

**Joslin Diabetes Center & Joslin Clinic**  
**Clinical Guideline for Pharmacological Management of Type 2 Diabetes**  
 10 28 2011

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)**

- Random plasma glucose  $\geq 200$  mg/dl and symptoms of diabetes (polyuria, polydipsia, ketoacidosis, or unexplained weight loss) **OR**
- Fasting plasma glucose (FPG)\*  $\geq 126$  mg/dl **OR**
- Results of a 2-hour 75-g Oral Glucose Tolerance Test (OGTT)\*  $\geq 200$  mg/dl **OR**
- Glycated Hemoglobin (A1C)  $\geq 6.5\%$ \*\* .

\* *These tests should be confirmed by a repeat test, on a different day, unless unequivocally high*

\*\* *Only an A1C test that has been referenced to an accepted laboratory method (standardized) should be utilized for diagnostic purposes*

**Goals of Glycemic Control for People with Diabetes**<sup>1</sup>

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

## 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 characteristics listed within each box)

- Mild or no symptoms *AND*
- Negative ketones *AND*
- No acute concurrent illness *AND*
- A1C  $\leq 7.0\%$

- FPG  $> 150$  mg/dl<sup>4</sup> *OR*
- Random  $> 250$  mg/dl<sup>4</sup> *AND/OR*
- A1C  $> 7.0\%$
- 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 metformin.  
Choose alternate drug if metformin is contraindicated

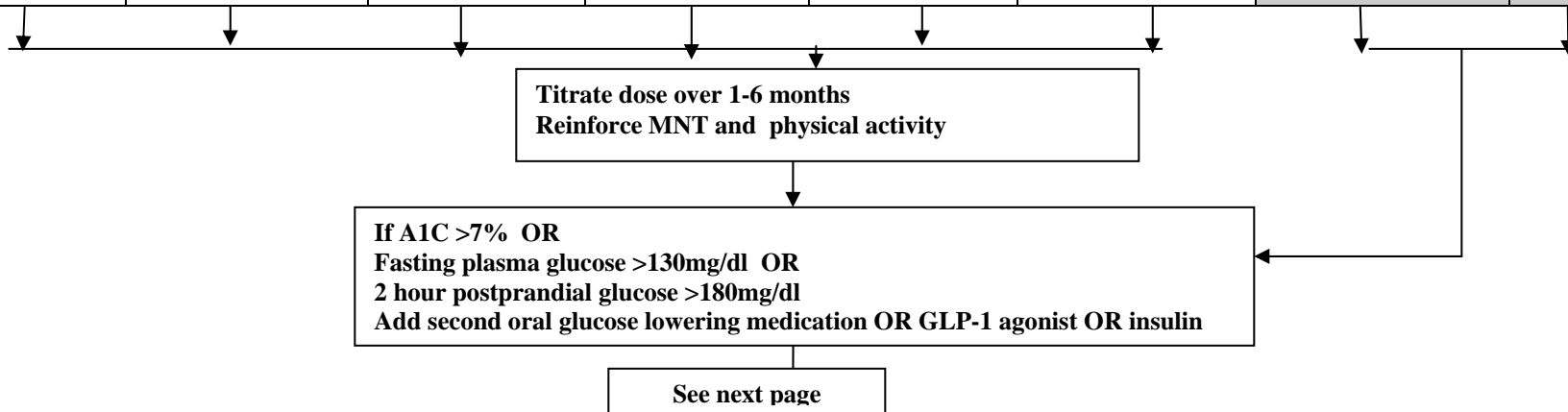
Start insulin immediately <sup>5</sup>

See page 5 – Add Insulin

See next page: CONSIDERATIONS FOR SELECTING NON-INSULIN GLUCOSE LOWERING MEDICATIONS

## CONSIDERATIONS FOR SELECTING NON-INSULIN GLUCOSE LOWERING MEDICATIONS

INITIAL THERAPY						ADJUNCT THERAPY	
<p><b>Metformin</b></p> <ul style="list-style-type: none"> <li>• Use only if renal/liver function normal</li> </ul> <p><b>Contraindicated with:</b></p> <ul style="list-style-type: none"> <li>• Creatinine &gt; 1.4 (women)</li> <li>• Creatinine &gt; 1.5 (men)</li> <li>• IV contrast use</li> <li>• Dehydration</li> <li>• Alcohol excess</li> <li>• &gt; 80 years age (unless creatinine clearance allows)</li> </ul>	<p><b>Insulin Secretagogue (sulfonylurea or meglitinide)</b></p> <ul style="list-style-type: none"> <li>• Repaglinide or nateglinide are useful for patients with postprandial hyperglycemia or with hypoglycemia on sulfonylurea</li> </ul> <p><b>Contraindicated:</b></p> <ul style="list-style-type: none"> <li>• Sulfonylureas in severe liver or renal disease</li> </ul>	<p><b>α-Glucosidase Inhibitor</b></p> <ul style="list-style-type: none"> <li>• Use if postprandial hyperglycemia is the predominant hyperglycemic pattern</li> </ul> <p><b>Contraindicated:</b></p> <ul style="list-style-type: none"> <li>• Chronic intestinal disorders</li> <li>• Acarbose in cirrhosis</li> <li>• Acarbose and miglitol in renal impairment (creatinine &gt; 2.0)</li> </ul>	<p><b>Thiazolidinediones (TZDs)</b></p> <ul style="list-style-type: none"> <li>• Follow LFT monitoring schedule<sup>7</sup></li> <li>• Can be used in renal impairment but may increase fluid retention</li> <li>• Consider risk for bone loss and fracture</li> </ul> <p>Note: <i>Full effect of initiation or titration of therapy may take 2-4 months to be seen</i></p> <p><b>Contraindicated:</b></p> <ul style="list-style-type: none"> <li>• Class III or IV CHF</li> <li>• LFTs &gt; 2.5 times upper limit of normal</li> </ul> <p><b>See footnotes 8, 9, 13 for CV and other risks</b></p>	<p><b>Dipeptidyl Peptidase IV Inhibitors (DPP-4 Inhibitors)</b></p> <ul style="list-style-type: none"> <li>• Use if postprandial hyperglycemia is the predominant hyperglycemic pattern</li> <li>• Weight neutral</li> <li>• Reduce dose in renal disease with some members of the class</li> <li>• Synergistic with metformin</li> <li>• Reports of post marketing pancreatitis</li> </ul> <p><b>Contraindicated:</b> hx of pancreatitis</p>	<p><b>GLP-1 agonist</b></p> <ul style="list-style-type: none"> <li>• Use if postprandial hyperglycemia predominates</li> <li>• To avoid hypoglycemia if using with a sulfonylurea or insulin glargine, consider initially decreasing sulfonylurea or glargine dose.</li> <li>• Use may be associated with weight loss</li> </ul> <p><b>Contraindicated:</b></p> <ul style="list-style-type: none"> <li>• Gastroparesis requiring treatment with metoclopramide</li> <li>• History of pancreatitis</li> <li>• Liraglutide is contraindicated in the setting of personal or fm hx of medullary thyroid cancer or patients with MEN2</li> </ul>	<p><b>Bile Acid Sequestrant (colesevelam)</b></p> <ul style="list-style-type: none"> <li>• Modest effect on A1C. Also lowers LDL-C</li> </ul> <p>Note: <i>Reduces gastric absorption of some drugs. If known interaction or unknown interaction with narrow therapeutic index drug, administer 1 hour prior or 4 hours after colesevelam</i></p> <p><b>Contraindicated:</b></p> <ul style="list-style-type: none"> <li>• Bowel obstruction</li> <li>• Serum triglyceride &gt; 500mg/dl</li> <li>• Hx of hypertriglyceridemia-induced pancreatitis</li> </ul>	<p><b>Centrally Acting Agent (bromocriptine mesylate)</b></p> <ul style="list-style-type: none"> <li>• Use as monotherapy or combination therapy</li> <li>• Most effective when used in combination with other antihyperglycemic medications</li> <li>• Modest effect on A1C</li> </ul> <p><b>Contraindicated:</b> Should not be taken by nursing mothers, or by patients who take ergot medicines or have syncopal migraines</p>



## ADVANCING GLUCOSE LOWERING MEDICATION THERAPY

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

↓  
**Add:**

Additional oral  
glucose lowering  
medication  
of Different Class<sup>10</sup>

*or*

Insulin<sup>10,11,12</sup>

*or*

GLP-1 agonist<sup>10</sup>

- 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, or 70/30 human insulin)
- Suggested starting dose for insulin: 0.1-0.2 units/kg ideal body weight
- Titrate/adjust insulin dosage to achieve glucose goals



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

- Combining exenatide with glargine
  - Adding pre-meal rapid or short-acting insulin (e.g. aspart, glulisine, lispro or regular) to bedtime intermediate or long-acting insulin
  - Adding 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
  - Changing to multidose insulin therapy using combination of rapid, short, intermediate, or long-acting insulin
  - Adding oral glucose lowering medication to improve glycemic control if already on insulin (metformin, TZDs<sup>13</sup>, sulfonylureas or meglitinides, sitagliptin,  $\alpha$ -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

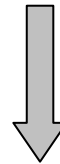
## GLUCOSE LOWERING MEDICATION COMBINATIONS

*Suggested well-studied combinations based on results of clinical studies.*

*These do not preclude other combinations:*

- metformin and insulin secretagogue \*\*
- metformin and dipeptidyl peptidase IV inhibitors \*\*
- metformin and GLP-1 agonists
- metformin and thiazolidinediones \*\*, <sup>9</sup>
- metformin and colesevelam
  
- sulfonylurea and  $\alpha$ -glucosidase inhibitor
- sulfonylurea and dipeptidyl peptidase IV inhibitors
- sulfonylurea and GLP-1 agonists
- sulfonylurea and colesevelam
  
- dipeptidyl peptidase IV inhibitors and pioglitazone
- pioglitazone and sulfonylurea\*\*, <sup>9</sup>
- pioglitazone and repaglinide <sup>9</sup>
- pioglitazone and GLP-1 agonists <sup>9</sup>
  
- glargine and exenatide

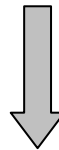
\* Also available in fixed combinations



*Continued on next page*

**ORAL GLUCOSE LOWERING MEDICATIONS AVAILABLE IN THE USA**

<b>Biguanides</b>	<b>TZDs (Thiazolidinediones)</b>	<b>α- Glucosidase Inhibitors</b>	<b>Insulin Secretagogues</b>	<b>Dipeptidyl Peptidase IV Inhibitors (DPP-4 Inhibitors)</b>	<b>Bile Acid Sequestrant</b>	<b>Centrally Acting</b>	<b>Fixed Combinations</b>
<ul style="list-style-type: none"> <li>• liquid metformin* (<i>Riomet</i>)</li> <li>• metformin (<i>Glucophage</i>)</li> <li>• metformin extended release (<i>Glucophage XR, Fortamet, Glumetza</i>)</li> </ul> <p><i>(metformin and metformin ER available as generic medication)</i></p> <p>* <i>Liquid formulation for patients unable to swallow pills</i></p>	<ul style="list-style-type: none"> <li>• pioglitazone (<i>Actos</i>)</li> <li>• rosiglitazone (<i>Avandia</i>)<sup>9</sup></li> </ul>	<ul style="list-style-type: none"> <li>• acarbose (<i>Precose</i>)</li> <li>• miglitol (<i>Glyset</i>)</li> </ul>	<p><b>Sulfonylureas</b></p> <ul style="list-style-type: none"> <li>• glimepiride (<i>Amaryl</i>)</li> <li>• glipizide (<i>Glucotrol</i>)</li> <li>• glipizide extended release (<i>Glucotrol XL</i>)</li> <li>• glyburide (<i>Micronase, Diabeta</i>)</li> <li>• micronized glyburide (<i>Glynase</i>)</li> </ul> <p><i>(glimepiride, glipizide and glyburide are available as generic medications)</i></p> <p><b>Meglitinides</b></p> <ul style="list-style-type: none"> <li>• repaglinide (<i>Prandin</i>)</li> </ul> <p><b>D-phenylalanine Derivatives</b></p> <ul style="list-style-type: none"> <li>• nateglinide (<i>Starlix</i>)</li> </ul>	<ul style="list-style-type: none"> <li>• sitagliptin (<i>Januvia</i>)</li> <li>• Saxagliptin (<i>Onglyza</i>)</li> <li>• Linagliptin (<i>Tradjenta</i>)</li> </ul>	<ul style="list-style-type: none"> <li>• colesevelam (<i>Welchol</i>)</li> </ul>	<ul style="list-style-type: none"> <li>• bromocriptine (<i>Cycloset</i>)</li> </ul>	<ul style="list-style-type: none"> <li>• metformin and glipizide (<i>Metaglip</i>)</li> <li>• metformin and glyburide (<i>Glucovance</i>)</li> <li>• metformin and pioglitazone (<i>Actoplus met</i>)</li> <li>• pioglitazone and glimepiride (<i>Duetact</i>)</li> <li>• rosiglitazone and glimepiride (<i>Avandaryl</i>)<sup>9</sup></li> <li>• rosiglitazone and metformin (<i>Avandamet</i>)<sup>9</sup></li> <li>• sitagliptin and metformin (<i>Janumet</i>)</li> <li>• saxagliptin and metformin ER (<i>Kombiglyze XR</i>)</li> <li>• repaglinide and metformin (<i>PrandiMet</i>)</li> <li>• sitagliptin and simvastatin (<i>Juvisync</i>)</li> </ul>



*Continued on next page*

## INJECTABLE DIABETES MEDICATIONS AVAILABLE IN THE USA

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

### Premixed Insulin Combinations

Insulin Type	
70% NPH; 30% Regular	Humulin 70/30
70% NPH; 30% Regular	Novolin 70/30
50% lispro protamine suspension, 50% lispro	Humalog 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
Liraglutide (Victoza)	Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins	2	1
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:

<sup>1</sup>Laboratory 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.

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

<sup>3</sup>The 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.

<sup>4</sup>If 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.

<sup>5</sup>Some 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.

<sup>6</sup>A 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%

<sup>7</sup>**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.

<sup>8</sup> Thiazolidinediones 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.

<sup>9</sup><sup>i</sup> On September 23, 2010, the Food and Drug Administration (FDA) announced regulatory actions with respect to products containing rosiglitazone: Avandia® (rosiglitazone maleate) Tablets, Avandamet® (rosiglitazone maleate and metformin hydrochloride) Tablets and Avandaryl® (rosiglitazone maleate and glimepiride) Tablets. The FDA is requiring GlaxoSmithKline (GSK) to implement restrictions on the use of these products through a program to assure their safe use (i.e., Risk Evaluation and Mitigation Strategy or REMS) and additional safety labeling changes in response to the agency's review of data that suggest an elevated risk of cardiovascular events. GSK will be working with the FDA to implement the agency's requirement for a REMS and additional labeling changes. Additional information will be communicated when these measures are finalized. It will take several months to put the REMS program in place. Until the REMS program is in place, the FDA's decision allows current or potential users of rosiglitazone to continue or start using the medication after consultation with their health care provider about treatment options. Once the REMS program is in place a) Health care providers will need to be enrolled in the program in order to prescribe rosiglitazone containing products. b) Pharmacists will need to be enrolled in order to dispense rosiglitazone containing products. c) Patients will need to be enrolled in the program by their physician in order for them to begin or continue receiving rosiglitazone. d) Health care providers will have to attest to and document their patient's eligibility if they believe that their patient is a candidate for rosiglitazone. e) Patients will have to review statements describing the cardiovascular safety concerns with rosiglitazone and sign an acknowledgment of their understanding of the information. f) Current users of rosiglitazone will only be able to continue using the medication if they acknowledge and document that they understand the risks associated with the drug. g) Patients not already taking rosiglitazone can receive the medicine only if they are unable to achieve glycemic control on other medications and, in consultation with their health care provider, decide not to take pioglitazone for medical reasons.

<sup>9</sup><sup>ii</sup> According to FDA advisory issued on June 15, 2011 re: potentially increased risk of bladder cancer with Pioglitazone use: a. Do not use pioglitazone in patients with active bladder cancer. b. Use pioglitazone with caution in patients with a prior history of bladder cancer. The benefits of glycemic control versus unknown risks for cancer recurrence with pioglitazone should be considered in patients with a prior history of bladder cancer.

<sup>10</sup> If therapeutic goals are not met, consider starting insulin. Stop exenatide when starting insulin other than glargine.

<sup>11</sup>May 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.

<sup>12</sup>Pre- 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.

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

Guideline Authors: Om Ganda, MD, Martin Abrahamson, MD, Jason Gaglia, MD, Richard Beaser, MD, Elizabeth Blair, ANP-BC, CDE, Alissa Segal Pharm D, CDE

Approved by Joslin Clinical Oversight Committee on 10/27/2011

### Glossary and Common Abbreviations

**A1C:** glycohemoglobin (hemoglobin A1C)

**ALT:** alanine aminotransferase

**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 glucoregulatory actions of naturally occurring incretins

**Kg:** kilogram

**LDL-C:** low density lipoprotein, cholesterol

**LFT:** liver function tests

**MEN2:** Multiple endocrine neoplasia type 2

**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.

**Rx:** treatment

**TZDs:** thiazolidinediones

#### Joslin Clinical Oversight Committee

Om Ganda, MD - Chairperson

Richard Beaser, MD

Elizabeth Blair, MS, ANP-BC, CDE

Amy Campbell, MS, RD, CDE

Cathy Carver, MS, ANP-BC, CDE

Jerry Cavallerano, OD, PhD

David Feinbloom, MD

William Hsu, MD

Richard Jackson, MD

Lori Laffel, MD, MPH

Melinda Maryniuk, MEd, RD, CDE

Medha Munshi, MD

Jo-Anne Rizzotto, MEd, RD, CDE

Susan Sjostrom, JD

Bijan Roshan, MD

William Sullivan, MD

Howard Wolpert, MD

John Zrebiec, LICSW

Martin J. Abrahamson, MD, *ex officio*

## References for Joslin's Pharmacological Management of Type 2 Diabetes Guideline

### Diagnosis

1. ADA Position Statement: Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 2011; 34 (suppl 1): S62-S69
2. Nathan, DM, Kuenen, J, Borg, H Translating the A1c assay into estimated average glucose values. *Diabetes Care* 2008; 31: 1473-1478

### Goals of Glycemic Control and Pharmacotherapy

1. American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2011; 34 ( suppl 1): S11-S 61
2. Beaser, RS and Staff of Joslin Diabetes Center. *Joslin's Diabetes Deskbook for Primary Care Providers*. Updated Second edition. Joslin Diabetes Center, Boston; 2010.
3. Diabetes Prevention and Control Program, Diabetes Guidelines Work Group. Massachusetts guidelines for adult diabetes care. Boston (MA): Massachusetts Department of Public Health; 2005 Jun.
4. Institute for Clinical Systems Improvement (ICSI). Management of type 2 diabetes mellitus. Bloomington (MN): Institute for Clinical Systems Improvement (ICS); 2005 Nov.

### Oral Antihyperglycemic Therapy

1. Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. *JAMA* 287:360-72, 2002.
2. Kimmel B and Inzucchi S. Oral agents for type 2 diabetes: an update. *Clinical Diabetes* 23:64-76, 2005.
3. Krentz AJ, Bailey CJ. Oral antidiabetic agents. *Drugs* 2005; 65(3):385-411.
4. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 131:281-303, 1999.
5. Kahn SE, Haffner SM, Heise MA, et. al. Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy. *New England Journal of Medicine* 2006; 355: 2427-2443
6. Nathan, DM et al Medical management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care* 2009; 32: 193-203
7. Rodbard H, Jellinger P, Davidson JA, Einhorn D, Garber AJ, Grunberger G, Handelsman Y, Horton ES, Lebovitz H, Levy P, Moghissi ES, Schwartz SS. Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on type 2 diabetes mellitus: An algorithm for glycemic control. *Endocr Pract* 2009;15: 540–559.

8. Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R et al. Comparative Effectiveness and Safety of Medications for Type 2 Diabetes: An Update Including New Drugs and 2-Drug Combinations. *Annals of Internal Medicine* 2011; 154(9):602-613.

## Metformin

1. Charpentier G, Riveline JP, Varroud-Vial M. Management of drugs affecting blood glucose in diabetic patients with renal failure. *Diabetes Metab* 26 Suppl 4:73-85, 2000.
2. Cryer DR, Nicholas SP, Henry DH, Mills DJ, Stadel BV. Comparative outcomes study of metformin intervention versus conventional approach. *Diabetes Care* 28:539-543, 2005.
3. Garber AJ, Duncan TG, Goodman AM, Millis DJ, Rohlf JL Efficacy of Metformin in Type II Diabetes: Results of a Double-Blind, Placebo-controlled, Dose-Response Trial. *Am J Med* 103:491-497, 1997.
4. Grant PJ. The effects of high and medium dose metformin therapy on cardiovascular risk factors in patients with type II diabetes. *Diabetes Care* 19: 64-66, 1996.
5. Holstein A, Stumvoll M. Contraindications can damage your health--is metformin a case in point? *Diabetologia* 48:2454-9, 2005.
6. Inzucchi SE. Metformin and heart failure: innocent until proven guilty. *Diabetes Care* 28:2585-2587, 2005.
7. Johansen K. Efficacy of metformin in the treatment of NIDDM. Meta-analysis. *Diabetes Care* 22:33-7, 1999.
8. McCormack J, Johns K, Tildesley H. Metformin's contraindications should be contraindicated. *CMAJ* 173:502-4, 2005.
9. UKPDS Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352: 854-865, 1998.
10. Saenz A, Fernandez-Esteban I, Mataix A, Ausejo M, Roque M, Moher D. Metformin monotherapy for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2006 Issue 4.
11. Salpeter S., Greyber E, Paternak G., Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Sys Rev* 2006 Issue 4.
12. Sulkin TV, Bosman D, Krentz AJ. Contraindications to metformin therapy in patients with NIDDM. *Diabetes Care* 20:925-8, 1997.

## Thiazolidinediones

1. Charbonnel B, Roden M, Urquhart J, Mariz S, Johns D, Mihm M, Wide M, Tan M. Pioglitazone elicits long-term improvements in insulin sensitivity in patients with type 2 diabetes: comparisons with glipazide-based regimens. *Diabetologia* 48:553-60, 2005.
2. Davidson JA, Perez A, Zhang J, The Pioglitazone 343 Study Group. Addition of pioglitazone to stable insulin therapy in patients with poorly controlled type 2 diabetes: results of a double-blind, multicentre, randomized study. *Diabetes Obes Metab* 8:164-74, 2006.

3. Kulenovic I. Impact of rosiglitazone on glycaemic control, insulin levels and blood pressure values in patients with type 2 diabetes. *Med Arh* 60:179-81, 2006.
4. Miyazaki Y, Mahankali A, Matsuda M et al. Improved glycaemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. *Diabetes Care* 24:710-719, 2001.
5. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, Le Winter M, Porte D, Semenkovich CF, Smith S, Young LH, Kahn R. American Heart Association; American Diabetes Association. Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Circulation* 108:2941-8, 2003.
6. Mazzone T, Meyer PM, Feinsein SB, Davidson MH, Kondos GT, D'Agostino RB, Sr. et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA* 2006; 296(21):2572-2581.
7. Yki-Jarvinen, H. Thiazolidinediones. *New England Journal of Medicine* 2004; 351: 1106-1118.
8. Nissen, SE, Wolski, K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *New England Journal of Medicine* 2007; 356: 2457-2471.
9. GlaxoSmithKline. GSK regulatory update on Avandia following EMA and FDA reviews: issued Thursday 23 September 2010. Available at: [http://www.gsk.com/media/pressreleases/2010/2010\\_pressrelease\\_10103.htm](http://www.gsk.com/media/pressreleases/2010/2010_pressrelease_10103.htm). Accessed September 2010.
10. U.S. Food and Drug Administration. Postmarketing drug safety information for patients and providers. Q&A: Avandia (rosiglitazone). Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm226976.htm>. Accessed September 2010.\*
11. Woodcock J. United States Food and Drug Administration, Center for Drug Evaluation and Research. Decision on continued marketing of rosiglitazone (Avandia, Avandamet, Avandaryl). Available at: <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM226959>. Accessed October 2010.\*
12. Piccinni, C, Motola, D, Marchesini, D, Poluzzi, E Assessing the association of pioglitazone use and bladder cancer through drug adverse reporting. *Diabetes Care* 2011; 34: 1369-1371
13. FDA Drug Safety Communication: Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer; June 15, 2011

## Insulin Secretagogues

1. Bailey CJ, Day C. Antidiabetic drugs. *Br J Cardiol* 10:128-36, 2003.
2. Del Prato S, Heine RJ, Keilson L, Guitard C, Shen SG, Emmons RP. Treatment of patients over 64 years of age with type 2 diabetes: experience from nateglinide pooled database retrospective analysis. *Diabetes Care* 26:2075-80, 2003.
3. Dornhorst M. Insulotropic meglitinide analogues. *Lancet* 358:1709-15, 2001.
4. Hazama Y, Matsuhisa M, Ohtoshi K, Grogawa S, Kato K, Kawamori D, Yoshiuchi K, Nakamura Y, Shiraiwa T, Kaneto H, Yamasaki Y, Hori M. Beneficial effects of nateglinide on insulin resistance in type 2 diabetes. *Diabetes Res Clin Pract* 71:251-5, 2006.
5. Plosker, GI, Figgitt, DP. Repaglinide: a pharmaco-economic review of its use in type 2 diabetes mellitus. *PharmacoEconomics* 22:389-411, 2004.

6. Shapiro MS, Abrams Z, Lieberman N. Clinical experience with repaglinide in patients with non-insulin-dependent diabetes mellitus. *Isr Med Assoc J*. 2005 7:75-7, 2005.

### **Alpha-Glucosidase Inhibitors**

1. Balfour JA, McTavish D. Acarbose. An update of its pharmacology and therapeutic use in diabetes mellitus. *Drugs* 46:1025-54, 1993.
2. Carlson RF. Miglitol and hepatotoxicity in type 2 diabetes mellitus. *Am Fam Physician* 62:315 -318, 2000.
3. Hanefeld M, Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Rupp M. Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. *Eur Heart J* 25:10-6, 2004.
4. Van de Laar FA, Lucassen PL, Akkermans RP, Van de Lisdonk EH, Rutten GE, Van Weel C. Alpha-glucosidase inhibitors for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 18; (2):CD003639, 2005.

### **GLP-1 receptor agonists**

1. DeFronzo RA et al. Effects of exenatide (Exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 28:1092-1100, 2005.
2. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD; Exenatide-113 Clinical Study Group. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 27:2628-35, 2004.
3. Fineman MS, Bicsak TA, Shen LZ, Taylor K, Gaines E, Varns A, Kim D, Baron AD. Effect on glycemic control of exenatide (synthetic exendin-4) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. *Diabetes Care* 26:2370-7, 2003.
4. Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG; GWAA Study Group. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. *Ann Intern Med* 143:559-69, 2005.
5. Iltz JL, Baker DE, Setter SM, Keith Campbell R. Exenatide: an incretin mimetic for the treatment of type 2 diabetes mellitus. *Clin Ther* 28:652-65, 2006.
6. Kendall, DM et al. Effects of exenatide (Exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 28:1083-1091, 2005.
7. Linnebjerg H, Kothare PA, Skrivaneck Z, de la Pena A, Atkins M, Ernest CS, Trautmann ME. Exenatide: effect of injection time on postprandial glucose in patients with type 2 diabetes. *Diabet Med* 23:240-5, 2006.
8. Poon T, Nelson P, Shen L, Mihm M, Taylor K, Fineman M, Kim D. Exenatide improves glycemic control and reduces body weight in subjects with type 2 diabetes: a dose-ranging study. *Diabetes Technol Ther* 7:467-77, 2005.
9. Russell-Jones D, Vaag A, Schmitz O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 Met+SU): a randomised controlled trial. *Diabetologia* 2009; 52: 2046–55.

10. Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. *Lancet* 2009; 373: 473–81.

### **DPP-IV Inhibitors**

1. Chia CW, Egan JM. Incretin-based therapies in type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2008; 93(10):3703-3716.
2. Miller S, St Onge EL. Sitagliptin: a dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. *Ann Pharmacother* 2006; 40(7-8):1336-1343.
3. Goldstein BJ, Feinglos MN, Luncelford JK, Johnson J, Williams-Herman DE. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. *Diabetes Care* 2007; 30(8):1979-1987.
4. DeFronzo RA, Hissa MN, Garber AJ, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. *Diabetes Care* 2009; 32:1649–55.
5. Scott, LJ Linagliptin in type 2 diabetes mellitus . *Drugs* 2011; 71: 611-624

### **Bile Acid Sequestrants**

1. Bays HE, Goldberg RB, Truitt KE, Jones MR. Colesevelam hydrochloride therapy in patients with type 2 diabetes mellitus treated with metformin: glucose and lipid effects. *Arch Intern Med* 2008; 168(18):1975-1983.
2. Fonseca VA, Rosenstock J, Wang AC, Truitt KE, Jones MR. Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. *Diabetes Care* 2008; 31(8):1479-1484.
3. Goldberg RB, Fonseca VA, Truitt KE, Jones MR. Efficacy and safety of colesevelam in patients with type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. *Arch Intern Med* 2008; 168(14):1531-1540.

### **Combination Therapy with insulin**

1. Aviles-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled insulin-treated type 2 diabetes mellitus. *Ann Intern Med* 131:182-88, 1999.
2. Belcher G, Lambert C, Goh1 KL, Edwards G, Valbuena1 M. Cardiovascular effects of treatment of type 2 diabetes with pioglitazone, metformin and glipazide. *Int J Clin Pract* 58:833-7, 2004.
3. Goudswaard AN, Furlong NJ, Valk GD, Stolk RP, Rutten GEHM. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. *Cochrane Database Sys Rev* 2006 Issue 4.
4. Jones TA, Sautter M, Van Gaal LF, Jones NP. Addition of rosiglitazone to metformin is most effective in obese, insulin-resistant patients with type 2 diabetes. *Diabetes Obes Metab* 5:163-70, 2003.

5. Roberts VL, Stewart J, Issa M, Lake B, Melis R. Triple therapy with glimepiride in patients with type 2 diabetes mellitus inadequately controlled by metformin and a thiazolidinedione: results of a 30-week, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther* 27:1535-47, 2005.
6. Rosenstock J, Sugimoto D, Strange P, Stewart JA, Soltes-Rak E, Dailey G. Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naïve patients. *Diabetes Care* 29:554-9, 2006.
7. Yki-Jarvinen H et al. Insulin glargine or NPH combined with metformin in type 2 diabetes: the LANMET study. *Diabetologia* 3:1-10, 2006.
8. Buse, JB et al Use of Twice-Daily Exenatide in Basal Insulin–Treated Patients With Type 2 Diabetes *Ann Intern Med* 2011; 154: 103-112.

## Insulin

1. Baker A, Ahmed E, Mallias J, Home PD. Optimization of evening insulin dose in patients using the short-acting insulin analog lispro. *Diabetes Care* 21:1162-66, 1998.
2. Davidson J, Vexiau P, Cucinotta D, Vaz J, Kawamori R. Biphasic insulin aspart 30: literature review of adverse events associated with treatment. *Clin Ther* 27:S75-88, 2005.
3. Hirsch B, Bergenstal RM, Parkin CG, Wright E, Buse JB. A real-world approach to insulin therapy in primary care practice. *Clin Diabetes* 23: 78-86, 2005.
4. Kennedy L, Herman WH, Strange P, Harris A for the GOAL A1C Team. Impact of active versus usual algorithmic titration of basal insulin and point-of-care versus laboratory measurement of HbA<sub>1c</sub> on glycemic control in patients with type 2 diabetes. *Diabetes Care* 29:1-8, 2006.
5. Kudva YC, Basu A, Jenkins GD, Pons GM, Quandt LL, Gebel JA, Vogelsang DA, Smith SA, Rizza RA, Isley WL. Randomized controlled clinical trial of glargine versus ultralente insulin in the treatment of type 1 diabetes. *Diabetes Care* 28:10-4, 2005.
6. Riddle MC. The Treat-to-Target Trial and related studies. *Endoc Pract.* 37:495-501, 2006.
7. Scholtz HE, Pretorius SG, Wessels DH, Becker RH. Pharmacokinetic and glucodynamic variability: assessment of insulin glargine, NPH insulin and insulin ultralente in healthy volunteers using a euglycaemic clamp technique. *Diabetologia* 48:1988-95, 2005.
8. Siebenhofer A, Plank J, Berghold A, Jeitler K, Horvath K, Narath M, Gfrerer R, Pieber TR. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *Cochrane Database Syst Rev.* 2006 Apr 19;(2):CD003287.
9. Taylor R, Davies R, Fox C, Sampson M, Weaver JU, Wood L. Appropriate insulin regimen for type 2 diabetes: a multicenter randomized crossover study. *Diabetes Care* 23:1612-18, 2000.
10. Valensi P, Cosson E. Is insulin detemir able to favor a lower variability in the action of injected insulin in diabetic subjects? *Diabetes Metab* 31:4S34-4S39, 2005.

## Pramlintide

1. Hollander P, Ratner R, Fineman M, Strobel S, Shen L, Maggs D, Kolterman O, Weyer C. Addition of pramlintide to insulin therapy lowers HbA<sub>1c</sub> in conjunction with weight loss in patients with type 2 diabetes approaching glycaemic targets. *Diabetes Obes Metab* 5:408-14, 2003.

2. Hollander PA et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care* 26:784-790, 2003.
3. Weyer C, Gottlieb A, Kim DD, Lutz K, Schwartz S, Gutierrez M, Wang Y, Ruggles JA, Kolterman OG, Maggs DG. Pramlintide reduces postprandial glucose excursions when added to regular insulin or insulin lispro in subjects with type 1 diabetes: a dose-timing study. *Diabetes Care* 26:3074-9, 2003.
4. Whitehouse F, Kruger DF, Fineman M, Shen L, Ruggles JA, Maggs DG, Weyer C, Kolterman OG. A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. *Diabetes Care* 25:724-30, 2002.

### **Bromocriptine**

1. Holt, RI et al Bromocriptine: old drug, new formulation, and new indication *Diabetes, Obesity, and Metabolism* 2010; 12: 1048-1057.