

QUICK REFERENCE GUIDE TO DIABETES FOR HEALTH CARE PROVIDERS

A special project of the Michigan Diabetes Outreach Network

Chapter 5 Oral Pharmacological Treatment of Type 2 Diabetes

Pharmacological therapy is recommended after 6-12 weeks if an individualized meal plan, activity, and weight loss trial (if needed) have failed to control blood glucose (BG). If the BG remains above 126 mg/dl fasting and over 200 mg/dl 1-2 hours postprandial, pharmacological treatment should be initiated.

Those with extremely high blood glucose and symptoms (polyuria and polydipsia) may need insulin to be started immediately. Insulin may be needed for a short period of time or indefinitely. A review and alteration of the other medications one is taking may help to control blood glucose; hyperglycemia may result from nicotinic acid, thiazide diuretics (large doses), beta blockers, Indocin, Dilantin, corticosteroids and fertility agents.

There are currently 8 classifications of oral therapy for type 2 diabetes

- Sulfonylureas
- Meglitinides
- D-Phenylalanine Derivatives
- Biguanides
- Thiazolidinediones
- Alpha Glucosidase Inhibitors
- DPP-4 Inhibitors
- Bile Acid Sequestrant

Medication Failures

- After 5 years, approximately 50% of patients will require medication adjustments.
- Fasting plasma glucose 126-200 mg/dl may respond to monotherapy along with dietary management.
- Fasting plasma glucose 200-275 mg/dl may respond to a combination therapy.
- If combination therapy fails to control BG, insulin or other injectible medication is the next line of treatment - see Chapter 6 "Insulin and Other Drugs in the Treatment of Type 2 Diabetes."

Sulfonylureas

Primary Function: Stimulate the pancreas to make more insulin. Over time, the body's ability to make insulin may lessen. If this happens, these drugs lose their ability to control blood glucose.

Agent	Typical Dosage	Max dosage
1st Generation		
Tolbutamide (Orinase)	0.25-2.0 g/day (divided)	3 g/day
Tolazamide (Tolinase)	100-1000 mg/day (divided)	1000 mg/day
Chlorpropamide (Diabinese)	100-500 mg bid	750 mg/day
2nd Generation		
Glyburide (DiaBeta, Micronase)	1.25 – 5 mg bid	20 mg/day
Glyburide (Glynase)	0.75 – 12.0 mg/day	12 mg/day
Glipizide (Glucotrol)	2.5 – 20.0 mg bid	40 mg/day
Glipizide (Glucotrol XL)	2.5 – 10 mg bid	20 mg/day
Glimepiride (Amaryl)	1-4 mg/day	8 mg/day

Dosing

- Start at lowest possible dose and increase every 1-2 weeks until glucose control or maximum dose is reached.
- Renal insufficiency may require dose reduction.
- There is no benefit to using two sulfonylureas (i.e. Diabeta and Glucotrol) together.
- Fasting plasma glucose (FPG) 126-200 mg/dl may respond to monotherapy along with dietary management.
- FPG greater than 200 mg/dl may need 2 agents or insulin.
- If sulfonylurea alone fails to control blood glucose, combination therapy or insulin may be used to achieve blood glucose control.

Side Effects

- Hypoglycemia
- Weight gain
- Hyperinsulinemia
- Disulfiram like reaction with alcohol (1st generation only)
- Skin rashes
- GI (5%)
- Hepatic changes (rare)

Contraindications

- Type 1 diabetes
- Pregnancy and lactation
- Diabetic Ketoacidosis (DKA)
- Severe renal or hepatic disease
- Elderly, debilitated or malnourished persons
- Allergy to sulfa drugs
- Serious illness/severe infection
- Surgery or trauma

Candidates for Initial Use:

Type 2 diabetes, no dyslipidemia, not overweight and FPG > 20 mg/dl above target

Meglitinides

Repaglinide (Prandin)

Primary Function: Enhances insulin secretion. Is a short-acting agent. The amount of repaglinide-induced insulin release depends on the blood glucose level. Insulin release diminishes as the glucose level declines.

Precautions

- Has the potential to cause hypoglycemia, but to a lesser extent than sulfonylureas.
- May be taken with decreased kidney function.
- Longer half-life may be found with antifungals, erythromycin and clarithromycin.
- Accelerated repaglinide metabolism and shortened drug effect may be found with use of rifampin, phenobarbital, carbamazepine, and troglitazone.

Dosing

- Available in 0.5 mg, 1 mg and 2 mg dosage units. Maximum dose is 16 mg daily.
- Initial dose for clients not previously treated with BG lowering agents: 0.5 mg/meal.
- Initial dose for clients previously treated with BG lowering agents or A1C > 8%: 1-2 mg/meal.
- Take at the start of the meal. Number of daily doses is determined by the number of meals eaten.
- If a meal is skipped, the dose is skipped; if a meal is added, a dose is added for that meal.

Side Effects

- Hypoglycemia (16-31%)
- GI (4%)
- Upper respiratory infections
- Back pain
- Headache

Contraindications

- Type 1 diabetes
- Pregnancy and lactation
- Diabetic Ketoacidosis
- Hypersensitivity to its active ingredients
- Impaired hepatic function
- Back pain
- Headache

Candidates for Initial Use:

Type 2 diabetes, no dyslipidemia, with or without renal failure, not overweight, and FPG > 20 mg/dl above target

D-Phenylalanine Derivative

Nateglinide (Starlix)

Primary Function: Stimulates insulin secretion when needed (postprandial), then allows insulin concentrations to return to baseline.

Precautions

- Is very rapid-acting.
- Not recommended for combination with a sulfonylurea or Prandin.

Dosing

- Is available in 60 mg and 120 mg tablets.
- Typical dose: 120 mg taken just before meals (60 mg tid can be used for those near their A1C goal).
- Take at the start of the meal. Number of daily doses is determined by the number of meals eaten.
- If a meal is skipped, the dose is skipped; if a meal is added, a dose is added for that meal.

Side Effects

- Hypoglycemia (2.4%)
- Dizziness (3.6%)
- Weight gain of < 1 kg

Contraindications

- Type 1 diabetes
- Pregnancy and lactation
- Diabetic Ketoacidosis
- Hypersensitivity to its active ingredients

Candidates for Initial Use:

Type 2 diabetes with the ability to produce insulin, significant postprandial hyperglycemia not controlled by nutrition therapy and exercise.

Alpha Glucosidase Inhibitors

Acarbose (Precose) and Miglitol (Glyset)

Primary Function: Lowers postprandial BG by delaying carbohydrate digestion and slows absorption.

Benefits

- Does not cause hypoglycemia.
- Can decrease postprandial blood glucose by about 50 mg/dl and A1c by approximately 0.5-1%.

Precautions

- Generally will not be effective in the treatment of significant fasting hyperglycemia.
- If hypoglycemic reactions occur, oral glucose or lactose (not sucrose) must be used for treatment.
- Should not be used if the client is using any rapid-acting insulin {lispro (Humalog), aspart (Novolog) or glulisine (Apidra)}. Their mechanisms of action are similar.
- Should not be used with metformin--severe GI side effects may occur.
- Check serum transaminase level every 3 months during the first year and then periodically. If elevated, discontinue acarbose. (Liver abnormalities do not seem to be a concern with miglitol.)

Dosing and Administration

- Both are available in 25 mg, 50 mg and 100 mg tablets.
- Given with the first few bites of major meals.
- **Precose:** starting dose 25 mg qd (to decrease side effects), add second dose after 2 weeks and third dose after an additional 2 weeks. Increase to 50 mg tid for 4-8 weeks .
 - Maximum dose for those under 60 kg : 50 mg tid
 - Maximum dose for those 60 kg and over: 100 mg tid
- **Glyset:** starting dose of 25 mg tid for 4-8 weeks, then 50 mg tid for 3 months. Increase to 100 mg tid if tolerated and needed.
 - Maximum dose: 100 mg tid
- May be used alone or in combination therapy.

Side Effects

- Most common: GI (abdominal pain, diarrhea, flatulence)
- Increased serum AST or ALT (Acarbose doses > 200 mg tid)

Contraindications

- Hypersensitivity to its active ingredients
- Safety not tested for pregnancy or lactation.
- Chronic intestinal problems or diseases present (inflammatory bowel disease, colonic ulceration, obstructive bowel disease and gastroparesis).
- Severe liver and renal disease (creatinine > 2.0).

Candidates for Initial Use:

Type 2 diabetes, dyslipidemia, obesity, and significant postprandial hyperglycemia

Biguanides

Metformin (Glucophage, Glucophage XR, Fortamet, Glumetza, Riomet)

Primary Function: Decreases glucose output from the liver. Does not stimulate insulin release.

Benefits

- Controls BG without causing hypoglycemia or weight gain in most people. A 2-5 kg weight loss is typical.
- Studies show a decrease in triglycerides (16%), LDL-cholesterol (8%) and total cholesterol (5%); along with an increase in HDL-cholesterol (2%).

Precautions

- Educate client to immediately report symptoms associated with lactic acidosis (severe weakness, cold, labored breathing, stomach pain, light headed or irregular heart rate).
- Evaluate kidney and liver (LFT) before initiating metformin. Test creatinine and LFTs every 6-12 months while on metformin therapy.

Dosing

- **Metformin (Glucophage)** is available in 500 mg and 850 mg and 1000 mg dosage units.
- Start at 500 mg twice a day or 850 mg once daily with meals. Increase by 500 mg (weekly) or 850 mg (every 2 weeks) to a usual dosage of 2000 mg. Maximum dosage is 2000 mg daily (ages 10-16 years) and 2550 mg (17 and older). Doses of 2550 mg is best taken three times daily. Clinically significant responses are NOT seen at doses less than 1500 mg per day.
- **Glumetza, Fortamet and Glucophage XR** are extended release formulas.
- Glucophage XR is available in a 500 mg and 750 mg dosage units. Maximum dosage is 2550 mg. Start at 500 mg with evening meal. Increase by 500 mg every week up to a maximum effective dose of 2000 mg once daily.
- Glumetza and Fortamet are available in 500 mg and 1000 mg dosage units. Start with 1000 mg once daily with the evening meal and titrate up (500 mg weekly) as tolerated to a maximum dosage of 2000 mg a day.
- **Riomet** is a liquid form of metformin. 5 ml of Riomet is equal to 500 mg of the tablet form of metformin.

Side Effects

- **Common:** GI (abdominal bloating, nausea, cramping, diarrhea, feeling of fullness)
- **Minor effects:** agitation, headache, metallic taste
- **Rare:** lactic acidosis, reduction of B12 levels

Contraindications

- Type 1 diabetes
- Pregnancy and lactation
- Hypersensitivity to its active ingredients
- Acute or chronic of lactic acidosis
- Hepatic dysfunction
- Renal dysfunction: serum creatinine >1.5 mg/dl (men) and >1.4 mg/dl (women)
- Over age 80
- Severe dehydration
- Severe infection
- Low blood oxygen levels
- History of alcoholism or binge drinking
- Metformin should be temporarily discontinued in any situation that predisposes the individual to acute renal dysfunction including:
 - Cardiac collapse
 - Acute myocardial infarctions
 - Acute exacerbated congestive heart disease.
 - Use of iodinated contrast media (withhold 48 hours before and after test)

Candidates for Initial Use:

Type 2 diabetes, dyslipidemia, obesity or genetic factors favoring insulin resistance and FPG > 20 mg/dl above target

Thiazolidinediones

Pioglitazone (Actos) and Rosiglitazone (Avandia)

Primary Function: Decreases insulin resistance and increases glucose uptake in muscle and adipose tissue.

Benefits

- Useful in those with renal dysfunction or other conditions in which metformin is contraindicated.
- Generally well tolerated.

Precautions

- Due to concern with Avandia causing new or worsened heart failure and other heart conditions leading to increased risk of angina or myocardial infarction, notify doctor with following side effects:
 - Swelling or fluid retention (especially the ankles or legs)
 - Shortness of breath or difficulty breathing
 - Unusually rapid weight gain
 - Chest pain or pressure

- Liver function testing should occur with Actos and Avandia. Check serum transaminase levels (ALT) prior to starting therapy, every 2 months during the first year, then periodically.
- Check liver function immediately if signs of hepatic dysfunction occur (nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice)
 - Do not use if ALT exceeds 2.5 times the upper limit of normal or if active liver disease is present.
 - If ALT exceeds 3 times the upper limit of normal during treatment, recheck as soon as possible. Discontinue drug if ALT remains > 3 times the upper limit of normal.

Dosing – Actos

- Approved for monotherapy or in combination with sulfonylurea, metformin or insulin
- Available in 15 mg, 30 mg and 45 mg tablets.
- Initial starting dose in monotherapy or combination therapy is 15 mg or 30 mg once daily, taken without regard to meal. Maximum dose is 45 mg once per day
- If used with insulin, may need to decrease insulin dose by 10-25% if hypoglycemia occurs.
- Sulfonylurea dose may need to be lowered if hypoglycemia occurs.
- May decrease triglycerides (5-26%) and increase HDL-cholesterol (6-13%).

Dosing - Avandia

- Approved for monotherapy or for use with sulfonylurea, metformin or insulin.
- Avandia is available in 2 mg, 4 mg and 8 mg tablets.
- Usual starting dose is 2 mg/day - single dose or divided into 2 doses/day.
- Max dose 8 mg/day. 4 mg bid is more effective than 8 mg once a day.
- Studies show small increases in HDL-cholesterol and LDL-cholesterol.

Side Effects

- Increased hepatic enzymes
- Weight gain
- Edema/fluid retention
- May make oral contraceptive less effective
- Bone fractures in females (hand, upper arm or foot)
- Macular edema
- Anemia

Contraindications

- Pregnancy or lactation
- Children
- Hepatic dysfunction
- Heart Failure (NYHA Class III or IV)
- Those with macular edema
- Pre menopausal anovulatory women with insulin resistance

Candidates for Initial Use:

Type 2 diabetes, obesity or genetic factors favoring insulin resistance and FPG > 20 mg/dl above target

DPP-4 Inhibitors

Januvia (sitagliptin phosphate)

Primary Function: Enhance a natural body system called the incretin system, which helps to regulate glucose by affecting the alpha and beta cells in the pancreas. The action of DPP-4 inhibitors is glucose –dependent, responding to the presence of elevated glucose and resulting in the release of insulin and decrease of glucagon only when needed

Benefit:

- Lower potential for hypoglycemia

Precautions:

- Because Januvia is renally eliminated, and to achieve plasma concentrations of Januvia similar to those with normal renal function, a dose adjustment is recommended in those with moderate renal insufficiency and in those with severe renal insufficiency or with end-stage renal disease(ESRD) requiring hemo- or peritoneal dialysis.
- Safety and effectiveness of Januvia in pediatric clients have not been established.
- There are no adequate and well-controlled studies in pregnant women, Januvia should be used during pregnancy only if clearly needed.
- Caution should be exercised when Januvia is administered to a nursing woman.
- Used in treatment of type 2 diabetes only.

Dosing:

- 100 mg once daily, with or without food, for all approved indications.
- Maximum daily dose is 100 mg once daily.

Side Effects:

- **Most common** (≥5 % and higher than placebo): stuffy/runny nose and sore throat, URI , headache and nausea

Contraindications

- Type 1 diabetes
- Pregnancy and lactation
- Diabetic Ketoacidosis
- Hypersensitivity to its active ingredients

Bile Acid Sequestrant Welchol (colesevelam HCL)

Primary Function: Lowers LD cholesterol. Unknown mechanism of lowering BG level. Theorized to impact GLP-1.

Benefit:

- Lower A1C (~0.5-0.8 %) as well as LDL cholesterol (15-18%)
- No weight gain
- Ok to use in those with renal and liver impairment

Precautions:

- May increase triglycerides (especially if used in combination with a sulfonylurea or insulin). Use caution if TG levels are greater than 300 mg/dl.
- May decrease absorption of fat soluble vitamins (A, D, E, K). Must take vitamins 4 hours prior to Welchol.
- Use caution in those treated for Vitamin K deficiency, bariatric surgery, GI problems or gastroparesis.
- May decrease absorption of glyburide, some oral contraceptives and levthyroxine. Must administer these meds 4 hours prior to Welchol.

Dosing:

- Available in 625 mg pills.
- Recommended dosage is 3.8 mg daily (Six 625 mg tablets at once or three 625 mg tablets bid or two 625 mg tablets tid).
- Take with meals and lots of liquids.

Side Effects:

- **Most common:** Constipation (~10%)
- Dyspepsia (8%)
- Nasopharyngitis (3%)
- Nausea (4%)

Contraindications:

- Pregnancy or lactation
- Children
- Type 1 or DKA
- Hypersensitivity to its active ingredients
- Those with TG levels greater than 500 mg/dl
- History of hypertriglyceridemia-induced pancreatitis
- History of bowel obstruction

Candidates for Initial Use:

For those with primary hyperlipidemia and/or type 2 diabetes who need additional A1C and LDL lowering. Can be used in combination with sulfonylureas, metformin and insulin.

Combination Therapy

Candidates for Combination Therapy: When other therapies reach maximum doses and target BG levels not met (FPG > 140 mg/dl, postprandial BG > 180 mg/dl, A1C > 7-8%).

Glucovance (glyburide/metformin)

- Available in 1.25 mg/250 mg, 2.5 mg /500 mg and 5 mg /500 mg dosage units.
- Take twice a day with meals. Start at a low dose and titrate up. Do not exceed 20 mg glyburide/2000 mg metformin.
- Side effects similar to those noted for glyburide and metformin.
- Contraindicated in those populations not indicated for use of glyburide and metformin.

Metaglip (glipizide/metformin)

- Available in 2.5 mg/250 mg, 2.5 mg/500 mg and 5 mg/500 mg dosage units.
- Take twice a day with meals. Start at a low dose and titrate up. Do not exceed 20 mg glipizide/2000 mg metformin.
- Side effects similar to those noted for glipizide and metformin.
- Contraindicated in those populations not indicated for use of glipizide and metformin.

AvandaMet (Avandia/metformin)

- Available in 1 mg /500 mg, 2 mg/500 mg, 4 mg/500 mg, 2 mg/1000 mg and 4 mg/1000 mg dosage units.
- Take twice a day with meals. Start at a low dose and titrate up. Do not exceed 8 mg Avandia/2000 mg metformin.
- Side effects similar to those noted for rosiglitazone (Avandia) and metformin.
- Contraindicated in those populations not indicated by use of rosiglitazone (Avandia) and metformin.

ACTOplus Met (Actos/metformin)

- Available in 15 mg/500 mg or 15 mg/850 mg dosage units.
- Take twice a day with meals. Start at a low dose and titrate up. Do not exceed 45 mg Actos/2550 mg metformin.
- Side effects similar to those noted for pioglitazone (Actos) and metformin.
- Contraindicated in those populations not indicated by use of pioglitazone (Actos) and metformin.

Avandaryl (Avandia/glimepiride)

- Available in 4 mg/1 mg, 4 mg/2 mg and 4 mg/4 mg dosage units.
- Take once a day with the first main meal. Start at a low dose and titrate up. Do not exceed 8 mg Avandia/8 mg glimepiride (Amaryl).
- Side effects similar to those noted for rosiglitazone (Avandia) and glimepiride (Amaryl).
- Contraindicated in those populations not indicated by use of rosiglitazone (Avandia) and glimepiride (Amaryl).

Duetact (Actos/glimepiride)

- Available in 30 mg/2 mg and 30 mg/4 mg dosage units.
- Take once a day with the first main meal. Start at a low dose and titrate up. Do not exceed 30 mg Actos/8 mg glimepiride (Amaryl).
- Side effects similar to those noted for pioglitazone (Actos) and glimepiride (Amaryl).
- Contraindicated in those populations not indicated by use of pioglitazone (Actos) and glimepiride (Amaryl).

Janumet (Januvia/metformin)

- Available in 50-mg/500mg and 50 mg/1000mg dosage units.
- Take twice daily with meals. Start at a low dose and titrate up. Do not exceed 100 mg of sitagliptin (Januvia)/2000 mg of metformin.
- Side effects are similar to those for sitagliptin (Januvia) and metformin. The most common being nasopharyngitis.
- Contraindicated in those populations not indicated by use of sitagliptin (Januvia) and metformin.

Prandimet (replaglinide/metformin)

- Available in 1-mg/500mg and 2-mg/500mg dosage units.
- Take 2-3 times a day with meal. Start at a low dose and titrate up. Do not exceed 10 mg of replaglinide (Prandin)/2500 mg of metformin per day or 4 mg replaglinide (Prandin)/1000 mg of metformin per meal.
- Side effects similar to those noted for replaglinide (Prandin) and metformin.
- Contraindicated in those populations not indicated for use of replaglinide (Prandin) and metformin.

References:

Mensing C et al. (2006). The Art and Science of Diabetes Self-Management Education. American Association of Diabetes Educators, Chicago.

American Diabetes Association (2008). Clinical Practice Recommendations. Diabetes Care. Supplement. Vol 31(1).