Patient Safety: A diabetes double take:  
The pharmacist’s role in managing double diabetes

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December 13, 2019

Disclosures

• I have no actual or potential conflicts of interest related to this activity. I do plan on discussing off-label uses of commercially available products.
Learning Objectives

At the conclusion of the presentation, the learner should be able to:

1. Define the pathophysiology of double diabetes
2. Identify the role and proper use of antidiabetic drugs for the management of double diabetes
3. Compare the risks and benefits of antidiabetic drugs in double diabetes
4. Given a patient case, optimize a treatment plan for a patient with double diabetes

Pre-assessment question 1

• Which of the following definitions best describes “double diabetes”? 
  A. Insulin dependent type 2 diabetes (T2DM) requiring two forms of insulin for treatment 
  B. A slow progressing form of autoimmune diabetes seen in adulthood 
  C. Insulin resistance seen in type 1 diabetes (T1DM)
Pre-assessment question 2

• Approximately, what percentage of patients with T1DM are overweight or obese?
  A. 10%
  B. 30%
  C. 50%

Pre-assessment question 3

• Which of the following antidiabetic drugs has been shown to lower A1c levels in patients with T1DM?
  A. Metformin
  B. Liraglutide
  C. Sitagliptin
Meet patient SB

• SB is a 48 year-old male with a history of T1DM
  • Insulin glargine U-100, 80 units daily
  • Insulin lispro, 20 units TID AC meals
  • HbA1c = 8.3% (down from 8.7%)
  • Wt: 265 lb. Ht: 6’0
• Expresses frustration at today’s visit about his inability to lose weight and recent A1c

More about SB

PMH
• T1DM (diagnosed at age 6)
• Obstructive sleep apnea
• HTN
• Hypothyroidism
• Insomnia
• Hx of pancreatitis
• Hx of *h. pylori*

• Owner of a landscaping company
• Recently started exercising to relieve stress and lose weight
• Has been self-titrating his basal insulin for the past month with little change in his glycemic control
• Working with insurance for CGM and possible insulin pump
What is double diabetes?

Islet cell auto-immunity (T1DM) + Insulin resistance (T2DM) → Double diabetes

Obesity in T1DM

- ~50% of patients with T1DM are overweight or obese
- SEARCH for Diabetes in Youth\(^1\)
  - 22.1% of youth with T1DM are overweight
- Pittsburgh Epidemiology of Diabetes Complications\(^2\)
  - Increase in overweight prevalence 29 to 42% in adults with T1DM
- Diabetes Control and Complications Trial\(^3\)
  - Intensive insulin therapy associated with 4.6 kg weight gain over 5 years
- Leads to insulin resistance, dyslipidemia and cardiometabolic dysfunction
- Current guidelines provide little guidance on how to manage “double diabetes”

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Mechanisms contributing to insulin resistance in double diabetes


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T1DM insulin-induced weight gain

- Insulin promotes lipogenesis
- Exogenous insulin delivery
- Intensity of insulin regimens
- Insulin type and associated technologies
- Feeding behaviors related to insulin therapy

Cardiovascular complications of diabetes

- Atherosclerotic cardiovascular disease (ASCVD) is leading cause of morbidity and mortality in patient with diabetes
- Hospitalizations related to heart failure are two-fold higher in patients with diabetes
- Risk factors:
- Obesity / overweight
- Dyslipidemia
- Smoking
- Family history of premature cardiovascular disease
- Chronic kidney disease
- Presence of albuminuria

Summary of cardiovascular outcomes data

<table>
<thead>
<tr>
<th>Trial name (study drug)</th>
<th>Study Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA (lixisenatide)</td>
<td>CV neutral</td>
</tr>
<tr>
<td>EXSCEL (exenatide ER)</td>
<td>CV neutral</td>
</tr>
<tr>
<td>LEADER (liraglutide)</td>
<td>CV benefit</td>
</tr>
<tr>
<td>SUSTAIN-6 (semaglutide)</td>
<td>CV benefit</td>
</tr>
<tr>
<td>REWIND (dulaglutide)</td>
<td>CV benefit</td>
</tr>
<tr>
<td>HARMONY (albiglutide)</td>
<td>CV benefit</td>
</tr>
<tr>
<td>EMPA-REG (empagliflozin)</td>
<td>CV benefit</td>
</tr>
<tr>
<td>CANVAS (canagliflozin)</td>
<td>CV benefit</td>
</tr>
<tr>
<td>DECLARE-TIMI (dapagliflozin)</td>
<td>CV neutral</td>
</tr>
<tr>
<td>EXAMINE (alogliptin)</td>
<td>CV neutral</td>
</tr>
<tr>
<td>SAVOR-TIMI 53 (saxagliptin)</td>
<td>CV neutral</td>
</tr>
<tr>
<td>TECOS (sitagliptin)</td>
<td>CV neutral</td>
</tr>
<tr>
<td>CAROLINA (linagliptin)</td>
<td>CV neutral</td>
</tr>
</tbody>
</table>
Rationale for adjunctive therapies in T1DM (Off-label)

Metformin

- Improves insulin sensitivity
- Minimal hypoglycemia
- No weight gain
- Reduces insulin doses

Incretin-based therapies

- Preserves β-cell function
- Decreases glucagon secretion
- Reduces PPG excursions
- Reduces insulin doses
- Weight loss

SGLT-2 inhibitors

- Glucose lowering independent of pancreatic function
- Weight loss

Metformin

- Extensively studied in adult and pediatric patients
- Evidence:
  - 13 RCTs (6 in adolescents)
    - n = 1183 patients
- Conclusion(s):
  - Metformin was associated with reductions in BMI, insulin requirements total cholesterol, and low-density lipoprotein cholesterol
  - Slight increased risk of severe hypoglycemia and gastrointestinal adverse events
  - No evidence that metformin improved glycemic control, TG or HDL levels
  - No evidence of increased risk of DKA

Safety considerations in T1DM

- Nausea, diarrhea, abdominal discomfort, metallic taste
  - “Start low, go slow”
- Rarely may increase plasma lactate
  - Renal dosing considerations:
    - Excreted unchanged; stop prior to IV contrast
    - Do not use if eGFR < 30 ml/min/1.73m²
    - Use with caution if eGFR < 45 ml/min/1.73 m²
      - Must monitor renal function and assess risk prior to using
- Increased risk of vitamin B₁₂ deficiency
  - HR 2.76 [1.28, 5.95]; p = 0.0094

GLP-1 receptor agonists

- Evidence:
  - 7 RCTs
    - n = 206 patients
    - Study duration: 3-15 months
    - Liraglutide (4), exenatide (3)
- Conclusion(s):
  - Addition of GLP-1 receptor agonist lowers A1c by 0.21% (p = 0.03), body weight by 3.5 kg (p < 0.05), and bolus insulin dose (p = 0.001) without increasing the risk of hypoglycemia

Safety considerations in T1DM

Gastrointestinal side effects
- Side effects are dose dependent
  - Daily formulations → nausea
  - Weekly formulations → diarrhea
- Co-treatment with metformin may increase risk of GI side effects
- Transient and should resolve after 1 week

Acute Pancreatitis
- Conflicting evidence
- Diabetes itself increase risk of pancreatitis
- Compared to placebo, treatment with GLP-1 agonist was not associated with increased risk of acute pancreatitis
  - OR 0.74 [95% CI, 0.47-1.17]

SGLT-2 inhibitors

<table>
<thead>
<tr>
<th>Study drug (dose)</th>
<th>Number of patients</th>
<th>Study duration (weeks)</th>
<th>Average age (years)</th>
<th>BMI @ baseline (kg/m²)</th>
<th>A1c @ baseline (%)</th>
<th>Change in A1c (%)</th>
<th>Change in weight (kg)</th>
<th>Incidence of DKA events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cana¹ (100 mg)</td>
<td>351</td>
<td>18</td>
<td>42</td>
<td>28.1</td>
<td>7.9%</td>
<td>-0.29</td>
<td>-2.8</td>
<td>4.3</td>
</tr>
<tr>
<td>Cana¹ (300 mg)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Soto² (400 mg)</td>
<td>1,402</td>
<td>24</td>
<td>43</td>
<td>28.2</td>
<td>8.2%</td>
<td>-0.46</td>
<td>-3</td>
<td>3</td>
</tr>
<tr>
<td>Dapa³ (5 mg)</td>
<td>833</td>
<td>52</td>
<td>42</td>
<td>28.3</td>
<td>8.5%</td>
<td>-0.33</td>
<td>-2.95</td>
<td>4</td>
</tr>
<tr>
<td>Dapa³ (10 mg)</td>
<td></td>
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</table>


Safety considerations in T1DM

• Euglycemic DKA:
  • DKA without marked hyperglycemia
    • BG < 200-250 mg/dL
  • Usually preceded by illness or reduction in insulin dose
  • Risk higher in patients with T1DM?
• Monitor:
  • Ketone testing
  • “Atypical” symptoms in the absence of hyperglycemia
  • Pump failures
  • Insulin titration


DPP-4 inhibitors

• Evidence:
  • 6 RCTs (4 double-blind RCT, 2 open-label RCT)
    • n = 238 patients
    • Study duration: 4-52 weeks
    • Sitagliptin (4), saxagliptin (1), vildagliptin (1)
• Conclusion(s):
  • DPP-4 inhibitors do not reduce A1c levels (p = 0.97), nor increase the risk of severe hypoglycemia (p = 0.64)
  • DPP-4 inhibitors significantly reduce insulin requirements by 2.41 units/day (p = 0.001)

Safety considerations in T1DM

• Severe and disabling arthralgia
  • Possible mechanism: DPP-4 inhibition increases expression pro-inflammatory cytokines
  • “DPP-4 inhibitors associated with a slight but significant increase in risk of overall arthralgia”
    • RR: 1.13, 95% CI: 1.04-1.22 (p = 0.003)

• Risk factors:
  • Longer duration of diabetes
  • Combination therapy
  • Hx of RA?


Weighing the available evidence

1. Yay! We have data! 😊

1. Small patient enrollments
2. Short study durations
3. Diverse patients, drugs and doses used
4. Cardiovascular data?
5. Cost effectiveness data?
6. Combination data?
Therapeutic considerations for use of adjunctive therapies in T1DM

• Consider for patients not reaching glycemic goals on insulin therapy who:
  • Are overweight / obese
  • Cannot continue with insulin titration due to side effects
  • Did not have improved glycemic control with insulin titration
  • Are highly motivated / engaged in care
• Use patient specific characteristics to guide therapy selection
• Use lower end of the dosing range to prevent side effects?
• Continued monitoring of insulin doses, hypoglycemia, and other side effects is sorely needed

Back to patient SB

• Do you think SB is a candidate for an adjunctive therapy?
• What recommendations do you have to optimize his diabetes care plan?
The role of the pharmacist

Identify patients who may have double diabetes
Identify patients who may be candidates for adjunctive therapies
Provide comprehensive medication reviews
Recommend medication adjustments
Counsel patients on how to monitor for side effects

Post-assessment question 1

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Questions?

Thank you for your time and attention!

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