

The Medication of Sadness

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Depression, a Disorder of Mind and Brain

- Lifetime prevalence of Major Depressive Disorder:
 - 10% in men
 - 20% in women
- Estimated annual workplace losses in U.S.: \$50 billion
- Substantial contributors to incidence and onset:
 - stressful life events (losses)
 - heritable genetic risk
 - interaction of genes X environment (e.g., promoter region of the serotonin transporter gene X life events)
- Genetic and environmental effects each impair the structure and function of:
 - the primitive (limbic) brain – supports emotions, basic drives
 - the neocortex (frontal lobes) – supports executive functions, including those that regulate emotion

Profound depression, from the inside

“I am now the most miserable man living. If what I feel were equally distributed to the whole human family, there would not be one cheerful face on earth.”

Profound depression, from the inside

“I am now the most miserable man living. If what I feel were equally distributed to the whole human family, there would not be one cheerful face on earth.”

Abraham Lincoln

Evidenced-based Somatic Treatments

- Electroconvulsive Therapy
 - Most effective, but least widely used
 - Cost, aversion to the procedure, memory effects explain limited use
- Antidepressant medications (ADM)
 - Introduced in 1950s (MAO-I; e.g., Nardil, selegiline patch)
 - 1960s: tricyclics (TCA; e.g., imipramine, Elavil)
 - 1980s: SSRIs (Prozac, Paxil)
 - 2000s: NSRIs (Effexor)
- Principle clinical differences between ADM classes:
 - Tolerability; nature and severity of side effects
 - Suicide risk potential
- All produce, on average, 15%-25% increment in response rates, relative to pill-placebo (e.g., 60% vs. 40%), in patient populations on which they have generally been tested

Evidenced-based Psychological Treatments for Major Depression

- Cognitive Therapy (CT)
 - Most extensively researched, most widely practiced
 - Compares favorably with ADM, even in more severe cases
 - Only treatment with substantial evidence of relapse prevention
- Interpersonal Therapy (IPT)
 - Has fared well as acute treatment in clinical trials, but with slower onset of effect than ADM or CT
 - Effective as a maintenance treatment, but not as prevention
 - Readily accepted by clinicians who trained psychodynamically
- Behavioral Activation (BA)
 - Excellent results in two clinical trials, both conducted in Seattle
 - May be better-suited for dissemination than CT or IPT

Key findings from the National Health and Nutrition Examination Surveys, 2005–2008

Americans 12+ yrs. old: 11% are on ADMs

- Among those with no symptoms: 8%
- Mild symptoms: 19%
- Moderate symptoms: 28%
- Severe symptoms: 33%

Key findings from the National Health and Nutrition Examination Surveys, 2005–2008

Of all those on ADMs

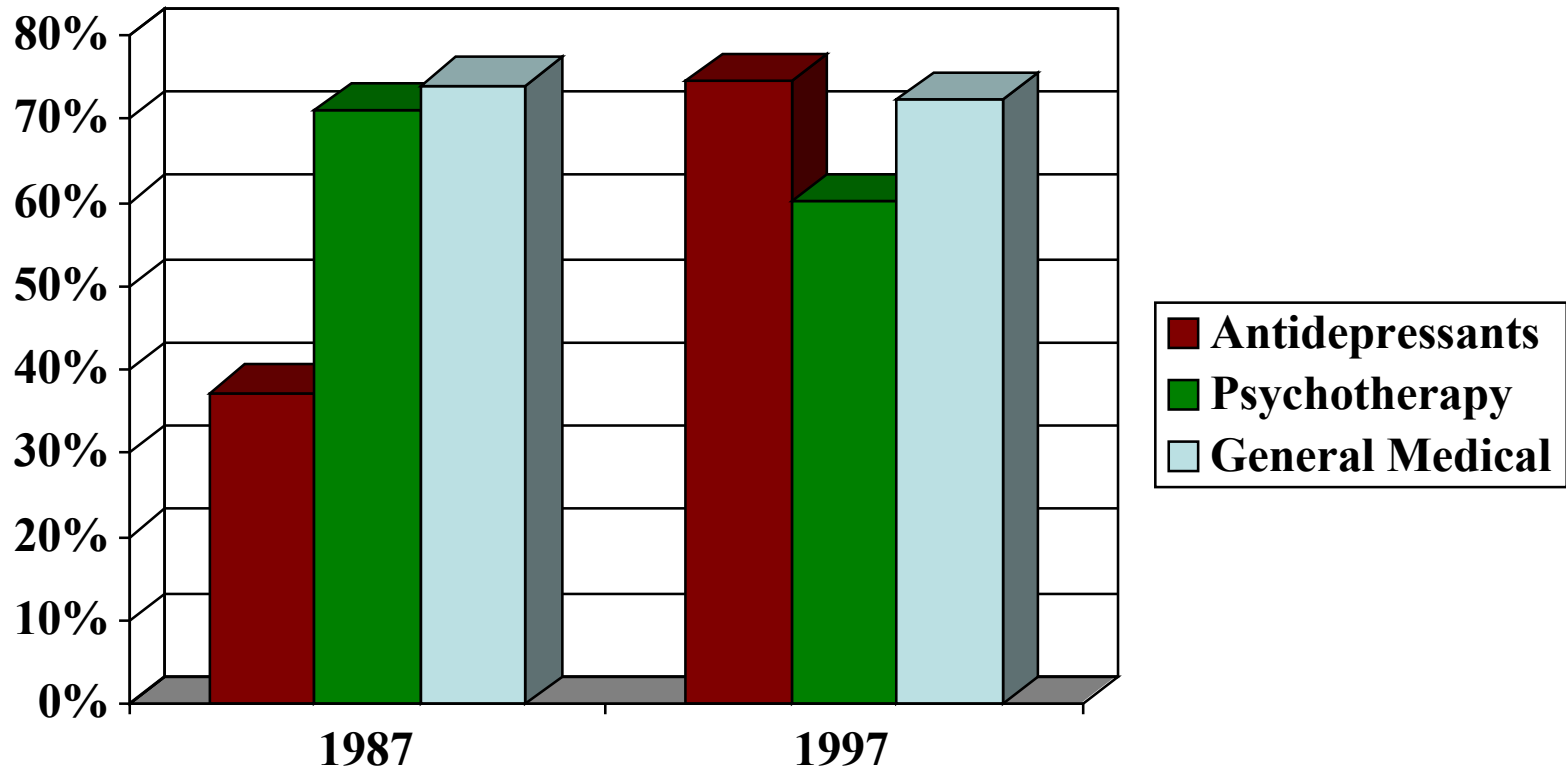
- 60% (7% of pop.) have been on them for 2+ years
- 14% (1.5% of pop.) have been on them 10+ years
- Less than 1/3rd of those on 1 ADM – and less than ½ of those on 2+ ADMs – have seen a mental health professional in the past year

Antidepressant use among undiagnosed: Patient's complaint

- Premenstrual tension
- Sleep disturbances
- Migraines
- Feeling tired

(Mojtabai & Olfson, 2011)

National Trends in Outpatient Treatment of Depression (Olfson et al 2002)



% Antidepressants increased ($p < .001$)
% Psychotherapy decreased ($p = .006$)
% General medical visits unchanged (ns)

Olfson et al 2002 (JAMA)

Reasons for Trends over Time

(Olfson et al 2002 JAMA)

- Safety and ease of prescribing newer antidepressant medications (SSRIs), relative to older medications
- Federal government (also NAMI, etc.) embarked on public health campaign to educate public about depression
- Promotion of sales through vigorous advertising campaigns to primary care doctors, and to consumers
- Growth of managed care resulted in shifts from specialty to primary care medical management
 - Psychotherapy reimbursed less generously than medications
 - Primary care physicians more likely to use medications

Antidepressant prescriptions in the U.S.

- 80% of prescriptions are made by physicians who are not psychiatrists
 - 62% written by PCPs
- Antidepressants increasingly prescribed for undiagnosed conditions (55-70%)

(Cascade et al., 2008; Mojtabai & Olfson, 2011)

Primary Care Physicians (PCPs)

- Treat at least 50% of depression cases
- 10-30% of patients in primary care are depressed
- > 50% of insured report they prefer going to a PCP for mental health issues

(Mickus, Colenda, & Hogan, 2000 ; Simon et al., 2002; Wang et al., 2005)

Treated vs. untreated depression in primary care

- After 1 year unrecognized cases did significantly better than those recognized (Goldberg et al., 1998)
- After 1 year patients not given drugs did significantly better than those receiving drugs (Goldberg et al., 1998)
- Unrecognized cases had comparable outcome after 12/39 months as recognized cases (Kamphuis et al., 2011)

Americans' Attitudes Toward Psychiatric Medications (1998–2006)

- 68% think medications help people feel better about themselves (vs. 60% in '98)
- 83% think medications help deal with day-to-day stresses (vs. 78% in '98)
- 47% would take medications to cope with life stresses (vs. 36% in '98)

(Mojtabai, 2009)

Reasons for Reduction in use of Psychotherapy over Time (DeRubeis)

- Lack of public education about the effectiveness of psychotherapies
- Lack of availability of professionals trained in evidence-based psychotherapy practice
- Persistence of the belief that psychotherapy is more expensive than medications (many reasons for this)
- Consumers' demand for antidepressants
 - high expectations
 - low cost (co-pays)
 - knowledge that they take little time from busy schedules and do not require speaking about embarrassing topics

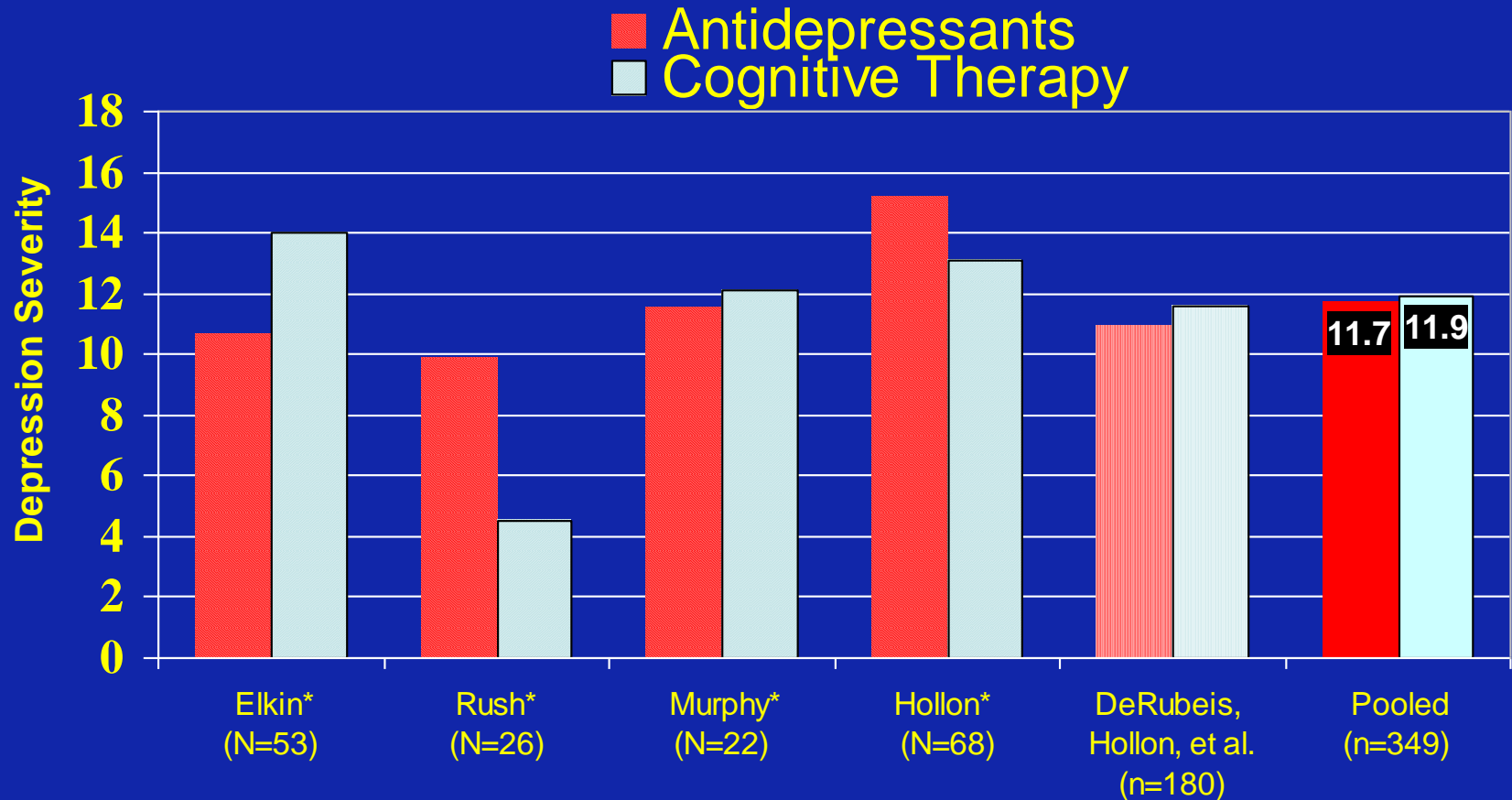
Have the shifts in treatment practices yielded greater benefits? Decreased costs?

- Rates of depression, and chronicity of depression, continue to increase
- Relapse rates on the most common treatments are as high as 50-80%
- Lifelong treatment is recommended for patients with recurrent depression (high cost)
- Patients often discontinue their medicines AMA; “discontinuation syndrome” can be quite unpleasant
- Question: Why haven't we developed more effective -- or more efficient -- treatments and treatment strategies?

Focus of Clinical Trials

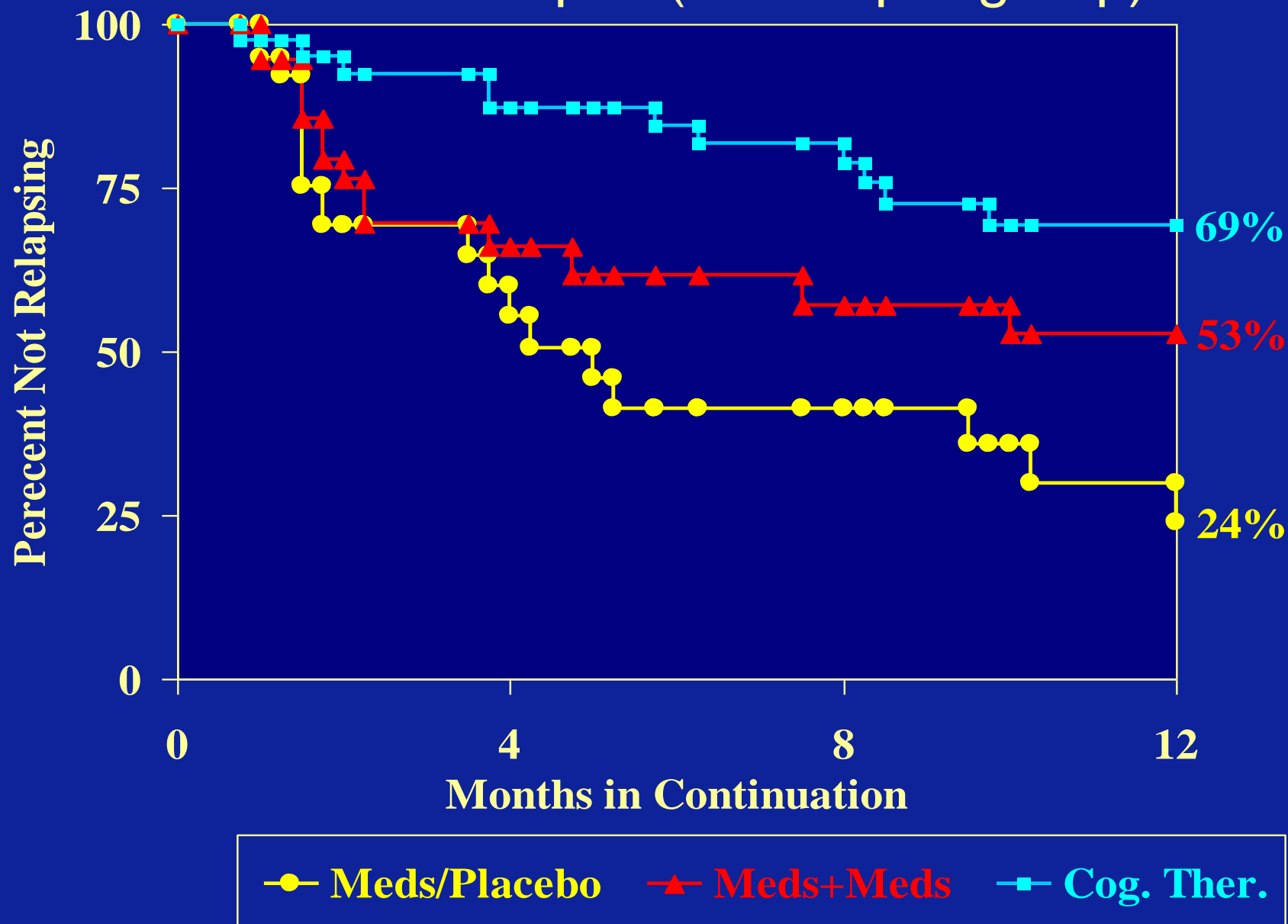
- Depressed patients with high severity symptoms
 - Group of greatest concern
 - Most likely to reveal difference between active treatment vs. control treatment (e.g., placebo)

Post-treatment Symptom Severity (Hamilton Scale) for Patients Who Were Severely Depressed Prior to Treatment

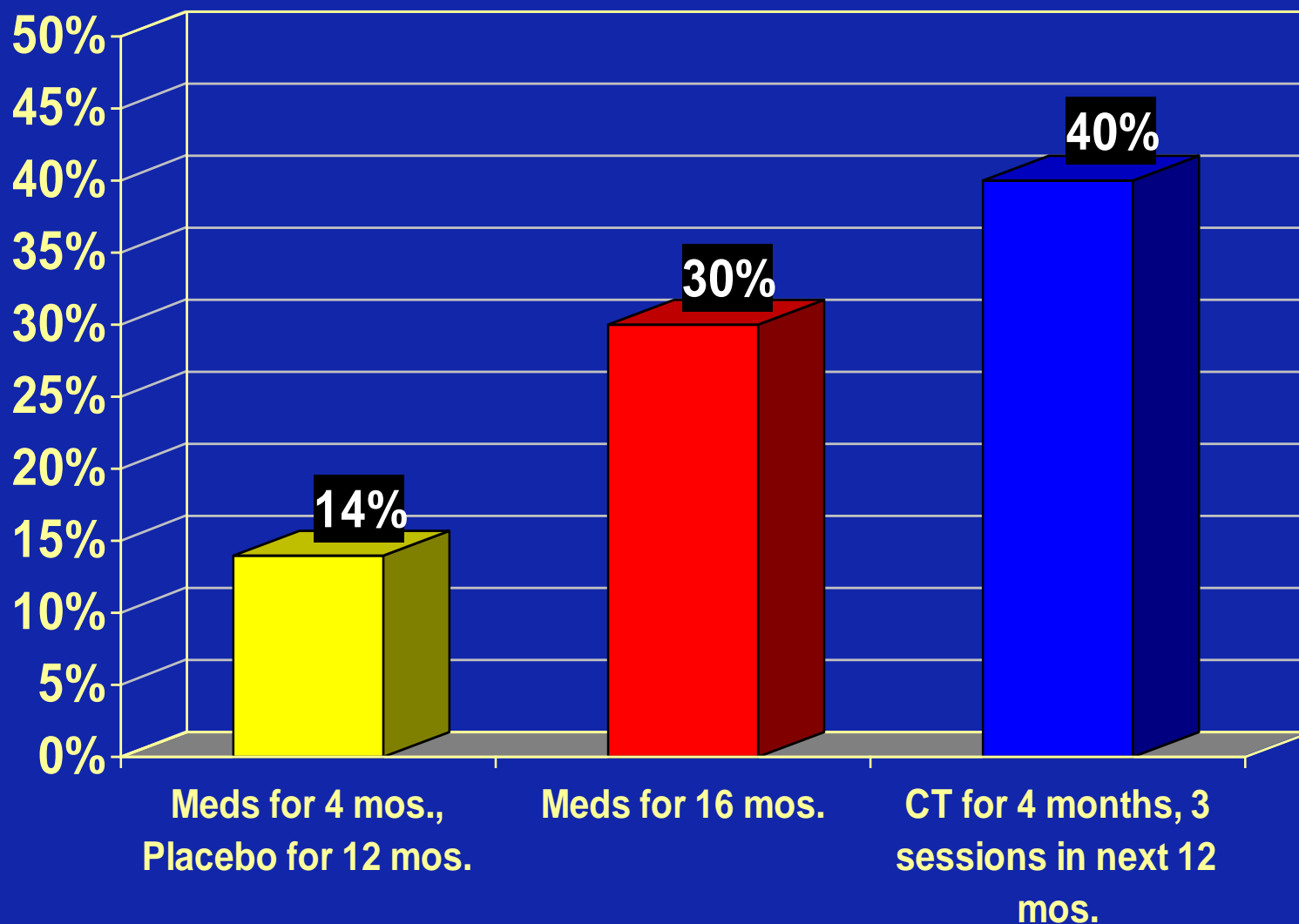


*(From DeRubeis, Gelfand, Tang, & Simons, 1999) ;

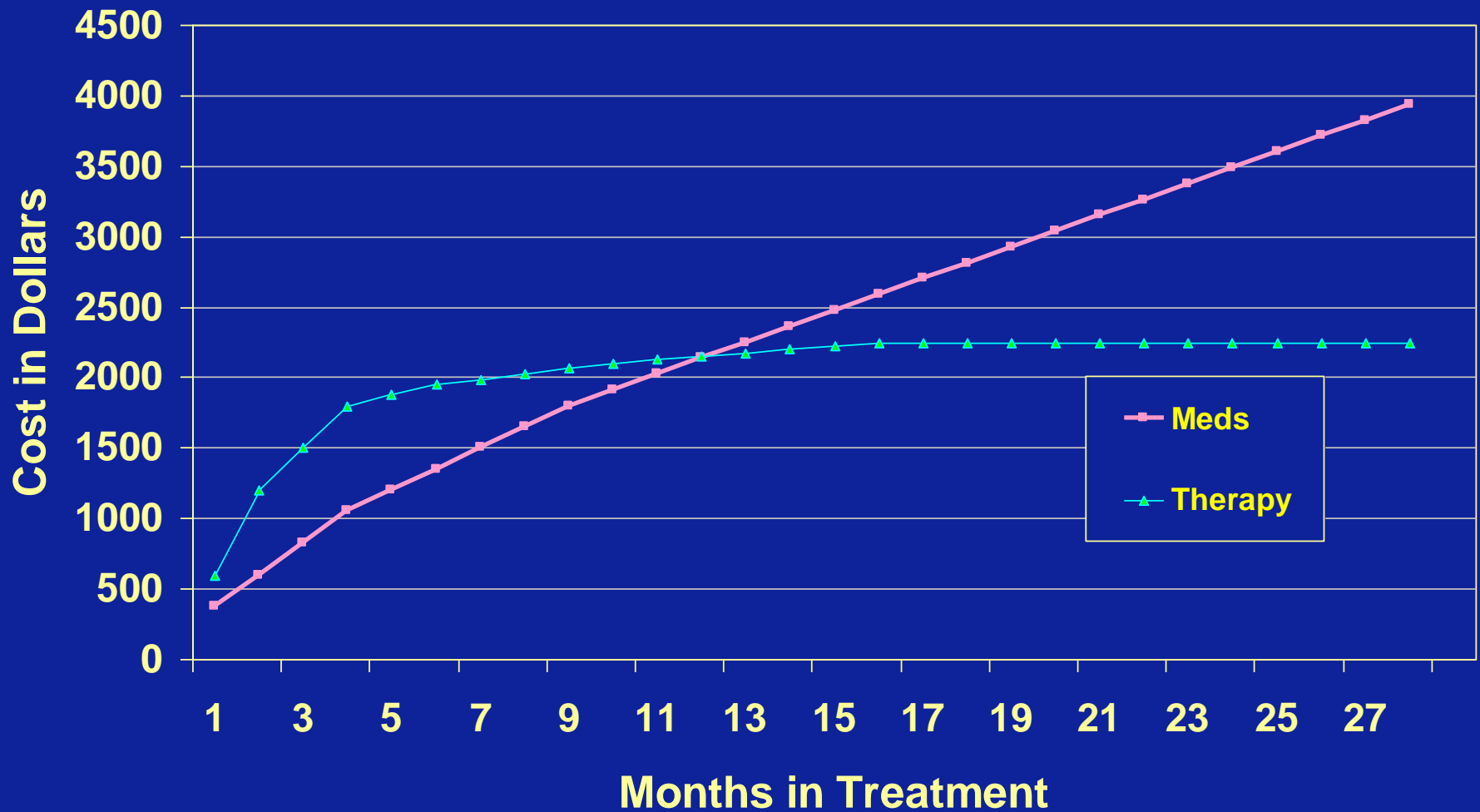
Time to Relapse (n = 35 per group)



Sustained Improvement through 16 months



Cumulative Direct Costs of Meds vs. Therapy



How did we get here?

- 1950s – excitement about the prospect of understanding and treating severe (real) depression by identifying and altering crucial (simple) brain mechanisms
- Destigmatization, fostered by advocacy groups, largely funded by the pharmaceutical industry
- Expansion of the definition of depression (DSM-III)
- Introduction of Prozac – and other SSRIs – whose side effects could be insidious, but not scary or unsettling
- Promotion of ADMs by the most powerful and persuasive members of the psychiatric establishment

How did we get here?

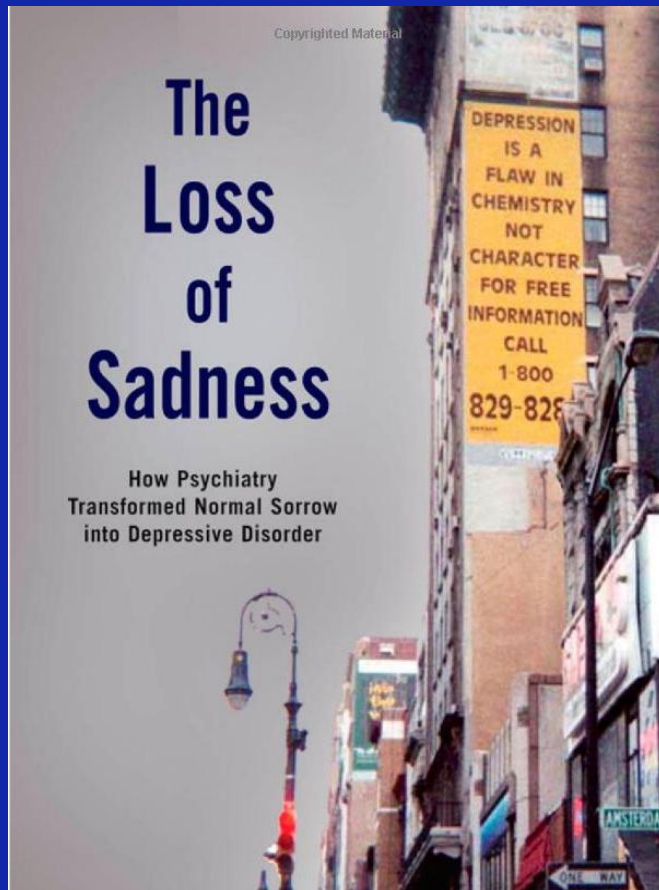
- The experiences of ADM-takers:
 - Worked on their depression
 - Other positive effects (calming, etc.)
 - Placebo effects
 - Discontinuation effects (confirming the benefits of the ADMs)
- Major campaigns to increase awareness of the benefits of ADMs (TV ads, websites, textbooks, etc.)

What happened next?

- Treatment of depression moved more and more to primary care (where ADMs are readily prescribed)
- Patient demand for medications increased; awareness of other means of dealing with depression did not

Major depressive disorder vs. understandable sadness

Major depressive disorder vs. understandable sadness



Allan Horwitz &
Jerome Wakefield

Sadness

- Universal emotion
 - Cross-cultural
 - Present in animals
- Functional loss response
 - Interpersonal
 - Hierarchical/social structure
 - Failure to achieve goals
- Has biological correlates
- Remits with recovery of loss or passage of time

Major Depressive Disorder

- Long recognized as an affliction
 - Cross-cultural
 - Animal models
- Often (85%) occurs in reaction to a stressor, but seen as dysfunctional
- Has biological correlates
- Can “spontaneously” remit

Features of a mental disorder

- A. Clinically significant psychological pattern occurring in an individual
- B. Associated with distress, disability, or risk of suffering death, pain, disability, or loss of freedom
- C. Must not be merely an expectable and culturally sanctioned response to a particular event
- D. A manifestation of a behavioral, psychological, or biological dysfunction in the individual
- E. Deviant behavior is NOT a mental disorders unless as a symptom of a dysfunction in the individual

According to the DSM IV TR

- “Periods of sadness are inherent aspects of human experience. These should not be diagnosed as MDD unless criteria are met for”:
 - Severity (5 or more symptoms)
 - Duration (≥ 2 weeks)
 - Distress or impairment

(APA, 2004; p. 355)

According to the DSM IV TR

- “Periods of sadness are inherent aspects of human experience. These should not be diagnosed as MDD unless criteria are met for”:
 - Severity (5 or more symptoms)
 - Duration (≥ 2 weeks)
 - ~~Distress or impairment~~ (Wakefield, Schmitz, & Baer, 2010)

(APA, 2004; p. 355)

Foreword to the Loss of Sadness

“...the DSM is not consistent even in applying its own definition of mental disorder to the diagnostic criteria sets for specific disorders.”

-Robert Spitzer

Loss of Sadness

- Sadness is an adaptive loss response
- Major Depression should involve a *dysfunction* of normal loss responses
- The symptoms of MDD can occur in response to a life stressor, without being indicative of dysfunction
- By ignoring the *context* in which symptoms occur, the DSM confuses sadness with MDD

Case

A 64-year-old married man has developed feelings of sadness and emptiness, lack of pleasure in activities, insomnia, fatigue and lack of energy, and feelings of worthlessness.

He is not interested in seeing friends and seems unable to concentrate on anything.

He yells at his wife when she attempts to console him and rejects her efforts to comfort him.

Case

The feelings were triggered 2 weeks before when the company the man worked for unexpectedly fired him as part of a corporate downsizing, just 6 months before he would have qualified for the company's retirement plan.

One of the major reasons the man chose to work for the company and then spend two decades with it had been the prospect of generous retirement benefits.

The loss of these benefits means that he and his wife will have very little retirement income other than Social Security.

Case

Subsequently, the couple is forced to sell their house and move to a small apartment.

The man finds part-time work that, along with Social Security, provides barely enough resources to sustain him and his wife.

He remains bitter about how he was treated, but his symptoms gradually subside over time.

Proposal, from “Loss of Sadness”

Sadness

1. Context specific to losses

AND

2. Proportional in intensity and duration

1. Cognitive

2. Affective

AND

3. Wanes with time, changes in circumstances, and internal coping

Proposal, from “Loss of Sadness”

Sadness

Major Depressive Disorder

1. Context specific to losses

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Proposal, from “Loss of Sadness”

Sadness

1. Context specific to losses

AND

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1. Cognitive
2. Affective

AND

3. Wanes with time, changes in circumstances, and internal coping

Major Depressive Disorder

1. Occurs “out of the blue”

OR

2. Disproportionate in intensity and duration

1. Cognitive
2. Affective

OR

3. Persists despite changes in circumstances or passage of time

Loss of Sadness: Endogenous vs. Reactive Revisited?

- Different assumption about the role of life events
- No assumption about symptom pattern
- No assumption about treatment response

Why does it matter?

- DSM as an obstacle to neuroscience (Nestler & Hyman, 2011)
- Research on etiology of mental disorder
- Unnecessary treatment
- Misleading prevalence rates

Bereavement (Kendler et al., 2008)

- Individuals with bereavement-related MDD and MDD related to other stressors are comparable in:
 - Demographics
 - Personality traits
 - Symptoms of depression
 - Co-morbidities
- The bereavement exclusion should be *removed* from DSM

Bereavement (Wakefield et al., 2007)

- Individuals with bereavement-related MDD and MDD related to other stressors are comparable
- Complicated vs. uncomplicated MDD differ in:
 - Impairment
 - Melancholic symptoms
 - Duration of episode
- The bereavement exclusion should be *expanded* in DSM

What do other people think?

- Lay people distinguish between depression coming “out of the blue” vs. depression following a life stressor (Holzinger et al., 2009)
- Psychologists extend the bereavement exclusion to other stressful life events (Kim et al., 2012)
- Mental disorders must not be merely an expectable and culturally sanctioned response to a particular event

What Should We be Doing to Develop a Rational Approach to Treatment?

- Develop methods to determine whether “treatment” is appropriate, vs.:
 - Watchful waiting
 - Psychoeducation
 - Coaching re diet, exercise, social engagement, etc.
- For those for whom treatment is indicated, ask more than whether a treatment is “evidence-based” (yes vs. no)

The enterprise of clinical science should aim to provide, for any treatment...

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- unbiased estimates of the magnitude...
 - of its costs, benefits, and ancillary effects...
 - both short-term and long-term...
 - relative to alternatives (nothing, placebo, other treatments)...
 - » across the range of those given the diagnosis...
 - » and for important subsets of those with the diagnosis

FDA approval requirements

- Two studies* in which the new drug beats placebo at the .05 level on the primary measure of depressive symptom severity
- Neither the number of trials it took to get to two -- nor any estimate of the magnitude of the effect -- plays a discernible role in the FDA verdict
- Verdict is “thumbs up” or “thumbs down” (not an estimate of degree or likelihood of benefit)
- No consideration of long-term benefit or harm, despite knowledge that depression is or can be chronic, and concerns about long-term side effects

Research Design Elements in FDA Registration Trials that Should Maximize the Likelihood of Obtaining an Effect

- Include only patients who are in the “golden zone”
- Employ a placebo run-in, to exclude placebo responders
- Do not use “active” placebos

Even so...

Overview of Turner study

N Engl J Med. 2008 Jan 17;358(3):252-60

- FDA reviews
- 12 antidepressants starting with Prozac
- Cohort of 74 trials *registered* with FDA
- Track each study into published literature
- Two questions:
 - Was the study published?
 - If published, how did the published results compare with the FDA results?

Breakdown by drug -- Journal view

Positive

							42					
							43					
			9				44					
			10		21	27	45			66		
		4	11		22	28	46			67		
		5	12	17	23	29	47	58		68		
		6	13	18	24	30	48	59	61	69	72	
1	7	14	19	25	31	39	49	60	62	71	73	

Not
positive

32

51

56

bupropion SR (Wellbutrin SR)

citalopram (Celexa)

duloxetine (Cymbalta)

escitalopram (Lexapro)

fluoxetine (Prozac)

mirtazapine (Remeron)

nefazodone (Serzone)

paroxetine (Paxil)

paroxetine CR (Paxil CR)

sertraline (Zoloft)

venlafaxine (Effexor)

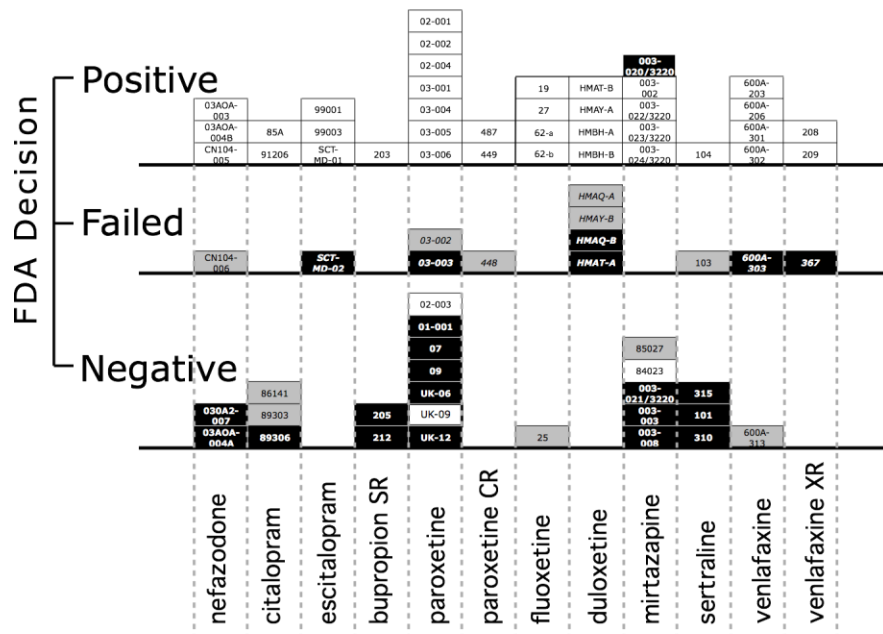
venlafaxine XR (Effexor XR)

Breakdown by drug -- FDA view

Positive								42				
								43				
						26		44				
			9		21	27		45		66		
			10	17	22	28	36	46		67		
		4	11	18	23	29	37	47	58		68	72
	1	5	12	19	24	30	38	48	59	61	69	73
Not positive	2	6	13	20	25	31	39	49	60	62	70	74
	3	7	14			32	40	50		63	71	
		8	15			33	41	51		64		
			16			34		52		65		
						35		53				
								54				
								55				
								56				
								57				
	bupropion SR (Wellbutrin SR)	citalopram (Celexa)	duloxetine (Cymbalta)	escitalopram (Lexapro)	fluoxetine (Prozac)	mirtazapine (Remeron)	nefazodone (Serzone)	paroxetine (Paxil)	paroxetine CR (Paxil CR)	sertraline (Zoloft)	venlafaxine (Effexor)	venlafaxine XR (Effexor XR)

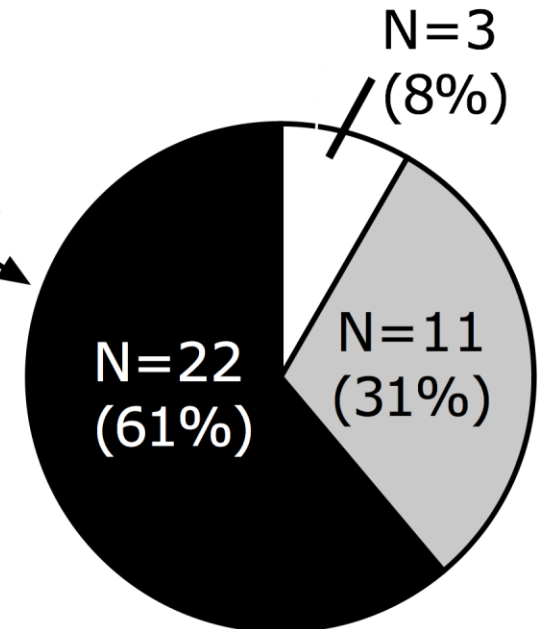
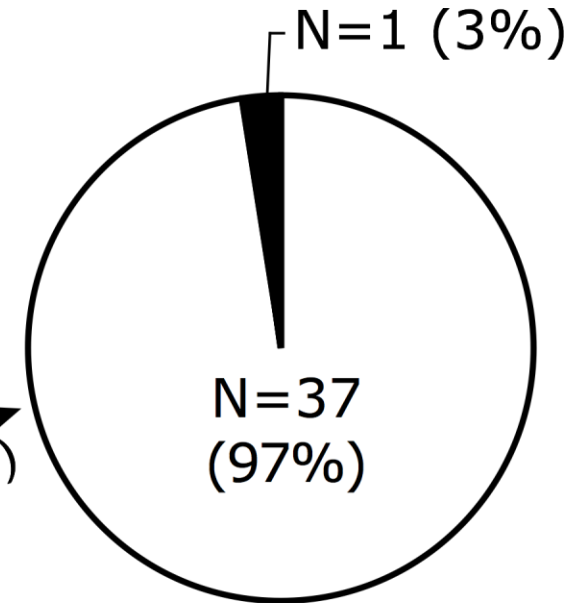
FDA decision → Publication fate

- Published, agree with FDA
- Published as positive, in conflict with FDA
- Not published



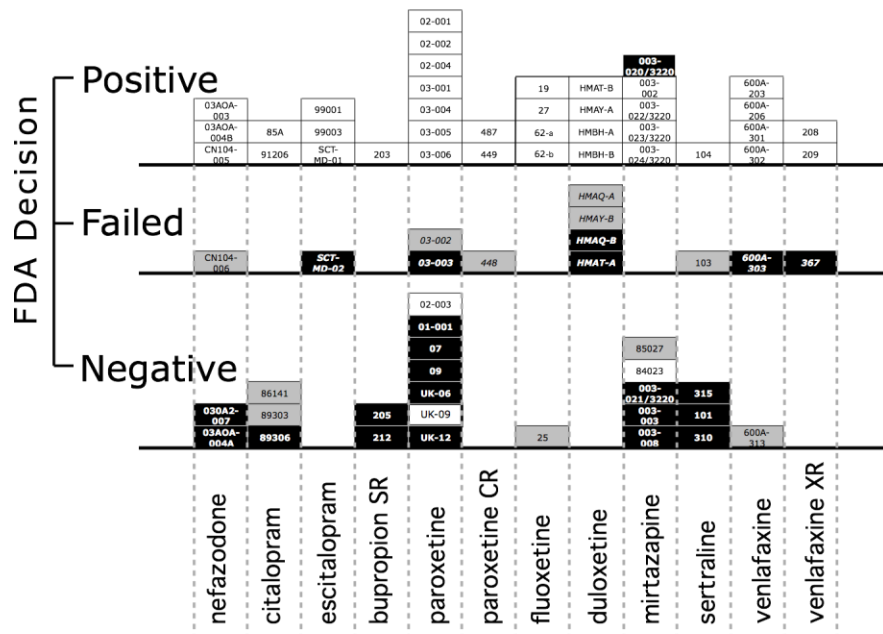
Positive
N=38 (51%)

Not positive
N=36 (49%)



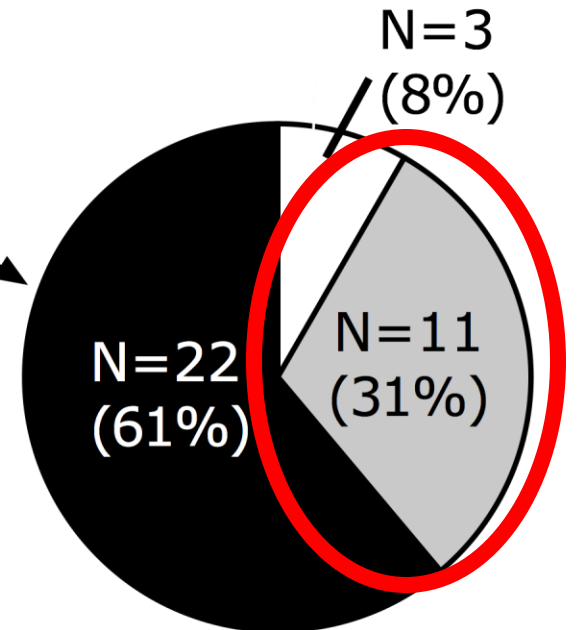
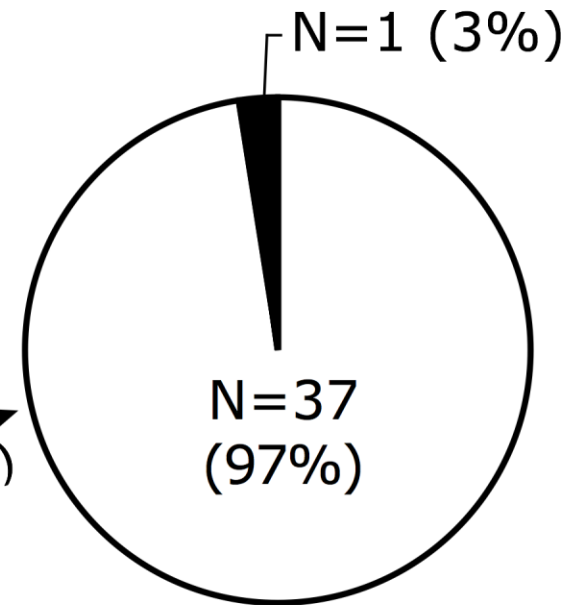
Spun trials

Published, agree with FDA
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Positive
N=38 (51%)

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N=36 (49%)

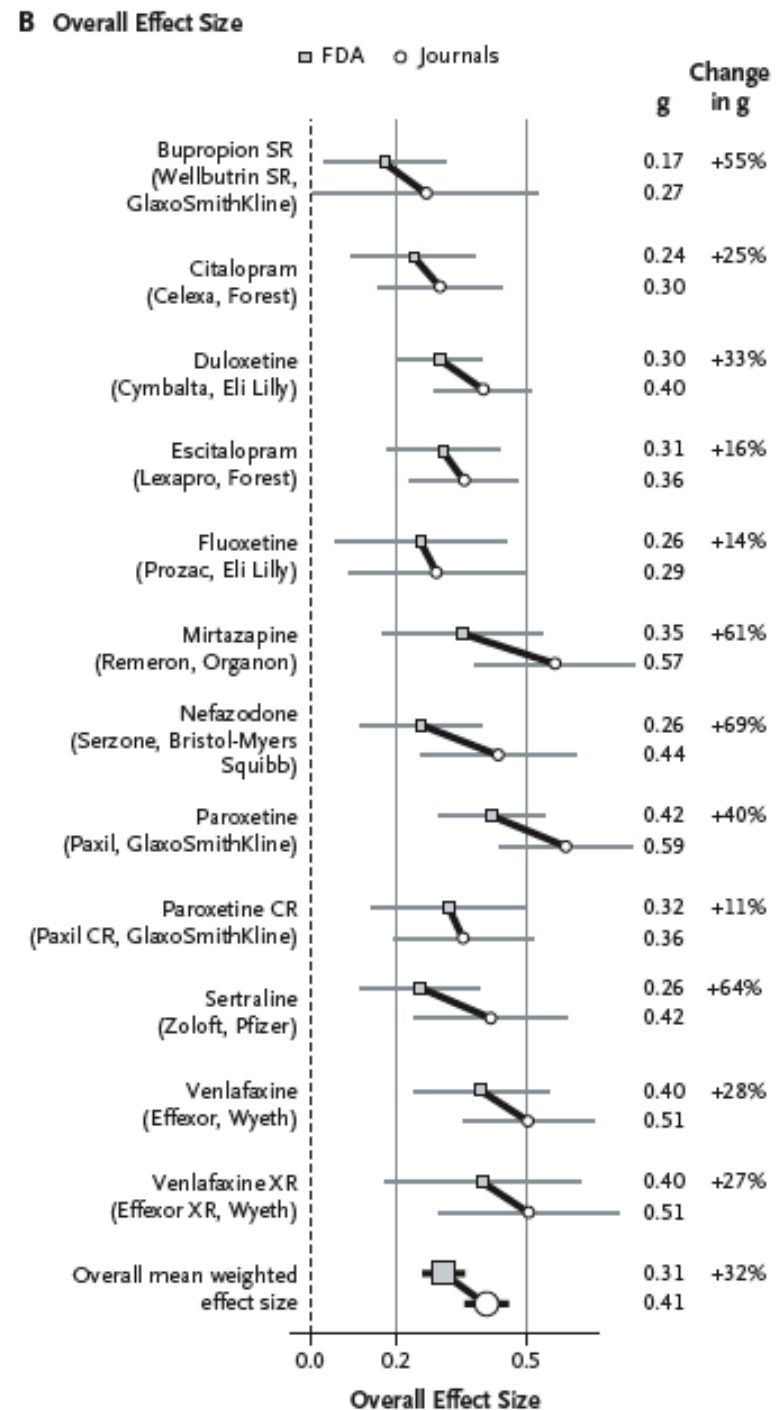


Effect size (ES) *with* CIs: FDA vs. journals

Journal-based ES > FDA-based ES
for each of the 12 drugs

Increase in effect size from FDA
to Journal:

- Minimum boost: 11%
- Maximum boost: 69%
- Average boost: 32%

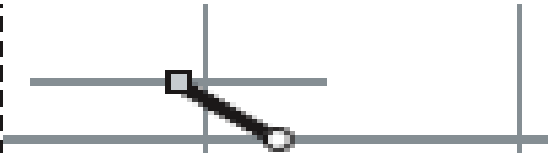


B Overall Effect Size

□ FDA ○ Journals

g
Change
in g

Bupropion SR
(Wellbutrin SR,
GlaxoSmithKline)



0.17
0.27
+55%

Citalopram
(Celexa, Forest)



0.24
0.30
+25%

Duloxetine
(Cymbalta, Eli Lilly)



0.30
0.40
+33%

Escitalopram
(Lexapro, Forest)



0.31
0.36
+16%

Fluoxetine
(Prozac, Eli Lilly)



0.26
0.29
+14%

Mirtazapine
(Remeron, Organon)

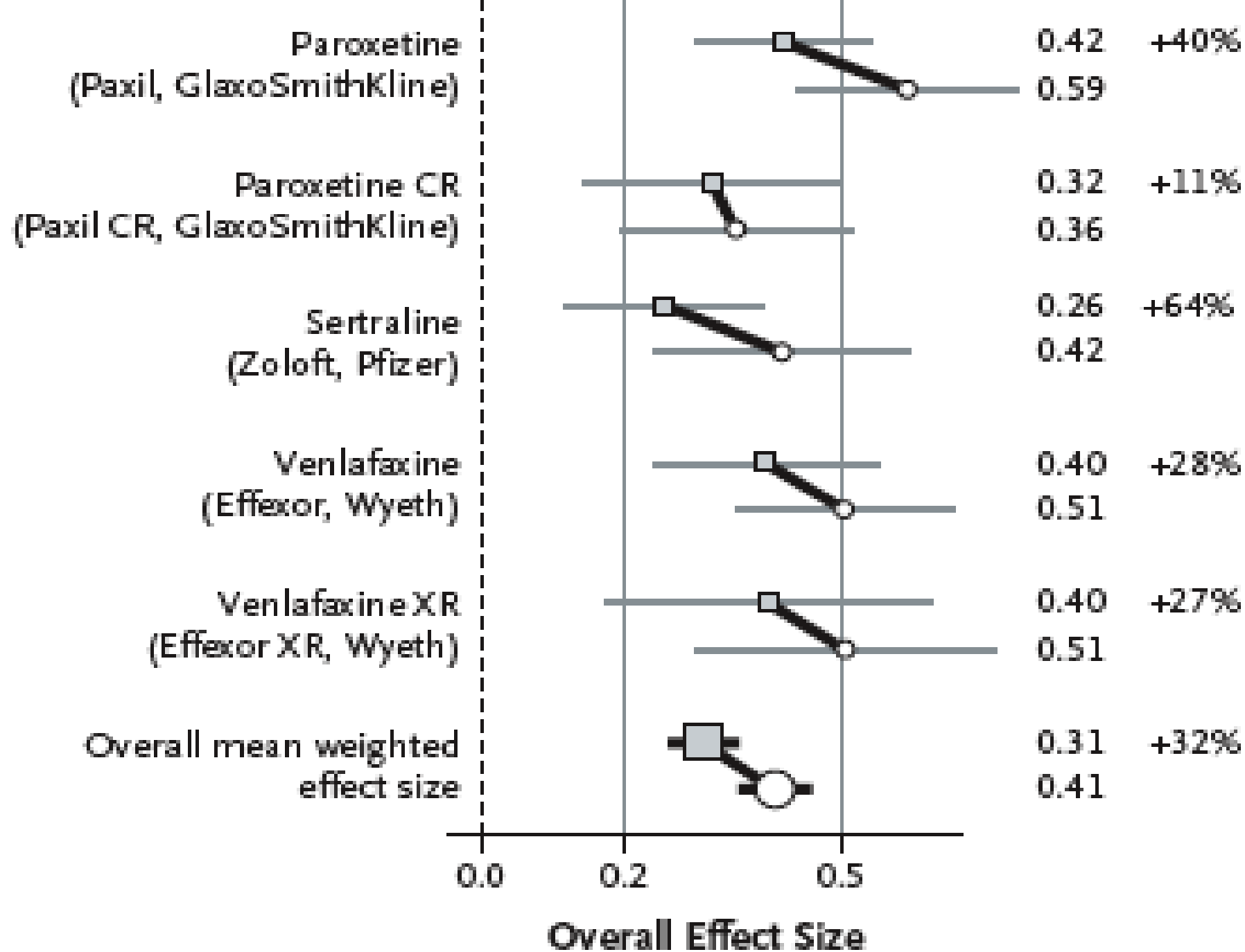


0.35
0.57
+61%

Nefazodone
(Serzone, Bristol-Myers
Squibb)



0.26
0.44
+69%



FDA-focused investigations are limited in their ability to provide crucial information

Investigators are discouraged from recruiting samples that include a broad range of depressive symptom severity

- Results cannot properly be generalized to the population of depressed patients
- Informative tests of the relation of symptom severity to the drug-placebo advantage cannot be conducted

Meta-Analyses of the FDA Database (Khan et al. and Kirsch et al.)

Both showed that the drug-placebo difference substantial for more severe patients, small at best for less severe cases

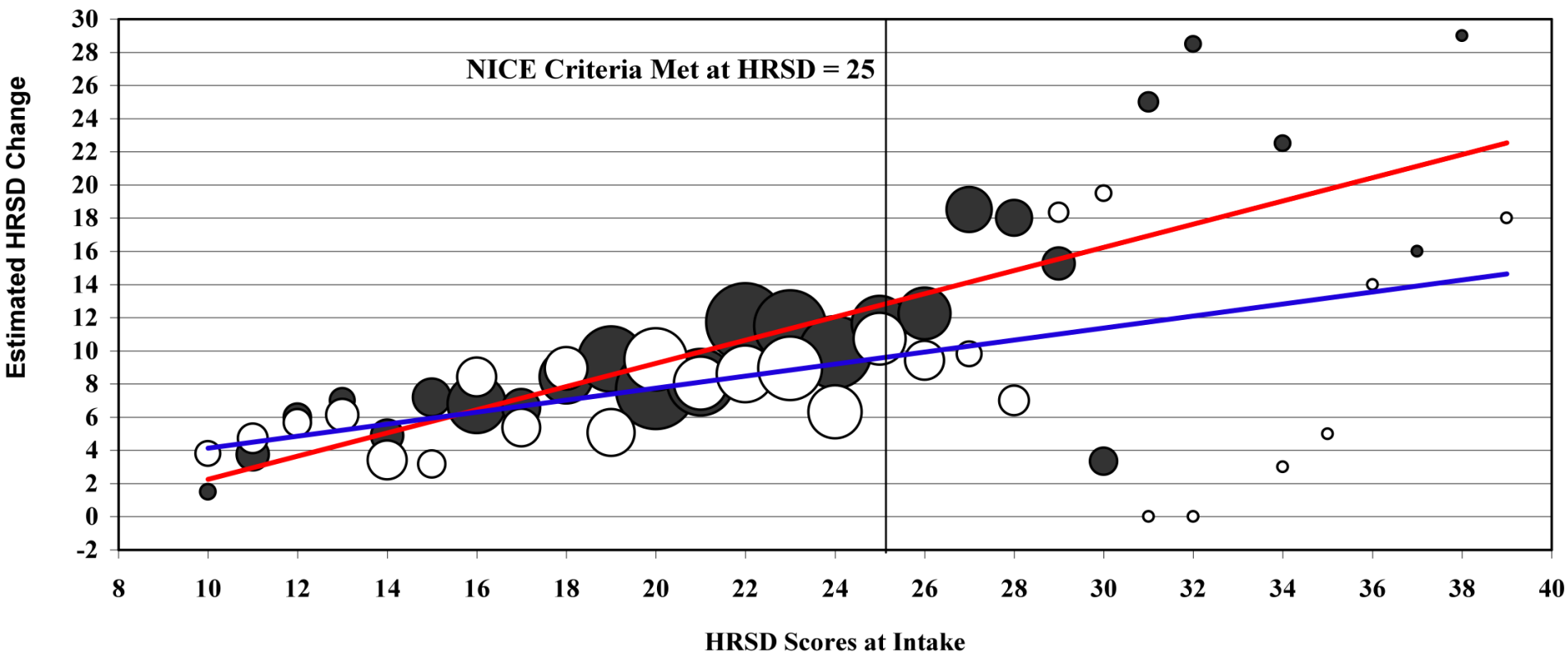
Most of the trials they included in their reports:

- Used a placebo washout design
- Excluded patients with HAMD of less than 20

Drug-placebo difference for typical depressed patient who is given an antidepressant could not be estimated:

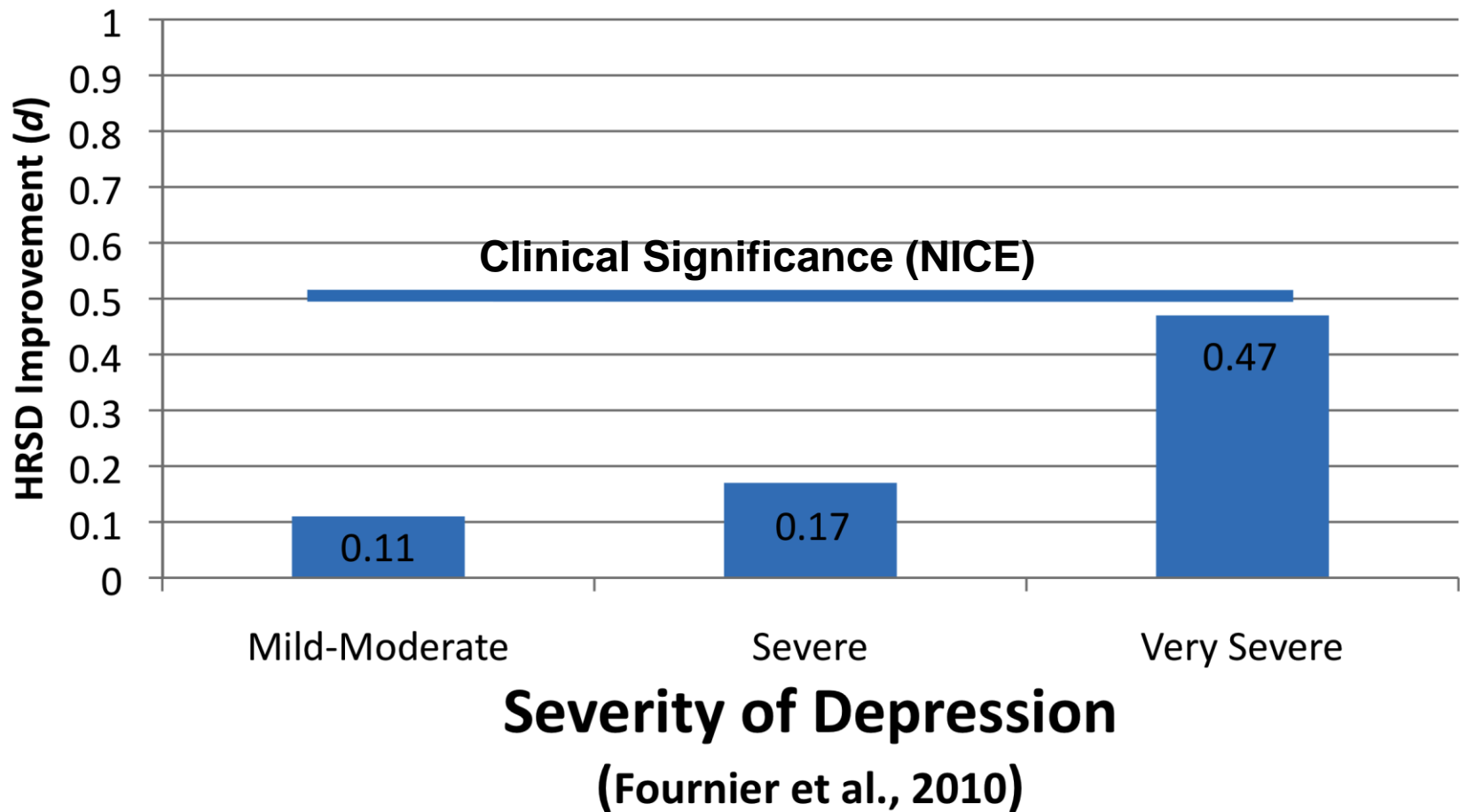
- In Khan et al., baseline mean < 23 in 0/45 studies
- In Kirsch et al., baseline mean < 23 in 2/27 studies

**Raw and Modeled Change in HRSD Scores
Following Treatment with ADM and Placebo**



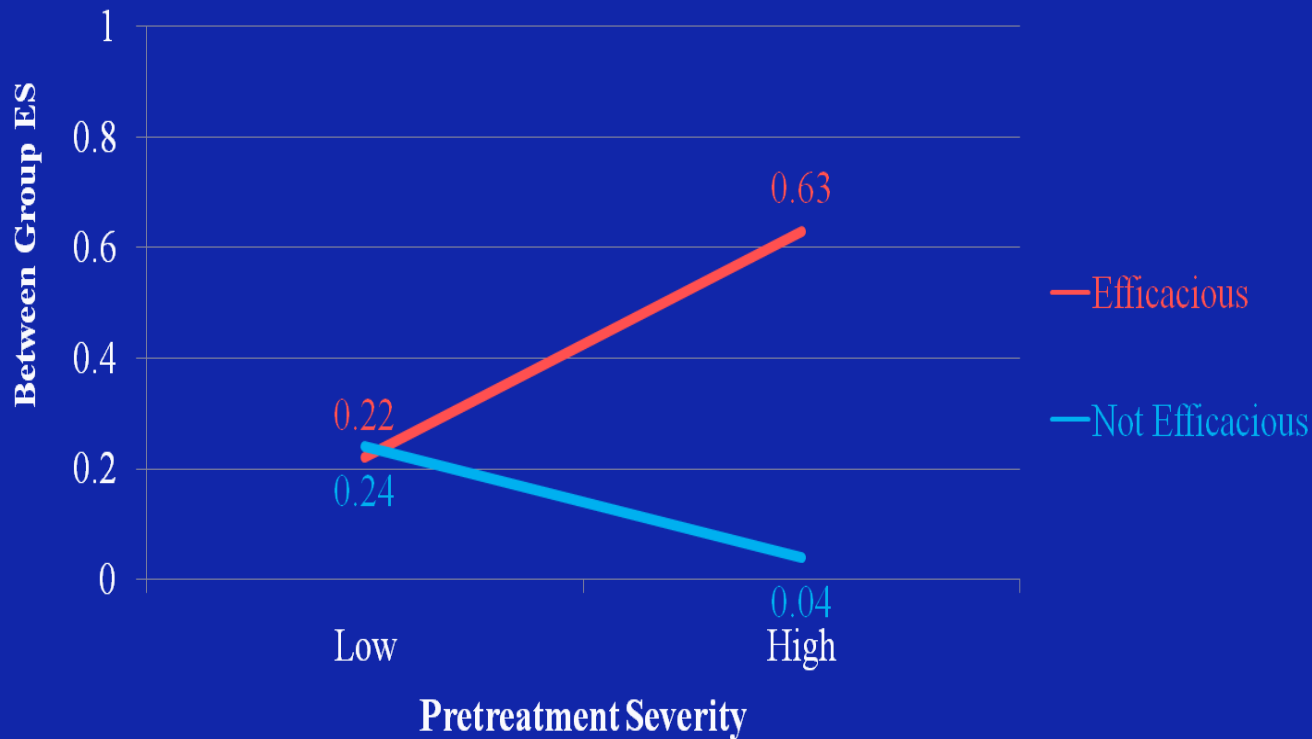
Fournier, DeRubeis, et al. (2010, JAMA)

Drug-Placebo Differences



Similar finding with psychotherapy

(Driessen et al., 2013)



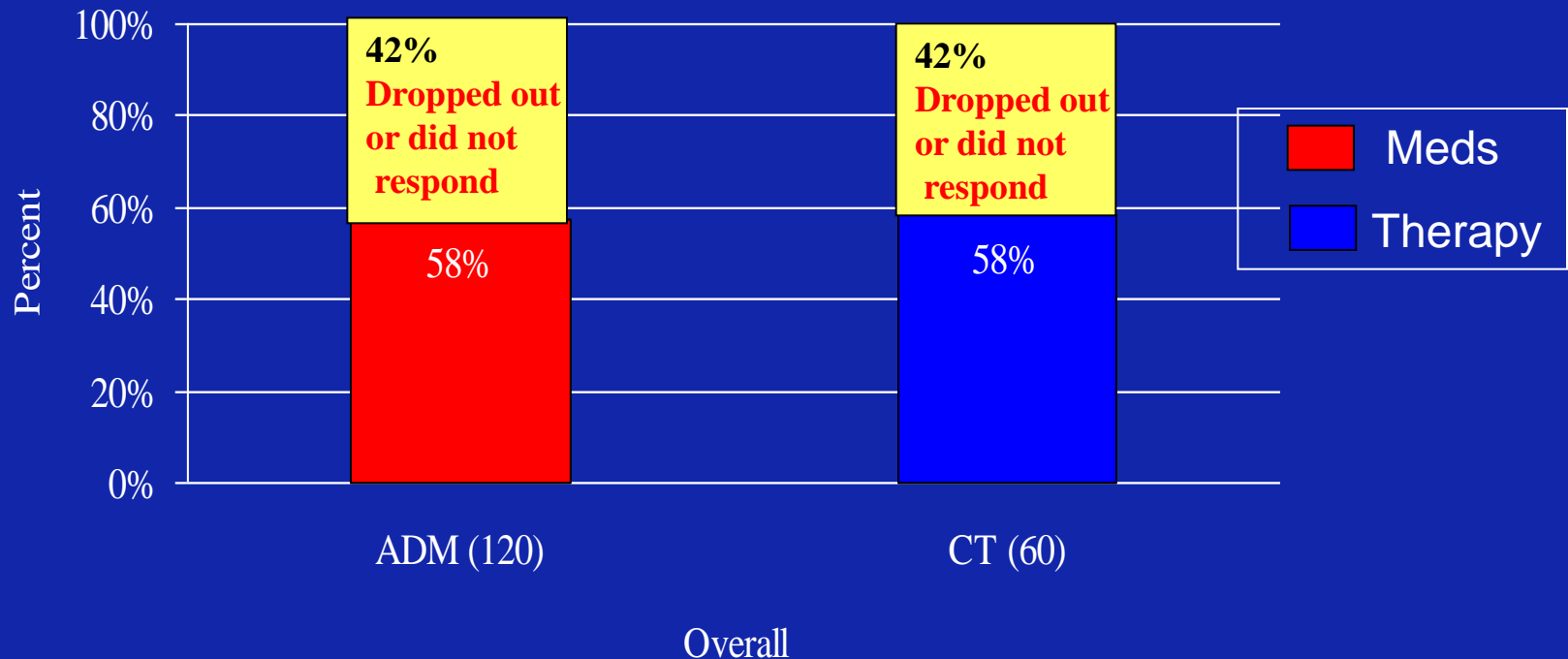
Efficacious: Elkin IPT; Dimidjian BA; Haringsma CDW; van Schaik IPT

Not Efficacious: Elkin CT; Dimidjian CT; Barlow SCT; Simpson DYN

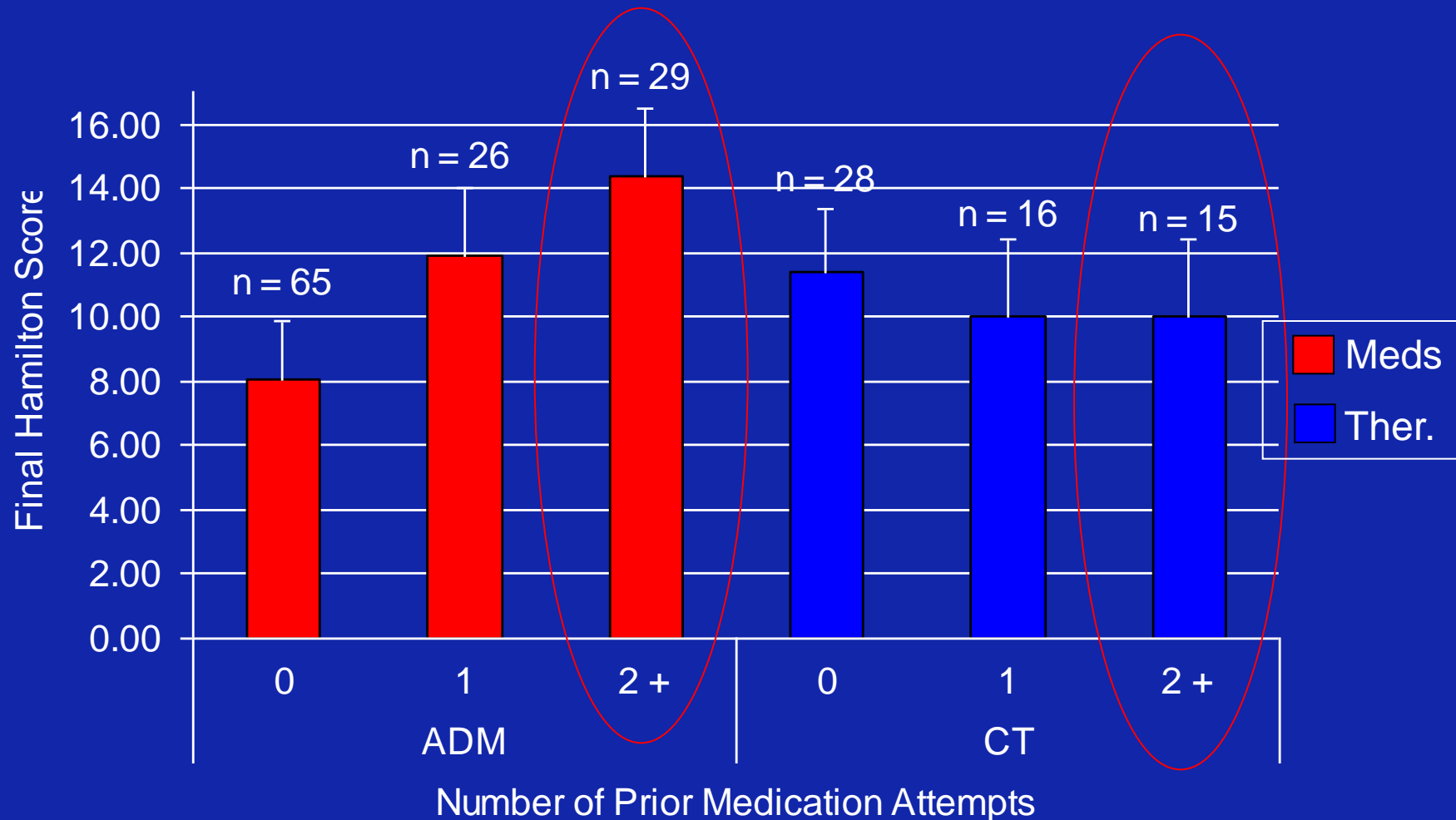
FDA-focused investigations are limited in their ability to provide crucial information

- Investigators are not encouraged to recruit samples that represent the important subsets of depressed patients
 - Results cannot properly be generalized to subsets of depressed patients who are not included in studies
 - Informative tests of the drug-placebo advantage in various subsets cannot be conducted

Percentage of Patients who Responded to 16 weeks of Treatment

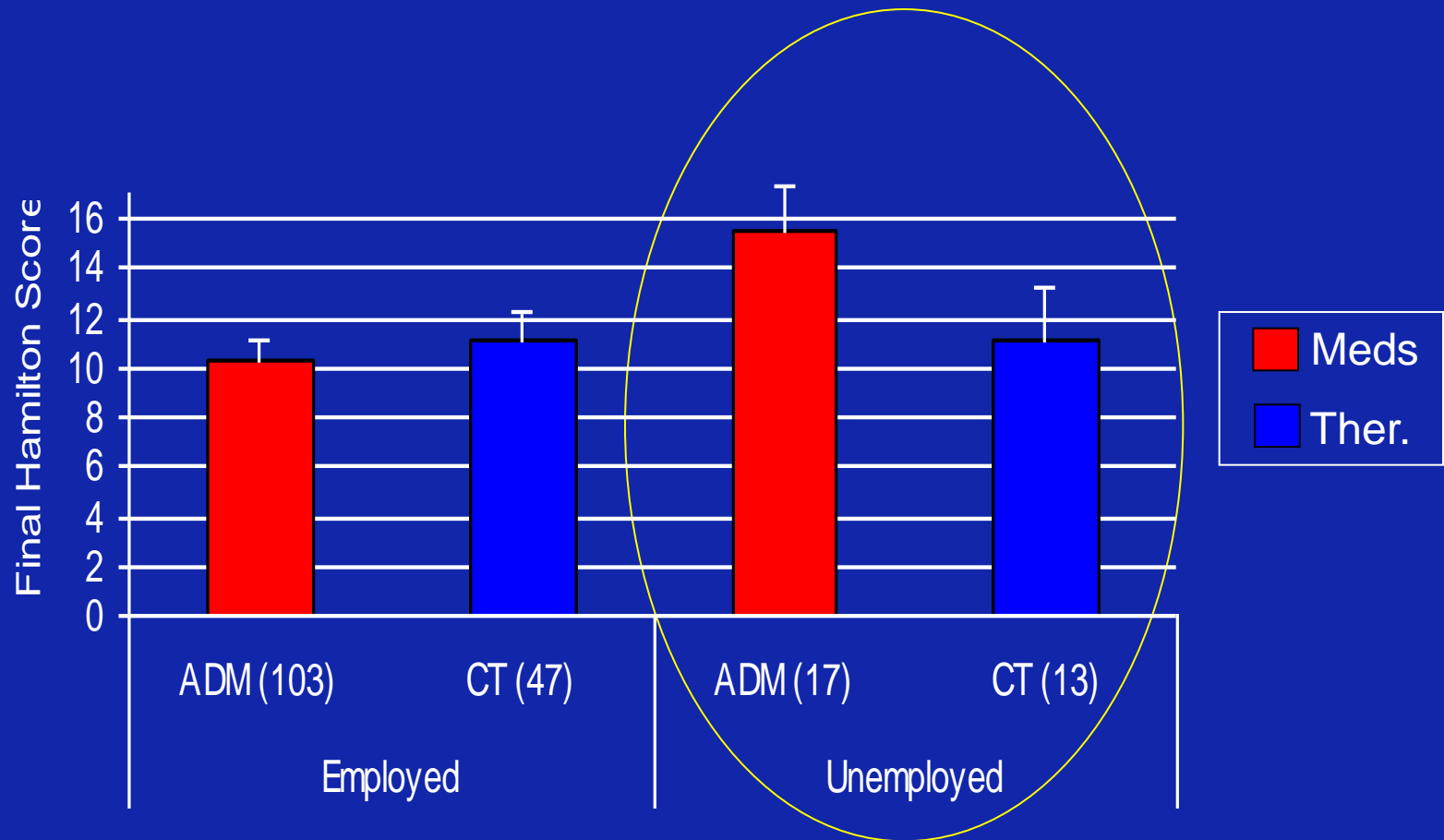


Prior Medication Treatment predicts differential response in the two treatments



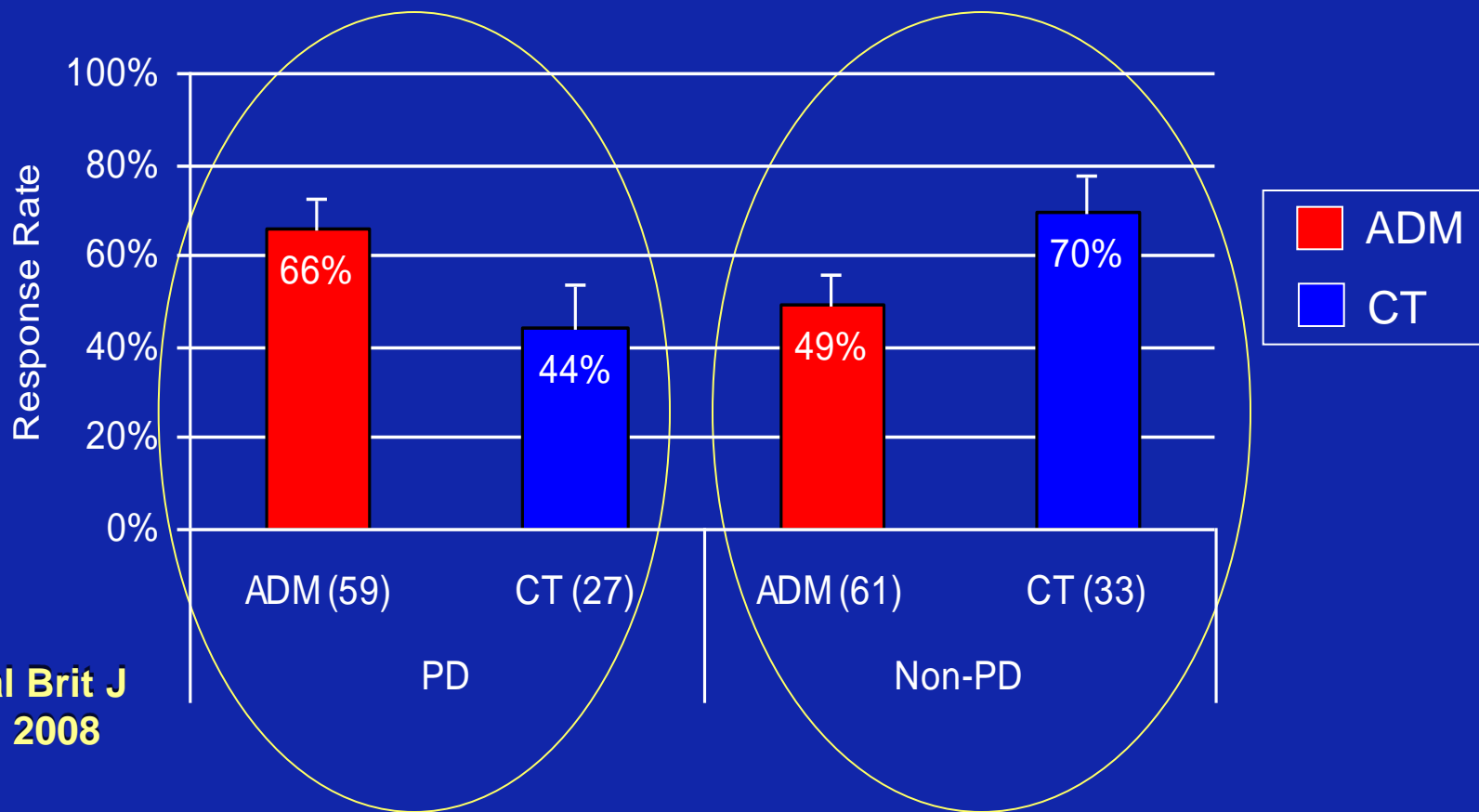
Employment Status

predicts differential response in the two treatments

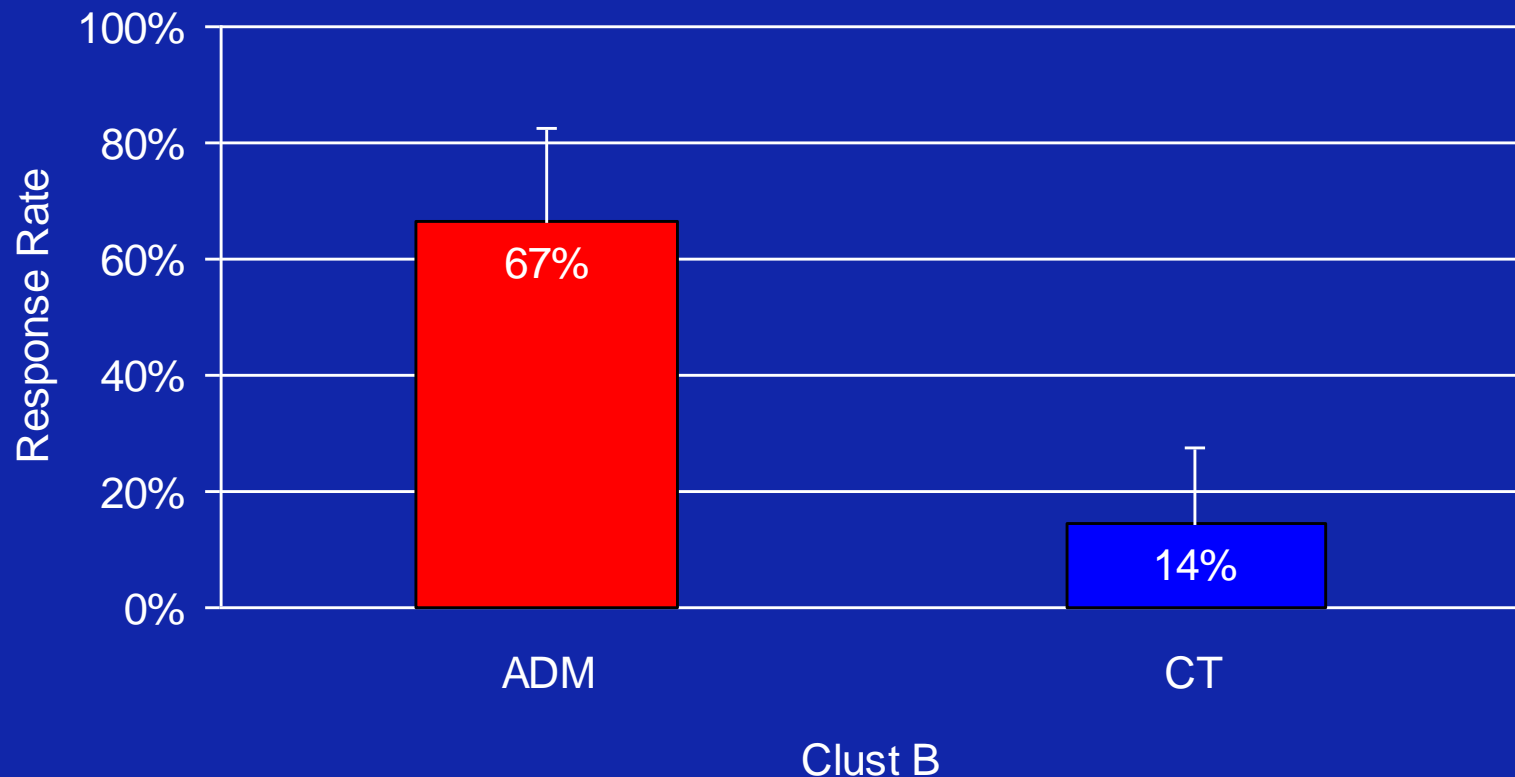


Diagnosis of Any Personality Disorder

The diagnosis of *any* Personality Disorder
predicts differential response in the two treatments

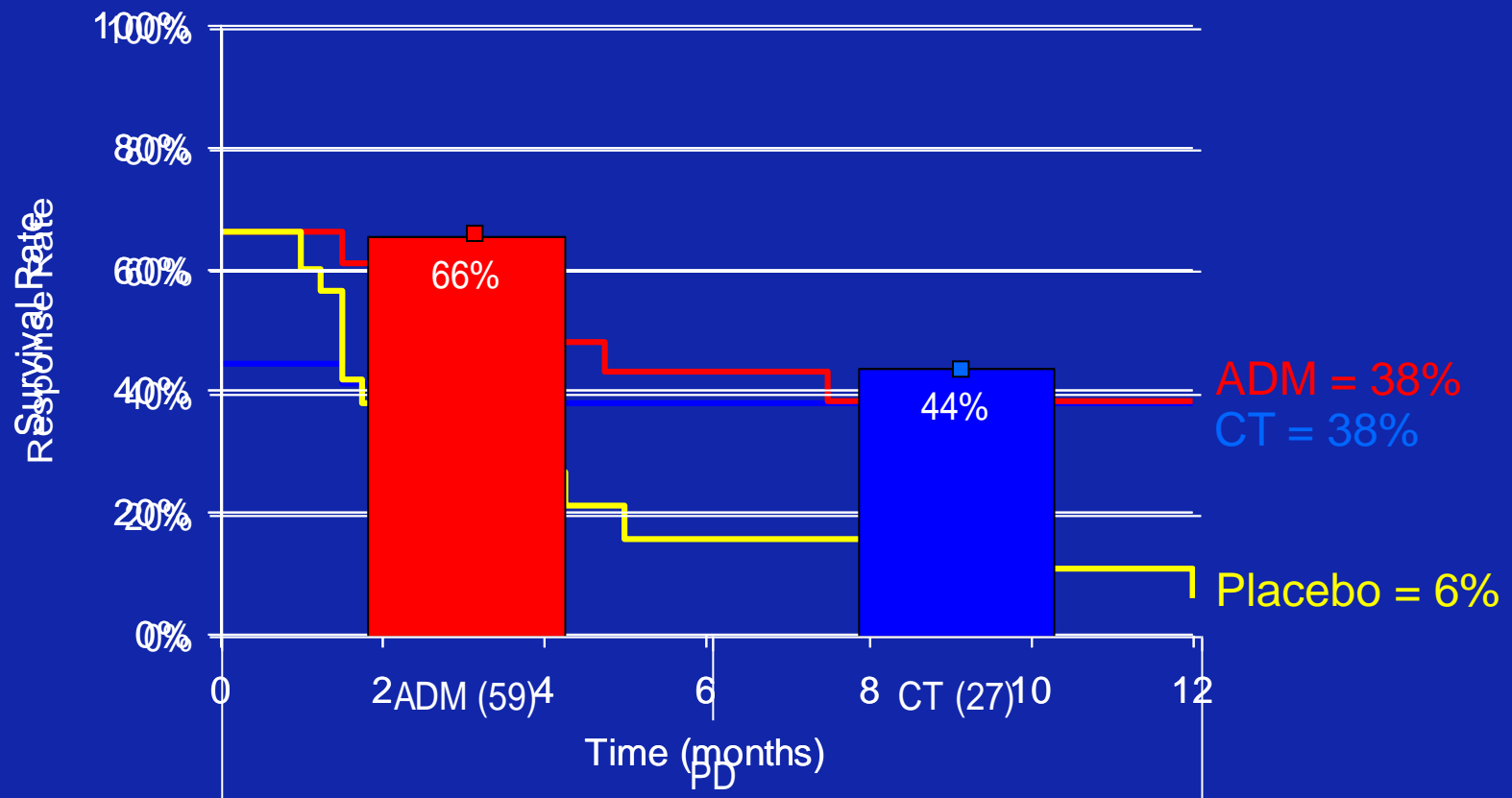


Patients Whose Personality Disorders Feature Very Poor Emotion-Regulation Responded Well to Medication, and Poorly to Cognitive Therapy



Percent of Patients who Remained on Well Criteria across Continuation

Response Rates Patients with Any Personality Disorder

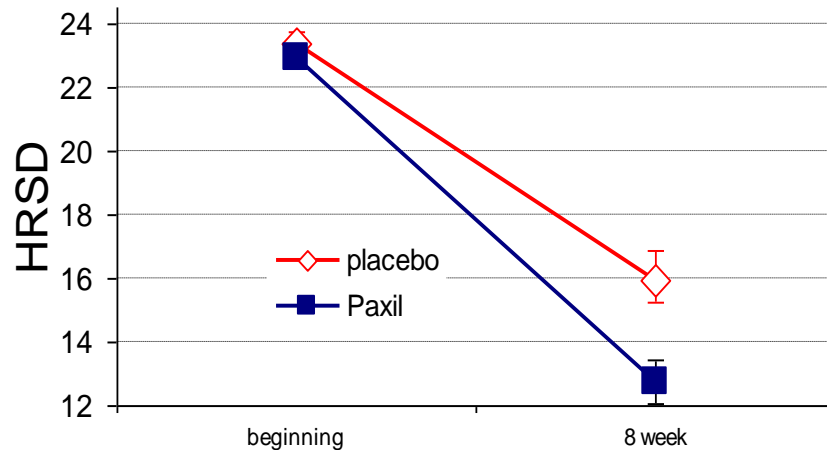


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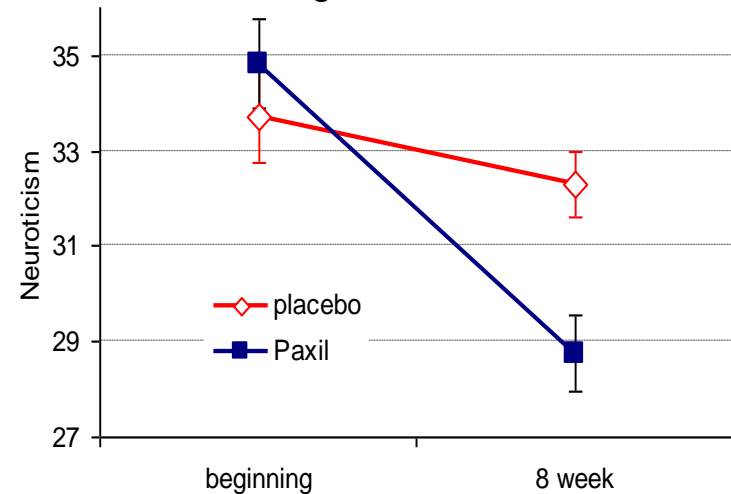
- Investigators are not encouraged to discern the effects of the medicines, other than on depression symptom severity and tolerability (side effects)

Personality Change during Pharmacotherapy for Depression: Drug-Placebo Differences

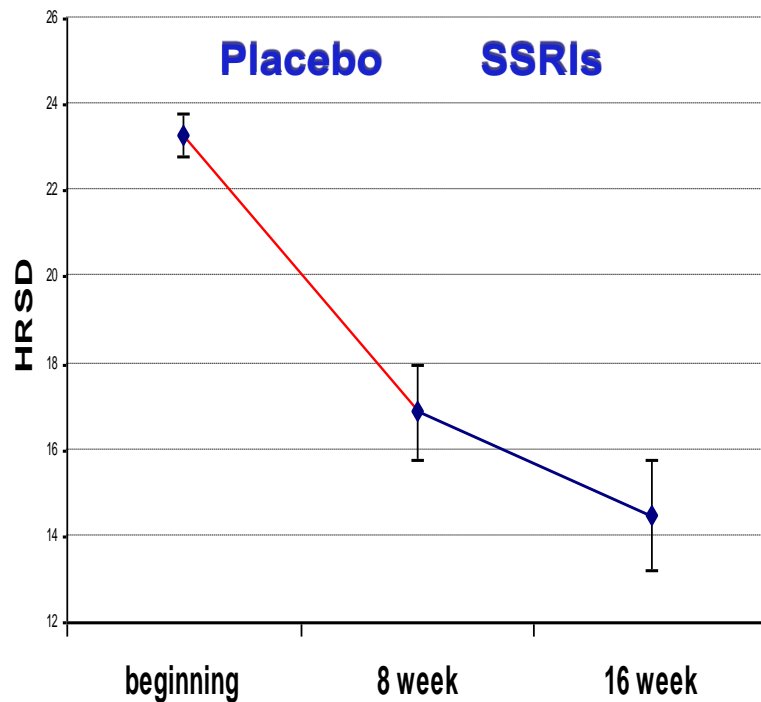
Change in depression severity



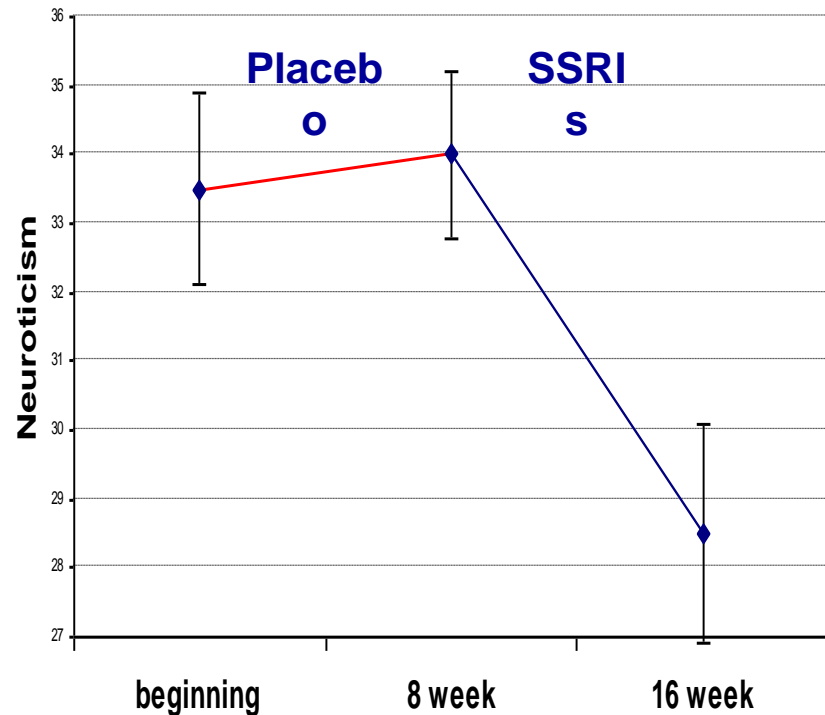
Change in Neuroticism



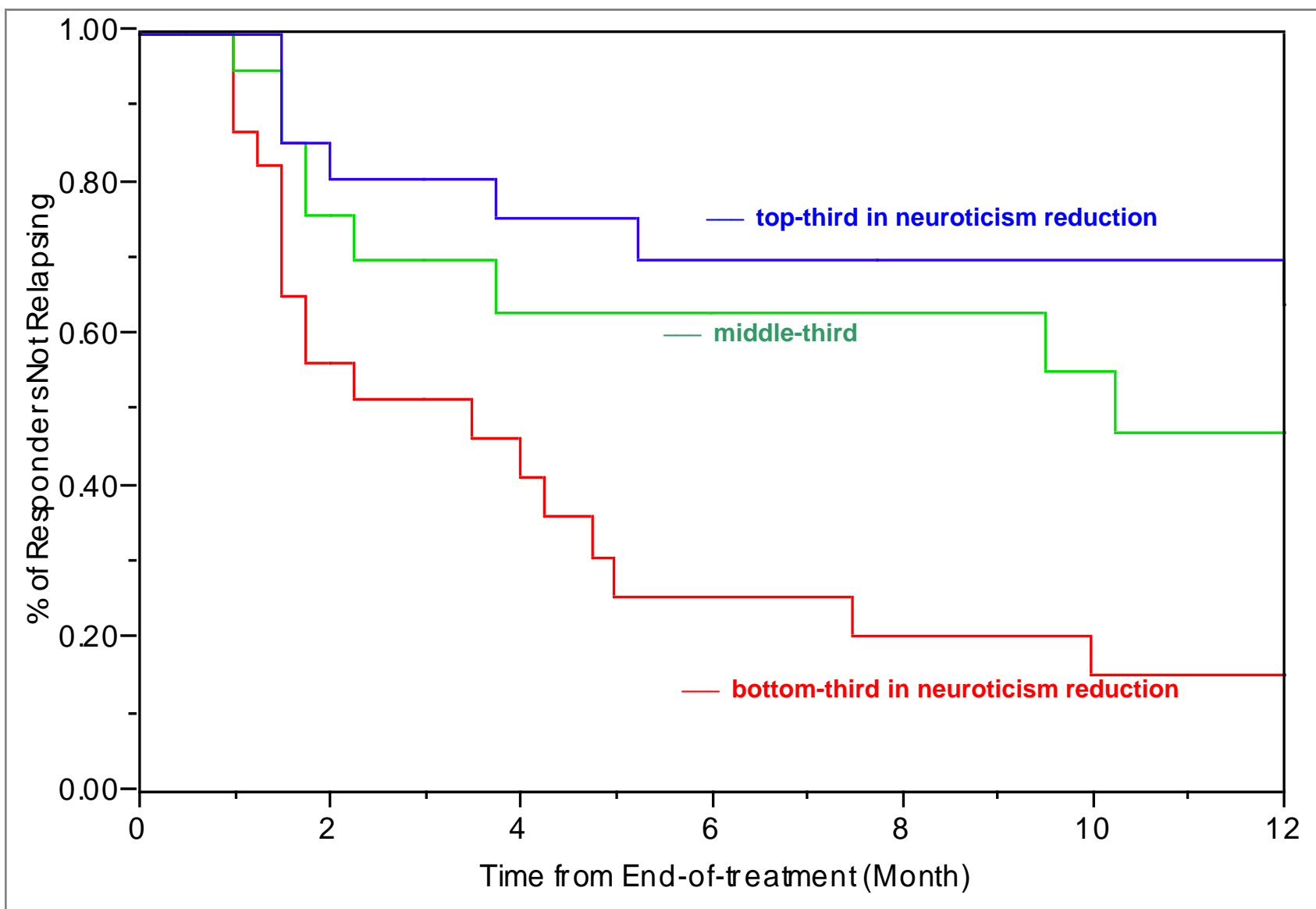
Personality Change during Pharmacotherapy for Depression: Switch to Medications

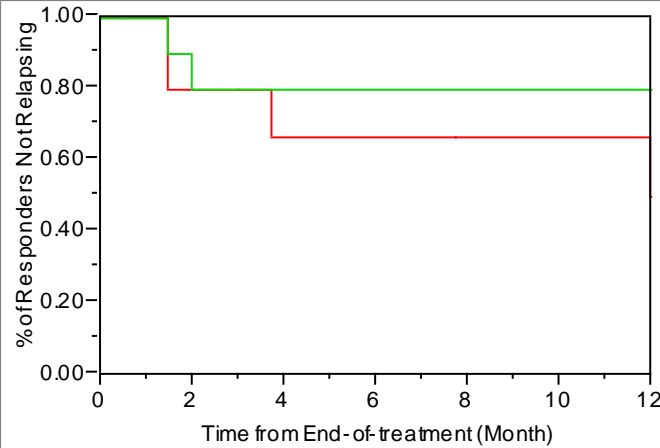


Depression

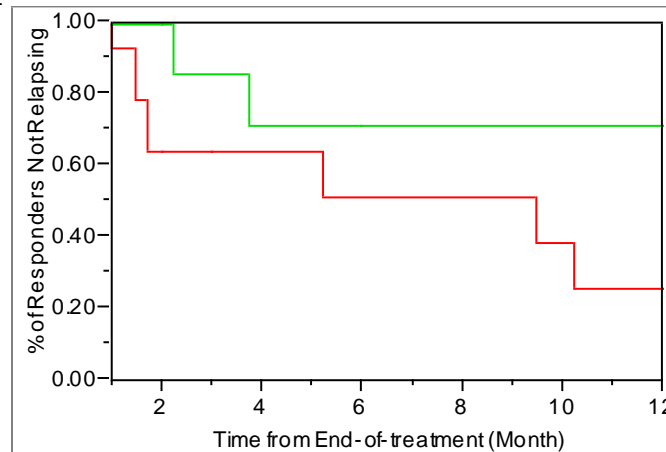


Neuroticism

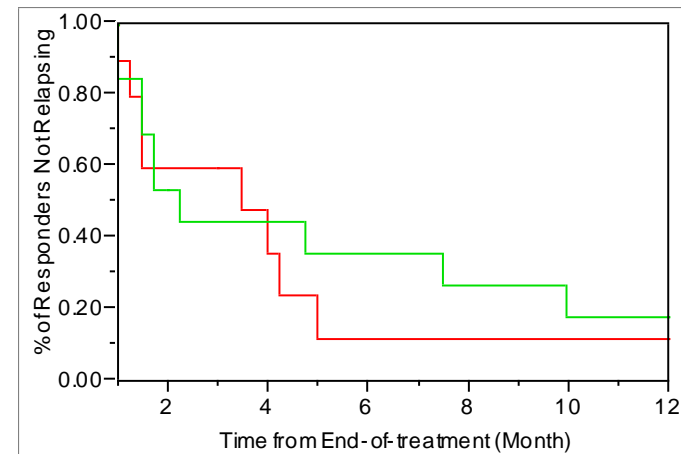




— medication continuation
— continuation on placebo



Lowest 1/3 of Δ Neuroticism (ns)



Relapse during Continuation, by Condition and Δ Neuroticism

To whom are antidepressants being prescribed? What other options are there?

Most patients, especially in primary care, would not qualify for pharmaceutical trials (Zimmerman et al. J Clin Psychopharmacol, 2002) on basis of severity

Look to the United Kingdom's NICE guidelines for mild depression: "Watchful waiting, guided self-help, computerised CBT, exercise, brief psychological interventions."

Be skeptical of combination treatments, at least as initial programs of care.

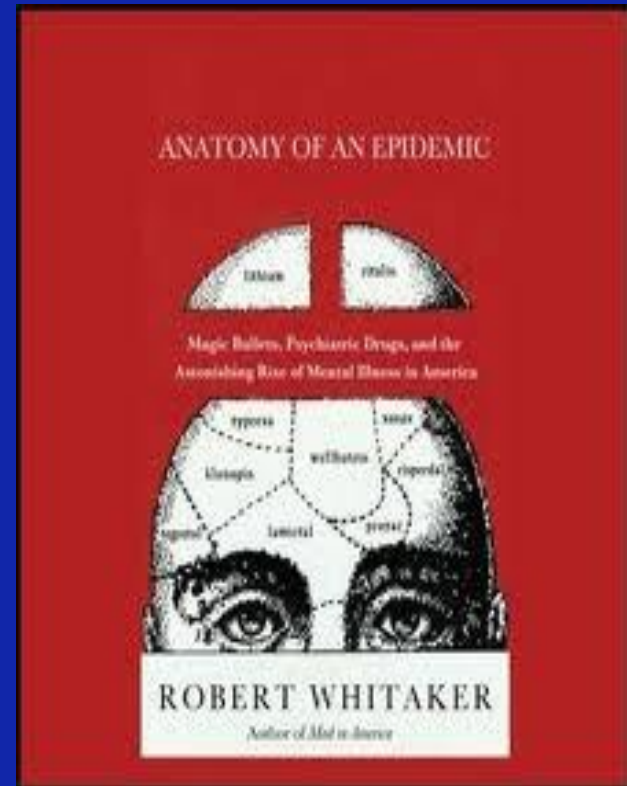
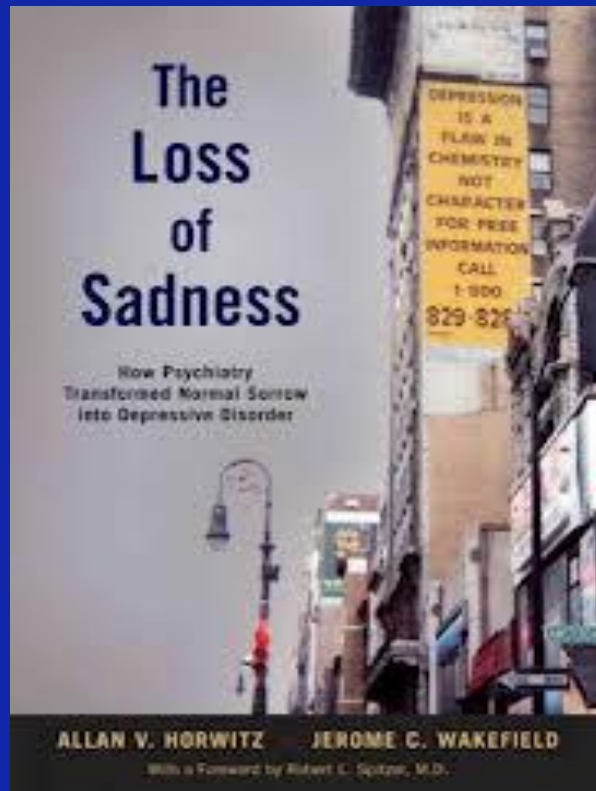
A Hot-Button Topic

Judith Warner: “The Wrong Story About Depression” (NYTimes, 1/8/2010)

Richard Friedman: “...on close inspection, the new study does not stand up to (the) mountain of earlier evidence.” (NYTimes, 1/11/2010)

Peter Kramer: “In Defense of Antidepressants.” “In the end, the much heralded overview analyses look to be editorials with numbers attached.” (NYTimes, 7/9/2011.)

Highly recommended



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