Joslin Diabetes Center & Joslin Clinic
Clinical Guideline for Pharmacological Management of Type 2 Diabetes
1-12-07

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.[1] 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 [2]		
Biochemical Index	**Normal**	**Goal**
Average Fasting Plasma Glucose or Preprandial Glucose (mg/dl)	**< 100**	**90 – 130**
Average Postprandial 2 hours (mg/dl)	**< 140**	**< 160**
Average Bedtime Glucose (mg/dl)	**< 120**	**110 – 150**
A1C (%) - sustained	**< 6%**	**< 7%** [3]

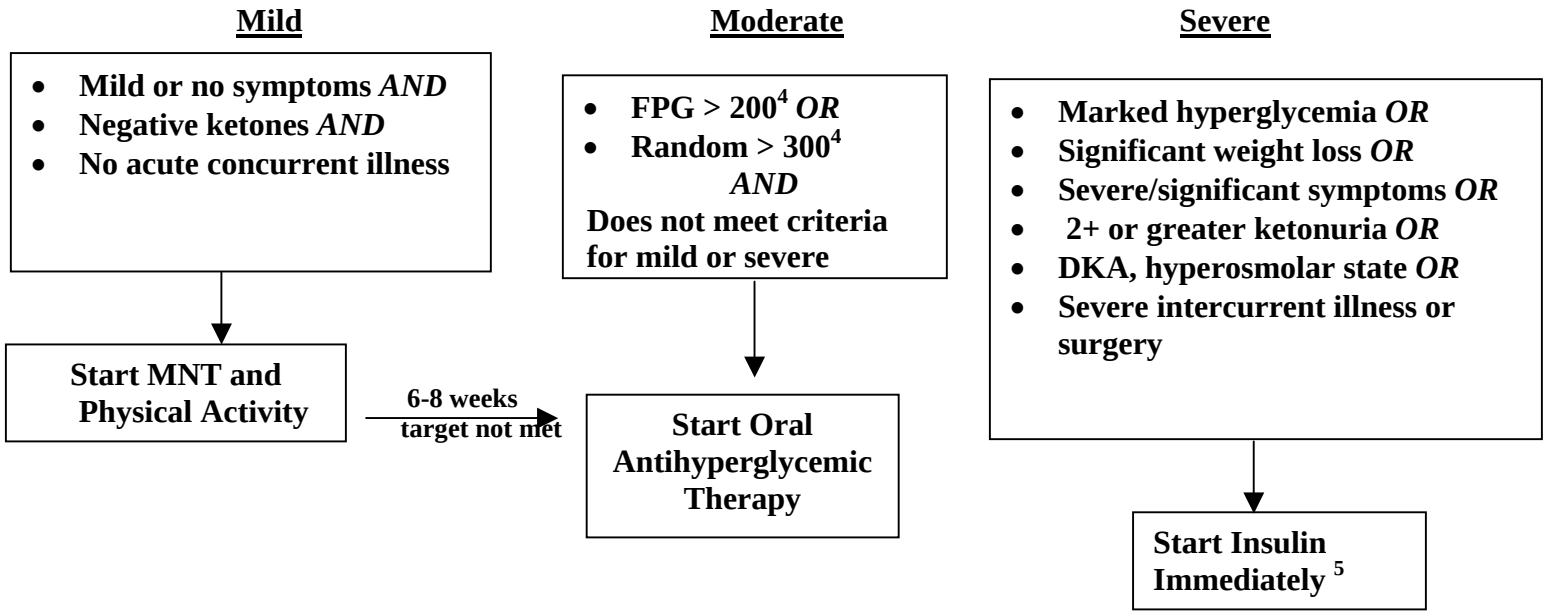
[2]Laboratory methods measure plasma glucose. Most glucose monitors approved for home use calibrate whole blood glucose readings to plasma values. Plasma glucose values are 10-15% higher than whole blood glucose values. It is important for people with diabetes to know whether their meters and strips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

[3]The 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**]

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)**



[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.

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CONSIDERATIONS FOR SELECTING INITIAL ORAL ANTIHYPERGLYCEMIC THERAPY[6]

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[7] [**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 [**2B**]
- 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)

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

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 [**1A**]
(See next page)

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

[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 < 8.0% .

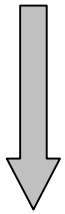
[7] ***FDA Requirements for LFT monitoring for thiazolidinediones (TZDs):***

- 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



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ANTIHYPERGLYCEMIC THERAPY, continued

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

Add:

Third Oral Antihyperglycemic Medication of Different Class[8] [1A]

(No proven benefit of adding two different insulin secretagogues in combination)

or

Insulin [9, 10] [1A]

- 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.[11] 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
  Suggested starting dose for inhaled insulin is based on body weight using mg instead of units. Follow recommended dosing according to package insert.
- 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]

or

Exenatide[8] [1A]

[8] If therapeutic goals are not met, consider starting insulin. Stop exenatide when starting insulin.
[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.
[11] Inhaled insulin not recommended if baseline FEV_1 or DL_{CO} < 70% predicted. Assess PFTs at baseline, after first 6 months of therapy and annually thereafter. If there is confirmed decline of ≥20% in FEV_1 or DL_{CO} from baseline spirometry or PFTs after initiation, discontinue the inhaled insulin.

Oral Antihyperglycemic Medications Available in the USA

Biguanides	TZDs (Thiazolidinediones)	α-Glucosidase Inhibitors	Insulin Secretagogues		Fixed Combinations
			Sulfonylureas *2nd generation*	Non-sulfonylurea *Secretagogues*	
• 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)*	• 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 *(Metaglip)* • metformin and glyburide *(Glucovance)* • metformin and pioglitazone *(Actoplus met)* • pioglitazone and glimepiride *(Duetact)* • rosiglitazone and glimepiride *(Avandaryl)* • rosiglitazone and metformin *(Avandamet)*

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INJECTABLE AND INHALABLE DIABETES MEDICATIONS

INSULIN CHART[12]

Insulin Type	Product	Onset	Peak	Duration
Rapid-Acting				
Insulin aspart analog	NovoLog	10 – 30 minutes	0.5 – 3 hours	3 – 5 hours
Insulin glulisine analog	Apidra	10 – 30 minutes	0.5 – 3 hours	3 – 5 hours
Insulin lispro analog	Humalog	10 – 30 minutes	0.5 – 3 hours	3 – 5 hours
Insulin human inhalation powder	Exubera	10 – 20 minutes	0.5 – 3 hours	Approx. 6 hours
Short-Acting				
Regular insulin	Humulin R Novolin R	30 minutes	1 – 5 hours	8 hours
Intermediate-Acting				
NPH insulin	Humulin N Novolin N	1 – 4 hours	4 – 12 hours	14 – 26 hours
Long-Acting				
Insulin detemir	Levemir	1 – 2 hours	Minimal peak	Up to 24 hours
Insulin glargine	Lantus	1 – 2 hours	Minimal peak	Up to 24 hours

Premixed Insulin Combinations

Insulin Type	Product
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
75% lispro protamine suspension, 25% lispro	Humalog Mix 75/25
70% aspart protamine suspension, 30% aspart	NovoLog Mix 70/30

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)

[12]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.

Guideline 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/m^2; overweight = 25.0-29.9 kg/m^2 (> 23 kg/m^2 in Asian populations); obese = ≥ 30 kg/m^2 (23-27 kg/m^2 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 gastronintestinal 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/m^2
Overweight: BMI = 25.0-29.9 kg/m^2
PFTs: pulmonary function tests
Rx: treatment
TAP: time action profile
TZDs: thiazolidinediones

Grading System Used in Guideline

Grade of Recommendation	Clarity of risk/benefit	Quality of supporting evidence
1A Strong recommendation High quality of evidence	Benefits clearly outweigh risk and vice versa.	Consistent evidence from well performed randomized, controlled trails 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 trails 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 uncertainly 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 trails 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.

[1]Guyatt G et al. Grading strength of recommendations and quality of evidence in clinical guidelines: Report from an American College of Physicians Task Force. *Chest* 129:174-181, 2006.