Diabetes Update: PBL

Jeffrey Unger, MD, FAAFP, FACE

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Director, Unger Primary Care Concierge Medical Group, Rancho Cucamonga, California; Director of Metabolic Studies, Catalina Research Institute, Montclair, California

Dr. Unger’s private practice is devoted to the comprehensive care of patients who have diabetes, addiction, mental illness, migraine, and other chronic disease states. He has published more than 190 peer-reviewed articles on diabetes, migraine, and pain management. In addition, he has written three medical textbooks on diabetes, including Diabetes Management in Primary Care, 2nd Edition, which was published in December 2012. Dr. Unger is board certified in family medicine and has served as a consulting physician for the Los Angeles Angels of Anaheim baseball club and the World Wrestling Federation.

Learning Objectives

1. Practice applying new knowledge and skills gained from Diabetes Update sessions, through collaborative learning with peers and expert faculty.
2. Identify strategies that foster optimal management of diabetes, within the context of professional practice.
3. Formulate an action plan to implement practice changes, aimed at improving patient care.

Associated Session

- Diabetes Update: Diabetes Management In Primary Care
Audience Engagement System

Step 1 Step 2 Step 3

Agenda

• Evaluate several “real world” patients who have unique and challenging problems.
• Each patient has suboptimal glycemic control
• Consider:
  – Correct diagnosis
  – Most effective workup
  – Best therapeutic intervention

Warning: Because these are real-world cases, not all patients will have a favorable outcome!

Case 1: A Patient Who Is Chronically “Non-Compliant”

Lydia

• 52 year old female
• T2DM for 14 years
• A1C is 12.8 % and has never been < 11 % (Has seen 3 endos in past 10 years and 3 CDEs)
• Clerical worker at an army base
• No family hx of diabetes

• Suddenly develops severe hypoglycemia x 2 in 1 week
• In ED BG level on visit # 1 was 28 mg/dL. Two days later BG level was 32 mg/dL
• Is this a case of “Brittle Diabetes”?

Case courtesy of Jeff Unger, MD, FACE

Does Lydia Have “Brittle Diabetes”?

Definition of Brittle Diabetes

“Patients with brittle diabetes defy all attempts at improving glycemic control using conventional therapies.”

• Recurrent and prolonged hospital stays are the rule
• Brittle diabetes disrupts the life of the patient and the lives of the family members living with the patient
• Have extreme glycemic variability
• Patients “taunt” diabetologist by their difficult challenges.
  – Be prepared to think outside the box!


Insulin Dosing Instructions

• Type of insulin: U500
• Breakfast: 5 units 15-30 minutes before eating
• Lunch: 5 units 15-30 minutes before eating
• Dinner: 8 units 15-30 minutes before eating
• 9 PM: Detemir-40 units
Notes: Check your blood sugar levels upon awakening each day, prior to each meal and 2 hours after dinner. Bring your meter in for downloading at each visit.

Meet Lydia…

Lydia

Case courtesy of Jeff Unger, MD, FACE

AES POLL QUESTION

What Is The Reason That Lydia Has Such Poorly Controlled Diabetes?

1. Numeracy or illiteracy?
2. Disordered eating?
3. Sleep apnea?
4. Major depression
5. Bipolar disorder
The Issues Facing PCPs Today Regarding Mental Illness

- Mental illness leads to disability, loss of productivity, loss of employment and healthcare.
- Suicide rates in patients with bipolar disorder are 20 times higher than the general population.
- Patients with mental illness are at high risk for developing metabolic disorders (obesity, diabetes, hyperlipidemia, CVD).
- PCPs are reluctant to deal with the emotional aspects of BPD, yet are well trained to manage their metabolic issues.

Depression and Diabetes

- Depression decreases the likelihood of successfully reducing A1C by 8%.
- Depressed patients and diabetes are more likely to relapse.
- Mortality rates are 2.3 x higher and medical costs are 4.5 x higher for depressed patients with diabetes.

Mental Illness Exposes the Body to Chronic Stress Leading to A State of Insulin Resistance

- Increased sympathetic activity stimulates the hypothalamus.
- Hypothalamus secretes adrenocorticotropin hormone (ACTH).
- ACTH stimulates the adrenal glands to release cortisol and corticotropin releasing factor (CRF).
- CRF stimulates the pituitary gland to release ACTH.
- ACTH stimulates the adrenal glands to release cortisol.

Relationship Between Depression and Type 2 Diabetes

- MDD precedes the onset of T2DM in 50% of cases within 6-8 years of the initial diagnosis of diabetes.

Troublesome Findings in Comorbid Mental Illness and Type 2 Diabetes

- Elevated CRP
- Higher fasting insulin levels
- Frequent nicotine addiction
- Higher daily caloric intake
- Higher systolic blood pressure
- Higher BMIs
- Reduced physical activity
- Increased risk of MI
- Less medication adherence

Suggested Evaluation of Patients With Diabetes Based on Their A1Cs

<table>
<thead>
<tr>
<th>A1C Level</th>
<th>7.5-9%</th>
<th>9.0-11%</th>
<th>&gt;11%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Consider lifestyle intervention</td>
<td>Consider medication options</td>
<td>Consider referral to specialist</td>
</tr>
</tbody>
</table>

Depressed patients with Diabetes Have Higher Medical Costs and Increased Risk of Mortality

- 4.5 x higher lifetime mortality
- 2.3 x increase risk of death
- Clinical events (CRF, CVD, MI)
- Medical costs
- Reduced physical activity
- Increased BMI
- Decreased physical functioning
- Cognitive impairment
- Sexual dysfunction
- Metabolic syndrome
**Mental Illness Rating Scales**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Number of Items</th>
<th>Administered By…</th>
<th>Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck Depression Inventory</td>
<td>21</td>
<td>Interviewer/Self</td>
<td>(10-15 minutes)</td>
</tr>
<tr>
<td>Geriatric Depression Scale</td>
<td>30</td>
<td>Self</td>
<td>(6-10 minutes)</td>
</tr>
<tr>
<td>HAM-D</td>
<td>21</td>
<td>Expert</td>
<td>**</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>25</td>
<td>Interviewer/Self</td>
<td>(5-6 minutes)</td>
</tr>
<tr>
<td>Columbia Suicide Severity Rating Scale</td>
<td>6</td>
<td>Interviewer/Self</td>
<td>***</td>
</tr>
<tr>
<td>MDQ (for mania)</td>
<td>15</td>
<td>Interviewer/Self</td>
<td>***</td>
</tr>
</tbody>
</table>

All rating scales can be downloaded at: [www.pscytoolkit.com/index.html](http://www.pscytoolkit.com/index.html)

**Medical management of Major Depression**

- Although lifestyle intervention and self-help techniques are helpful for minor depression, most patients with MDD will require SSRIs or SNRIs – SSRIs reduce the risk of death, non-fatal MI and all-cause mortality by 43% compared to non-SSRI users!
- Fluoxetine and sertraline have been shown to improve both depression and glycemic control in patients with T2DM.
- Duloxetine and venlafaxine are excellent choices for patients with depression and chronic pain syndromes.
- TCAs cause weight gain, urinary hesitancy, orthostasis, and blurred vision.

**Bipolar Depression**

- Misdiagnosed in 70% of patients
- Each patient will experience 3.5 misdiagnoses and 4 consults before receiving an accurate diagnosis.
- Lifetime prevalence of BPD is 1% vs 10-25% of general population experience MDD.
- Prevalence of T2DM in BPD is 7 %. Pre DM prevalence is 24%.
- 15% will successfully commit suicide.
- 60% will have coexisting substance abuse.
- Women are at high risk of suicide, irrational behavior, manic episodes and substance abuse during the postpartum period.
- 60% of patients are overweight or obese.

**Differentiating MDD from BPD**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MDD</th>
<th>BPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>&gt; Age 40</td>
<td>&lt; age 25, recurrent + mania</td>
</tr>
<tr>
<td>Family history</td>
<td>Possible</td>
<td>Very common</td>
</tr>
<tr>
<td>History of suicide attempts</td>
<td>No</td>
<td>Yes (11 %)</td>
</tr>
<tr>
<td>History of substance abuse</td>
<td>Uncommon</td>
<td>&gt; 60%</td>
</tr>
<tr>
<td>Response to SSRIs</td>
<td>Good</td>
<td>Multiple treatment failures. Can induce mania</td>
</tr>
<tr>
<td>Other features</td>
<td>Guilt, sleep disturbance, appetite, loss of concentration</td>
<td>Mania, mood swings, irritability, diurnal variation, grandiosity, hypersexuality, aggressiveness, poor judgment</td>
</tr>
</tbody>
</table>

**Lydia Treatment Plan**

- **Antidepressant First:**
  - Lithium 900 mg BID (mood stabilizer)
  - Clonazepam: Baseline 2 mg qd
  - Vitamin D3 5000 IU qd
- **Adjunctive therapy for patients with bipolar disorder:**
  - Treatment regimen simplified
    - Lithium 900 mg BID
    - Sertraline 150 mg BID
- **Suicide risk:**
  - If suicidal risk > 10% use Clobazam 10 mg qd or 10 mg TID
  - If suicidal risk > 20% use Clobazam 20 mg qd
  - If suicidal risk > 30% use Clobazam 30 mg qd

**Discussion**
Case 2: Ken The Stockbroker

- 27 year old stockbroker
- Developed T1DM at age 15
- On CSII x 9 years. Refused CGM (too constraining). SMBG 3/d.
- 4 ED visits and hospital admits in the past year for nausea, vomiting, DKA, and “feeling dirty.”
- Admissions typically occur on Saturday evening and by Monday he is ready for discharge.
- Denies alcohol or drug use, but admits to “partying heavily on weekends.”
- Download of his pump and meter show that he is bolusing insulin appropriately even when he is ill.

Today in ED:
- BG= 650 mg/dL
- Urine ketone bodies +
- pH= 7.1

AES POLL QUESTION
What Is The Reason For Ken’s Frequent Bouts of DKA?
1. Gastroparesis?
2. Intestinal parasite?
3. Migraine variant?
4. Illicit drug use?
5. Mechanical dysfunction of the insulin pump?
6. Bipolar mania?

Cannabinoid Hyperemesis
Initially described in 1994 by Allen
Patients have cyclic vomiting in the setting of long-term cannabis use and resolves once the drug is stopped
- Associated symptoms include vomiting, colicky abdominal pain, compulsive hot showering, and cessation of sex upon cessation of drug use and appearance of a neg UDT
- Typical pt is white, employed, average age 33 years
- Lack of awareness of CH will lead to extensive, expensive and invasive testing as well as frustration on behalf of the patient and clinician.

Duration of Cannabis Use Before Onset of Symptoms And Frequency Of Use/Week
Criteria For CH
- Long-term cannabis use
- Cyclic nausea and vomiting
- Relief of symptoms with hot showers or baths
- Resolution with cannabis cessation
- Abdominal pain, epigastric or periumbilical
- Frequent use of drug
- Neg. lab, xray and endoscopic studies

How Do You Manage Patients With Co-Existing Drug Abuse and Diabetes In Your Practice?
- Do you use naltrexone (vivitrol)?
- Do you use buprenorphine/naloxone? (suboxone)

Ken Epilogue
- Refused to stop using MJ
- Received a medical MJ card “for anxiety”
- Referred to addictionologist
- Fired from job 2 months after his most recent hospitalization
- Found dead at home from an OD of heroin on 4/12/12
Case 3: "I Prefer To Be Low"

- 82 y/o retired family doctor with repeated episodes of nocturnal and confirmed hypoglycemia
- Wife administers glucagon 3 times a week
- T1DM for 60 years. Only diabetes-related complication is hypoglycemia awareness autonomic failure!
- He is developing signs of cognitive impairment
- Patient uses an insulin pump and "injects extra insulin" if his glucose levels go too high.
- A1C=6.6%

82 Year Old Physician With Hypoglycemia Unawareness

Chronic Hypoglycemia

- Would you report him to the DMV as "high risk driver"?
- The patient has had glycemic variability for > 60 years. Why does he not have any microvascular or macrovascular complications?
- What would you do to minimize this patient’s risk of hypoglycemia?
- What are the dangers of hypoglycemia?

Question…

- Patient # 1 has A1C of 10%. Diabetes x 18 years. No complications.
- Patient # 2 has an A1C of 5.7%. Diabetes x 18 years. Complications include painful neuropathy, retinopathy, stage 4 CKD (eGFR= 18 mL/Min.
- Why?

Genetic of Diabetes Complications (The Joslin Medalist Story)

- High-risk patients?
  - Complications appear soon after diagnosis
  - Complications appear at lower threshold A1C
- Low-risk patients?
  - Few complications
  - Few complications despite glycemic burden
Hurdles to Intensive Therapy
Rates of Severe Hypoglycemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Rates of Severe Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS5</td>
<td>4.6%</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>2.8%</td>
</tr>
<tr>
<td>ACCORD</td>
<td>3.8%</td>
</tr>
<tr>
<td>VADT</td>
<td>12.1%</td>
</tr>
</tbody>
</table>

Frequency of Adverse Outcomes
Among Patients With T2DM Experiencing Severe Hypoglycemia

<table>
<thead>
<tr>
<th>Months from severe hypoglycemia to event</th>
<th>Microvascular event</th>
<th>Cardiovascular death</th>
<th>Noncardiovascular death</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>13-24</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>25-36</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>37-48</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Conclusion – severe hypoglycemia is associated with a higher risk of mortality.

ADVANCE
Severe Hypoglycemia vs Adverse Endpoints

Unreported Asymptomatic Episodes of Hypoglycemia

- >45% of patients with T2DM had asymptomatic (unrecognized) hypoglycemia, identified via continuous glucose monitoring.
- Similar findings in other studies.

Why Is Hypoglycemia Associated With Increase Cardiovascular Mortality in High Risk Patients?

Effects of Hypoglycemia on Thrombosis in T2DM
Abnormal QT prolongation and T-wave morphology during hypoglycaemia in a single patient

Baseline QTc = 456 ms
Glucose nadir = 2.5 mmol/L

Progressive flattening of T wave is noted with fall in glucose over time

Example of cardiac arrhythmia: sinus bradycardia with trigeminy

Glucose = 49 mg/dL

Pathophysiologic CV Consequences of Hypoglycaemia

Effect of Experimental Hypoglycaemia on QT Interval Prolongation

Prior hypoglycaemia blunts subsequent counter-regulatory response (non-diabetic adults)

Driving Under The Influence
Driving Under the Influence

Risk Factors For Collisions

- Recent hx of hypo (regardless of treatment)
- T1DM with a hx of prior accident within 12 months

"Any patient with type 1 diabetes who has had a recent car accident should be carefully evaluated for HAAF and educated on the effects of driving while hypoglycemic." ADA. Diabetes and Driving: Position Statement. Diabetes Care. 2012. 35 (Suppl 1. S81-S86)

Current Status Of The Hypo Patient

- Pt. started on CGM (paid cash because not covered by Medicare)
- No "high alert" programmed. Low alert set at 70 mg/dL
- Educated on insulin stacking and "driving under the influence of severe hypoglycemia"
- Pt. understood that his cognition was deteriorating. He now believes that hypoglycemia is more worrisome at his age than hyperglycemia

Addendum On Hypoglycemia Patient

3 years ago patient committed suicide
- Gun shot to the mouth in front of his wife
- Patient’s memory was deteriorating which upset him significantly

Case 4: Downhill Diabetes

Mike
- 42 year old engineer with a history of T1DM for 30 years
- On insulin pump and CGM
- No diabetes-related complications except for HAAF (hypoglycemia awareness autonomic failure)
- Very adherent to suggested treatment regimen
- Exercises 5-7 days a week (paintball, hockey, mixed martial arts, "anything I can get my hands on.")
- In January 2012 A1C is 6.7%
- A1C is now 9.8%

AES POLL QUESTION

What Can Be Causing This Wide Glycemic Variability?

1. Mail order insulin
2. Pump occlusions
3. Sensitivity to preservative in the insulin vials
4. Nodularity at infusion sites
5. Lipodystrophy
6. Prolonged use of infusion sets (> 72 hours)
7. All of the above
What Should You Do Next For Mike?

1. Order some labs
2. Suggest that he stop exercising
3. Send him to a CDE for "an analysis."
4. Perform a physical exam
5. Drug test him
6. Watch him insert his infusion set
7. Send him to an endocrinologist. (If you are an endocrinologist you would send him back to his PCP who would send him to a CDE for "an analysis").

Fixing Mike…

Summary

- Diabetes is a complex, progressive and challenging disease state for patients and clinicians
- When times get tough, LISTEN to the patient. They will often tell you why they may have wandered off track from their diabetes self-management program
- NEVER blame a patient for losing control. They depend on you for help.
- Telling a patient, colleague, consultant or family member that a patient is "non-compliant" is irresponsible and does little to help the patient regain some control.
- Use drugs which minimize risk of hypoglycemia
- Patients with persistence of HbA1c > 9% screen for mental illness

The 5 Strategies Which Guarantee Successful Diabetes Self-Management

- Know your metabolic targets
- Know how to achieve your metabolic targets
- Take your medicines
- Don’t smoke
- Receive care from clinicians who are knowledgeable about diabetes pathogenesis and management

Practice Recommendations

- Patients presenting with mental illness and diabetes should have their mental illness stabilized prior to attempting to intensify diabetes therapy. (SOR A)
- Hypoglycemia increases risk of cardiovascular mortality. (SOR A)
- Buprenorphine and naltrexone are effective interventions for opioid dependency. (SOR A)