Acute Treatment of Schizophrenia
Multiple-treatments meta-analysis

Prof. Stefan Leucht
Vice chairman
Department of Psychiatry and Psychotherapy
Technische Universität München

Aims

I. To understand the principle of simple pairwise meta-analyses and of network meta-analyses

II. To know the relative effects of second-generation antipsychotics in major efficacy and side-effect outcomes

III. To understand that single antipsychotics differ enormously in their effects which allows to adapt them to the needs of individual patients

IV. To understand the principle of shared decision making

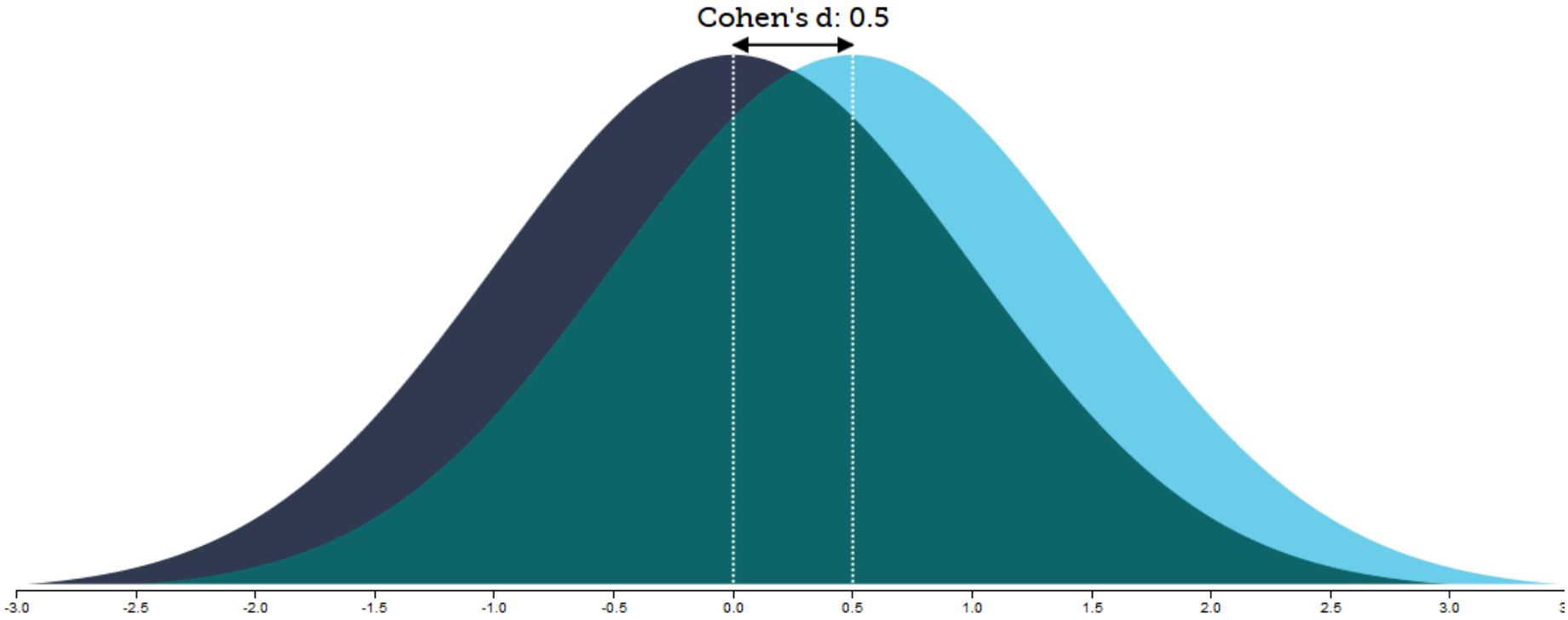
Two important measures in meta-analyses: p-value versus effect size

- Meta-analyses try to calculate the mean of several studies on the same topic
- They present **p-values** to indicate the **probability** of whether difference between two interventions is only a chance finding. The lower the p-value, the lower this probability
- But the p-value is not a measure of the magnitude of the difference between two interventions. For example, it depends in part on the sample size. If the sample size is very high, an excellent p-value may results although the magnitude of the difference is small
- Therefore, meta-analyses also present **effect sizes** which are measures of the **magnitude of the difference** between two interventions
- **Both are important, but once a significant p-value is established, the effect size is relevant to understand the clinical meaningfulness of a difference**

Calculation of Effect Sizes for Continuous Variables

- **Effect size is a measure for the magnitude of the difference between interventions**
- **Effect size = (mean A – mean B)/pooled standard deviation**
- **Example (PANSS total score): (90 – 80)/20 = 0.50**

Ilustration of the meaning of effect size



source : http://rpsychologist.com/d3/cohend/

Cohen‘s rule

Standardised mean difference („effect size“) of:

0.20 = small

0.50 = medium

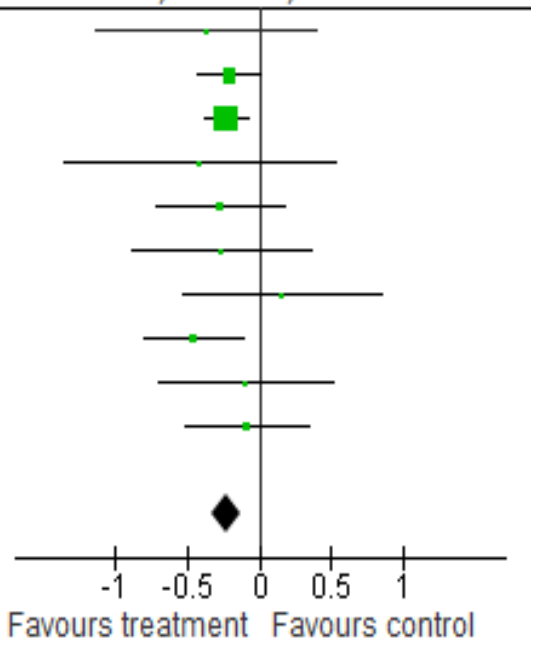
0.80 = large

Principle of meta-analysis, example: Olanzapine versus quetiapine for schizophrenia

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Atmaca 2003	74.86	6.41	13	77.24	6.08	14	1.8%	-0.37 [-1.13, 0.39]
Kinon 2006b	-11.3	18.3	166	-7.2	21.2	169	23.2%	-0.21 [-0.42, 0.01]
Lieberman 2005	-11.27	22.31	330	-6.08	22.31	329	45.6%	-0.23 [-0.39, -0.08]
McEvoy 2006	-7.7	9.8	10	-1.3	19.23	8	1.2%	-0.41 [-1.36, 0.53]
McEvoy 2007	-18.4	9.73	37	-15.6	10.68	44	5.5%	-0.27 [-0.71, 0.17]
Mori 2004	69.4	10.8	20	72.9	15.1	20	2.8%	-0.26 [-0.88, 0.36]
Riedel 2007	-17.88	20.71	17	-21.5	23.39	16	2.3%	0.16 [-0.52, 0.84]
Stroup 2006	-8.2	22.31	66	2	22.31	63	8.7%	-0.45 [-0.80, -0.10]
Svestka 2003b	-45.65	11.96	20	-43.91	20.94	22	2.9%	-0.10 [-0.70, 0.51]
Voruganti 2007	48.5	9.9	42	49.4	12	43	5.9%	-0.08 [-0.51, 0.34]
Total (95% CI)			**721**			**728**	**100.0%**	**-0.23 [-0.34, -0.13]**

Heterogeneity: Tau² = 0.00; Chi² = 3.85, df = 9 (P = 0.92); I² = 0%

Test for overall effect: Z = 4.39 (P < 0.0001)



Komossa et al. Cochrane review 2010

Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis

Stefan Leucht, Caroline Corves, Dieter Arbter, Rolf R Engel, Chunbo Li, John M Davis

4166 abstracts screened

150 double-blind studies with 21,533 participants included

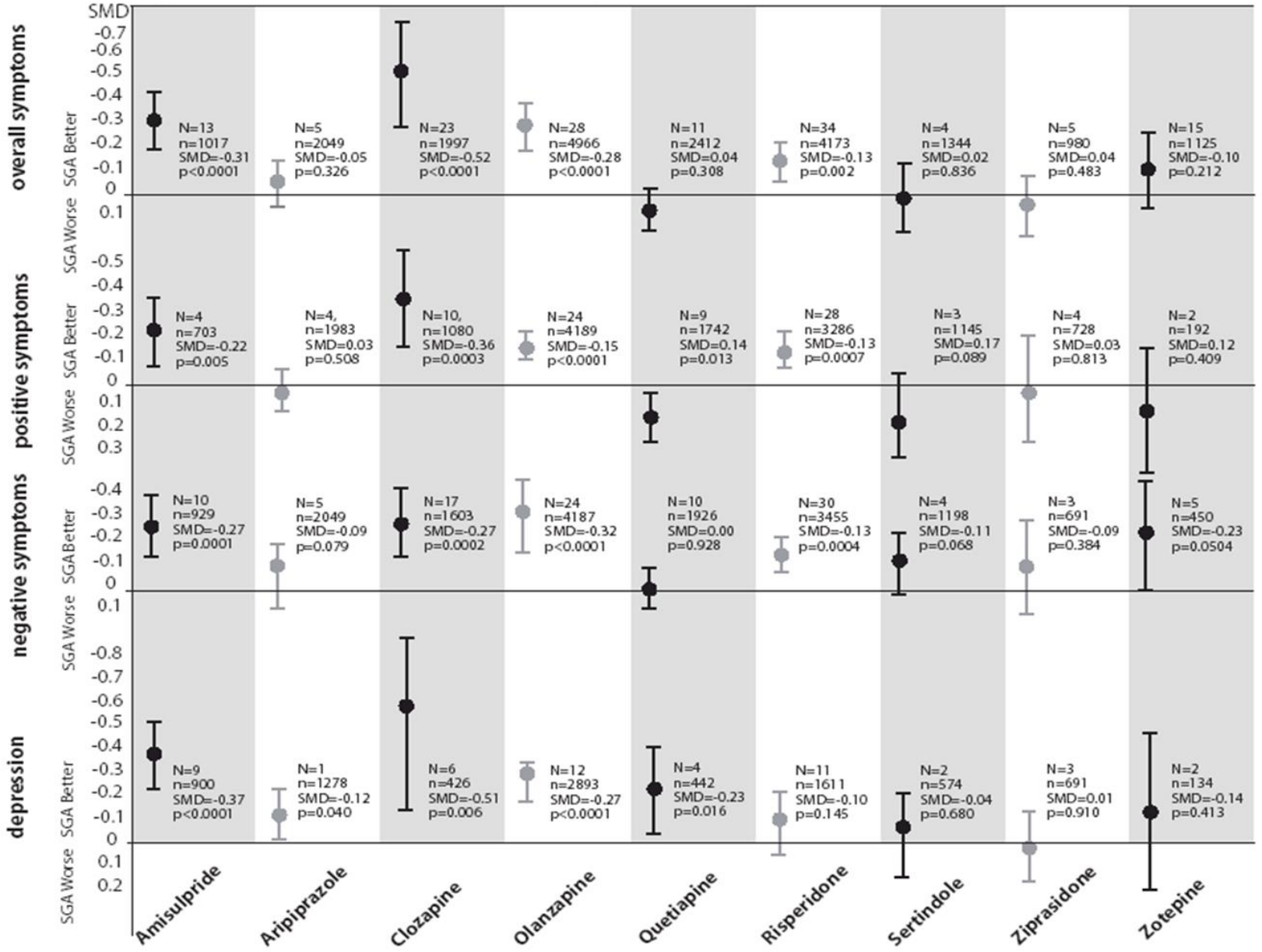
Most frequent comparators: Haloperidol (N=95), chlorpromazine (N=28)
35 from China and other Asian countries, 5 first episode, 81% <= 12 weeks, mean age 36.2 years

<u>Nine Outcomes analysed:</u>

Overall symptoms (PANSS total), positive symptoms, negative symptoms, depression, quality of life, relapse, EPS, weight gain, sedation

Leucht et al. Lancet 2009

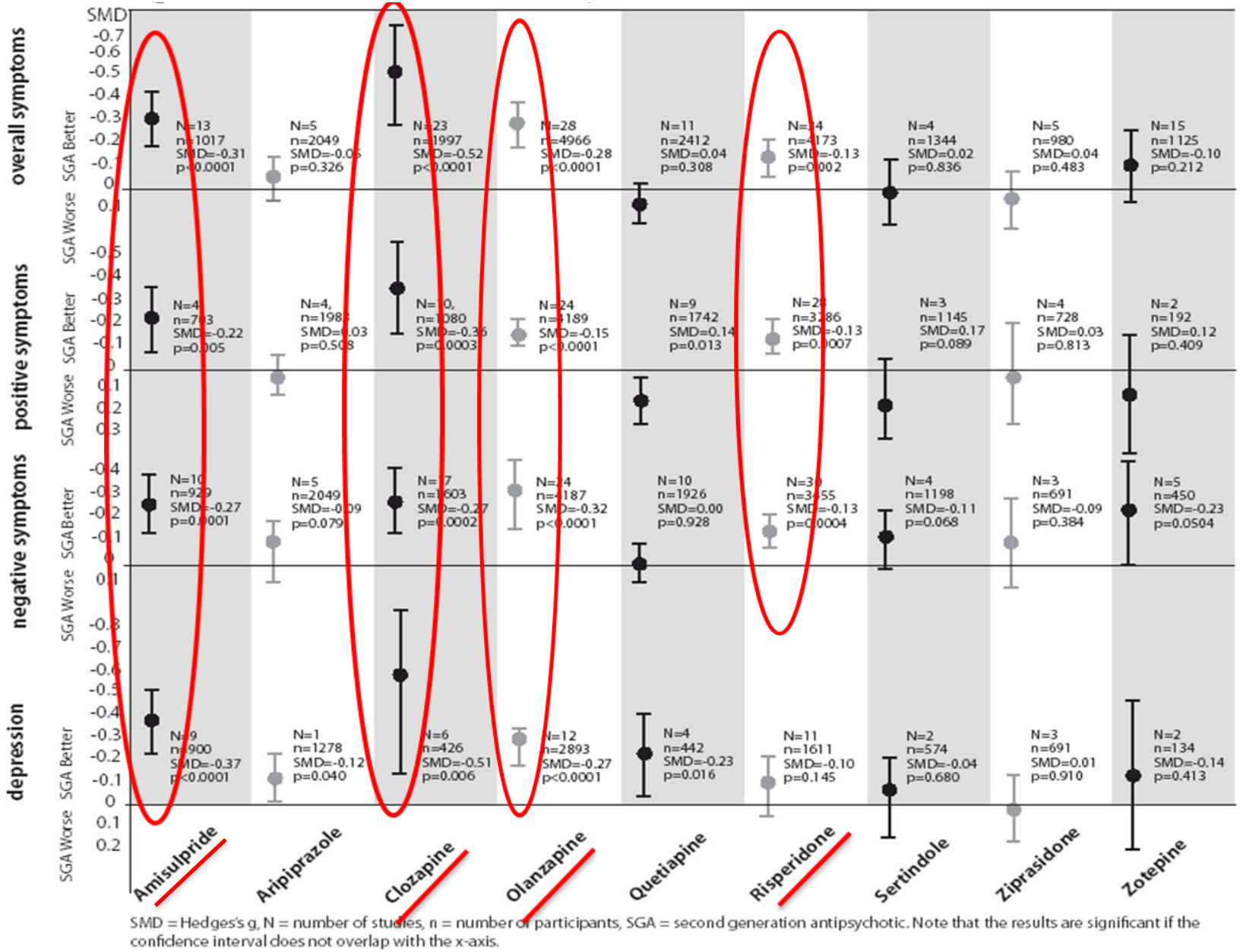
Second-generation versus first-generation antipsychotics – efficacy



SMD = Hedges's g, N = number of studies, n = number of participants, SGA = second generation antipsychotic. Note that the results are significant if the confidence interval does not overlap with the x-axis.

Leucht et al. Lancet 2009

Second-generation versus first-generation antipsychotics – efficacy



SMD = Hedges's g, N = number of studies, n = number of participants, SGA = second generation antipsychotic. Note that the results are significant if the confidence interval does not overlap with the x-axis.

Leucht et al. Lancet 2009

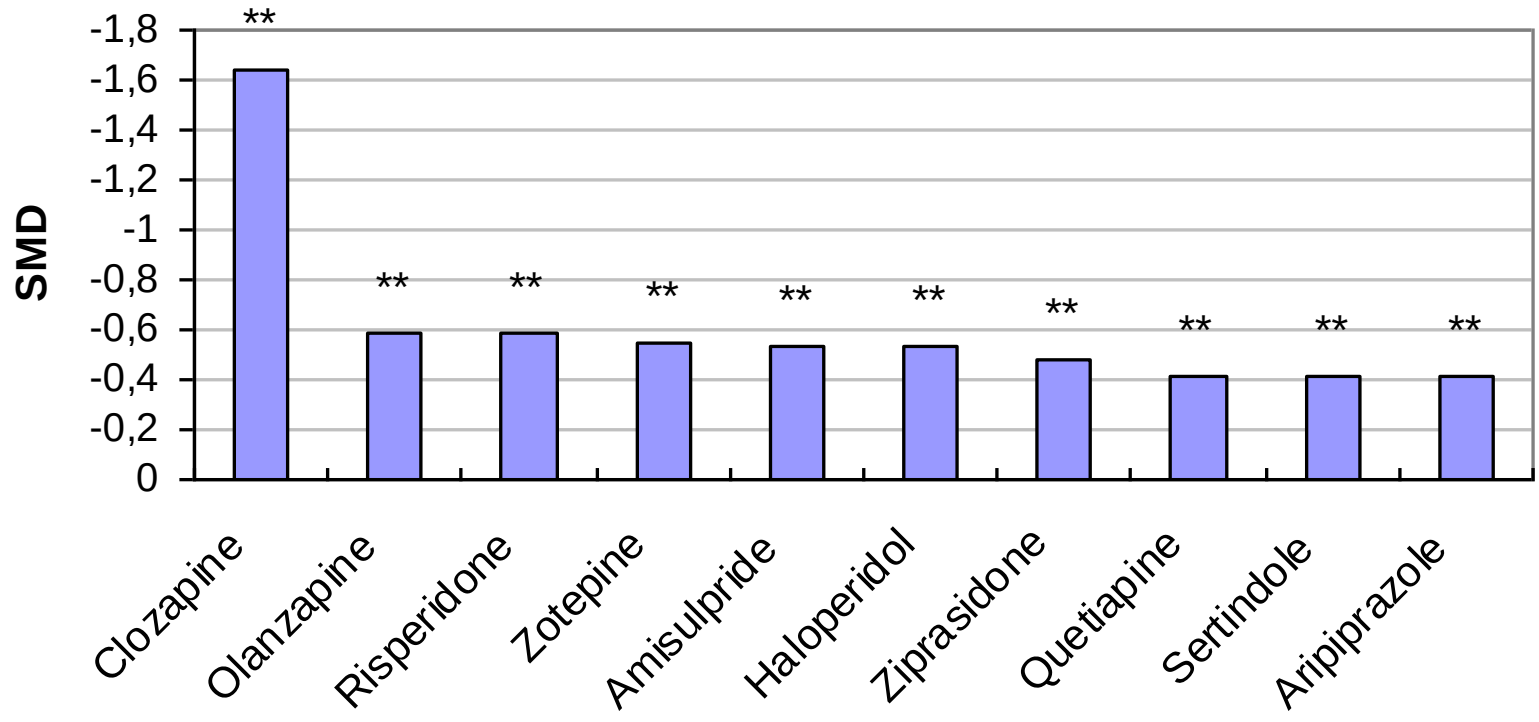
ORIGINAL ARTICLE

How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials

S Leucht[1], D Arbter[1], RR Engel[2], W Kissling[1] and JM Davis[3]

Molecular Psychiatry (2008), 1–19

PANSS/BPRS: antipsychotics vs placebo



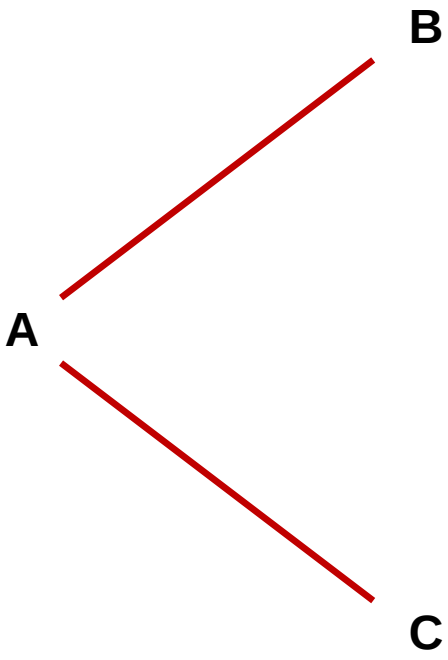
A Meta-Analysis of Head-to-Head Comparisons of Second-Generation Antipsychotics in the Treatment of Schizophrenia

Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, Schwarz S, Davis JM. American Journal of Psychiatry 2009

	Amisulpride	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Risperidone	Sertindole	Ziprasidone
Aripiprazole								
Clozapine								
Olanzapine	↔ 701	**OLA ↑** 794	↔ 619					
Quetiapine			↔ 232	**OLA ↑** 1449				
Risperidone	↔ 291	↔ 372	↔ 466	**OLA ↑** 2404	**RIS ↑** 1953			
Sertindole						↔ 493		
Ziprasidone	↔ 122		↔ 146	**OLA ↑** 1291	↔ 710	**RIS ↑** 1016		
Zotepine			**CLO ↑** 59					

Blank fields indicate that no study is available. ↑ Statistically significantly superior, ↔ no significant difference between groups. The numbers below the arrows represent the number of participants included in the comparison.

Latest development: Network meta-analysis Principle

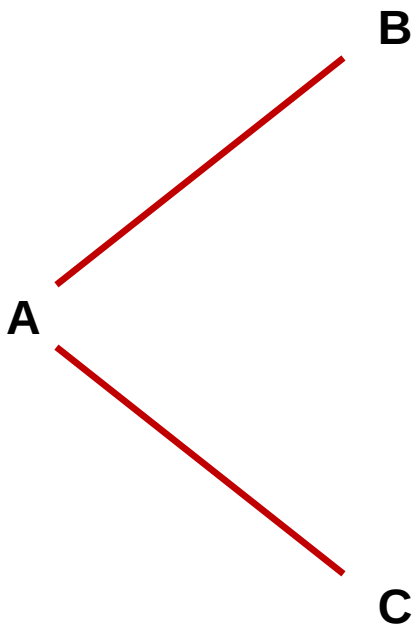


There are trials of:

- A versus B
- A versus C

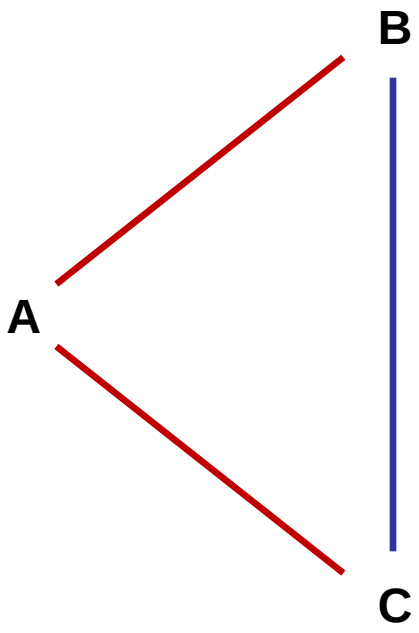
but **not** B versus C

Principle of network meta-analysis continued



There are trials of:
- A versus B
- A versus C

but **not** B versus C



B vs C can be estimated from A vs B and A vs C

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

Stefan Leucht, Andrea Cipriani, Loukia Spineli, Dimitris Mavridis, Deniz Örey, Franziska Richter, Myrto Samara, Corrado Barbui, Rolf R Engel, John R Geddes, Werner Kissling, Marko Paul Stapf, Bettina Lässig, Georgia Salanti, John M Davis

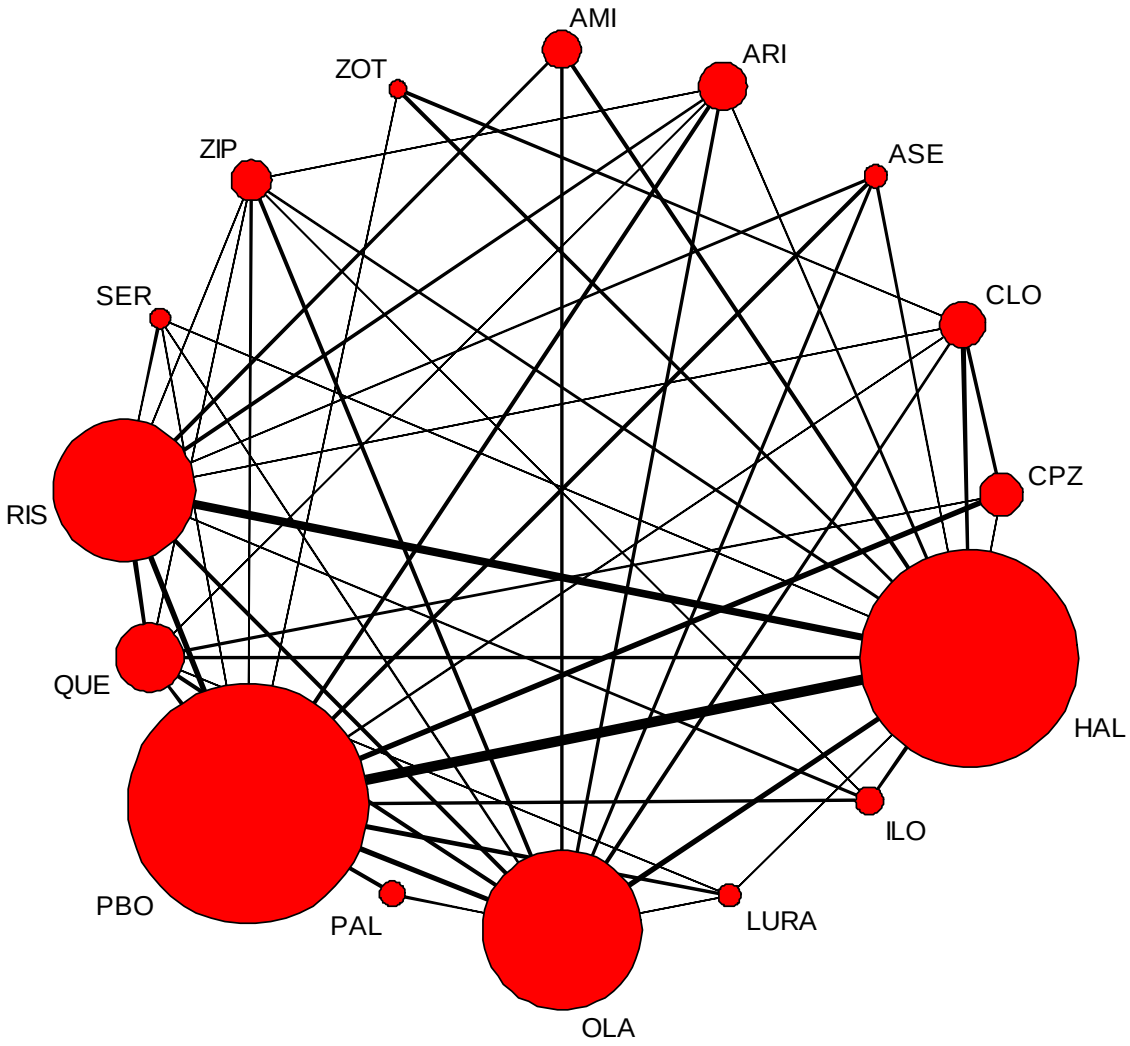
Lancet 2013

Multiple-treatments meta-analysis: characteristics

- **212 RCTs, 43,049 participants**
- **At least single-blind RCTs (94% double-blind)**
- **4-12 weeks duration (requirement of MTM to have a homgeneous sample)**
- **Exclusion of studies in treatment resistant patients, patients with predominant negative symptoms**
- **15 drugs:** amisulpride, aripiprazole, asenapine, chlorpromazine, clozapine, haloperidol, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, zotepine or placebo
- **Mean age** 38.4 (SD 6.9), **mean duration of illness** 12.4 (SD 6.6) years, **nine first-episode studies**

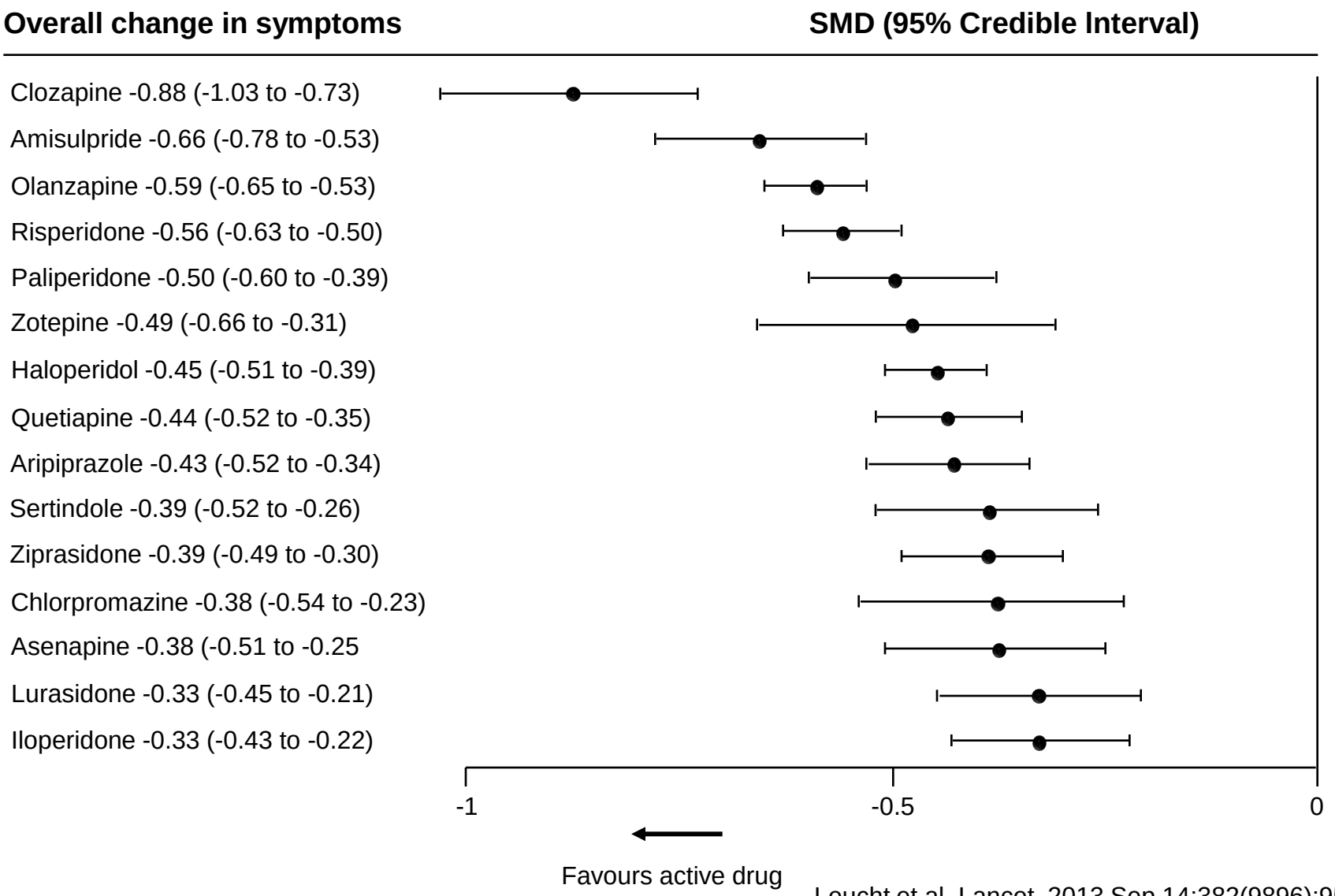
Leucht et al. Lancet. 2013 Sep 14;382(9896):951-62

Network meta-analysis of 15 antipsychotic drugs in schizophrenia (212 studies, 43,049 participants)



Leucht et al. Lancet. 2013 Sep 14;382(9896):951-62

Overall efficacy of antipsychotic drugs vs placebo



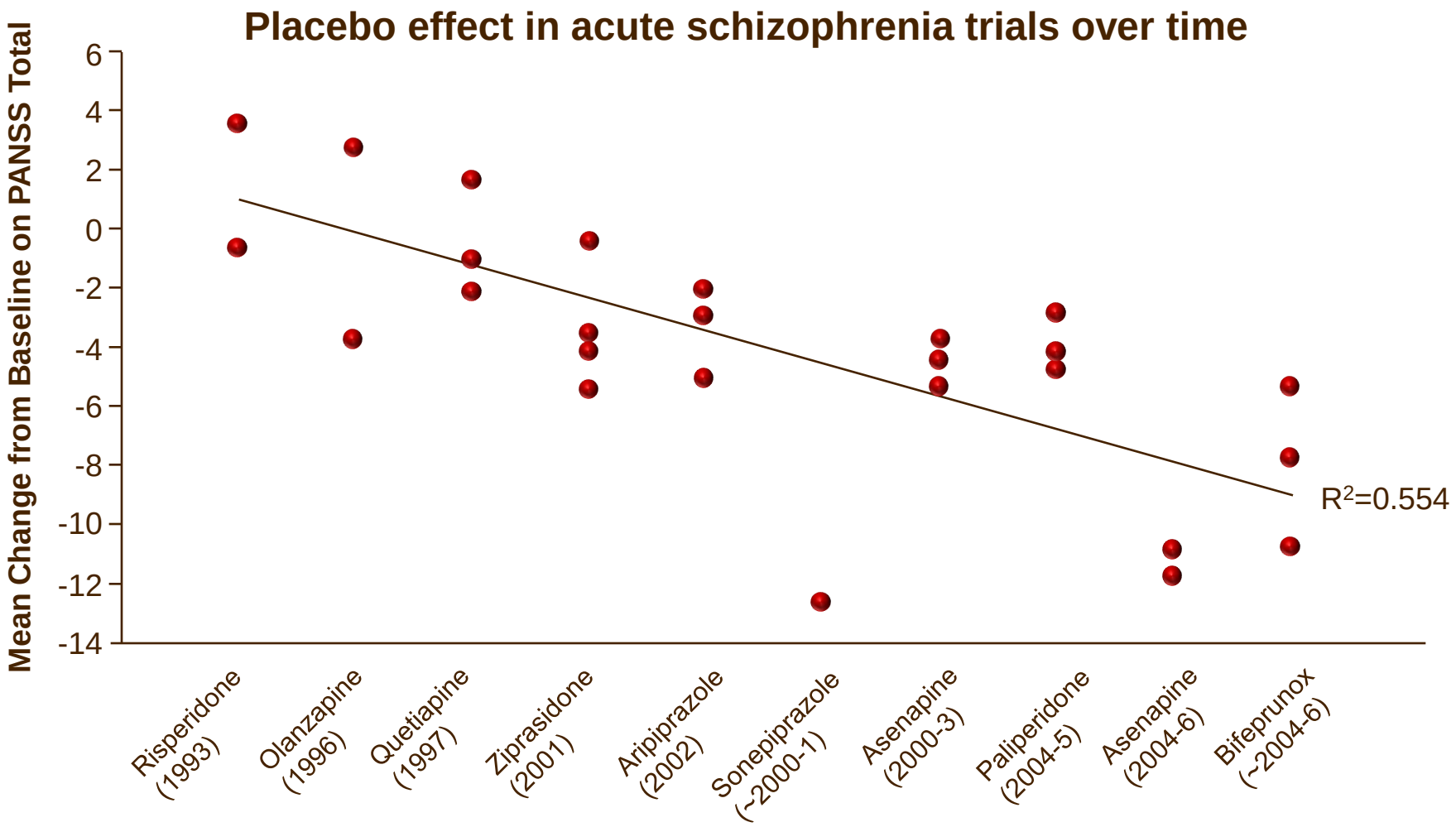
Leucht et al. Lancet. 2013 Sep 14;382(9896):951-62

Confounders ruled out by sensitivity, subgroup and meta-regression analyses

- **Increasing placebo response**: Exclusion of placebo, publication year as a continuous co-variate
- **Differences in haloperidol comparator dose**: Exclusion of haloperidol, haloperidol ≤12 mg/day and >12 mg/day and ≤7.5 mg/day and
  >7.5 mg/day, same for chlorpromazine ≤600 (or 500) mg/day and >600 (or 500) mg/day
- **Unfair doses**: Exclude studies that compared high-doses of one drug with low-doses of the other, dose of all antipsychotics in chlorpromazine equivalents as a co-variate
- Exclude **single-blind studies, first-episode studies**, 'failed' studies (both the new antipsychotic and the active comparator were not more efficacious than placebo), **completer analyses**
- **Pharmaceutical sponsor**, participants' mean age (measure of **chronicity**), **length** of the follow up and overall **percentage of dropout**

Leucht et al. Lancet. 2013 Sep 14;382(9896):951-62

Increasing placebo response in recent schizophrenia trials

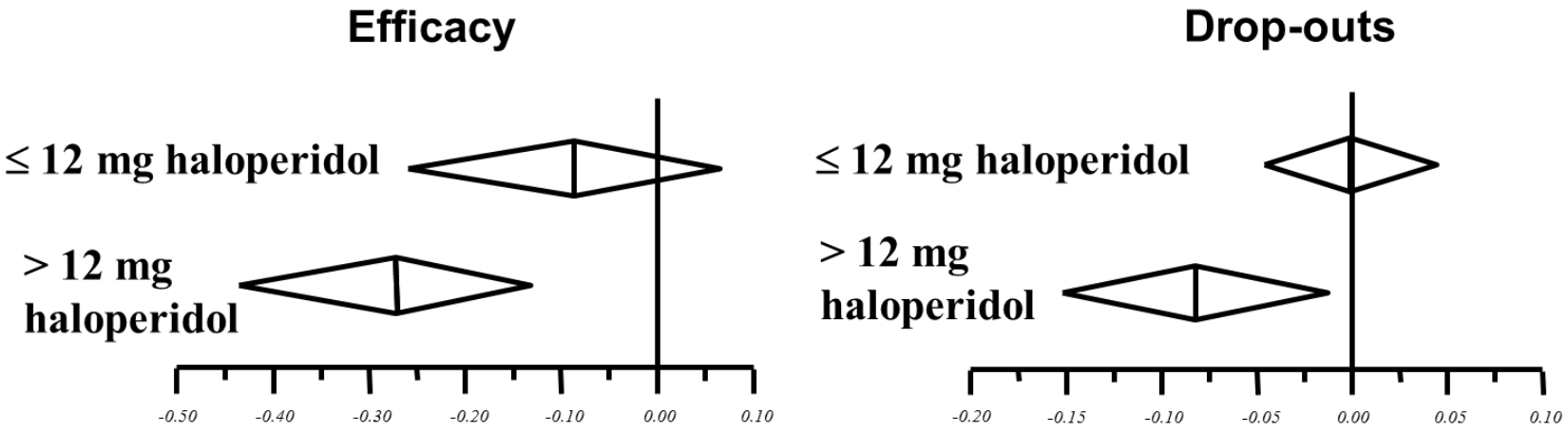


Adapted from Kemp AS, et al. Schiz Bull. 2011;36:504–9.

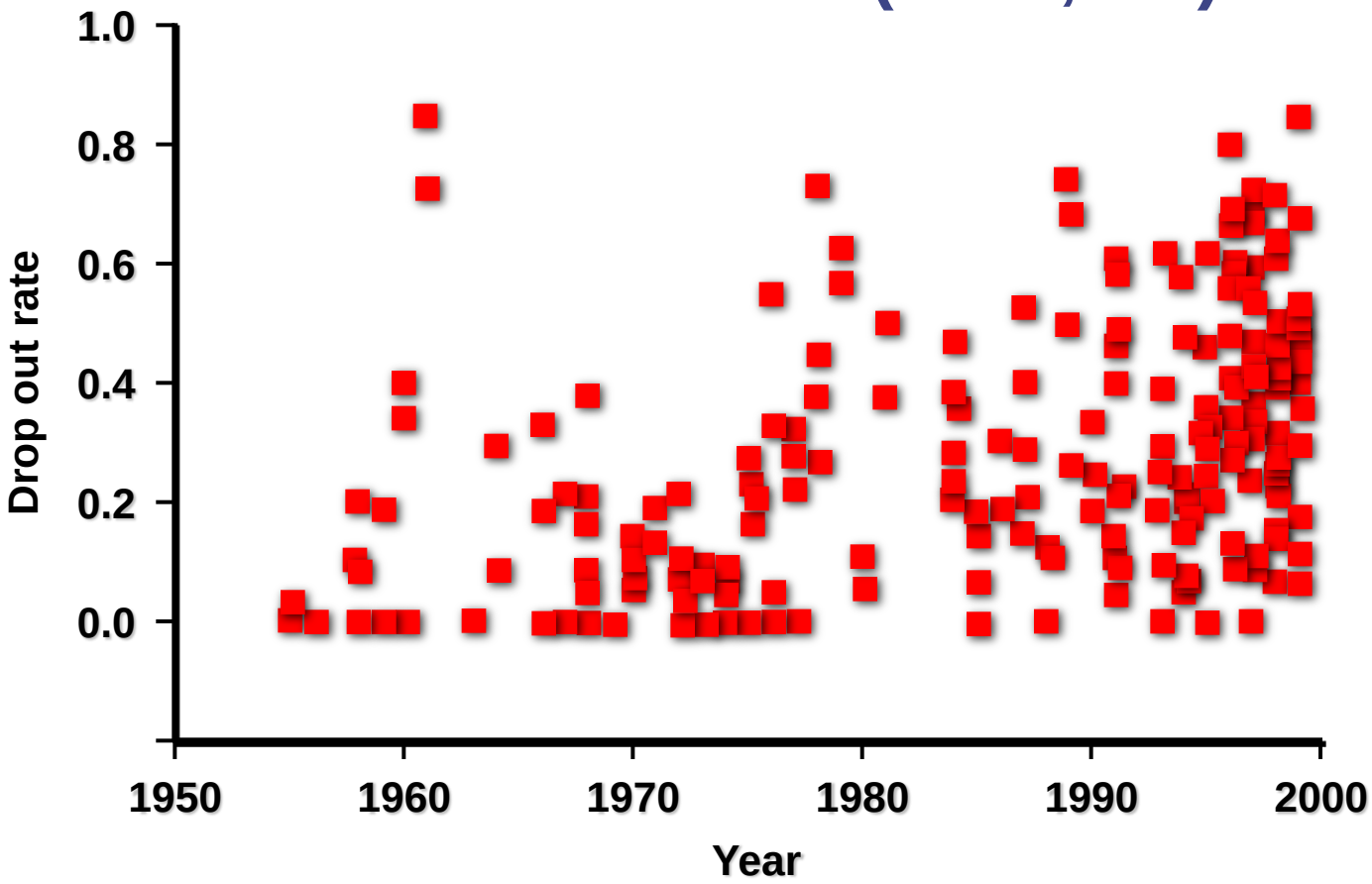
“Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta.regression analysis

Geddes et al. British Medical Journal (2000) 321:1371-6“

„No superiority of the new antipsychotics in terms of efficacy and drop-out rates when conventional antipsychotics were used at doses lower than 12mg/day haloperidol or its equivalent“



Continuous Increase of Drop-out Rates by 1%/year in Randomised Schizophrenia Drug Trials Since 1950 (n=18,000)



Another important problem are high dropout rates in schizophrenia trials, often more than 50% already in short-temr studies

Wahlbeck et al. have shown that they have increased since the 1950s

It is difficult to statistically analyse data in such a situation

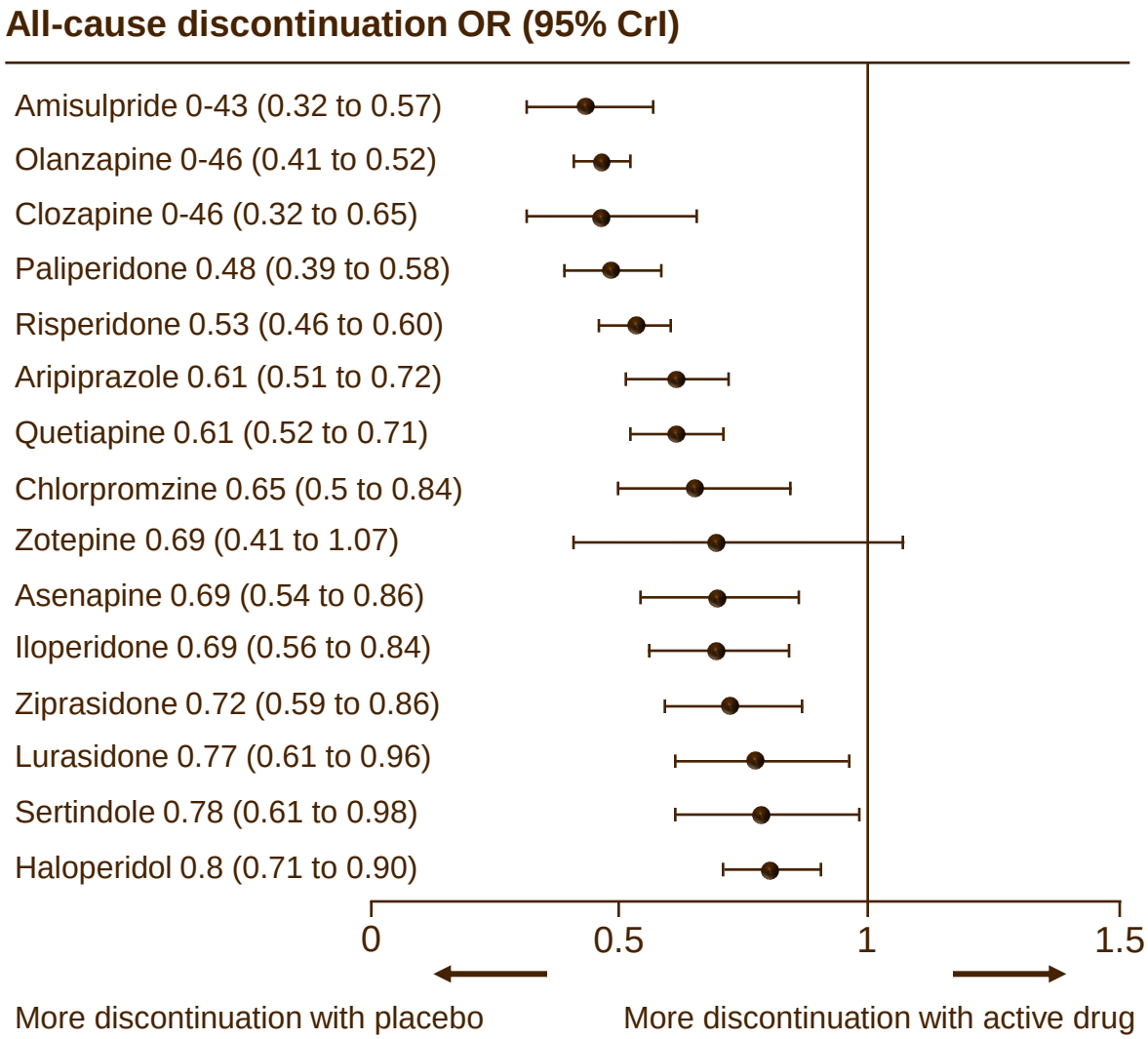
Wahlbeck et al. Psychopharmacology 2001

Confounders ruled out by sensitivity, subgroup and meta-regression analyses

- **Increasing placebo response**: Exclusion of placebo, publication year as a continuous co-variate
- **Differences in haloperidol comparator dose**: Exclusion of haloperidol, haloperidol ≤12 mg/day and >12 mg/day and ≤7.5 mg/day and
  >7.5 mg/day, same for chlorpromazine ≤600 (or 500) mg/day and >600 (or 500) mg/day
- **Unfair doses**: Exclude studies that compared high-doses of one drug with low-doses of the other, dose of all antipsychotics in chlorpromazine equivalents as a co-variate
- Exclude **single-blind studies, first-episode studies**, 'failed' studies (both the new antipsychotic and the active comparator were not more efficacious than placebo), **completer analyses**
- **Pharmaceutical sponsor**, participants' mean age (measure of **chronicity**), **length** of the follow up and overall **percentage of dropout**

Leucht et al. Lancet. 2013 Sep 14;382(9896):951-62

All-cause discontinuation of antipsychotic drugs vs placebo



OR=odds ratio

Leucht et al. Lancet. 2013 Sep 14;382(9896):951-62

What is the best term?

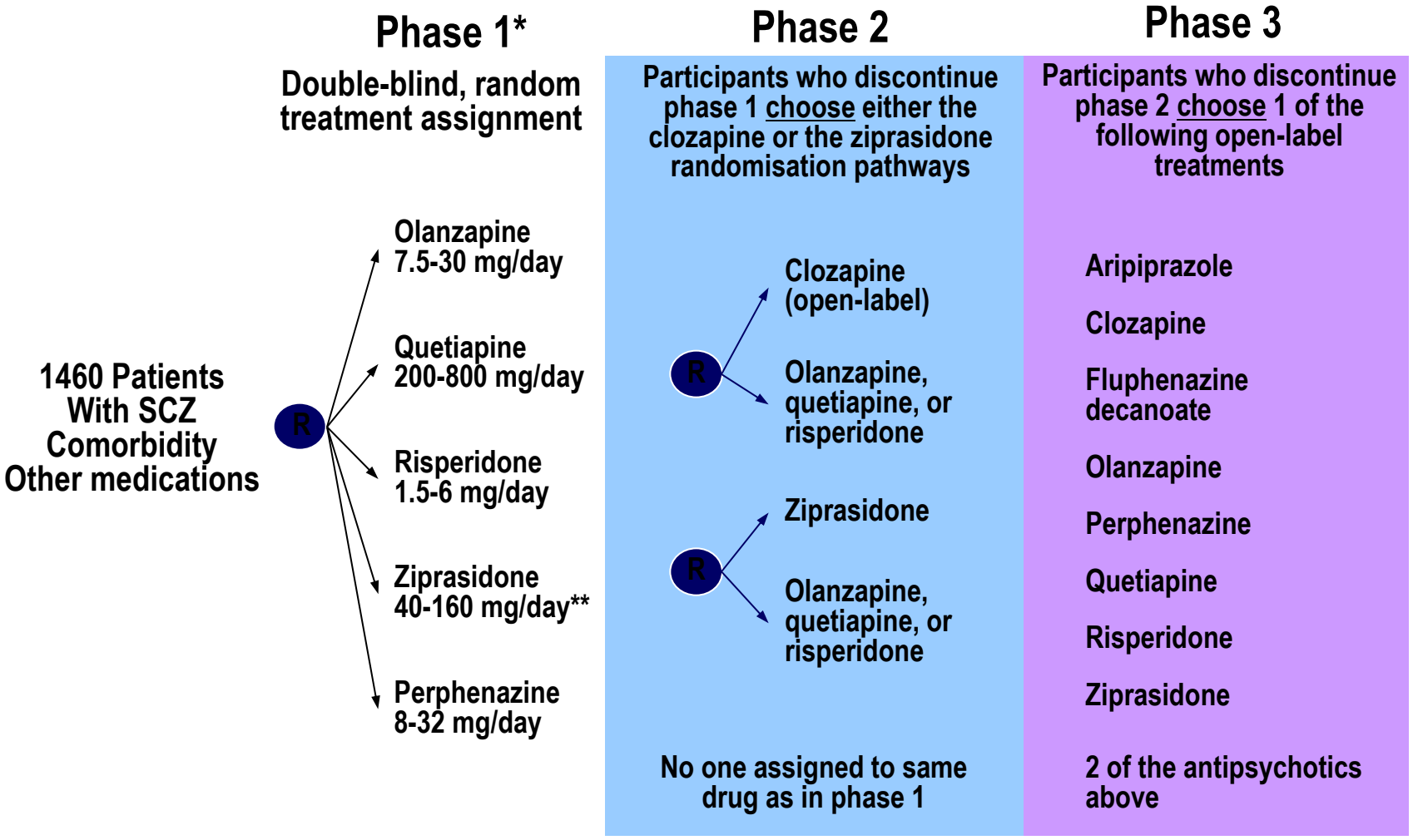
Dropout for any reason: no immediate clinical meaning

Acceptability of treatment: readers confuse it with tolerability, but it combines efficacy and tolerability

All-cause discontinuation: neutral term, but it is negative blurring the clinical important

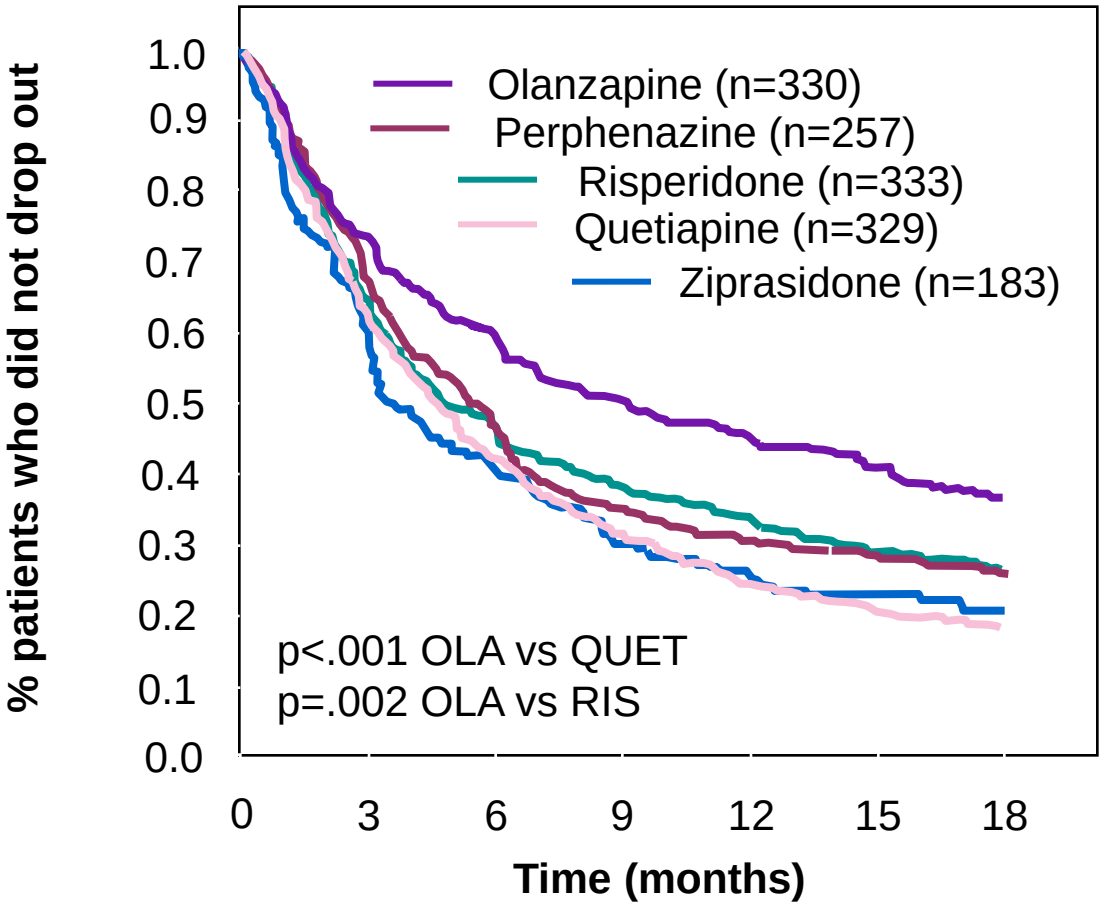
Retention/staying in treatment: positive, clinically meaningful?

CATIE Schizophrenia Trial Design



*Phase 1A: participants with tardive dyskinesia (N=231) do not get randomised to perphenazine; phase 1B: participants who fail perphenazine will be randomised to an atypical (olanzapine, quetiapine, or risperidone) before eligibility for phase 2.
**Ziprasidone added after 40% sample enrolled.
Stroup TS, et al. *Schizophr Bull.* 2003;29(1):15-31.

CATIE: All cause discontinuation (%)

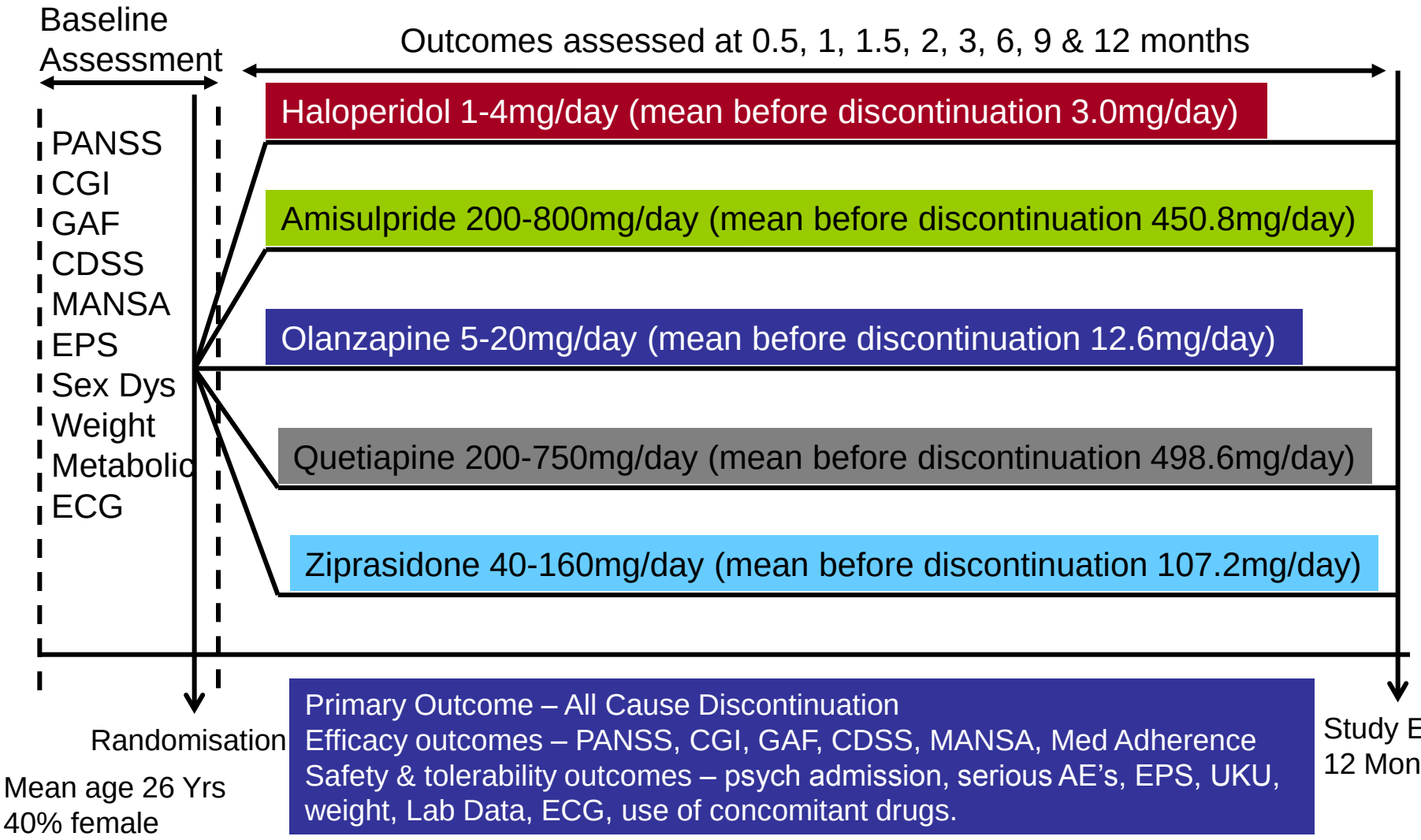


Drop-out (%)	
Total	74
Ola	64
Ris	74
Per	75
Zip	79
Quet	82

Lieberman et al, N ENGL J Med 353;12; 2005

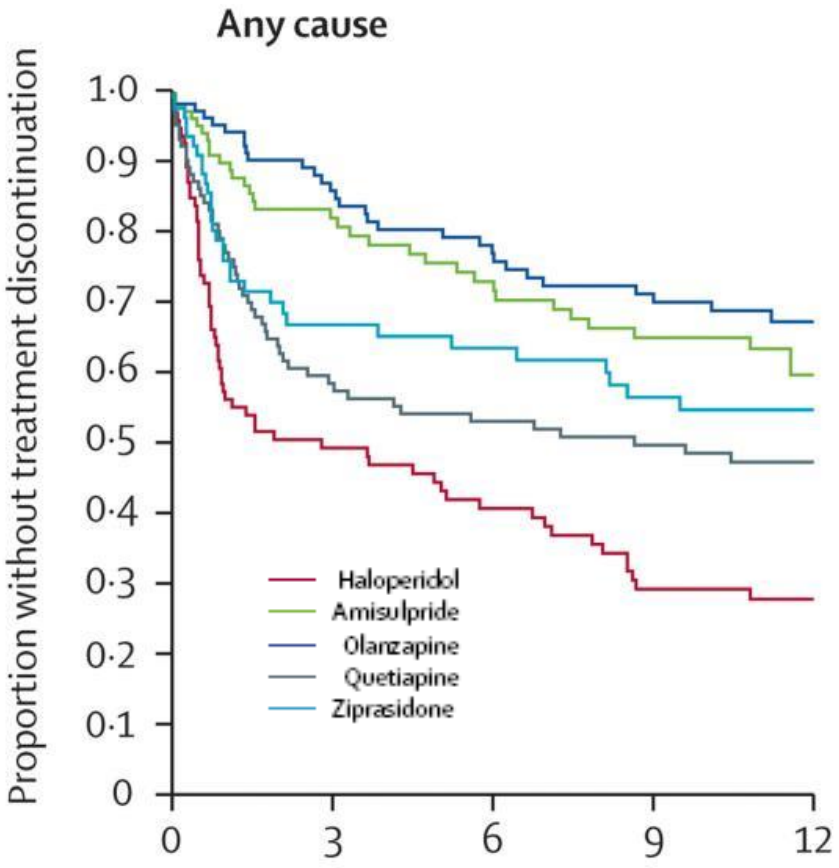
EUFEST Study: design of an open RCT in first-episode schizophrenia

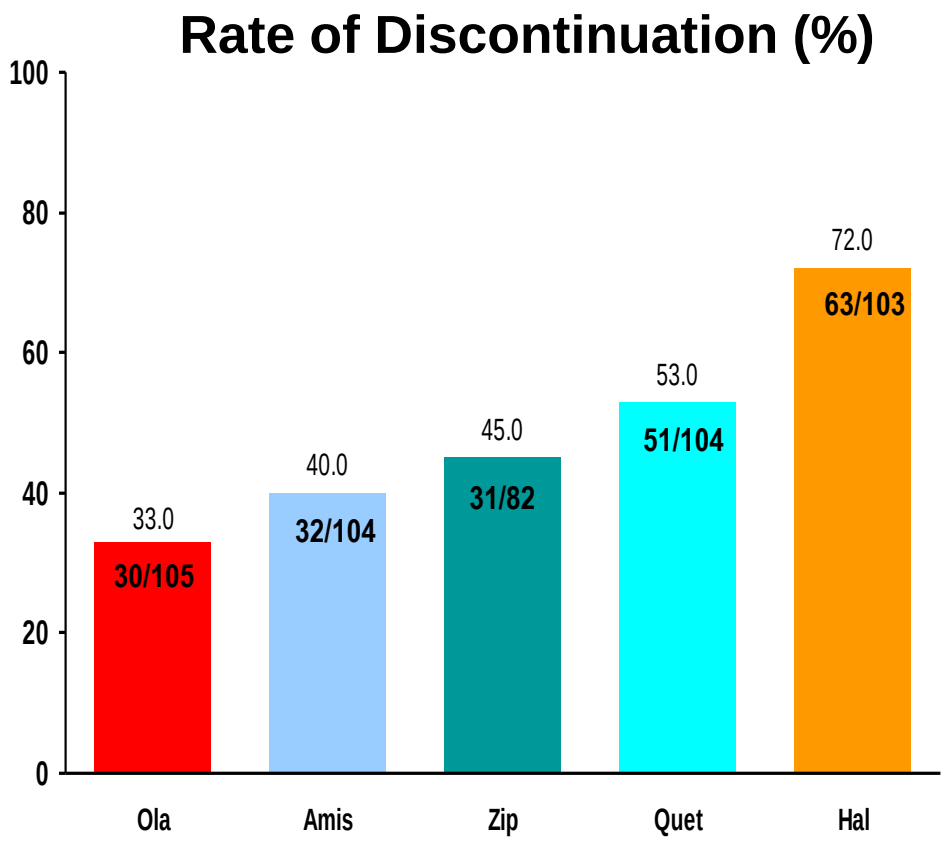
N=496



Kahn R.S. et al. Lancet 2008;371:1085-97

Time To & Rates of All-Cause Discontinuation Within 12 Months

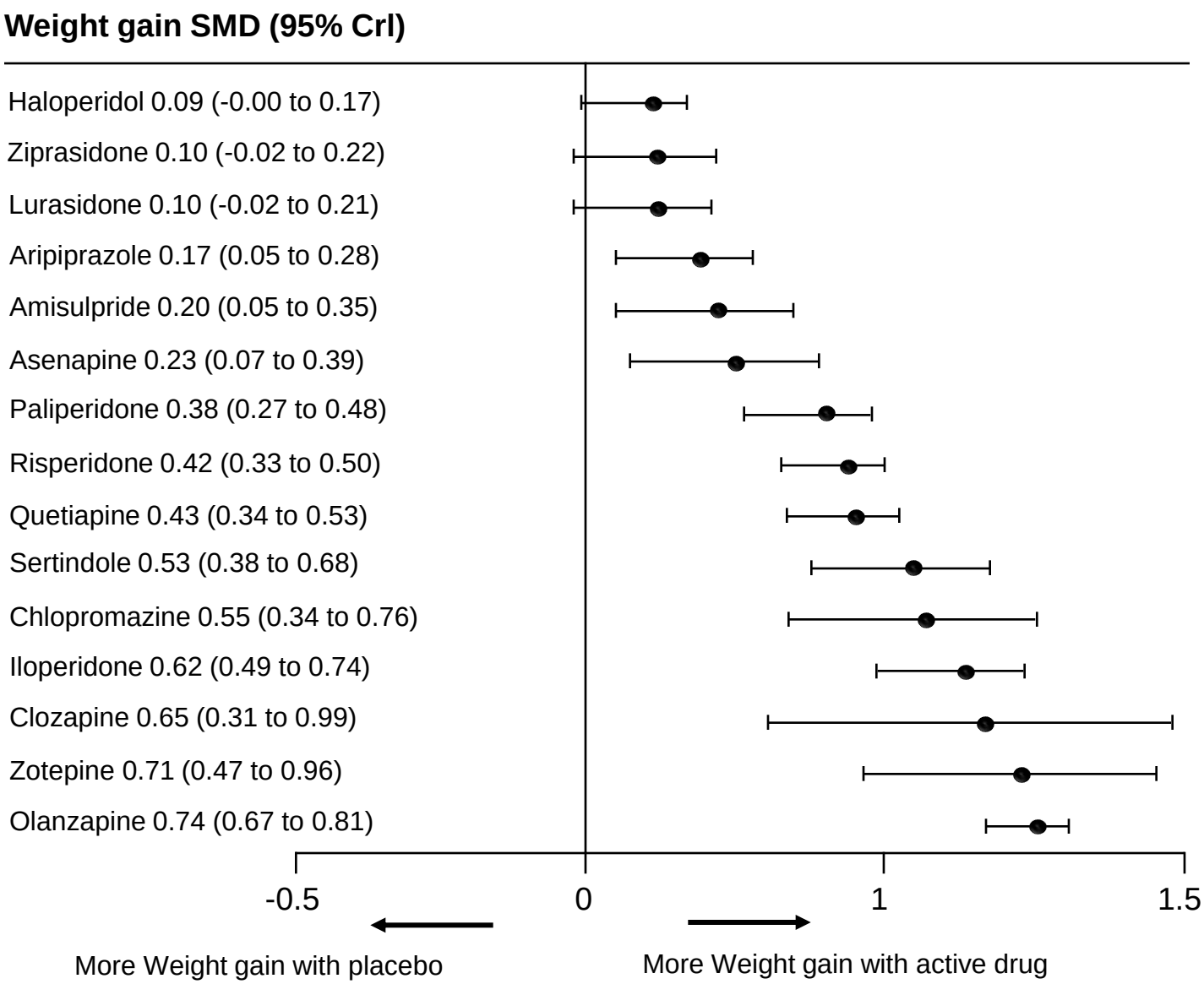




Treatment discontinuation for any cause differed between treatment groups (p<0.0001)

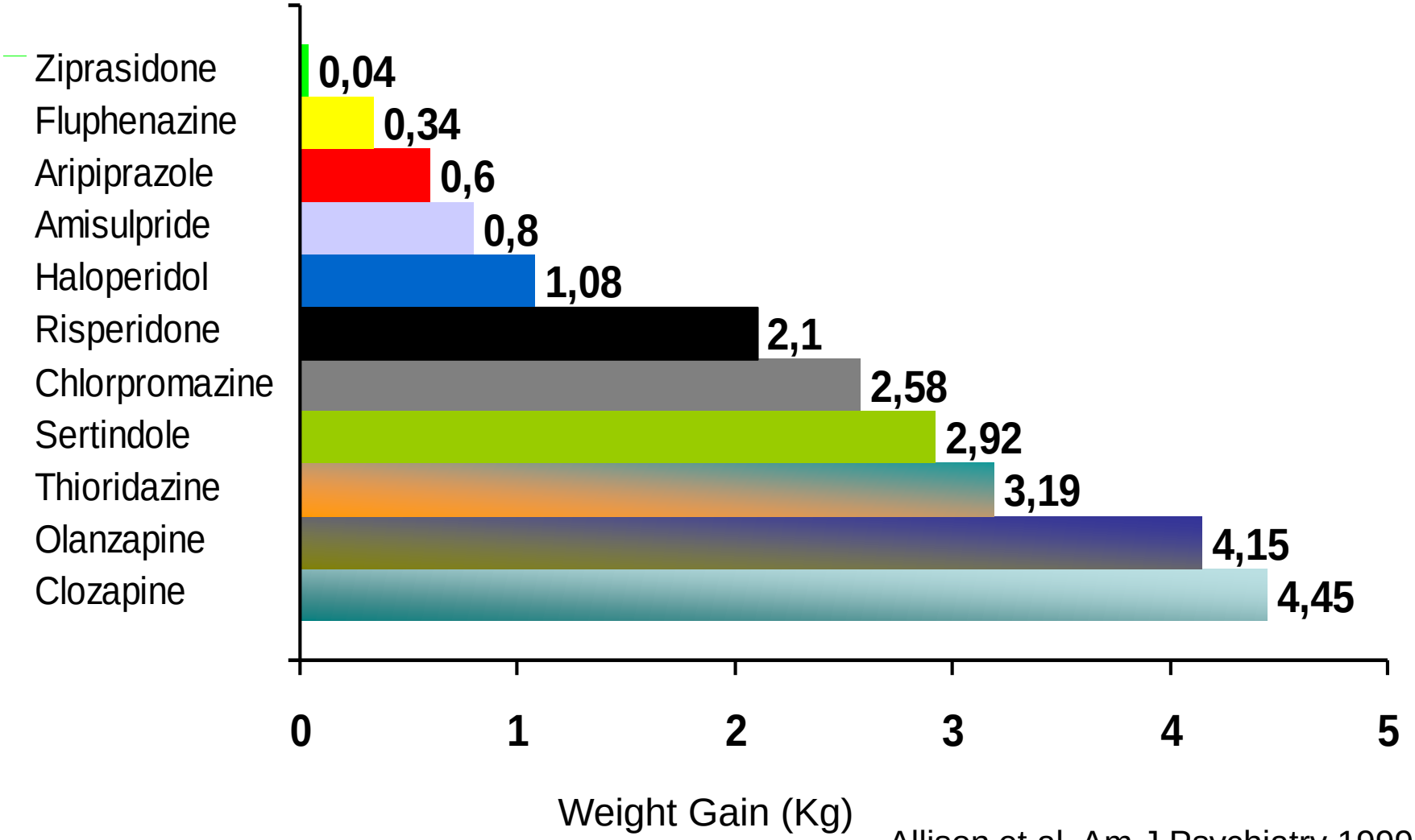
Kahn R.S. et al. Lancet 2008;371:1085-97

Weight gain antipsychotic drugs vs placebo



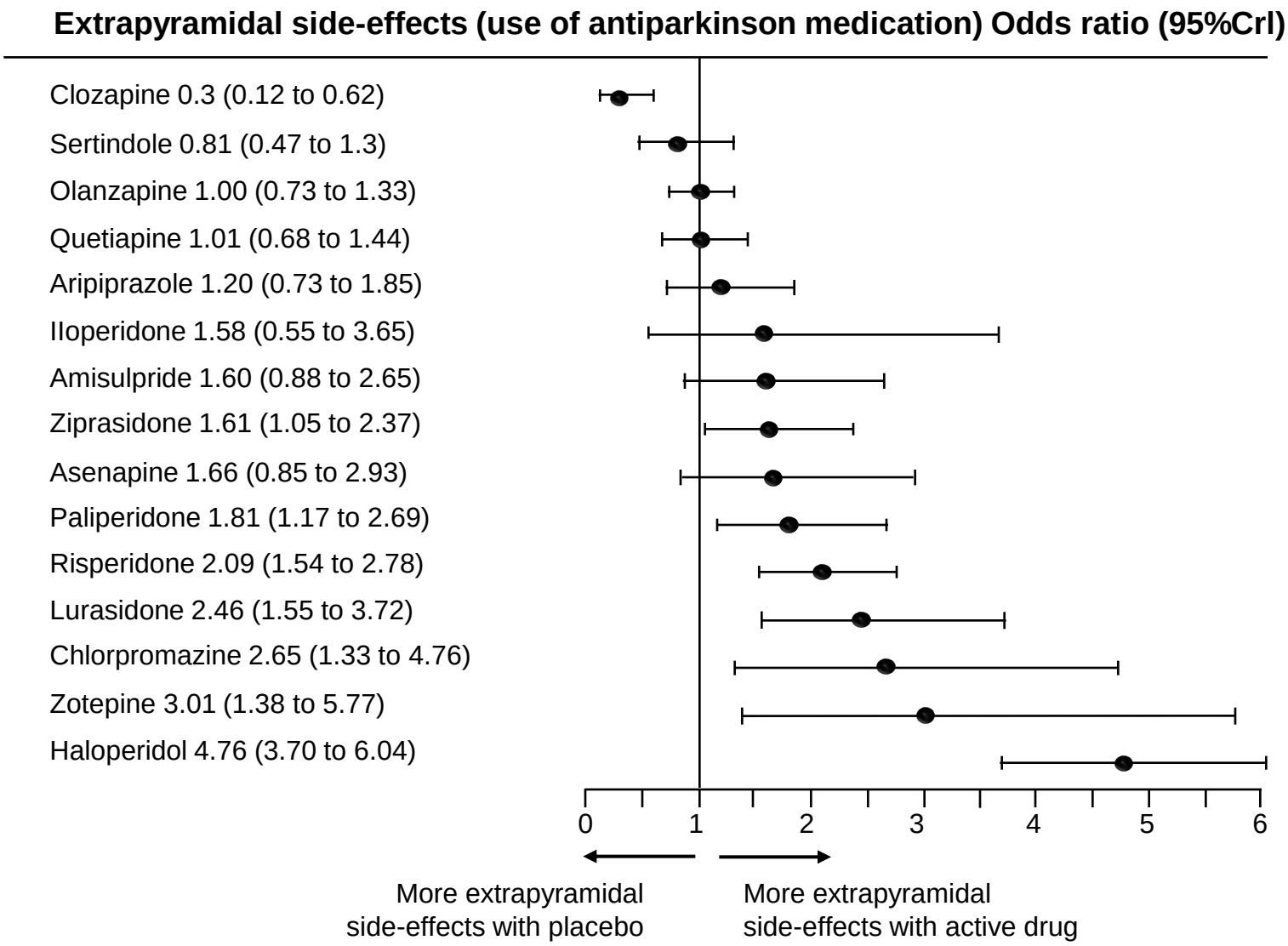
Leucht et al. Lancet. 2013 Sep 14;382(9896):951-62

Meta-analysis of Weight Gain Liabilities: 4–10 Week Studies (n=72)



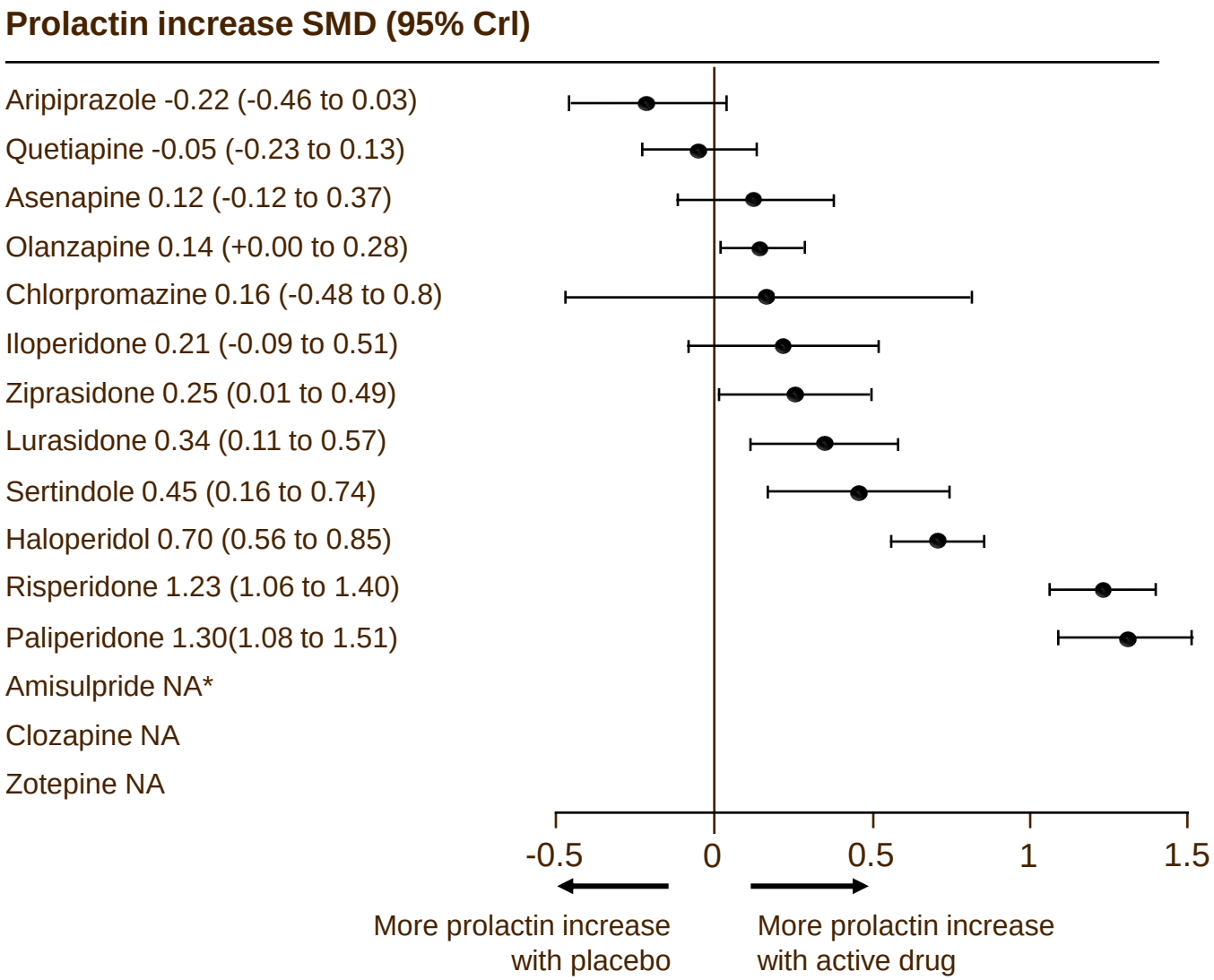
Allison et al. Am J Psychiatry 1999

EPS (use of antiparkinson medication): Antipsychotic drugs vs placebo



Leucht et al. Lancet. 2013 Sep 14;382(9896):951-62

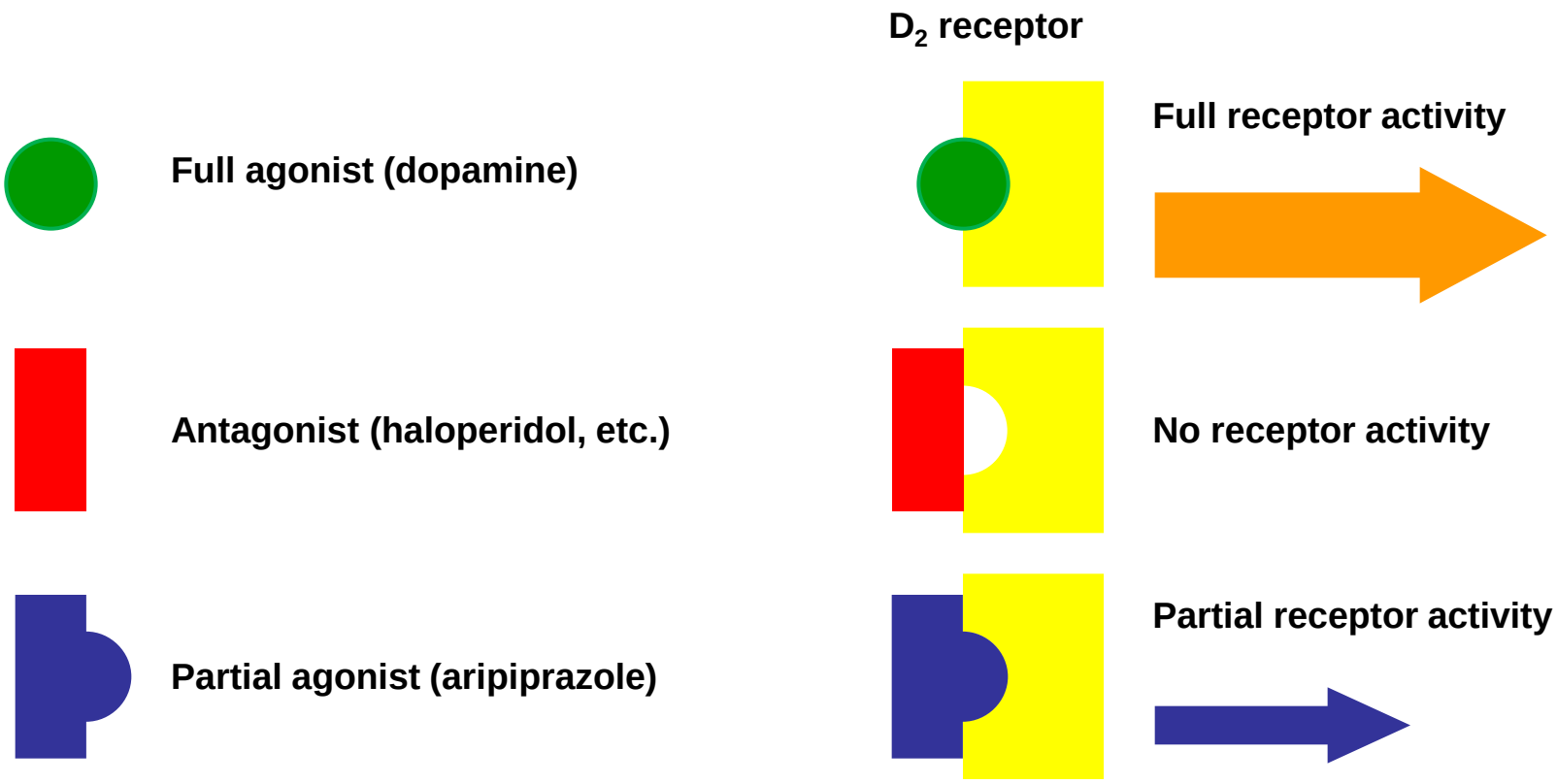
Prolactin increase: Antipsychotic drugs vs placebo



Leucht et al. Lancet. 2013 Sep 14;382(9896):951-62

Illustration of the mechanism of action of partial dopamine agonists such as aripiprazole

Intrinsic activity describes the ability of a compound to stimulate receptors



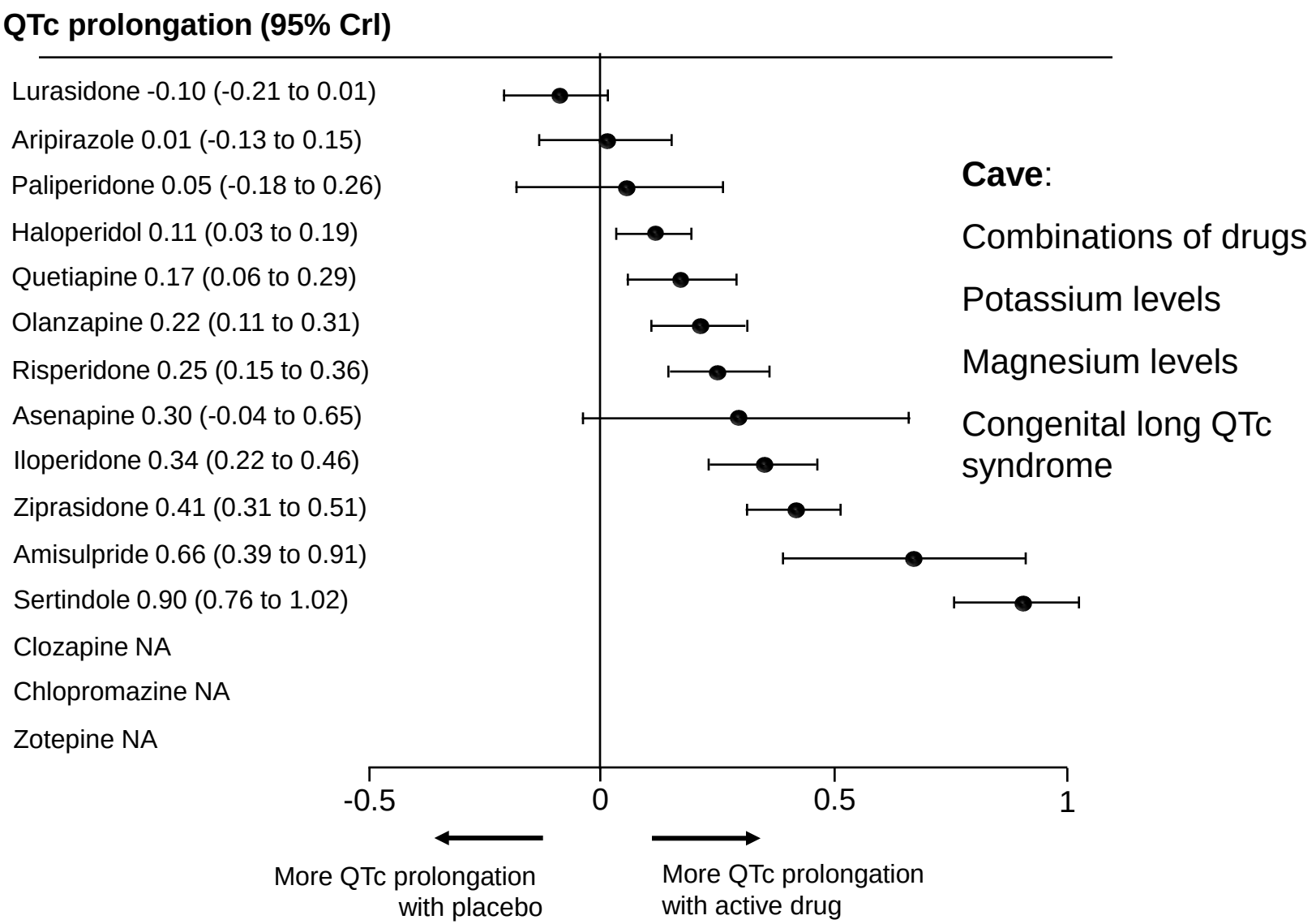
Tamminga J Neural Transm 2002

Prolactin increase is only a laboratory value, it may not be necessary to change treatment as long as there are no side-effects

It is clearly linked to sexual side-effects such as amenorrhea or galactorrhea

The link to side-effect such as erectile dysfuntion or lack of libido is more complex, e.g. negative symptoms of schizophrenia also play a role

QTc prolongation: Antipsychotic drugs vs placebo



Leucht et al. Lancet. 2013 Sep 14;382(9896):951-62

Article

Comparative Mortality Associated With Ziprasidone and Olanzapine in Real-World Use Among 18,154 Patients With Schizophrenia: The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC)

QTc prolongation is primarily only a ECG parameter. To understand whether it is also associated with increased cardiac mortality, the manufacturer of ziprasidone Pfizer had to conduct a large randomised, but then observational study, in which 18.154 patients received either ziprasidone or olanzapine.

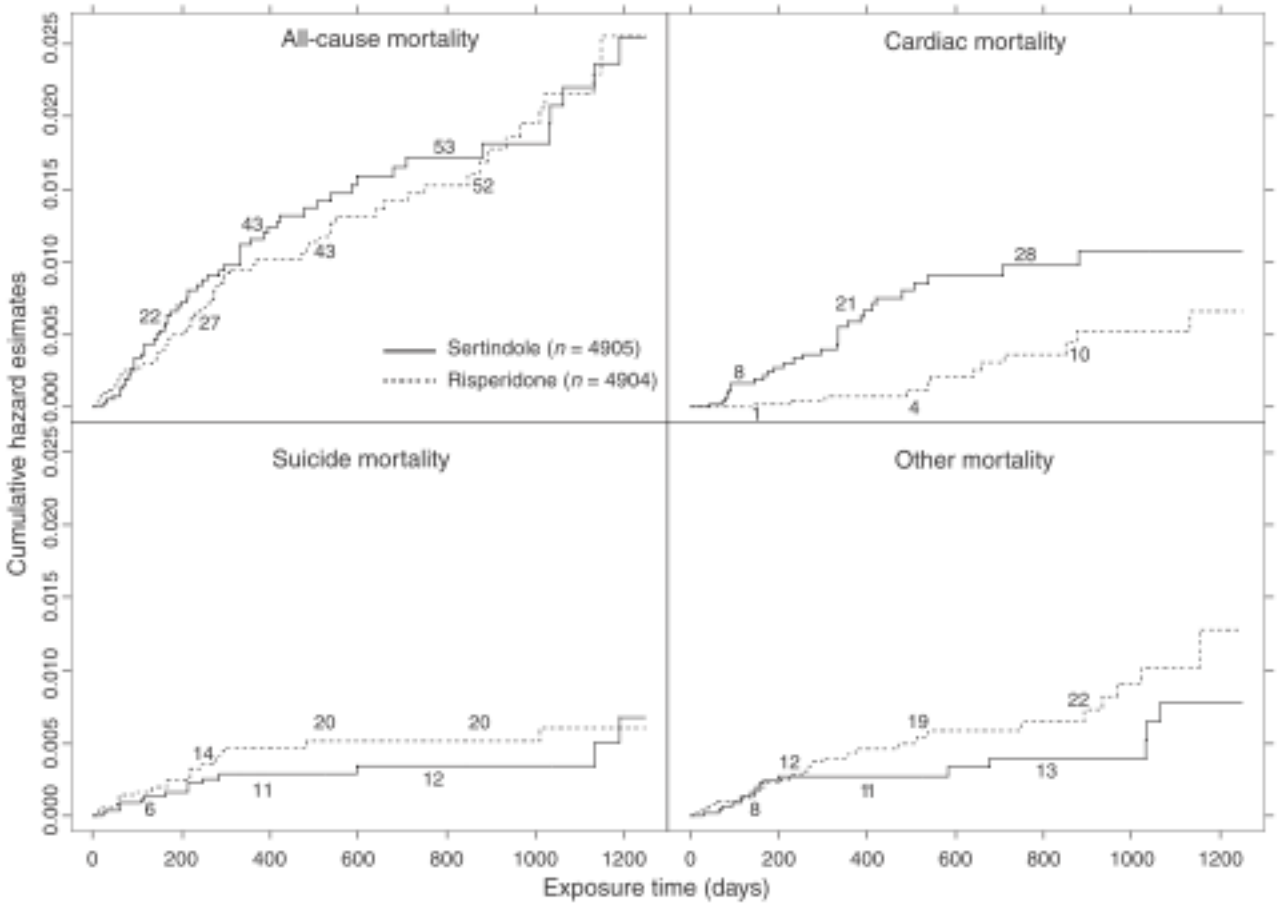
There was no increased cardiac mortality, and a relative risk larger than 1.39 could be excluded with high probability.

Therefore, there are no specific requirements for the use of ziprasidone

Nevertheless, risk factors of QTc prolongation such as electrolyte imbalances (e.g. hypokalemia, hypomagnesemia, drug interactions, congenital long QT syndrome) should always be considered

Strom et al. Am J Psychiatry 2011

Safety of sertindole versus risperidone in schizophrenia: principal results of the sertindole cohort prospective study (SCoP)

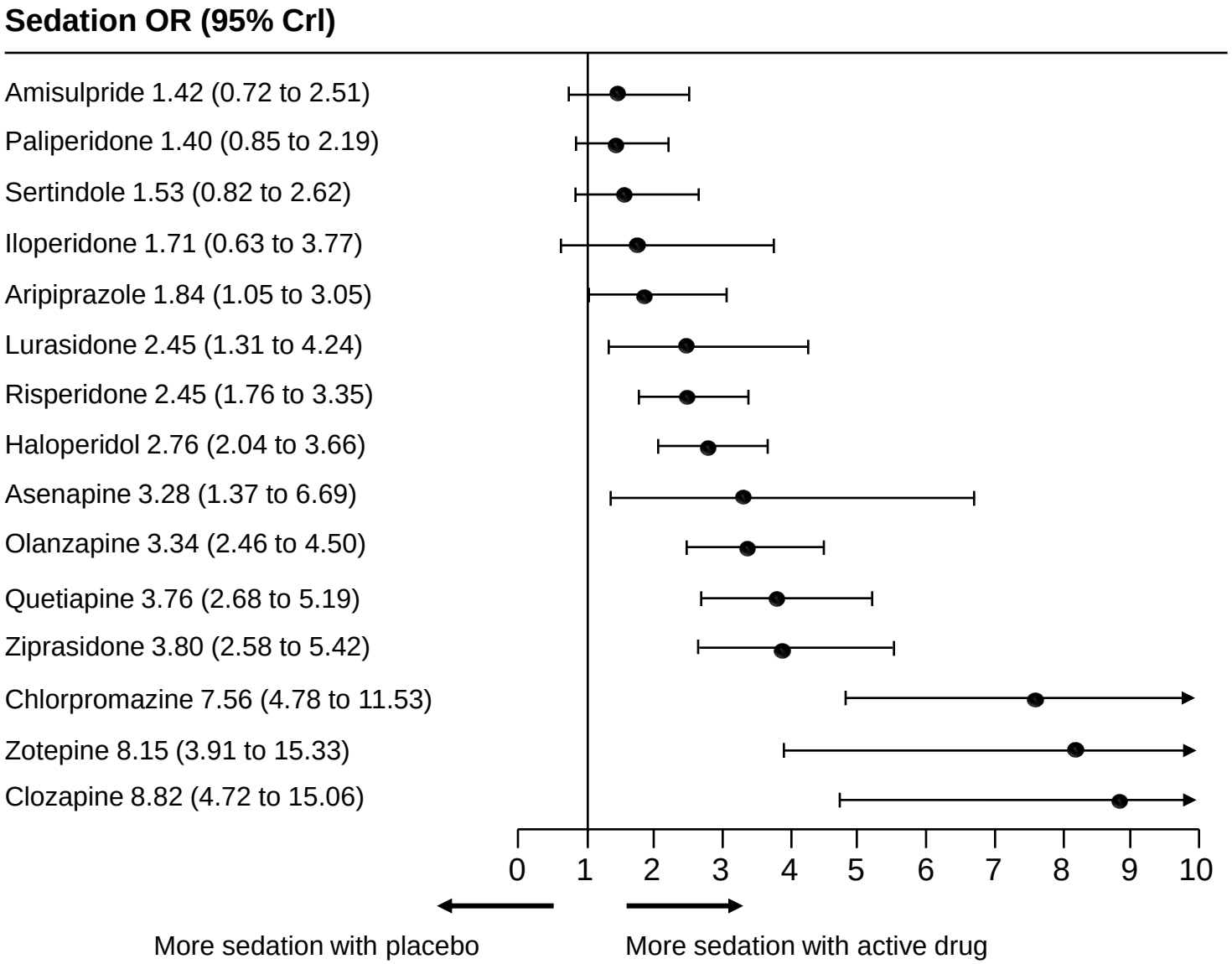


The values indicated on the graphs are the accumulated numbers of events at time points where 75%, 50%, and 25% of the patients remained at risk for each treatment group.

In a similar study, the ScOP study (9858 participants), there was no significant difference between sertindole and risperidone in all cause mortality, but cardiac mortality was higher in the sertindole group. In contrast suicide mortality tended to be lower in the sertindole group.

Thomas et al. Acta Psych Scand 2010

Sedation: Antipsychotic drugs vs placebo



Leucht et al. Lancet. 2013 Sep 14;382(9896):951-62

As so many different antipsychotics are available, which vary substantially in their effects, choice of drug should be adapted to the needs of the individual patients

Important subgroups such as treatment resistant patients or patients with predominant negative symptoms were excluded from the network
We will now extend the network to such subgroups

First-episode vs multiple episode patients (relapse 7–12 months)[1–2]

Rationale:

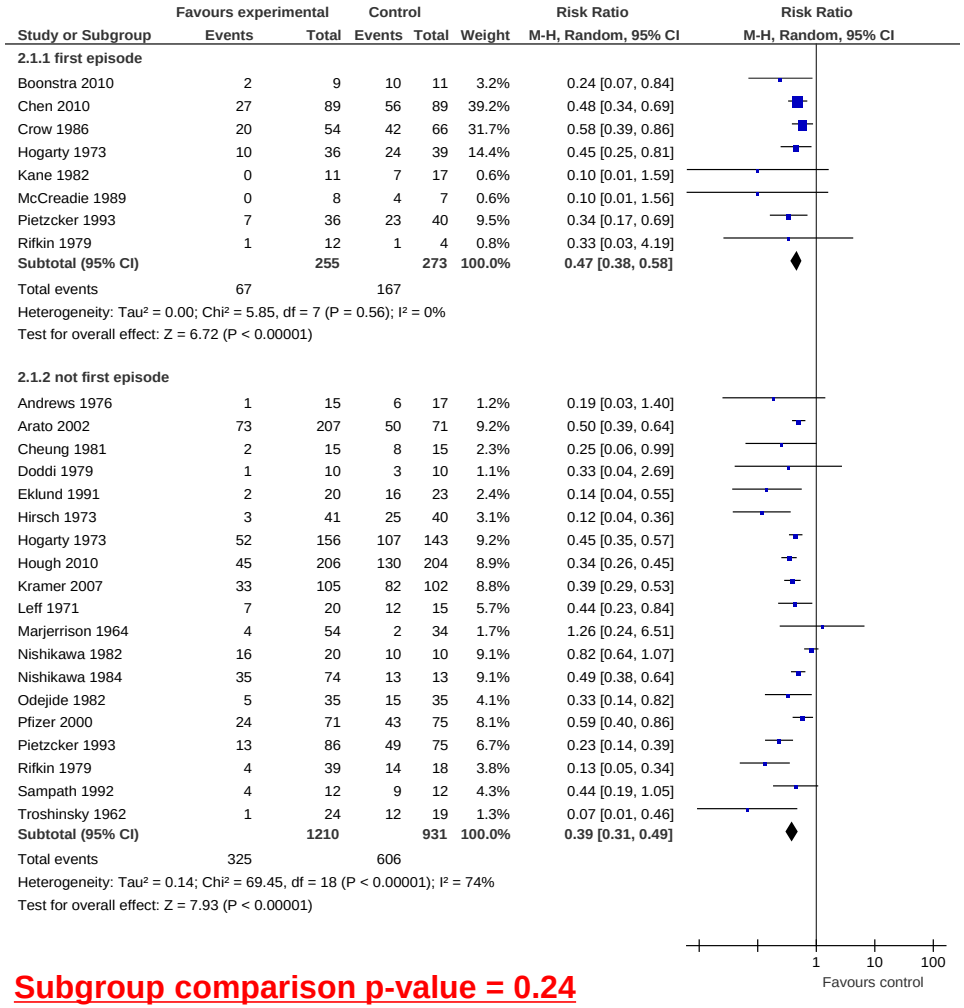
- Approximately 10%-20% of first-episode patients will not have a second episode within 5 years
- They are thought to have a better prognosis

Result:

- They benefit as much from maintenance treatment as multiple episode patients!

Problem:

- The 10%-20% without a second episode cannot be identified in advance



Study or Subgroup	Favours experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 first episode						
Boonstra 2010	2	9	10	11	3.2%	0.24 [0.07, 0.84]
Chen 2010	27	89	56	89	39.2%	0.48 [0.34, 0.69]
Crow 1986	20	54	42	66	31.7%	0.58 [0.39, 0.86]
Hogarty 1973	10	36	24	39	14.4%	0.45 [0.25, 0.81]
Kane 1982	0	11	7	17	0.6%	0.10 [0.01, 1.59]
McCreadie 1989	0	8	4	7	0.6%	0.10 [0.01, 1.56]
Pietzcker 1993	7	36	23	40	9.5%	0.34 [0.17, 0.69]
Rifkin 1979	1	12	1	4	0.8%	0.33 [0.03, 4.19]
Subtotal (95% CI)		**255**		**273**	**100.0%**	**0.47 [0.38, 0.58]**
Total events	67		167			
Heterogeneity: Tau² = 0.00; Chi² = 5.85, df = 7 (P = 0.56); I² = 0%						
Test for overall effect: Z = 6.72 (P < 0.00001)						
2.1.2 not first episode						
Andrews 1976	1	15	6	17	1.2%	0.19 [0.03, 1.40]
Arato 2002	73	207	50	71	9.2%	0.50 [0.39, 0.64]
Cheung 1981	2	15	8	15	2.3%	0.25 [0.06, 0.99]
Doddi 1979	1	10	3	10	1.1%	0.33 [0.04, 2.69]
Eklund 1991	2	20	16	23	2.4%	0.14 [0.04, 0.55]
Hirsch 1973	3	41	25	40	3.1%	0.12 [0.04, 0.36]
Hogarty 1973	52	156	107	143	9.2%	0.45 [0.35, 0.57]
Hough 2010	45	206	130	204	8.9%	0.34 [0.26, 0.45]
Kramer 2007	33	105	82	102	8.8%	0.39 [0.29, 0.53]
Leff 1971	7	20	12	15	5.7%	0.44 [0.23, 0.84]
Marjerrison 1964	4	54	2	34	1.7%	1.26 [0.24, 6.51]
Nishikawa 1982	16	20	10	10	9.1%	0.82 [0.64, 1.07]
Nishikawa 1984	35	74	13	13	9.1%	0.49 [0.38, 0.64]
Odejide 1982	5	35	15	35	4.1%	0.33 [0.14, 0.82]
Pfizer 2000	24	71	43	75	8.1%	0.59 [0.40, 0.86]
Pietzcker 1993	13	86	49	75	6.7%	0.23 [0.14, 0.39]
Rifkin 1979	4	39	14	18	3.8%	0.13 [0.05, 0.34]
Sampath 1992	4	12	9	12	4.3%	0.44 [0.19, 1.05]
Troshinsky 1962	1	24	12	19	1.3%	0.07 [0.01, 0.46]
Subtotal (95% CI)		**1210**		**931**	**100.0%**	**0.39 [0.31, 0.49]**
Total events	325		606			
Heterogeneity: Tau² = 0.14; Chi² = 69.45, df = 18 (P < 0.00001); I² = 74%						
Test for overall effect: Z = 7.93 (P < 0.00001)						

Subgroup comparison p-value = 0.24

M-H, Mantel–Haenszel; Random, random effects model;
CI, confidence interval

1. Leucht et al. Lancet 2012;379:2063–2071; 2. Leucht et al. Cochrane Database Syst Rev 2012;5:CD008016;

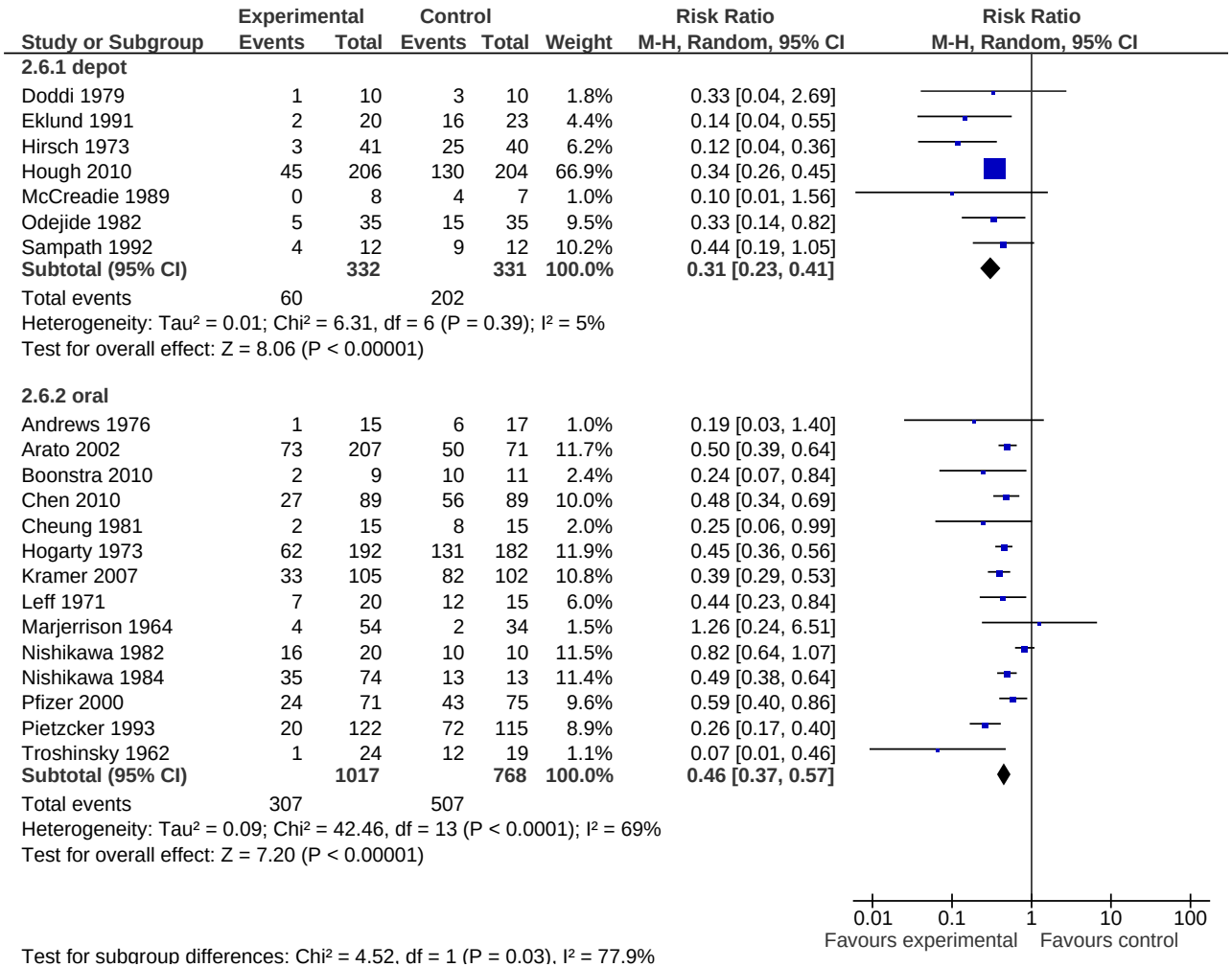
Depot versus oral medication (relapse 7-12 months)

Rationale:

- Depot drugs are thought to be superior in relapse prevention due to improved compliance

Problem:

- Indirect comparison, there are many possible confounders
- Only head-to-head comparisons can tell whether depots are better



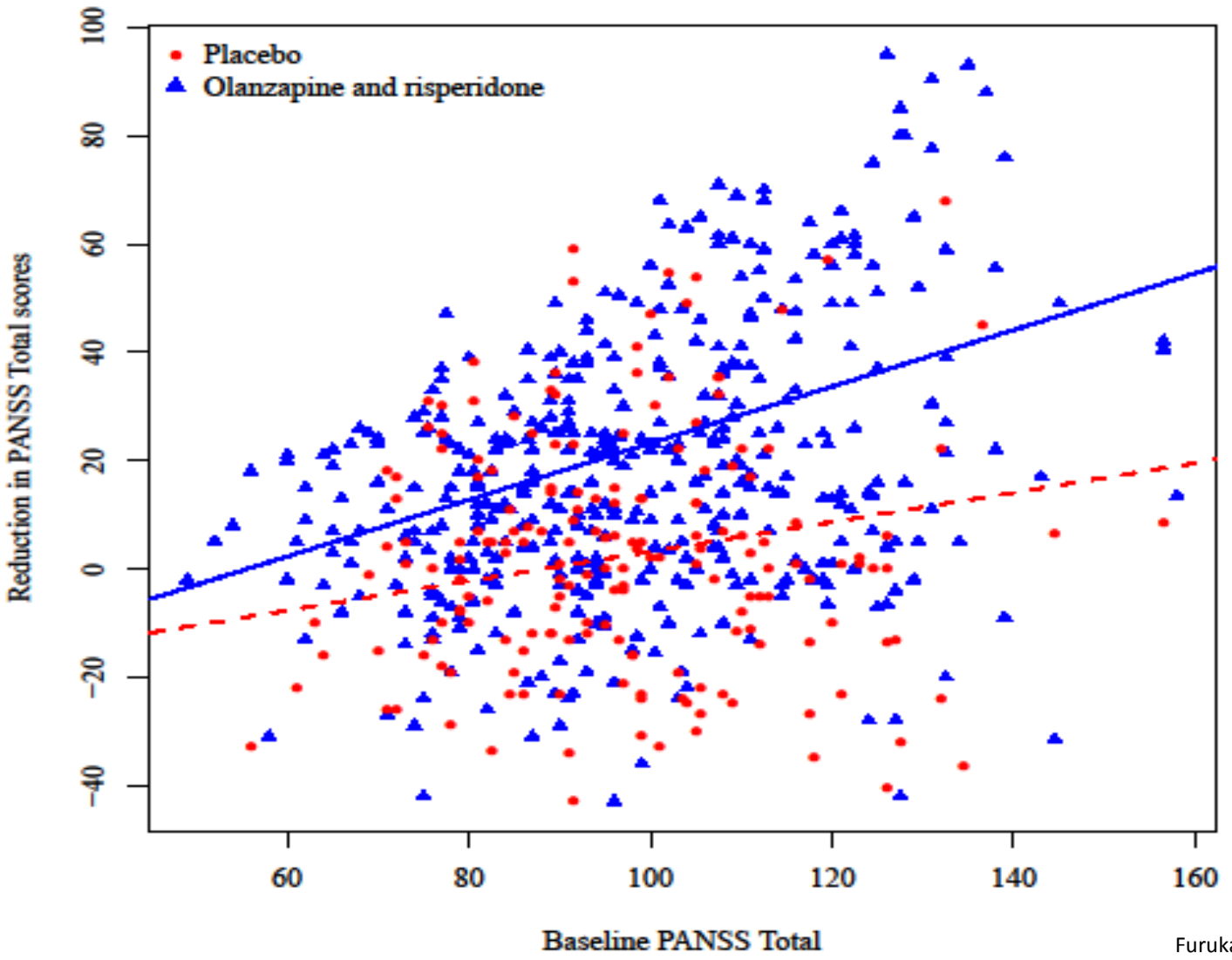
Studies that allowed both depot and oral medication (Crow et al. 1986, Kane et al. 1982, Rifkin et al. 1979) were excluded from this analysis
MH = Maentel-Haenszel, random = random effects model, 95% CI = 95% confidence interval

Leucht et al. Lancet 2012
Cochrane Database Syst Rev 2012

Individual patient data (IPD) meta-analysis would be more appropriate to examine whether different subgroups respond differently to antipsychotics, because with aggregated data we always work on a group level which is not very sensitive

For example, if one wants to examine the effects of age on antipsychotic response, within a trial there is a lot of variability, but the average ages in trials are usually similar (in schizophrenia mid-thirties)

Example for IPD meta-analysis: Effects of baseline severity on antipsychotic drug vs placebo differences in schizophrenia



Furukawa et al. under reivew

As so many different antipsychotics are available, which vary substantially in their effects, choice of drug should be adapted to the needs of the individual patients

Currently, the selection might be done in a shared decision making process

This concept is explained in the subsequent slides

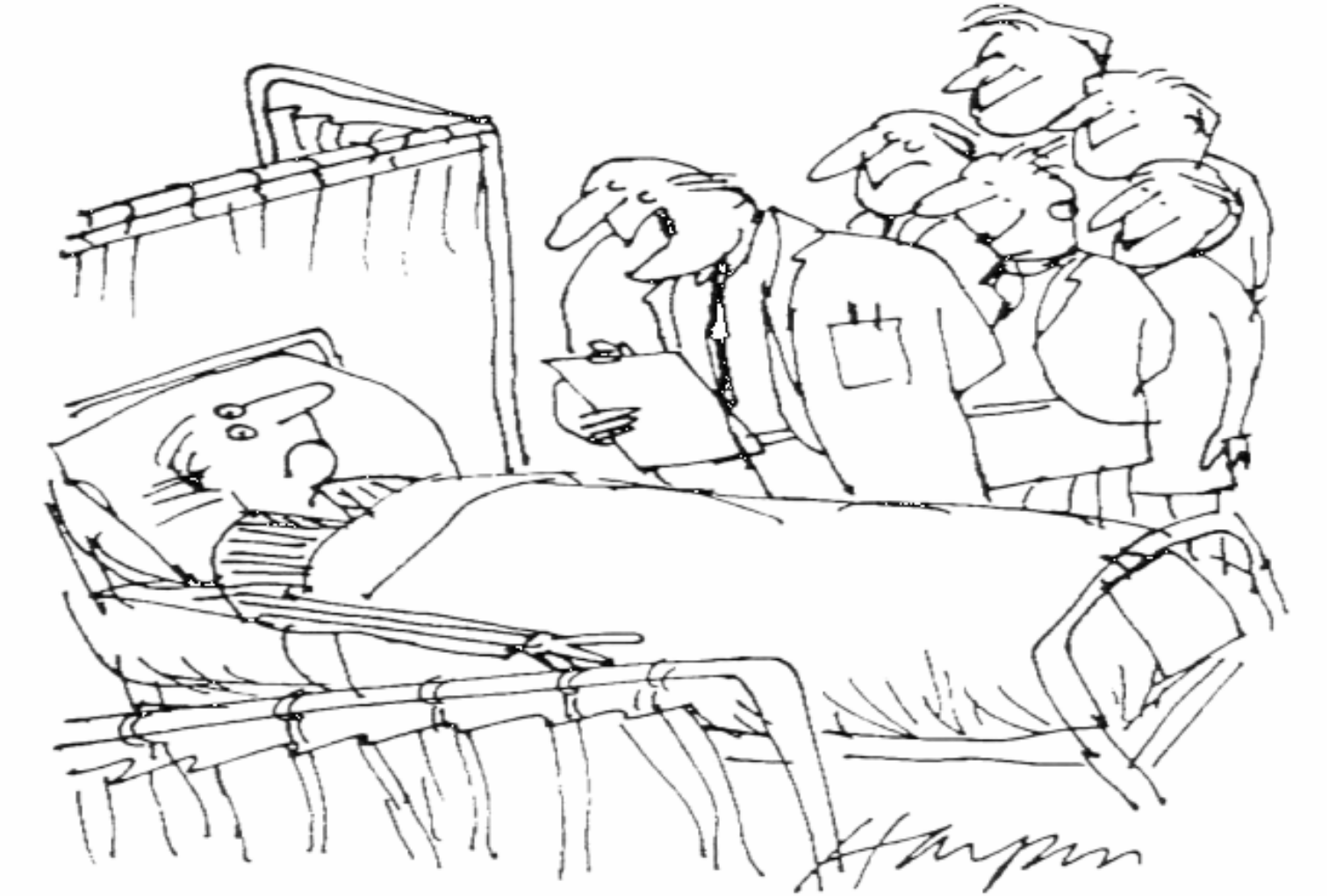
The model of ‘Shared decision making’

The concept of shared decision making can be easily understood, if it is contrasted with other models of patient-doctor interactions.

	Paternalistic model	**Shared decision making**	**Informed choice** (e.g. information on vaccines for tropical regions)
Role of doctor	The doctor chooses the medication they consider most appropriate for the patient	Doctor communicates all important information and treatment options to patient. The doctor can recommend an option. Doctor and patient decide on a therapy together	Doctor communicates all important information and treatment options to patient. Patient chooses from available options without consulting the doctor.
Role of patient	Patient ‘accepts’ doctor’s suggestions. Patient’s duty is to collaborate in treatment.	Patient receives all information. Patient considers all options and discusses preferences with the doctor. Decisions are made together with doctor.	The patient receives all information, considers all options and chooses the therapy.
Responsibility for decision	Doctor	Doctor and patient	Patient

Hamann J, et al. Acta Psychiatr Scand. 2003;107:403–9.

Caricature of the paternalistic model



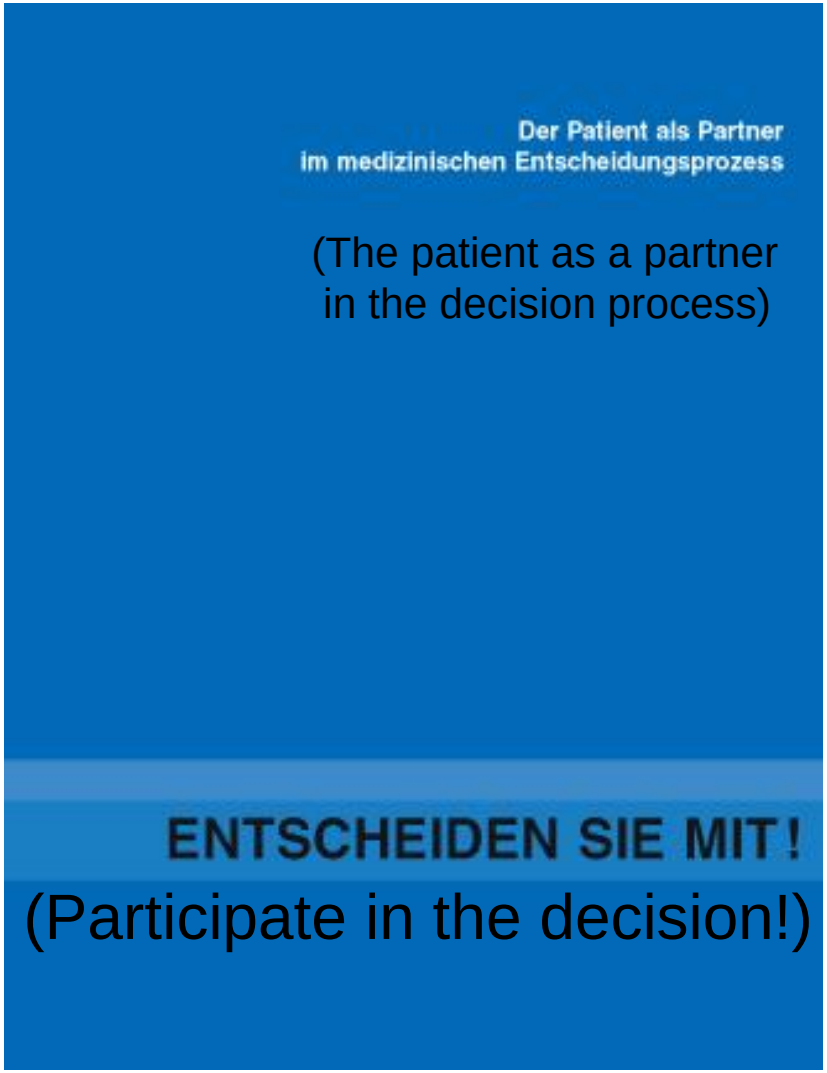
"When we want your opinion, we'll give it to you"

Example of a Decision Aid

16-page booklet

Patients work through it together with nurse

Serves as a basis for discussion with the doctor



For a review on shared decision making read
Hamann et al. Acta Psychiatr Scand 2003

Example for a Decision Aid to Choose between Oral or Depot Medication

Wie können die Medikamente eingenommen werden?

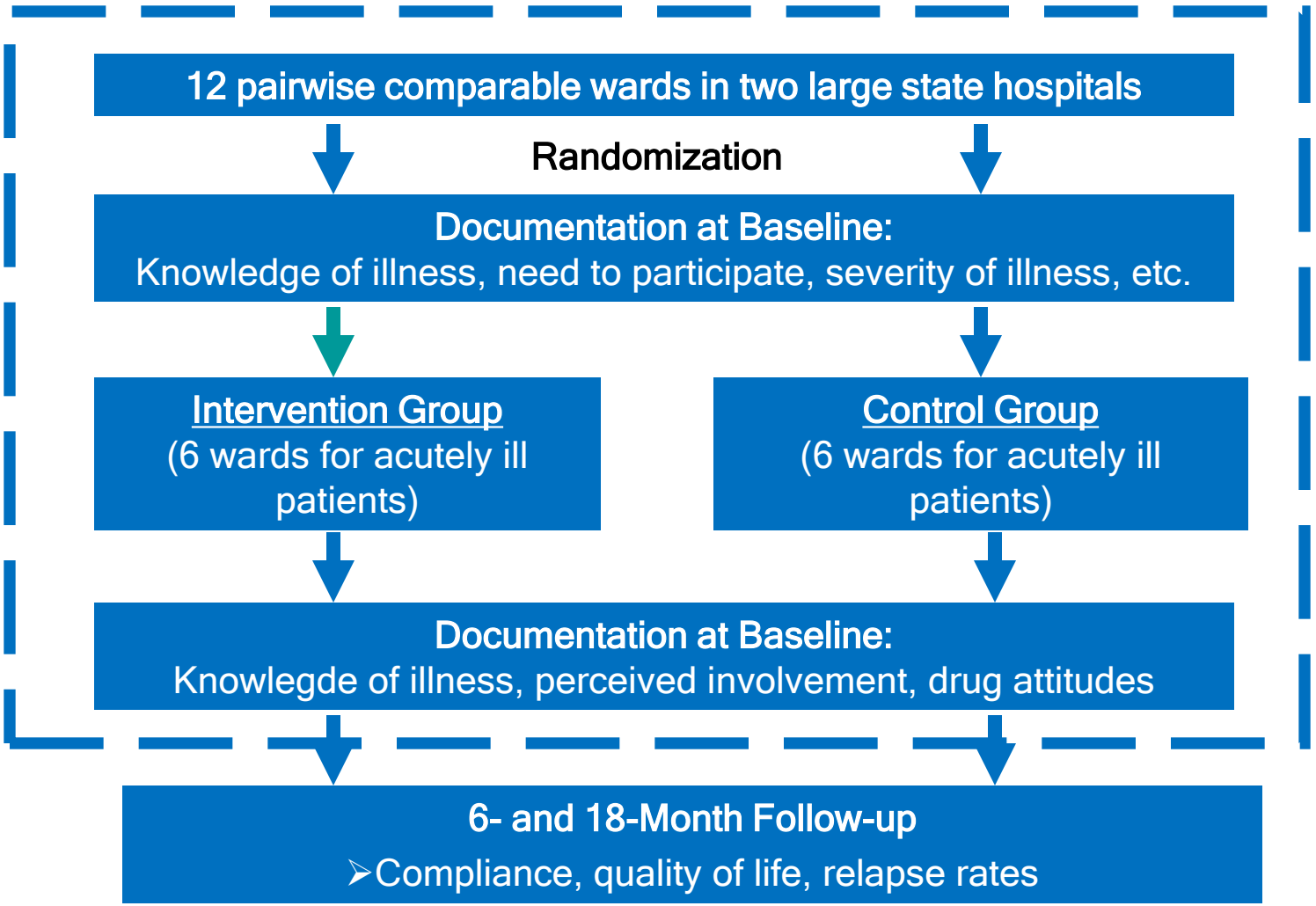
(How can drugs be ingested)

Medikamente (Neuroleptika) zur Behandlung von Psychosen gibt es in verschiedenen Formen

TABLETTEN (TROPFEN)	DEPOT (SPRITZEN)
Tabletten (und Tropfen) müssen regelmäßig eingenommen werden. Wenn Sie die Medikamente vergessen, kann es zu einem Rückfall kommen.	Ein Depot wird vom Arzt alle 2-4 Wochen in den Muskel gespritzt. Sie müssen also regelmäßig alle 2-4 Wochen zu Ihrem Arzt gehen, sonst kann es zu einem Rückfall kommen. Ansonsten müssen Sie aber nicht jeden Tag an Ihre Medikamente denken.
Fast alle Medikamente gibt es als Tabletten, manche auch als Tropfen.	Allerdings gibt es nicht jedes Medikament als Depot.

For a review on shared decision making read Hamann et al. Acta Psychiatr Scand 2003

Design of a cluster randomised study in schizophrenia (N = 107)



Hamann J et al. Acta Psychiatr Scand 2006

Acute phase results of a trial on shared decision making in schizophrenia

	Intervention	Control	Analysis		
			F	**df**	***P***
COMRADE (involvement)	79.5 (SD 18.6) after the Intervention	69.7(SD 20.0) at baseline	4.00	1	0.05
COMRADE (before discharge)	76.8 (SD 20.9)	73.5(SD 19.3)	1.26	1	0.27
Knowledge of the disease	15.0 (SD 4.4)	10.9 (SD 5.4)	5.65	1	0.02
DAI (drug attitude)	6.9 (SD 2.8)	5.5 (SD 2.9)	5.13	1	0.03
ZUF8 (patient satisfaction)	16.3	16.4	1.17	1	0.28

Hamann J et al. Acta Psychiatr Scand 2006

Long-term effects of a trial on shared decision making in schizophrenia

At 18 months follow-up a trend in terms of fewer hospitalisations in the shared decision making group were found (p=0.08)

Overall non-compliance and rehospitalisation rates were high

The major limitation of the trial was that it was based on a single shared decision making talk

Hamann et al. J Clin Psych 2007

Major take home points

(1) Antipsychotics differ in efficay and side-effects

(2) The efficacy differences are overall smaller than the differences in side-effects

(3) The heterogeneity of all drugs calls the classification into “typical and atypical” (or first-generation versus second-generation) antipsychotics into question

(4) The profiles of the individual drugs should be used to adapt drug choice to the needs of individual patients

(5) Ideally in a shared decision making process