

# Clinical Practice Guidelines

## Antipsychotic Drugs, Weight Gain, and Diabetes

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**DISCLOSURE STATEMENT**

Dr. Casimir has received honoraria as a speaker and/or consultant for:

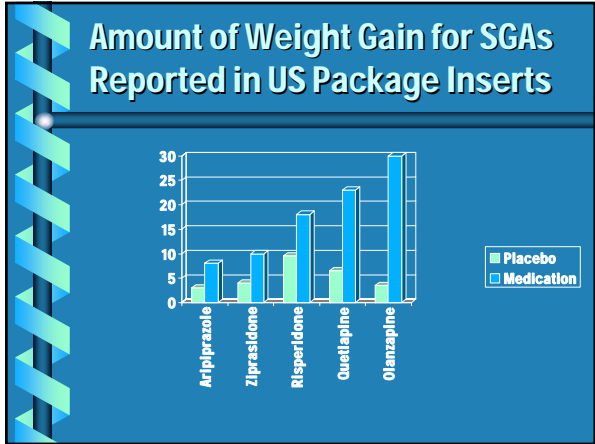
- Pfizer Inc.
- Abbott Laboratories
- Forest Pharmaceuticals
- Eli Lilly and Company

**Educational Objectives**

- Briefly consider current research data regarding the relationship between antipsychotic drugs and metabolism
- Review the Consensus Development Conference Paper on Antipsychotic Drugs, Obesity, and Diabetes
- Outline Clinical Practice Guidelines at MMHI and how they will be integrated into the clozapine/olanzapine DUE process

**The Impact of Second Generation Antipsychotics on Metabolism**

- Acute complications: diabetic ketoacidosis
- Intermediate-term complications: weight gain, glucose intolerance, insulin resistance (pre-diabetes), dyslipidemia
- Long-term complications: diabetes mellitus, hypertension, cardiovascular disease



## Consensus Development Conference on Antipsychotic Drugs, Obesity, and Diabetes

An expert panel was convened from November 19-21, 2003, with its purpose being to gain a better understanding of the relationship between the use of SGAs, weight gain, and associated metabolic abnormalities

## Who was represented on the conference panel?

- Ω American Diabetes Association
- Ω American Psychiatric Association
- Ω American Association of Clinical Endocrinologists
- Ω North American Association for the Study of Obesity

(Presentations were also made by representatives of the U.S. FDA, AstraZeneca, Bristol-Myers Squibb, Janssen, Eli Lilly, and Pfizer)

## Consensus positions were developed for the following questions:

- Ω What is the current use of SGAs?
- Ω What is the prevalence of obesity and metabolic abnormalities in populations in which SGAs are used?
- Ω What is the relationship between the use of SGAs and the incidence of obesity and/or diabetes?

## Questions (continued):

- Ω Given these risks, how should patients be monitored for development of weight gain, dyslipidemia, and diabetes, and how should they be treated if diabetes develops?
- Ω What research is needed to better understand the relationship between SGAs and weight gain, dyslipidemia, and diabetes?

### 1. What is the current use of antipsychotic drugs?

- Ω First-generation antipsychotics are still widely available, and are effective at treating positive symptoms of psychosis
- Ω FGAs are less effective at treating negative symptoms, cognitive impairment, and affective symptoms
- Ω Due to their better tolerability and efficacy, SGAs have become first-line agents in the treatment of psychotic illness

### 2. What is the prevalence of obesity and DM in the populations in which SGAs are used?

- Ω Data from most studies suggest that the prevalence of both diabetes and obesity among individuals with schizophrenia and affective disorders is approximately 1.5 to 2.0 times higher than in the general population
- Ω Methodologic limitations make it difficult to determine whether this relationship is more direct or indirect

### 3. What is the relationship between the use of SGAs and the incidence of metabolic abnormalities ?

Based on current data, three types of metabolic abnormalities have caused clinical concern:

- ∩ Weight Gain
- ∩ Diabetes
- ∩ Dyslipidemia

### SGAs and metabolic abnormalities

Drug	Weight gain	Risk for DM	Dyslipidemia
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole	+/-	--	--
Ziprasidone	+/-	--	--

### Weight Gain

- ∩ Treatment with SGAs can cause a rapid increase in body weight in the first few months of treatment which may not reach a plateau even after one year of treatment
- ∩ At 10 weeks of therapy, estimated average weight gain with drug treatment compared with placebo varies from 0.5 kg to 5.0 kg

### Diabetes Mellitus

- ∩ Numerous case reports have documented the onset or exacerbation of DM following initiation of therapy with SGAs
- ∩ Onset may occur as rapidly as within a few weeks of initiating drug treatment
- ∩ In some, but not all cases, hyperglycemia promptly resolved after the SGA was discontinued

### Diabetes (continued)

- ∩ Data consistently show an increased risk for diabetes in patients treated with clozapine or olanzapine
- ∩ The risk for patients taking risperidone and quetiapine is less clear; some studies show an increased risk for diabetes, while others do not

### Diabetes (continued)

- ∩ Aripiprazole and ziprasidone have relatively limited epidemiological data, but available clinical trial experience with these drugs has not shown an increased risk for diabetes
- ∩ Insulin resistance appears to be integrally related to development of hyperglycemia, but precise mechanism remains unclear

## Dyslipidemia

### Parameters of primary concern:

- ∩ Elevation of total cholesterol
- ∩ Increase in LDL cholesterol
- ∩ Elevation of triglycerides
- ∩ Decrease in HDL cholesterol

## 4. Given the above risks, how should patients be monitored and treated ?

### The consensus panel recommends :

- ∩ Baseline monitoring before, or as soon as clinically feasible after initiating SGA treatment
- ∩ Follow-up monitoring at 4, 8, and 12 weeks after initiating or changing SGA therapy, and quarterly thereafter

## Baseline monitoring

- ∩ Personal or family history of obesity, diabetes, dyslipidemia, hypertension, or cardiovascular disease
- ∩ Weight and height
- ∩ Waist circumference (at umbilicus)
- ∩ Blood pressure
- ∩ Fasting plasma glucose
- ∩ Fasting lipid profile

## Other considerations when initiating SGA pharmacotherapy

- ∩ If obesity, hyperglycemia, dyslipidemia, or hypertension are diagnosed, appropriate treatment should be initiated
- ∩ Nutrition and physical activity counseling
- ∩ In patients at risk for development of above conditions (e.g., poor diet, sedentary lifestyle, other medications), it may be preferable to initiate treatment with a relatively more weight - neutral SGA

## Follow-up monitoring

- ∩ The patient's weight should be reassessed at 4, 8, and 12 weeks after initiating or changing SGA therapy, and quarterly thereafter
- ∩ If a patient gains >5% of his or her initial weight at any time during therapy, one should consider switching the SGA

## Monitoring protocol for patients on SGAs (consensus guidelines)

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 yrs
Family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting glucose	X			X		X	
Fasting lipid profile	X			X			X

**IN SUMMARY, the panel recommends the following:**

- ⌚ Consideration of metabolic risks when starting SGAs
- ⌚ Patient, family, and caregiver education
- ⌚ Baseline screening
- ⌚ Regular monitoring
- ⌚ Referral to specialized services, when appropriate

**5. What additional research is needed in this area ?**

- ⌚ Better measures of body composition
- ⌚ Contribution of neuroendocrine function
- ⌚ Better studies of insulin sensitivity, beta cell function, and lipid metabolism

**Additional research (continued)**

- ⌚ Baseline characteristics and possible prediction of serious complications
- ⌚ Risks of SGA therapy in different ethnic groups
- ⌚ Relationship between psychiatric diagnosis and SGA side effects

**Additional research (continued)**

- ⌚ Alterations in energy intake and expenditure
- ⌚ CNS vs. peripheral actions of SGAs
- ⌚ Studies of genetic markers and possible relationships to SGA-associated metabolic disturbances (e.g. serotonin, histamine receptors)

**Clinical Guidelines at Mendota Mental Health Institute**

How do we assess and treat patients with SGA-associated metabolic disturbances at MMHI ?

**MMHI Clinical Practice Guideline: Metabolic Effects of Antipsychotic Medication**

MMHI standard of care with regard to SGAs and metabolic side effects is defined with regard to five basic areas

## 1. Consideration of metabolic risk factors when initiating SGA

- ∩ Obesity (BMI > 30)
- ∩ Glucose intolerance
- ∩ Diabetes Mellitus
- ∩ Dyslipidemia

## 1. Metabolic risk factors (continued)

- ∩ Hypertension
- ∩ Tobacco use
- ∩ Coronary artery disease
- ∩ Family history of coronary artery disease

## 2. Informed consent

- ∩ Careful documentation
- ∩ To include patient, family, and caregiver education

## 3. Baseline screening

- ∩ Weight
- ∩ Vital signs
- ∩ Fasting blood glucose
- ∩ Fasting lipid profile

## 4. Follow-up monitoring

- ∩ Weight (monthly)
- ∩ Vital signs (monthly)
- ∩ Fasting blood glucose (one month, 6 months, 12 months)
- ∩ Fasting lipid profile (one month, 6 months, 12 months)

## 5. Careful choice of SGA

- ∩ In patients at higher risk for weight gain, diabetes, or dyslipidemia (e.g. poor diet, limited exercise, or other medications), it may be preferable to initiate treatment with an SGA which appears to have a lower propensity for weight gain or metabolic side effects

## 5. Careful choice of SGA (continued)

∞ If a patient gains > 5% of his or her initial weight at any time during therapy, the attending physician should consider switching the SGA to a more weight-neutral SGA

## 5. Careful choice of SGA (continued)

∞ If a patient develops hyperglycemia or dyslipidemia while receiving antipsychotic therapy, one should consider switching to an SGA which has a lower propensity for inducing weight gain, diabetes, or dyslipidemia

## How do we monitor our practice at MMHI ?

Data are gathered and feedback is provided to physicians using the Drug Utilization Evaluation (DUE) process

## MMHI Clozapine/Olanzapine Drug Utilization Evaluation

- ∞ In 2001, MMHI Pharmacy and Therapeutics Committee data indicated that institute-wide, the most prevalent Adverse Drug Reaction was weight gain and metabolic abnormalities in patients receiving treatment with clozapine or olanzapine
- ∞ Based on this determination, a DUE was initiated to gather additional data in this area

## Standard MMHI DUE Protocol

- ∞ Pharmacy staff generates sample of patients (typically, n=20) using computerized database
- ∞ Using DUE instrument, charts are examined to determine whether based on agreed-upon criteria, the attending physician has deviated from recommended practice
- ∞ If criteria are met, peer review is undertaken by a P & T committee physician

## DUE protocol (continued)

- ∞ If P & T physician concurs, a letter is sent to the attending physician encouraging him/her to compare their practice to the standard of care adopted for MMHI
- ∞ Results are summarized and reported in Pharmacy and Therapeutics Committee

## Clozapine/Olanzapine Database Information Sheet

- Identifying data
- Height
- Date of clozapine or olanzapine initiation
- Recommended progress note
- Risk factors
- Serum testing results
- Weight (monthly)
- Vital signs (monthly)

## IN SUMMARY:

- Research data indicates a clear relationship between treatment with second generation antipsychotic medications and metabolic side effects such as weight gain, diabetes, and lipid abnormalities
- Evidence of such a relationship has also been found in patients at MMHI

## SUMMARY (continued)

- A Drug Utilization Evaluation has been undertaken by the MMHI Pharmacy and Therapeutics Committee to gather data regarding metabolic side effects of second generation antipsychotic medications

## SUMMARY (continued)

- Elements of the ADA/APA Consensus Guidelines have been adopted as a desirable standard of care for patients at Mendota Mental Health Institute

## CONCLUSION

- To facilitate assessment and management of weight gain and metabolic side effects associated with SGA pharmacotherapy, MMHI Clinical Practice Guidelines have been integrated into the Drug Utilization Evaluation process