2010

Weight Gain in Psychiatric Treatment: Risks, Implications, and Strategies for Prevention and Management

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Weight gain and Psychotropic's

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Disclosure

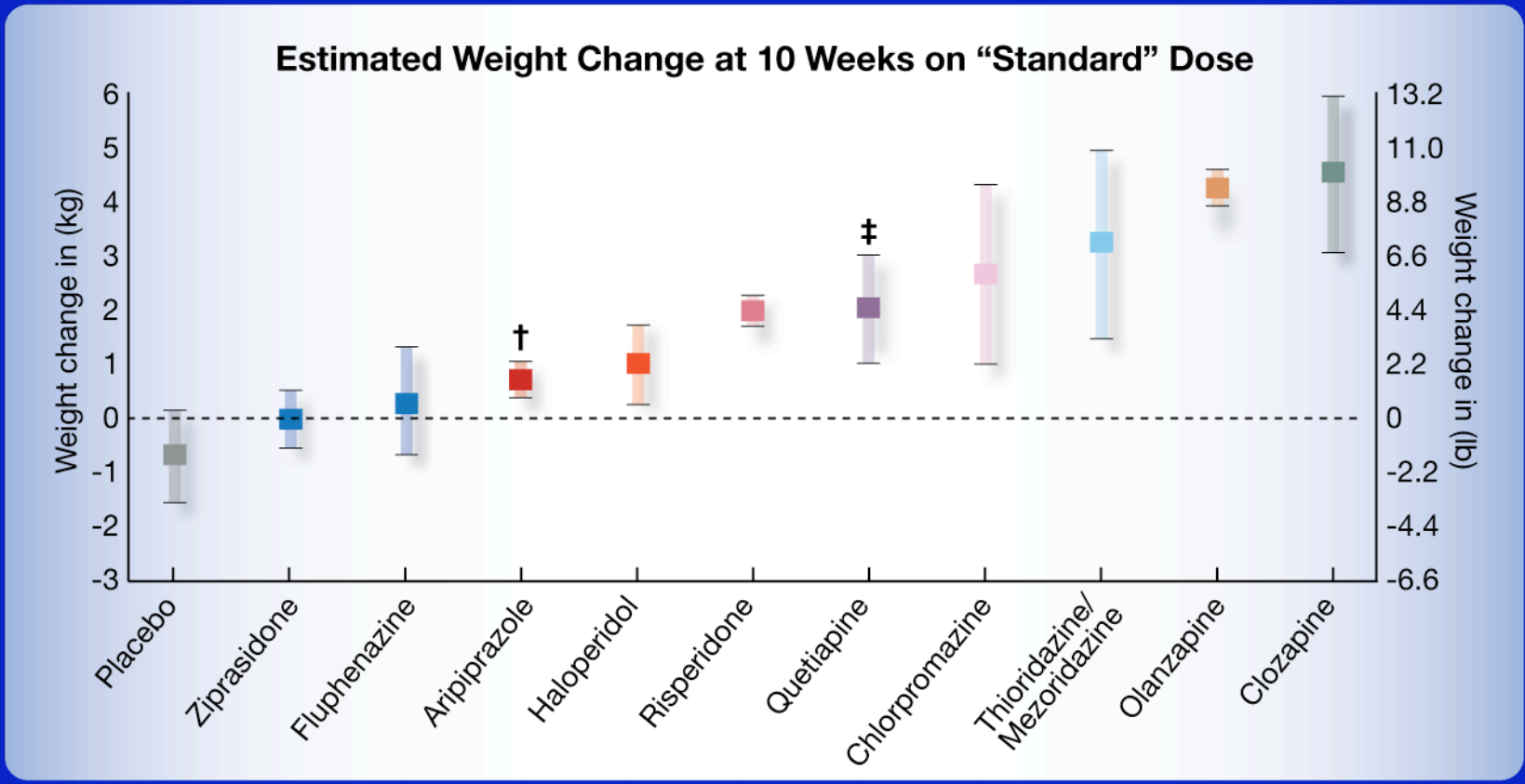
Research, education & travel grant.
Speakers group & advisory panels

- Janssen Cilag
- Janssen Ortho
- Astra zeneca.Canada & UK
- Pfizer
- Roche pharmaceuticals
- Nicolus Pharmaceuticals
- SUN Pharma
- Prempharma

non-pharmacological interventions reduce antipsychotic induced weight gain

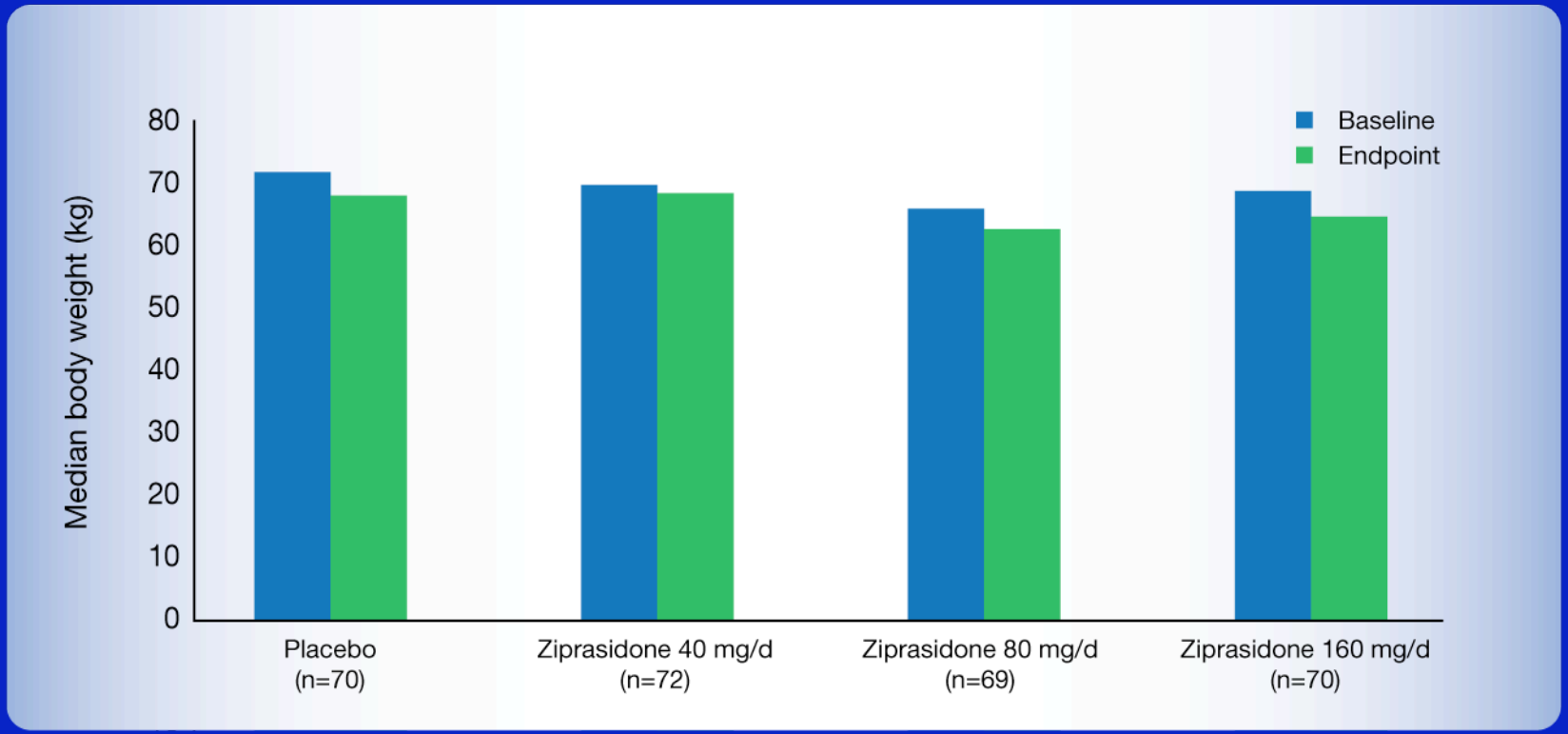
- Six RCTs assessed the effects of cognitive behavioural therapy (CBT), three assessed nutritional coun- selling and one assessed a combination of nutritional counselling and exercise. Non-pharmacological interventions significantly reduced weight and BMI compared with treat- ment as usual (WMD in weight 22.56 kg, 95% CI 23.2 to 21.9 kg; p,0.001; I2 = 28.9%; WMD in BMI 20.91 kg/m2, 95% CI 21.1 to 20.7 kg/m2; p,0.001; I2 = 28.9%). The reduction in weight with non-pharmacological interventions was maintained at 2–3 months of follow-up (three RCTs; WMD 24.1 kg, 95% CI 25.8 to 22.5 kg; p,0.001). Analyses of subgroups found no statistically significant differences in the treatment effect sizes between trials that aimed to prevent weight gain (four trials) and those that aimed to produce weight loss (six trials); between group (five trials) and individual (five trials) forms of intervention;

Meta-Analysis of Antipsychotic-Related Weight Gain: Estimate at 10 Weeks



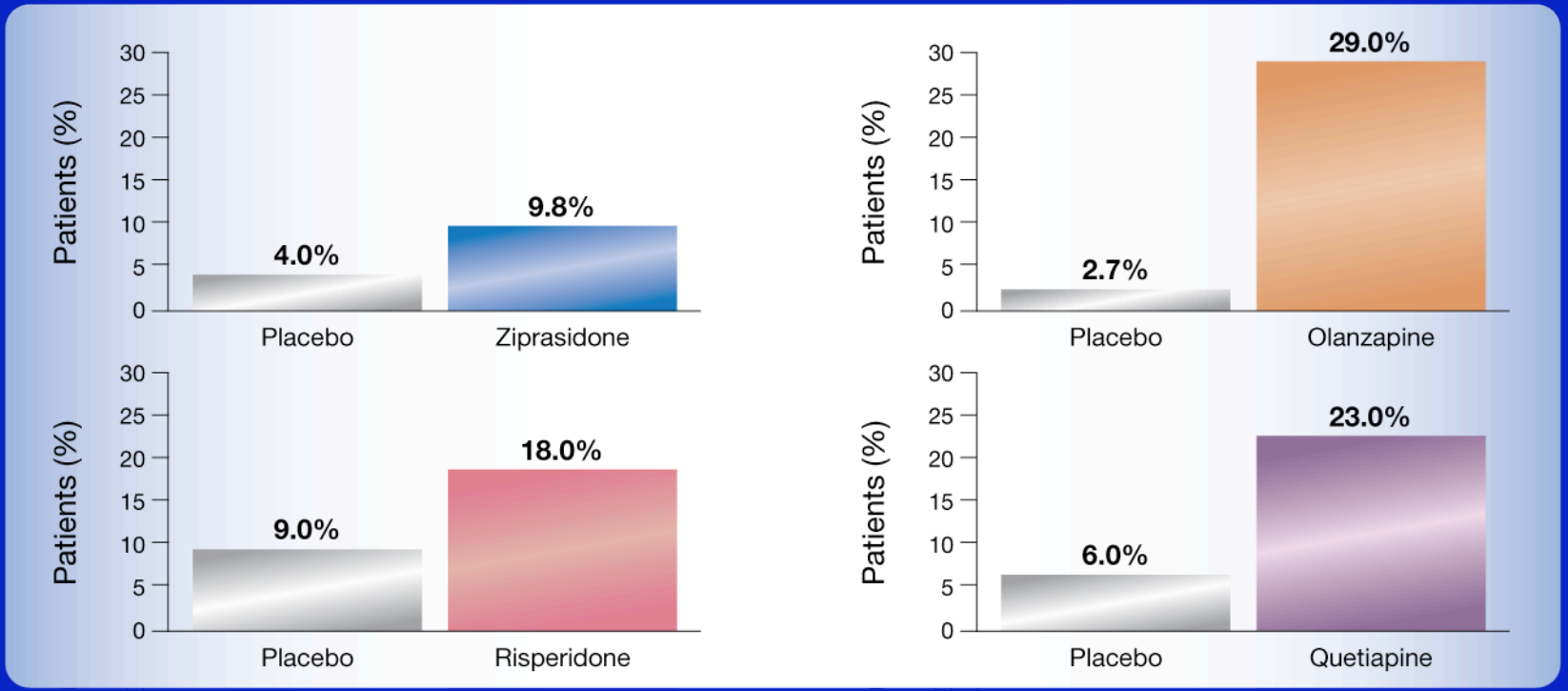
† 4-6 week pooled data (Marder SR *et al. Schizophr Res* 2003;1;61:123-136).
‡ 6-week data adapted from Allison DB, Mentore JL, Heo M *et al. Am J Psychiatry* 1999;156:1686-1696; Jones AM *et al.* ACNP, 1999.

Ziprasidone vs. Placebo (ZEUS Study): Median Body Weight at Baseline and Endpoint



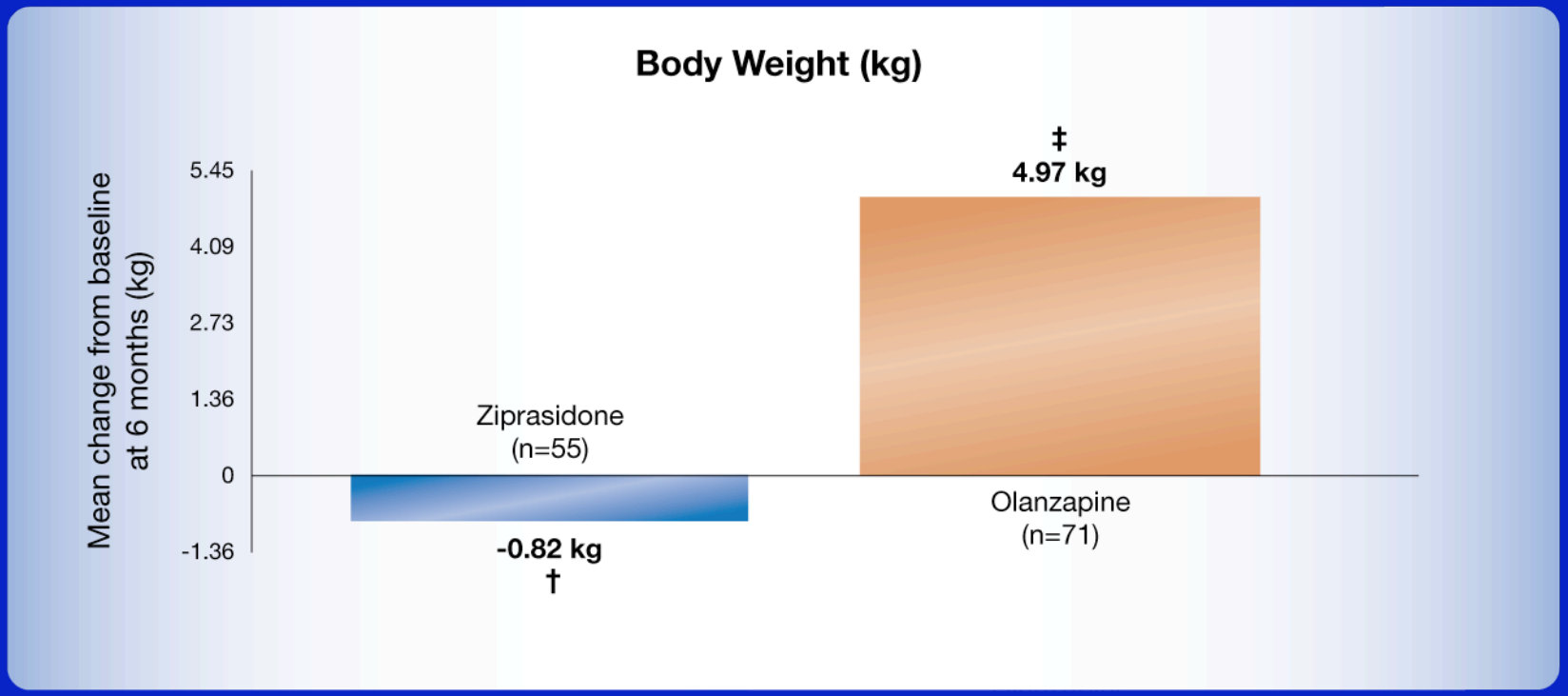
Arato M *et al. Int Clin Psychopharmacol* 2002;17:207-215.

Incidence of Clinically Significant (≥7%) Weight Gain in Short-Term Studies



Tandon *et al*. *J Ser Res* 1997;4:159-177.
Zyprexa USPI.
Risperdal USPI.
Seroquel USPI.

Ziprasidone Safety and Tolerability (6-Month Continuation Study): Demonstrated a Favourable Effect on Weight vs. Olanzapine

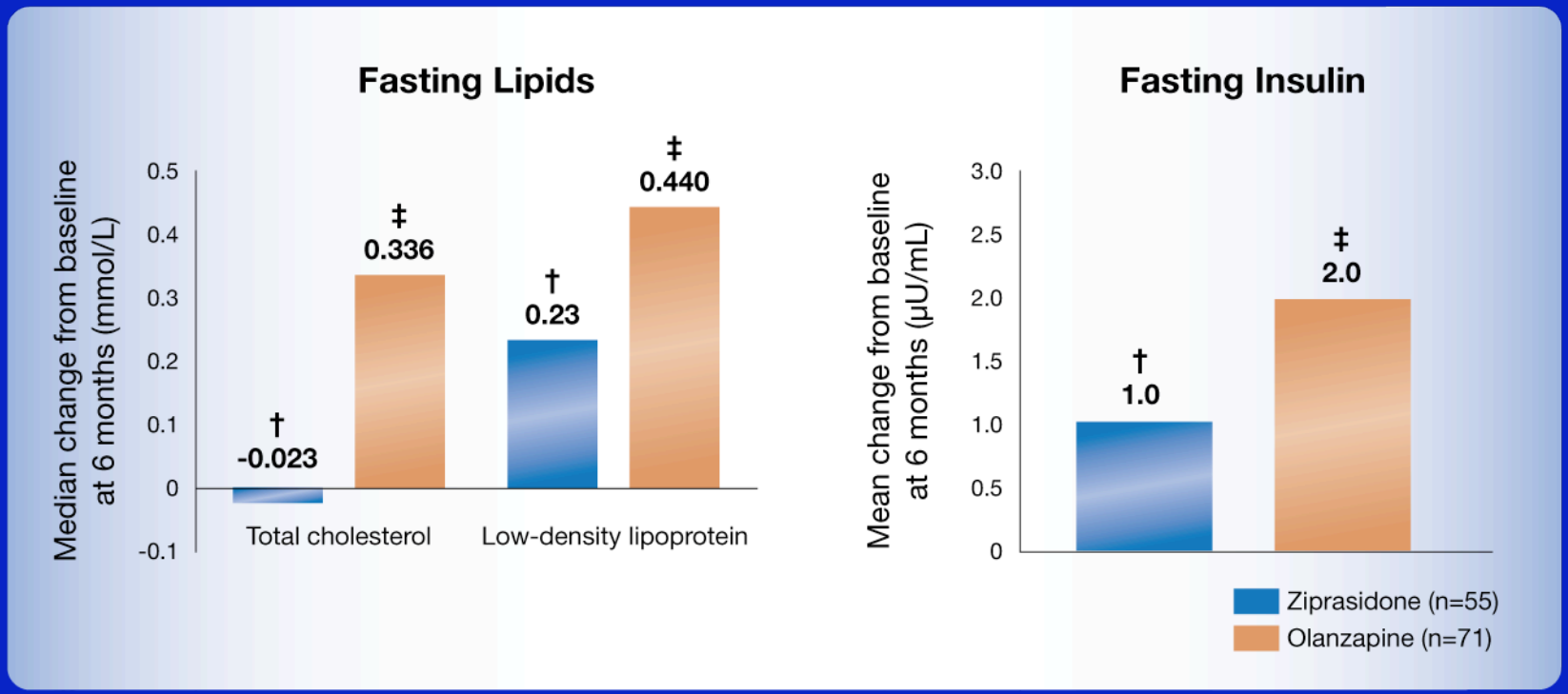


† $p<0.001$ between groups
‡ $p<0.05$ vs. baseline
Simpson GM *et al. Am J Psychiatry* 2005;162:1535-1538.

Mean Dose

Ziprasidone	135.2 mg/d
Olanzapine	12.6 mg/d

Ziprasidone Safety and Tolerability (6-Month Continuation Study): Demonstrated Favourable Effects on Lipids and Insulin vs. Olanzapine

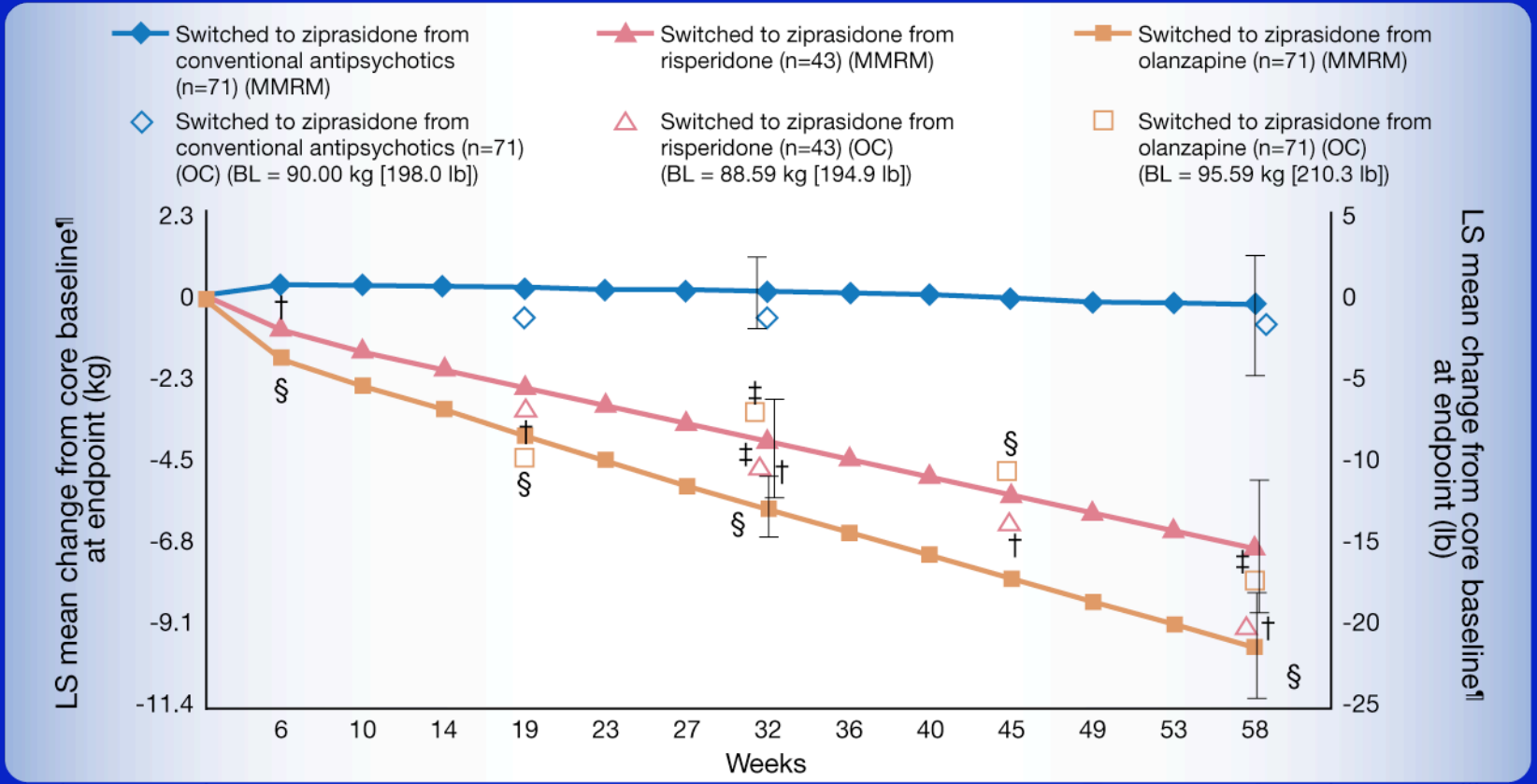


† *p*=NS vs. baseline
‡ *p*<0.05 vs. baseline
p=NS between treatment groups
Simpson GM *et al. Am J Psychiatry* 2005;162:1535-1538.

Mean Dose

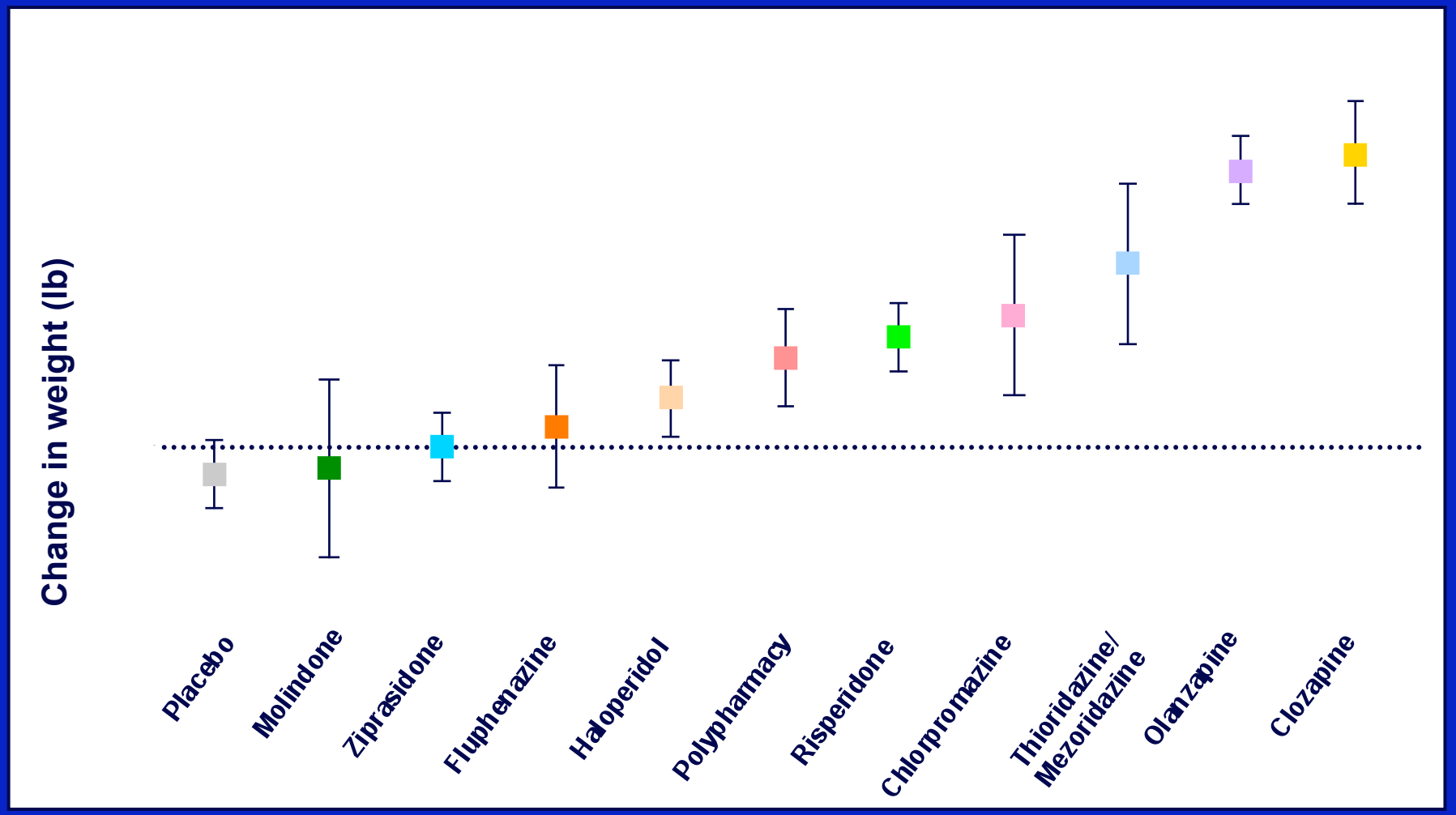
Ziprasidone	135.2 mg/d
Olanzapine	12.6 mg/d

Ziprasidone Safety and Tolerability (1-Year Switch Extension Studies): Change in Weight from Baseline 58 Weeks After Switching to Ziprasidone



MMRM = Mixed-model repeated measures
OC = Observed cases
BL = Baseline
† $p<0.05$; ‡ $p<0.01$; § $p<0.0001$; ¶ Core baseline – 6-week trial.
Weiden PJ *et al*. *Neuropsychopharmacology* 2008;33:985-994.

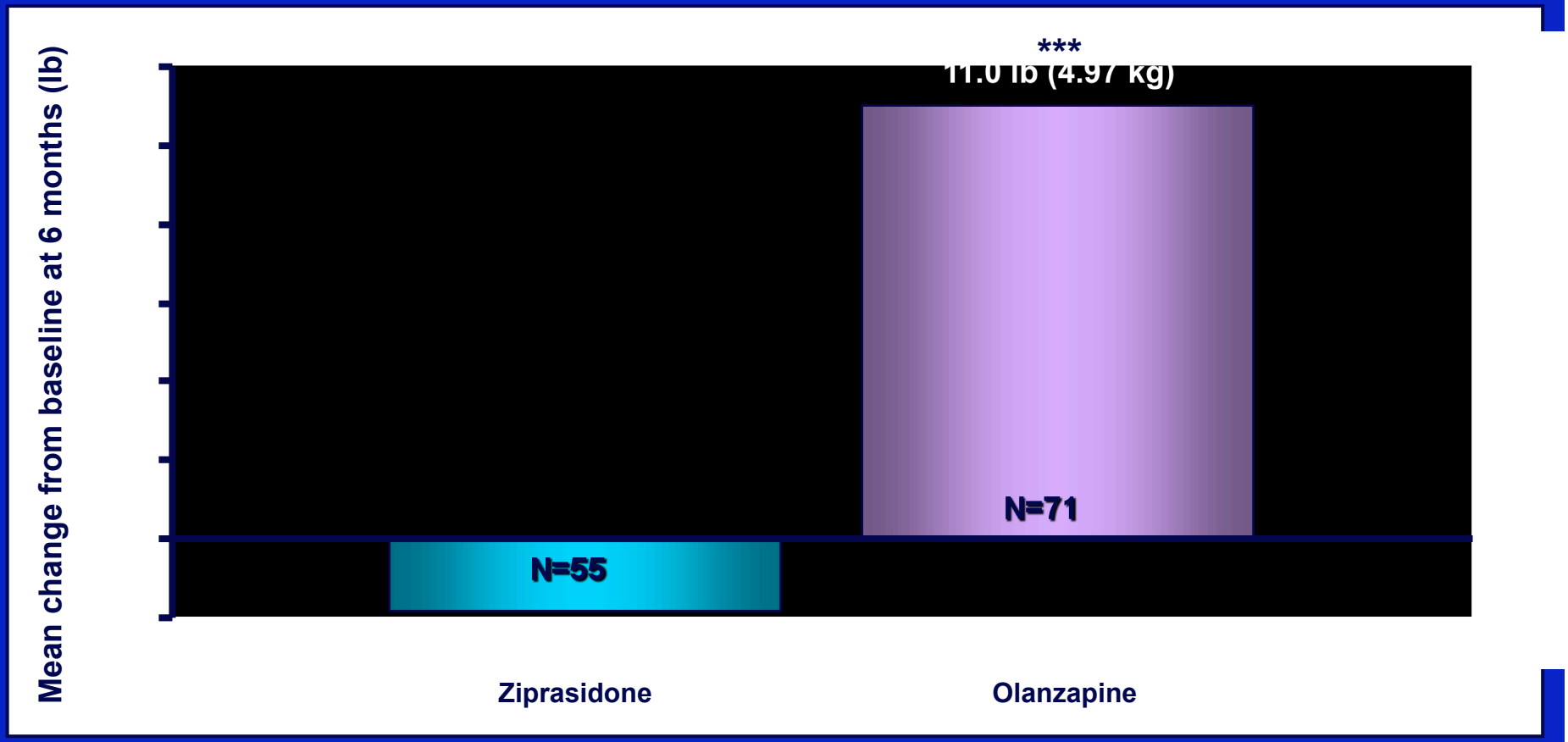
Antipsychotics and Weight Gain After 10 Weeks of Treatment



Adapted from Allison DB, et al. *Am J Psychiatry.* 1999;156:1686-1696.

Favorable Weight vs Olanzapine

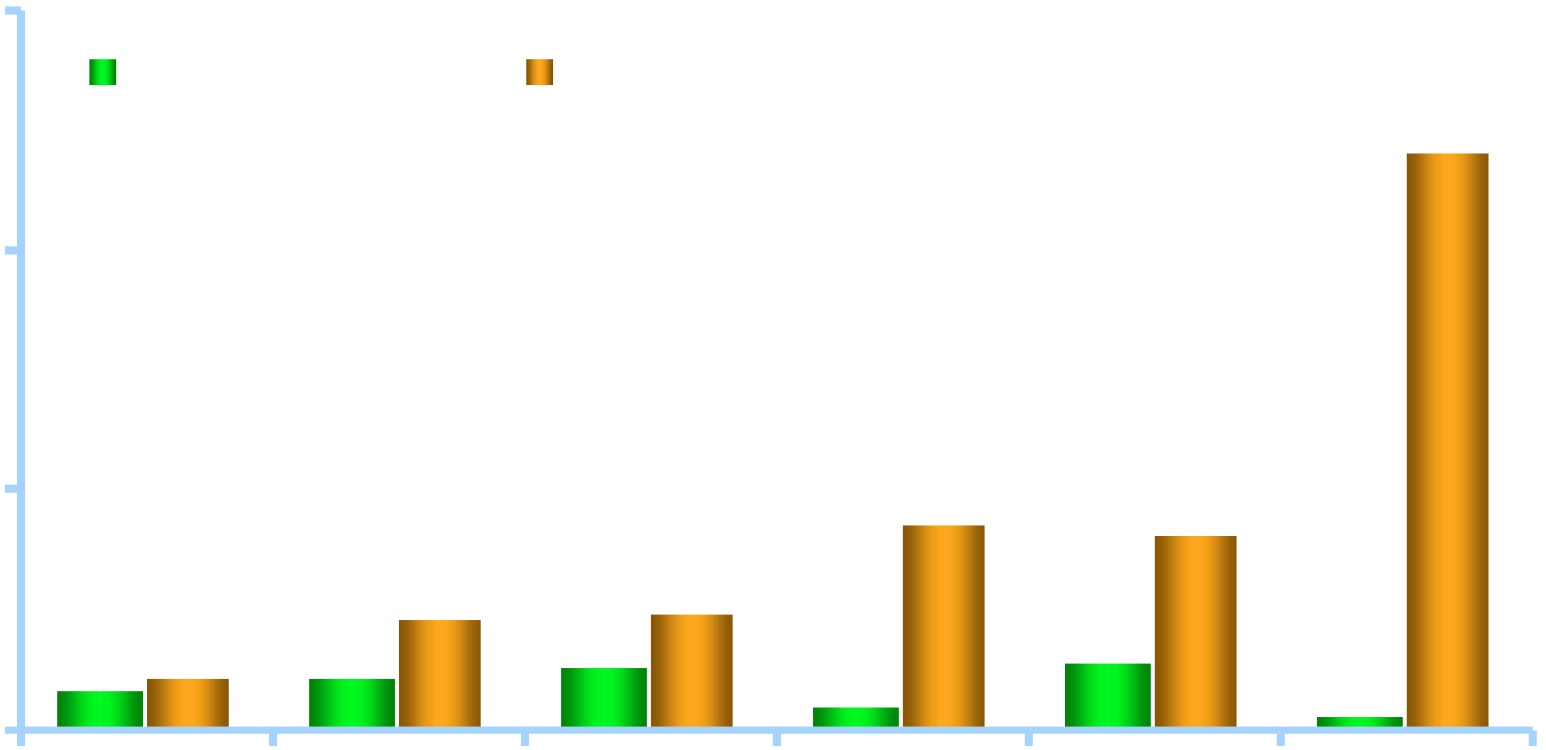
Body Weight (lb)



*$P<0.05$ vs baseline
***$P<0.001$ vs between groups
Simpson GM, et al. *Am J Psychiatry.* 2005;162:1535-1538.

Mean Modal Dose	
Ziprasidone	135.2 mg/d
Olanzapine	12.6 mg/d

Distribution of Weight Change in Double-blind, Comparative, Short-term (4-12 wk) Studies



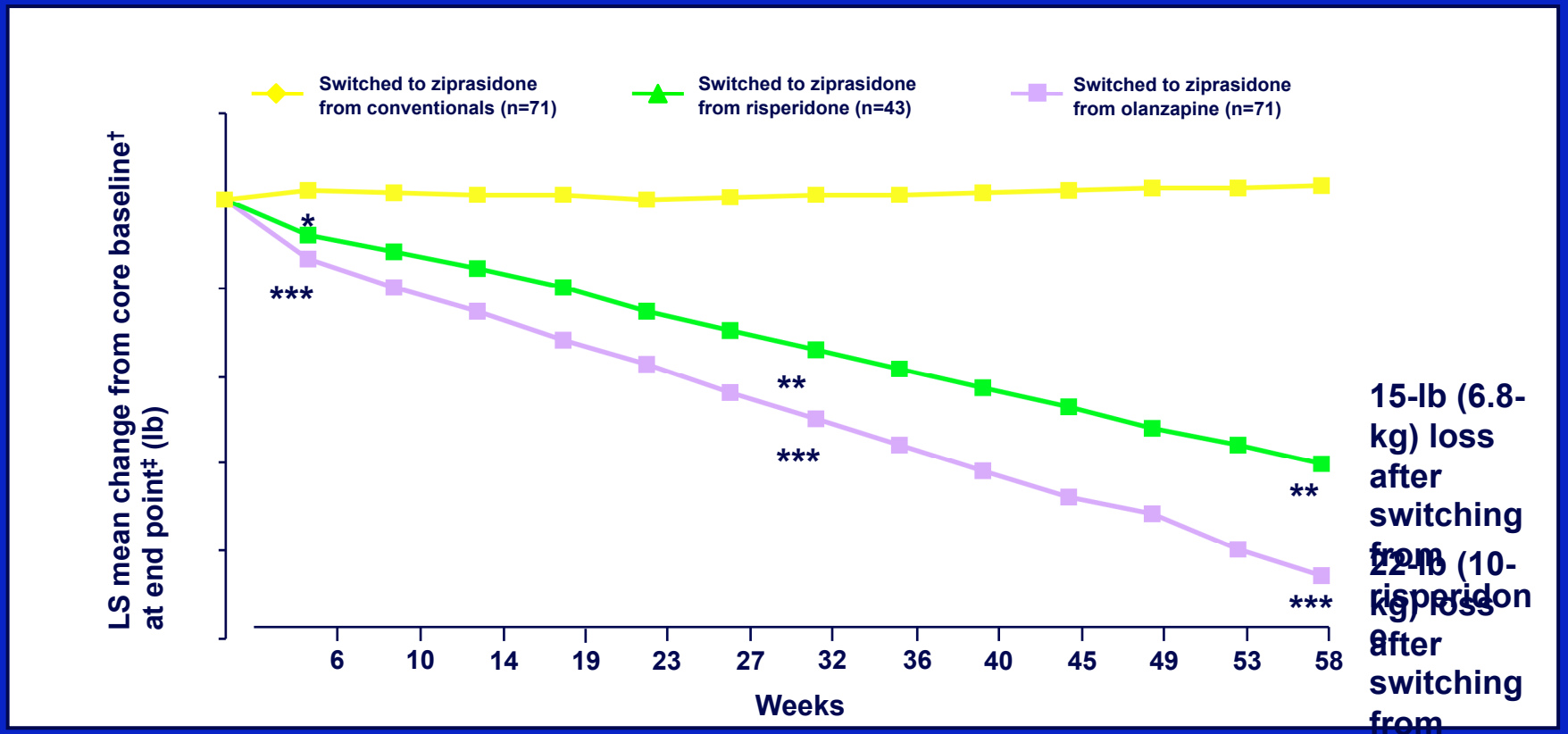
	N=187	N=1067	N=230	N=112	N=55	N=92
Mean change (lb)	-0.7	1.3	-0.02	4.2	2.9	11.2

***P*<0.01, ****P*<0.001, *****P*<0.0001 (vs placebo for distribution of weight change from baseline).

Parsons B et al. APA. May 2006.

Safety and Tolerability: Sustained Decrease in Weight After Switching

Mean Body Weight Change Over 58 Weeks



15-lb (6.8-kg) loss after switching from risperidone

22-lb (10-kg) loss after switching from olanzapine

*P<0.05, **P<0.001 ***P<0.0001.
†Core baseline—6-week trial. ‡Mixed-model analysis.
Weiden PJ, et al. APA 2004

Does weight gain matter ?

- **Psychological effects**

- low self esteem, depression, sleeping poorly

- **Social effects**

- Isolation, reluctance to participate in activities

- **Financial Effects**

- unemployment , additional purchases

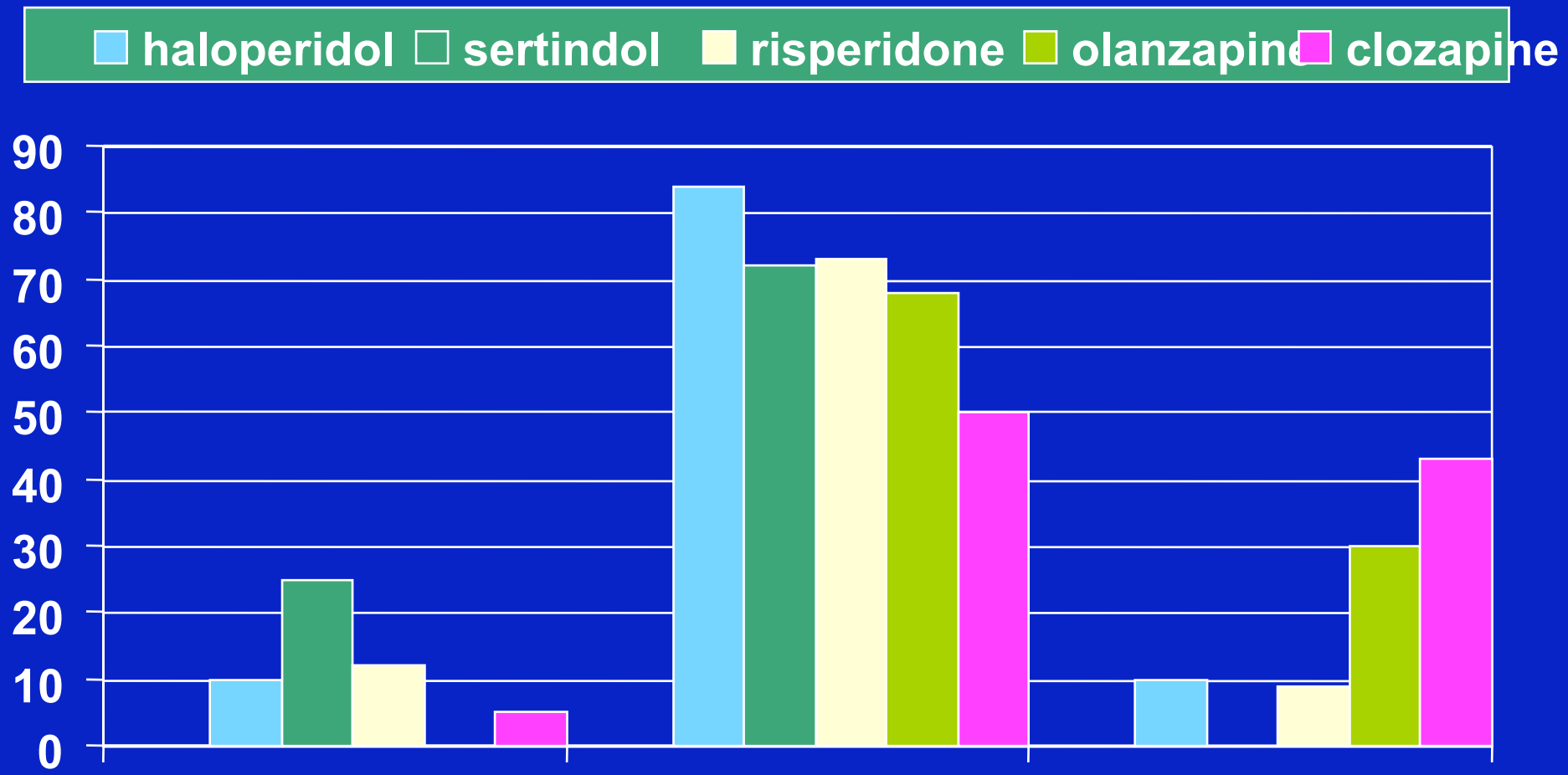
- **Physical symptoms**

- tiredness, sweating, back pain, arthritis, shortness of breath, stress incontinence, snoring

- **Metabolic problems**

-hypertension, hyperlipidaemia, ischemic heart disease, diabetes, major cancers, menstrual problems

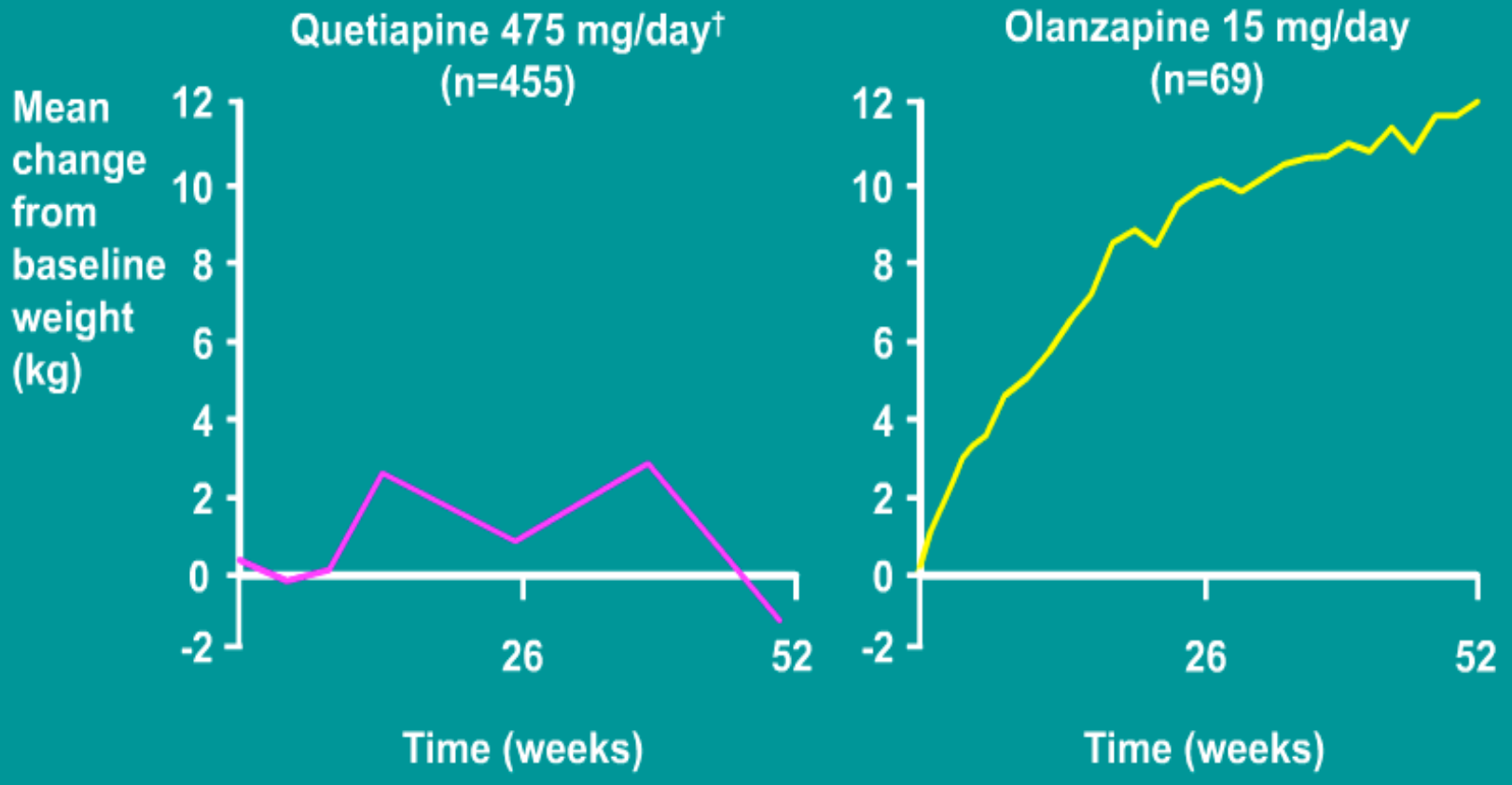
Weight gain and atypical APD



Weight gain and Quetiapine

- "Drug was associated with weight gains of approx. 2.1;3.5;and 5.6 kg after treatment for 4 to 6 weeks,18 to 26 weeks and 1 year respectively"
- "Clinically significant weight gain [>7% increase in body weight] occurred in up to 25% of quetiapine recipients in some clinical trials"
- There is evidence to indicate that weight gain may be more common with Quetiapine than with classical antipsychotics
- In multiple fixed dose comparative trial 10 to 16 % of patients receiving Quetiapine had clinically significant weight gain compared to 4% receiving haloperidol
- Mean weight gain in 6 weeks study ranged between 0.9 to 2.9 kg in Quetiapine patients compared with 0.3 kg receiving haloperidol, and a reduction of 0.8 kg in placebo
- In CPZ trial , 27% of Quetiapine- treated patients had significant weight gain compared to 18% in CPZ group

Long-term weight change - differences between atypical antipsychotics

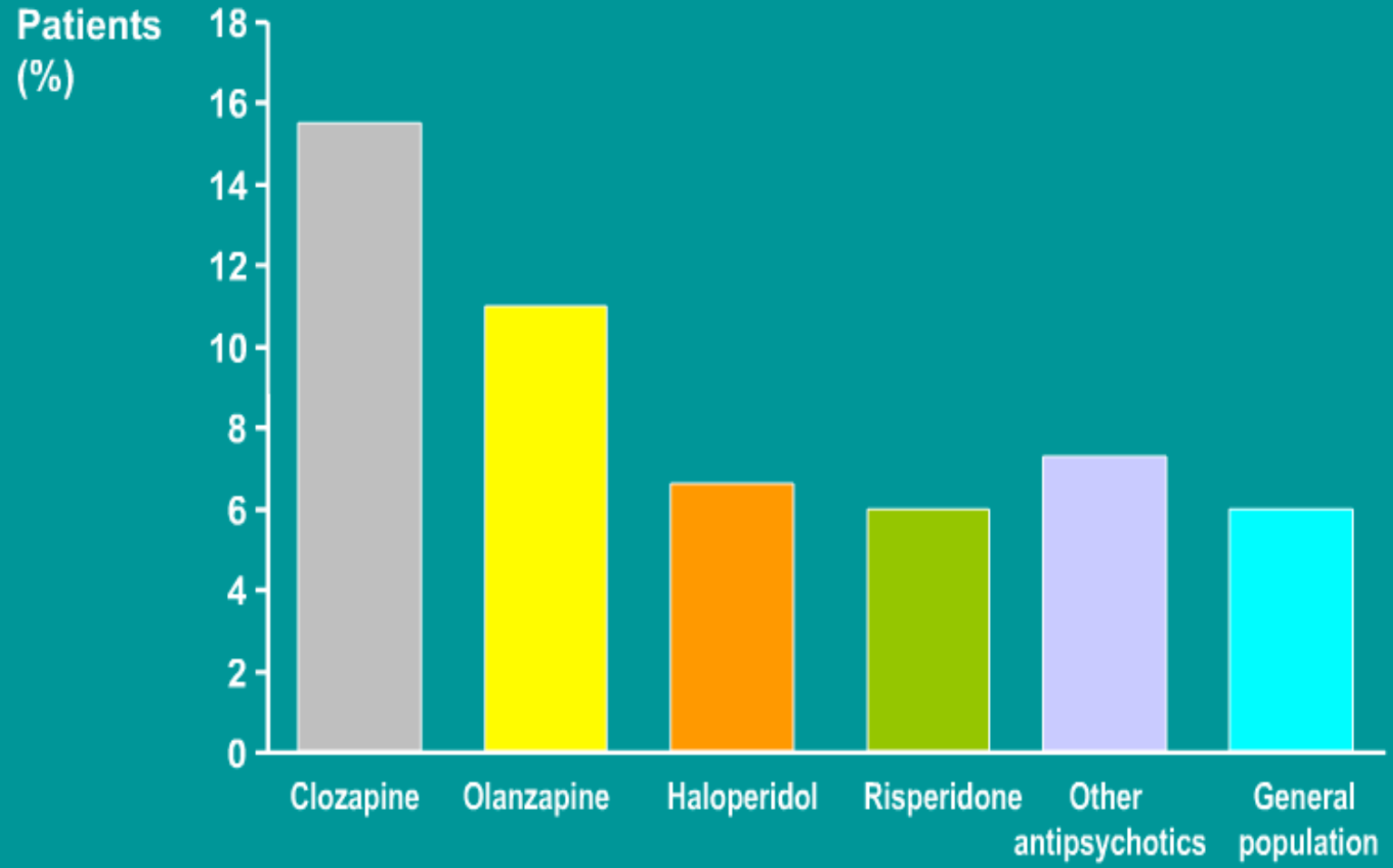


†Mean dose at completion of trial

Kasper & Müller-Spahn 2000

Adapted from Nemeroff 1997

Incidence of type 2 diabetes associated with antipsychotic use in schizophrenia



Cross-sectional study (n=396)

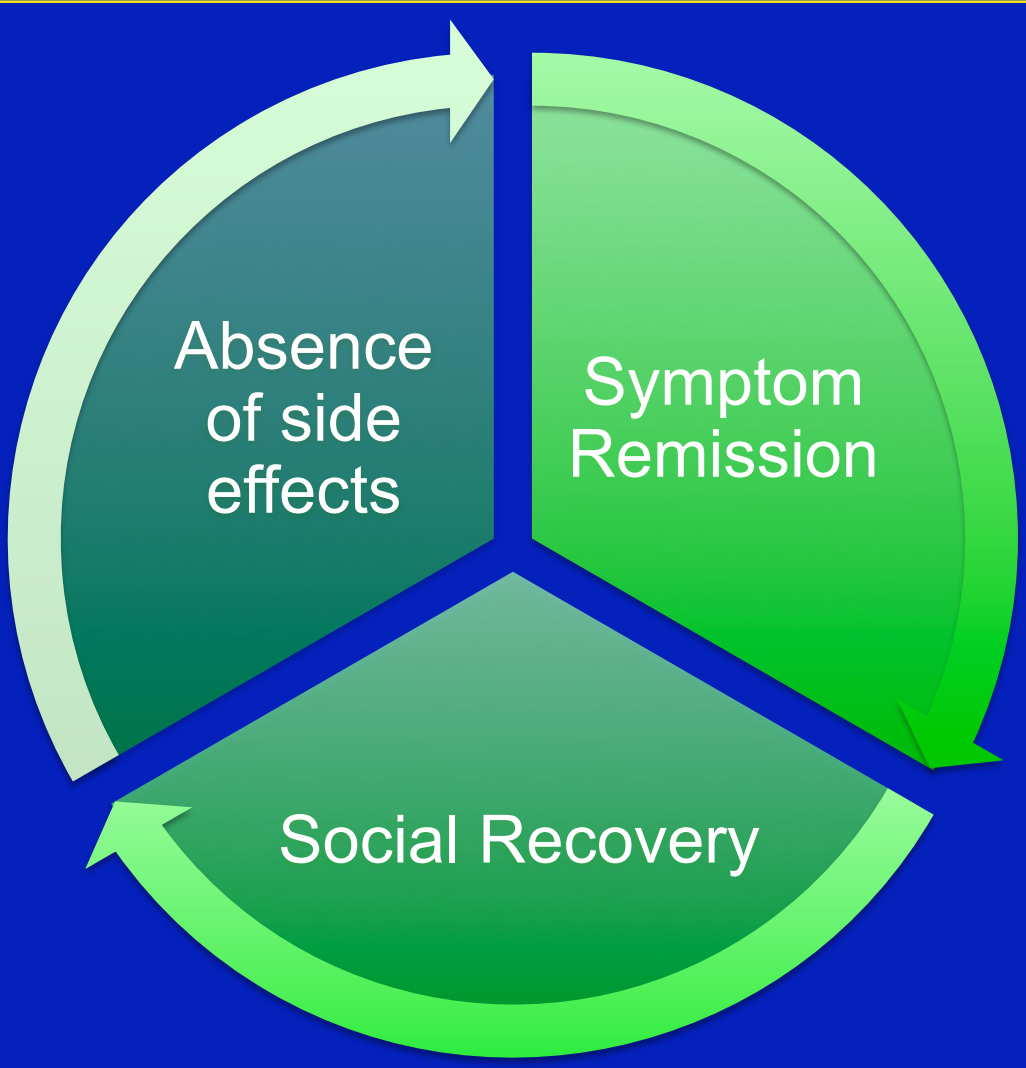
Zoler and Ganguli 1999;
Canadian Guidelines on the Treatment of Diabetes 1999

New onset diabetes Mellitus and diabetic ketoacidosis: analysis of 45 cases

Jim,H.;Meyer JM;Jeste DV ;Ann.Cl.Psy march 22002

- **Clozapine 20 cases**
- **Olananzapine 19**
- **Quetiapine. 03**
- **Risperidone . 03**
- **NS for duration, weight gain, family history of DM ,exposure to drug**
- **87% were male**
- **84% were over-weight at base**
- **42% presented with DKA**
- **DKA was seen in young, female, less weight**

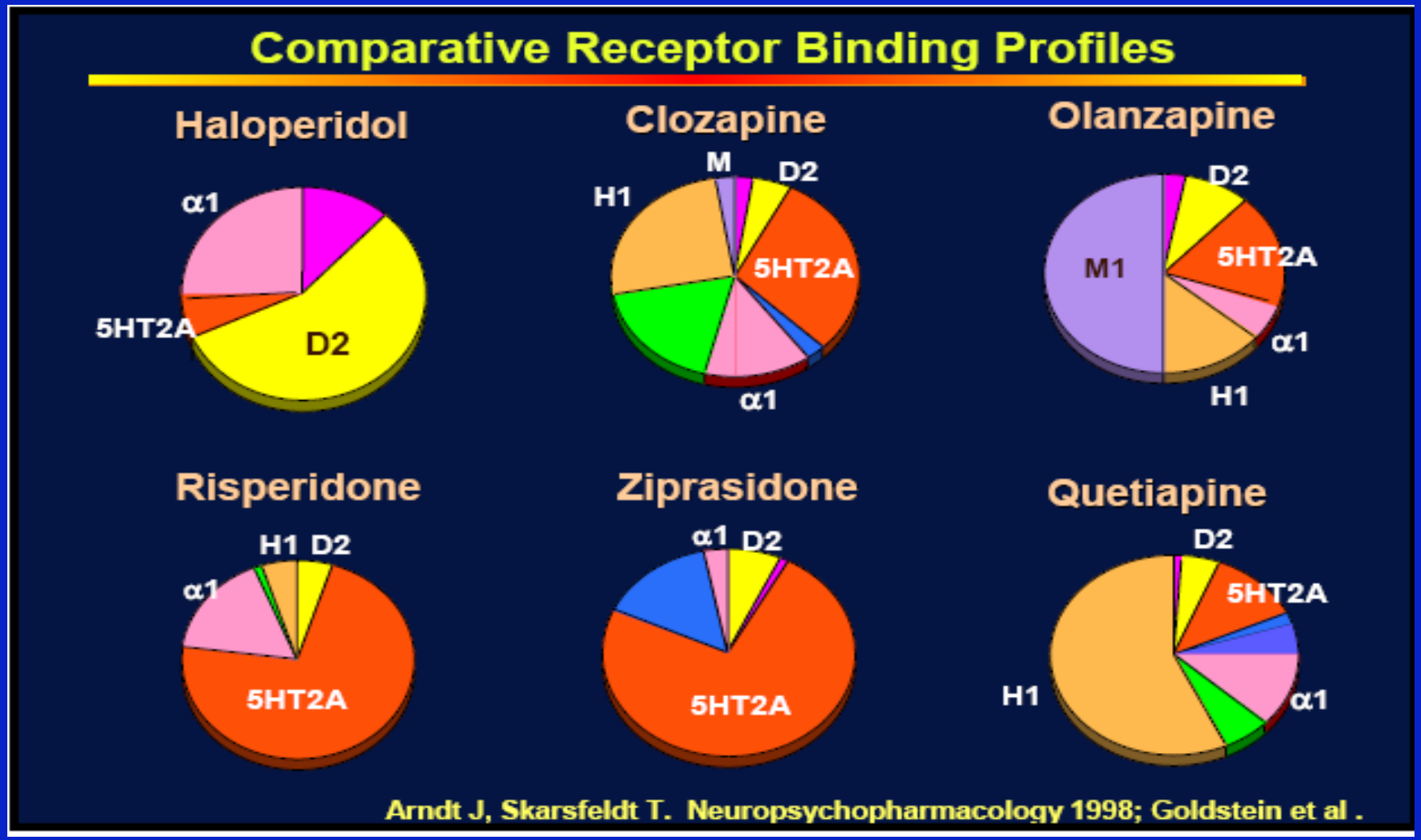
Differences are expected on efficacy & side effect



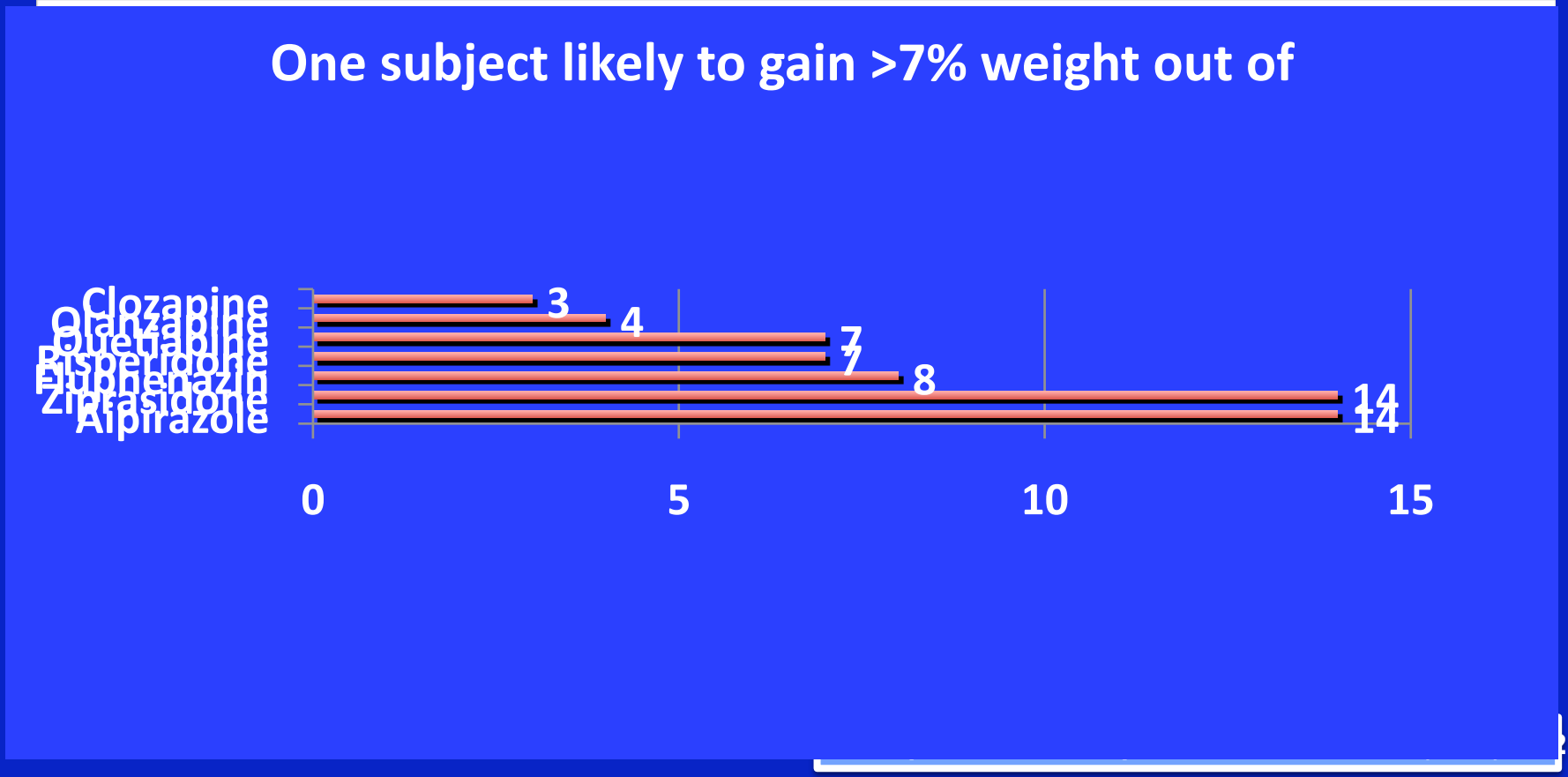
Atypical antipsychotics:

SDA: Ratio- D2/5HT$_{2A}$

Does Receptor occupancy correlate with symptom Control ?

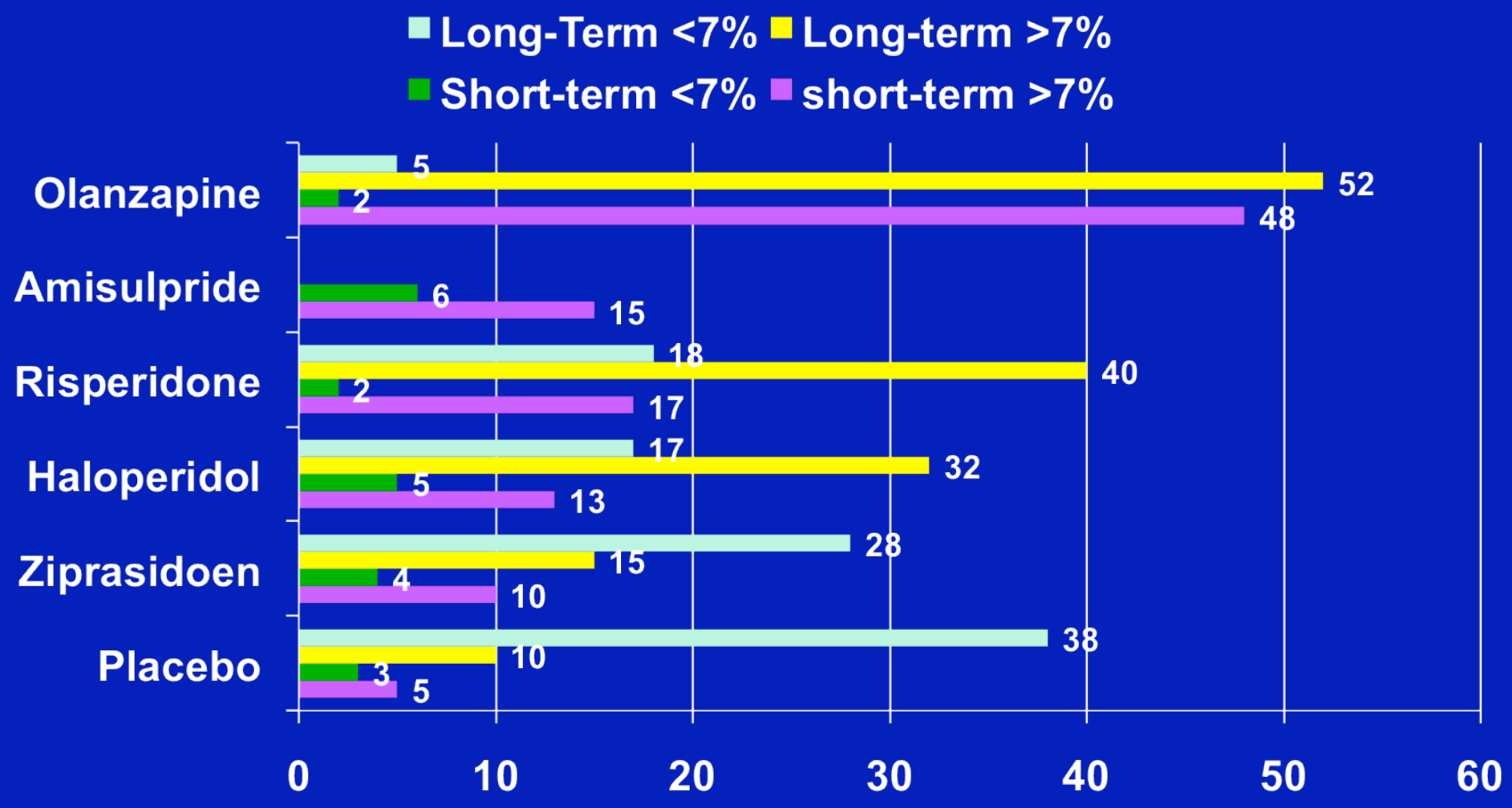


Weight Gain and AAPD



Early Weight gain persists

Short (N=1717, 4-12 wks) & Long-term (N=1649, 52 wks),



Bruce,P et al, Weight effects associated with antipsychotics: A comparative database analysis, Schizophrenia research 110 (2009) 103-110

What We Should Be Doing

Inquiry	Measure	Lab
• Personal or family history: – Diabetes – Hypertension – CHD (MI or Stroke) – Cigarette smoking – Diet – Physical Activity	• Height • Weight • Waist circumference • Blood Pressure	• Fasting Glucose • Fasting Lipids

And - trying to use medications which have fewer metabolic side effects!

ADA/APA Consensus Conference on Antipsychotic Drugs and Obesity and Diabetes
Summary

Drug	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine (Clozaril)	+++	++	++
Olanzapine (Zyprexa)	+++	++	++
Risperidone (Risperdal) Paliperidone (Invega)	++	+/-	+/-
Quetiapine (Seroquel)	++	+/-	+
Aripiprazole* (Abilify)	+/-	-	-
Ziprasidone* (Geodon)	+/-	-	-

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

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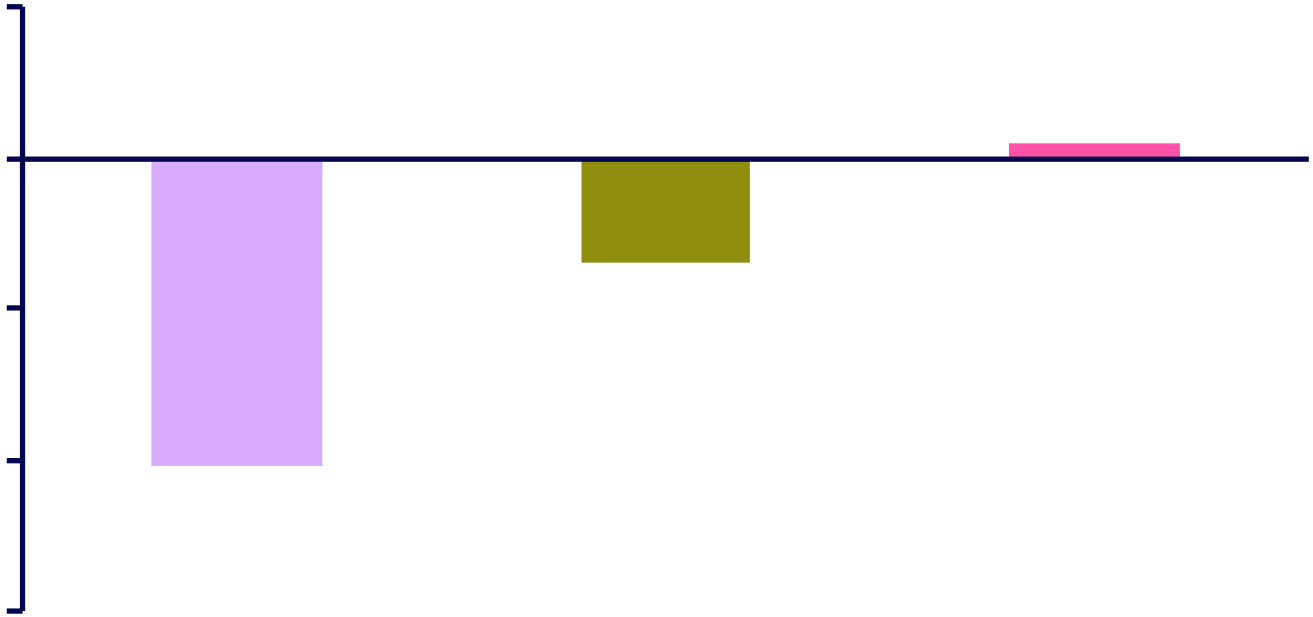
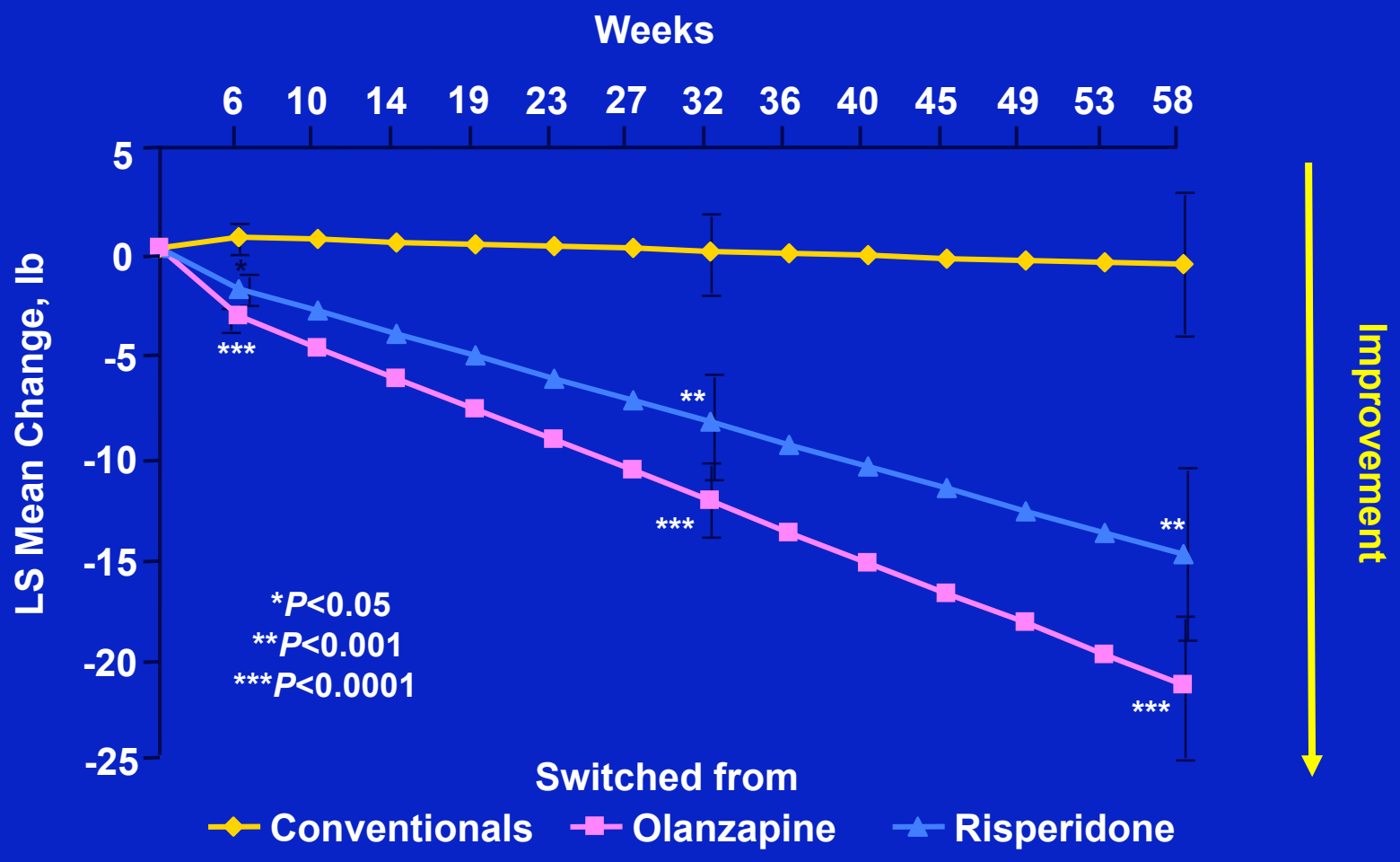
Change in Body Weight Following Switch to Aripiprazole-8 Wk Study



*$p<0.001$; †$p=0.077$
LOCF analysis.

Casey, et al. *Int J Neuropsychopharmacol*. 2002;5(suppl 1):S187.

Estimated Weight Change (lb) After Switch to Ziprasidone†



†Repeated measures analysis

Presented at APA 2004, New York, NY

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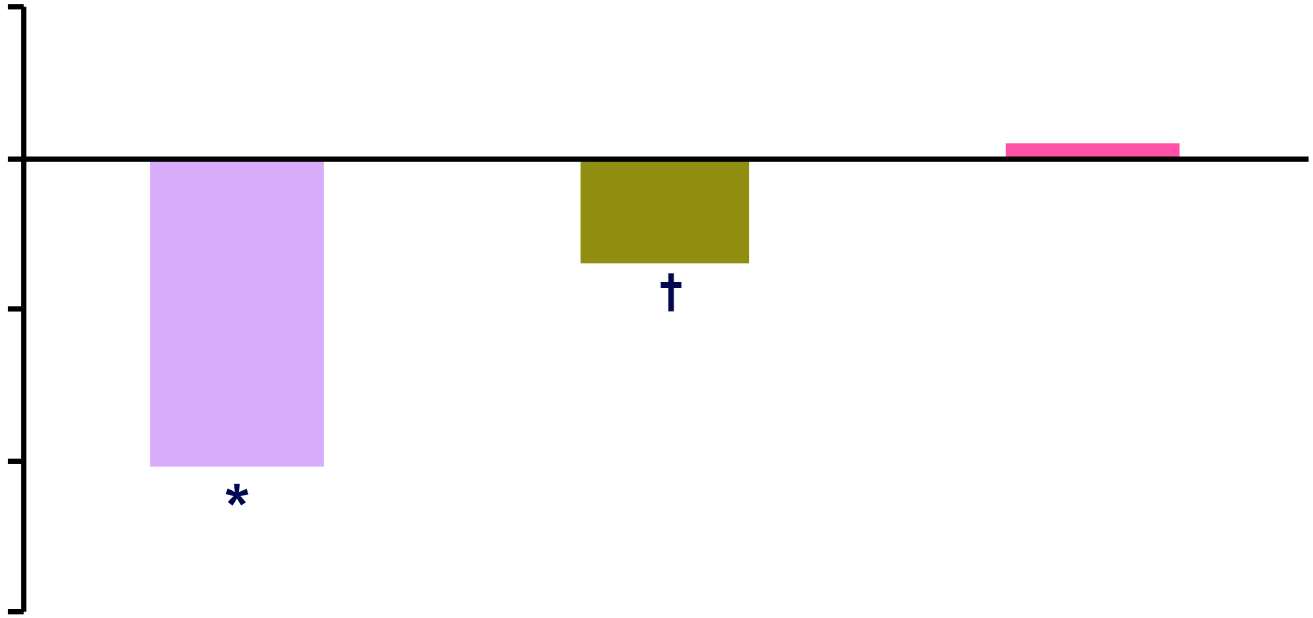

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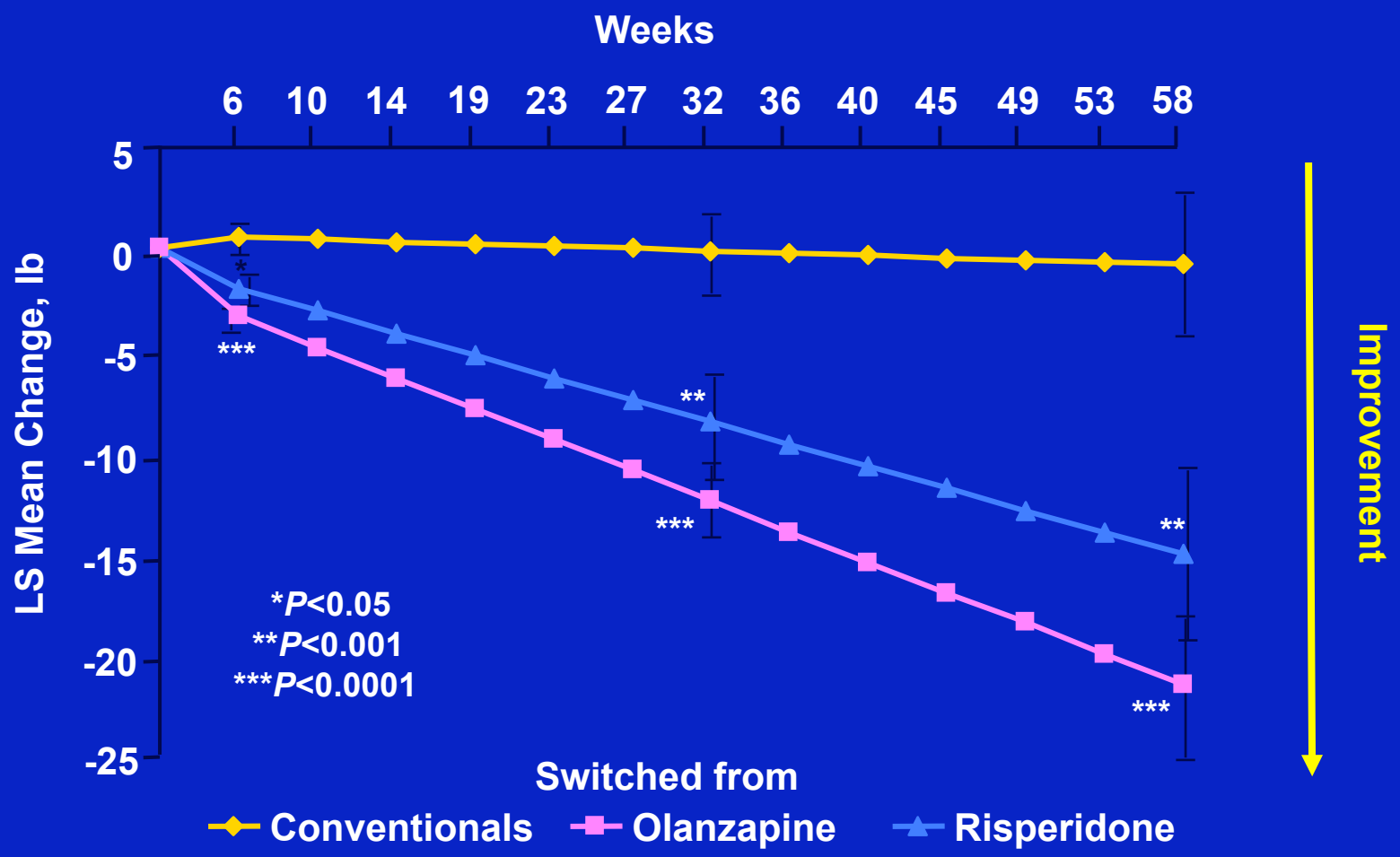

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Presented at APA 2004, New York, NY

What's New?

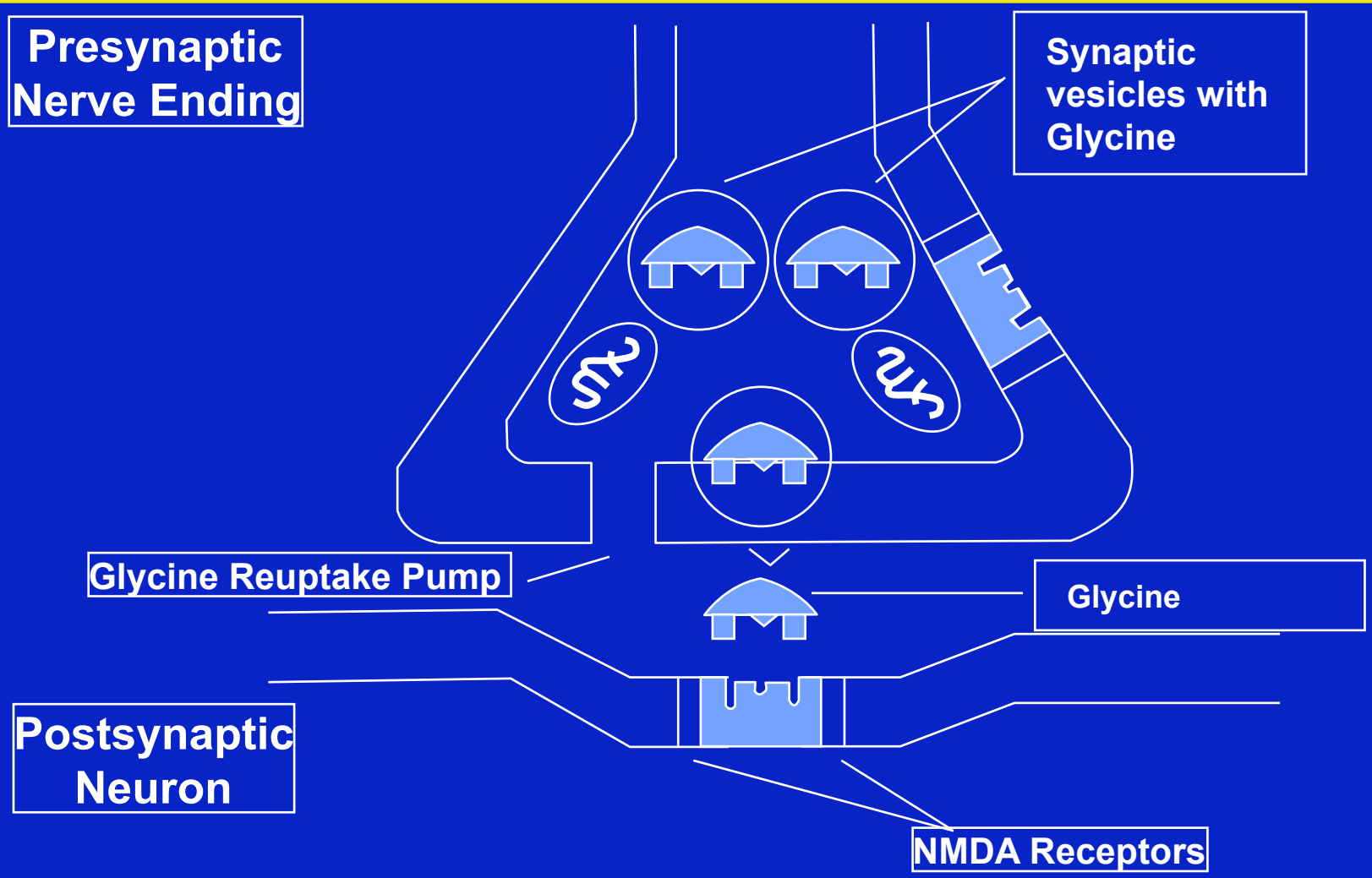
Newer Antipsychotics

- Paliperidone (Invega®) - Risperdal metabolite
  - Very similar side effect profile to Risperdal
  - Very similar effectiveness to Risperdal
- Bifeprunox - similar in mechanism to Abilify
  - More nausea than Abilify -> Long titration (8 days) - not for acute use
  - Questions about effectiveness - awaiting FDA decision
- Asenapine - another atypical antipsychotic
  - No major efficacy or safety benefits - awaiting FDA decision
- Iloperidone - another atypical antipsychotic
  - No major efficacy benefits, QTc concerns - awaiting FDA decision
- Long-Acting Injectables (Not Yet Approved)
  - Olanzapine Pamoate: 2-4 wks, effective, major safety concerns
  - Paliperidone Palmitate: 4 wks, not yet filed with FDA (?2009)

On the Horizon

- Some features of schizophrenia may be due to decreased levels of activity at a certain type of receptor (NMDA glutamate receptors)
- Glycine can stimulate those receptors and might prove useful as a treatment for schizophrenia
- Glycine Transport Inhibitors (GlyT1 Blockers)
  - The GlyT1 transporter is localized to important areas of the brain
  - Interesting data in animal models of psychosis induced by PCP

How A Reuptake Inhibitor Works



Conclusions

- Except for clozapine, most of the currently available agents, and those on the horizon, are more alike than different in terms of effectiveness
- Safety and avoidance of metabolic side effects are major reasons to choose certain medications
- Providers have a duty to monitor weight, blood pressure, blood sugar and cholesterol (lipids)
- Long-acting injectable medications are useful, will have more options in the next few years
- Ongoing research may help identify newer classes of medications

Case

1. **Why did he develop diabetes and diabetic ketoacidosis?**

   Do 2nd Generation (Atypical) antipsychotics have adverse metabolic effects?

2. **Could this metabolic decompensation have been predicted and prevented?**
3. **How should his psychotic symptoms be treated now?**

Table 3: Etiologic classification of diabetes mellitus

Type 1 diabetes mellitus (beta-cell destruction, usually leading to absolute insulin deficiency)
- Immune mediated
- Idiopathic

Type 2 diabetes mellitus (may range from predominantly insulin resistance with relative insulin deficiency to predominantly secretory defect with insulin resistance)

Gestational diabetes mellitus (onset or recognition of glucose intolerance in pregnancy)

Other specific types

Genetic defects of beta-cell function
- Chromosome 12, HNF-1α (formerly MODY 3)
- Chromosome 7, glucokinase (formerly MODY 2)
- Chromosome 20, HNF-4α (formerly MODY 1)
- Mitochondrial DNA
- Others

Diseases of the endocrine pancreas
- Pancreatitis
- Trauma pancreatectomy
- Neoplasia
- Cystic fibrosis
- Hemochromatosis
- Fibrocalculous pancreatopathy
- Others

Infections
- Congenital rubella
- Cytomegalovirus
- Others

Drug or chemical induced
- Vacor
- Pentamidine
- Nicotine acid
- Glucocorticoids
- Thyroid hormones
- Diazoxide
- Beta-adrenergic agonists
- Thiazine
- Dilantin
- Alpha-interferon
- Others

Genetic defects in insulin action
- Type A insulin resistance
- Leprechaunism
- Rabson–Mendenhall syndrome
- Lipoatrophic diabetes
- Others

Endocrinopathies
- Acromegaly
- Cushing's syndrome
- Glucagonoma
- Pheochromocytoma
- Hyperthyroidism
- Somatostatinoma
- Aldosteronoma
- Others

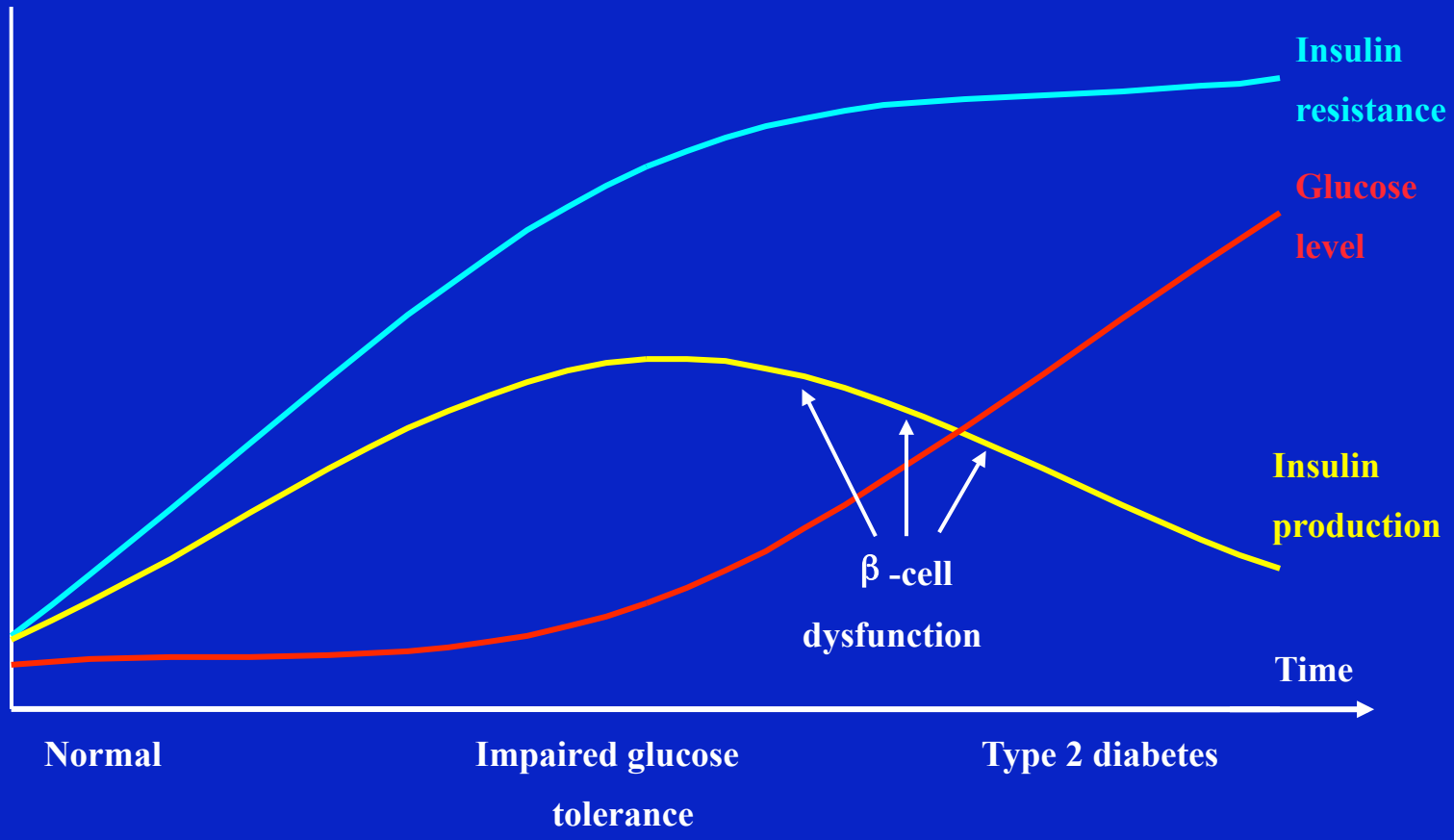
Uncommon forms of immune-mediated diabetes
- "Stiff-man" syndrome
- Anti-insulin receptor antibodies
- Others

Other genetic syndromes sometimes associated with diabetes
- Down's syndrome
- Klinfelter's syndrome
- Turner's syndrome
- Wolfram's syndrome
- Friedreich's ataxia
- Huntington's chorea
- Laurence–Biedel syndrome
- Myotonic dystrophy
- Porphyria
- Prader–Willi syndrome
- Others

DKA risk factors

- T1DM
  - 1st presentation
  - Acute-illness
  - Insulin omission (inappropriate sick-day management, noncompliance, Eating Disorders)
- T2DM
  - During stress
  - Ethnicity: African-American, Hispanic
- Extremes of age
- Poor glycemic control
- CSII

Natural History of Type 2 Diabetes



Henry. *Am J Med* 1998;105(1A):20S-6S.

Antipsychotic Agents That Decrease Neuronal Response in the Cerebral Cortex to Incoming Stimuli

Mechanism	Type of Agent	Result
Dopamine D2 antagonism	First-generation (haloperidol)	Blockade of dopamine facilitation of pyramidal-neuron response
D2 and 5-HT_{2A} antagonism	Second-generation (olanzapine, risperidone, quetiapine, ziprasidone)	Blockade of dopamine facilitation of pyramidal-neuron response and serotonin facilitation of glutamate release
Multiple actions	Clozapine	D1, D2, and 5-HT_{2-3} antagonism, leading to decreased pyramidal-neuron responses; increased acetylcholine release and norepinephrine antagonism, leading to increased interneuron regulation of pyramidal neurons
Mixed dopaminergic agonism and antagonism	Aripiprazole	Facilitation of low-level stimulation of dopamine receptors, blockade of higher levels of stimulation
Dopamine D2 and D3 antagonism	Amisulpride	Blockade of cortical dopamine receptors, but not those in basal ganglia

Schizophrenia & Diabetes Mellitus

- Many studies shown ↑ risk in schizophrenia:
  - IGT, Insulin resistance
  - Type 2 Diabetes mellitus
    - 10% Schizophrenia > 6–8% general population
- Studies over several decades, predating both typical & atypical neuroleptics
- Many recent case reports/series:
  - Treatment emergent DM (sometimes severe with DKA)
  - Atypical > 1st Generation Antipsychotics
- Alternative hypothesis:
  - Worsening DM phenotype in schizophrenia population mirrors general population

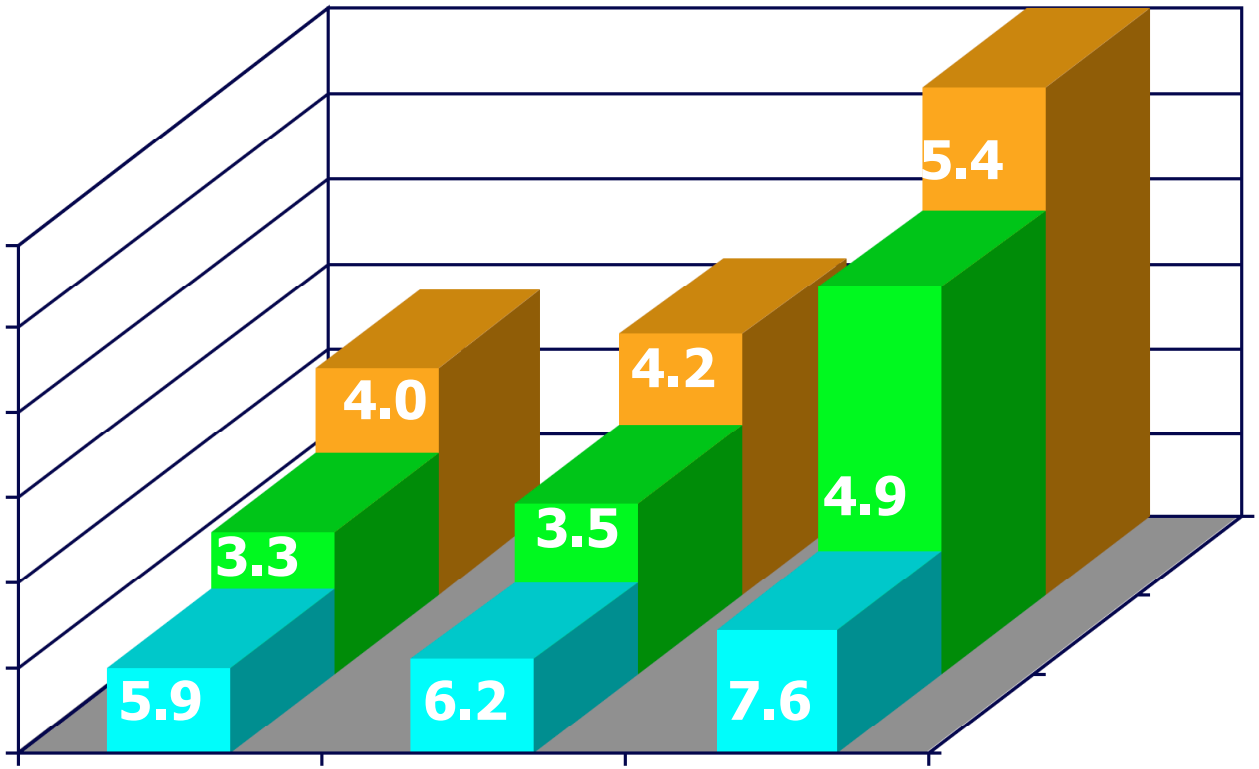
Diabetes Mellitus (DM) in Canada
Magnitude of the Problem

Year	Number of People	% of Population	Cardiovascular Hospitalization	Lower Limb Amputation	New Dialysis/Yr
1996	1.2 mill.	4	80,000	6,000	1,500
2006	1.9 mill.	6	158,000	10,000	2,500
2016	2.7 mill.	7	228,000	15,000	3,500

Based on diagnosed diabetes.

Blanchard et al.

Rising DM Prevalence (*Diagnosed*)



RCT Data

- 1 study (Pubmed “Antipsychotics & Diabetes”)
- *Lindenmayer et al, Am J Psych 160:290-6, Feb 2003*
- 157 inpatients: schizophrenia or schizoaffective dx
- Randomized to:
  - clozapine, olanzapine, risperidone, or haloperidol
- 2 Periods: 8 week fixed dose → 6 week variable dose
- FBG, fasting cholesterol (Baseline, 8 wk, 14 wk)

RCT Data

- 157 patients to start:
  - 49 failed to complete 1st 8 wk period (initial 31% loss to F/up)
    - Breakdown of f/up as per Rx group not reported
  - 28 failed to complete 2nd 6 wk period (18% loss to F/up)
  - Overall 49% loss to F/up
- Baseline Characteristics:
  - Only statistical difference between groups FBS:
  - clozapine, risperiodone > haloperidol ($P < 0.05$)

RCT Data

- 7 (4.4%) patients had DM at baseline
  - Rx with OHA
  - BS dropped despite antipsychotic Rx (haloperidol, olanzapine, risperidone)
- 14 (8.9%) developed new DM over course of study
  - 6 clozapine, 4 olanzapine, 3 risperidone, 1 haloperidol (NS)
- Effect of Antipsychotics on FBS:
  - Clozapine ↑ 0.9 mM ($P < 0.01$)
  - Olanzapine ↑ 0.8 mM ($P < 0.02$)
  - Haloperidol ↑ 0.5 mM ($P < 0.03$)
  - Risperidone NS

RCT Data

- **Effect of Antipsychotics on Fasting cholesterol:**
  - Clozapine ↑ 0.4 mM ($P < 0.02$)
  - Olanzapine ↑ 0.5 mM ($P < 0.04$)
  - Haloperidol NS
  - Risperidone NS
- **Weight Gain:**
  - Olanzapine 7.3 Kg ($P < 0.0001$)
  - Clozapine 4.8 Kg ($P < 0.0003$)
  - Risperidone 2.4 Kg ($P = 0.09$)
  - Haloperidol NS

RCT Data - Summary

- Only 1 RCT Study
- Study Flaws:
  - 49% loss to F/up
  - Very short F/up to P/up Adverse Metabolic Rxns
  - Baseline: higher FBS clozapine, risperidone groups
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  - 9% of all patients Rx with antipsyhotics developed new DM
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  - No correlation between weight gain and FBS in this study

Cohort Data

- *Caro et al, J Clin Psychiatry 63(12):1135-9, Dec 2002*
- Regie de l'Assurance Maladie du Quebec database
- 33,946 patients
  - Prescription for olanzapine or risperidone
- Jan 1, 1997-Dec 31, 1999.
- Development of DM:
  - Determined by censoring
  - Greater risk with olanzapine
  - Crude OR 1.08 (95% CI 0.89-1.31, P = 0.43)
  - Adjusted OR 1.20 (95% CI 1.0-1.43, P = 0.05)
    - » Adjusted for age, sex, haloperidol use
- Their conclusion: ↑ DM risk olanzapine > risperidone
- Reality: Negative study

Cohort Data

Buse et al:

- **Risk increased with all antipsychotics**
- **Risk increased with schizophrenia in general?**

Table 3
Incidence and hazard ratio of diabetes mellitus in patients during treatment with antipsychotics

Cohort	New cases (*n*)	Patients (*n*)	Patient-years	Incidence (per 1000 patient-years)		HR[a]		
				Rate	95% CI	Ratio	95% CI	*P* value
Conventional antipsychotics								
All combined	307	19,782	3645.57	84	75–94	3.5	3.1–3.9	≤0.0001
Haloperidol	133	8476	1568.39	85	70–100	3.1	2.6–3.7	≤0.0001
Thioridazine	62	3133	654.28	95	71–119	4.2	3.2–5.5	≤0.0001
Atypical antipsychotics								
All combined	641	38,969	9571.18	67	62–72	3.1	2.9–3.4	≤0.0001
Clozapine	7	277	103.95	67	16–118	3.3	1.4–8.0	0.0070
Olanzapine	194	13,863	3374.57	58	49–66	3.0	2.6–3.5	≤0.0001
Quetiapine	40	4196	1025.75	39	27–51	1.7	1.2–2.4	0.0020
Risperidone	400	20,633	5066.90	79	71–87	3.4	3.1–3.8	≤0.0001
General patient population	45,513	5,816,473	2,908,236.5	15.7	15.5–15.8			

Cohort Data

- *Mahmoud et al, J Clin Psychiatry 63(10) 920-30, Oct 2001.*
- Claims data for 2.5 million pyschotic patients within health plans, analyzed retrospectively
- Increased risk of new DM:
  - conventional low-potency antipsychotics (OR 4.16)
  - conventional hi-potency antipsychotics (OR 2.13)
  - clozapine (OR 7.44), olanzpaine (3.10)
- No increased risk with risperidone (OR 0.88)

Case Series Data: DKA

- 19 reported cases of DKA associated with atypical antipsychotics
- Increased risk: women, younger age, lower weight

Table 2. Comparison of Patient Characteristics for Those Who Developed Diabetes Mellitus (DM) Only With Those Who Developed Diabetic Ketoacidosis (DKA) Associated With Usage of Atypical Antipsychotics

Variables	DM only, $N = 26$ (%)	DKA, $N = 19$ (%)	t test or χ^2	p
Gender (female)	3.8	26.3	4.79	0.029
Race (African American)	42.3	52.6	1.07	0.585
Adjunctive medications	81.8	69.2	0.73	0.392
Overweight at baseline	100	58.3	9.44	0.002
Weight gain	47.6	36.4	0.372	0.542
Family history of diabetes	36.0	38.9	0.039	0.981
	Mean (SD)			
Age (years)	43 (6.8)	37 (8.9)	2.712	0.010
Weeks on atypical	20.9 (27.2)	18.0 (20.5)	0.385	0.702
Blood glucose (mg/dL)	481 (360)	750 (396)	2.34	0.024

Case Series Data

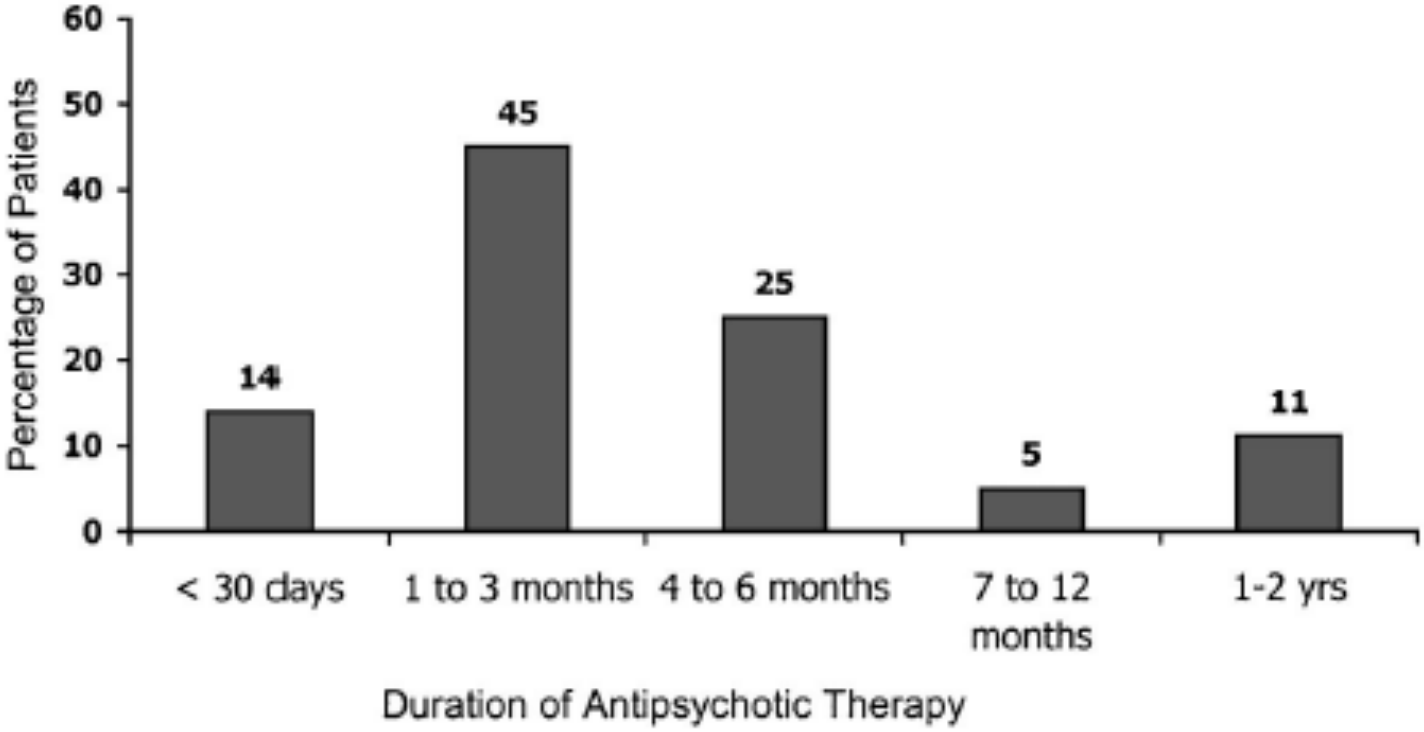

Fig. 1. Time to presentation with diabetes mellitus or diabetic ketoacidosis after instituting atypical antipsychotic therapy ($N = 45$).

Basic Science

TABLE 3. Baseline to end point changes in steady state glucose infusion rate, insulin levels, and insulin sensitivity index

Therapy	Change in M [mmol/min·kg ($\times 10^{-3}$)]	Change in I (pmol/liter)	Change in M/I ($\times 10^{-5}$)
Olanzapine	−2.4 (16.0)	111.0 (266.4)	−4.63 (11.0)[a]
Risperidone	−7.8 (11.6)	81.6 (266.4)	−3.7 (7.4)
Placebo	0.3 (16.0)	−112.8 (260.4)	0.92 (7.4)

Data collected during the final hour of the clamps were used to calculate the steady state glucose infusion rate (M; millimoles per kg BW/min), steady state insulin level (I; picomoles per liter), and an insulin sensitivity index (M/I). Results are shown as the group mean change from baseline in M, I, and M/I. SDs are shown in *parentheses*.

[a] $P < 0.05$ within a group.

Basic Science

- *Sowell et al, JCEM 87(6):2918-23, June 2002.*
- **Summary:**
  - **Olanzapine and risperidone cased 3 Kg wt. Gain**
  - **No evidence of reduced insulin secretion/β-Cell function**
  - **Increased insulin resistance**
    - » **Only statistically significant with olanzapine**
    - » **Became nonsignificant when multivariate analysis controlled for weight gain**

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  - **Less DM risk with Risperidone?**
- **Cohort Studies**
  - **Increased risk of DM due to schizophrenia itself or Rx with any antipsychotic (atypical or conventional)**
  - **Some studies suggest less DM risk with risperidone**
- **Case Reports/Studies**
  - **DKA, ? Positive de-challenge and re-challenge**
- **Basic Science**
  - **Normal insulin secretion, ↓ insulin sensitivity with ↑ weight**

Why did this patient develop DKA?

- clozapine? quetiapine?
- Type 2 DM related to schizophrenia?
  - Underlying precipitant(s): pancreatitis, ileus, esophageal tear, pneumonia
- Pancreatitis with endocrine dysfn?
  - GB stone, EtOH, Triglycerides
  - Psychiatric co-interventions: Valproate

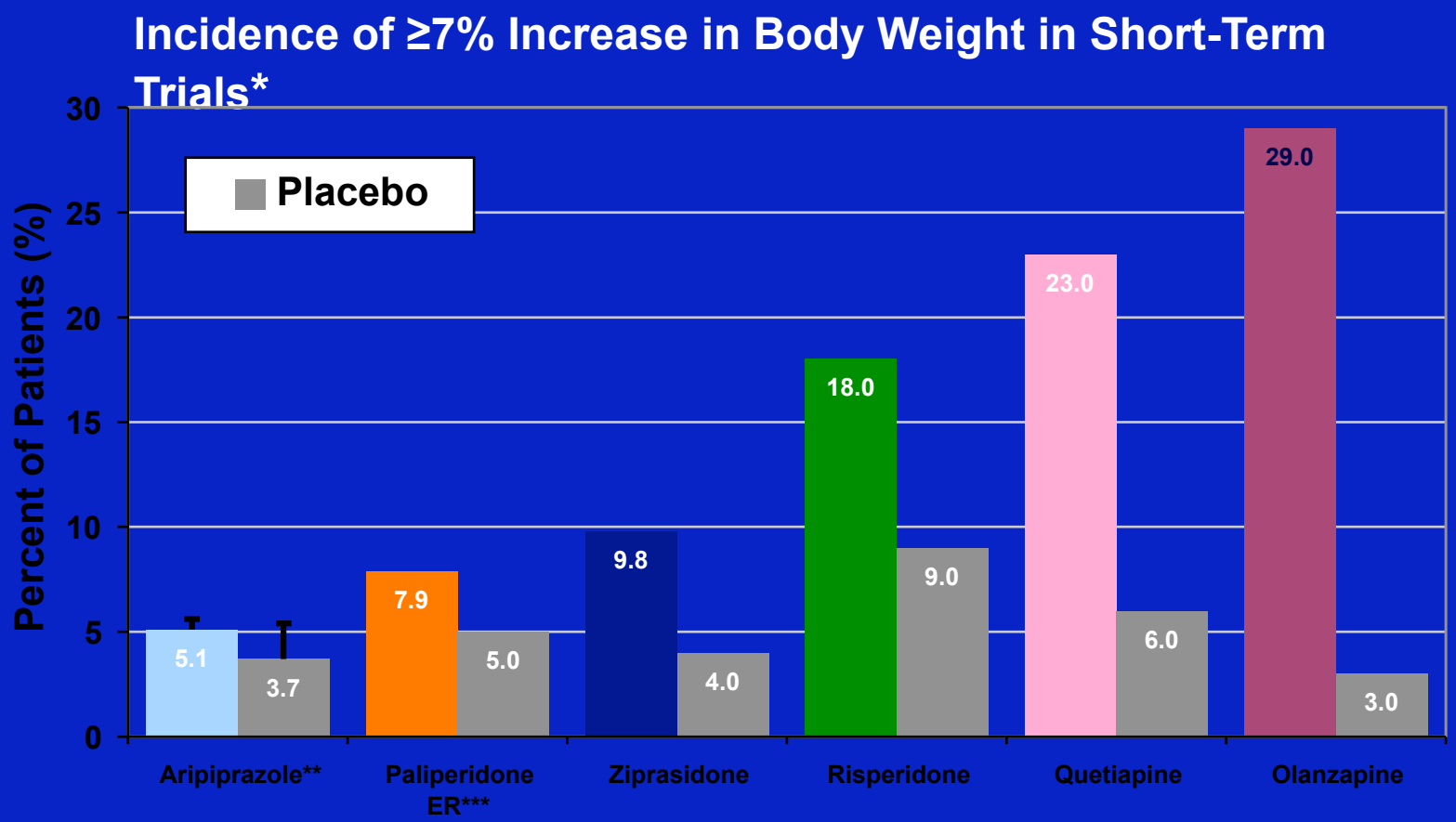
Could this have been predicted or prevented?

- **Risk factors for T2DM**
  - **Obese, older, ethnic groups, FHx DM, etc.**
- **Risk factors for DKA**
  - **Thin, younger, female?**
- **CDA 2003 Guidelines:**
  - **Schizophrenia: " more frequent (than q3y) testing with either FPG or OGTT "**
  - **My suggestion: baseline and q6mos FBS, HbA1c, lipid profile**
    - » **Not Evidence Based Suggestion!**
  - **Ideal screening/surveillance method needs to be investigated**

Need for more Research…

- **Better RCTs, Cohort Studies**
  - **Is there a risk or not with atypical antipsychotics?**
  - **Are some safer than others: risperidone?**
  - **Can DM complications be prevented if started on a new antipsychotic?**
    - **Screening/Surveillance**
    - **Exercise/diet**
    - **Prophylactic anti-diabetic Rx: metformin, acarbose, orlistat, TZD's, sulfonylureas, insulin glargine**
- **Basic Science**
  - **Mechanisms?**

Weight Gain Comparision of Atypical Antipsychotics



*Based on United States Product Inserts
**Error bars reflect reporting of weight gain in PI by baseline BMI
***confirmation of US PI

Schizophrenia & Diabetes Mellitus

- Many studies shown ↑ risk in schizophrenia:
  - IGT, Insulin resistance
  - Type 2 Diabetes mellitus
    - 10% Schizophrenia > 6–8% general population
- Studies over several decades, predating both typical & atypical neuroleptics
- Many recent case reports/series:
  - Treatment emergent DM (sometimes severe with DKA)
  - Atypical > 1st Generation Antipsychotics
- Alternative hypothesis:
  - Worsening DM phenotype in schizophrenia population mirrors general population

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