



DIFFICULTIES IN ESTABLISHING LONG-TERM EFFICACY FOR PSYCHOTROPIC DRUGS

**Basis for current regulatory
requirements: Need for
change?**



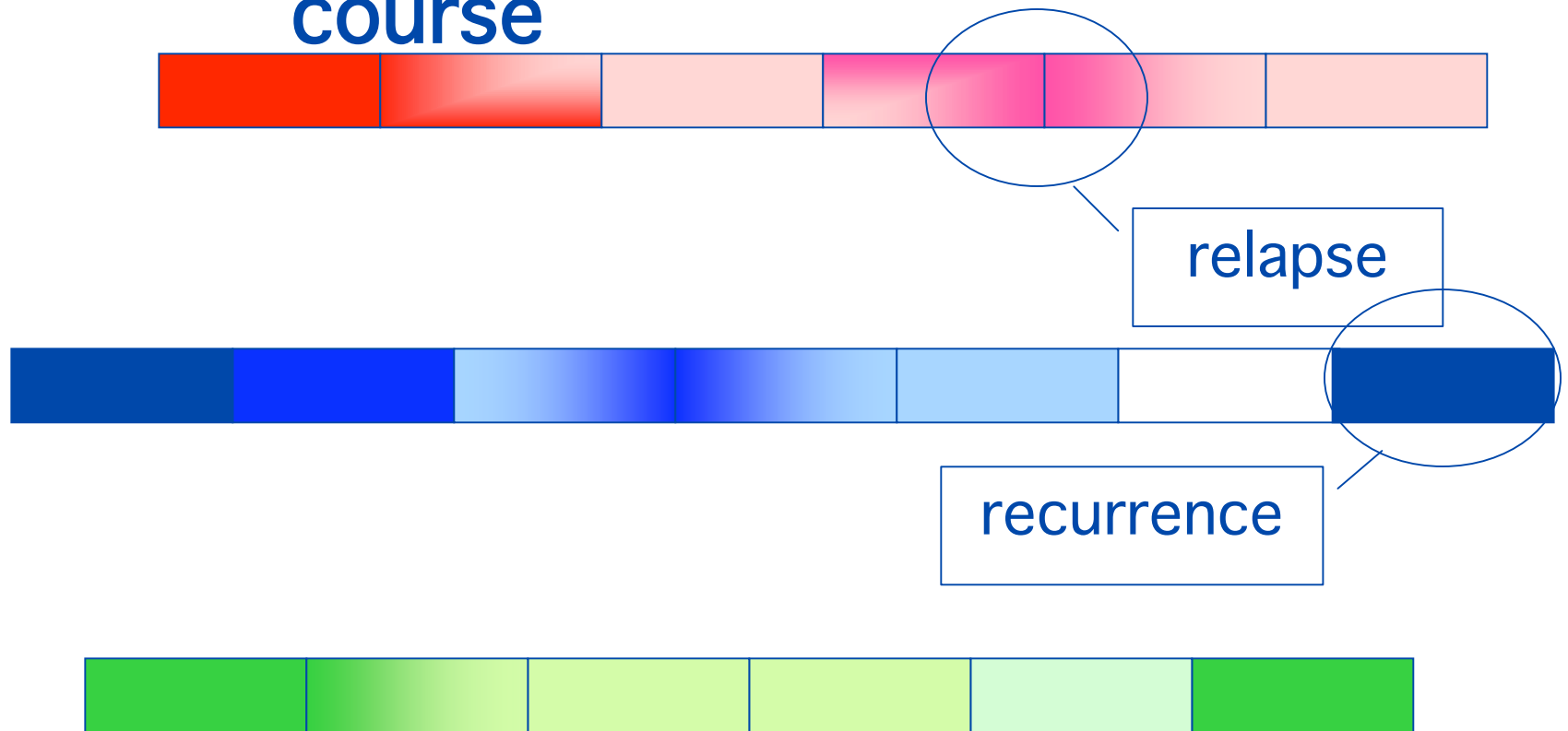
Summary

- The problem framework :
 - _ *To study long term efficacy of psychotropic drugs is difficult.*
- Knowledge gaps
 - _ What European regulators demand to know?
 - _ What clinicians want to know?
- Room for improvement
- Conclusions



Problem framework

Psychiatric disorders: clinical course





Problem framework (1)

- Psychiatric diseases are chronic disorders.
- PsyD phenomenology can be a sign/symptom of almost any other medical condition.
- Drugs are approved for clear clinical entities and only rarely for isolated signs or symptoms.
- Drugs intended for chronic disorders must be efficacious on the long-term.

— Thus, the long-term efficacy must be proven.



Divergence among partners in a era o global development!



USA is the most important pharmaceutical market thus FDA rules!

Free market
without constraints!

Prescription drugs
paid out of the
pocket.

High prices.

The largest number
of consumers.

Direct advertising.



EU cannot be ignored,
at least, by big
Pharma. Thus, lets
make some effort to
comply!

Market has
reimbursement
constraints!

Prescription drugs paid
by NHS or insurance

Lower prices.

High number
consumers.

(500 x10⁶ inhabitants)



Class effects

Always an hot topic!

- Some would argue that any antipsychotic/*antidepressant* will have some degree of long-term efficacy.
 - Therefore as far as a new compound is considered as belonging to the antipsychotics/*antidepressant* class it is admissible that long-term efficacy is present what would waive the need to demonstrate it.

However long term B/R will still be needed.

- But long-term trials could focused in more interesting goals than efficacy upon positive symptoms.

•What is a Class?
•How is a class effect demonstrated?
•Is industry interested in CE?



Problem framework (2)

- Efficacy has to be demonstrated by short-term studies showing an effect in schizophrenia and in addition maintenance of efficacy has to be shown.

_ CPMP/EWP/559/95

- 1 year, DB, extension studies, with an active comparator.
- 6 m relapse-prevention studies
- 6 m, DB, placebo-controlled studies.



Problem framework (3)

- Depression: For licensing it should be shown that a short-term effect can be maintained during the episode. For this a randomized withdrawal study, also called relapse prevention study, is probably the best design.

CPMP/EWP/518/97/rev1



Problem framework (4)

- GAD: In addition to the short-term trials, long-term studies are needed demonstrating that the effect of the product is maintained over time. The optimal design for demonstrating maintenance of effect is by means of RWS.

_CHMP/EWP/4284/02



Test

Active comparator

← Test 1 year →

Placebo

← 6 M →

Ethical concerns;
Difficulties with the interpretation due to allowance for rescue

Problems:

Dropouts _ Imputation methods;
Definition of the outcome (multiple dimensions)
Definition on the non-inferiority margin;
Large sample-size;
Complex logistics.

Test

Responders

Placebo

NR

← 6 M →

Acute



LEUCHT, BARNES, KISSLING, ET AL.
Am J Psychiatry 160:7, July 2003

Up to 2002: 29 LT
 RCTs, 17 reporting
 on relapses.
 DO not relapse:

44%

FIGURE 1. Differences in Risk of Relapse in Patients With Schizophrenia in Studies Comparing New-Generation Antipsychotic Medications With Placebo^a

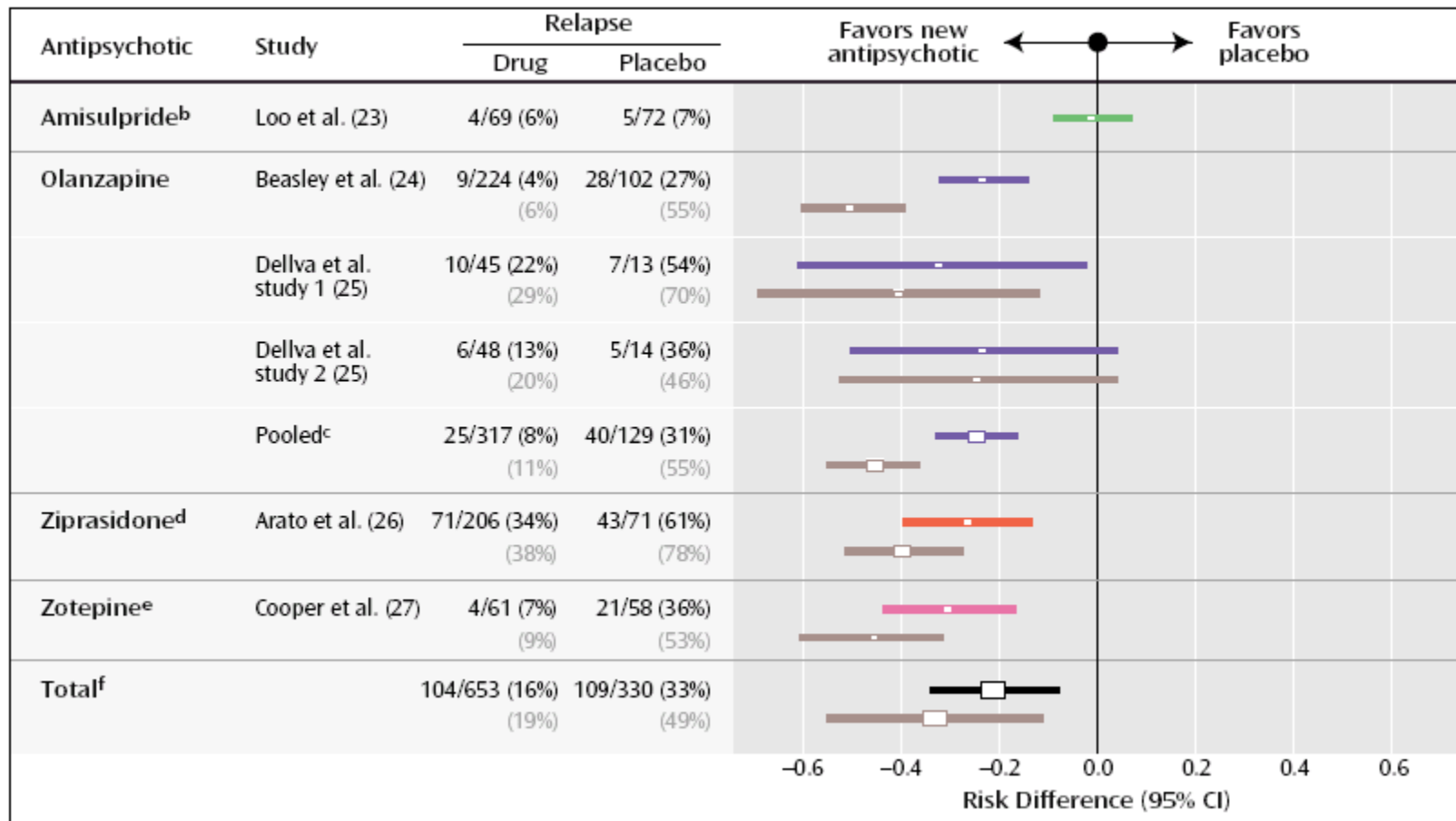
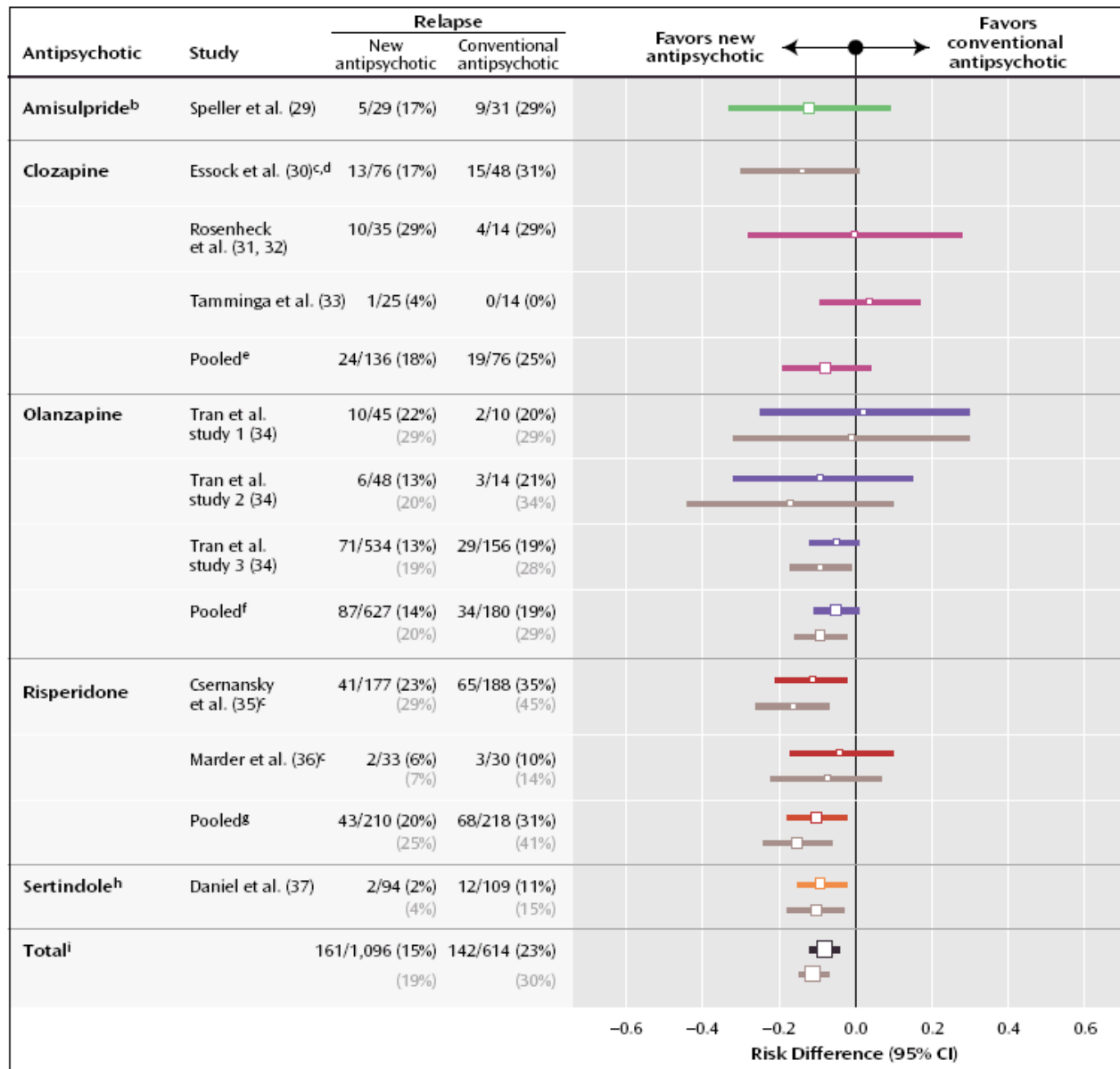




FIGURE 4. Differences in Risk of Relapse in Patients With Schizophrenia in Studies Comparing New-Generation Antipsychotic Medications With Conventional Antipsychotics^a





Aripiprazole vs haloperidol: 1 year, DB, trial

Ref No	Trial Design	Trial Population	Treatment	Efficacy Results (*primary efficacy parameters)				
5	Two 52 week double blind active controlled trials (one in the US, one worldwide). Results of the trials were pooled (prospectively planned)	1294 patients in acute relapse with chronic schizophrenia Primary efficacy outcome- time to failure to maintain response in responders. Response defined as a $\geq 20\%$ decrease from baseline in PANSS total score at a single time point. A more stringent criteria was also used, defined as a $\geq 30\%$ decrease from baseline in PANSS total score for at least 28 days.	Aripiprazole 30mg od (n=861) Haloperidol 10mg od (n=433) A one-time dose reduction to 20mg daily of aripiprazole and 7mg daily of haloperidol was allowed for tolerability.	Response rate	Aripiprazole	Haloperidol	P value	
				$>20\%$ improvement in PANSS	72%	69%	0.362	
				$>30\%$ improvement in PANSS over ≥ 28 days	52%	44%	0.003	
				*Kaplan-Meier estimates for patients maintaining responses at week 52				
				Time to failure to maintain response	Aripiprazole	Haloperidol	Risk ratio	P value
				$>20\%$ improvement in PANSS	77%	73%	0.88	0.427
				$>30\%$ improvement in PANSS over ≥ 28 days	85%	79%	0.7	0.098



FDA vs CHMP

CLINICAL PHARMACOLOGY/Clinical Studies

Efficacy information from the 52 week, active-controlled study should be removed since this trial, by design, cannot demonstrate the longer-term efficacy of aripiprazole in schizophrenia.

FDA Clinical review 2003

The data on long-term efficacy used aripiprazole in a targeted dose of 30 mg/d and compared it to haloperidol 10 mg. The trial was designed as a superiority trial on rate of maintenance of response at 52 weeks. Although there was no statistical difference between arms, the data available supports that aripiprazole is efficacious for maintenance therapy.

EMA EPAR 2004



Up to 2000: 37 trials, 21 analysed, large majority 12 m duration (14); data suggest that relapse and recurrence behave similarly.

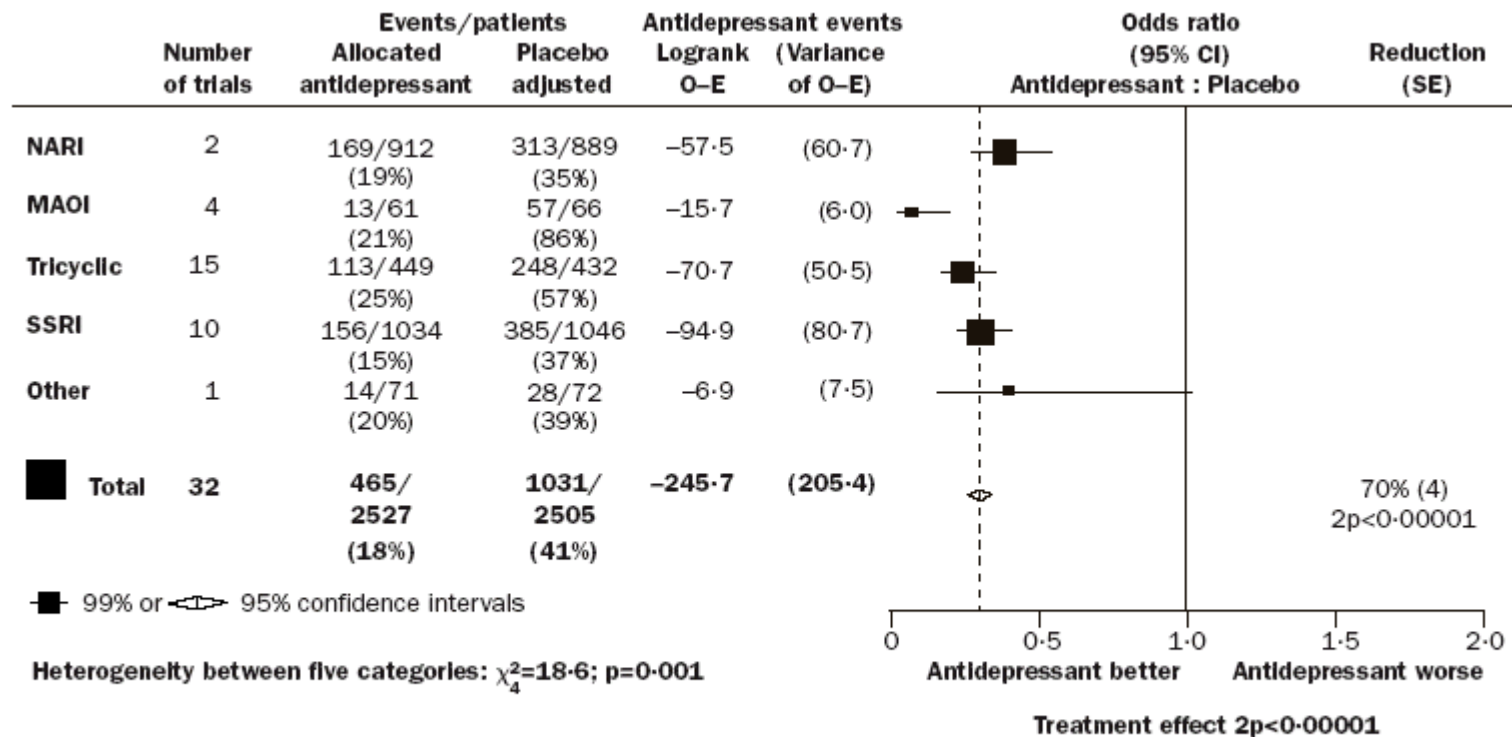


Figure 1: Risk of relapse: odds ratios by drug type

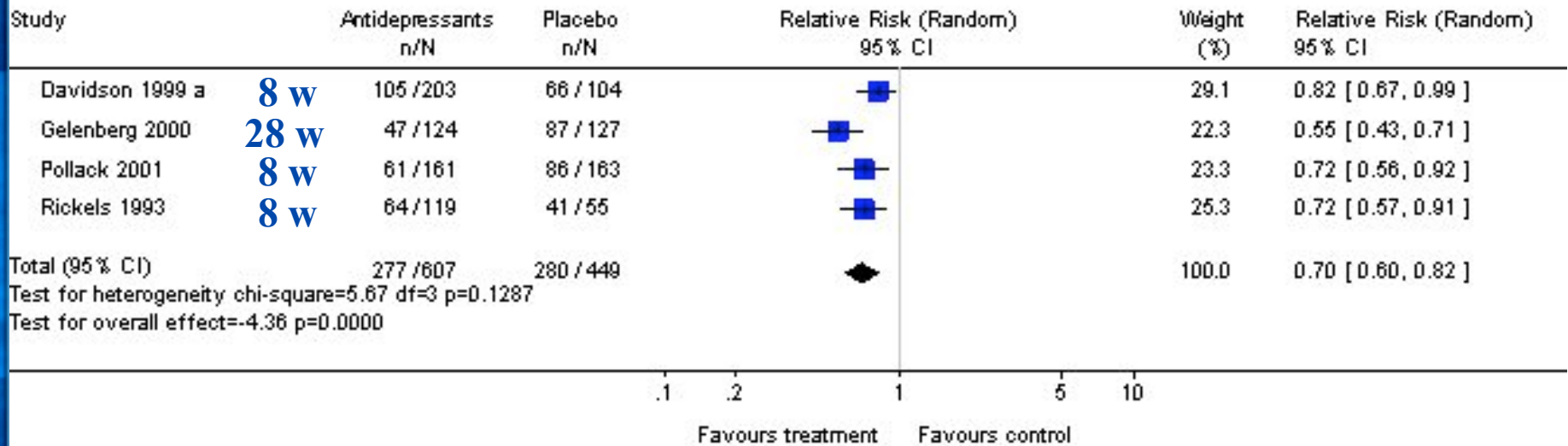
NARI=noradrenaline (norepinephrine) reuptake inhibitor. MAOI=monoamine oxidase inhibitor. SSRI=selective serotonin reuptake inhibitor.

Geddes et al. Lancet 2003; 361: 653–51



Another important research question is whether the long-term efficacy described for venlafaxine (Gelenberg 2000, Hackett 1999) also applies to other antidepressants!

Review: Antidepressants for generalized anxiety disorder
 Comparison: 01 Antidepressants vs placebo
 Outcome: 01 No treatment response



Kapczinski F, Lima MS, Souza JS, Cunha A, Schmitt R.
The Cochrane Database of Systematic Reviews 2003, Issue 2.



Knowledge gap (1)

- Demonstration of long-term efficacy is systematically required by CHMP.
_is this unreasonable?
NO
- However...



Knowledge gap (2)

- Are the goals of the long-term studies the most relevant?
 - _ probably not.

There is a lot to do. Namely harmonizing the definition of relapse in operational terms!



Schizophrenia

Most common goals:

- Relapses defined mostly as recurrence of positive symptoms.

Most relevant clinical outcomes:

- Negative symptoms
 - _ social integration;
- Safety profile, not only EPS.
- Impact on cognition



Are long-term trials in Psy D useless for industry?

- NO
- They are critical to:
 - _ Reimbursement (in Europe);
 - _ To gain a place in therapeutic guidelines.



Conclusions

- Long-term clinical trials in Psy D are technical and logistically difficult.
 - _ The solution is not to avoid them but rather to optimized their conduction and output.
 - _ Relapse prevention studies are systematically recommended but they do not provide the most interesting clinical answers.
 - _ Industry should rethink their clinical development plans moving from a strategy “just for the sake of *European* regulators” .
 - _ Clinicians should established clinical research networks to harmonized concepts, goals and procedures to facilitate clinical research success.



Conclusions

- Regulatory requirements: Need for change?
 - _ A revolutionary change _ EMEA reverting to FDA standards?
 - Unlikely
 - Undesirable
 - _ A change in continuity?
 - Possible
 - Desirable



Conclusions

- What changes?
 - _ Tailored long-term trials to highlight the potential advantages of each new drug.
 - _ Trials that address the issues of relapse and recurrence in a clear but cost-effective way.
 - _ Safety outcomes evaluated by protocol specification.