

# Zyprexa & the Prescribing Physician



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# Zyprexa multimedia game

*Designed for Lilly by:*

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# Zyprexa is approved to treat:

- Schizophrenia
- Bipolar disease

# Drugs used to treat bipolar disease.

Antidepressants

Typical  
Atypical  
SSRI  
Dual uptake

Mood stabilizers

MAOI  
Antiseizure  
Lithium

Anxiolytics

Antipsychotics

Typical  
Atypical

# Antidepressants used to treat bipolar disease.

## *Typical*

Elavil  
Asendin  
Anafranil  
Norpramin  
Sinequan/Zonalon  
Tofranil  
Vivactil  
Surmontil  
Pamelor/Aventyl

## *Atypical*

Wellbutrin/Zyban  
Remeron  
Desyrel  
Effexor  
Serzone\*

## *SSRI*

Celexa  
Lexapro  
Paxil  
Luvox  
Zoloft  
Prozac

## *DUI*

Effexor  
Cymbalta

\*Gone but not forgotten

# Mood stabilizers used to treat bipolar disease.

## *Lithium*

## *MAOI*

Marplan

Nardil

Parnate

## *Anticonvulsant*

Tegretol

Neurontin\*

Lamictal\*

Depakote

Topamax\*

\*Unapproved

# Antipsychotics used to treat bipolar disease.

## *Atypical*

Clozaril

Seroquel

Risperdal

Geodon

Abilify

Zyprexa

## *Typical*

Prolixin

Haldol

Trilafon

Navane

Stelazine

Loxitane

Moban

Thorazine

Serentil

Mellaril

## Anxiolytics used to treat bipolar disease.

Librium	Xanax
Klonopin	Dalmane
Tranxene	Serax
ProSom	Halcion
Ativan	Buspar
Restoril	Nembutol
Valium	

# Conventional theories for suing doctors in prescription drug cases:

- Wrong drug for the person.
- Wrong drug for the problem.
- Wrong dose.
- Wrong combination of drugs.
- Unapproved use (off label).
- Failure to monitor.
- Lack of informed consent (some states).

## Other motives

- Avoid removal.
- Venue selection.
- Payback for:
  - Testifying against you in another case.
  - Contributing to vile 527 that lies about candidate supported by trial lawyers.
  - Refusing to treat families and employees of trial lawyers.
  - Making you wait two hours and charging you \$1000 to tell you your client is a sociopath who deserves nothing.
- Doc is a nasty bastard who needs sued no matter what.
- All of the above.

# Physician interviews - October 2004

## What do you think of Zyprexa?

- Neurologist: “I quit using it, because they all blow up like toads. I use Seroquel.”
- Family practice physician: “I won’t give it to a person who is functional and takes some pride in appearance, because the weight gain can be devastating. Remeron is even worse.”
- Psychiatrist: “It works, and although it has risks, the alternatives are even riskier, except lithium and Depakote, and they don’t work for a lot of people.”

## Physician interviews - October 2004

### Do you monitor for glucose in patients you put on atypical antipsychotics?

- Neurologist: “It’s really the other way around. They have to monitor themselves by going to the lab. I don’t do lab work in my office.”
- Family practice physician: “I give them standard, written instructions for people at risk for diabetes, but I don’t know if a patient has followed them, until the next time I see the patient.”

## Physician interviews - October 2004

# Do you monitor for glucose in patients you put on atypical antipsychotics?

- “The people who need antipsychotics are not a compliant group. I have no way of knowing at the time if they get lab work done, any more than I know if they’re taking their medications.”
- “What I’d really like to know is how long is the risk period? If nothing happens in six months, or year, or whatever, is the person out of the woods? I’ve asked the drug reps, but they say they don’t have this information.”

# Zyprexa: wrong drug for the person

- Pediatric/adolescent population.
- Diabetics
- Ties into off label prescribing.
- People with risk factors for diabetes. But remember that schizophrenia itself is a risk factor for diabetes, and both typical and atypical antipsychotics produce weight gain.\*

“Weight control and antipsychotics: how to tip the scales away from diabetes and heart disease,”  
Adler, Current Psychiatry, Aug. 2002

# Zyprexa: wrong drug for the problem

- Use for weight gain.
- Use for inability to sleep.
- Use for Alzheimer's or senility.
- Use for ADD.
- Ties into off label prescribing.
- Unsupported misdiagnosis of schizophrenia or bipolar disorder.

# Zyprexa: wrong combination of drugs

Probably the only cases will be where a doc prescribes a drug, in addition to Zyprexa, that increases the risk of glucose control dysfunction, independently or in combination with Zyprexa, e.g., Clozaril with Zyprexa or Remeron with Zyprexa.

# Zyprexa: failure to monitor

- At what point in time did monitoring become, or should it have become, standard practice? Experts will probably disagree.
- Suggestive literature around for years, but Lilly sales reps told docs, at least up through end of 2003, that diabetes is a result of weight gain, so was it reasonable at that time for docs not to be concerned with diabetes in the absence of weight gain?
- Consensus Guidelines published in February 2004.
- Lilly DHCP letter is dated March 1, 2004, but who got it?
- Other sources of drug risk information for physicians: PDR monthly supplements, Monthly Prescribing Reference (MPR), Prescribers' Letter, etc.

# Guidelines for assessing the impact of antipsychotic drugs on obesity and diabetes

## *At baseline, assess the following factors:*

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

## *At follow-up visits, reassess the following factors:*

- Weight (at 4, 8, and 12 wk and then quarterly)
- Fasting plasma glucose, fasting lipid profile, and blood pressure at 3 mo, fasting plasma glucose and blood pressure annually, and fasting lipid profile every 5 yr

American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004;27(2):596-601

# Zyprexa: lack of informed consent

- If the cause of action is available, the failure to provide diabetes risk information is probably a good informed consent case.
- At what point in time was the risk known? Probably early on, because the mechanism of risk materialization, weight gain or direct effect, is irrelevant to the existence of the risk.

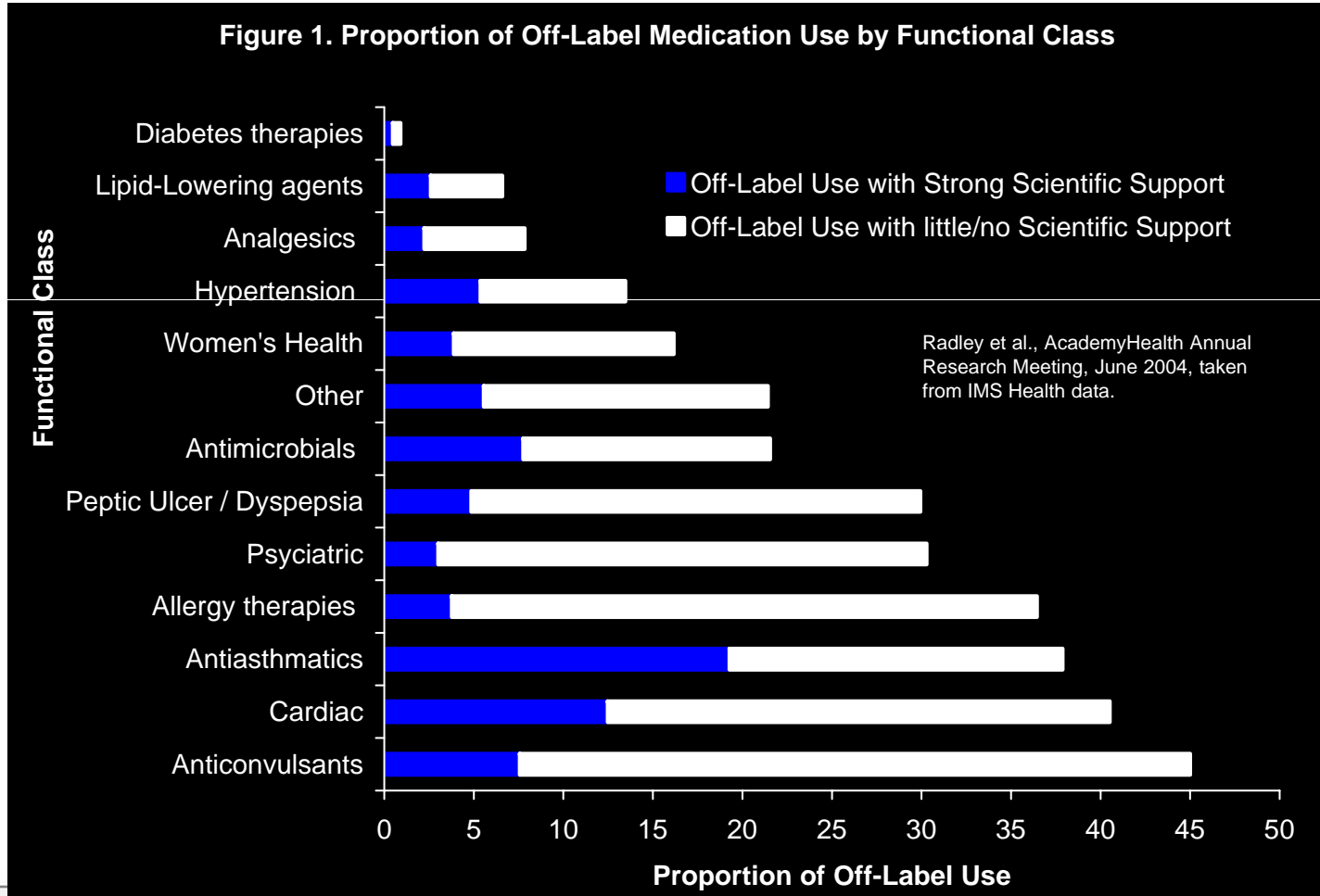
# Zyprexa: unapproved use

- Use for weight gain.
- Use for ADD
- Use for Alzheimer's or senility
- Pediatric/adolescent use
- Unapproved use does not establish negligence.
- Substantial off label use of Risperdal shows that many physicians prescribe atypical antipsychotics off label.

# Why are drugs prescribed off label?

- The FDA doesn't regulate physicians.
- Lack of market incentive for manufacturer to try to get approval, *e.g.*,
  - generics
  - market segment too small.
- No drug approved for the purpose in a market segment, *e.g.*, pediatric.
- Failure of approved drug(s) to work for an individual.
- Doctor is an idiot or doesn't like the patient.

# Proportion of Off-Label Prescribing by Functional Class



# Drugs with highest proportion Off-Label use

## Neurontin (anticonvulsant)

83%: **20% support / 80% no support**

## amitriptyline (psychiatric: tricyclic antidepressant)

79%: **25% support / 75% no support**

## isosorbide mononitrate (cardiac: nitrate)

75%: **64% support / 36% no support**



## digoxin (cardiac: dysrhythmia)

66%: **38% support / 62% no support**

## Risperdal (psychiatric: antipsychotic)

66%: **<1% support / 99+% no support**

Radley et al., AcademyHealth Annual Research Meeting, June 2004, taken from IMS Health data.

### Off-Label Prescribing with Strong Scientific Support

Medication	Functional Class	Drug Mentions: Strong Support (millions)	Proportion: Off-Label Mentions with Strong Support (%)
albuterol	Antiasthmatic	6.8	67
amoxicillin	Antimicrobial	4.4	54
azithromycin	Antimicrobial	2.7	75
atenolol	HTN	1.8	78
digoxin	Cardiac: rhythm	1.7	38

### Off-Label Use with Little/No Scientific Support

Medication	Functional Class	Drug Mentions: Little/No Support (millions)	Proportion: Off-Label Mentions with Little/No Support (%)
amoxicillin	Antimicrobial	3.7	46
albuterol	Antiasthmatic	3.3	33
digoxin	Cardiac: rhythm	2.8	62
gabapentin	Anticonvulsant	2.8	80
loratadine / pseudoephedrine	Allergy	2.8	95

Radley et al., AcademyHealth Annual Research Meeting, June 2004, taken from IMS Health data.

### Off-Label Use with Strong Scientific Support

Indication	Supported Off-Label Mentions (million)	Proportion of Supported Off-Label Therapy (%)	Most Frequent Concomitant Off-Label Drug
Chronic Sinusitis	6.2	32	amoxicillin (59%)
COPD	4.2	19	albuterol (77%)
Chronic Ischemic Disease	2.7	19	atorvastatin (21%)
Asthma	1.6	8	loratadine (36%)
Cardiac_Arrhythmias	1.3	40	metoprolol (31%)

### Off-Label Use Little / No Scientific Support

Indication	Un-Supported Off-Label Mentions (million)	Proportion of Un-Supported Off-Label Therapy (%)	Most Frequent Concomitant Off-label Drug
Chronic Sinusitis	5.5	28	fluticasone (15%)
Chronic Ischemic Disease	4.2	29	digoxin (22%)
Ac. Respiratory Infection	4.3	26	loratadine (16%)
Depression	4.0	14	alprazolam (29%)
COPD	3.9	17	amoxicillin (46%)

Radley et al., AcademyHealth Annual Research Meeting, June 2004, taken from IMS Health data.

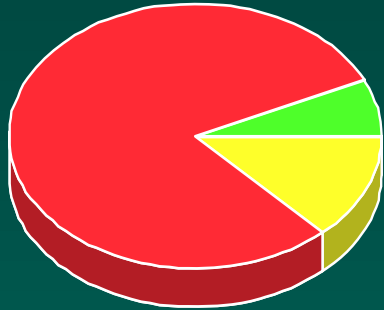
# Natural history of schizophrenia



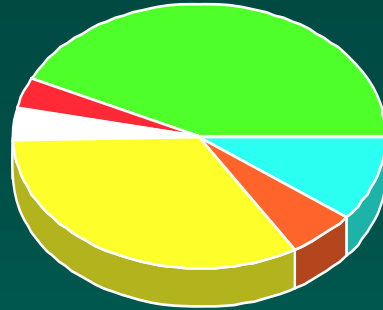
# Outcome targets for schizophrenia treatment

- Relief of symptoms: positive, negative, affective, cognitive
- Freedom from despair and suicidal ideation
- Absence of drug related side effects
- Prevention of hospitalization
- Improved general health
- Ability to live independently
- Ability to pursue occupational objectives
- Overall adequate quality of life and social interaction

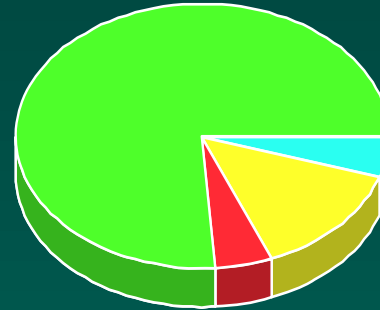
# Atypical Antipsychotics In Vivo Binding Affinities



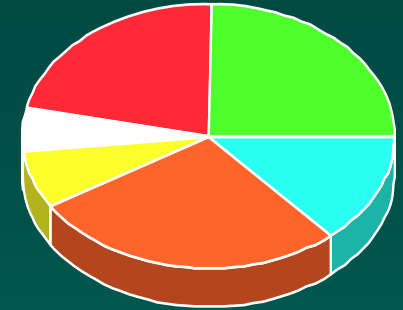
Haloperidol



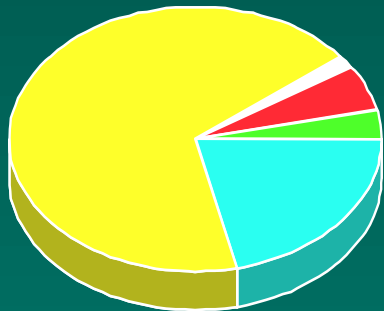
Clozapine



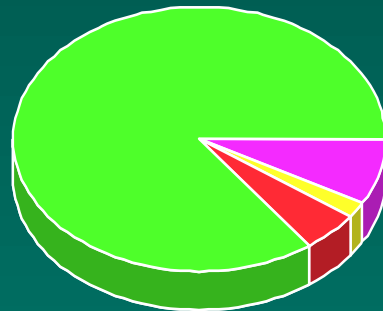
Risperidone



Olanzapine



Quetiapine



Ziprasidone

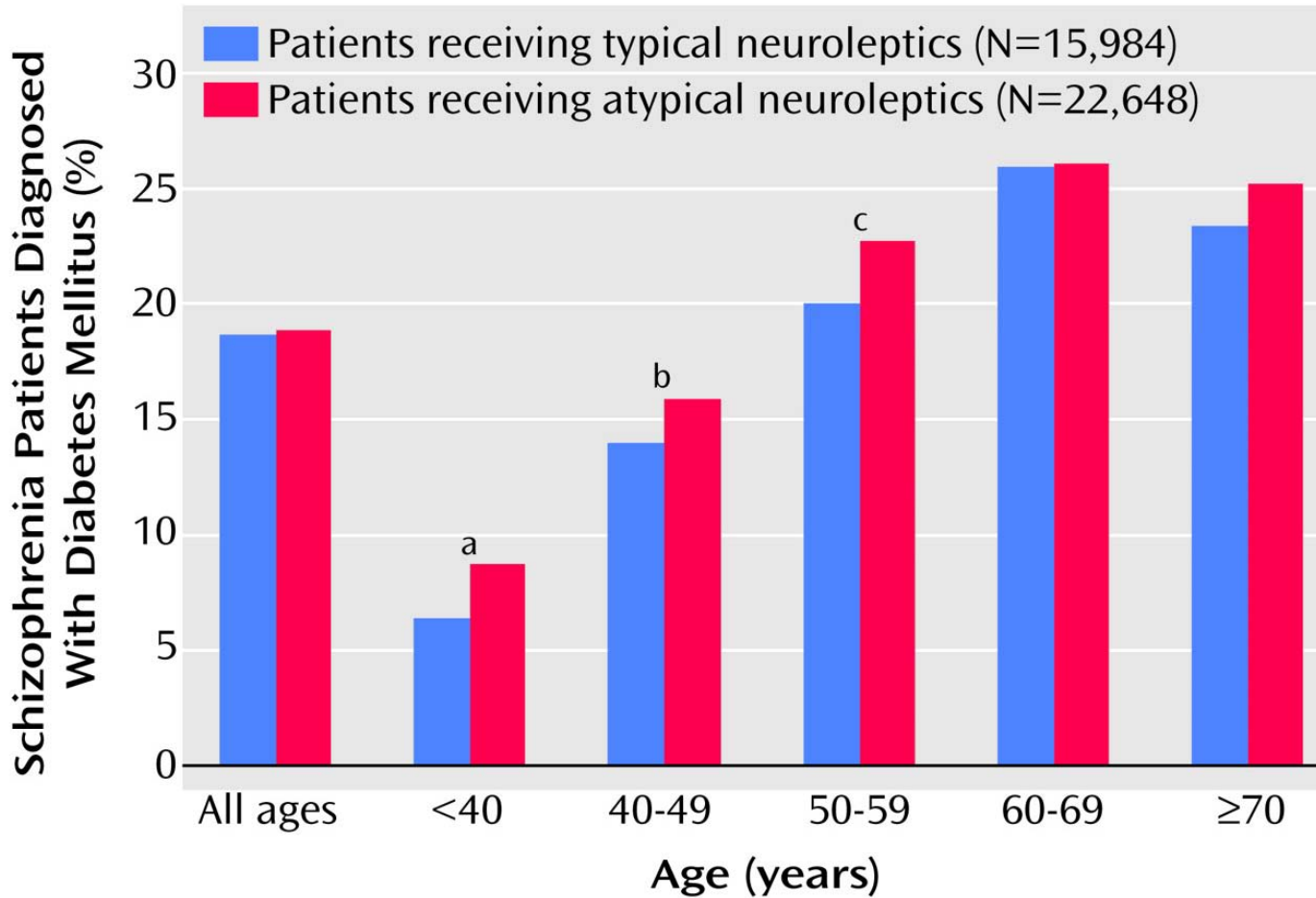


# Basic pharmacology and clinical effects of antipsychotics

D1-like blockade	Blunts cocaine euphoria
D2-like blockade	Antipsychotic, antimanic; EPS
AChM blockade	Dry mouth; protects against EPS
H1 blockade	Sedation, weight gain
NA a1 blockade	Postural hypotension, initial sedation
NA a2 blockade	Antidepressant
5-HT2A blockade	Reduces EPS; increases slow wave sleep; improves mood?
5-HT2C blockade	Weight gain; improves mood?

# Side effects of antipsychotics

	typical antipsychotics	Clozaril	Risperdal	Zyprexa	Seroquel
<b>Sedation</b>	+ to +++	+++	+	++	++
<b>EPS</b>	+ to +++	0	+	0 to +	0
<b>Antichol. Effects</b>	+ to +++	+++	0	+ to ++	0 to +
<b>Weight gain</b>	+	++++	+	+++	++
<b>Prolactin Increase</b>	+ to ++	0	+ to ++	+/-	0
<b>AST/ALT Increase</b>	+	+	0	0 to +	+
<b>Orthostatic Hypotension</b>	+ to +++	+++	++	+	++
<b>Prolonged QT</b>	+/-	+	0	0	0
<b>Agranulocytosis</b>	0	+++	0	0	0
<b>Tardive Dyskinesia</b>	+++	0	+?	+?	?

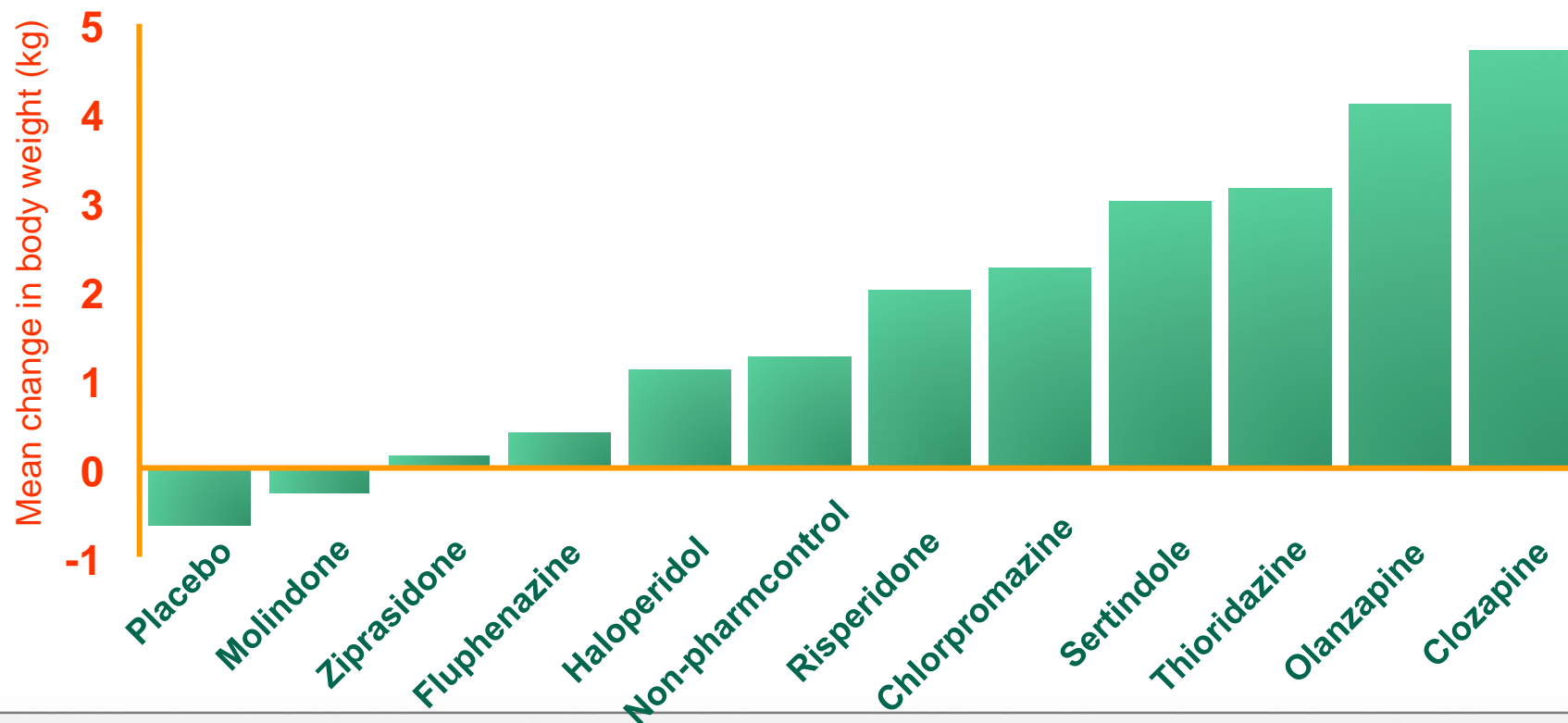


Association of Diabetes Mellitus With Use of Atypical Neuroleptics in the Treatment of Schizophrenia  
 Michael J. Sernyak, M.D.,  
 Douglas L. Leslie, Ph.D.,  
 Renato D. Alarcon, M.D.,  
 Miklos F. Losonczy, M.D.,  
 Ph.D.,  
 and Robert Rosenheck, M.D., Am J Psychiatry 159:561-566, April 2002

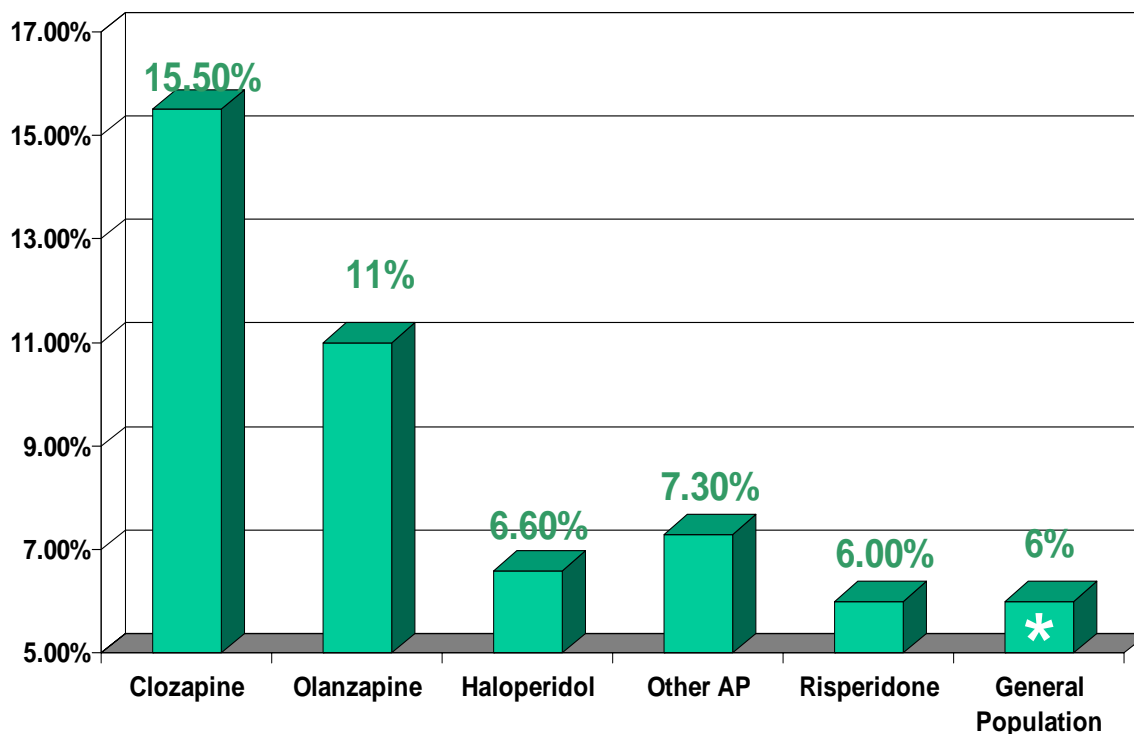
## Estimated mean weight gain at ten weeks

A comprehensive literature search identified 78 studies that included data on weight change in patients treated with a specific antipsychotic. For each agent a meta-analysis and random effects regression estimated the change in weight at 10 weeks of treatment.

Allison, D.B., Mentore, J.L., Heo, M. et al: Weight gain associated with conventional And newer antipsychotics: a meta analysis, Am J Psychiatry 1999



# Incidence Of Type 2 Antipsychotic Associated Diabetes



Pittsburgh Schizophrenia  
Treatment and Research  
Center Zoler, Ganguli, '99  
Canadian Guidelines on the  
Treatment of diabetes 1999

# Atypical Antipsychotics and diabetes

- **Hierarchy of diabetes risk increase with atypicals: olanzapine 12-35%, clozapine 17-37%**  
(Casey, Smith, Henderson, Hagg, Melkersson, Zoler)
- **Hierarchy of weight gain with atypicals: clozapine ≥ olanzapine > quetiapine > risperidone**  
(Wirshing, Allison)
- **Differential direct effects on insulin resistance: clozapine > olanzapine > risperidone > ziprasidone**  
(Newcomer, Henderson, Glick, Fryburg, Cohn, Chue)
- **Olanzapine: DM 1 (32% of case reports), DM 2 (17% of case reports), DKA (51% case reports), direct effect on glucose & insulin resistance**  
(Newcomer, Henderson)