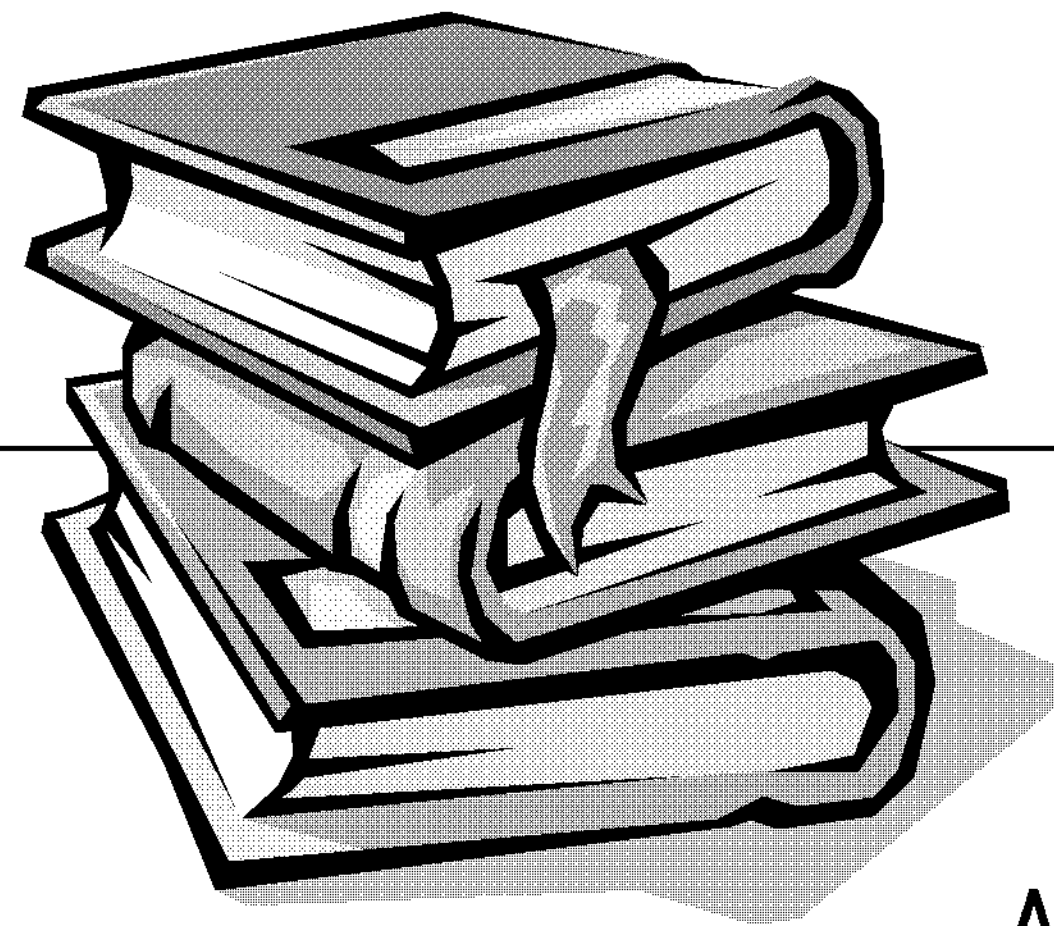

Quetiapine, Risperidone, and Ziprasidone: Metabolic Abnormalities

A literature review



Lilly

Answers That Matter.

“Facts and Comparisons”^{1,2,3}

■ **Quetiapine (Seroquel®)**

- Indication: Schizophrenia and Bipolar Mania
- MOA: Antagonist at dopamine D_{1,2}; serotonin 5-HT_{1a,2}; H₁ receptor; adrenergic $\alpha_{1,2}$

■ **Risperidone (Risperdal®)**

- Indication: Schizophrenia and Bipolar Mania
- MOA: Antagonist at dopamine D₂ and serotonin 5-HT₂

■ **Ziprasidone (Geodon®)**

- Indication: Schizophrenia
- MOA: Antagonist at dopamine D₂ and serotonin 5-HT_{2a, 1d} receptor; adrenergic α_1 ; moderate H₁ receptor activity; 5-HT_{1a} receptor agonist

Yu BP, et al.²⁹

FACTS TO CONSIDER...

- Incidence of diabetes in patients with schizophrenia and bipolar disorder is 2-4 times greater than in the general population.
- Increased rates of insulin resistance and glucose dysregulation were noted in psychiatric patients even before the introduction of antipsychotic or mood-stabilizing drugs.
- The true question in our hands → Maybe antipsychotic therapy is not the risk factor for diabetes, but rather the disorder it is treating predispose patients to be at a greater risk for developing diabetes???
- GA Maguire and colleagues studies olanzapine in stuttering and found NO worsening of fasting blood glucose levels.

Metabolic Abnormalities

- **Weight gain:** multifactorial process involving serotonergic, histaminergic, and/or adrenergic neurotransmission
 - Antipsychotic drugs with high affinity for H₁ receptor are associated with significant weight gain → deemed most likely molecular target responsible for drug-induced weight gain
 - Blockade of 5-HT_{2c} receptor that controls appetite and body weight however variable effects, not a good predictor
 - Dose-related vs. non-dose related elevations
- **Lipid abnormalities:** exact mechanism unknown
 - Increases in serum triglycerides (some trials)
 - Due to increases in body weight?
- **Glucose abnormalities:** numerous mechanisms proposed
 - Impaired glucose tolerance
 - Increases in body weight → increased serum glucose levels

Atypical Antipsychotics & Metabolic Abnormalities⁴

Drug	Weight Gain	Risk for diabetes	Worsening lipid profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
*Aripiprazole	+/-	+	--
*Ziprasidone	+/-	--	--

+ = increase effect; -- = no effect; **D** = discrepant results; * Newer drugs with limited data

Weight Gain



- Weight gain assessed using two parameters in most trials:
 - Clinically significant weight gain: $\geq 7\%$ increase from baseline
 - Mean body weight change from baseline

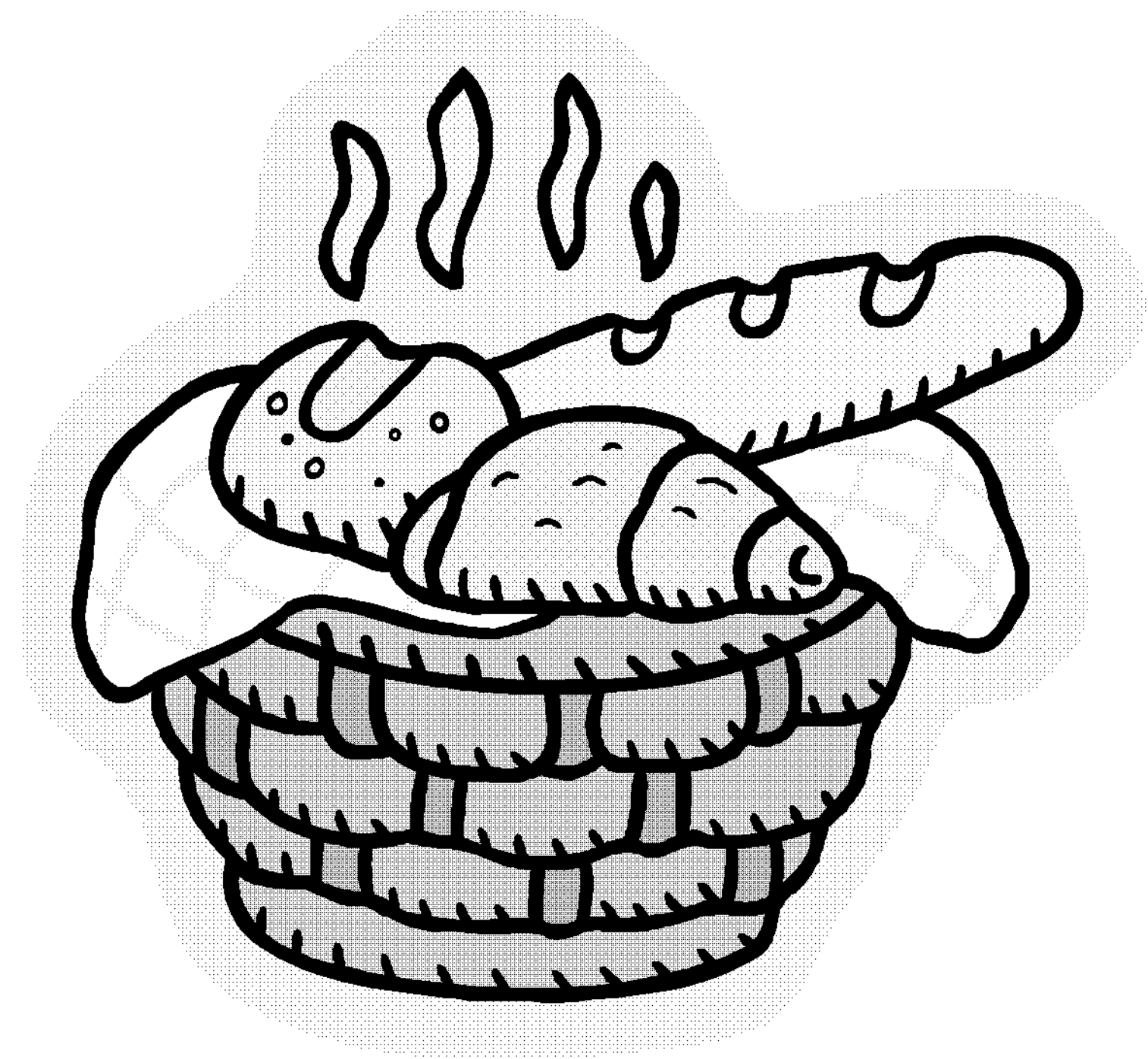
Glucose and Lipid Abnormalities

■ Pre-diabetic hyperglycemia

- Increases in glucose
- Insulin intolerance

■ Hyperlipidemia

- Increases in total cholesterol
- Increases in triglycerides
- Increases in LDL



Let us get started with...



Kingsbury SJ, *et al.*⁶

- Objective: Examined the effects of ziprasidone on body mass index (BMI) and serum levels of glucose, cholesterol, and triglycerides
- Methods: 6 week, randomized, multi-center, flexible-dosing, comparator switching study (n=37)
 - All patients started on ziprasidone 40mg BID on day 1 and d/c previous antipsychotic by day 7
 - Only 15 patients previously treated with olanzapine
- Results:
 - Weight gain
 - Prior to start, no differences in BMI based on previous meds
 - No significant change in BMI during 6 week trial
 - No differential changes based upon patients' previous medication

Continued →

Kingsbury SJ, *et al.*⁶

■ Results (cont'd)

■ Glucose changes

- Serum glucose levels did not significantly change during 6-weeks
- Neither previous meds, 6-week trial, nor interaction of previous meds with the 6-week trial significantly affected glucose levels.

■ Lipid changes

- Serum cholesterol levels significantly decreased ($p < 0.001$) from baseline
- Serum TG levels significantly decreased ($p = 0.018$) from baseline

■ Author note: Decrease in cholesterol levels was independent of change in BMI

Weiden PJ, et al.⁷

- Objective: Efficacy and tolerability when switching to ziprasidone
- Methods: 6 week, open-label, multi-center (n=270), pooled-analysis of 3 separate 6 week studies (only difference was previously used antipsychotic med)
- Results:
 - Weight data
 - Mean body weight decreased significantly in patients switched from olanzapine to ziprasidone ($p<0.0001$)
 - Mean weight loss → women = 1.85kg; men = 1.58kg ($p<0.0001$)
 - BMI significantly decreased in olanzapine group ($p<0.0001$)
 - Mean body weight decreased significantly in patients switched from risperidone to ziprasidone (-0.86kg; $p<0.02$) and significant drop in BMI too.
 - Prior treatment with conventionals → mean body weight INCREASE of 0.27kg ($p=0.3$) and mean increase in BMI of 0.08 ($p=0.33$)

Weiden PJ, *et al.*⁷

■ Results: (cont'd)

- Lipid changes
 - Non-fasting TG and TC levels decreased significantly from baseline to endpoint in patients switched from olanzapine or risperidone to ziprasidone
 - Median changes in TG
 - Olanzapine = -50mg/dL (p<0.0001)
 - Risperidone = -29mg/dL (p<0.01)
 - Median changes in TC
 - Olanzapine = -17mg/dL (p<0.0001)
 - Risperidone = -12mg/dL (p<0.005)
 - Note: TC levels declined in 76% of patients switched from olanzapine, 72% of those switched from risperidone

Fryburg DA, *et al.*⁸

- Objective: Determine effects of ziprasidone and olanzapine on weight, lipids, and metabolic parameters associated with insulin resistance in schizophrenic patients
- Methods: 6-week, double-blind, randomized, acute inpatients (n=92)
- Results
 - Body weight
 - Median body weight after treatment significantly higher in olanzapine group (3kg) than ziprasidone group (0.5kg) (p=0.0001)
 - Insulin and insulin resistance
 - Median fasting plasma insulin increased by 5.6μU/mL in olanzapine group vs. 0.9μU/mL in ziprasidone group (p=0.001)
 - However, is this clinically significant??

Fryburg DA, *et al.*⁸

■ Results (cont'd)

- No significant changes from baseline in fasting glucose were observed in either group of patients.
- Lipid changes (all significant)
 - Fasting TC (p<0.001)
 - Olanzapine = +18mg/dL
 - Ziprasidone = -5.5mg/dL
 - Fasting LDL (p=0.023)
 - Olanzapine = +12mg/dL
 - Ziprasidone = -5.5mg/dL
 - Fasting HDL (p=0.0049)
 - Olanzapine = -1mg/dL
 - Ziprasidone = -4mg/dL
 - Fasting TG (p=0.029)
 - Olanzapine = +28mg/dL
 - Ziprasidone = +1mg/dL

Simpson GM, *et al.*⁵

- Objective: Safety, efficacy, and tolerability of ziprasidone vs. olanzapine
- Methods: 6 week, double-blind, multi-center, inpatient, randomized (n=269)
 - Ziprasidone 40-80 mg BID (n=136)
 - Olanzapine 5-15 mg QD (n=133)
- Results
 - Weight gain ($p < 0.0001$)
 - Olanzapine = 3.57kg
 - Ziprasidone = 0.93kg
 - Lipid Changes
 - Fasting TC → Ziprasidone = -1mg/dL vs. olanzapine = +20mg/dL ($p < 0.0001$)
 - Fasting LDL → Ziprasidone = -1mg/dL vs. olanzapine = +13mg/dL ($p = 0.0004$)

Simpson GM, *et al.*⁹

- Objective: Continuation data from previously reviewed trial
- Results:
 - Weight gain/loss (p=0.001)
 - Olanzapine = +4.72 kg
 - Ziprasidone = -1.31 kg
 - Insulin and Glucose
 - Mean fasting insulin levels increased by 2.0mU/mL with olanzapine and by 1.0 mU/mL with ziprasidone → no significance between two groups
 - Mean fasting plasma glucose increased by 5mg/dL with olanzapine and by 2mg/dL with ziprasidone → no significance between two groups
 - Serum Lipids
 - Treatment with olanzapine significantly increased median TC vs. baseline (+13; p<0.05). No significant change in ziprasidone group
 - Fasting LDL levels increased significantly in olanzapine group (+17; p<0.05) but not in ziprasidone (+9; p=ns) → no significance between two groups

Addington D, *et al.* ¹⁰

- Objective: Efficacy and tolerability of ziprasidone and risperidone in the treatment of acute exacerbation of schizophrenia or schizoaffective disorder
- Methods: 52 week, randomized, comparative (n=296)
- Results:
 - Mean weight gain/loss during initial treatment period (8 weeks)
 - Risperidone
 - Men = +1.36kg
 - Women = +2.27kg
 - Ziprasidone
 - Men and women = -0.45kg
 - 44 week continuation
 - Risperidone
 - Men and women ~ +3.8 kg
 - Ziprasidone
 - Men = +0.1 kg
 - Women = +0.5 kg

Cohen S, *et al.* ¹¹

- Objective: Study effects of ziprasidone in individuals with mental retardation and maladaptive behavior
- Methods: 24-week, switch from another agent (70% previously on risperidone, 5% on olanzapine), tracked weight trends 6 months prior to study, caloric consumption monitored, all blood tests were fasting (n=40)
- Results:
 - Weight gain 6 months prior to trial = 1.8kg
 - 6 months after ziprasidone initiation = -3.6kg (p<0.0001)
 - Additional changes defined on next slide (Table 1)

Cohen S, et al. ¹¹

Table 1: Weight, lipid and glucose levels in patients receiving ziprasidone

Measure	N	Mean @ Baseline	Mean @ 6 months after ziprasidone addition	P value
*Weight (lb)	40	169.2	161.1	P<0.0001
*Cholesterol (mg/dL)	30	200.5	176.4	P=0.032
*Triglycerides (mg/dL)	29	147.8	123.4	P=0.035
Glucose (mg/dL)	27	87.0	83.4	P=0.498
LDL (mg/dL)	19	113.9	110.7	P=0.555
HDL (mg/dL)	19	41.3	41.5	P=0.885

*Statistically significant decreases

Note: During 6 months prior to study, caloric restriction due to weight gain. Upon initiation of ziprasidone, caloric restriction lifted and some patient's intake doubled. One patient lost 25 lbs in the first month after switching to ziprasidone.

Kane JM, *et al.* ¹²

- Objective: Efficacy and safety of olanzapine compared with ziprasidone
- Methods: 28-week, multi-center, randomized, double-blind, parallel, in- and outpatients (n=548)
 - Olanzapine 10-20 mg/day
 - Ziprasidone 80-160 mg/day
- Results: Table 2 (next slide)
- Study conclusion: Authors concluded that olanzapine resulted in significantly better improvement in psychopathology than ziprasidone. Despite the fact that olanzapine had greater weight gain and elevated lipids, ziprasidone patients experienced significantly more EPS and treatment-emergent adverse effects.

Kane JM, et al. ¹²

Table 2: Mean change from Baseline to Endpoint in Weight, Glucose, and Lipids

Measure	Therapy	N	Mean @ baseline	Endpoint Change	P value
Weight (kg)	OLZ	269	77.7	3.06	P<0.001
	ZIP	260	77.1	-1.12	
Fasting Glucose (mmol/L)	OLZ	261	5.27	0.26	P=0.485
	ZIP	244	5.31	0.00	
TC	OLZ	250	4.99	0.09	P<0.001
	ZIP	241	4.97	-0.31	
HDL	OLZ	246	1.24	-0.07	P<0.001
	ZIP	239	1.21	0.03	
LDL	OLZ	235	3.01	0.04	P=0.005
	ZIP	233	3.01	-0.25	
TG	OLZ	250	1.63	0.36	P<0.001
	ZIP	241	1.66	-0.23	

Hirsch SR, *et al.* ¹³

- Objective: Compare ziprasidone with the conventional antipsychotic haloperidol in outpatients with stable schizophrenia.
- Methods: 28-week, randomized, double-blind, multi-center, parallel-group, flexible dosing (n=301)
 - Ziprasidone 80-160 mg/day
 - Haloperidol 5-15 mg/day
- Results: Similar results in both treatment groups
 - Ziprasidone = +0.31kg
 - Haloperidol = +0.22 kg

Atypical Antipsychotics & Metabolic Abnormalities⁴

ADA/APA Guidelines

Drug	Weight Gain	Risk for diabetes	Worsening lipid profile
Clozapine	++++	+	+
Olanzapine	++++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
*Aripiprazole	+/-	+	--
*Ziprasidone	+/-	--	--

Suggested Effects

Drug	Weight Gain	Risk for diabetes	Worsening lipid profile
Clozapine	++++	+	+
Olanzapine	++++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
*Aripiprazole	+/-	+	--
*Ziprasidone	+/-	*+	--

+ = increase effect; -- = no effect; **D** = discrepant results; * Newer drugs with limited data

*There is little long-term data with glucose control and insulin resistance but short-term studies (<6 months) show no differences compared to olanzapine

Continuing on with ...



AND



File name/location

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www.seroquel.com, www.risperdal.com

Atypical Antipsychotics & Metabolic Abnormalities⁴

ADA/APA Guidelines

Drug	Weight Gain	Risk for diabetes	Worsening lipid profile
Clozapine	++++	+	+
Olanzapine	++++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
*Aripiprazole	+/-	+	--
*Ziprasidone	+/-	--	--

Suggested Effects

Drug	Weight Gain	Risk for diabetes	Worsening lipid profile
Clozapine	++++	+	+
Olanzapine	++++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
*Aripiprazole	+/-	+	--
*Ziprasidone	+/-	+	--

+ = increase effect; -- = no effect; **D** = discrepant results; * Newer drugs with limited data

Note: We will address diabetes risk and lipid profile. Weight gain has previously been established.

Reinstein MJ, *et al.* ¹⁴

- Objective: Assess changes in weight and diabetes status for patients initially treated with clozapine who developed diabetes and who were then switched to clozapine-quetiapine combination therapy
- Methods: 10-month, open-label, non-randomized, retrospective comparative study (n=65, only 13 had developed diabetes)
- Results: (In terms of glycemic control)
 - 20% of diabetic patients showed significant clinical improvement
 - HgBa1c levels dropped to normal (<7%) with combination therapy by the end of the study (A1c's had increased to 10-15% with clozapine monotherapy)
 - Weight loss in 13 diabetic patients = -4.68kg (10.3lbs)
 - Normalization of blood glucose at end of 10 months for majority of patients
 - Decreases in insulin requirements
 - Discontinuation of insulin with addition of oral hypoglycemic agent
 - 3 patients discontinued oral agent and were maintained on diet alone

Sussman N, *et al.* ¹⁵

- Objective: Review article assessing weight changes and diabetes incidence with atypical antipsychotics

- Results:

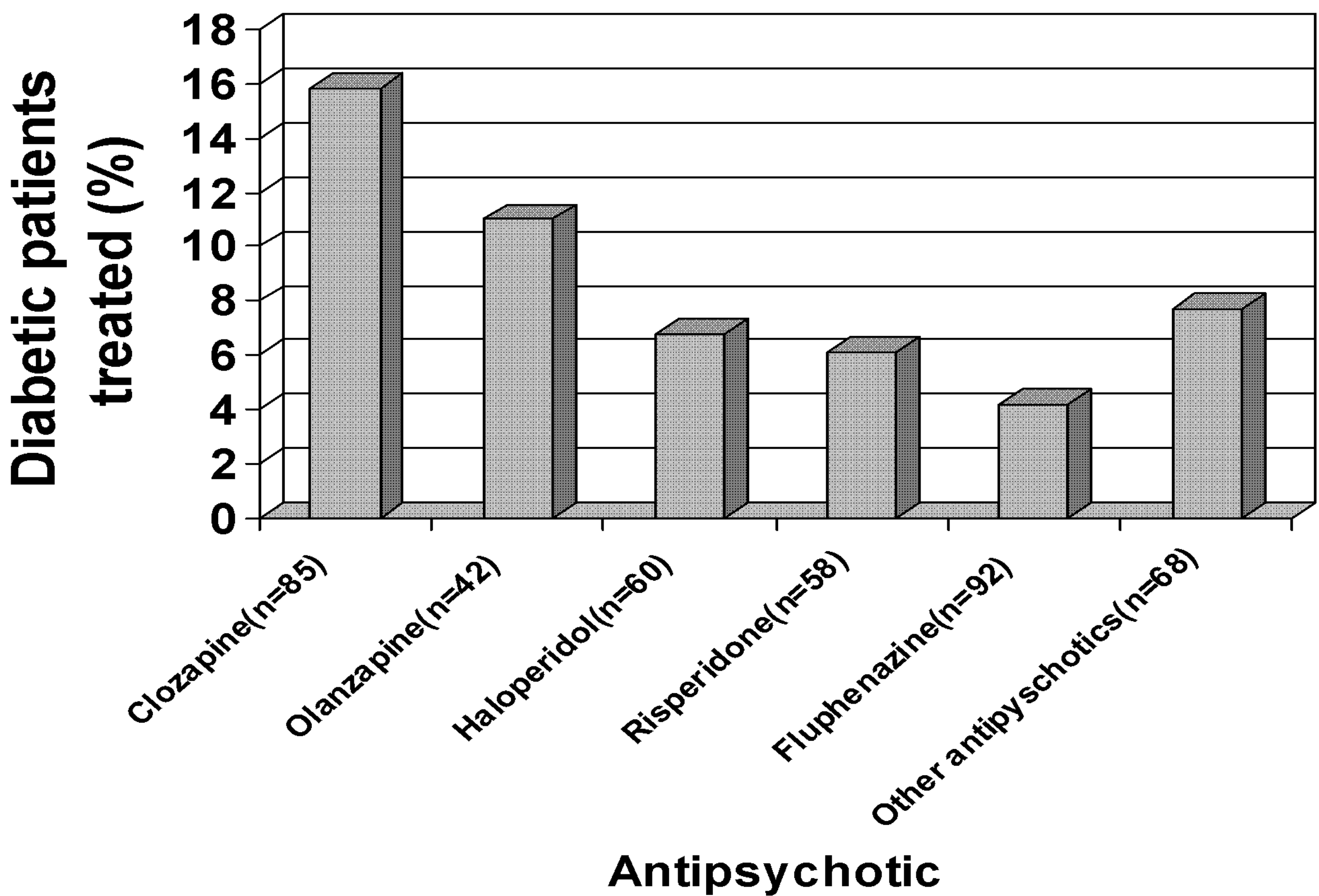
- Quetiapine not sufficiently studied to make conclusive statements on association with diabetes mellitus → available data suggests treatment does not confer a measurable risk of developing Type II DM.
- Clinical trials and post-marketing surveillance data shows NO relationship between treatment and development of Type II DM.
- Phase II/III clinical trials (n=1,256) → <1% incidence of diabetes mellitus, hyperglycemia, and other symptoms associated with deleterious changes in glucose metabolism.
- Of the atypical's, risperidone, followed by quetiapine, was associated with the lowest risk of diabetes in patients older than 40 years of age. Prevalence of DM was similar for clozapine, olanzapine, risperidone, and quetiapine in younger patients.¹⁶

Zoler M.¹⁷

- Objective: Compare prevalence of DM in patients receiving different neuroleptics
- Methods: All outpatients with schizophrenia treated with selected drugs over 4 months reviewed
- Results:
 - Under 40-age group → odds significantly greater for all atypicals
 - 40-49 age-group → Clozapine, olanzapine, or quetiapine associated with significantly increased odds for having diagnosis of diabetes but risperidone was not.
 - 50-59 age-group → Only olanzapine and risperidone were associated with significantly increased prevalence of diabetes diagnosis
 - 60-69 age-group → Clozapine associated with a significantly decreased prevalence

Zoler M.¹⁷

Table 3: Proportion of patients with Type II DM according to medication



Wirshing DA, *et al.* ¹⁸

- Objective: Determine the relative liability of an individual novel antipsychotic to affect glucose and lipid levels.
- Methods: Retrospective chart review (n=590, only 215 included due to adequate data), average patient overweight (BMI >25kg/m²)
 - Clozapine n=39
 - Olanzapine n=32
 - Risperidone n=49
 - Quetiapine n=13
 - Haloperidol n=41
 - Fluphenazine n=41

Wirshing DA, *et al.* ¹⁸

■ Results

- Glucose
 - No significant increases b/w those patients receiving risperidone and quetiapine, yet all agents had a significant increase compared to typicals
- Total Cholesterol
 - Risperidone patients → significant decrease from baseline (-6%; p=0.04)
 - Four patients (13%) of olanzapine required addition of lipid-lowering therapy.
- Triglycerides
 - Olanzapine patients → significant increase from baseline (+38%; p=0.02)
- LDL
 - Olanzapine, quetiapine, and risperidone → significant decreases in mean LDL (-14%; p=0.03 olanzapine) (-11%; p=0.006 risperidone) (-13%; p=0.04 quetiapine)

Wirshing DA, et al. ¹⁸

Table 4: Percentage of Patients with Clinically Significant Changes in Glucose and Lipid Values.

Value (mg/dL)	<u>Olanzapine</u>		<u>Risperidone</u>		<u>Quetiapine</u>		p-value
	N	%	N	%	N	%	
Glucose \geq 126	6/22	27.3	9/25	36.0	1/8	12.5	0.5
Glucose \geq 200	1/22	4.6	2/25	8.0	0/18	0	0.8
Cholesterol \geq 200	5/20	25.0	4/19	21.1	2/8	25.0	0.4
Triglycerides \geq 200	5/13	38.5	5/16	31.3	2/5	40.0	0.0002
LDL \geq 160	1/13	7.7	0/16	0	0/6	0	0.3
HDL $<$ 35	5/22	22.7	1/22	4.6	1/8	12.5	0.1

* Clinically significant changes are defined in the chart above

Meyer JM, *et al.* ¹⁹

- Objective: Evaluate novel antipsychotics and their association with hyperlipidemia
- Methods: Case series, retrospective over 1 year, inpatient facility (n=46 cases referred with severe hypertriglyceridemia >600, only 14 included in review)
- Results:
 - Year's monthly avg. = 172 patients receiving olanzapine, 50 receiving quetiapine
 - 9/14 (64%) patients had prior history of TG increases of >200mg/dL at some point in their hospitalization
 - Overall mean weight gain 11.8lb (p<0.02), only 6.25lb for newly onset DM cases
 - ↑ serum TG NOT correlated with weight ↑ nor antipsychotic dosage schedule
 - 7 patients (6 olanz, 1 quet) TG>1,000mg/dL → 3 developed new-onset DM, 1 pre-existing DM
 - 5/7 (71%) had prior history of high TG → Question: Do novel antipsychotics primarily aggravate this condition rather than cause it?

L'Italien GJ, *et al.* ²⁰

- Objective: Determine the contributions of olanzapine and risperidone on body weight and diabetes
- Methods: case-control (n=744; 112 olanzapine, 150 risperidone, 482 typicals)
- Results:
 - Total of 96 cases of new-onset diabetes identified (16 olanzapine, 10 risperidone, 70 typicals [controls])
 - Significantly more olanzapine cases compared to typical control (14.3% vs. 7.3%; p=0.015)
 - No significant difference in # of risperidone cases compared to typicals (6.7% vs. 7.3%; p=0.805)
 - Weight gain of 10lbs or more was seen at a higher rate in both olanzapine (54.5%) and risperidone (50%) compared to typicals (30.3%; p<0.001)
 - Authors conclusions: Olanzapine associated with clinically significant weight gain and onset of diabetes while risperidone was only associated with significant weight gain.

Other trials, data, and opinions...

- Yu and colleagues²⁹: Chart review of established diabetic patients (n=22)
 - No significant differences b/w medications were found to suggest that one atypical agent had a greater effect on glucose regulation than another.
 - All 3 agents (olanz, risp, quet) showed improvement in blood glucose levels (p=0.01).
 - Conclusion: Atypical agents not associated with worsening of DM in patients with preexisting disease.

- Lee and colleagues²⁸: Cohort study, non-diabetic patients initiated on atypical or typical antipsychotic therapy, determine 1yr relative risk of developing DM (n=2315)
 - Patient medications: Olanzapine = 38.5%; Risperidone = 56.2%
 - 1-yr rate of DM onset nearly identical for atypical (3%) and typical (3.2%) groups (p=0.8237)
 - Conclusion: Determination of atypical therapy should not be based on concern for development of DM.

Other trials, data, and opinions...

- Ollendorf and colleagues²⁶: Retrospective, claims data used to determine rate of new-onset diabetes b/w conventional and atypical agents (n=1316)
 - Crude incidence of DM did not differ b/w two agents (2.46% atypical vs. 2.76% conventional agents; p=0.525)
 - Hazard ratio 1.17 → atypical agents significant, moderate increased risk of DM relative to conventional agents
 - No significant differences in DM among atypical agents

- Lage and colleagues²²: Retrospective analysis, rate of new-onset (n=6440)
 - No evidence of a higher probability of becoming diabetic b/w two agents (atypical vs. conventional)
 - No significant difference b/w olanzapine/risperidone and conventional agents
 - Fewer new DM cases with olanzapine vs. risperidone, but not significant

Other trials, data, and opinions...

- Caro and colleagues²¹: Retrospective database analysis (n=33,946)
 - 20% increased risk of DM with olanzapine vs. risperidone (p=0.05)
 - First 3 months of olanzapine treatment associated with increased risk of DM of 90% (p<0.001)

- Gianfrancesco and colleagues²⁷: Retrospective claims data (n=7933)
 - Risperidone patients were no more likely to acquire or exacerbate DM than untreated patients.
 - Olanzapine, clozapine, and conventionals had a significantly greater risk of developing DM than untreated patients.

Other trials, data, and opinions...

- Sernyak and colleagues¹⁶: Retrospective claims data, VA hospital (n=38,632)
 - All atypicals (except risperidone) found higher odds of being associated with DM
 - Study did not control for preexisting DM or the level of patient exposure to each of the antipsychotic medications
 - Patients < 40 years of age were associated with a significant increased prevalence of DM despite the atypical agent in use.

Summary

■Risperidone:

- After my literature review, I feel as though it would be reasonable to add a “+/-” defined as a possible increased risk for diabetes or no effect in terms of risk of diabetes. The data available provides mixed information, however, more favors this addition to the chart.
- At this point in time, I don’t feel there is sufficient data to make a conclusion on risperidone’s effects on lipids. The data is sparse and not well defined. I will leave a “D” for discrepant data.

■Quetiapine:

- Currently, I feel as though the little data available supports the chart addition of “+/-” or possible increased or no effect in terms of risk of diabetes. However, more long-term data is needed to make a final conclusion.
- At this point in time, I don’t feel there is sufficient data to make a conclusion on quetiapine’s effects on lipids. The data is sparse and not well defined. I will leave a “D” for discrepant data.

Atypical Antipsychotics & Metabolic Abnormalities⁴

ADA/APA Guidelines

Drug	Weight Gain	Risk for diabetes	Worsening lipid profile
Clozapine	++++	+	+
Olanzapine	++++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
*Aripiprazole	+/-	+	--
*Ziprasidone	+/-	--	--

Suggested Effects

Drug	Weight Gain	Risk for diabetes	Worsening lipid profile
Clozapine	++++	+	+
Olanzapine	++++	+	+
Risperidone	++	+/-	D
Quetiapine	++	+/-	D
*Aripiprazole	+/-	+	--
*Ziprasidone	+/-	+	--

+ = increase effect; -- = no effect; **D** = discrepant results; * Newer drugs with limited data

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