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Next step treatments for depression

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Disclosure / conflict of interest

I have an interest in relation to one or more organisations that could be perceived as a possible conflict of interest in the context of the subject of this presentation. The relationships are summarised below:

Interest	Name of organisation
Speaker fees	AstraZeneca, Bristol Myers-Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Merck Sharp & Dohme, Pfizer, Servier, Wyeth
Consultancy fees	AstraZeneca, Bristol Myers-Squibb, Cyberonics, Eli Lilly, Janssen-Cilag, Lundbeck, Merck Sharp & Dohme, Servier, Wyeth
Independent investigator-led research support	AstraZeneca, Eli Lilly, Wyeth

I do not hold any shares in, nor have any ongoing financial relationship with, any pharmaceutical company

Outcome of STAR*D: effect of treatment step

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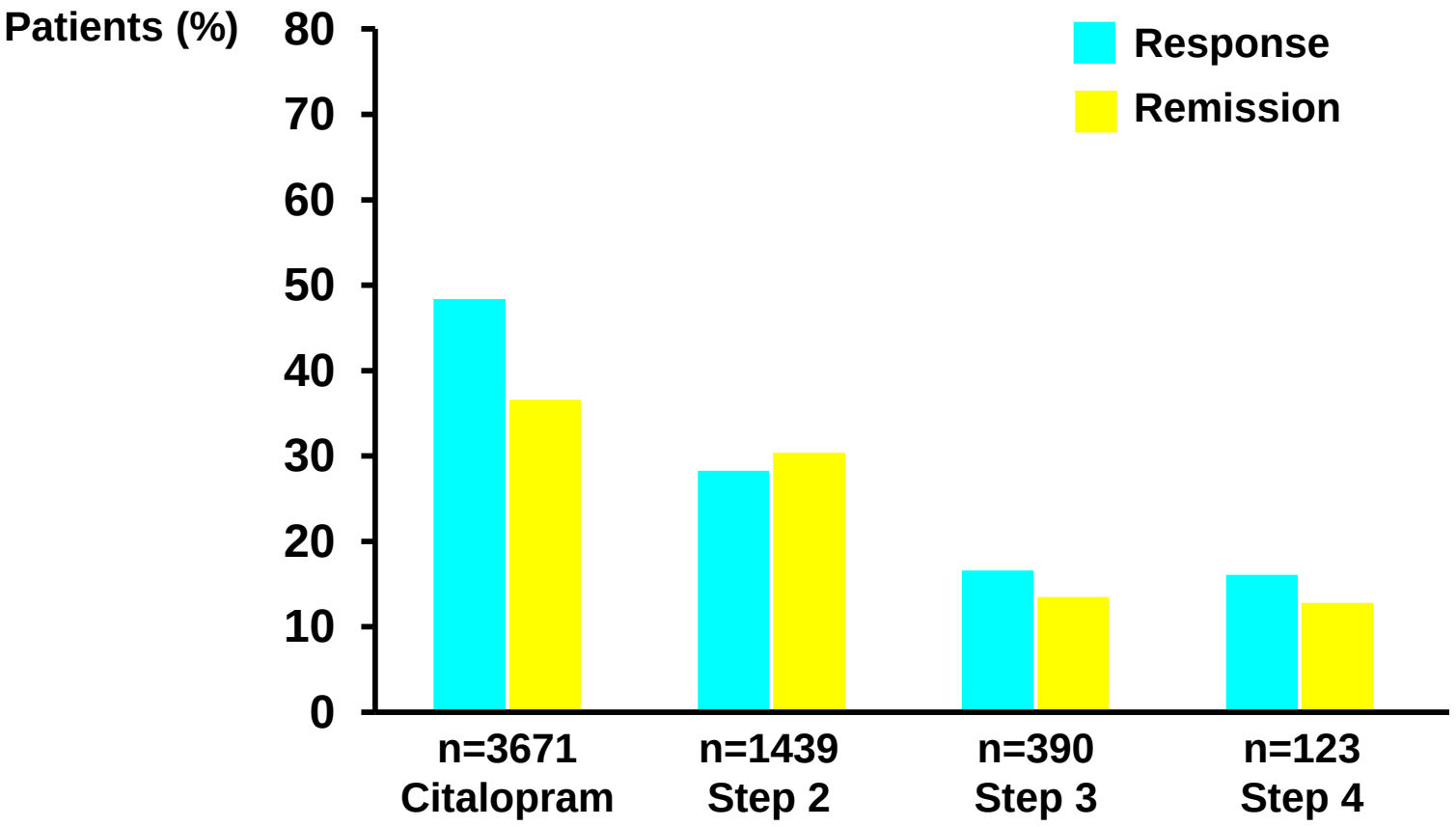
Entry: 80% recurrent or chronic depression

Mean episodes, 6; mean duration, 25 months



STAR*D, Sequenced Treatment Alternatives to Relieve Depression

Rush et al. *Am J Psychiatry* 2006;163:1905

Model of depression and treatment

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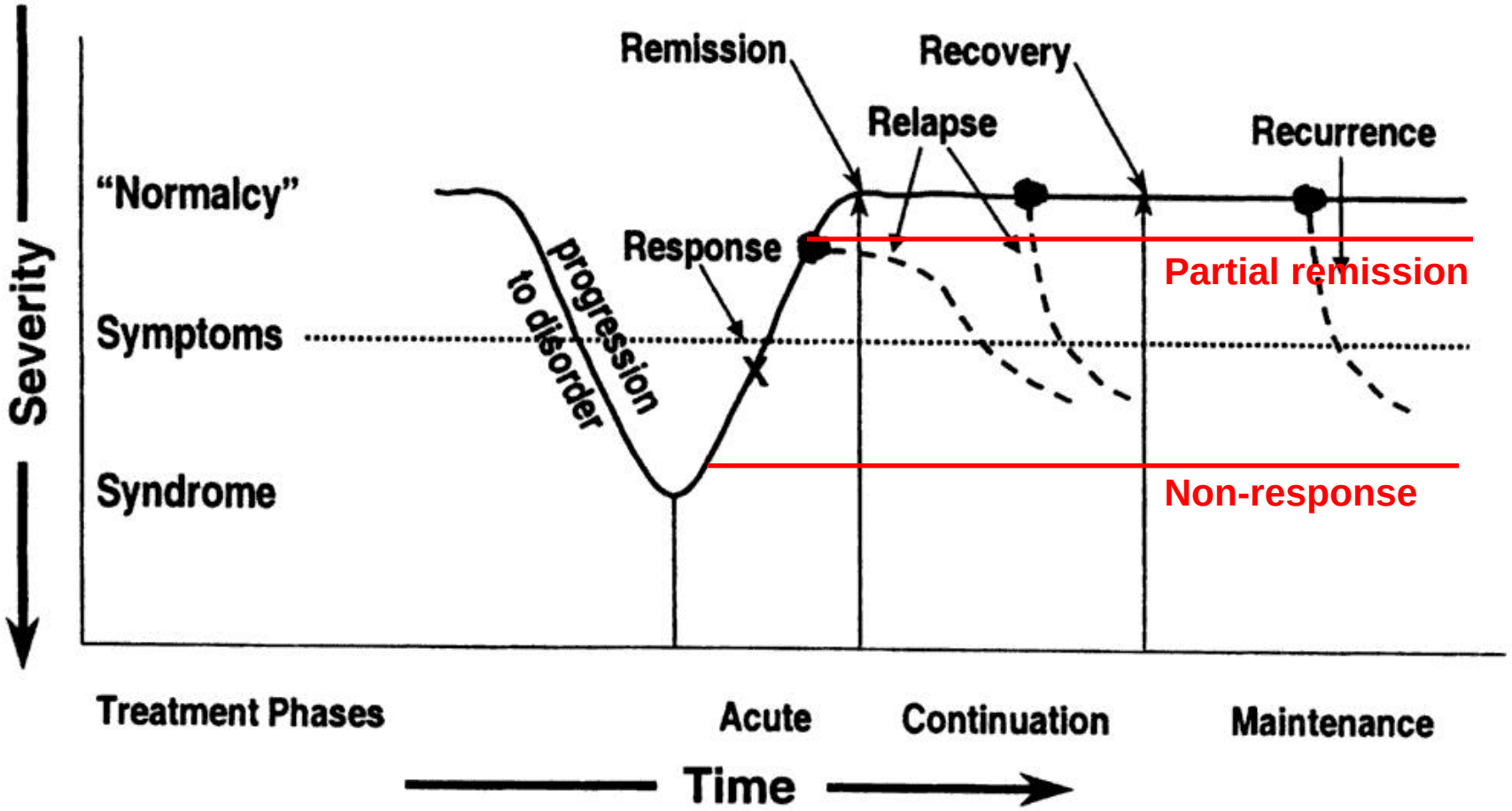

Frank et al 1991

Reasons for poor outcomes in MDD

Patient related

Doctor related

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Reasons for poor outcomes in MDD

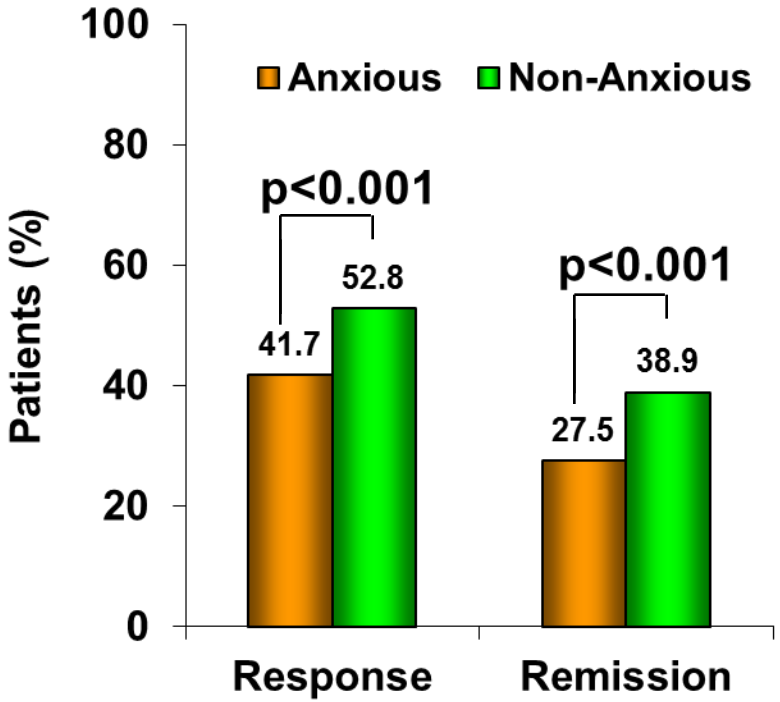
Patient related (assuming correct diagnosis!)

- Non-adherence
- Comorbidity
  - Personality
  - Substance misuse
  - Physical illnesses / Pain
  - Anxiety
  - Psychosis
  - Ongoing stress
- Chronicity
- Frequent relapse

Doctor related

STAR*D suggests anxious depression is less likely to respond or remit with treatment

- STAR*D study N=2,876
- Patients with MDD
- Treated with citalopram for 12 weeks
- Anxious patients defined as:
  - ≥ 7 on anxiety/somatisation
- Response and remission rated with HAMD and QIDS-SR



Fava M, et al. *Am J Psychiatry* 2008;165:342–51.

Addressing patient factors

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Thorough assessment of predisposing, precipitating and perpetuating factors

Address any that are tractable – consider all interventions available

Ensure adequate prophylaxis

Reasons for poor outcomes in MDD

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Patient related

Doctor related

- **Lack of clarity of thought**
- **Lack of awareness of the evidence base**
- **Unsystematic approach**
- **Therapeutic nihilism**

Addressing doctor-related factors

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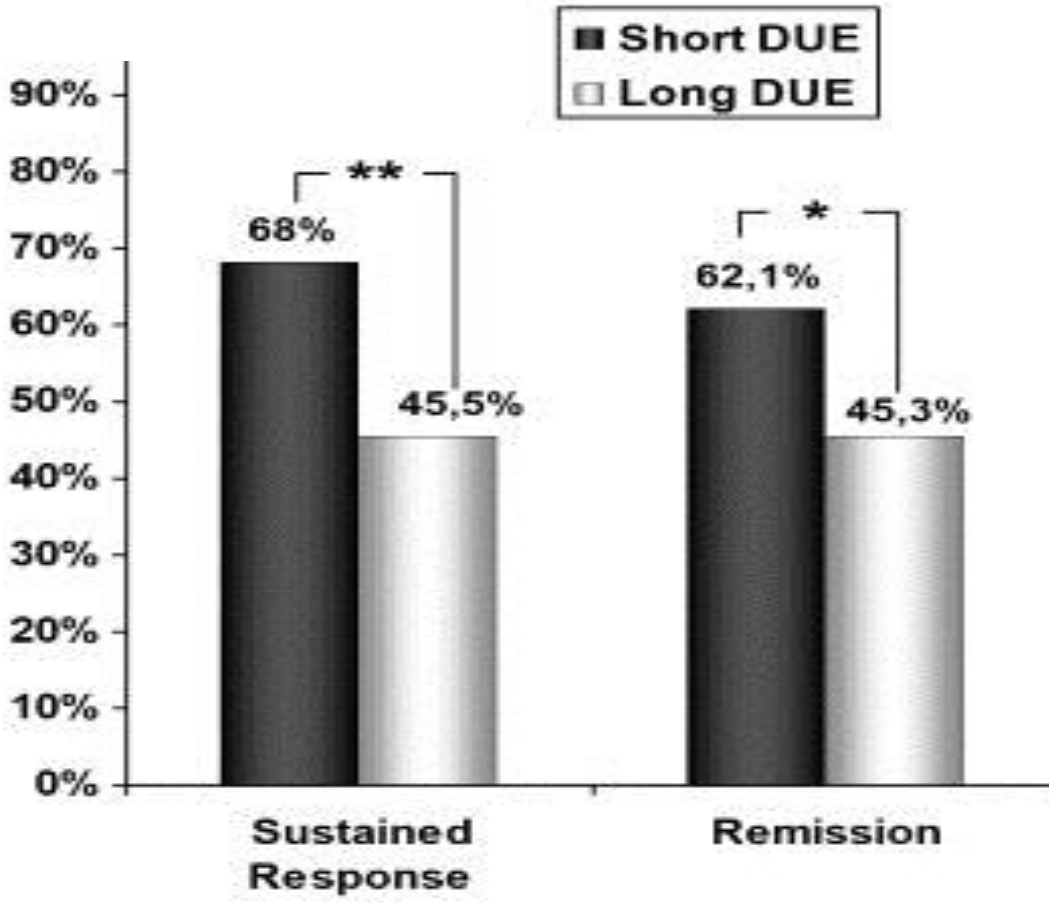
Avoid delays

Effect of duration of un-treated depression on response and remission



De Diego-Adelino et al. (2010) J Affect Disorders 120:221 - 225

Addressing doctor-related factors

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Avoid delays

Clear pharmacological strategy

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Which antidepressant?

AIM- find one that the patient makes at least some response to

Sexual dysfunction associated with antidepressants

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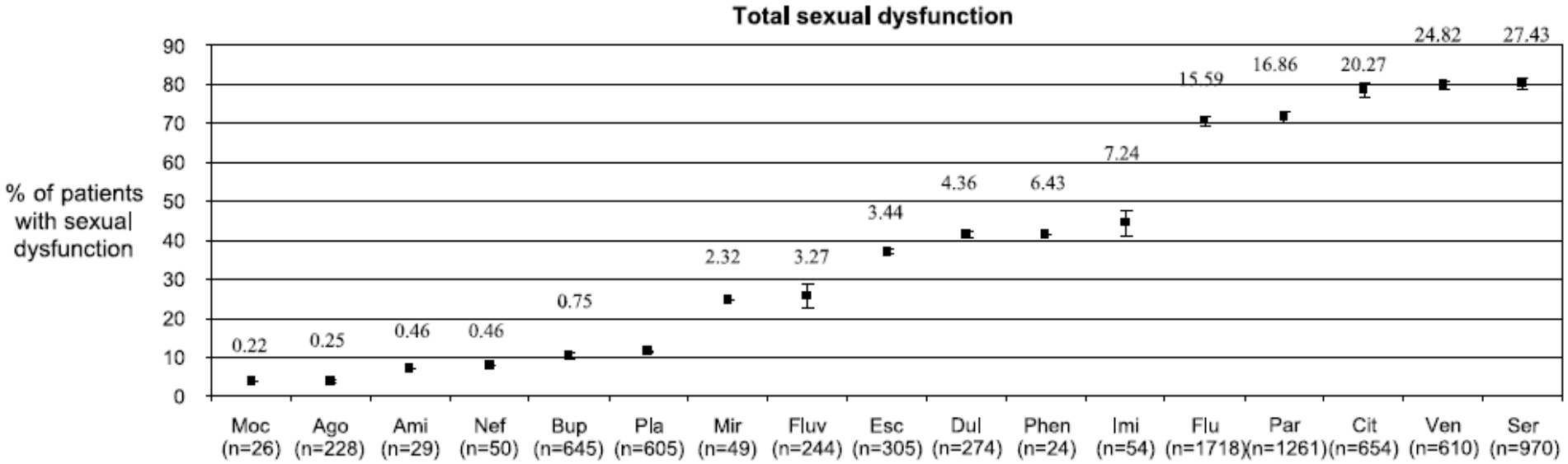
Meta analysis of antidepressant trials which included a direct measure of sexual function (direct question or rating scale). Studies including patients that had a primary sexual dysfunction were excluded.



Mean total sexual dysfunction with placebo was 14.2%. The absolute % values and odds ratios vs. placebo are reported for each antidepressant.

Ago indicates agomelatine; Ami, amineptine; Bup, bupropion; Cit, citalopram; Clo, clomipramine; Dul, duloxetine; Esc, escitalopram; Flu, fluoxetine; Fluv, fluvoxamine; Im, imipramine; Mr, mirtazapine; Moc, moclobemide; Nef, nefazodone; Par, paroxetine; Phe, phenelzine; Pla, placebo; Sel, selegiline; Ser, sertraline; Ven, venlafaxine

Serretti A & Chiesa A. *J Clin Psychopharmacol* 2009;29:259-266

Which antidepressant? Differences in efficacy?

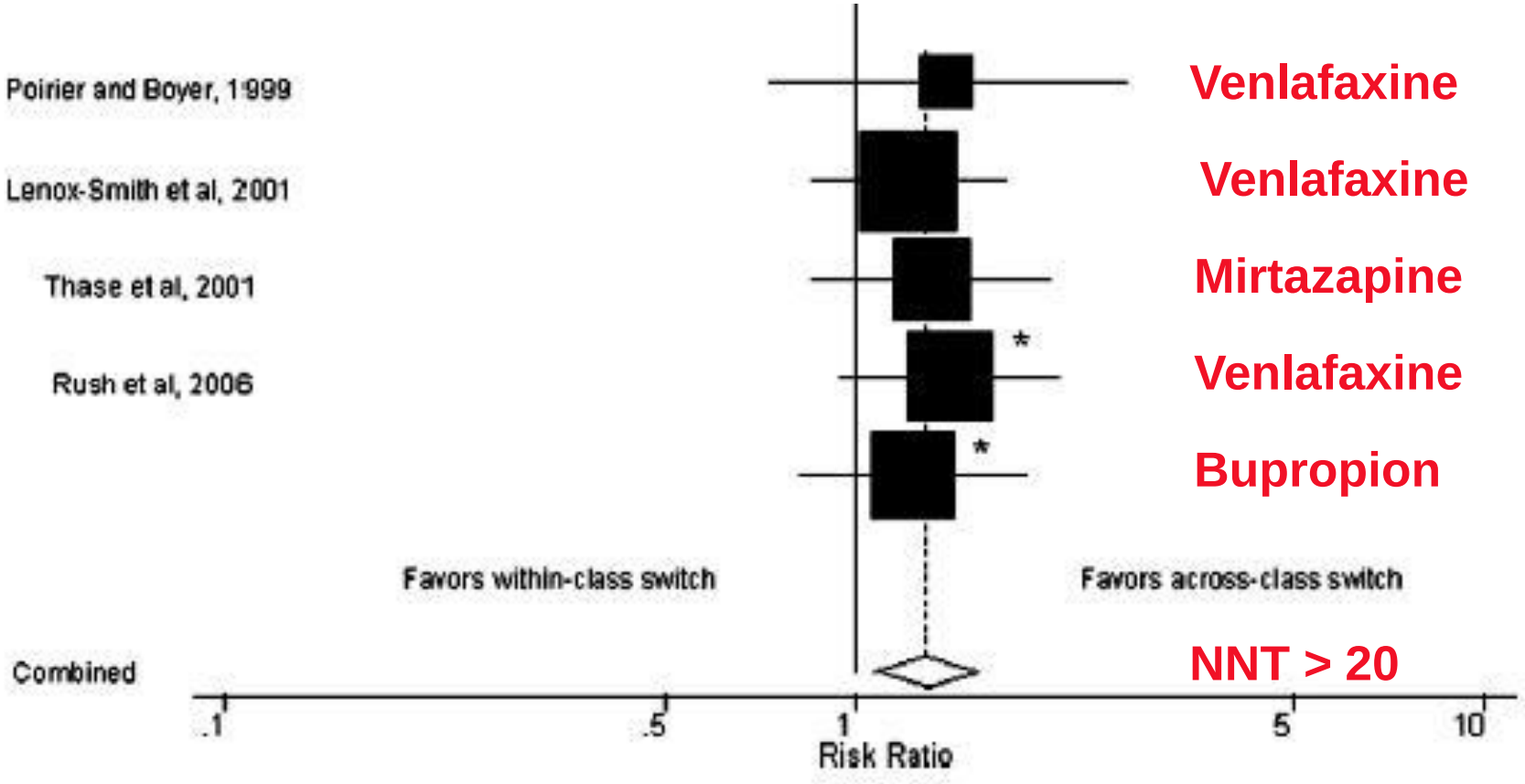
- There is evidence of differences in efficacy between antidepressants but the effect size is small
- Meta-analysis support for[1,2]
  - Amitriptyline vs SSRIs
  - Venlafaxine, escitalopram, mirtazepine and sertraline vs “second generation” antidepressants
- More than 1 RCT showing benefit over another AD for[3,4]
  - Clomipramine, venlafaxine, escitalopram, agomelatine
- Theoretical support for blockade of both 5-HT and NA[5]

1. Anderson et al. 2000 J Affect Disord. 58(1):19-36; 2. Cipriani et al. 2009 Lancet. 373(9665):746-58; 3. Montgomery et al. 2007 Int Clin Psychopharmacol. 22(6):323-9; 4. Hale et al. 2010 Int Clin Psychopharmacol. 25(6):305-14; 5. Nelson JC, et al. Biol Psychiatry. 2004;55:296–300

Which antidepressant?
Patient past history

- Is there evidence of preferential response to 5-HT uptake blockade?
  - try escitalopram, clomipramine or sertraline
- Is there evidence of preferential response to NA blockade?
  - try reboxetine, lofepramine or desipramine
- If neither (or in doubt) try a dual action drug
  - Venlafaxine, duloxetine, amitriptyline, mirtazepine
- Has there been response, but poor tolerability of a TCA?
  - try venlafaxine or duloxetine
- Issue with poor tolerability?
  - Escitalopram, agomelatine or vortioxetine
- Has there been a trial of an MAOI?

RCTs of switching antidepressants: SSRI to SSRI vs SSRI to another AD (remission)



Remission rates 28% (for non-SSRIs) and 23.5% (for SSRIs)

Papakostas et al 2008

Switch or Augment/Combine?

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Treating Depression After Initial Treatment Failure

*Directly Comparing Switch and Augmenting Strategies in STAR*D*

Bradley N. Gaynes, MD, MPH, Stacie B. Dusetzina, PhD,† Alan R. Ellis, MSW,‡ Richard A. Hansen, PhD,§|| Joel F. Farley, PhD,|| William C. Miller, MD, PhD,¶ and Til Stürmer, MD, MPH¶*

- 1292 patients who did not remit with citalopram and opted to go with medication at level 2
  - N = 565 augmentation (cit.+bupropion (279); cit.+buspirone (286))
  - N = 727 switch (bupropion (239); sertraline (238); venlafaxine (250)
- When matched, no difference in RR for remission:
  - RR 1.07 (95% CI 0.76 – 1.50))
- **If had received 12 weeks of initial therapy:**
  - **Augmentation > switch: RR 1.9 (95% CI 1.16–3.11)**
- **Patients with residual symptoms:**
  - **Augmentation > switch: RR 1.32 (95% CI 1.03–1.70)**

J Clin Psychopharmacol 2012; 32: 114-119

Lithium augmentation in TRD: 1st vs 2nd generation ADs

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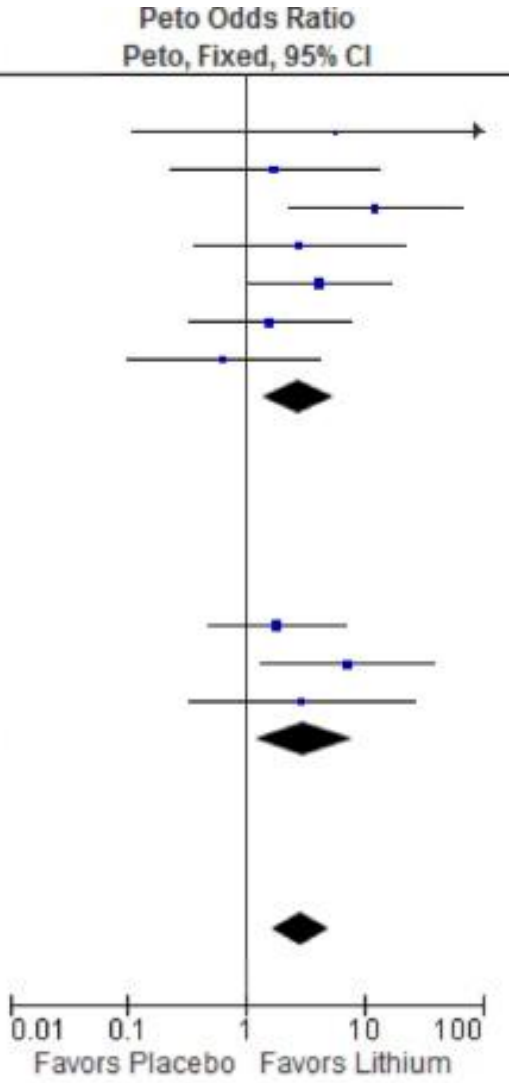
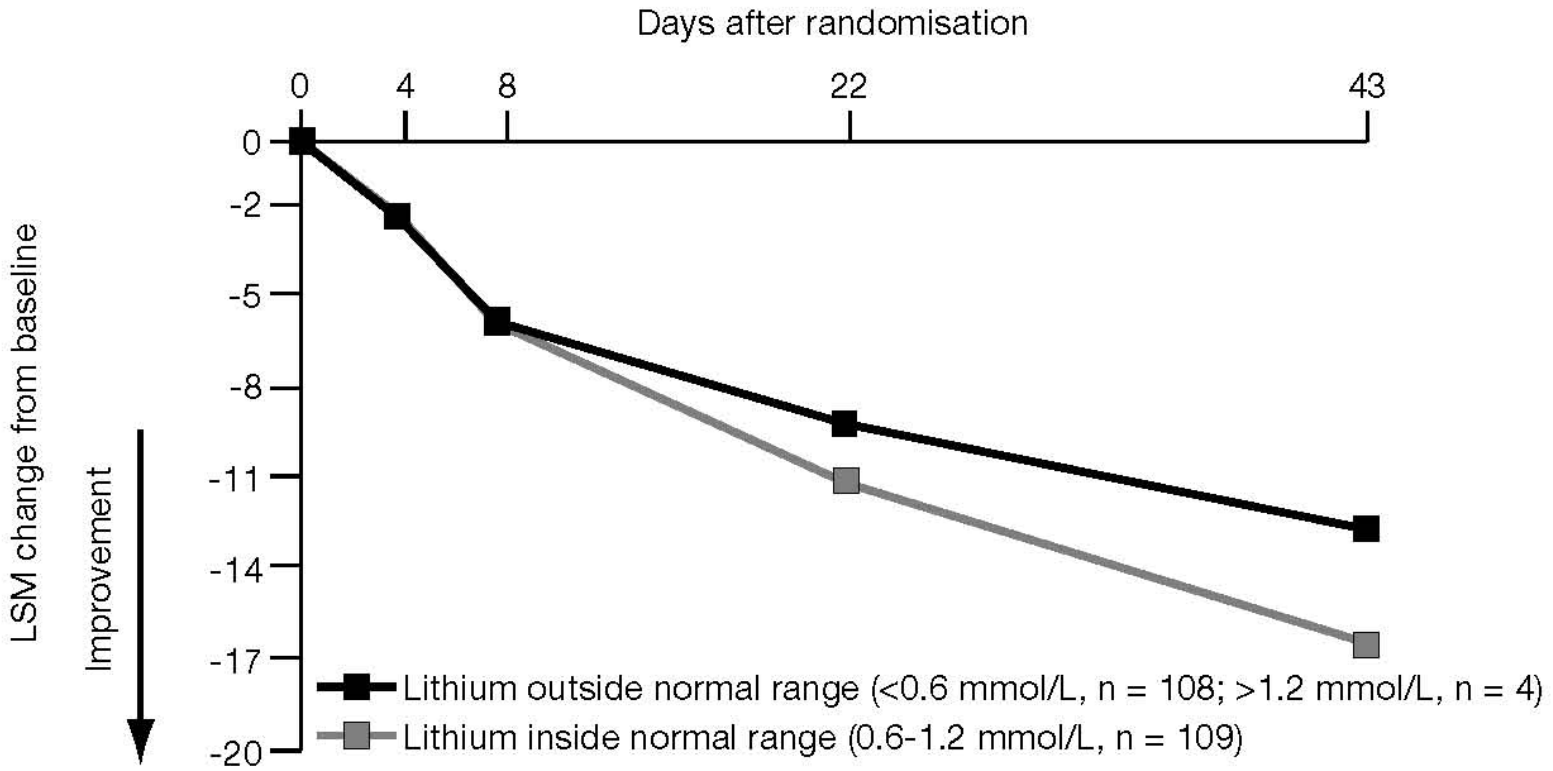
Study or Subgroup	Lithium Events	Lithium Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.1 TCAs or 1st Generation Agents						
Kantor et al 1986	1	4	0	3	2.0%	5.75 [0.11, 302.04]
Zusky et al 1988	3	8	2	8	7.4%	1.73 [0.22, 13.36]
Schöpf et al 1989	7	14	0	13	10.9%	12.27 [2.26, 66.53]
Brown et al 1990	3	7	2	10	7.4%	2.82 [0.36, 22.04]
Joffe et al 1993	9	17	3	16	16.0%	4.19 [1.04, 16.95]
Katona lofepramine 1995	9	12	11	17	12.7%	1.59 [0.33, 7.64]
Nierenberg et al 2003	2	17	3	17	8.9%	0.63 [0.10, 4.12]
Subtotal (95% CI)		**79**		**84**	**65.2%**	**2.80 [1.40, 5.59]**
Total events	34		21			
Heterogeneity: Chi² = 6.52, df = 6 (P = 0.37); I² = 8%						
Test for overall effect: Z = 2.92 (P = 0.003)						
1.1.2 SSRIs or 2nd Generation Agents						
Katona fluoxetine 1995	10	17	7	16	17.2%	1.80 [0.47, 6.89]
Baumann et al 1996	6	10	2	14	11.0%	7.18 [1.33, 38.73]
Joffe et al 2006	3	9	1	8	6.6%	2.97 [0.34, 26.26]
Subtotal (95% CI)		**36**		**38**	**34.8%**	**3.06 [1.19, 7.88]**
Total events	19		10			
Heterogeneity: Chi² = 1.59, df = 2 (P = 0.45); I² = 0%						
Test for overall effect: Z = 2.31 (P = 0.02)						
Total (95% CI)		**115**		**122**	**100.0%**	**2.89 [1.65, 5.05]**
Total events	53		31			
Heterogeneity: Chi² = 8.13, df = 9 (P = 0.52); I² = 0%						
Test for overall effect: Z = 3.72 (P = 0.0002)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						



Nelson et al. 2014 J Affective Disorders 168:269-275

Response to lithium within and outside normal levels

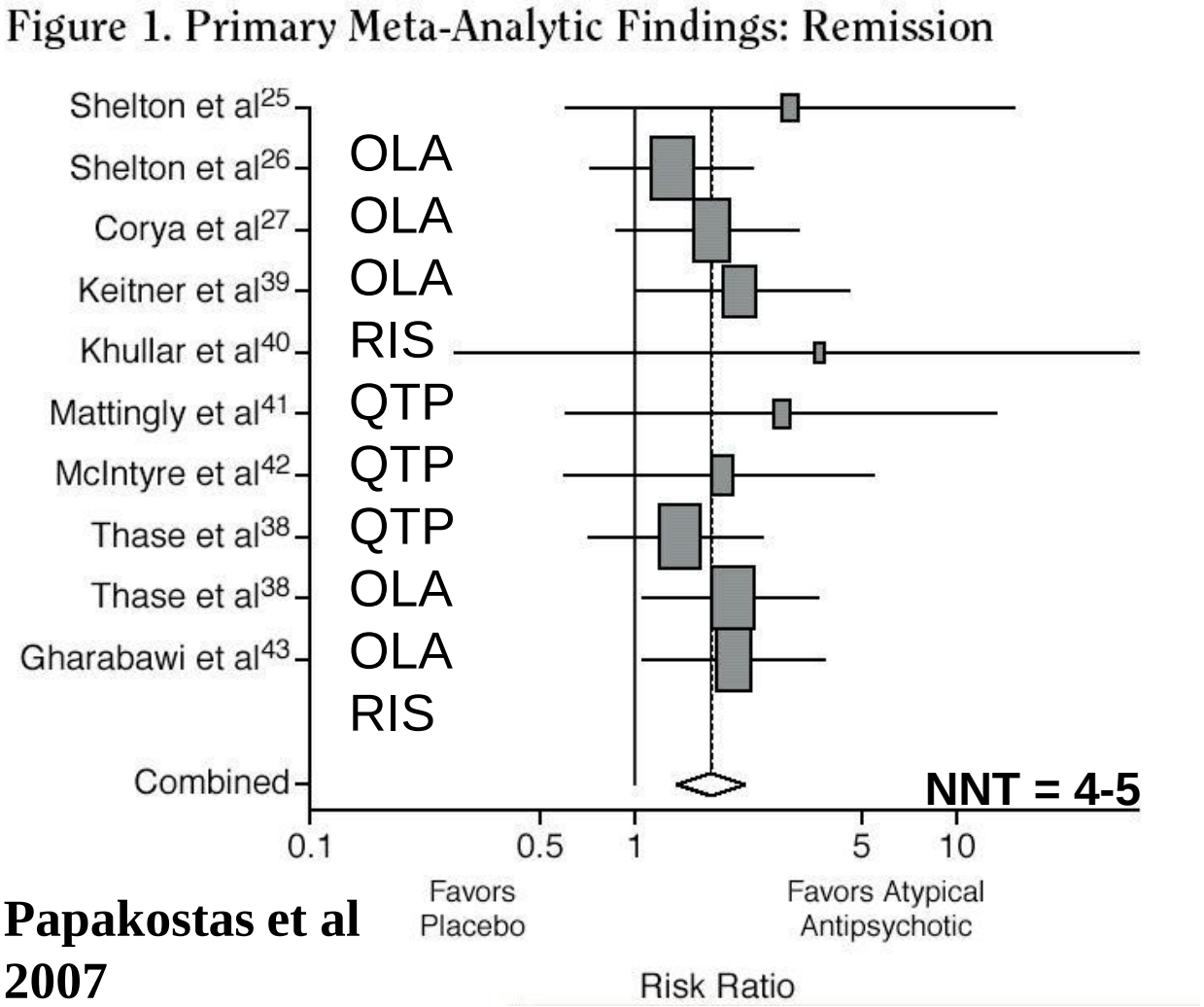
post hoc analysis



LOCF, last observation carried forward; LSM, least squares means;
MADRS, Montgomery-Åsberg Depression Rating Scale; MITT, modified intent-to-treat

Bauer et al 2010

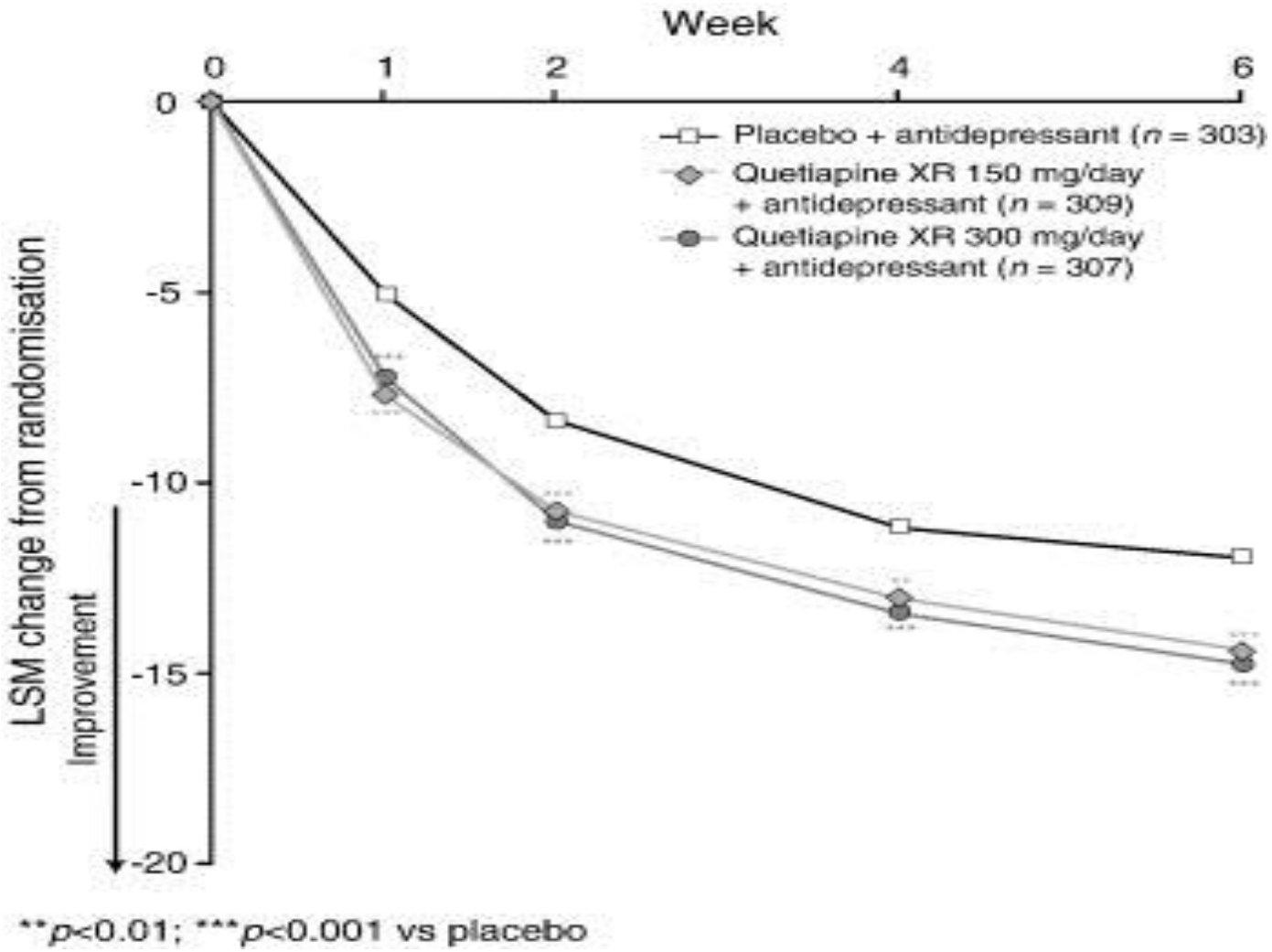
Atypical antipsychotic augmentation in TRD/inadequate response to ADs



Papakostas et al 2007

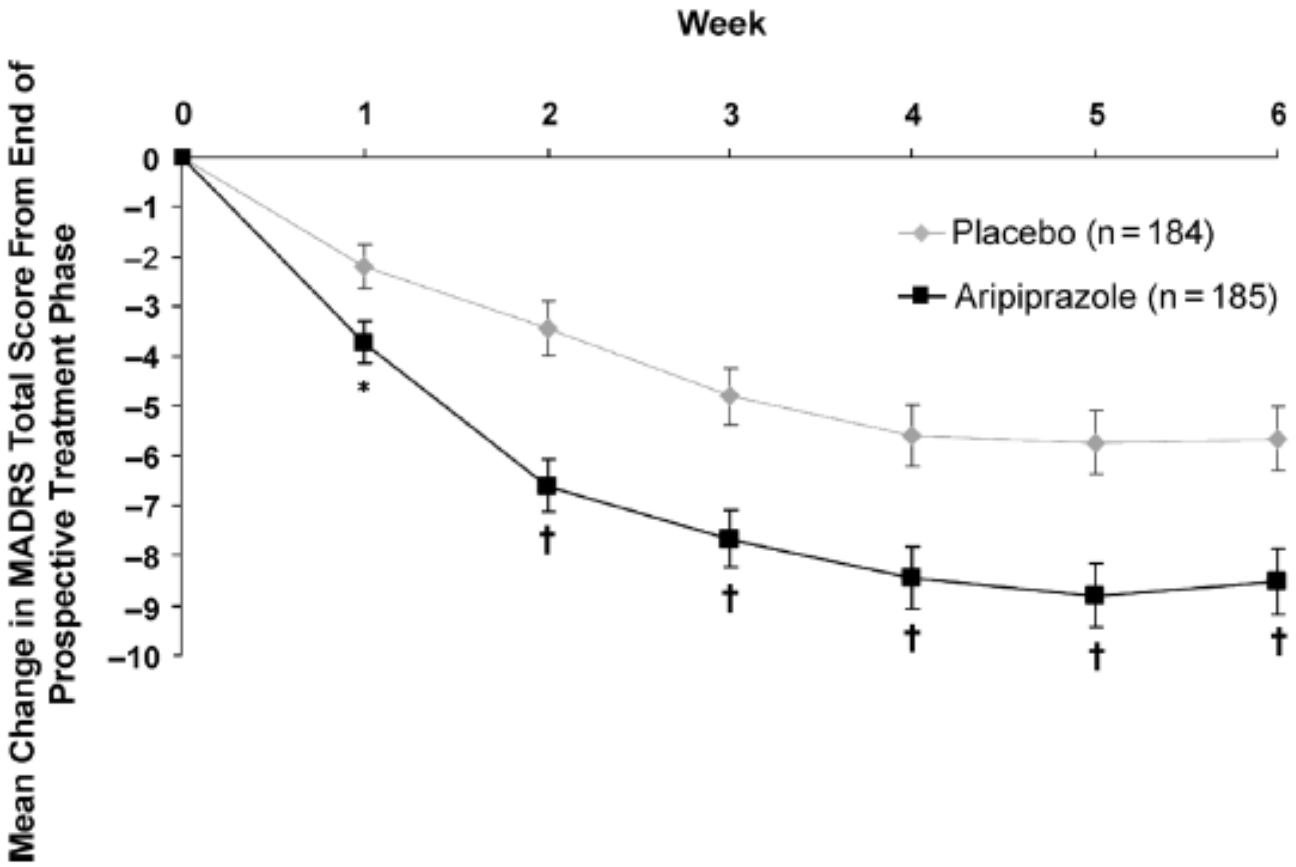
NOTE: Olanzapine and risperidone do not have a licence for augmentation of antidepressants in unipolar depression in Europe

Quetiapine augmentation of antidepressants following sub-optimal response



Bauer et al. (2010) J Affect Dis 127:19 - 30

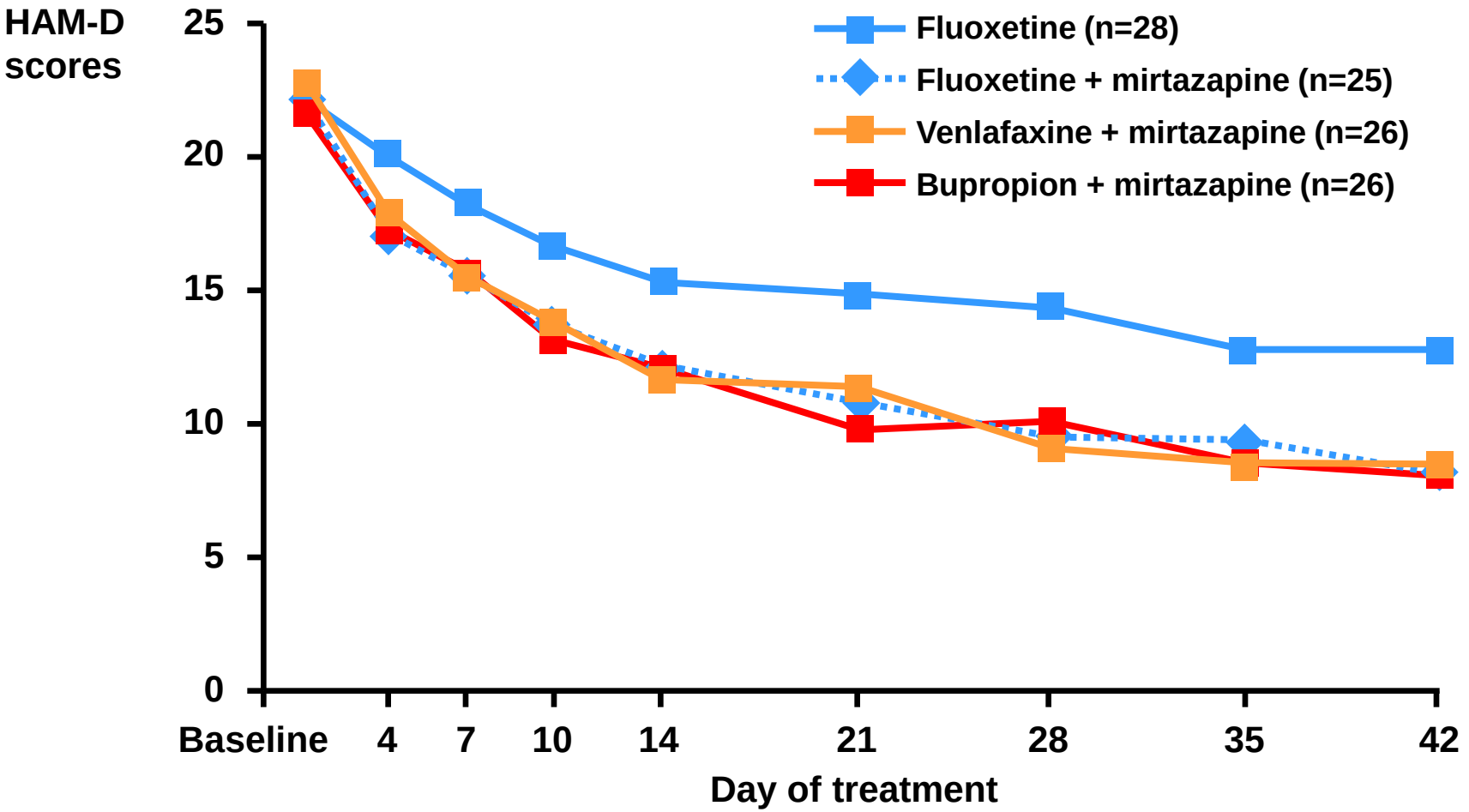
Aripiprazole augmentation after inadequate response to SSRI/SNRIs



Aripiprazole does not have a licences for augmentation in refractory depression in Europe

Marcus, R. N., McQuade, R. D., Carson, W. H., et al (2008) The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychopharmacology,* **28**, 156-165.

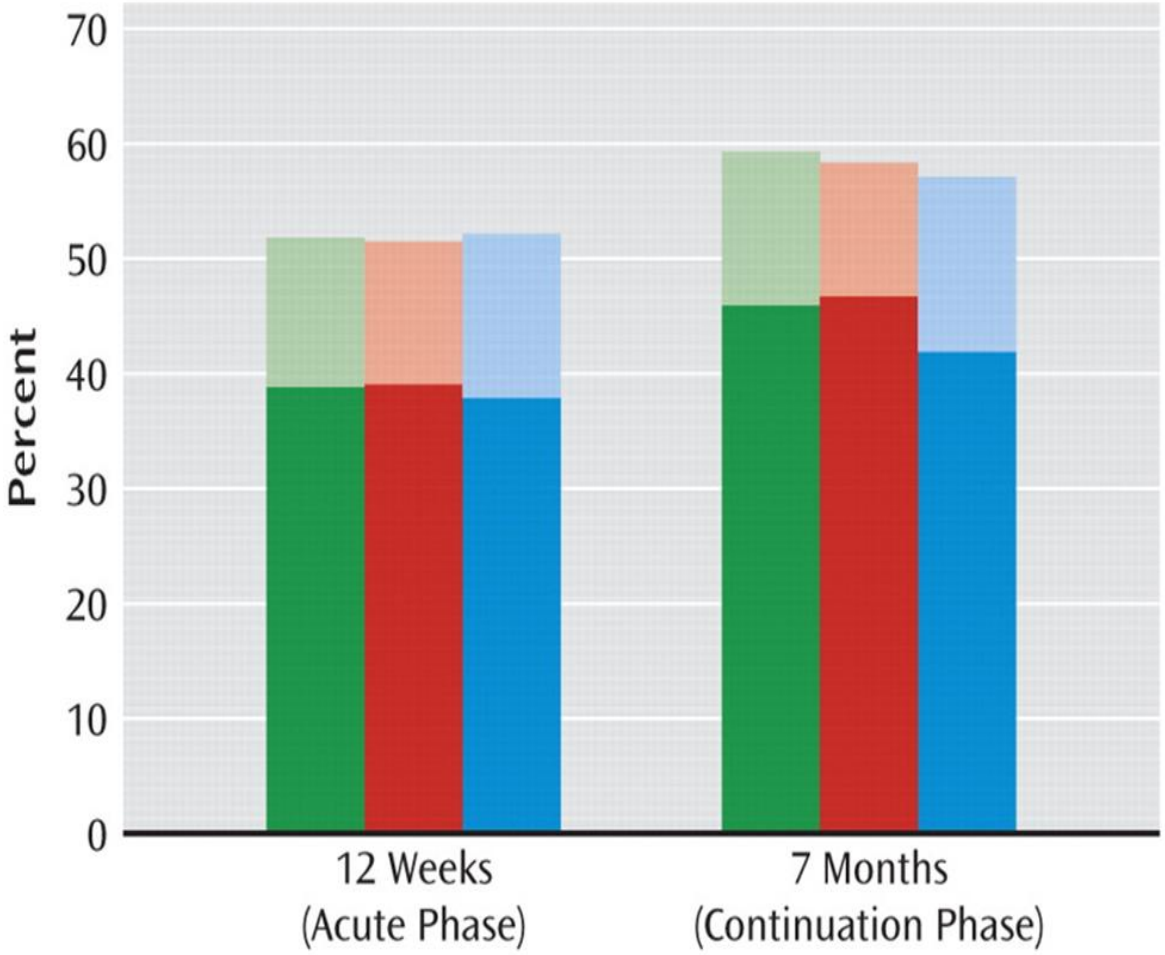
Antidepressant combinations



p=0.011, difference between fluoxetine monotherapy and all combination treatment groups

Blier et al. *Am J Psychiatry* 2010;167:281

CO-MED – Outcomes



Monotherapy: escitalopram + placebo (N=224)
- Remission
- Response

Sustained-release bupropion + escitalopram (N=221)
- Remission
- Response

Extended-release venlafaxine + mirtazapine (N=220)
- Remission
- Response

Rush, A. J., Trivedi, M. H., Stewart, J. W., *et al* (2011) Combining Medications to Enhance Depression Outcomes (CO-MED): Acute and Long-Term Outcomes of a Single-Blind Randomized Study. *American Journal of Psychiatry*, **168**, 689-701.

Other augmentation options
(Hidden slides)

- T3
  - Positive and negative studies. Better tolerated than Lithium
- Modafinil
  - Positive meta-analysis of 4 studies in MDD
  - Other psychostimulants very little data
- Lamotrigine
  - Four RCTs negative on primary outcome
- L-tryptophan
  - Safe but only anecdotal evidence
- Pramipexol
  - Limited data from small RCTs
- Ketamine
  - Positive RCTs but effects are short lived
- Other options under study
  - Anti-inflammatories, anti-glucocorticoids

Addressing doctor-related factors

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- Avoid delays
- Clear pharmacological strategy
- Use adequate trials of medication

Standard v high dose venlafaxine after SSRI failure/intolerance

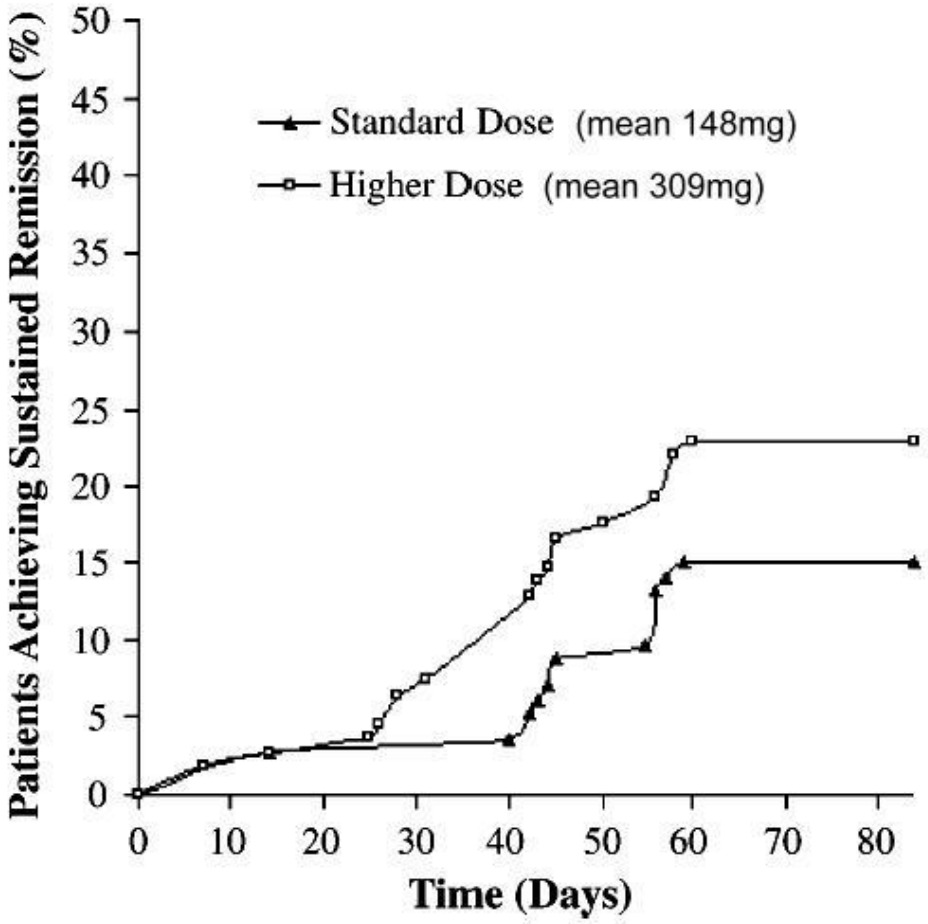

FIGURE 1. Time to remission during treatment with standard or higher dose venlafaxine XR.

Thase et al 2006

BAP Guidelines: Treatment trial duration

- Lack of significant improvement after 2–4 weeks treatment substantially reduces the probability of eventual sustained response (A).

- After 4 weeks adequate treatment:
  - if there is at least some improvement continue treatment with the same antidepressant for another 2–4 weeks (B),
  - if there is no trajectory of improvement undertake a next-step treatment (B);
    - in patients who have failed a number of treatments consider longer trials (D)
- After 6–8 weeks adequate treatment:
  - if there is moderate or greater improvement continue the same treatment,
  - if there is minimal improvement undertake a next-step treatment (B)
    - in patients who have failed a number of treatments consider longer trials before changing treatment (D).

BAP Guidelines: Treatment trial duration

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Addressing doctor-related factors

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- Avoid delays
- Clear pharmacological strategy
- Use adequate trials of medication
- Holistic treatment

CBT + AD v AD

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Review: Dep Up: Psychology: Cognitive and behavioural therapies
Comparison: 09 Cognitive and behavioural therapies + ADs v ADs (with clinical management or GP care)
Outcome: 04 Depression scores: continuous measures post-treatment

Study or sub-category	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)	SMD (fixed) 95% CI
02 HRSD scores post-treatment					
Hautzinger (in-pats)	20	9.30 (7.50)	22	11.30 (7.60)	
Murphy 1984 (US)	22	8.23 (7.00)	24	10.92 (8.22)	
Miller 1989 (US)	14	15.30 (13.84)	17	23.80 (14.84)	
Hautzinger 1996 (Ge)	32	8.00 (5.50)	24	8.80 (6.80)	
Scott 1997 (UK)	18	13.50 (5.30)	16	16.50 (6.80)	
Keller 2000 (US)	226	10.80 (9.47)	220	15.80 (9.49)	
Thompson 2001 (US)	36	12.00 (6.90)	33	15.00 (6.20)	
Subtotal (95% CI)	368		356		
Test for heterogeneity: Chi² = 2.64, df = 6 (P = 0.85), I² = 0%					
Test for overall effect: Z = 6.10 (P < 0.00001)					
Total (95% CI)	368		356		
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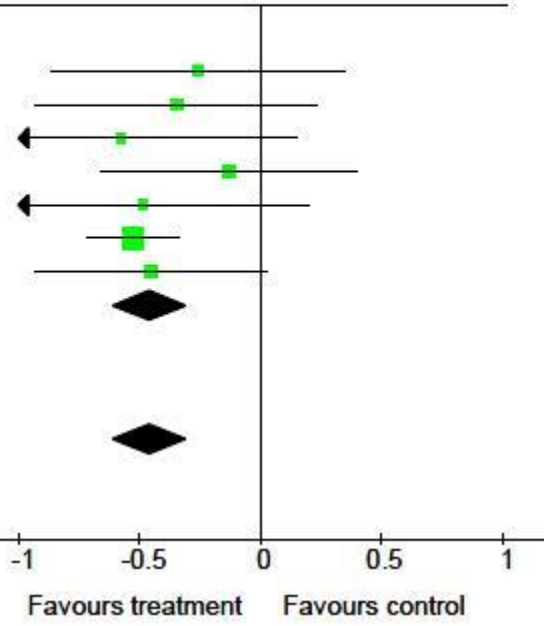

NICE guideline 2009

ECT vs Pharmacotherapy

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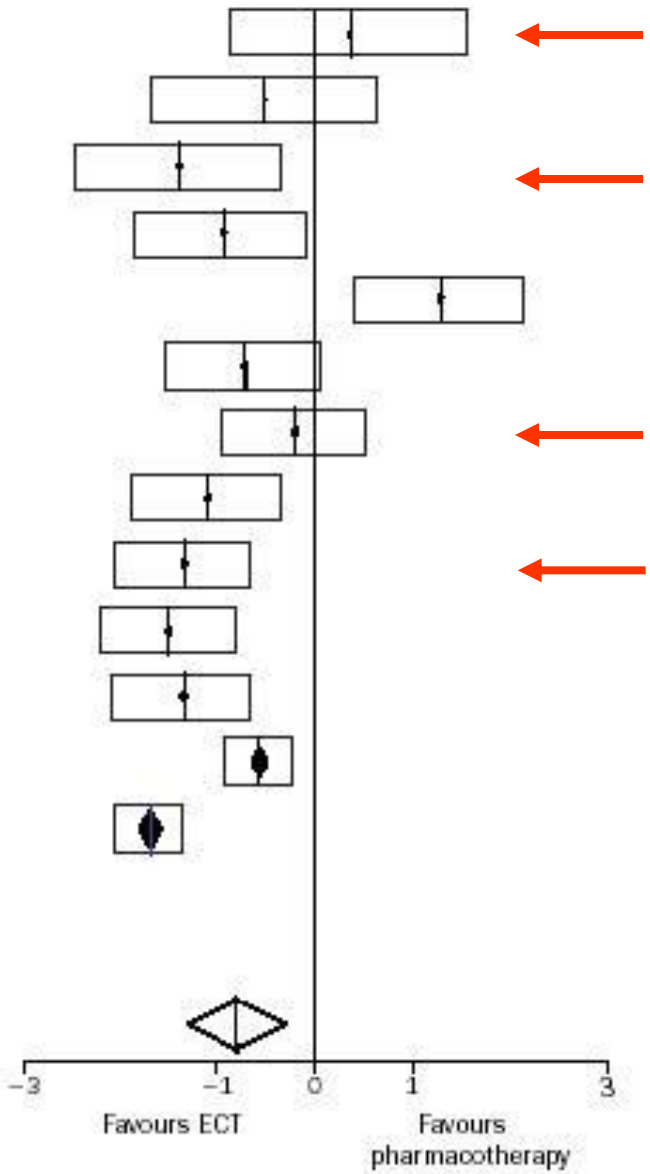
Trial*	Number of participants	Standardised effect size (95% CI)
Steiner 1978[16]	12	0·369 (–0·840 to 1·578)
Wilson 1963[10]	12	–0·513 (–1·663 to 0·637)
Davidson 1978[17]	19	–1·389 (–2·449 to –0·328)
McDonald 1966[18]	22	–0·930 (–1·813 to –0·047)
Gangadhar 1982[19]	32	1·287 (0·406 to 2·169)
MacSweeney 1975[20]	27	–0·714 (–1·492 to 0·065)
Dinan 1989[21]	30	–0·196 (–0·926 to 0·534)
Janakiramaiah 2000[22]	30	–1·095 (–1·863 to –0·328)
Folkerts 1997[23]	40	–1·336 (–2·032 to –0·640)
Herrington 1974[24]	43	–1·497 (–2·174 to –0·821)
Stanley 1962[25]	47	–1·342 (–2·047 to –0·638)
Medical Research Council 1965[26]	204	–0·559 (–0·883 to –0·234)
Greenblatt 1964[27]	242	–1·683 (–2·020 to –1·346)
Pooled fixed effects		–1·010 (–1·170 to –0·856)
Pooled random effects		–0·802 (–1·290 to –0·289)



UK ECT Review Group 2003

Addressing doctor-related factors

Avoid delays

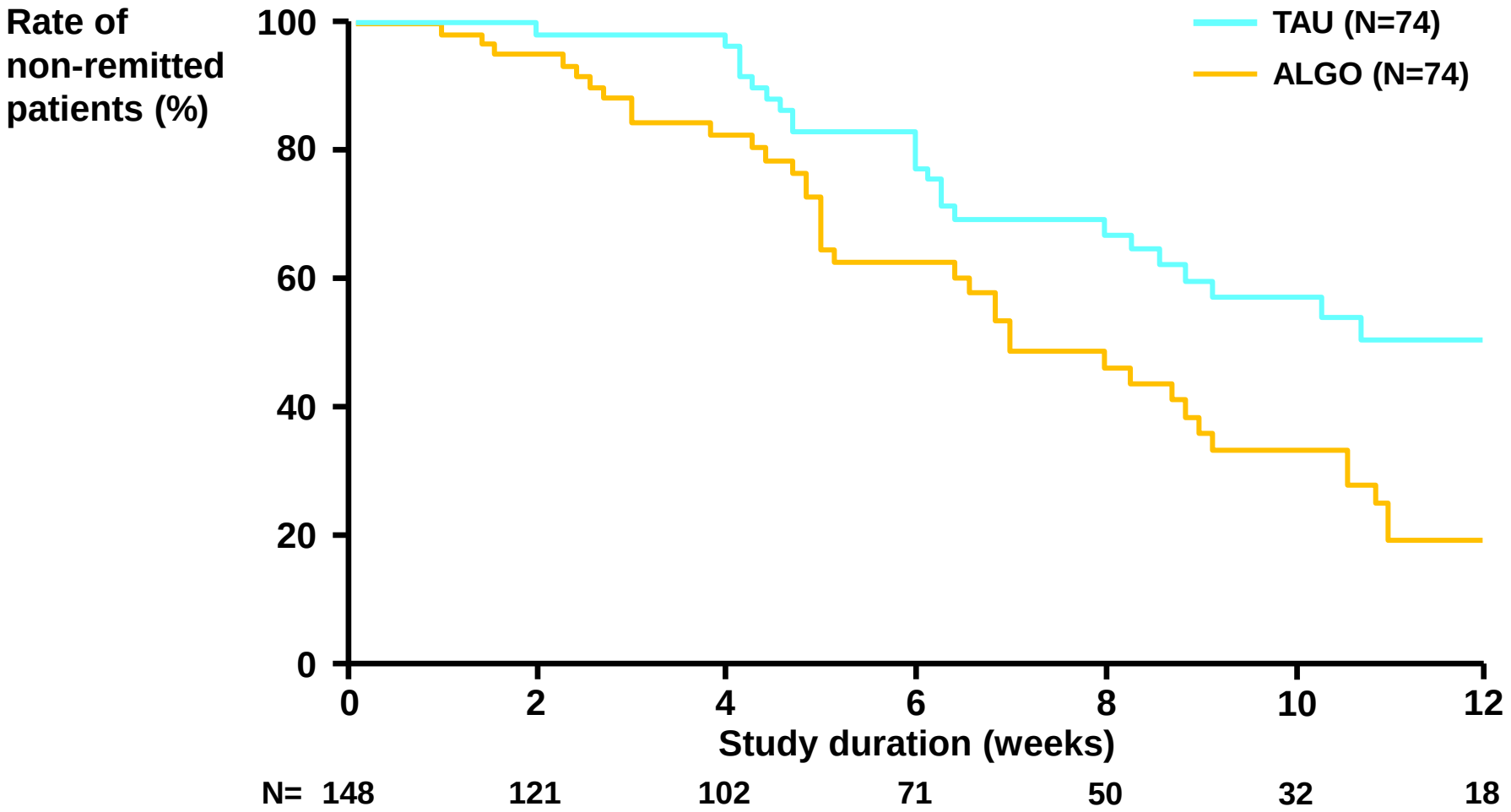
Clear pharmacological strategy

Use adequate trials of medication

Holistic treatment

Monitor response and use critical decision points

Algorithm (ALGO) vs treatment as usual (TAU)



HR=2.0 (p=0.004)
Survival analysis (ITT group)

Bauer et al. *J Clin Psychopharmacol* 2009;29:327

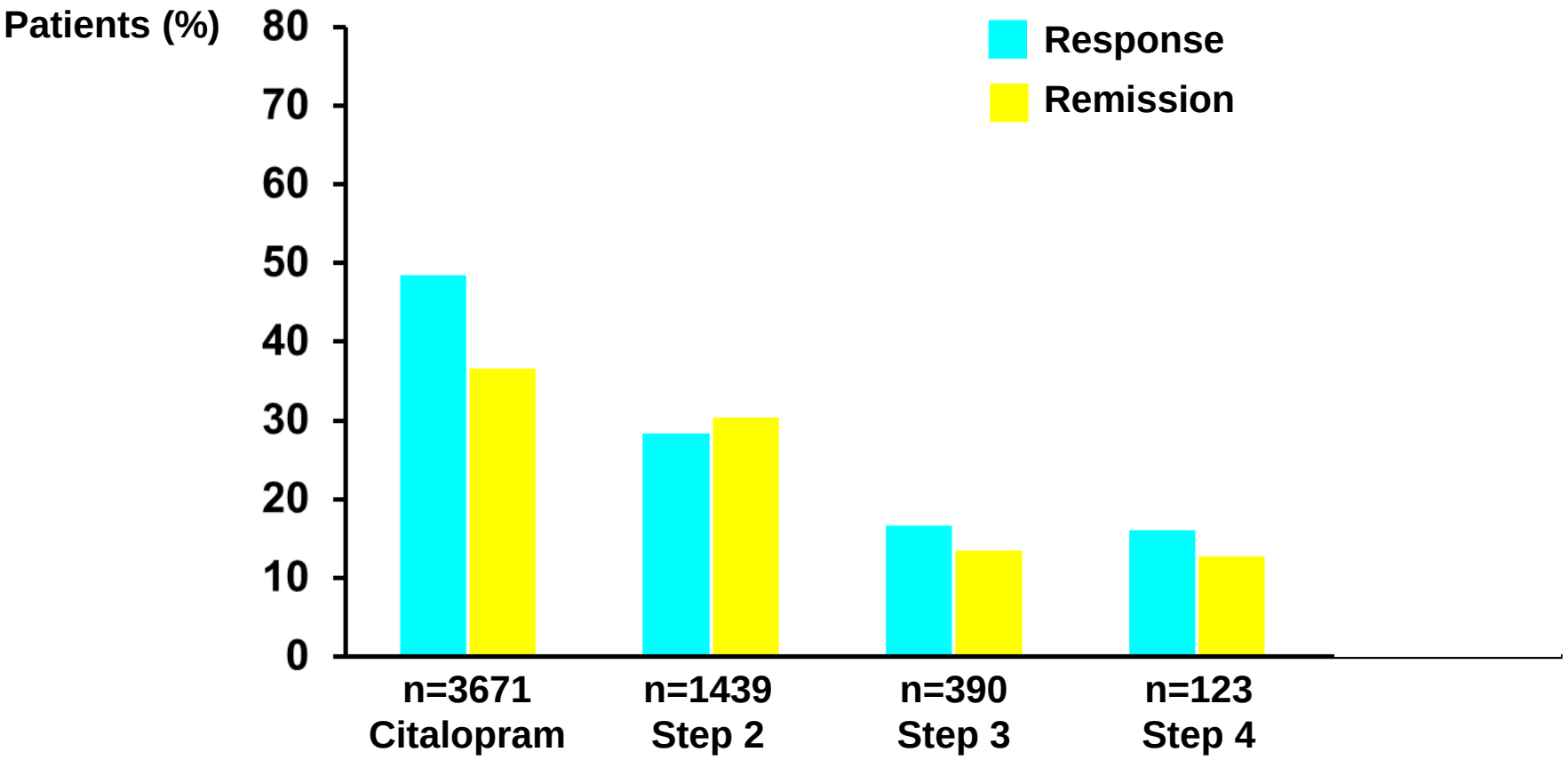
Addressing doctor-related factors

- Avoid delays
- Clear pharmacological strategy
- Use adequate trials of medication
- Holistic treatment
- Monitor response and use critical decision points
- Avoid therapeutic nihilism and instil hope

Outcome of STAR*D: effect of treatment step

Entry: 80% recurrent or chronic depression

Mean episodes, 6; mean duration, 25 months



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Rush et al. *Am J Psychiatry* 2006;163:1905

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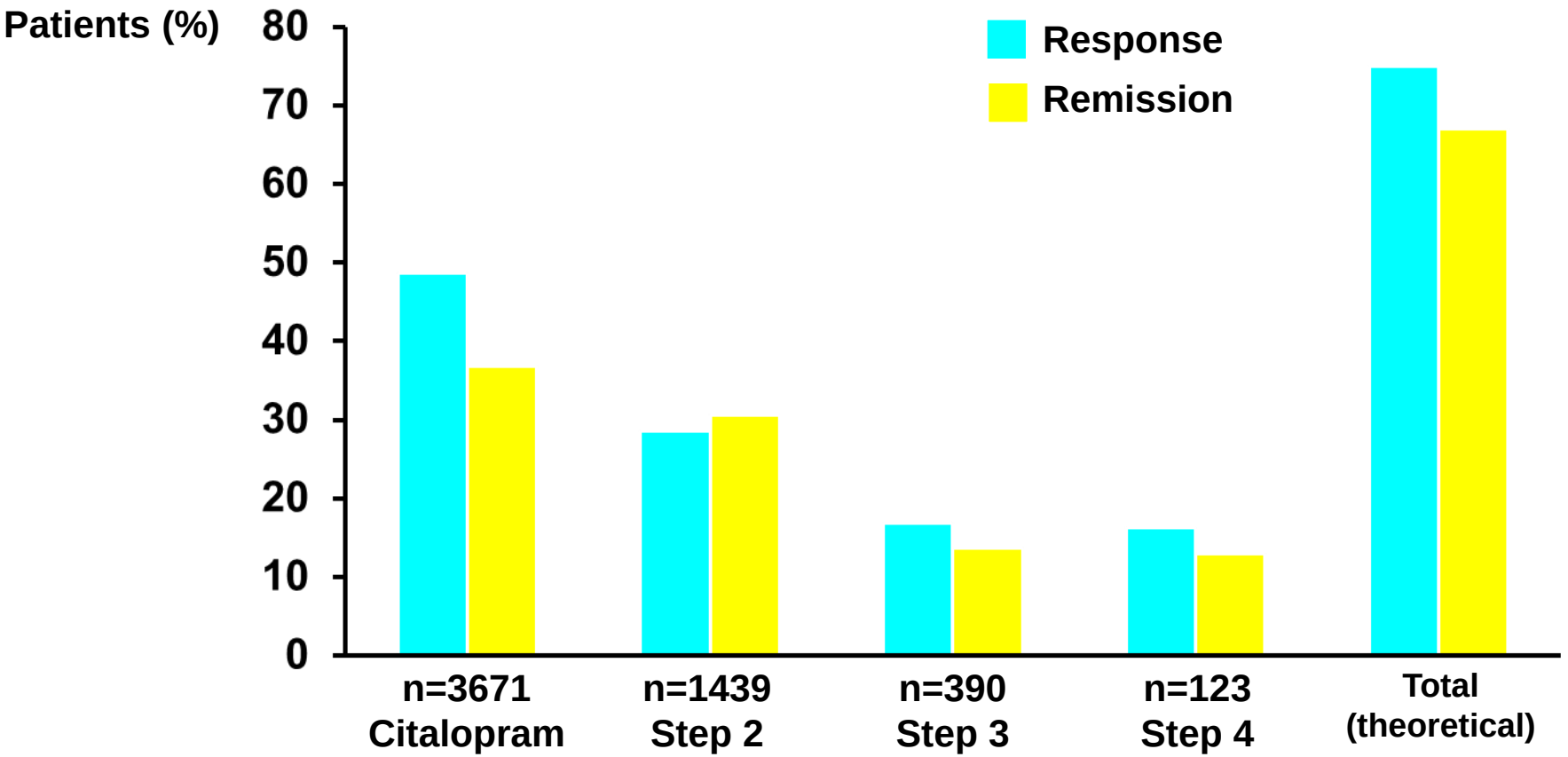

STAR*D, Sequenced Treatment Alternatives to Relieve Depression

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Conclusions

- Beware malignant psychodynamics
- All antidepressants are not the same
- Have non-response strategies
  - Instil (realistic) hope
  - Do something!!
  - Work to an algorithm with critical decision points
  - If stuck then refer