ECHO Diabetes

Atypical Antipsychotic Agents & Diabetes

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Pre-Question

2) Diabetes occurring in association with Zyprexa (olanzapine) :

A. Is entirely due to olanzapine-induced weight gain
B. Is more common in younger patients <40 or 50 and less common >60
C. Is usually mild and gradual in onset
D. Can be severe and result in DKA

- A and B
- B and C
- B and D
- C and D
- A, B, and D
- B, C and D
- All of above

Atypical Antipsychotic Medications Use

- Atypical antipsychotic drugs (also called “second generation” antipsychotic drugs) differ from typical antipsychotic agents in producing significantly fewer extrapyramidal symptoms (EPS) and having a lower risk of tardive dyskinesia (with equal or better efficacy)
  - used primarily to treat psychotic disorders, such as hallucinations, delusions or abnormal behavior/thought
  - Used for sedative and tranquillizing effects in very disturbed or aggressive patients (associated with dementia, anxiety disorder, autism spectrum disorder, and PTSD and obsessive-compulsive disorder (off-label use))
  - Some atypical antipsychotics have received regulatory approval for schizophrenia, bipolar disorder, autism, and as an adjunct in major depressive disorder.

Atypical antipsychotic agents are associated with a different spectrum of side effects, including

- weight gain,
- alterations in glucose metabolism and
- increased concentrations of blood lipids

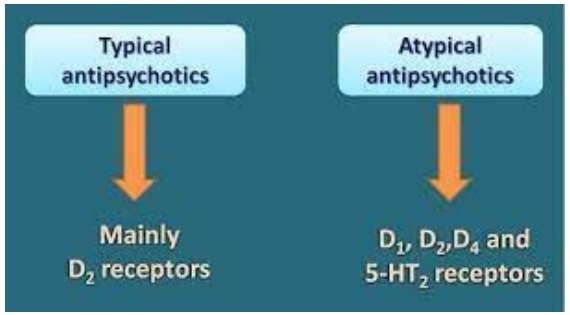
CLASSIFICATION OF ANTIPSYCHOTIC DRUGS

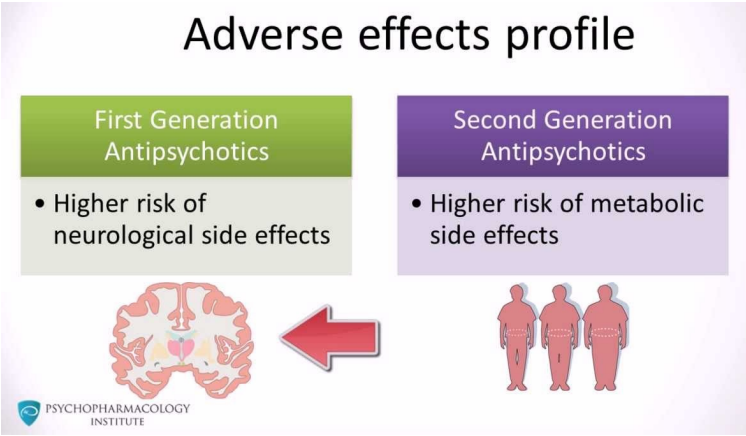
Typical antipsychotics

- Phenothiazines
  - e.g. chlorpromazine, fluphenazine, thioridazine
- Butyrophenones
  - e.g. haloperidol, droperidol
- Thioxanthines
  - e.g. chlorprotixen, thiothixene

Atypical antipsychotics

- Clozapine
- Risperidone
- Sulpiride
- Sertindole
- Seroquel
- Olanzapine
- Quetiapine.





What has been learned about atypical antipsychotic medications and diabetes?

Diabetes Risk Associated with Use of Olanzapine, Quetiapine, and Risperidone in Veterans Health Administration Patients with Schizophrenia

Bruce L. Lambert et al

American Journal of Epidemiology, Volume 164, Issue 7, 1 October 2006

- Epidemiologic studies have largely confirmed the association of **new-onset diabetes with use of second-generation antipsychotic agents**
  - Compared with conventional antipsychotic agents, ***clozapine*** has been associated with more than a twofold increased risk of diabetes in ***younger patients (ages 20–34 years***).
- In the present study, ***olanzapine***, ***risperidone***, and ***quetiapine*** appeared ***to increase risk by 60–70 percent*** in comparison with haloperidol***. Elevations in risk were higher among younger patients***.

Comparison of metabolic effects of atypical antipsychotics

Drug	Weight gain	Dyslipidemia	Hyperglycemia
Clozapine	+++	+++	+++
Olanzapine	+++	+++	+++
Risperidone	++	+	+
Quetiapine	++	++	++
Ziprasidone	+/0	+/0	+/0
Aripiprazole	+/0	+/0	+/0
Iloperidone[a]	++	+/0	+/0
Paliperidone	+	+	+
Asenapine[a]	+/0	+/0	+/0
Lurasidone[a]	+/0	+/0	+/0

+++: significant; ++: intermediate; +: low; +/0: low or neutral

[a]Limited data and/or long-term data are not available

Bahrain Medical Bulletin, Vol. 29, No.4, December 2007

Severe Diabetic Ketoacidosis Precipitated by an Atypical Antipsychotic Drug

Mohammad Naeem Niazy, MRCP et all

- The relative risk (RR) of olanzapine induced DM is
  - 4.2 compared to the risk associated with conventional antipsychotics
  - 5.8 compared to those patients with no treatment (schizophrenia itself has higher risk of DM)
- Patients developing secondary diabetes mellitus following olanzapine are about **10 years younger**, than what is seen in the community
- Hyperglycemia and DKA related to olanzapine may occur approximately ***10 days to 18 months following the initiation of the drug***

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Severe Diabetic Ketoacidosis Precipitated by an Atypical Antipsychotic Drug

Mohammad Naeem Niazy, MRCP et all

- The most likely mechanism of abnormal glucose homeostasis with olanzapine and other atypical antipsychotics are probably through
  - **weight gain and obesity**, **mediated by central nervous system blockade of the serotonin receptor 5HT2C**.
  - Olanzapine also induces hyperinsulinemia and **insulin resistance**.
  - Postulated **that olanzapine has an inhibitory role in insulin secretion** through potent ***anticholinergic activity at the islet cells of pancreas***

Severe Insulin Resistance Associated with Atypical Antipsychotic Agents ADA abstract 2011

- Two cases of **DKA** as new onset presentation
  - one ***required 530 units of insulin/day***
- The mechanism of action may be attributed to the decrease in uptake of neurotransmitters like norepinephrine at the cellular level.
- ***Metformin may help in the treatment of this insulin resistance, but adequate insulin is essential***.

[the more common presentation is ***gradual onset or worsening of pre-existing diabetes mellitus, weight gain and metabolic syndrome*** - severe DKA as a presenting manifestation is very rarely reported]

A consensus statement by the American Diabetes Association, American Psychiatry Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity

- Recommend that *all patients receiving antipsychotics* should receive appropriate baseline screening and ongoing monitoring of whether they have diabetes or not.
- A prospective cohort study in Japan showed that 5.2% of patients who used second-generation antipsychotics developed diabetes
  - *hyperlipidemia* and a *family history of diabetes* were risk factors

How to manage?

How do we help our patients when they need these agents?

Weight gain - only part of the Risk

- The association between second-generation antipsychotic agents and diabetes risk first came to light in **case reports** among patients initiating either clozapine or olanzapine - the two agents that have been on the market for the longest time and most often been associated with ***weight gain***.
- While *the weight gain associated with use of these agents may contribute to the increased risk of diabetes*, the ***mechanism appears to be complex***, possibly involving
  - direct effects of the agents on insulin sensitivity and serotonin receptor activity (Serotonin is known to play a role in glucose homeostasis)
  - weight gain, overeating, and metabolic disorders mediated by antagonists of multiple receptors especially H1and serotonin 5-HT2C receptors.
    - 5-HT1A antagonism leads to a decrease in insulin secretion secondary to decreased pancreatic β-cell responsiveness to plasma glucose levels.

Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis

Varuni Asanka de SilvaEmail author et all BMC PsychiatryBMC series 2016

- *Meta analysis of 12 published studies* with a total of 743 patients found that in patients treated with antipsychotics***, metformin treatment resulted in significantly better anthropometric and metabolic parameters than placebo.***
  - The mean change in weight was −3.27 kg
  - Metformin compared to placebo resulted in significant reduction in BMI −1.13 kg/m2 and insulin resistance index but not fasting blood sugar [−2.48 mg/dl (95 % CI −5.54 to 0.57].
- Conclusion: This meta-analysis confirms that ***metformin is effective in treating antipsychotic induced weight gain***

GLP-1 receptor agonist liraglutide reverses long-term atypical antipsychotic treatment associated behavioral depression and metabolic abnormalities in rats

Ajaykumar N Sharma et al, Metab Brain Dis. 2015 PMID: 25023888 DOI: 10.1007/s11011-014-9591-7

Abstract

- Mood disorder patients that are on long-term **atypical antipsychotics treatment** frequently experience metabolic dysfunctions. In addition to this, accumulating evidences points to **increased risk of structural abnormalities, brain volume changes, altered neuroplasticity and behavioral depression** with long-term antipsychotics use. However, there is paucity of preclinical evidences for long-term antipsychotic associated depression-like behavior.

- 3-week **liraglutide treatment partially reversed metabolic abnormalities and depression-like behavior** with long-term olanzapine-treatment *in rats*.

In summary, add-on GLP-1 receptor agonists promise novel alternatives to counteract long-term antipsychotics associated behavioral and metabolic complications.

Glucagon-like peptide-1 agonists combating clozapine-associated obesity and diabetes

Karla Mayfield, Dan Siskind, Karl Winckel, ...
J Psychopharmacol. 2016 Mar;30(3):227-36. doi: 10.1177/0269881115625496.

- Recent studies suggest that glucagon-like peptide-1 (GLP-1) may play a key role in clozapine's metabolic effects, possibly ***suggesting*** that ***clozapine-associated obesity and diabetes are mediated independently through reduced GLP-1.***
  - As a result, GLP-1 agonists could show promise in reversing antipsychotic-induced metabolic derangements, providing mechanistic justification that they may represent a novel approach to treat, and ultimately prevent, both diabetes and obesity in patients on clozapine.
  - GLP-1 agonists are already used for diabetes, and they provide a unique combination of glycemic improvement and metabolically relevant weight loss in diabetic and non-diabetic patients, in the context of a currently favorable safety profile.
- **Using GLP-1 agonists for clozapine-associated obesity and diabetes** could be a potentially effective intervention that ***may reduce cardiometabolic morbidity and mortality*** in this vulnerable patient population.

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

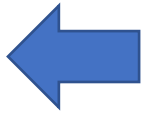
JAMA Psychiatry. 2017;74(7):719-728. doi:10.1001/jamapsychiatry.2017.1220

Randomized clinical trial of 103 patients with schizophrenia spectrum disorders treated with clozapine or olanzapine (*at least 6 months on* clozapine or olanzapine)

- Participants randomly assigned in a double-blind fashion, to 16 weeks of treatment with either subcutaneously injections of liraglutide or placebo prefilled pen injectors (up-titration schedule of 0.6 mg per week to 1.8 mg (remained at 1.2 mg week if intolerant of higher dosages)
  - In the liraglutide group, 30 participants (63.8%) changed status ***from prediabetes to normal glucose tolerance*** compared with 8 (16.0%) in the placebo group, corresponding to a *number needed to treat of 2*.
  - The liraglutide group had ***significantly reduced glycated HbA1c*** level compared with the placebo group.
  - An ***increased C-peptide secretion and a decreased glucagon secretion*** during the oral glucose tolerance test was found with liraglutide compared with placebo indicated an **increased beta cell function**

Table 2. Change in End Points From Baseline to Week 16[a]

Characteristic	Liraglutide Treatment Group (n = 47)	Placebo Treatment Group (n = 50)	Estimated Treatment Difference, Liraglutide vs Placebo (95% CI)[b]	*P* Value[c]
Clinical, mean (SE)				
Body weight, kg	−4.7 (0.5)	0.5 (0.7)	−5.3 (−7.0 to −3.7)	<.001[d]
Waist circumference, cm	−4.0 (0.6)	0.5 (0.7)	−4.1 (−6.0 to −2.3)	<.001[d]
BMI	−1.6 (1.2)	0.08 (0.2)	−1.8 (−2.4 to −1.3)	<.001[d]
Systolic blood pressure, mm Hg	−1.4 (2.0)	1.1 (1.8)	−4.9 (−9.5 to −0.3)	.04
Diastolic blood pressure, mm Hg	0.5 (1.5)	2.4 (1.1)	−3.0 (−6.8 to 0.9)	.13
Prediabetes status, No. (%)[e]	−30 (63.8)	−8 (16.0)	9.2 (2.6 to 32.7)	<.001[d]
Elevated fasting plasma glucose level	−13 (85.7)	−6 (40.0)	2.1 (0.9 to 3.3)	<.001[d]
Elevated glycated hemoglobin level	−5 (83.3)	0 (0.0)	NA (too few events)	NA (too few events)
Impaired glucose tolerance	−28 (37.8)	−6 (12.5)	2.1 (0.8 to 3.5)	.002[d]
Glucose metabolism				
Glycated hemoglobin level, %	−0.2 (0.04)	0.06 (0.04)	−0.2 (−0.3 to −0.1)	<.001[d]
Fasting plasma glucose level, relative change	0.90	0.99	0.90 (0.88 to 0.95)	<.001[d]
Fasting C-peptide level, mean (SE), ng/mL	0.26 (0.15)	−0.20 (0.16)	0.46 (−0.02 to 0.94)	.06
Fasting glucagon level, mean (SE), pg/mL	−4.6 (2.4)	2.0 (2.8)	−4.7 (−8.6 to −0.05)	.02
Insulin resistance[f]	1.02	0.96	1.08 (0.96 to 1.22)	.21
Beta cell function[f]	1.28	0.99	1.29 (1.18 to 1.42)	<.001[d]
Insulin sensitivity[f]	0.99	1.04	0.93 (0.82 to 1.06)	.26
2-h, 75-g OGTT value	0.47	0.95	0.77 (0.70 to 0.85)	<.001[d]
Body composition				
Visceral fat, mean (SE), g	−315.8 (75.3)	−24.0 (41.7)	−250.19 (−459.9 to −40.5)	.02
Android to gynoid fat ratio	0.99	1.01	0.98 (0.94 to 1.01)	.23
Total body fat	0.91	0.99	0.96 (0.94 to 0.99)	.01
Cholesterol level				
Total, mean (SE), mg/dL	−19.3 (3.5)	3.5 (3.1)	−19.3 (−30.9 to −7.7)	<.001[d]
LDL, mean (SE), mg/dL	−15.4 (3.1)	−2.3 (1.9)	−15.4 (−23.2 to −7.7)	<.001[d]
HDL	0.95	0.99	0.96 (0.90 to 1.03)	.27
VLDL	0.94	0.94	0.93 (0.79 to 1.10)	.39



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Outcomes:

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

Antipsychotic-Induced Weight Gain (AIWG)

- Antipsychotic-induced weight gain and metabolic disturbances are ***most profound at the beginning of treatment***
- Interventions for antipsychotic-induced weight gain and metabolic disturbances have been examined
  - Several meta-analyses of adjunct pharmacologic intervention to antipsychotic medications found **metformin** hydrochloride to be superior to placebo but only induced a body weight loss of ~3 kg for 2 to 4 months.
  - In meta-analyses of other interventions, such as ***adjunctive treatment with topiramate***, ***switch of antipsychotic medication***, and ***behavioral interventions***, had similar or *smaller effects* and *less consistent improvements* across metabolic parameters
  - further research is needed to **determine whether liraglutide can be used as a *preventive* adjunctive treatment during the *emergence* of weight gain** and metabolic abnormalities.

Take Home Summary

- Think about – could it be antipsychotic-induced or exacerbated hyperglycemia (weight gain, dyslipidemia)?
- Screen and monitor patients on these agents
  - Clozapine and olanzapine are considered the worst offenders for contributing to hyperglycemia, dyslipidemia, and weight gain
  - higher odds ratios in *younger* patients, at least for olanzapine and risperidone (<50 yo, especially <40 yo; less >60 or 70 yo cohorts)) – contribute to *premature CVD and mortality*
- Metformin treatment shown to help reduce AIWG/ some weight loss
- GLP1 RA medications – promising studies – anecdotal reports
  - Shown to improve glycemia in patients with atypical antipsychotic associated diabetes
  - More studies needed on using it early on to *prevent* weight gain

Pre-Question

2) Diabetes occurring in association with Zyprexa (olanzapine) :

A. Is entirely due to olanzapine-induced weight gain
B. Is more common in younger patients <40 or 50 and less common >60
C. Is usually mild and gradual in onset
D. Can be severe and result in DKA

- A and B
- B and C
- B and D
- C and D
- A, B, and D
- B, C and D
- All of above

Efficacy of Metformin in Type II Diabetes

Garber, A. J., Duncan, T. G., Goodman, A. M.,…The American Journal of Medicine, 103(6), 491–497. https://doi.org/10.1016/s0002-9343(97)00254-4

- Randomized, double-blind, placebo-controlled dose-response study (n=451)
- After 3-week, single-blind, placebo-controlled washout phase, patients received 500, 1000, 1500, 2000, or 2500mg metformin daily x 8 wks (minimum)
  - Dose titrated weekly to target
  - 500mg once daily; 500mg BID; 500mg TID; 1000mg BID; 1000mg w/breakfast/dinner and 500mg w/lunch
- Primary outcome:
  - Antihyperglycemic activity of metformin is generally dose-dependent
  - Well tolerated beyond digestive disturbances
  - Most patients achieve maximal efficacy at a daily dosage of 2000mg (1000mg BID)

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TABLE II

Adjusted Mean Changes from Baseline in Glucose Variables During Double-Blind Treatment

Variable	Placebo (n = 79)	Metformin Dose (mg) 500 (n = 73)	1000 (n = 73)	1500 (n = 76)	2000 (n = 73)	2500 (n = 77)
Fasting plasma glucose (mg/dL)						
Week 7	+0.4	−24**	−41***	−49***	−84***	−62***
Week 11	−8	−29*	−43**	−52***	−88***	−73***
Endpoint	−8	−27†	−39**	−49***	−86***	−70***
HbA_{1c} (%)						
Week 7	+1.1	+0.4**	−0.01***	−0.3***	−0.5***	−0.1***
Week 11	+1.2	+0.2***	−0.1***	−0.6***	−0.9***	−0.5***
Endpoint	+1.2	+0.3**	+0.01***	−0.5***	−0.8***	−0.4***

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ for mean difference from placebo, adjusting for center effect in linear model.
† $P = 0.054$ for mean difference from placebo, adjusting for center effect in linear model.