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 Diabetes

<table>
<thead>
<tr>
<th>Biochemical Index</th>
<th>Normal</th>
<th>Goal²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Plasma Glucose or Preprandial Glucose (mg/dl)</td>
<td>&lt; 100</td>
<td>70 – 130</td>
</tr>
<tr>
<td>Postprandial 2 hours (mg/dl)</td>
<td>&lt; 140</td>
<td>&lt; 180</td>
</tr>
<tr>
<td>Bedtime Glucose (mg/dl)</td>
<td>&lt; 120</td>
<td>90 – 150</td>
</tr>
<tr>
<td>A1C (%) - sustained</td>
<td>&lt; 6%</td>
<td>&lt; 7%³</td>
</tr>
</tbody>
</table>

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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)**

<table>
<thead>
<tr>
<th>Mild or no symptoms AND</th>
<th>FPG &gt; 150 mg/dl(^4) OR</th>
<th>Marked hyperglycemia OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative ketones AND</td>
<td>Random &gt; 250 mg/dl(^4) AND/OR</td>
<td>Significant weight loss OR</td>
</tr>
<tr>
<td>No acute concurrent illness AND</td>
<td>A1C &gt; 7.5%</td>
<td>Severe/significant symptoms OR</td>
</tr>
<tr>
<td>A1C ≤ 7.5%</td>
<td>Does not meet criteria for mild or severe</td>
<td>2+ or greater ketonuria OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DKA/ hyperosmolar state OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe intercurrent illness or surgery</td>
</tr>
</tbody>
</table>

- [ ] Start MNT and Physical Activity and Consider Addition of Metformin
- [ ] If after 6-8 weeks, target not met, Start Oral Antihyperglycemic Therapy
- [ ] Start Insulin Immediately\(^5\)

**Continued on next page**
### CONSIDERATIONS FOR SELECTING INITIAL NON-INSULIN ANTIHYPERGLYCEMIC THERAPY

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Thiazolidinediones (TZDs)</th>
<th>Insulin Secretagogue (sulfonylurea or short-acting secretagogue)</th>
<th>α-Glucosidase Inhibitor</th>
<th>Dipeptidyl Peptidase IV Inhibitors (DPP-4 Inhibitors)</th>
<th>Bile Acid Sequestrant (colesevelam)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <em>Overweight/obese</em>&lt;br&gt;• Renal/liver function normal&lt;br&gt;<strong>Contraindicated:</strong>&lt;br&gt;• Creatinine &gt; 1.4 (women)&lt;br&gt;• Creatinine &gt; 1.5 (men)&lt;br&gt;• IV contrast&lt;br&gt;• Dehydration&lt;br&gt;• Alcohol excess&lt;br&gt;• &gt; 80 years age (unless creatinine clearance allows)&lt;br&gt;<em>Defined in glossary</em></td>
<td>• <em>Overweight/obese, signs of insulin resistance</em>&lt;br&gt;• Liver function normal: need to follow LFT monitoring schedule&lt;br&gt;• Can be used in renal impairment but may increase fluid retention&lt;br&gt;• Consider risk for bone loss and fracture&lt;br&gt;Note: <em>Full effect of initiation or titration of therapy may take 2–4 months to be seen</em>&lt;br&gt;<strong>Contraindicated:</strong>&lt;br&gt;• Class III or IV CHF&lt;br&gt;• LFT &gt; 2.5 times upper limit of normal&lt;br&gt;• See footnotes 8, 9 for CV risk</td>
<td>• Normal/overweight&lt;br&gt;• Repaglinide or nateglinide are useful for patients with postprandial hyperglycemia or with hypoglycemia on sulfonylurea&lt;br&gt;<strong>Contraindicated:</strong>&lt;br&gt;• Sulfonylureas in severe liver or renal disease</td>
<td>• Milder presentation&lt;br&gt;• Use if postprandial hyperglycemia is the predominant hyperglycemic pattern&lt;br&gt;• No GI symptoms&lt;br&gt;<strong>Contraindicated:</strong>&lt;br&gt;• Chronic intestinal disorders&lt;br&gt;• Acarbose in cirrhosis&lt;br&gt;• Acarbose and miglitol in renal impairment (creatinine &gt; 2.0)</td>
<td>• Use if postprandial hyperglycemia is the predominant hyperglycemic pattern&lt;br&gt;• Weight neutral&lt;br&gt;• Reduce dose in renal disease&lt;br&gt;<strong>Contraindicated:</strong>&lt;br&gt;None known at this time</td>
<td>• Adjunct to other treatment modalities&lt;br&gt;• Modest effect on A1C. Also lowers LDL-C&lt;br&gt;Note: <em>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</em>&lt;br&gt;<strong>Contraindicated:</strong>&lt;br&gt;• Bowel obstruction&lt;br&gt;• Serum triglyceride &gt; 500 mg/dl&lt;br&gt;• Hx of hypertriglyceridemia-induced pancreatitis</td>
</tr>
</tbody>
</table>

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**Titrate Dose over 1–6 months**<br>Reinforce MNT and Physical Activity<br>If A1C > 7.0% OR<br>Fasting Plasma Glucose > 130 mg/dl OR<br>2 Hour Postprandial Glucose > 180 mg/dl<br>Add second oral antihyperglycemic OR GLP-1 agonist OR insulin<br>(See next page)

GLP-1 agonist<br>• Administered subcutaneously twice daily<br>• Use if postprandial hyperglycemia predominates<br>• To avoid hypoglycemia if using with a sulfonylurea, consider initially decreasing sulfonylurea dose. Use may be associated with weight loss<br>**Contraindicated:**<br>• Gastroparesis requiring treatment with metoclopramide<br>• History of pancreatitis
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

Continued on next page
ANTIHYPERTENSION 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

  • 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

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, TZDs, 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

<table>
<thead>
<tr>
<th>Biguanides</th>
<th>TZDs (Thiazolidinediones)</th>
<th>α-Glucosidase Inhibitors</th>
<th>Insulin Secretagogues</th>
<th>Dipeptidyl Peptidase IV Inhibitors (DPP-4 Inhibitors)</th>
<th>Bile Acid Sequestrant</th>
<th>Fixed Combinations</th>
</tr>
</thead>
</table>
| **• liquid metformin** *(Riomet)*  
**• metformin** *(Glucophage)*  
**• metformin extended release** *(Glucophage XR, Fortamet, Glumetza)* *(metformin and metformin ER available as generic medication)*  
* Liquid formulation for patients unable to swallow pills | **• pioglitazone** *(Actos)*  
**• rosiglitazone** *(Avandia)* | **• acarbose** *(Precose)*  
**• miglitol** *(Glyset)* | **Sulfonylureas**  
• glimepiride *(Amaryl)*  
• glipizide *(Glucocontrol)*  
• glipizide extended release *(Glucotrol XL)*  
• glyburide *(Micronase, Diabeta)*  
• micronized glyburide *(Glynase)*  
(glimepiride, glipizide and glyburide are available as generic medications)  
**Non-sulfonylurea Meglitinides**  
• repaglinide *(Prandin)*  
**D-phenylalanine Derivatives**  
• nateglinide *(Starlix)* | **• sitagliptin** *(Januvia)* | **• colesevelam** *(Welchol)* | **• metformin and glipizide** *(Metaglip)*  
**• metformin and glyburide** *(Glucovance)*  
**• metformin and pioglitazone** *(Actoplus met)*  
**• pioglitazone and glimepiride** *(Duetact)*  
**• rosiglitazone and glimepiride** *(Avandaryl)*  
**• rosiglitazone and metformin** *(Avandamet)*  
**• sitagliptin and metformin** *(Janumet)*  
**• repaglinide and metformin** *(PrandiMet)* |

Continued on next page
# INJECTABLE DIABETES MEDICATIONS

## INSULIN CHART

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

## Premixed Insulin Combinations

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% NPH; 50% Regular</td>
<td>Humulin 50/50</td>
</tr>
<tr>
<td>70% NPH; 30% Regular</td>
<td>Humulin 70/30</td>
</tr>
<tr>
<td>70% NPH; 30% Regular</td>
<td>Novolin 70/30</td>
</tr>
<tr>
<td>50% lispro protamine suspension, 50% lispro</td>
<td>Humalog Mix 50/50</td>
</tr>
<tr>
<td>50% aspart protamine suspension, 50% aspart</td>
<td>Novolog Mix 50/50</td>
</tr>
<tr>
<td>75% lispro protamine suspension, 25% lispro</td>
<td>Humalog Mix 75/25</td>
</tr>
<tr>
<td>70% aspart protamine suspension, 30% aspart</td>
<td>NovoLog Mix 70/30</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Product</th>
<th>Mechanism of Action</th>
<th>Type of Diabetes</th>
<th># of Injections Per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide (Byetta)</td>
<td>Incretin mimetic that enhances glucose-dependent insulin secretion and several other antihyperglycemic actions of incretins.</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pramlintide (Symlin)</td>
<td>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.</td>
<td>1 and 2</td>
<td>1-4 (with meals)</td>
</tr>
</tbody>
</table>
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.

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

3 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.

4 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.

5 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.

6 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%

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.

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.

A 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.

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

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.

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.

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

The 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.

Guideline Authors: Martin Abrahamson, MD, Richard Beaser, MD, Elizabeth Blair, ANP-BC, Om Ganda, MD, James Rosenzweig, MD, Howard Wolpert, MD, Alissa Segal Pharm D, CDE, Amy Campbell, MS, RD, CDE

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 glucoregulatory 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

Joslin Clinical Oversight Committee

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
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<td>William Sullivan, MD</td>
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<tr>
<td>Martin J. Abrahamson, MD, ex officio</td>
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</tr>
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</table>
References for Joslin’s Pharmacological Management of Type 2 Diabetes Guideline  
1-9-09

Diagnosis


Goals of Glycemic Control and Pharmacotherapy


Oral Antihyperglycemic Therapy


Metformin


**Thiazolidinediones**


**Insulin Secretagogues**


**Alpha-Glucosidase Inhibitors**


**Exenatide**


DPP-IV Inhibitors


Bile Acid Sequestrants


Combination Therapy with insulin


### Insulin


### Pramlintide


