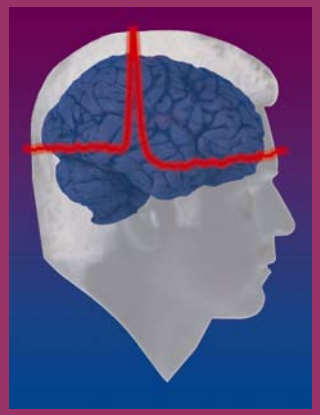
Newcastle University

Psychobiology Research Group



Management of Depression: Some observations

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NICE Clinical Guideline 23

December 2004

National Institute for Clinical Excellence

Depression: management of depression in primary and secondary care

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Original Papers

Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines

I. M. Anderson[1], D. J. Nutt[2] and J. F. W. Deakin[1], on behalf of the Consensus Meeting and endorsed by the British Association for Psychopharmacology

[1]*University of Manchester Department of Psychiatry, University of Manchester, Oxford Road, Manchester and* [2]*University of Bristol, Psychopharmacology Unit, School of Medical Sciences, Bristol, UK*

A revision of the British Association for Psychopharmacology guidelines for treating depressive disorders with antidepressants was undertaken in order to specify the scope and target of the guidelines and to update the recommendations based explicitly on the available evidence. A consensus meeting, involving experts in depressive disorders and their treatment, reviewed key areas and considered the strength of evidence and clinical implications. The guidelines were drawn up after extensive feedback from participants and interested parties. A literature review is given which identifies the quality of evidence followed by recommendations, the strength of which are based on the level of evidence. The guidelines cover the nature and detection of depressive disorders, acute treatment with antidepressant drugs, choice of drug versus alternative treatment, practical issues in prescribing, management when initial treatment fails, continuation treatment, maintenance treatment to prevent recurrence and stopping treatment.

Key words: antidepressants; depressive disorder; evidence-based guidelines; treatment

Treatment of Depression: Basic Steps

- Identify depressive syndrome
- Educate patient and others
- Select treatment
- Monitor response and adjust treatment
- Maintenance treatment
- Non-response strategy

Diagnostic dilemmas

- “Normal” misery vs depression
- Unipolar vs bipolar disorder
  - Between 9 and 24% of unipolar depression patients end up with a different diagnosis, mainly bipolar affective disorder (Angst & Preisig, 1995)

Treatment of Depression: Basic Steps

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Factors influencing choice between antidepressants: Draft BAP 2007 guidelines

- Antidepressants have similar efficacy in the majority of patients with major depression

- Factors to consider in choosing an antidepressant include:
  - Previous response to drug (D)
  - Tolerability and adverse effects to previous drug (D)
  - Response and/or side effects in family members (D)
  - Side effect profile (C)
  - Low lethality if suicide risk (D)
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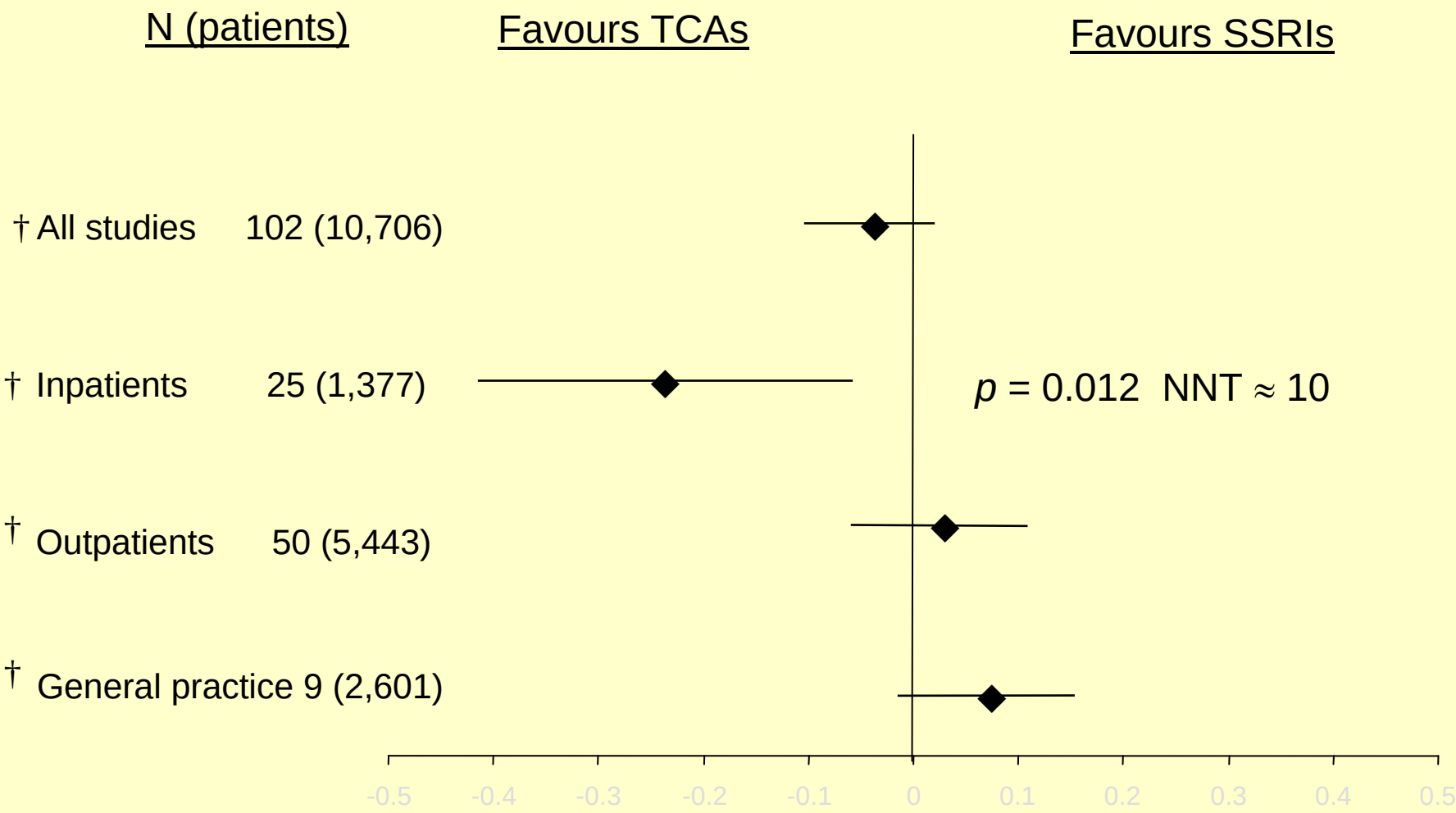
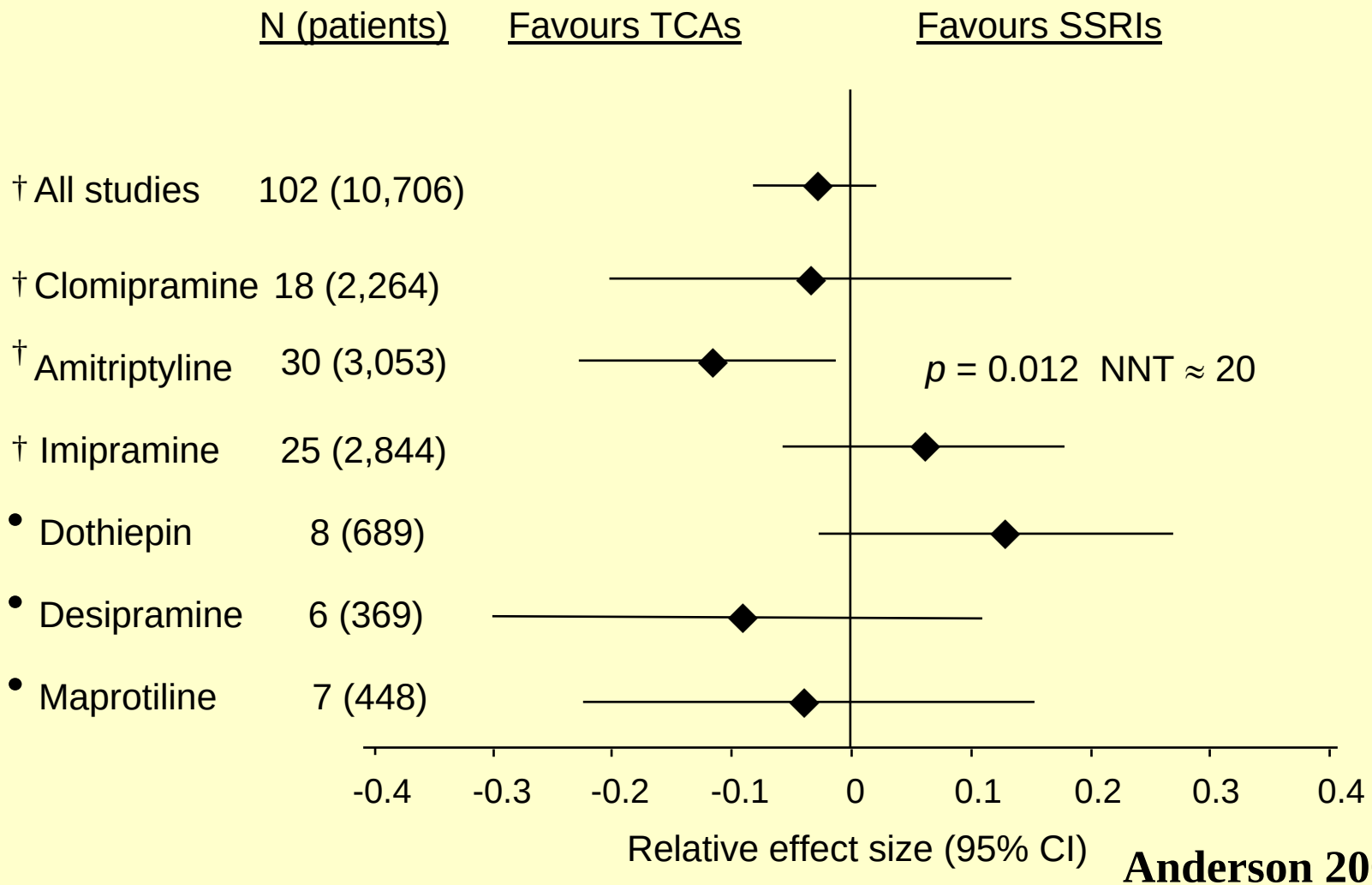
Efficacy: SSRIs versus TCAs



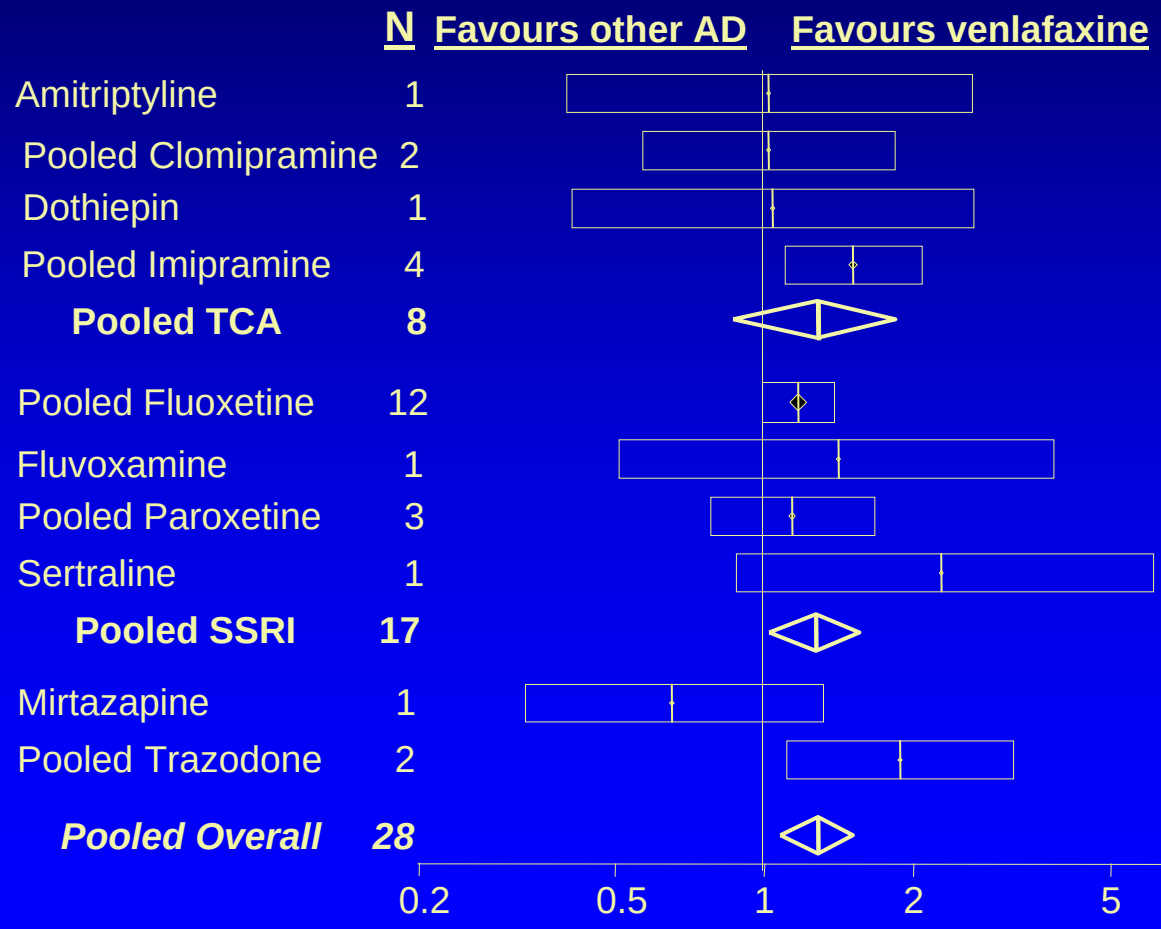
Anderson 2000

Efficacy: TCAs vs SSRIs



Anderson 2000

Efficacy of venlafaxine vs other antidepressants

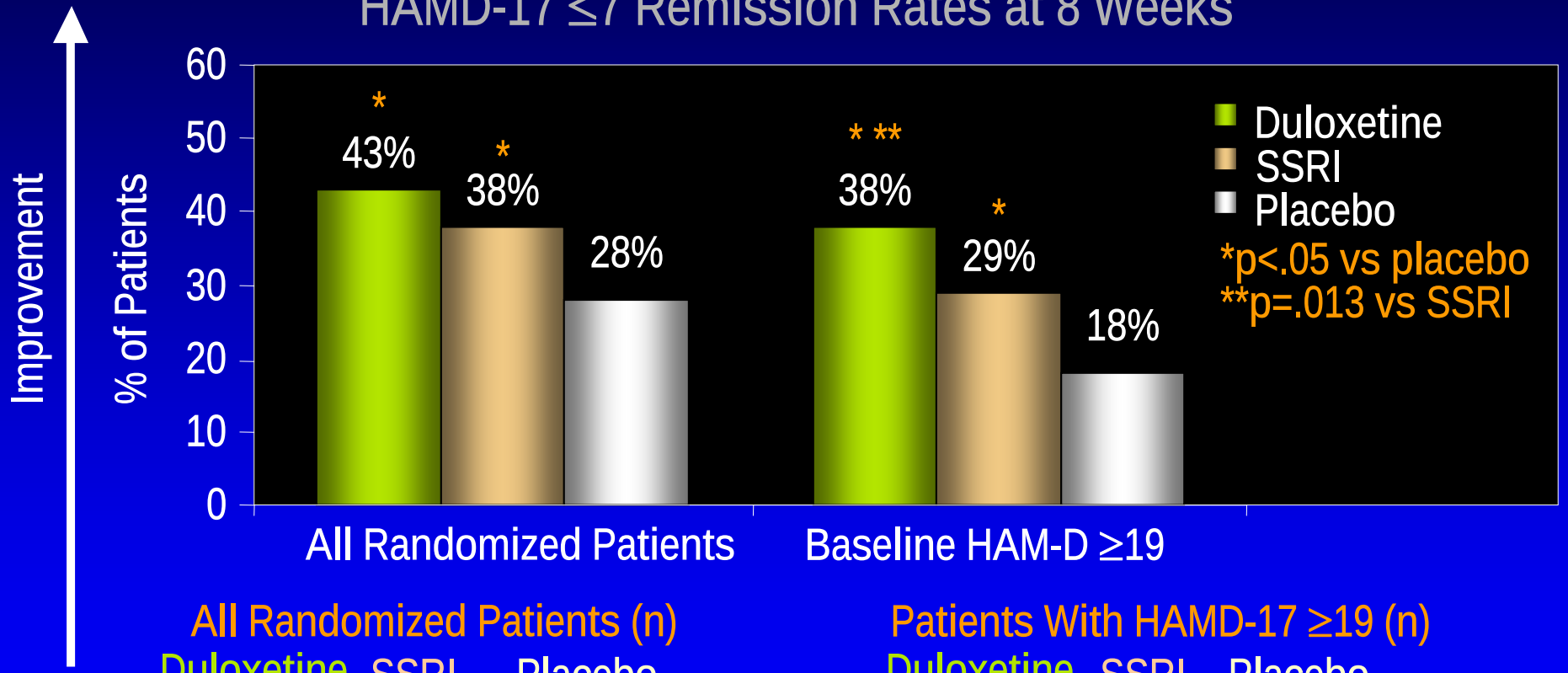


NNT = 19

Smith et al 2002

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

HAMD-17 ≤7 Remission Rates at 8 Weeks



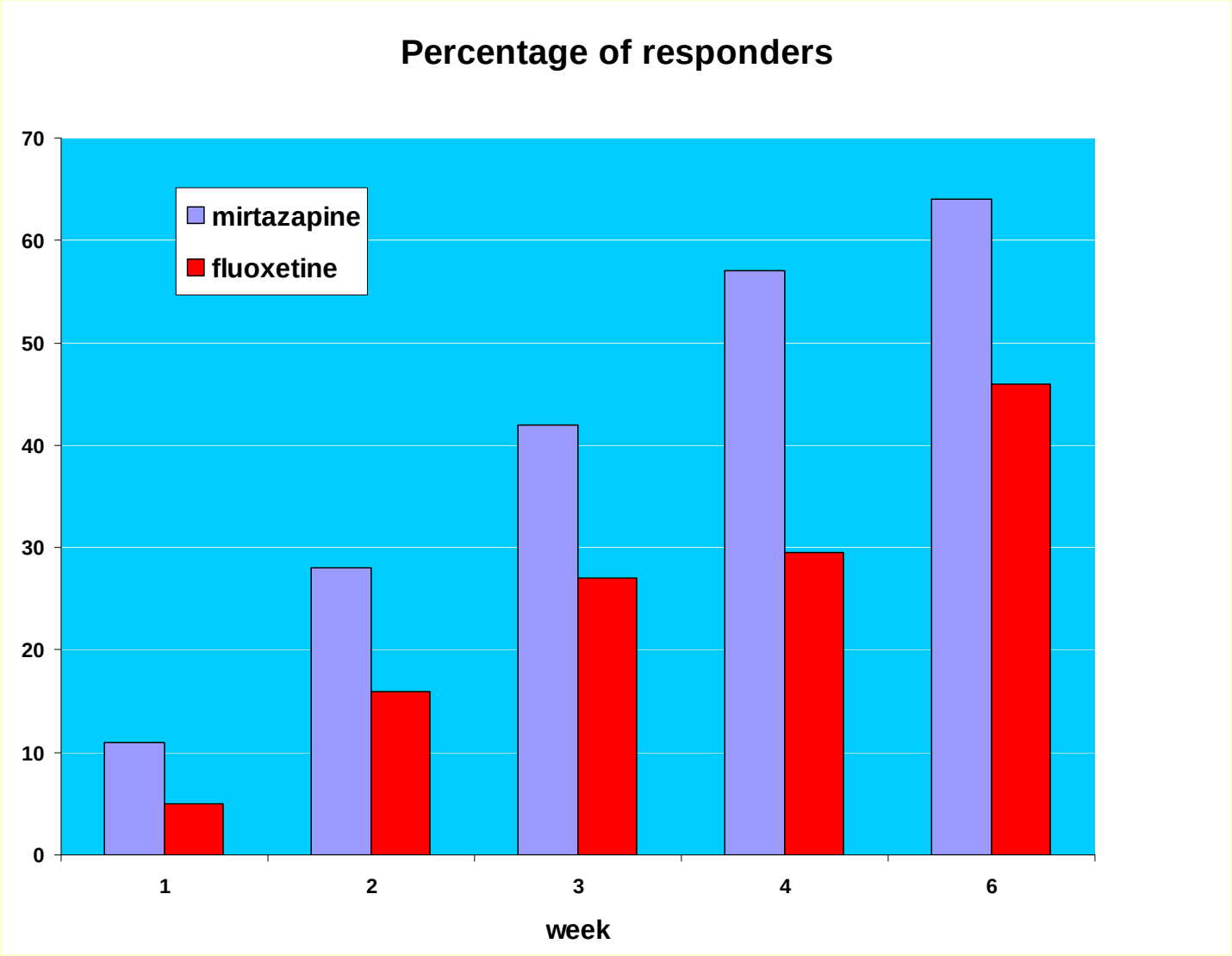
All Randomized Patients (n)		
Duloxetine	SSRI	Placebo
(711)	(429)	(516)

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

NICE conclusions….

- Amitriptyline
  - Significant benefit of AMT over other ADs in IP
    - Clinically significant?
    - NB less well tolerates in OP but no diff in IP
- Venlafaxine
  - Significantly better than SSRIs at achieving response or remission
    - Clinically significant?
    - Effects more evident at doses at 150mg + (when Mirtaz excluded)
    - Effects more evident in severely ill
- Mirtazepine
  - Significantly better at achieving remission than other antidepressants
    - Clinically significant?
    - NB less likely to leave treatment early

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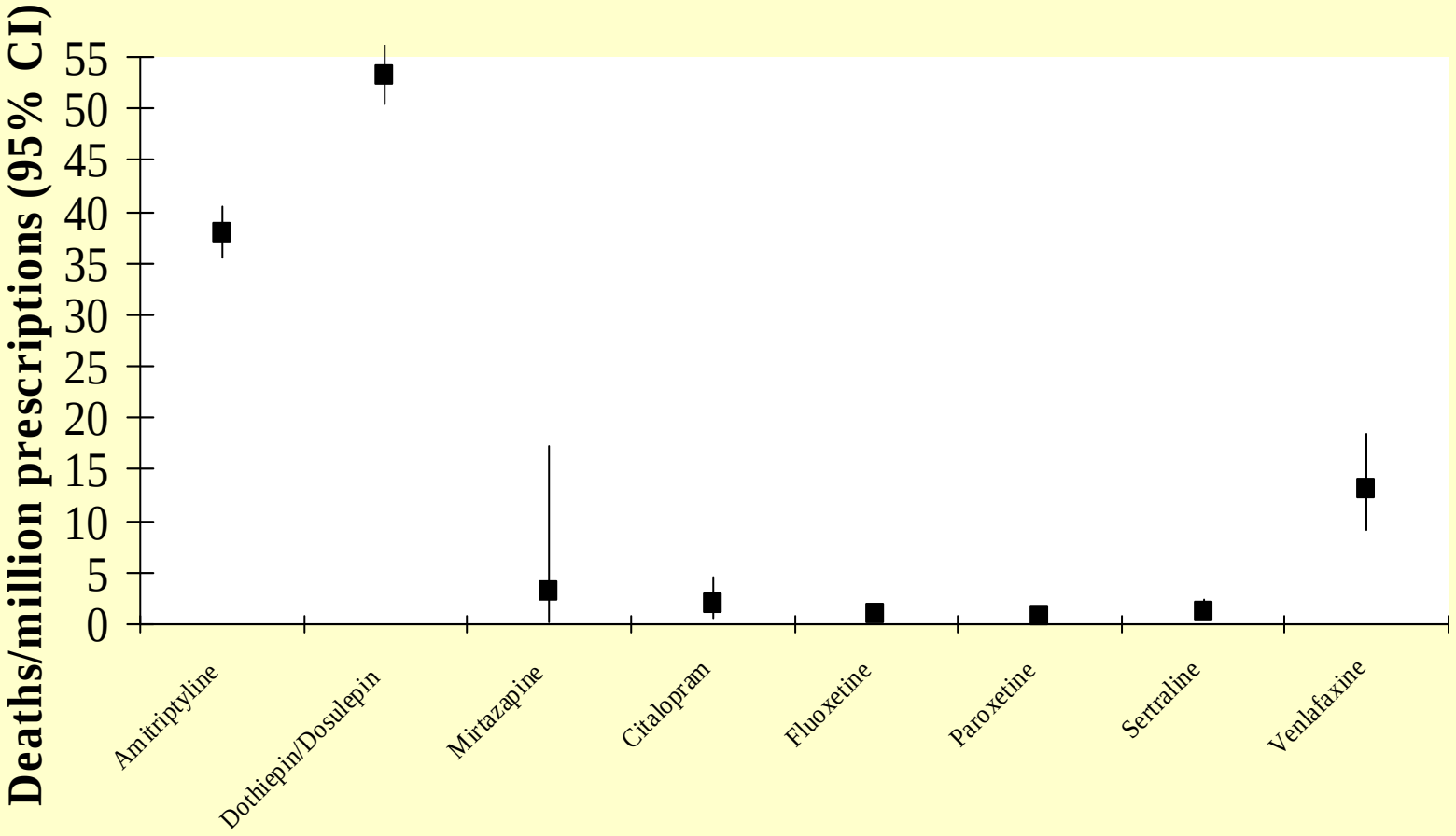
Fatal toxicity of serotonergic and other antidepressant drugs

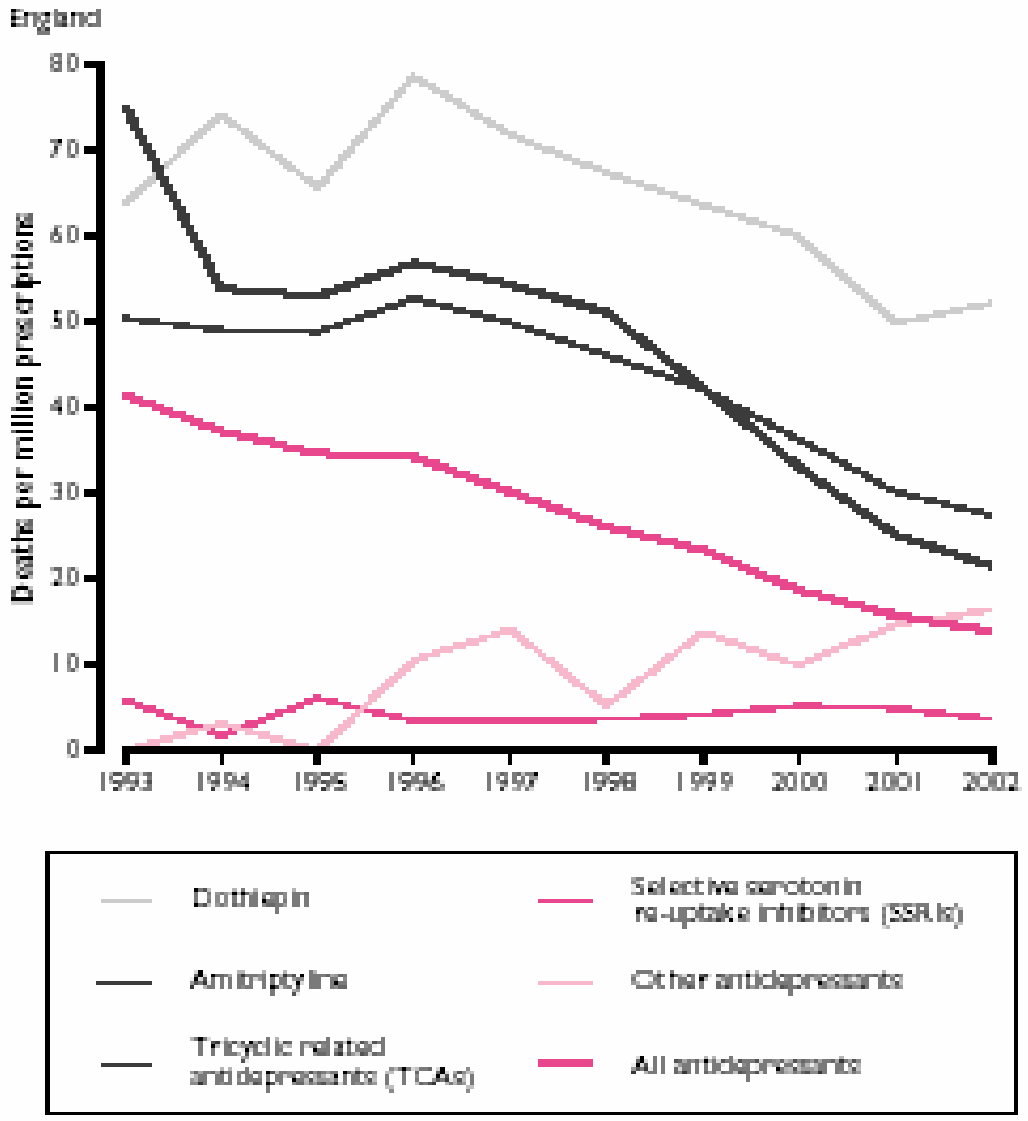
"1993-1999, Single ingestions ± alcohol:England,Wales & Scotland"

FTI= fatal toxicity index expressed as deaths per million prescriptions.



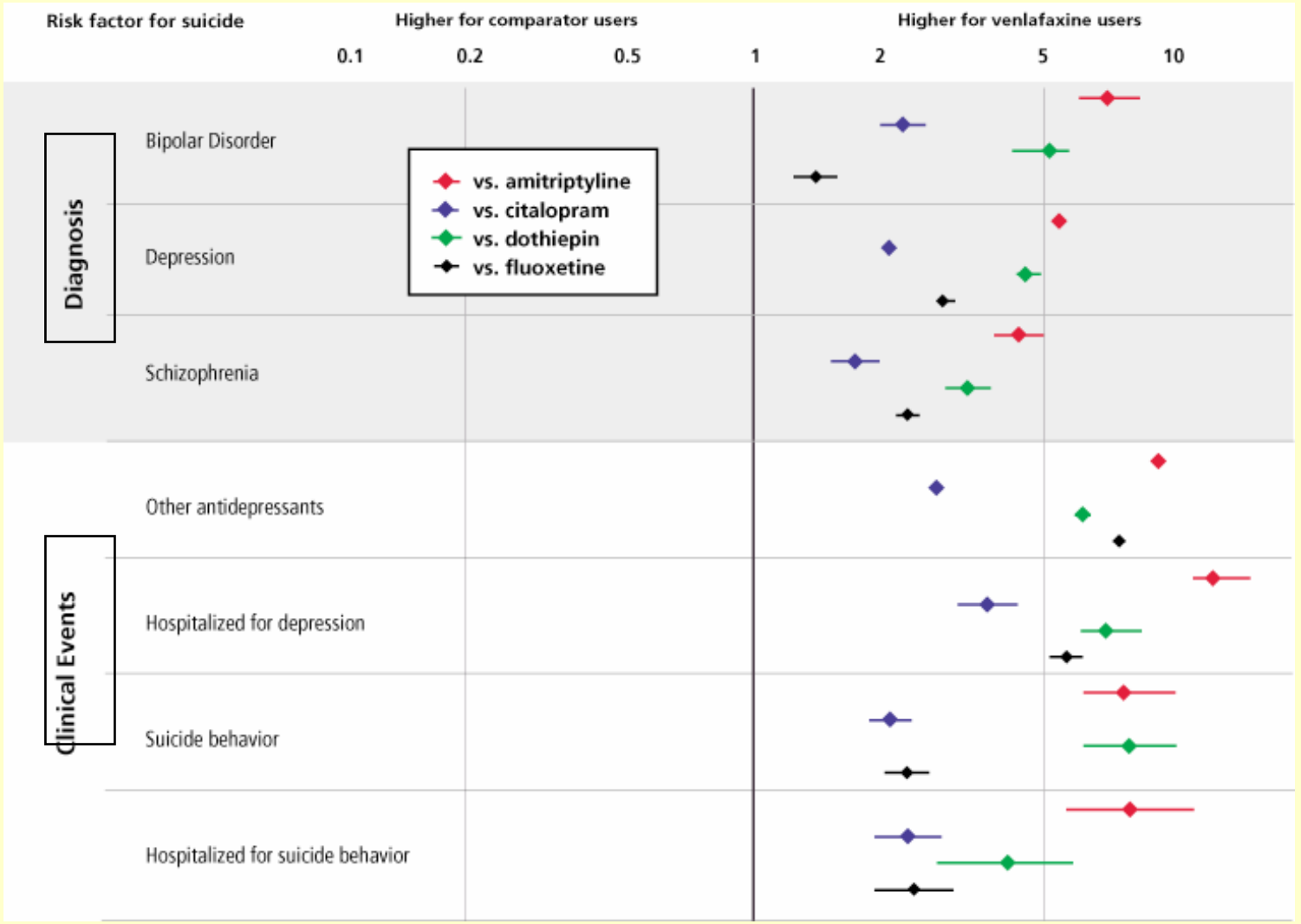
Buckley N and McManus P, BMJ 2002 325 : 1332-1333

Figure 4 Antidepressant-related deaths per million prescriptions for selected antidepressants, 1993–2002



Morgan O, Griffiths C, Bajer A, Majeed A. Health Statistics Quarterly, Autumn 2004.

GPRD study: Burden of pre-existing risk factors



Adapted from Mines D et al, Pharmacoepidemiol and Drug Safety 2005;14:367-72 &
Data on file.Wyeth GPRD Report, 17 Jan 2005

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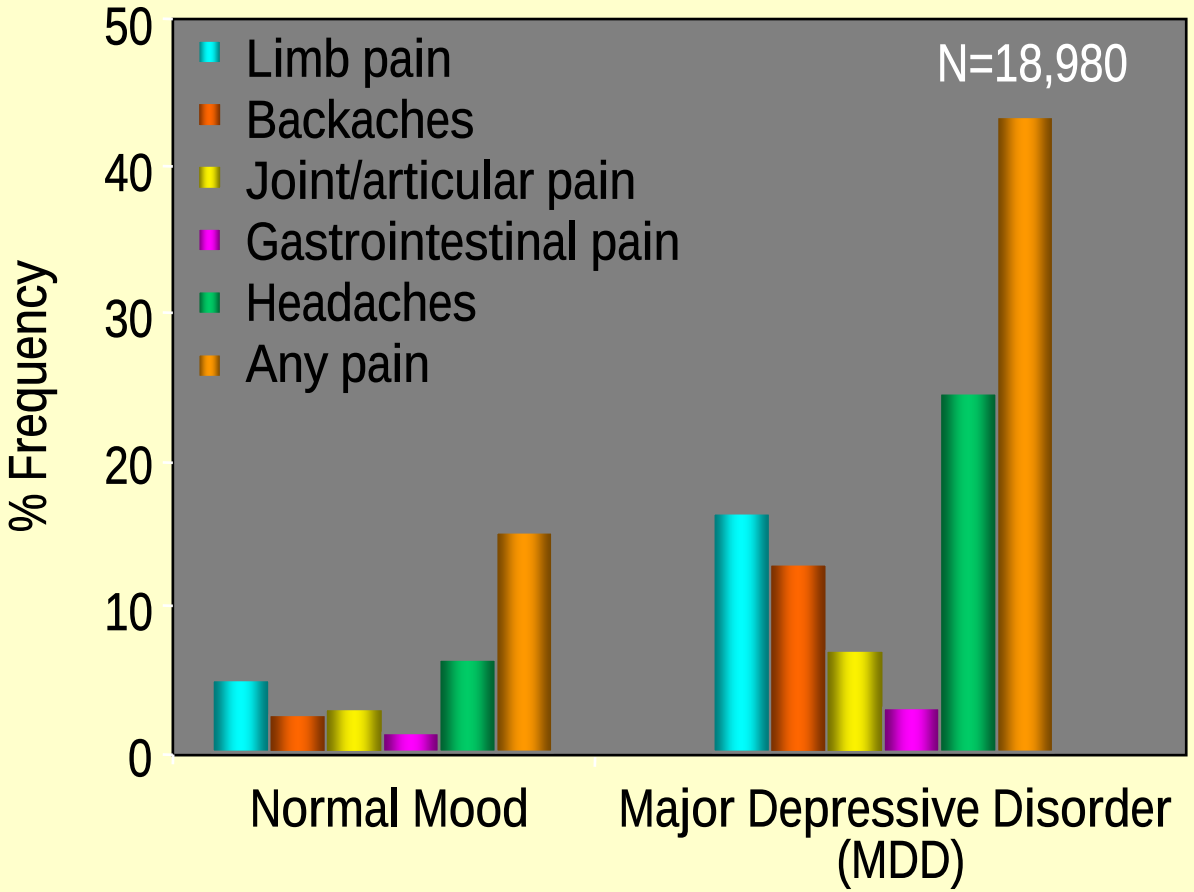
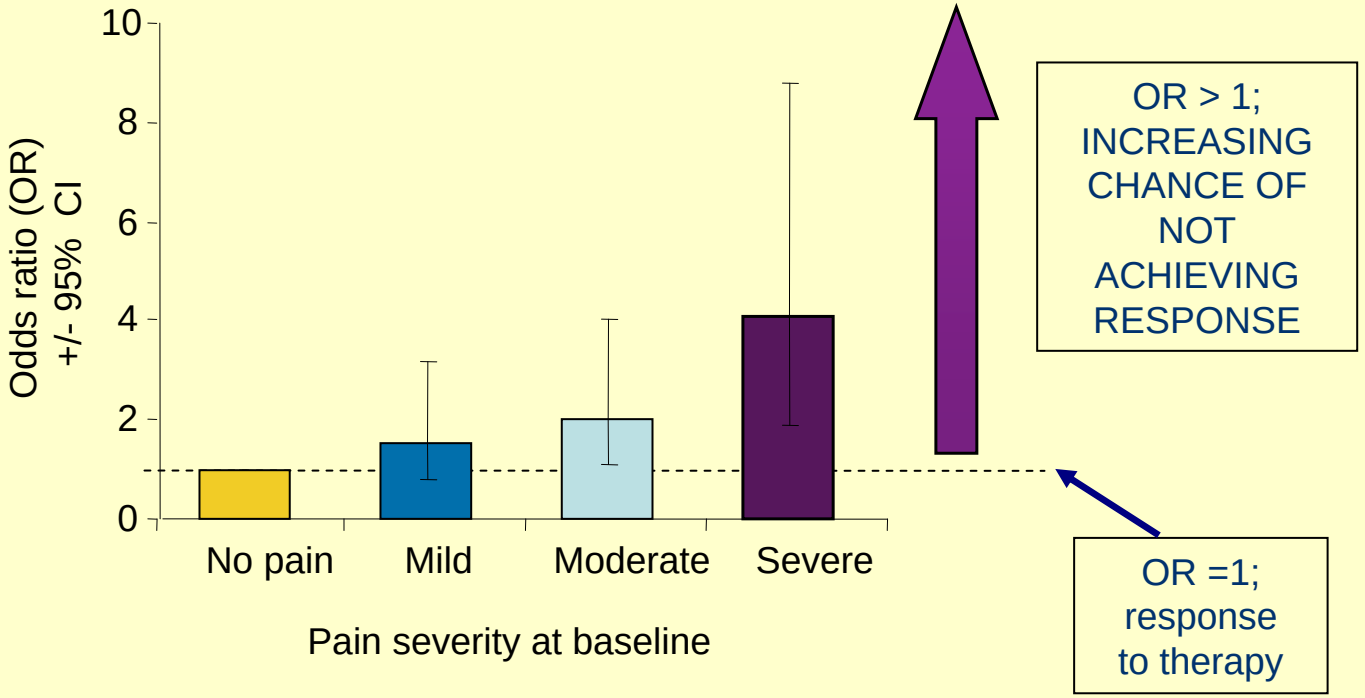
Painful Symptoms Are Highly Correlated With Depression



Ohayon MM, Schatzberg AF. *Arch Gen Psychiatry.* 2003;60(1):39-47.

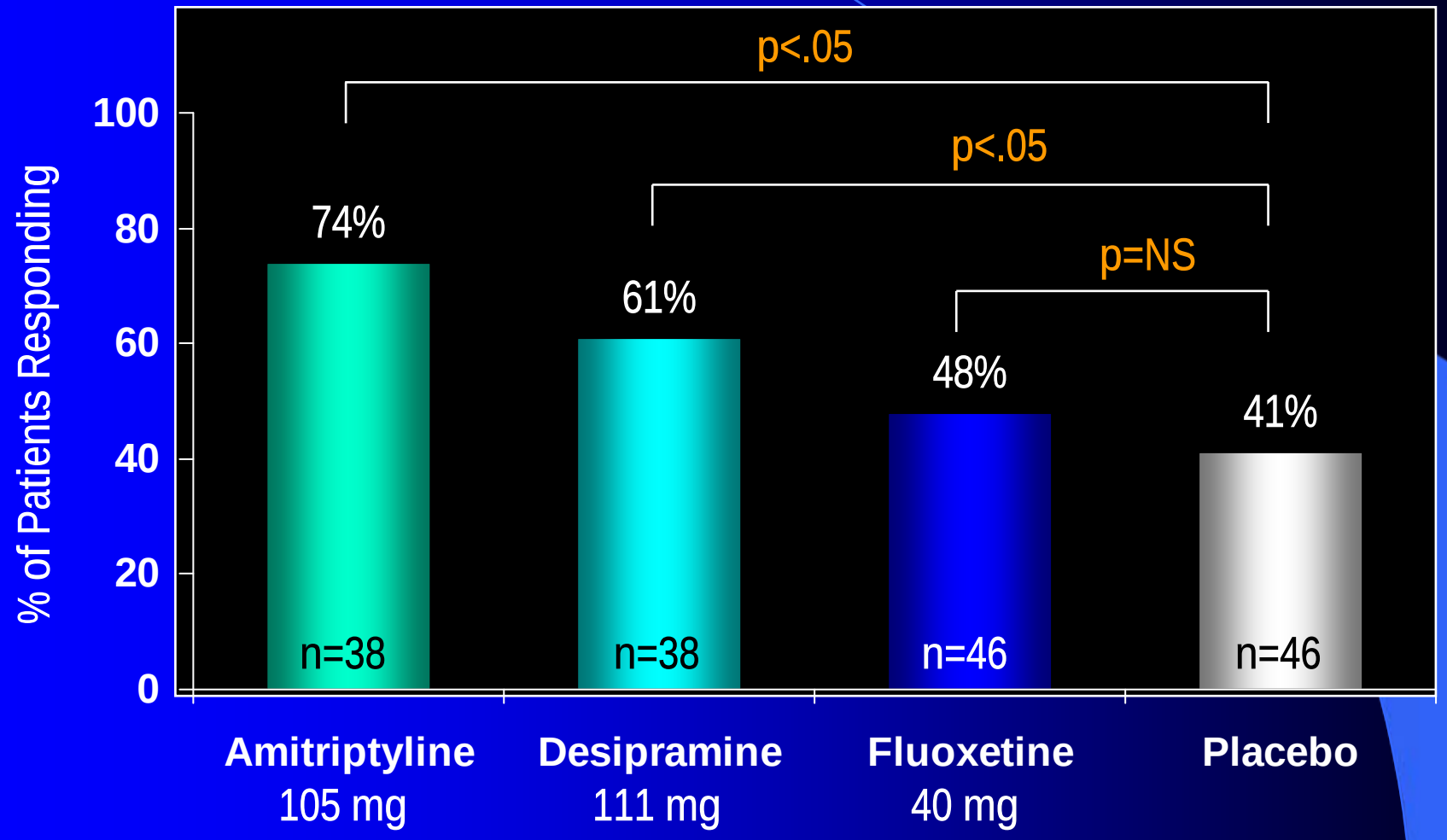
Severity of pain and response to SSRI therapy



N=573
SF-36 scale

Bair MJ *et al*. *Psychomsomatic Med* 2004; **66**:17–22.

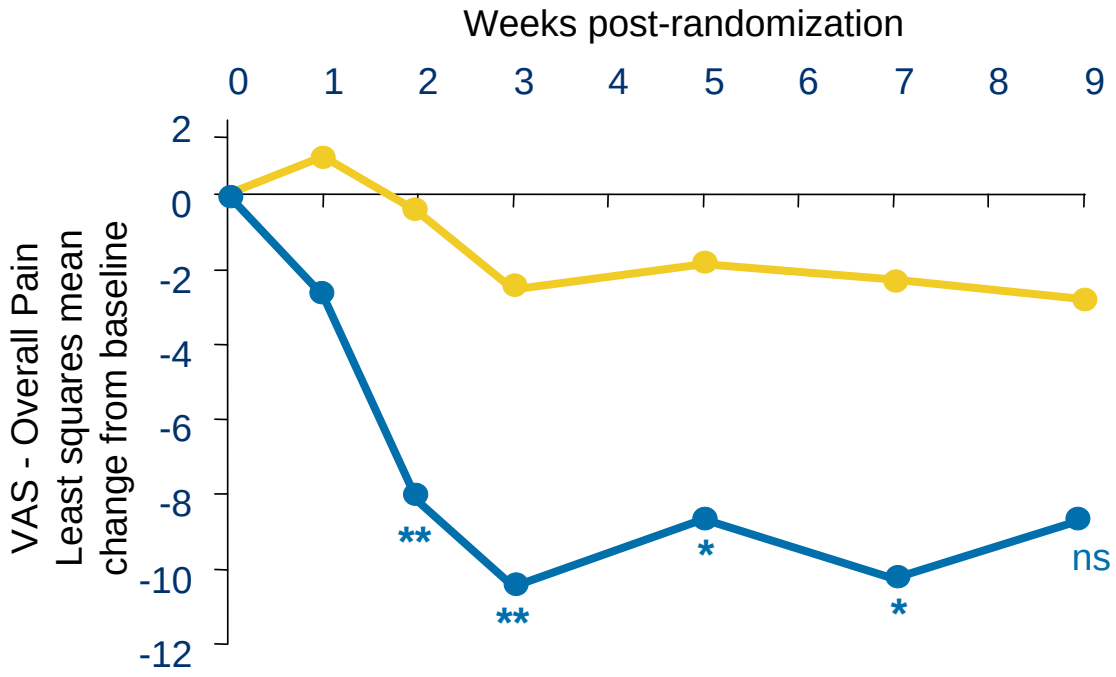
Amitriptyline, Desipramine, and Fluoxetine for Pain



Max MB, et al. *N Engl J Med.* 1992;326(19):1250-1256.

General aches and pains relief in depressed patients – 60 mg OD study

In a large study (N=18,980) 43% of patients with depression experienced general aches and pains (GAPs)[1]



*p<0.05 vs. placebo
**p<0.01 vs. placebo
ns p=0.055
MMRM

Placebo (n = 122)
Duloxetine 60mg OD (n = 123)

Detke, *et al*. *J Clin Psychiatry* 2002; **63**: 308-315.

Treatment of Depression: Basic Steps

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- Educate patient and others
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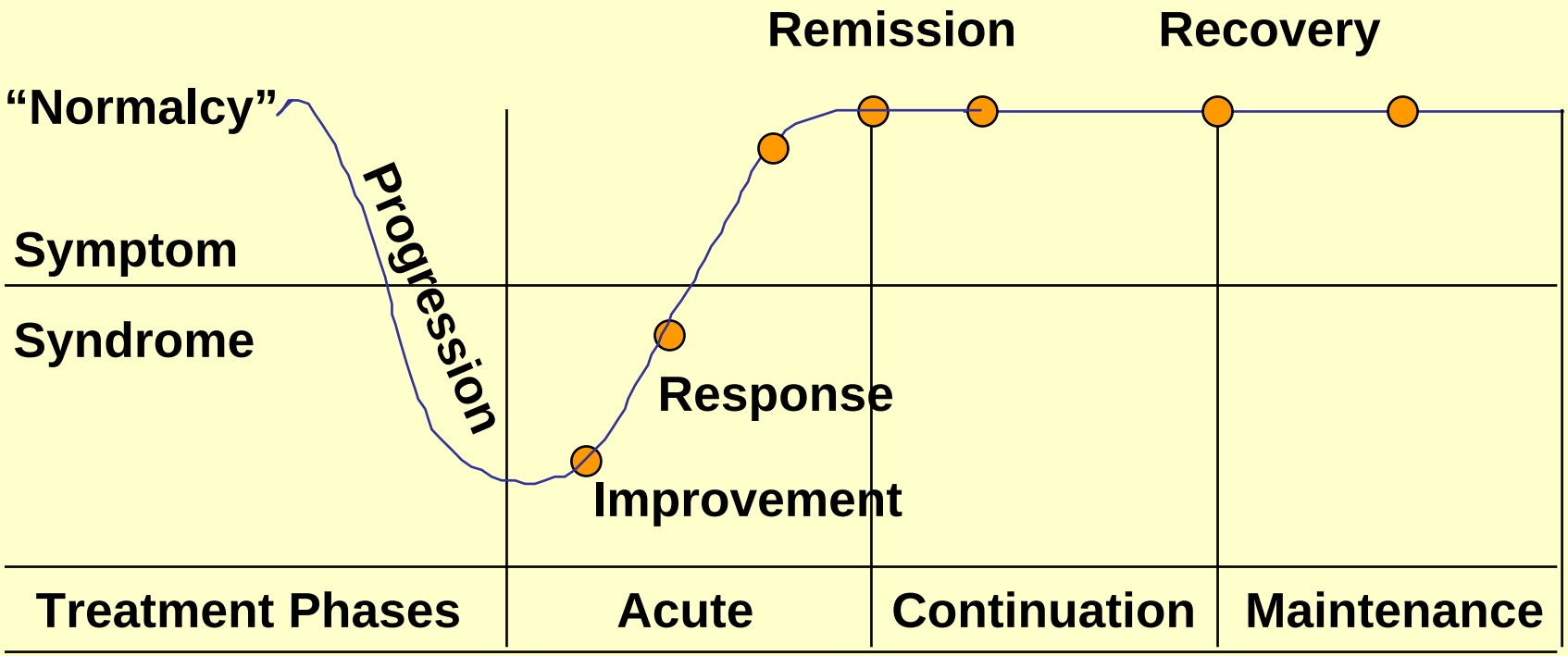
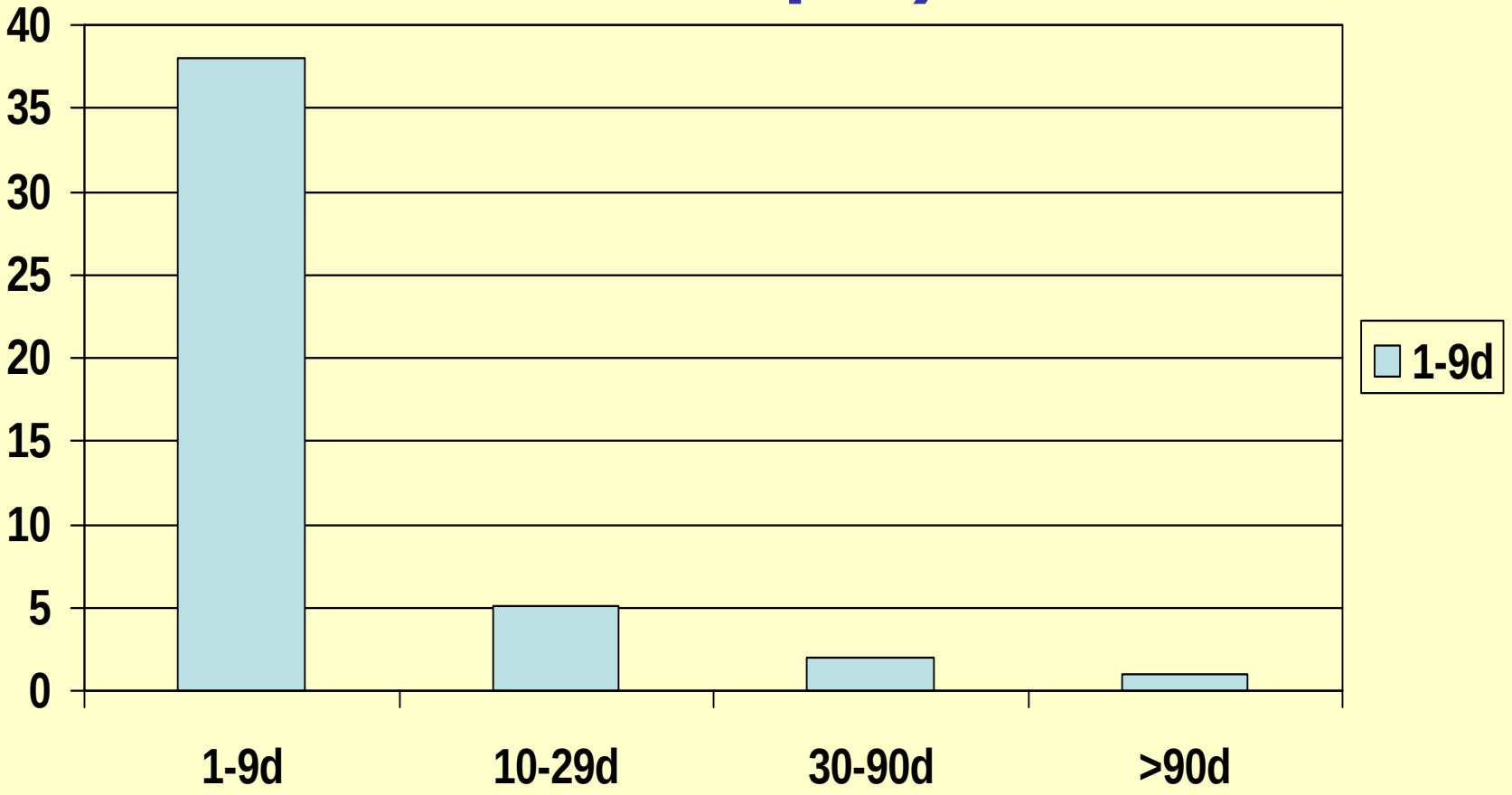
- Maintenance treatment
- Non-response strategy

Course and outcome of depression



Adapted from Kupfer 1991.

Risk of Suicidal Behaviour in Relation to Onset of Treatment (Fatal Attempts)



Treatment of Depression: Basic Steps

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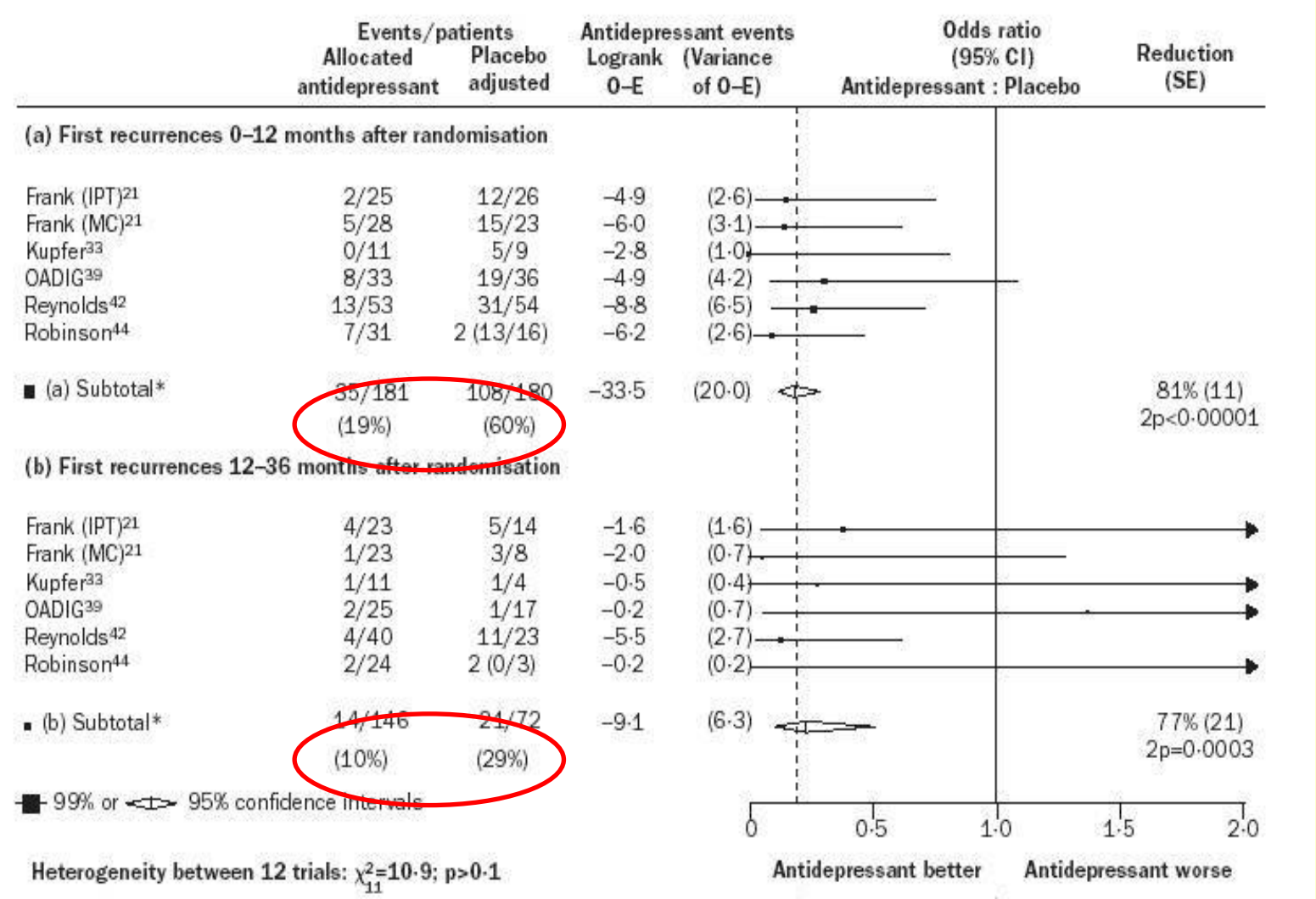
Reduction in the risk of relapse with continuation of antidepressants



Geddes et al 2003

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“Real World” Efficacy of SSRIs (STAR*D)

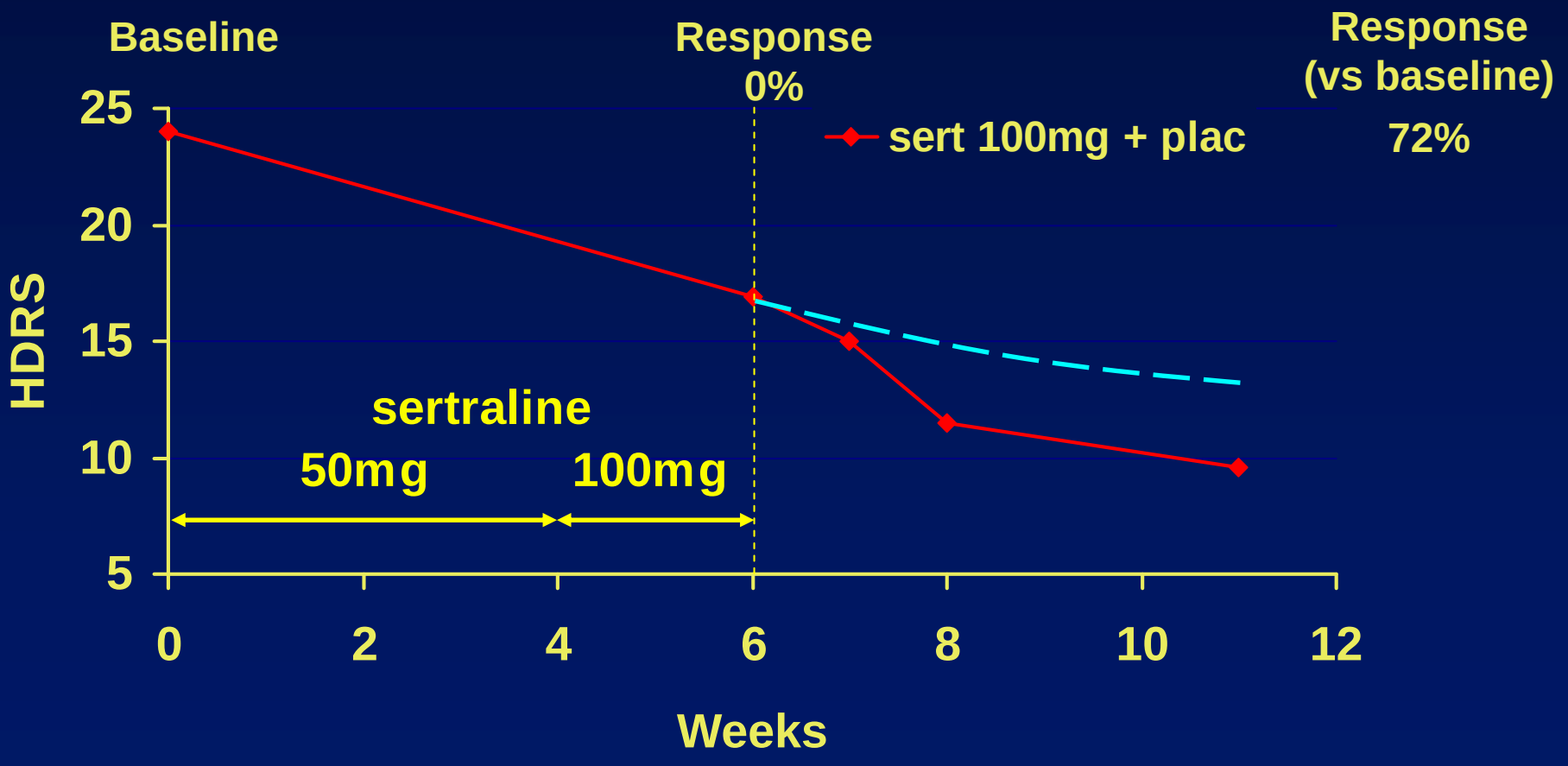
- 2,876 patients with major depression treated in primary care and psychiatric settings
- Flexible dose of citalopram upto 14 weeks (mean dose 42mg daily)
- 80% subjects had chronic or recurrent depression
- Remission rate 28%, Response rate 47%

(Trivedi et al, 2006)

General Management Strategies

1. Assessment and investigations
2. Instillation of hope, education, collaboration
   - involve carers
   - general support/CPN
3. Psychotherapy
   - Psychodynamic issues
   - CBT
   - IPT
4. Develop Psychopharmacological plan
   - clear strategy
   - avoid poly pharmacy
   - care with changeovers
   - adequate trial
   - Maintenance
5. Monitor response assiduously and objectively

TRD: Do something
Continuation of same dose sertraline



Licht & Qvitzau 2002

Management Strategies

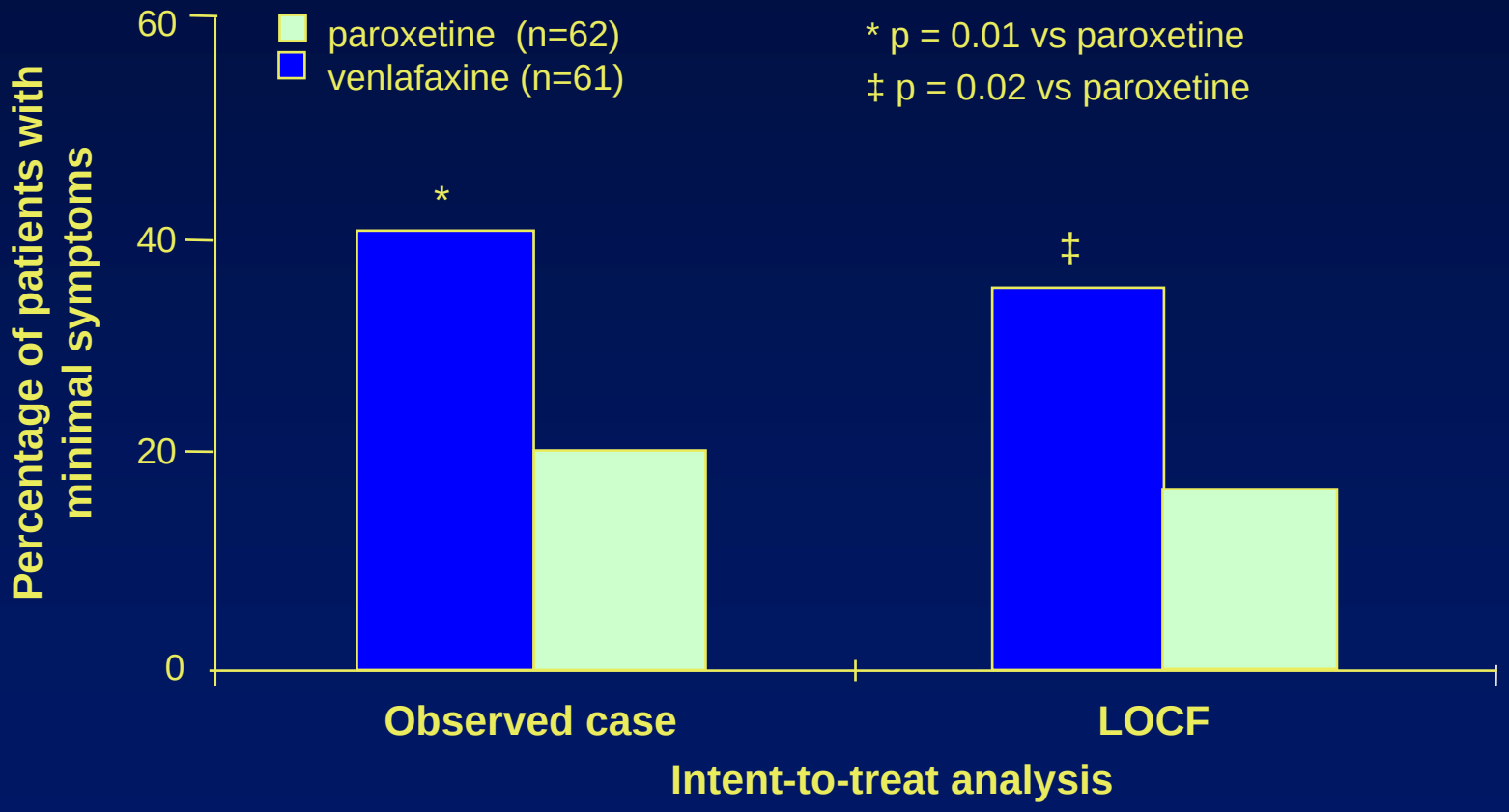
- One drug strategies
- Augmentation
- Combination strategies
- Non-pharmacological strategies

Management Strategies

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

Venlafaxine vs paroxetine in treatment-resistant depression

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



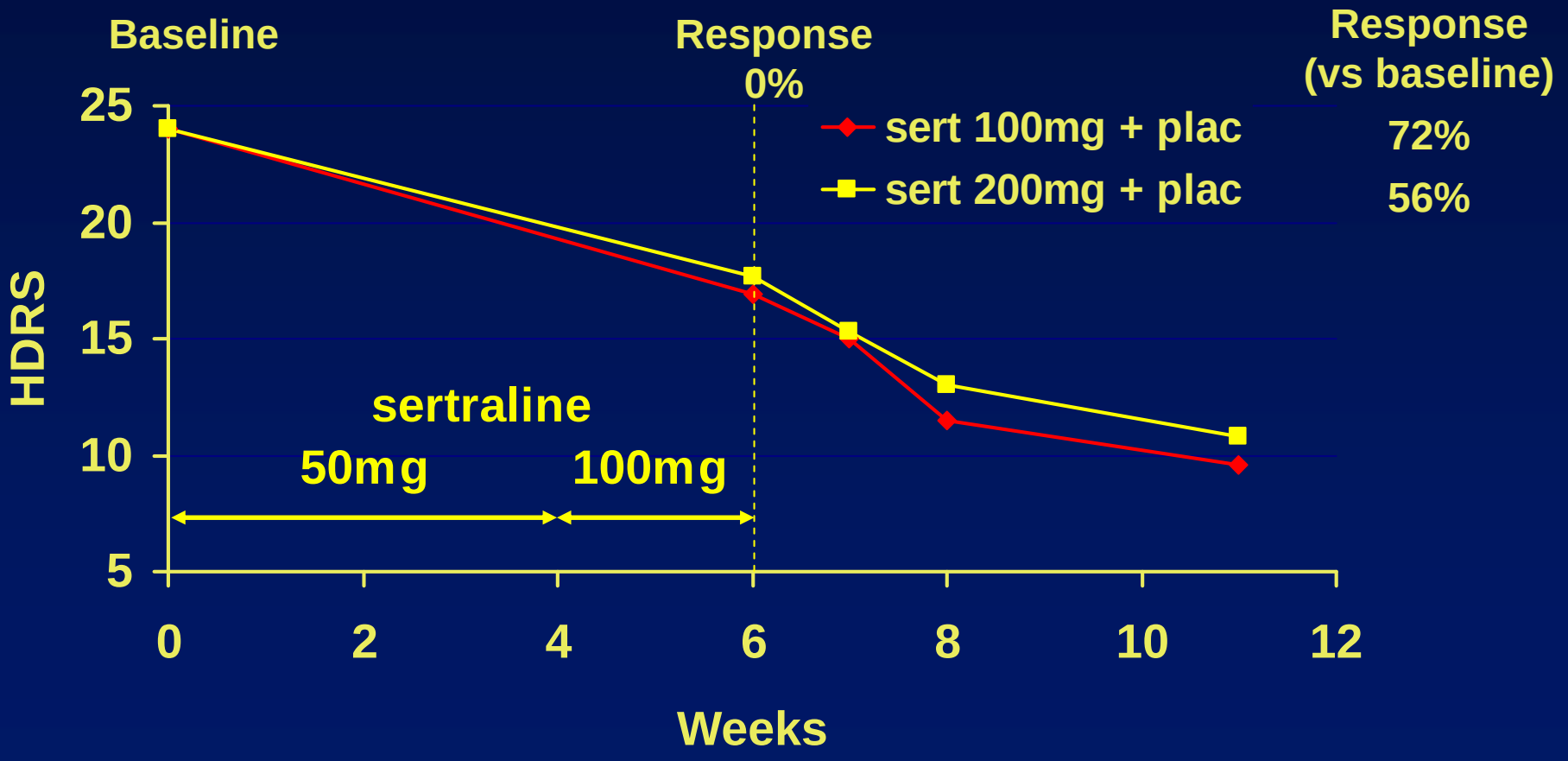
Poirier MF and Boyer P. BJP 1999 175 12-16

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**
  - **Little evidence of benefits of increased dose**

[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

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  - **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

Management Strategies

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

Nefazodone vs CAT vs Nefazodone + CAT

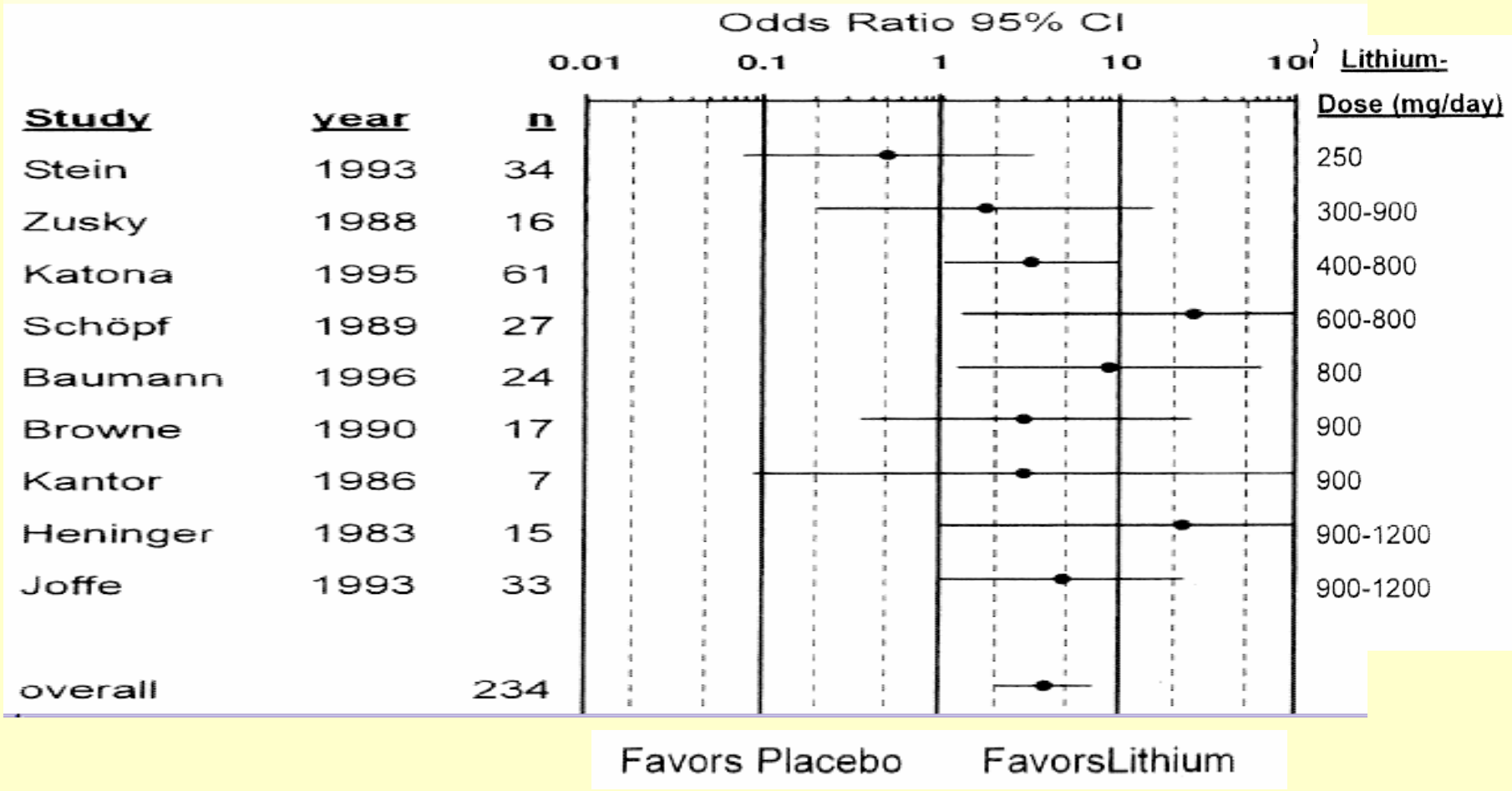
Drug	Psychotherapy	Combination
55%	**52%**	**85%**

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

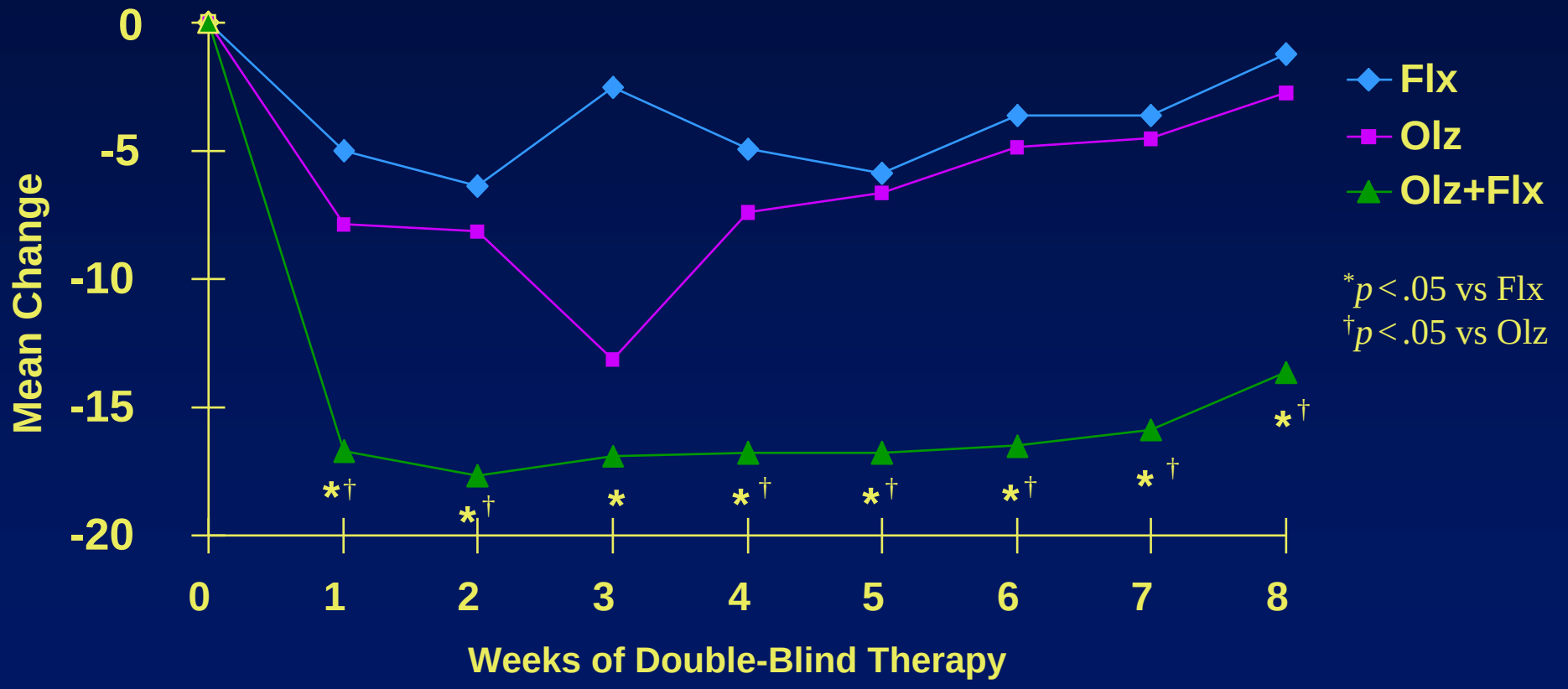
Augmentation with thyroid hormones

- 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

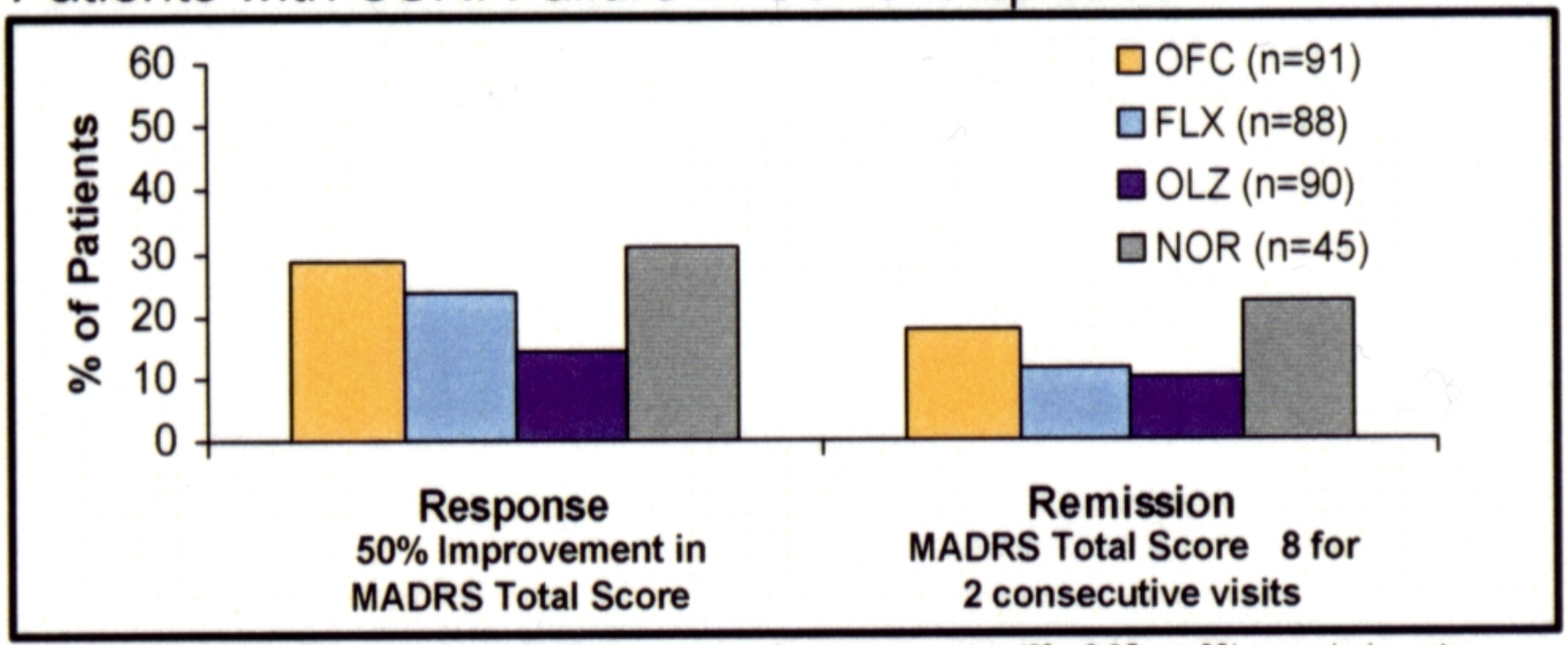


Shelton et al 2001

From **Dube et al 2002 European Psychiatry 17 (suppl 1): 98**
8 week RCT in 500 patients with history of SSRI failure and prospective failure to respond to 7 weeks nortriptyline randomised to olanzapine, fluoxetine, OFC or nortriptyline. OFC > olanzapine but not fluoxetine or nortriptyline.

TRD STUDY 1 - RESPONSE AND REMISSION RATES AT ENDPOINT (LOCF)

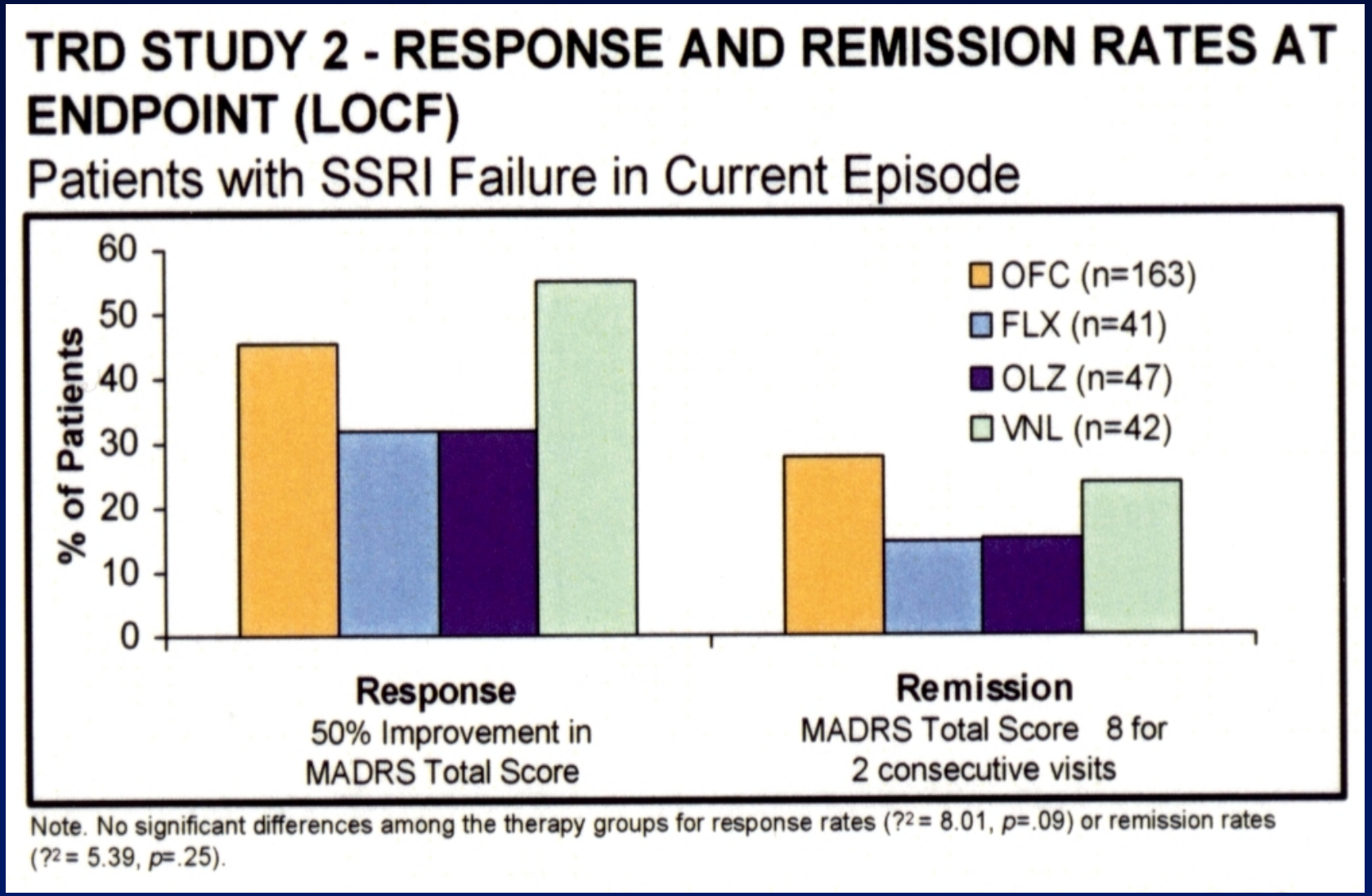
Patients with SSRI Failure in Current Episode



Note. No significant differences among the therapy groups for response rates ($?^2 = 6.85$, $p=.08$) or remission rates ($?^2 = 5.07$, $p=.17$).

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



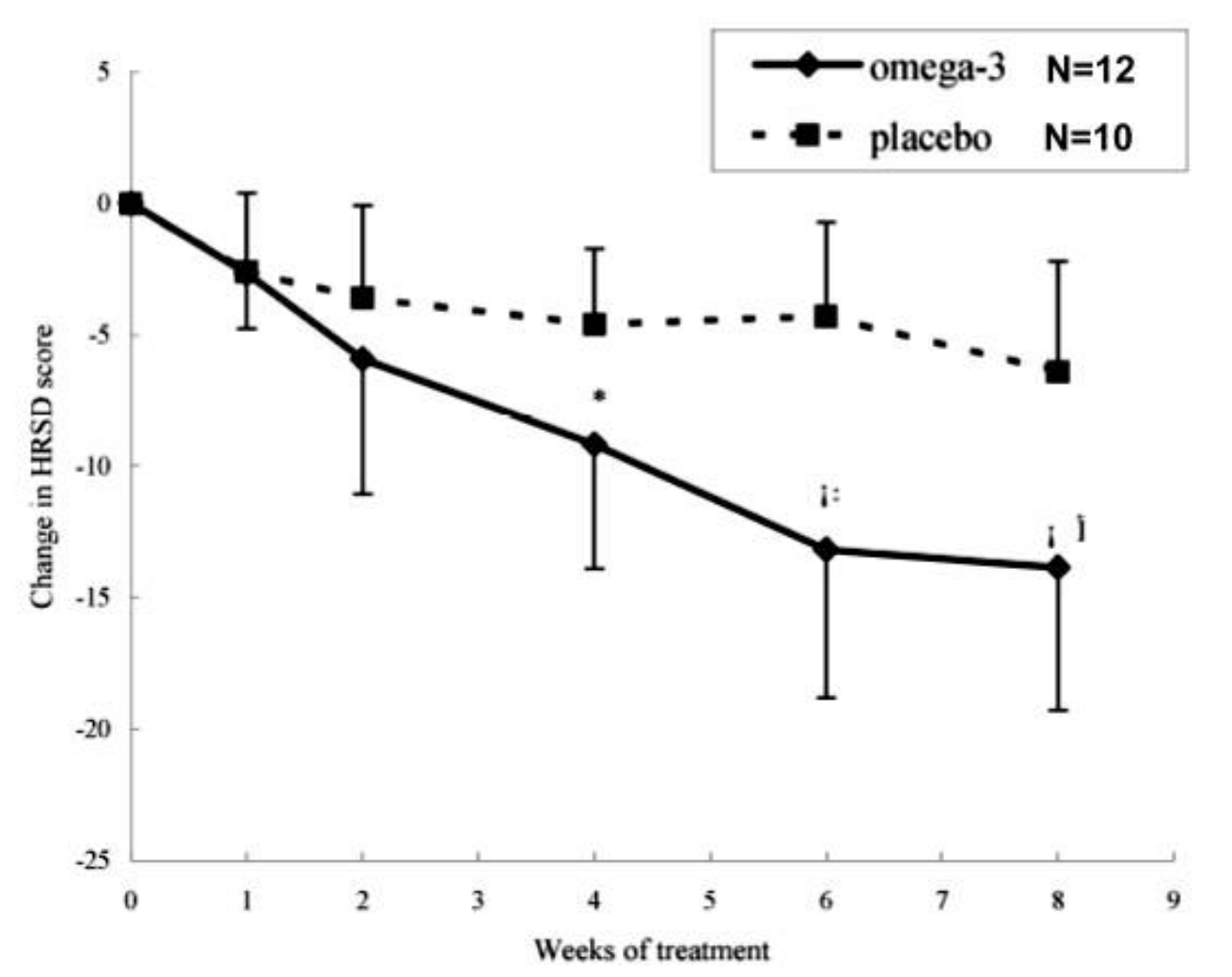
Other augmentation strategies

- 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

Folate and depression

- Papakostas et al. (2004)
  - 55 patients non-responsive to fluoxetine 20 mg
  - Randomised to fluox 40mg, fluox+li or fluox + desipramine
  - Low serum folate associated with non-response
- Taylor et al. (2004)
  - Meta-analysis of folate augmentation
  - 2 studies – n's of 13 and 49 (smaller one folate deficient)
  - Significant benefit of folate augmentation - ? Magnitude of effect

Omega3 fatty acid addition to antidepressants



Su et al 2003

Metyrapone augmentation of antidepressants (Jahn et al. 2004)

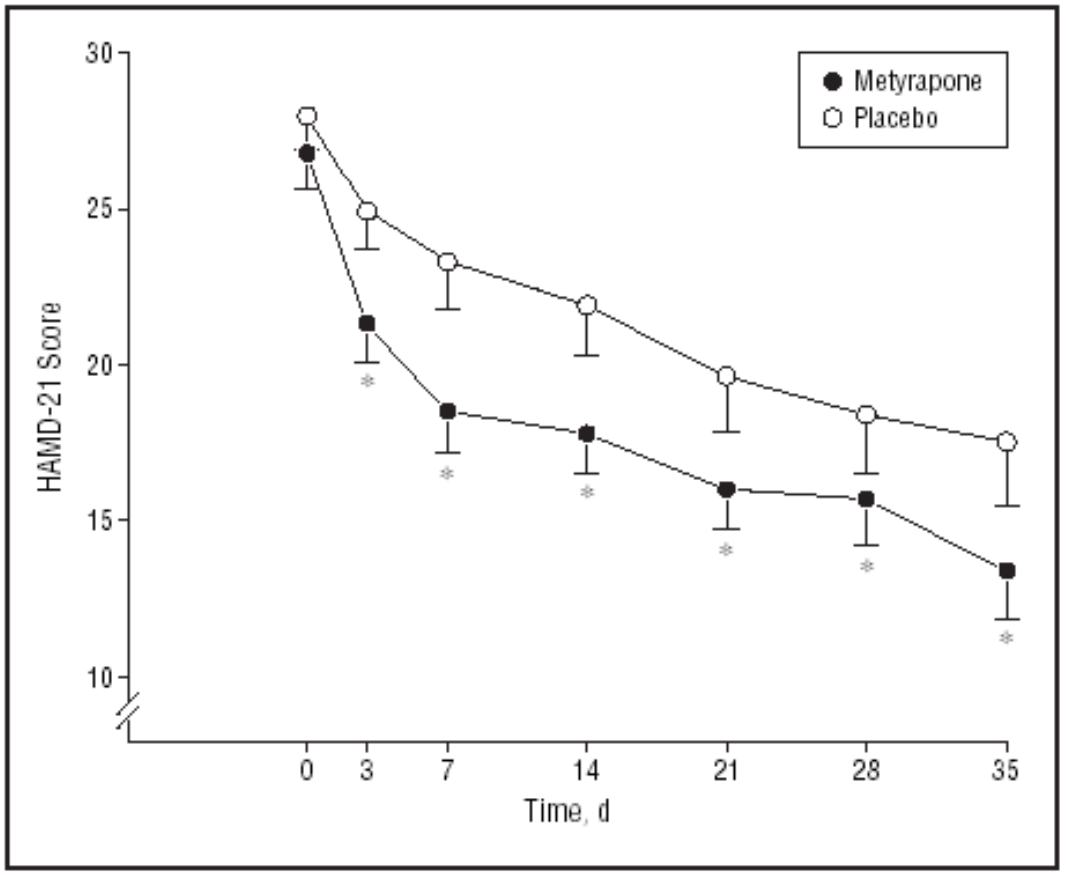


Figure 2. Hamilton Rating Scale for Depression, 21-item version (HAMD-21) scores for the metyrapone group (solid circles) and the placebo group (open circles) for days 0, 3, 7, 14, 21, 28, and 35 on the intention-to-treat sample. Data are presented as mean ± SEM. Asterisks indicate time points with significant group differences. The y-axis is cut below a HAMD score of 10.

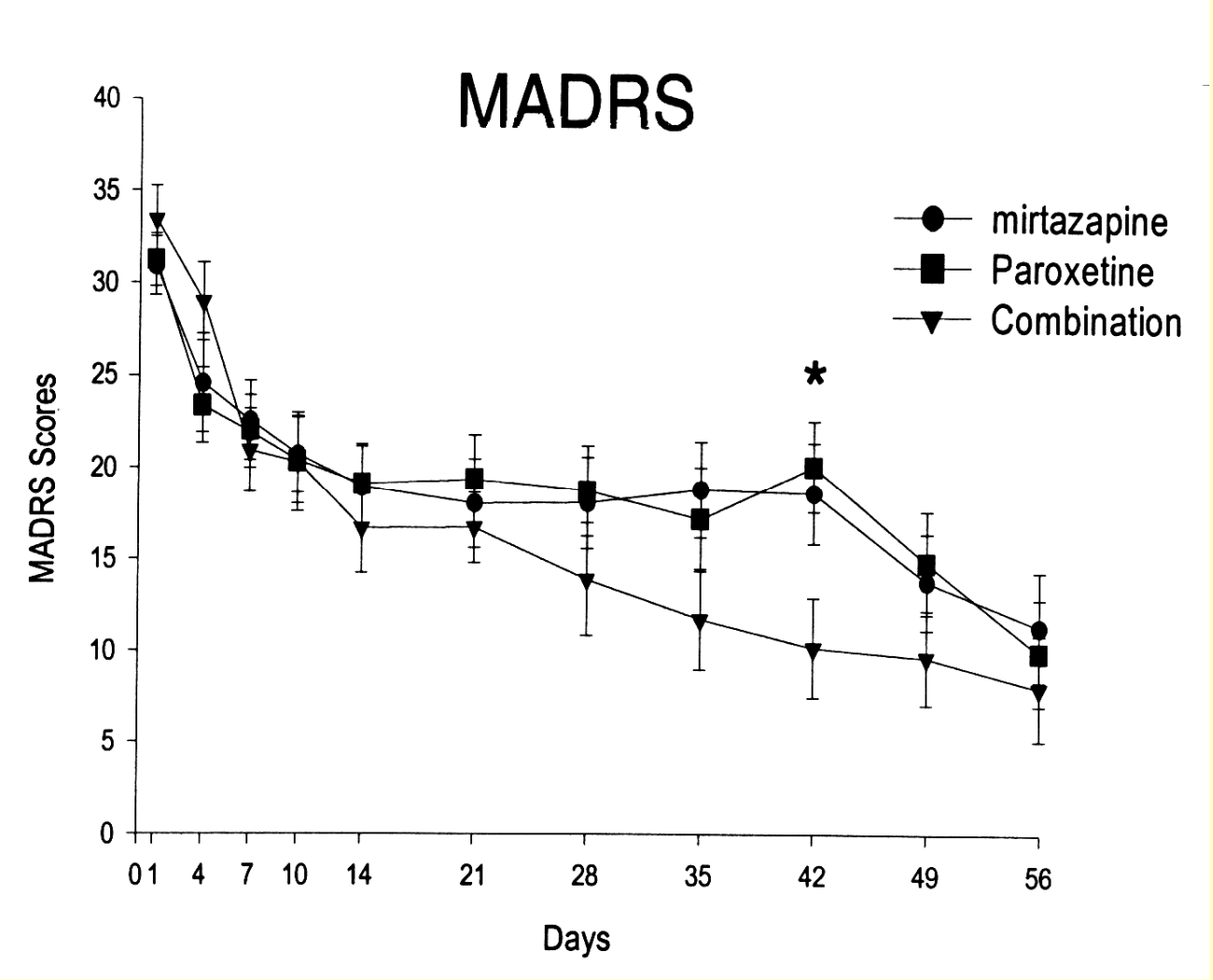
n = 63

Antidepressants = nefazadone or fluvoxamine

Management Strategies

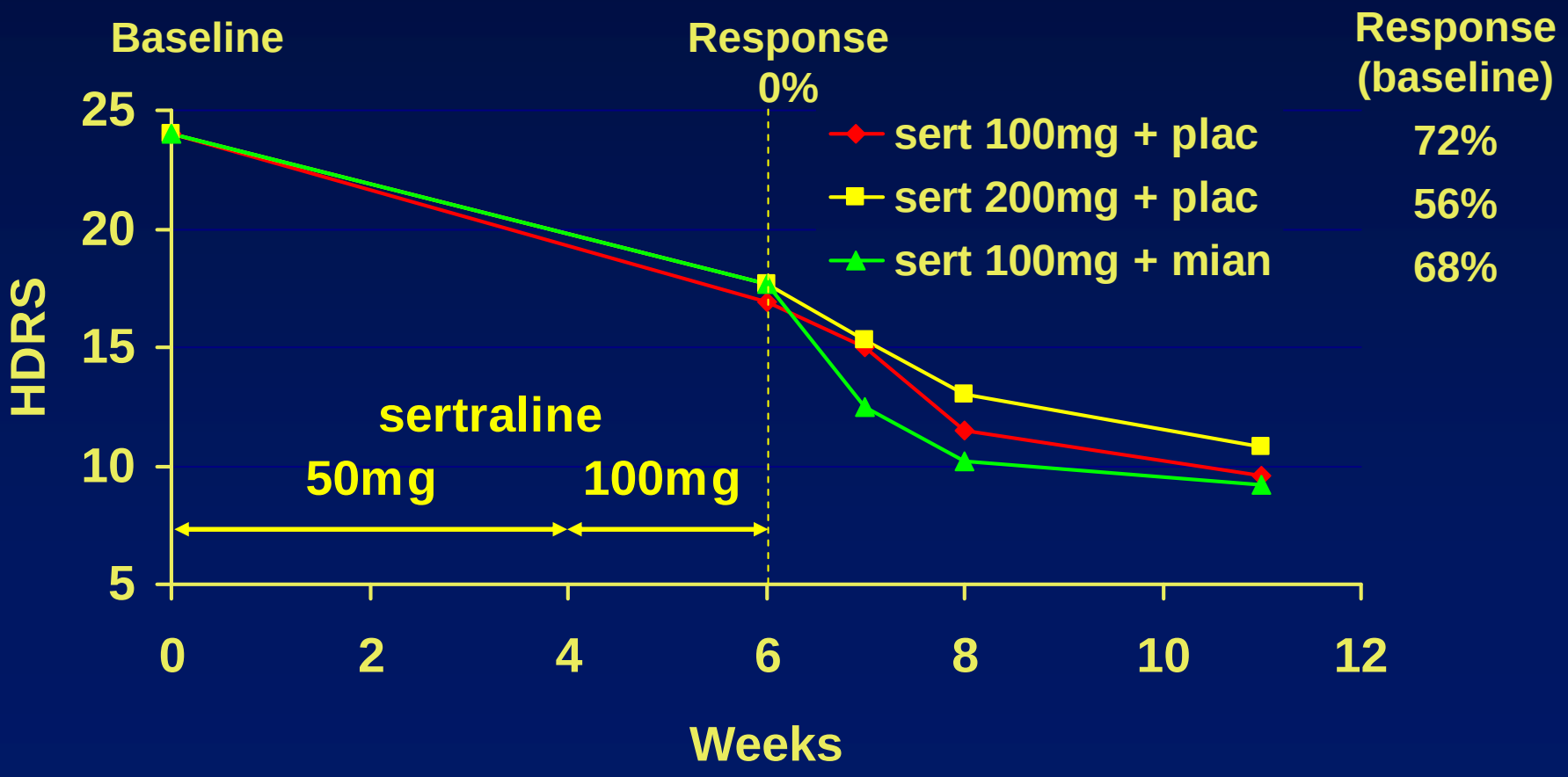
- One drug strategies
- Augmentation
- Combination strategies
  - SSRI + TCA
  - MAOI + TCA
  - SSRI + reboxetine
  - SSRI + Trazodone
  - Mirtazepine/mianserin + Venlafaxine/SSRI/reboxetine
- Non-pharmacological strategies

Combined paroxetine + mirtazapine in depression



Debonnel et al 2000

Non-response at 6 weeks: augmentation with mianserin



Licht & Qvitzau 2002

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]

Management Strategies

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

Second opinions

- Depressed patients rarely say “I could be doing better”
- If you get to the point that you feel there is nothing left to try, then it is time for a second opinion

Conclusions

- Beware bipolar masquerading as unipolar
- Educate patients and their families
- Use appropriate length treatment trials
- Aim for remission
- Have clear non-response strategies
  - Single treatments
  - Augmentation
  - Combinations
- Several new treatments are currently under evaluation, so “watch this space”

Annual Residential Meeting of the Faculty of General and Community Psychiatry

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Twin themes: Vulnerability and Service Delivery

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