"When I die, I hope it's in a meeting. The transition from life to death will be barely perceptible."

Richard Balon

TREATMENT RESISTANT ANXIETY : DEFINITION, RISK FACTORS AND TREATMENT CHALLENGES

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Faculty Disclosure

- Dr. Roy-Byrne has in the past 3 years:
  - Received research support from
    - National Institute of Mental Health
    - National Institute of Drug Abuse
  - Been a paid (stock options) consultant for
    - Valant Medical Systems (Behavioral Health EMR Company)
  - Been paid as Editor-in-Chief for
    - *Depression and Anxiety* (Wiley Press)
    - *Up-to-Date Psychiatry*
    - *Journal Watch Psychiatry (Mass Medical Publishing)*

THE FUNDAMENTAL TENSION

- “Evidence-Based Practice”---Data from placebo-controlled RCTs (control for variability in patient and care process characteristics) show what “works”. But Placebo controlled trials will NOT detect true therapeutic effects in a tiny proportion of the group being studied i.e. <10%
- “Practice-Based Evidence”—Information from clinical practice experience (no control for the “clinicians illusion” where once something works, you do it more and more, with an evident and communicated bias that promotes placebo responses). Some “ineffective” treatments COULD work for a given patient, but should NOT be tried until more effective ones have been given a chance.

TREATMENT RESISTANT ANXIETY

- Definition and Prevalence
- Determinants
  - "Pseudo-Resistance"
  - True Treatment Resistance
- Treatment Approaches

TREATMENT-RESISTANT ANXIETY DEFINITION & PREVALENCE

- Includes failure to remit (60%), or respond (30%), or respond persistently i.e. not relapse (10-30% over 1-10 years)
- So 70% cases may be "refractory" at some point
- Since each syndrome has multiple components, need to consider all relevant response dimensions (i.e. for some, "response" may be limited to one domain and so they could be "non-responders")
- Panic as the most complex example with multiple domains
  - Panic frequency & intensity
  - Phobic avoidance
  - Panic sensation avoidance
  - Anticipatory anxiety
  - Work & Social Disability

DETERMINANTS OF TREATMENT-RESISTANT ANXIETY

- Pseudo-Resistance—lack of adequate treatment (clinician driven) or failure to adhere to treatment (patient driven)
- True Treatment Resistance—failure to respond due to wrong diagnosis, complicating comorbidities, or exogenous anxiogenic factors

PSEUDO-RESISTANCE: CLINICIAN AND PATIENT CONTRIBUTIONS

- Clinician factors (“error”) a more common contributor to psychotherapy pseudo-resistance
- Patient factors (adherence) , a more common contributor to medication psuedo-resistance
- This reflects the relative difficulty of delivering good psychotherapy vs good pharmacotherpy (concept of “robustness”)

ANXIETY TREATMENT EFFICACY

- Medication and CBT equally effective for: Panic, GAD, SAD
- CBT more effective than medication for OCD
- Medication and CBT probably equivalent for PTSD (Zoellner and Feeny study results pending)

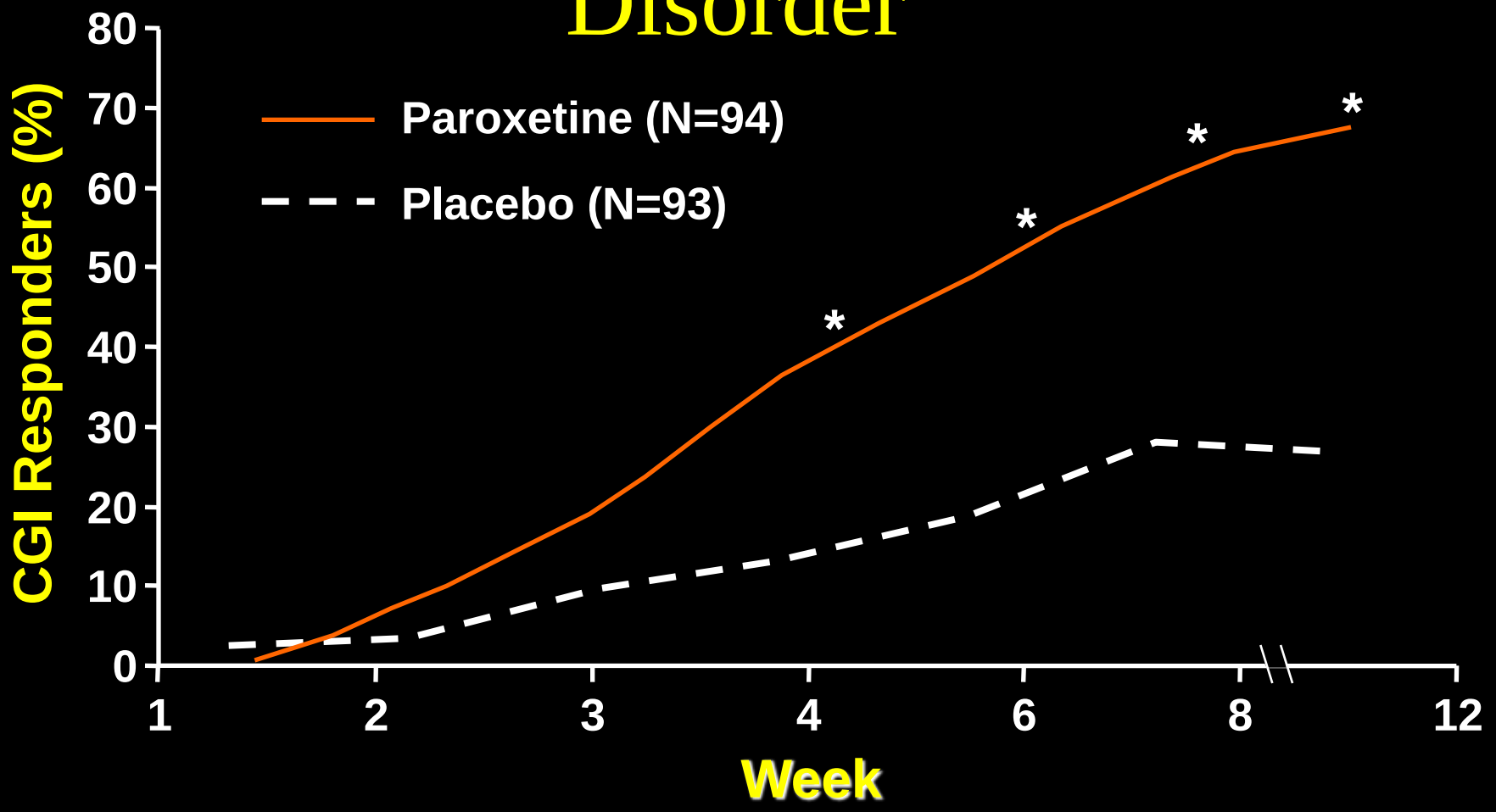
ASSURING ADEQUATE MEDICATION TREATMENT FOR ANXIETY

- SSRI, SNRI, probably MAOI for all four disorders; only SSRI or CMI for OCD
- Bzs do not work for OCD PTSD
- TCAs do not work for SAD or OCD
- Buspirone and Trazadone work ONLY for GAD
- Beta-Blockers work ONLY for performance SAD and at a weak level for GAD
- Bupropion does not work for ANY anxiety disorder (but agitated depression may respond very well!)

ASSURING ADEQUATE MEDICATION TREATMENT FOR ANXIETY: DURATION IS CRUCIAL!

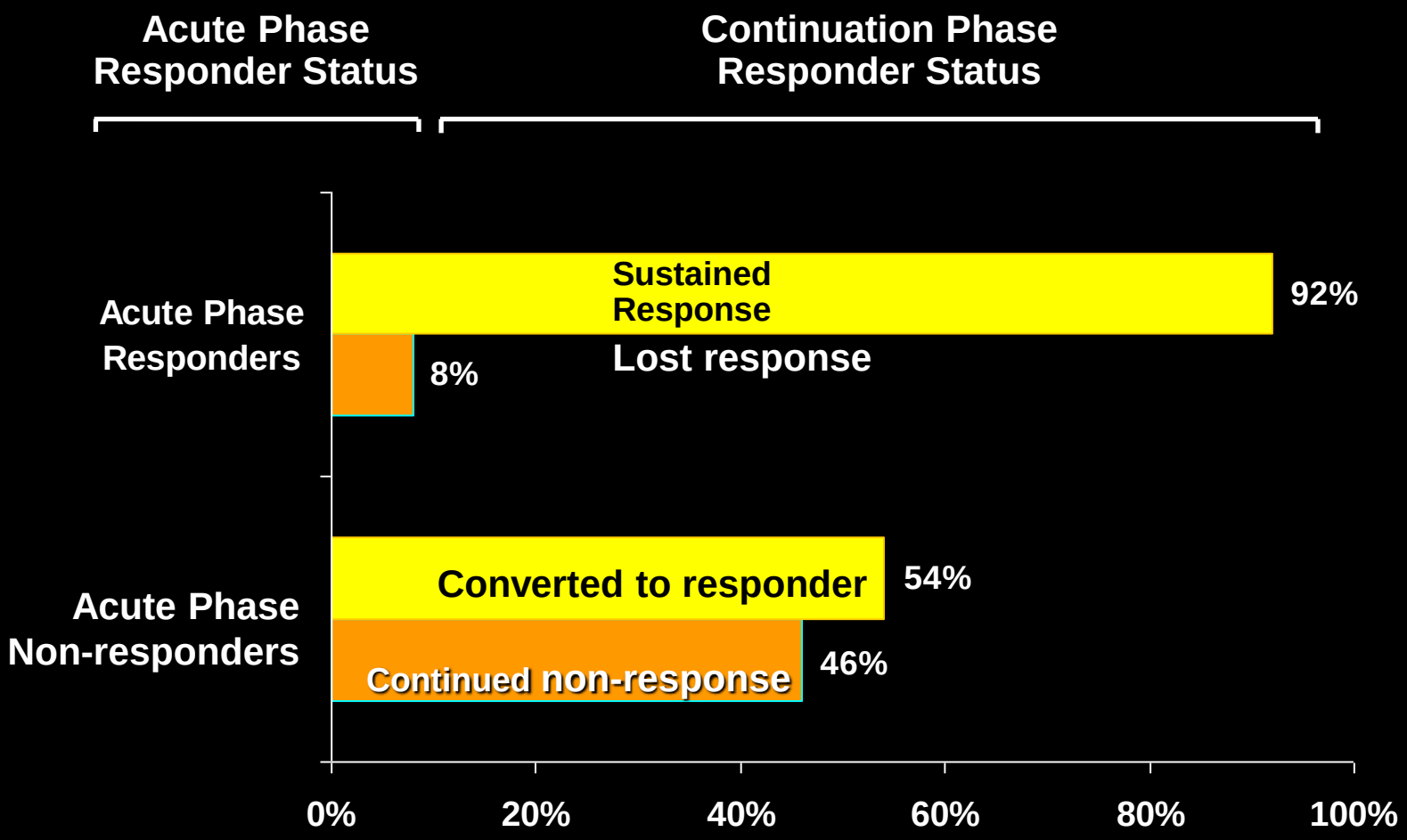
- Anxiety requires a longer time to respond than depression—get dose up during same time
- Acute treatment takes 8-12 weeks
- Even after this, because of the disabling behavioral effects of anxiety, further benefit can accrue over the next 3 months
- This is the biggest challenge for clinicians and requires psychotherapeutic expertise i.e. to help patient be patient!

Paroxetine Treatment of Social Anxiety Disorder



*p≤0.001 vs. placebo Adapted with permission from Stein et al. JAMA. 1998;280:708

Continuation Phase Outcome with Sertraline Treatment of PTSD Based on Acute Phase Response Category



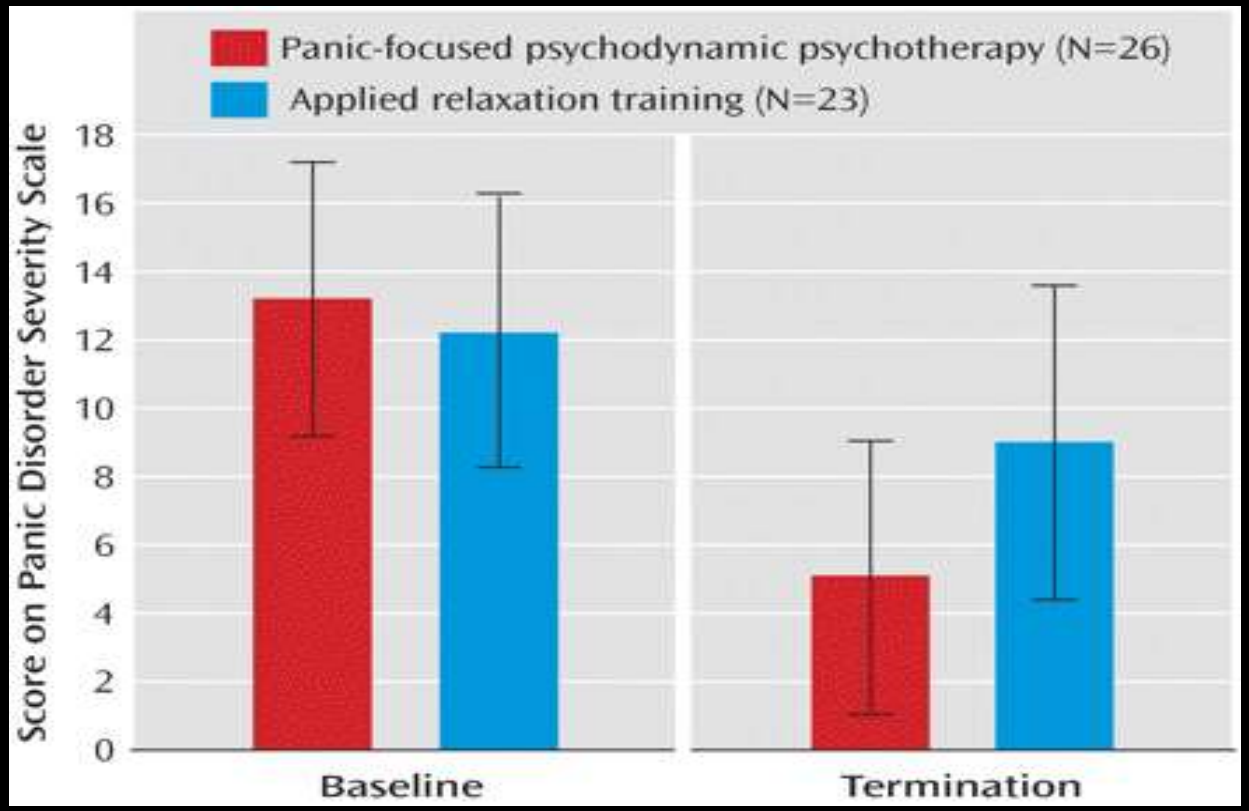
Responder = ≥ 30% decrease CAPS and CGI-S = 1 or 2

Londborg et al. *J Clin Psychiatry*, in press.

ASSURING ADEQUATE PSYCHOTHERAPY FOR ANXIETY

- CBT (various forms and versions) is the only treatment that works for all five disorders (but PE better for PTSD and ERP better for OCD)
- Mindfulness (GAD), psychodynamic psychotherapy (Panic, GAD, SAD) and IPT (PTSD) have some efficacy but far fewer studies and testing often done in mixed diagnostic groups
- Psychotherapy is much harder to deliver adequately than medication (more expertise is required), and any non-CBT treatment is harder to deliver adequately than CBT

Psychodynamic Therapy for Panic



Milrod B et al., Am J Psychiatry 2007

PSYCHODYNAMIC PSYCHOTHERAPY FOR SAD: NOT EQUAL TO CBT

TABLE 3. Outcomes for Cognitive-Behavioral Therapy, Psychodynamic Therapy, and Waiting List Among Patients With Social Anxiety Disorder (Intent-to-Treat Sample; N=495)[a]

	Cognitive-Behavioral Therapy (N=209)			Psychodynamic Therapy (N=207)			Waiting List (N=79)		
Measure and Assessment Time	Mean	SD	95% CI	Mean	SD	95% CI	Mean	SD	95% CI
Liebowitz Social Anxiety Scale									
Baseline	72.06	22.39	69.00–75.11	73.26	22.13	70.22–76.30	73.32	20.93	68.66–77.99
Week 8 of treatment	67.49	23.12	64.25–70.74	71.88	24.47	68.46–75.29			
Week 15 of treatment	59.10	24.03	55.70–62.49	66.32	26.67	62.54–70.10			
End of treatment	42.94	25.41	39.25–46.64	50.71	27.49	46.52–54.90	68.13	25.34	61.82–74.45
Social Phobia and Anxiety Inventory									
Baseline	90.19	19.26	87.34–93.04	90.09	19.88	87.12–93.07	89.91	18.09	85.58–94.24
End of treatment	66.28	26.86	62.26–70.31	76.67	24.89	72.58–80.76	85.70	22.17	80.09–91.31
Beck Depression Inventory									
Baseline	14.78	8.94	13.38–16.19	14.18	9.93	12.64–15.72	15.14	9.16	12.86–17.42
End of treatment	10.40	10.98	8.53–12.27	12.58	12.40	10.48–14.68	15.37	11.74	12.36–18.37
Inventory of Interpersonal Problems									
Baseline	14.27	3.52	13.73–14.81	14.11	3.69	13.56–14.66	14.53	3.83	13.63–15.44
End of treatment	11.67	4.83	10.92–12.42	13.12	4.38	12.45–13.80	13.82	3.98	12.77–14.87

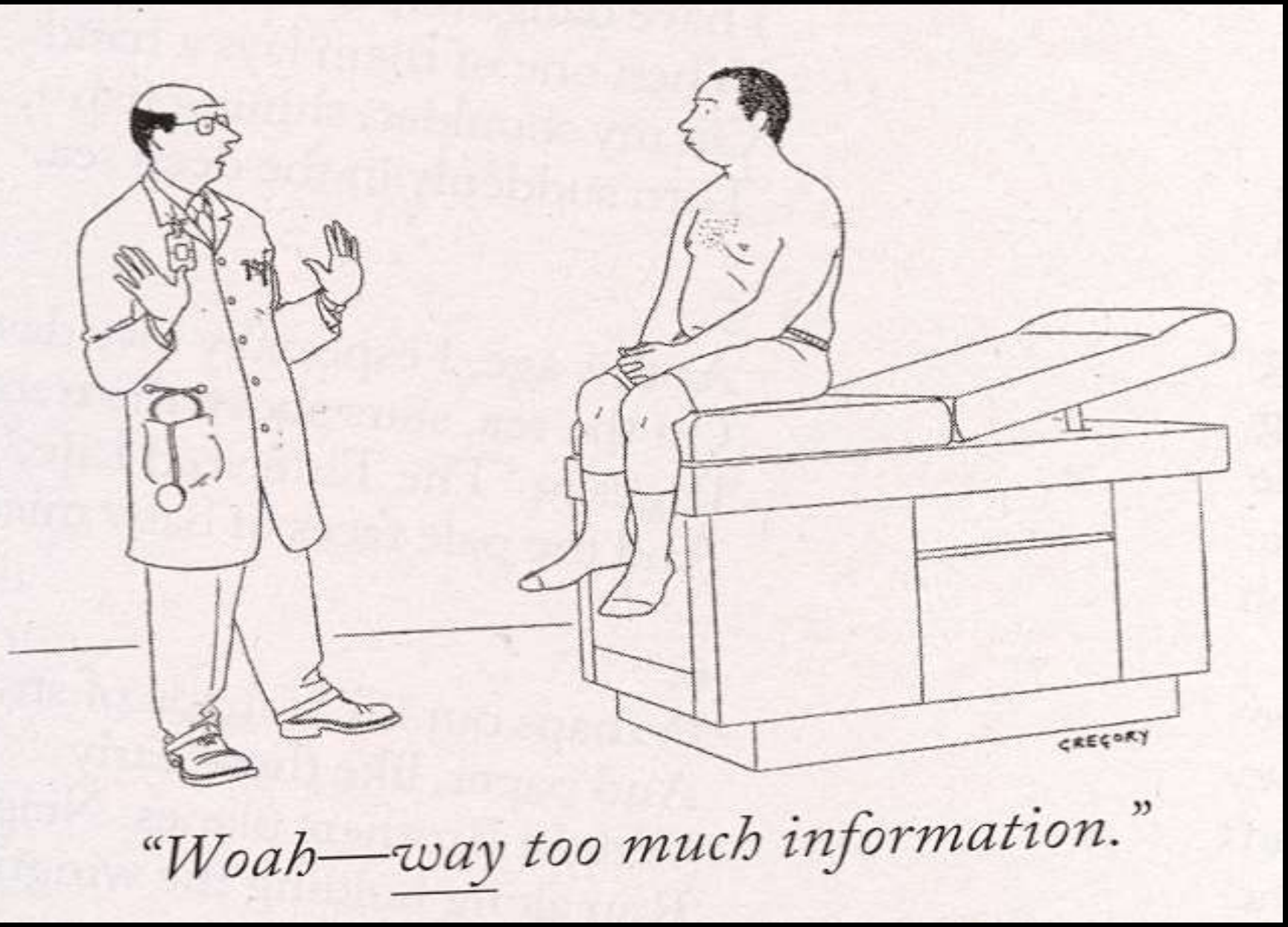
Remission CBT, PD, WL= 36%, 26%, 9% (CBT>PD>WL)
Response CBT, PD, WL= 60%, 52%, 15% (CBT=PD>WL)

Leichsenring et al 2013, Am J Psychiatry

CBT DELIVERY FAILURE

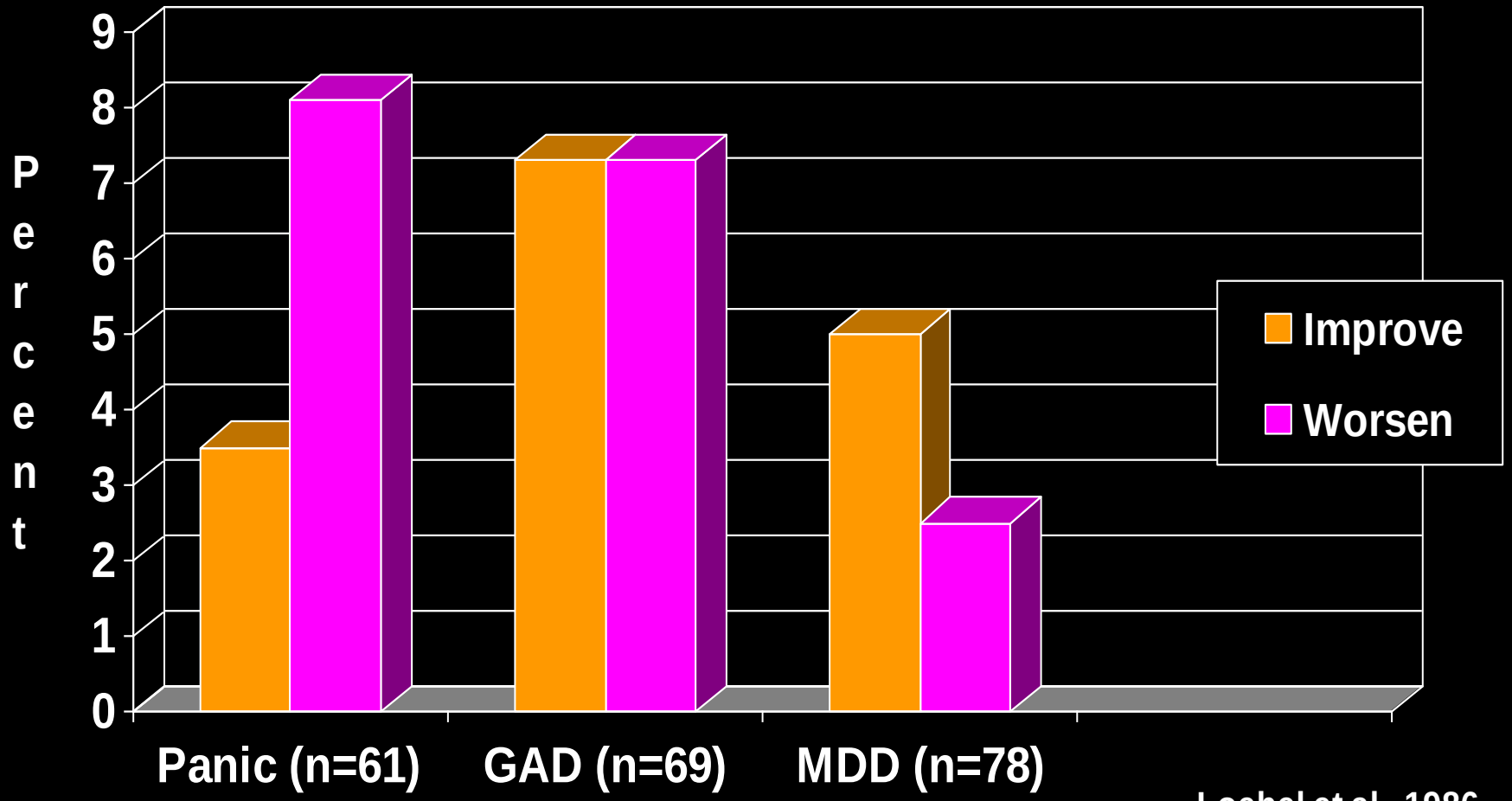
- Most common is failure to progress to exposure due to clinician discomfort or inadequate training
- Sometimes failure to focus sufficiently on cognitive themes

PATIENT CONTRIBUTORS TO PSEUDO-RESISTANCE



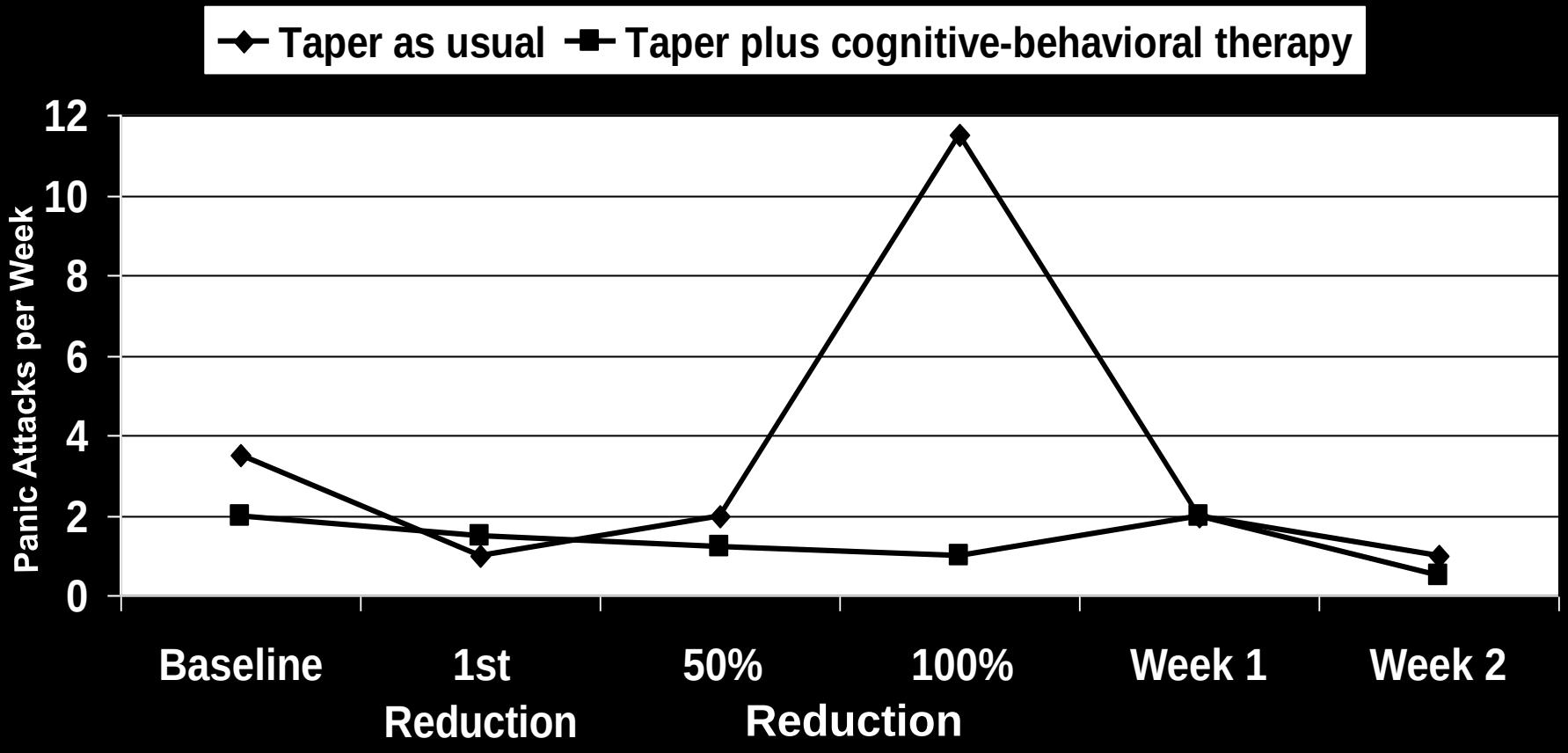
"Woah—way too much information."

TREATMENT INTOLERANCE: HIGH RATE OF NEGATIVE PLACEBO RESPONSE IN ANXIOUS PATIENTS



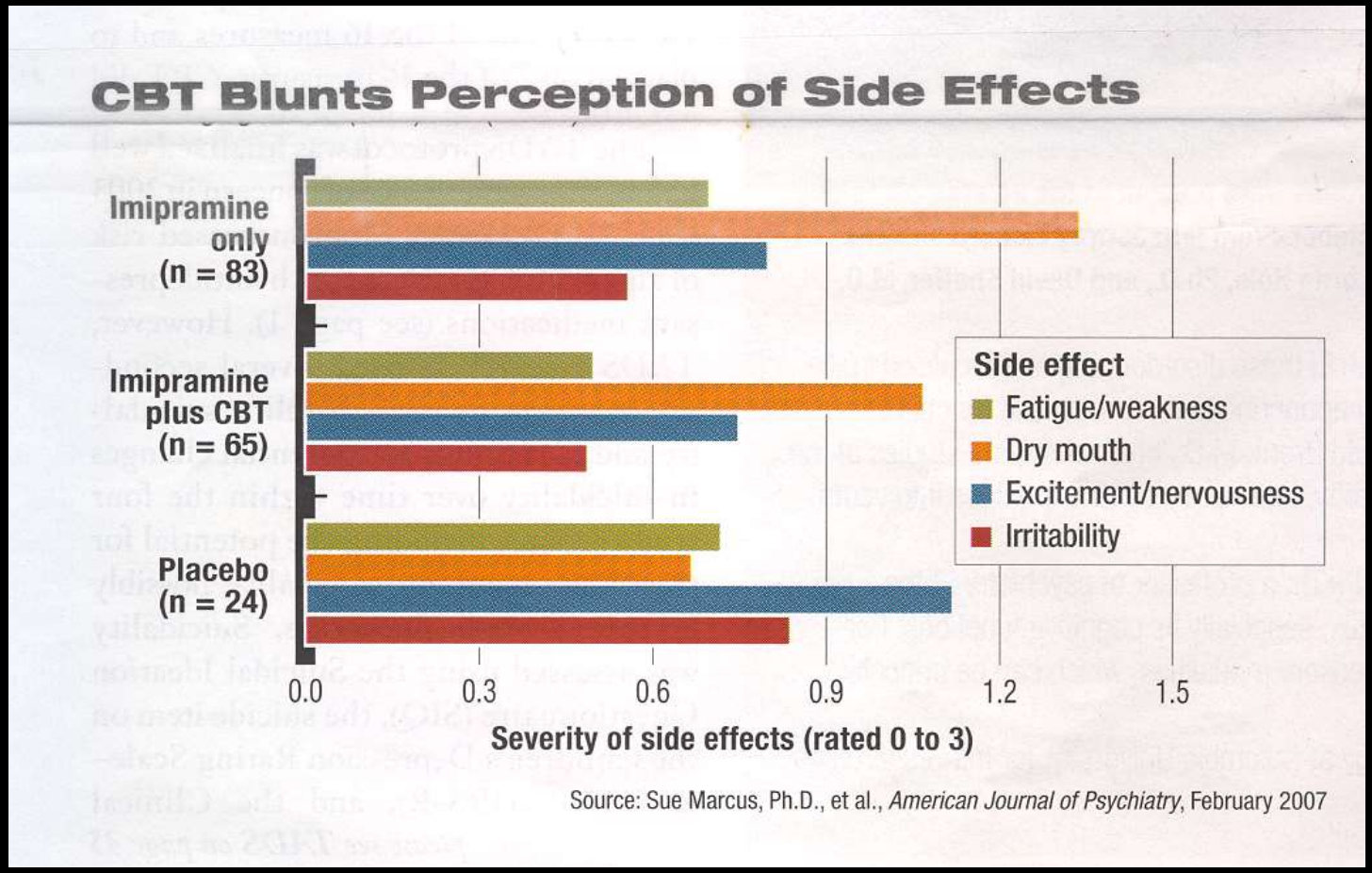
Loebel et al., 1986

CBT ATTENUATES PANIC DURING BZ DISCONTINUATION



Otto et al., 1993

CBT Increases Medication Tolerability



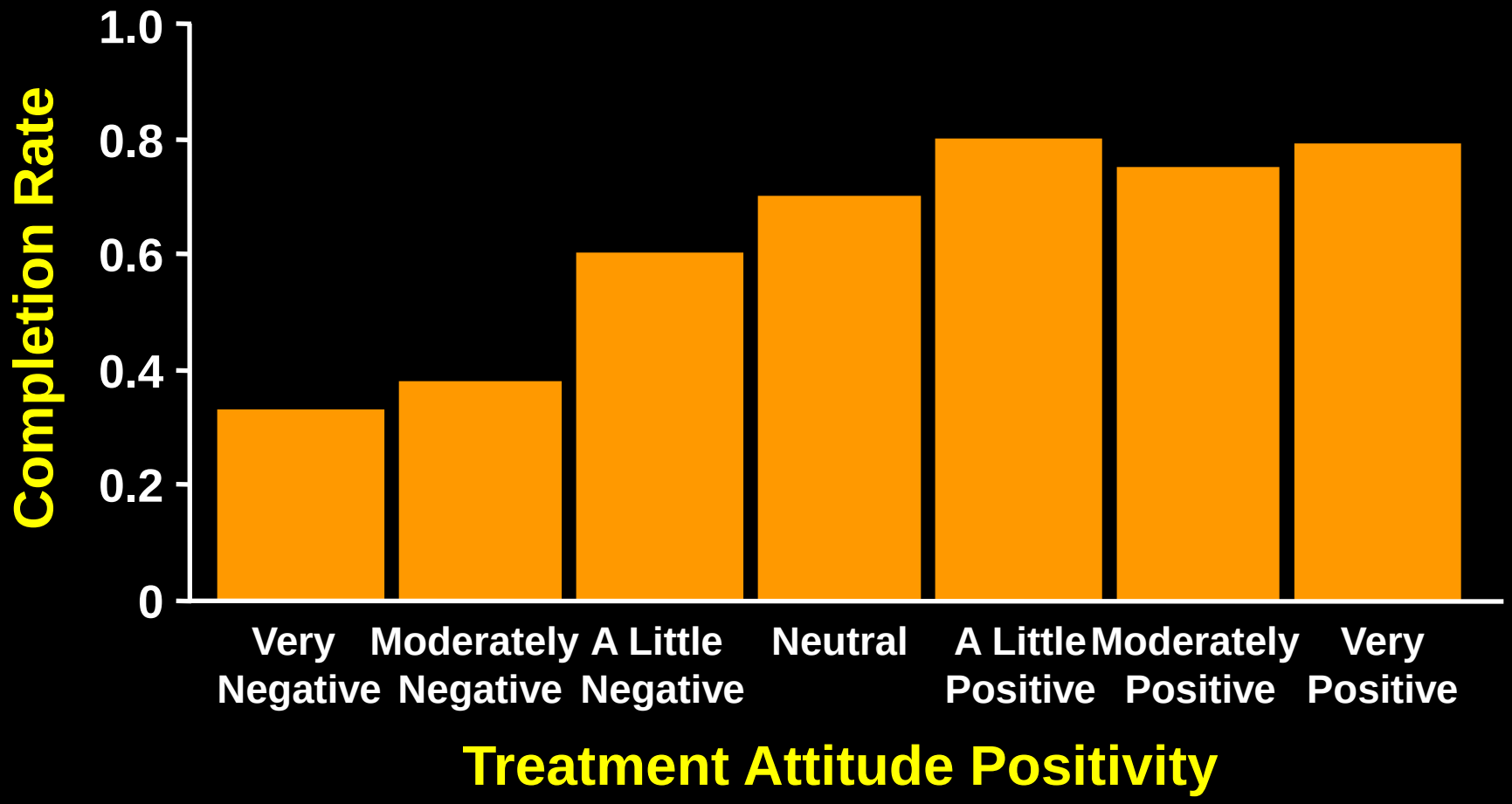
MEDICATION TREATMENT INTOLERANCE: APPROACHES

- Education and patient preparation (Explanatory model, past experience, time course)
- Baseline ratings of anxiety (=side effects)
- Close (2x weekly) monitoring by phone or message for first few weeks
- CBT Techniques--exposure with low dose, slow titration, side effects reframing consistent with patients own model of illness (most important)

TREATMENT NON-ADHERENCE IN ANXIETY DISORDERS

- Hypersensitivity to Medication (especially in Panic)
- "Normalizing attitudes" about anxiety—attribution to stress (Panic and GAD), to personality (SAD), to trauma (PTSD)
- Negative Beliefs about Treatment Efficacy—sometimes related to prior adverse personal or familial experiences with medication or psychotherapy
- Fear of Medication "Dependence" (sometimes confused also with fears of medication "addiction"
- Recovery and Acute Illness Model (late non-adherence)
- Structural and other barriers to treatments—low income, culture and ethnicity

Panic Patients with Negative Beliefs About Treatment Efficacy Drop Out More Often



Grilo CM, Money R, Barlow DH, et al. Compr Psychiatry. 1998(Nov-Dec);39(6):323-332

NOT GETTING PREFERRED TREATMENT REDUCES ADHERENCE

	PE (*n* = 116)		**Sertraline** (*n* = 84)		
	Prefer PE (*n* = 95)	**Prefer SER (*n* = 21)**	**Prefer SER (*n* = 54)**	**Prefer PE (*n* = 30)**	**Cohen's *d* (preference)**
% Treatment Completer	67 (70.5%)	10 (47.6%)	42 (77.8%)	15 (50.0%)	.22*
SER Dosage (mg/d)	--	--	144.20 (66.46)	62.03 (69.63)	1.18***
PE: In vivo Exposure Hwk	19.52 (11.71)	13.57 (14.56)	--	--	0.38*
PE: Imaginal Exposure Hwk	15.21 (9.71)	10.19 (10.73)	--	--	0.39*

TREATMENT RESISTANCE: KEY FACTORS

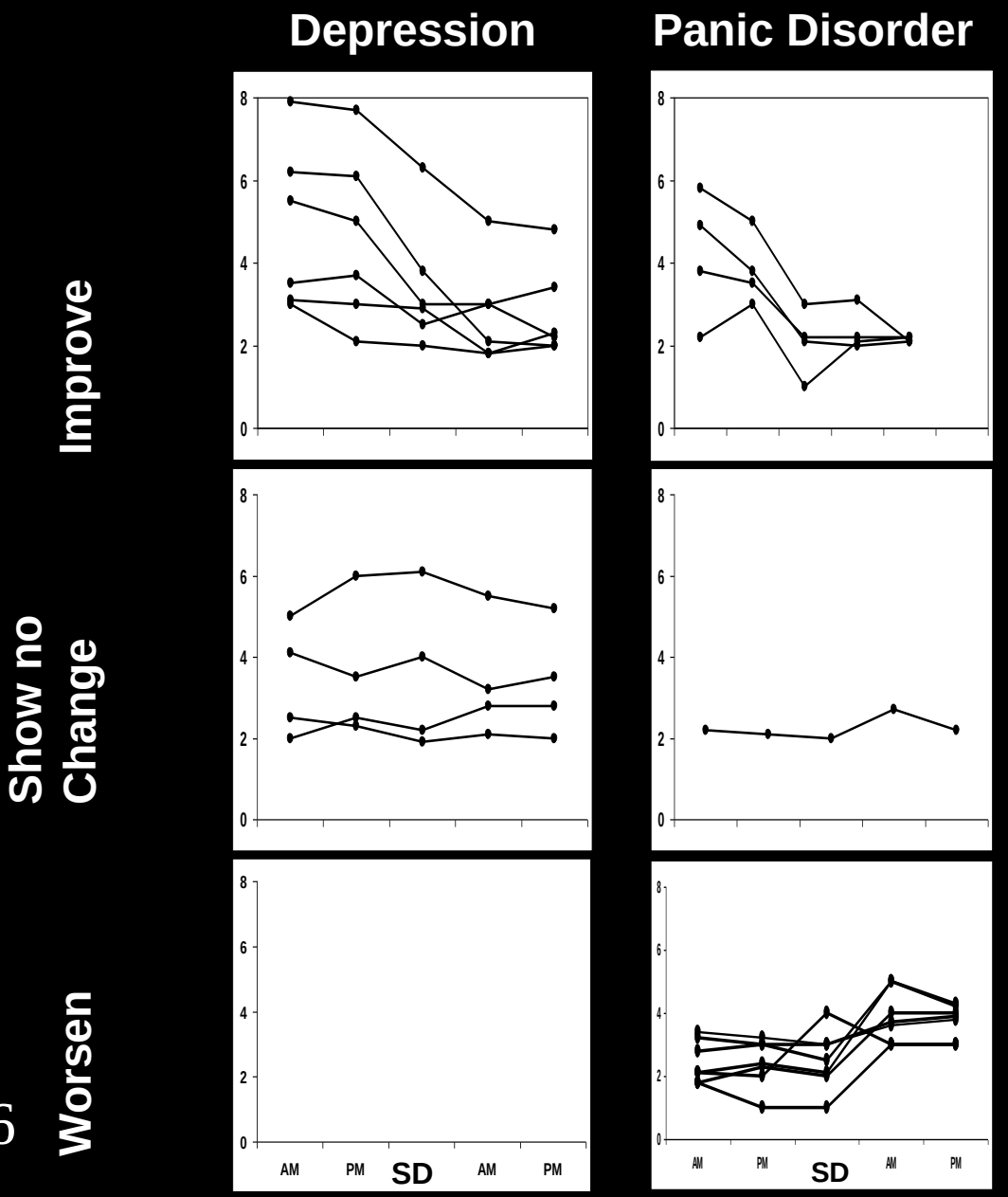
- Exogenous Factors
- Unrecognized Medical Illness
- Wrong “Primary” Diagnosis—Somatic Symptom Disorder, BP, AHDD, Substance Abuse

TREATMENT RESISTANCE: ROLE OF EXOGENOUS ANXIOGENIC FACTORS

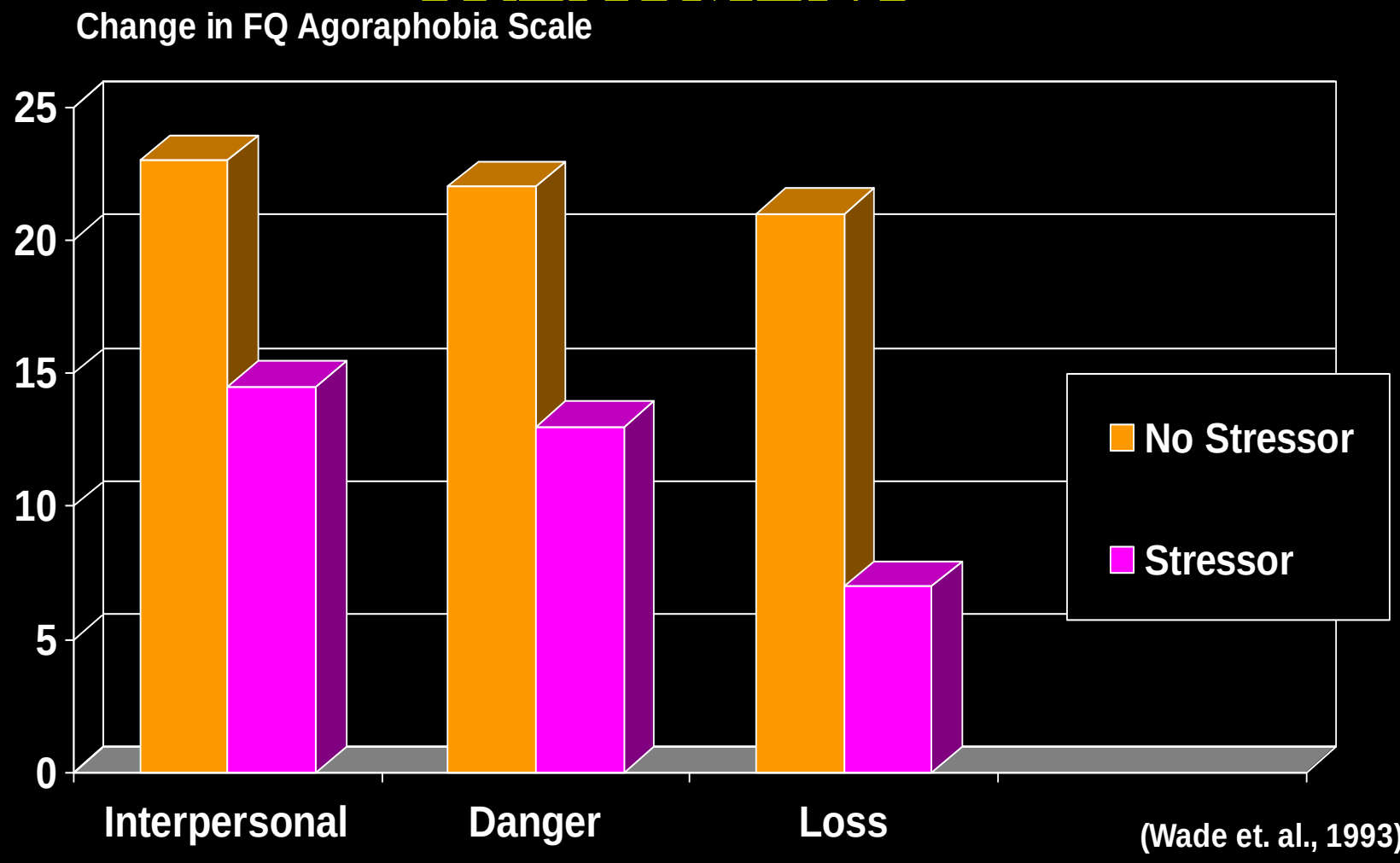
- Health Habits
  - Caffeine
  - Alcohol
  - OTC Cold Preparations
  - Lack of Exercise/ Deconditioning
  - Sleep Deprivation
  - Nicotine (panic risk)
- Life Events/Stress
  - Acute
  - Chronic (low SES; lack of social support)
  - Systems Readjustment (Marital)
- Substance Use
  - Marijuana
  - Alcohol

Differential Anxiety Response to Sleep Deprivation

Roy-Byrne et al 1986

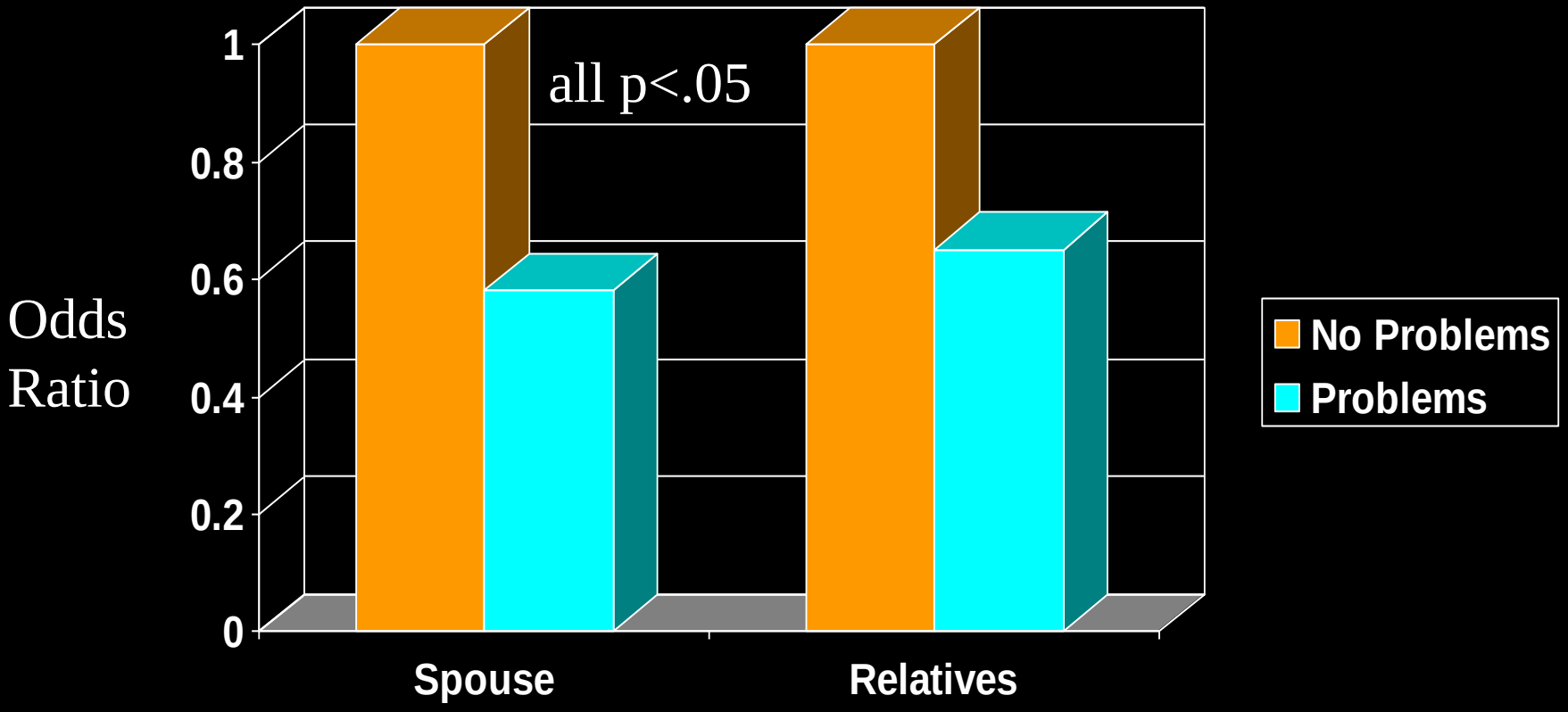


CHRONIC LIFE STRESSORS: EFFECT ON ANTI-PANIC TREATMENT



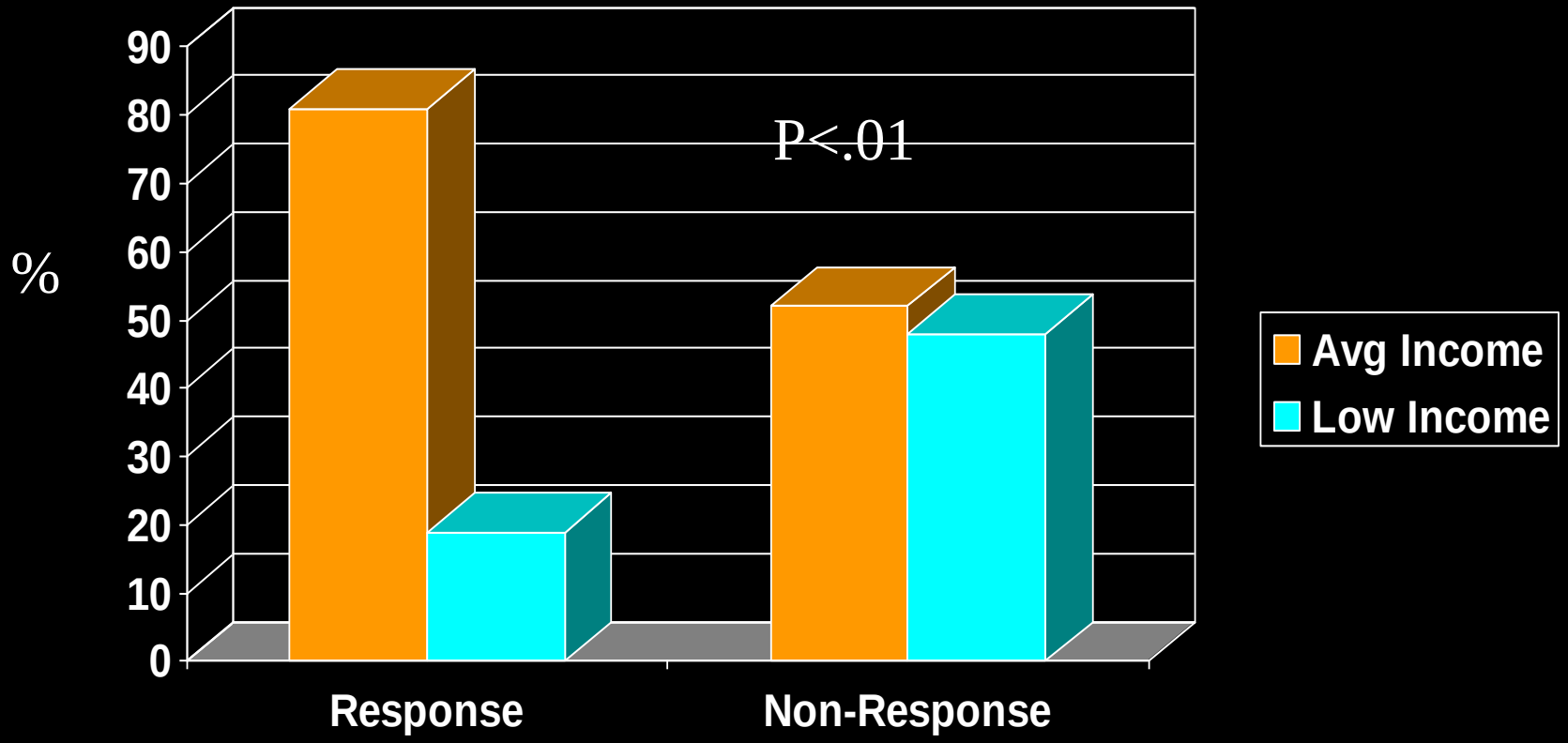
(Wade et. al., 1993)

DISTURBED SPOUSE AND FAMILY RELATIONSHIPS PREDICT LACK OF REMISSION IN GAD



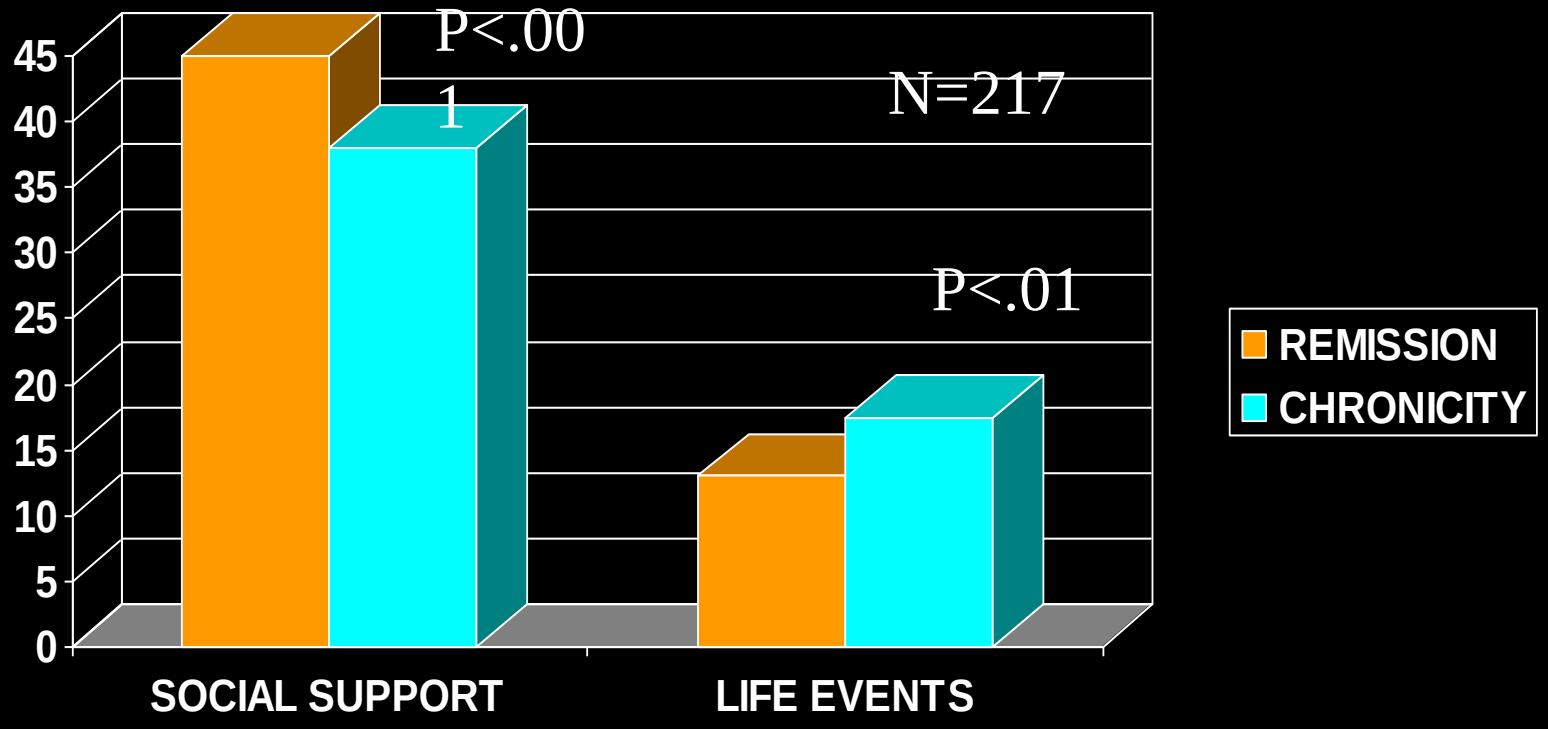
Yonkers et al 2000

POORER SSRI RESPONSE IN LOW INCOME PANIC DISORDER PATIENTS



Roy-Byrne et al 2003

POORER SOCIAL SUPPORT AND MORE LIFE EVENTS PREDICTS PTSD CHRONICITY



Udwin et al 2000

MJ USE AND POORER OUTCOME AFTER VA PTSD PROGRAM

Table 2. Relationship Between Marijuana Use and Clinical Outcomes at 4-Month Follow-Up

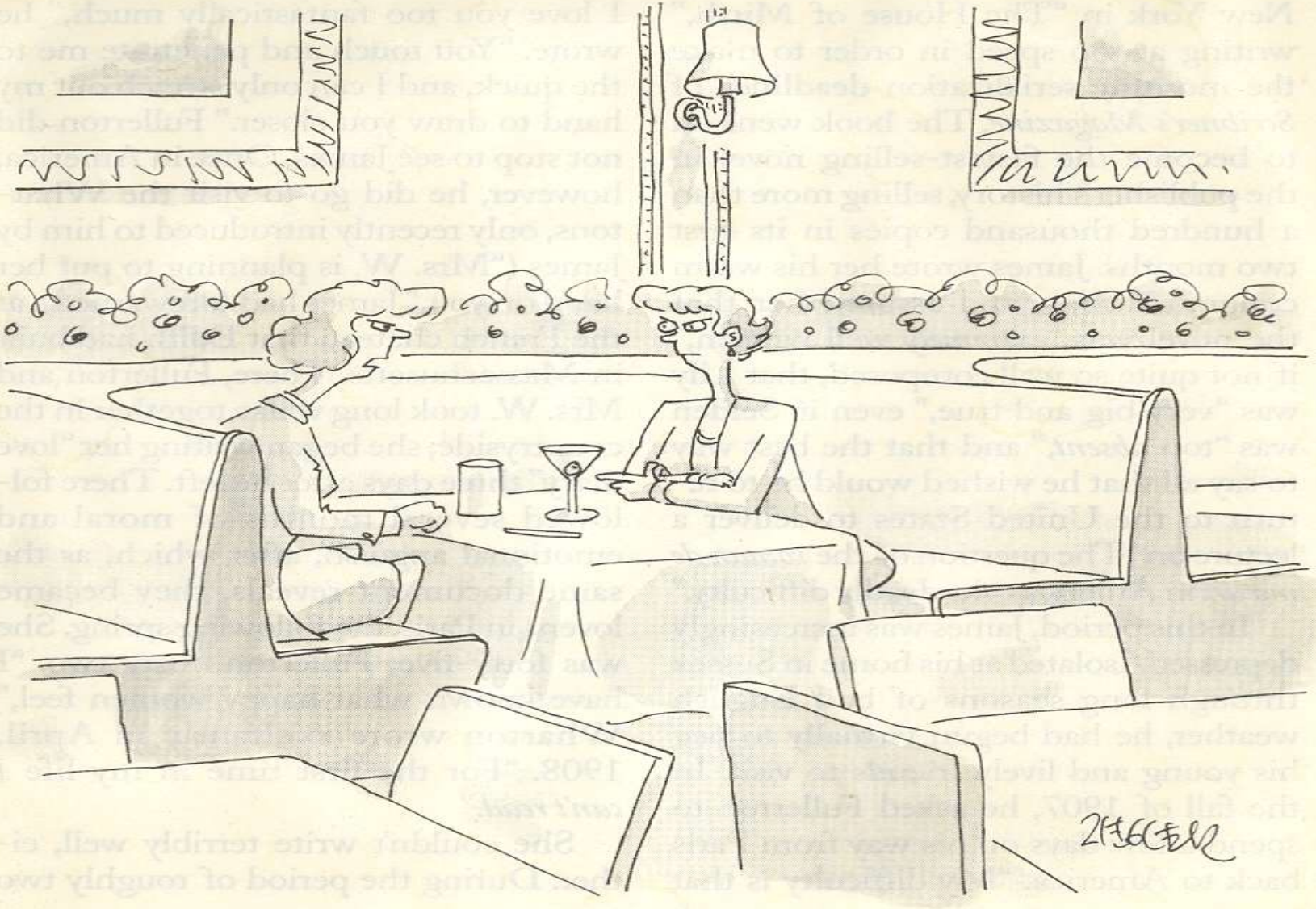
Outcome Variable[a]	Never-Users [1] (n = 767)	Stoppers [2] (n = 263)	Continuing Users [3] (n = 268)	Starters [4] (n = 738)	*F*	*P*	Paired Comparison
PTSD symptom severity (SF-MISS)	37.71 (0.228)	36.64 (0.385)	38.92 (0.383)	39.67 (0.226)	21.47	< .0001	3, 4 > 1, 2
Violence	0.87 (0.041)	0.76 (0.068)	0.93 (0.068)	1.25 (0.040)	21.28	< .0001	4 > 1, 2, 3
Alcohol abuse (ASI)	0.096 (0.007)	0.079 (0.011)	0.129 (0.011)	0.229 (0.006)	88.51	< .0001	4 > 1, 2, 3; 3 >
Drug abuse (ASI)	0.037 (0.0033)	0.034 (0.0056)	0.128 (0.0056)	0.130 (0.0033)	176.26	< .0001	3, 4 > 1, 2
Employment status (ASI)	0.578 (0.007)	0.575 (0.011)	0.594 (0.011)	0.577 (0.007)	0.66	.5752	

[a]Data presented as least-squares mean (SE), covarying for marital status, age, race, history of incarceration, waiting list status, psychosis, chronic medical problems, war zone service, length of stay, expulsion from treatment, and baseline measures of violence, PTSD, drug and alcohol abuse, an employment.

*$P < .01$.

Abbreviations: ASI = Addiction Severity Index; PTSD = posttraumatic stress disorder; SF-MISS = Mississippi Scale for Combat-Related PTSD, Short Form; SE = standard error

J Clin Psychiatry 2015 Rosenheck

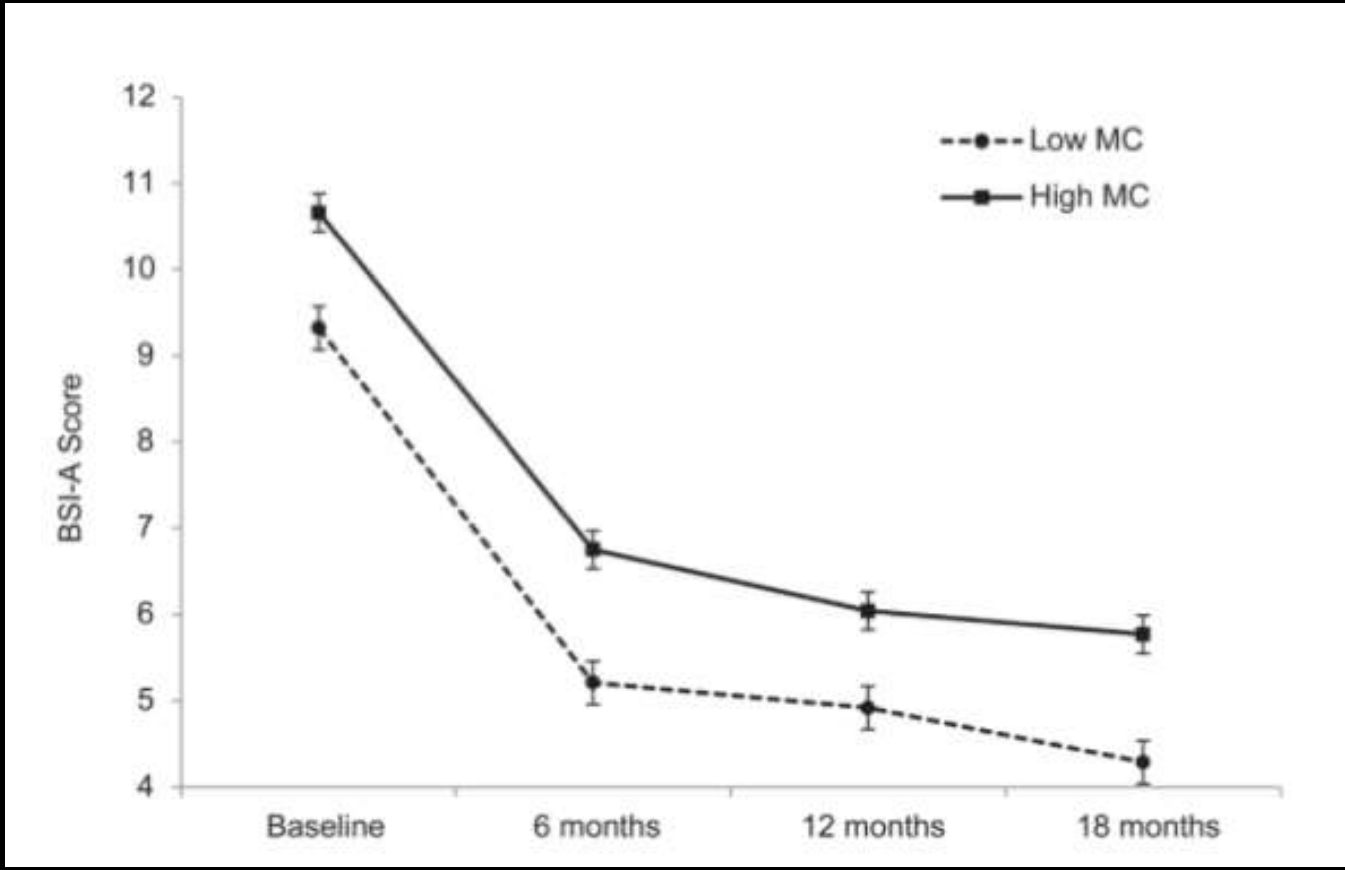


"I was on hormone replacement for two years before I realized that what I really needed was Steve replacement."

ANXIETY AND UNRECOGNIZED MEDICAL ILLNESS

- In practice this is not very common, but failure to recognize can be serious
- Commonly missed syndromes: occult pulmonary embolism in medically healthy young women, complex partial seizures due to early head trauma (sports concussion?) or more serious neuropathology
- Pheochromocytoma (“cold fear”) or hyperthyroidism (easy to test for) are rare

EFFECTS OF MEDICAL ILLNESS ON ANXIETY TREATMENT OUTCOME IN THE CALM STUDY



Campbell-Sills et al: PsychoMed 2015

ANXIETY AND WRONG PRIMARY DIAGNOSIS

- Somatic Symptom Disorder—Somatic symptoms a core part of anxiety
- Atypical Bipolar Disorder with alternating mixed anxious states and more dysphoric depressions
- ADHD—most often confused with GAD
- Occult Substance Abuse—much more common than you think, especially in middle and upper income patients

Somatic Symptom Disorder

- Formerly Somatization Disorder-low rate
- Somatic symptoms causing distress/dysfunction
- Cognitions, or anxiety, or behavior change focused on “seriousness” of symptoms
- Not explained by another disorder
- The key differentiating factor is often the persistence of thoughts, feelings or behaviors, persistent help seeking despite normal tests, antagonism to psychological explanations
- Relation to anxiety probably dimensional

Somatic Symptom Presentations Common to all Mood and Anxiety Disorders

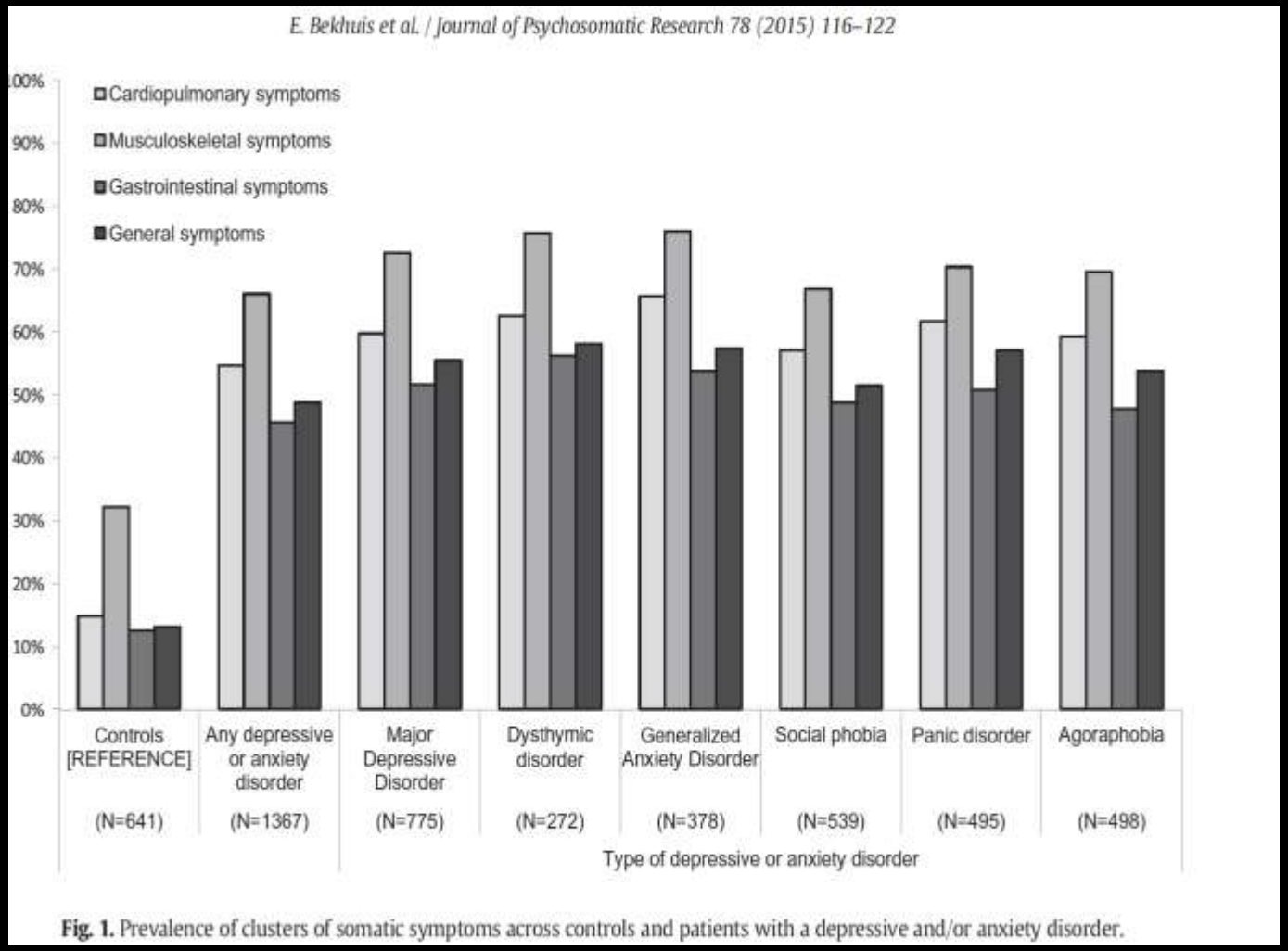


Fig. 1. Prevalence of clusters of somatic symptoms across controls and patients with a depressive and/or anxiety disorder.

Differential Diagnosis

- Panic more episodic but not when chronic!
- Depression has depressive symptoms
- GAD has multiple worries not just one
- Conversion has loss of neurologic function and so an “objective” finding
- Delusional disorder—beliefs are more firmly held and sometimes bizarre
- BDD—concern is appearance
- OCD—symptoms more intrusive

Somatic Symptom Disorder

- In general, pharmacotherapy is not very effective. There are no RCTs but even observational series are underwhelming—I would use SSRIs along with an atypical antipsychotic
- CBT has been more effective—Cochrane review (2014) of 21 studies indicates ES of 0.34 (small to moderate) for all therapies but CBT studies the most rigorous and numerous(n=14)

CBT for Somatic Symptom Disorder

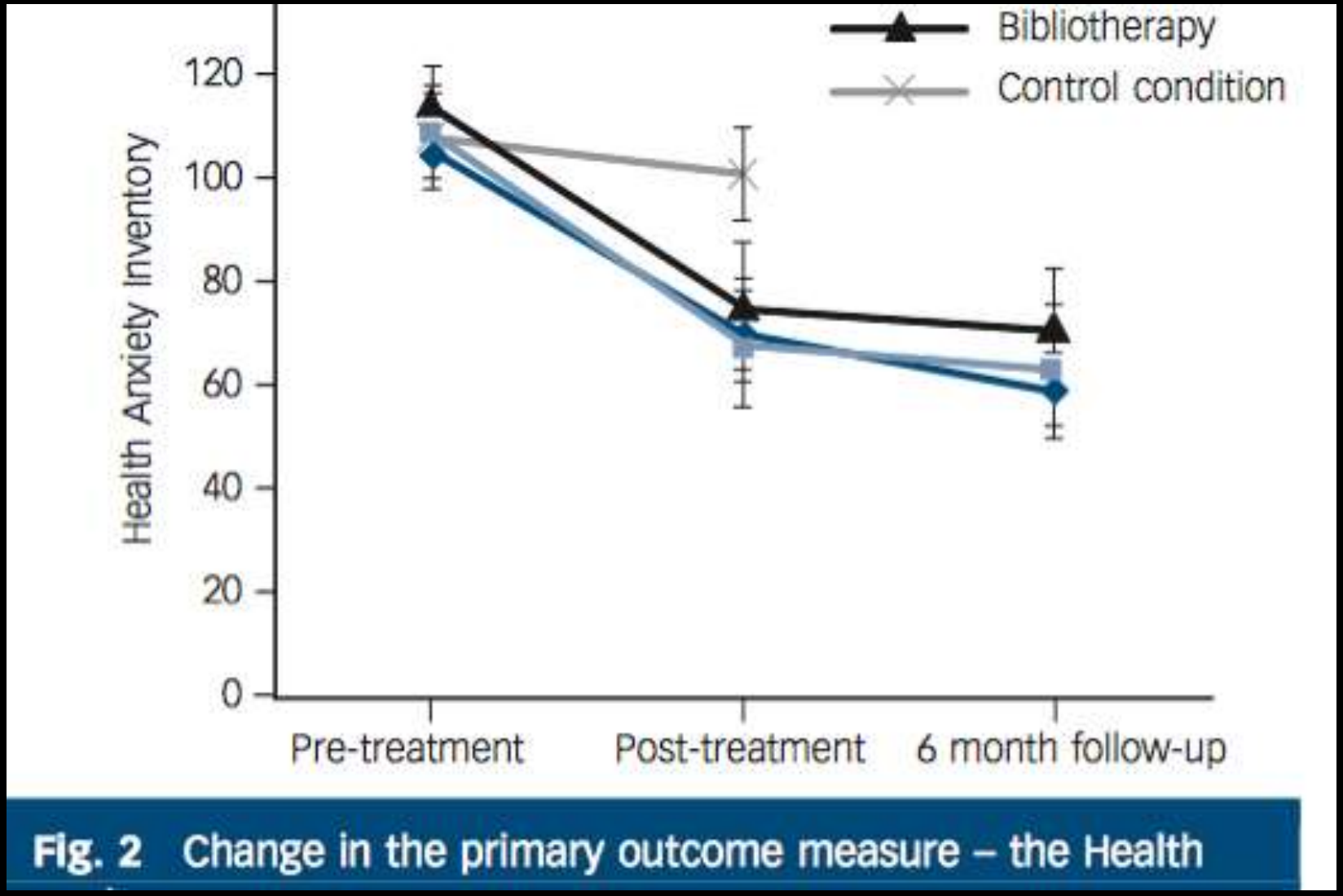


Fig. 2 Change in the primary outcome measure – the Health

Hedman et al The British Journal of Psychiatry 2016 Aug 6 online
doi: 10.1192/bjp.bp.116.181396

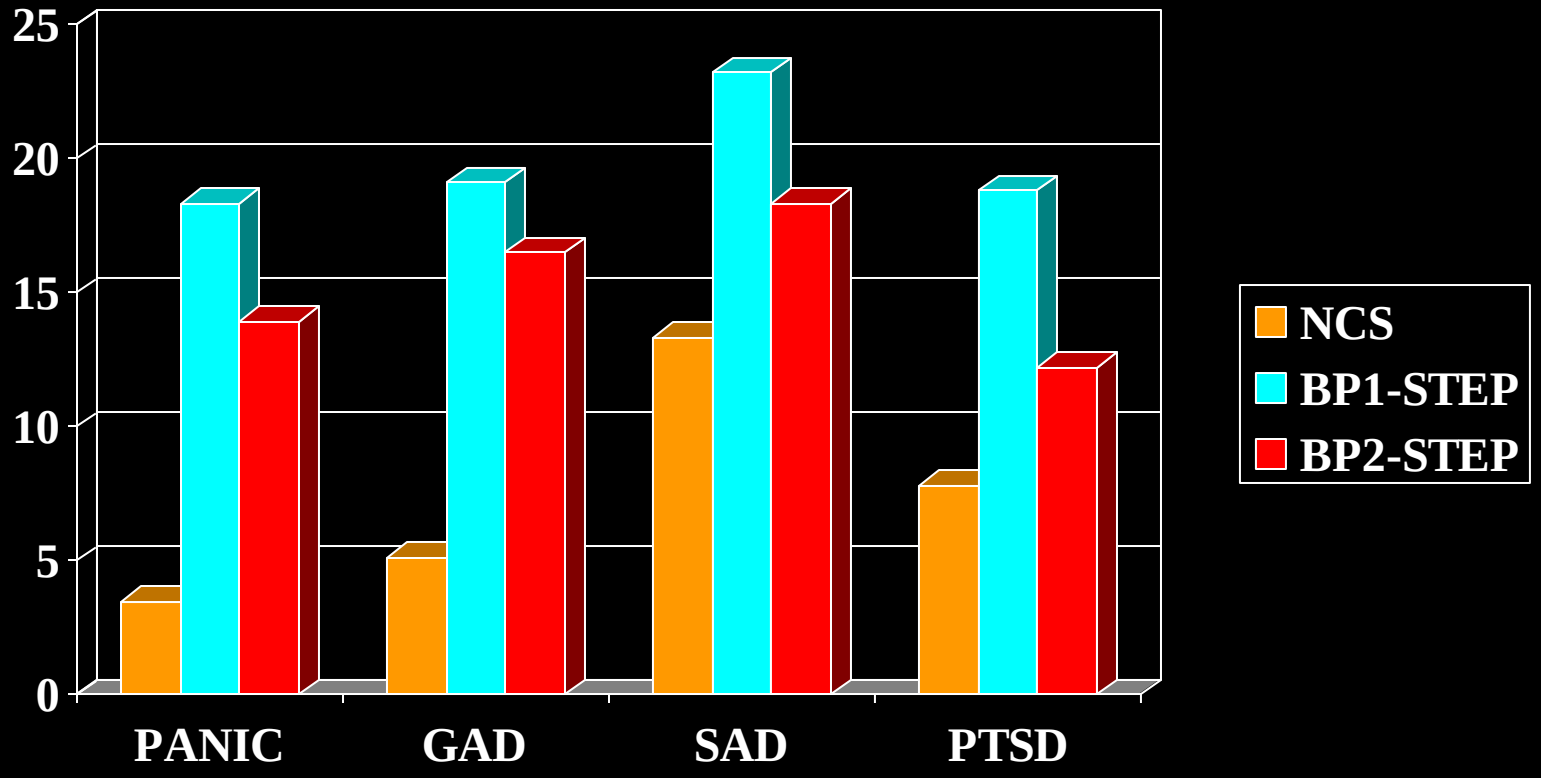
CBT for Somatic Symptom Disorder

Table 2 Means and effect sizes (Cohen's *d*) on primary outcome measure

Health Anxiety Inventory (scale range: 0–192)	Mean (s.d.)			Effect size (95% CI)		
	Pre-treatment	Post-treatment	6-month follow up	Within-group, pre–post treatment	Within-group, pre–post treatment, pre–6-month follow-up	Between-group,[a] post-treatment
ICBT	105.5 (21.4)	69.7 (24.8)	59.5 (31.3)	1.55 (0.87–2.22)	2.23 (1.31–3.14)	1.27 (0.72–1.79)
U-CBT	109.1 (25.8)	68.3 (35.6)	62.9 (34.2)	1.31 (0.84–1.78)	1.52 (0.90–2.15)	1.02 (0.49–1.53)
Bibliotherapy	114.5 (21.3)	75.5 (35.0)	71.5 (31.3)	1.35 (0.88–1.82)	1.61 (1.05–2.16)	0.80 (0.28–1.30)
Control condition	108.2 (24.1)	100.1 (26.1)	–	0.29 (0.15–0.42)	–	Reference

ICBT, therapist-guided internet-delivered exposure-based cognitive–behavioural therapy; U-ICBT, unguided internet-delivered exposure-based cognitive–behavioural therapy; Bibliotherapy, unguided exposure-based cognitive–behavioural bibliotherapy.
a. Between-group effect sizes are based on the control condition as comparator.

ELEVATED RATES OF ANXIETY DISORDER IN BP ILLNESS



CAN ANXIETY BE A DISGUISED "MIXED" BP STATE?

- In comorbid anxiety and BP, anxiety precedes BP diagnosis by 3 years
- Anxiety predicts transition from MDD to BP illness in adults
- Anxious children of BP parents have high rate of agitation/irritability with antidepressants
- Mixed states often misdiagnosed as anxiety
- What does preference for BZs mean in these cases?

Mixed features of depression: why DSM-5 is wrong (and so was DSM-IV)

Athanasios Koukopoulos, Gabriele Sani and S. Nassir Ghaemi

The DSM system has never acknowledged a central position for mixed states; thus, mixed depressions have been almost completely neglected for decades. Now, DSM-5 is proposing diagnostic criteria for depression with mixed features that will lead to more misdiagnosis and inadequate treatment of this syndrome. Different criteria, based on empirically stronger evidence than exists for the DSM-5 criteria, should be adopted.

The British Journal of Psychiatry **(2013) 203, 3–5.**

TREATMENT APPROACHES

- Combination Treatment
- RCTs in Treatment Resistance
- Novel Approaches

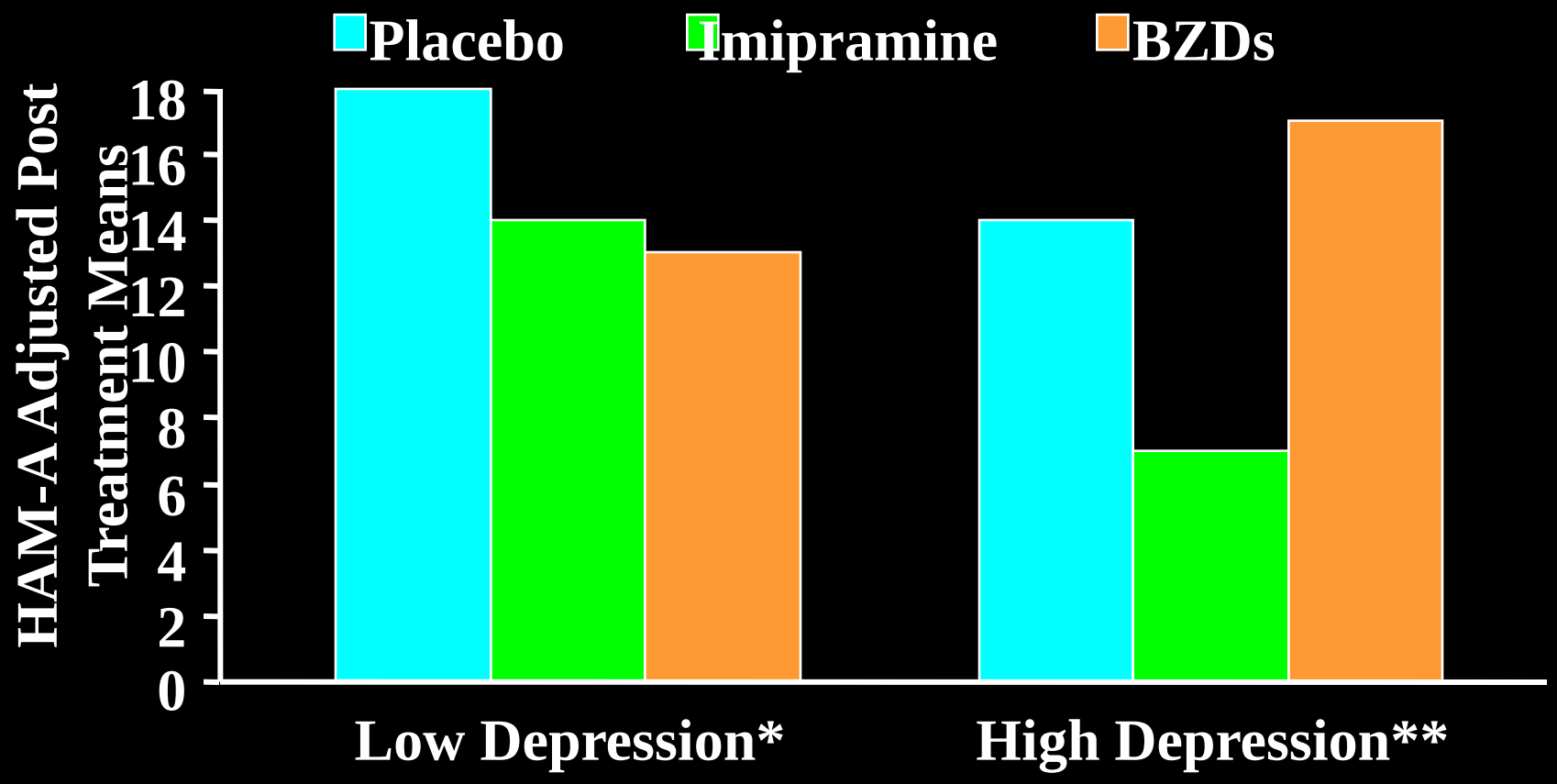
COMBINATION TREATMENT

- Most studies done in non-refractory anxiety
- Slight advantage of combination treatment in panic disorder
- Equivocal evidence of combination treatment advantage in GAD
- Consistent evidence of combination treatment advantage in SAD
- Combination treatment not better than ERP in OCD
- No data in PTSD—ongoing UW study

CAN BZS ADVERSELY IMPACT THE EFFICACY OF PSYCHOTHERAPY?

- Old literature suggests BZs may impair desensitization to specific phobias
- Uncontrolled studies suggest BZ use is associated with increased anxiety sensitivity since patients improve with BZ cessation (Fava et al 1994)
- Westra et al (2002) show prn BZ users have poorer CBT outcome than non-users or regular users
- As needed (prn) use of BZs is often employed in addition to regular dosing by users
- PRN use reduces self-efficacy (reinforces pill taking as a coping mechanism) and interferes with stress tolerance by linking anxiety contexts with BZ intake and promoting conditioned tolerance (Westra and Steward 2002)

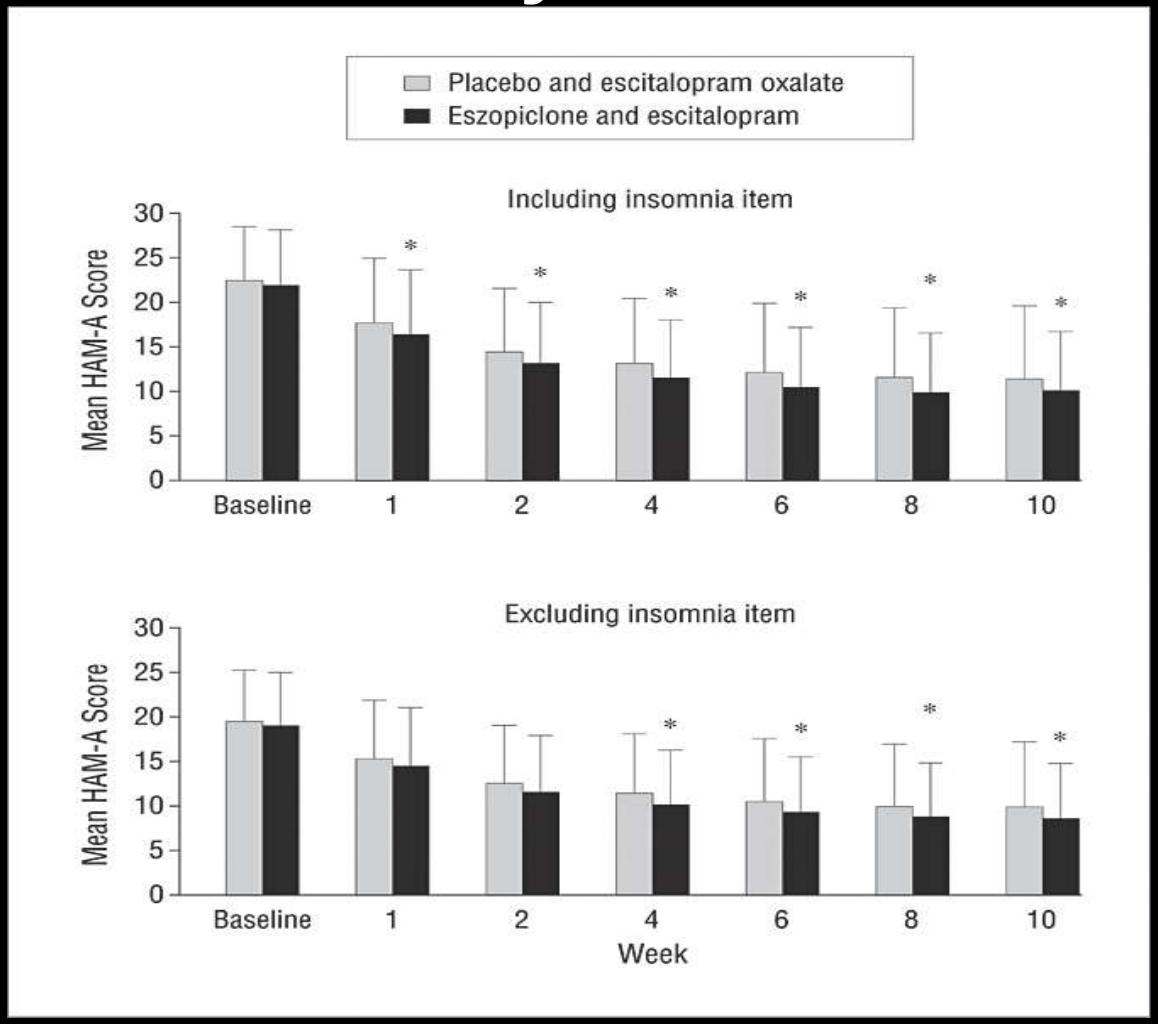
GAD With Depressive Symptoms: Could BZs Make Anxiety Worse?



* Imipramine/diazepam > placebo *P* <0.05.
** Imipramine > diazepam *P* <0.05.
BZD = benzodiazepine.

Rickels K, et al. *Arch Gen Psychiatry.* 1993;50:884-895.

Eszopiclone Added to an SSRI Improves Anxiety Outcomes in GAD



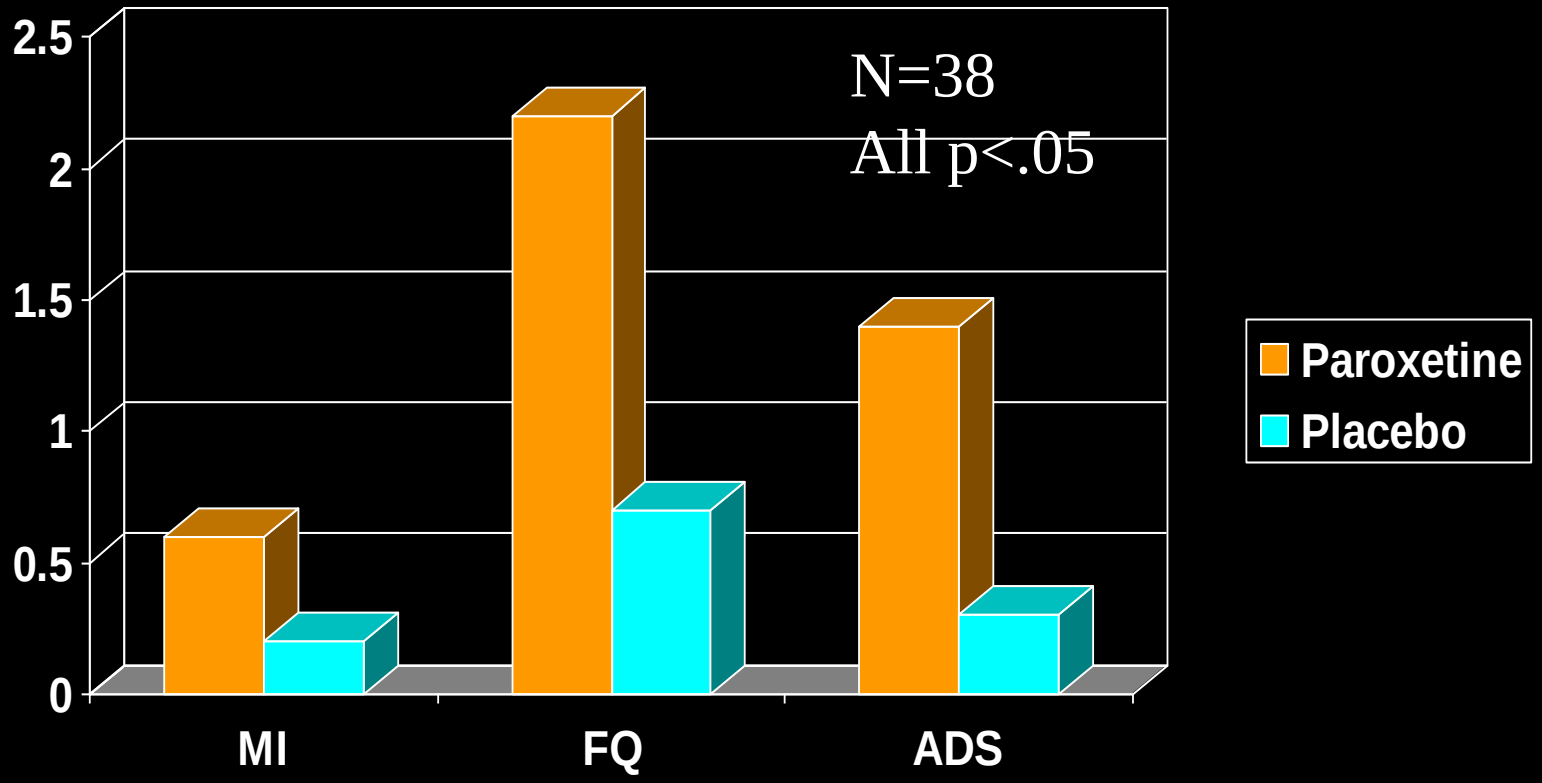
NNT for: Response=6 Remission= 15

Pollack, M. et al. Arch Gen Psychiatry 2008;65:551-562.

ARCHIVES OF GENERAL PSYCHIATRY

RCTS IN TREATMENT RESISTANT ANXIETY

Adjunctive Paroxetine in Panic Disorder Non-Responders to CBT



Kampman et al 2002

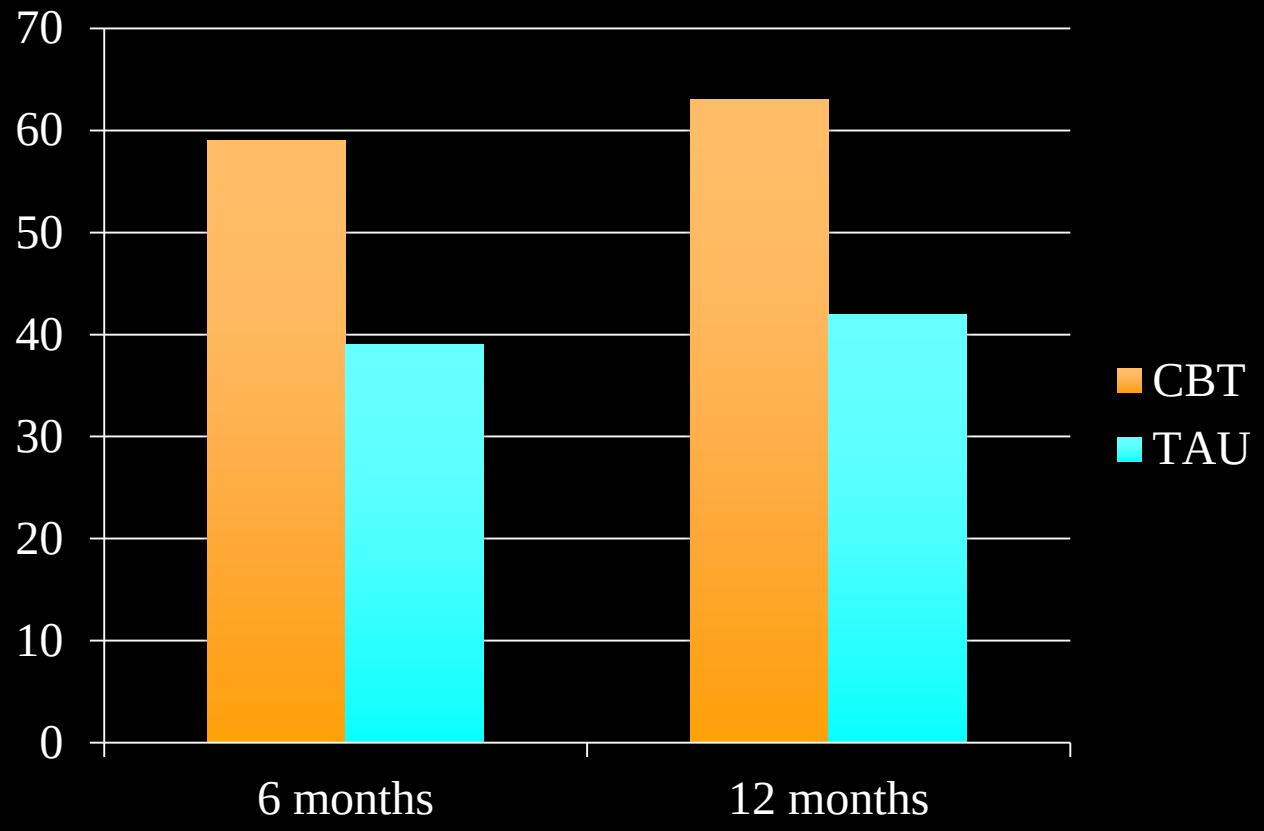
IN CBT REFRACTORY PANIC, WOULD MORE CBT WORK AS WELL AS PAROXETINE?

Response to treatment in assessed participants.

Assessment	SSRI n (%)	Continued CBT n (%)	Odds Ratio	95% Confidence Interval
Time 3 (3 months)	18/31 (58%)	8/21 (38%)	2.25	.72 – 6.99
Time 4 (12 months)	13/23 (57%)	8/15 (53%)	1.24	.41 – 3.70

Depression and Anxiety, in revision

RESPONSE RATES FOR CBT VS TAU IN MEDICATION RESISTANT ANXIETY: THE CALM STUDY (N=258)



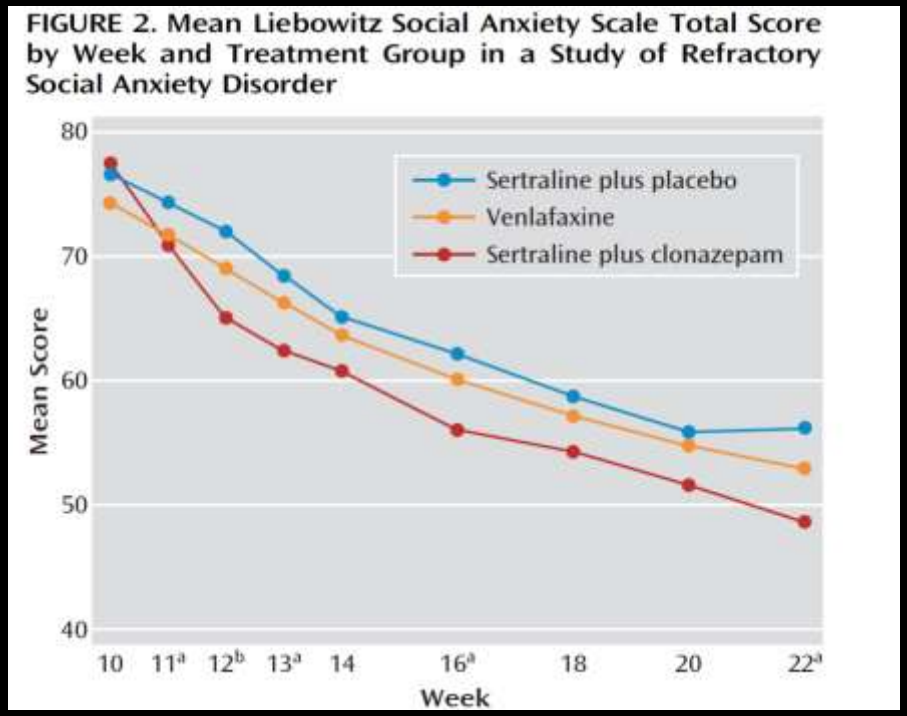
NNT=5

Roy-Byrne et al unpublished; from Roy-Byrne et al 2010 JAMA

TREATMENT-REFRACTORY ANXIETY: AUGMENTATION RCTS

- BZ to SSRI for SAD
- Pregabalin to SSRI for SAD
- Risperidone augmentation for GAD (but largest trial negative in PTSD)
- Olanzapine augmentation for GAD and PTSD
- Open trials for anticonvulsant augmentation (Gabapentin, Tiagabine, Leviracetam for all four disorders); buspirone augmentation (SAD); antidepressant combinations (Panic)

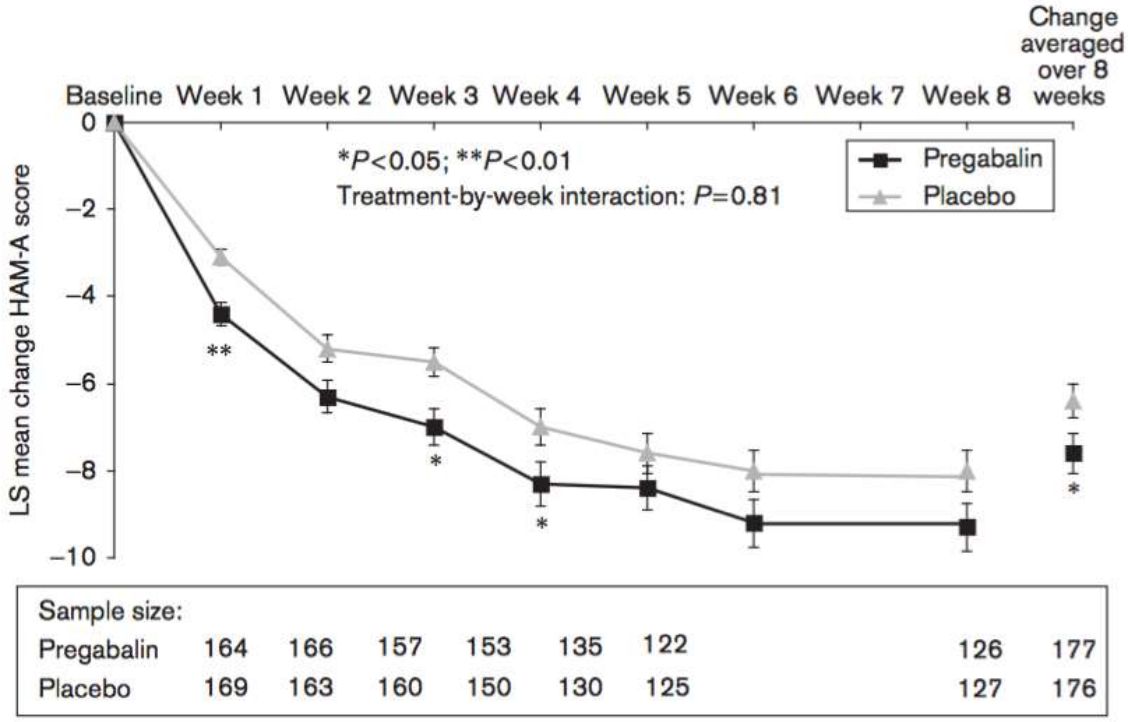
SSRI-REFRACTORY SAD: BZ ADVANTAGE?



Remission CZ, VEN, SERT= 27%, 19%, 17% NS
Response CZ, VEN, SERT= 56%, 46%, 36% CZ>SERT

Pollack et al, 2014

ADJUNCTIVE PREGABALIN FOR SSRI REFRACTORY SAD



mean change in HAM-A total score. On the basis of repeated measures analysis of covariance using the heterogeneous autoregressive ariance structure with treatment, center, week, and treatment-by-week as fixed effects and baseline HAM-A total score as a continuous covariate. M-A, Hamilton Anxiety Rating Scale; LS, least squares.

Rickels et al 2012

ATYPICAL NEUROLEPTICS; HIGH RISK, LIMITED GAIN?

- **Strongest data** support adjunctive use, added to SSRI, **in OCD** (Olanzapine, Risperidone, Quetiapine, Aripiprazole)—but inferior to add on ERP!
- Remaining data possibly supports adjunctive use (olanzapine and risperidone) **only** in **some** cases of PTSD (but recent large negative risperidone study).
- No studies in panic, no efficacy in GAD, unclear in SAD
- **Adverse effects on lipids, glucose and weight much better established than clinical benefits!**
- **Thus, Quetiapine monotherapy results were NOT sufficient to get FDA approval for GAD**
- **Adjunctive use** is third line option in disabling, resistant anxiety—**Bzs are probably much safer overall, and with better evidence for efficacy!**

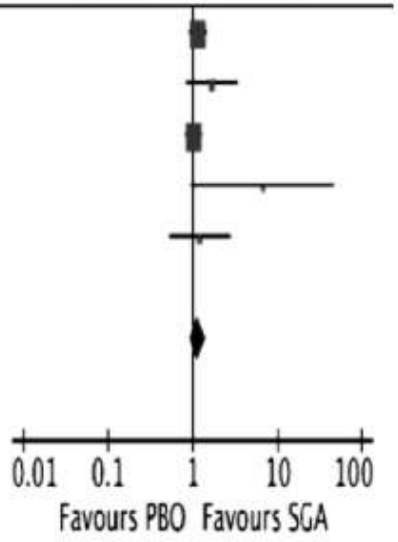
ATYPICAL NEUROLEPTICS NOT EFFECTIVE IN REFRACTORY GAD

i. Response

Study or Subgroup	2nd Gen. Antipsychotic Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Astra Zeneca Palladium	84	204	72	198	42.0%	1.13 [0.88, 1.45]
Brawman-Mintzer 2005	11	19	7	20	8.2%	1.65 [0.81, 3.36]
Pandina 2007	79	196	77	194	42.7%	1.02 [0.80, 1.30]
Pollack 2006	5	9	1	12	1.1%	6.67 [0.93, 47.59]
Simon 2008	6	11	5	11	5.9%	1.20 [0.52, 2.79]
Total (95% CI)		**439**		**435**	**100.0%**	**1.14 [0.92, 1.41]**
Total events	185		162			

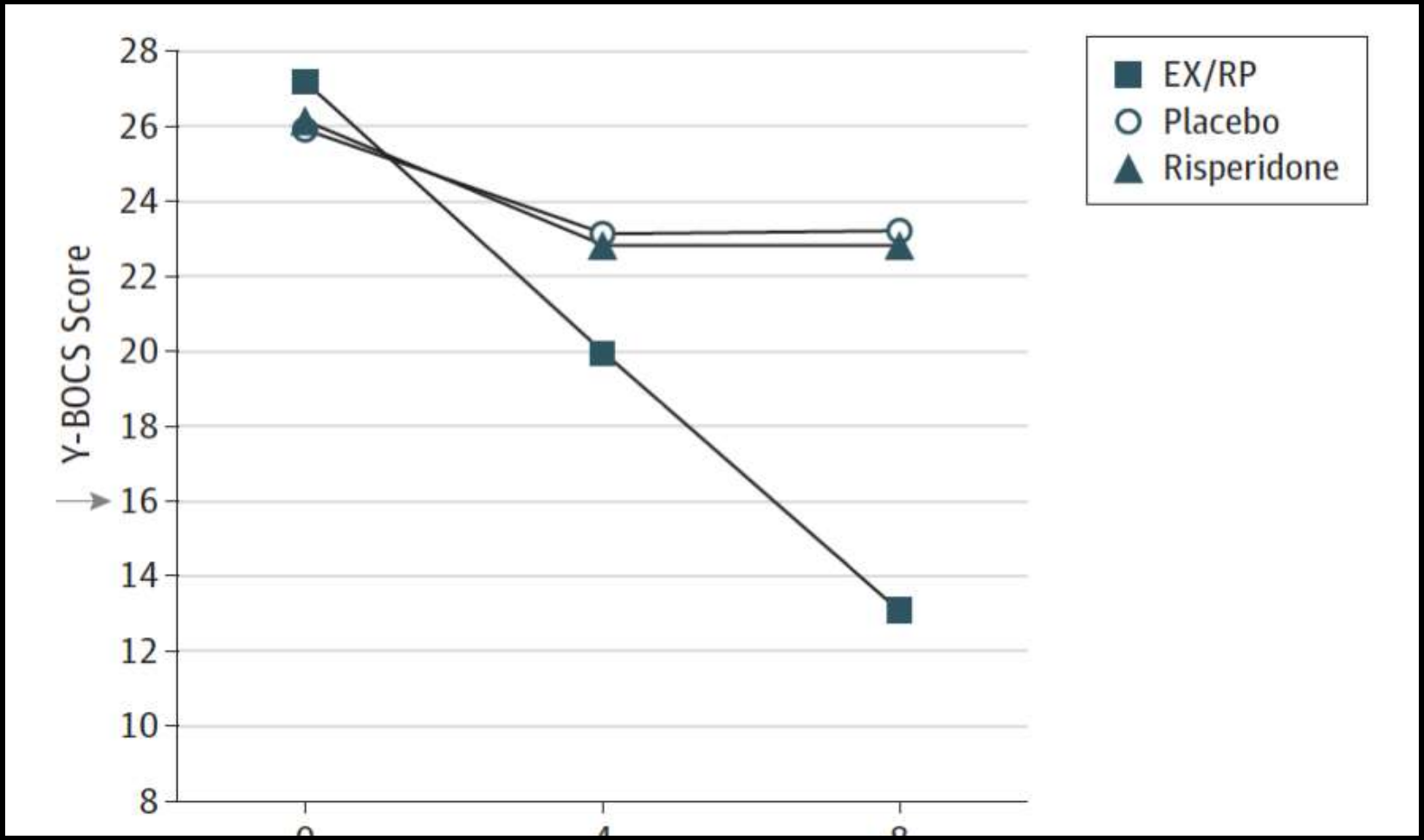
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.00$, df = 4 (P = 0.29); $I^2 = 20\%$

Test for overall effect: Z = 1.23 (P = 0.22)



LaLonde et al 2011 J Clin Psychopharmacol

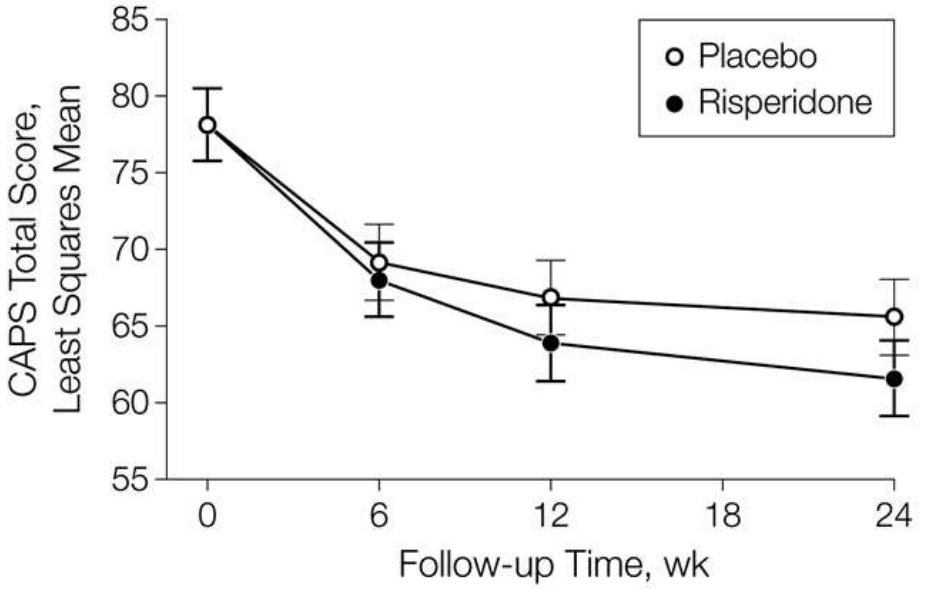
ERP BEATS RISPERIDONE IN REFRACTORY OCD



Simpson et al 2013, JAMA Psychiatry

Adjunctive Risperidone Treatment for Antidepressant-Resistant Symptoms of Chronic Military Service–Related PTSD

Change in CAPS Total Score During Treatment



No. of patients				
Placebo	134	122	127	124
Risperidone	133	128	122	123

Krystal, J. H. et al. JAMA 2011;306:493-502

NOVEL MEDICATION APPROACHES: RCTS

- Anticonvulsants

  --Gabapentin (panic, SAD); Pregabalin (GAD,SAD)

  --Valproate (panic, but 2 negative trials in PTSD)

  --Tiagabine (GAD, but follow up trial negative)

  --Lamotrigine (PTSD, but very small study)
- Atypical Neuroleptics

  ---Quetiapine (Robust data in GAD)

  ---Olanzapine (SAD, but negative trial in PTSD)
- **Prazosin (PTSD nightmares)**
- Inositol (2 studies in panic)
- Open trials support ACs in panic, SAD, PTSD, and atypicals in PTSD—**But don't believe open trials!**

NOVEL NON-MEDICATION APPROACHES: RCTS

- Exercise (in panic, but may apply to others)
- Imagery Rehearsal (PTSD, but could apply to GAD and other ruminative syndromes)
- Mindfulness?

LIMITED BENEFIT OF EXERCISE FOR ANXIETY?

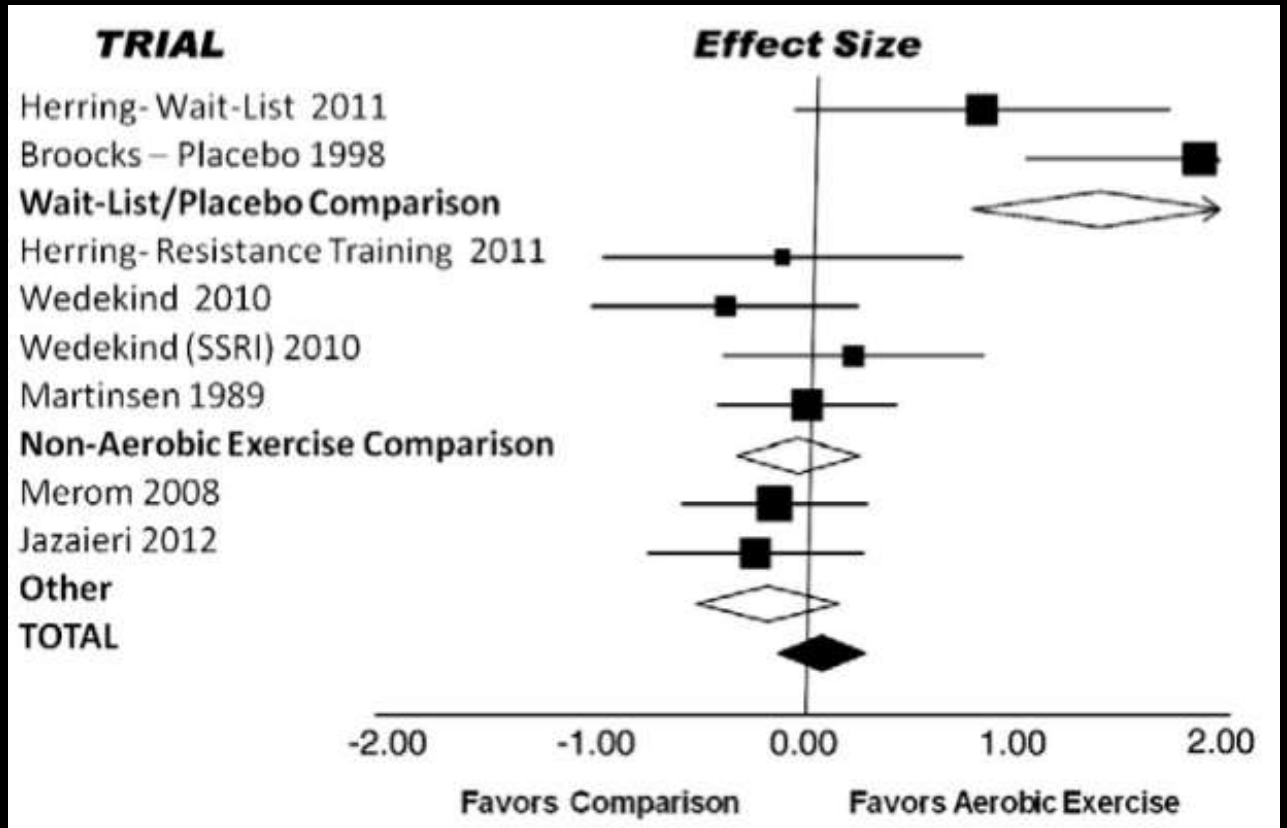
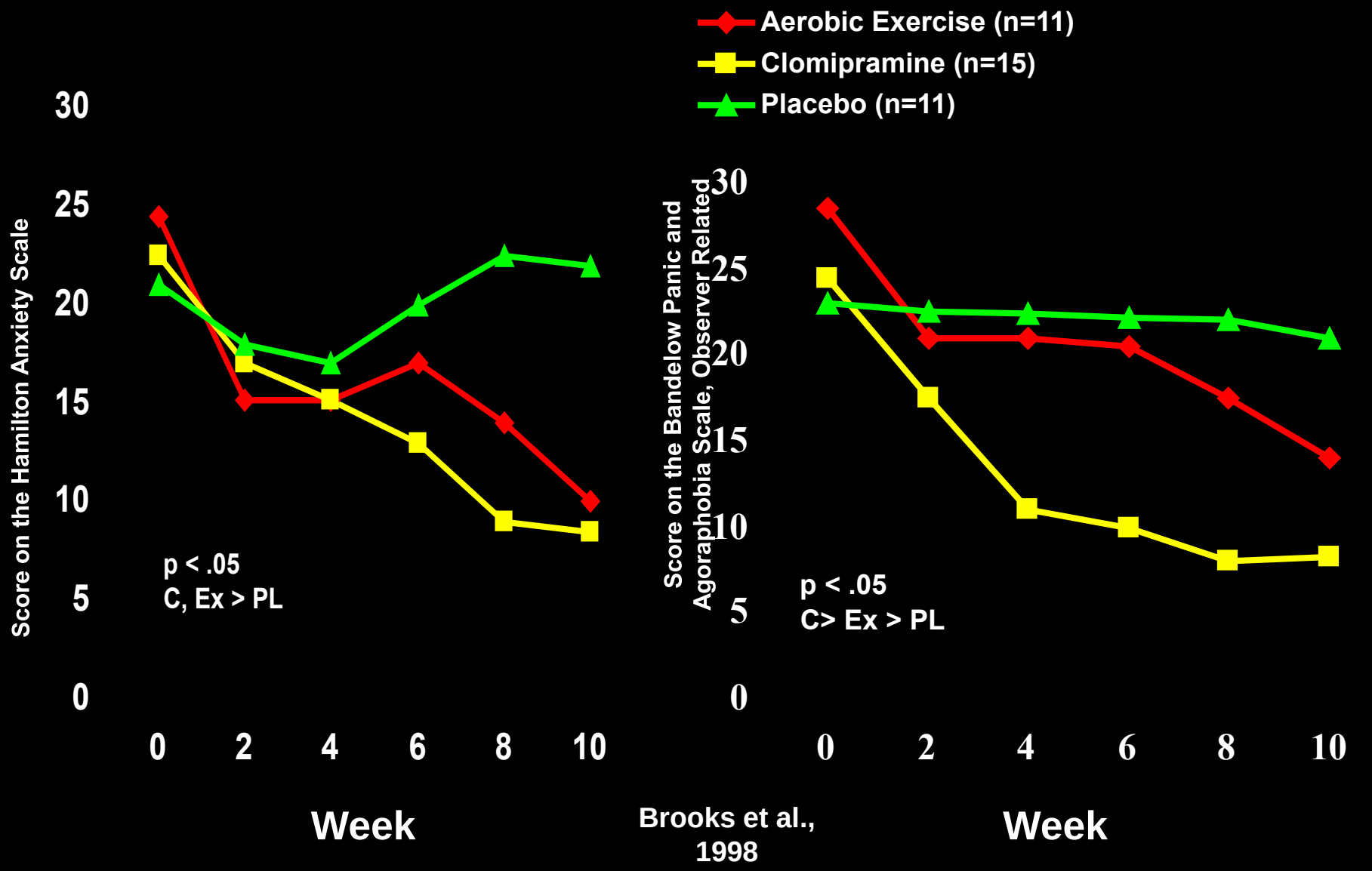


Fig. 3. Measured effect size of aerobic exercise for anxiety disorder stratified by the type of comparison condition.

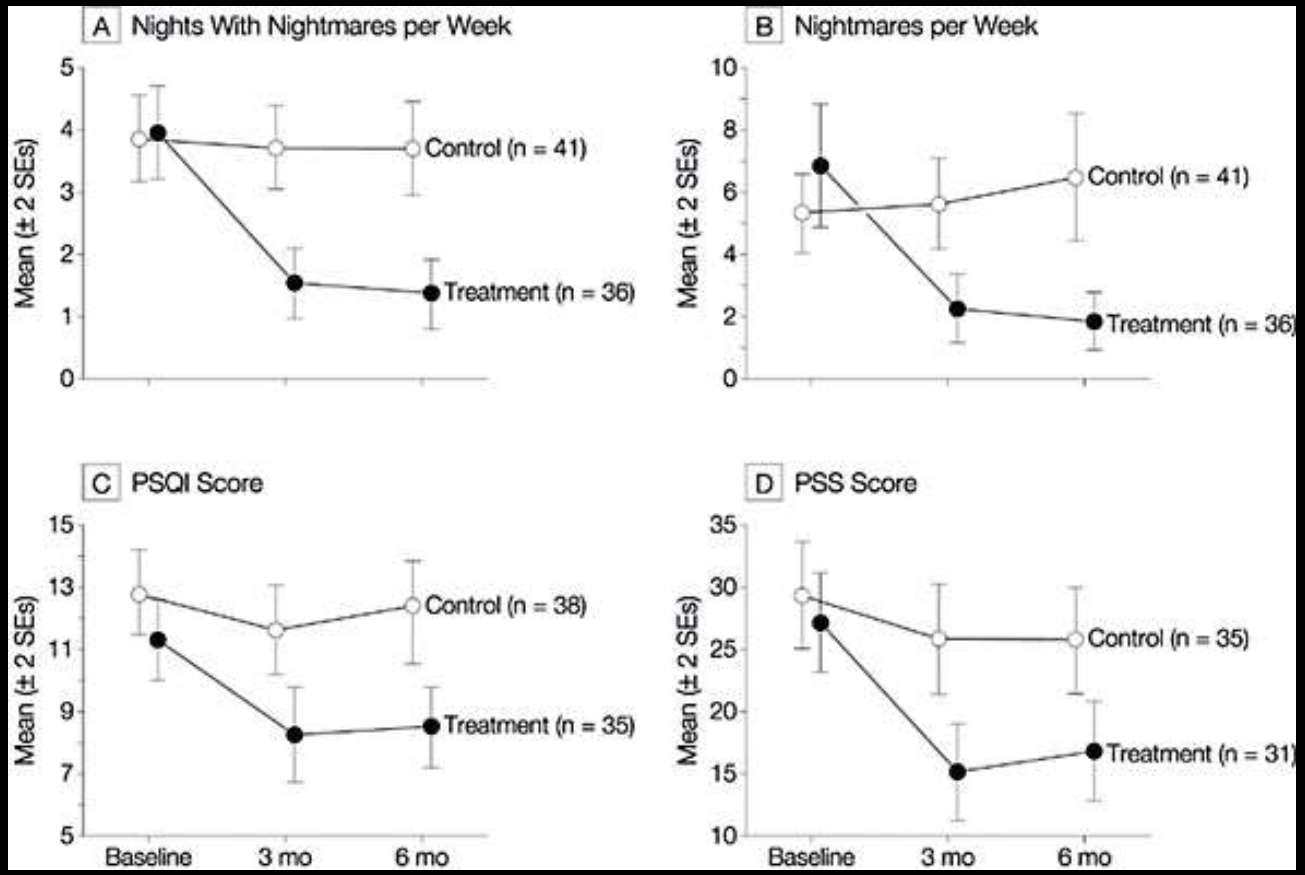
EXERCISE, CLOMIPRAMINE, AND PLACEBO FOR PANIC



Brooks et al., 1998


24 HOUR
FITNESS

Imagery Rehearsal vs. Wait List for Nightmares in PTSD



Krakow et al 2001

MBSR FOR GAD

Measure & Condition	Pre-Treatment *M (SD)*	Post-Treatment *M (SD)*	3-month FU *M (SD)*
Primary Outcomes			
Clinician's Severity Rating			
MBSR	6.02 (1.09)	3.09 (2.59)	2.18 (2.66)
CBT	6.08 (.86)	3.22 (2.81)	2.94 (2.83)
Penn State Worry Questionnaire			
MBSR	45.46 (9.83)*	39.37 (13.59)	44.73 (13.02)
CBT	39.75 (12.32)*	39.75 (12.59)	40.00 (11.58)
MASQ-Anxious Arousal Scale			
MBSR	21.05 (8.64)	20.30 (8.41)	17.69 (7.15)
CBT	20.23 (8.60)	17.14 (8.02)	16.85 (8.53)
Secondary Outcomes			
Beck Depression Inventory-II			
MBSR	25.97 (11.61)	21.36 (15.26)	24.53 (15.68)
CBT	22.12 (12.32)	19.10 (14.81)	20.42 (16.55)

Arch et al 2013 Beh Res Therapy

"I was able to get in one last lecture about diet and exercise."

TREATMENT RESISTANCE: ASSESSMENT APPROACH

- Is it treatment resistance—rating scale data!
- Is it pseudo-resistance—are you delivering correct type, “dose” (therapy elements) for long enough? Is the patient adherent?
- If true treatment resistance, assess: health habits, wrong diagnosis, medical comorbidity

TREATMENT RESISTANCE: PHARMACOLOGIC APPROACHES

- Start with antidepressant baseline (SSRI vs venlafaxine?)
- Wait long enough (?) for complete response
- Adjunctive treatments—consider another AD, BZD, atypical antipsychotic, anticonvulsant, pindolol?
- Other possibilities—NAC, SAMe, Deplin?
- Simplify regimen after 6–12 months

TREATMENT RESISTANCE: PSYCHOTHERAPY APPROACHES

- CBT useful alone or in combination with medication for
  - Refractory symptoms
  - Persistent cognitive factors, behavioral patterns and anxiety sensitivity
  - Comorbid conditions
  - Early intervention for PTSD prophylaxis
- CBT may be facilitated by medication if it did not work alone
- Some anxious patients may need an alternate approach
- Psychodynamic psychotherapy, IPT, Mindfulness could be tried

.

"Why should I settle for good self-esteem when, with the right medication, I could have great self-esteem?"