Goals

- To appreciate the associations between psychiatric disorders and cardiovascular disease
- To identify medications associated with metabolic syndrome
- To recognize potential magnitude of these side-effects and clinical relevance thereof
- Begin evidence based treatment when necessary.
Risk of Heart Disease

Those with mood disorders had twice the risk of heart disease in the World Mental Health Surveys.


Risk of Heart Disease

In the representative NCS-R (N=5,692)

- Vascular disease equivalents and risk factors were more common in those with mood disorders, particularly women with bipolar disorder

- This finding was independent of sociodemographic and clinical variables as well as several traditional risk factors for vascular disease:
  - diabetes mellitus
  - family hx of heart disease
  - high blood pressure
  - obesity
  - smoking


Mortality

In representative age samples, patients with schizophrenia and bipolar disorder have approximately twice the risk of dying. Most of the excess mortality occurs secondary to suicide and vascular disease.

**Mortality**

54,000 former inpatients with mood disorders from Sweden. All cause mortality SMR 2.6 in bipolar disorder and 2.0 in unipolar major depression. Excess death by cause:

![Mortality Chart](image-url)


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**Life Expectancy**

- Life expectancy was assessed in national cohort of 6.5 million Swedish adults, 6,618 identified with bipolar disorder from outpatient or inpatient dx.
  - Men: -9 years
  - Women: -8.5 years
  - Adjusting for age, sociodemographics and substance use HR 2.1 (95% C.I. 1.9-2.5) for women and 1.7 (95% C.I. 1.5-1.8) for men


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**Life Expectancy**

- More interesting, elevated risk for risk factors not as high as mortality (diabetes 1.7 women, 1.6 men; CVD 1.3 women, 1.2 men). No ↑ in hypertension, lipid disorders. Suggested risk factors under-identified.
- When stratified by risk factors, mortality risk drops significantly, leading to conclusion: “…better provision of primary care may effectively reduce premature mortality…”

Life Expectancy

- Life expectancy at 15 y/o was compared for those hospitalized with serious mental disorders in Denmark, Finland, and Sweden (1987-2006).

- Men: -20 years
- Women: -15 years


Medical Co-morbidity Rx

Patients with psychiatric disorders are less likely to be monitored for and to receive adequate treatment of medical conditions, such as risk factors for vascular disease.


Adverse Effects of Treatments

Weight Gain

Adolescent Data
Meta-analysis of 21 studies (2,455 pts) of drug vs. placebo in children and adolescents:
• Olanzapine 3.45 kg (95% C.I. 2.93-3.98)
• Risperidone 1.77 kg (95% C.I. 1.35-2.20)
• Aripiprazole 0.94 kg (95% C.I. 0.65-1.24)
Mean study duration of 9 weeks.

Almendi NB et al. Pediatric Drugs 2013.

Individual Variability
Antipsychotic naïve youth treated with risperidone for 3 months

Correll CU et al. Trends in Molecular Medicine 2011.
Antipsychotic Comparisons

Adapted from Lieberman et al. *NEJM* 2005.

**Head-to-head Comparisons**

*Short-term (≤12 weeks) studies:*
- Clozapine > Risperidone (MD 3.2 kg)
- Olanzapine > Risperidone (MD 2.5 kg)
- Olanzapine > Quetiapine (MD 2.7 kg)
- Olanzapine > Ziprasidone (MD 2.5 kg)


**Head-to-head Comparisons**

*Long-term (>12 weeks) studies:*
- Clozapine > Risperidone (MD 1.9 kg)
- Olanzapine > Risperidone (MD 2.5 kg)
- Olanzapine > Quetiapine (MD 2.7 kg)
- Olanzapine > Aripiprazole (MD 3.9 kg)
- Olanzapine > Ziprasidone (MD 4.4 kg)

Some Head-to-head Comparisons

Weight gain:
Valproate (1.1 kg) vs. Lithium (0.2 kg) in 12 weeks
Quetiapine (3.3 kg) vs. Lithium (1.0 kg) in 12 weeks


Individual Variability Reminder

Even with aripiprazole, 8-11% of patients may gain >7% of baseline weight after four weeks of treatment.

All antipsychotics carry potential for extreme weight gain in vulnerable individuals!


Antidepressants

Mirtazapine → greatest risk
TCAs and MAOIs > SSRIs
SSRIs weight loss acutely (< 12 weeks) with some weight gain thereafter.
- In some studies more weight gain with paroxetine than sertraline or fluoxetine
Bupropion associated with weight loss

Antidepressants – Meta-analysis

Effect on Weight Change During Medium and Long-term Treatment (≥4 mo)

Mean Difference, kg (95% CI)


Antidepressants – Long-term

Claims data on 22,610 patients for weight changes 3-12 months.


Antidepressants – Long-term

Antidepressants – Long-term


Antidepressants – Long-term


Psychotropic Propensity for Weight Gain

Risk for Weight Gain

Greatest risk of weight gain in:
- Those with lower baseline BMI (for short-term, not long-term weight gain)
- Higher BMI in parents
- Higher BMI in patients (long-term)
- Female gender
- Younger age


Clinical Relevance of Weight Changes

Clinical relevance is not straightforward.

Large weight gains (3 to 5 units BMI) in those with Class II or greater obesity associated with 33-53% mortality increase independent of other risk factors.


Identifying Those At Risk

Early weight gain of >5% in 1 month is best predictor of long-term weight gain.

Dyslipidemia

Dyslipidemia Players

Clozapine and olanzapine are known to cause hypertriglyceridemia and hypercholesterolemia (esp. triglycerides). Olanzapine and quetiapine > risperidone and haloperidol, ziprasidone, aripiprazole (not studied with quetiapine)
Risperidone > aripiprazole and ziprasidone


Dyslipidemia Magnitude

Study of medication-naïve participants x 1 year with haloperidol, risperidone, or olanzapine:
- 36.6 mg/dL increase in triglycerides (2 mmol/L)
- 22.2 mg/dL increase in total cholesterol
Case reports of doubling in triglycerides in 2 weeks!

Dyslipidemia Impact

Changes in triglycerides of 1 mmol/L (88 mg/dL) associated with mortality increases of 18% in women and 8% in men independent of other risk factors.

Changes in cholesterol of 36 mg/dL associated with twice the risk of CV mortality.


Diabetes Mellitus

Risk with Antipsychotics

Bobo WV et al. *JAMA Psychiatry* 2013.
Risk with Antipsychotics

Agents Most Implicated

60% greater risk of new-onset type 2 diabetes mellitus in new users of olanzapine, risperidone, and quetiapine relative to haloperidol

Divalproex consistently associated with insulin resistance.

Head-to-head Comparisons

Glucose Change:
Olanzapine > Quetiapine, Risperidone, Aripiprazole, and Ziprasidone

Bibo WV et al. JAMA Psychiatry 2013.
Diabetes Mechanisms

Indirect Mechanisms

Fig. 2. Central receptor blockade by atypical antipsychotics in the VMHn and the PVN respectively, could cause adiposity by increasing food intake and decreasing energy expenditure. A high SOCS-3 level might lead to leptin resistance. Adiponectin and TNFα influence glucose homeostasis.


Direct Mechanisms

Fig. 3. Atypical antipsychotics may inhibit insulin secretion in pancreatic β-cells through inhibition of M3-receptor mediated insulin release. Furthermore, antagonism of the 5HT1a-receptor might decrease glucose sensitivity, whereas α2-receptor antagonism might stimulate insulin release, both resulting in disturbance of dynamic control.

Direct Mechanisms

Fig. 4. Atypical antipsychotics may inhibit glucose uptake in skeletal and liver cells through inhibition of the GLUT glucose transporter.


Elevated Blood Pressure

Agents Implicated

Increases in blood pressure have consistently been reported with:
- Stimulant medications (~4 mm Hg)
- Atomoxetine (~2 mm Hg)
- Antidepressants which inhibit norepinephrine reuptake (venlafaxine, duloxetine, tricyclic antidepressants)

Antipsychotics
Hypertension has been associated several antipsychotics:
- Aripiprazole, clozapine, olanzapine, risperidone


Individual Variability


Individual Variability

Magnitude of Change

For venlafaxine and imipramine, a 2-3 mm Hg difference in systolic blood pressure. Although small, even within the usual range of blood pressure down to 115/75, changes of this magnitude may be associated with a 15-20% higher risk of CV mortality. More extreme changes may be seen in vulnerable individuals.


Monitoring

Divalproex Monitoring

From guidelines: CBC and hepatic function every 6 months.

Data above would suggest:
Consider monitoring BMI and fasting glucose (or hemoglobin A1c)

APA Practice Guidelines.
**Antipsychotic Monitoring**

- BMI: Baseline, 4, 8, 12 weeks, then quarterly
- Fasting glucose: Baseline, 12 weeks, then annually
- Lipid profile: Baseline, 12 weeks, every 2-5 years if normal

**Conclusions**

- Psychotropic medications may have a variety of adverse cardiometabolic effects.
- There is considerable individual variability in propensity to have cardiometabolic adverse effects.
- Routine clinical care should include monitoring of these adverse effects.

**Management**

- To manage may consider:
  - Using lower doses or alternative agents
  - Address diet, physical activity
  - Change regimen with early weight gain (first four weeks for antipsychotics)
Adjunctive Therapies

Metformin Efficacy

<table>
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<th>Study</th>
<th>Baseline Weight (kg)</th>
<th>Metformin Weight (kg)</th>
<th>Metformin Weight (kg)</th>
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<td>Wu et al. 2008</td>
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</tr>
</tbody>
</table>


Metformin Dosing

Studies in antipsychotic-associated weight gain have used doses of **750-2250** mg/day. Only one study exceed 1700 mg/day (Baptista et al. 2007).

Best results when combined with lifestyle intervention (Wu et al. 2008).


**Metformin Tolerability**

Common side-effects include:
- GI: Diarrhea, N/V, abdominal discomfort
- Weakness

Less common
- Metallic taste in mouth

Fiedorowicz JG. *Unpublished Review.*

**Metformin Monitoring**

Periodic monitoring of renal function, glucose and CBC.

Rare risk of lactic acidosis (contraindicated if serum creatinine ≥ 1.4 in women or 1.5 mg/dL in men, CHF).

Vitamin B12


**Topiramate Efficacy**

**Topiramate Dosing**

Can titrate in 25-50 mg increments to 100 mg bid. Doses in obesity studies range from 50-200 mg/day.

Fiedorowicz JG. Unpublished Review.

**Topiramate Tolerability**

As of 2013, more than 9,000 subjects have been enrolled in RCTs of topiramate, alone or in combination, for weight loss or binge eating associated with obesity. 10% more w/d on topiramate than placebo.
- Paresthesias (metabolic acidosis), sedation, decreased concentration
- Acute angle closure glaucoma and nephrolithiasis (Micromedex 1-3%), Stevens-Johnsons

Fiedorowicz JG. Unpublished Review.

**Naltrexone and Bupropion**

References (40)


