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 provides 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 presentation and treatment strategies in the adult non-pregnant patient population. Refer to Joslin’s Clinical Guideline for Adults with Diabetes.

Joslin’s Guidelines are evidence-based; in order to allow the user to evaluate the quality of the evidence used to support each standard of care, a modification of the GRADE system has been adopted. The table provided on page 9 describes the categories in which methodological quality and strength of recommendations have been classified. Evidence levels are graded 1A through 2C, as indicated in brackets.

### 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

### Goals of Glycemic Control for People with Diabetes

<table>
<thead>
<tr>
<th>Biochemical Index</th>
<th>Normal</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Fasting Plasma Glucose or Preprandial Glucose (mg/dl)</td>
<td>&lt; 100</td>
<td>90 – 130</td>
</tr>
<tr>
<td>Average Postprandial 2 hours (mg/dl)</td>
<td>&lt; 140</td>
<td>&lt; 160</td>
</tr>
<tr>
<td>Average Bedtime Glucose (mg/dl)</td>
<td>&lt; 120</td>
<td>110 – 150</td>
</tr>
<tr>
<td>A1C (%) - sustained</td>
<td>&lt; 6%</td>
<td>&lt; 7%^3</td>
</tr>
</tbody>
</table>

^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.

^2The true goal of care is to bring A1C as close to normal as safely possible. [1C] 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. [1B]
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</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
</table>
| • Mild or no symptoms AND  
• Negative ketones AND  
• No acute concurrent illness | • FPG > 200\(^4\) OR  
• Random > 300\(^4\) AND  
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 | Start Oral Antihyperglycemic Therapy | Start Insulin Immediately \(^5\) |

\(^4\)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 oral antihyperglycemic therapy.

Continued on next page
CONSIDERATIONS FOR SELECTING INITIAL ORAL ANTIHYPERGLYCEMIC THERAPY

Metformin [1A]
- Overweight/obesity* present [1A]
- Renal/liver function normal [1C]

Contraindicated:
- Creatinine ≥ 1.4 (women)
- Creatinine ≥ 1.5 (men)
- IV contrast
- CHF
- Dehydration
- Alcohol excess
- ≥ 80 years age (unless creatinine clearance is normal)

* Defined in glossary

Thiazolidinediones [1A] (TZDs)
- Overweight/obese*, signs of insulin resistance [1A]
- Liver function normal; need to follow LFT monitoring schedule [2C]
- Can be used in renal impairment but may increase fluid retention [1B]

Note: Full effect of initiation or titration of therapy may take 2-4 months to be seen

Contraindicated:
- Class III or IV CHF
- LFT > 2.5 times upper limit of normal

Insulin Secretagogue (sulfonylurea or short-acting secretagogue) [1A]
- Normal/overweight
- Repaglinide or nateglinide are useful for patients with postprandial hyperglycemia or hypoglycemia on sulfonylurea [1B]

Contraindicated:
- Sulfonylureas in severe liver or renal disease

α-Glucosidase Inhibitor [1A]
- Milder presentation [1C]
- Use if postprandial hyperglycemia is the predominant hyperglycemic pattern [1A]
- No GI symptoms [1C]

Contraindicated:
- Chronic intestinal disorders
- Acarbose in cirrhosis
- Acarbose and miglitol in renal impairment (creatinine > 2.0)

Exenatide
- Administered subcutaneously twice daily
- Use if postprandial hyperglycemia predominates [1B]
- Approved for use with metformin and/or a sulfonylurea [1A]
- If using with a sulfonylurea, to avoid hypoglycemia, consider initially decreasing sulfonylurea dose [1C]
- Use may be associated with weight loss [2B]

Contraindicated:
- Gastroparesis requiring treatment with metoclopramide

If A1C ≥ 7.0% OR
Fasting Plasma Glucose > 130 mg/dl OR
2 Hour Postprandial Glucose > 160 mg/dl
Add second oral antihyperglycemic or incretin mimetic

Tritrate Dose over 2 – 4 Months
Reinforce MNT and Physical Activity [1A]

* 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 < 8.0%.

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

- Insulin secretagogue and metformin** [1A]
- Sulfonylurea and α-glucosidase inhibitor [1B]
- Thiazolidinediones and sulfonylurea** [1A]
- Thiazolidinediones and metformin** [1A]
- Thiazolidinediones and repaglinide [1A]
- Sulfonylurea and exenatide [1A]
- Metformin and exenatide [1A]

** Also available in fixed combinations

Continued on next page
ANTIHYPERGLYCEMIC THERAPY, continued

A1C ≥ 7.0% OR
Fasting Plasma Glucose > 130 mg/dl OR
2 Hour Postprandial Plasma Glucose > 160 mg/dl

Add:

- Several options available:
  - Consider starting with a single bedtime dose of long- or intermediate-acting insulin.
    - Intermediate-acting insulin (NPH) once or twice daily as part of a conventional program. [1A]
    - Long-acting insulin (detemir or glargine) once or twice daily for basal therapy [1A]
  - Pre-supper insulin mixture (75/25 lispro, 50/50 lispro, 70/30 aspart, 70/30 human insulin, or 50/50 human insulin) [1B]
    - Inhaled insulin before meals one to three times per day. [1A] (Obtain spirometry or full PFTs prior to use.) Contraindicated in smokers, recent smokers and patients with underlying lung disease.
  - Suggested starting dose for injectable insulin: 0.1-0.2 units/kg ideal body weight
  - Titrate/adjust insulin dosage until glucose goals met [1A]

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 [1A]
- Adding pre-meal rapid or short-acting insulin (e.g. aspart, glulisine, lispro or regular) [1A] or inhaled insulin pre-meals to bedtime intermediate or long-acting/basal insulin [1B]
- If on pre-meal insulin and postprandial glucose targets are met but fasting glucose is elevated, add bedtime basal insulin and adjust the rapid or short-acting or inhaled insulin as needed [1A]
- Adding oral antihyperglycemic medication to reduce insulin resistance or improve glycemic control if already on insulin (Metformin, TZDs, sulfonylureas, and α-glucosidase inhibitors are approved for use in combination with insulin) [1A]
- Refer to endocrinologist for intensification of therapy [1C] or for consideration of pramlintide use [2A]

- Inhaled insulin not recommended if baseline FEV₁ or DLCO < 70% predicted. Assess PFTs at baseline, after first 6 months of therapy and annually thereafter. If there is confirmed decline of ≥20% in FEV₁ or DLCO from baseline spirometry or PFTs after initiation, discontinue the inhaled insulin.

If there are any proven benefits of adding two different insulin secretagogues in combination

Third Oral Antihyperglycemic Medication of Different Class [1A]

Insulin [9,10] [1A] or Exenatide [8] [1A]

9 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.
10 Pre- and postprandial blood glucose should be checked. Frequency may vary 1-4 times/day depending on individual patient and status of glycemic control.

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### 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>Non-sulfonylurea Secretagogues</th>
<th>Fixed Combinations</th>
</tr>
</thead>
</table>
| • liquid metformin* (Riomet)  
• metformin (Glucophage)  
• metformin extended release (Glucophage XR, Fortamet, Glumetza)  
* Liquid formulation for patients unable to swallow pills | • pioglitazone (Actos)  
• rosiglitazone (Avandia) | • acarbose (Precose)  
• miglitol (Glyset) | • glimepiride (Amaryl)  
• glipizide (Glucotrol)  
• glipizide extended release (Glucotrol XL)  
• glyburide (Micronase, Diabeta)  
• micronized glyburide (Glynase)  
(glimepiride, glipizide and glyburide are available as generic medications) | D-phenylalanine Derivatives  
• nateglinide (Starlix) | Meglitinides  
• repaglinide (Prandin)  
| | | | | | • metformin and glipizide (Metagliz)  
• metformin and glyburide (Glucovance)  
• metformin and pioglitazone (Actoplas met)  
• pioglitazone and glimepiride (Duetact)  
• rosiglitazone and glimepiride (Avandaryl)  
• rosiglitazone and metformin (Avandamet) |

Continued on next page
### INJECTABLE AND INHALABLE DIABETES MEDICATIONS

#### INSULIN CHART\(^2\)

<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>0.5 – 3 hours</td>
<td>3 – 5 hours</td>
</tr>
<tr>
<td>Insulin glulisine analog</td>
<td>Apidra</td>
<td>10 – 30 minutes</td>
<td>0.5 – 3 hours</td>
<td>3 – 5 hours</td>
</tr>
<tr>
<td>Insulin lispro analog</td>
<td>Humalog</td>
<td>10 – 30 minutes</td>
<td>0.5 – 3 hours</td>
<td>3 – 5 hours</td>
</tr>
<tr>
<td>Insulin human inhalation powder</td>
<td>Exubera</td>
<td>10 – 20 minutes</td>
<td>0.5 – 3 hours</td>
<td>Approx. 6 hours</td>
</tr>
<tr>
<td><strong>Short-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular insulin</td>
<td>Humulin R</td>
<td>30 minutes</td>
<td>1 – 5 hours</td>
<td>8 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>NPH insulin</td>
<td>Humulin N</td>
<td>1 – 4 hours</td>
<td>4 – 12 hours</td>
<td>14 – 26 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>1 – 2 hours</td>
<td>Minimal peak</td>
<td>Up to 24 hours</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Lantus</td>
<td>1 – 2 hours</td>
<td>Minimal peak</td>
<td>Up to 24 hours</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>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>

#### 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>

\(^2\)The onset, peak and duration of any insulin type depend 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.

Insulins listed alphabetically by generic name; TAP derived from information provided by manufacturers.
Goldline Authors: Martin Abrahamson, MD, Richard Beaser, MD, Elizabeth Blair, CS-ANP, Om Ganda, MD, James Rosenzweig, MD, Howard Wolpert, MD

Approved by Joslin Clinical Oversight Committee on 1/12/07.

Glossary

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
FDA: Food and Drug Administration
FPG: fasting plasma glucose
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: kilograms
Mg: milligrams
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>
</tr>
</thead>
<tbody>
<tr>
<td>James Rosenzweig, MD</td>
<td>Chairperson</td>
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<tr>
<td>Richard Beaser, MD</td>
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<tr>
<td>Elizabeth Blair, MS, CS-ANP, CDE</td>
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<td>Patty Bonsignore, MS, RN, CDE</td>
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<td>Amy Campbell, MS, RD, CDE</td>
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<td>Cathy Carver, ANP, CDE</td>
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<td>Om Ganda, MD</td>
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<td>Melinda Maryniuk, MEd, RD, CDE</td>
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<td>William Petit, MD</td>
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<td>Kristi Silver, MD</td>
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<td>Howard Wolpert, MD</td>
<td></td>
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<tr>
<td>Martin J. Abrahamson, MD, ex officio</td>
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</tr>
</tbody>
</table>
Grading System Used in Guideline

<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Clarity of risk/benefit</th>
<th>Quality of supporting evidence</th>
</tr>
</thead>
</table>
| **1A**  
Strong recommendation  
High quality of evidence | Benefits clearly outweigh risk and vice versa. | Consistent evidence from well performed randomized, controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. |
| **1B**  
Strong recommendation  
Moderate quality of evidence | Benefits clearly outweigh risk and burdens, or vice versa. | Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other research design. Further research is likely to have an impact on our confidence in the estimate of the benefit and risk and may change the estimate. |
| **1C**  
Strong recommendation  
Low quality of evidence | Benefits outweigh risk and burdens, or vice versa. | Evidence from observational studies, unsystematic clinical experience, or from randomized controlled trials with serious flaws. Any estimate of effect is uncertain. |
| **2A**  
Weak recommendation  
High quality of evidence | Benefits closely balanced with risks and burdens. | Consistent evidence from well performed randomized controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk. |
| **2B**  
Weak recommendation  
Moderate quality of evidence | Benefits closely balanced with risks and burdens; some uncertainty in the estimates of benefits, risks and burdens. | Evidence from randomized controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other research design. Further research is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate. |
| **2C**  
Weak recommendation  
Low quality of evidence | Uncertainty in the estimates of benefits, risks and burdens; benefits may be closely balanced with risks and burdens. | Evidence from observational studies, unsystematic clinical experience, or from randomized controlled trials with serious flaws. Any estimate of effect is uncertain. |

Evidence graded less than “A” is acceptable to support clinical recommendations in a guideline. It is also assumed that for many important clinical recommendations, it would be unlikely that level A evidence be obtained because appropriate studies may never be performed.