Association of British Clinical Diabetologists 27 October 2005

Diabetes & Anti-psychotic drugs: Genuine Concern or Industry Hype?

Richard IG Holt

Senior Lecturer in Endocrinology & Metabolism

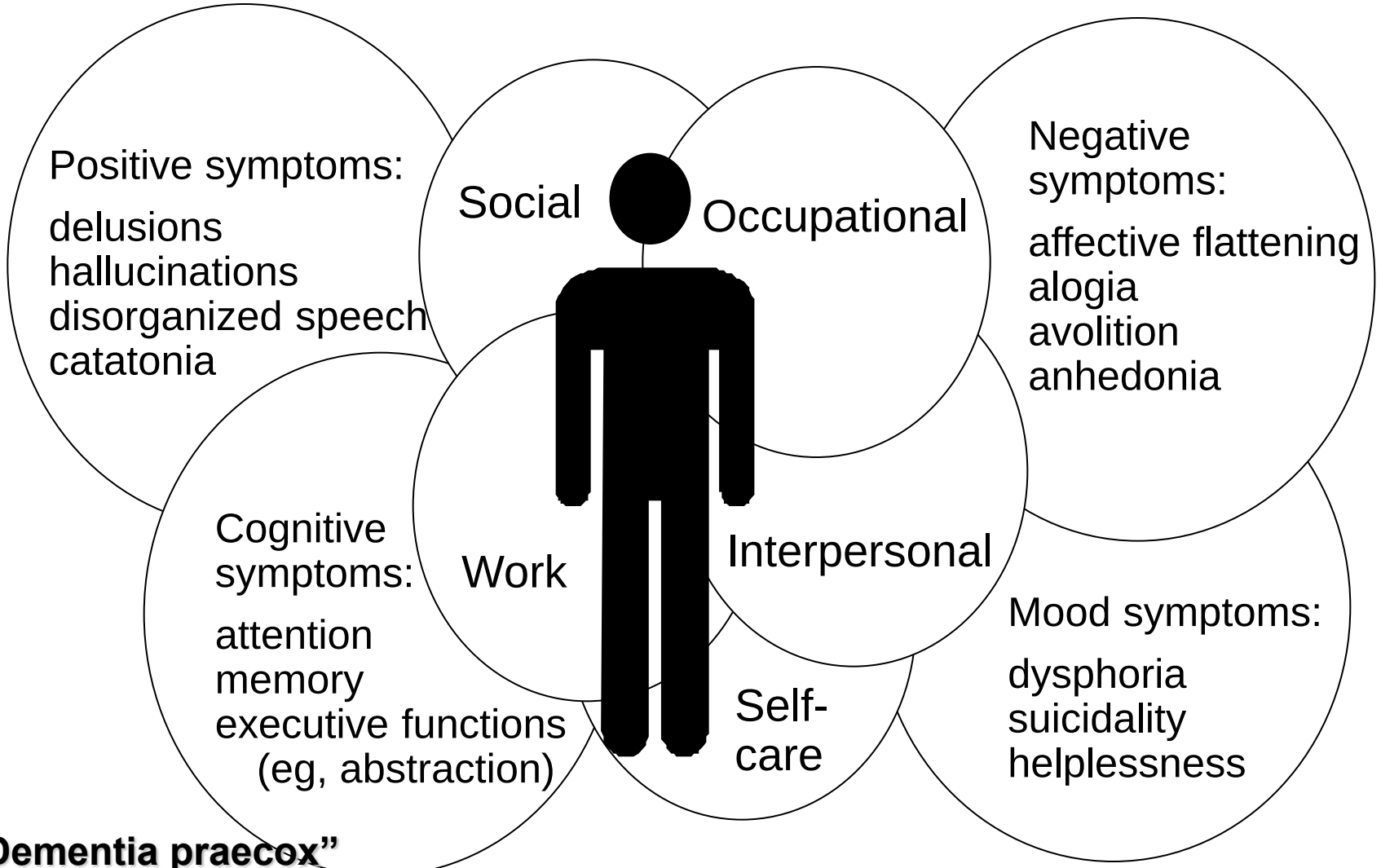
University of Southampton

Conflict of Interest: I have received educational awards & fees for consultancy from Eli Lilly & Co, GSK and BMS for work in this area

Audience Questions

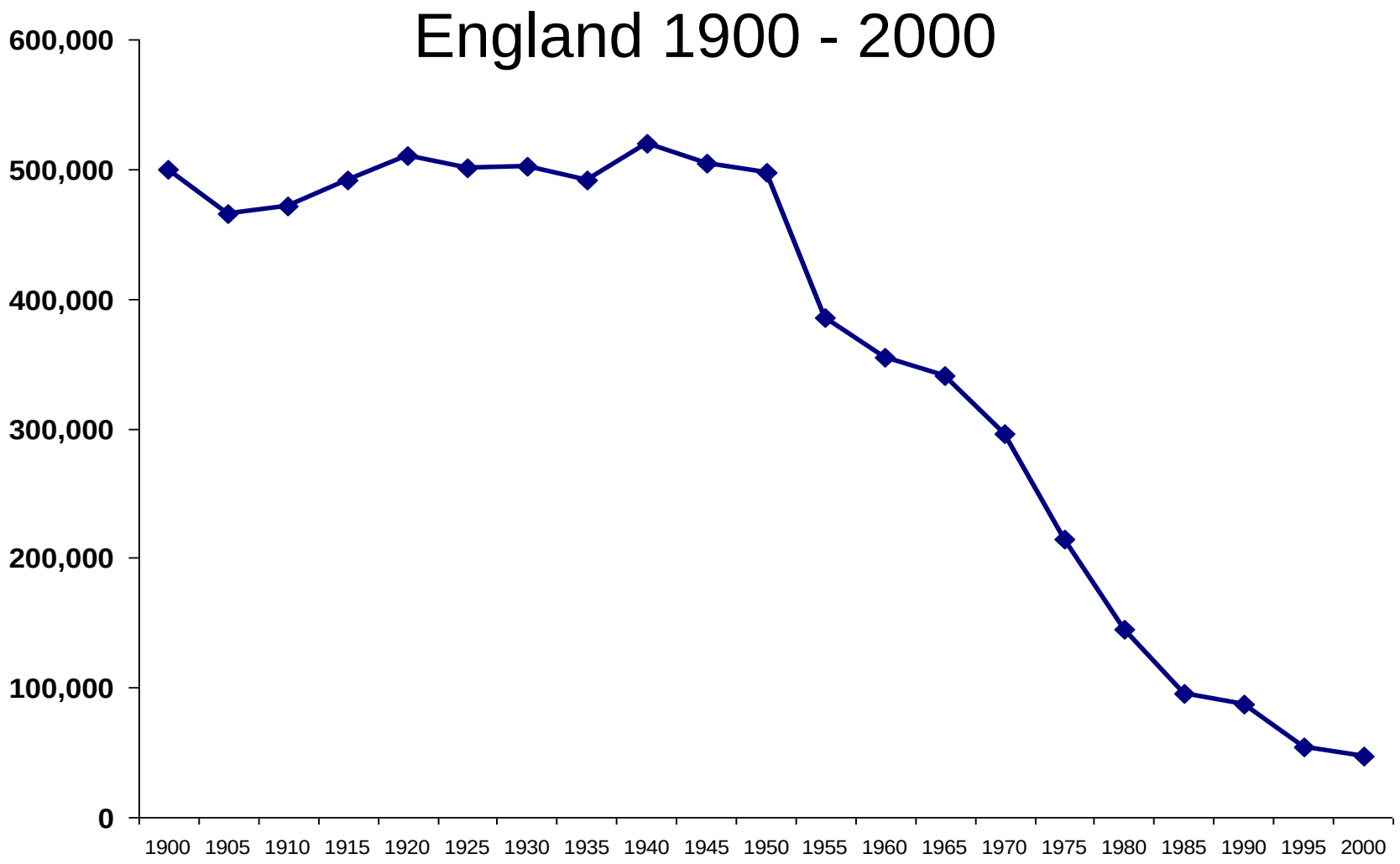
- How many of you believe diabetes is a serious clinical problem among people with schizophrenia?
- How many of you believe the anti-psychotic drugs cause diabetes?
- How many of you believe the anti-psychotic drugs are a major cause of diabetes in this patient group?

Impact of Schizophrenia on Overall Functioning



“Dementia praecox”

Number of psychiatric hospital beds



Extra-pyramidal symptoms (EPS)

- Four syndromes
  - Parkinsonism
  - Akathisia
  - Dystonia
  - Dyskinaesia
- May occur early or late in treatment
- Alone or in combination

Eight atypicals available in UK and potential advantages

- Amisulpride
- Aripiprazole
- Clozapine
- Olanzapine
- Quetiapine
- Risperidone
- Sertindole
- Zotepine

- ⬇ EPS and TD
- Improved -ve symptoms
- Prolactin sparing
- ⬇ relapse
- ⬇ hospitalisation
- Improved compliance
- Improved cognition

Marketing of AAPDs

- Atypical anti-psychotic drugs generate more than $8 billion a year
- Marketing on efficacy & effectiveness
  - No studies till recently
- Marketing on side effects….
  - Diabetes and weight gain

Physical Consequences of Schizophrenia

- Overall SMR: 298
- Unnatural Causes: 1273
- Natural Causes SMR: 232
  - Accounted for ¾ of deaths
  - 1/3rd of all deaths were CVD
  - Diabetes & metabolic syndrome may explain some of the increase

Brown et al: Br J Psychiatry. 2000 Sep;177:212-7

Schizophrenia & Diabetes

- Association documented from early 1900s
- Prevalence rates is ~10-15% in Western societies
- High prevalence of undiagnosed disease
  - As many as 70% may be undiagnosed

Holt 2005, Subramanian 2003, Taylor 2005

Why might Diabetes be increased in Schizophrenia?

-Genetics

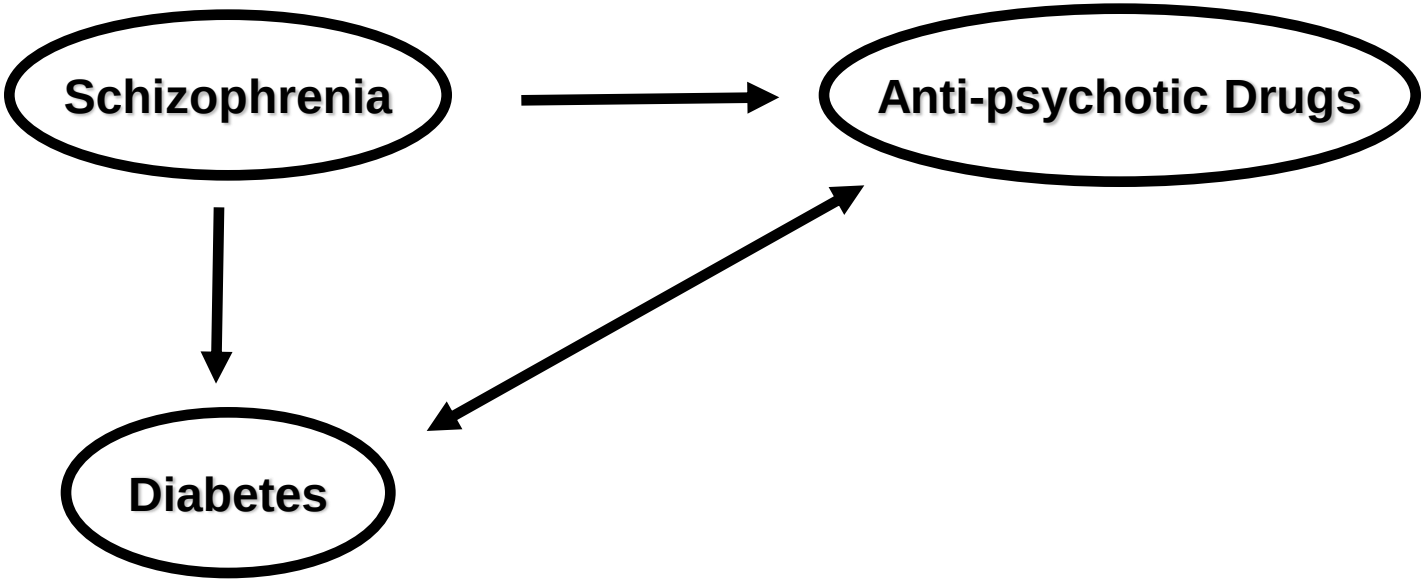
-Low Birth Weight

-Lifestyle

-The illness of Schizophrenia

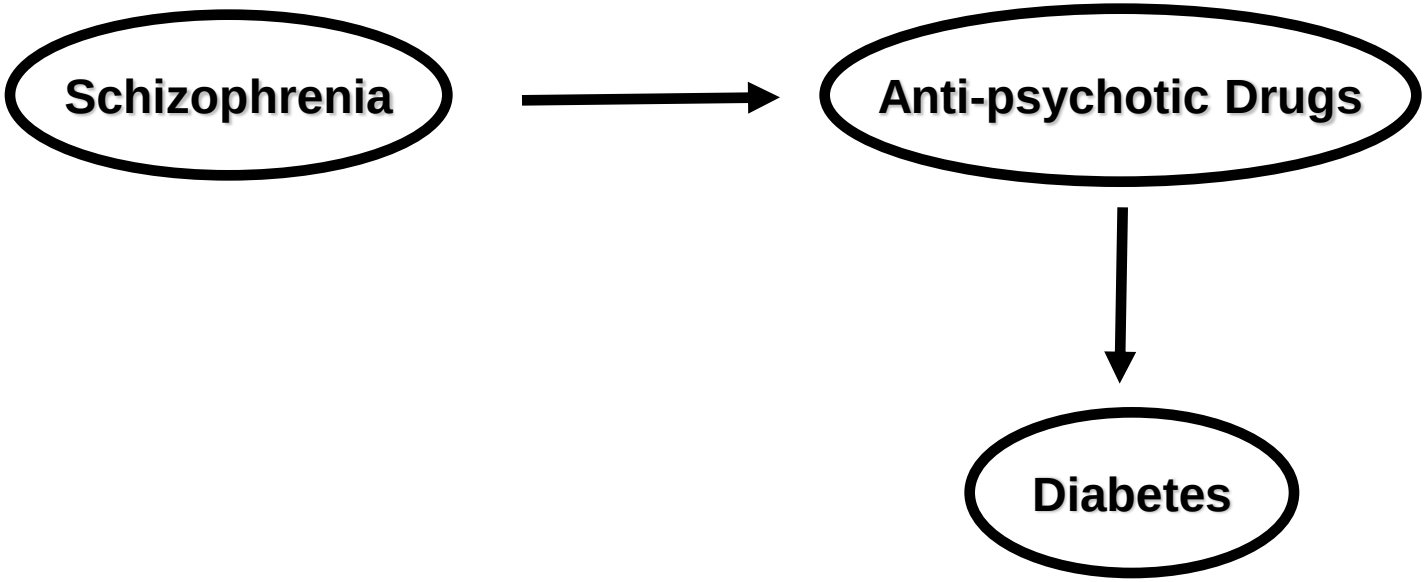
-Drugs

Association or Causation?



Clinical implication: Management of diabetes risk is important for all patients with schizophrenia

Association or Causation?



Clinical Implication: Discovery of new better APDs will see ↑ diabetes rate fall to background population rate

Methodology for evaluating side effects

- Case Reports & Drug Safety Studies
  - Descriptive, generate hypotheses
- Observational analytical studies
  - Cohort (prospective or retrospective)
  - Case-control
  - Cross sectional
- Experimental analytical studies
  - Gold standard placebo controlled double blind RCT

Austin Bradford Hill Criteria

- Strength
- Consistency
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experimental evidence
- Analogy

Strength of Association

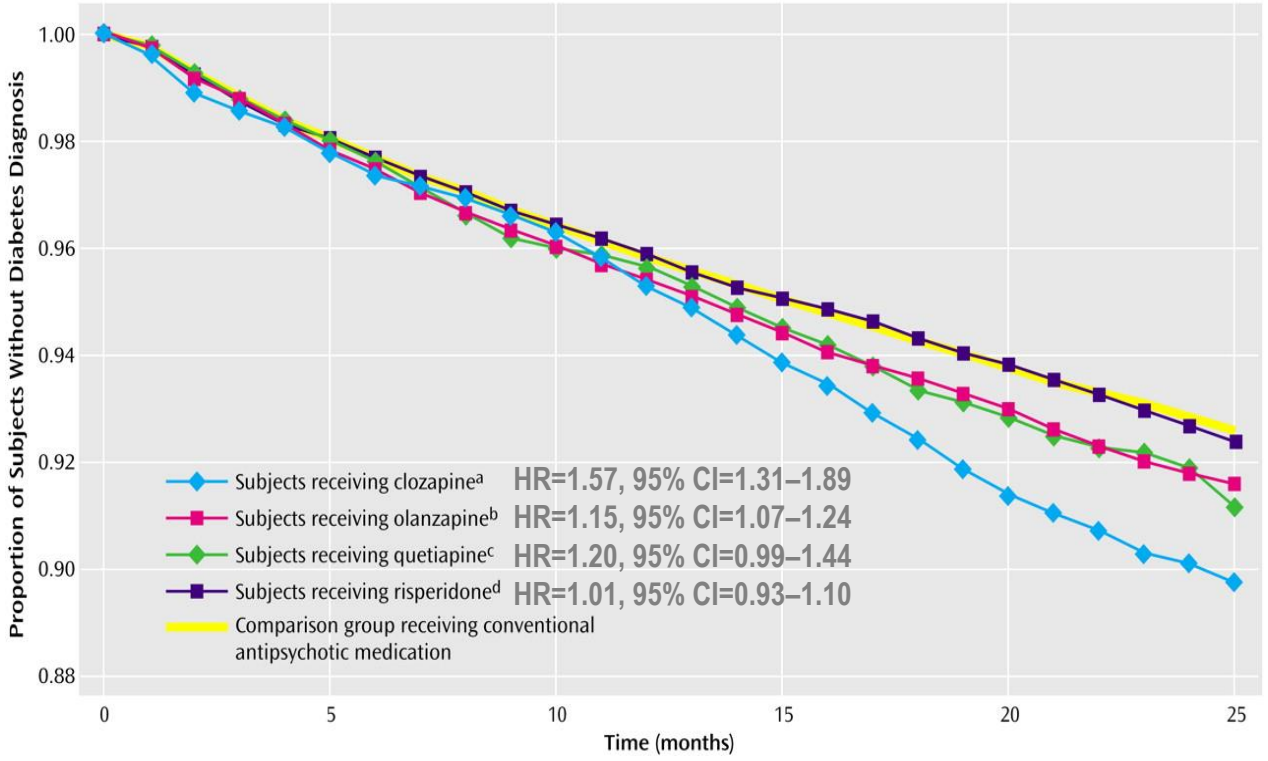
- “A strong association is more likely to be causal than a weak association and is less likely to be explained by unrelated biases”

	HR,OR,RR
• Strong Association	>3.0
• Moderate Association	2-3
• Weak Association	1-2

Strength of Association

Strong		Moderate		Weak	
Risk factor	RR,OR, HR	Risk factor	RR.OR, HR	Risk factor	RR,OR, HR
Family history	4.1	Afro-American vs White	2.0	TNFα gene polymorphism	1.8
Obesity	3.0	Irregular menstrual cycle	2.08	Low birth weight	1.75
Physical Inactivity	3.85	Low grade inflammation	2.7	Anti-psychotic drugs	1.0-1.57

Risk Attributable to AAPD v FGAs



- 60,000 Veterans Administration patients
- The attributable risk was highest for clozapine (2.03%), followed by quetiapine (0.80%), olanzapine (0.63%), & risperidone (0.05%)

Leslie & Rosenheck 2004

Consistency

"Repeated observations of an association in different populations under different circumstances provide additional support for a causal association"

Comparisons of Risk of Diabetes by Exposure to Atypical Antipsychotic drugs

First Author	CLO	RIS	OLZ	QUE	SGA
Lund	↑	NA	NA	NA	NA
Sernyak	↑	↑	↑	↑	↑
Wang	±	±	NA	NA	NA
Koro	NA	±	↑	NA	NA
Kornegay	?	?	?	?	? ↑
Gianfrancesco	↑	±	↑	NA	NA
Caro	NA	±	↑	NA	NA
Buse	±	↑	±	±	±
Gianfrancesco	NA	±	↑	NA	NA
Gianfrancesco	NA	±	↑	±	NA
Fuller	NA	±	↑	NA	NA
Etminan	NA	NA	NA	NA	±
Citrome	↑	±	±	↑	↑

Adapted from Citrome & Jaffe: Annals of Pharmacotherapy 37:1849-57, 2003; Citrome: Drugs of Today 40(5):445-464, 2004

Summary….

Drug	Number of studies showing increased risk	Number of studies showing no increased risk
Clozapine	4	2
Risperidone	2	8
Olanzapine	7	2
Quetiapine	2	2
Any 2nd generation APD	3	2

……olanzapine looks to have the highest risk!

Comparisons of Risk of Diabetes by Exposure to Atypical Antipsychotic drugs

First Author	CLO	RIS	OLZ	QUE	SGA	Industry Sponsor
Lund	↑	NA	NA	NA	NA	None
Sernyak	↑	↑	↑	↑	↑	None
Wang	±	±	NA	NA	NA	None
Koro	NA	±	↑	NA	NA	Bristol-Myers Squibb (ARI)
Kornegay	?	?	?	?	? ↑	None
Gianfrancesco	↑	±	↑	NA	NA	Janssen (RIS)
Caro	NA	±	↑	NA	NA	Janssen (RIS)
Buse	±	↑	±	±	±	Eli Lilly (OLZ)
Gianfrancesco	NA	±	↑	NA	NA	Janssen (RIS)
Gianfrancesco	NA	±	↑	±	NA	AstraZeneca (QUE)
Fuller	NA	±	↑	NA	NA	Janssen (RIS)
Etminan	NA	NA	NA	NA	±	None
Citrome	↑	±	±	↑	↑	None

Adapted from Citrome & Jaffe: Annals of Pharmacotherapy 37:1849-57, 2003; Citrome: Drugs of Today 40(5):445-464, 2004

Summary….

Drug	Number of independent studies showing increased risk	Number of independent studies showing no increased risk
Clozapine	3	1
Risperidone	1	2
Olanzapine	1	1
Quetiapine	2	0
Any 2nd generation APD	3	1

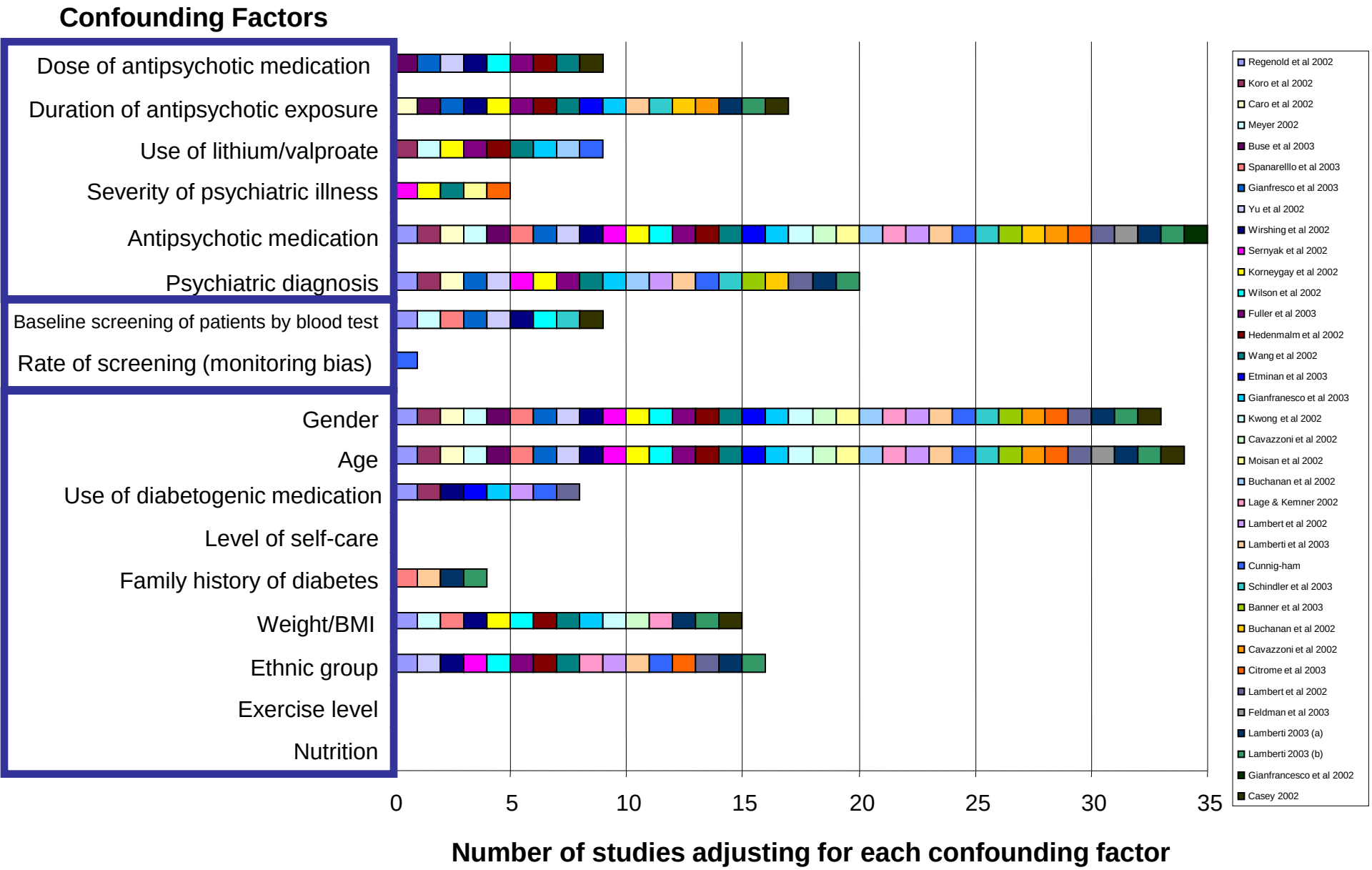
……no overall pattern!

Explanations for discrepant results

- Non-publication of unfavourable results!

- Treatment assignment bias
- Screening or surveillance bias
- Inadequate and incomplete information on, and knowledge of, all relevant confounders

Number of Studies Adjusting for Each Confounding Factor



16 Prospective Clinical Trials

- No differences in glucose abnormalities between anti-psychotic drugs or placebo
- Most studies are funded through industry
- CATIE is the one independent study
  - No change in glucose but HbA1c was increased by 0.4% in those treated with OLZ
  - HbA1c measured in a subset
  - No separation of diabetic from non-diabetic individuals

N Engl J Med. 2005 Sep 22;353(12):1209-23.

Weaknesses of Prospective studies

- Post hoc analysis
- Selected patients
- The duration of the studies were often too short
- A mixture of fasting and random blood samples were used
- Few of these studies were in drug naive patients
  - ?carry-over effect from previous treatment

Specificity

“A cause leads to a single effect not multiple effects, but cautioned that although the concept of specificity is sometimes helpful, it could be misleading”

Specificity

	Weight gain	Hyperprolactinaemia	EPS
Clozapine	++	+/-	+/-
Olanzapine	++	+/-	+/-
Risperidone	+	++	+
Quetiapine	+	+/-	+/-
Ziprasidone	+/-	+/-	+/-
Aripiprazole	+/-	+/-	+/-

Temporality

“Cause precede effect in time”

Diabetes and SZ preceded introduction of AAPD

- “Diabetes is a disease which often shows itself in families in which insanity prevails”
  - Henry Maudsley 1879

- Glucose, IR and central adiposity found in 1st episode, drug naïve patients

Thonnard-Neumann E. *Am J Psychiatry* 1968; 124: 978-982
Ryan. Am J Psychiatry. 2003;160(2):284-9

Diabetes follows APD

- Marked ↑ in diabetes after introduction of phenothiazines
  - "Phenothiazine diabetes"

- Case reports for each of the AAPDs
  - Including re-challenge

Biological Gradient

“The biological gradient as demonstrated by a dose response curve is well known in epidemiology”

Biological Gradient

- Most studies have not examined dose response
  - Those prospective studies that have do not show a dose response
- Insulin, C-peptide and triglycerides correlated with clozapine serum concentration and to the ratio of olanzapine to N-desmethylolanzapine concentrations
- For weight gain there seems to be a threshold response

Psychopharmacology (Berl). 2003 Nov;170(2):157-66
J Clin Psychopharmacol. 2005 Jun;25(3):250-4

Plausibility

"Biological plausibility of a hypothesis is another aspect to be considered for causal inference"

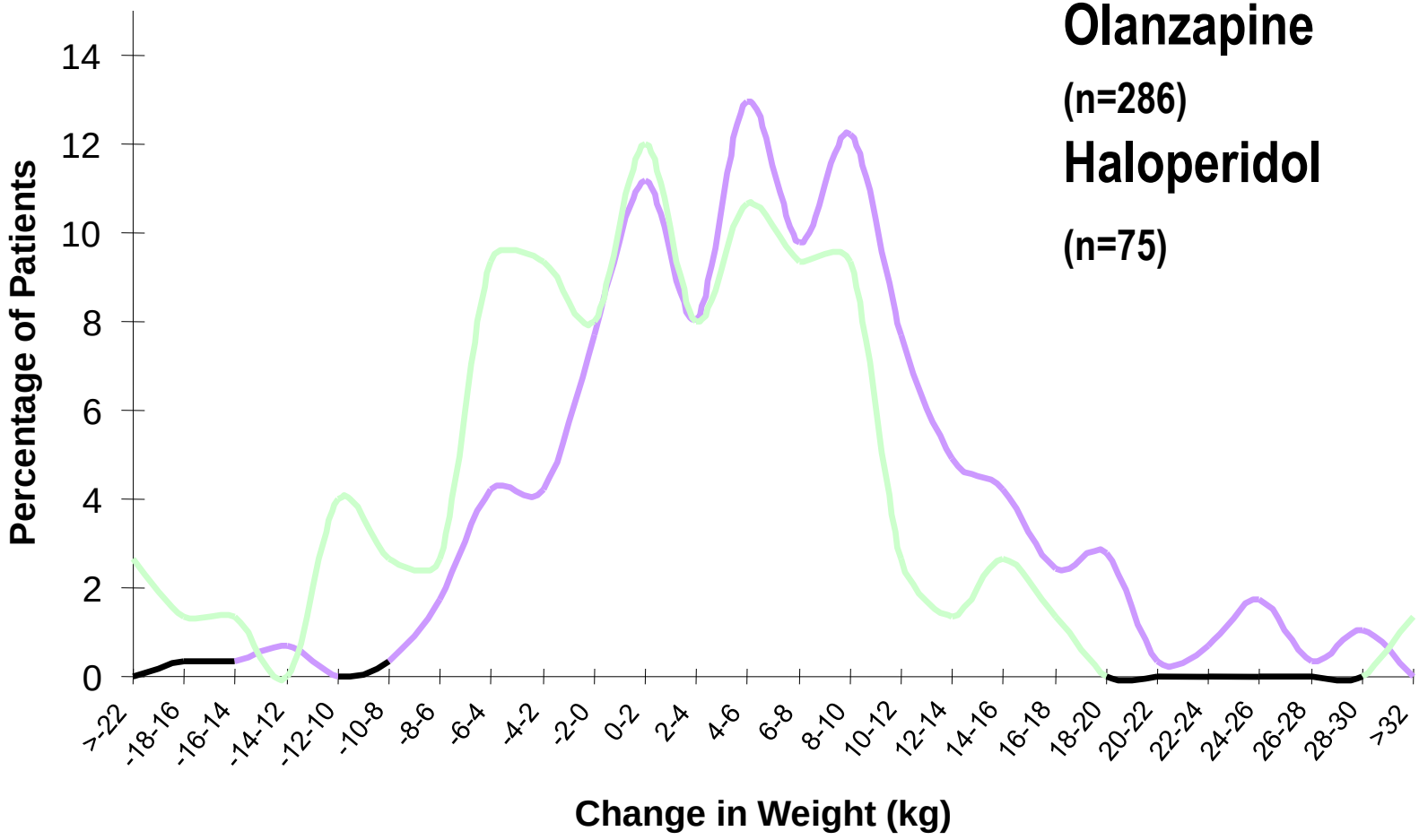
Plausibility

- Insulin resistance
  - Weight gain
  - ?other cause
- β-cell failure

Weight Gain in different anti-psychotics

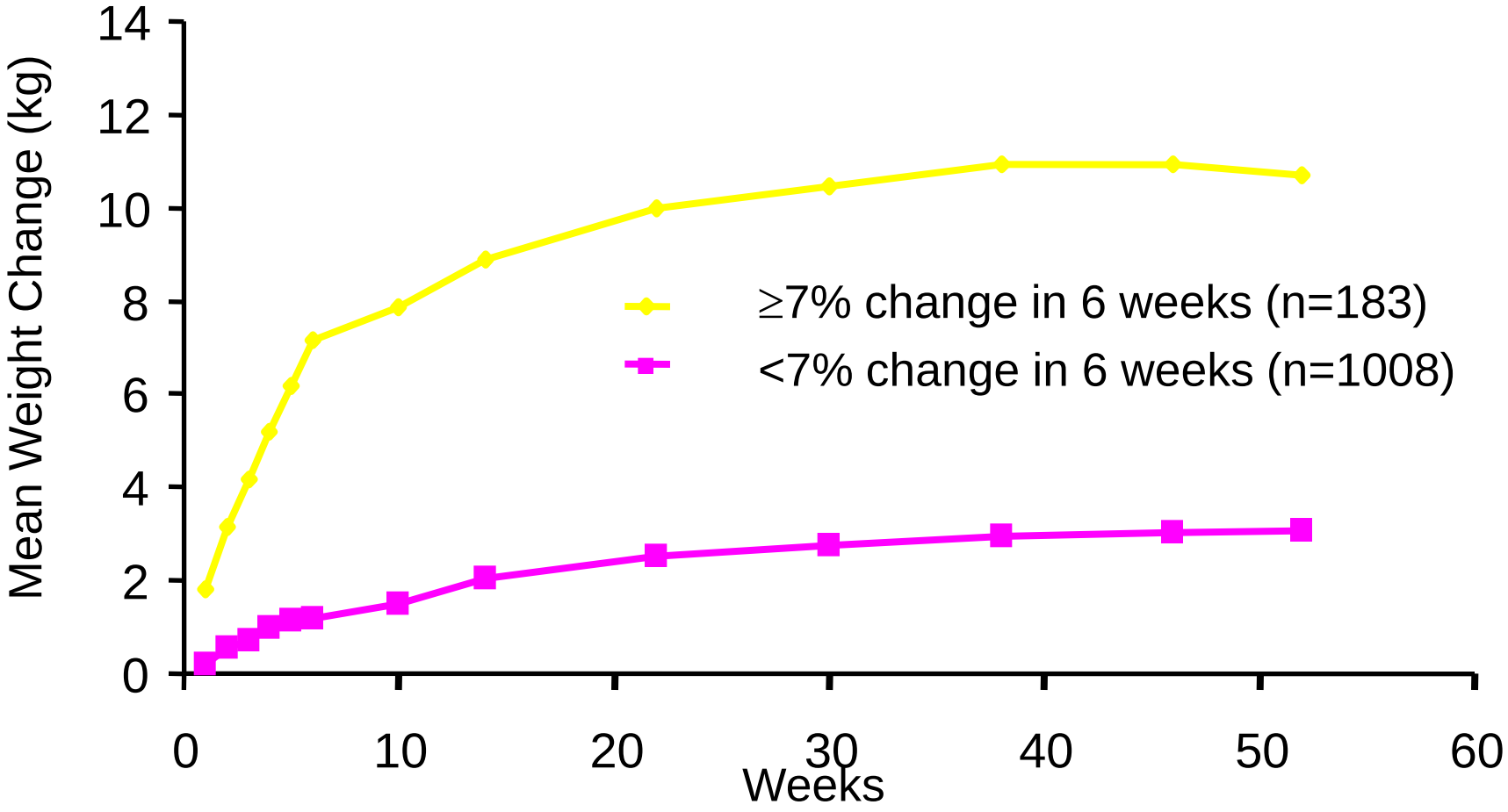
	Meta-analysis of weight gain during 10/52 clinical trials	Weight gain during 6/12 observational study
Clozapine	4.45	2.3
Risperidone	2.1	1.4
Olanzapine	4.15	2.4
Quetiapine	2.7	0.6
Amisulpride	-	1.4

Weight Gain During Olanzapine or Haloperidol Treatment



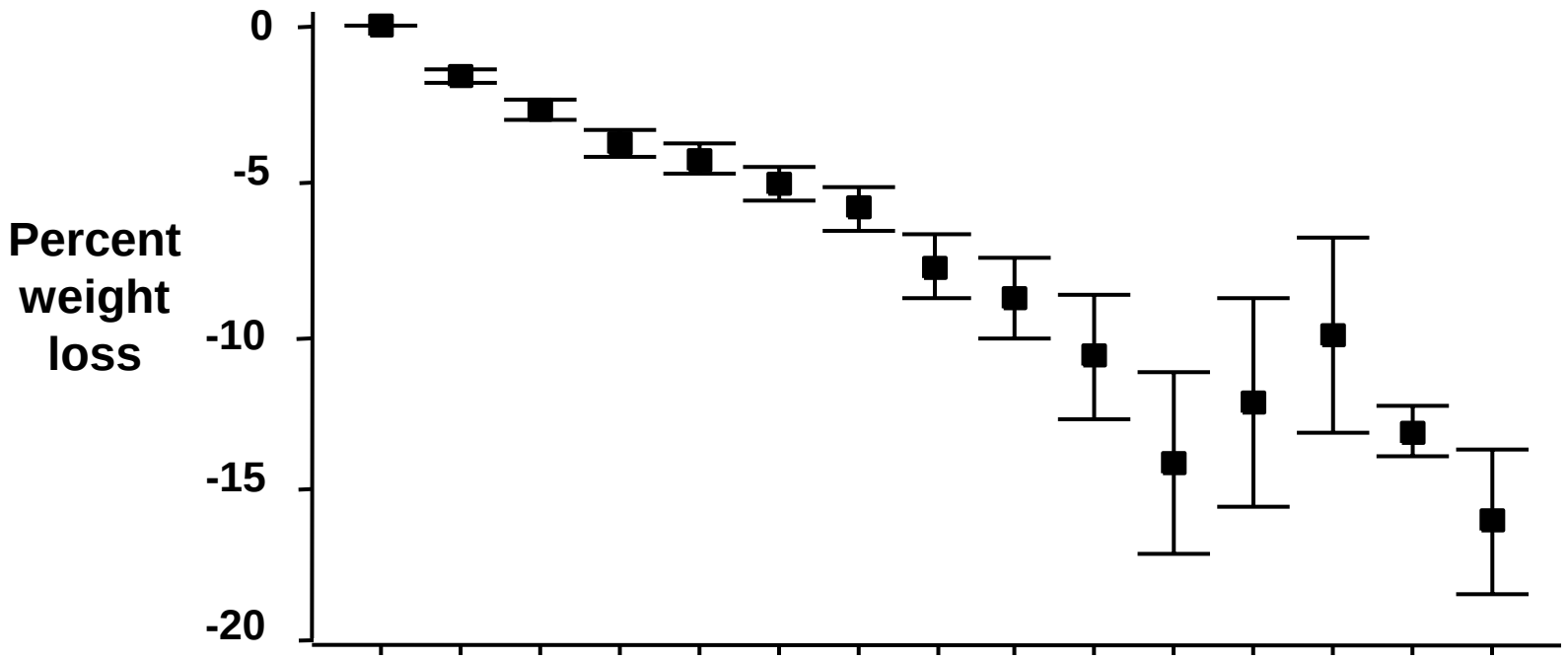
Tollefson GD, Am J Psych, 1997;154:457-65.)

Rate of initial weight gain predicts long term wt gain in patients treated with olanzapine



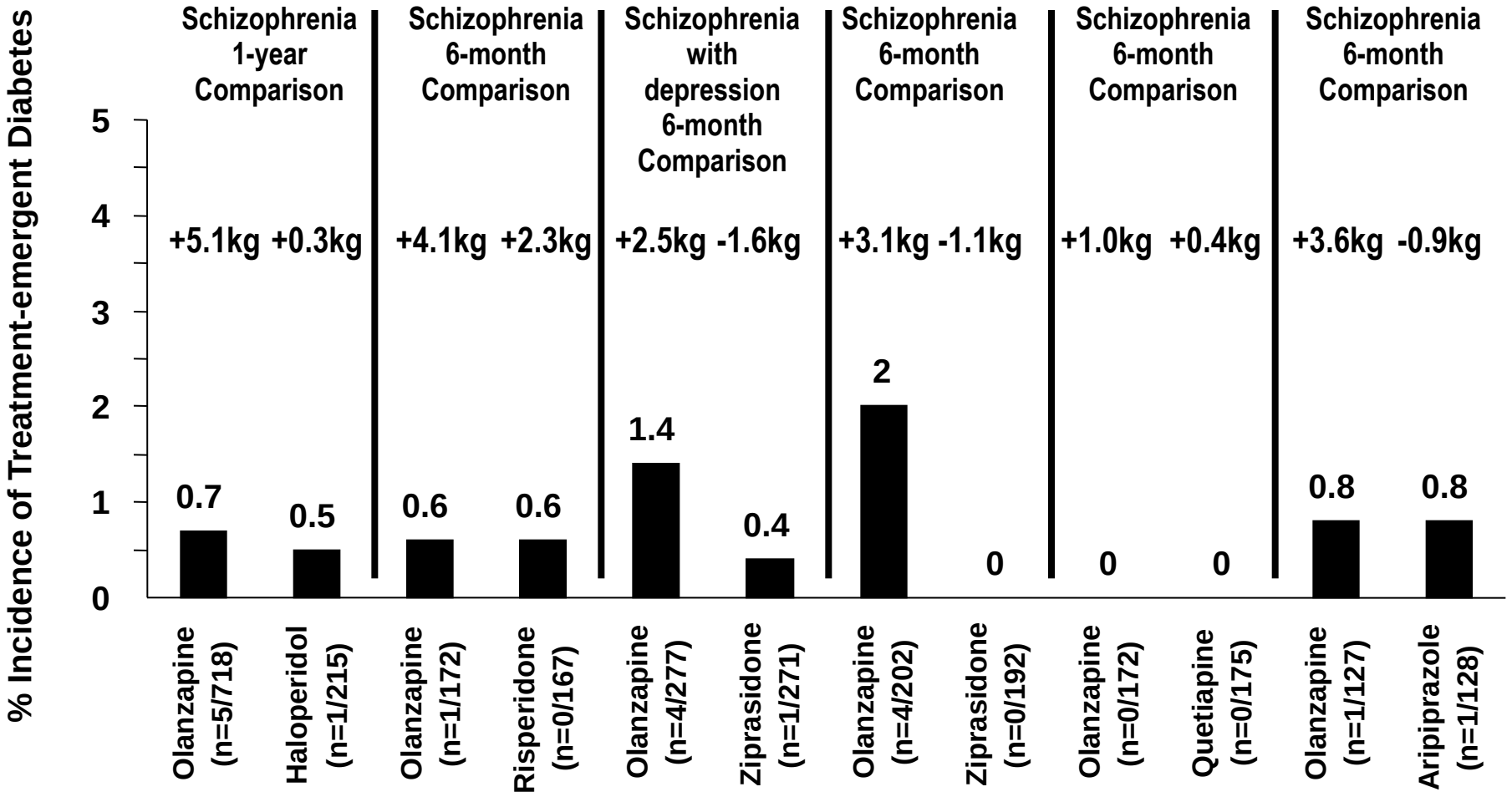
Data from Kinon BJ, APA *2003:*

Effect of weight management clinic



Number	103	94	78	69	62	60	54	46	41	26	16	8	7	2	3
Time (weeks)	0	4	8	12	16	20	26	39	52	78	104	130	156	182	208

Incidence of Treatment-emergent Diabetes: Longer-term Comparisons from Schizophrenia Clinical Trials



Treatment-emergent diabetes defined as new diagnosis of diabetes, worsening of preexisting diabetes, or initiation of diabetic pharmacotherapy.

Food and Drug Administration Center for Drug Evaluation and Research Medical Review 21-436 accessed at http://www.fda.gov/cder/foi/nda/2002/21-436_Abilify.htm

Other effects on insulin resistance

- Basic science evidence
  - OLZ inhibits insulin signalling in myotubes
- Animals
  - ↑hepatic insulin resistance
- Normal humans
  - Δ insulin resistance explained by Δ weight

Mol Psychiatry. 2005 Aug 30 epub; Diabetes. 2005 Mar;54(3):862-71; J Clin Endocrinol Metab 2002; 87: 2918-23

β-cell failure

- In vitro
  - Clozapine and Olanzapine ↑ insulin release
  - No Δ with quetiapine, risperidone and ziprasidone
- Animal models
  - OLZ caused ↓ in compensatory insulin secretion
- Human studies
  - No change

Neuro Endocrinol Lett. 2005 Jun;26(3):205-8; Eur Neuropsychopharmacol. 2004 Mar;14(2):115-9 Diabetes. 2005 Mar;54(3):862-71; J Clin Endocrinol Metab 2002; 87: 2918-23

Coherence

“Cause and effect interpretation should not conflict with generally known facts of natural history and biology of disease”

Coherence

- Incidence of DM is ↑ in people with SZ
- Use of AAPDs is also ↑

…however screening for DM is also ↑

  - only 41% of patients at the Maudsley received screening
  - those receiving AAPDs had more screening

Taylor et al Br J Psychiatry 2004, 185, 152-6.

Experimental Evidence

Analogy

Other drugs that cause weight gain or insulin resistance are associated with development of diabetes eg steroids

Austin Bradford Hill Criteria

• Strength	Weak
• Consistency	X
• Specificity	X
• Temporality	√ in a few
• Biological gradient	+/-
• Plausibility	√
• Coherence	√
• Experimental evidence	+/-
• Analogy	√

Audience Questions?

- How many of you believe diabetes is a clinical problem among people with schizophrenia?
- How many of you believe the anti-psychotic drugs cause diabetes?
- How many of you believe the anti-psychotic drugs are a major cause of diabetes in this patient group?
- DM is serious clinical problem among people with schizophrenia
- APDs do cause DM in a few patients
- Attributable risk associated with APDs is low

Are anti-psychotic drugs always bad for diabetes?

- Need to treat the mental state adequately!
  - To empower the patient manage their diabetes
- Case reports showing improved HbA1c

Seeing the full picture

- Metabolic side effects are only one consideration
- Effectiveness
- Other side effects
  - EPS
  - Hyperprolactinaemia
  - ECG

Clinical Implications

- Diabetes should be actively sought in those with severe mental illness
- Treatment of the mental state should be the primary concern
  - Don’t deny the patient effective treatment
- A multi-disciplinary approach is needed to manage diabetes and diabetes risk in this vulnerable group