

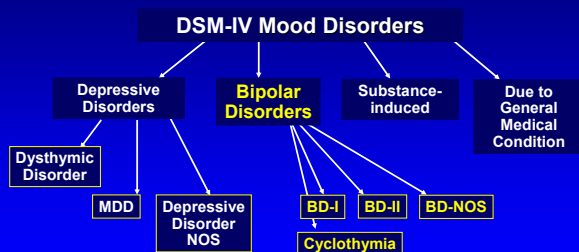
## Modern Day Mood Stabilizers: Let Your Pharmacist Introduce You to the Side Effects

Steven M. Burghart, DPh, MBA, BCPP  
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Jerry Overman, Pharm.D., BCPP

## Bipolar Disorder

- Prevalence: 1-4% (narrow vs. spectrum)
- Onset in young adulthood (>60 years: medical)
- Chronic episodic course
- Significant morbidity (disability, hospitalization, adjustment, substance problems, psychiatric disorder, medical issues)
- Significant mortality (suicide, accidents, and medical co-morbidities)

## Mood Disorders: DSM-IV Classification



APA (1994). Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, D.C.: APA

## Bipolar Disorders: DSM-IV

- Bipolar I disorder
  - Hypomanic, manic, mixed, depressed, unspecified
- Bipolar II disorder
- Cyclothymic disorder
- Bipolar disorder NOS (not otherwise specified)

## General Treatment Principles

- Psychosocial interventions
- Pharmacologic interventions
- Promote education
- Enhance adherence

## Classes of Medications for Bipolar Disorder

- “Classic” Mood Stabilizers
  - Lithium, Divalproex Sodium, Carbamazepine
- Newer Antiepileptic Agents
- Atypical Antipsychotics

## Treatment Goals

- Acute mania  
Rapid onset of action, relief of symptoms, no depression induction
- Bipolar depression  
Relief of symptoms, no mania induction
- Maintenance  
Prevention of relapse into depression or mania; reduction of co-morbid anxiety

## Improving Treatment Adherence

- Therapeutic alliance
- Education
- Availability and support
- Psychotherapy
- Medication -- minimize side effects, complexity, cost

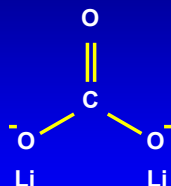
## Choice of Medication(s)

- Phase of illness
- Prior response and tolerability
- Medical and psychiatric comorbidities
- Side effects
- Drug interactions
- Patient preferences

## “Classic” Mood Stabilizer Side Effects: Lithium, Carbamazepine, Divalproex

Steven M. Burghart, DPh, MBA, BCPP

## Lithium Carbonate



## Lithium-History

- 1817; elemental lithium was first isolated.
- Late 19<sup>th</sup> century; benefit was first noted in psychiatric illnesses.
- 1929; 7-Up introduced containing lithium citrate, intended as a hangover cure.
- 1949; Australian psychiatrist, John Cade, notes efficacy of lithium in patients with mania.
- 1970; Lithium Carbonate approved for use in Bipolar mania.

## Lithium-Mechanism of Action

- Although the mechanism of the antimanic and antidepressant action in the CNS is not known, evidence suggests that Lithium interferes with the synthesis, storage, release, and reuptake of monoamine neurotransmitters. Lithium enhances the uptake of tryptophan, increases the synthesis of serotonin, and may also enhance the release of serotonin in the CNS.

## Lithium Side Effects

Subjective Side Effects	% Patients Reporting
Excessive Thirst (Polydipsia)	35.9
Excessive Urination (Polyuria)	30.4
Memory Problems (Cognition)	28.2
Tremor	26.6
Hypothyroidism	20
Weight Gain	18.9
Drowsiness/Fatigue	12.4
Diarrhea	8.7

Goodwin and Jamison 1990; Lenox and Manji 1995

## Management of Lithium Side Effects

Side Effect	Specific Symptoms	Clinical Management
Excessive Thirst/Excessive Urination	Kidney damage rare at usual doses but may occur with toxicity. Edema may occur but is not related to kidney function.	May be decreased if most of daily dose is given at bedtime. Some diuretics (amiloride) will reduce urination/edema and not affect lithium levels.
Memory problems	May be related to peak plasma concentrations; symptoms include memory impairment /slowing.	Reduce dose or increase interval between doses.
Tremor	Tremor, lethargy, weakness. Increase in tremor severity may be sign of high lithium levels.	Reduce dose or increase interval between doses. Reduce caffeine, stimulant, or tricyclic antidepressant use. Beta-blocker (propranolol or atenolol) may be helpful.

Pies,RW 2005

## Management of Lithium Side Effects

Side Effect	Specific Symptoms	Clinical Management
Weight Gain	May have insulin-like effects on carbohydrate metabolism. Also, increase liquids intake may increase weight.	Comprehensive weight management program. Consider medication change if clinically feasible. Avoid diuretics that may increase lithium levels.
Drowsiness/Fatigue	Usually improves with time. Increase in severity may indicate toxicity.	Reduce dose or increase interval between doses.
Diarrhea	Nausea, vomiting, anorexia, cramping, diarrhea. Common when therapy started and improves with time.	Slow rate of dose increases. Give with meals. Slow release lithium preparations improve nausea but not diarrhea.

Pies,RW 2005

## Management of Lithium Side Effects

Side Effect	Specific Symptoms	Clinical Management
Hypothyroidism	More common in females or within first 3 months of treatment	Monitor thyroid function and provide thyroid supplement if needed.
Dermatological	Acne, worsening of psoriasis, hair loss	Conventional treatments for acne or psoriasis are effective. Hair loss most commonly due to low thyroid levels.

Pies,RW 2005

## Lithium Monitoring

- Lithium Blood Level
  - Usually ordered 4-5 days after starting treatment or after dose change then every 3-6 months when stabilized.

Devane, L, Fundamentals of Monitoring Psychoactive Drug Therapy, Williams and Wilkins, 1990

## Lithium Toxicity

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Stage	Lithium Level (mEq/L)	Clinical Picture
Early toxicity	1.2-1.5	Slight ataxia, dysarthria, lack of coordination.
Mild toxicity	1.5-2.0	Listlessness, nausea, slurring of speech, diarrhea, coarse tremor.
Moderate toxicity	2.0-2.5	Coarse tremor, confusion, delirium, pronounced ataxia.
Severe toxicity	2.5 or greater	Stupor, spontaneous hyperextension of extremities, choreoathetosis, seizures, coma.

Pies, RW 2005

## Lithium Monitoring Tests

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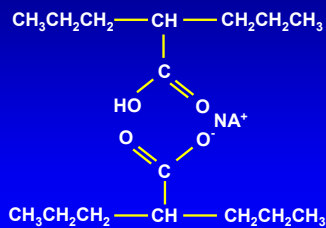
- Thyroid function tests (T3,T4,TSH)
- Renal function tests (UA, SCr, BUN)
- Blood function tests (CBC with differential)
- Electrolytes (especially Sodium level)
- Electrocardiogram (ECG)

**These tests are generally ordered before treatment, after treatment is stabilized and then every 6-12 months.**

Devane, L. Fundamentals of Monitoring Psychoactive Drug Therapy, Williams and Wilkins, 1990

## Divalproex Sodium

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## Divalproex Sodium

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- Available as valproic acid, sodium valproate or divalproex sodium.
- First synthesized in 1882 by Burton as an analog of valeric acid, found naturally in valerian.
- Anti-seizure activity discovered in 1962.

## Divalproex-Mechanism of Action

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- Indirectly acts on voltage-gated sodium channels.
- Indirect potentiation of GABA.

## Divalproex-Side Effects

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Side Effect	% Patients Reporting
Nausea/Vomiting	23-34
Platelet abnormalities	13-54
Elevated Liver Functions	20
Alopecia	6
Weight gain	5

Sillanpaa 1981, Divalproex Sodium Package Labeling

## Management of Divalproex Side Effects

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Side Effect	Clinical Management
Nausea/Vomiting	Divalproex better tolerated than Valproic Acid. Take with food.
Platelet abnormalities	Thrombocytopenia (low platelet counts) more common in older patients. Usually not clinically significant. Monitor platelet counts periodically.
Elevated Liver Functions	Usually benign and dose related. If liver function test 3 times normal levels may need to discontinue treatment.
Alopecia	Usually transient. May improve with use of zinc and selenium supplements.
Weight gain	Exercise and dietary changes may be helpful. May be refractory.

Pies,RW 2005

## Divalproex Monitoring Tests

cpnp

- Liver function tests (AST, ALT)
- Blood function tests (CBC with differential)
  - Generally ordered before treatment, every few months for six months then annually.
- Plasma level
  - Four days after starting or changing dose then every 3 months.

Devane, L. Fundamentals of Monitoring Psychoactive Drug Therapy, Williams and Wilkins, 1990

## Carbamazepine

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## Carbamazepine

cpnp

- Carbamazepine was discovered by chemist Walter Schindler at J.R. Geigy AG (now part of Novartis) in Basel, Switzerland, in 1953. Schindler then synthesized the drug in 1960.
- In 1971, Drs. Takezaki and Hanaoka first used carbamazepine to control mania in patients refractory to antipsychotics (Lithium was not available in Japan at that time). Dr. Okuma, working independently, did the same thing with success.

## Carbamazepine-Mechanism of Action

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- Directly blocks presynaptic voltage-gated sodium channels, leading to reduced action potentials and reduced release of glutamate from presynaptic neurons; also indirect augmentation of GABA.

## Carbamazepine-Side Effects

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Side Effect	% Patients Reporting
Dizziness	35
Drowsiness	29
Nausea	13
Skin reactions	12
Asthenia	11
Leukopenia	10
Liver enzyme elevations	10
Thyroid dysfunction	8

Sillanpaa 1981

## Management of Carbamazepine Side Effects

Side Effect	Clinical Management
Dizziness	Usually transient; reversible with dose reduction.
Drowsiness	Usually transient; reversible with dose reduction.
Nausea	Usually improves after a few weeks. Dose reduction or more frequent dosing may help.
Skin reactions	Rash improves with topical steroids. Discontinue treatment if rash includes fever, bleeding or exfoliate skin lesions (Stevens-Johnson Syndrome).
Asthenia	Usually transient; reversible with dose reduction.

Pies, RW 2005

## Management of Carbamazepine Side Effects

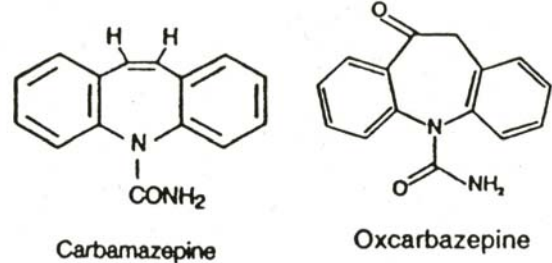
Side Effect	Clinical Management
Leukopenia	Usually transient and benign. May improve with dose reduction. Aplastic anemia very rare (1 in 575,000).
Liver enzyme elevations	Usually benign. Improves with dose reduction. Discontinue treatment if levels are three times normal.
Thyroid dysfunction	May be dose related. Usually not severe enough to require treatment with thyroid supplements.

Pies, RW 2005

## Carbamazepine Monitoring Tests

- Liver function tests (AST, ALT)
- Blood function tests (CBC with differential)
- Electrolytes (especially Sodium level)
  - Generally ordered before treatment, monthly for 2-3 times then annually.
- Plasma level
  - Four days after starting or changing dose then every 3 months.

Devane, L, Fundamentals of Monitoring Psychoactive Drug Therapy, Williams and Wilkins, 1990



## Oxcarbazepine Side Effects

- AE dropouts
  - monotherapy 9%
  - pediatrics 11%
- Common – nausea, vomiting, dizziness, somnolence, ataxia
- Uncommon – hyponatremia (< 125 mEq/L, 2.5%)
- Rare: Stevens-Johnson syndrome and toxic epidermal necrolysis

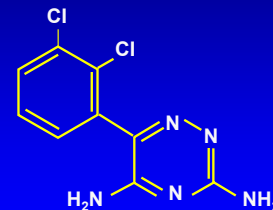
## Newer antiepileptic drugs used in mood stabilization

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## Not all Anticonvulsants Are Antimanic

- For example –
  - Lamotrigine
  - Gabapentin
  - Topiramate
  - Zonisamide
- etc.

## Lamotrigine



## Lamictal (lamotrigine)

- Brought to US market as an antiepileptic medication.
- Has been found to be useful in mood stabilization.
- No blood monitoring needed.
- Potential side effect and suggestions for management of the problem are listed on the next slide.

## Side Effects of Lamotrigine

### Dose Related

Dizziness  
Diplopia  
Ataxia  
Blurred vision  
Nausea and vomiting  
Insomnia

### Not Dose Related

Headache  
Dermatologic  
10% benign rash  
3/1,000 adults—severe rash  
Do not rapidly escalate dose  
Warn patients about rash  
Malformations: 2.7%  
(Messenheimer JA, 2006)

## Rash with Lamotrigine Use

- Black box warning
- Overall rash prevalence: 10%
  - 0.3% severe in adults
  - 1% severe in children (not for those <15yoa)
- Predictors of rash: starting dose, titration, concurrent divalproex, use in children, history of prior rash
- Stevens-Johnson syndrome with lamotrigine
  - 1993: 5/4,450
  - 1999: 3/17,648

Messenheimer et al. Drug Safety. 1998;18:281-96; Physicians' Desk Reference. 55th ed. 2001

## Lamotrigine Dosing

- Monotherapy
  - Weeks 1 and 2: 12.5-25 mg/day
  - Weeks 3 and 4: 25-50 mg/day
- With valproate: ↓ dose by 50%
- Maintenance: 50-400 mg/day

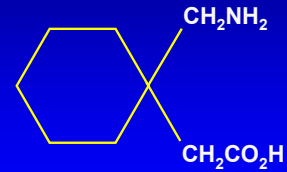
## Lamictal (lamotrigine)

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Potential Side Effect	Suggestion for Management
Skin rash	Slowly increasing the dose to a point that it is working best for the patient is useful. If this side effect occurs contact your physician <b>immediately</b> .
Clumsiness, dizziness, drowsiness	Discuss problem with your provider. Take the medication at bedtime.
Upset stomach	Tell your provider you are having this problem and inquire about whether or not the dose can be decreased/changed. Take with food.

## Gabapentin

cpnp



## Neurontin (gabapentin)

cpnp

- At one time considered an option for mood stabilization.
- Current evidence suggests it is less likely to be useful in mood stabilization.
- No blood monitoring needed.
- Potential side effects and management strategies are listed on the next slides.

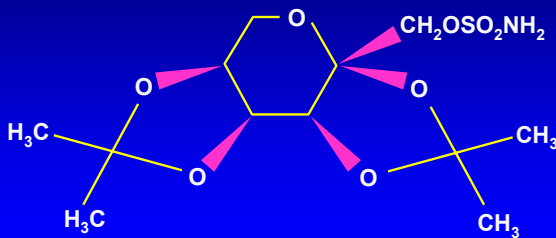
## Neurontin (gabapentin)

cpnp

Side Effect	Suggestion for Management
Dizziness, clumsiness, sleepiness, fatigue	Discuss problem with your provider. Take the medication at bedtime.
Nystagmus = jerky eye movement	Discuss problem with your provider <b>immediately</b> .
Weight gain	Increase activity through regular exercise such as walking around the block or other physical activity that fits your lifestyle.

## Topiramate

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## Topiramate for Bipolar Disorders

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- No double-blind controlled efficacy studies in bipolar
- Dose range: 25-400 mg/day
- Open-label results:

moderate/marked improvement	52%
minimal/no improvement	36%
worse	11%
- Adverse events dropouts (6/58) 10%

**Topamax (topiramate)** cpnp

Side Effect	Suggestion for Management
Fatigue or drowsiness	Take larger portion of medication at bedtime.
Difficulty with concentration	Discuss the side effect with provider. Inquire about whether or not the dose could be changed.
Difficulty finding the right word (word retrieval)	Discuss the side effect with provider. Inquire about whether or not the dose could be changed.
Confusion	Discuss the side effect with provider. Inquire about whether or not the dose could be changed.
Dizziness, clumsiness	Discuss this problem with provider. Take larger portion of medication at bedtime.
Tingling feeling in hands or feet	Discuss this problem with provider.

- Topiramate** cpnp
- AE dropouts (epilepsy trials): 28%
  - More common: somnolence, cognitive impairment, dizziness, ataxia, psychomotor slowing, paresthesias, weight loss
  - Kidney stones: 1.5%



- Topiramate and Kidney Stones** cpnp
- Occurred in 1.5% (32/2086)
  - 2 to 4 times ↑ risk
  - Men > women
  - Reported in kids
  - One bipolar II woman
  - Carbonic anhydrase inhibition

- Zonegran (zonisamide)** cpnp
- Could be used as adjunctive treatment with other mood stabilizers, studies ongoing.
  - If a patient is taking this medication, it is important that they be monitored for the potential development of metabolic acidosis.
  - Potential other side effects and management strategies are on the following slide.

**Zonegran (zonisamide)** cpnp

Potential Side Effect	Suggestion for Management
Sleepiness or fatigue	Ask provider if the dose can be adjusted (ie a larger amount taken at night).
Dizziness	Discuss problem with provider and take medications at night.
Loss of appetite (ie. anorexia), stomach upset	Tell your provider you are having this problem and inquire about whether or not the dose can be decreased/changed. Take with food.
Headache	Discuss side effect with provider. Consider taking an over the counter pain relieving medication.

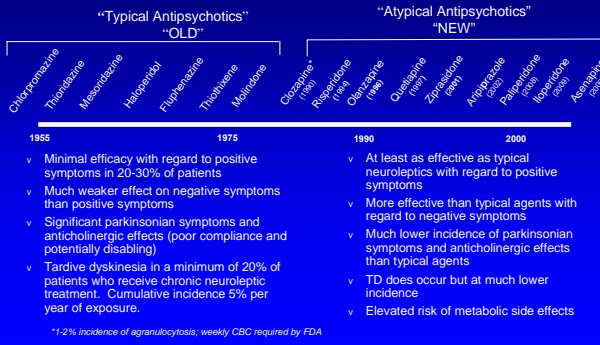
## Atypical Antipsychotic Use in Bipolar Disorder

Jerry Overman, Pharm.D., BCPP

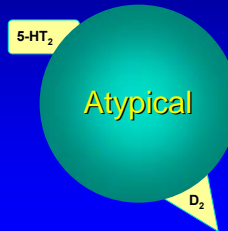
## Atypical (Second Generation) Antipsychotics in Mania

- All such agents apparently effective
- Generally no worsening of depression (unlike conventional antipsychotics)
- Limited antidepressant effects, some adjunctive mood stabilization effects
- Less EPS but must be wary of metabolic risks, especially weight gain and deviations in glucose, lipids, or prolactin

## Antipsychotic Drugs: Development Timeline



## Atypical Antipsychotics



- Clozapine (Clozaril®)
- Olanzapine (Zyprexa®)
- Risperidone (Risperdal®)
- Quetiapine (Seroquel®)
- Aripiprazole (Abilify®)
- Ziprasidone (Geodon®)
- Paliperidone (Invega®)
- Asenapine (Saphris®)
- Iloperidone (Fanapt®)

## 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

## Adverse Effects of Receptor Blockade

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

## The Old Concerns and the New Concerns of Atypical Antipsychotics

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 Concerns of Atypical Antipsychotics

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

## 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

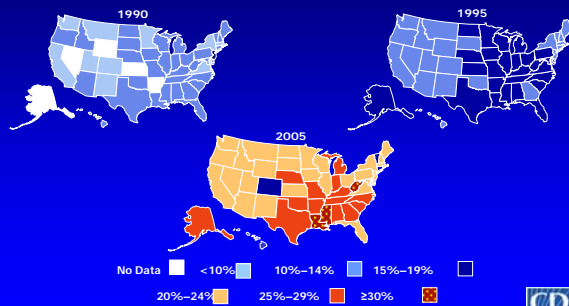
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- Body Mass Index (BMI)
  - Is a measure of body fat based on height and weight that applies to both adult men and women
  - To calculate:  $\frac{\text{Weight in Kilograms}}{\text{Height in Meters}^2}$
  - Underweight = <18.5
  - Normal weight = 18.5-24.9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

## Obesity Trends Among U.S. Adults

1990, 1995, 2005

(BMI  $\geq 30$ , or about 30 lbs overweight for 5'4" person)

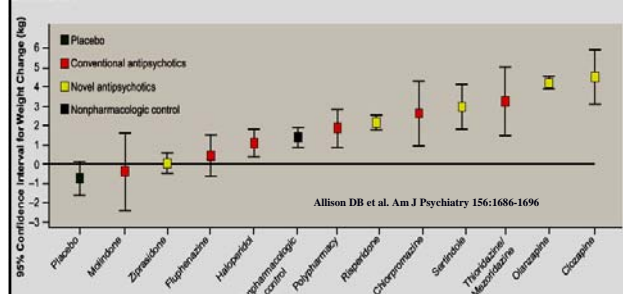


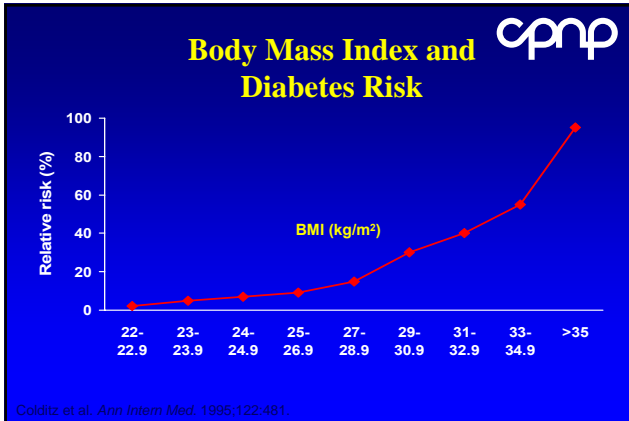
Source: Behavioral Risk Factor Surveillance System, CDC.

## Atypical Antipsychotics: Clinically Significant Weight Gain

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





- ### 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 Circumference	X					X	
Blood Pressure	X			X		X	
Fasting Plasma Glucose	X			X		X	
Fasting Lipid Profile	X			X			X

### Antipsychotic Drugs - Metabolic Risk

Metabolic Effects Compared – Change from Baseline (CATIE trial. *NEJM* 2005; 353: 1209-23)

Medication	Weight (lbs)	Glucose (mg/dL)	A1c (%)	TG (mg/dL)
Olanzapine	9.4 ± 0.9	13.7 ± 3.5	0.4 ± 0.07	40.5 ± 8.9
Perphenazine	-2.0 ± 1.1	5.4 ± 2.8	0.09 ± 0.09	9.2 ± 10.1
Quetiapine	1.1 ± 0.9	7.5 ± 2.5	0.04 ± 0.08	21.2 ± 9.2
Risperidone	0.8 ± 0.9	6.6 ± 2.5	0.07 ± 0.08	-2.4 ± 9.1
Ziprasidone	-1.6 ± 1.1	2.9 ± 3.4	0.11 ± 0.09	-16.5 ± 12.2

### Questions ?