Meds for Type 2 –
What you need to know

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Diabetes Meds for Type 2: What You need to Know

1. Describe the main action of the 6 different categories of type 2 diabetes medications.
2. Discuss strategies to determine the right medication for the right patient.
3. List the side effects and clinical considerations of each category of medication.

Registered Nurses and CA Pharmacists
DES is accredited as a provider of continuing nursing education by the California Board of Registered Nursing (CEP # 12940). This Education program will provide 2.0 contact hours of continuing education credit. CA Pharmacists also earn 2.0 CE (since we are accredited by the BRN).

Registered Dietitians
DES is a Continuing Professional Education (CPE) Accredited Provider with the Commission on Dietetic Registration (CDR) Provider # DI002. Registered dietitians (RDs) will receive 2.0 continuing professional education units (CPEUs) for completion of this program.
ABCs of Diabetes –

- **A1c less than 7%** (avg 3 month BG)
  - Pre-meal BG 70-130
  - Post meal BG <180
- **Blood Pressure** < 140/80 (changed in 2013)
- **Cholesterol**
  - HDL >40
  - LDL <100 (if CHD, <70)
  - Triglyceride < 150

American Diabetes Association Standards of Care

Resource Page Underline = Link

- We have added hyperlinks that you can click on for more information.
- So, if you see words underlined click on them to review additional information.
- Diabetes Medication PocketCards

What is Type 2 Diabetes?

- Complex metabolic disorder ….
  (Insulin resistance and deficiency)
with social, behavioral and environmental risk factors unmasking the effects of genetic susceptibility.
Natural Progression of Type 2 Diabetes

[Graph showing the progression of plasma glucose, postprandial glucose, fasting glucose, and relative β-cell function over years of diabetes, with data points indicating increased insulin resistance and decreased insulin secretion before and after diagnosis.]

Adapted from Bergenstal et al. 2000; International Diabetes Center.

Ominous Octet

Increased
1. liver production of glucose
2. free fatty acid circulation
3. alpha cell secretion of glucagon
4. glucose reabsorption from the kidney

Decreased
5. insulin/amylin secretion (80% of beta cells lost at dx)
6. muscle absorption of glucose
7. gut hormones GLP-1 and GIP
8. neurotransmitter function from the brain (affects appetite control)

From the Triumvirate to the Ominous Octet – a new paradigm for the treatment of T2DM. DeFronzo at the 2008 Banting Lecture.
Resources for Medications

- Partnership for Prescription Assistance
  - www.pparx.org
- NeedyMeds.org
- www.rxassist.org

Action/Classes of Type 2 Meds

1. Suppressor
   - Biguanide – Metformin
2. Squirter
   - Sulfonylureas
   - Meglitinides
3. Satiators
   - AmylinMimetics
   - Incretin Mimetics
   - DPP-4 Inhibitors
4. Sensitizer
   - Thiazolidinediones (TZD)
5. Glucoretics
   - SGLT2 Inhibitors
6. Circadian Switchers
   - Dopamine Receptor Agonists
7. Slower
   - Alpha-glucosidase inhibitors

Diabetes Agents Considerations

- Diabetes medications can be used as monotherapy, in combo or with insulin
- Combining agents from different classes has additive effect
- Most reduce A1c 0.5 – 2.0%
- Not to be used during preconception, pregnancy or when breastfeeding
ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

Patient-Centered Approach – Meds Part 2

“...providing care that is respectful of and responsive to individual patient preferences, needs, and values - ensuring that patient values guide all clinical decisions.”

• Gauge patient’s preferred level of involvement.
• Explore, where possible, therapeutic choices.
• Utilize decision aids.
• Shared decision making – final decisions re: lifestyle choices ultimately lie with the patient.

Ideal Diabetes Med -

- No hypoglycemia
- No weight gain
- Affordable
- Lowers CV risk
- Most people can tolerate/use?

Biguanides – Suppressor Metformin (Glucophage®)

- Action: suppresses release of glycogen from the liver
- Who?
  - Fasting hyperglycemia
  - Dysmetabolic Syndrome
  - For pediatrics starting age 10
    - (XR age 17)
Biguanides - Metformin

**Action:** decrease hepatic glucose (glycogen)

**Names:**
- Metformin (Glucophage)
  - Starting dose: 500 BID, max 2500mg daily
- Metformin extended release (3 different versions)
  - Starting dose 500mg at dinner, max dose 2000 to 2500 mg daily

**Efficacy:**
- Decrease fasting plasma glucose 60-70 mg/dl
- Reduce A1C 1.0-2.0%

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Biguanides - Metformin

**Side effects**
- Diarrhea and abdominal discomfort
- Lactic acidosis if improperly prescribed
- Decrease LDL cholesterol and triglycerides
- No weight gain, with possible modest weight loss
- Watch for B12 deficiency

**Considerations**

**Biguanide - Metformin (Glucophage®)**

**Contraindications due to lactic acidosis:**
- creatinine >1.4 females, >1.5 males
- liver disease
- alcohol abuse
- over 80 years old
- risk of acidosis
- during IV dye study
- CHF requiring meds
Metformin – How does it rate?

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What questions would you ask?

35 yr old, BMI 28, A1c 6.7% x 2. LDL 154, enjoys “occasional” beer.

Sulfonylureas –

- Action: tells pancreas to squirt insulin all day
- Who?
  - Lean type 2
**Sulfonylureas - Squirts**

- **Action:** Increase endogenous insulin secretion
- **Efficacy:**
  - Decrease FPG 60-70 mg/dl
  - Reduce A1C by 1.0-2.0%
- **Primary failures:** about 20% no response
  - R/O glucose toxicity or low beta cell function
- **Secondary failures:** 5-10% shortly after initial response, many more later
  - Usually after 5 or more years of therapy due to natural history of DM 2

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**Sulfonylureas: 1st Generation**

<table>
<thead>
<tr>
<th>Trade</th>
<th>Generic</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Diabinese*</td>
<td>Chlorpropamide</td>
<td>72 hr</td>
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<tr>
<td>Tolinase</td>
<td>Tolazamide</td>
<td>10-14 hrs</td>
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<tr>
<td>Orinase</td>
<td>Tolbutamide</td>
<td>6-12 hrs</td>
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*Longest duration. Use with caution in elderly and those with renal disease. Can cause flushing reaction with alcohol.

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**Sulfonylureas: 2nd Generation**

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<tr>
<th>Generic</th>
<th>Trade, Micronase,</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Glyburide</td>
<td>Glynase Prestaba</td>
<td>12-24 hrs</td>
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<tr>
<td>Glipizide*</td>
<td>Glucotrol, Glucotrol XI</td>
<td>12-24 hrs</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Amaryl</td>
<td>16-24 hrs</td>
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*take short acting product on empty stomach
Sulfonylureas

- Other Effects
  - Hypoglycemia
  - Weight gain
  - Cleared by kidney, use caution for pts with kidney problems
  - Generally the least expensive class of medication

Indication for “Fast Acting” Insulin Secretagogues- Meglitinides

- Action: tells pancreas to squirt insulin with meals
- Who?
  - Targets post-prandial hyperglycemia

Meglitinides - Squirts

- Action: stimulate insulin secretion (rapid and short duration) when glucose present
- Names:
  - repaglinide (Prandin)
    - **Dosing:** 0.5 to 4 mg a.c. Max dose 16mg
    - Metabolized by liver and mostly excreted in feces (some renally).
  - nateglinide (Starlix)
    - **Dosing:** 120 mg tid with meals
    - Metabolized by liver, excreted by kidney
- Efficacy:
  - Decreases peak postprandial glucose
  - Decreases plasma glucose 60-70 mg/dl
  - Reduce A1C 1.0-2.0%
Meglitinides

Other Effects
- Hypoglycemia (less than with sulfonylureas if patient has a variable eating schedule)
- Minimal weight gain
- No significant effect on plasma lipid levels
- Safe at higher levels of serum Cr than sulfonylureas

Squirters – How does they rate?

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What questions?

- 72 yr old, thin, lives alone, A1c 7.3%. History of MI, stroke. DM for 12 yrs, “diet controlled”. Creat 1.6
**Indications for Amylin Mimetics**

**Incretin Mimetics**

**DPP-4 Inhibitors**

- **Action:** Satiates
- **Who?**
  - Target post-prandial hyperglycemia
  - Avoid hypoglycemia, wt gain
  - For type 2s only, except Amylin Mimetics used in type 1 and 2.

**Amylin Mimetic Pramlintide (Symlin) 2005**

- **Action:**
  - Prevents post-meal rise in glucagon
  - Slowing gastric emptying
  - Increases satiety
- **Efficacy:** Decreases A1c by 0.7%, wt by 3lbs
- **Dosing:**
  - Type 2 – max 120 mcg, BID before meals
  - Type 1 – max 60 mcg ac meals (meal = 30 gms carbs)
- **Other:** approved only as adjunct to insulin therapy – can’t mix in same syringe with insulin

**Pramlintide (Symlin) Considerations**

- Sub-Q injection in abd or thigh prior to meal
- Reduce insulin by 50% when starting pramlintide
- Side effects include hypoglycemia, nausea, loss of appetite, redness, swelling at inject site
- Don’t use in pts with gastroparesis, hypoglycemia unawareness
- Store unopened vials in refrig, toss after 28 days
- Cost: $100 for 5 ml vial

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### Amylin Mimetic – How does it rate?

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### Great time to Take a Break

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### Incretin Mimetics – “Gut Hormones”

- **DPP-IV Inhibitors**
  - How do they work?
GLP-1 Effects in Humans
Understanding the Natural Role of Incretins

GLP-1 secreted upon the ingestion of food
Promotes satiety and reduces appetite

↑ Beta-cell response

Alpha cells: ↓ Postprandial glucagon secretion
Liver: ↓ Glucagon reduces hepatic glucose output

Betacells: Enhances glucose-dependent insulin secretion

Stomach: Helps regulate gastric emptying

GLP-1 degraded by DPP-4 within minutes

Incretin Mimetics
Exenatide (Byetta), Liraglutide (Victoza)

Action:
- Insulin release in response to meal
- Slows gastric emptying
- Causes Satiety

Exenatide Dosing: ~ 5-10 mcg ac break, dinner
- Long acting version in pipeline (LAR)

Efficacy: Decreases A1c by 0.7%, wt by 3lbs

Indication: For type 2s only - mono or in combo

Other: In prefilled pens in 5 or 10 mcg doses

Incretin Mimetics — Exenatide XR - Bydureon

Once a Week Dosing: 2mg

Efficacy: Decreases A1c by 1.6%, wt by ~6lbs

Indication: For type 2s only

Other: Pt will need to mix powdered form and inject

Caution: not indicated for those with history of medullary thyroid tumor - pancreatitis warning
$323.44 for four doses, or about $4,200 a year.

Incretin Mimetics – GLP-1 Analog
Liraglutide (Victoza)

**Liraglutide Dosing:** 1x daily, time not critical
- 0.6 x 1 week – if tolerated (nausea), go to >
- 1.2 x 1 week – if tolerated go to >
- 1.8 mg daily

- **Efficacy:** lowers; A1c by 1%, body wt by ~ 2.5kg
- **Indication:** Monotherapy or in combo . Type 2 only
- **Other:** In pen, with preset dosing
- **Black box**–thyroid tumor warning (avoid if family hx, notify MD of hoarseness, lump).

Incretin Mimetics Considerations
Exenatide, Liraglutide

- Store pens in refrig, toss after 30 days
- Sub-Q Injection in abd, thigh, upper arm
- To prevent hypoglycemia , reduce sulfonylurea/insulin dose when starting
- Side effects include nausea, diarrhea
- Pancreatitis warning (instruct pt to report abd pain, vomiting)
- Don’t use w/ gastroparesis, severe renal disease
- Exenatide Cost : $150-175 for month supply of pen devices
Incretin Mimetics – How do they rate?

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<td>Yes/No</td>
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DPP-4 Inhibitors – “Incretin Enhancers”
Januvia (sitagliptin) – Tradjenta (linagliptin)
Onglyza (saxagliptin) - Nesina (alogliptin)

- **Action:**
  - Increase insulin release w/ meals
  - Suppress glucagon
- **Dosing:**
  - Januvia – 100mg a day
  - Onglyza – up to 5mg a day
  - Tradjenta – 5mg a day
  - Nesina – 25 mg a day
- **Efficacy:** Decreases A1c by 0.6 -0.8%
- **Indication:** For type 2s

Januvia, Onglyza eliminated via kidney, lower dose needed
Tradjenta reduced efficacy in combo w/ CYP 3A4 inducer (e.g., rifampin).
Do not cause wt gain or hypoglycemia
Side effects – headache, runny nose, sore throat - watch for pancreatitis
Cost $100 - $150 mo
DPP-IV Inhibitors – How do they rate?

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For all the Previous GLP-1 Enhancers

- Pancreatitis Warning
  - Please tell all patients to report signs right away and discontinue meds
  - Signs include:
    - Sudden abdominal pain, nausea and vomiting
  - May also be associated w/ increased risk of pancreatic cancer? Studies ongoing.

What questions?

- 69 year old male, BMI 25, on Metformin 1000mg BID and Exenatide 5mcg before breakfast and dinner. AM glucose 120s, A1c 8.1%. Creat 1.4
Indications for Insulin Sensitizers
Rosiglitazone (Avandia®), Pioglitazone (Actos®)

- **Action:** Sensitizers
- **Who?**
  - Insulin resistant patient
  - Dysmetabolic syndrome

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Thiazolidinediones – TZD’s

- **Action:** decrease insulin resistance by making muscle and adipose cells more sensitive to insulin. Decrease free fatty acids
- **Names:**
  - pioglitazone (Actos)
    - Dosing: 15-45 mg daily
  - rosiglitazone (Avandia) - restricted
    - Dosing: 4-8 mg daily
- **Efficacy:**
  - Decrease fasting plasma glucose ~35-40 mg/dl
  - Reduce A1C ~0.5-1.0%
  - 6 weeks for maximum effect
  - $30 a month

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rosiglitazone (Avandia) Warning

- Avandia FDA Restricted.
  - NO new pts can start. Mail order only. Not in pharmacies
    - Associated w/ increase risk of Myocardial Infarction
  - Restriction includes combo meds
    - Avandamet
    - Avandaryl

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Pioglitazone (Actos) Warning

Bladder Cancer Risk
- Risk increased with increasing dose and duration
- France has pulled Actos, Germany restricted access
- FDA Recommends
  - Do not use in pts with active bladder cancer.
  - Use with caution in pts w/ prior history of bladder CA
  - “Benefits of BG control should be weighed against the unknown risks for cancer recurrence”

Patient Instructions
- Report symptoms of bladder cancer: blood or red color in urine; urgent need to urinate or pain while urinating; pain in back or lower abdomen.

TZD Actos—How does it rate?

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SGLT2 Inhibitor—

- **Action:** “Glucoretic” decreases renal reabsorption in the proximal tubule of the kidneys (reset renal threshold and increase glucosuria)
- **Name:**
  - Canagliflozin (Invokana)
- **Dosing:** 100 – 300 mg once daily ac first meal
  - If eGFR 45-60: do not exceed 100mg a day
  - If eGFR <45, do not use
- **Efficacy:**
  - Weight loss of 1-3 lbs
  - Reduce A1C ~0.7-1.0%
SGLT2 Inhibitors - Considerations

- Monitor B/P, K+ & renal function.
- Side effects: hypotension, UTI, increased urination, genital yeast infections.
- Improves beta cell function?
  - Reverses glucose toxicity by increasing GLUT4 transport in muscle
  - Increase liver sensitivity to insulin and decreases gluconeogenesis.

“Circadian Switchers” Dopamine Receptor Agonist bromocriptine mesylate QR “Quick Release”

- Action: Increases dopamine levels
  - Decreases insulin resistance
  - Decreases dyslipidemia
  - No weight gain

“Circadian Switchers” Increased Dopamine Levels =

Decreased:
- Insulin resistance
- Hepatic Glucose Output
- Lipolysis / FFA
- Lipogenesis / TG
- Vascular pathology

Increased:
- Glucose tolerance
- Insulin Sensitivity

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Dopamine Agonists – Circadian Re-Setters

- **Action:** Increase am dopamine levels
- **Name:** bromocriptine mesylate QR (Cycloset)
  - **Dosing:** 1.6 to 4.8 mg per day
  - Each tab 0.8 mg, start at one tab a day, increase one tab a week
  - Give w/in 2 hrs of waking (before food)
- **Efficacy:**
  - Reduces A1C 0.6 – 0.9%
  - Reduces death from CV events
- **Side Effects:**
  - Nausea, vomiting, headaches, fatigue (watch for syncope)

“Circadian Switchers” bromocriptine mesylate QR

- **Other considerations:**
  - Avoid in patients:
    - With syncopal migraines
    - With psychotic disorders
    - Who are breastfeeding (stops lactation)
  - Eval for somnolence
  - Watch for drug/drug interaction w/ meds that affect CYP450 isoenzyme

Cycloset– How does it rate?

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Indications for Glucosidase Inhibitors
Acarbose (Precose®), Miglitol (Glyset®)

Action: Slower
- Target postprandial blood glucose
- Minimal systemic absorption

Alpha-glucosidase Inhibitors

- **Action:** blocks enzymes that digest starches in the small intestine
- **Name:** acarbose (Precose)
  - Dosing: 75-300mg based on weight
- **Efficacy**
  - Decrease postprandial glucose 40-50 mg/dl
  - Decrease A1C 0.5-1.0%
- **Other Effects**
  - Flatulence or abdominal discomfort
  - Contraindicated in patients with inflammatory bowel disease or cirrhosis
- **Special Consideration**
  - In case of hypoglycemia, treat with glucose tabs or milk
  - (other starches are blocked by medication)

Acarbose—How does it rate?

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Juvisync
Januvia + Simvastatin

- Incretin Enhancer + Cholesterol Lowering
- 3 Doses:
  - 100 mg sitagliptin + 10 mg simvastatin
  - 100 mg sitagliptin + 20 mg simvastatin
  - 100 mg sitagliptin + 40 mg simvastatin
- Plan to develop 50 mg sitagliptin dose
- Observe precautions of each.
- Pancreatitis & muscle weakness/ soreness

Juvisync– How does it rate?

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Combo Pills for Type 2

- Sulfonylurea + Biguanide
  - Glyburide + Metformin - Glucovance Metaglip
  - Glipizide + Metformin -
- Thiazolidinedione + Biguanide
  - Pioglitazone + Metformin - Actoplus Met
- Thiazolidinedione + Sulfonylurea
  - Actos + Amaryl - Duetact
- DPP-4 Inhibitor + Biguanide
  - Januvia + Metformin - Janumet
  - Onglyza + Metformin XR Kombiglyze
- DPP-4 Inhibitor + Statin
  - Januvia + Zocor - Juvisync
Ominous Octet

Incretin Mimetics
- satiation neurotransmission
- Pramlintide, amylin, Secretagogues 
- β-cell secretion

Metformin
- glucose production

TZDs
- lipolysis

Incretin Mimetics, DPP-IV inhibitors
- Bile Acid Sequestrants
- Gut hormones

SGLT2 Inhibitors
- glucose renal reabsorption

Incretin Mimetics, DPP-IV inhibitors
- Bile Acid Sequestrants

J. R.

49 year old with type 2 diabetes for 9 years.
Weight – 370 lbs
A1c 13.9%
Creat 2.0
Gave up checking BG
Meds for past year:
- Januvia
- Byetta
- Detemir 20units at hs

Consider these Clinical Books as additional resources
Other Resources

- Medications and Insulin Online Courses
- PocketCards
- Other Free Webinars
- Resource Page for Meds and Insulin

Thank you for joining our Web Clinic

Wrap up notes
1. You have 1 year to complete this program and take the post test to receive your CE credit (from time of purchase)
2. Complete the post test - click test button
3. Complete program survey - we appreciate your feedback
4. Now, your certificate is ready to print out
5. Join us on Facebook for special events

Keep in touch!
Beverly Thomassian and Lainey Koski