

Joslin Diabetes Center & Joslin Clinic
Clinical Guideline for Pharmacological Management of Type 2 Diabetes
1/09/2009

The objective of the *Joslin Diabetes Center & Joslin Clinic Clinical Guideline for Pharmacological Management of Type 2 Diabetes* is to support clinical practice and influence clinical behavior to improve outcomes and assure quality of care according to accepted standards. The Guideline was established after careful review of current evidence, literature and clinical practice. This Guideline will be reviewed periodically and modified to reflect changes in clinical practice and available pharmacological information.

This Clinical Guideline is not intended to serve as a mandatory standard, but rather to provide a set of recommendations for patient care management. These recommendations are not a substitute for sound and reasonable clinical judgment or decision-making and do not exclude other options. Clinical care must be individualized to the specific needs of each patient and interventions must be tailored accordingly. The Guideline has been created to address initial presentations and treatment strategies in the adult non-pregnant patient population. The Guideline is not a substitution for full prescribing information. Refer to Joslin's *Clinical Guideline for Adults with Diabetes* for additional, more comprehensive information on diabetes care and management.

Diabetes Mellitus – Diagnostic Criteria (Non-Pregnant Adults)

- Casual plasma glucose ≥ 200 mg/dl and symptoms of diabetes (polyuria, polydipsia, ketoacidosis, or unexplained weight loss) **OR**
 - Fasting plasma glucose (FPG)* ≥ 126 mg/dl **OR**
 - Results of a 2-hour 75-g Oral Glucose Tolerance Test (OGTT)* ≥ 200 mg/dl
- * *These tests should be confirmed by a repeat test, on a different day, unless unequivocally high*

Goals of Glycemic Control for People with Diabetes¹

Biochemical Index	Normal	Goal ²
Fasting Plasma Glucose or Preprandial Glucose (mg/dl)	< 100	70 – 130
Postprandial 2 hours (mg/dl)	< 140	< 180
Bedtime Glucose (mg/dl)	< 120	90 – 150
A1C (%) - sustained	< 6%	< 7% ³

INITIAL TREATMENT STRATEGY

Medical nutrition therapy (MNT), physical activity, blood glucose monitoring and patient education are the cornerstones of diabetes management for all patients. Pharmacological management should be used in combination with MNT and physical activity. Current weight status and lifestyle should be considered when choosing initial pharmacological therapy.

Initial Presentation (Based on presentation of the items listed within each box)

- Mild or no symptoms *AND*
- Negative ketones *AND*
- No acute concurrent illness *AND*
- A1C \leq 7.5%

- FPG $>$ 150 mg/dl⁴ *OR*
- Random $>$ 250 mg/dl⁴ *AND/OR*
- A1C $>$ 7.5%
- Does not meet criteria for mild or severe

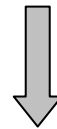
- Marked hyperglycemia *OR*
- Significant weight loss *OR*
- Severe/significant symptoms *OR*
- 2+ or greater ketonuria *OR*
- DKA/ hyperosmolar state *OR*
- Severe intercurrent illness or surgery

Start MNT and Physical Activity and Consider Addition of Metformin

If after 6-8 weeks, target not met

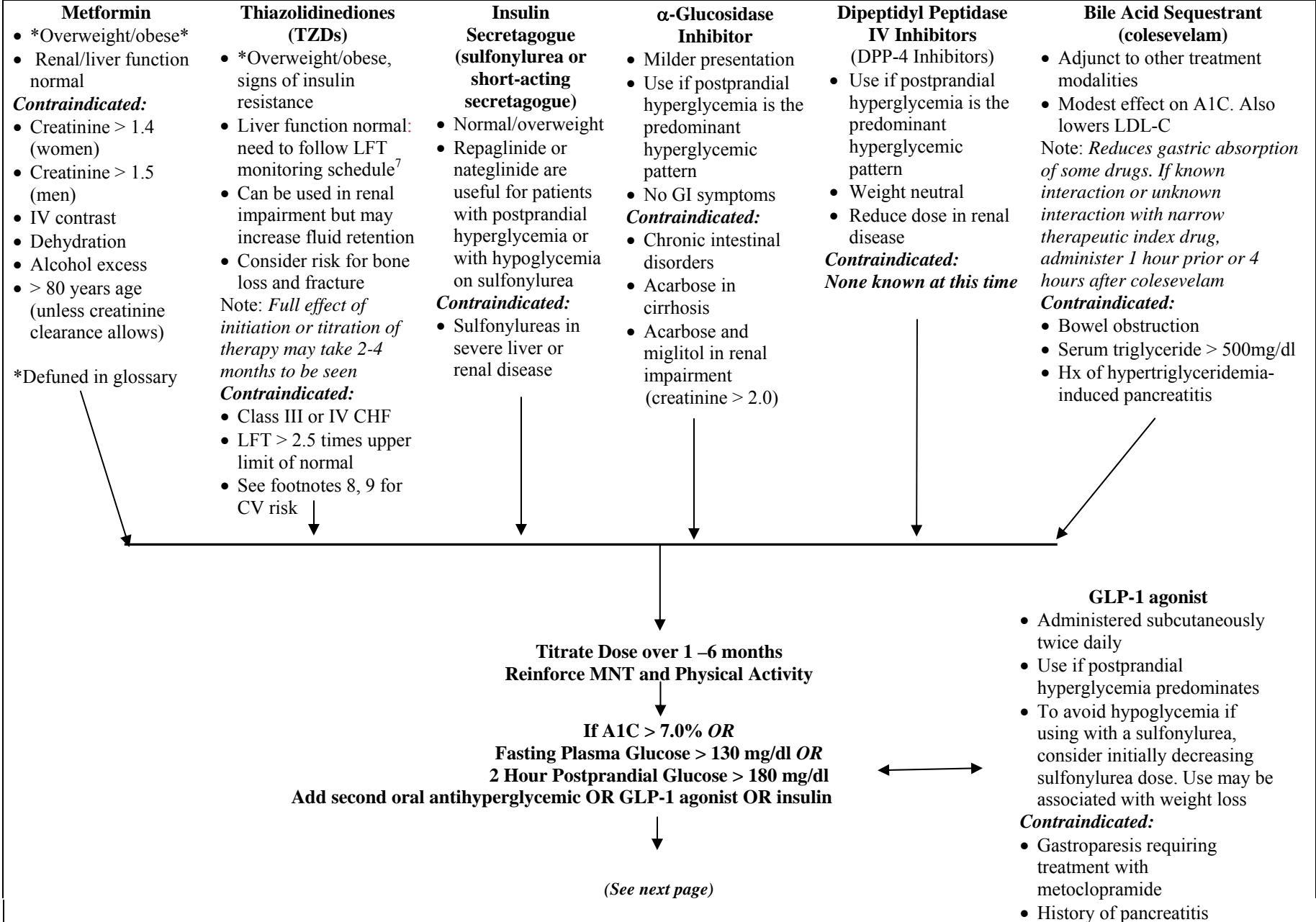
Start Oral Antihyperglycemic Therapy

Start Insulin Immediately⁵



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CONSIDERATIONS FOR SELECTING INITIAL NON-INSULIN ANTIHYPERGLYCEMIC THERAPY⁶

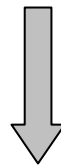


ANTIHYPERGLYCEMIC THERAPY . continued

Suggested well-studied combinations based on results of clinical studies. These do not preclude other combinations:

- Insulin secretagogue and metformin**
- Sulfonylurea and α -glucosidase inhibitor
- Thiazolidinediones and sulfonylurea**
- Thiazolidinediones and metformin**
- Thiazolidinediones and repaglinide
- Thiazolidinediones and exenatide
- Sulfonylurea and exenatide
- Metformin and exenatide
- Dipeptidyl Peptidase IV Inhibitors and sulfonylurea
- Dipeptidyl Peptidase IV Inhibitors and metformin**
- Dipeptidyl Peptidase IV Inhibitors and pioglitazone
- Colesevelam and sulfonylurea
- Colesevelam and metformin

** Also available in fixed combinations



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ANTIHYPERGLYCEMIC THERAPY, continued

A1C > 7.0% *OR*
Fasting Plasma Glucose > 130 mg/dl *OR*
2 Hour Postprandial Plasma Glucose > 180 mg/dl

Add:

**Additional Oral
Antihyperglycemic
Medication
of Different Class**¹⁰

- or*
- Insulin**^{10,11,12}
- or*
- GLP-1
agonist**¹⁰
- Consider starting with.
 - Intermediate-acting insulin (NPH) once or twice daily as part of a conventional program
 - Long-acting insulin (detemir or glargine) once or twice daily for basal therapy
 - Pre-supper insulin mixture (75/25 lispro, 50/50 lispro, 50/50 aspart, 70/30 aspart, 70/30 human insulin, or 50/50 human insulin)
 - Suggested starting dose for injectable insulin: 0.1-0.2 units/kg ideal body weight
 - Titrate/adjust insulin dosage to achieve glucose goals

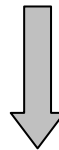
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If target glucose not met after 2-4 months, consider:

- Changing to multidose insulin therapy using combination of rapid, short, intermediate, or long-acting insulin
 - Adding pre-meal rapid or short-acting insulin (e.g. aspart, glulisine, lispro or regular) pre-meals, to bedtime intermediate or long-acting insulin
 - Adding bedtime basal insulin and adjusting the rapid or short-acting insulin as needed if taking pre-meal insulin and postprandial glucose targets are met, but fasting glucose is elevated
 - Adding oral antihyperglycemic medication to reduce insulin resistance or improve glycemic control if already on insulin (metformin, TZDs¹³, sulfonylureas, α -glucosidase inhibitors, and colesevelam are approved for use in combination with insulin)
- ↓
- If post-prandial excursions predominate, refer to endocrinologist for intensification of therapy or for consideration of pramlintide use

Oral Antihyperglycemic Medications Available in the USA

Biguanides	TZDs (Thiazolidinedi- ones)	α - Glucosidase Inhibitors	Insulin Secretagogues	Dipeptidyl Peptidase IV Inhibitors (DPP-4 Inhibitors)	Bile Acid Sequestrant	Fixed Combinations
<ul style="list-style-type: none"> liquid metformin* (<i>Riomet</i>) metformin (<i>Glucophage</i>) metformin extended release (<i>Glucophage XR</i>, <i>Fortamet</i>, <i>Glumetza</i>) <p>(metformin and metformin ER available as generic medication)</p> <p>* Liquid formulation for patients unable to swallow pills</p>	<ul style="list-style-type: none"> pioglitazone (<i>Actos</i>) rosiglitazone (<i>Avandia</i>) 	<ul style="list-style-type: none"> acarbose (<i>Precose</i>) miglitol (<i>Glyset</i>) 	<p>Sulfonylureas</p> <ul style="list-style-type: none"> glimepiride (<i>Amaryl</i>) glipizide (<i>Glucotrol</i>) glipizide extended release (<i>Glucotrol XL</i>) glyburide (<i>Micronase</i>, <i>Diabeta</i>) micronized glyburide (<i>Glynase</i>) <p>(glimepiride, glipizide and glyburide are available as generic medications)</p> <p>Non-sulfonylurea Meglitinides</p> <ul style="list-style-type: none"> repaglinide (<i>Prandin</i>) <p>D-phenylalanine Derivatives</p> <ul style="list-style-type: none"> nateglinide (<i>Starlix</i>) 	<ul style="list-style-type: none"> sitagliptin (<i>Januvia</i>) 	<ul style="list-style-type: none"> colesevelam (<i>Welchol</i>) 	<ul style="list-style-type: none"> metformin and glipizide (<i>Metaglip</i>) metformin and glyburide (<i>Glucovance</i>) metformin and pioglitazone (<i>Actoplus met</i>) pioglitazone and glimepiride (<i>Duetact</i>) rosiglitazone and glimepiride (<i>Avandaryl</i>) rosiglitazone and metformin (<i>Avandamet</i>) sitagliptin and metformin (<i>Janumet</i>) repaglinide and metformin (<i>PrandiMet</i>)



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INJECTABLE DIABETES MEDICATIONS

INSULIN CHART¹⁴

Insulin Type	Product	Onset	Peak	Duration
Rapid-Acting				
Insulin aspart analog Insulin glulisine analog Insulin lispro analog	NovoLog Apidra Humalog	10 – 30 minutes	30 minutes – 3 hours	3 – 5 hours
Short-Acting				
Human Regular	Humulin R Novolin R	30-60 minutes	2 – 5 hours	up to 12 hours*
Intermediate-Acting				
Human NPH insulin	Humulin N Novolin N	90 minutes – 4 hours	4 – 12 hours	up to 24 hours**
Long-Acting				
Insulin detemir Insulin glargine	Levemir Lantus	45 minutes -4 hours	Minimal peak	up to 24 hours ***

Premixed Insulin Combinations

Insulin Type	
50% NPH; 50% Regular	Humulin 50/50
70% NPH; 30% Regular	Humulin 70/30
70% NPH; 30% Regular	Novolin 70/30
50% lispro protamine suspension, 50% lispro	Humalog Mix 50/50
50% aspart protamine suspension, 50% aspart	Novolog Mix 50/50
75% lispro protamine suspension, 25% lispro	Humalog Mix 75/25
70% aspart protamine suspension, 30% aspart	NovoLog Mix 70/30

*Usual clinical relevance can be less than 12 hours

** Usual clinical relevance can be less than 24 hours. Often requires twice daily dosing

*** Individual response may require twice daily dosing

INCRETIN MIMETICS AND NON-INSULIN SYNTHETIC ANALOGS

Product	Mechanism of Action	Type of Diabetes	# of Injections Per Day
Exenatide (Byetta)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins.	2	2
Pramlintide (Symlin)	Synthetic analog of human amylin, a naturally occurring hormone made in the beta cells, which slows gastric emptying, suppresses glucagon secretion, and regulates food intake. A significant reduction in insulin dose may be required when insulin is used in conjunction with pramlintide.	1 and 2	1-4 (with meals)

Footnotes:

¹Laboratory methods measure plasma glucose. Most glucose monitors approved for home use calibrate whole blood glucose readings to plasma values. Plasma glucose values are 10-15% higher than whole blood glucose values. It is important for people with diabetes to know whether their meters and strips record whole blood or plasma results.

²Goals should be individualized based on the following, including: co-morbidity, age, duration of diabetes, hypoglycemic awareness.

³The true goal of care is to bring the A1C as close to normal as safely possible. A goal of < 7% is chosen as a practical level for most patients using medications that may cause hypoglycemia to avoid the risk of that complication. Achieving normal blood glucose is recommended if it can be done practically and safely.

⁴If diet history reveals markedly excessive carbohydrate intake, may consider initial trial of MNT and physical activity before initiating oral agent therapy even though glucose levels are above the thresholds listed.

⁵Some patients with type 2 diabetes initially stabilized on insulin may be considered for transition to non-insulin anti-hyperglycemic therapy as blood glucose control permits.

⁶A combination of two drugs of different classes may be used as initial pharmacotherapy when there is marked hyperglycemia or when MNT and physical activity alone have not resulted in an A1C of < 7.0%

FDA Requirements for LFT monitoring for thiazolidinediones (TZDs):

If initial ALT is > 2.5 times normal, do not start this medication

Once TZD is started, monitor ALT periodically thereafter according to clinical judgement.

If ALT is > 2.5 times normal during treatment, check weekly. If rise persists or becomes 3 times > normal, **discontinue** TZD.

⁸Thiazolidinediones cause or exacerbate congestive heart failure in some patients. After initiation of TZDs and after dose increases, observe patients carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of the TZD must be considered. TZDs are not recommended in patients with symptomatic heart failure or in patients with established NYHA Class III or IV heart failure.

⁹A meta-analysis of 42 clinical studies (mean duration 6 months; 14,237 total patients), most of which compared rosiglitazone to placebo, showed rosiglitazone to be associated with an increased risk of myocardial ischemic events such as angina or myocardial infarction. Three other studies (mean duration 41 months; 14,067 total patients), comparing rosiglitazone to some other approved oral antihyperglycemic agents or placebo, have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive.

¹⁰If therapeutic goals are not met, consider starting insulin. Stop exenatide and DPP-IV inhibitor when starting insulin.

¹¹May need to taper and discontinue some or all oral antihyperglycemic medications as insulin is initiated and adjusted, particularly if using short or rapid-acting and basal insulins.

¹²Pre- and postprandial blood glucose should be checked. Frequency of checking may vary between 1-4 times/day depending on individual patient and status of glycemic control.

¹³There is an increased risk for edema when insulin and a thiazolidinedione are used together. Rosiglitazone should not be used in combination with insulin.

¹⁴The onset, peak and duration of any insulin type depends on many factors. Patients may experience variations in timing and/or intensity of insulin activity due to dose, site of injection, temperature of the insulin, level of physical activity, in addition to other factors. Therefore, the time action profile (TAP) should be considered as only reasonable estimates of the action of an insulin.

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Approved by Joslin Clinical Oversight Committee on 01/09/2009.

Glossary and Common Abbreviations

A1C: glycohemoglobin (hemoglobin A1C)

ALT: alanine aminotransferase

BMI: body mass index; normal = 18.5-24.9 kg/m²; overweight = 25.0-29.9 kg/m² (> 23 kg/m² in Asian populations); obese = ≥ 30 kg/m² (23-27 kg/m² in Asian populations)

Casual plasma glucose: a random plasma glucose

CHF: congestive heart failure

CV: cardiovascular

DPP-4: Dipeptidyl Peptidase IV Inhibitors

FDA: Food and Drug Administration

FPG: fasting plasma glucose

G: gram

GLP-1: Glucagon-like peptide-1 is secreted by the intestinal L cell in response to food intake, impacting glucose regulation.

HS: bedtime

Incretin: hormone produced by the gastrointestinal tract in response to food intake and necessary for glucose homeostasis

Incretin mimetics: a class of agents used for managing type 2 diabetes that mimics the enhancement of glucose-dependent insulin secretion and other gluco-regulatory actions of naturally occurring incretins

Kg: kilogram

LDL-C: low density lipoprotein, cholesterol

LFT: liver function tests

Mg: milligram

Mg/dl: milligram per deciliter

MNT (Medical Nutrition Therapy): Begins with assessment of overall nutrition status, followed by individualized prescription for treatment. Registered dietitian considers food intake, physical activity, course of any medical therapy, individual preferences and other factors.

Obesity: BMI ≥ 30 kg/m²

Overweight: BMI = 25.0-29.9 kg/m²

PFTs: pulmonary function tests

Rx: treatment

TAP: time action profile

TZDs: thiazolidinediones

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