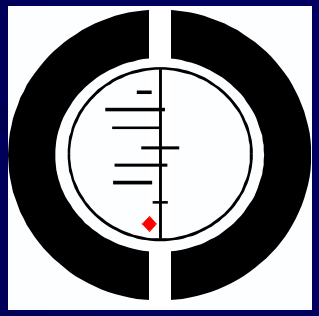
Methodological problems of long-term studies in schizophrenia



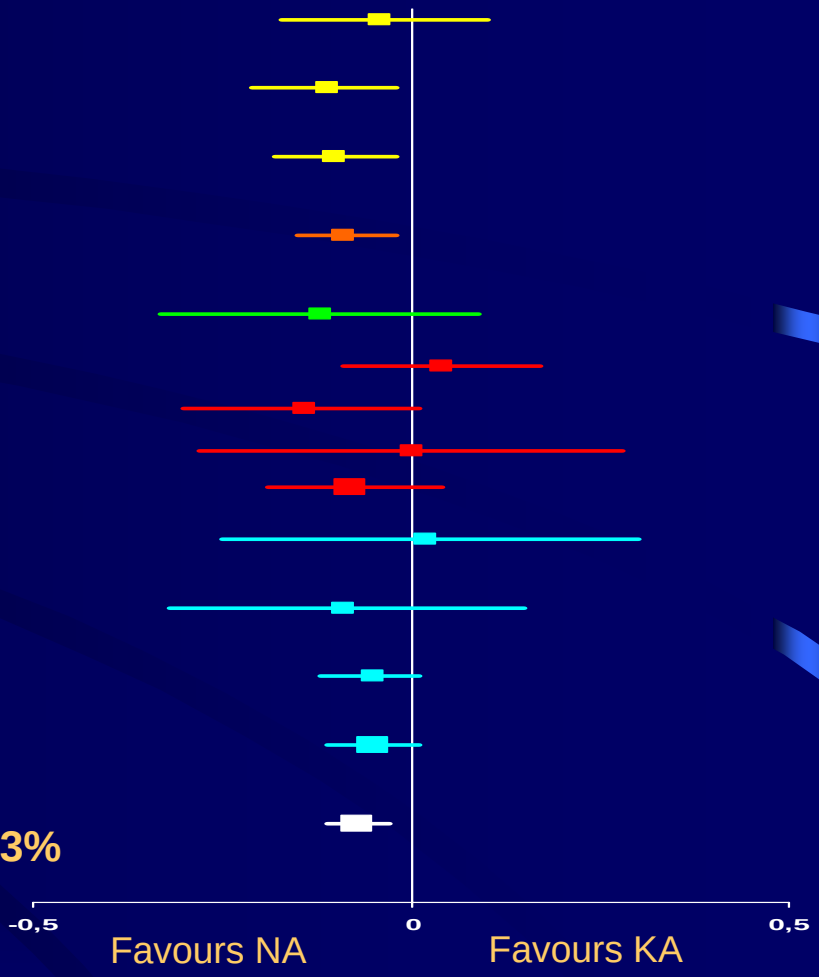
Cochrane
Schizophrenia Group

OA PD Dr. Stefan Leucht
Klinik für Psychiatrie und Psychotherapie der TU-München

Relapse prevention: new generation vs conventional antipsychotics

	NA n/N	%	KA n/N	%
Marder 2002 - risperidon	2/33	6%	3/30	10%
Csernansky 2000 - risperidon	41/177	23%	65/188	35%
Risperidone pooled	43/210	21%	68/218	31%
Daniel 1998 - sertindol	2/94	2%	12/109	11%
Speller 1997 - amisulprid	5/29	17%	9/31	29%
Tamminga 1993 - clozapin	1/25	4%	0/14	0%
Essock 1996 – clozapin	13/76	17%	15/48	31%
Rosenheck 1999 - clozapin	10/35	29%	4/14	29%
Clozapine pooled[d]	24/136	18%	19/76	25%
Tran 1998a - olanzapin	10/45	22%	2/10	20%
Tran 1998b - olanzapin	6/48	13%	3/14	21%
Tran 1998c - olanzapin	71/534	13%	29/156	19%
Olanzapin pooled	87/627	14%	34/180	19%
Total	**161/1096**	**15%**	**142/614**	**23%**

p=0.0001 in favour of atypical drugs



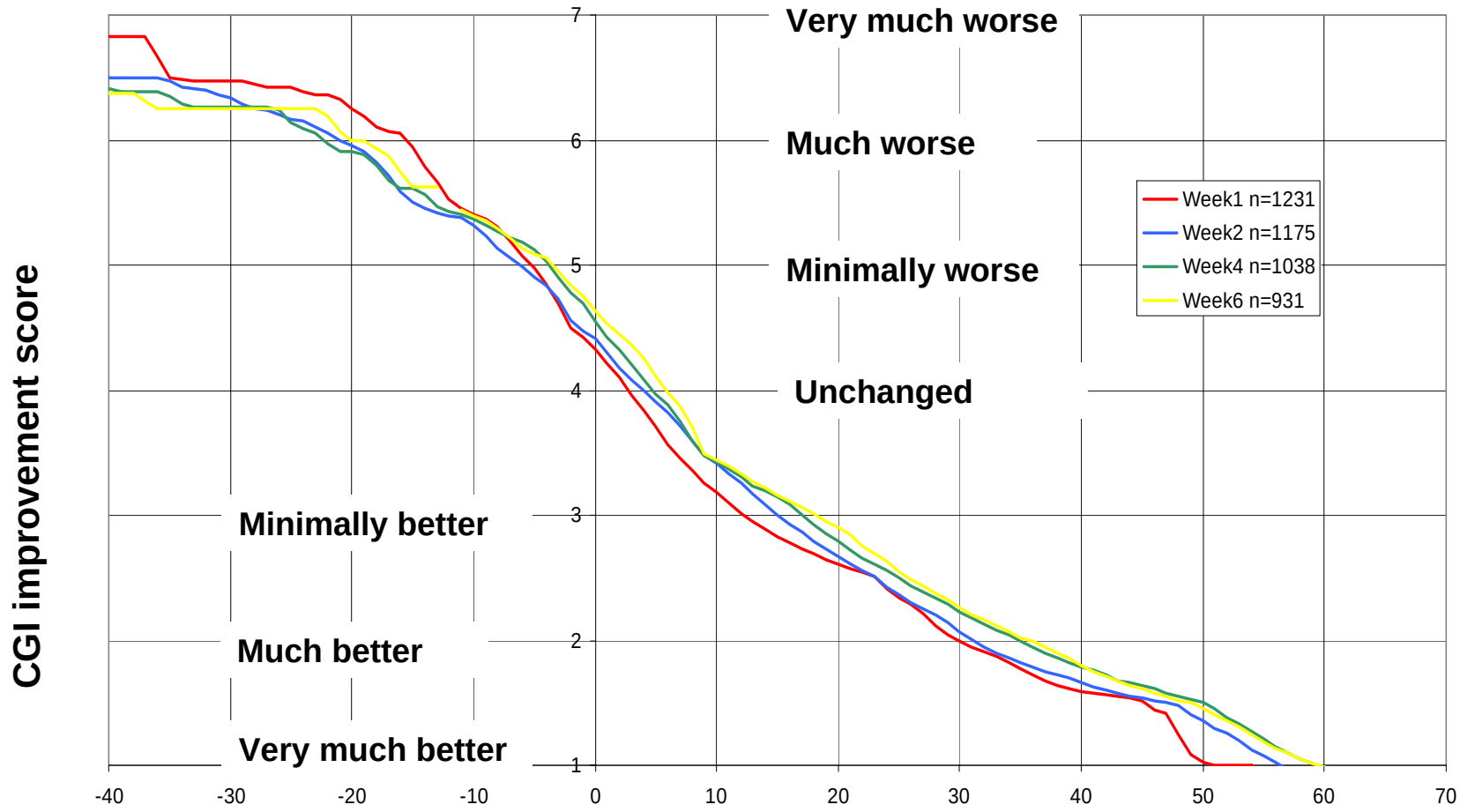
Leucht et al. Am J Psychiatry 2003; 160:1209- 1222

METHODOLOGICAL PROBLEMS IN THE RELAPSE PREVENTION STUDIES

- Several maintenance studies do not report relapse rates
- Relapse criteria of unclear clinical relevance
- Absence of a systematic assessment of compliance

  (pill-count: Csernansky 2002, Rosenheck 1997, Cooper 2000)
- Inclusion of only partially remitted patients (Cooper 2000, Arato 1999)
- High drop-out rates (Median 33%)
- Fixed doses (Daniel 1997 and most placebo-controlled trials)
- Too high doses of conventional antipsychotics (low-dose strategy only Speller 1997)
- No comparisons with mid/low-potency antipsychotics
- No comparisons with depot conventional antipsychotics

Linking of CGI Change with absolute Reduction of PANSS Total Score from Baseline (n=1231)



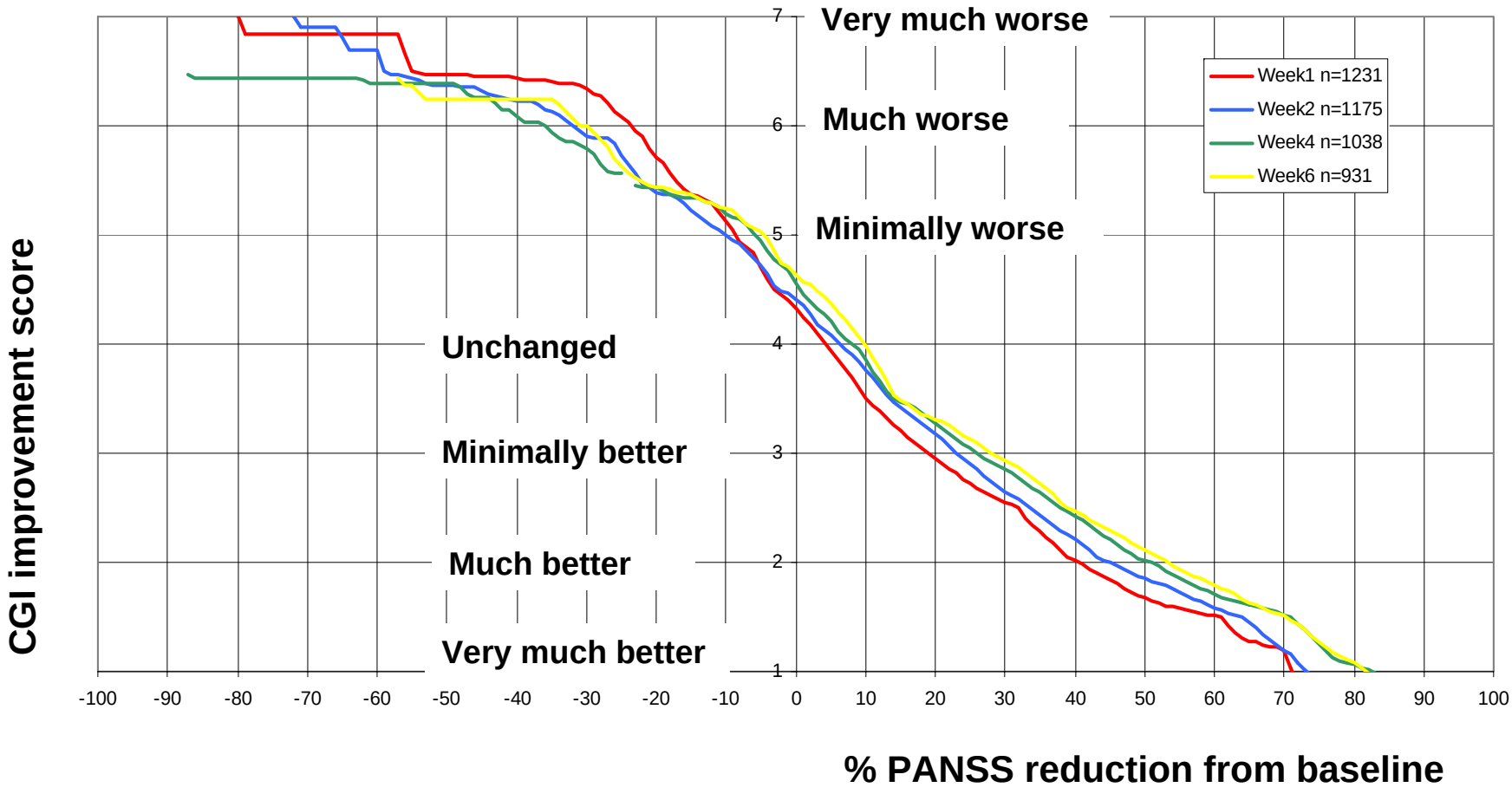
Leucht et al. Neuropsychopharmacology, in press

METHODOLOGICAL PROBLEMS IN THE RELAPSE PREVENTION STUDIES

- Several maintenance studies do not report relapse rates

- Relapse criteria of unclear clinical relevance, for example the inability to maintain a 20% reduction of the PANSS in the acute treatment phase, e.g Tran et al. Olanzapine vs Risperidone, J Clin Psychopharmacol. 1997;17:407-18 ; but also all Janssen studies

Linking of CGI Change with Percent Reduction of PANSS Total Score from Baseline (n=1231)



Leucht et al. Schizophrenia Research 2005

Suggestion of a simple table for the display of response rates

	Total n	0% - 25% PANSS/BPRS reduction	25% - 50% PANSS/BPRS reduction	50% - 75% PANSS/BPRS reduction	75% - 100% PANSS/BPRS reduction
Intervention Group	n	n (%)	n (%)	n (%)	n (%)
Control Group	n	n (%)	n (%)	n (%)	n (%)

Leucht et al. submitted

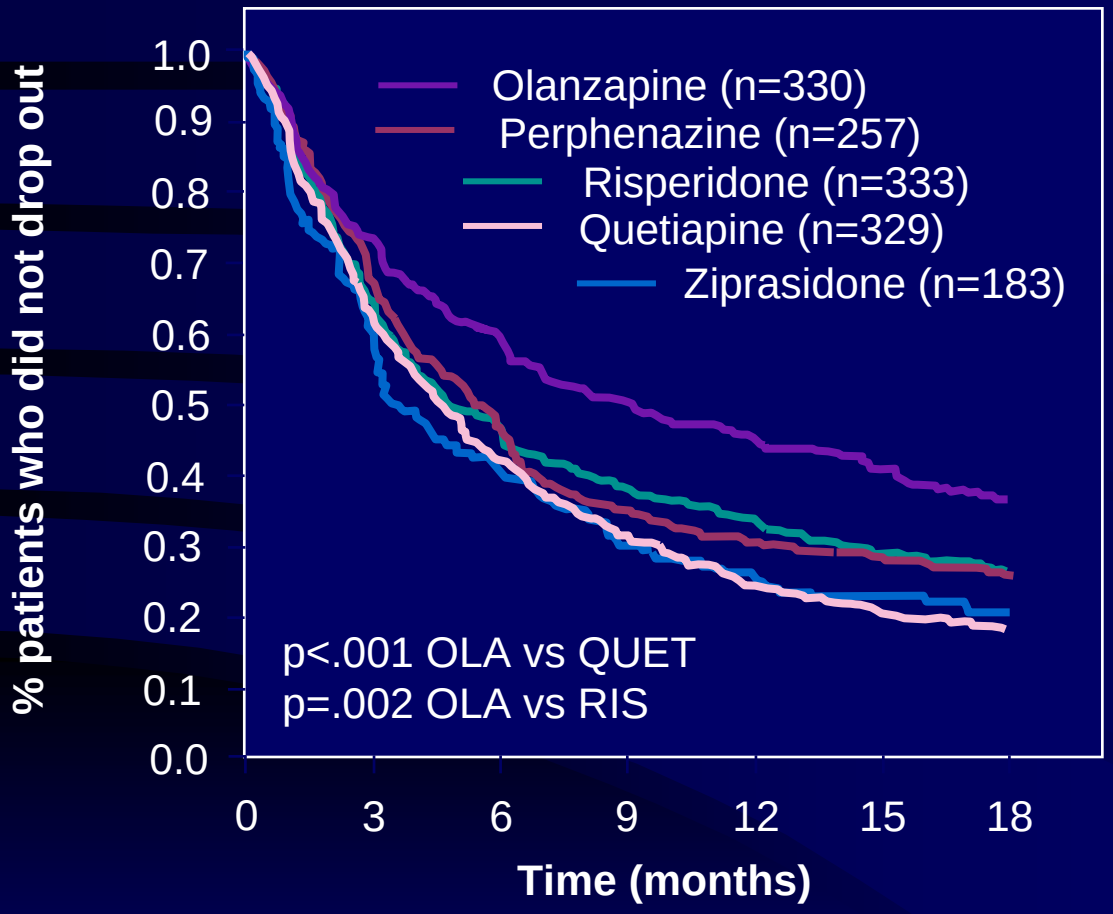
METHODOLOGICAL PROBLEMS IN THE RELAPSE PREVENTION STUDIES

- Several maintenance studies do not report relapse rates

- Relapse criteria of unclear clinical relevance: for example the inability to maintain a 20% reduction of the PANSS in the acute treatment phase, e.g Tran et al. Olanzapine vs Risperidone, J Clin Psychopharmacol. 1997;17:407-18 ; but also all Janssen studies

- Relapse is difficult to define, there is no unanimously accepted definition, most of the studies included in our meta-analysis had their own criteria (increase of positive symptom items or suicidality or rehospitalization ...) , a consensus would be useful

CATIE: Study discontinuation due to any reason (%)



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

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

Global Expert Working Group
Criteria Foundation: Illness symptoms

DSM-IV	PANSS
Delusions	Delusions (P1)
	Unusual thought content (G9)
Hallucinations	Hallucinatory behavior (P3)
Disorganized speech	Conceptual disorganization (P2)
Grossly disorganized or catatonic behavior	Mannerisms/ posturing (G5)
Negative symptoms	Blunted affect (N1)
	Social withdrawal (N4)
	Lack of spontaneity (N6)

Severity criterion:

All 8 symptoms mild or better

Time criterion:

For at least 6 months (problem: how often must it be measured)

Andreasen et al Am J Psychiatry 2005

Clinical Global Impressions (CGI)

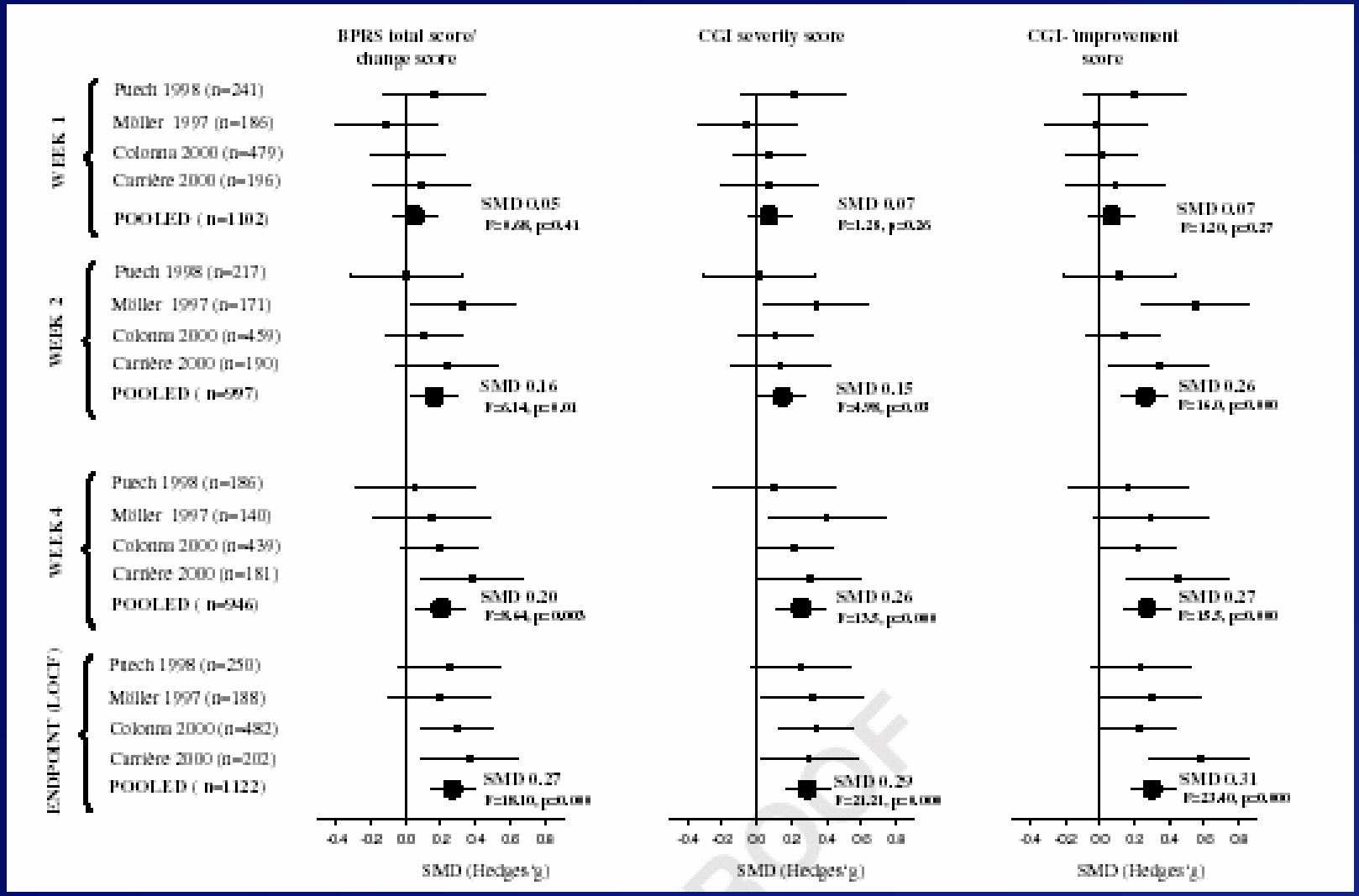
- Advantage:
  - Can be understood intuitively
- Problem:
  - The psychometric properties of the CGI are unclear

THE PANSS IS TOO LONG

NEW IMPROVED VERSIONS FOR BIPOLAR DISORDER AND SCHIZOPHRENIA EXIST (Haro et al. Acta Psychiatrica Scandinavica 2004)

SURPRISINGLY, THE SENSITIVITY OF THE CGI SEEMS TO BE SIMILAR TO THAT OF THE BPRS

The sensitivity of the BPRS and the CGI to detect differences between antipsychotics is similar



Leucht et al. Neuropsychopharmacology 2005

Clinical Global Impressions (CGI)

- Advantage:
  - Can be understood intuitively
- Problem:
  - The psychometric properties of the CGI are unclear

THE PANSS IS TOO LONG

NEW IMPROVED VERSIONS FOR BIPOLAR DISORDER AND SCHIZOPHRENIA EXIST (Haro et al. Acta Psychiatrica Scandinavica 2004)

SURPRISINGLY, THE SENSITIVITY OF THE CGI SEEMS TO BE SIMILAR TO THAT OF THE BPRS

METHODOLOGICAL PROBLEMS IN THE RELAPSE PREVENTION STUDIES

- Several maintenance studies do not report relapse rates
- Relapse criteria of unclear clinical relevance
- Absence of a systematic assessment of compliance

  General options: pill-count, questionnaires, plasma levels, specific medication containers, depot

METHODOLOGICAL PROBLEMS IN THE RELAPSE PREVENTION STUDIES

- Several maintenance studies do not report relapse rates
- Relapse criteria of unclear clinical relevance
- Absence of a systematic assessment of compliance (pill-count: Csernansky 2002, Rosenheck 1997, Cooper 2000)
- Patient characteristics: Inclusion of only partially remitted patients (Cooper 2000, Arato 1999)

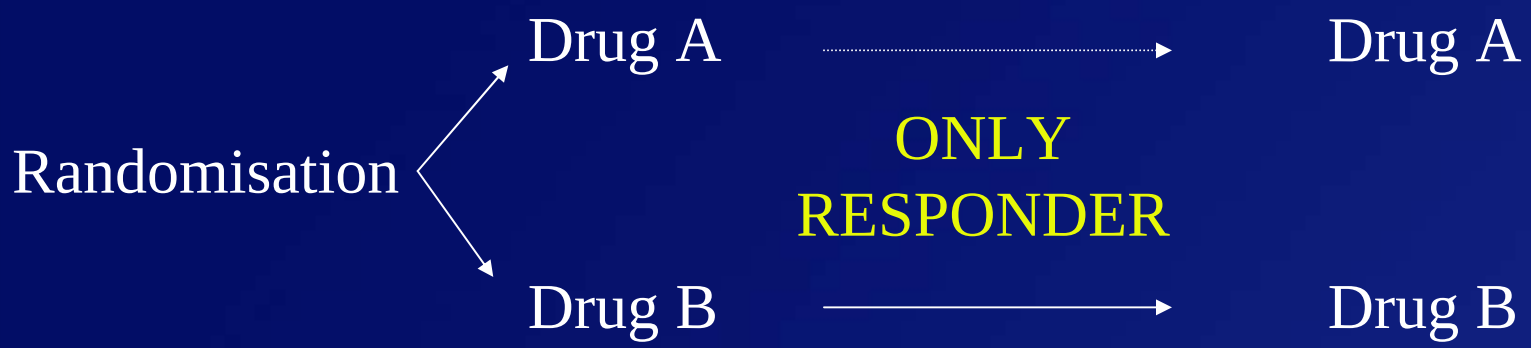
METHODOLOGICAL PROBLEMS IN THE RELAPSE PREVENTION STUDIES

- Several maintenance studies do not report relapse rates
- Relapse criteria of unclear clinical relevance
- Absence of a systematic assessment of compliance (pill-count: Csernansky 2002, Rosenheck 1997, Cooper 2000)
- Patient characteristics: Inclusion of only partially remitted patients (Cooper 2000, Arato 1999)
- **Follow up of responders of the acute phase corrupts randomisation**

METHODOLOGICAL PROBLEMS IN THE RELAPSE PREVENTION STUDIES

Acute Phase

Maintenance Phase

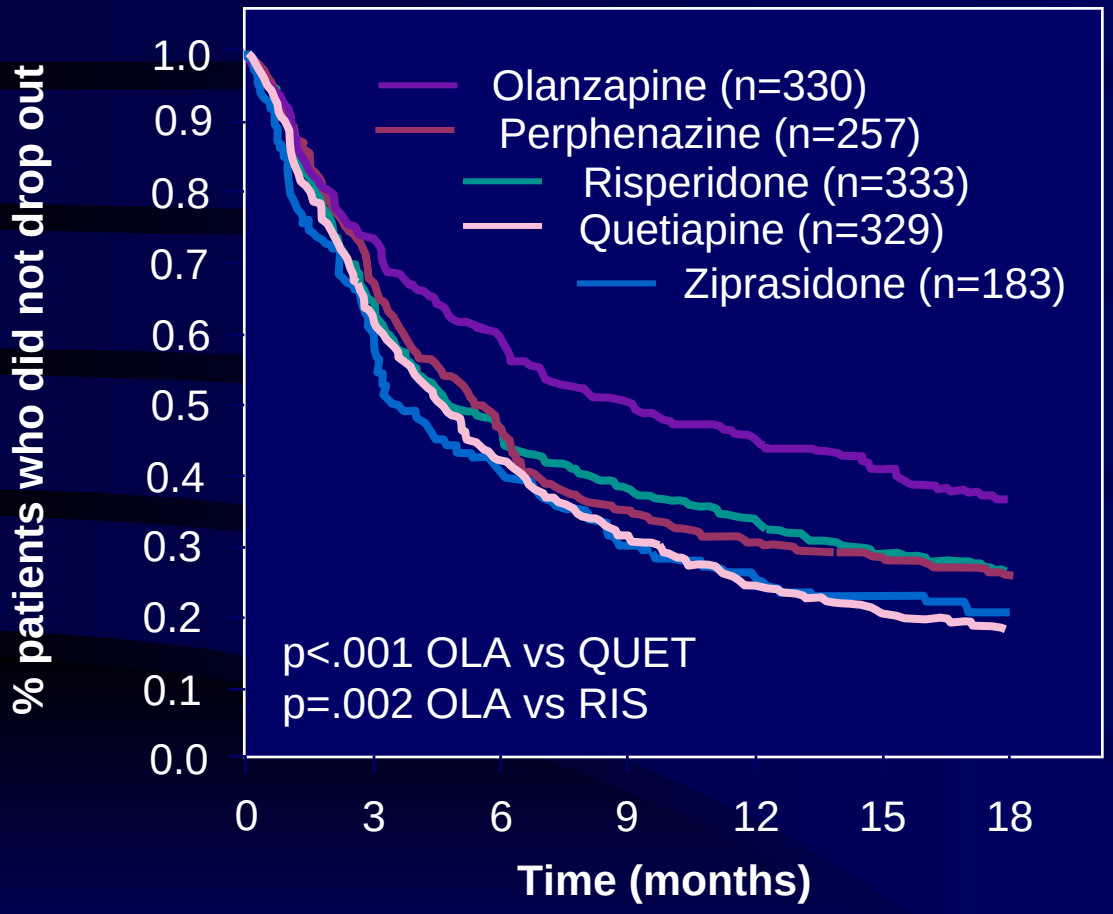


METHODOLOGICAL PROBLEMS IN THE RELAPSE PREVENTION STUDIES

- Several maintenance studies do not report relapse rates
- Relapse criteria of unclear clinical relevance
- Absence of a systematic assessment of compliance

  (pill-count: Csernansky 2002, Rosenheck 1997, Cooper 2000)
- Inclusion of only partially remitted patients (Cooper 2000, Arato 1999)
- High drop-out rates

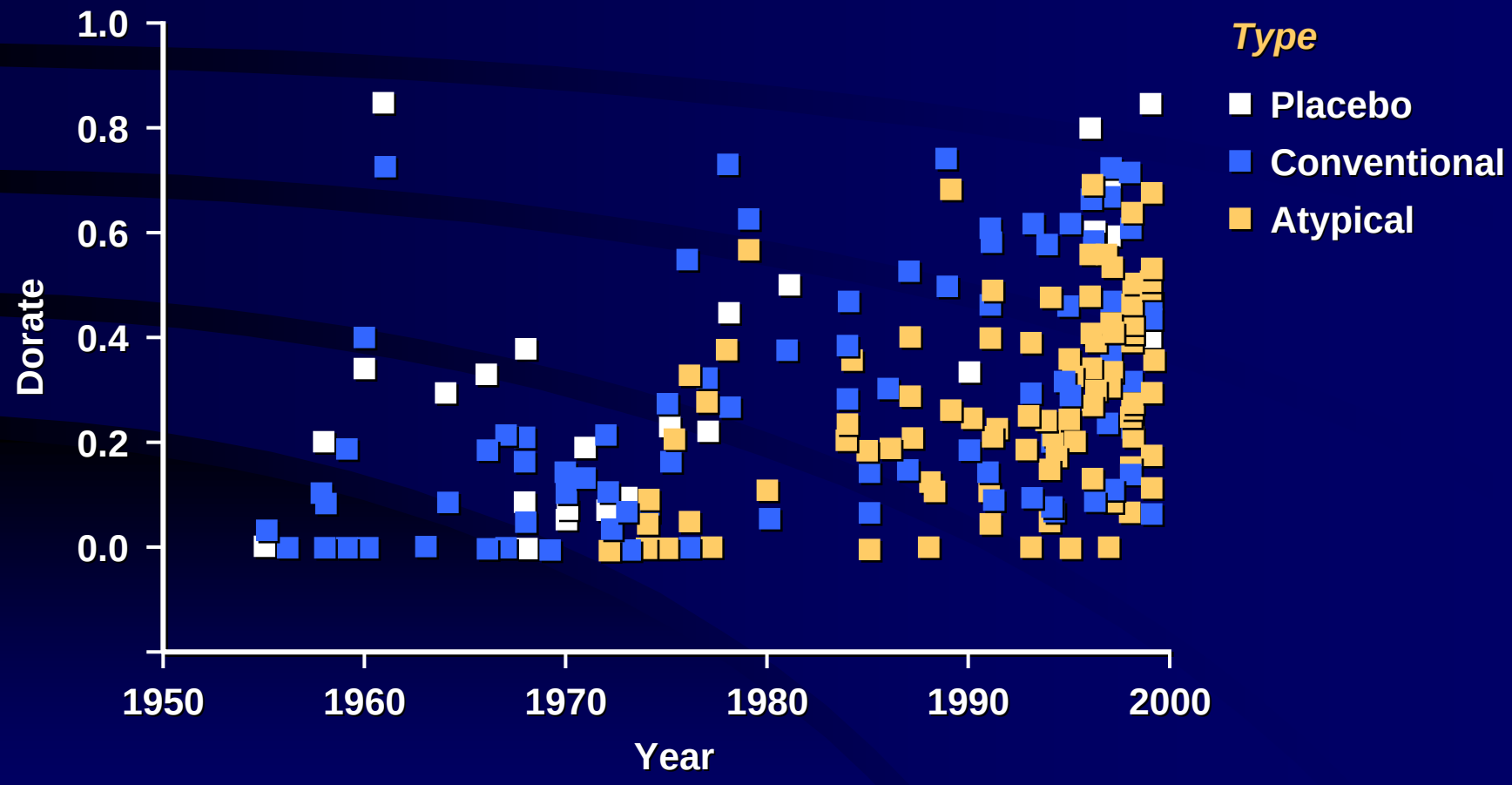
CATIE: Study discontinuation due to any reason (%)



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

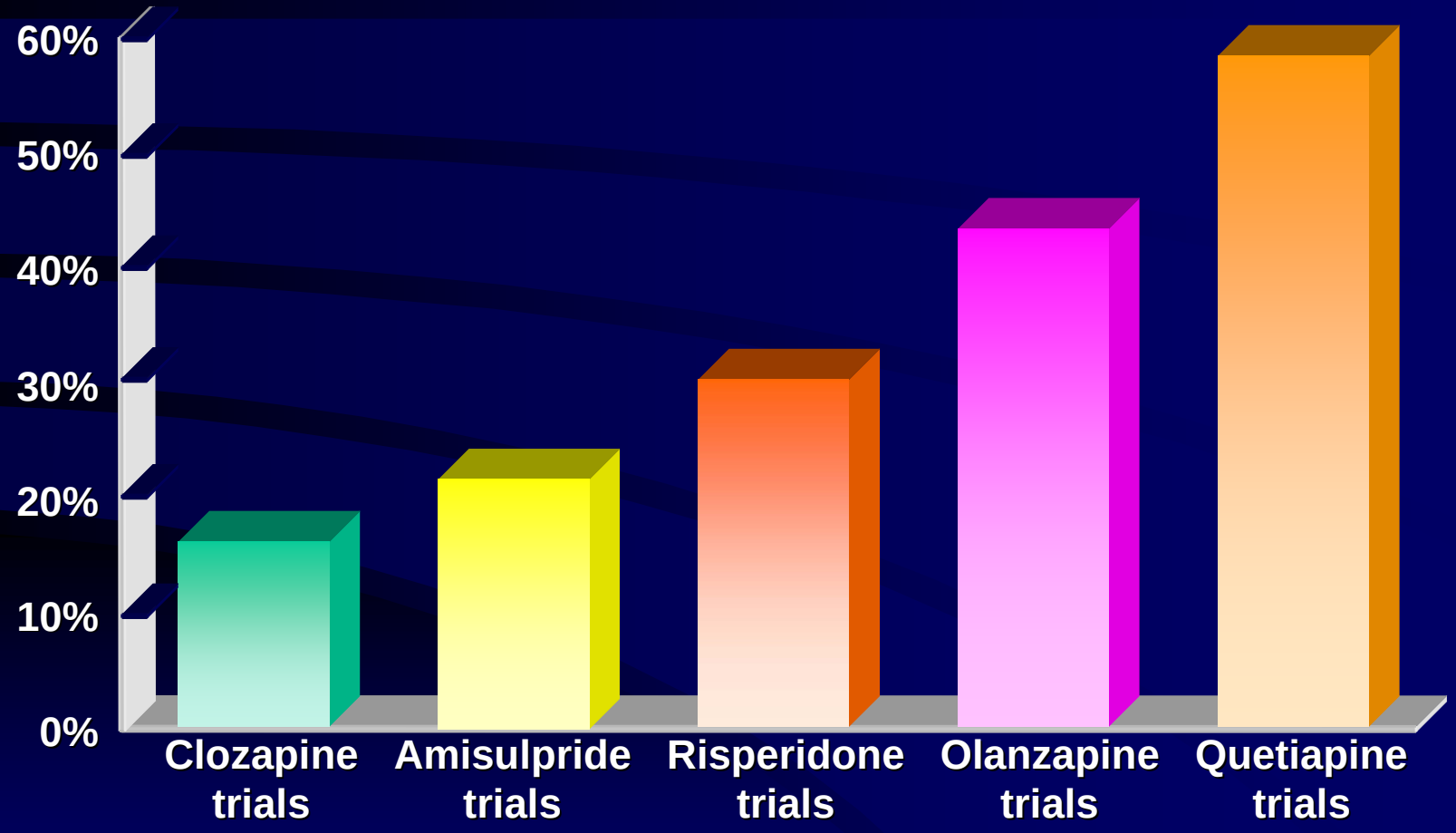
Lieberman et al, N ENGL J Med 353;12; 2005

Continuous increase of dropout rates in randomised schizophrenia studies since 1950 (n=18,000)



Wahlbeck et al. Psychopharmacology 2001

Drop-out rates by 6-12 weeks in trials of new antipsychotics



Adapted from Thornley and Adams, BMJ 1998

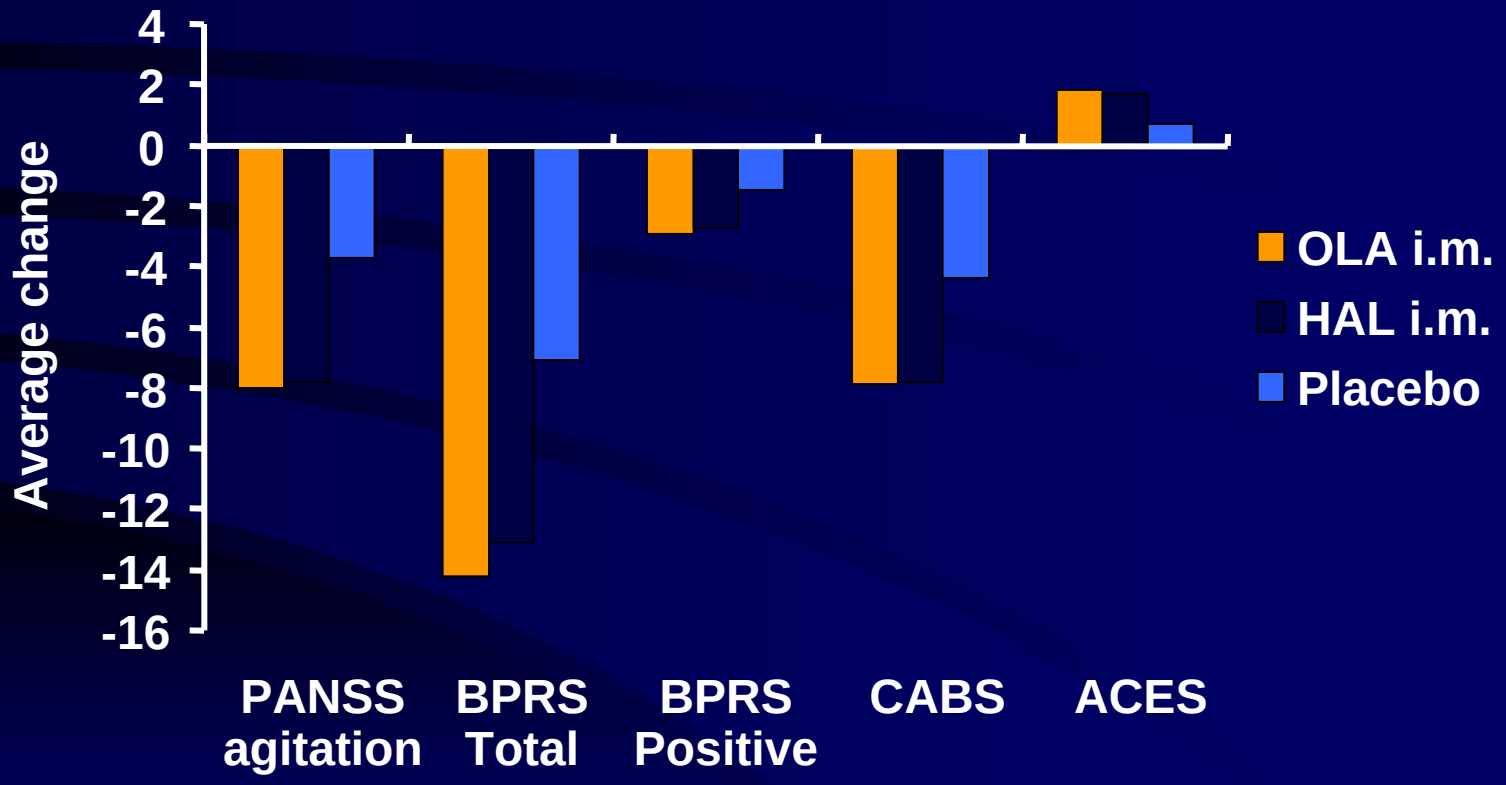
METHODOLOGICAL PROBLEMS IN THE RELAPSE PREVENTION STUDIES

- Several maintenance studies do not report relapse rates
- Relapse criteria of unclear clinical relevance
- Absence of a systematic assessment of compliance

  (pill-count: Csernansky 2002, Rosenheck 1997, Cooper 2000)
- Inclusion of only partially remitted patients (Cooper 2000, Arato 1999)
- High drop-out rates
- Too tight designs, e.g. fixed doses (Daniel 1997 and most placebo trials)

  A solution may be more pragmatic, large and simple studies

Olanzapine i.m. vs Haloperidol i.m. Agitated Patients with Schizophrenia, Randomised, DB, N=325



All comparisons with placebo statistically significant ($p < 0.05$)

TREC Trial (n=301, 15000 USD, 6 months)

Time after injection	Patient outcomes	**Midazolam** (n=151)	**Haloperidol-promethazine** (n=150)	Relative risk (CI)	Difference in % risk (CI)*
20 minutes	**Tranquil or asleep**	**134 (89%)**	**101 (67%)**	1.32 (1.16-1.49)	22 (12-30)
	Asleep	93 (62)	43 (29)	2.15 (1.48-3.11)	33 (19-47)
	Serious adverse effect	1 (1)	1 (1)	-	-
	Unknown	1 (1)	2 (1)	-	-
40 minutes	Tranquil or asleep	141 (93)	124 (83)	1.13 (1.01-1.26)	10 (1-20)
	Asleep	118 (78)	69 (46)	1.70 (1.32-2.19)	32 (18-46)
	Unknown	1 (1)	2 (1)	-	-
60 minutes	Tranquil or asleep	141 (93)	131 (87)	1.07 (0.97-1.18)	6 (-3-15)
	Asleep	120 (79)	83 (55)	1.44 (1.16-1.78)	24 (11-38)
	Unknown	1 (1)	2 (1)	-	-
120 minutes	Tranquil or asleep	144 (95)	138 (92)	1.04 (0.96-1.12)	3 (-4-11)
	Asleep	125 (83)	95 (63)	1.31 (1.08-1.57)	20 (7-32)
	No additional tranquilising drugs	149 (99)	143 (95)	1.04 (0.98-1.09)	4 (-2-8)
	Not needing restraints	118 (78)	110 (73)	1.07 (0.90-1.26)	5 (-8-18)
	Unknown	1 (1)	2 (1)	-	-
24 hours	No other episode of aggression:	107 (71)	111 (74)	0.96 (0.80-1.15)	-3 (-16-10)
	Unknown	2 (1)	7 (5)		
	Doctor not called to see patient:	**100 (66%)**	**107 (71%)**	0.93 (0.76-1.13)	-5 (-19-8)
	Unknown	2 (1)	4 (3)		
	Accepting oral medication	135 (89)	139 (93)	0.96 (0.88-1.06)	-4 (-12-5)
	Unknown	7 (5)	5 (3)		
2 weeks	Discharged	73 (48)	69 (46)	1.05 (0.77-1.44)	2 (-12-17)
	Unknown	0	3 (2)		

TREC collaborative group, BMJ 2003

How pragmatic should a study be considering internal and external validity, for example should all patients be included in the analysis, even if they changed the antipsychotic?

Do we always need informed consent in the light that only ~ 10% of eligible patients are finally included in schizophrenia RCTs (Hofer et al. 2003, Riedel et al. 2004)?

METHODOLOGICAL PROBLEMS IN THE RELAPSE PREVENTION STUDIES

- Several maintenance studies do not report relapse rates
- Relapse criteria of unclear clinical relevance
- Absence of a systematic assessment of compliance

  (pill-count: Csernansky 2002, Rosenheck 1997, Cooper 2000)
- Inclusion of only partially remitted patients (Cooper 2000, Arato 1999)
- High drop-out rates (Median 33%)
- Fixed doses (Daniel 1997 and most placebo-controlled trials)
- Continuous debate about the dose of the comparator drug used

  ASK THE MANUFACTURER

Reviews and Overviews

Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation Antipsychotics

The overall outcome reported in the abstract of head to head comparisons of atypical antipsychotics strongly depends on the sponsor

In a blinded analysis of the abstracts of 33 head to head comparisons of atypical antipsychotics in about 90% the overall outcome was in favour of the sponsor

Heres et al. Am J Psych 2006

The End