Update on Diabetes Treatment Strategies

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Objectives

- Highlight current guidelines regarding glycemia control and diabetes pharmacotherapy in diabetes mellitus
- Highlight the current pharmacologic classes available for the treatment of diabetes mellitus
- Identify patients with diabetes mellitus appropriate for insulin therapy
Prevalence Of Diabetes In The US

- Diabetes affects 25.8 million people
- 8.3% of the US population (13% Montgomery County)
  - Diagnosed: 18.8 million
  - Undiagnosed: 7.0 million
- Leading cause of kidney failure, nontraumatic lower-limb amputation, new cases of adult blindness
- Major cause of heart disease and stroke
- 7th leading cause of death in US (6th in Ohio)

www.cdc.gov/diabetes/
DM2 Is A Progressive Disease

Obesity  Pre-DM  Diabetes  Uncontrolled Hyperglycemia

MICROVASCULAR DISEASE

Post-meal Glucose

Fasting Glucose

Glucose (mg/dL)

Years of DM

Relative Function (%)

Insulin Resistance  β-cell Failure  Insulin Level

MACROVASCULAR DISEASE

-10  -5  0  5  10  15  20  25  30

Adapted from International Diabetes Center, Minneapolis, Minnesota.
## Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Micro</th>
<th>Macro</th>
<th>Mortality</th>
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**Legend:**
- Initial Trial: ![grey_box](grey_box.png)
- Long Term Follow-up: ![light_blue_box](light_blue_box.png)

Anti-hyperglycemic Therapy: Glycemia targets

- HbA1c < 7.0% (MPG ~150 mg/dL)
- Pre-prandial PG <130 mg/dL
- Post-prandial PG <180 mg/dL
- Avoidance of hypoglycemia
- Individualization is key:
  - More stringent (6.0-6.5%) - short disease duration, healthier, no CVD
  - Less stringent (7.5-8.0%+) - comorbidities, complications, hypoglycemias, short life expectancy
Many Patients Are Not At The ADA/EASD Recommended A1c Goal Of < 7%

Patients (%) at A1c < 7%

1999-2002: 43.1%
2003-2006: 57.1%

## Approach to Management of Hyperglycemia

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>More stringent</th>
<th>Less stringent</th>
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<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia, other adverse events</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Disease duration</td>
<td>Newly diagnosed</td>
<td>Long-standing</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>Absent</td>
<td>Few/mild</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>Absent</td>
<td>Few/mild</td>
</tr>
<tr>
<td>Resources, support system</td>
<td>Readily available</td>
<td>Limited</td>
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Antihyperglycemic Therapy in DM2

- Initial drug monotherapy
  - Efficacy (+ HbA1c)
  - Hypoglycemia
  - Weight
  - Side effects
  - Costs

- Two-drug combinations
  - Efficacy (+ HbA1c)
  - Hypoglycemia
  - Weight
  - Major side effect(s)
  - Costs

- Three-drug combinations

- More complex insulin strategies

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with one or two noninsulin agents:

- Insulin (multiple daily doses)

Sequential Insulin Strategies in T2DM

Non-insulin regimens

Basal insulin only (usually with oral agents)

Basal insulin + 1 (meal-time) rapid-acting insulin injection

Basal insulin + ≥2 (meal-time) rapid-acting insulin injections

Premixed insulin twice daily

Number of injections Regimen complexity

1 low

2 mod.

3+ high

more flexible less flexible Flexibility

Diabetes Care, Diabetologia. 19 April 2012.
The Ominous Octet-Type 2

- Islet \( \beta \)-cell
  - Impaired Insulin Secretion
- Increased Glucagon Secretion
  - Increased HGP
- Increased Lipolysis
- Decreased Glucagon Secretion
  - Decreased Glucose Reabsorption
- Decreased Incretin Effect
  - Decreased Glucose Uptake
- Increased Glucose Uptake
  - Increased Lipolysis
- Neurotransmitter Dysfunction

## Anti-hyperglycemic Therapy: Oral agents & non-insulin injectables

- Biguanides
- Sulfonylureas
- Thiazolidinediones
- Meglitinides
- Alpha-glucosidase inhibitors
- DPP-4 inhibitors
- SGLT-2 inhibitors
- Dopamine-2 agonists
- Bile acid sequestrants
- GLP-1 receptor agonists
- Amylinomimetics

# Efficacy Of Oral Diabetes Agents*

<table>
<thead>
<tr>
<th>Drug</th>
<th>A1c Reduction (%)</th>
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<tr>
<td>Metformin</td>
<td>1.5-2.0</td>
</tr>
<tr>
<td>SFU</td>
<td>1.5-2.0</td>
</tr>
<tr>
<td>TZD</td>
<td>1.0-1.2</td>
</tr>
<tr>
<td>Glinide</td>
<td>1.5-2.0</td>
</tr>
<tr>
<td>α–GI</td>
<td>0.7-1.0</td>
</tr>
<tr>
<td>DPP4i</td>
<td>0.5-1.0</td>
</tr>
<tr>
<td>SGLT2i(^1)</td>
<td>0.8-1.0</td>
</tr>
<tr>
<td>Bromocriptine IR(^1)</td>
<td>0.6-0.9</td>
</tr>
<tr>
<td>Colesevelam(^1)</td>
<td>0.3-0.5</td>
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</table>

*Not head to head. Baselines differ. Background therapies differ.

\(^1\)Information taken from manufacturer PI.

Fowler MJ. *Clinical Diabetes* October 2007 vol. 25 no. 4 131-134.
BIGUANIDES
Metformin

- Weight neutral
- Low cost
- GI side effects common (~25%)
  - Slow titration and administration with meals
  - Consider extended release
- Vitamin B12 malabsorption
- Cardioprotective?

Metformin

• **Lactic acidosis**
  - 1 case per 30,000 patient-years
  - Women: creatinine > 1.4 mg/dL
  - Men: creatinine > 1.5 mg/dL
  - Decompensated CHF, renal or hepatic insufficiency; comorbid conditions/drugs which predispose to hypoxia
  - Contrast: Hold day of procedure and restart at 48 hours if creatinine is acceptable

SULFONYLUREAS
Sulfonylureas

• **1\textsuperscript{st} Generation**
  – Chlorpropamide, tolazamide, acetohexamide or tolbutamide

• **2\textsuperscript{nd} Generation**
  – Glyburide, glipizide or glimepiride

• **Can target fasting hyperglycemia/postprandial**
  – Enhance insulin secretion
Sulfonylureas

- Secondary failure rate
- Hypoglycemia
  - Elderly
  - Impaired renal function
  - Irregular meal schedule
- Weight gain
- Low cost
- Increase cardiovascular events?

THIAZOLIDINEDIONES
Pioglitazone and Rosiglitazone

• **Directly reduce insulin resistance**
  – Targets fasting and postprandial hyperglycemia

• **No hypoglycemia**

• **Indirect markers of CVD**

• **$\beta$-cell preservation**
Thiazolidinediones

- Weight gain
- Edema
- CHF
- Anemia
- Bone fractures
- Bladder cancer
- Cardiovascular events?

Lewis JD et al. *Diabetes Care.* April 2011 vol. 34 no. 4 916-922.
MEGLITINIDES
Repaglinide and Nateglinide

- Targets postprandial hyperglycemia
  - Stimulates insulin secretion
  - Rapid onset; short acting
- No dose adjustment in renal insufficiency
- Less hypoglycemia than sulfonylureas
- No sulfa moiety

α-GLUCOSIDASE INHIBITORS
Acarbose and Miglitol

- Target postprandial hyperglycemia
- Inhibit saccharidases of small intestine
  - Delay glucose entry into the circulation
- Flatulence (80%), diarrhea (27%), n/v (8%)
- No hypoglycemia or weight gain
  - Treatment of hypoglycemia in combination treated patients may be affected. Use simple sugars

DIPEPTIDYL PEPTIDASE-4 INHIBITORS
GLP-1 and GIP Are Degraded by the DPP-4 Enzyme

Meal

Intestinal GLP-1 and GIP release

DPP-4 enzyme

Active GLP-1 and GIP

Rapid inactivation

Inactive metabolites

DPP4 Inhibitors

- Side effects comparable to placebo
- No significant hypoglycemia or weight gain
- Can be used in CKD/ESRD
- Pancreatitis

“FDA has not concluded these drugs may cause or contribute to the development of pancreatic cancer.”

www.fda.gov/drugs/drugsafety/ucm343187.htm.
Sodium-glucose co-transporter 2 (SGLT-2) inhibitor
SGLT-2 Inhibitor

Canagliflozin

• Usual dose is 100 mg orally once daily initially
  – May increase to 300 mg once daily
  – Max dose of 100 mg daily if eGFR of 45-59 mL/min
  – Contraindicated eGFR < 45 mL/min

• Reduction of BP and weight

• Increased genital mycotic infections

• UGT inducers (e.g., rifampin) reduce levels.
  – Consider increasing dose from 100 mg to 300 mg

• Monitor digoxin levels

• Hyperkalemia, renal insufficiency, hypotension and LDL elevation
Centrally Acting Dopamine Agonist
Bromocriptine IR

- **Increases CNS dopaminergic activity**
  - Diabetes patients may have low morning levels of hypothalamic dopamine, which is thought to lead to hyperglycemia and dyslipidemia

- **PPG reductions, without increasing plasma insulin concentrations**
  - Not prone to hypoglycemia or weight gain

- **Side effects**- nausea, dizziness, fatigue, HA

Bile Acid Sequestrant
Colesevelam

• **Lowers LDL cholesterol**

• **Mechanism to improve glycemic control is uncertain**
  – May act in the gastrointestinal tract to reduce glucose absorption.

• **Side effects** constipation, nausea, dyspepsia and increase TG ~20%

Incretins and Amylinomimetic
Multihormonal Regulation of Glucose: Insulin, Glucagon, GLP1 and Amylin

- **Postprandial Glucagon**
- **Amylin**
- **Insulin**
- **Pancreas**
- **Liver**
- **Stomach**
- **Brain**
- **Gut**
- **Plasma Glucose**
- **Rate of glucose appearance**
- **Rate of glucose disappearance**
- **Tissues**
- **Food Intake**
- **Gastric Emptying**
- **GLP-1**

Incretins and Amylin: The Diabetes Treatment Continuum

- **IGT**
- **Diet + Exercise**
- **Basal**
- **Meal Time**

- **Orals**
  - Indication: Incretin
  - **Time: Years**

- **Insulins**
  - Indication: Amylin
  - **Time: Years**

- **Relative function**
  - **β-cell workload**
  - **β-cell response**
  - **Time - Years**
Insulin
Anti-hyperglycemic Therapy: Insulin

- Regular
- Neutral protamine Hagedorn (NPH)
- Rapid analogues (aspart, glulisine, lispro)
- Basal analogues (detemir, glargine)
- Pre-mixed varieties

Insulin Therapy in DM2: Indications

- Significant hyperglycemia at presentation
- Hyperglycemia on effective doses of oral agents
- Intolerance of orals
- Need more flexibility
- Renal or hepatic disease

- Surgery
- Pregnancy
- Unable to afford orals
- Decompensation
  - Acute injury, stress, infection, myocardial ischemia, stroke
  - Hyperglycemia with ketones, weight loss
  - Use of diabetogenic medications

Anti-hyperglycemic Therapy: Insulin

Hours after injection:

- Rapid (Lispro, Aspart, Glulisine)
- Intermediate (NPH)
- Long (Detemir)
- Long (Glargine)

Insulin level:

The Basal/Bolus Insulin Concept
Persons With DM Require Both Basal And Prandial Insulin

• **Basal insulin:**
  – Suppresses glucose between meals and overnight
  – Maintains nearly constant levels
  – Provides ~50% of daily needs

• **Prandial insulin:**
  – Limits hyperglycemia after meals
  – Produces immediate rise and sharp peak at 1 hour
  – Provides ~10%-20% of daily requirement per meal

• **Supplemental/Correctional insulin:**
  – Addresses unanticipated hyperglycemia
Basal vs Mealtime Hyperglycemia

AUC from normal basal >1875 mg/dL·hr; Est HbA1c >8.7%
Basal vs Mealtime Hyperglycemia In Diabetes: Basal Corrected

Plasma Glucose (mg/dL)

AUC from normal basal 900 mg/dL·hr; Est HbA1c 7.2%
Basal vs Mealtime Hyperglycemia In Diabetes: *Mealtime Corrected*

- **Plasma Glucose (mg/dL)**
  - 0
  - 50
  - 100
  - 150
  - 200
  - 250

**Time of Day**
- 0600
- 1200
- 1800
- 2400
- 0600

**AUC from normal basal 1425 mg/dL·hr; Est HbA1c 7.9**

**Basal hyperglycemia**

**Mealtime hyperglycemia**

Basal vs Mealtime Hyperglycemia In Diabetes: *Basal & Mealtime Corrected*

AUC from normal basal 225 mg/dL·hr; Est HbA1c 6.4%

Initiating Basal/Bolus De Novo

• **Total Daily Dose**
  – Type 2 Diabetes: 0.5 to 1 unit/kg/d
  – Type 1 Diabetes: 0.4 to 0.8 unit/kg/d

• **Basal**
  – Half the total daily dose

• **Bolus**
  – Half the total daily dose
  – Often reduced until adequately eating

• **Correction**
  – Based upon total daily dose

Limitations Of Human Insulin

- **Does not mimic endogenous insulin**
  - Variable onset, peak and duration of action

- **Potential for unpredictable hypoglycemia**
  - Major factor limiting insulin adjustments and aggressive glucose control

- **More weight gain**
Long-Acting Analogs: Medical Rationale

- Mimic basal physiological insulin profile
- Less hypoglycemia
- More predictable insulin delivery
- Improve glycemic excursions
- Less weight gain

Rapid-Acting Analogs: Medical Rationale

- Convenient administration with meals
- Faster onset of action
  - Reduce postprandial hyperglycemia
- Shorter duration of activity
  - Reduce late postprandial hypoglycemia
- More predictable insulin delivery
- Mimic physiologic insulin profile

Human Insulin Time-Action Patterns

- Normal Insulin Secretion at Meal Time
- Regular insulin

Change in Serum Insulin vs. Time (hours)

s.c. Injection
Baseline Level

A More Physiologic Time-Action

- Normal Insulin Secretion at Meal Time
- Analog insulin

Change in Serum insulin

s.c. injection

Time (hours)

Baseline Level

Spectrum Of Options

Conventional Insulin Therapy

Intensive Insulin Therapy

Insulin Pump Therapy

Sensor Augmented Pumps

Key Points

• Glucose targets & therapies must be individualized
• Diet, exercise & education = foundation
• Unless contraindicated, metformin 1st-line drug
• After metformin, data are limited
  – Combination therapy with oral and/or injectables is reasonable
  – Minimize side effects
• Many patients will require insulin therapy