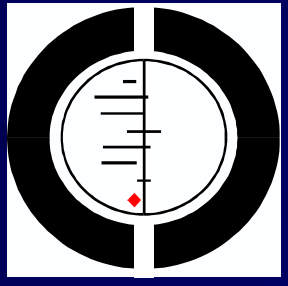
Metaanalytische Evaluierung atypischer Antipsychotika

TECHNISCHE UNIVERSITÄT MÜNCHEN



Cochrane
Schizophrenia Group

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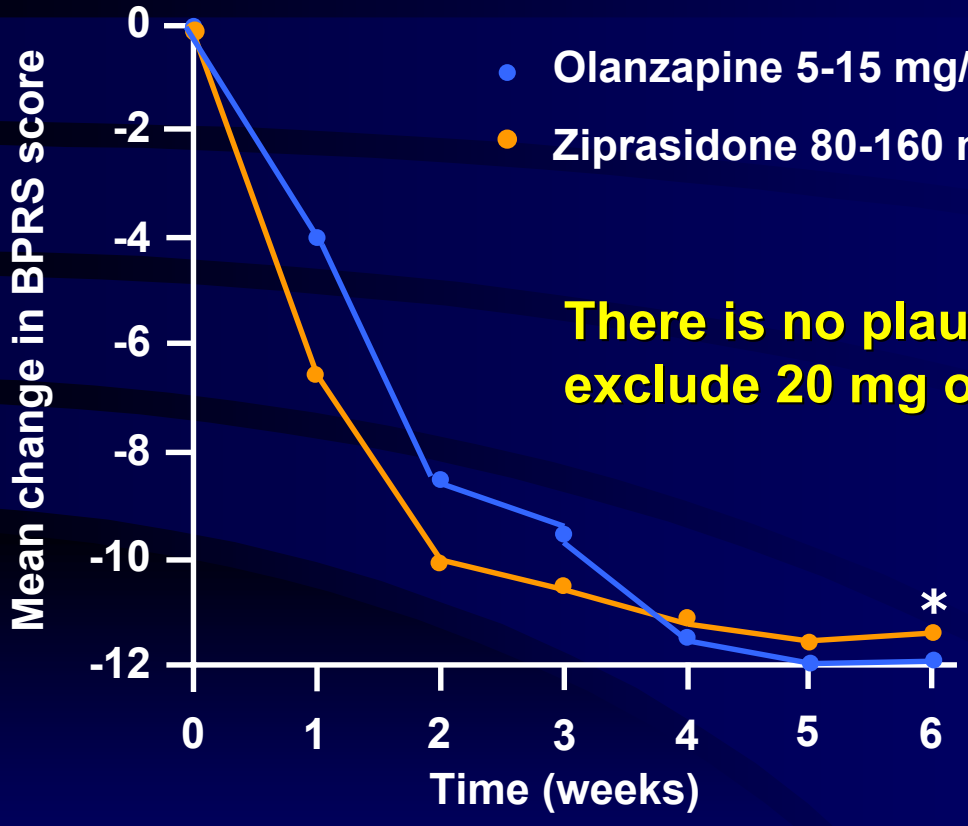
Klinik für Psychiatrie und Psychotherapie der TU-München

Pfizer Study: Ziprasidone as Effective as Olanzapine

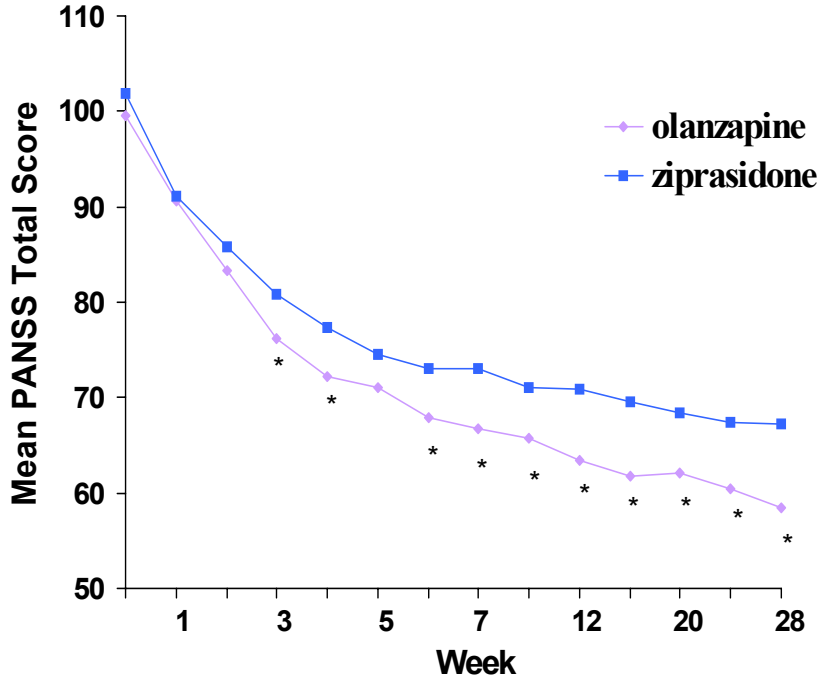


There is no plausible reason to exclude 20 mg olanzapine!

* No significant differences between groups (llast observation carried forward) (p=0.77, 95% CI=-2.36 to 3.18)

Simpson et al. 2004

Lilly study: Olanzapine significantly more effective than ziprasidone



Dose ranges:

Olanzapine

5-20 mg/day

Ziprasidone

80-160 mg/day

Breier et al. 2005

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

Why do we need meta-analyses?

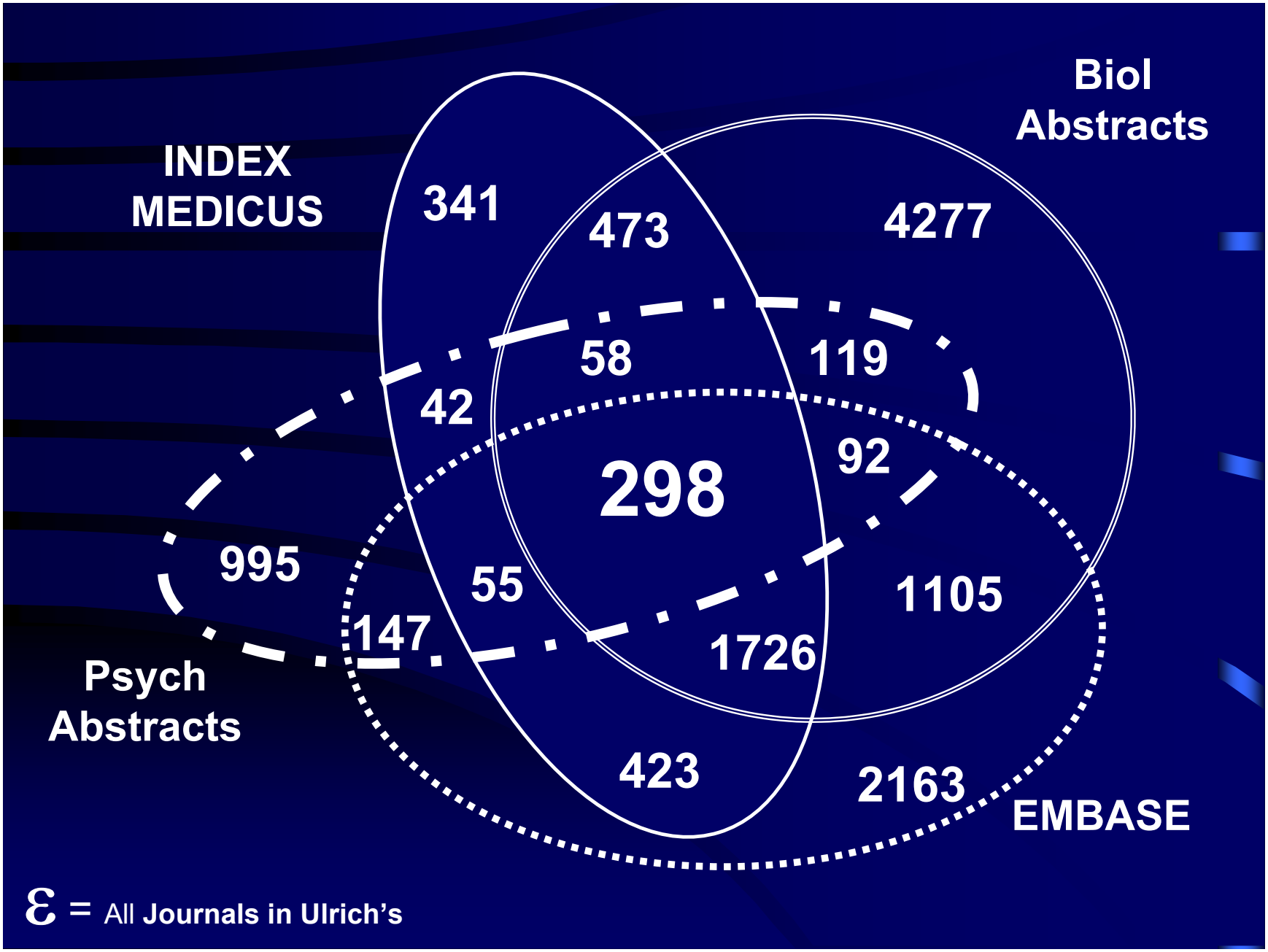
- In 10000 medical journals 2 million articles are published every year
- A general practicioner would have to read 19 articles everyday, 365 days per year to cover relevant reports
- Almost 300 randomised controlled studies about the „atypical“ antipsychotics are available

I. BEFORE: Writing a protocol

- Which patients
- Which interventions
- Which outcomes
- Literature search (data bases, search strings)
- Statistical method

II. Literature search

- Not only MEDLINE
- Not only English/Dutch
- Electronic databases, conference abstract books, book chapters, contacting pharmaceutical companies, contacting study authors, FDA webpage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ε = All Journals in Ulrich's

III. Data extraction (2 Reviewers!)

1. Continuous variables

(e.g. blood pressure, rating scales)

For both groups:

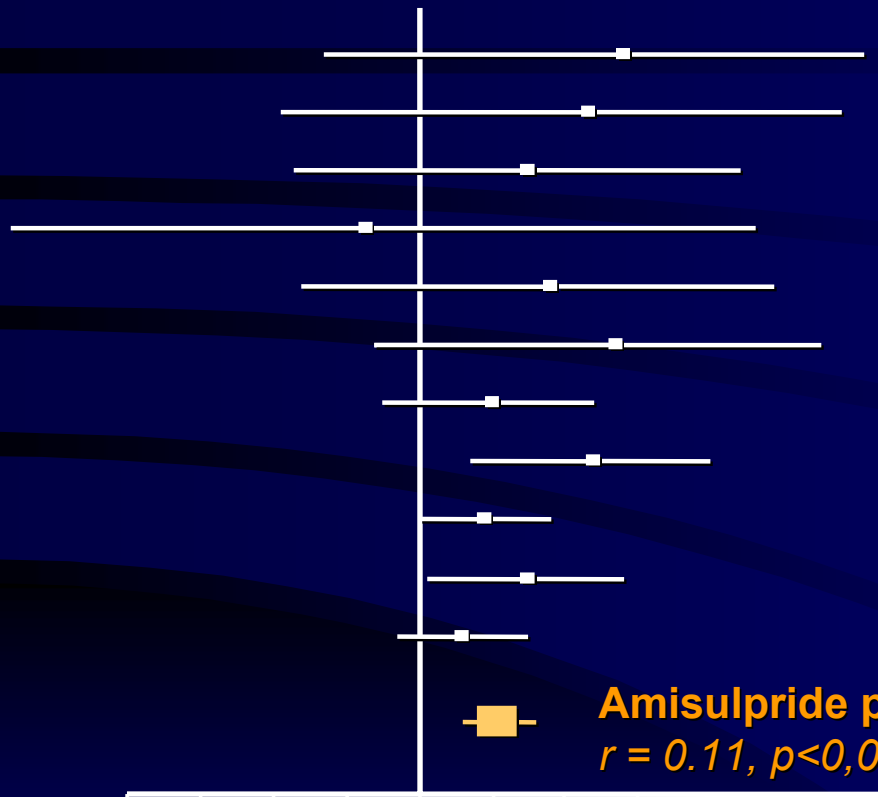
Mean, standard deviation, n

(can be calculated back from t-value, F-Value, p-value)

Effect size measures:

Mean difference, Standardised mean difference (Cohen‘s D, Hedges‘ g etc.), R

BPRS: Amisulpride vs. typical antipsychotics



Rüther (1989) **vs. perazine**[1]
Pichot (1988)
Ziegler (1989)
Klein (1985)
Costa e Silva (1989)
Delcker (1990)
Möller (1997)
Wetzel (1999) **vs. flupentixol**
Puech (1998)
Carrière (2000)
Colonna (2000)

Amisulpride pooled:
r = 0.11, p<0,0001, 10 studies, n = 1654

-0.4 -0.3 -0.2 -0.1 0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 *r (95% CI)*

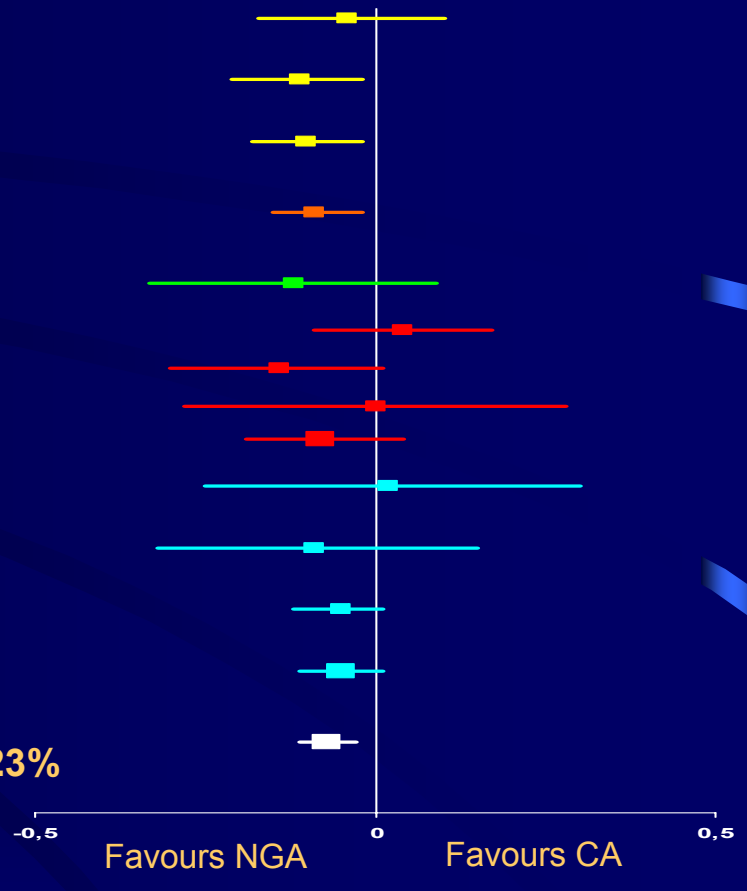
[1] endpoint analysis, not used for mean effect size

Leucht et al. Am J Psychiatry 2002

Relapse prevention – first vs new generation antipsychotics

	SGA n/N	%	FGA n/N	%
Marder 2002 - risperidone	2/33	6%	3/30	10%
Csernansky 2000 - risperidone	41/177	23%	65/188	35%
Risperidone pooled	43/210	21%	68/218	31%
Daniel 1998 - sertindole	2/94	2%	12/109	11%
Speller 1997 - amisulpride	5/29	17%	9/31	29%
Tamminga 1993 - clozapine	1/25	4%	0/14	0%
Essock 1996 – clozapine	13/76	17%	15/48	31%
Rosenheck 1999 - clozapine	10/35	29%	4/14	29%
Clozapine pooled[d]	24/136	18%	19/76	25%
Tran 1998a - olanzapine	10/45	22%	2/10	20%
Tran 1998b - olanzapine	6/48	13%	3/14	21%
Tran 1998c - olanzapine	71/534	13%	29/156	19%
Olanzapine 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

Interpretation of these numbers

One year Relapse rates: New drugs 15% Haloperidol 23%

SMALL: Absolute risk difference (RD) 8%,
NNT = 13, but...

if 1000 patients are treated for one year with new antipsychotics instead of haloperidol, 80 relapses are avoided

HIGH: Relapse reduction by 35%

Reduction in the Risk of Dying From Breast Cancer

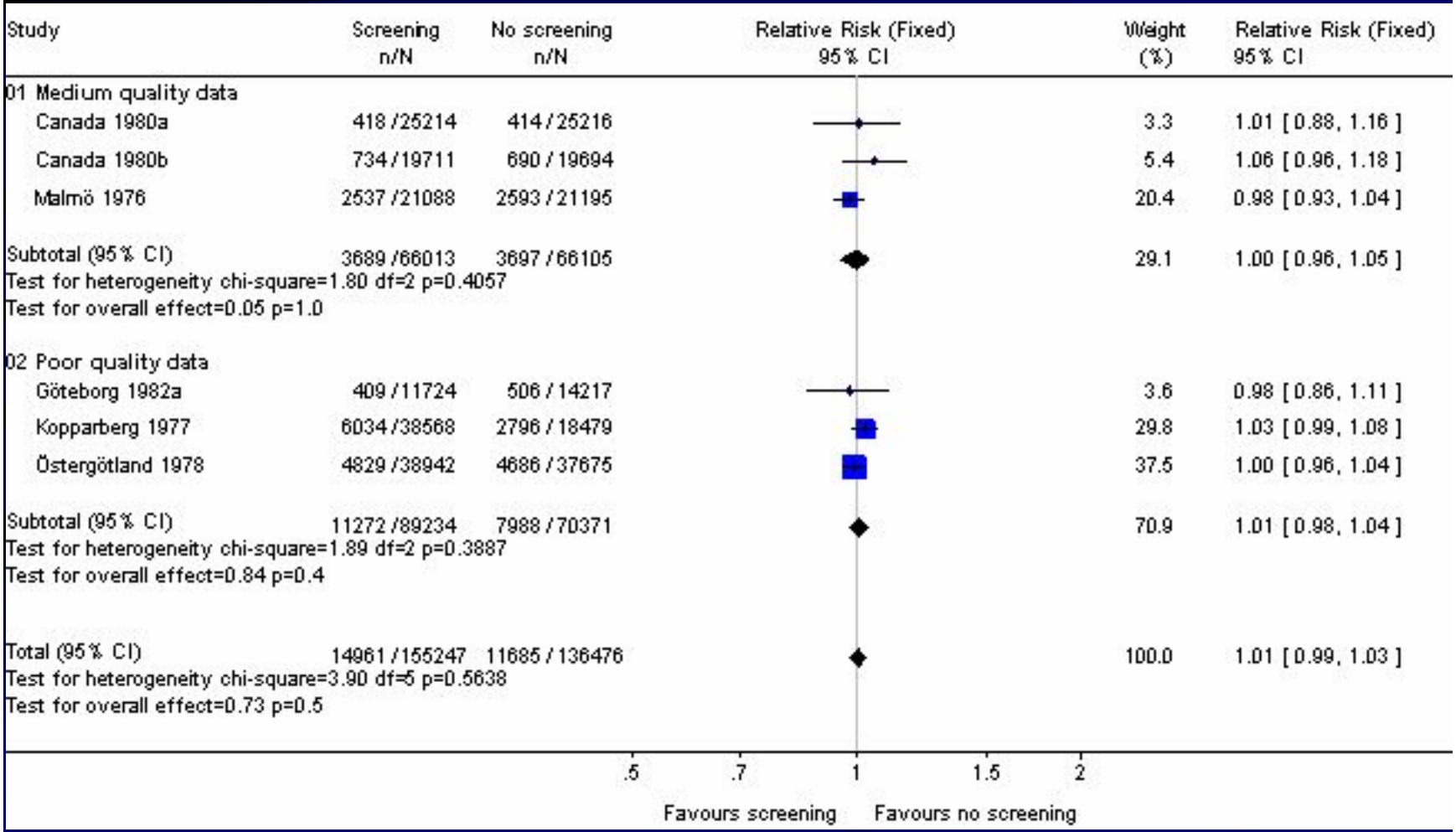
	100,000 Women without mammography	100,000 Women with mammography
Breast cancer mortality in 10 years	0.36% (360/100,000)	0.29% (290/100,000)

Relative mortality reduction = **20%** (1 – [0.29%/0.36%])

Absolute mortality reduction = **0.07%** (0.36%-0.29%)

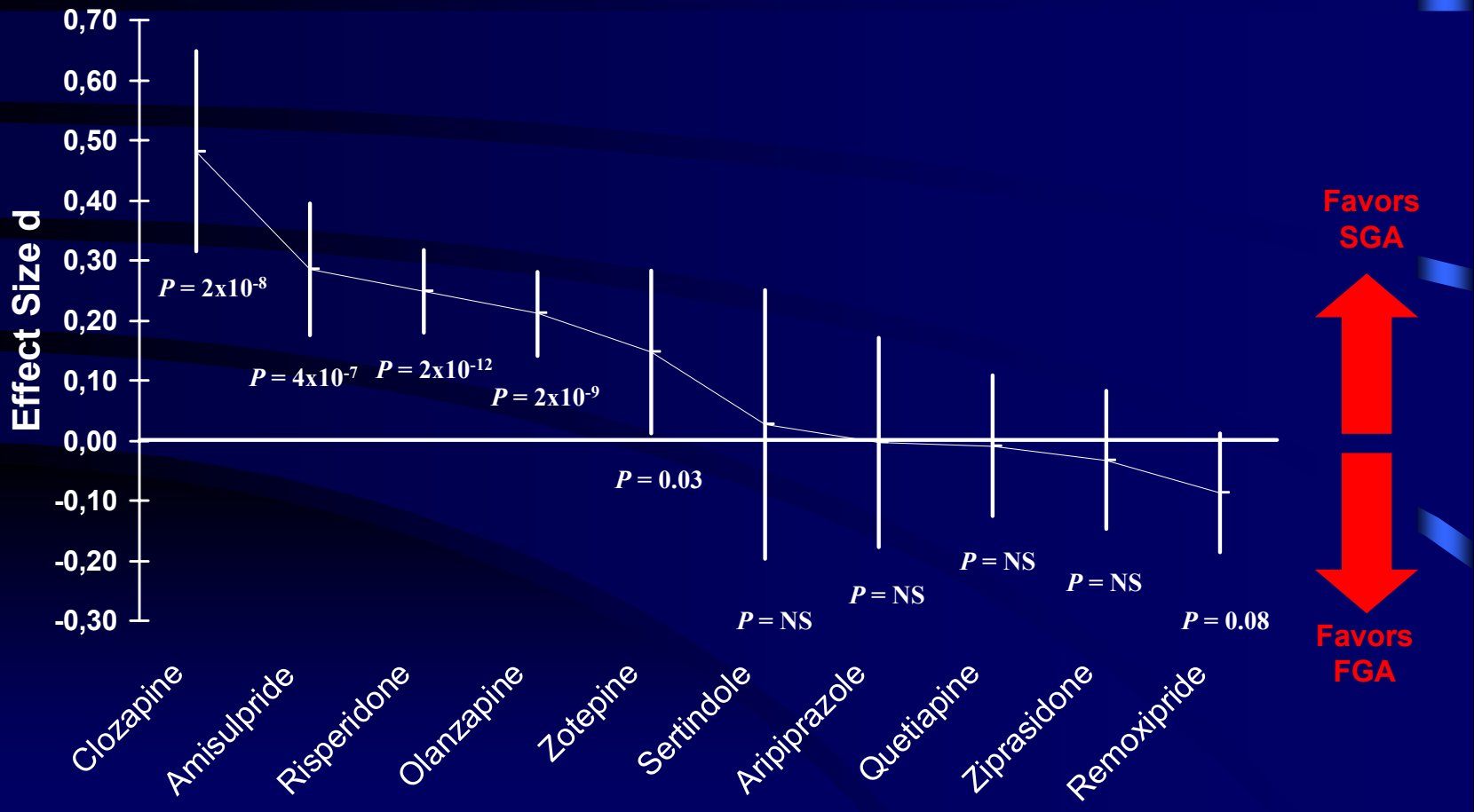
Data from Kürzl Deutsches Ärzteblatt 9/2004

Breast cancer screening – mortality after 13 years



Olson and Goetzsche Cochrane Library 2002

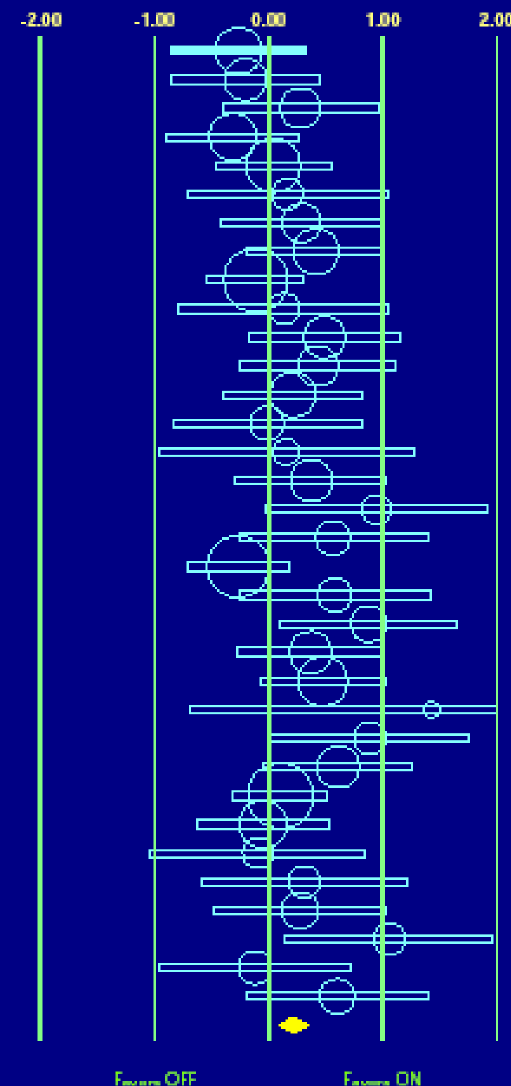
Effect sizes of ten second generation antipsychotics



Davis et al. Arch Gen Psychiatry 2003

Meta-analysis of the cognitive effects of conventional antipsychotics (Mishara and Goldberg Biol Psych 2004)

	Citation	CogFunction	N1	N2	Effect	Lower	Upper	PValue
	Allen et al, 1997	Multiple Cog Domains	25	22	-.27	-.86	.33	.36
	Allen et al, 2000	Executive/ Motor	19	19	-.21	-.87	.45	.52
	Braff & Saccuzzo, 1982	Speed of Proc/Verbal Ability	20	16	.28	-.41	.96	.41
	Chapman & Knowles, 1964	Conceptual Breadth	24	24	-.32	-.90	.27	.27
	Cleghorn et al, 90	Multiple Cog Domains	37	27	.04	-.47	.56	.87
	David, A. 1995	Semantic Priming	6	40	.17	-.72	1.05	.70
	Earle-Boyer et al, 1991	Attention (Sustained)	17	17	.29	-.42	.99	.40
	Epstein et al, 1996	Attention (Sustained)	23	23	.41	-.19	1.01	.16
	Finkelstein et al, 1997	Attention (Sustained)/WM	44	44	-.11	-.54	.31	.59
	Gilbertson&Kemp, 1997	Attention/ Memory	12	9	.14	-.79	1.06	.76
	Gold and Hurt, 1990	General intelligence	19	19	.49	-.18	1.16	.13
	Harvey & Pedley, 1989	Attention (Selective)	18	18	.43	-.26	1.12	.20
	Heilizer, 1959	RT/Perceptual/Practice	22	22	.21	-.40	.82	.48
	Hirschfeld et al., 1996	Multiple Cog Domains	10	16	-.01	-.85	.82	.97
	Hammer et al., 1991	Oculomotor	8	7	.15	-.97	1.27	.76
	Killian, Holzman et al, 1984	Multiple Cog Domains	13	34	.37	-.29	1.04	.25
	Litman et al, 1989	Oculomotor	11	10	.95	-.03	1.92	.04
	Marder et al, 1984	Attention (Visual)	13	13	.56	-.27	1.39	.15
	Mann, 1993	Multiple Cog Domains	40	43	-.27	-.71	.17	.22
	Nestor et al, 1991	Attention (Sustained)	12	13	.58	-.27	1.43	.15
	Oltmanns et al, 1978	Attention (Selective)	15	16	.88	.10	1.65	.02
	Pigache, 1993	Attention (auditory)	20	20	.37	-.28	1.01	.24
	Purdon et al, 2001	Multiple Cog Domains	27	27	.48	-.08	1.03	.08
	Serper et al, 1990	Learning/Auto Proc/Atten	4	4	1.43	-.69	3.55	.06
	Serper et al, 1994	Learning/Auto Proc/Atten	12	13	.89	.01	1.76	.03
	Spohn et al, 1977	Attention (Selective)	20	20	.61	-.05	1.27	.06
	Spohn et al., 1989	Oculomotor	36	64	.10	-.31	.52	.62
	Sweeney et al., 1994	Oculomotor	24	24	-.05	-.63	.53	.86
	Sweeney et al., 1997	Oculomotor	10	10	-.09	-1.03	.85	.83
	Sommer et al., 1999	Language	11	11	.31	-.59	1.21	.46
	Tomer & Flor-Henry, 1989	Hemispheric Proc	15	15	.27	-.48	1.03	.45
	Tomer, 1990	Verbal Ability/Hemispher Proc	12	12	1.06	.14	1.97	.01
	Ulferts et al, 1999	Time Perception	12	12	-.12	-.97	.73	.76
	Zahn et al, 1994	Atten/Sensory Dominance	14	14	.60	-.19	1.40	.11
Random	Combined (34)		625	698	.22	.10	.34	.00

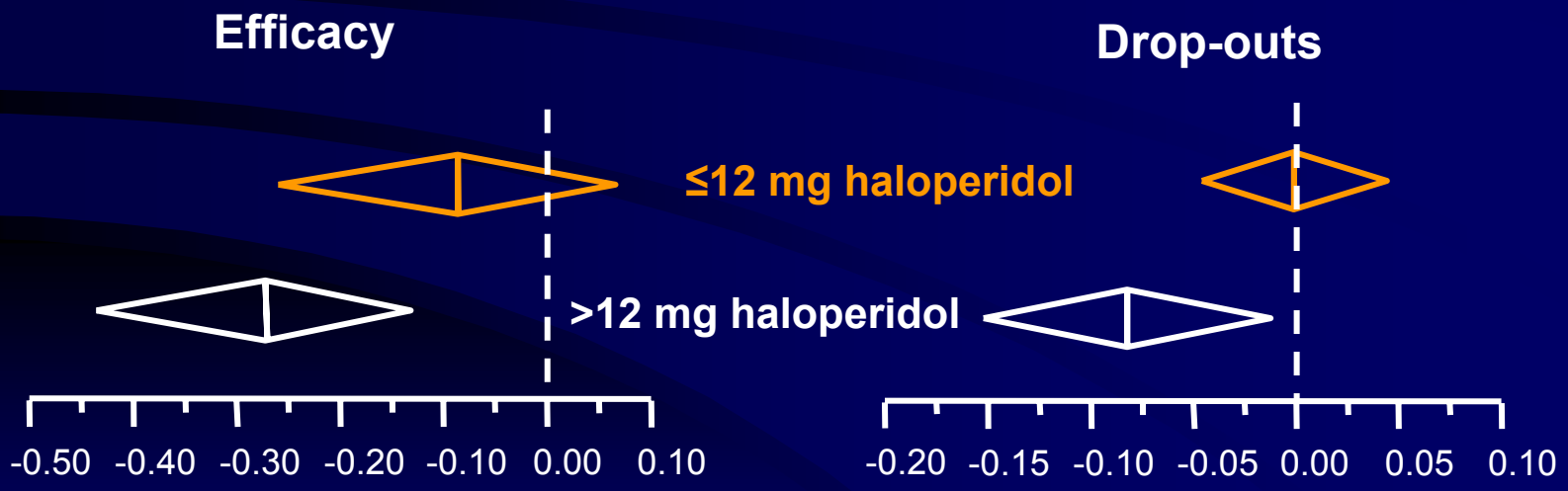


Meta-regression

- Is used for the analysis of the influence of further variables on the outcome
- For example, the influence of the doses used on the results

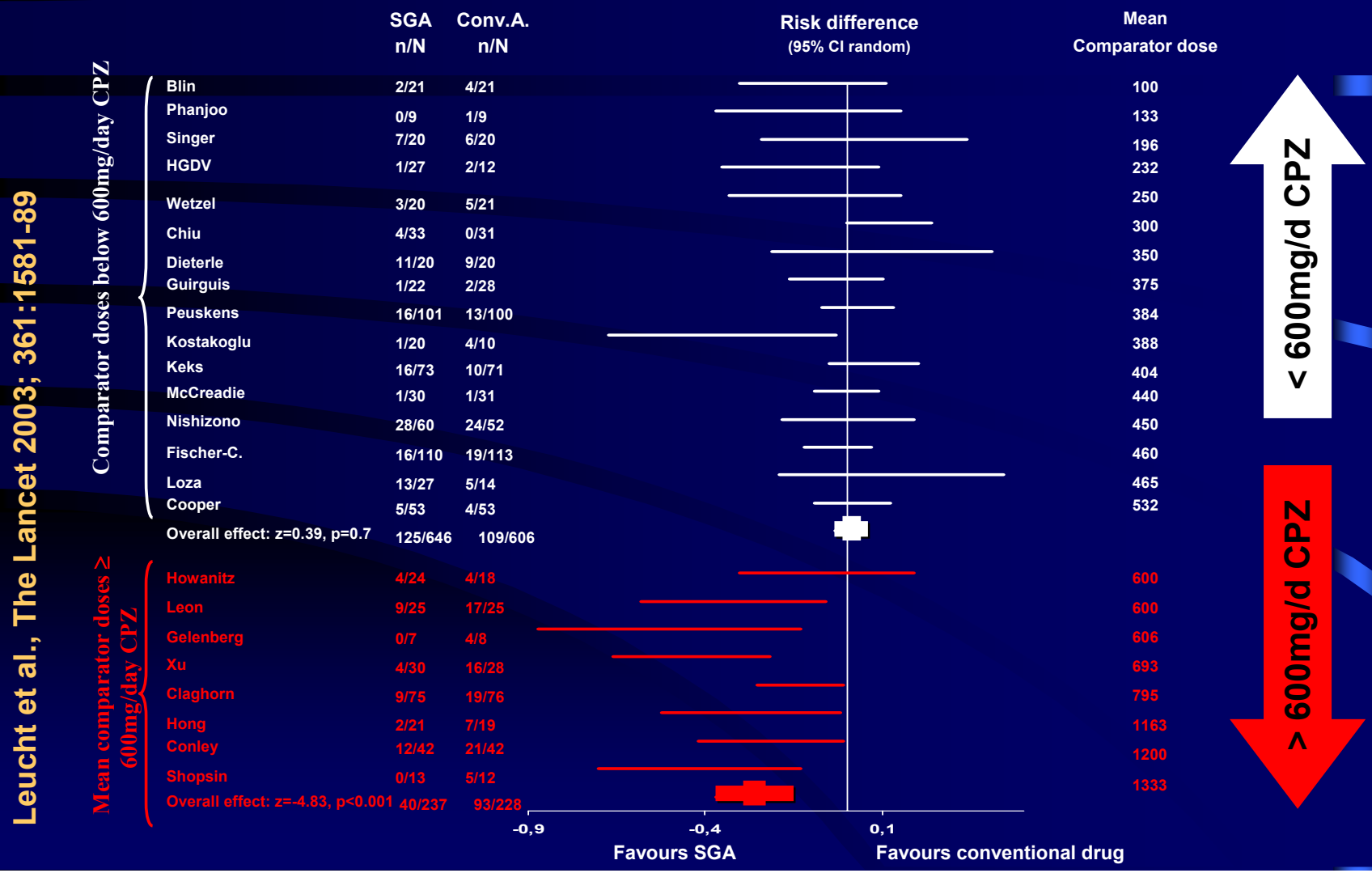
Atypical Antipsychotics in the Treatment of Schizophrenia: Systematic Overview and Meta-regression Analysis

"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"



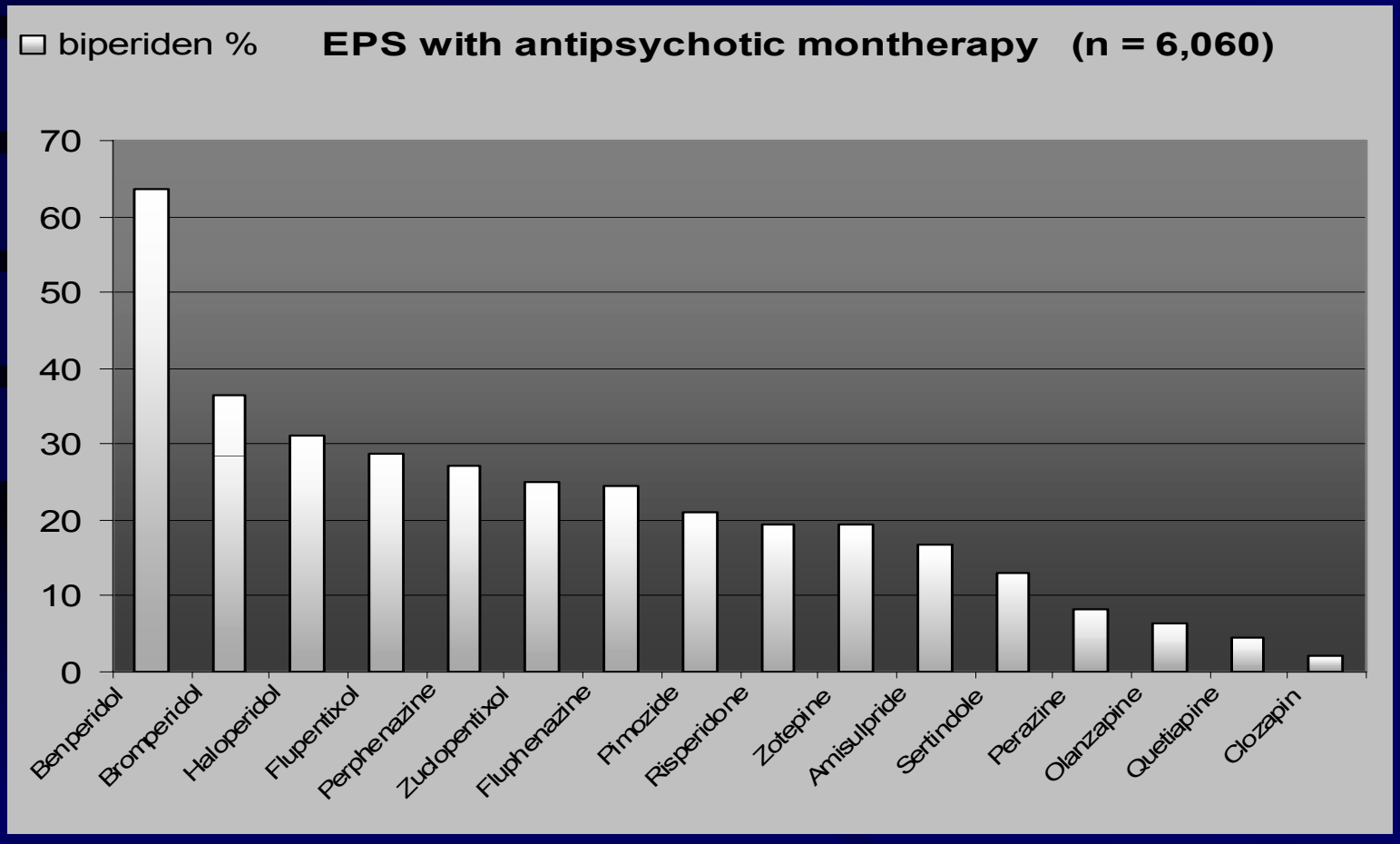
Geddes et al. 2000

Number of patients with at least a single occurance of EPS



Leucht et al., The Lancet 2003; 361:1581-89

Cross-sectional evaluation of EPS in 6060 patients AGATE project, Fischer-Barnicol et al. 2003



Limitations of Meta-analyses

- Methodological problems of meta-analysis, especially the apples and oranges problem, different study quality etc.

- In meta-analysis there are many judgement calls

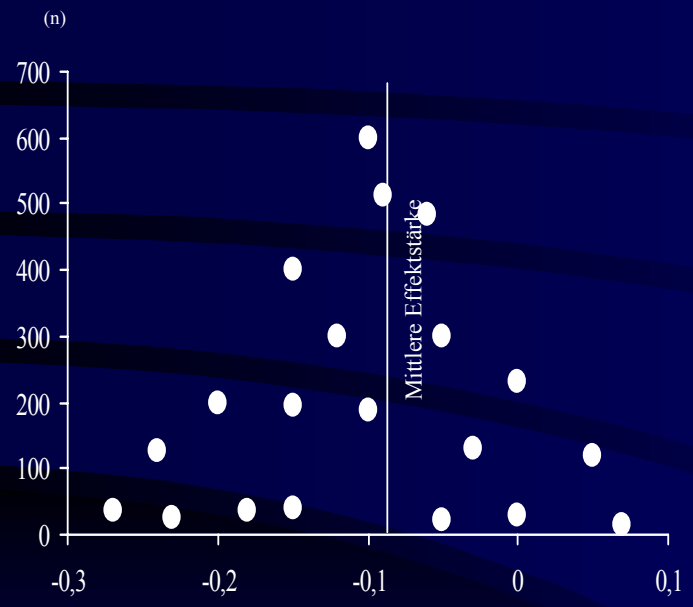
- The original studies are frequently so poorly reported that meta-analytic procedures are not possible

- Publication bias

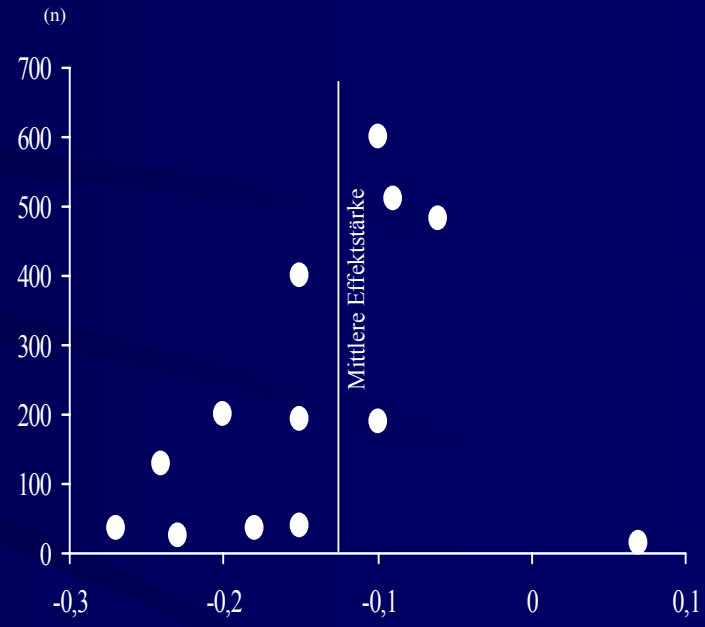
Publication Bias

- Is probably the greatest problem of ‘evidence based medicine’
- Studies without significant results are considered less interesting by journals and thereby have a reduced likelihood of getting published
- Pharmaceutical companies are understandably not interested in publishing studies with results that were unfavourable for their product.
  - Example 1: paroxetine for depressed children.
  - Example 2: It has been suggested that 25% of trials comparing antidepressants with placebo are negative

„Funnel-plot“ without publication bias



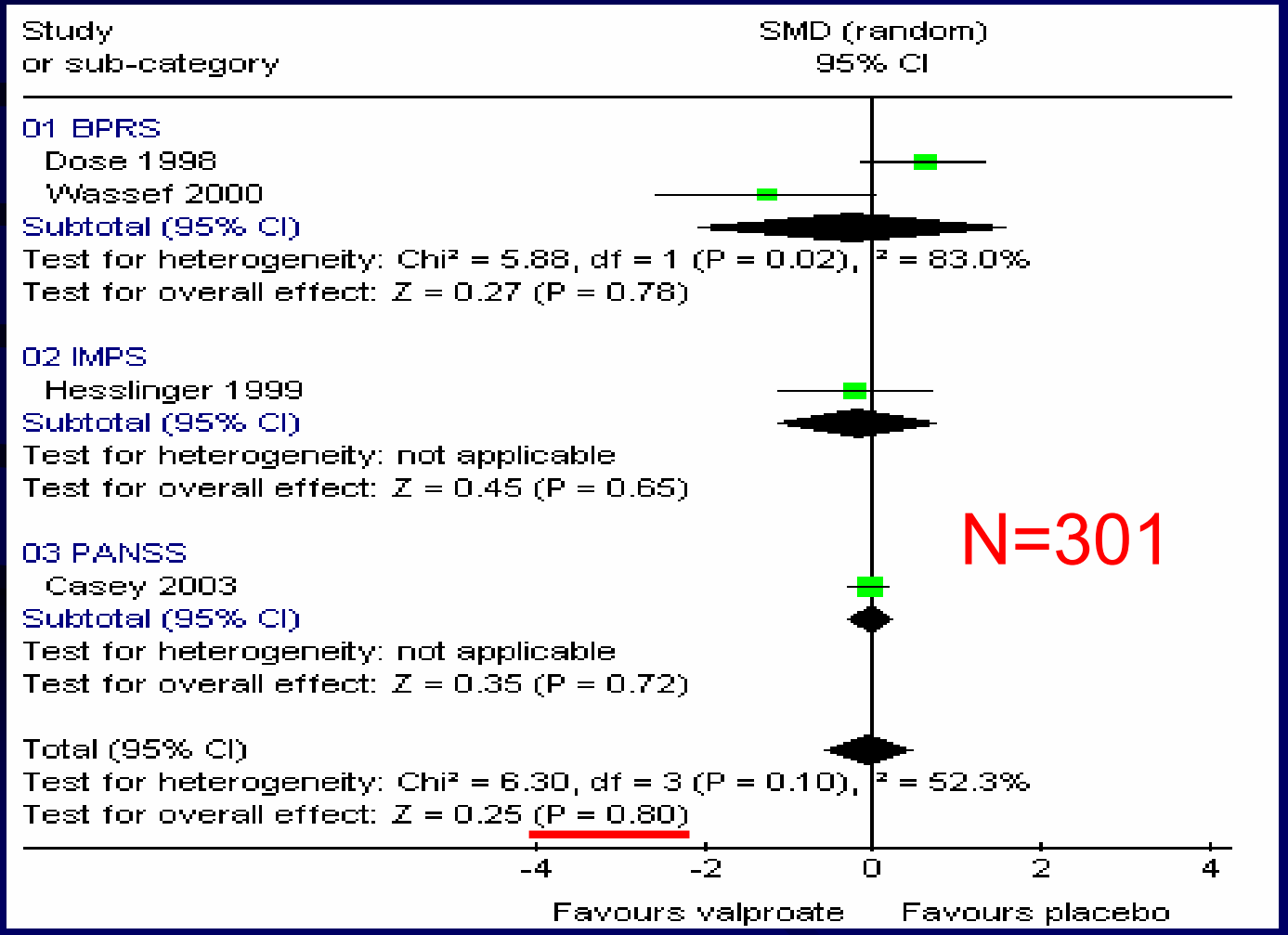
„Funnel-plot“ showing possible publication bias



Metaanalysis

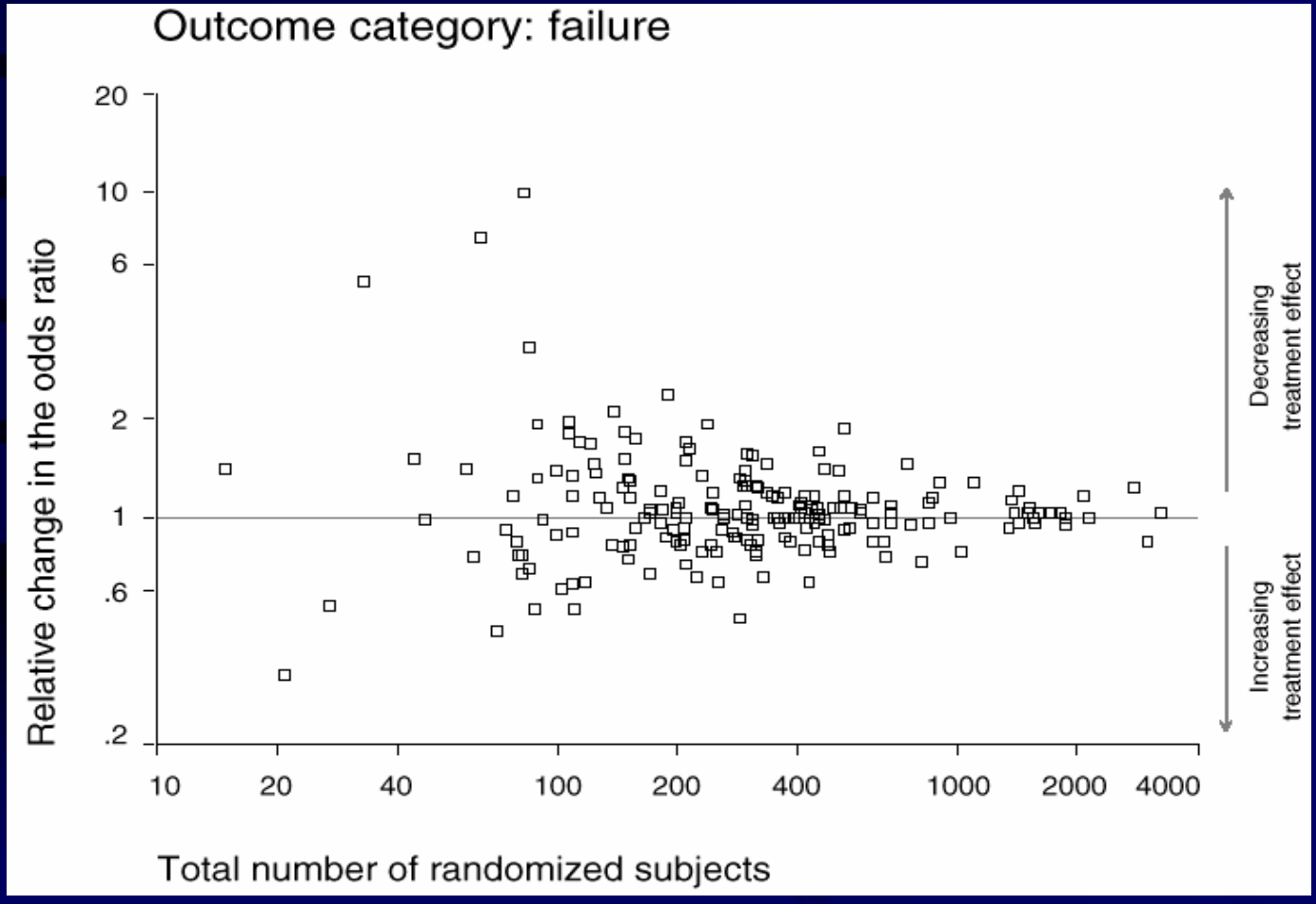
A goldstandard?

Valproate augmentation of antipsychotics for schizophrenia



Basan et al. Schizophrenia Research 2004

Ab welcher Fallzahl sind die Ergebnisse von Metaanalysen stabil?



EU-Psy group et al. Am J Epidmiol 2005

Vielen Dank für Ihre Aufmerksamkeit