Metabolic Side Effects of Atypical Antipsychotics

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Goals and Objectives

• Goals
  • To understand metabolic risks associated with atypical antipsychotics and how to apply this knowledge your treatment approach to patients

• Objectives
  • Review specific metabolic side effects associated with atypical antipsychotics and pathophysiology involved
  • Review clinical approaches to these side effects in regard to choice of medication, switching or lowering doses, lifestyle interventions, and pharmacological intervention
Prescription of atypical antipsychotics (AAP)

- Use of AAP common in psychiatric practice very common
  - (Camsari 2014)
    - 25% of psychiatric outpatients prescribed at least one AAP
    - More than half for off-label use
- Often prescribed for patients without psychosis
  - Sleep, anxiety, mood disorders, anger, agitation, etc.
- Not uncommon to see used in children and adolescents
- Risperidone, quetiapine, and olanzapine most commonly prescribed atypical antipsychotics for off-label use

Metabolic side effects of AAP (Deng 2013, Ryan 2003)

- Treatment with AAP is associated with higher incidence of weight gain, insulin resistance, dyslipidemia, and “metabolic syndrome”
  - Patients with lower baseline BMI gain the most
  - Younger patients and women seem to be most vulnerable
  - Typical antipsychotics, even high potency agents, may cause weight gain and other metabolic side effects though not to degree as AAP’s
  - Taken together, this increases risk of cardiovascular disease and DM II
Metabolic side effects of AAP (Deng 2013, Ryan 2003)

• Patients with mental illness share a disproportionate share of cardiovascular disease than the general population
  • Especially so in patients with schizophrenia, schizoaffective disorder, bipolar disorder, and treatment resistant depression
  • Even antipsychotic naïve schizophrenic patients may demonstrate insulin resistance which isn’t necessarily secondary to obesity

Metabolic side effects of AAP

• Multiple factors for increased risk of CVD in these patients
  • Medications
  • Poor access to care
  • Poor adherence to medical treatment
  • Smoking
  • Sedentary lifestyle
  • Diet
Metabolic side effects of AAP

• Oklahoma
  • 2015 Data (Robert Wood Johnson Foundation, Trust for America’s Health)
    • Adult obesity 33.9% (8/24)
    • Diabetes 11.7% (9/81)
    • HTN 36.2% (9/25)
  • Recall that American Indians, Hispanics, and African Americans have higher risk for DMII, heart disease, and stroke

Mechanisms of AAP weight gain (Balt 2011)

• Appetite and food intake regulated by
  • Input to the brain from the periphery
  • Action of hypothalamic neurotransmitters and neuropeptides
• Hypothalamic input
  • Higher cortical areas
  • Reward pathways
  • Peripheral messengers
• Serotonin
  • Enhances satiety by stimulating pro-opiomelanocortin (POMC) secretion from the hypothalamus
  • Mediated by 5-HT2C receptors
  • 5-HT2C knockout mice show increased appetite and obesity
Mechanisms of AAP weight gain (Balt 2011, Chandran 2013, Wysokinski 2014)

- Histamine
  - Suppresses food intake
  - Increases thermogenesis
  - Increases SANS activated lipolysis
  - Seems to be necessary for action of leptin’s appetite suppressing effects
  - H1 antagonists are well known to cause weight gain

- Dopamine
  - Overall decrease in limbic DA activity → reward seeking behaviors such as food intake (dopaminergic agents such as amphetamine suppress appetite)
  - D2 blockade may be associated with hyperprolactinemia → increased fat deposition and decreased insulin sensitivity

- Acetylcholine
  - M3 antagonists cause impaired glucose tolerance and reduced insulin secretion from pancreatic β cells

- Noradrenergic
  - α₁ activation reduces appetite (amphetamine, phentermine) and antagonism could stimulate appetite
Mechanisms of AAP weight gain (Balt 2011, Chandran 2013, Wysokinski 2014)

- Neuropeptide hormones involved in weight regulation affected by AAP’s
  - Leptin resistance
    - Levels increase but do not decrease appetite as expected
  - Ghrelin increase
    - Appetite stimulant
  - Adiponectin decrease
    - Unclear if this is a direct effect or secondary to weight gain and insulin resistance
    - Increases insulin sensitivity
    - Decreases vascular inflammation

Insulin resistance (Samuel and Shulman 2016, Deng 2013)

- In face of chronic energy surplus, ectopic lipid accumulation occurs in liver and skeletal muscle
- This triggers pathways that impair insulin signaling
  - Reduced muscle glucose uptake
  - Decreased hepatic glycogen synthesis
  - Increased hepatic production of fatty acids and dyslipidemia
- AAP’s may induce insulin resistance and even DM independent of weight gain
Weight Gain and Dyslipidemia (Jung 2014)
↑FFA delivery to liver
↑TG and VLDL production→

↑LDL and ↓HDL

Insulin Resistance (Abel 2012)

• Many molecular mechanisms of insulin resistance may result in cardiovascular disease
  • Impaired vascular function
    • Impaired vasorelaxation→HTN and increased risk of atherosclerosis
    • Genetic manipulation of insulin on the vasculature may increase risk of atherosclerosis
  • May contribute to macrophage accumulation in vessel wall→increased atherosclerosis and unstable plaques
  • Increases extent of myocardial injury in myocardial ischemia→increased risk of heart failure in affected individuals

**Metabolic Syndrome**

American Heart Association criteria - 3 or more of the following:

- Waist circumference ≥ 40” for males / ≥ 35” for females
- Triglycerides ≥ 150 mg/dl
- HDL < 40 mg/dl for males / <50mg/dl for females
- BP ≥ 130/85
- Fasting glucose ≥ 100mg/dl

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**Differences between AAP (Musil 2015)**

- All first generation and second generation antipsychotics may lead to weight gain but this will vary significantly between agents
- Risk factors for weight gain with antipsychotics
  - Younger age
  - Female
  - Lower BMI at baseline
  - Combination therapy with mood stabilizers and AAP seems to be associated with even higher rates of weight gain
- Meta analysis and review
  - Highest risk - clozapine and olanzapine
  - Medium risk - iloperidone, paliperidone, quetiapine, and risperidone
  - Lowest risk - lurasidone, aripiprazole, and ziprasidone
Differences between AAP (Lieberman 2005)

• Clinical Antipsychotic Trials of Intervention Effectiveness Trial (CATIE)
  • Proportion of patients gaining ≥7% of body weight
    • Olanzapine 30%
    • Quetiapine 16%
    • Risperidone 14%
    • Perphenazine 12%
    • Ziprasidone 7%

Differences between AAP (Kahn 2008)

• European First Episode Schizophrenia Trial (EUFEST)
  • Olanzapine +30.6 lbs
  • Quetiapine +23.1 lbs
  • Haloperidol +7.3 lbs
  • Ziprasidone +4.8 lbs
Managing CV risk with AAP

• Before starting/continuing an antipsychotic
  • Do they need it in the first place?
  • Does it need to be continued?
  • If possible start an agent with a more favorable metabolic profile especially in patients with personal or family history of
    • Obesity
    • Dyslipidemia
    • HTN
    • DM II
    • CV disease

Managing CV risk with AAP (Shulman 2014)

• Clozapine and olanzapine are the worst offenders in regards to metabolic side effects however..
  • Olanzapine was shown to have longer duration of use until discontinuation in the CATIE phase 1 suggesting greater efficacy
  • Clozapine outperformed other agents in CATIE phase 2 including olanzapine
  • Olanzapine very commonly used on inpatient units as a first line agent and also for use in the agitated patient
Managing CV risk with AAP

• Monitoring (National Collaborating Centre for Mental Health guidelines 2014)
  • Take a good medical history and family medical history
  • Prior to starting an antipsychotic medication
    • Measure the baseline weight and height for BMI
    • Waist circumference (at the level of the umbilicus)
    • Blood pressure and pulse
    • Fasting glucose, HgbA1C, and lipid profile

Managing CV risk with AAP

• Monitoring (National Collaborating Centre for Mental Health guidelines 2014)
  • Continued Monitoring
    • Weight checks every week for first 6 weeks, again at 12 weeks, 1 year, and then annually
    • Blood pressure and pulse 12 weeks after initiation and then at one year
    • Fasting glucose, HgbA1C, and lipids 12 weeks after initiation, 1 year, and then annually
Managing CV risk with AAP (Shulman 2014)

• Switching to another antipsychotic with more favorable profile
  • Most data show that this can be effective for weight gain
• Dose reduction
  • Possibly effective for weight gain but some studies have shown that this side effect may not be fully dose related
• These strategies would need to be weighed against the possibility of destabilization

Managing CV Risk with AAP

• Lifestyle modifications
  • Group and individual weight-management sessions and exercise may help significantly in patients taking antipsychotics
  • Daumit, 2013
    • Patients with schizophrenia, schizoaffective disorder and Mood disorders (n=291)
      • 89% on FGA or SGA
      • Baseline BMI (both) 36.3 ±7.3
      • Group and individual weight-management sessions
      • Group exercise sessions
      • Control received standard nutrition and exercise information at baseline
      • Outcome was weight change
Managing CV Risk with AAP

- Dietary changes
  - Caloric need (UCLA Student Nutrition Awareness Campaign)
    - Healthy body weight = BMI 19-25
    - HBW x 10 = to meet your BMR
    - HBW x 13 = to meet your BMR and a sedentary lifestyle
    - HBW x 15 = to meet your BMR and light activity
    - HBW x 17 = to meet your BMR and moderate activity (exercising an hour 4-5x/wk)
    - HBW x 20 = to meet your BMR and heavy activity (athlete)
  - Recall that BMR can differ among patients


Figure 2. Mean Weight Change, According to Study Group.
The model-based estimates of the mean difference in changes in weight (the change in the intervention group minus the change in the control group) between the two groups at 6, 12, and 18 months were −1.5 kg (95% CI, −2.6 to −0.4; P=0.007), −2.5 kg (95% CI, −4.1 to −0.8; P=0.004), and −3.2 kg (95% CI, −5.1 to −1.2; P=0.002), respectively. To convert values for weight to pounds, multiply by 2.2.
Managing CV Risk with AAP (UCLA Student Nutrition Awareness Campaign 2005)

<table>
<thead>
<tr>
<th>Height</th>
<th>HBW</th>
<th>BMR</th>
<th>Light activity</th>
<th>Mod. activity</th>
<th>Heavy activity</th>
</tr>
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<tbody>
<tr>
<td>5'4&quot;</td>
<td>110-145</td>
<td>1100-1450</td>
<td>1650-2175</td>
<td>1870-2465</td>
<td>2200-2900</td>
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<tr>
<td>5'6&quot;</td>
<td>118-155</td>
<td>1180-1550</td>
<td>1770-2325</td>
<td>2006-2635</td>
<td>2360-3100</td>
</tr>
<tr>
<td>5'8&quot;</td>
<td>125-164</td>
<td>1250-1640</td>
<td>1875-2460</td>
<td>2125-2788</td>
<td>2500-3280</td>
</tr>
<tr>
<td>5'10&quot;</td>
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<td>1320-1740</td>
<td>1980-2610</td>
<td>2244-2958</td>
<td>2640-3480</td>
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<td>6'0&quot;</td>
<td>140-184</td>
<td>1400-1840</td>
<td>2100-2760</td>
<td>2380-3128</td>
<td>2800-3680</td>
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<tr>
<td>6'2&quot;</td>
<td>148-194</td>
<td>1480-1940</td>
<td>2220-2910</td>
<td>2516-3298</td>
<td>2960-3880</td>
</tr>
</tbody>
</table>

Managing CV Risk with AAP

- **Dietary changes**
  - 3500 calories in pound of fat
  - 500 calorie restriction daily = 1 pound lost in a week
  - Smaller portions of higher calorie foods and larger portions of lower calorie foods
    - Protein and carbohydrate = 4 calories/g
    - Fat = 9 calories/g
    - 200 gram apple = about 100 calories
    - 200 grams of bacon = about 1000 calories
- **Regular exercise (McDaniels 2016)**
  - In addition to burning calories needed for the activity increases in metabolic may be seen for several hours after exercise is over
  - May decrease appetite
Managing CV risk with AAP (Shulman 2014)

- Pharmacological approach may be called for when lifestyle modifications have failed or are otherwise impractical
- Several medications may be of some help but metformin seems to have the strongest evidence for weight gain and metabolic changes
- Meta analysis of pharmacologic interventions for metabolic changes in patients with schizophrenia taking antipsychotics (Mizuno 2014)
  - 40 trials with metformin being the most extensively studied
  - Mean difference of -3.17 kg (95% CI: -4.44 to -1.90) compared to placebo
  - Pooled effects for topiramate, sibutramine, aripiprazole, and reboxetine also separated from placebo for weight gain
  - Metformin and rosiglitazone improved insulin resistance
  - Metformin, aripiprazole, and sibutramine decreased blood lipids

Managing CV risk with AAP

- Metformin
  - Inhibits hepatic gluconeogenesis
  - Lowers TG and cholesterol
  - Improves insulin sensitivity peripherally
  - Low risk of hypoglycemia
  - Lactic acidosis?
    - Cochrane review (Salpeter 2010) found no cases of fatal or nonfatal lactic acidosis in studies of about 70,000 patient-years of use and average lactate levels during metformin tx no different than placebo
Managing CV risk with AAP

• **Metformin** (Kalantar-Zadeh 2016)
  - Though risk may be low this may occur in those with CKD
  - Use should be reviewed in those patients with eGFR 60–45 mL/min/1.73 m² (but may be continued if eGFR is ≥60 mL/min/1.73 m²)
  - Discontinued in those with eGFR <45 mL/min/1.73 m²
  - Temporarily held at any eGFR with a concurrent serious illness that increases the risk of AKI
  - Recall other illness burden placing patients at higher risk of lactic acidosis
    - Sepsis, CHF, MI, liver failure, etc.
  - May cause B12 deficiency

Managing CV risk with AAP

• **Dyslipidemia**
  - Clozaril > Olanzapine > Quetiapine > Risperidone > Ziprasidone > Aripiprazole (Koch 2016)
  - Metformin may help lower LDL, raise HDL, total cholesterol, and TG in patients taking antipsychotics (Wu 2016)
Managing CV Risk with AAP (AHA guideline 2013)

• Using metformin might be the best initial approach but statins may be considered in those without benefit
  • Pharmacologic therapy is recommended for otherwise healthy patients over 21 years of age with low-density lipoprotein (LDL) greater than or equal to 190 mg/dL
  • For diabetic patients who are 40–75 years of age with LDL above or equal to 70 mg/dL,
  • For patients 21–75 years of age who have clinical cardiovascular disease, and for those who are 40–75 years of age with a 10 year cardiovascular disease risk greater than or equal to 7.5% and LDL above or equal to 70 mg/dL

Managing CV Risk with AAP

• Cardiovascular risk calculation involves several parameters
  • Age
  • Sex
  • Race
  • Total and HDL cholesterol
  • Systolic BP (and treatment for such)
  • Smoking
  • Diabetes

• cvriskcalculator.com
Managing CV risk with AAP

• AHA Guidelines
  • Statin therapy is classified into three categories based on effects on LDL cholesterol:
    • High-intensity for a 50% or more decrease or diabetes or CVD (e.g., atorvastatin 40–80 mg daily)
    • Moderate-intensity for 30%–50% decrease (e.g., atorvastatin 10–20 mg daily)
    • Low-intensity for less than 30% decrease (e.g., pravastatin 10–20 mg).
  • Check and ALT and CK prior to starting and repeat only if signs of muscle damage or hepatotoxicity (Shulman 2014)

Comparison of Atypical Antipsychotics
(Pharmacist’s Letter 2015)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>Diabetes Risk</th>
<th>Dyslipidemia</th>
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</thead>
<tbody>
<tr>
<td>Aripiprazole (Abilify)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Asenapine (Saphris)</td>
<td>Low to Moderate</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Brexpiprazole (Rexulti)</td>
<td>Moderate</td>
<td>Low to Moderate</td>
<td>Low to Moderate</td>
</tr>
<tr>
<td>Caripiprazine (Vraylar)</td>
<td>Low</td>
<td>Low to Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Clozapine (Clozaril)</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Iloperidone (Fanapt)</td>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Lurasidone (Latuda)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Paliperidone (Invega)</td>
<td>Low to Moderate</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Ziprasidone (Geodon)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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</table>
Summary

• Treatment with antipsychotics, particularly atypical antipsychotics, is associated with weight gain, insulin resistance, and dyslipidemia, increasing risk for cardiovascular disease.

• Atypical antipsychotics may result in these metabolic derangements through a variety of mechanisms.

• There can be significant differences between atypical antipsychotics in terms of metabolic side effects.

• To avoid morbidity and mortality in patients taking these medications providers should choose or continue such drugs carefully, monitor appropriately, and to intervene if such side effects do occur.

Sources


