Diabetes Mellitus (Type II)

Sometimes it definitely takes “Two to Tango”

Place in therapy with GLP-1 RA
Objectives

• Appreciate and outline the challenges to treat DM in clients with comorbid mental disorders (SMI population)

• What are some of the realistic goals for the control of DM in these clients

• Outline the medications that are available commercially for the treatment of diabetes, with focus on GLP-1 receptor agonists
What is the definition of SMI (Serious Mental Illness)?

• Old term of “chronic mental illness”, applies only to adults >18 yo
• Have had a diagnosable mental, behavioral or emotional disorder of sufficient duration during the past year to meet DSM-V criteria
  
  AND

• Must have at least moderate impairment in at least 4 areas from the following domain: feeling/mood/affect, thinking, family, interpersonal, role performance, social-legal, self-care/basic needs.
• Excludes developmental disorders and substance use disorders
Question #1

• What are some of the obvious challenges in dealing with patients with behavioral health disorders that has concomitant diabetes?
• What are some of the reasons that put SMI population at risk to getting primary care?
Possible answers to question #1

• Medication adherence in patients with mental disorders has always been historically low and hence this may “carry over” to medications for other disease states

• Mental illness and the symptoms of the disease itself sometimes mitigates the “fighting spirit” to overcome other disease states

• Lack of motivation, lack of energy

• Poor support, from family and friends

• Financial issues, insurance barriers
Relationship of psychiatric medications (antipsychotics) and diabetes (blood glucose dysregulation)

- Incidence of atypical antipsychotic-induced Type 2 DM
  - 2006 study, 78% of patients on antipsychotics experienced weight gain greater than 7% compared with baseline
  - ADA article, estimated prevalence of obesity in the medicated schizophrenic population is 40 to 60% vs 30% of the general adults
- Mechanisms for development of diabetes in this group
  - simple weight gain, antagonism of the hypothalamic H1 receptors, serotonergic 5-HT2C receptors, and/or adrenergic alpha-2 receptors.
  - for the non-weight gainers, alterations (antagonism) on pancreatic beta-cells, alpha-2 receptors, and other receptors.
  - alterations in glucose transporters on hepatic and skeletal muscle tissues
Question #2, 3, 4 and 5

• What is the average life expectancy of an SMI patient?

• How many years earlier do SMI patients die than the general population?

• Name at least 3 reasons that put the SMI population at risk to getting to primary care?

• What are the top 4 medical conditions SMI population are at risk for?
Potential reasons for increased diabetes in this population group/use of antipsychotics

- Schizophrenia is an independent risk factor for diabetes?
- Patients younger than 40, the odds ratio for developing diabetes is 1.63 if they are taking an atypical antipsychotic
- More intra-abdominal fat correlate with increased insulin resistance?
- Sedentary lifestyle
- Greater prevalence of smoking in this population group
- Lack of understanding of disease (diabetes and mental)
- Lack of support and inadequate financial resources
- Lack of availability of a central medical provider (PCP)
Patient #1

• BC, 62 yo asian female, 5’3”, 129 lbs, nonsmoker
• Unemployed, homemaker, has 2 grown children that are supportive
• MDD with psychosis
  - Aripiprazole LAI 400 mg IM every month
• Medical history
  - Benign essential hypertension (on amlodipine and losartan)
  - Dyslipidemia (on atorvastatin)
  - Chronic kidney insufficiency?  (no meds)
Current regimen for diabetes

• Albiglutide (Tanzeum®) 50 mg subcutaneously once weekly
• Glipizide-XL 5 mg once daily
• Patient had initially been started on Glucophage 500 mg bid, but about 3 months into treatment, serum creatinine continue to rise (up to 1.46 mg/DL) and so glucophage was discontinue. Patient had severe adverse fear to use of needles and there were some questions surrounding patient’s knowledge of diabetes and medication adherence.
• Further investigations revealed that patient has a history of renal issues as well as the fact that patient may been “diabetic” for a while now before coming to JP clinic.
Timeline of medication and HgA1c

<table>
<thead>
<tr>
<th>Date</th>
<th>Medication/changes</th>
<th>A1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/31/16</td>
<td>Glucophage 500 mg bid</td>
<td>10.6%</td>
</tr>
<tr>
<td>8/9/16</td>
<td>Albiglutide 30 mg, home meter Glucophage discontinued due to rising serum creatinine</td>
<td></td>
</tr>
<tr>
<td>10/5/16</td>
<td>Random BG in office in high 190s Added Glipizide-XL 5 mg daily</td>
<td>7.9%</td>
</tr>
<tr>
<td>1/26/17</td>
<td>Albiglutide increase to 50 mg</td>
<td></td>
</tr>
<tr>
<td>4/12/17</td>
<td>Albiglutide 50 mg weekly Glipizide-XL 5 mg daily</td>
<td>6.3%</td>
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</tbody>
</table>
Patient #2

• SB, 65 yo Caucasian female, 5’4”, 140 lbs, nonsmoker
• Widow, unemployed, on disability.
• Schizophrenia, chronic paranoid
  - Fluphenazine 10 mg orally bid
• Medical history
  - Irritable bowel disease (on omeprazole, dicyclomine)
  - Dyslipidemia (on atorvastatin)
Current regimen for diabetes

• Exenatide (Bydureon®) 2 mg subcutaneously once weekly
• Canagliflozin (Invokana®) 100 mg orally once daily
• Patient initially came to clinic on Insulin glargine (Lantus®) and Glucophage 500 mg bid. HgA1c at that time was 9.7%. It took a few months before the clinic got a better picture of the home situation of the patient and that she was very inconsistent with taking her diabetes medications. Patient had problems with swallowing the “big” Glucophage tablets and she did not like using the insulin glargine. Her diet was “bad”, consisting mostly of carbs and sugars, and she was not checking her blood glucose at home. Home environment and financial reason were major barriers for success with diet. Random blood glucose readings at clinic were mostly in the 200s, occasionally in the middle 300s.
## Timeline of medication and HgA1c

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<tr>
<td>8/10/15</td>
<td>Insulin glargine, Glucophage</td>
<td>9.1%</td>
</tr>
<tr>
<td>3/24/16</td>
<td>DC Insulin glargine, continue Glucophage, started Exenatide</td>
<td>9.7%</td>
</tr>
<tr>
<td>4/26/16</td>
<td>Exenatide, increase Glucophage to 850 mg bid</td>
<td>8.5%</td>
</tr>
<tr>
<td>8/7/16</td>
<td>Same, had really not been taking the glucophage, patient has lost about 7 lbs</td>
<td>6.7%</td>
</tr>
<tr>
<td>11/16/16</td>
<td>Glucophage stopped a month ago</td>
<td>6.9%</td>
</tr>
<tr>
<td>3/28/17</td>
<td>Added Canagliflozin 100 mg Exenatide 2 mg SQ weekly</td>
<td>8.6%</td>
</tr>
</tbody>
</table>
Patient #3

- JS, 33 yo African-American male, 6’3”, 264 lbs, smoker
- Single, not married, on disability
- Schizoaffective disorder, depressed
  - Aripiprazole LAI 400 mg IM every month
  - Citalopram 40 mg daily
  - Benztropine 1 mg orally bid prn EPS symptoms
- Medical history
  - Dyslipidemia (on Fenofibrate 48 mg daily)
Current regimen for diabetes

- Glucophage 500 mg, 2 tabs daily with dinner
- Albiglutide 30 mg subcutaneously once weekly
- On 1\textsuperscript{st} initial visit to clinic, routine screening revealed an A1c of 6.1%. Patient did not disclose that he had an alcohol misuse problem and was admitted to hospital in March 2016 for acute pancreatitis and also had an A1c of 11.4%.
- Following a post-discharge to clinic, NP decided to start Insulin glargine bid but blood glucose were still in the 200 range for a few months and then it was decided to add Glucophage to regimen. Apparently, it was later disclosed that patient had been non adherent with diet and medications and was quite “passive and stubborn”.
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<th>A1c</th>
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<tbody>
<tr>
<td>3/26/16</td>
<td>Insulin glargine 65 units daily</td>
<td>11.4%</td>
</tr>
<tr>
<td>5/4/16</td>
<td>Insulin glargine 40 units bid Glucophage 500 mg bid (insurance wanted a failed trial)</td>
<td></td>
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<tr>
<td>7/28/16</td>
<td>Albiglutide 30 mg weekly</td>
<td></td>
</tr>
<tr>
<td>10/13/16</td>
<td>Albiglutide 30 mg weekly Not taking Glucophage and insulin glargine</td>
<td>7.6%</td>
</tr>
<tr>
<td>2/2/17</td>
<td>Albiglutide 30 mg weekly</td>
<td>7.1%</td>
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Glucagon-like peptide-1 receptor agonist (GLP-1)

Uses/Indications:
• Type 2 diabetes mellitus
• Obesity/weight reduction in those with or without Type 2 diabetes
  - only approved one is Liraglutide (at higher dose of 3 mg) (Saxenda®)
Mechanism of action:
• Acts on GLP-1 receptors on pancreatic beta cells (incretin mimetic)
• Enhances glucose-dependent insulin secretion from pancreatic cells
• Delays gastric emptying
• Reduces glucagon secretion
GLP-1 agonists

Contraindications:
• Multiple endocrine neoplasia syndrome type 2
• Personal or family history of medullary thyroid carcinoma

Black box warning:
• Thyroid C-cell tumors may occur

Precautions:
• Severe gastrointestinal disease (ex. gastroparesis) – use is not recommended
• Acute/history of pancreatitis – use is cautioned
• Severe renal impairment (CrCl <30 ml/min) – use is not recommended particularly with Exenatide
GLP-1 and A1c reduction

<table>
<thead>
<tr>
<th>GLP-1 Agonist</th>
<th>A1c Reduction</th>
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<tbody>
<tr>
<td>Albiglutide (Tanzeum®)</td>
<td>~ 1%</td>
</tr>
<tr>
<td>Dulaglutide (Trulicity®)</td>
<td>~ 1.5%</td>
</tr>
<tr>
<td>Exenatide IR (Byetta®)</td>
<td>~ 1%</td>
</tr>
<tr>
<td>Exenatide ER (Bydureon®)</td>
<td>~ 1.5%</td>
</tr>
<tr>
<td>Liraglutide (Victoza®)</td>
<td>~ 1.5%</td>
</tr>
<tr>
<td>Lixisenatide (Adlyxin®)</td>
<td>~ 1%</td>
</tr>
</tbody>
</table>
GLP-1 agonists potential significant adverse effects

• Common
  - abdominal pain
  - nausea, vomiting, diarrhea
  - decrease in appetite – may cause some weight loss
  - injection site reactions
  - upper respiratory infection - Tanzeum®
GLP-1 agonists potential significant adverse effects and monitoring

• Serious
  - malignant tumor of thyroid gland (calcitonin levels, nodules)
  - pancreatitis (need for routine monitoring)
  - renal failure (routine labs)
  - atrioventricular block, 1st degree - Trulicity®
  - pneumonia - Tanzeum®
Conclusion

• Treatment of diabetes in the SMI population may have to “deviate” from standard recommended treatment guidelines.

• Keep in mind that nonadherence to medications and lifestyle modifications may require healthcare providers to take a more “hand-holding” approach.

• Reductions as in A1c may not totally be attributable to the use of the GLP-1 agents but it certainly is an option to consider due to ease of use of these agents.
Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost and causes of death among public mental health clients in eight states. Prev Chronic Dis. 2006;3(2):A42


Saha S, Chant D, McGrath J. A systemic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch Gen Psychiatry. 2007;64(10):1123-1131


