The Biggest Loser: GLP-1 Receptor Agonists Join the Race for Antipsychotic-Induced Weight Gain

Kevin Zhao, PharmD
PGY2 Ambulatory Care/Behavioral Health Pharmacy Resident
South Texas Veterans Health Care System
The University of Texas at Austin College of Pharmacy
UT Health San Antonio
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Objectives

1. Discuss the pathophysiology of antipsychotic-induced weight gain (AIWG)
2. Describe the relationship between glucagon-like peptide-1 (GLP-1) and AIWG
3. Analyze available literature for GLP-1 receptor agonists (GLP1-RAs) use in patients with AIWG
4. Create recommendations to support the use of GLP1-RAs in patients with AIWG
I. Introduction
   A. Background
      i. Weight gain and obesity have become critical public health issues
         a. Within the United States, medical costs associated with obesity could reach $147 billion a year
      ii. Obesity is an additional health burden for those with mental illnesses, negatively affecting medication therapies, quality of life, and cardiovascular risk
      iii. Unhealthy lifestyle and mental illness can affect an individual’s cardio-metabolic status, as can certain pharmacological treatments, such as second-generation antipsychotics (SGAs)
   B. Health Impact
      i. Weight gain is not only pronounced in the administration of SGAs, but also early in mental illnesses such as schizophrenia
         a. In the EUFEST study, newly diagnosed patients with schizophrenia were found to have greater than 7% weight gain even when given less orexigenic agents
      ii. Schizophrenia has suggested risks for type 2 diabetes mellitus (T2DM) and metabolic dysregulation without medication treatment
         a. For every 1 kg/m² increase in Body Mass Index (BMI), the risk of developing new-onset T2DM increases by 8.4%
      iii. Cardiovascular disease (CVD) is also a main contributor to reducing life expectancy in people with schizophrenia
         a. Risk factors for CVD include smoking, overweight/obesity, and alcohol misuse
      iv. Patients with schizophrenia have a 2.5 times greater risk of mortality compared with age-matched people from the general population
         a. Mortality risk is likely attributed to health care availability and the utilization of psychosocial treatments, but also the modifiable risks of undesirable medication effects

II. Atypical antipsychotics or SGAs
   A. Background
      i. First-line treatment for psychotic disorders
      ii. Adjunctive use in non-psychotic disorders
      iii. Several medications within this class are more likely to cause weight gain and metabolic syndrome than the first-generation antipsychotics (FGAs)
         a. Metabolic syndrome is associated with a 2- to 3-fold increase in cardiovascular mortality and a 2-fold increase in all-cause mortality
   B. Indications
      i. Psychotic disorders
         a. Schizophrenia
         b. Schizoaffective disorder
         c. Agitation associated with schizophrenia
         d. Bipolar disorder
         e. Bipolar depression
         f. Treatment-resistant major depression
      ii. Non-psychotic disorders
         a. Irritability associated with autistic disorder
         b. Autism spectrum disorder
C. Mechanism of action
   i. Antagonize D₂ receptor with some 5-HT₂A antagonism
   ii. Dissociate rapidly from D₂ receptors
   iii. Higher affinity for 5-HT₂A

D. Common side effects (Table 1)
   i. Drug-induced weight gain
   ii. Metabolic abnormalities
      a. Glucose dysregulation/T2DM
      b. Dyslipidemia
   iii. Tachycardia
      iv. Constipation
   v. Excessive salivation
   vi. Somnolence

Table 1. Side Effects with Atypical Antipsychotic Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Weight Gain</th>
<th>Glucose Metabolism Abnormalities</th>
<th>Dyslipidemia</th>
<th>Metabolic Syndrome</th>
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<tbody>
<tr>
<td>Asenapine</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Clozapine</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Risperidone</td>
<td>+++</td>
<td>+++</td>
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<td>+++</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+</td>
<td>+</td>
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<td>+</td>
</tr>
</tbody>
</table>

+ 0-10% incidence; ++ 10-20% incidence; +++ 20-30% incidence; ++++ >30% incidence

E. Monitoring
   i. Metabolic Syndrome
      a. Definition: meeting of ≥3 out of 5 criteria below
         1. Waist circumference >40 inches (men) or >35 inches (women)
         2. BP ≥130/85 mmHg
         3. Fasting TG ≥150 mg/dl
         4. Fasting HDL <40 mg/dl (men) or <50 mg/dl (women)
         5. FPG ≥100 mg/dl
   ii. Significant weight gain can be identified within 6-8 weeks of SGA initiation
      a. Early weight gain appears to be a predictor of longer term weight gain
         1. A prospective study found that weight gain of more than 5% after 1 month
            is the best predictor of long-term weight gain
   iii. Recommendations for metabolic risk factor monitoring per American Diabetes Association/American Psychiatric Association (ADA/APA) Consensus Guidelines (Table 2)
III. Pathophysiology of AIWG

A. Background
   i. AIWG and obesity can result from a medication-induced or -aggravated imbalance between energy intake and energy expenditure
   ii. Data have been inconclusive on whether antipsychotics can increase weight via increased appetite and food intake, decreased activity, or decreased metabolism
   iii. Several moderators and mediators for weight gain during antipsychotic treatment have been reported including treatment setting, comediations, and changes in diet and activity during antipsychotic exposure

B. Pathways (Figure 1)
   i. Behavioral mechanism
      a. Individuals exposed to most antipsychotics have greater appetites and eat more but the composition of their food may not be altered
      b. In addition to increased appetite, delayed or dampened satiety signaling has also been observed to increased weight gain
   ii. Neurohormonal mechanism
      a. SGAs increase levels of leptin, a peptide hormone that regulates appetite and is produced by adipocytes in response to AIWG
         1. Macrophages and adipocytes produce higher amounts of inflammatory markers
      b. In the early course of antipsychotic treatment, there is a decrease in fasting morning ghrelin (appetite-stimulating hormone) levels and then an increase after chronic use

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Table 2. Consensus Guidelines for Baseline Assessment and Monitoring for Patients Receiving Atypical Antipsychotic Medications*

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>Quarterly</th>
<th>Annually</th>
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<tr>
<td>Personal/family history</td>
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<td></td>
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<tr>
<td>Weight (BMI) ≥30</td>
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<tr>
<td>Waist circumference</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Men: &gt;40 inches</td>
<td>X</td>
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<td>Women: &gt;45 inches</td>
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<td>Blood pressure (BP)</td>
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<td>Fasting plasma glucose</td>
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<td>(FPG) ≥100 mg/dl</td>
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<td>Fasting lipid profile</td>
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<td>TG: ≥150 mg/dl</td>
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<td>X</td>
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<td>HDL: Men &lt;40 mg/dl,</td>
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<td>Women &lt;50 mg/dl</td>
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</tbody>
</table>

*Per British Association of Psychopharmacology (BAP) Guidelines – recommend monitoring weight, BP, FPG, and fasting lipid profile at 6 months mark, as well as weight annually

TG = triglyceride; HDL = high-density lipoprotein (HDL)
iii. Pharmacodynamic neurotransmitter targets\textsuperscript{13,14}
   a. Antipsychotics have various targets and interacts with receptors with varying degrees of affinity
   b. Dopamine
      1. Strong binding (agonism or partial agonism) at dopamine D\textsubscript{2} receptors is the only common mechanism to all currently-approved antipsychotics
      2. D\textsubscript{2} blockade can potentially impact energy metabolism through alterations in reward signaling and decrease psychomotor activity
   c. Serotonin
      1. Serotonin has a potential role in regulating feeding behavior and satiety signaling
      2. Blockade of 5-HT\textsubscript{2C} receptor will increase food intake by impairing satiety
   d. Histamine
      1. Histamine H\textsubscript{1} agonism suppresses food intake, whereas hypothalamic H\textsubscript{1} receptor antagonism increases food intake
      2. H\textsubscript{1} receptor-linked activation of hypothalamic adenosine monophosphate (AMP)-kinase mediates AIWG binding to histamine H\textsubscript{1} receptor in weight gain liabilities\textsuperscript{15}

iv. Many other mechanisms have been explored, but pathways involving GLP-1 and peptide YY (PYY) 3-36 have yet to be explored in depth\textsuperscript{16}
C. Management strategies

i. Behavioral interventions - considered first line approach and should be continued with any additional interventions
   a. Randomized controlled trials (RCTs) have demonstrated positive weight-loss effects from lifestyle interventions
      1. Results showed a mean weight loss of approximately 2.5 kg versus placebo
   b. Diet
      1. Restrict consumptions of high-carbohydrates, high-fat, and low-fiber foods
      2. Limit total caloric intake to 1500-1800 kcal/day in males and 1200-1500 kcal/day in females
   c. Physical exercise
      1. Endurance activities are preferable, but not resistance training
      2. May start at lower activity level for inactive patients, then increase to 2-3 times weekly for 30 minutes
      3. Goal: 200-300 minutes per week of physical activity
   d. Weight loss
      1. Goal: reduce weight by ≥3 kg and BMI ≥1 kg/m²
   e. Smoking cessation and alcohol moderation

ii. Antipsychotic switching
   a. Consider patients’ entire psychiatric and physical condition, in addition to pharmacological profiles of current and proposed antipsychotics
   b. Clinician must balance the possible weight-reducing benefits against the risks of inducing relapse of core psychotic symptoms
   c. May consider switching to antipsychotic medications with lower propensities for weight gain, such as ziprasidone, lurasidone, aripiprazole, or asenapine
   d. APA/ADA Consensus Guidelines recommend switching to a SGA with a lower weight gain risk in patients who experience more than a 5% weight increase from their initial weight
   e. BAP Guidelines
      1. Only four RCTs have directly examined the weight reducing effects of antipsychotic switching on AIWG
      2. Studies observed an average of 3 kg weight reduction when switching from olanzapine to either aripiprazole or quetiapine

iii. Adjunctive pharmacotherapy
   a. Recommended therapies (see Table 3)
      1. Metformin
         a) A systematic review of studies in non-diabetic, obese young people indicated that metformin reduced BMI by 1.42 kg/m² when compared to placebo
         b) A meta-analysis of 10 RCTs evaluating the addition of metformin at various therapy times to existing antipsychotic medications (clozapine, olanzapine or risperidone) concluded an average weight reduction of 3.17 kg
c) Jarskog et al. was the largest study carried out in 17 locations in the USA (n=116)
   1) Patients included in the study had a diagnosis of schizophrenia or schizoaffective disorder and were ill for more than 12 months and had a BMI of 27 kg/m² or greater
   2) Participants received weekly diet and exercise counseling, and treatments with either metformin or placebo for 16 weeks
      - Final average total daily metformin dose: 1887mg daily
      - Mean weight loss of 3 kg with metformin (1 kg with placebo)
      - Significant lowering of TG and hemoglobin A1c (HbA1c) levels

d) Wu et al. was the longest study at a single site in China (n=84) for 24 weeks
   1) Female patients were included in the study if within their first year of antipsychotic treatment and have experiencing amenorrhea
   2) All patients received metformin 1000mg daily
   3) No diet and exercise interventions provided in the study
   4) Significant weight loss of 2.3 kg and BMI reduction of 0.93 kg/m² observed

e) These studies suggest that metformin can benefit AIWG with a weight decrease of approximately 3 kg compared to placebo, with or without additional lifestyle interventions

2. Aripiprazole
   a) Meta-analyses found small effects of weight increase in aripiprazole compared to other antipsychotic medications
   b) Henderson et al. was a 6-week, open-label trial looking at the effects of aripiprazole in clozapine-treated patients (n=13)
      1) Dose of aripiprazole used was between 15-30 mg daily
      2) People were included in the study with a diagnosis of chronic schizophrenia
      3) Significant weight reduction of 2.7 kg observed
   c) Henderson et al. later performed a 10-week, placebo-controlled, double-blind crossover study looking at aripiprazole’s effects in individuals treated with olanzapine (n=15)
      1) Dose of aripiprazole used was 15 mg daily
      2) Participants were included in the study who were overweight and obese with diagnoses of schizophrenia and schizoaffective disorder
      3) Significant weight loss of 1.3 kg and BMI reduction of 0.4 kg/m² observed
      4) Other significant metabolic effects included decrease in TG and total very LDL cholesterol (VLDL)
   d) Fleischhacker et al. was a 38-week, multicenter, double-blinded, and RCT examining the effects of adjunctive therapy of clozapine with aripiprazole against clozapine alone (n=207)
      1) Dose of aripiprazole used had a mean dose of 12 mg daily
2) Patients were included in the study with a diagnosis of schizophrenia and a greater than 2.5 kg weight gain on clozapine
3) Significant weight decrease of 2.15 kg was observed
4) Other significant effects were in the reduction of BMI, waist circumference, total cholesterol (TC), and low-density lipoprotein (LDL) cholesterol
e) The addition of aripiprazole to clozapine or olanzapine has been shown to provide significant weight loss of around 2 kg compared to placebo
1) Data regarding the lipid effects of aripiprazole use is inconsistent

b. Other therapies
1. Topiramate
   a) Weight loss has been reported in some individuals with epilepsy who were prescribed topiramate
   b) A meta-analysis found a weight loss of 5.34 kg compared to placebo when looking at the effects of topiramate in overweight and obese people in the general population
   c) Some studies have proposed the weight loss mechanism of topiramate to be a reduction in visceral fat, leading to a decrease in plasma leptin concentration
   d) Four double-blind, placebo controlled RCTs have examined the effects of topiramate on weight and/or BMI as adjunctive therapy to antipsychotics; three studies found significant benefits
      1) Nickel et al. (n=49) studied topiramate in combination with olanzapine for 10 weeks with significant weight difference of 5.3 kg between the groups
         • Topiramate dosing in this study started at 50mg daily and titrated to 250 mg daily
      2) Ko et al. (n=66) studied topiramate in combination with clozapine, olanzapine, quetiapine, or risperidone for 12 weeks
         • Significant difference found in weight loss for topiramate daily doses of 100 mg (1.68 kg) and 200 mg (5.35 kg)
      3) Narula et al. studied topiramate in combination with olanzapine for 12 weeks and found significant weight reduction of 1.27 kg plus other improvements in FPG, TC and LDL cholesterol
         • Dosing used in the study was topiramate 100 mg daily
   e) Modest amount of evidence from RCTs suggest topiramate may help to mitigate weight gain and potentially induce weight loss

2. Orlistat
   a) Two trials with small effects only seen in men
   b) Medication was poorly tolerated and had high rates of discontinuation

3. Amantadine, Melatonin, Naltrexone
   a) RCTs with beneficial effect, but data was either too limited or effect size was too small

4. Atomoxetine, H2 Antagonists, Antidepressants
   a) Clinical trials failed to show benefits
Table 3. Summary of Adjunctive Pharmacological Medications for AIWG\textsuperscript{3,6}

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Usual Dose</th>
<th>Monitoring</th>
<th>Side Effects</th>
<th>Metabolic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>&quot;Weight neutral SGA&quot; Dopamine D2 receptor partial agonist</td>
<td>5-30 mg daily</td>
<td>Metabolic monitoring</td>
<td>Nausea, headache, insomnia, anxiety, restlessness</td>
<td>\downarrow weight (\textasciitilde 2 kg) \downarrow TC &amp; TG</td>
</tr>
<tr>
<td>Metformin</td>
<td>Reduces hepatic glucose production, increase insulin sensitivity in muscle</td>
<td>500 mg BID, titrate 500 mg Qweek Max: 2,550 mg daily</td>
<td>Baseline, annual Scr FPG, HbA1c</td>
<td>N/V/D, headache</td>
<td>\downarrow weight (2-3 kg) \downarrow lipids \downarrow glucose intolerance</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Sodium channel blocker, mixed GABAergic, and anti-glutamatergic activity</td>
<td>50-400 mg daily</td>
<td>Baseline BMI, Scr, bicarbonate Yearly BMI, Scr</td>
<td>Paresthesia, drowsiness, fatigue, memory impairment, nephrolithiasis</td>
<td>\downarrow weight (\textasciitilde 4 kg) \downarrow TC &amp; LDL \downarrow FPG</td>
</tr>
</tbody>
</table>

GLP-1 Receptor and Weight Gain

I. GLP-1 receptor system and weight gain\textsuperscript{20} (Figure 2)
   A. GLP-1 is an endogenous peptide hormone secreted by endocrine L-cells of gastric mucosa in response to meal intake
      i. Peptide hormone is produced by proteolytic processing of the proglucagon pro-hormone, resulting in the major active form of a 30 amino acids peptide GLP-1
   B. GLP-1 is metabolized and inactivated rapidly by dipeptidyl peptidase IV to generate an inactive metabolite that competitively antagonizes the GLP-1 receptor
   C. Receptors are widespread throughout the body, including the pancreas, gastrointestinal tract, kidney, and brain

II. Proposed mechanisms leading to weight gain\textsuperscript{21,22}
   i. Acute and reversible derangement of glucose metabolism through suppression of GLP-1
   ii. Elevated glucagon secretion
   iii. Increased hepatic gluconeogenesis

III. Literature\textsuperscript{23}
   A. Smith et al. proposed clozapine and olanzapine can induce rapid and reversible reductions of active GLP-1 levels, and cause changes to food preferences, secretion of glucagon, and ultimately glucose tolerance
   B. Nasrallah et al. postulated a clozapine-related mechanism of inhibition of GLP-1 secretions through antagonism of muscarinic M1 and M2 receptors
   C. Peters et al. and Shin et al. revealed that GLP-1 plays an active role in the macronutrient selection and helps to regulate intake of high-sugar foods, which can be suppressed by clozapine to cause hyperphagia and weight gain
I. Background\textsuperscript{21,22}
   A. GLP1-RAs constitute an anti-diabetic and anti-obesity drug class that mimics the effects of endogenous gut hormone GLP-1
   B. GLP1-RAs lower blood glucose and body weight, but also moderately reduce BP and lipids through peripheral and central actions

II. Mechanisms\textsuperscript{24,25}
   A. GLP-1 is essential for normal glucose tolerance, which contributes to amplification of insulin secretion and inhibition of glucagon secretion
   B. Inhibits gastrointestinal motility and secretion
   C. Physiological regulator of appetite and food intake

III. Current FDA approved indications\textsuperscript{24,25}
   A. T2DM
   B. Obesity – only liraglutide

IV. Available GLP-1RAs and Dosages\textsuperscript{6,24,25}

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Initial Dosing</th>
<th>Max Dosing</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>Byetta</td>
<td>5mcg BID</td>
<td>10mcg BID</td>
<td>~$690/pen</td>
</tr>
<tr>
<td>Exenatide ER</td>
<td>Bydureon</td>
<td>2mg weekly</td>
<td>2mg weekly</td>
<td>~$644/kit</td>
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<tr>
<td>Liraglutide</td>
<td>Victoza</td>
<td>0.6mg daily</td>
<td>1.8mg daily</td>
<td>~$769/carton</td>
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<tr>
<td>Dulaglutide</td>
<td>Trulicity</td>
<td>0.75mg weekly</td>
<td>1.5mg weekly</td>
<td>~$698/carton</td>
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<tr>
<td>Albiglutide</td>
<td>Tanzeum</td>
<td>30mg weekly</td>
<td>50mg weekly</td>
<td>~$541/carton</td>
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<tr>
<td>Lixisenatide</td>
<td>Adlyxin</td>
<td>10mcg daily</td>
<td>20mcg daily</td>
<td>~$580/carton</td>
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<tr>
<td>Semaglutide</td>
<td>Ozempic</td>
<td>0.25mg weekly</td>
<td>1mg weekly</td>
<td>~$700/carton</td>
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</table>
V. Adverse drug events (ADEs)\textsuperscript{6}
   A. Common: injection site pruritus, gastrointestinal disturbances: nausea, vomiting, diarrhea, and constipation, hypoglycemia, headache, dizziness
   B. Serious: acute pancreatitis, medullary thyroid carcinoma, acute renal failure, angioedema

VI. Special warnings\textsuperscript{24,25}
   A. Thyroid C-cell tumors may occur with use
   B. Pancreatitis or pancreatic duct metaplasia has been reported, including fatal/nonfatal hemorrhagic and necrotizing pancreatitis

VII. Literature
   A. There is limited head-to-head evidence evaluating GLP1-RAs for weight loss, but limited data suggests superior effects with exenatide and liraglutide\textsuperscript{26,27}
      i. Twice-daily exenatide was found to be superior to lixisenatide and non-inferior to liraglutide 1.8 mg, once-weekly exenatide, and dulaglutide 1.5 mg
      ii. Liraglutide 1.8 mg was found to be superior to albiglutide, once-weekly exenatide and dulaglutide 1.5 mg
   B. Based on current evidence, liraglutide and exenatide are two GLP1-RAs with promising outcomes for patients experiencing AIWG

| Clinical question: Could GLP1-RAs be considered a safe, effective, and recommended adjunctive therapy option for AWIG? |

Studies

Larsen JR, et al. Effect of Liraglutide Treatment on Prediabetes and Overweight or Obesity in Clozapine- or Olanzapine-Treated Patients with Schizophrenia Spectrum Disorder: A Randomized Clinical Trial. JAMA Psychiatry.\textsuperscript{28}

<table>
<thead>
<tr>
<th>Design and Methods</th>
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<tr>
<td>Objective</td>
</tr>
<tr>
<td>Design</td>
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<tr>
<td>Inclusion Criteria</td>
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<tr>
<td>Exclusion Criteria</td>
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</table>
### Intervention

- At baseline and after 16 weeks, complete a 4-hour, 75-g oral glucose tolerance test
- Blood sample obtained before oral intake of glucose and at specific times thereafter
- After baseline examinations, eligible participants randomly assigned in a double-blind fashion, to 16 weeks of treatment with either subcutaneously injections of liraglutide or placebo prefilled pen injectors
  - Dosages were followed by a fixed up-titration schedule of 0.6 mg per week to 1.8 mg
  - Remained at 1.2 mg week intolerant of higher dosages
- Every 4 weeks from day of randomization
  - Blood samples obtained: plasma glucose, C-peptide, and glucagon
  - Body weight, waist circumference, and BP measured
  - ADEs documented

### Outcomes

**Primary outcome:**
- Change in glucose tolerance from baseline to week 16

**Secondary outcomes:**
- Changes in glycaemia
  - FPG levels
  - Impaired glucose tolerance
  - Glycated HbA1c levels
- Body weight
- Waist circumference
- BP
- Secretion of C-peptide and glucagon (during oral glucose tolerance test)
- Beta cell function
- Insulin sensitivity
- Body composition – Dual energy x-ray absorptiometry (DXA)
- Lipid profile
- Quality of life and daily functioning
- ADEs

### Results

**Baseline**

103 individuals with schizophrenia spectrum disorder were randomized from May 1, 2013 to February 25, 2016

At baseline, there were no significant differences between the two groups except with the number of treatment with either olanzapine (olanzapine 31.9% vs. placebo 6%) or clozapine (clozapine 68.1% vs. placebo 82.05%)
- Liraglutide (n=47)
- Placebo (n=50)

**Results**

**Primary outcome:**
- Change in glucose tolerance from baseline to week 16 (p<0.001)
  - Treatment with liraglutide resulted in a 23% larger reduction in 2-h plasma glucose level test
### Secondary outcomes:

#### Changes in Secondary Outcomes

<table>
<thead>
<tr>
<th>Glucose metabolism</th>
<th>Liraglutide Group (n=47)</th>
<th>Placebo Group (n=50)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG levels</td>
<td>0.90</td>
<td>0.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>-28</td>
<td>-6</td>
<td>0.002</td>
</tr>
<tr>
<td>Glycated HbA1c levels</td>
<td>-0.2</td>
<td>0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>0.99</td>
<td>1.04</td>
<td>0.26</td>
</tr>
<tr>
<td>Mean secretion of C-peptide level</td>
<td>0.26</td>
<td>-0.20</td>
<td>0.06</td>
</tr>
<tr>
<td>Mean fasting glucagon level</td>
<td>-4.6</td>
<td>2.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Beta cell function</td>
<td>1.28</td>
<td>0.99</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

#### Clinical, mean

| Body weight, kg                     | -4.7                     | 0.5                  | <0.001  |
| Waist circumference, cm             | -4.0                     | 0.5                  | <0.001  |
| BMI                                 | -1.6                     | 0.08                 | <0.001  |
| Systolic BP, mmHg                   | -1.4                     | 1.1                  | 0.04    |
| Diastolic BP, mmHg                  | 0.5                      | 2.4                  | 0.13    |

#### Body composition (Dual energy x-ray absorptiometry (DEXA))

| Mean visceral fat                  | -315.8                   | -24                  | 0.02    |
| Total body fat                     | 0.91                     | 0.99                 | 0.01    |

#### Lipid profile

| Mean TC, mg/dL                     | -19.3                    | 3.5                  | <0.001  |
| Mean LDL, mg/dL                    | -15.4                    | -2.3                 | <0.001  |
| HDL                                | 0.95                     | 0.99                 | 0.27    |

#### Rating scales

| Schizophrenia Quality of Life Scale (SQLS) | -1.8 to -5.5 | -0.8 to -2.6 | 0.30 to 0.55 |
| Global Assessment of Functioning scale (GAF) | -0.3 | 0.8 | 0.06 |

#### ADEs

| Nausea                              | 31/50 (62%)              | 16/50 (32%)         | 0.008   |
| Orthostatic hypotension             | 4/49 (8.2%)               | 0                   | 0.04    |
| Total serious ADEs                  | 6/51 (11.8%)              | 13/51 (25.5%)       | 0.04    |

#### Author’s Conclusion

In this study, liraglutide, as an adjunctive treatment to clozapine or olanzapine in patients with schizophrenia spectrum disorder, is a safe and effective intervention for AIWG. Liraglutide improved glucose tolerance and metabolic variables, as well as induced significant body weight loss compared to placebo and without adversely affecting mental statuses.

#### Reviewer’s Critique(s)

**Strengths**
- Randomized, placebo-controlled and double-blinded study
- Low dropout rate to maintain adequate power
- Extensive list of outcomes to provide clear and measurable results

**Weaknesses**
- Specific patient population, limiting generalizability to a broader audience
- Low baseline of pre-diabetic patients, resulting in skewed data in outcomes regarding glucose levels
### Design and Methods

#### Objective
To investigate the metabolic effects of the GLP1-RA, exenatide once-weekly, in non-diabetic, antipsychotic-treated, obese patients with schizophrenia.

#### Design
Investigator-initiated, randomized, placebo-controlled, double-blinded, parallel group, 3-month intervention trial.

#### Inclusion Criteria
- Adults ages 18–65 years
- Diagnosed within the schizophrenia spectrum
- Receiving current and unchanged antipsychotic treatment for ≥3 months
- HbA1c <6.5%
- BMI ≥30 kg/m²

#### Exclusion Criteria
- Substance dependence
- T2DM or HbA1c ≥6.5%
- Pregnancy, lactation
- Severe somatic disease
- Allergy to exenatide
- Suicidal ideations

#### Intervention
- All patients were randomized after baseline examinations
- Intervention arms: exenatide 2mg once weekly or placebo
- First 2 doses given in the hospital with subsequent injections provided at patients’ homes
- Clinical examination and recordings of any ADEs were performed
- Baseline examinations followed by a weekly injection of trial medication with 3 scheduled visits at 1 week, 4 weeks, and at end-of-trial

#### Outcomes
- **Primary outcome:** Weight loss after 3 months of treatment
  - Secondary outcomes:
    - Waist and hip circumference measurements
    - 24-hour BP measurement
    - Dual-energy X-ray absorptiometry (DEXA)
    - Blood sampling
    - Experimental procedures regarding exenatide, anti-exenatide antibodies and glucagon
    - Adverse events

#### Statistics
- Within-subject factor between time points was denoted “Time”
- Between-subject factor between exenatide vs placebo was denoted “Group”
- “Time × Group interaction” indicated a difference between the two treatment groups

#### Results
40 patients were enrolled into the trial between March 2013 and June 2015
- Exenatide (n=20)
- Placebo (n=20)
At baseline, there were no significant differences between groups, except persons who smoked (p=0.02)
Results

Primary outcome:
- Body weight
  - Exenatide and placebo groups experienced similar reductions in body weight (2.2 ± 3.3 and 2.2 ± 4.4 kg, respectively) (p=0.98)
- BMI
  - Both groups experienced BMI reduction (p=0.97)
    - Exenatide group changed from 39.5 ± 3.5 to 38.7 ± 3.7 kg/m$^2$
    - Placebo group changed from 38.6 ± 6.3 to 37.8 ± 6.7 kg/m$^2$

Secondary outcomes: mostly found significance within treatment groups but not when compared with each other

### Results of Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Exenatide Group (n=20)</th>
<th>Placebo Group (n=20)</th>
<th>Time P Value</th>
<th>Time x Group P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference, cm</td>
<td>Baseline 128.4</td>
<td>End of Trial 127.7</td>
<td>Baseline 125.3</td>
<td>End of Trial 124.4</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
<td>Baseline 124.0</td>
<td>End of Trial 122.0</td>
<td>Baseline 118.5</td>
<td>End of Trial 118.1</td>
</tr>
<tr>
<td>Central 24-h systolic BP, mmHg</td>
<td>Baseline 122.4</td>
<td>End of Trial 115.6</td>
<td>Baseline 110.5</td>
<td>End of Trial 111.9</td>
</tr>
<tr>
<td>Central 24-h diastolic BP, mmHg</td>
<td>Baseline 83.7</td>
<td>End of Trial 81.6</td>
<td>Baseline 78.1</td>
<td>End of Trial 78.6</td>
</tr>
<tr>
<td>Body fat mass (%)</td>
<td>Baseline 47.0</td>
<td>End of Trial 47.0</td>
<td>Baseline 46.9</td>
<td>End of Trial 45.7</td>
</tr>
</tbody>
</table>

Blood sampling

<table>
<thead>
<tr>
<th></th>
<th>Exenatide Group (n=20)</th>
<th>Placebo Group (n=20)</th>
<th>Time P Value</th>
<th>Time x Group P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c, mmol/mol</td>
<td>Baseline 33.3</td>
<td>End of Trial 36.2</td>
<td>Baseline 34.7</td>
<td>End of Trial 39.15</td>
</tr>
<tr>
<td>FPG, mmol/L</td>
<td>Baseline 5.1</td>
<td>End of Trial 5.8</td>
<td>Baseline 5.3</td>
<td>End of Trial 6.1</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>Baseline 1.5</td>
<td>End of Trial 2.4</td>
<td>Baseline 1.4</td>
<td>End of Trial 2.1</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>Baseline 4.5</td>
<td>End of Trial 5.2</td>
<td>Baseline 4.2</td>
<td>End of Trial 5.0</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>Baseline 2.6</td>
<td>End of Trial 3.3</td>
<td>Baseline 2.4</td>
<td>End of Trial 3.1</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>Baseline 0.9</td>
<td>End of Trial 1.1</td>
<td>Baseline 1.0</td>
<td>End of Trial 1.1</td>
</tr>
<tr>
<td>Plasma exenatide, pmol/L</td>
<td>Baseline 3.4</td>
<td>End of Trial 84.9</td>
<td>Baseline 0.0</td>
<td>End of Trial 0.0</td>
</tr>
<tr>
<td>Anti-exenatide antibody binding (%)</td>
<td>Baseline 3.75</td>
<td>End of Trial 17.8</td>
<td>Baseline 0.0</td>
<td>End of Trial 0.0</td>
</tr>
<tr>
<td>Plasma glucagon</td>
<td>Baseline 10.1</td>
<td>End of Trial 10.5</td>
<td>Baseline 9.1</td>
<td>End of Trial 9.1</td>
</tr>
</tbody>
</table>

Adverse events: exenatide group reported more diarrhea (n=5, P=0.02) and fatigue (n=4, P=0.04) compared to 0% in the placebo group

Author’s Conclusion

In this study, treatment with once-weekly exenatide for AIWG did experience significant weight loss, though not when compared to placebo. The results could suggest that the body weight-lowering from AIWG may involve multiple signaling pathways and require blockade of numerous receptor systems. Nevertheless, anti-obesity regimens effective in the general population may not be readily implemented in antipsychotic-treated patients with schizophrenia.

Reviewer’s Critique(s)

**Strengths**
- Well-designed study with weight loss as the primary outcome
- Powered appropriately for primary endpoint
- Detailed monitoring and examination

**Weaknesses**
- Inclusion of multiple antipsychotics varying in weight gain propensities
- Short study with no long-term effects of treatment examined
### Design and Methods

<table>
<thead>
<tr>
<th>Objective</th>
<th>To assess whether an exogenous GLP1-RA, exenatide, would be feasible and tolerable in obese people with schizophrenia on clozapine with or without T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Open-label, parallel, randomized, controlled pilot trial</td>
</tr>
</tbody>
</table>
| Inclusion Criteria | • Adults ages 18–64 years  
• Diagnosed with schizophrenia or schizoaffective disorder  
• Receiving treatment of oral clozapine for at least 18 weeks  
• Patients with stable body weight (defined as less than 5 kg change in weight over the past 3 months before inclusion)  
Arm A:  
• Diagnosed with T2DM (HbA1c ≥7.5%)  
• BMI ≥30 kg/m² and <45 kg/m²  
Arm B:  
• BMI ≥30 kg/m² and <45 kg/m² |
| Exclusion Criteria | • Pregnancy, lactation  
• Severe gastrointestinal disease  
• Severe renal impairment or end stage renal disease  
• Allergy/hypersensitivity to study products  
• Obesity induced by other endocrinological disorder  
• Treated with corticosteroids or other hormone therapy for > 10 days  
• Current use of any weight-Lowering therapies  
• History of thyroid adenoma or carcinoma  
• Acute/chronic pancreatitis or high risk of pancreatitis  
Arm B: diagnosis of type 1 diabetes mellitus (T1DM) or T2DM |
| Intervention | Patients were randomized to either exenatide (intervention group) or treatment as usual (control group) for 24 weeks  
• Intervention group received weekly subcutaneous injections of exenatide 2 mg  
• Control group received no additional treatments and were followed up every 4 weeks  
• Both groups received case management and psychiatrist appointments while remaining on their usual medications  
Measurements:  
• Weight and waist measurements were taken at baseline and weeks 4, 8, 12, 16, 20 and 24  
• Fasting blood tests and Brief Psychiatric Rating Scales (BPRS) were collected at baseline and at weeks 12 and 24  
• Glycated HbA1c values were collected at baseline and week 24  
• Appetite and food preferences were rated via visual analogue scales created for this study at baseline and at weeks 12 and 24 |
Outcomes

Primary outcome: Baseline to 24 weeks
- Difference in the proportion of participants with >5% weight reduction between the two groups

Secondary outcomes: baseline to 12 weeks to 24 weeks
- Changes in metabolic markers (lipid profile, BP, and FPG)
- Change in symptoms of psychosis using BPRS scale
- Change in insulin sensitivity
- Change in weight loss
- Changes in appetite/food preferences
- Adverse effects (only in exenatide group)

Results

Baseline
123 people were assessed for eligibility and 28 people in total were randomized from February 2016 to July 2017

Baseline characteristics had no significant differences between the exenatide and usual care (control) groups
- Arm A: 5 (3 to exenatide and 2 to usual care)
- Arm B: 23 (11 to exenatide and 12 to usual care)

Results
Primary outcome: More participants in the treatment group had lost more than 5% of their baseline weight (p=0.029)
- Exenatide group vs. usual care group
  - Baseline weight (108 kg vs. 102.7 kg)
  - Changes at 12 weeks (-3.66 kg vs. -0.75 kg)
  - Changes at 24 weeks (-5.29 kg vs. -1.12 kg)

Secondary outcomes:
- No differences for changes in appetite and food preference
- Exenatide group reported transient nausea (n=8), vomiting (n=7), dizziness (n=7) and diarrhea (n=7)

<table>
<thead>
<tr>
<th>Changes in variables at 12 weeks and 14 weeks</th>
<th>Exenatide Group (n=14)</th>
<th>Placebo Group (n=14)</th>
<th>Time x Group P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 Weeks</td>
<td>24 Weeks</td>
<td>12 Weeks</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>-1.22</td>
<td>-1.78</td>
<td>0.24</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>-2.89</td>
<td>-4.18</td>
<td>-0.80</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>-1.93</td>
<td>-2.29</td>
<td>-1.64</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>-1.29</td>
<td>-1.50</td>
<td>0.07</td>
</tr>
<tr>
<td>HbA1c</td>
<td>--</td>
<td>-0.21</td>
<td>--</td>
</tr>
<tr>
<td>FPG, mmol/L</td>
<td>-0.21</td>
<td>-0.34</td>
<td>0.36</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>-0.21</td>
<td>-0.24</td>
<td>0.94</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>BPRS</td>
<td>-0.43</td>
<td>-1.29</td>
<td>-1.50</td>
</tr>
</tbody>
</table>
In this study, more patients treated with once-weekly exenatide achieved a greater than 5% weight loss, at an average of 4.16 kg, than those receiving usual care. There were also significantly greater reductions in BMI, waist circumference and FPG with exenatide, but not for other metabolic syndrome components. Exenatide was well tolerated, with mild nausea, vomiting and diarrhea being the main ADEs. Mental states were unchanged. Participants on exenatide reported high levels of satisfaction, but less than half felt confident in their ability to self-administer injections.

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion/exclusion criteria assisted to draw appropriate patients</td>
<td>Open-label and therefore subject to bias</td>
</tr>
<tr>
<td>Measurable and specific outcomes</td>
<td>Participant and clinicians knew of treatment allocation</td>
</tr>
<tr>
<td></td>
<td>Small sample size</td>
</tr>
</tbody>
</table>
Summary

- Individuals with schizophrenia commonly experience significant weight gain, which is associated with greater risk of developing T2DM and hypertension
- FGAs and SGAs can be used for similar indications but have differences in their side effects
- AIWG can be caused by SGAs but without a uniformly recognized mechanism
- Behavioral interventions aim to improve diet and increase physical activity, with average reductions in weight by 3 kg and BMI by 1 kg/m²
- Recommendations surrounding antipsychotic switching for AIWG vary, but evidence suggests an average weight reduction of 3 kg
- Multiple adjunctive therapies, including GLP1-RAs, may offer reasonable alternatives to those unable to achieve weight loss with lifestyle modifications alone
- Exenatide has shown mixed benefits for weight loss (an average of 2 kg) in AIWG, but can provide positive metabolic effects including glucose, lipid level, and BP lowering
- Liraglutide is not only approved for obesity and T2DM, but has displayed a significant weight loss potential of 4.7 kg and various secondary benefits including glucose control, systolic BP lowering, and lipid profile improvements in AIWG

Recommendations

- Patients with AIWG should first consider a trial of recommended lifestyle modification
- Patients receiving SGAs who experience a weight gain of 5% or greater should consider additional interventions – antipsychotic switching or adjunctive therapy
- Patients receiving SGAs who are unable to switch their antipsychotics should consider adjunctive therapy for AIWG
- Preferred adjunctive therapies for AIWG should remain metformin and aripiprazole, given similar potentials for weight loss and metabolic benefits, though additional supports from guidelines and evaluated literature
- However, if preferred adjunctive therapies are unable to be considered, recommendations for GLP1-RAs can be equally stratified with that of topiramate, given their similar potentials for weight loss and metabolic benefits, including FPG and lipid profile
- Selection of adjunctive therapy with GLP-1RAs versus topiramate may be considered in patients with an indication for anti-diabetic therapy, questionable medication compliance, and access to administrations by providers.
- Dosing:
  - Liraglutide 0.6 mg, 1.2 mg, 1.8 mg subcutaneous daily (titrate)
  - Exenatide ER 2 mg subcutaneous weekly
- Future GLP1-RAs research
  - Comparative trials of GLP1-RAs against all other well-studied potential pharmacological agents would help improve treatment recommendations
  - Studies of GLP1-RAs with the use of other antipsychotic agents would further assist with clinical decisions
References: