Disclosure of Interests

- **Research Support**
  NIH DK36452, DK53060, DK59364

- **Consulting Relationships**
  None

- **Speaker’s Bureau(s)**
  None

- **Stock Equity (> $10,000)**
  None
Comorbid Depression and Diabetes

A Case Presentation

- 56-year old white female with T2DM x 6 yrs; poorly controlled on diet and oral agents
- PMHx: obesity, hypertension, CHD with myocardial infarction 1 yr ago
- Called after hearing an ad about a study of depression in persons with diabetes
Comorbid Depression and Diabetes

*A Case Presentation*

- Presents with untreated MDD, BDI =32, no SI/HI
- First episode age 26 resolved after 1 yr without treatment, ~10 episodes in the last 20 years, longest lasting 2 years
- 2 yrs ago, placed on sertraline by PCP; she stopped after 2 weeks because of headaches
Diabetes Type

- **Type 1 diabetes**

  An autoimmune disease that destroys insulin-producing pancreatic cells and leads to insulin deficiency with hyperglycemia. 5-10% of diabetes cases are type 1; most present before adulthood.

- **Type 2 diabetes**

  Results from insulin resistance (a condition in which the body fails to properly use insulin), combined with relative insulin deficiency. 90-95% of diabetes cases are type 2; most present during adulthood.
## Prevalence (%) of Diabetes in the US

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>%</th>
<th>million</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overt Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosed Diabetes</td>
<td>5.9</td>
<td>11.8</td>
</tr>
<tr>
<td>Undiagnosed Diabetes</td>
<td>2.4</td>
<td>4.9</td>
</tr>
<tr>
<td>Total Overt Diabetes</td>
<td>8.3</td>
<td>16.7</td>
</tr>
<tr>
<td><strong>Prediabetes (age ≥20 yrs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired Fasting Glucose</td>
<td>6.1</td>
<td>12.3</td>
</tr>
<tr>
<td>Impaired Glucose Tolerance</td>
<td>2.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Total Prediabetes</td>
<td>8.6</td>
<td>16.7</td>
</tr>
<tr>
<td><strong>Total Overt or Prediabetes</strong></td>
<td>16.9</td>
<td>33.4</td>
</tr>
</tbody>
</table>

"A majority of Americans -- now 64% -- are overweight or obese."

---

**Age-Adjusted Prevalence of Obesity (Adults 20-74 Years)**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Both</td>
<td>23.3</td>
<td>30.9</td>
</tr>
<tr>
<td>Men</td>
<td>20.6</td>
<td>27.7</td>
</tr>
<tr>
<td>Women</td>
<td>25.9</td>
<td>34.0</td>
</tr>
</tbody>
</table>

Flegal et al, JAMA 2002
Atherosclerosis and Coronary Heart Disease (CHD) in Diabetes

**Diabetes:**

- Is a powerful independent risk factor for CHD
- Increases the risk for CHD 2-4 times over the general population.

_Atherosclerosis accounts for:_

- 80% of all deaths in diabetes (50% from CHD).
- 75% of all hospitalizations for diabetic complications.

Aronson & Rayfield, 1998
Type 2 Diabetes and CHD: 7-Year Incidence of Fatal/Nonfatal MI

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetes n=1373</th>
<th>Diabetes n=1059</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior MI*</td>
<td>4%</td>
<td>45%</td>
</tr>
<tr>
<td>MI</td>
<td>19%</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

Changes in CAD Mortality Rates in Patients with and without Diabetes*

Nondiabetes
Men: -43.8
Women: -20.4

Diabetes
Men
Women: 10.6

P = 0.001
P = 0.012
P = 0.76

*NHANES I (1971-1975) and NHANES II (1982-84)
Gu et al., JAMA 1999; 281:1291-1297
## Prevalence (%) of Depression in Persons with and without Diabetes

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>%</th>
<th>(Millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Population</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-month</td>
<td>6.6</td>
<td>13.3</td>
</tr>
<tr>
<td>Lifetime</td>
<td>16.2</td>
<td>32.6</td>
</tr>
<tr>
<td><strong>Diabetes (16.7 Million)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>11.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Lifetime</td>
<td>28.6</td>
<td>4.8</td>
</tr>
<tr>
<td>Elevated symptoms</td>
<td>31.0</td>
<td>5.2</td>
</tr>
</tbody>
</table>

* Kessler (NCS-R 2003)
** Anderson et al, 2001
The odds of depression were doubled in diabetics compared to controls.

*Anderson et al., 2001*
Depression Doubles the Risk of T2DM

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-up Interval</th>
<th>Incidence T2DM</th>
<th>Covariates</th>
<th>Depression Measure</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eaton ’96 (ECA, n=1715)</td>
<td>13 yrs</td>
<td>5.2%</td>
<td>Demographics, SES, health use comorbidity, weight</td>
<td>Diagnosis per DSM</td>
<td>2.2 (0.9-5.6)</td>
</tr>
<tr>
<td>N=1715</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kawakami ’99 (Japan, n=2764 ♂)</td>
<td>8 yrs</td>
<td>2.3%</td>
<td>Demographics, BMI, comorbidity activity level, smoking, ETOH</td>
<td>Zung Scale</td>
<td>2.3 (1.0-5.2)</td>
</tr>
<tr>
<td>Carnethon ’03 (NHANES, n=6190)</td>
<td>15.6 yrs</td>
<td>7.3%</td>
<td>Diabetes risk factors</td>
<td>GWB Dep Scale</td>
<td>1.8 (1.1-2.9)</td>
</tr>
<tr>
<td>Golden et al ’04 (ARIC, n=11,615)</td>
<td>6 yrs</td>
<td>6.2%</td>
<td>Age, race, sex, education</td>
<td>Vital Exhaustion Scale</td>
<td>1.6 (1.3-2.0)</td>
</tr>
</tbody>
</table>
## Risk of T2DM by Quartiles of Depressive Symptoms

<table>
<thead>
<tr>
<th>Adjusted for:</th>
<th>Quartile of depressive symptoms</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: Age, race, education and sex</td>
<td></td>
<td>1.0</td>
<td>1.2</td>
<td>1.3</td>
<td>1.6</td>
<td>$&lt;$0.0001</td>
</tr>
<tr>
<td>Model 2: Metabolic covariates*</td>
<td></td>
<td>1.0</td>
<td>1.1</td>
<td>1.1</td>
<td>1.4</td>
<td>0.0071</td>
</tr>
<tr>
<td>Model 3: Lifestyle covariates†</td>
<td></td>
<td>1.0</td>
<td>1.2</td>
<td>1.1</td>
<td>1.5</td>
<td>0.0005</td>
</tr>
<tr>
<td>Model 4: Lifestyle covariates and BMI‡</td>
<td></td>
<td>1.0</td>
<td>1.2</td>
<td>1.0</td>
<td>1.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Model 5: Metabolic and lifestyle covariates§</td>
<td></td>
<td>1.0</td>
<td>1.1</td>
<td>1.0</td>
<td>1.3</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Model 2: adjusted for Model 1 + fasting insulin, fasting glucose, log triglycerides, HDL cholesterol, BMI, waist-to-hip ratio, and systolic blood pressure.
†Model 3: adjusted for Model 1 + physical activity, total caloric intake, and smoking status.
‡Model 4: adjusted for Model 3 + BMI and waist-to-hip ratio.
§Model 5: adjusted for Model 2 + Model 3.
$P < 0.05$

Golden et al., 2004
Association of Depression with Diabetes Complications

Any Complications
- All Studies (k=22)
- Type 1 DM
- Type 2 DM

Specific Complications
- Retinopathy
- Neuropathy
- Nephropathy
- Macrovascular (k=9)

Weighted Effect Size $r$
- de Groot et al., 2002
Manifest CHD in Relation to Depression: A 10-yr prospective study in diabetic women

- Subjects free of CHD (%)

  - Not depressed
    - n = 60
  - Depressed
    - n = 16

- Time from interview (yr)

  - p < 0.01 between groups

- Age-adjusted hazard ratio 5.2 (1.4-18.9, p = 0.01)

Clouse RE et al., Psychosom Med, 2002
Summary of Epidemiologic Observations

- Depression rates are doubled in the presence of diabetes (both type 1 and type 2).
- Depression occurs in the course of diabetes (primarily type 1).
- Depression increases the risk for diabetes (type 2).
- Depression is more likely in the face of complications (both types).
- Depression predicts morbidity from CHD (both types).
How treatable is depression in a diabetic patient?

Does treatment of depression improve medical outcome?
Comorbid Depression and Diabetes
*A Case Presentation*

- Entered maintenance trial, started on sertraline in open treatment phase

- Achieved depression remission and mild GHb improvement (-0.2%) on 100 mg/d. Randomly assigned to continue sertraline treatment for 1 year or to recurrence

- Remained depression free over 52 weeks of follow-up; GHb deteriorated to its baseline level
**Efficacy of Antidepressant Medication: Meta-analysis of FDA Data Base**

<table>
<thead>
<tr>
<th>Drug</th>
<th>$K$</th>
<th>$N$</th>
<th>Drug/D</th>
<th>PBO/P</th>
<th>D-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>5</td>
<td>1,132</td>
<td>8.3</td>
<td>7.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>12</td>
<td>1,289</td>
<td>9.9</td>
<td>6.7</td>
<td>3.2</td>
</tr>
<tr>
<td>Sertraline</td>
<td>3</td>
<td>779</td>
<td>10.0</td>
<td>7.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>6</td>
<td>1,148</td>
<td>11.5</td>
<td>8.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>8</td>
<td>1,428</td>
<td>10.7</td>
<td>8.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Citalapram</td>
<td>4</td>
<td>1,168</td>
<td>9.7</td>
<td>7.7</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Overall average benefit per HAM-D: 2.2

*Kirsch et al., 2002*
Treatment Effectively Relieves Depression

Significantly Improved, %

<table>
<thead>
<tr>
<th>Treatment Effectively Relieves Depression</th>
<th>Nortriptyline</th>
<th>Fluoxetine</th>
<th>CBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Improved</td>
<td>57.1</td>
<td>66.7</td>
<td>70</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>35.7</td>
<td>37</td>
<td>36.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p <0.05 for all comparisons

21.4 29.7 33.4 Treatment – Control (%)
Treatment Effectively Relieves Depression

Patients in Remission, %

Nortriptyline: Treatment 57.1, Control 35.7
Fluoxetine: Treatment 61.9, Control 31.3
CBT: Treatment 85, Control 27.3

* p < 0.05

21.4 30.6 57.7 Treatment – Control (%)
Treatment of Depression Produces Improvement in Glycemic Control

**GHb (%)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nortriptyline</td>
<td>-0.6%</td>
<td><strong>p&lt;0.05</strong></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>-0.4%</td>
<td>p=0.12</td>
</tr>
<tr>
<td>CBT</td>
<td>-0.7%</td>
<td><strong>p=0.04</strong></td>
</tr>
</tbody>
</table>

*Effect of depression improvement.*
Nortriptyline in Diabetes

All Subjects
(HbA1c >9.5%)

Psychiatric Diagnosis

Major Depression
RA
Nortriptyline
Placebo
Treatment to 50-150 ng/ml
Measurement of Outcome

Psychiatrically Well
RA
Nortriptyline
Placebo
Effect of Depression Relief on GHb

Depression remission = ↓ GHb of 0.8% - 1.2%
Progression Rate of Retinopathy as a Function of GHb

Depression remission = ↓ GHb of 0.8% - 1.2%
# Depression in Diabetes is a Recurrent Problem

<table>
<thead>
<tr>
<th></th>
<th>Recurrence during 5 yr follow-up</th>
<th>Within 1 yr</th>
<th># of depression episodes during follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lustman et al 1983</td>
<td>80</td>
<td>--</td>
<td>4.2</td>
</tr>
<tr>
<td>Lustman et al 1997</td>
<td>90</td>
<td>60</td>
<td>4.8</td>
</tr>
<tr>
<td>Psychiatric Samples</td>
<td>40-70</td>
<td>25-50</td>
<td></td>
</tr>
</tbody>
</table>
Sertraline Maintenance Therapy for Prevention of Depression Recurrence

The proportion of patients remaining in remission was higher with sertraline than placebo (65% vs. 42%).

The proportion of patients remaining in remission was higher with sertraline than placebo (65% vs. 42%).
Change in A1C During Open Label and Maintenance Treatment

- **SRT** = Sertraline
- **PBO** = Placebo

All Subjects (N=116)

- **SRT** = Downward trend from 8.2 to 7.8

NonRecurs (N=51)

- **SRT** = Upward trend from 8.2 to 8.6

* *p<0.05; **p<0.01
Optimizing Management of Diabetes and Depression

Initial intervention

Progressive escalation in diabetes management regimen

Evaluate depression as a contributor to the development of type 2 diabetes

Evaluate depression as a contributor to poor metabolic control in any type of diabetes

Treat clinically significant depression

Maintenance Rx for relapsing depression
Summary

- Depression in diabetic patients is effectively treated using conventional approaches.
- The effects of depression treatment on mood and glycemic control are not always parallel nor stable over time.
- Response to therapy and reassessment for evidence of relapse or recurrence are essential; maintenance strategies are often required to achieve lasting remission.
- The interaction between depression and hyperglycemia may be bidirectional.