Matching Pharmacology to Pathophysiology

Peripheral Insulin Resistance

- Elevated Glucose
- Hepatic Glucose Output
- Insulin Sensitizers: Exercise! TZD
  - Biguanides (Metformin)
  - GLP-1 Mimetics
  - Bromocriptine Mesylate
- Sulfonylureas
- Insulin DPP-4 Inhibitors
- GLP-1 Mimetics

Insulin Secretion

- Excess CHO Intake & Absorption
- Altered Satiety

Classification Based on Target Pathology

- Insulin Resistance
  - Biguanides
  - Thiazolidinediones (TZD)
- β-Cell Dysfunction / Failures
  - Sulfonylureas (SU)
  - Meglitinides
  - DPP-4 inhibitors
  - GLP-1 agonists
  - Alpha-glucosidase inhibitors
  - Bile acid sequestrant

Biguanides: Metformin

- Mechanism of Action
  - Reduces hepatic glucose production
  - Depends upon presence of insulin
- Safety and Efficacy
  - Decreases A1C 1–2%
  - Adverse events: Diarrhea and nausea, B12; worry: lactic acidosis
  - Contraindications: Renal, cardiac, hepatic insufficiency; IV contrast
- Dosing
  - Initial dose: 500 mg once a day; dosing: usually BID (range, OD–QID)
  - Maximum effective dose: 2000 mg per day; max. dose 2550 mg
  - Titration frequency: Week(s) to months
  - Alternative formulations: “XR” and combo w/ glyburide, glipizide and rosiglitazone


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**Metformin Reduces Cardiovascular Risk in Type 2 Diabetes**

UKPDS: Intensive glucose control in overweight type 2 diabetes patients using metformin as primary therapy

- Reduced A1C by 0.6% over 10 years
- Reduced the risk of diabetic complications

<table>
<thead>
<tr>
<th>Change in risk*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes-related endpoint</td>
<td>32%</td>
</tr>
<tr>
<td>Diabetes-related deaths</td>
<td>42%</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>36%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>39%</td>
</tr>
</tbody>
</table>

*vs conventional treatment


**Metformin Safety**

**Lactic Acidosis Avoidance: Prescribing Considerations**

- Metformin should not be prescribed to patients with:
  - Renal dysfunction as indicated by Scr ≥1.5 in males, ≥1.4 in females; in patients ≥80 years of age, creatinine clearance should be assessed prior to initiating therapy
  - Recent myocardial infarction or CHF requiring pharmacologic management
  - Liver dysfunction
  - History of alcohol abuse or binge drinking
  - Acute or chronic metabolic acidosis

**Thiazolidinediones (TZDs or Glitazones): Pioglitazone and Rosiglitazone**

- **Mechanism of Action**
  - Enhance insulin sensitivity in muscle, adipose tissue
  - Inhibit hepatic gluconeogenesis
  - Perhaps, stabilize beta-cell dysfunction
- **Safety and Efficacy**
  - Decrease A1C 1–2%
  - Adverse events: Edema, weight gain, anemia; worry: liver / heart failure
- **Dosing**
  - Initial dose: Pio 15 mg OD
  - Maximum effective dose: Maximum dose (pio 45 mg OD, rosi 8 OD)
  - Titration frequency: Weeks to month(s)


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Antidiabetes Medications 2011: Issues and Perspectives

**Insulin Resistance: TZD Effects**

- Accelerated Atherosclerosis
- Type 2 diabetes
- Hypertension
- Inflammation
- Dyslipidemia
- Coagulation/fibrinolytic defects
- Endothelial dysfunction
- Obesity (central)


**Insulin Resistance: TZD Effects**

- Improves glycemic control
- Reverses coagulation and fibrinolytic defects
- Reduces blood pressure
- Decreases TG (P)
- Increases HDL
- Improves LDL size
- Reduces central obesity
- Improves endothelial dysfunction


**TZDs: Minimizing Adverse Effects**

- Warn patients about the possible (liver) and expected (edema and weight gain) adverse effects; develop prospectively a plan for home evaluation and management
- ALT measurements prior to initiating therapy and intermittently thereafter; avoid use in active liver disease
- Start with a low dose in high-risk patients (pre-existing edema, insulin-treated, or known heart disease)

  - Pioglitazone 15 mg PO QD or rosiglitazone 2–4 mg PO QD
  - At 1–2 month follow-up visit, increase dose as needed
  - If edema develops, salt restriction ± low-dose thiazide diuretic ± loop diuretic ± dose reduction
  - Consider role of ACE inhibition, CCBs, NSAIDs

**PROactive Summary**

- Funded by the manufacturer Takeda Pharmaceuticals
- Technically, a negative study from a statistical point of view
  - Analogous to UKPDS
- Nevertheless, it suggests a 16% reduction in stroke, MI, and death
  - Largely accounted for by a reduction in A1C, triglycerides, and blood pressure and an increase in HDL-C
- Benefits were in part mitigated by an increase in CHF, edema, and weight


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**TZDs and Cardiovascular Events: Pioglitazone**

- Highly efficacious in reducing insulin resistance and glucose without hypoglycemia
- Side effects limiting use: Weight gain, edema
- Cardiovascular issues incompletely resolved
  - Clear data for CHF → contraindication
  - Ischemic CVD: Insufficient data, individual judgment required
- Increased bone fracture rates in women
- Observational trials suggest possible association with bladder cancer

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**TZD: Summary**

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Approximately 50% of patients with newly diagnosed type 2 diabetes achieve acceptable glycemic control. 15%-20% of patients have little or no glycemic response. Long-term failure in 30% of patients (sulfonylureas).

Risk of hypoglycemia:
- Age, decreased carbohydrate intake, renal and hepatic dysfunction, potentiating effects of alcohol
- Consistent timing and quantity of food intake required
- Less hypoglycemia with repaglinide or nateglinide

May increase hyperinsulinemia and weight gain.

Mechanism of Action:
- Stimulate basal and postprandial insulin secretion
- Require functioning beta cells

Safety and Efficacy:
- Decrease A1C approximately 1–2%
- Adverse events: Weight gain, allergy (rare); main risk, hypoglycemia

Dosing:
- Initial dose: 1/8 to 1/4 maximum dose; dosing: 1–2 times/day (SFU), 3 times/day (glinides)
- Maximum effective dose: 1/2 maximum (full dose with nateglinide)
- Titration frequency: Day(s) to weeks

Insulin Secretagogues: Sulfonylureas and “Glinides”

K<sub>ATP</sub> Channels in Pancreatic β Cells

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Acarbose, miglitol

- Delay absorption of carbohydrates by inhibiting disaccharidases
- Decrease A1C 0.5–1%
- Adverse events: Flatulence, rare liver enzyme elevations

**Dosing**
- Initial: ¼ max dose premeals (25 mg), usually maximal effective dose 50 mg
- Titration frequency: Weeks to months
- Use glucose when treating hypoglycemia or may delay recovery speed

**GLP-1 Secretion and Metabolism**

Intestinal GLP-1 Release → GLP-1 (7–36) Active → Rapid Inactivation (>80% of pool) → Renal Clearance

**GLP-1 Actions**

- Stomach: Reduces gastric emptying
- Brain: Promotes satiety and reduces appetite
- Liver: Glucagon reduces hepatic glucose output
- Pancreatic cells: Promotes insulin secretion postprandial glucagon secretion

**Incretin Hormone:**

Glucose-dependent insulin secretion by pancreas


GLP-1: Secreted upon the ingestion of food


Exenatide: Effects on Glycemic Control in Combination with Current Therapies

Effect of Exenatide on Weight: Open-Label Extension – Combined

Liraglutide Monotherapy: A1C Change Over 52 Weeks

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Liraglutide Use Is Associated with Weight Loss

Data are mean (±2 SE).

+1.1 kg
-2.1 kg
-2.5 kg

Inactive GLP-1
Other Peptides

GLP-1 (7–36)
Active

DPP-4

DPP-4 Inhibitors: Enhance Insulin Secretion via Reduction in Incretin Inactivation

Sitagliptin
Saxagliptin

No weight gain
Good combination with metformin
Well-tolerated

DPP-4 Inhibitors: Physiologic Action

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**Effect of Sitagliptin on A1C, FPG, and 2-Hour PPG**

- **A1C**
  - Mean Baseline: 8.0%
  - Mean Baseline: 7.7%
  - Mean Baseline: 7.5%
- **FPG**
  - Mean Baseline: 170 mg/dL
  - Mean Baseline: 170 mg/dL
  - Mean Baseline: 170 mg/dL
- **2-hr PPG**
  - Mean Baseline: 275 mg/dL
  - Mean Baseline: 275 mg/dL
  - Mean Baseline: 275 mg/dL

*Compared with placebo.
†Least squares means-adjusted for prior antihyperglycemic therapy status and baseline value.
‡Difference from placebo.

**Sitagliptin Added to Metformin: Effect on A1C, FPG, and 2-Hour PPG**

- **A1C**
  - Mean Baseline A1C: 8.0%
  - Mean Baseline: 7.7%
  - Mean Baseline: 7.5%
- **FPG**
  - Mean Baseline: 170 mg/dL
  - Mean Baseline: 170 mg/dL
  - Mean Baseline: 170 mg/dL
- **2-hour PPG**
  - Mean Baseline: 275 mg/dL
  - Mean Baseline: 275 mg/dL
  - Mean Baseline: 275 mg/dL

*Compared with patients inadequately controlled on metformin monotherapy.
†Compared with placebo plus metformin.
‡Least squares means-adjusted for prior antihyperglycemic therapy status and baseline value.
§Difference from placebo.

**Effect of Saxagliptin on A1C, FPG, and 2-Hour PPG**

- **A1C**
  - Mean Baseline: 8.0%
  - Mean Baseline: 7.7%
  - Mean Baseline: 7.5%
- **FPG**
  - Mean Baseline: 170 mg/dL
  - Mean Baseline: 170 mg/dL
  - Mean Baseline: 170 mg/dL
- **2-hour PPG**
  - Mean Baseline: 275 mg/dL
  - Mean Baseline: 275 mg/dL
  - Mean Baseline: 275 mg/dL

*Compared with placebo.
†Least squares means-adjusted for prior antihyperglycemic therapy status and baseline value.
‡Difference from placebo.
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**Saxagliptin Added to Metformin:**
**Effect on A1C, FPG, and 2-Hour PPG**

- **A1C**
  - Mean Baseline A1C: 8.1%
  - Change from Baseline: -0.8% (95% CI: -1.00, -0.50)
- **FPG**
  - Mean Baseline: 179 mg/dL
  - Change from Baseline: -23 mg/dL (95% CI: -30, -16)
- **2-hour PPG**
  - Mean Baseline: 296 mg/dL
  - Change from Baseline: -40 mg/dL (95% CI: -56, -4)

*In patients inadequately controlled on metformin monotherapy.
†Compared with placebo plus metformin.
‡Least squares means-adjusted for prior antihyperglycemic therapy status and baseline value.
Difference from placebo.

**Linagliptin Shows Significant A1C Reductions Across All Pivotal Phase III Trials**

- **Monotherapy**
  - Mean Baseline A1C: 121.8
  - Change from Baseline: -0.89
- **Metformin**
  - Mean Baseline A1C: 121.8
  - Change from Baseline: -0.64
- **Metformin + Pioglitazone**
  - Mean Baseline A1C: 121.8
  - Change from Baseline: -0.67
- **vs. Placebo in Japanese**
  - Mean Baseline A1C: 121.8
  - Change from Baseline: -0.87

**Linagliptin Is the Only DPP-4 Inhibitor Not Primarily Excreted via the Kidneys**

- Linagliptin: 5%
- Sitagliptin: 75–80%
- Vildagliptin: 85%
- Saxagliptin: 75%
- Alogliptin: 60–70%

Linagliptin is primarily excreted via the enterohepatic system.

- All other DPP-4 inhibitors are primarily excreted via the kidneys.
- All of them have dose adjustments or are not recommended for patients with moderate or severe renal impairment.

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**FDA-Approved Indications for Colesevelam**

- Reduction of LDL-C in monotherapy, or in combination with HMG-CoA inhibitors (statins)*
- Adjunct treatment for glycemic control, after diet and exercise, type 2 diabetes**
- Contraindications: Triglycerides >500 mg/dL

*Statins remain the first choice for LDL-C reduction for most patients.
**Colesevelam has not been studied for glycemic control in monotherapy, or in combination with incretin-mimetics or DPP-4 inhibitors.

---

**Effects of Colesevelam on A1C Levels in Add-on Therapy Trials**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change in A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLOWS Week 12</td>
<td>-0.50</td>
</tr>
<tr>
<td>Metformin Week 26</td>
<td>-0.54</td>
</tr>
<tr>
<td>Sulfonylurea Week 26</td>
<td>-0.54</td>
</tr>
<tr>
<td>Insulin Week 16</td>
<td>-0.50</td>
</tr>
</tbody>
</table>

---

**Bromocriptine Mesylate RA Tablets**

- A novel approach to treating type 2 diabetes in adults
  - Quick-release formulation of bromocriptine that increases CNS dopaminergic activity
  - Controls glucose throughout the day
    - Once-daily dosing provided significant PPG reductions, without increasing plasma insulin concentrations
    - Improved A1C by 0.6–0.9% vs placebo when added to other agents
  - Has demonstrated cardiovascular safety and overall safety
    - 1.5% of patients on bromocriptine vs 3% on placebo experienced a composite CVD endpoint

Dose: 1.2–4.8 mg within 2 hours of waking in the morning
Patients with diabetes may have low morning levels of hypothalamic dopamine, which is thought to lead to hyperglycemia and dyslipidemia.

Bromocriptine RA resets aberrant low morning hypothalamic dopaminergic activity, which may reset neuroendocrine metabolic control.


Decreased lipolysis in adipose tissue
Decreased postprandial hepatic glucose output
Decreased insulin resistance

0.6–0.9% A1C reductions vs placebo when bromocriptine RA added to other oral antidiabetes drug (OAD)

Data on file, Santarus, Inc.

Efficacy data in combination with thiazolidinediones are limited. Efficacy has not been confirmed in combination with insulin.

Placebo
Bromocriptine

Failing Any OAD (n=412)
Failing Metformin ± OAD (n=282)
Failing Metformin + Sulfonylurea (n=192)
Failing TZD ± OAD (n=81)

Average baseline A1C 8.3%

P<0.0001
P<0.0001
P=0.0002
P=0.0026

0.57
0.69
0.69
0.91

Type 2 Diabetes and Reduced Renal Function

Medications contraindicated
- Glyburide (CrCl ≤ 50)
- Exenatide (CrCl < 30)
- Metformin (creatinine > 1.4 in women or > 1.5 in men)  
- α-Glucosidase inhibitors (creatinine > 2.0)

No adjustment needed
- Thiazolidinediones
- Liraglutide
- Nateglinide
- Bromocriptine

Medications requiring a reduction in dose
- Glipizide
- Gilmeperide
- Rapagliflud
- DPP-4 Inhibitors

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Most Patients with Type 2 Diabetes May Fail to Attain A1C Goal with Conventional Treatment Paradigm

OAD=oral antidiabetes drug.


Earlier and More Aggressive Intervention May Improve Patients’ Chances of Reaching Goal

OAD=oral antidiabetes drug.


Progressive Hyperglycemia Despite Insulin, Sulfonylurea, or Metformin

OAD=oral antidiabetes drug.


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**Patients Remain on Monotherapy >1 Year after First A1C >8.0%**

<table>
<thead>
<tr>
<th>Duration of Monotherapy</th>
<th>Metformin Only</th>
<th>Sulfonylurea Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 months</td>
<td>n = 334</td>
<td></td>
</tr>
<tr>
<td>20 months</td>
<td>n = 2517</td>
<td></td>
</tr>
</tbody>
</table>

*May include up-titration. Length of time between first A1C >8% and switch/addition in therapy could include periods when patients had subsequent A1C test values below 8%. Based on nonrandomized retrospective database analysis. Data from Kaiser Permanente Northwest 1994–2002. Patients had to be continuously enrolled for 12 months with A1C lab values.


---

**Treatment Titration for Type 2 Diabetes**

**Why use early combination therapy?**

- Combination pharmacotherapy addresses multiple pathophysiologic defects
- Dual therapy is titrated simultaneously rather than sequentially
- Early stepwise titration aimed at glycemic targets
- Medication chosen for titration based on glucose patterns


---

**Effects of Metformin on FPG in Glyburide-Treated Patients**

**P value**

- 0.001

Combination Therapy: Estimated Improvements in Glycemic Control

<table>
<thead>
<tr>
<th>Regimen</th>
<th>↓ A1C</th>
<th>↓ FBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea + metformin</td>
<td>~1.7%</td>
<td>~65 mg/dL</td>
</tr>
<tr>
<td>Sulfonylurea + rosiglitazone</td>
<td>~1.4%</td>
<td>~60 mg/dL</td>
</tr>
<tr>
<td>Sulfonylurea + pioglitazone</td>
<td>~1.2%</td>
<td>~50 mg/dL</td>
</tr>
<tr>
<td>Sulfonylurea + acarbose</td>
<td>~1.3%</td>
<td>~40 mg/dL</td>
</tr>
<tr>
<td>Repaglinide + metformin</td>
<td>~1.4%</td>
<td>~40 mg/dL</td>
</tr>
<tr>
<td>Pioglitazone + metformin</td>
<td>~0.7%</td>
<td>~40 mg/dL</td>
</tr>
<tr>
<td>Rosiglitazone + metformin</td>
<td>~0.8%</td>
<td>~50 mg/dL</td>
</tr>
<tr>
<td>Insulin + antidiabetes agents</td>
<td>Open to target</td>
<td>Open to target</td>
</tr>
</tbody>
</table>

Schneider et al. [Diabetes. 1999;48(suppl 1):A106] | Egan et al. [Diabetes. 1999;48(suppl 1):A117] |
Fonseca et al. [Diabetes. 1999;48(suppl 1):A100] |

Using Noninsulin Therapy Wisely in Type 2 Diabetes

- Select medication based on understanding of pathophysiology
- Beta-cell dysfunction determines progression
- Combination therapies should be considered earlier
- Consider nonglycemic effects of drugs
- Treat to goal

Links to Guidelines