Newcastle University

Psychobiology Research Group

The Pharmacological Management of Difficult to Treat and Treatment-Resistant Disorders

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Plan

- Can’t cover the whole of clinical psychiatry!!
- Concentrate on general adult psychiatry and psychopharmacology of:
  - Schizophrenia
  - Anxiety disorders
  - Depression
  - Bipolar disorder
- Concentrate on **clinical use of drugs**, rather than pharmacodynamic and pharmacokinetics
- Cover generalities then specifics of pharmacotherapy
  - NB guidelines

Some general principles of managing difficult to treat patients

1. Reassessment of diagnosis
2. Reassessment of comorbidity, maintaining factors etc
3. Assess concordance

Assessment

4. Collaborative approach
5. Education of all
6. Instillation of hope
7. Do something
8. Non-pharmacological strategies

General Issues

9. Have clear pharmacological plans
10. Have adequate trials of medication
11. Monitor response assiduously and objectively
12. Take care with change overs
13. Avoid polypharmacy where possible
14. Maintenance therapy

Pharmacology

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Depression “sub-types” and “treatment-resistance”

- Atypical depression
  - To TCAs but not MAOIs (Quitkin et al. 1993)
- Psychotic depression
  - Response rate less than half that for non-psychotic depression to antidepressant monotherapy (Charney & Nelson, 1981)
  - ? similar response rate to ECT or AD+antipsychotic
- Bipolar depression
  - Median time to stabilisation = 24/52 (Kupfer et al. 2000)
  - Poor response to TCAs and SSRIs
  - ? Better response to MAOIs (Thase et al. 1992)

Problems with bipolar disorder diagnosis

- Nationwide Community Study in US
- Procedure
  - 127,800 MDQs sent to a sample representative of US adult population
  - 66.8% usable returns
- Results
- 3.7% identified positive (weighted/adjusted for non-response)
- Of these…
  - **19.8% had previously received a diagnosis of bipolar disorder from a physician**
  - **31.2% had received a diagnosis of unipolar depression**

Hirschfeld RM, et al. J Clin Psychiatry 2003;64:53–9

Unipolar vs Bipolar disorder

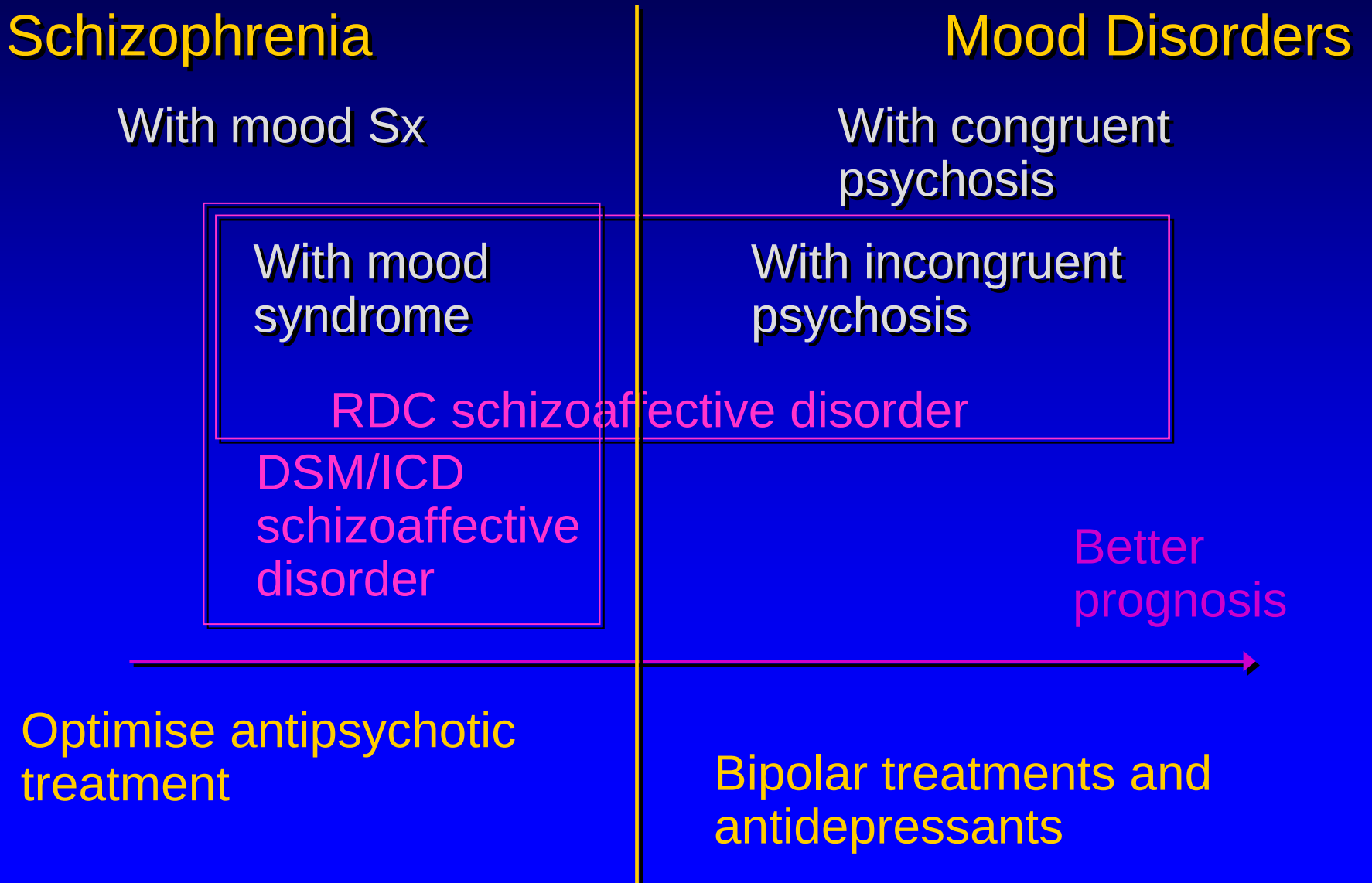
- Clues that “unipolar” depression may be bipolar
  - Onset of illness:
    - Prepubertal or adolescent
    - Postpartum onset
  - Characteristics of episode:
    - Hypersomnic-retarded
    - Psychotic
  - Family history:
    - Bipolar family history
    - Consecutive generation mood disorder
  - Pharmacological hypomania

Geller & Luby. *J Am Acad Child Adolesc Psychiatry*. 1997;36:1168-76. Akiskal et al. *J Affect Disord*. 1983;5:115-28.

Schizoaffective disorder

- RDC (1981) defined schizoaffective disorder (SAD) as mood syndrome plus core schizophrenic symptoms
  - schizophrenia and affective subtypes depending on the duration of psychotic symptoms
- DSM and ICD define SAD as just the schizophrenic subtype defined by RDC on the basis of
  - Genetics
  - Treatment response
- Reasonable inter-rater reliability for RDC
- Poor inter-rater reliability for DSM and ICD SAD

Schizophrenia - Affective disorders diagnoses



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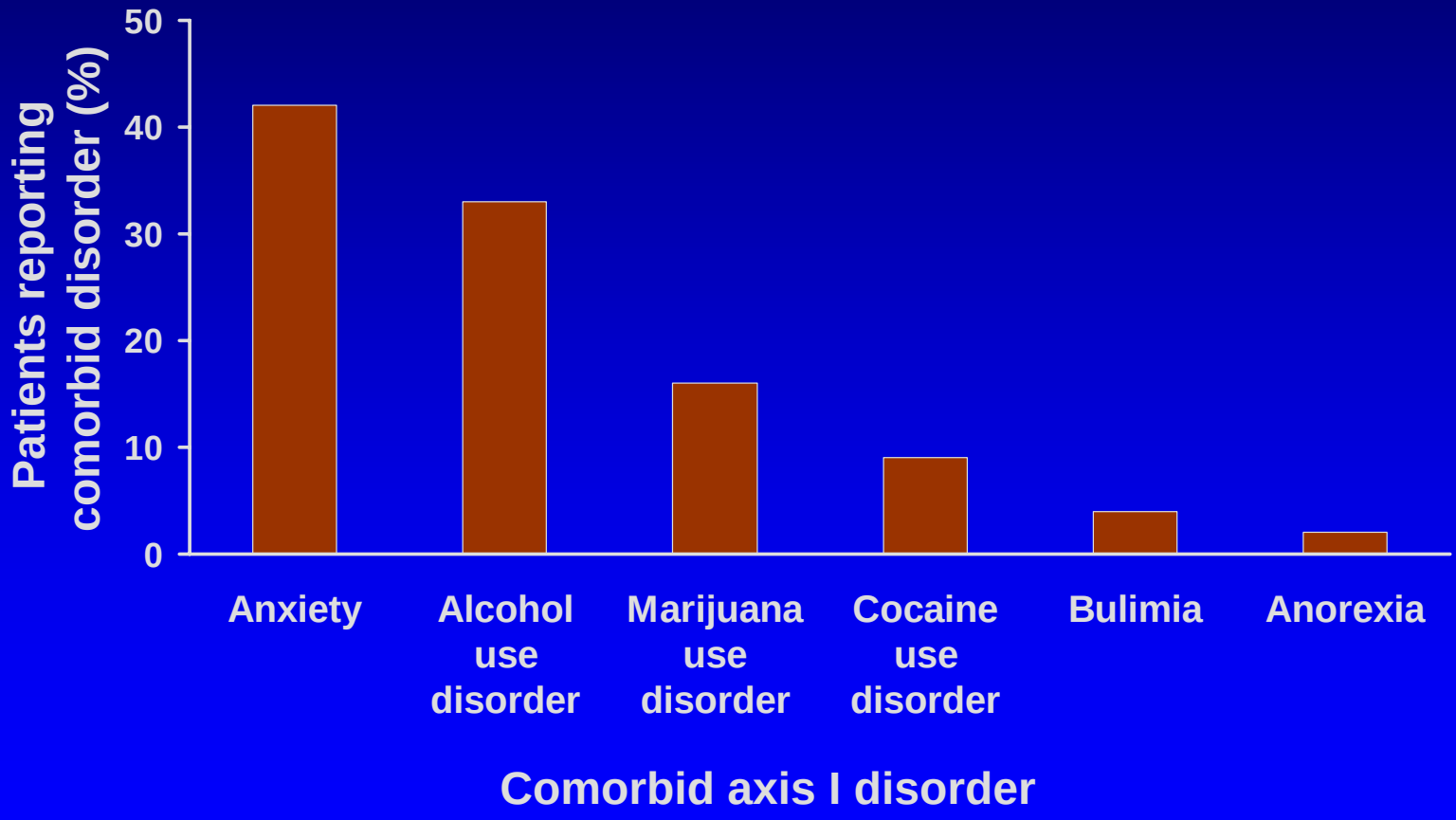
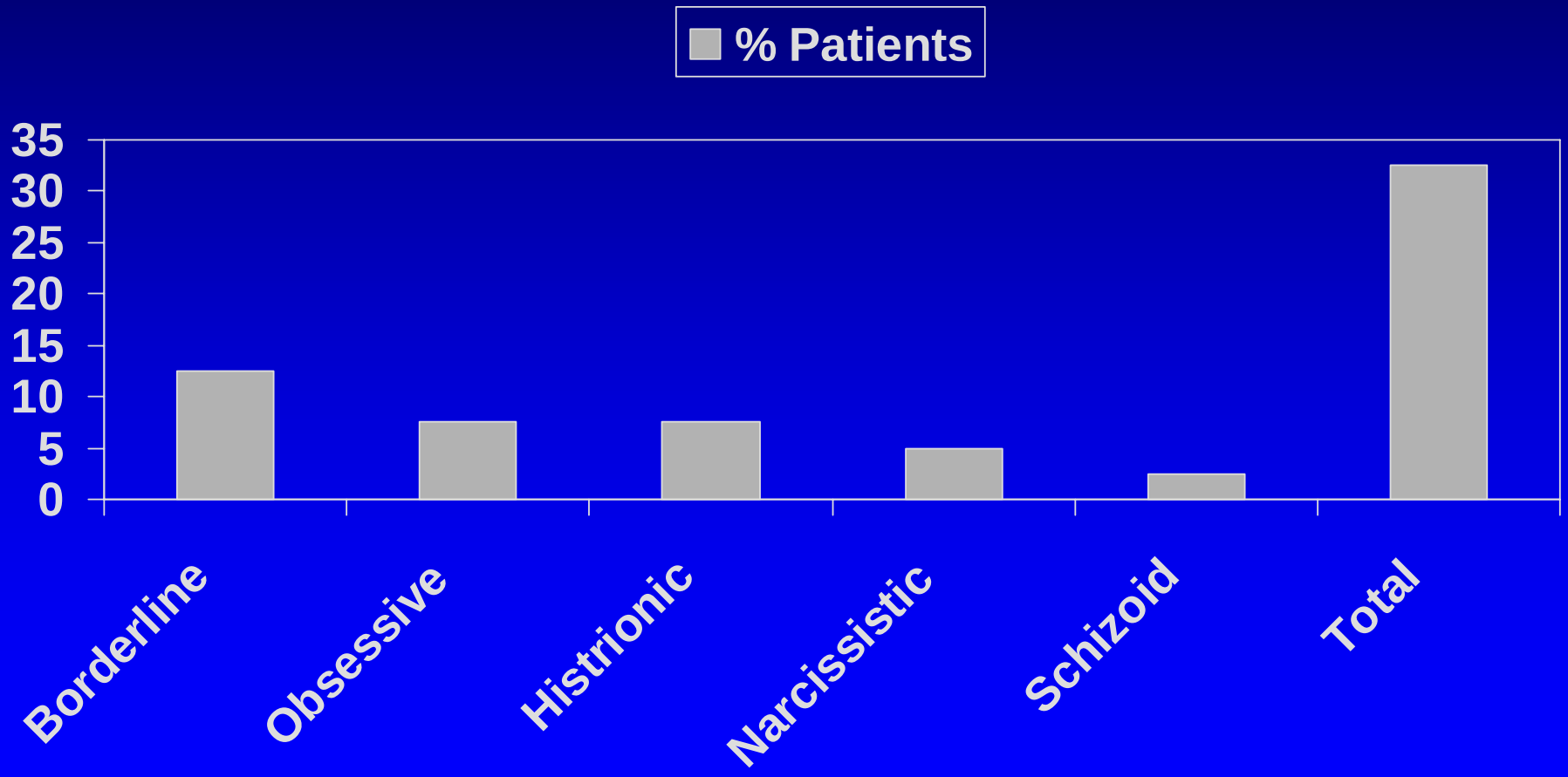
Bipolar disorder comorbidity



McElroy S, et al. Am J Psychiatry 2001;158:420–6

Personality disorders in bipolar II



Vieta et al 1999

Risk factors for difficult-to-treat depression

- Comorbid personality disorders
  - Inconsistent views re impact: Negative (e.g. Thase 1996), no difference (e.g. Perry et al. 1999)
- Comorbid anxiety disorders (Rosenbaum et al. 2001)
  - Comorbid panic associated with longer time to remission, increased suicide, increase recurrence and greater impairment (Alpert & Lagomasino 2001)
- Comorbid substance abuse (Nunes et al. 1996)
  - Even moderate use of alcohol has negative impact on outcome (Worthington et al. 1996)
- Comorbid medical illnesses (O'Reardon & Amsterdam, 2001)
- Other factors (Fagiolini & Kupfer, 2003)
  - Female sex, older patients, early onset, delay in treatment onset, family history,
  - Lower SE status, non-supportive environment, family stress, multiple losses, work dysfunction
  - Poor compliance (accounts for 20% of TRD)

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Depression: Interpersonal

- The patient
  - Thinks you could save her but consider herself too insignificant
  - Thinks you must think her to be as worthless as she thinks she is
- You
  - Want to rescue the patient and do too much
  - Can get angry, bored, unduly pessimistic

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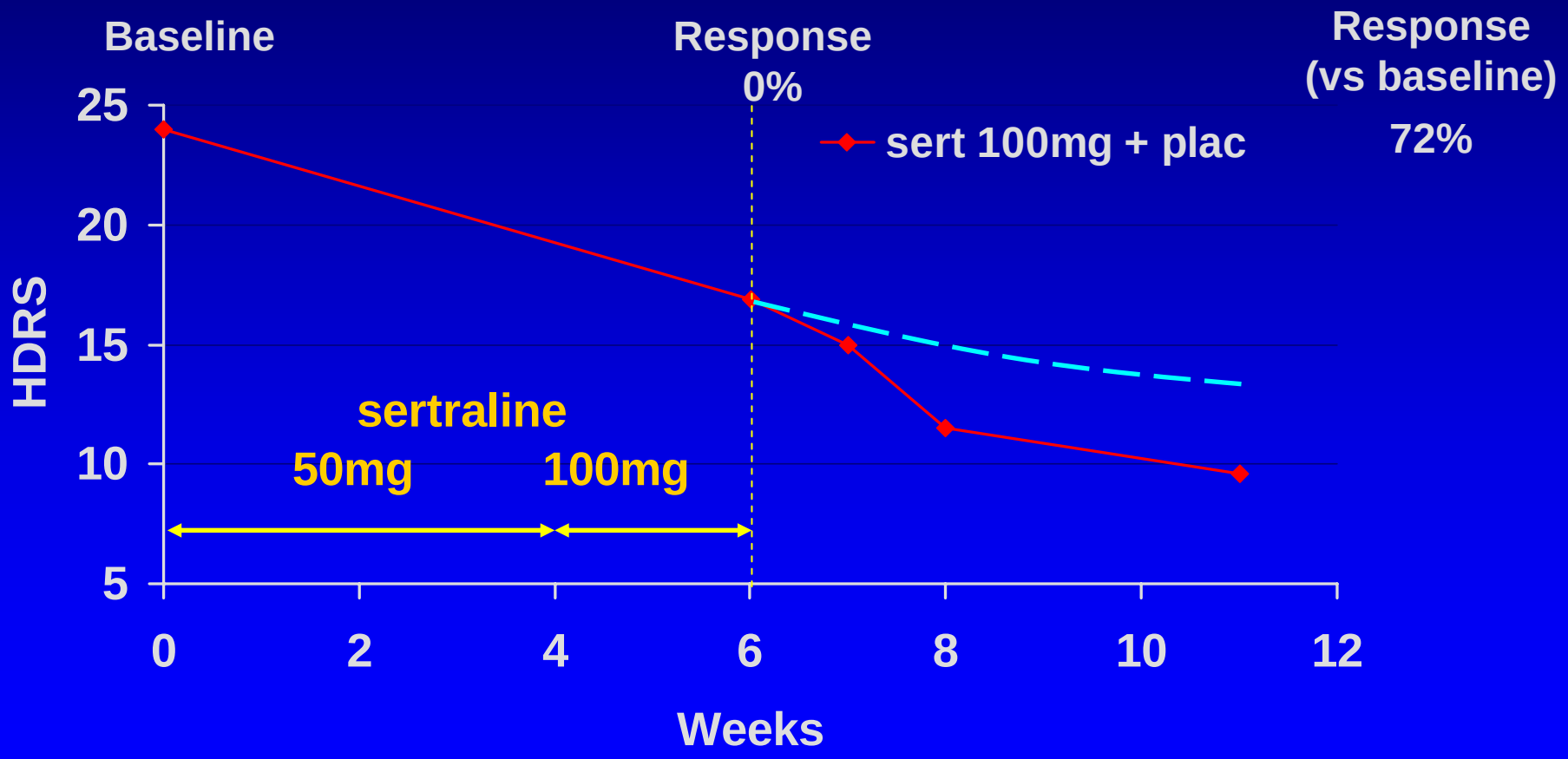
Non-response at 6 weeks: continuation of same dose sertraline



Licht & Qvitzau 2002

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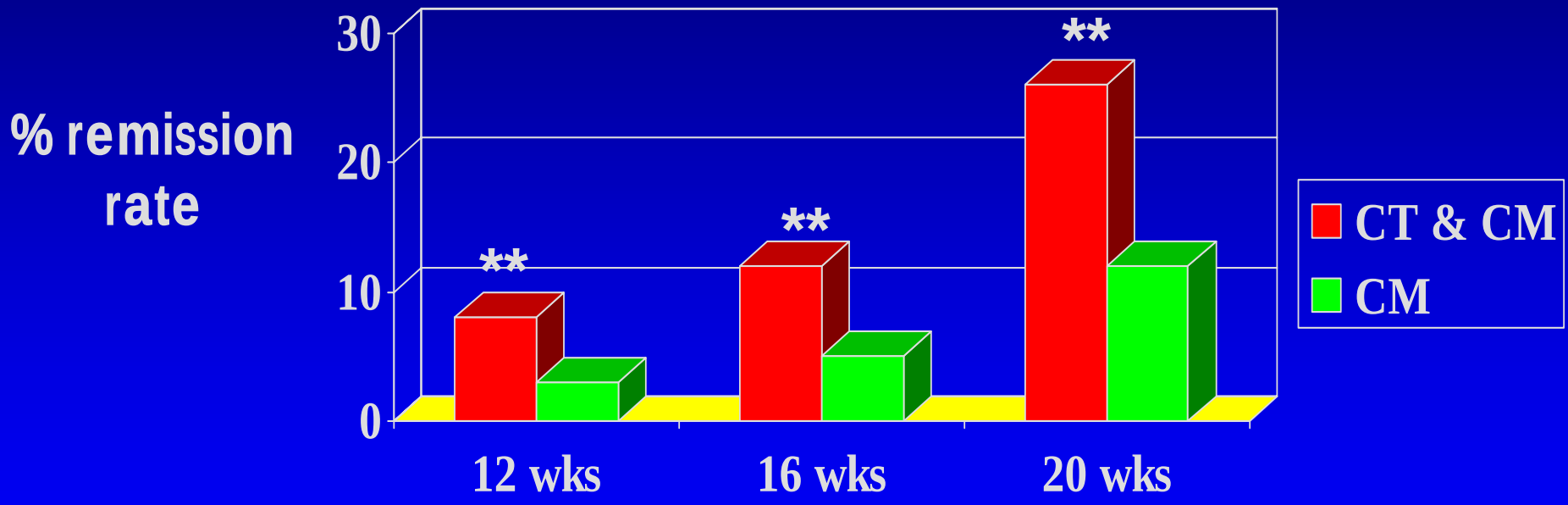
Non-pharmacological strategies: Schizophrenia

- Brief CBT for schizophrenia
- Turkington et al. (2002) B.J.Psych 180, 523-527
  - Pragmatic RCT of 422 patients (2:1)
  - CPN delivered CBT of up to 6 X 1hr sessions
    - Assessment and engagement, developing explanations, symptom management, adherence, core beliefs in relapse prevention
  - Booklets for patients and carers
  - Improvement in symptomatology and insight

MRC RCT of adjunctive CBT in depression: cumulative remission rates

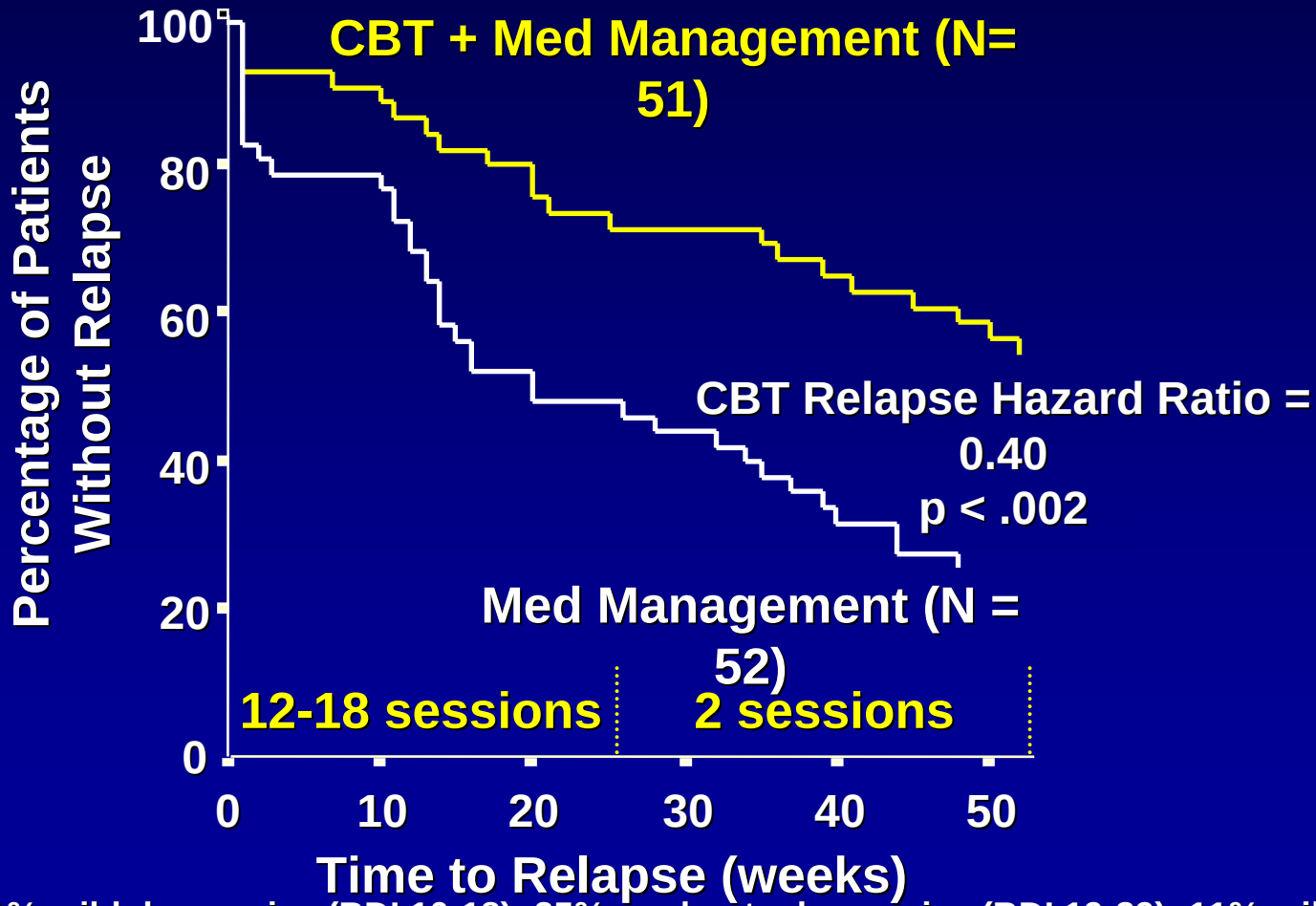


** Adjusted hazard ratio for remission = 2.42 (95% ci 1.1-5.5); p=0.03

Paykel et al 1999

12-Month Randomized Adjunctive Cognitive Behavioral Therapy Versus Med Management for Bipolar I Relapse Prevention

Cognitive Behavioral Therapy Effective Over First 12 Months

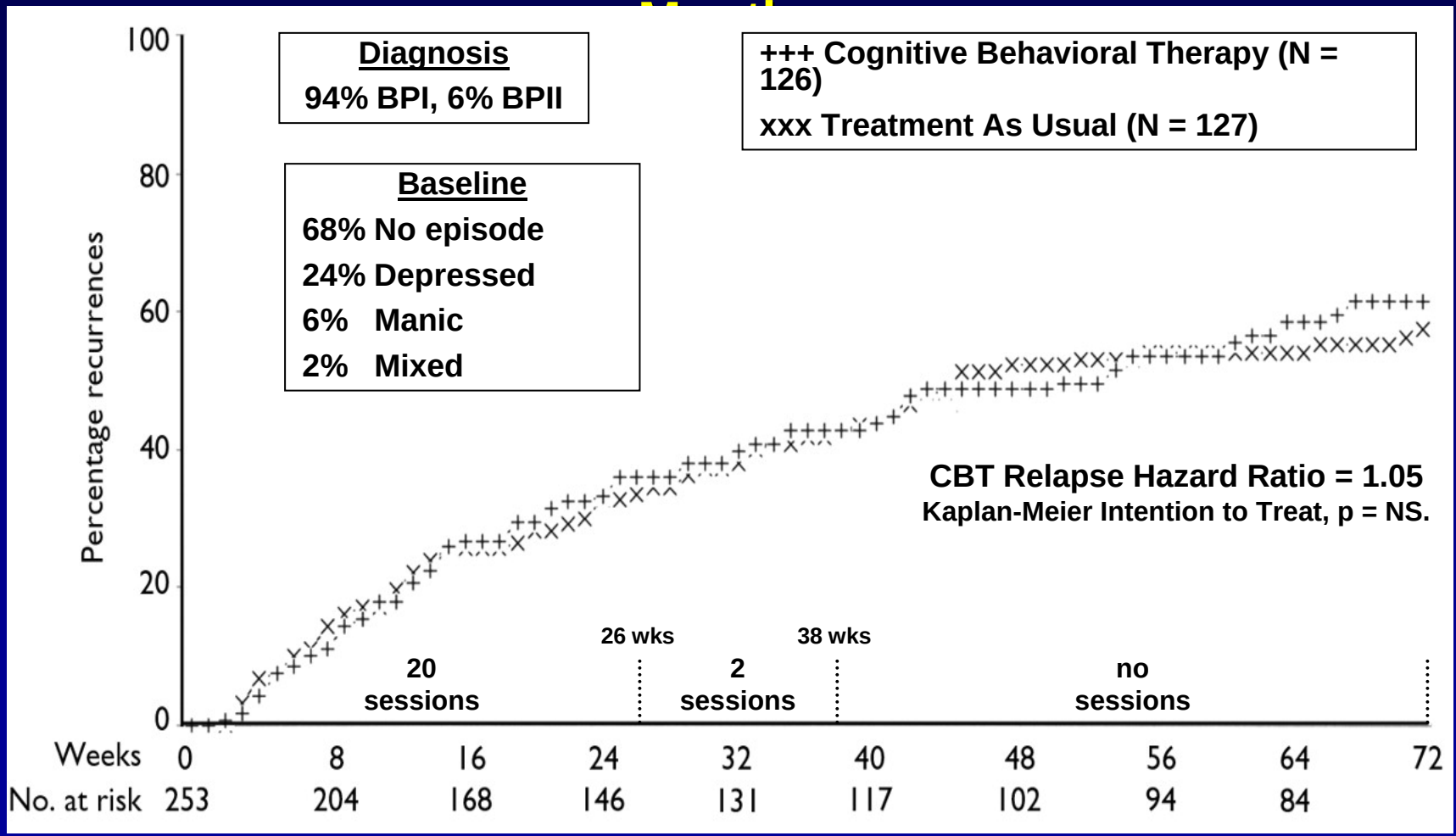


Baseline: 31% mild depressive (BDI 10-18); 25% moderate depressive (BDI 19-29); 11% mild hypomanic (MRS 6-9)

Lam DH, et al. Arch Gen Psychiatry 2003;60:145-52.

18-Month Randomized Adjunctive Cognitive Behavioral Therapy Versus Treatment As Usual in Severe Recurrent Bipolar Disorder

Cognitive Behavioral Therapy Not Effective Over 18 Months



Scott J, et al. Br J Psychiatry 2006;188:313-20.

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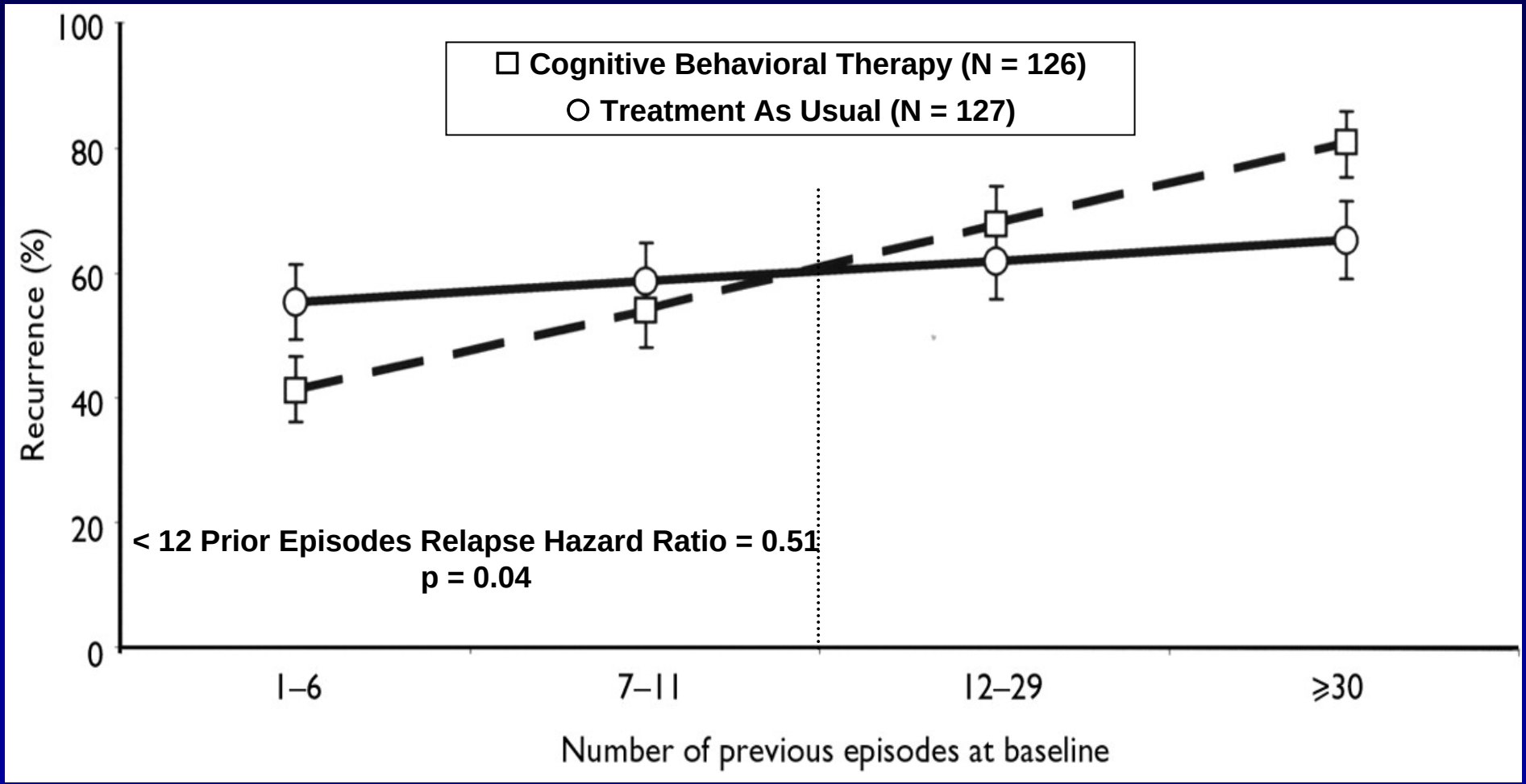
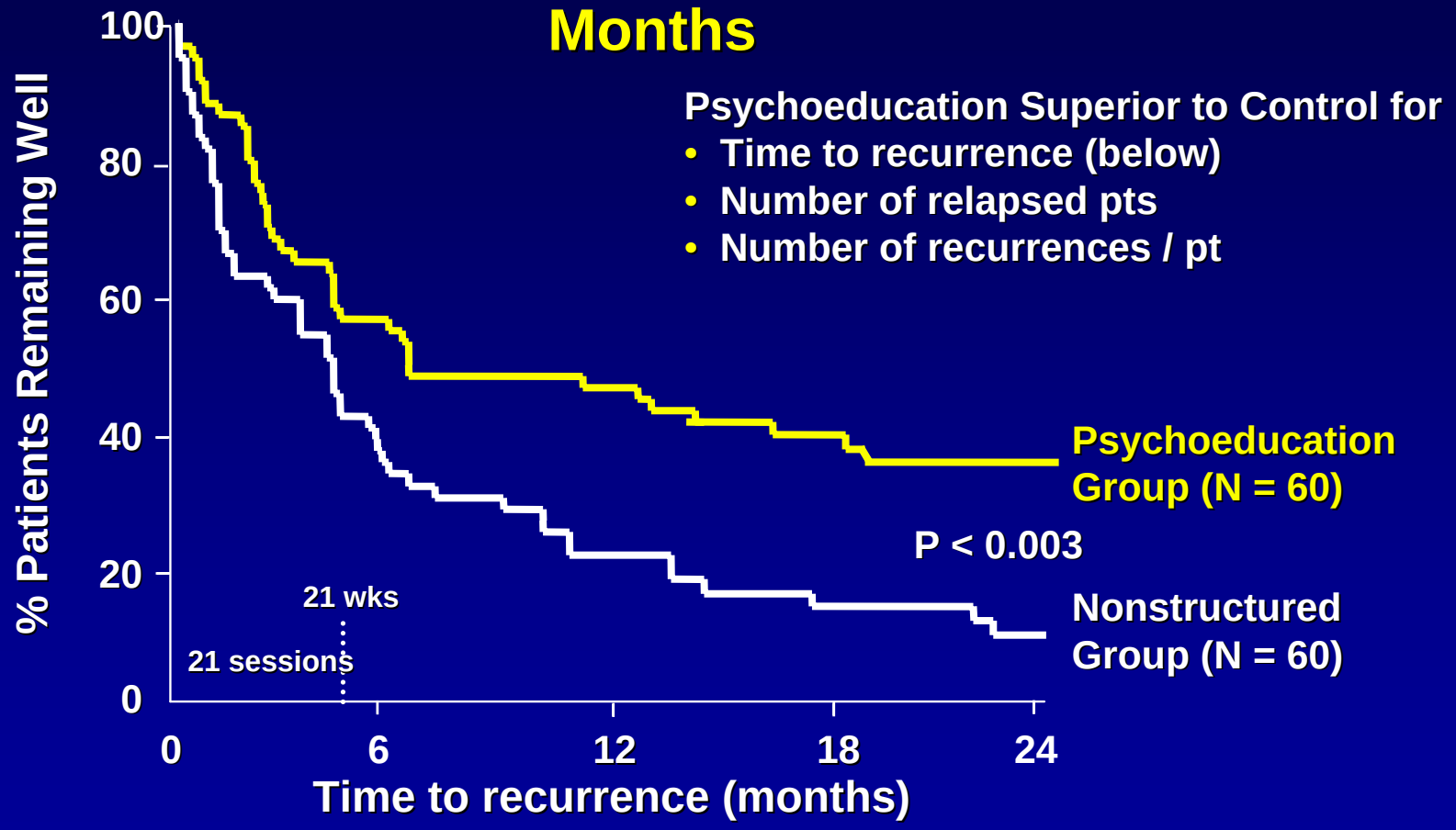
CBT Only Effective in Patients with < 12 Prior Episodes



Scott J, et al. Br J Psychiatry 2006;188:313-20.

24-Month Randomized Adjunctive Psychoeducation Versus Nonstructured Group Prophylaxis in Bipolar Disorder

Psychoeducation Group Effective Over 24 Months



83% BPI, 17% BPII, euthymic > 6 months at baseline.

Colom F, et al. Arch Gen Psychiatry. 2003;60:402-7.

Benefit evident after end of 21-week psychoeducation group.

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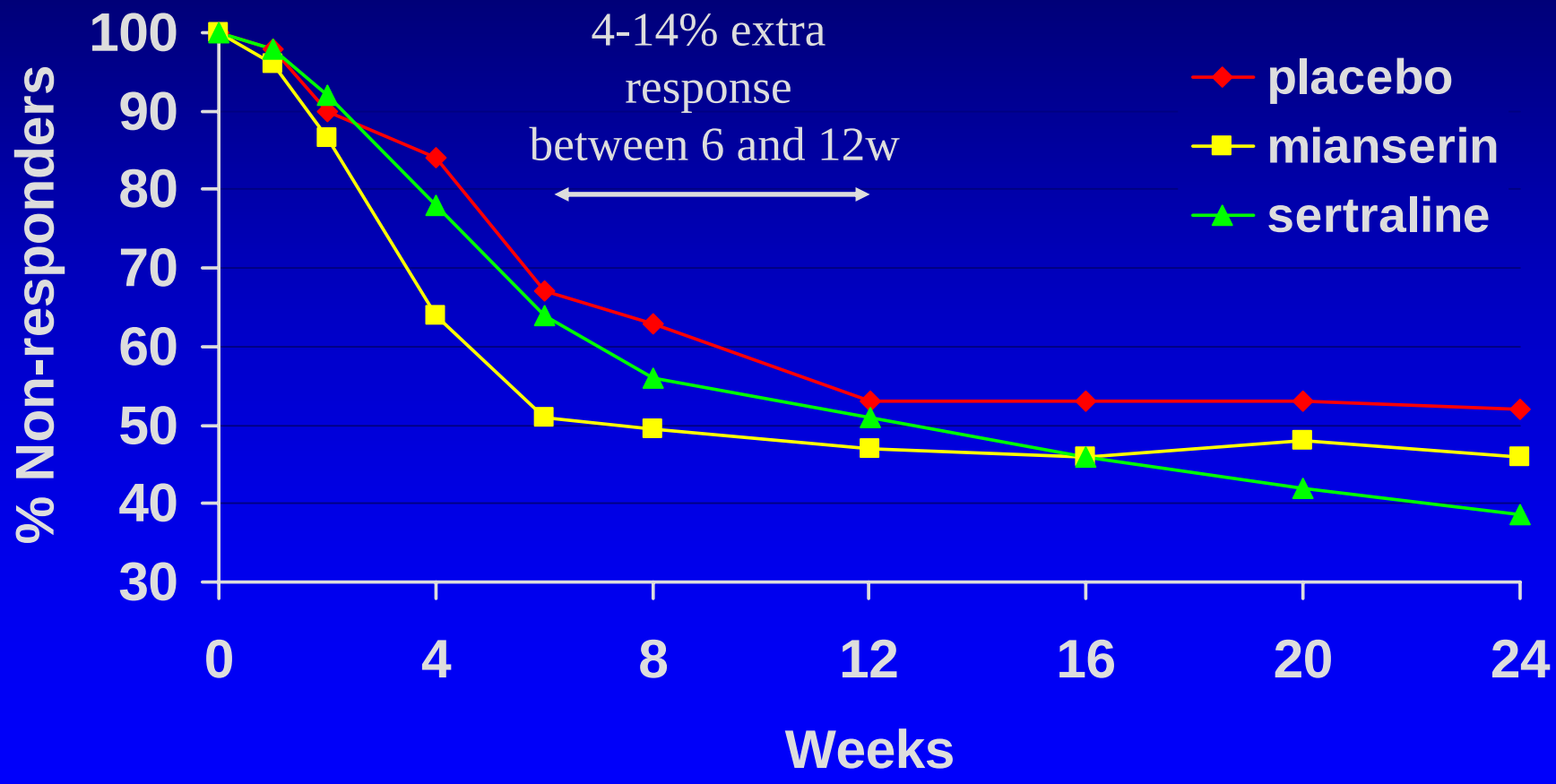
Depression: how long is an adequate trial?



Malt et al 1999

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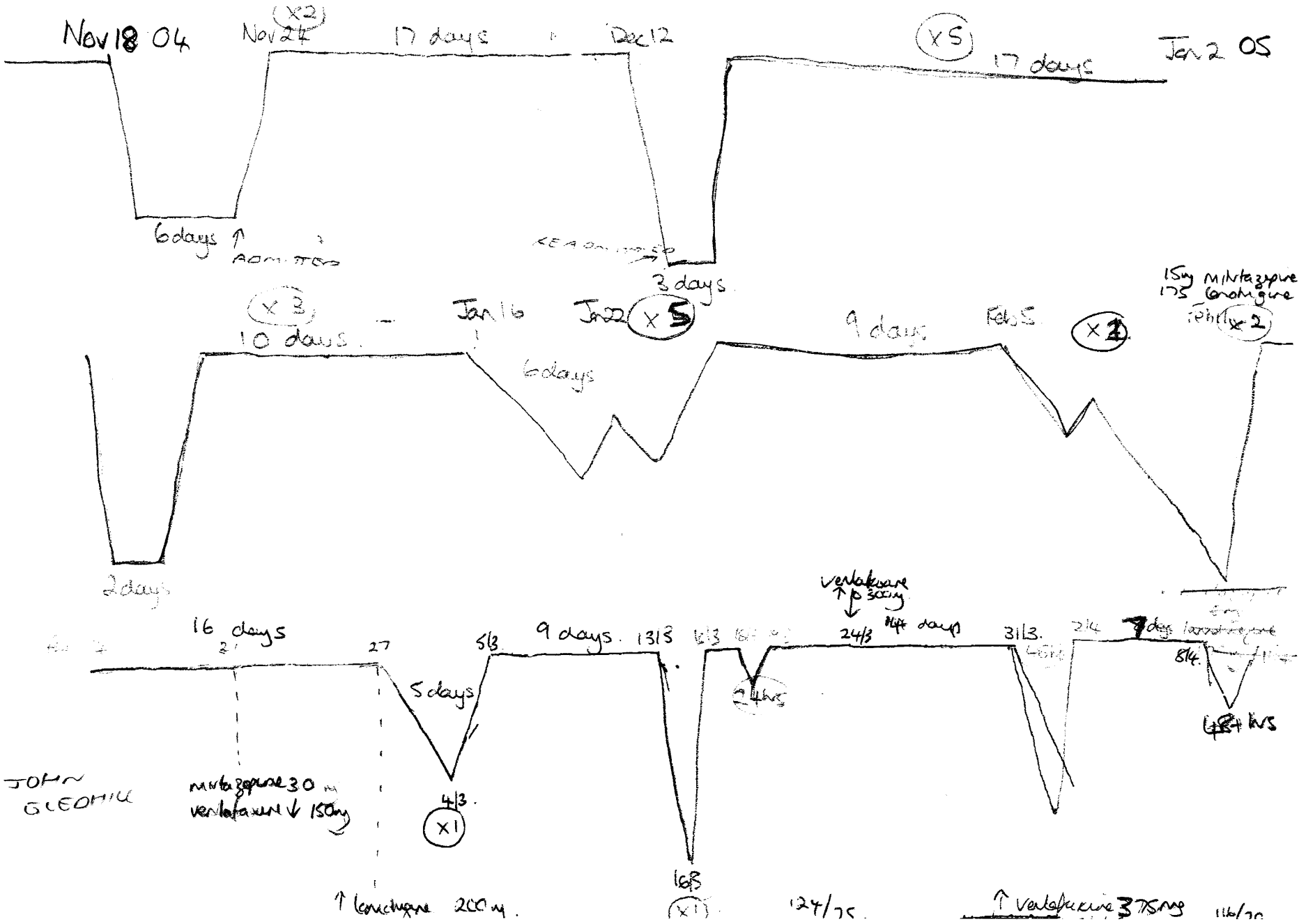
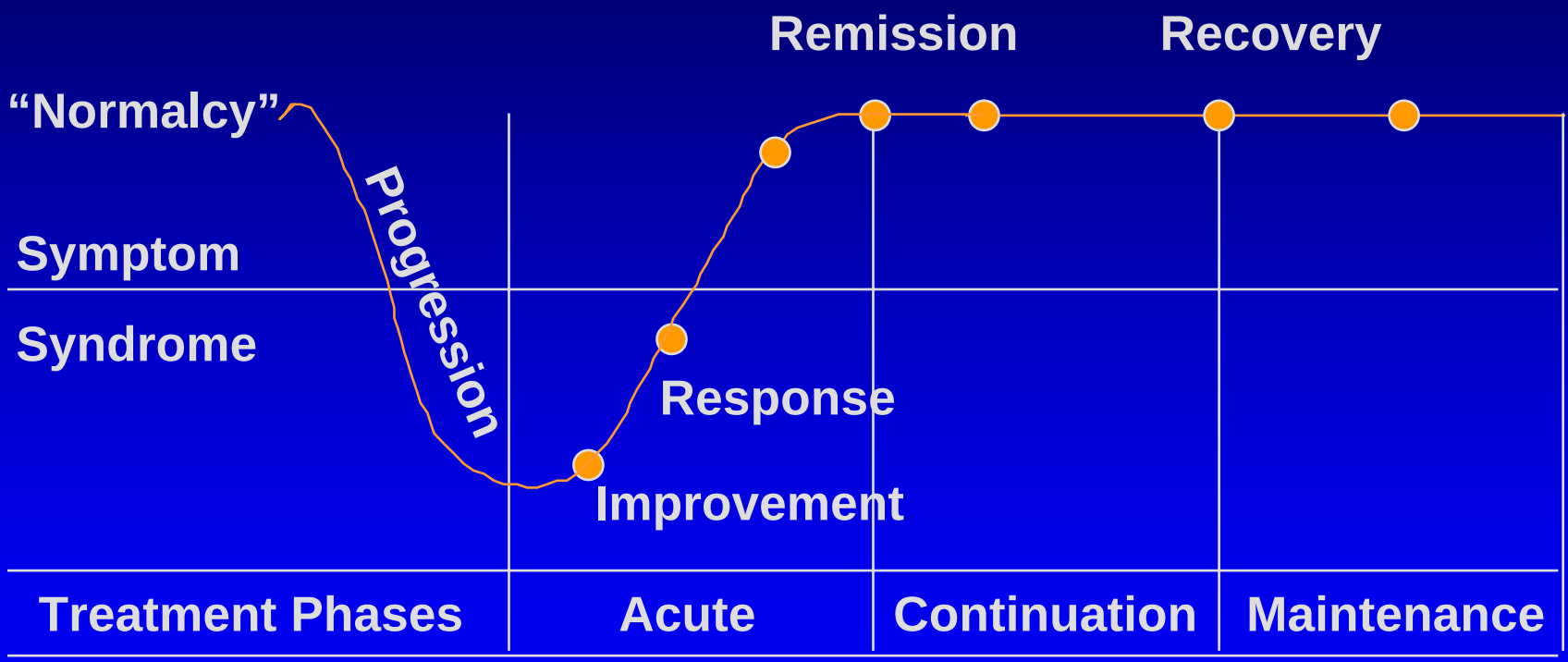

Nov 18 04
Nov 24
(X2)
17 days
Dec 12
X5
17 days
Jan 2 05
6 days
3 days
X3
10 days
Jan 16
Jan 22
X5
6 days
9 days
Feb 5
X1
X2
2 days
16 days
5 days
9 days
5/3
4/3
X1
16/3
X1
24/3
31/3.
8/4.
JOHN
GLEOHIU
124/75.

Course and outcome of depression



Adapted from Kupfer 1991.

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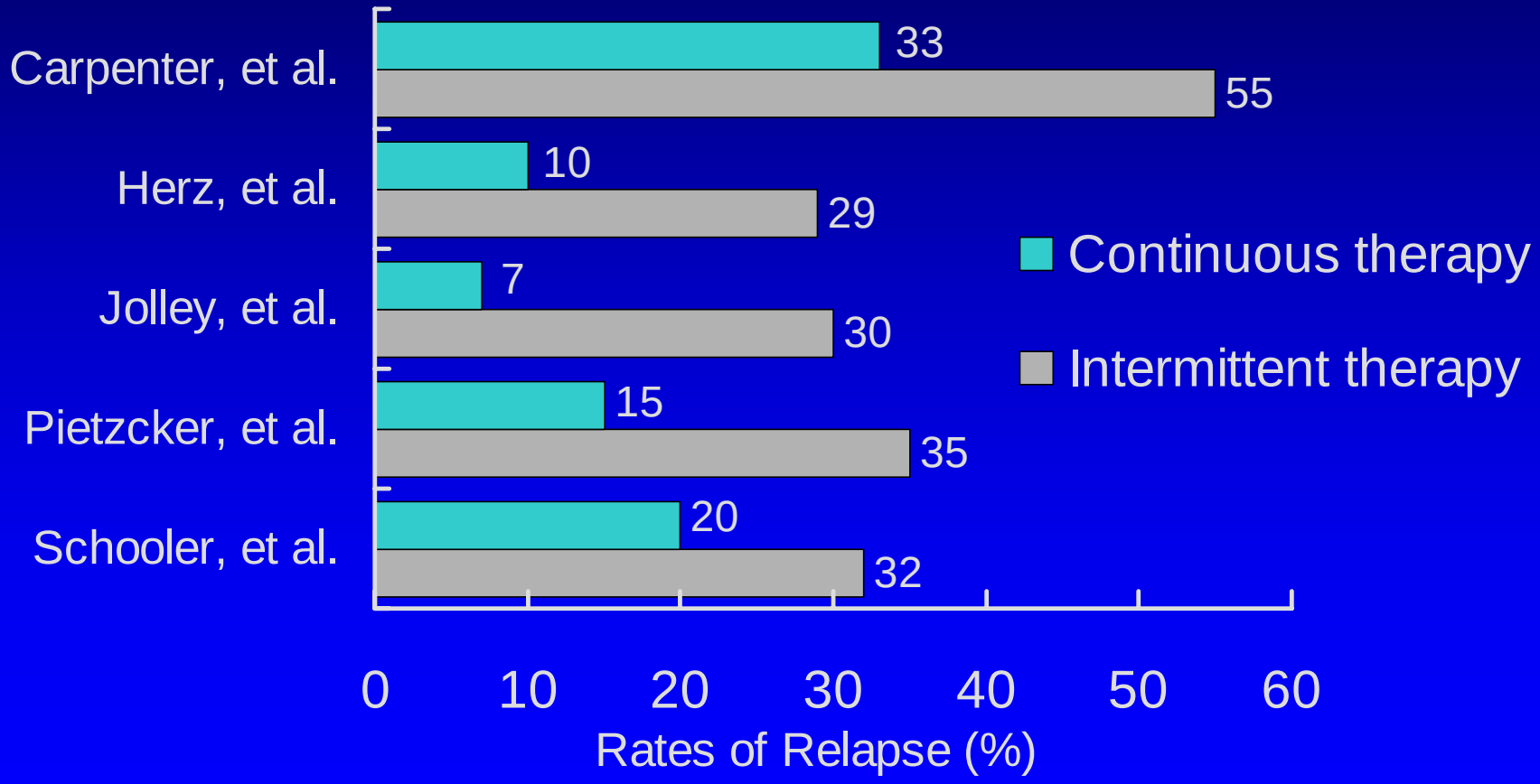
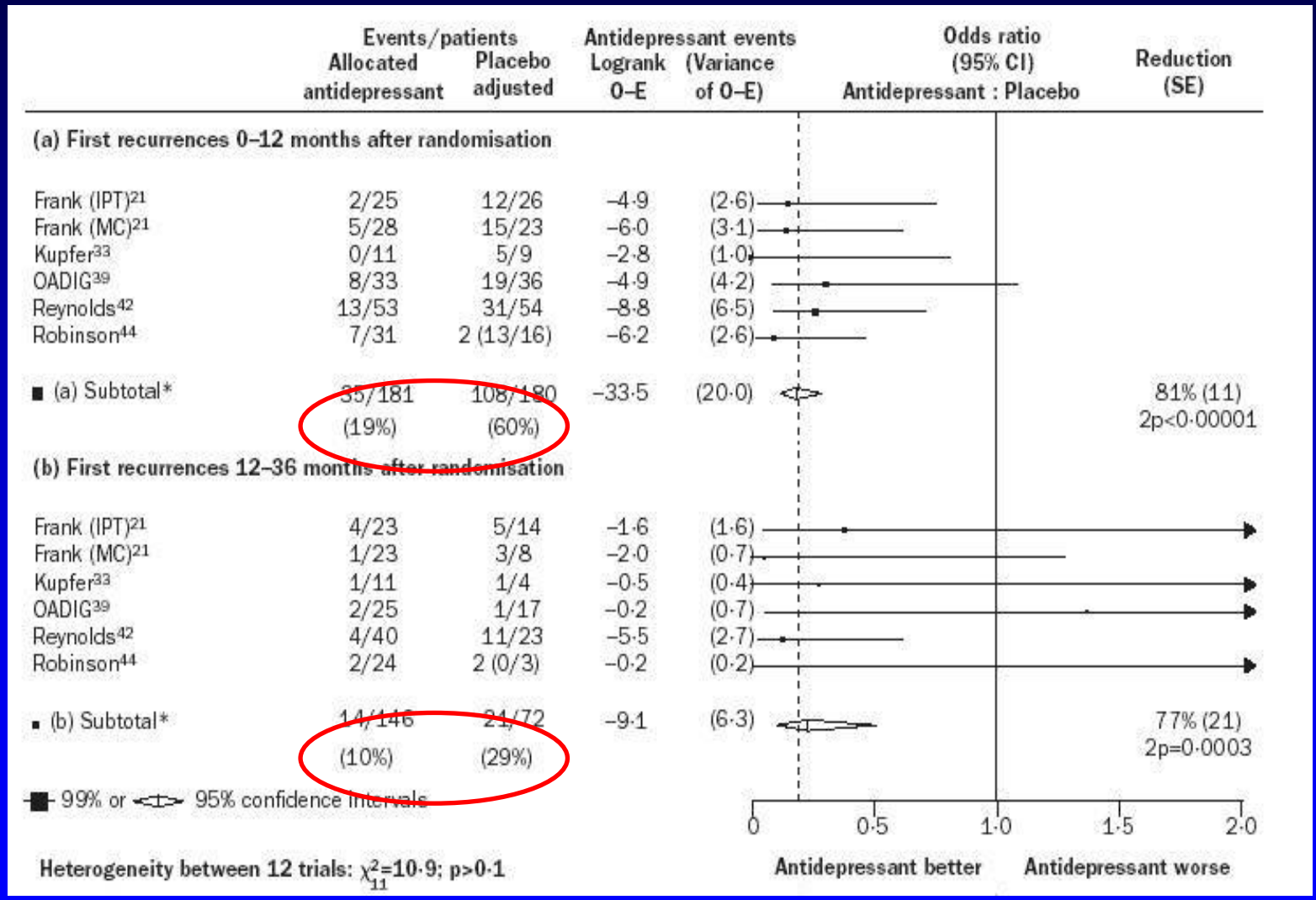
Continuous vs intermittent maintenance: 1 year relapse rates



Kane et al, 1996. N Engl J Med;334:34-41.

Reduction in the risk of relapse with continuation of antidepressants



Geddes et al 2002

Schizophrenia

NHS
National Institute for Clinical Excellence

NICE Clinical Guideline

Core interventions in the treatment and management of schizophrenia in primary and secondary care

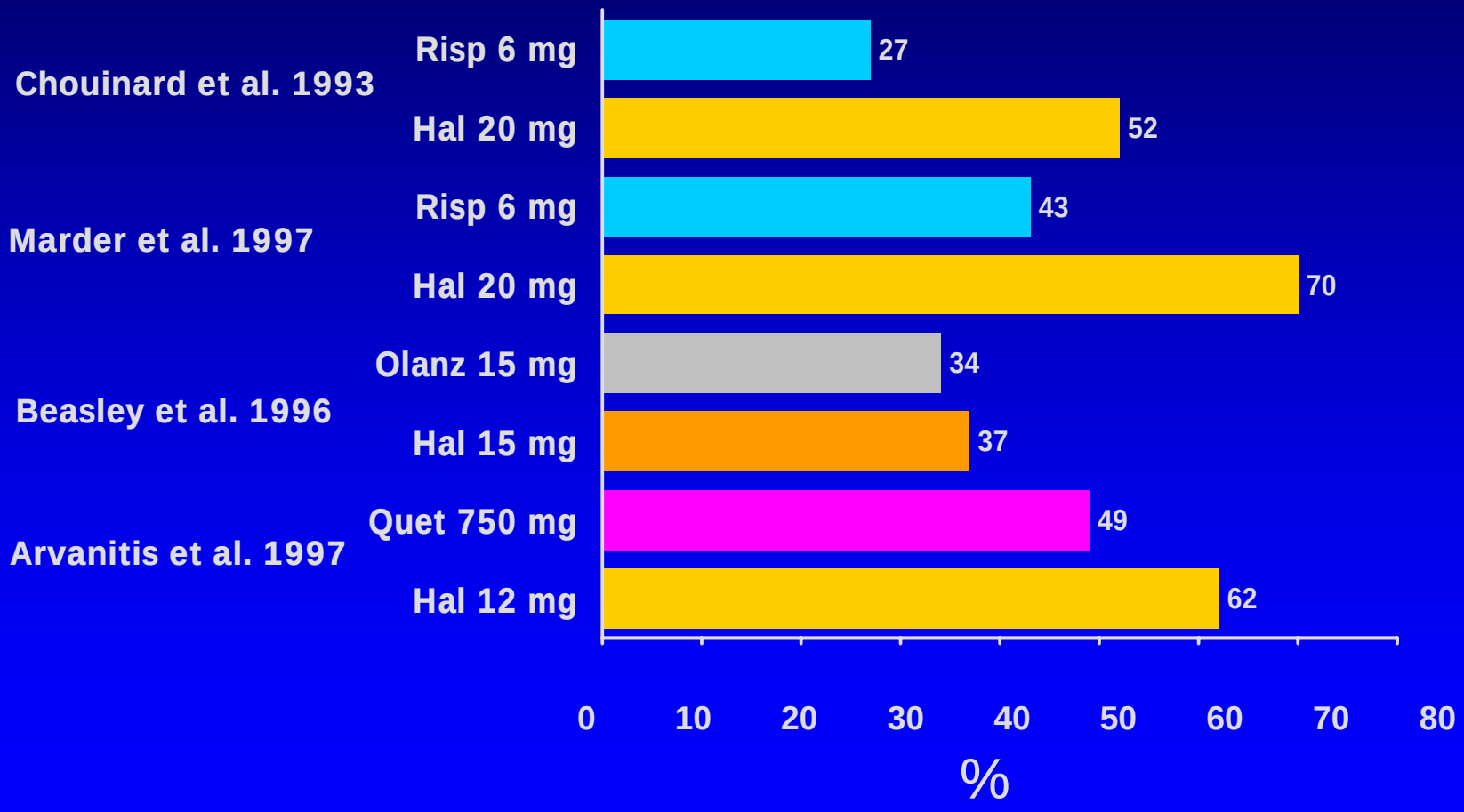
Treatment-resistant Schizophrenia: Pharmacological Strategies

Antipsychotic drugs

- SGA vs FGA
- High-dose antipsychotics
- Clozapine
- Other SGAs
- Combined antipsychotics

- Adjunctive treatment
  - Lithium
  - Carbamazepine
  - Sodium valproate
  - Lamotrigine
  - Antidepressant
  - Benzodiazepine
  - ECT

RCTs: SGAs v FGAs
Proportion Of Patients Not Meeting 20% Improvement Criteria



High V Standard Dose Conventional Antipsychotics

- No RCTs shows a significant advantage for high dose
- Lack of consistent criteria for TRS in RCTs
- Wide variation in high/mega doses used
- Improvement in a proportion of patients in both standard and high-dose treatment groups
- Findings do not preclude individual responses to high dosage
- High/mega dosages associated with greater frequency/severity of EPS

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Clozapine

Landmark, 6-week, double-blind trial *(Kane et al 1988)*

Patients

- 319 (256 male, 63 female) with schizophrenia
- Mean age 36 years
- Rigorous criteria for treatment resistance + prospective study of high dose haloperidol

Method

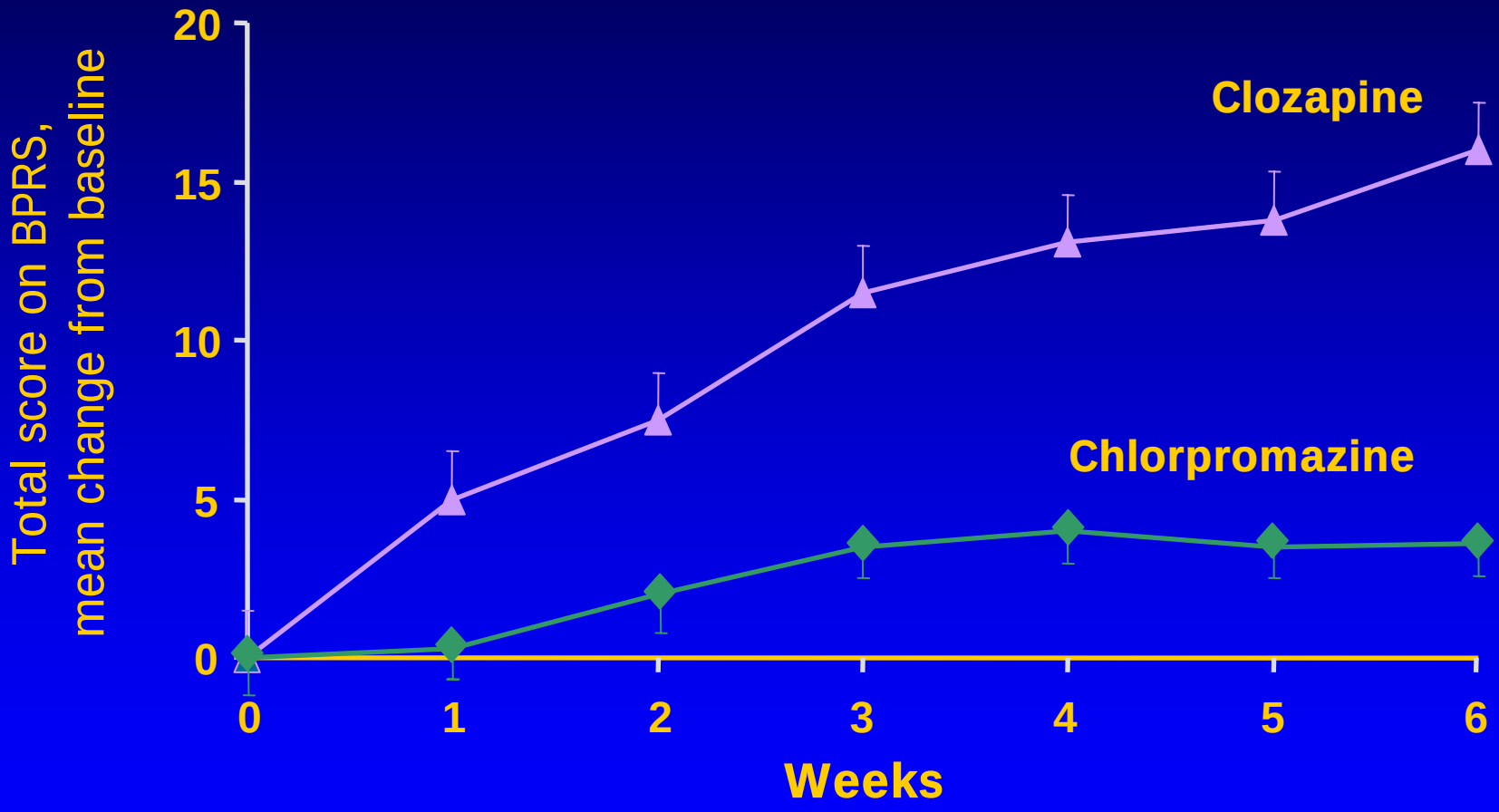
Random assignment to either:

clozapine (up to 900 mg a day) alone, or

chlorpromazine (up to 1800 mg a day)

+ benztropine mesylate (up to 6 mg a day)

Clozapine vs Chlorpromazine in Treatment-resistant Schizophrenia



***P*<0.001** during each week of study.
BPRS = Brief Psychiatric Rating Scale.

Kane et al. *Arch Gen Psychiatry*. 1988;45:789.

Clozapine
Efficacy in TRS

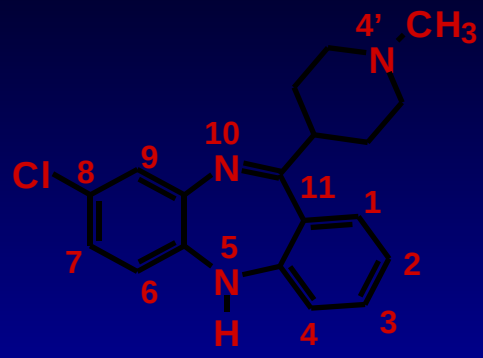
Systematic review/meta-analysis of 31 RCTs
(Wahlbeck et al 1999)

- Convincing superiority in clinical improvement, relapse prevention and acceptability
- Greater clinical improvement in TRS studies
- Relative absence of functional and social outcomes

BUT

- 20-30% reduction in symptom scores in less than half *(Chiene et al 1999, Chakos et al 2001)*
- Around 30% have inadequate response *(Buckley et al 2001)*

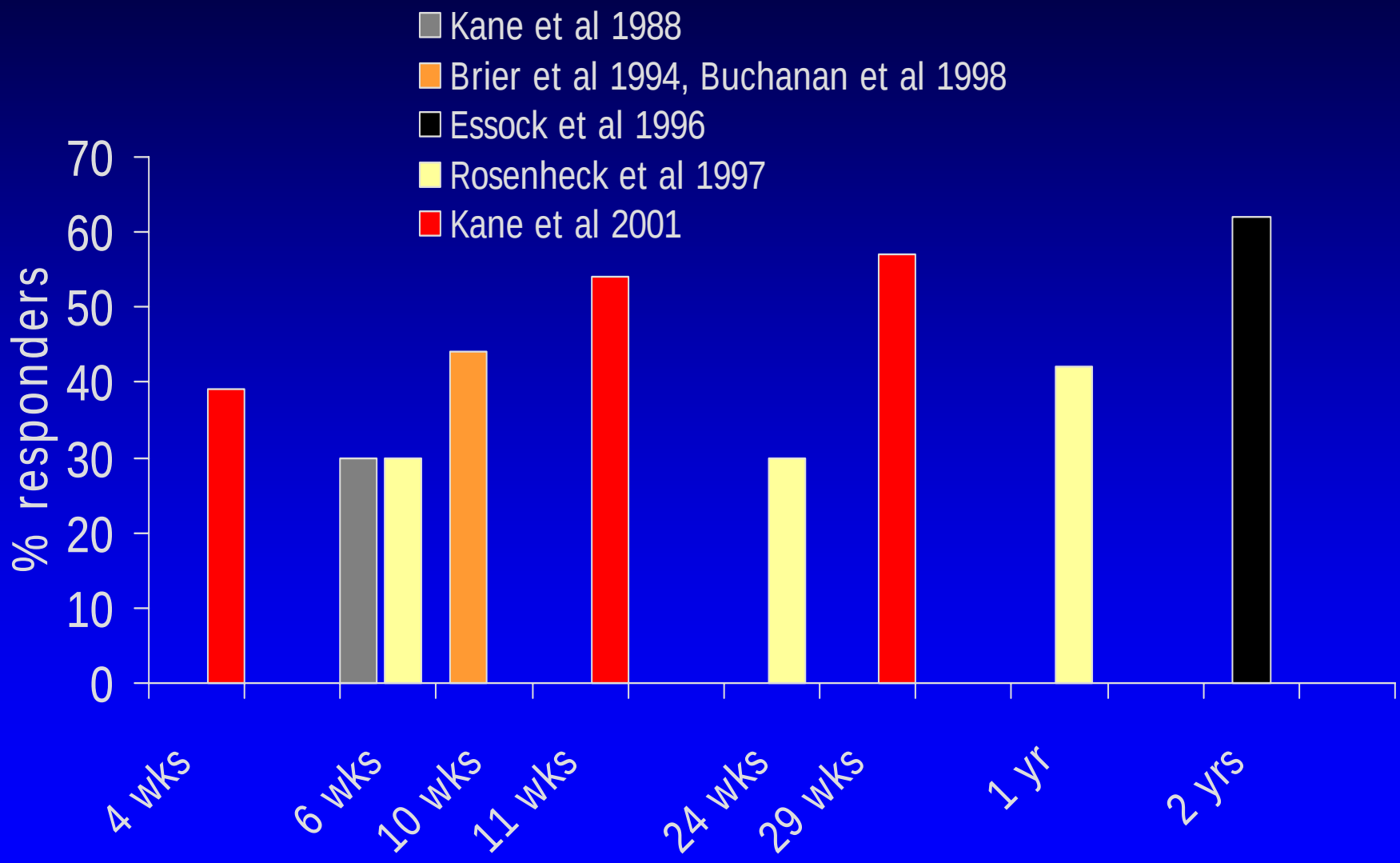
Clozapine Efficacy



Claims for specific, positive effects on:

- Hostility/aggression
- Disorganisation and affective symptoms in schizoaffective disorder
- Cognitive function (verbal fluency/attention)
- Suicidality *(Meltzer et al 2003)*
- Smoking

Response To Clozapine In Comparative Trials



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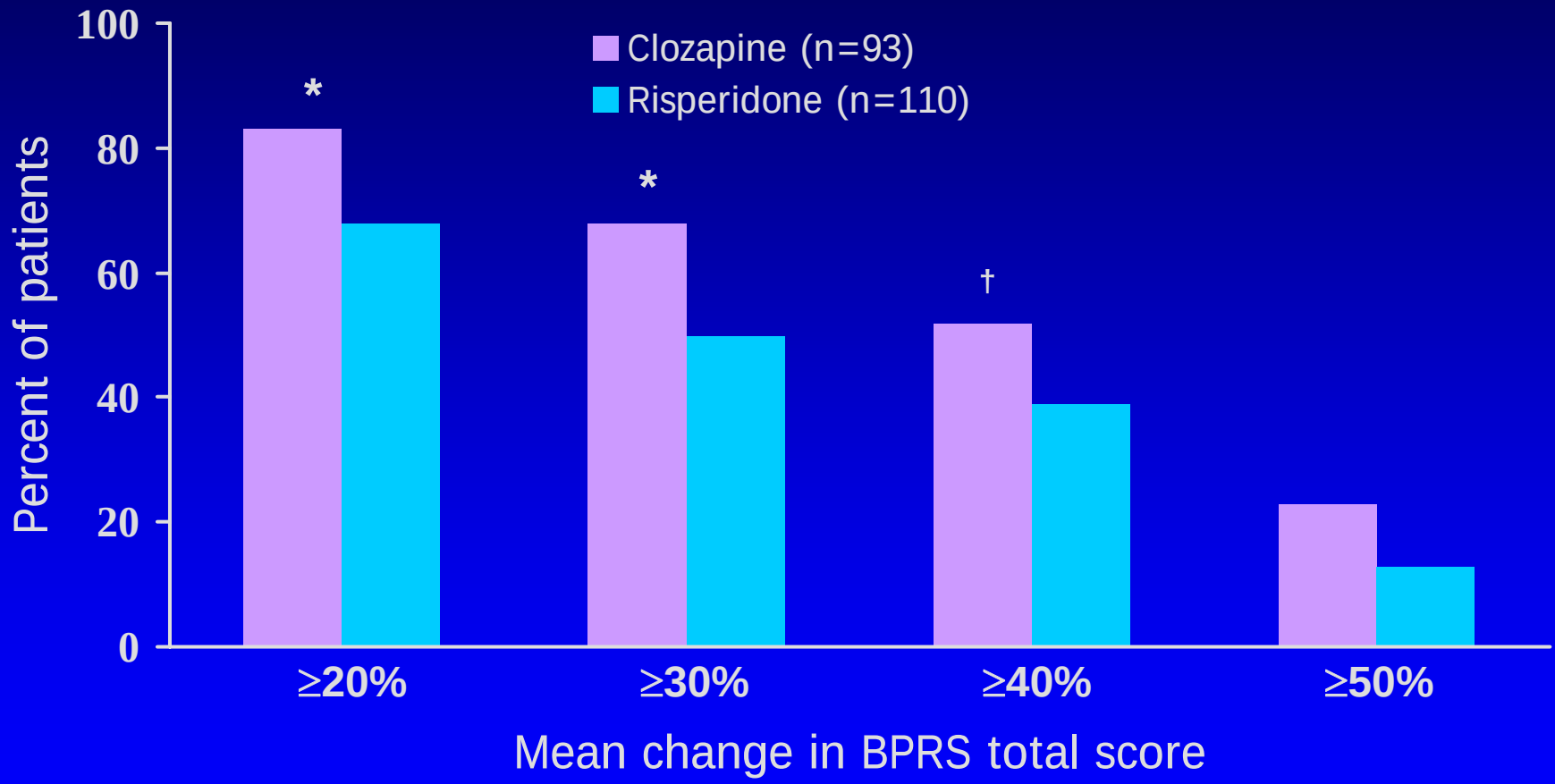
Clozapine vs Risperidone in Severe Chronic Schizophrenia: Mean Change In BPRS



*$P<0.01$, †$P<0.05$.

Azorin et al. *Am J Psychiatry*. 2001;158:1305.

Treatment-resistant Schizophrenia: Olanzapine

- Early clinical reports
  - Possible role for high-dose olanzapine in the management of treatment-resistant schizophrenia

    (Launer 1998, Baldacchino et al 1998, Martin et al 1997, Sheitman et al 1997)
- Controlled studies
  - Versus chlorpromazine (*Conley et al 1998)*
  - Versus clozapine *(Tollefson et al 2001)*
  - Findings not entirely consistent
- Whether moderate to high doses of olanzapine (up to 40mg a day) offer an advantage over standard doses for patients with treatment-resistant schizophrenia, remains to be determined

  (*Dursun et al 1999, Lerner 2003)*

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Treatment-resistant Schizophrenia: Combined Antipsychotics

Consistent recommendations for monotherapy with antipsychotic drugs *(Lehman & Steinwachs 1998, NICE guideline 2002)*

Literature review

- 40% of schizophrenic patients receiving antipsychotic combination *(Cannales et al 1999, Taylor et al 2000)*

Possible Reasons for antipsychotic polypharmacy

- Cross-titration (active or aborted)
- Poor communication between services
- Different target symptom
- Reduce adverse effects
- Different route of administration
- Enhance therapeutic effect

Potential problems with Antipsychotic Polypharmacy

- Higher than necessary total dosage
- Increased side effects (acute or long-term)
- Drug-drug interactions
- Increased risk of non-adherence
- Difficulty determining cause and effect
- Cost
- ? increased mortality
- Lack of evidence

Treatment-resistant Schizophrenia: Combinations with Clozapine

- Combination of **clozapine** and conventional antipsychotic common in clinical practice
  - Conventional antipsychotics added in 30-35% of cases in Denmark *(McCarthy & Terkelsen 1995)*
  - US survey of 906 patients: 18% clozapine + antipsychotic *(Buckley et al 2001)*
- Controlled data lacking but ‘safe and may be potentially efficacious when clozapine has produced less that optimal improvement’ *(Chong & Remington 2000)*

Treatment-resistant Schizophrenia: Combinations with Clozapine

Sulpiride

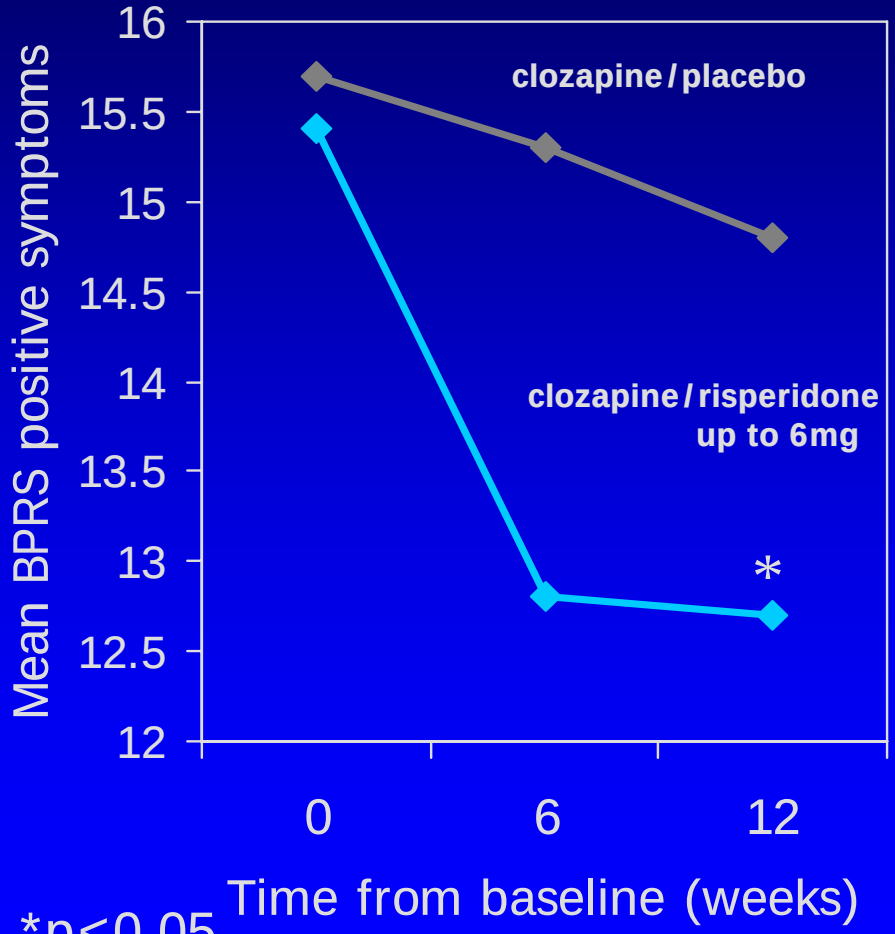
- Double-blind study *(Shiloh et al 1998)*
- Greater reduction in BPRS ($p<0.05$) with sulpiride
- Small sample size (n=28), short duration (10 wks)
- Treatment groups not matched
- Exclusion of complete responders to clozapine

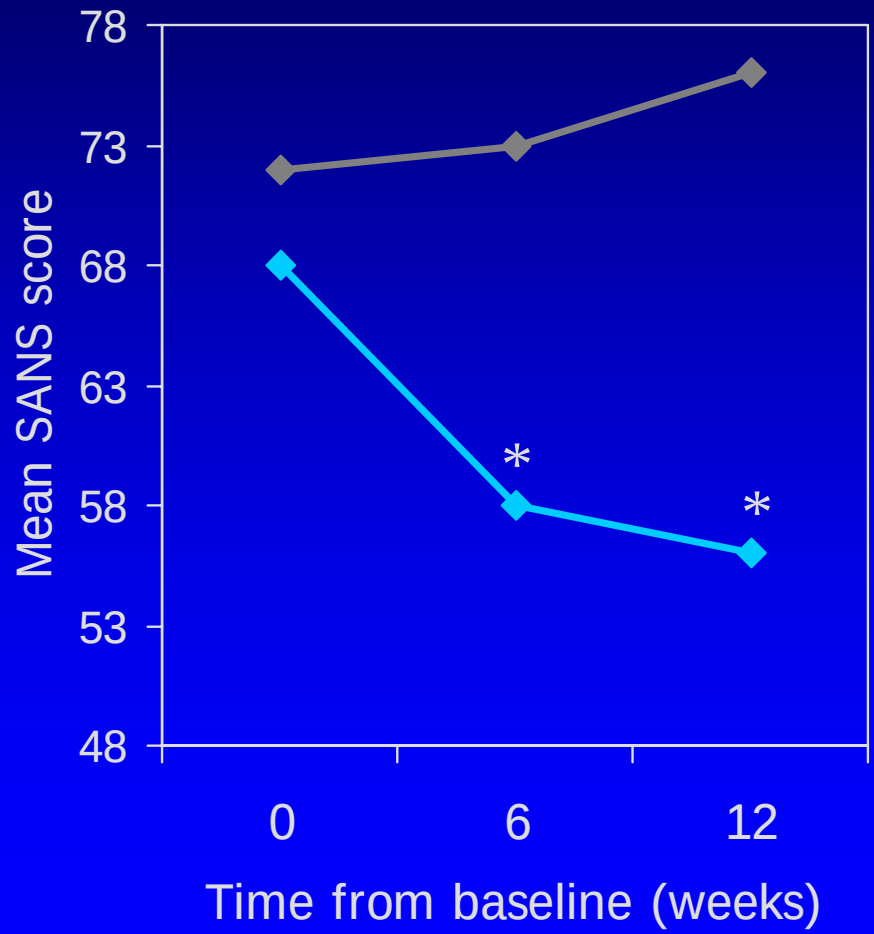
Amisulpride

- Naturalistic study *(Matthiasson et al 2002)*
- 28 of 33 patients completed 6-month study
- 20 (74%) responders (>20% decrease in BPRS)
- No worsening of side effect burden
- Possible pharmacokinetic interaction *(Frick et al 2003)*

Clozapine - Risperidone Combination

- Randomised, double-blind trial of 40 pts
- Unresponsive/partially-responsive to clozapine monotherapy





*p<0.05

Josiassen et al 2005

Clozapine - Risperidone Combination

- 2 other placebo-controlled double-blind studies showing **no** significant benefit

- 6-week, double-blind study *(Yağcioğlu et al 2005)*
- 30 patients with partial response to clozapine
- Risperidone up to 6mg
- Significant improvement in both groups
- Greater improvement in placebo-treated patients on PANSS positive subscale

- 8-week, double-blind study *(Honer et al 2005)*
- 71 patients with partial response to clozapine
- Risperidone 3mg (?low dose)
- Responders (>20% decrease in PANSS):
  - placebo 26%, risperidone 18%
- No significant differences on any variable.

Treatment-resistant Schizophrenia: Pharmacological Strategies

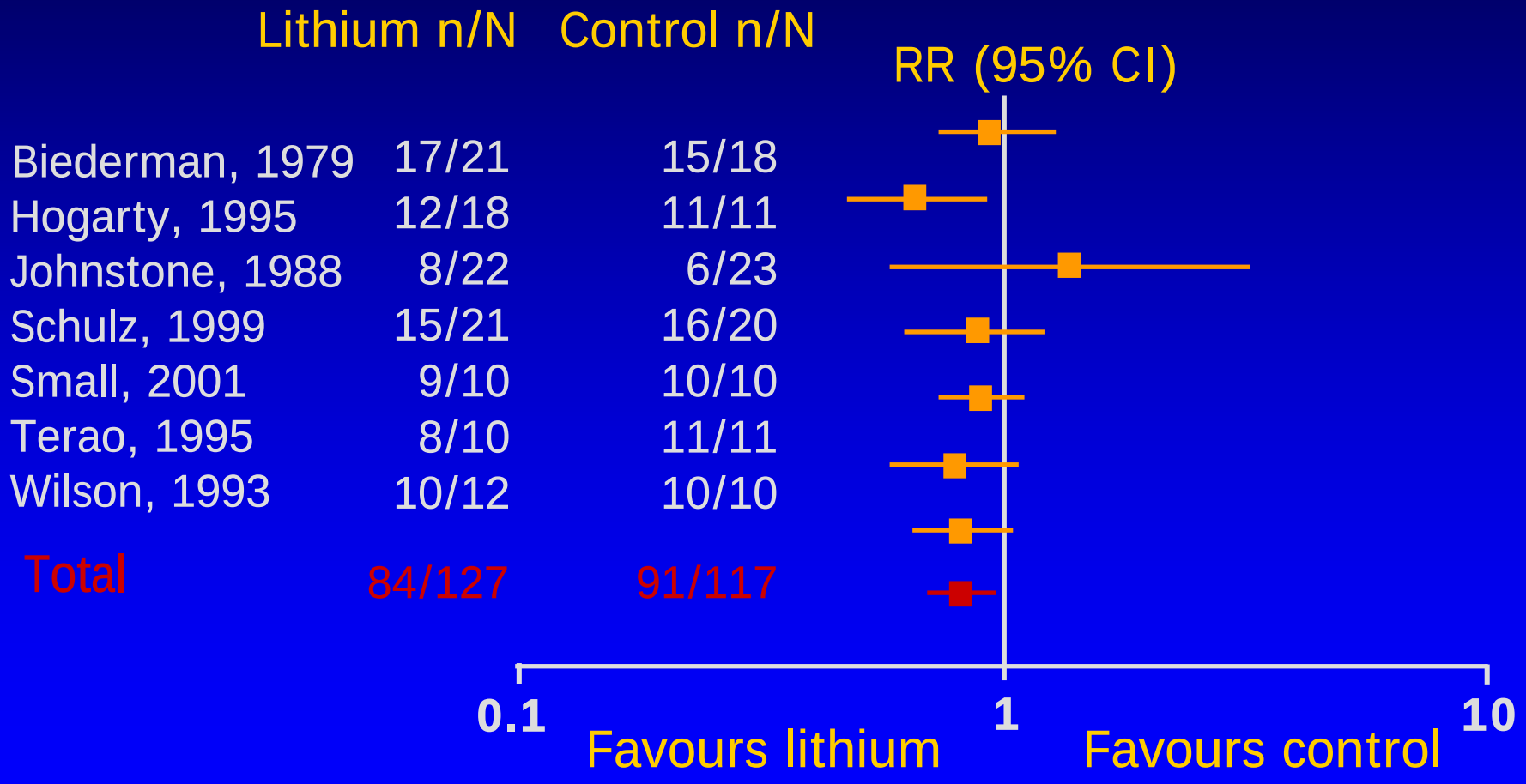
Antipsychotic drugs

- SGA vs FGA
- High-dose antipsychotics
- Clozapine
- Other SGAs
- Combined antipsychotics

- Adjunctive treatment
  - **Lithium**
  - Carbamazepine
  - Sodium valproate
  - Lamotrigine
  - Antidepressant
  - Benzodiazepine
  - ECT

Lithium vs. Placebo Augmentation

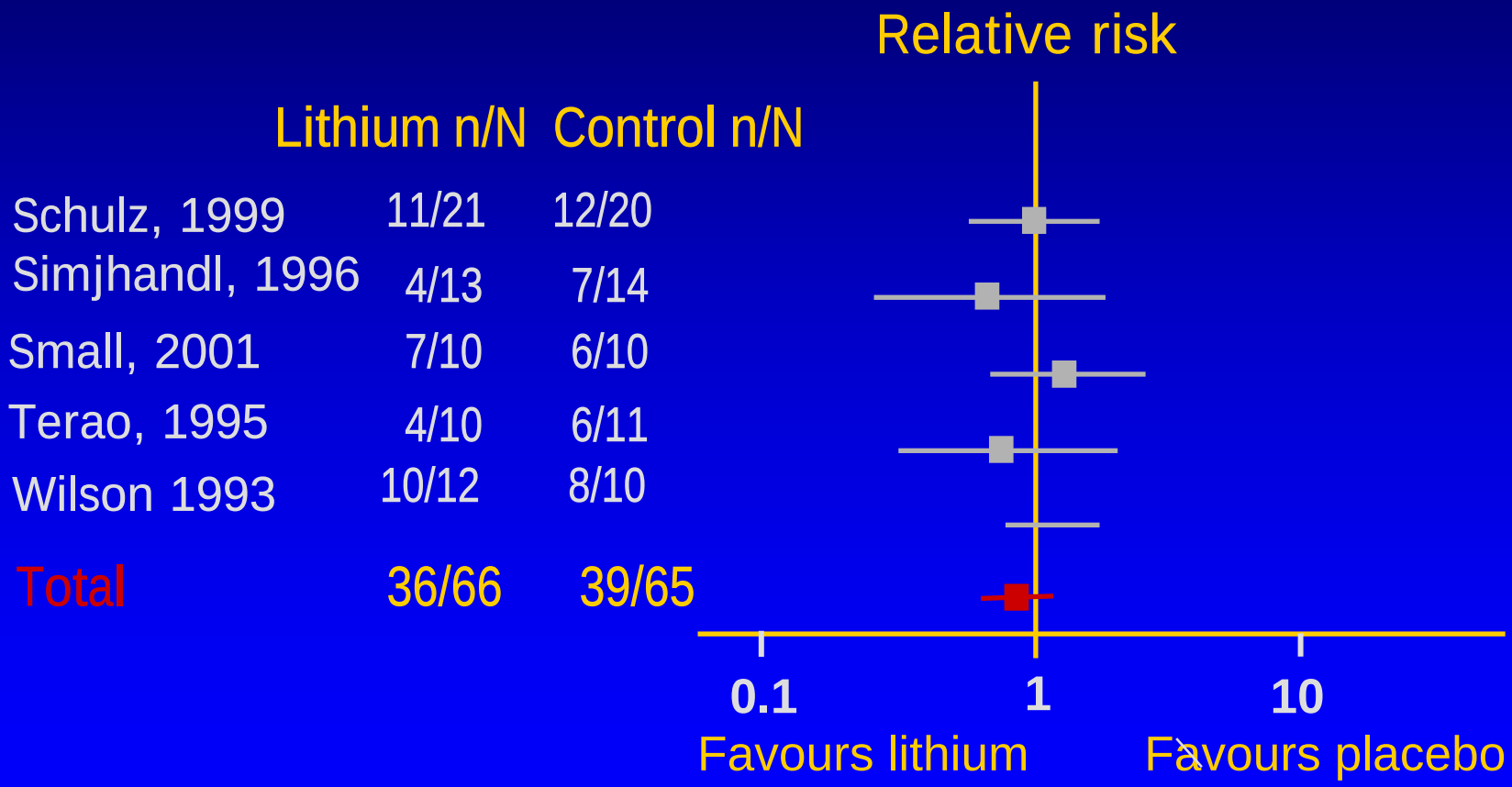
At least 50% scale reduction or CGI much improved



Overall z = -2.51, p=0.01; Leucht S et al.2004. J Clin Psych 65:177-186

Lithium vs. Placebo Augmentation

Number of patients with at least 20% BPRS reduction



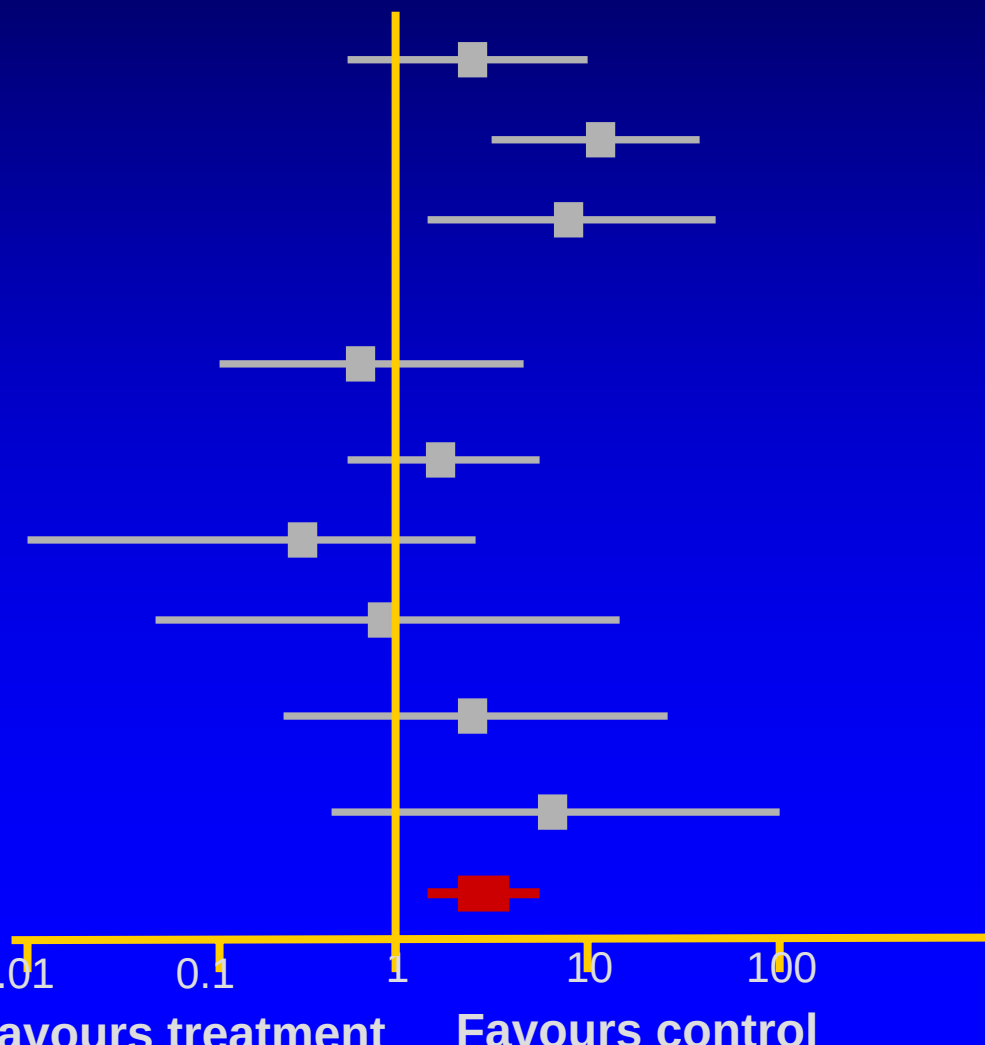
p=0.4; Leucht S et al. J Clin Psychiatry. 2003;160(7):1209-1222

Lithium vs. Placebo Augmentation

Drop out rates

	Lithium n/N	Placebo
Biederman 1979	7/21	3/18
Collins 1991	11/21	1/23
Hogarty 1995	7/18	0/11
Huang 1984	0/6	0/4
Lerner 1988	2/20	3/21
Schulz 1999	14/21	11/20
Simhandl 1996	0/13	2/14
Small 1975	1/12	1/10
Terao 1995	2/10	1/11
Wilson 1993	2/12	0/10
Total	46/154	22/142

2.62 (1.46, 4.71), p=0.0006



Leucht et al. J Clin Psychiatry 2004

Treatment-resistant Schizophrenia: Pharmacological Strategies

Antipsychotic drugs

- SGA vs FGA
- High-dose antipsychotics
- Clozapine
- Other SGAs
- Combined antipsychotics

- Adjunctive treatment
  - Lithium
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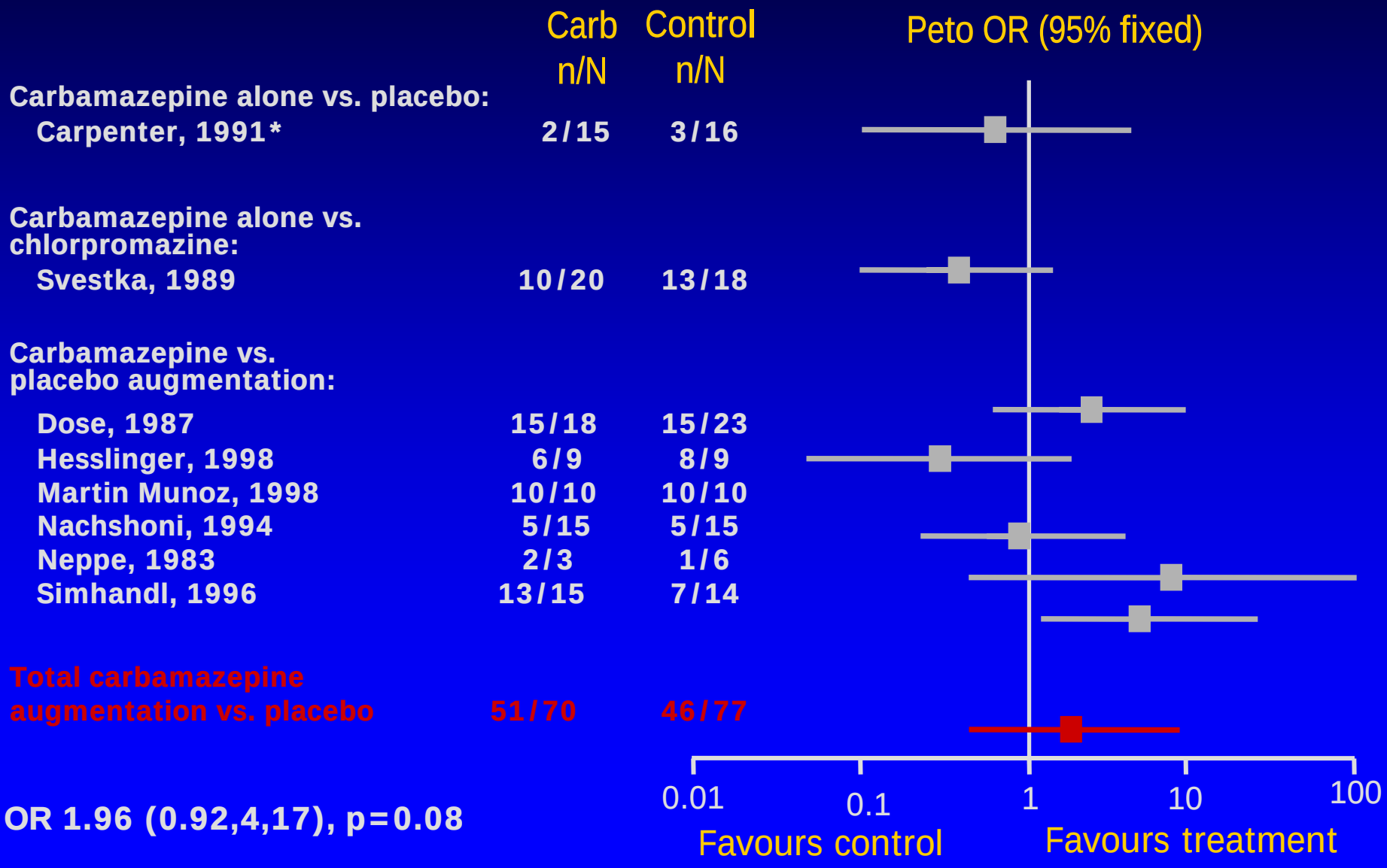
  - Antidepressant
  - Benzodiazepine
  - ECT

Carbamazepine For Schizophrenia

Number of patients with at least 20% BPRS reduction



OR 1.96 (0.92,4,17), p=0.08

Treatment-resistant Schizophrenia: Pharmacological Strategies

Antipsychotic drugs

- SGA vs FGA
- High-dose antipsychotics
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- Other SGAs
- Combined antipsychotics

- Adjunctive treatment
  - Lithium
  - Carbamazepine
  - **Sodium valproate**
  - Lamotrigine
  - Antidepressant
  - Benzodiazepine
  - ECT

Treatment-resistant Schizophrenia: Valproate Augmentation

Adjunctive use increased in schizophrenia in USA

- 12% in 1994, 35% in 1998 *(Citrome et al 2000)*

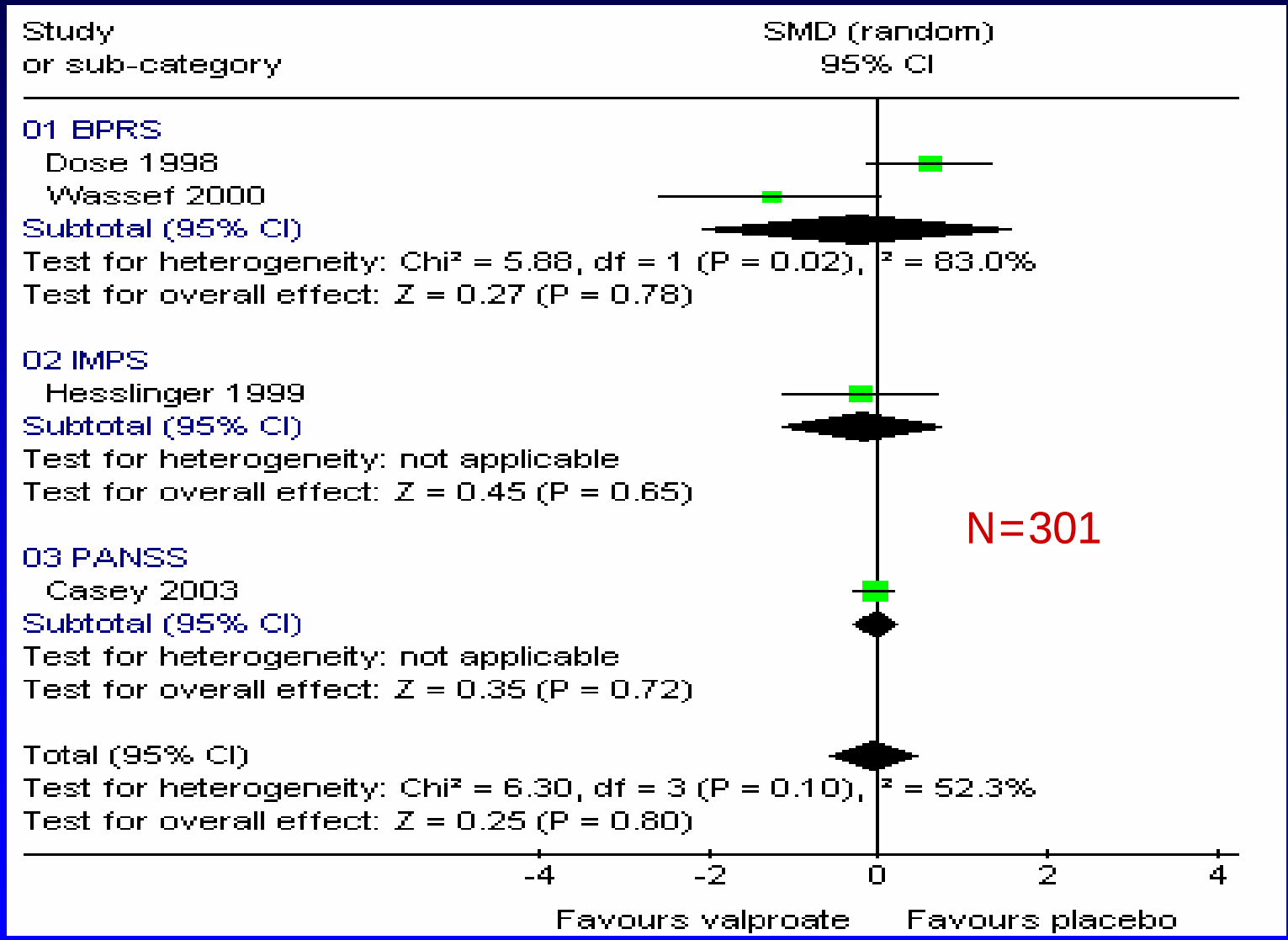
Prophylaxis against clozapine-induced seizures

Improve efficacy of drug regime

Retrospective studies

- Conflicting evidence for benefit
- Reduced hospitalisations *(Reinstein et al 1998)*
- Symptomatic benefit *(Kando et al 1994)*
- Better outcome with clozapine alone *(Wilson 1995)*

Treatment-resistant Schizophrenia: Valproate Augmentation



Basan et al. Schizophrenia Research 2004

Treatment-resistant Schizophrenia: Pharmacological Strategies

Antipsychotic drugs

- SGA vs FGA
- High-dose antipsychotics
- Clozapine
- Other SGAs
- Combined antipsychotics

- Adjunctive treatment
  - Lithium
  - Carbamazepine
  - Sodium valproate
  - **Lamotrigine**
  - Antidepressant
  - Benzodiazepine
  - ECT

Treatment-resistant Schizophrenia: Pharmacological Strategies

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- High-dose antipsychotics
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- Other SGAs
- Combined antipsychotics

- Adjunctive treatment
  - Lithium
  - Carbamazepine
  - Sodium valproate
  - Lamotrigine
  - **Antidepressant**
  - Benzodiazepine
  - ECT

Treatment-resistant Schizophrenia: Antidepressant Augmentation

TCAs

- No reports with clozapine
- Concern about combined anticholinergic effects

SSRIs

- Suggested as adjunctive treatment for negative symptoms *(Zullino et al 2002)*
- Augmenting clozapine
  - Double-blind comparison of adjunctive fluoxetine and placebo. No significant differences in symptomatology between the two treatment groups. *(Buchanan et al 1996)*
  - Increased clozapine plasma level, risk greater for fluvoxamine, fluoxetine and paroxetine *(Hiemke et al 1994, 1996, Spina et al 1998)*

Treatment-resistant Schizophrenia: Pharmacological Strategies

Antipsychotic drugs

- SGA vs FGA
- High-dose antipsychotics
- Clozapine
- Other SGAs
- Combined antipsychotics

- Adjunctive treatment
  - Lithium
  - Carbamazepine
  - Sodium valproate
  - Lamotrigine
  - Antidepressant
  - **Benzodiazepine**
  - ECT

Treatment-resistant Schizophrenia: Benzodiazepine Augmentation

- Reduction reported in anxiety, hostility, excitement, and positive psychotic symptoms
- Therapeutic effects develop rapidly but diminished after a few weeks
- As adjunct to antipsychotic drugs, positive effects are modest and transient.
- No long-term efficacy data

(Wolkowitz and Pickar 1991, Hollister et al 1993 , Hosák & Libiger 2002)

Treatment-resistant Schizophrenia: Benzodiazepine Augmentation

Adverse events

- Sedation
- Dependence
- Withdrawal symptoms
- Disinhibition
- Euphoria
- Aggressive behaviour

Adverse events with Clozapine

- Hypersalivation
- Lethargy
- Delirium/ataxia
- Loss of consciousness
- Cardiorespiratory collapse

(Hosák & Libiger 2002)

Treatment-resistant Schizophrenia: Pharmacological Strategies

Antipsychotic drugs

- SGA vs FGA
- High-dose antipsychotics
- Clozapine
- Other SGAs
- Combined antipsychotics

- Adjunctive treatment
  - Lithium
  - Carbamazepine
  - Sodium valproate
  - Lamotrigine
  - Antidepressant
  - Benzodiazepine
  - **ECT**

Treatment-resistant Schizophrenia: ECT Augmentation

- No controlled studies
- Published anecdotal reports/retrospective studies
  - Proportion will benefit substantially
  - ?duration of effect / ?predictors of response

  (Shear 1978, Sajatovic & Meltzer, Gujavarty et al 1987)
- ECT and Clozapine
  - 'Safe and effective' *(Chong and Remington 2000)*
  - 'Marked clinical improvement' in 24 of 36 patients with treatment-resistant schizophrenia *(Kupchik et al 2000)*
  - Risks
    - Tachycardia
    - Seizures
    - BP elevation

Treatment-resistant Schizophrenia: Pharmacological Strategies

Antipsychotic drugs

- SGA vs FGA
- High-dose antipsychotics
- Clozapine
- Other SGAs
- Combined antipsychotics

- Adjunctive treatment
  - Lithium
  - Carbamazepine
  - Sodium valproate
  - Lamotrigine
  - Antidepressant
  - Benzodiazepine
  - ECT
  - **Glycine, Omega-3 FAs**

NICE: Treatment resistant schizophrenia

NHS
National Institute for Clinical Excellence

- Establish that there have been adequate trials of antipsychotics
  - Dose, duration, adherence
  - Substance misuse, medication or physical illness mitigating against response
- If Sx unresponsive to a conventional then use an atypical before consider TRS
  - Olanzapine or risperidone (but advice pt that less evidence in TRS than for clozapine)
- If TRS (min 2 antipsychotics each for 6-8/52, at least one atypical) consider clozapine sooner rather than latter
- Avoid multiple antipsychotics except for pts who have not fully responded to clozapine

Anxiety Disorders

(briefly!!)

Treatment-resistant Anxiety Disorders

- Generally virtually no evidence to support practice.
- Few RCTs:
- Panic disorder:
  - combination of paroxetine and CBT superior to continued CBT in patients non-responsive to 15 CBT sessions (Kampman *et al.*, 2002)
- GAD
  - No placebo-controlled or comparator controlled studies
- PTSD
  - ? combination of drug and psychological treatment
  - ? Olanzapine augmentation
- OCD
  - Lithium ineffective (McDougle *et al.*, 1991)
  - haloperidol effective with co-morbid tics (McDougle *et al.,* 1994)
  - quetiapine (Atmaca *et al.*, 2002; Denys et al. 2004)
  - risperidone (McDougle *et al.*, 2000; Hollander *et al.*, 2003)
  - Olanzapine –ve RCT (Shapira et al. 2004)

NICE: Anxiety: Management of anxiety in adults in primary and secondary care

NHS
National Institute for Clinical Excellence

- Guideline covers panic disorder and GAD
- Choose one out of:
  - Psychological interventions
  - Pharmacological therapy
  - Self-help
- If fail two types of intervention – refer into secondary care

NICE Anxiety Guidelines
Panic Disorder
Pharmacotherapy

NHS
National Institute for Clinical Excellence

- SSRI licensed for panic (citalopram, escitalopram, paroxetine)
- If SSRI not suitable or patient fails 12/52 course consider imipramine or clomipramine
- Long term treatment and doses at the higher end of the dose range may be needed

- In specialist care: “consider a full exploration of pharmaco-therapy”

NICE PTSD guidelines
Pharmacotherapy

NHS
National Institute for Clinical Excellence

- Consider:
  - mirtazepine or paroxetine (general use)
  - amitriptyline or phenelzine (specialist use)
  - N.B. sertraline not recommended
- NOT first line
- Use if:
  - Patient prefers drugs
  - Delay in getting trauma-focused CBT
  - If trauma-focused CBT fails
  - Sleep disturbance (or short term BZ)
- If drug fails, consider increasing the dose or adding adjunctive olanzapine

NICE OCD and BDD guidelines

NHS
National Institute for Clinical Excellence

- If mild functional impairment: CBT (brief or group) or ERP
- If moderate functional impairment: CBT or SSRI
- If severe impairment: SSRI + CBT
- Pharmacotherapy:
  - An SSRI with evidence
  - N.B. may take at least 12/12 for a response
  - Increase dose after 4-6/52 if no response
- If no response after 12/52 then CBT +SSRI
- If no response switch SSRI or use clomipramine (ECG and BP monitoring)
- If no response refer to secondary care. Consider:
  - More CBT (including ERP)
  - Antipsychotic + SSRI or clomipramine (Busp + SSRI for BDD)
  - Clomipramine + citalopram
- If no response refer to tertiary care to consider neurosurgery

Depression

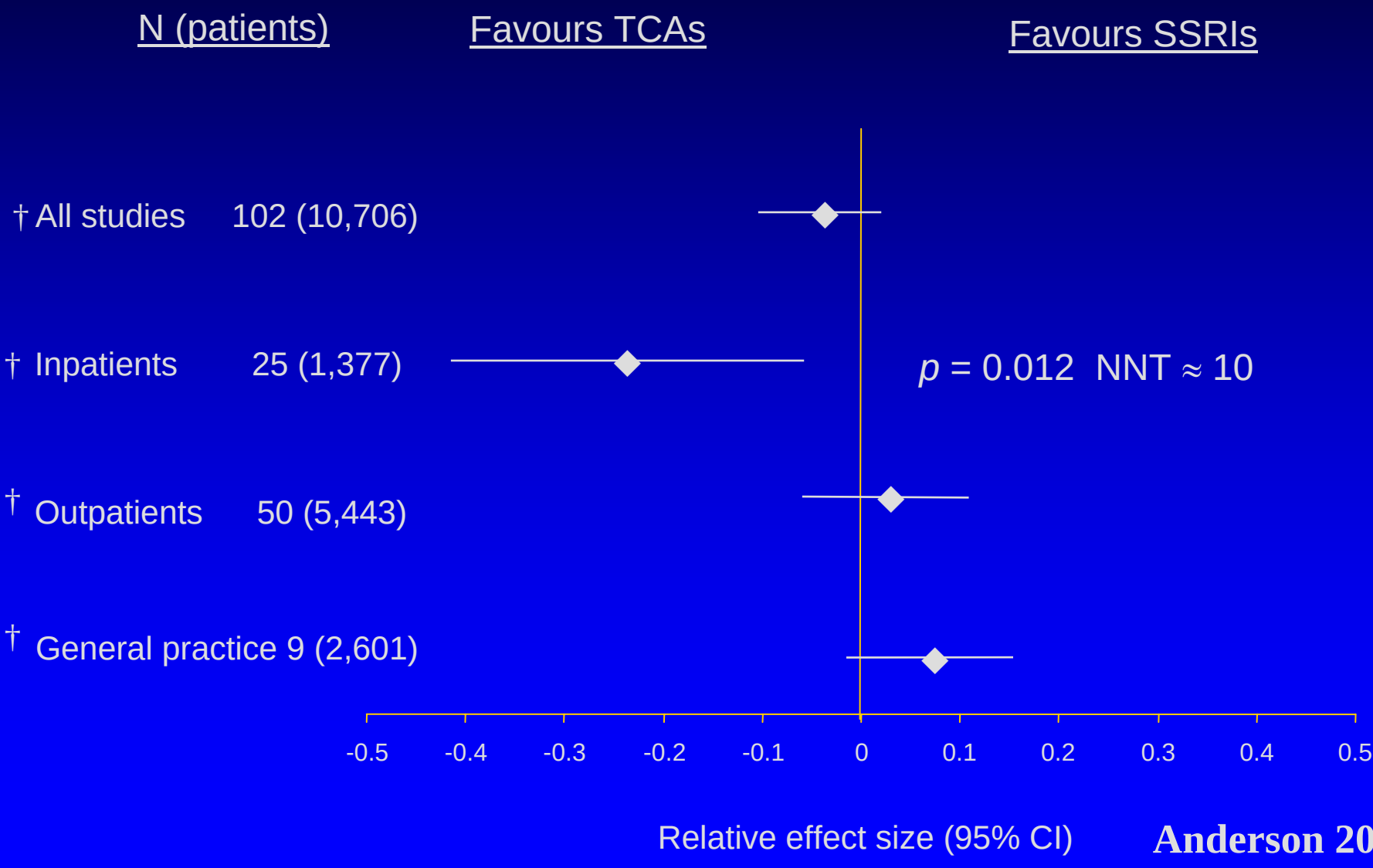
TRD Pharmacological Strategies

- One drug strategies
- Augmentation
- Combination strategies
- Non-pharmacological strategies

TRD Pharmacological Strategies

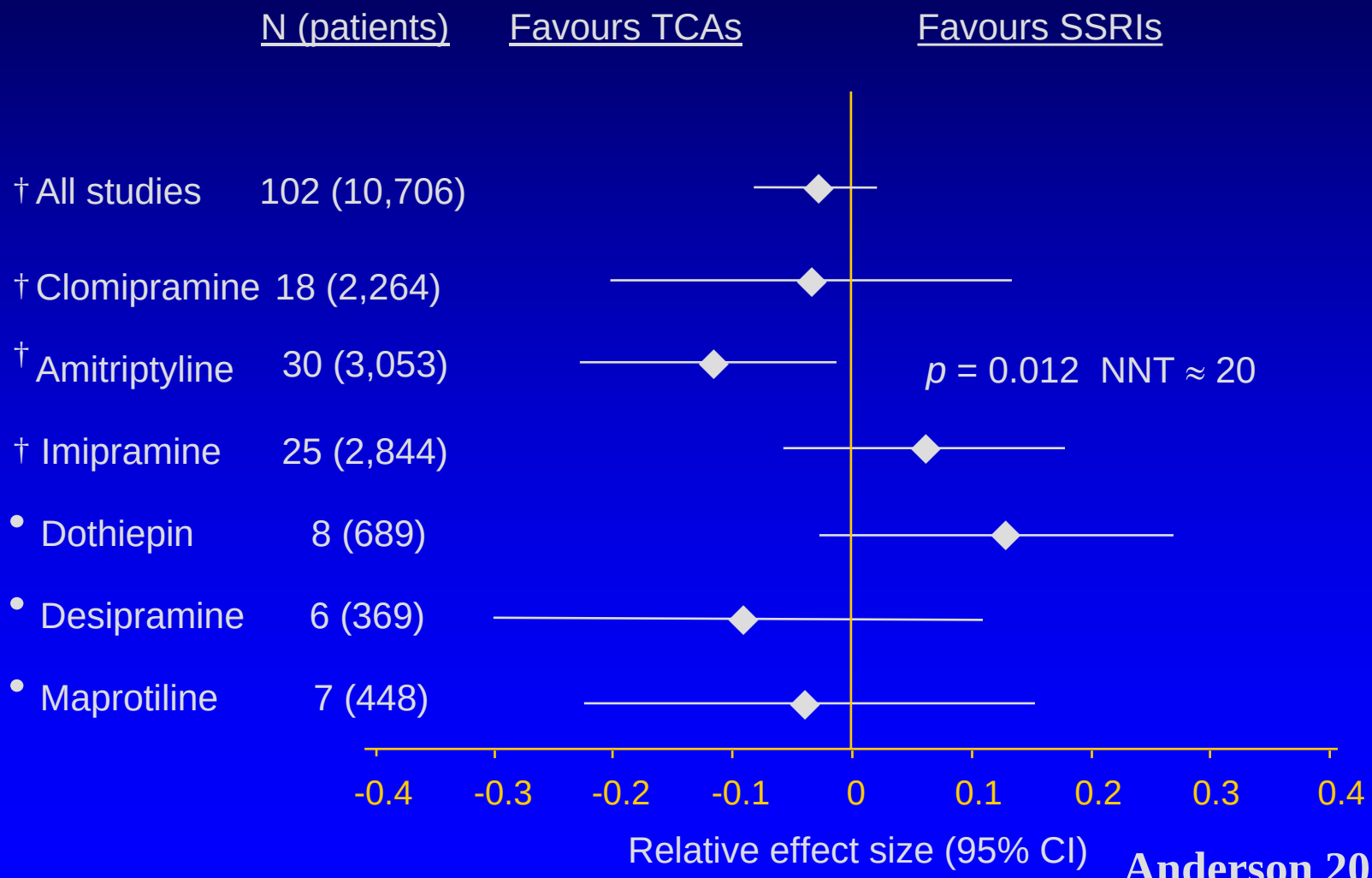
- One drug strategies
  - Choice of drug
  - Increased dose
  - Switch drug
- Augmentation
- Combination strategies
- Non-pharmacological strategies

Efficacy: SSRIs versus TCAs



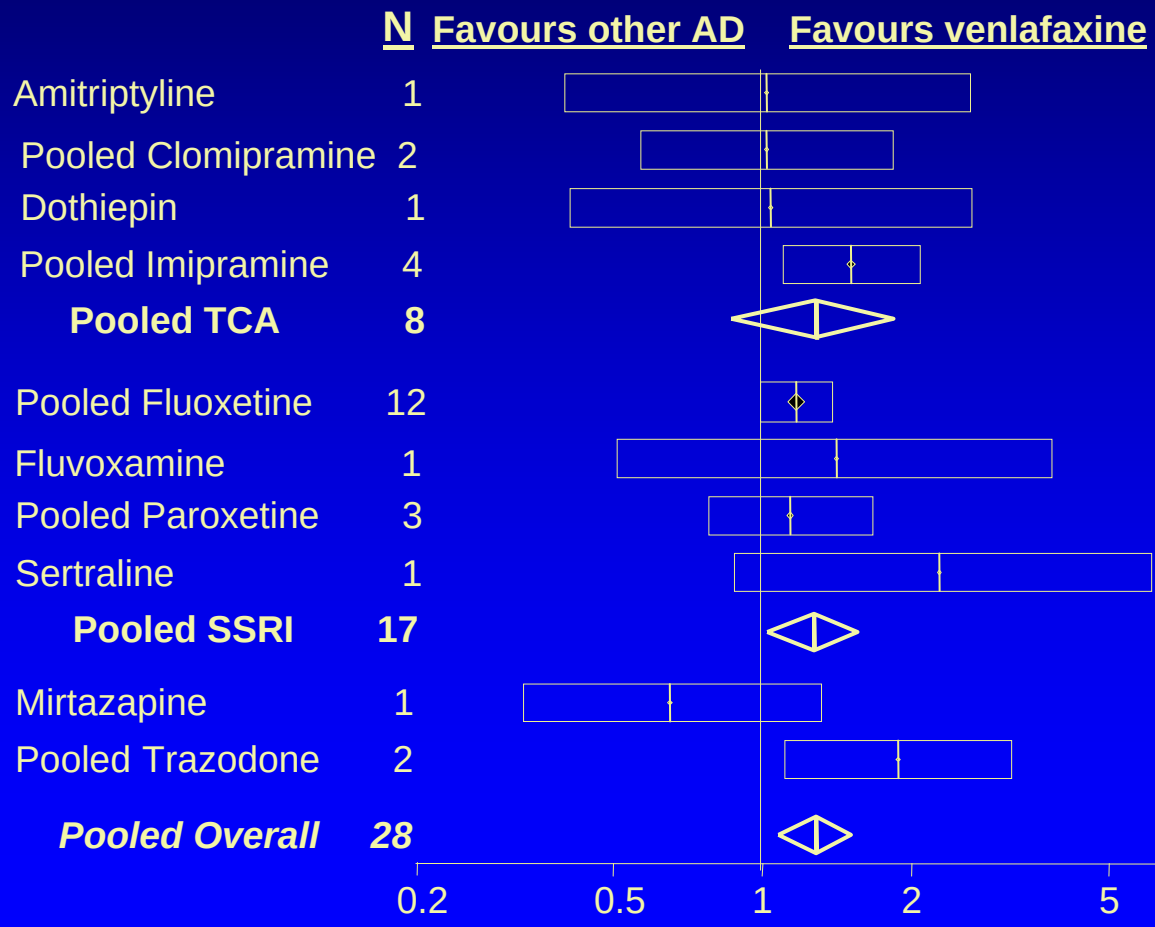
Anderson 2000

Efficacy: TCAs vs SSRIs



Anderson 2000

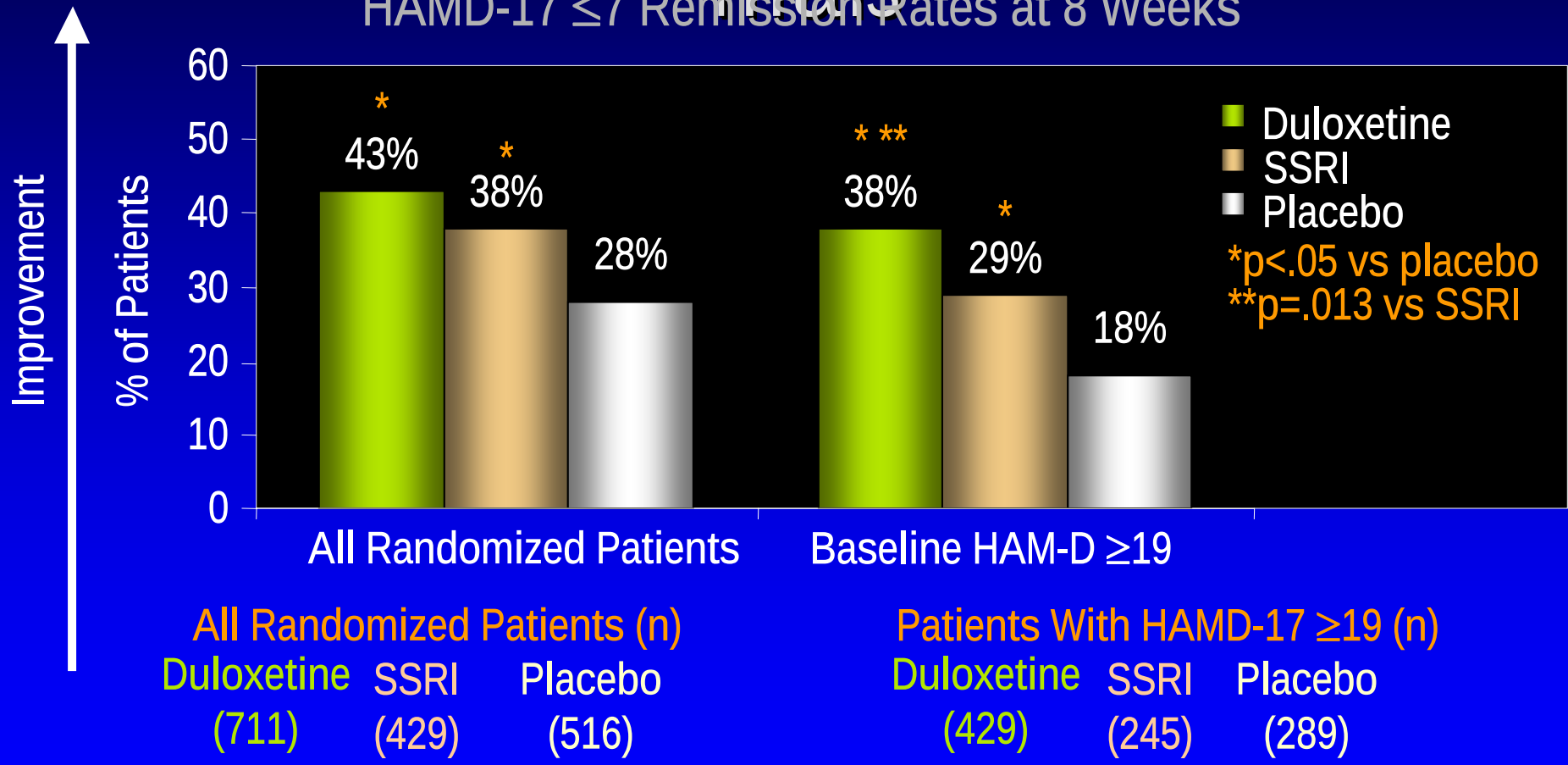
Efficacy of venlafaxine vs other antidepressants



NNT = 19

Smith et al 2002

Pooled Analysis of Remission in 6 Placebo and SSRI-Controlled Trials



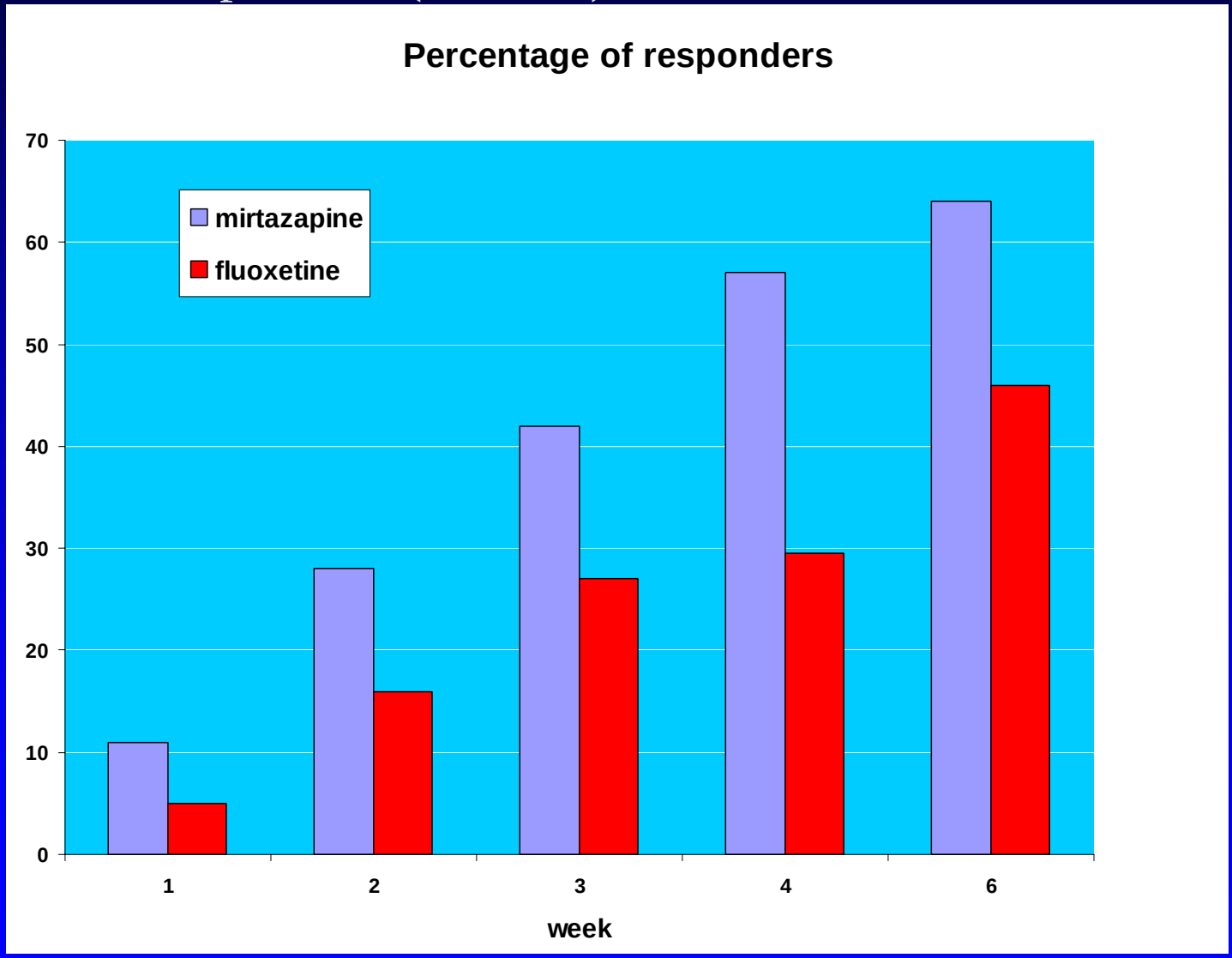
All Randomized Patients (n)		
Duloxetine	SSRI	Placebo
(711)	(429)	(516)

Patients With HAMD-17 ≥19 (n)		
Duloxetine	SSRI	Placebo
(429)	(245)	(289)

Thase ME, et al. Presented at: 156th APA Annual Meeting; May 17-22, 2003; San Francisco, Calif.

Mirtazapine v fluoxetine

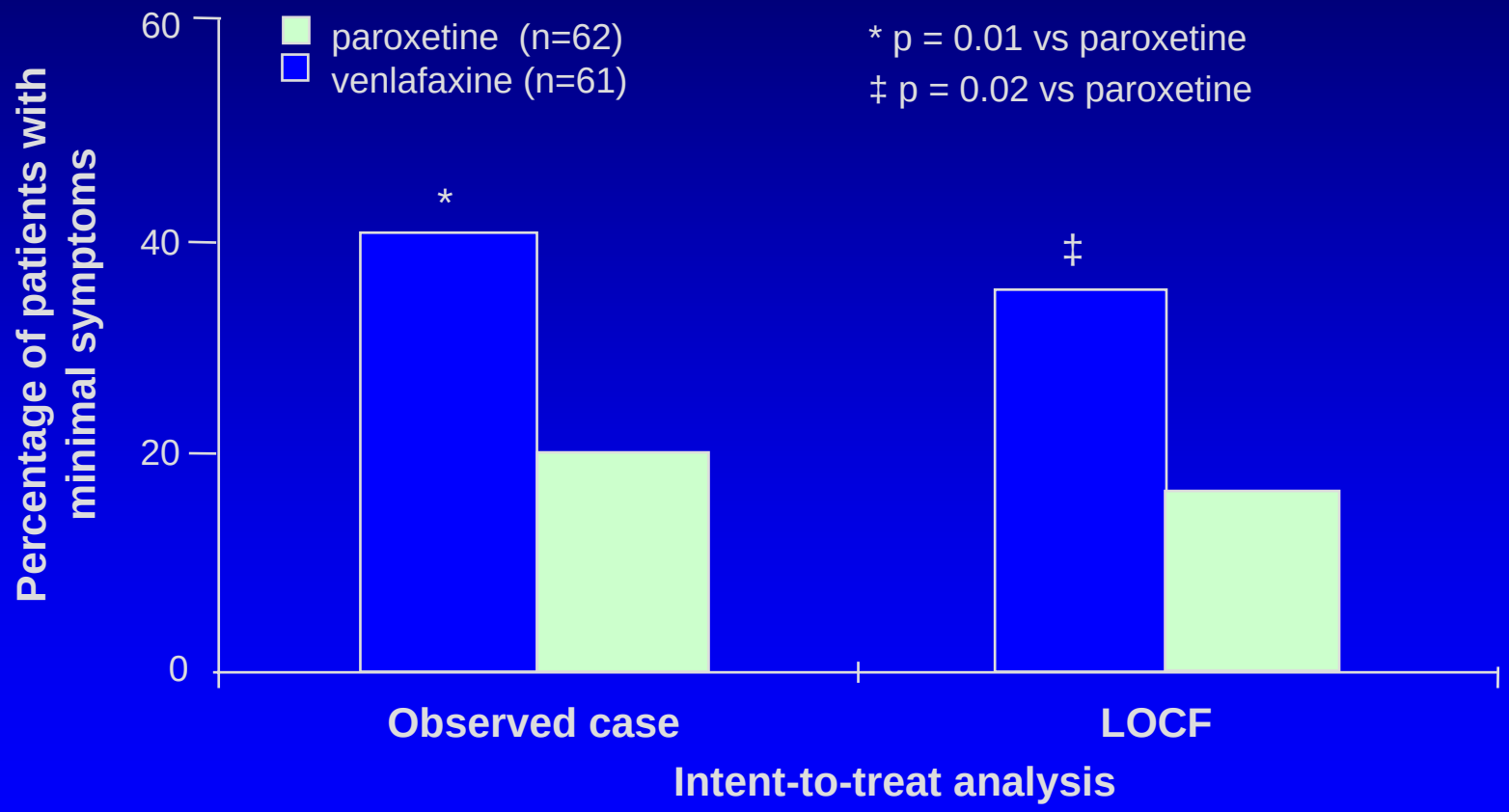
Depressed outpatients (n = 123)



Wheatley et al J Clin Psychiatry (1998) 59(6) 306-312

Venlafaxine vs paroxetine in treatment-resistant depression

Remission = final 17-item HAM-D Score <10 at week 4



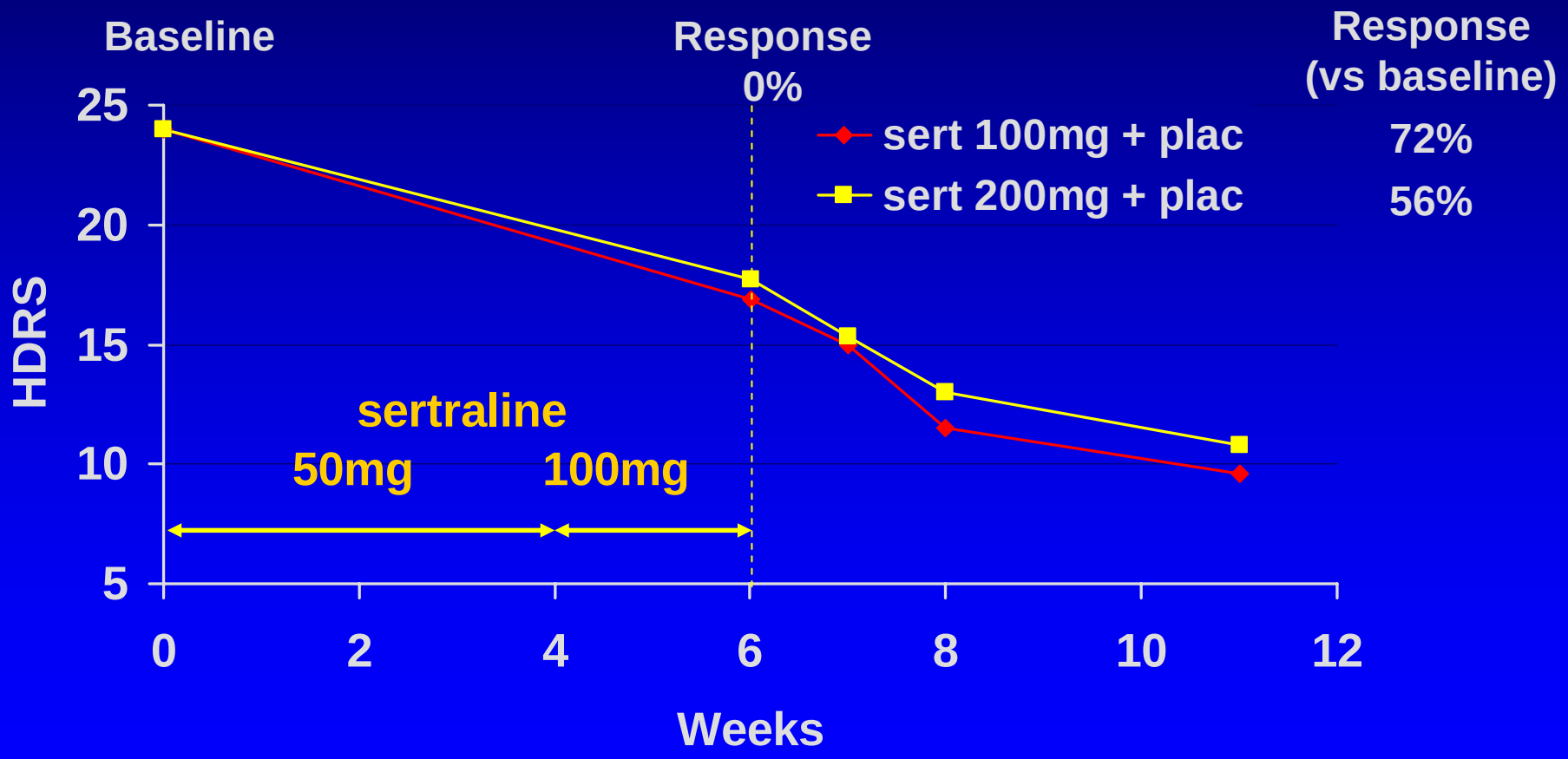
Poirier MF and Boyer P. BJP 1999 175 12-16

Increased Dose

- **TCAs**
  - **An effective dose of a TCA is not less than 125mg[1]**
  - **300mg/day of imipramine is superior to 150mg/day [2]**
  - **large variation in plasma levels of TCAs**
- **SSRIs**

[1] Paykel et l 1992 BMJ [2] Simpson 1976 Archives 1372
[4] Cowen 1998 APT

Non-response at 6 weeks: increased dose of sertraline



Licht & Qvitzau 2002

Increased Dose

- **TCAs**
  - **An effective dose of a TCA is not less than 125mg[1]**
  - **300mg/day of imipramine is superior to 150mg/day [2]**
  - **large variation in plasma levels of TCAs**
- **SSRIs**
  - **Little evidence of benefits of increased dose**
- **MAOIs**
  - **increased response with 90 mg of phenelzine[4]**
- **Venlafaxine**

[1] Paykel et l 1992 BMJ [2] Simpson 1976 Archives 1372
[4] Cowen 1998 APT

TRD Pharmacological Strategies

- One drug strategies
- Augmentation
  - Psychotherapy
  - Lithium
  - L-tryptophan
  - Thyroid hormones
  - Antipsychotics
  - Others
- Combination strategies
- Non-pharmacological strategies

Nefazodone vs CAT vs Nefazodone + CAT

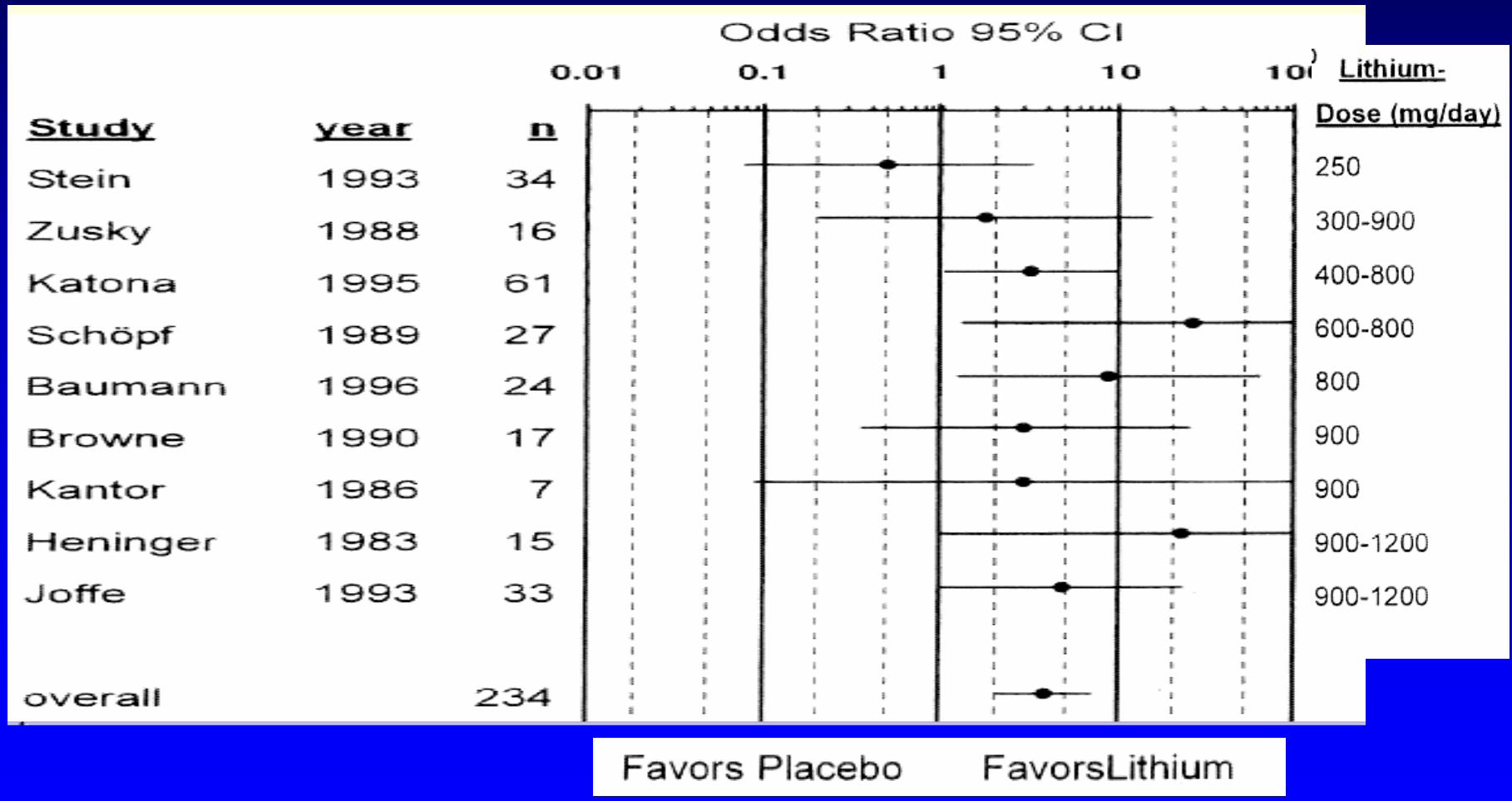
Drug	Psychotherapy	Combination
55%	**52%**	**85%**

Response Rates (50% reduction on Hamilton Depression Rating Scale)

Keller et al. (2000)

- ? Multiple psychotherapies combined, e.g. IPT for depression and CBT for comorbid panic (Grote & Frank, 2003)

Lithium augmentation in TRD: a meta-analysis of placebo controlled studies



Bauer M and Dopfmer S 1999 J Clin Psychopharm

Augmentation with l-tryptophan

- Tryptophan alone may have antidepressant properties (RCT, n=28 over 12/52: Thomson et al. 1982)
- Only one RCT as augmentation (Levitan et al. 2000)
  - N= 30, fluoxetine +/- tryptophan 2-4g over 8/52
  - Improved response at 1/52 and increased SWS
- Anecdotes of:
  - Newcastle cocktail (Phenelzine+Li+tryp: Barker et al. 1987)
  - London cocktail (Clomip+Li+tryp: Hale et al. 1987)
  - Dalhousie cocktail (nefaz+pind+tryp: Dursun et al. 2001)
- Eosinophilia due to contaminant? (Kilbourne et al. 1996)
- Recent SPC change

- N.B. tryptophan discontinuation

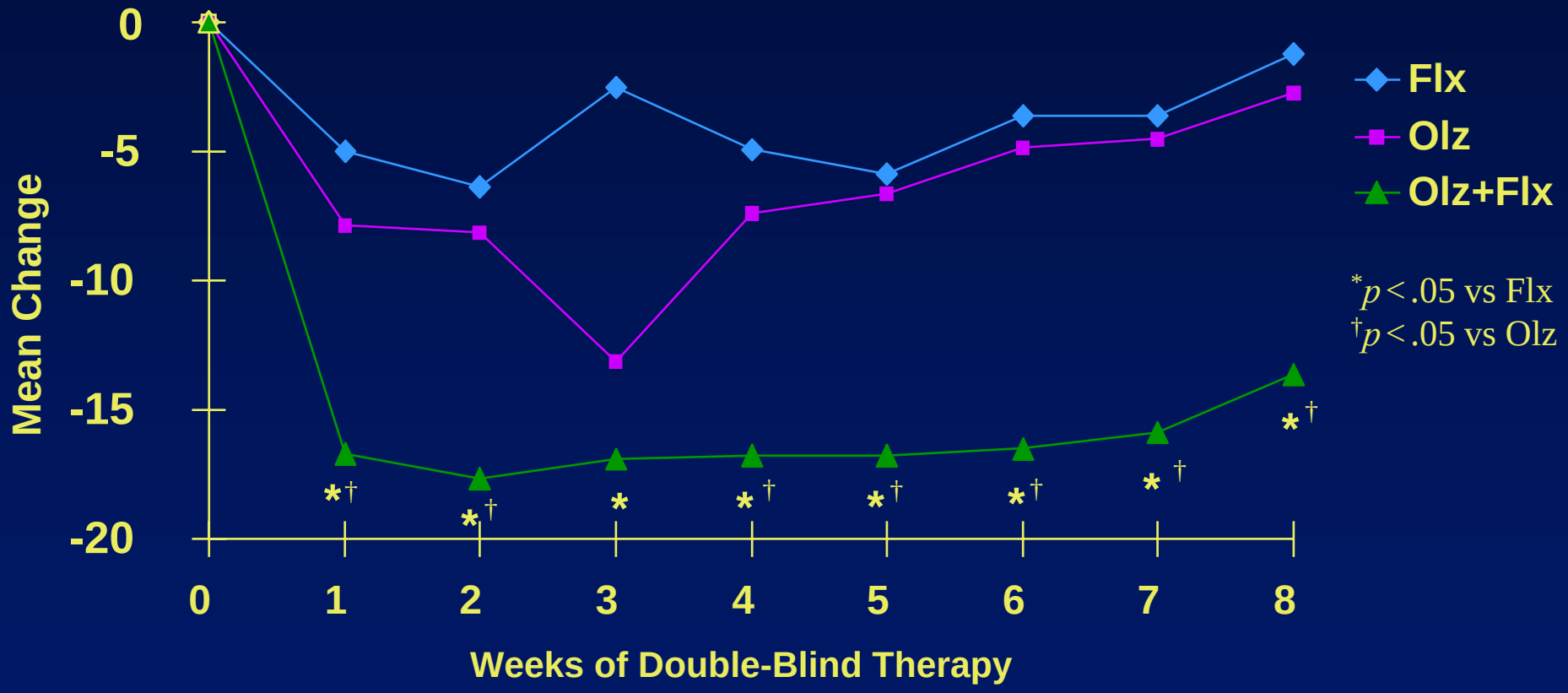
Augmentation with thyroid hormones

- Remission with supraphysiological T_4 in 50% of TRD patients (Bauer et al. 2000)
- Numerous open studies suggest 25-50 microgrammes T_3 leads to response in 25-60% of patients with TRD
- RCT showed T_3 = Li > placebo (Joffe et al. 1993)
- Meta-analysis – no effect of T_3 (Aronson et al. 1996)
- RCT of T3 + SSRIs (Lerer et al. 2006)
  - Placebo n=60, T3 n= 64
  - Response – pl – 50%, T3 – 70%
- ? reserve strategy for clinical and subclinical hypothyroidism

Augmentation with antipsychotics

- Psychotic MDD (Spiker et al. 1985; Rothschild et al. 1993)
- Severe non psychotic MDD
  - Non-specific effects – anxiolytic, sedative, reduce psychomotor agitation
  - ? true augmenting effect on mood
  - RCT of olanzapine augmentation (Shelton et al. 2001)

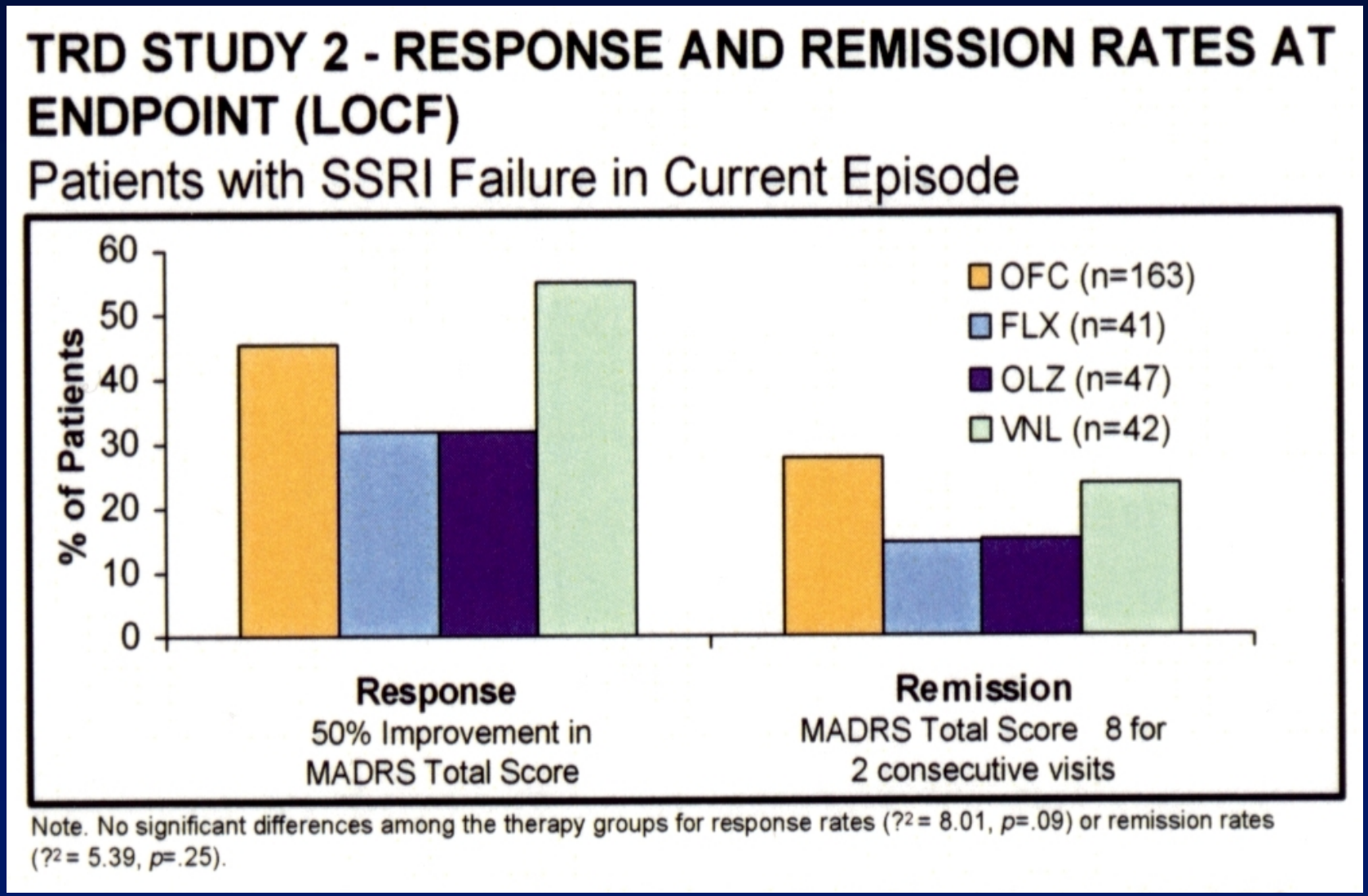
Olanzapine, fluoxetine, + combination in patients not responding to fluoxetine



Shelton et al 2001

From **Dube et al 2002 ACNP**

12 week RCT in 483 patients with history of SSRI failure and prospective failure to respond to 7 weeks venlafaxine randomised to olanzapine, fluoxetine, OFC or venlafaxine. OFC = venlafaxine > olanzapine but not fluoxetine



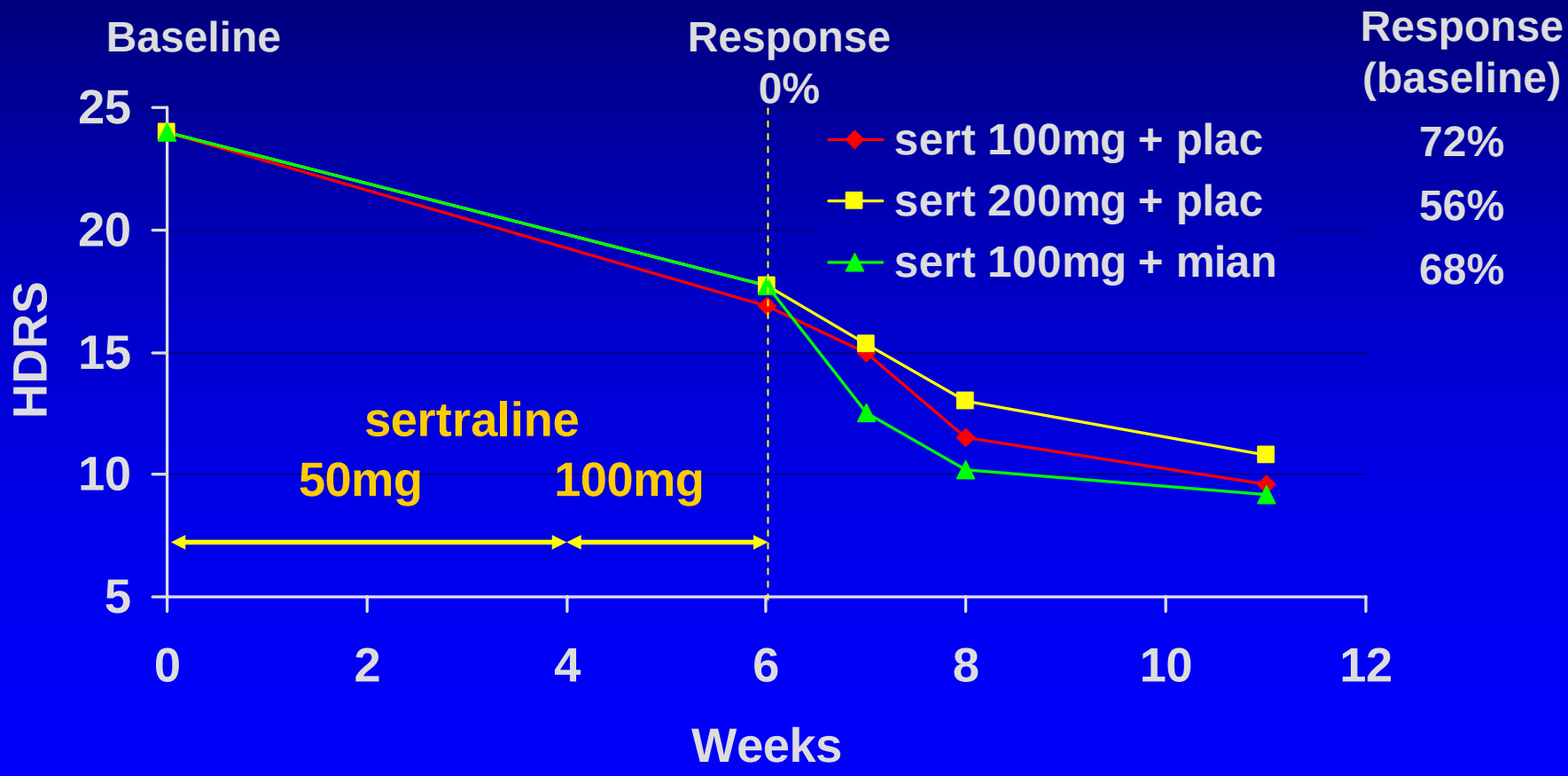
Other augmentation strategies

- Buspirone
  - RCT suggests effect size small (Appleberg et al. 2001)
- Benzodiazepines
  - Cochrane review – 63% response to combo vs 38% for ADs alone (plus 37% less likely to drop out)
- Anticonvulsants
  - Valproate and carbamazepine been used. No RCTs
- Pindolol
  - May accelerate response but probably not effective in TRD (McAllister-Williams & Young, 1998)
- Stimulants
  - Used extensively in USA
  - ? Use tranylcypromine in UK
- Others
  - Folate, Omega fatty acids, Metyrapone, DHEA

TRD Pharmacological Strategies

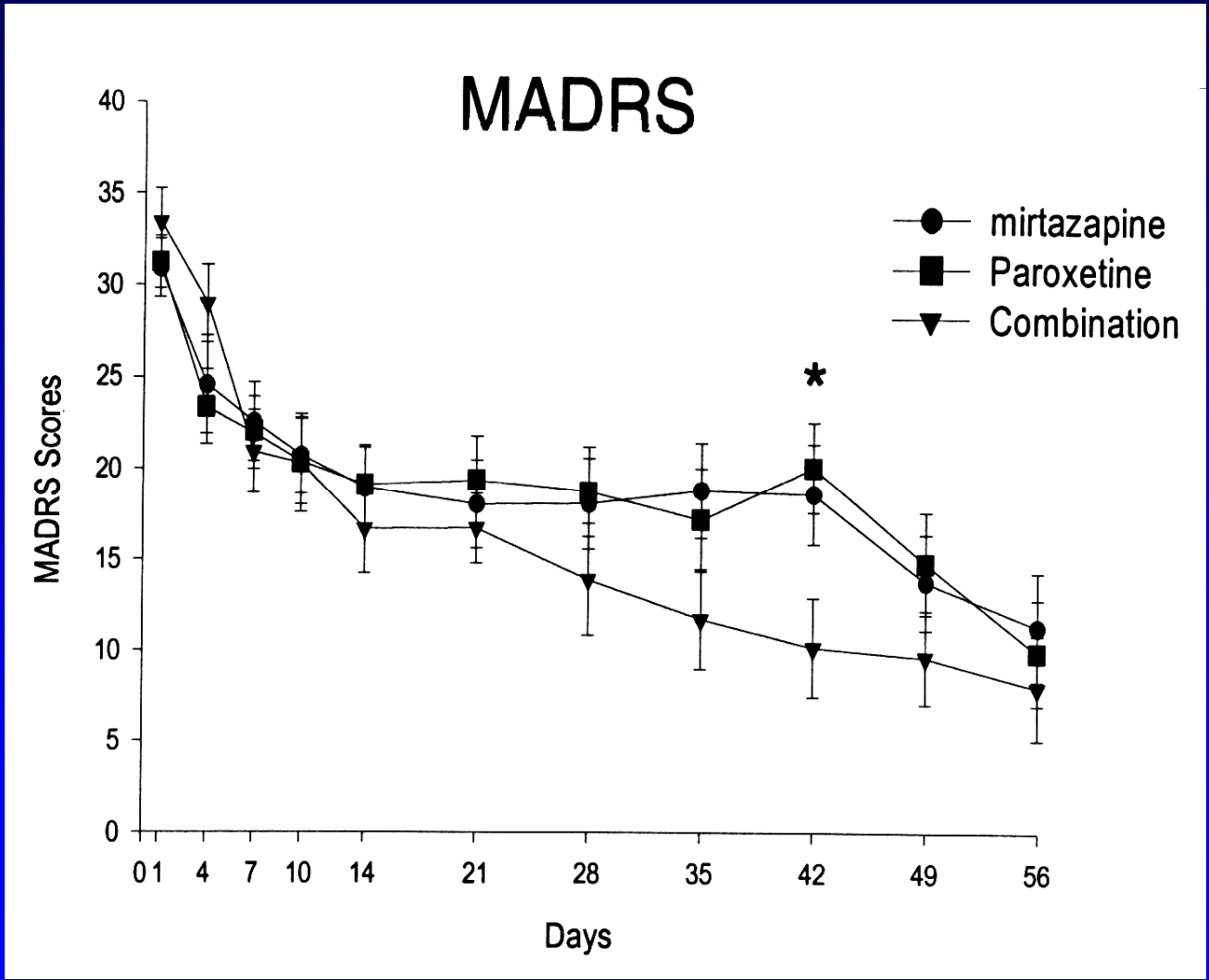
- One drug strategies
- Augmentation
- Combination strategies
  - SSRI + TCA
  - MAOI + TCA
  - SSRI + reboxetine
  - SSRI + Trazodone
  - Mirtazepine or mianserin + uptake blocker
- Non-pharmacological strategies

Non-response at 6 weeks: augmentation with mianserin



Licht & Qvitzau 2002

Combined paroxetine + mirtazapine in depression



Debonnel et al 2000

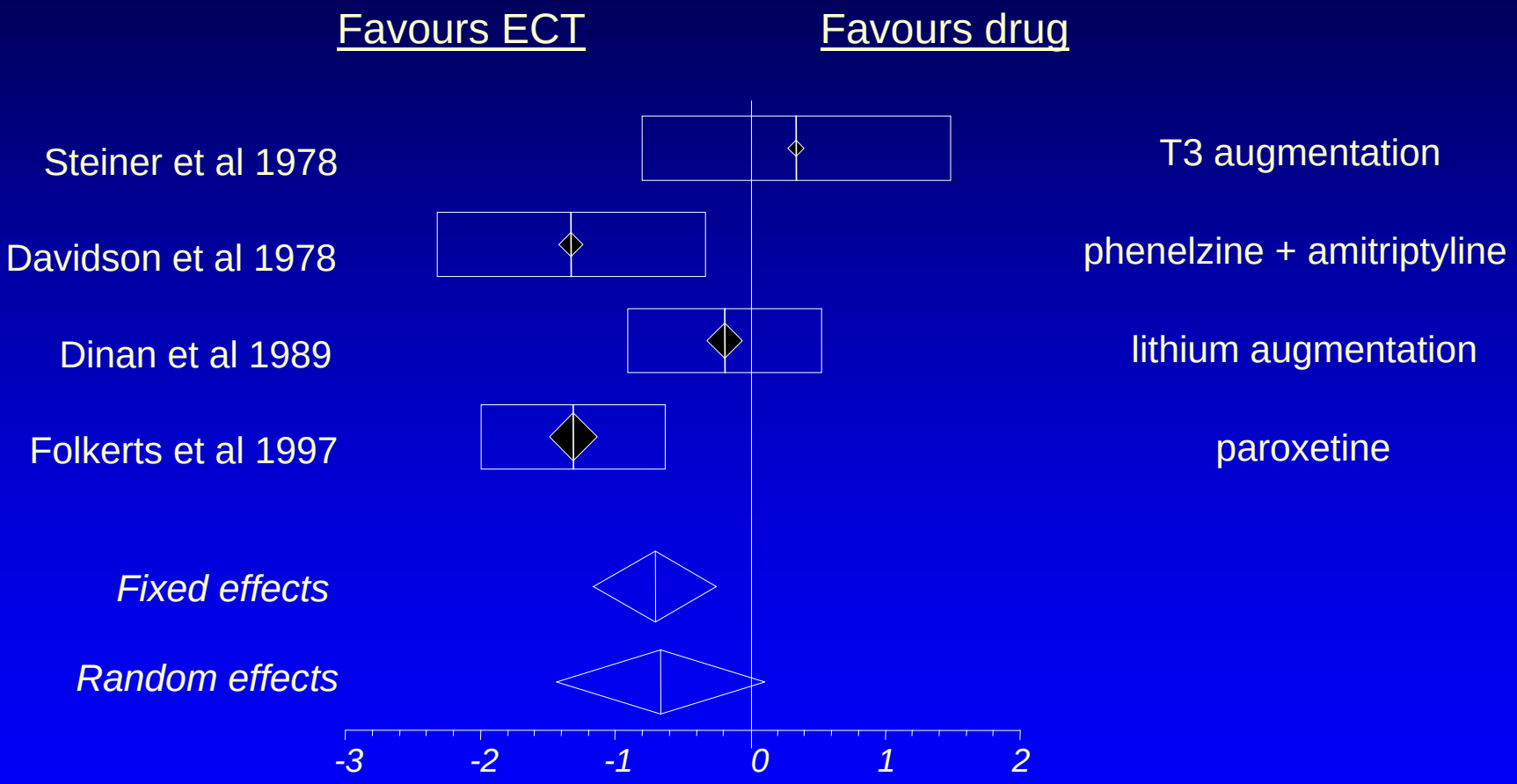
TRD Pharmacological Strategies

- One drug strategies
- Augmentation
- Combination strategies
- Non-pharmacological strategies
  - ECT
  - TMS
  - VNS
  - Psychosurgery

ECT

- 60-80% remission rates (Kennedy et al. 2001)
- Symptom profile
  - Psychosis, retardation, refusal of food intake, severe suicidality, pregnancy
- Previous response

ECT vs pharmacotherapy in TRD



Random effects pooled effect size = -0.66 (95% CI = -1.43 to 0.11)

Analysis of data from UK ECT Review Group 2003

ECT

- 60-80% remission rates (Kennedy et al. 2001)
- Symptom profile
  - Psychosis, retardation, refusal of food intake, severe suicidality, pregnancy
- Previous response
- Relapse rate of 50-95% (Bourgon & Kellner, 2000)
  - What drug do you use for continuation therapy?
  - Sackheim et al. 2001
    - Placebo (84%)
    - Nortiptyline (60%)
    - Nortiptyline + lithium (39%)

Step 4 - Refractory depression

National Institute for Clinical Excellence

- Failure to respond to 2 or more ADs
- Refer for re-evaluation of symptoms, risks etc.
- Consider everything in step 3. [GPP]
- Consider the following options:
  1. ADs plus CBT
  2. Lithium augmentation (even after 1 AD) – NB SEs and toxicity [C]
  3. Venlafaxine up to BNF limits [C]
  4. SSRI + mianserin or mirtazepine [C]
     - Monitor carefully for SEs [GPP]
     - Use mianserin with caution esp. in elderly – agranulocytosis [C]
  5. Consider phenelzine [C]
  - Don't augment with BZs [C]
  - Carbamazepine, lamotrigine, buspirone, pindolol, valproate, thyroid hormone augmentation not recommended routinely [B]
- If thinking of other strategies, think of second opinion or tertiary referral – document discussions in notes [C]

Bipolar Disorder

NICE Clinical Guideline

July 2006

Bipolar Disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care

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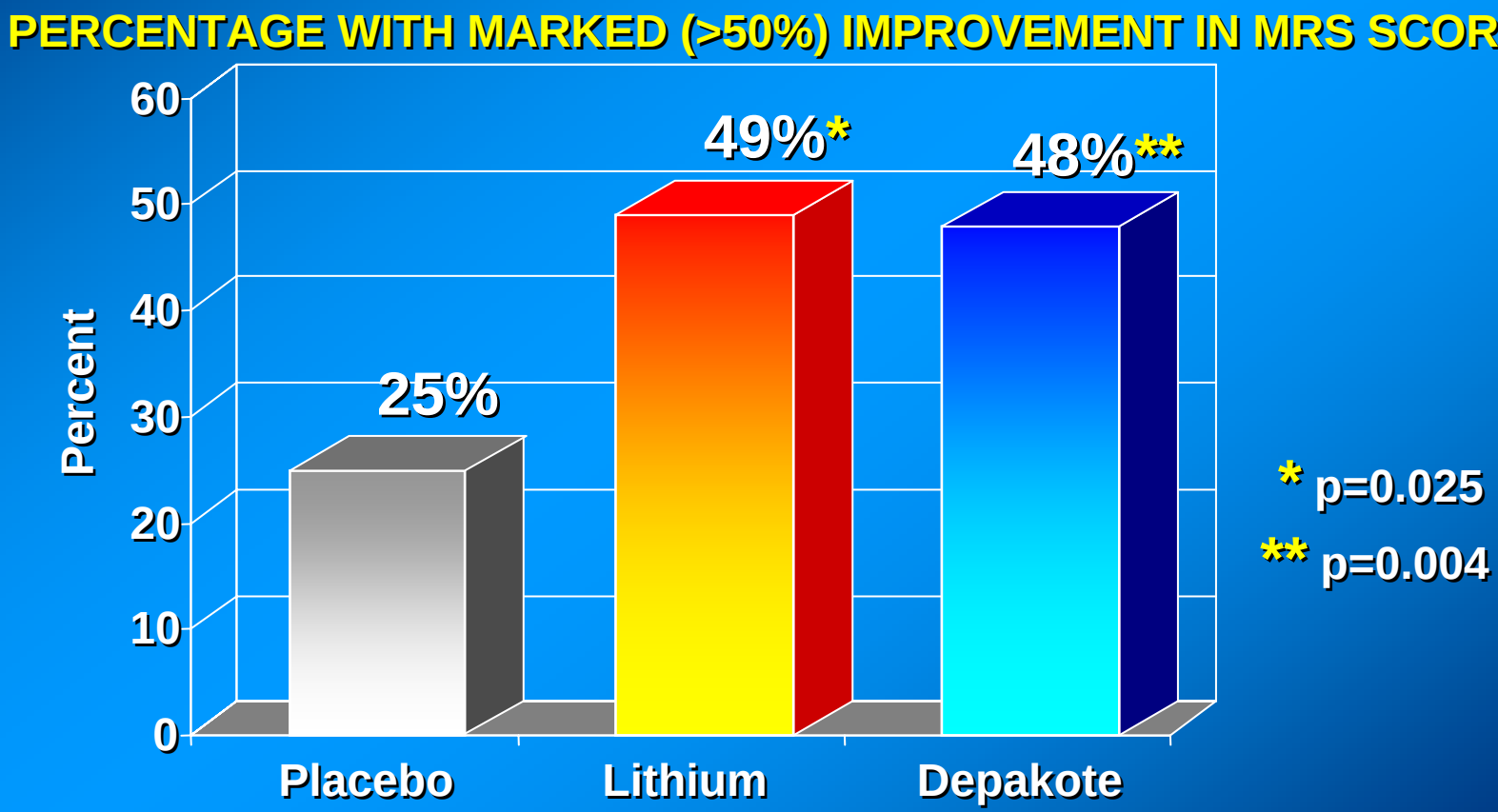
Guidance

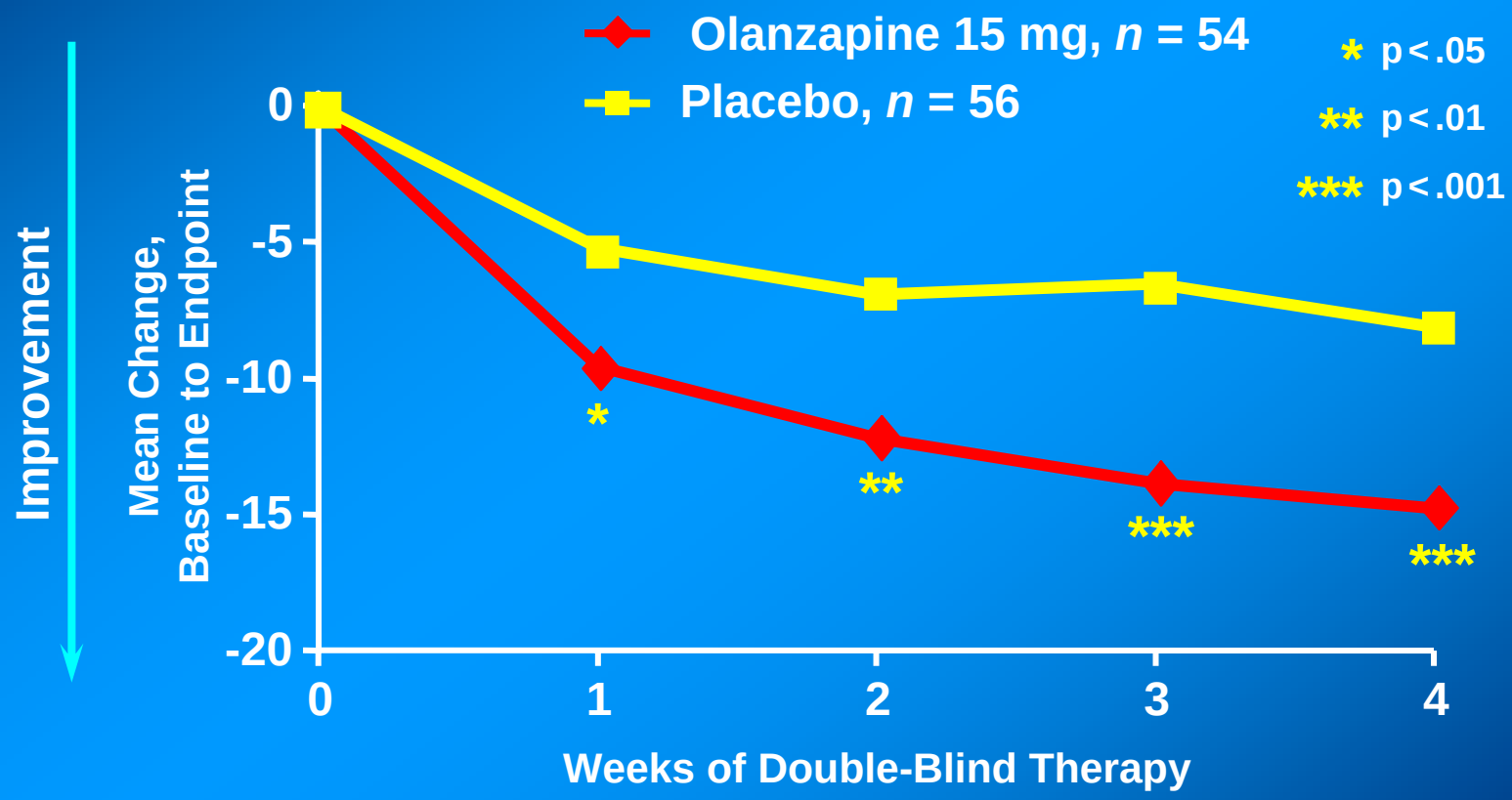
- Common aspects of care for all people with bipolar disorder
- Assessment, recognition and diagnosis
- Treatment setting and pathways to care
- Physical care
- Treatment and management of bipolar disorder
- Long-term management
- Treatment and management of women of child-bearing potential
- Assessment, diagnosis and treatment of children and adolescents

Valproate and Lithium in acute mania Bowden et al 1994



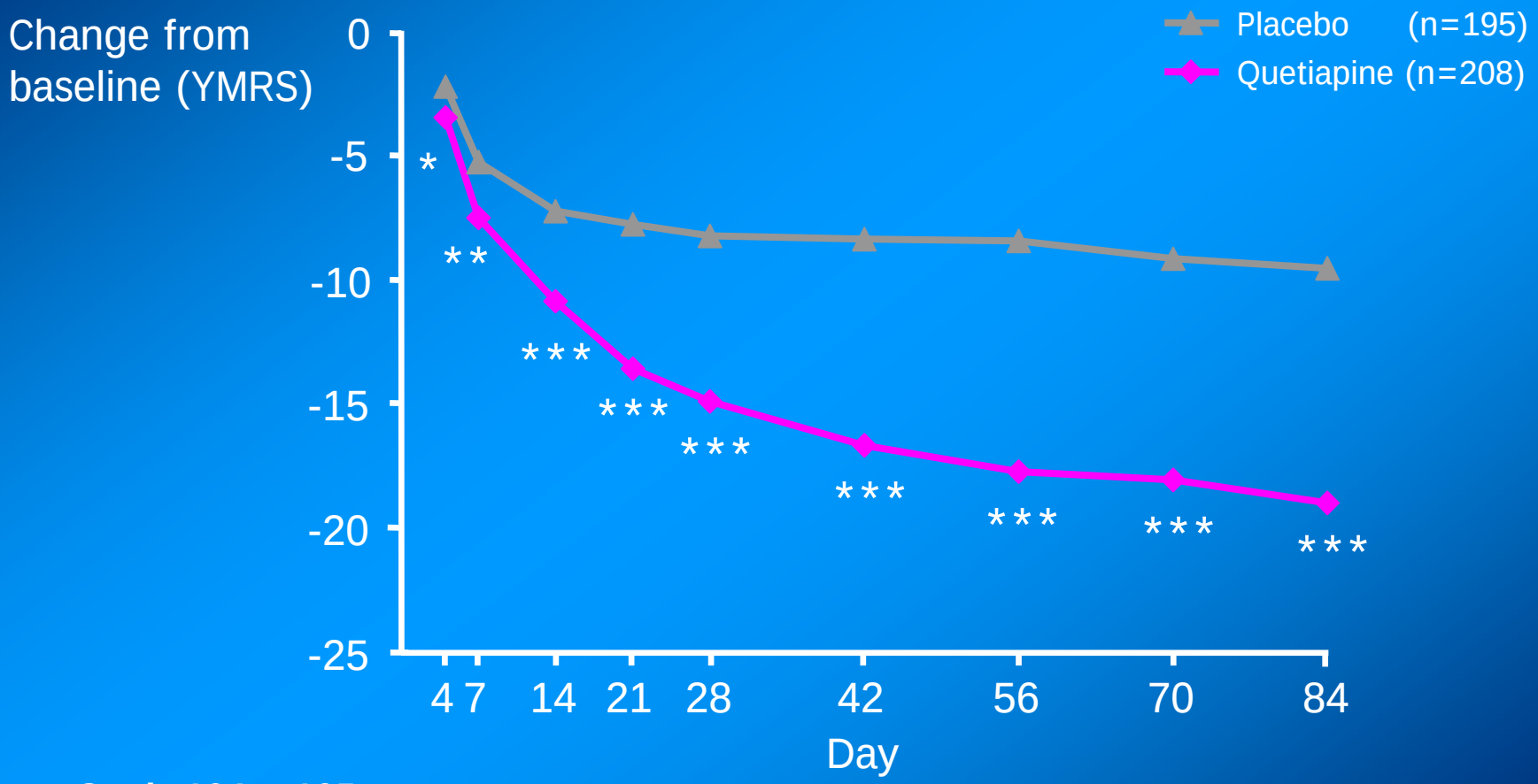
N.B. Efficacy of Depakote independent to prior responsiveness to Lithium

Olanzapine in acute mania



Compared to placebo, olanzapine patients had a statistically significantly greater LOCF mean improvement at week 1 which was maintained throughout the study

Quetiapine in acute mania

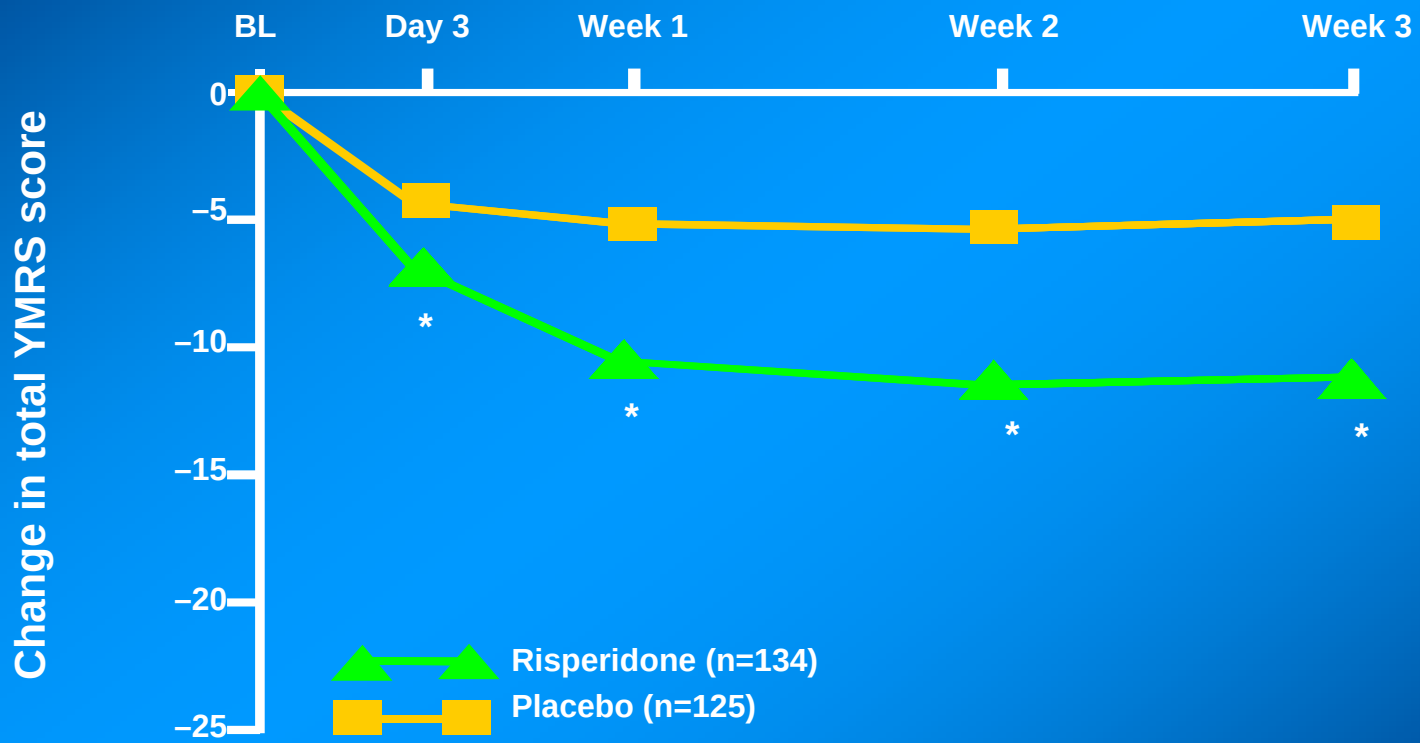


Study 104 + 105

***p<0.05; **p<0.01; ***p<0.001**

Brecher & Huizar 2003; Paulsson & Huizar 2003; Jones & Huizar 2003

Risperidone in acute mania

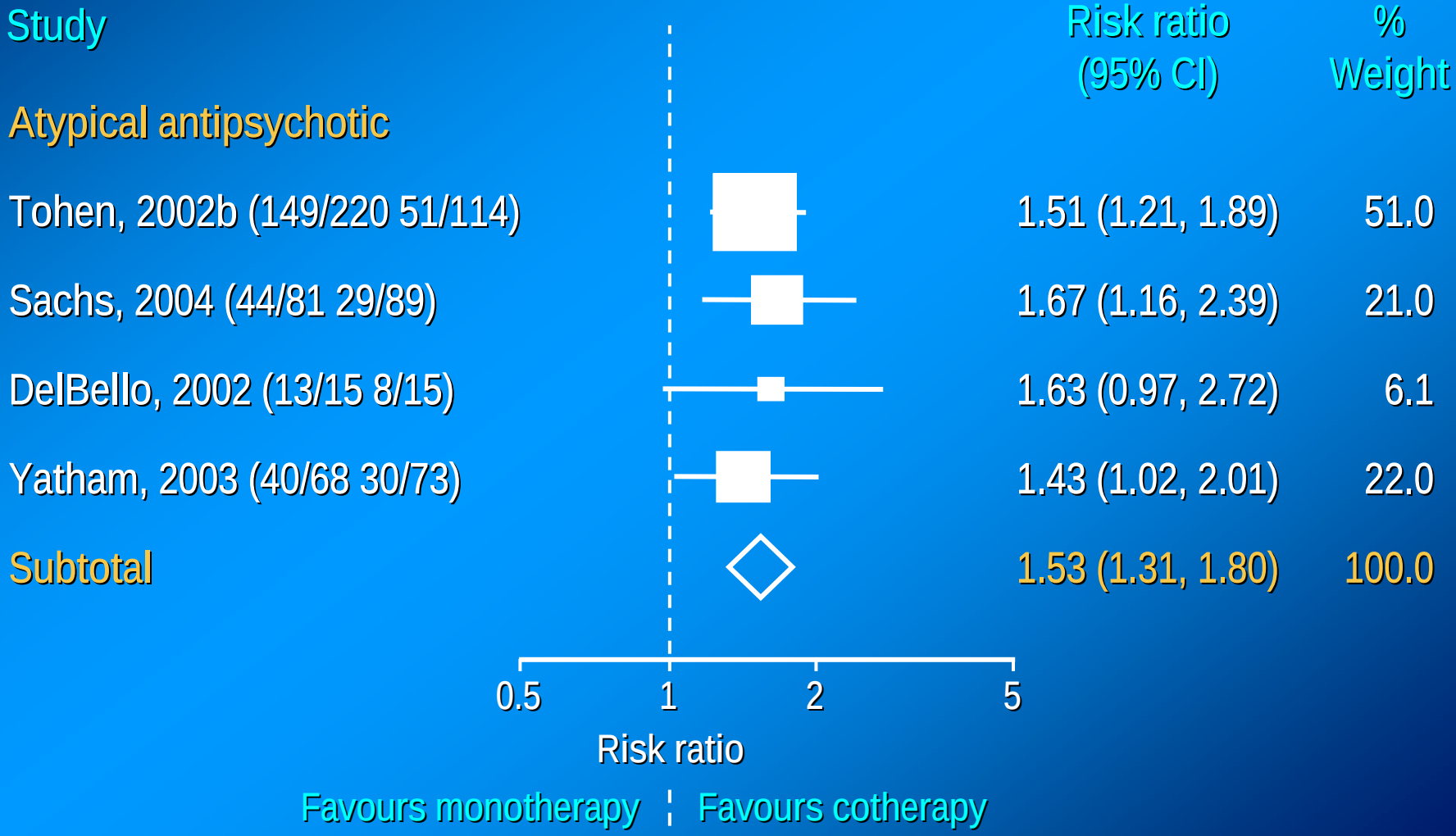


Median dose 4mg/day
BL: Risperidone = 29.1; placebo = 29.2

LOCF analysis; *P<0.001 risperidone vs placebo;
Hirschfeld RM, et al. Am J Psychiatry 2004;161:1057–65

Cotherapy vs monotherapy in mania

RESPONSE



Acute Mania:
Those not on anti-manic treatment

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- Atypical antipsychotic (olanzapine, risperidone, quetiapine) for those with severe mania
  - If ineffective consider adding Li or valproate
- Valproate or Li if previous good response and compliance
  - Avoid valproate in women of child baring potential
  - Li only if less severe
- Don’t use carbamazepine routinely and avoid gabapentine, lamotrigine and topiramte

Acute Mania:
Those on anti-manic treatment

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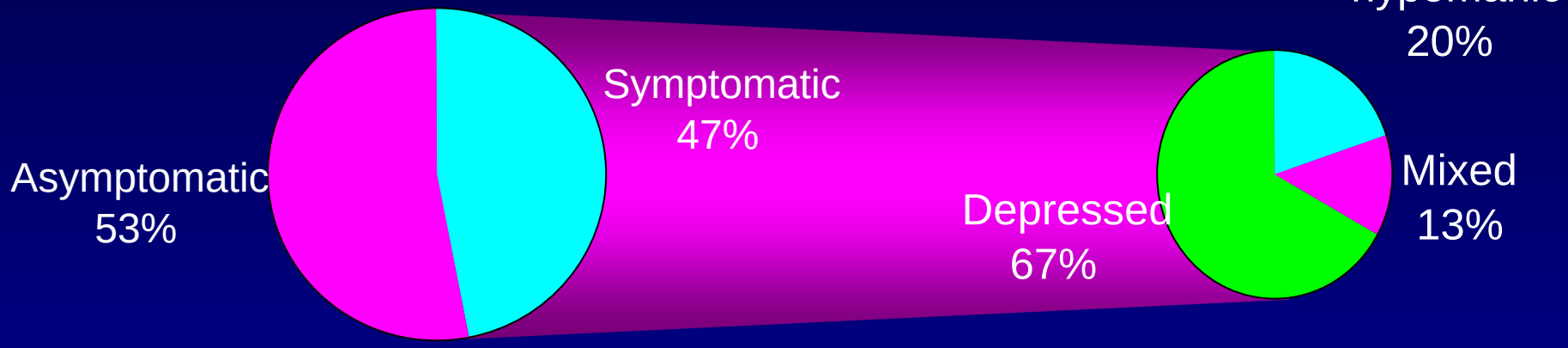
- Optimise treatment
  - Li level 0.8-1.0
  - Valproate to max. licensed dose (depending on SEs)
  - Don’t generally increase carbamazepine
- Add olanzapine, risperidone or quetiapine

Depression is THE Problem

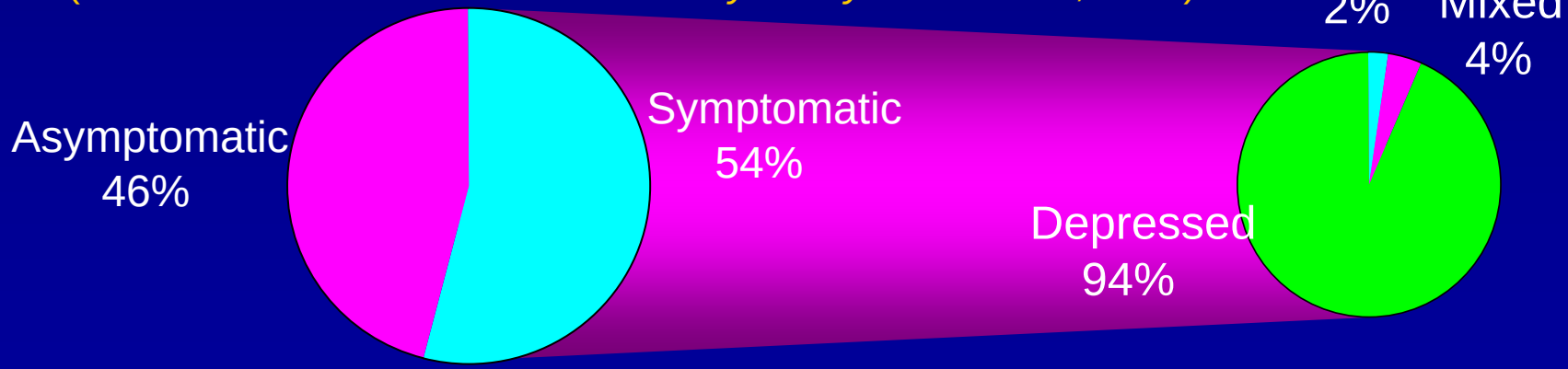
Bipolar I

(Judd et al. *Archives of General Psychiatry* 59:530-537, 2002)

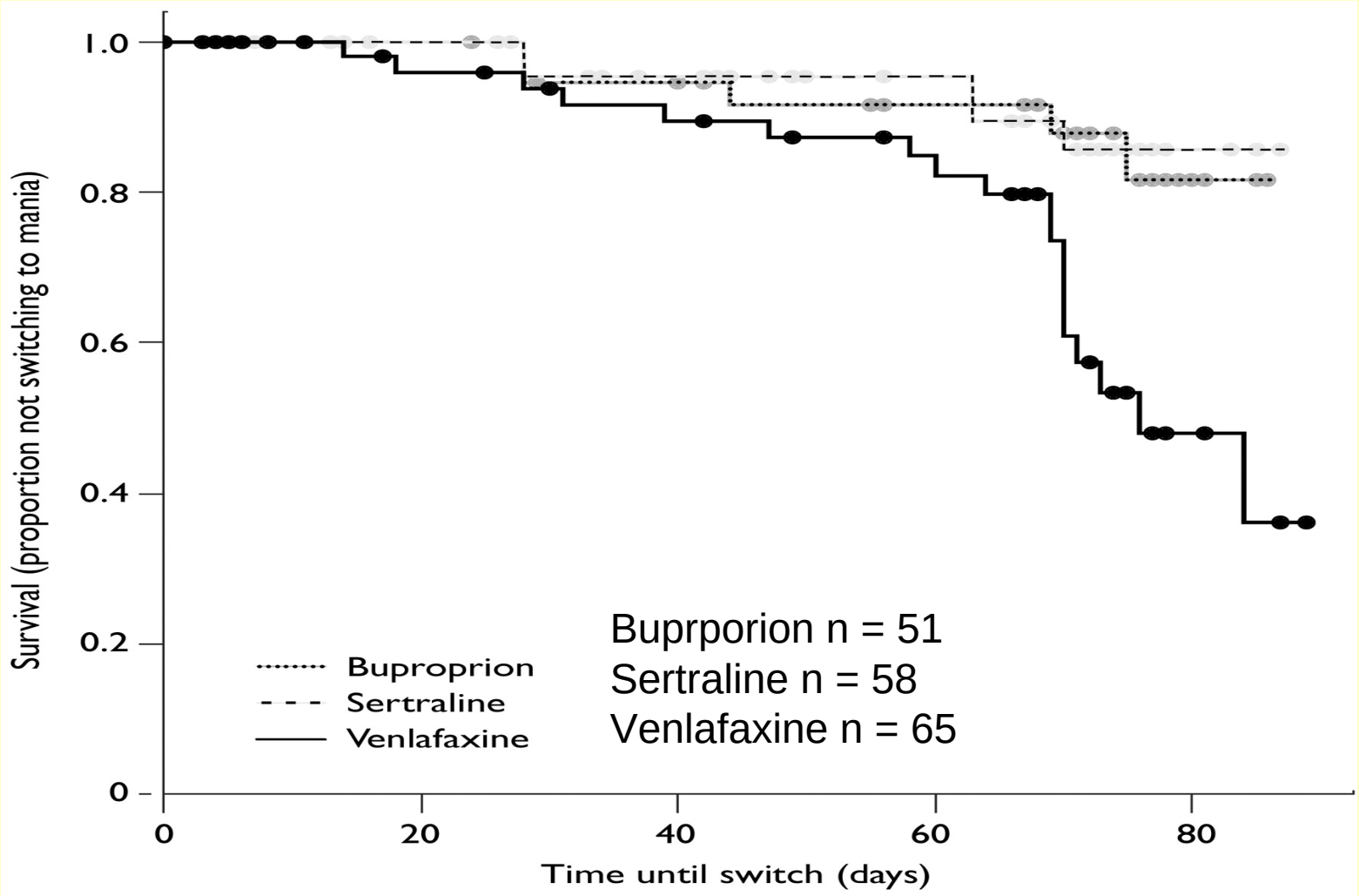


Bipolar II

(Judd LL et al. *Archives of General Psychiatry* 60:261-269, 2003)

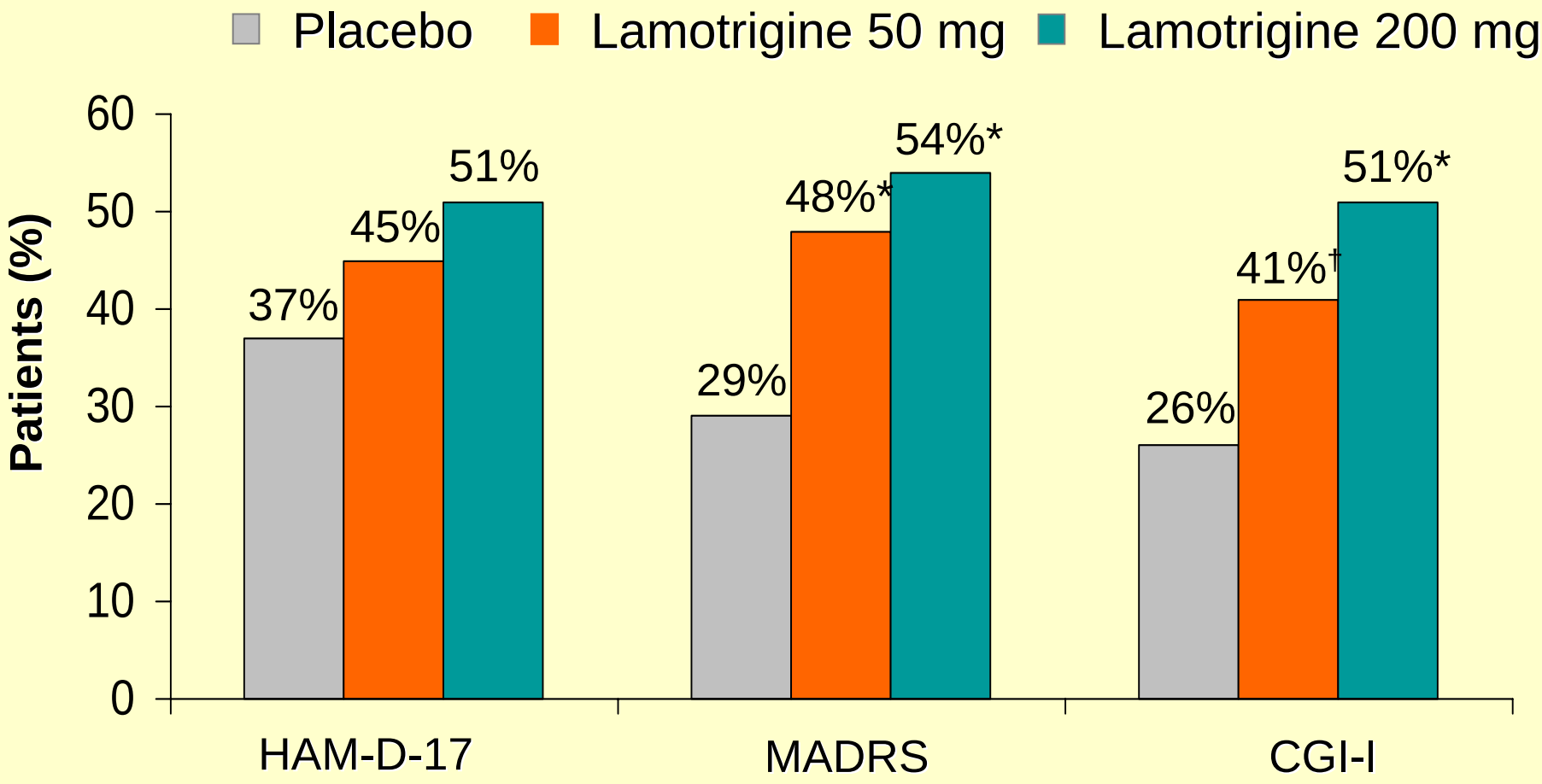


Switching with different antidepressants: Post et al. 2006



Switch defined as a 2-point increase in manic severity score on CGI - Bipolar

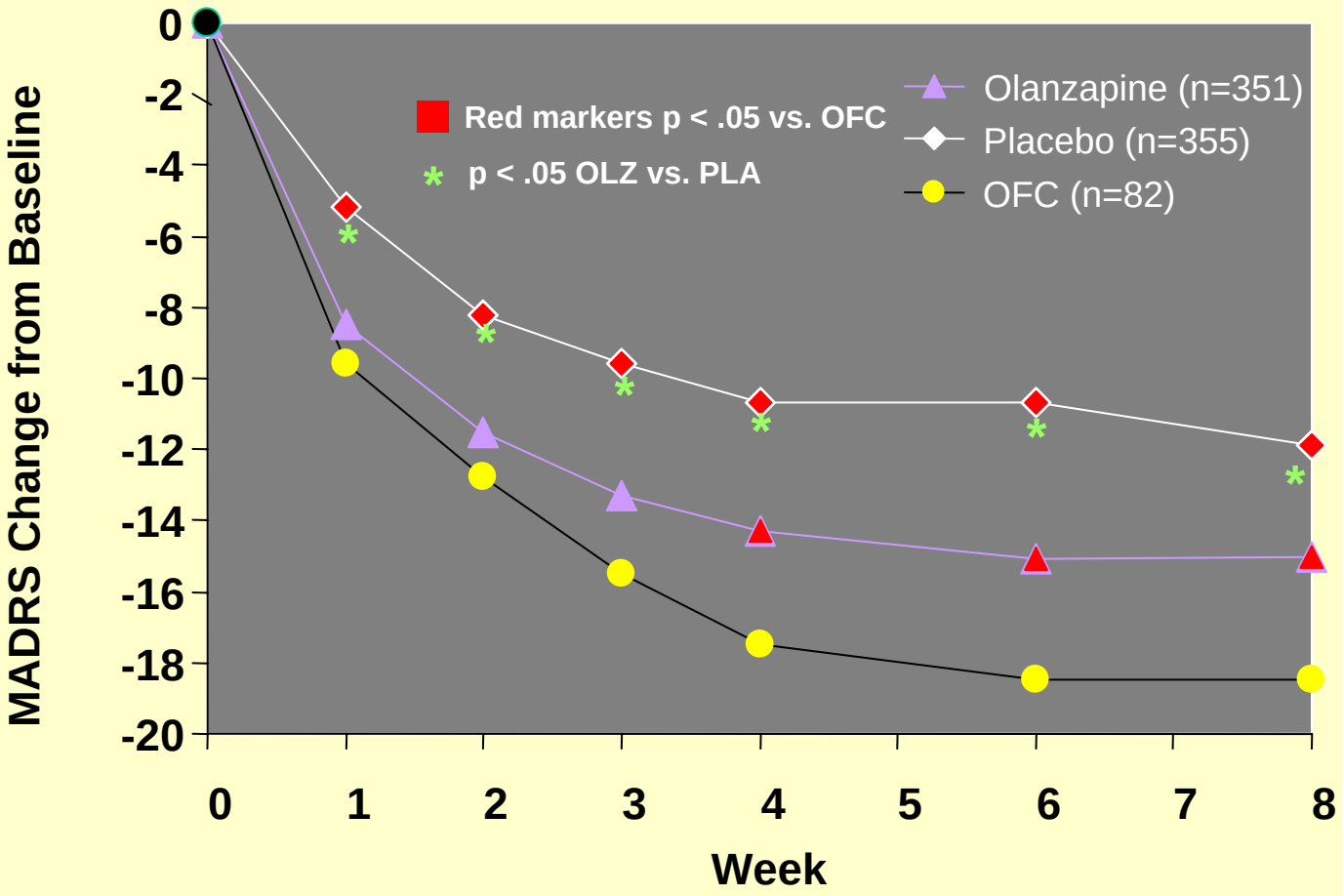
Lamotrigine vs Placebo in Bipolar Depression: Acute Treatment



* *P*<0.05 vs placebo. † *P*<0.1 vs placebo.

Calabrese et al. *J Clin Psychiatry*. 1999;60:79-88.

Olanzapine + fluoxetine in bipolar depression

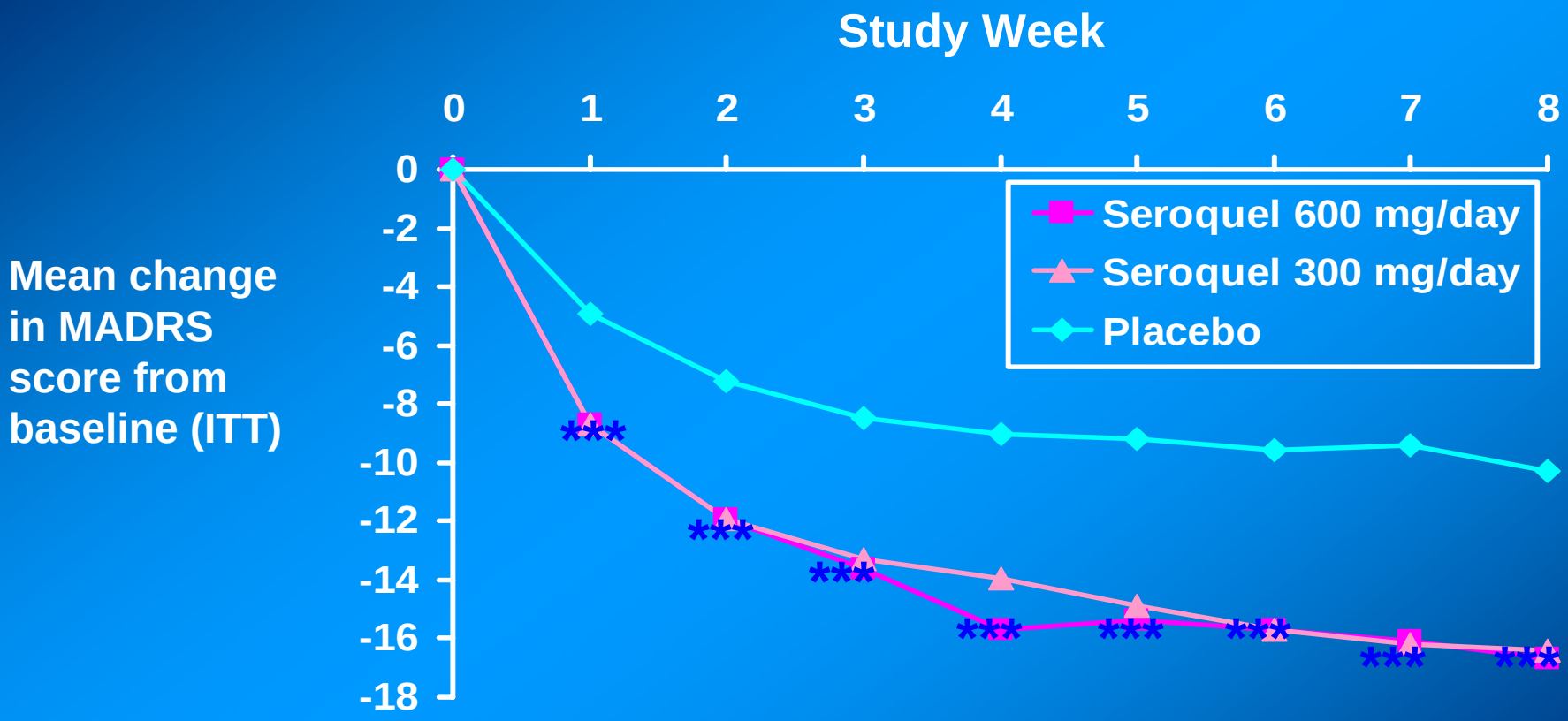


***MMRM = Mixed-Model Repeated Measures**

F1D-MC-HGGY

Tohen M et al. *Arch Gen Psychiatry* 60:1079-1088, 2003

Quetiapine monotherapy in bipolar depression



***p<0.001 vs placebo for both active arms at all time points
Mean baseline scores: BP I 30.5; BP II 30.2

Calabrese J et al. 2005 Am J Psychiatry 162;1351-60.

Acute Depression

- First line: SSRI plus antimanic agent
- If on antimanic: SSRI or quetiapine (if not on antipsychotic)
- If recent unstable mood: avoid antidepressants – increase antimanic and consider lamotrigine
  - NB avoid lamotrigine as a single first line agent in bipolar I but consider this in bipolar II
- If doesn't respond to SSRI switch to mirtazepine or venlafaxine or add quetiapine or olanzapine if not on an antipsychotic
- Taper antidepressants after symptoms reduced for 8 weeks

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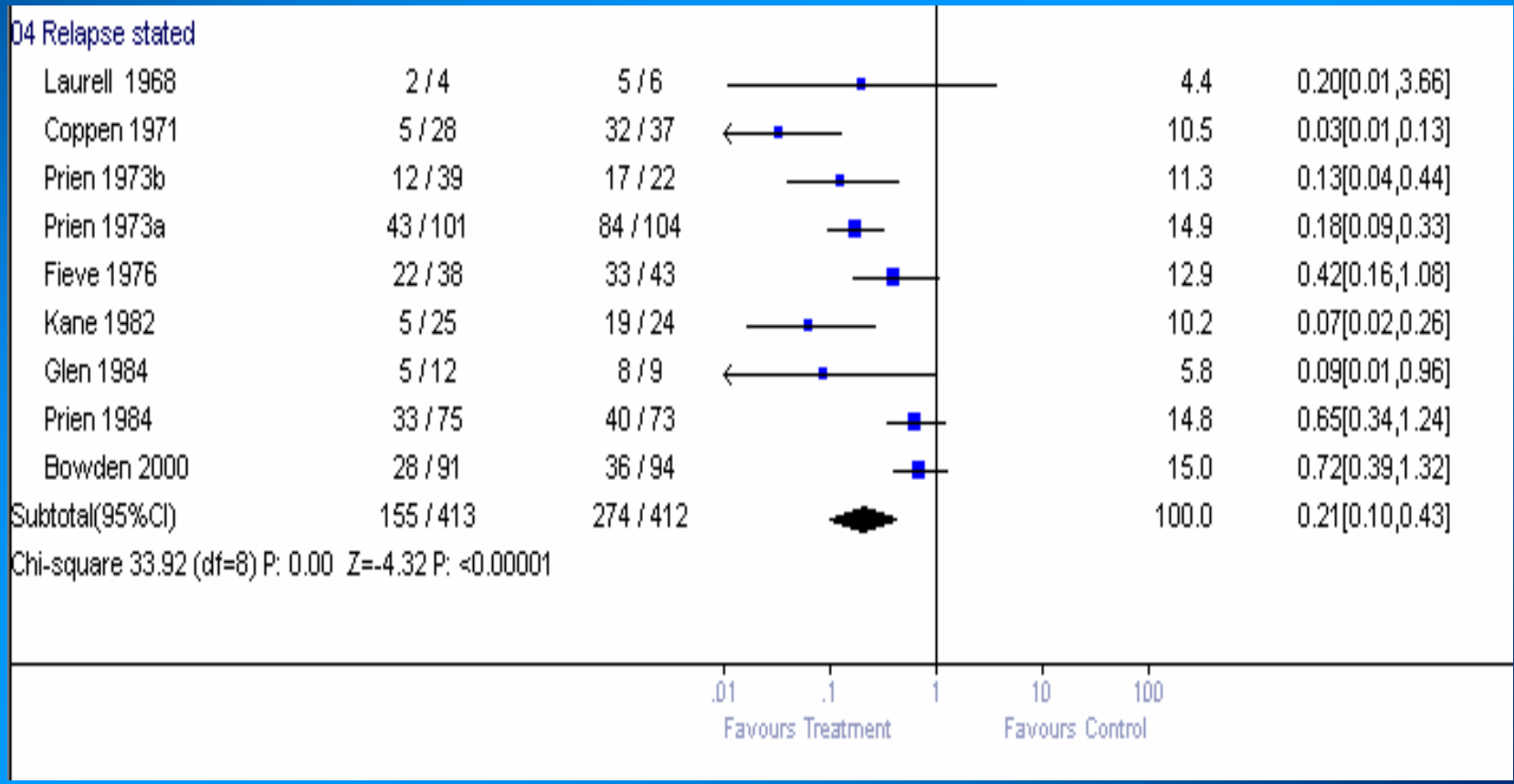
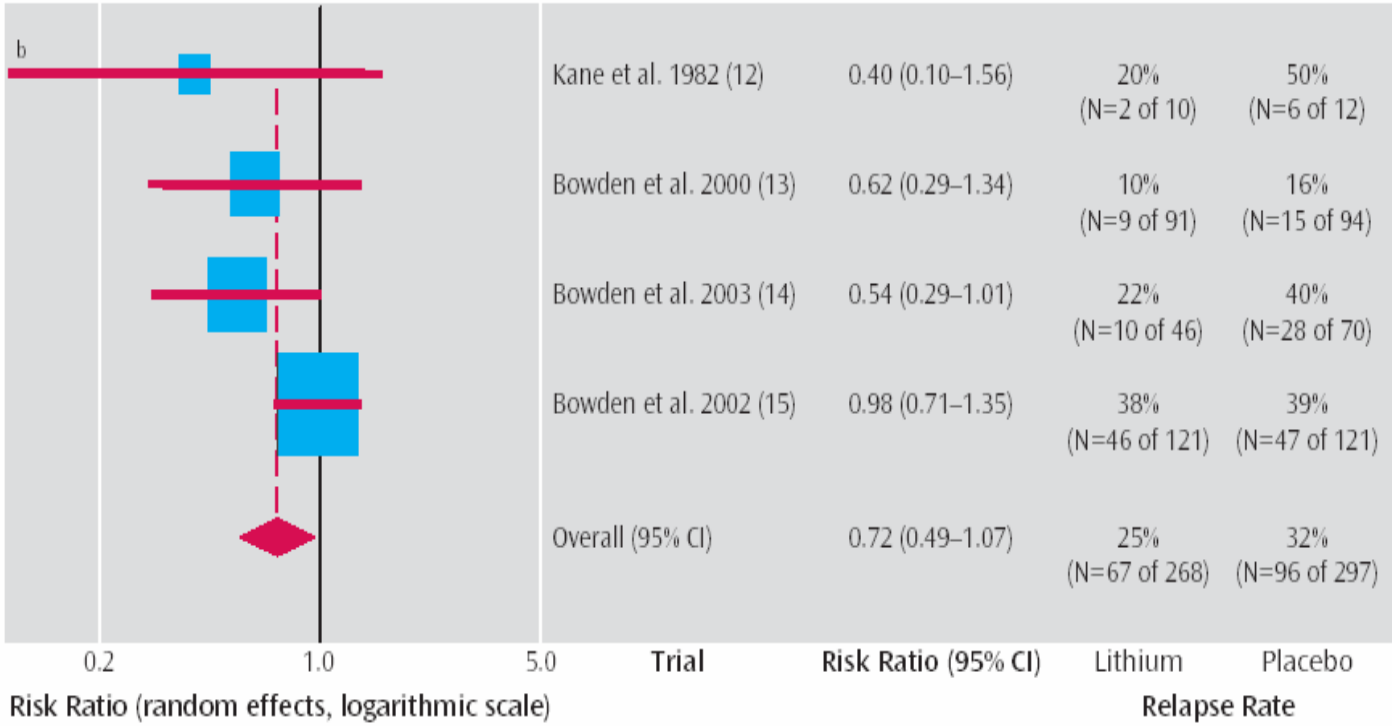
Lithium v placebo, maintenance in bipolar disorder



Lithium *Not* Clearly Superior to Placebo in Preventing Depression

FIGURE 3. Randomized, Placebo-Controlled Trials Assessing the Effectiveness of Lithium for the Prevention of Depressive Relapse in Bipolar Disorder Patients[a]

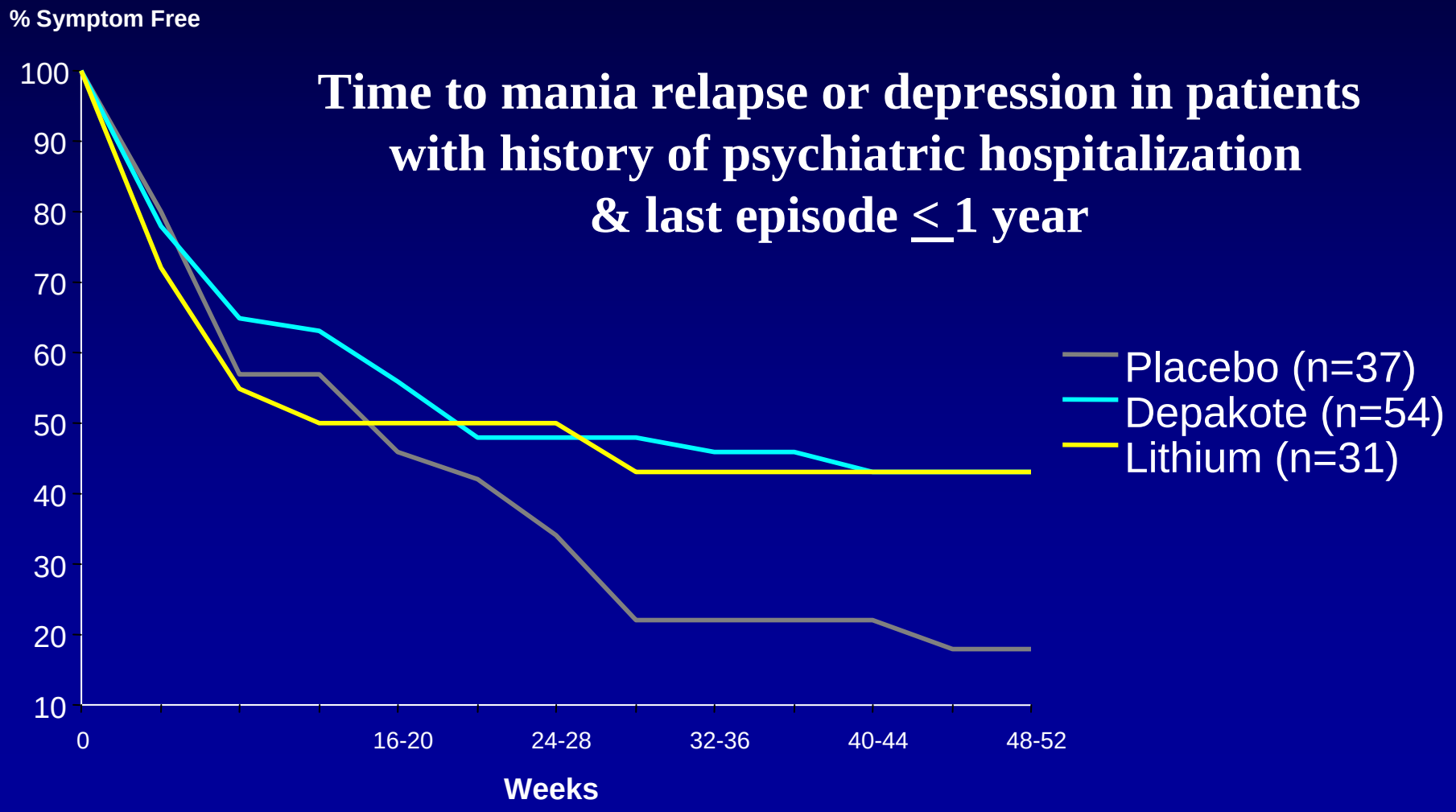


[a] The area of the blue box represents the weighting given to the trial in the overall pooled estimate and takes into account the number of participants and events and the amount of between-studies variation (heterogeneity).
[b] Lower confidence interval extends beyond graph (0.10).

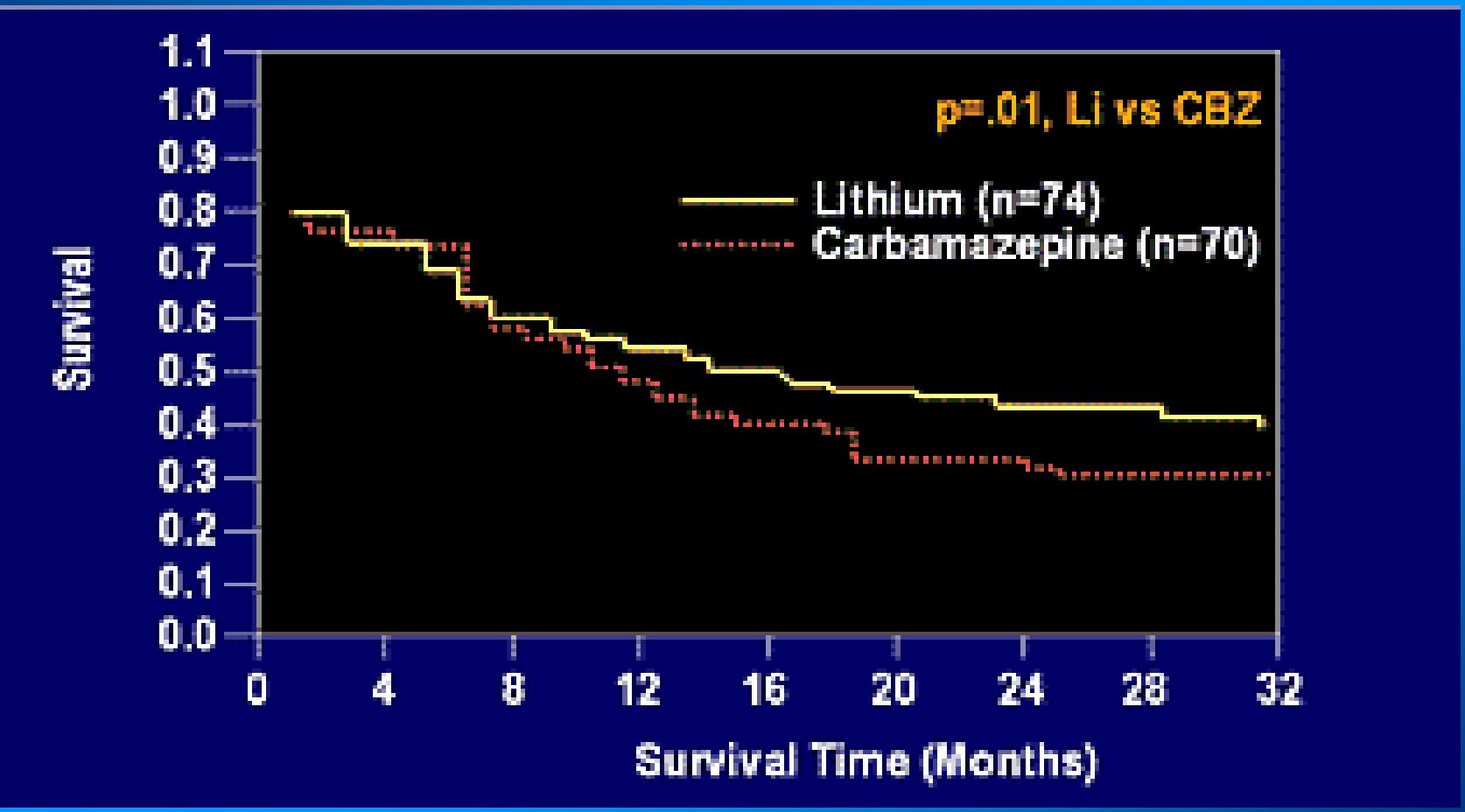
Random effects $p = 0.10$

Geddes J et al. *Am J Psychiatry* 161:217-222, 2004

Evidence base for use of valproate for prophylaxis in bipolar disorder

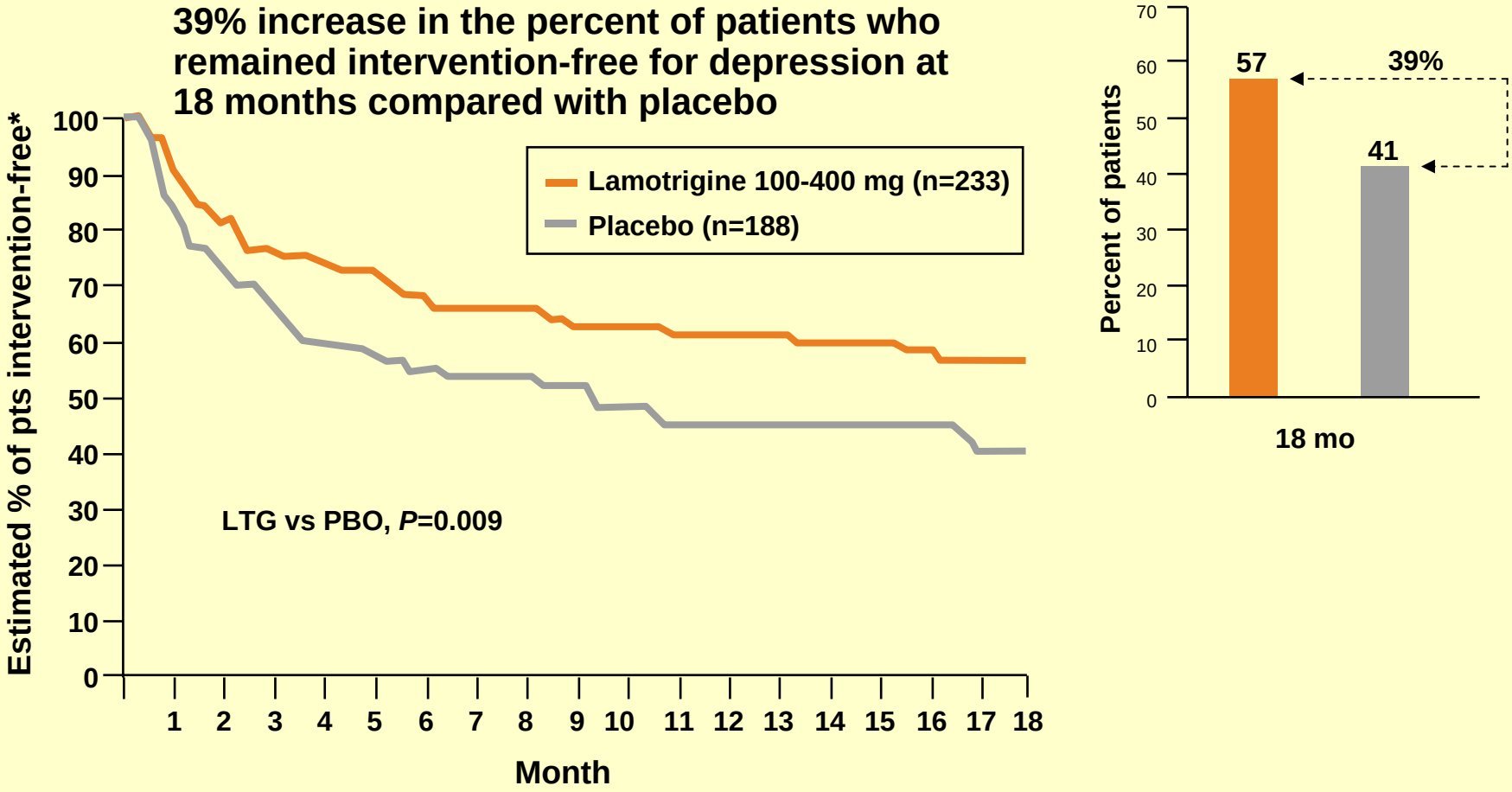


Long Term Treatments – Carbamazepine



Greil et al J Affect Disord 1997

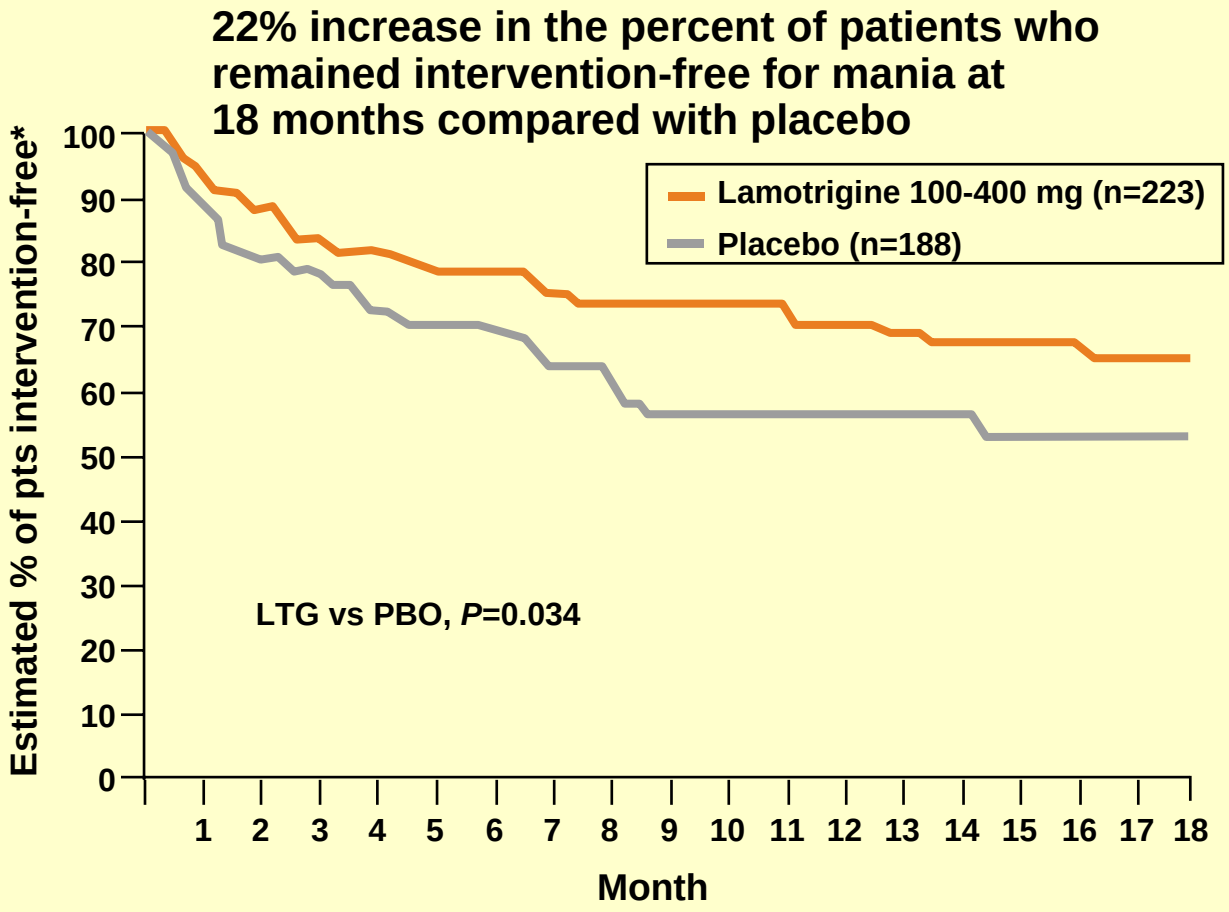
Lamotrigine protection against depressive episodes: Combined analysis

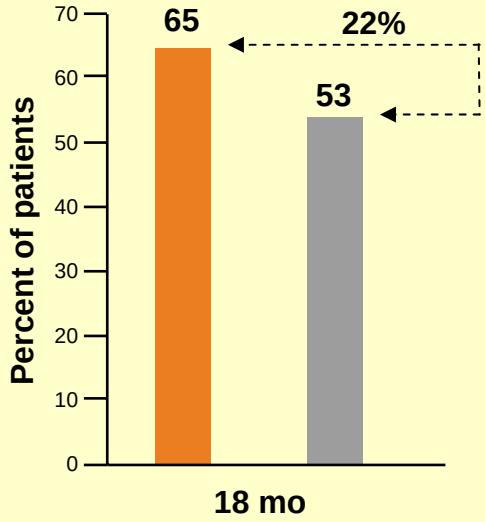


* Some patients considered intervention-free for depressive episodes could have had intervention for manic episodes.

Goodwin et al. 2004 J. Clin. Psychiatry

Lamotrigine protection against manic episodes: Combined analysis

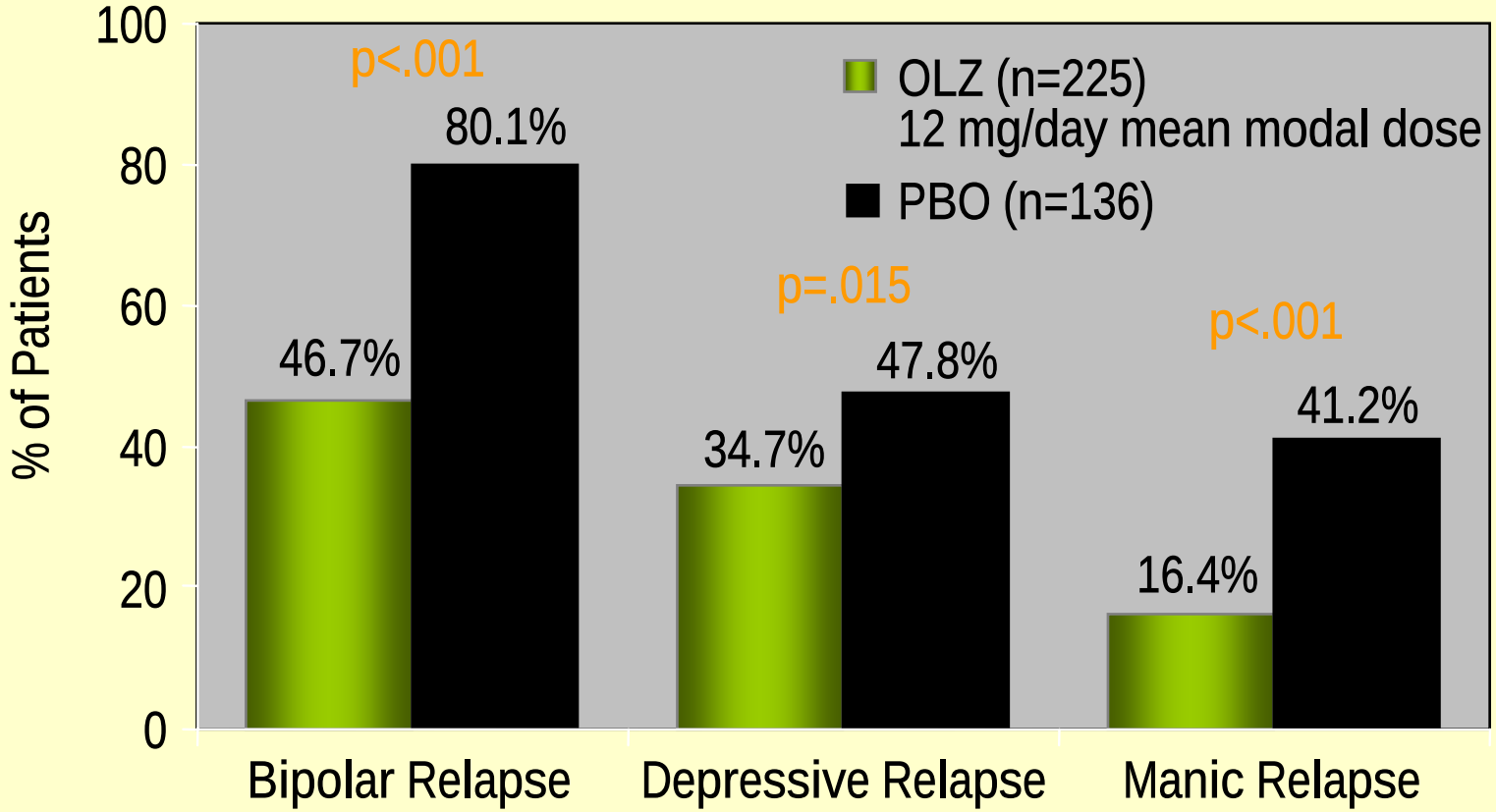




* Some patients considered intervention-free for manic episodes could have had intervention for depressive episodes.

Goodwin et al. 2004 J. Clin. Psychiatry

Olanzapine 12 month continuation in bipolar disorder



Tohen, Calabrese, Sachs et al., *Am J Psychiatry,* 2006; 163(2).

Long-term Treatment: What?

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- First line: lithium, olanzapine or valproate
- If fails monotherapy over 6 months
  - Li + valp, Li + olanz, Valp + olanz
- If combination fails
  - Consider lamotrigine (esp. BPII), carbamazepine, referral to tertiary centre
- NOT antidepressants routinely (unless no mania X 5 yrs)
- Normally treat for at least 5 years

Treatment Resistant BD

Now What?

Clozapine

- Multiple case reports
- Suppes et al 2003
  - Open label, 1-year, RCT in treatment refractory BDI
  - Clozapine add-on vs usual care
  - Improvement noted in the Clozapine treatment group
- Ciapparelli et al 2000
  - Open-label, 2-year, naturalistic study in treatment refractory SZ and BD patients
  - Significant improvements on Clozapine in all patients, greater for BD than SZ

ECT

- ?Unique bi-modal efficacy
- Safe

- Vaidya et al J ECT 2003
  - **Effective in Refractory Bipolar Disorder (both acute and maintenance treatment)**


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Daily Mail
Evening Standard
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