

The Pharmacological Basis of Schizophrenia Treatment and Tolerability

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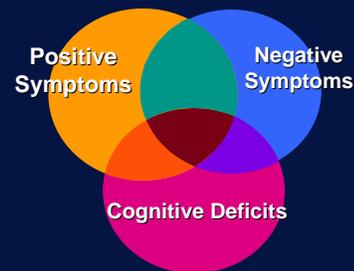
Learning Objectives

- ♦ Briefly describe schizophrenia, its manifestations, clinical course, and prognosis
- ♦ Review the diagnosis of schizophrenia, distinguishing between positive, negative and cognitive symptoms
- ♦ Discuss the different treatment options for schizophrenia, listing the atypical antipsychotics currently available on the market
- ♦ Understand the characteristics of antipsychotic medications and their different receptor effects
- ♦ Describe the tolerability of antipsychotics focusing on extrapyramidal symptoms and the metabolic syndrome

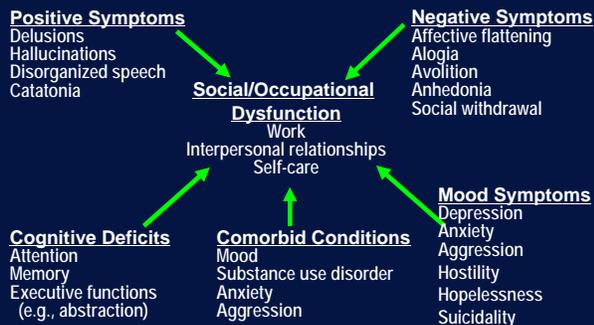
Definition of Schizophrenia

- ♦ A syndrome of disorganized and bizarre thoughts, delusions, hallucinations, inappropriate affect, impaired social functioning and cognitive deficits
- ♦ A complex disorder with many possible etiologies: biological, psychosocial, and environmental

Clinical Symptoms



Features of Schizophrenia



Diagnosis Multiaxial Assessment System

- ♦ **Axis I** Clinical Disorders
- ♦ **Axis II** Personality Disorders, Mental Retardation
- ♦ **Axis III** General Medical Conditions
- ♦ **Axis IV** Psychosocial and Environmental Problems
- ♦ **Axis V** Global Assessment of Functioning

Diagnostic and Statistical Manual of Mental Disorders (DSM) Fourth Edition; American Psychiatric Association (APA)

Diagnosis of Schizophrenia

- ◆ **DSM-IV-TR Diagnostic Criteria for Schizophrenia**
 - ◆ Characteristic symptoms; two or more of the following
 - ◆ Delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms
 - ◆ Social/occupational dysfunction
 - ◆ Duration of at least 6 months
 - ◆ Schizoaffective or mood disorder has been excluded
 - ◆ Disorder is not due to a medical disorder or substance abuse
 - ◆ History of pervasive developmental disorder

Diagnostic and Statistical Manual of Mental Disorders (DSM) Fourth Edition; American Psychiatric Association

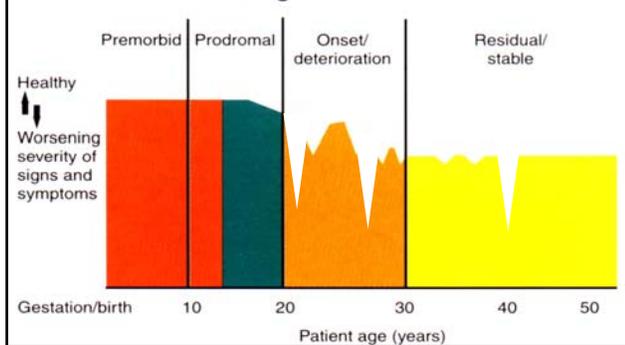
Epidemiology

- ◆ Lifetime prevalence ranges from 0.6%-1.9%
- ◆ Worldwide prevalence is similar among all cultures
- ◆ Onset is most common in late adolescence and early adulthood
- ◆ Male: Female is 1:1
- ◆ Men may develop earlier than women

Natural history of schizophrenia

Lieberman JA. J Clin Psychopharmacol. 1998;18:20s.

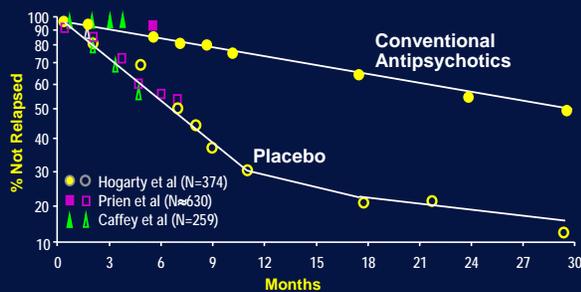
Stages of illness



Clinical Course/Prognosis

- ◆ Usually poor long-term outcome prognosis
- ◆ First episode patient may have a relapse rate of 60% in the first two years following the initial episode
- ◆ Remission is sustained in only a small group of patients

Relapse in Schizophrenia



Baldessarini RJ et al. Tardive Dyskinesia. APA Task Force Report 18; 1980

Long-term Outcomes

- ◆ Lifetime risk of suicide is approximately 10%
- ◆ Approximately 50% of people discharged on conventional antipsychotics will be rehospitalized within 1 year
- ◆ About two-thirds of first-episode patients continue to have positive symptoms after 1 year
- ◆ About 2/3 of people on conventional antipsychotics have persistent parkinsonism
- ◆ Subjective and objective measures of quality of life are poor, even when compared with other chronically ill patients.
- ◆ Less than 20% of patients with schizophrenia are employed in competitive work at any time

Weiden et al, J Clin Psychiatry 1996

Goals for Improving Long-term Outcomes

- ♦ Foundation for stability and reducing relapse
- ♦ Improving positive, negative and cognitive symptoms
- ♦ Reducing side effect burden
- ♦ Maintain adherence

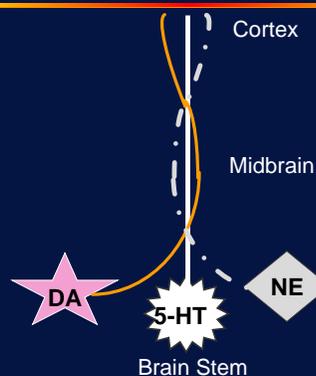
Etiology

- ♦ Various abnormalities in brain structure and function
- ♦ Genetic susceptibility
- ♦ Early developmental insults
- ♦ Environmental

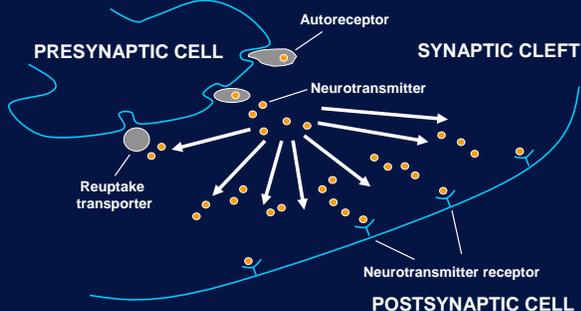
Pathophysiology-Neuroanatomical

- ♦ Enlarged lateral and third ventricles
 - ♦ Imply changes in the limbic-striatal area
- ♦ Decreased size of frontal and temporal lobes

Pathophysiology-Neurochemical

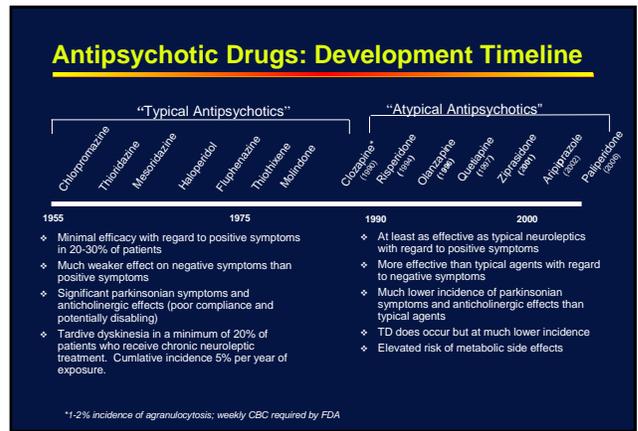
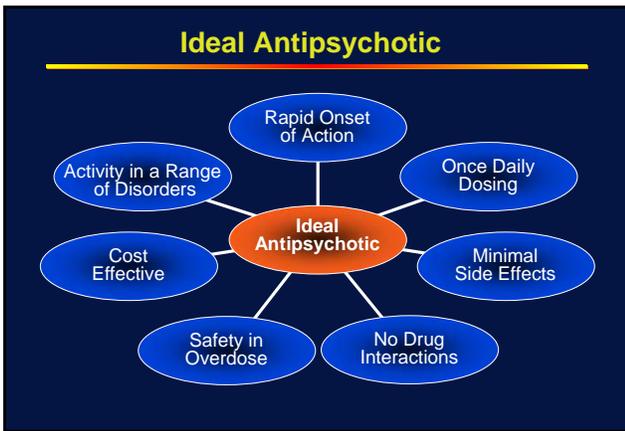


Neurotransmitters—Mechanisms of Action



Treatment

- ♦ **Goals:**
 - ♦ Induce remission
 - ♦ Prevent recurrence
 - ♦ Restore baseline level of functioning
- ♦ **There is no cure at this time**
- ♦ **Decrease target symptoms**
- ♦ **Non-drug therapy is important- helps with social difficulties**



Typical Antipsychotics

-the older agents

Examples

- Chlorpromazine (Thorazine®)
- Thioridazine (Mellaril®)
- Mesoridazine (Serentil®)
- Haloperidol (Haldol®)
- Fluphenazine (Prolixin®)
- Thiothixene (Navane®)
- Molindone (Moban®)

London: Martin Dunitz, 1999.

Typical Antipsychotics

-the older agents

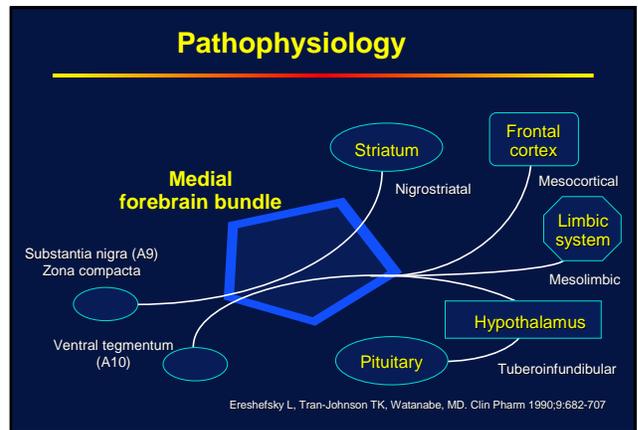
- ♦ **Mechanism of action:**
 - ♦ Most of these agents work specifically by blocking post-synaptic dopamine receptors in the brain
 - ♦ Most of these agents have more selectivity for dopamine-2 receptors
 - ♦ Increased dopamine receptor blockade can lead to extrapyramidal side effects, tardive dyskinesia, and increased prolactin release

Haloperidol and D₂ Occupancy

11C-Raclopride PET Scan (Before Treatment)

11C-Raclopride PET Scan Haloperidol 2 mg/day (74% occ.)

From Kapur, 1999 (presentation)



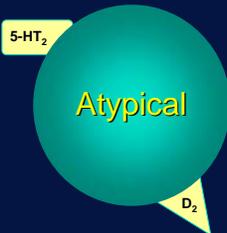
Dopaminergic Tracts

Dopamine Tract	Origin	Innervation	Function	Dopamine Antagonist Effect
Nigrostriatal	Substantia nigra (A9 area)	Caudate nucleus Putamen	Extrapyramidal System, movement	Movement Disorders
Mesolimbic	Midbrain ventral tegmentum (A10 area)	Limbic areas (e.g., amygdala, olfactory tubercle, septal nuclei, Cingulate gyrus)	Arousal, memory, stimulus processing, motivational behavior	Relief of psychosis
Mesocortical	Midbrain ventral tegmentum (A10 area)	Frontal and pre-frontal lobe cortex	Cognition, communication, social function, response to stress	Relief of psychosis, cognition
Tuberoinfundibular	Hypothalamus	Pituitary gland	Regulates prolactin release	Increased prolactin concentrations

Movement Disorders

Reaction	Features	Maximum Risk	Proposed Mechanism	Treatment
Acute Dystonia	Spasm of muscles of tongue, face, neck, back	1-5 days	Unknown	Antiparkinson agents
Akathisia	Motor restlessness	5-60 days	Unknown	Reduce dose; Change drug; Propranolol, BZDs
Parkinsonism	Bradykinesia, rigidity, tremor, mask facies, shuffling gait	5-30 days	Dopamine antagonism	Antiparkinson agents
Tardive Dyskinesia	Oral-facial dyskinesias; widespread choreoathetosis or dystonia	Months or years of treatment; worse upon withdrawal	?Excess dopaminergic functioning	Treatment is unsatisfactory; PREVENTION is key

Atypical Antipsychotics

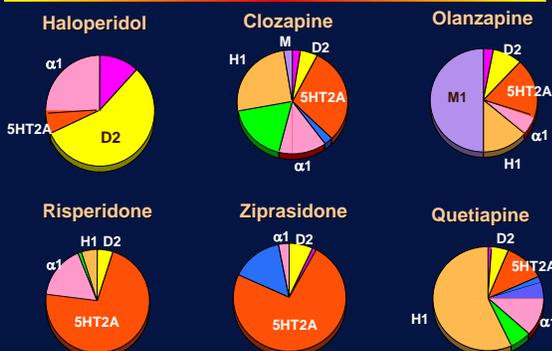


Clozapine (Clozaril®)
 Olanzapine (Zyprexa®)
 Risperidone (Risperdal®)
 Quetiapine (Seroquel®)
 Aripiprazole (Abilify®)
 Ziprasidone (Geodon®)
 Paliperidone (Invega®)

Atypical Antipsychotics

- ♦ Mechanism of action:
- ♦ Like the typical antipsychotics, atypical medications also block post-synaptic dopamine receptors in the brain
- ♦ Unlike most of the typical agents, atypicals also have antagonistic effects at serotonin receptors, specifically 5HT2a receptors
- ♦ These agents also work at many other receptors

Comparative Receptor Binding Profiles



Arndt J, Skarsfeldt T. Neuropsychopharmacology 1998; Goldstein et al .

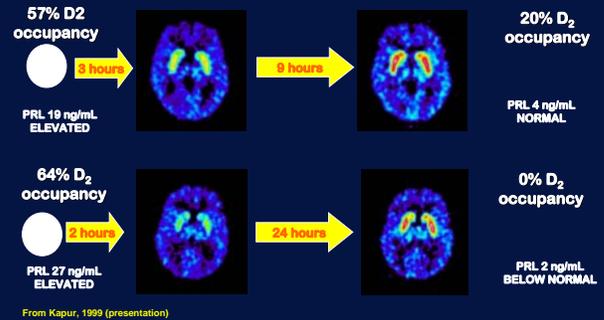
Adverse Effects of Receptor Blockade

RECEPTOR	ASSOCIATED ADVERSE EFFECTS
Dopaminergic(D ₂)	EPS, prolactin elevation
Histaminergic (H ₁)	Sedation, weight gain
Muscarinic (M ₁)	Dry mouth, urinary retention, blurred vision, constipation, sinus tachycardia, cognitiona and memory problems
α ₁ -adrenergic	Orthostatic hypotension, reflex tachycardia, sexual dysfunction

Aripiprazole and Bifreprunox

- ♦ **Partial agonist at D₂ receptors**
 - ♦ Functional antagonist under conditions of dopamine hyperactivity (i.e. possible control of positive symptoms)
 - ♦ Functional agonist in conditions of dopamine hypoactivity (i.e. possible improvement in negative symptoms, cognitive improvement, minimal EPS)
- ♦ **Antagonist at 5-HT_{2a} receptors**
- ♦ **Partial agonist at 5-HT_{2a} receptors**

Transient D₂ Receptor Occupancy with Quetiapine



Relative Dissociation of Antipsychotics From the D₂ Receptor



The Old Concerns and the New Ones in Schizophrenia Management

Issue	Old Era	New Era
EPS	Major patient tolerability issues, effects on medication compliance	Infrequent Not major concerns
Tardive dyskinesia	Major long-term risk	Seems rare Not major concern
Social, cognitive, and vocational efficacy	Disappointment Accepted	New hope and expectations
Negative symptoms and refractory patients	Disappointment Accepted	New hope and expectations
Poor patient adherence	Common	Expected improvement

(cont)

The Old Concerns and the New Ones in Schizophrenia Management

Issue	Old Era	New Era
Cardiovascular health	Not on the radar screen	Major public health issue
Glucose and lipid problems	Not on the radar screen	Major public health issue
Weight gain	Never thought of	Major patient concern
Cognitive dysfunction	Lack of progress Accepted	New hope for improvement
Depression	Assumed to be part of the illness	New hope and expectations

Baseline Risk of Medical Illness Is High in Schizophrenia

- ♦ **Patients with schizophrenia have about a twofold increased risk of death from medical causes^{1,2}**
- ♦ **Cardiovascular death is a major contributor to increased mortality in schizophrenia^{1,3}**

1. Harris and Barraclough. *Br J Psychiatry*. 1998;173:11.
 2. Dwyer et al. *Ann Clin Psychiatry*. 2001;13:103.
 3. Gausset et al. *Encephale*. 1992;18:93.

Metabolic Syndrome

*a multiplex risk factor for cardiovascular disease (CVD)

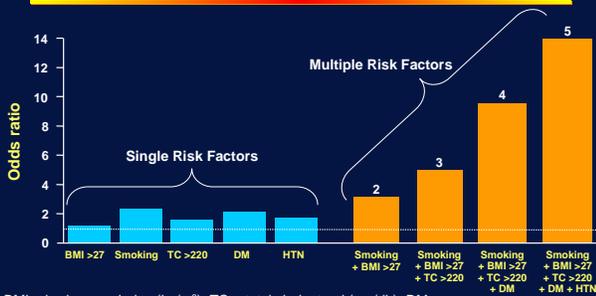
- ♦ Central obesity as measured by waist circumference:
Men — Greater than 40 inches
Women — Greater than 35 inches
- ♦ Fasting blood triglycerides greater than or equal to 150 mg/dL
- ♦ Blood HDL cholesterol:
Men — Less than 40 mg/dL
Women — Less than 50 mg/dL
- ♦ Blood pressure greater than or equal to 130/85 mmHg
- ♦ Fasting glucose greater than or equal to 100 mg/dL (ADA guidelines)

Body Mass Index

♦ Body Mass Index (BMI)

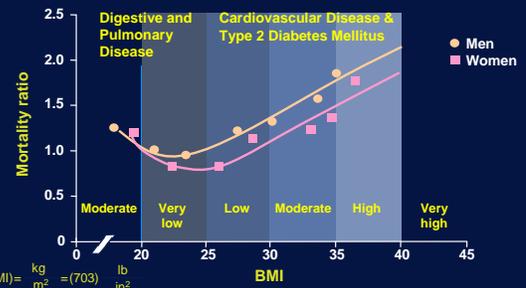
- ♦ Is a measure of body fat based on height and weight that applies to both adult men and women
- ♦ To calculate: $\frac{\text{Weight in Kilograms}}{\text{Height in Meters}^2}$
- ♦ Underweight = <18.5
- ♦ Normal weight = 18.5-24.9
- ♦ Overweight = 25-29.9
- ♦ Obesity = BMI of 30 or greater

Risk Factors for Heart Disease in the General Population



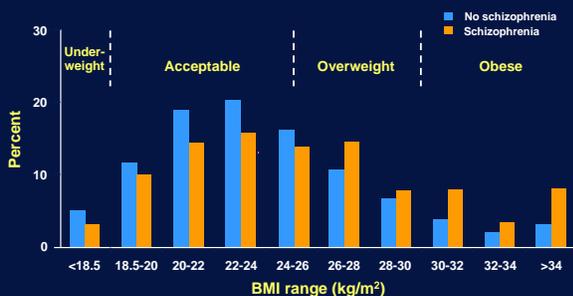
BMI = body mass index (kg/m²); TC = total cholesterol (mg/dL); DM = diabetes mellitus; HTN = hypertension.
Wilson et al. *Circulation*. 1998;97:1837.

Obesity and Mortality Risk in the General Population



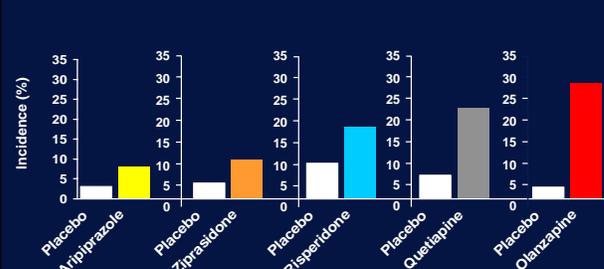
Adapted from: Gray et al. *Med Clin North Am*. 1989;73:1;
Based on data from: Lew and Garfinkel. *J Chronic Dis*. 1979;32:563; American Cancer Society study of 750,000 men and women.

BMI Distributions in General Pop. and in Patients With Schizophrenia



Allison et al. *J Clin Psychiatry*. 1999;60:215.

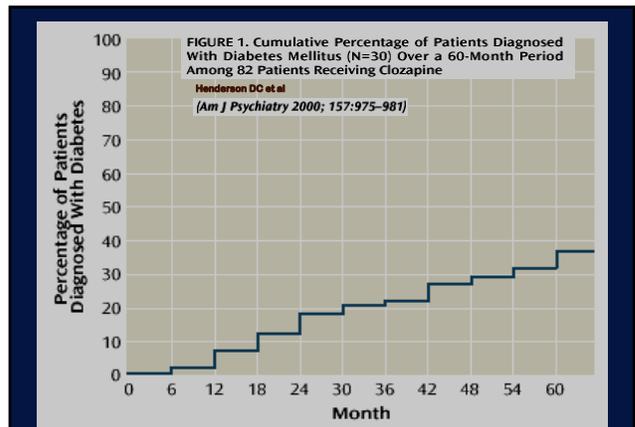
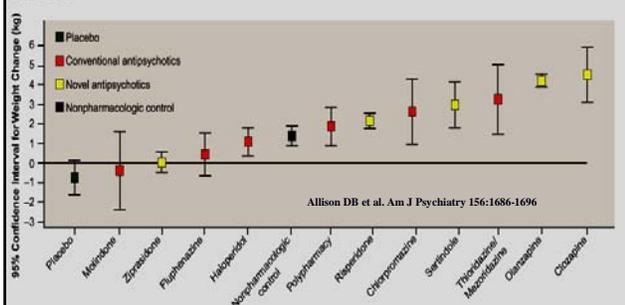
Atypical Antipsychotics: Clinically Significant (≥7%) Weight Gain



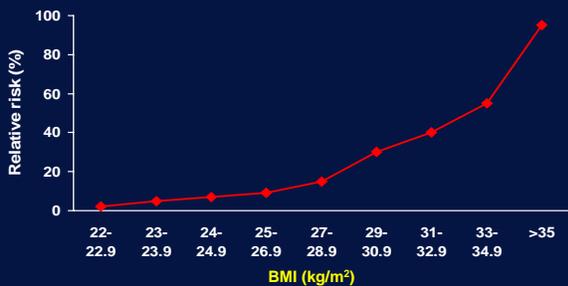
Data for aripiprazole, ziprasidone, risperidone, quetiapine, and olanzapine are from US product labels.

Atypical Antipsychotics: Clinically Significant Weight Gain

FIGURE 1. 95% Confidence Intervals for Weight Change After 10 Weeks on Standard Drug Doses, Estimated From a Random Effects Model



Body Mass Index and Diabetes Risk



Schizophrenia and Diabetes

- ◆ Prevalence of adult-onset diabetes in schizophrenia populations is about 13%¹
 - ◆ Adjusted odds ratio ~2
- ◆ Increased risk for diabetes predates arrival of antipsychotics^{1,2}

1. Dixon et al. *Schizophr Bull.* 2000;26:903.
2. Newcomer et al. *Arch Gen Psychiatry.* 2002;59:337.

Atypical Antipsychotics and Diabetes

◆ New data suggest 2 separate issues

◆ Diabetic ketoacidosis

- ◆ May occur early in treatment
- ◆ May not be associated with weight gain

◆ New/ongoing diabetes cases

- ◆ Impaired glucose tolerance/new cases of diabetes occur over extended time frame
- ◆ Often, but not always, associated with weight gain

Changes in Fasting Lipids Levels Associated with Atypical Antipsychotics



Pfizer study 054; BMS data on file

Identification of Metabolic Syndrome

≥ 3 Risk Factors Required for Diagnosis	
Risk Factor	Defining Level
Abdominal Obesity Men	Waist Circumference >40 in
Women	>35 in
Triglycerides	≥150 mg/dL
HDL cholesterol Men	<40 mg/dL
Women	<50 mg/dL
BP	130/85 mmHg
Fasting blood glucose	≥ 110 mg/dL

HDL = high density lipoprotein; BP = Blood pressure
NCEP III. Circulation 2002;106:3143-3421

Modifiable Risk Factors

- ♦ Overweight/Obesity
- ♦ Insulin Resistance
- ♦ Diabetes/hyperglycemia
- ♦ Dyslipidemia

Newcomer JW. CNS Drugs 2005;19(Suppl 1):1-93.

Hyperglycemia/Diabetes

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 long-term data

Monitoring and Treatment

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/ Family History	X					X	
Weight (BMI)	X	X	X	X	X		
Waist Circum- ference	X					X	
Blood Pressure	X			X		X	
Fasting Plasma Glucose	X			X		X	
Fasting Lipid Profile	X			X			X

Prevalence of Metabolic Syndrome

CATIE Study - Individuals with schizophrenia

(Schizophrenia Research 2005; 80: 19-32)

- ♦ 1,458 subjects enrolled in the CATIE Study
- ♦ Baseline Characteristics
 - ♦ Mean Age = 40.4 yrs, BMI = 29.7, Male (74%)
 - ♦ White (60%), Black (35.2%), Hispanic (11.6%)
- ♦ Prevalence of metabolic syndrome
 - ♦ NCEP Criteria – 42% (only 14% had no risk factors)
 - ♦ Men = 39% and women = 52%*
 - ♦ White = 44.2%, Black = 29.6%, and Hispanic = 39.5%

*Note: Women were significantly older than men in this trial

Prevalence of Metabolic Syndrome

CATIE Study – Prevalence of Risk Factors

(Schizophrenia Research 2005; 80: 19-32)

- ♦ HDL cholesterol ≤ 40 or 50 mg/dL = 52.7%
- ♦ Triglycerides ≥ 150mg/dL = 48.5%
- ♦ Blood Pressure ≥ 130/85 mmHg = 47.2%
- ♦ Waist Circumference ≥ 40 or 35 inches = 46.1%
- ♦ Glucose ≥ 110 mg/dL = 16.1%
- ♦ Glucose ≥ 100 mg/dL = 25.7%

Prevalence of Metabolic Syndrome

CATIE Study – Cardiovascular Risk

(Schizophrenia Research 2005; 80: 45-53)

Baseline CV risks in subjects enrolled in CATIE trial vs. NHANES III (matched controls)

Smokers 68% vs. 35% ($p < 0.0001$)

Diabetes 13% vs. 3% ($p < 0.0001$)

Hypertension 27% vs. 17% ($p < 0.0001$)

HDL Cholesterol 43.7 vs. 49.3 mg/dL ($p < 0.0001$)

Antipsychotic Drugs - Metabolic Risk

Do antipsychotic medications increase the risk of developing the metabolic syndrome?

(CATIE trial. NEJM 2005; 353: 1209-23)

- ♦ Subjects: Previously treated schizophrenia but not treatment resistant (n=1432)
- ♦ Randomized to olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone.
- ♦ Outcome – treatment discontinuation was high (74%)
- ♦ From a metabolic standpoint, olanzapine-treated subjects had significantly poorer outcomes
 - More likely to discontinue tx due to weight gain or metabolic effect

Current Challenges in Treatment of Schizophrenia

- ♦ Cure remain elusive
- ♦ More medication choices than ever before
- ♦ Uncertainty about
 - ♦ Finding the right treatment objectives
 - ♦ Balancing competing goals
 - ♦ What is amenable to psychopharmacology Vs other interventions?
 - ♦ When is the right time to increase the dose or decrease the dose?
 - ♦ When is the right time to switch to another antipsychotic