ecnp
Neuroscience applied

ECNP WORKSHOP
on Clinical Research Methods

Methodology of Clinical Trials

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Disclosure / conflicts of interest

Concept	Company
Research	AB-Biotics, Abbvie, Almirall, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celon, Cephalon, Dainippon Sumitomo Pharma, Elan, Ferrer, GH Research, GlaxoSmithKline, Janssen, Lilly, Lundbeck, Orion, Otsuka, Pfizer, Sanofi-aventis, Servier, Sunovion, Takeda
Education	Abbott, Abbvie, Angelini, AstraZeneca, Bristol-Myers Squibb, Cambridge University Press, Elsevier, Farmindustria, Ferrer, Galenica, GlaxoSmithKline, Janssen, Johnson & Johnson, Lilly, Lundbeck, Oxford University Press, Otsuka, Pfizer, Sanofi-aventis, Viatris
Consultancy	Abbvie, Angelini, AstraZeneca, Biogen, Biohaven, Bristol-Myers Squibb, Celon, Compass, Ferrer, GH Research, Gedeon Richter, HMNC, Idorsia, Janssen, Jazz, Lilly, Lundbeck, Merck Sharp & Dohme, Novartis, Organon, Otsuka, Pfizer, Roche, Sage, Sanofi-aventis, Servier, Shire, Sunovion, Takeda, Teva

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Aciphex
ACEON
ULTRACET
FLOMAX
Macrobid
TriCor

Psychiatry: from interest in conflicts to conflicts of interest

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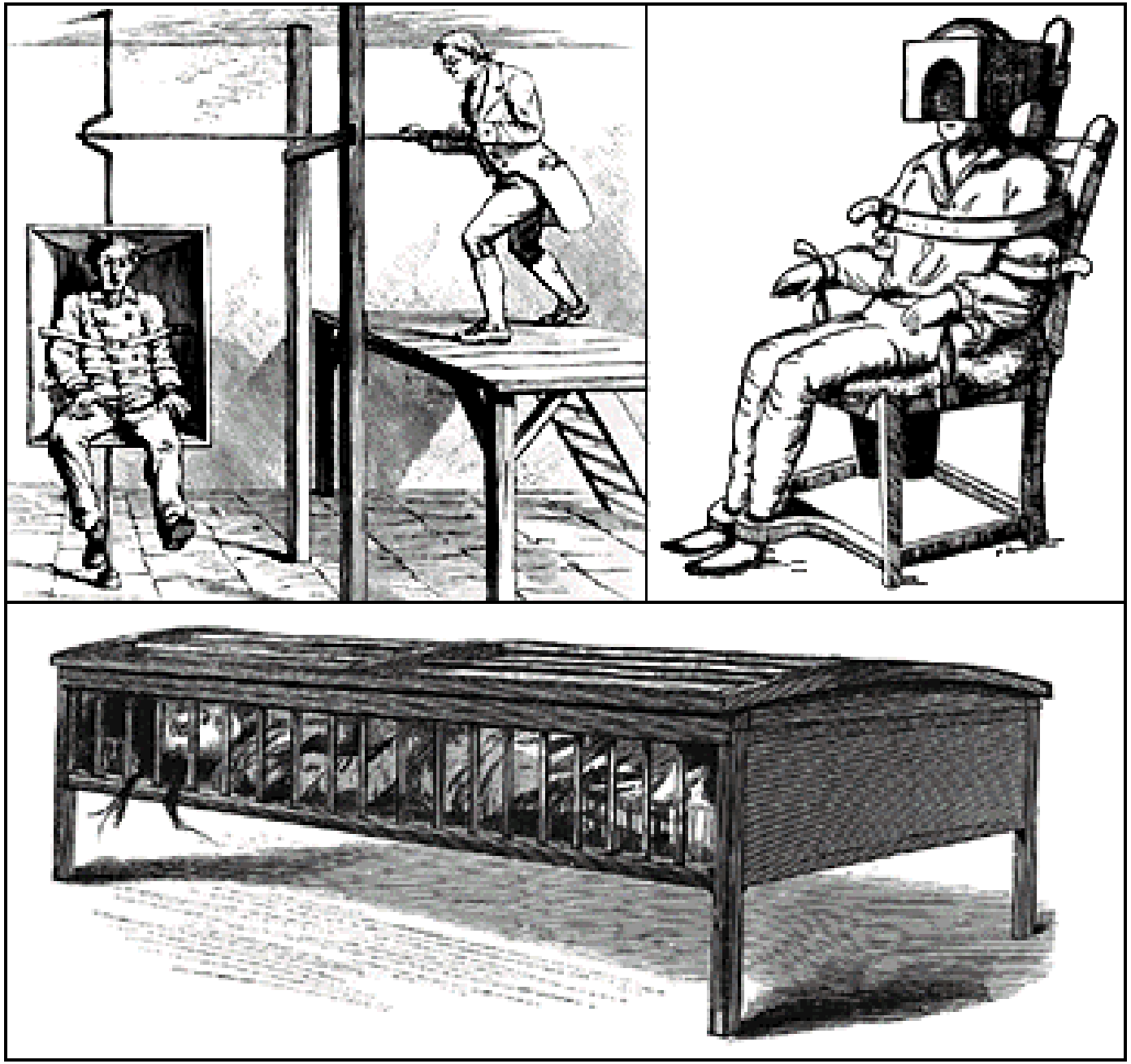
There was a time when psychiatry was largely influenced by the view that most mental conditions were the result of unsolved inner conflicts. That was a time when the availability of effective drugs for psychiatric disorders was extremely limited, and access to mental health care was also restricted to the very wealthy or to very sick patients, who would be confined in institutions for the mentally ill for long periods of time, and kept apart from society. The

I think that we should take a global approach to it. Hence, as Giovanni Fava rightly points out, clinical medicine and psychiatry are suffering from an unprecedented crisis of credibility, and this has more to do, in my opinion, with increased awareness about this issue rather than with decreased ethical standards or malpractice. Our society is increasingly aware of potential conflicts of interest and this is good for transparency, although one of my arguments will be that some conflicts are more visible than others and, to be fair, our responsibility as clinicians, educators or researchers is to disclose all of them, regardless of their nature. At the

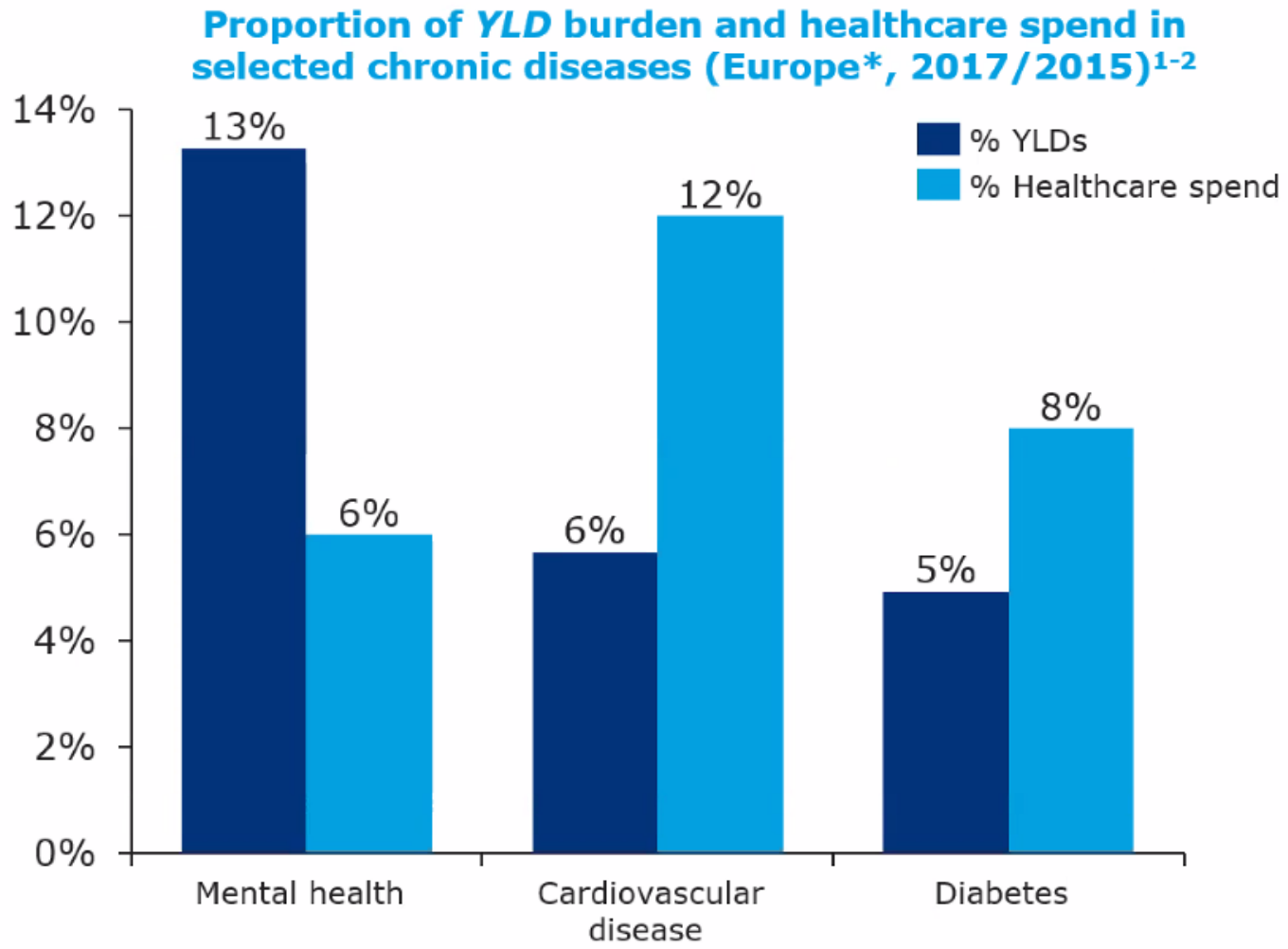


World mental health report

- Most people living with mental illness do not get care
- Mental illness is a leading cause of disability worldwide
- Care in many countries is concentrated in long-term psychiatric hospitals
- Need of shifting care away from long-term inpatient settings toward community-based approaches integrated with primary care
- Importance of respecting human rights, raising mental health awareness, and developing stigma prevention plans
- People who live with mental illness give voice, choice and influence to the mental health care system
- Governments must work across sectors, such as schools and workplaces, to promote good mental health
- Technology can also help scale up care

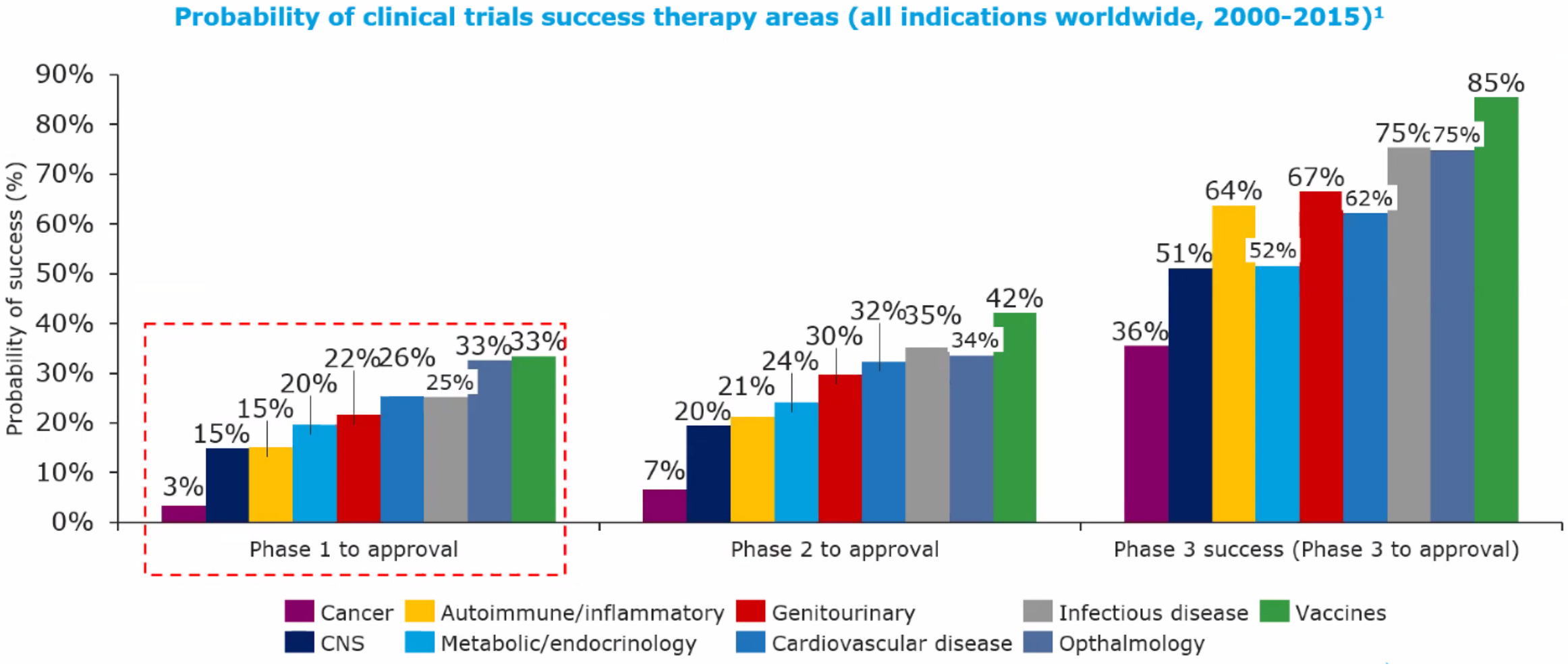
WHO, 2022

Mental Disorders: More disability, less investment



Sources: [1]WHO, 2017a (data for WHO European region, for country list see here), [2]Institute for Health Metrics & Evaluation
Healthcare expenditure data for mental health disorders were taken from the WHO Mental Health Atlas (2017 data) as an average of 14 countries for which data was available.

Clinical trial success in Neuroscience



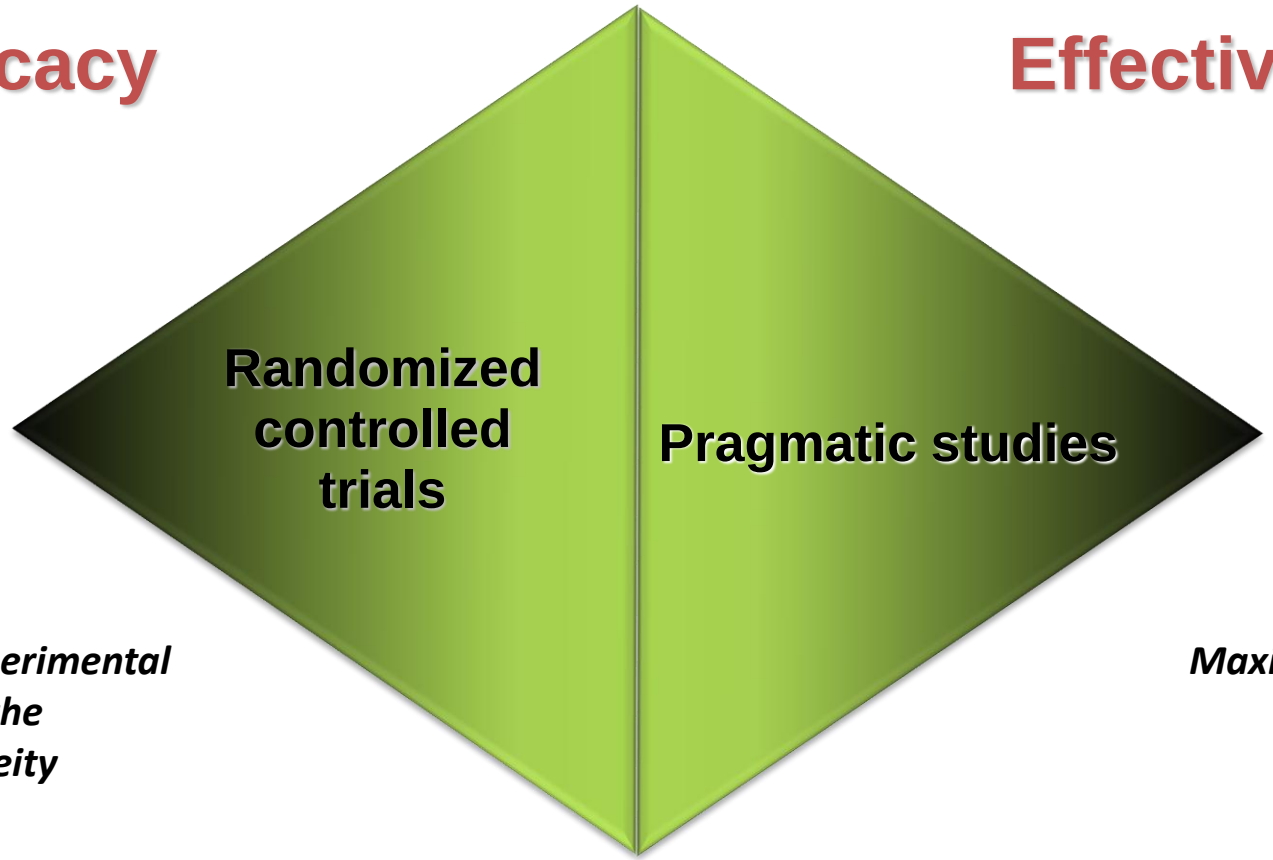
Clinical trials

- **Clinical trials** are experiments done in clinical research.
  Such prospective biomedical or behavioral research studies on human participants are designed to answer specific questions about biomedical or behavioral interventions, including new treatments (such as novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison.
- Types of clinical trials
  - Phase I
  - Phase II
  - Phase III
  - Phase IV

A Randomized, Double-blind, Placebo-controlled, Flexible-dose, Parallel-group Study of DRUG X Adjunctive to Lithium or Divalproex for the Prevention of Recurrence in Subjects With Bipolar I Disorder

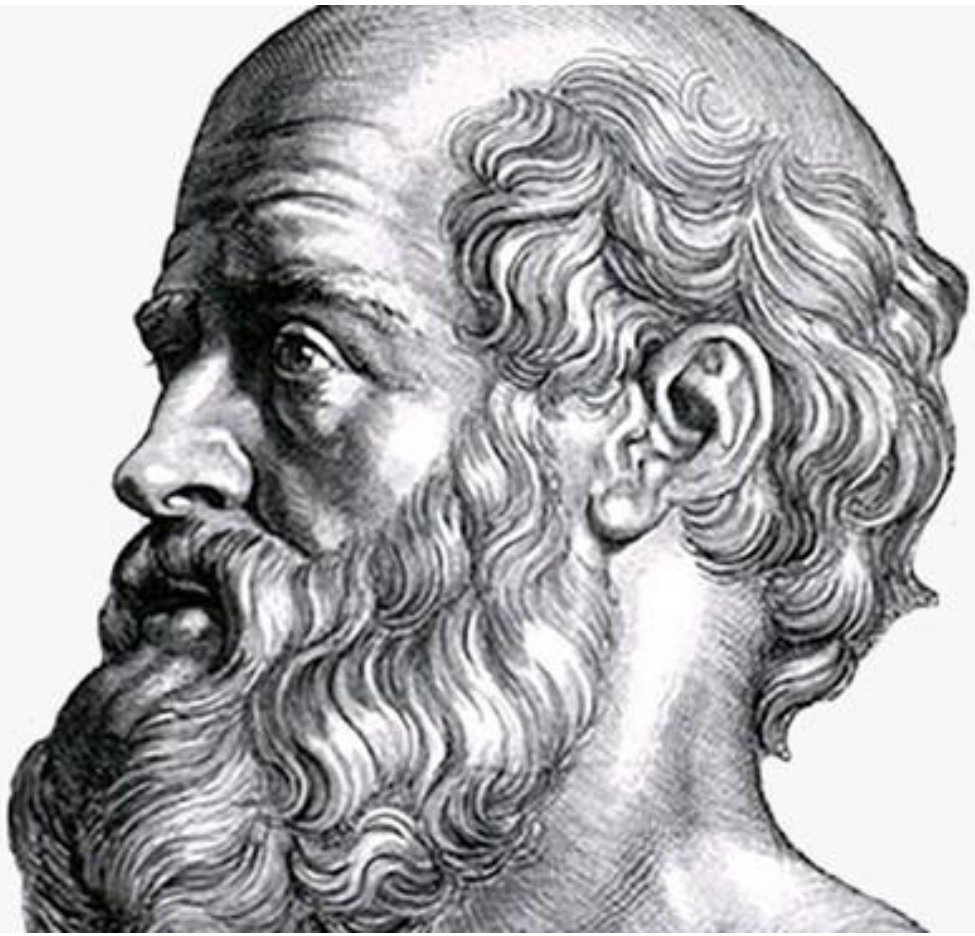
TRIAL METRICS	Relapse Prevention (*i.e.,* Maintenance) Design
N	~1000-1100
Pt. Population	• 18 Year of Age or Older
Design Details	• Open label stabilization phase of up to 20 weeks followed by randomization and 28 week double blind prevention study
Inclusion	• Open Label Phase: Bipolar I (DSM-IV)Bipolar I; At least 1 manic, mixed manic or depressed episode within 2 years; YMRS or MADRS total score ≥ 14 on Li or DVP. ≥ 18 if not. • Double Blind Phase: Consistent clinical stability, defined as ≤ 12 on the YMRS and MADRS over at least 12 weeks, with the allowance of two excursions (YMRS and/or MADRS total scores up to 13 or 14, respectively) except during the last 4 weeks before randomization
Exclusion	• Open Label Phase: Diagnosis of Axis I or Axis II disorder (other than BPI) within 3 months; subjects whom diagnostic agreement between investigator and CRO cannot be reached; ultra fast cycling; substance abuse; unstable medical illness; suicidal ideation • Double Blind Phase: Subjects who have not been compliant within stabilization phase; subjects who have not stabilized during open label phase; drug abuse
Allocation	• Randomized
Intervention Model	• Parallel Assignment
Masking	• Double Blind (Note: Stabilization phase is open label)
Arms	1. Exp. Active + Li/DVP 2. Placebo = Li/DVP
Length	• Open Label: Up to 20 Weeks • Double Blind Phase: 28 Weeks
Primary Outcome	• Time to recurrence of mood event during the double blind treatment phase [Time Frame: 28 weeks][Designated as safety issue: No]
Secondary Outcome	• Global severity assessed by the Clinical Global Impression-Bipolar Version-Severity of Illness [Time Frame: 28 weeks] [Designated as safety issue: No]
US + ROW Sites	21 US + 83 ROW = 94 Total

‘Evidence’ versus ‘effectiveness’



"It is far more important to know what person the disease has, than what disease the person has."

Hippocrates
(ca. 400 BCE)

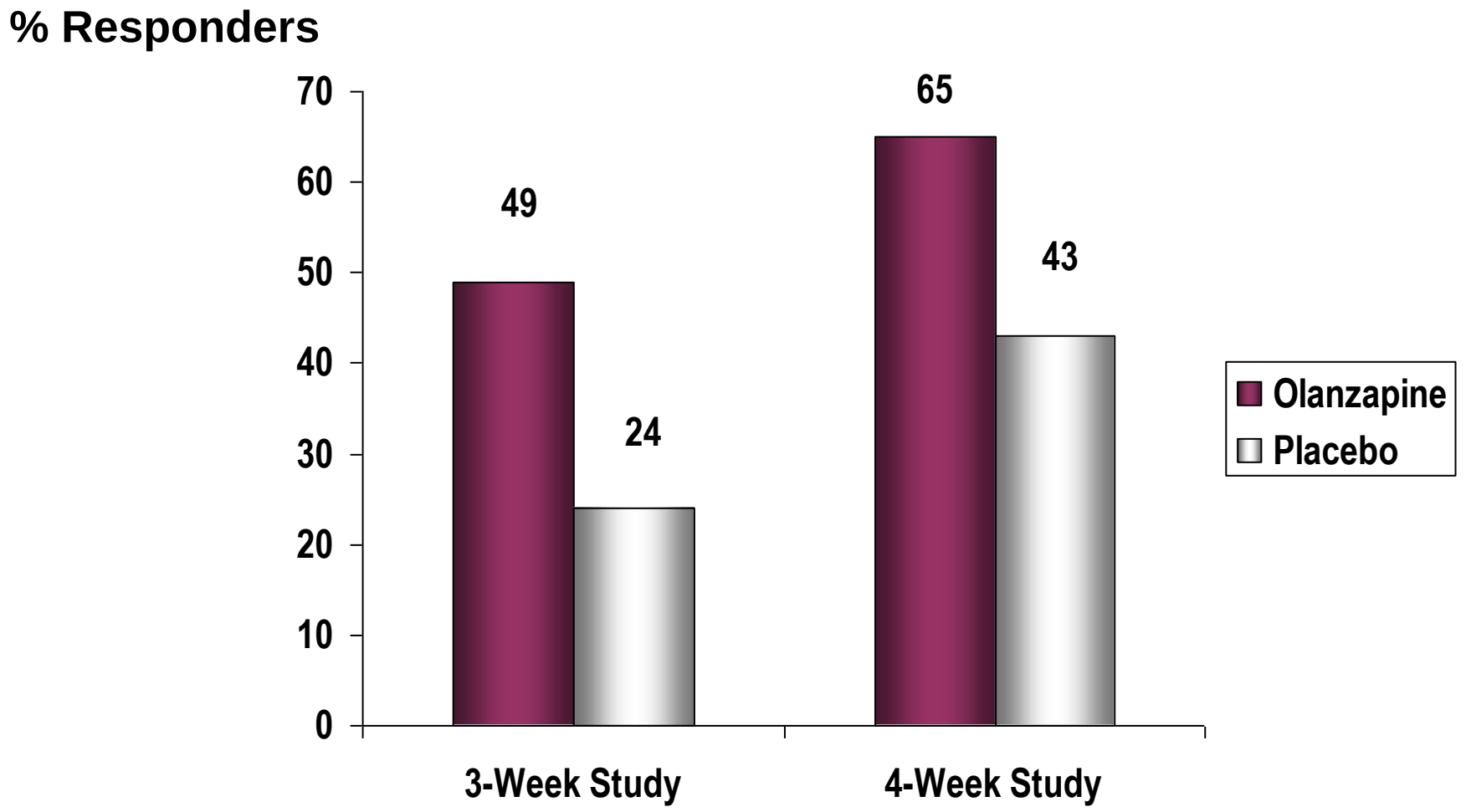


Range of movement after thoracotomy

Placebo Analgesia

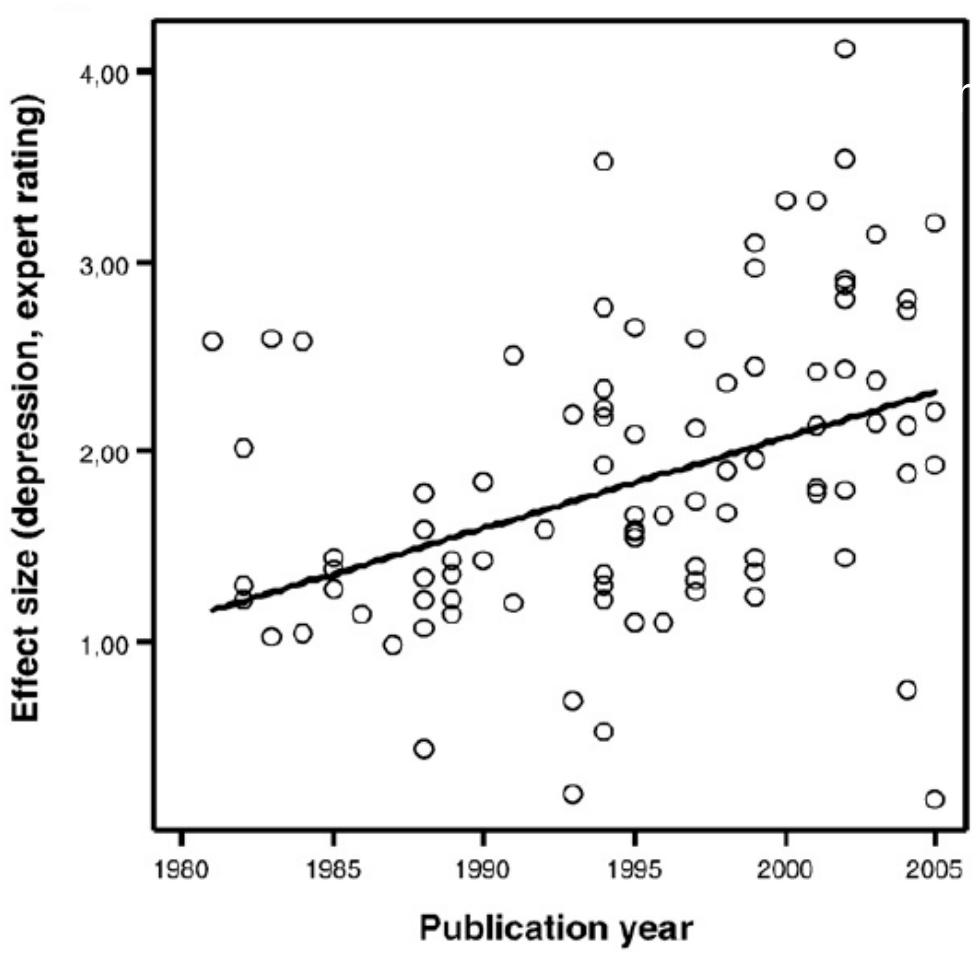
Courtesy of Fabrizio Benedetti

Placebo response may be high, even in acute Mania



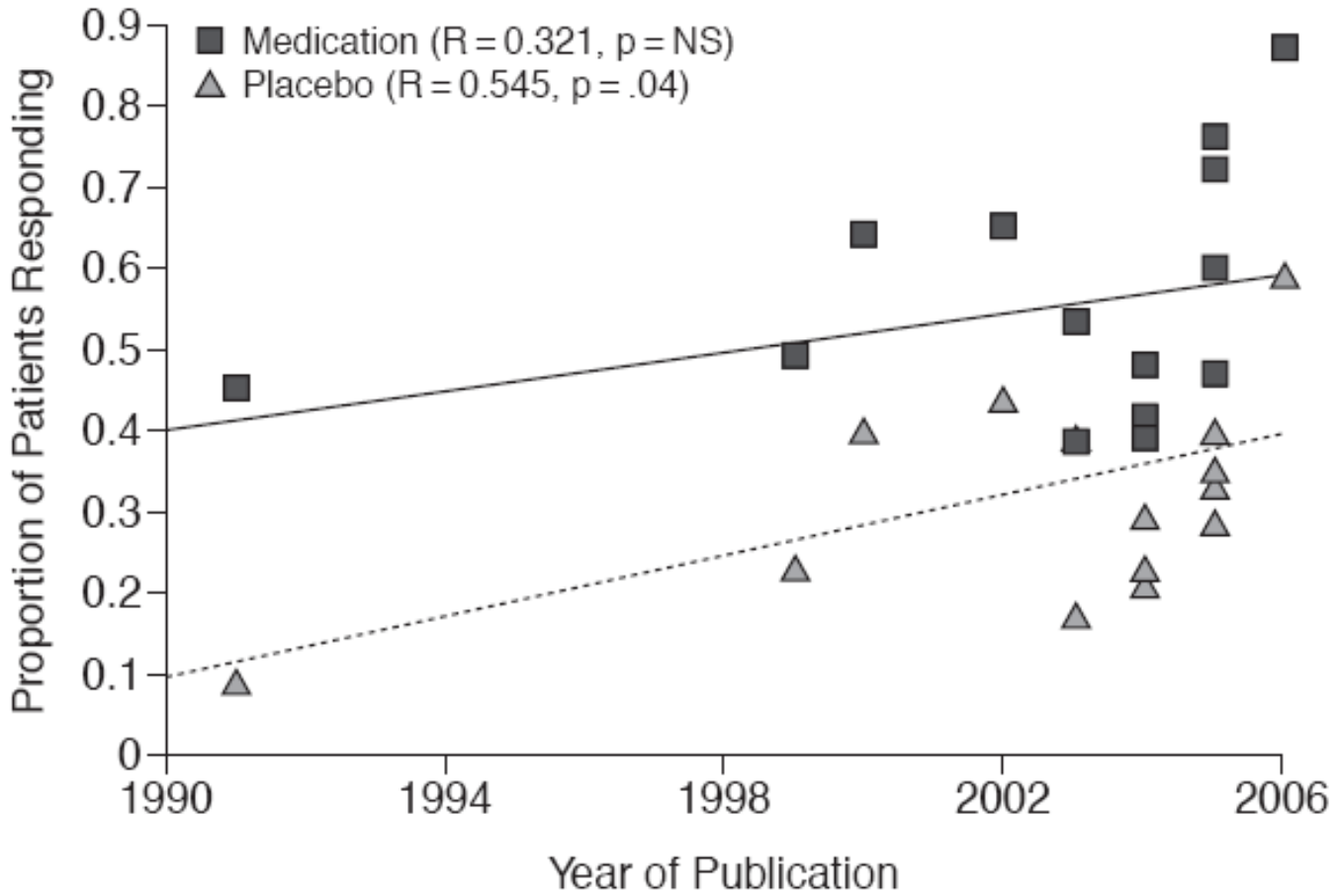
Tohen et al 1999 and 2000

Increased Placebo response over time in Depression Trials



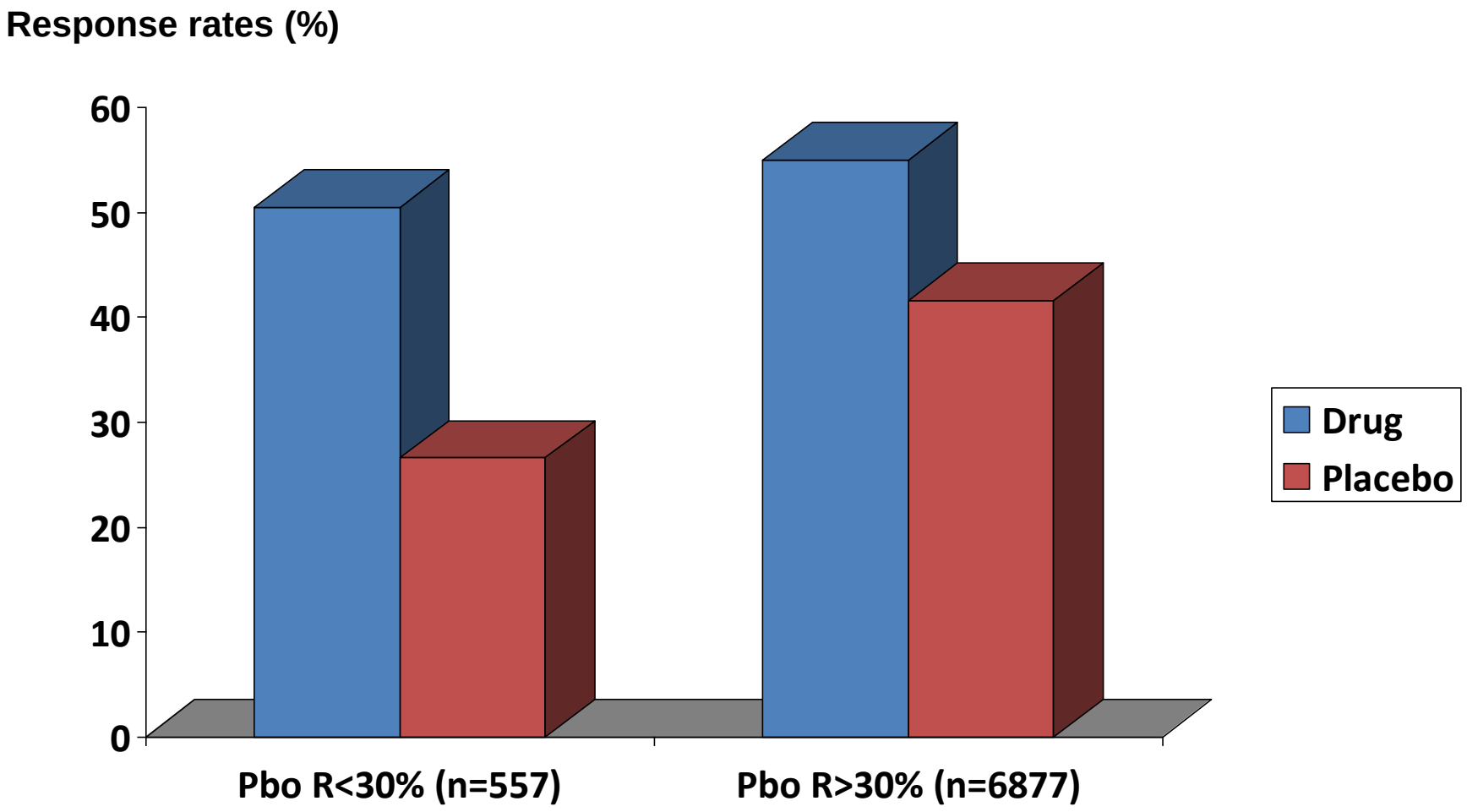
Rief et al, JAD 2009

Figure 1. Proportion of Patients Who Showed a 50% or Greater Improvement in Young Mania Rating Scale Score by Year of Publication



Sysko & Walsh, J Clin Psychiatry 2007; Vieta & Cruz, J Clin Psychiatry 2008

Efficacy of drug versus placebo as a function of placebo response rates in bipolar depression trials



Iovieno et al, IJNP 2016

Reasons for Placebo response in Bipolar Disorder Trials

1. Less severe populations
2. Continued care in trial
3. Collaborative patients
4. “Professional” patients
5. Subjective outcome measures
6. Spontaneous remission
7. Diagnostic uncertainity
8. Benzos and hypnotics allowed
9. Rater drift and “noise”
10. Baseline inflation
11. Regression to the mean
12. Trial design and expectations

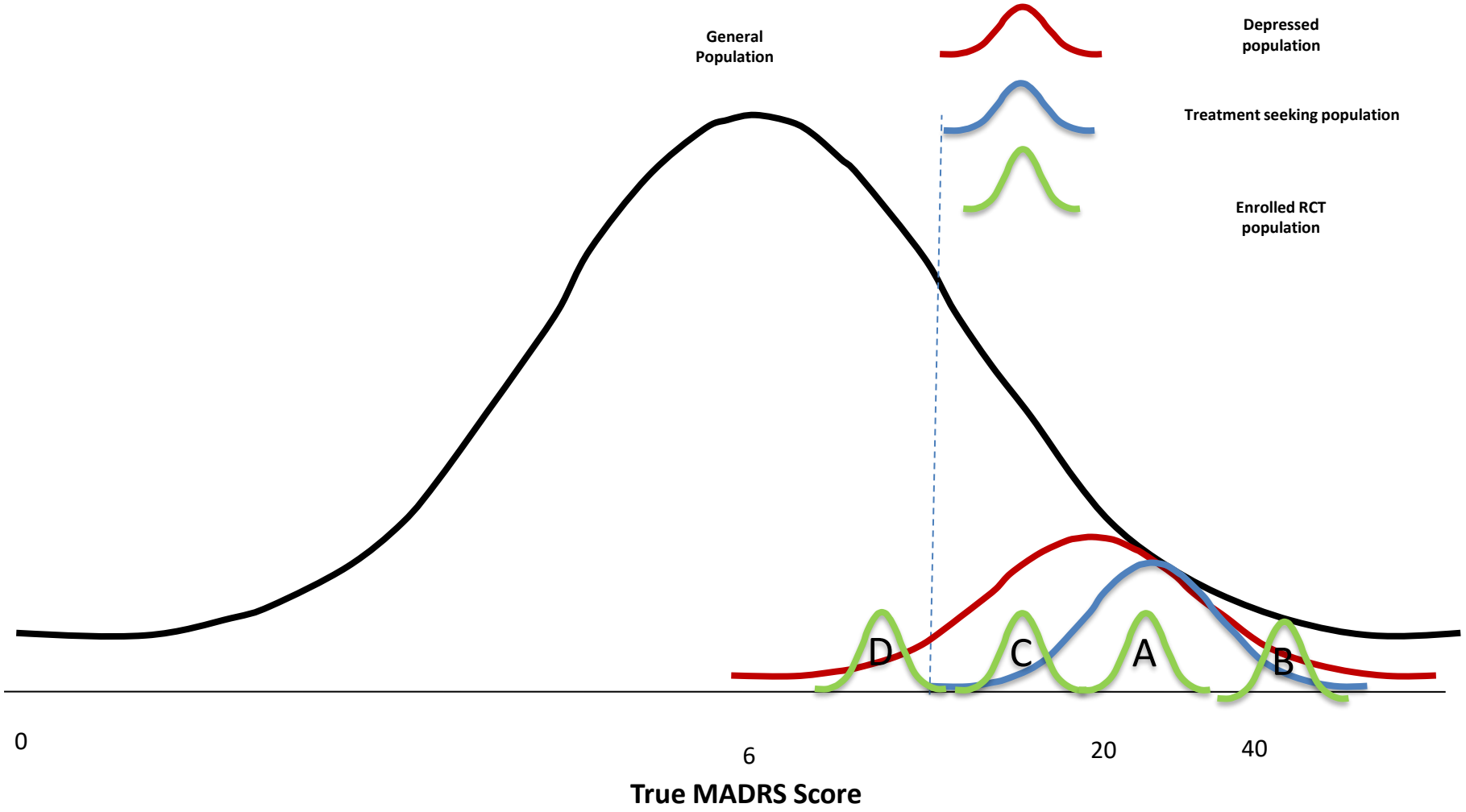
Vieta & Carne, Psychotherapy Psychosom 2005

What leads the increase in placebo response over time?

Variable	Reason
1. Less severe populations	Increased ethical standards
2. Continued care in trial	Financial incentives
3. Collaborative patients	Both of the above
4. “Professional” patients	Financial incentives
5. Subjective outcome measures	Lack of biomarkers
6. Spontaneous remission	Trial design
7. Diagnostic uncertainity	Emphasis on paperwork over inner quality
8. Benzos and hypnotics allowed	Feasibility
9. Rater drift and “noise”	Cost issues: multisite studies
10. Baseline inflation	Financial incentives
11. Regression to the mean	Financial incentives and cost issues
12. Trial design and expectations	High patient & investigator motivation

Vieta, 2015

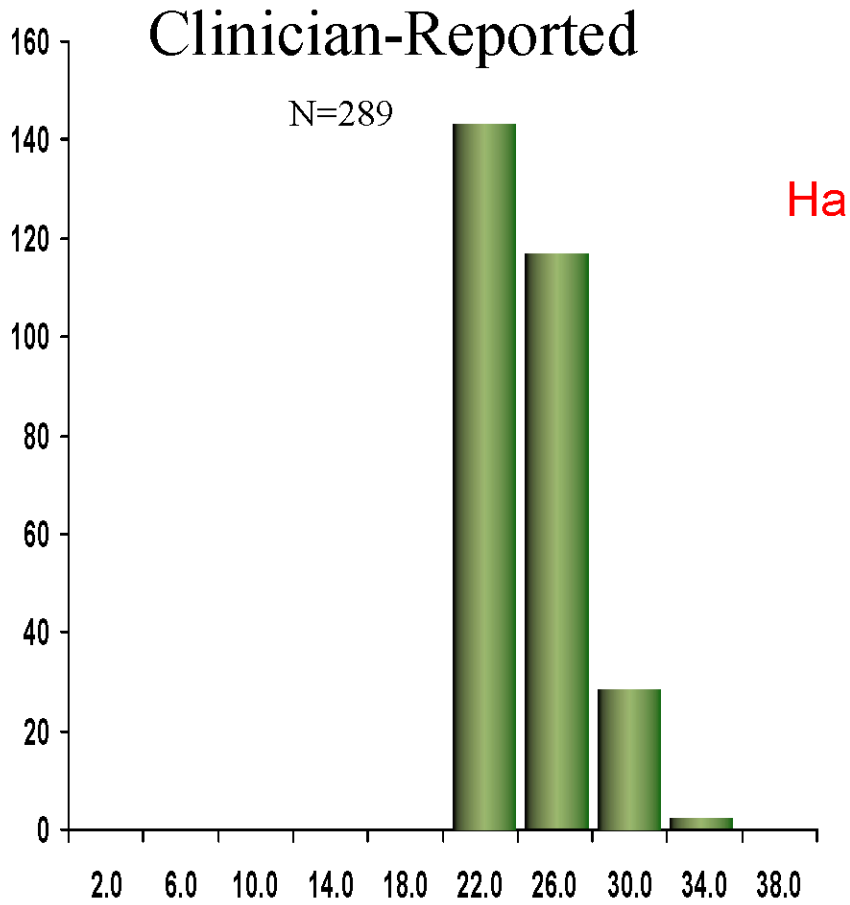
When are clinical trials most likely to succeed?

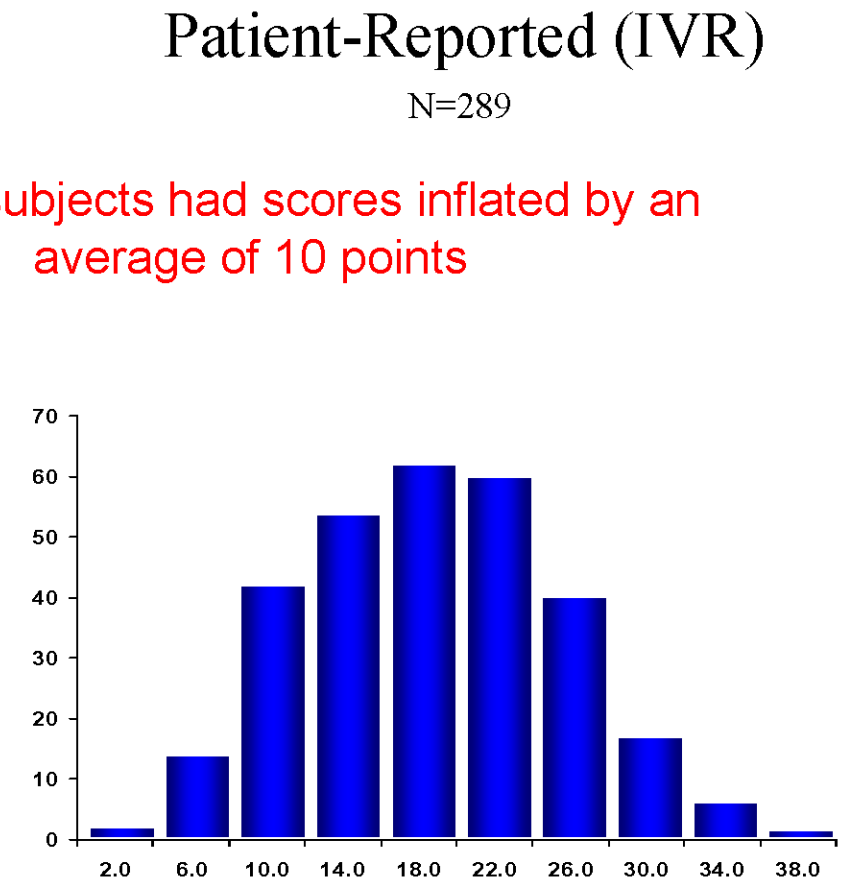


Sachs, 2001

Antidepressant RCT: Baseline HAM-D Ratings

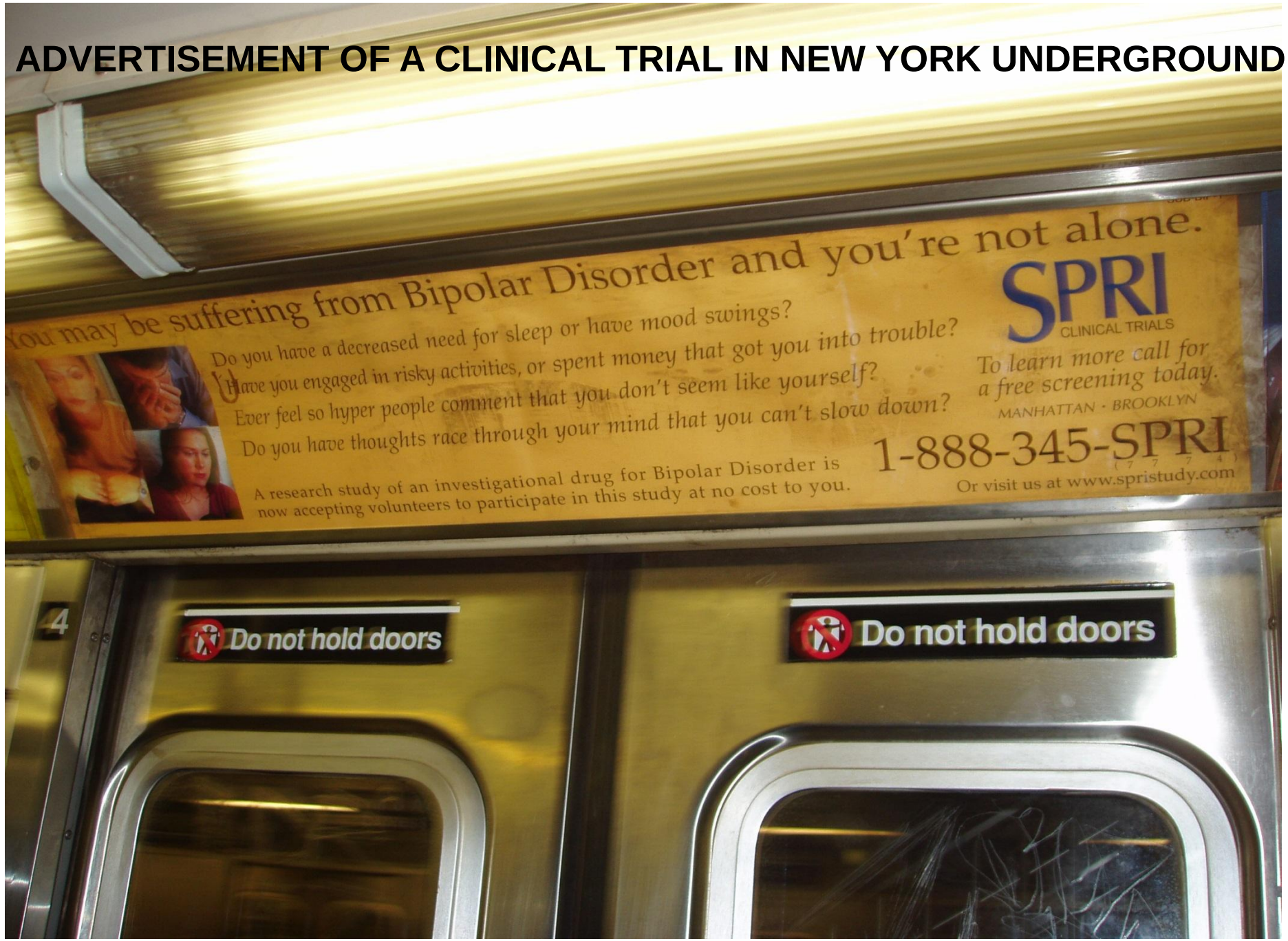
Evidence of Baseline Inflation



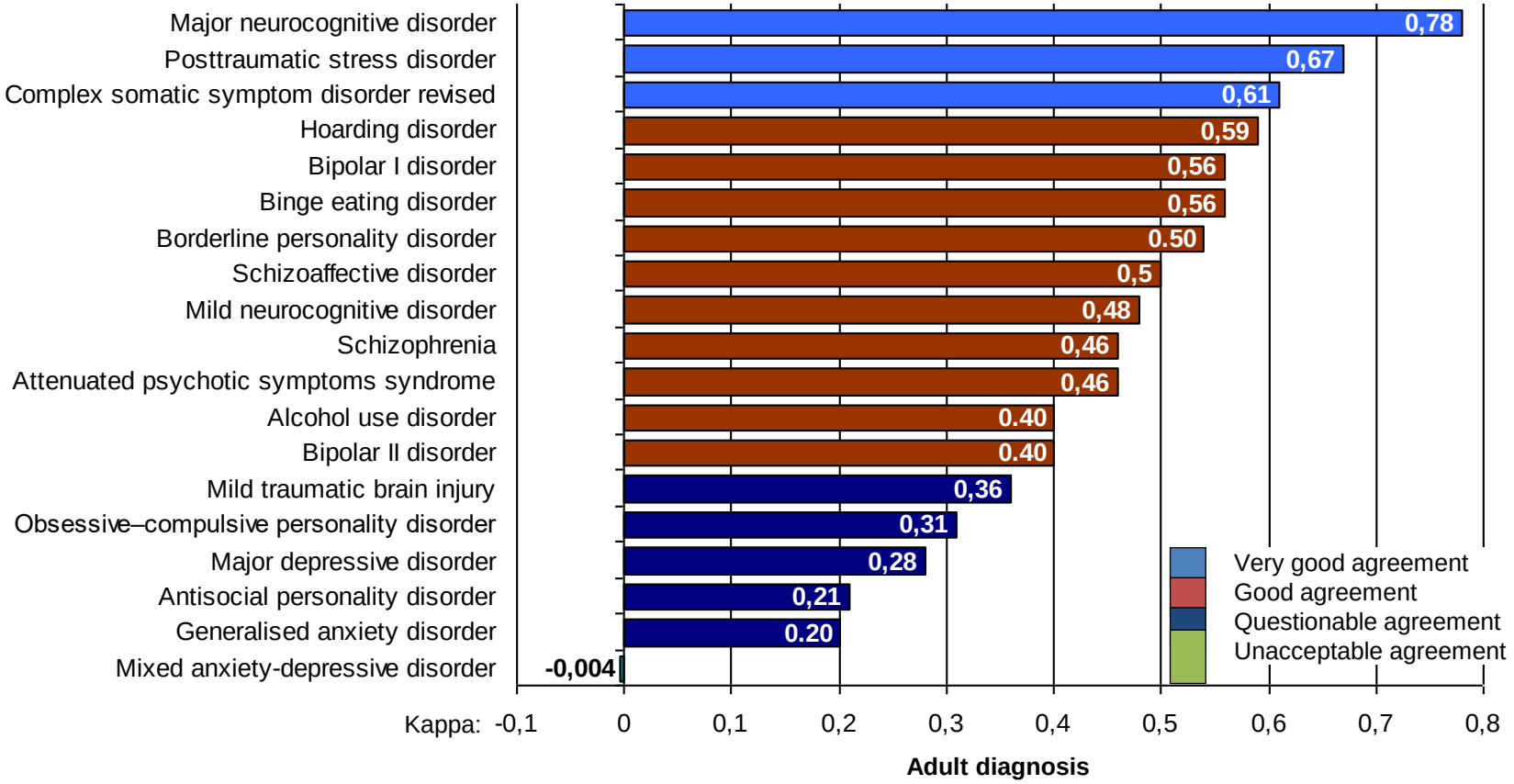


Half the subjects had scores inflated by an average of 10 points

ADVERTISEMENT OF A CLINICAL TRIAL IN NEW YORK UNDERGROUND

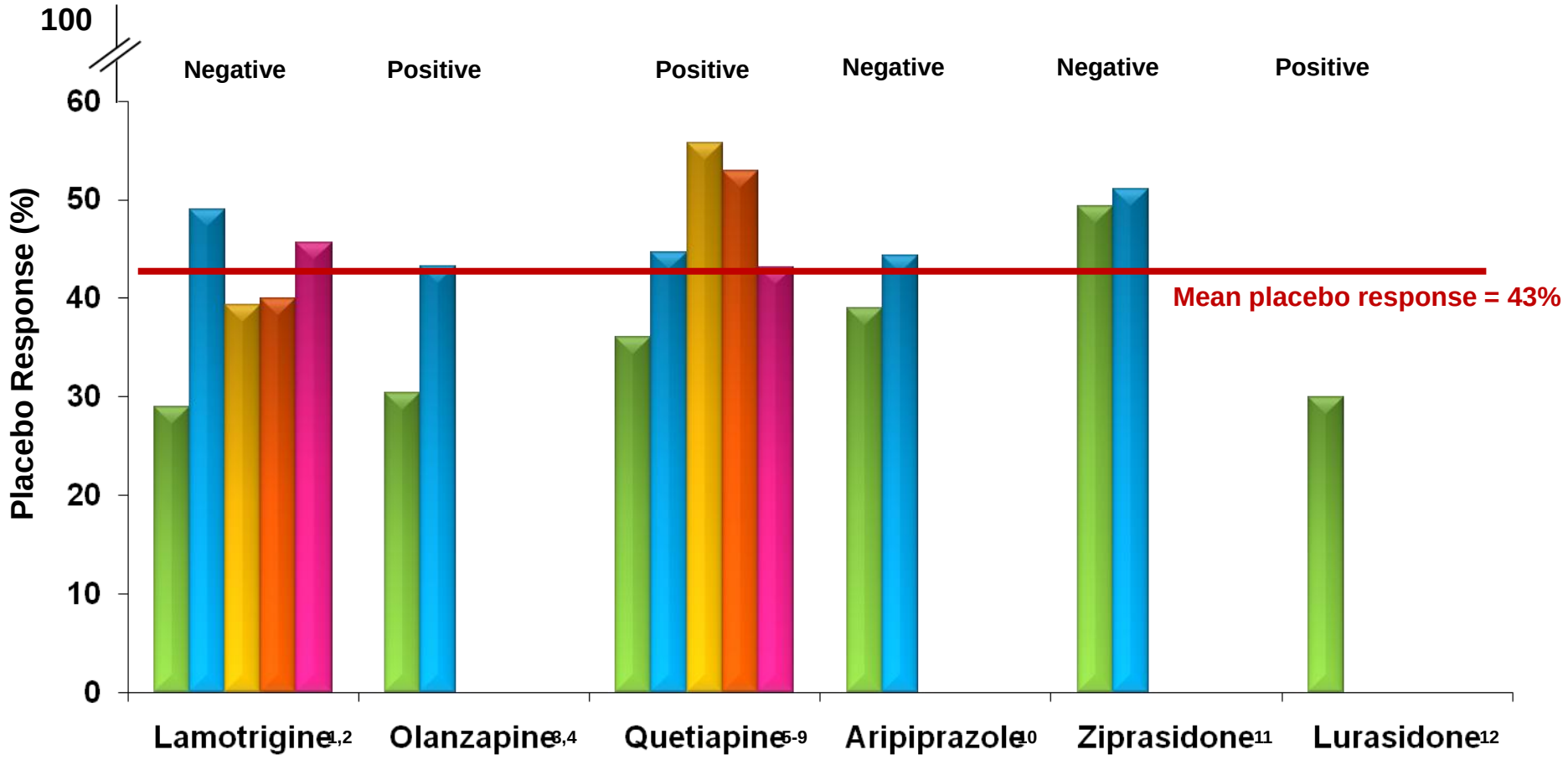


A critical problem: phenotype reliability (DSM-5)



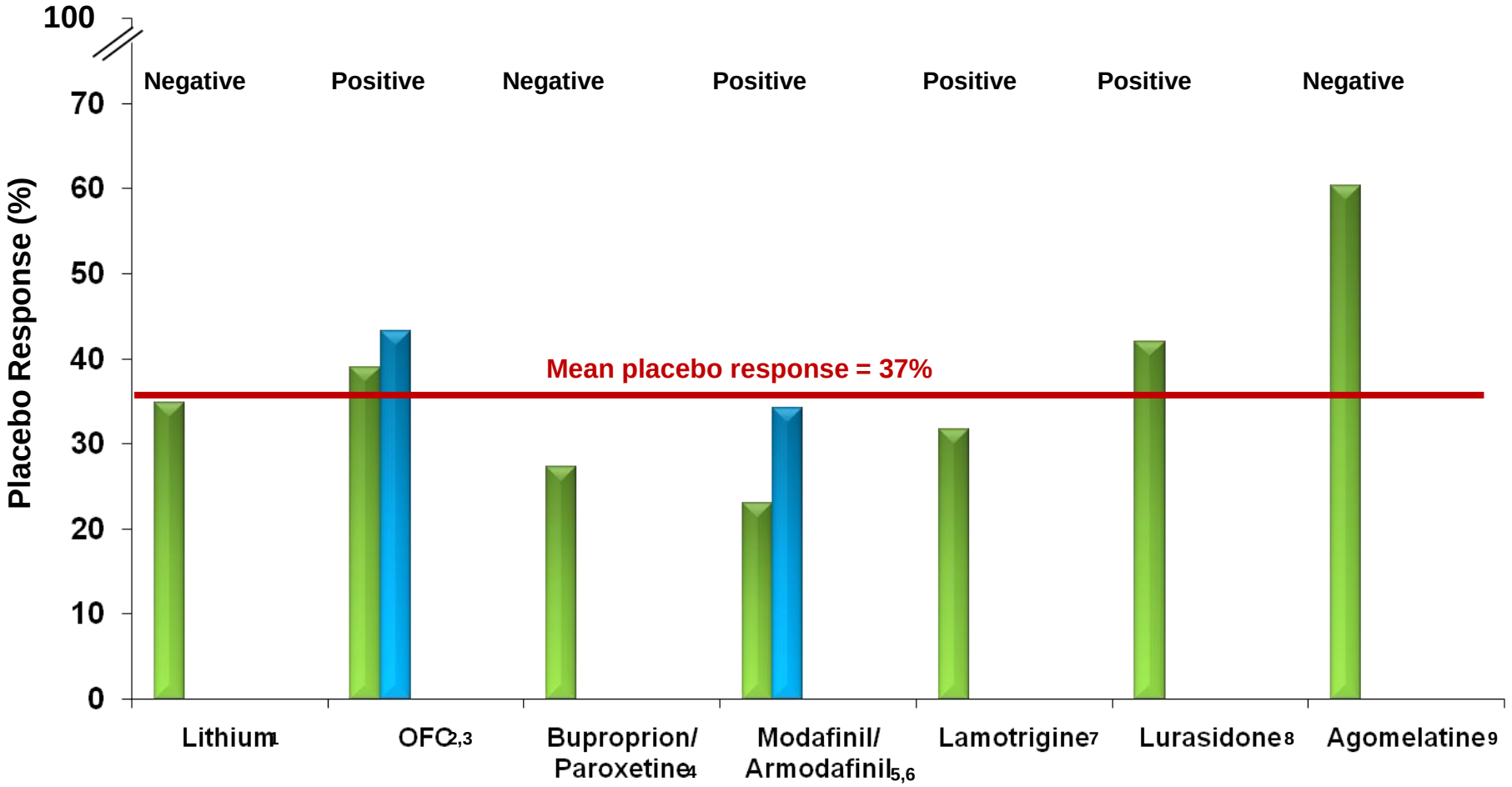
Freedman et al, Am J Psychiatry 2013

Placebo Response Rates in Monotherapy Trials of Acute Bipolar Depression



1. Calabrese JR, et al. *J Clin Psychiatry*. 1999;60(2):79-88. 2. Calabrese JR, et al. *Bipolar Disord*. 2008;10(2):323-333. 3. Tohen M, et al. *Br J Psychiatry.* 2012;201(5):376-382. 4. Tohen M, et al. *Arch Gen Psychiatry*. 2003;60(11):1079-1088. 5. Young AH, et al. *J Clin Psychiatry*. 2010;71(2):150-162. 6. McElroy SL, et al. *J Clin Psychiatry*. 2010;71(2):163-174. 7. Thase ME, et al. *J Clin Psychopharmacol*. 2006;26(6):600-609. 8. Calabrese JR, et al. *Am J Psychiatry*. 2005;162(7):1351-1360. 9. Suppes T, et al. *J Affect Disord*. 2010;121(1-2):106-115. 10. Thase ME, et al. *J Clin Psychopharmacol*. 2008;28(1):13-20. 11. Lombardo I, et al. *J Clin Psychopharmacol*. 2012;32(4):47-48. 12. Loebel A, et al. *Am J Psychiatry*. 2014;171(2):160-168.

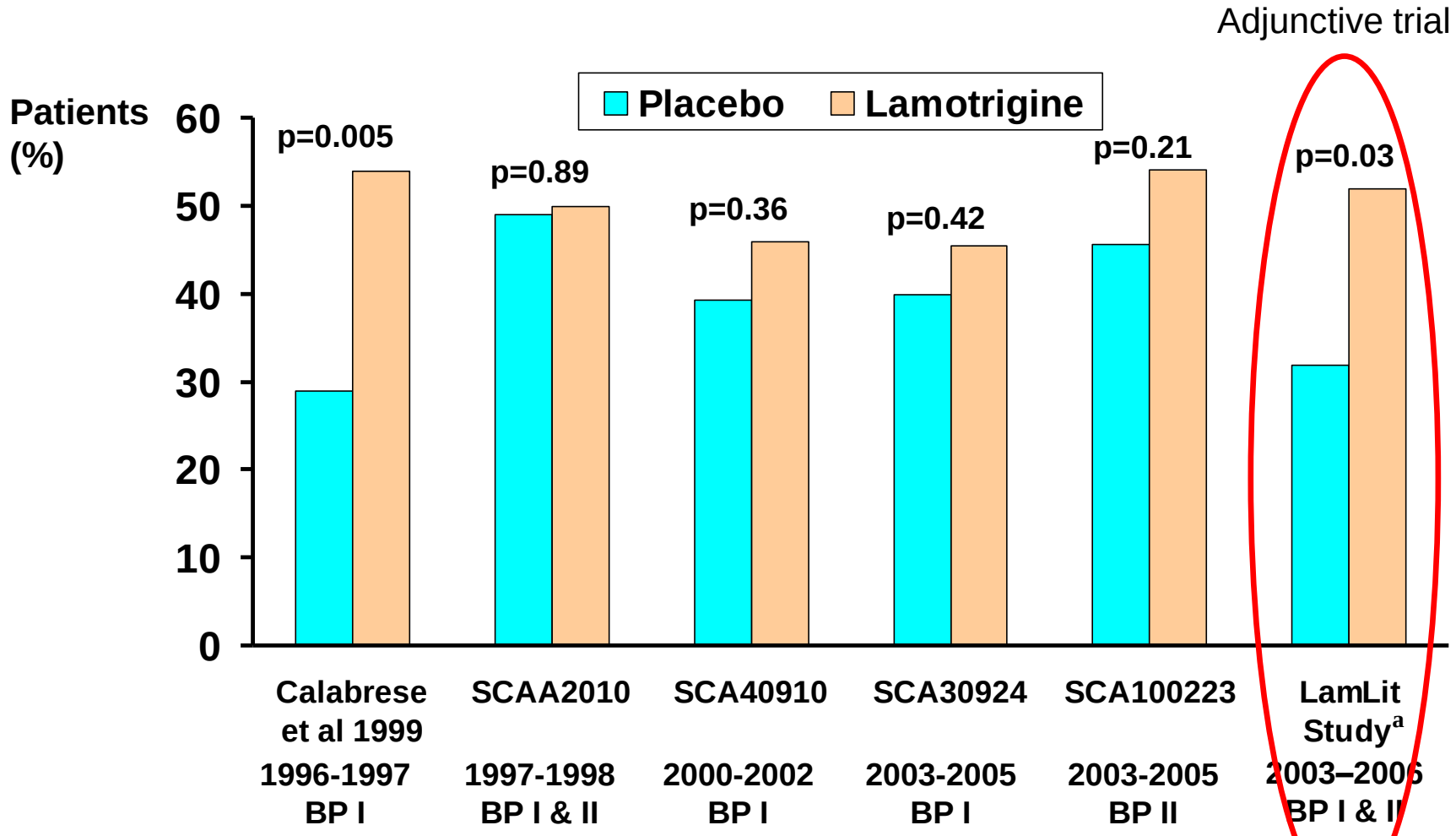
Placebo Response Rates in Adjunctive Therapy Trials of Acute Bipolar Depression



OFC, olanzapine-fluoxetine combination.

1. Nemeroff CB, et al. *Am J Psychiatry*. 2001;158(6):906-912. 2. Tohen M, et al. *Arch Gen Psychiatry*. 2003;60(11):1079-1088. 3. SYMBYAX [package insert]. Indianapolis, IN: Eli Lilly and Company; 2013. 4. Sachs GS, et al. *N Engl J Med*. 2007;356(17):1711-1722. 5. Frye M, et al. *Am J Psychiatry*. 2007;164(8):1242-1249. 6. Ketter T, et al. Poster presented at: 25th Annual US Psychiatric and Mental Health Congress; November 8-11, 2012; San Diego, CA. 7. van der Loos ML, et al. *J Clin Psychiatry.* 2009;70(2):223-231. 8. Loebel A, et al. *Am J Psychiatry*. 2014;171(2):169-177. 9. Yatham LN, et al. Unpublished data.

MADRS response rates across six lamotrigine multicentre acute bipolar depression studies



MADRS response = 50% improvement over baseline

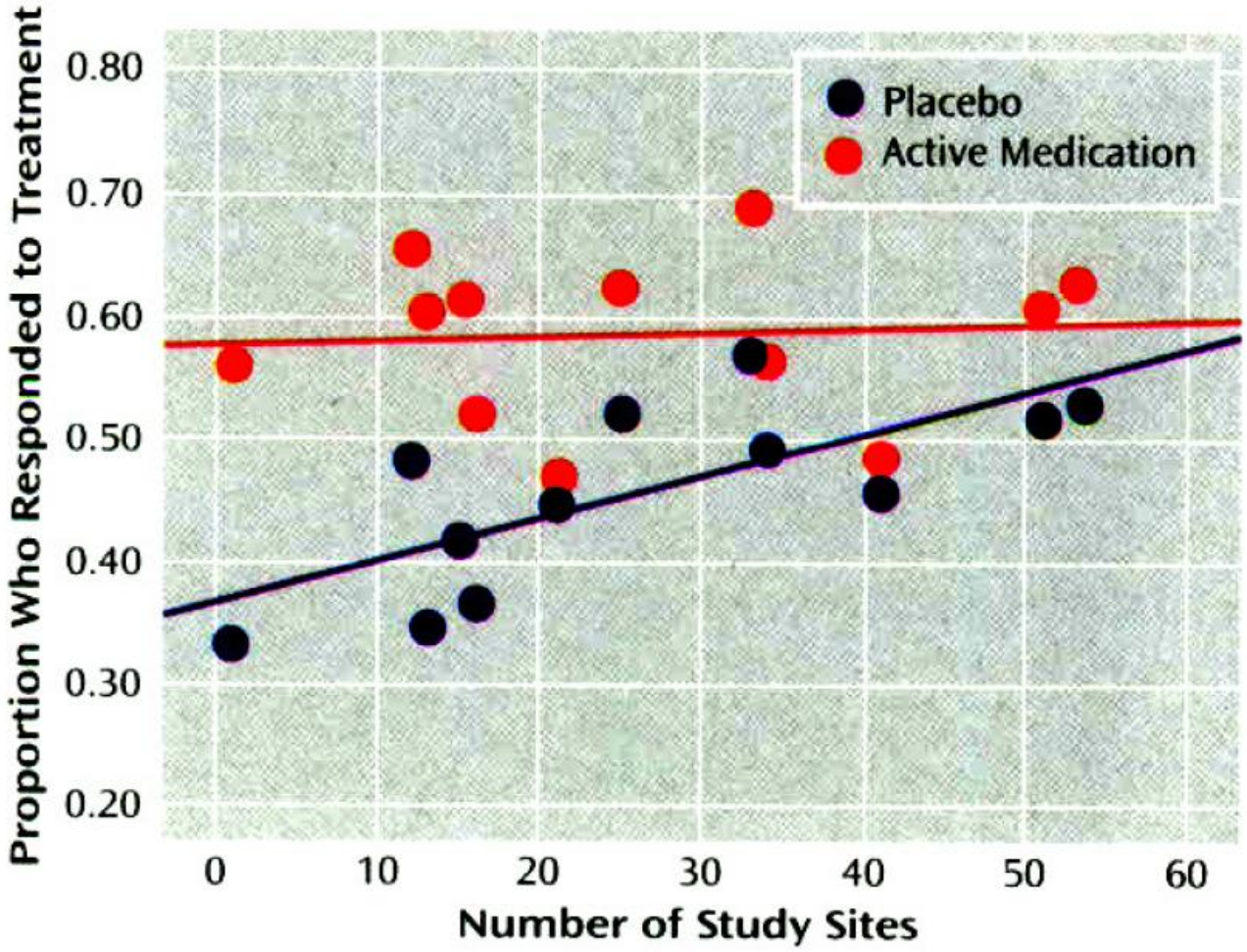
Pooled Relative Risk of Response: 1.22 CI 1.06-1.41. p=0.005. Geddes et al 2007

Calabrese et al 1999; Calabrese et al 2008;

[a]Van der Loos et al, 2009

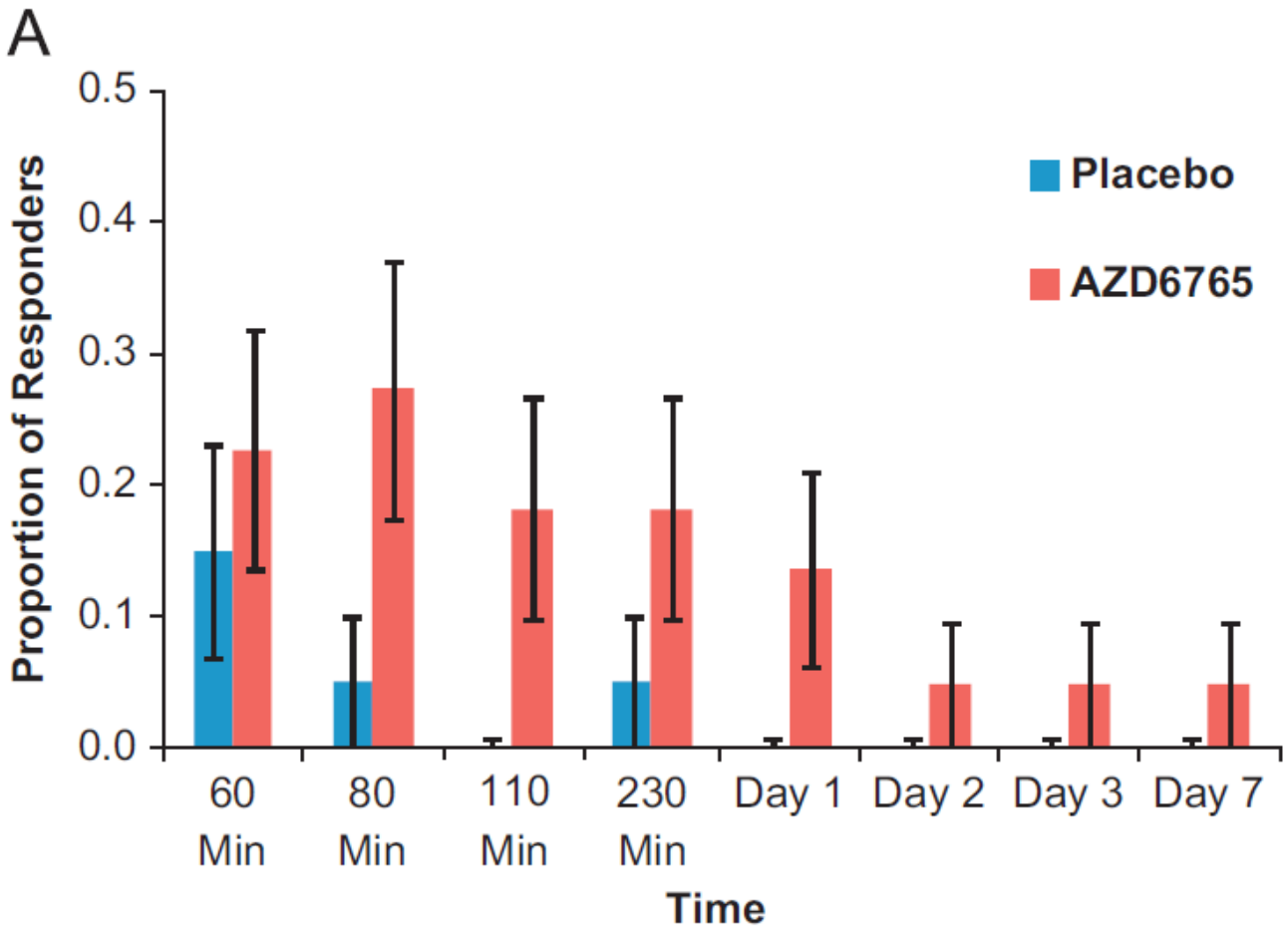
Placebo response and number of study sites

Placebo-controlled trials in Pediatric depression



Bridge et al, Am J Psychiatry 2009

Placebo response mimicks drug response: timing

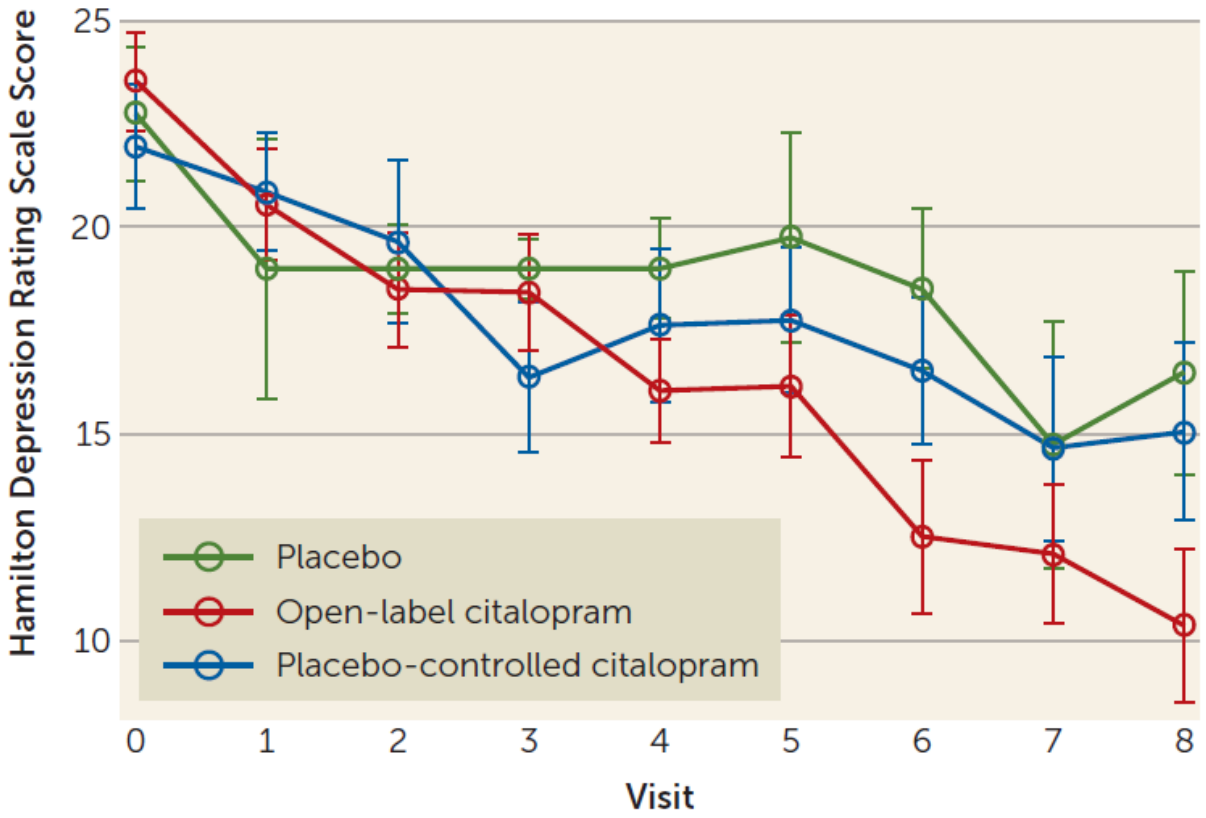


Zarate et al, Biol Psychiatry 2012

Patients' expectancy: Blinding mitigates drug response

PATIENT EXPECTANCY AND PLACEBO EFFECTS IN ANTIDEPRESSANT TRIALS

FIGURE 3. Change in Depressive Symptoms Over Time for Study Conditions[a]



[a] Error bars represent standard error.

Rutherford et al, Am J Psychiatry 2017

Table 2. Factors associated with improvement in mania ratings in placebo- and drug-arms, and drug-placebo contrasts.

Factors	Mania Improvement with Treatment		Drug–Placebo Contrasts
	Placebo	Drug	
More collaborating sites (n)	Increased	No Effect	Decreased
Sample size	Increased	No Effect	Decreased
Higher initial mania score	No Effect	Increased	Increased
Higher %-max mania score	No Effect	Increased	Increased
More with psychotic features (%)	Decreased	Increased	Increased
Younger age (years)	Decreased	Increased	Increased
More men (%)	Decreased	Increased	Increased
More mixed-state diagnoses (%)	No Effect	Decreased	Decreased
Trial completers: drug arms (%)	——	Increased	Increased
Trial completers: placebo arms (%)	Increased	——	No Effect

Only effective drugs were considered for drug effect and drug-placebo contrasts (N= 28 studies, 40 contrasts), but all available placebo arms were included for placebo effect, from randomized, monotherapy trials (N= 32 studies). Improvement was measured by MD, as defined in Methods.

Yildiz, et al, Int J Neuropsychopharmacol, 2011.

Body mass affects treatment response in depression

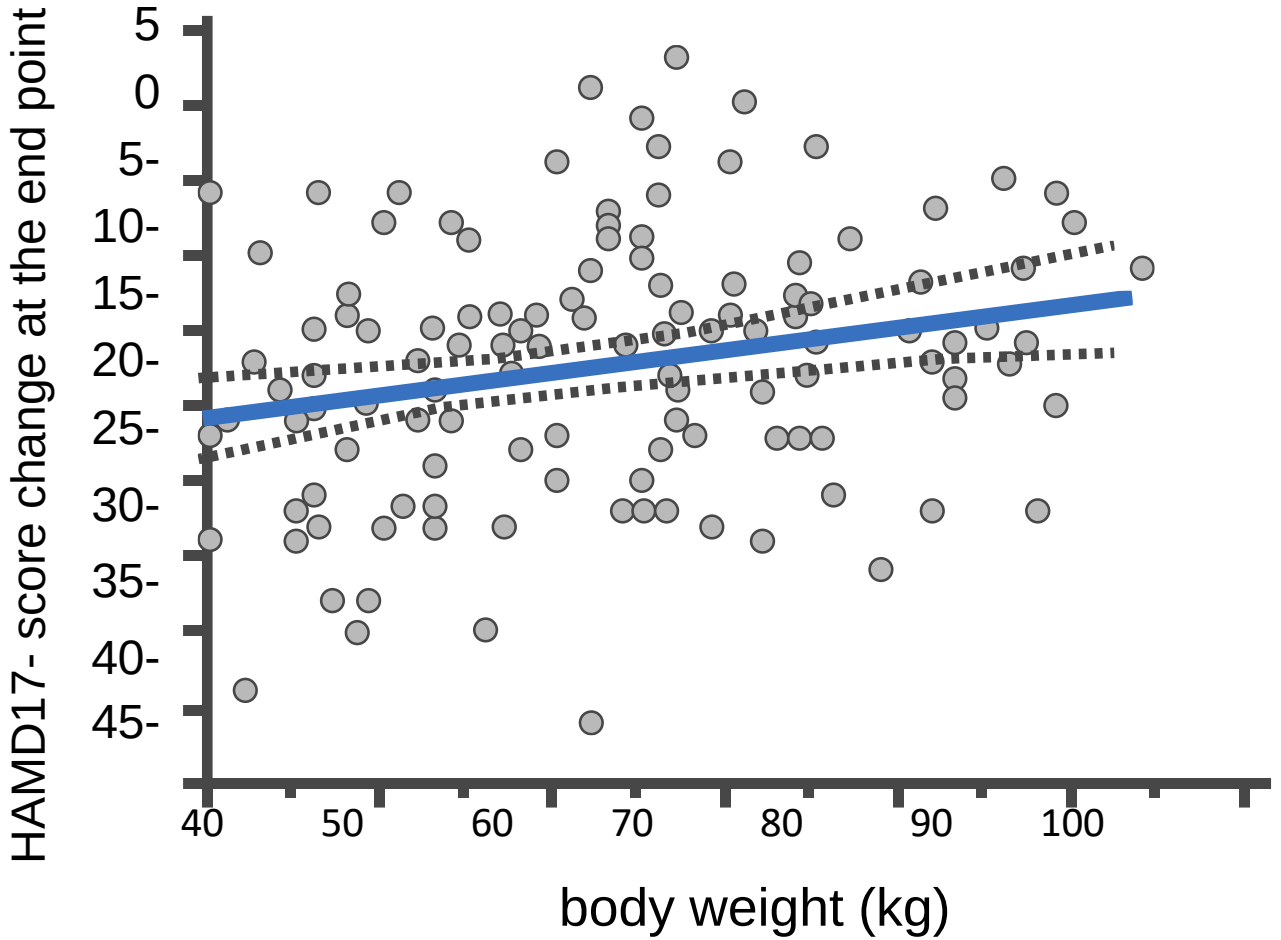
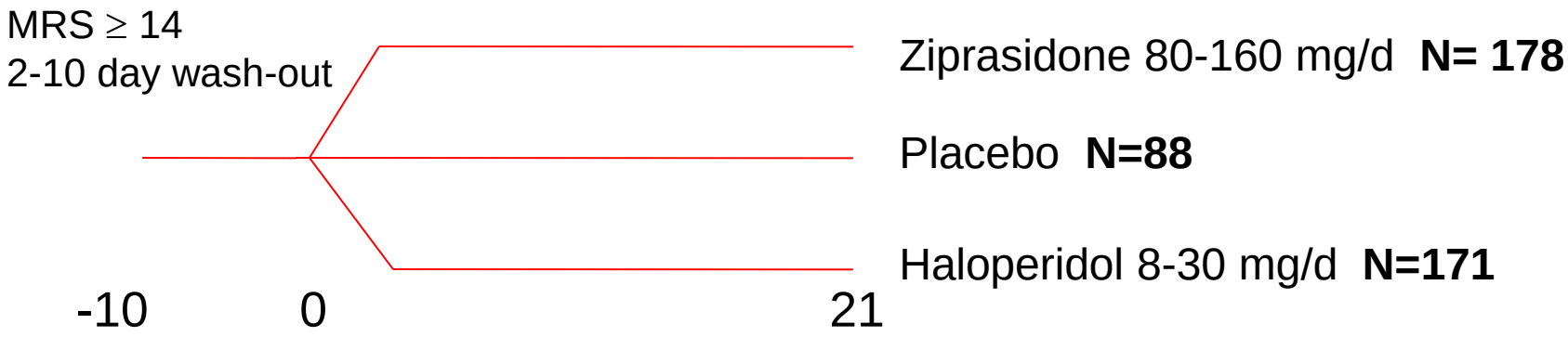


Fig. 1. Scatter plot of the association between the baseline body weight and the 17-item Hamilton Depression Rating Scale (HAMD-17) reduction at the end point

Lin CH et al, JAD 2014

Baseline geographical variations in clinical trials

3-week, double-blind, placebo and active controlled randomized multinational study on 438 adults with bipolar I disorder (most recent manic or mixed episode)



Vieta E, et al. *Int J Neuropsychopharmacol.* 2011.

Baseline geographical variations in clinical trials

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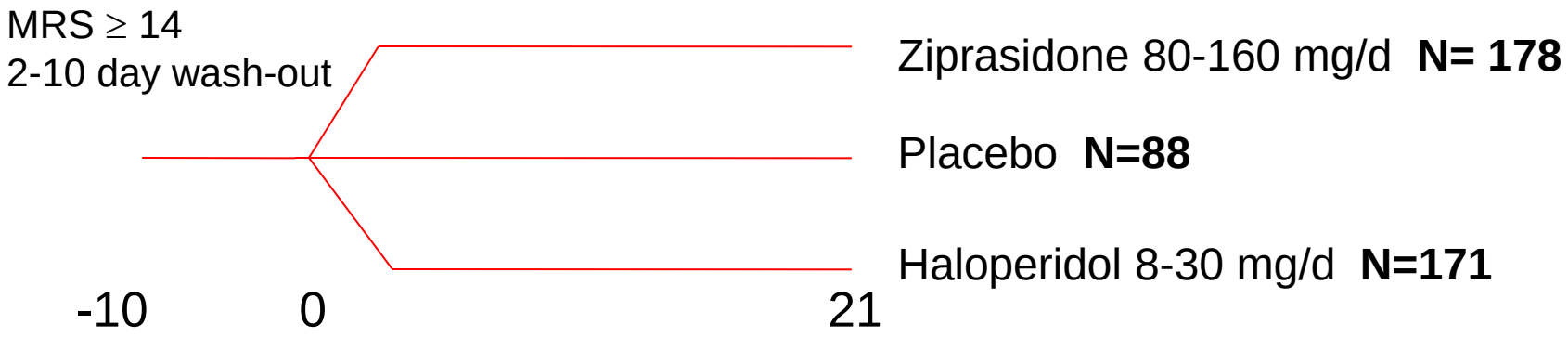
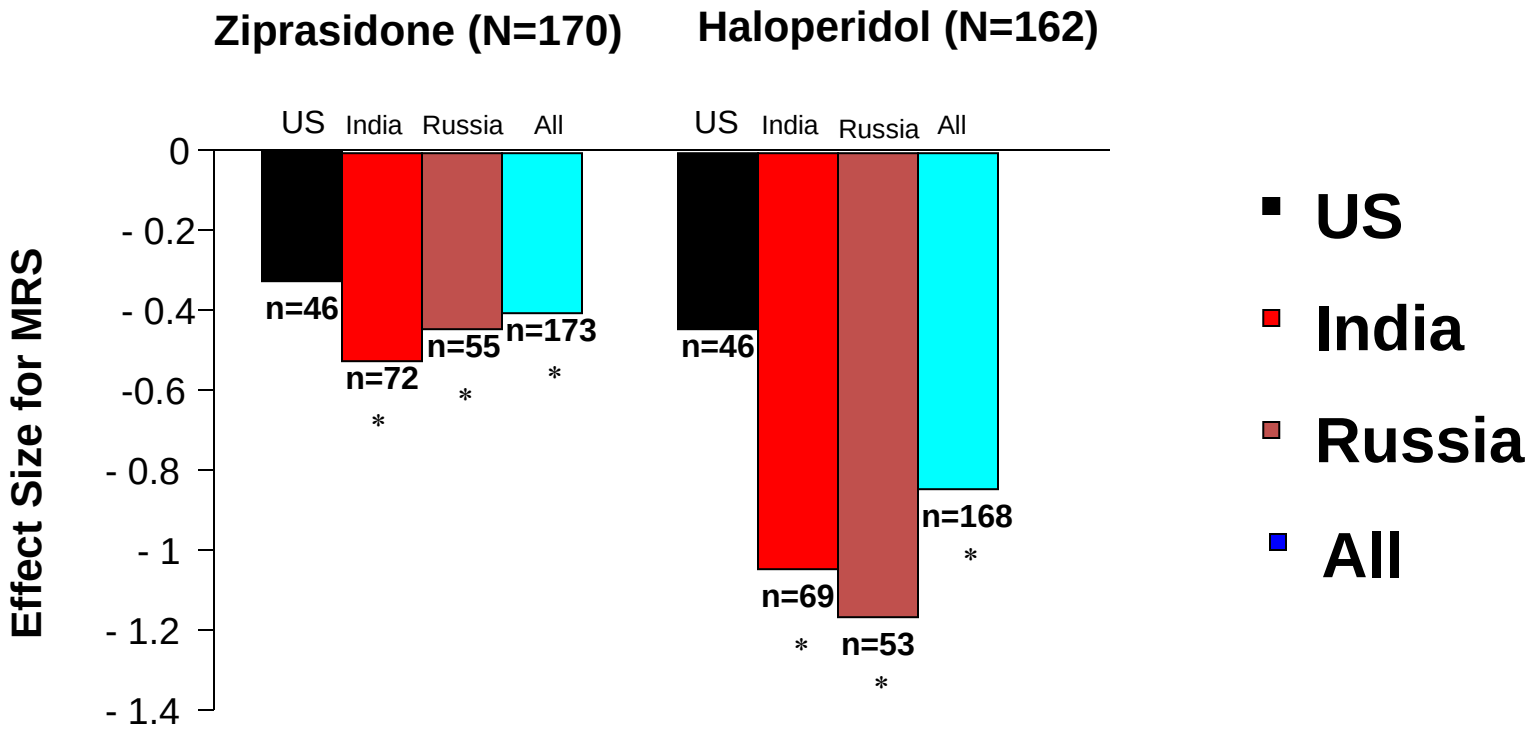


3 countries, 33 centers

	9 India	9 Russia	15 USA
Baseline severity	34.4	28	23.8
Baseline weight	57.1 Kg	73.9 Kg	82.4 Kg

Vieta E, et al. *Int J Neuropsychopharmacol.* 2011.

Country effect-size findings in MRS (week 3 LOCF*)

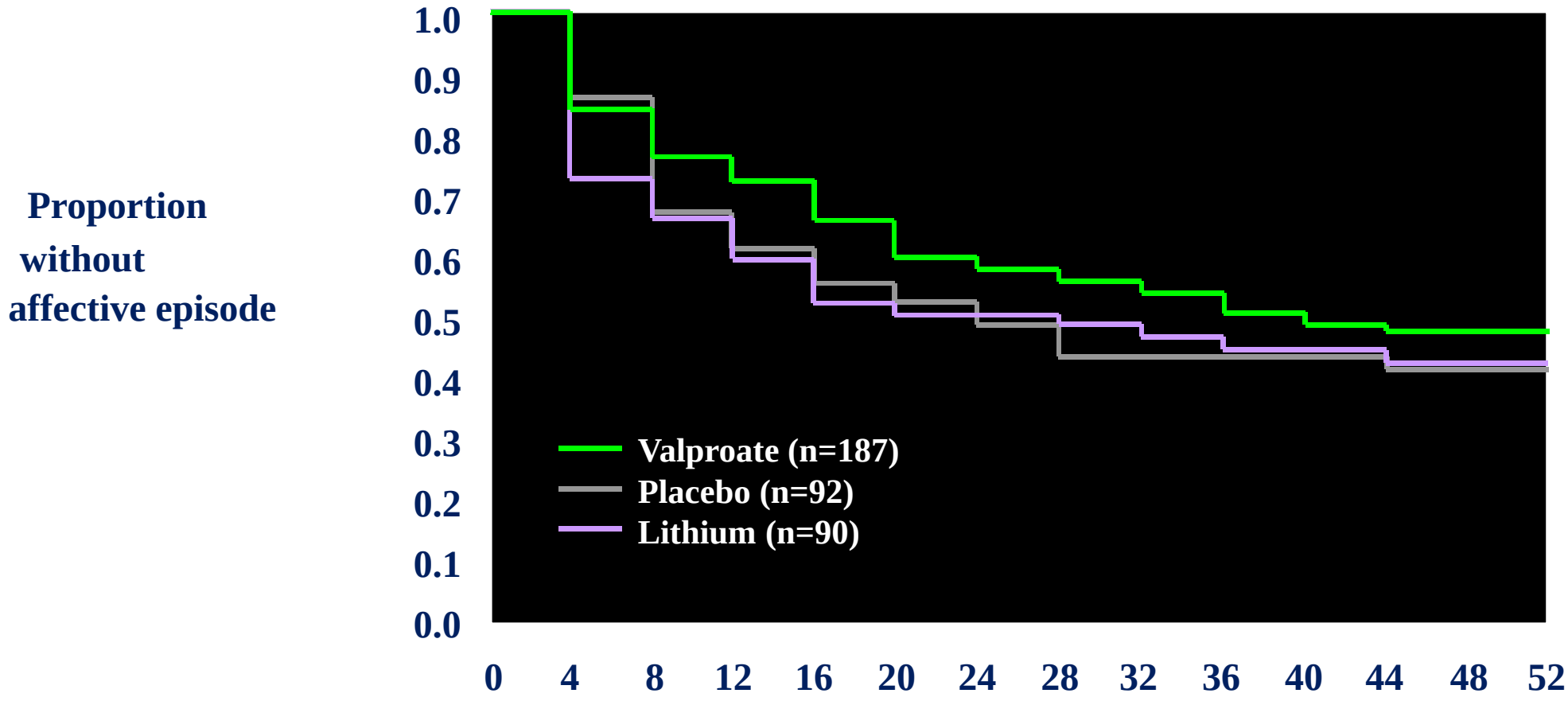


* *P* < 0.05 (95%) CI of effect size. Effect size (Cohen's *d)*= placebo corrected treatment effect/root mean square.

***** LOCF, last observation carried forward

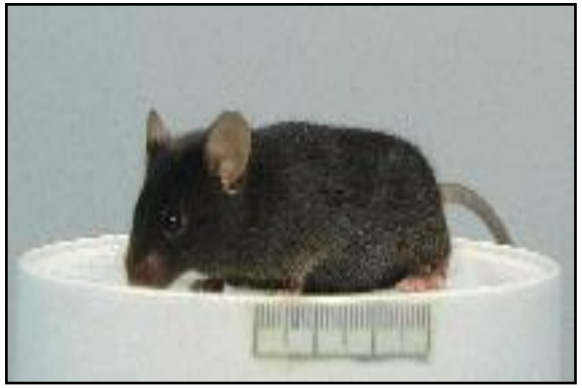
Vieta E, et al. *Int J Neuropsychopharmacol.* 2011.

Valproate vs Lithium vs Placebo
During the remission period

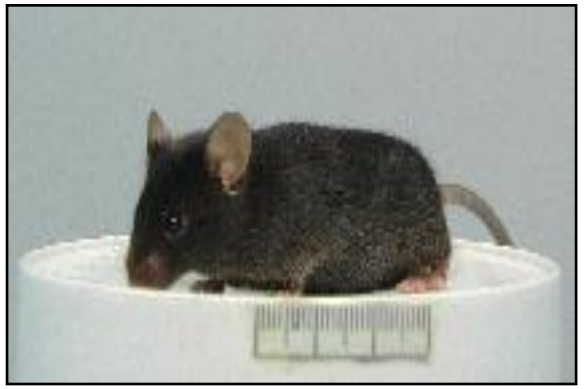


Bowden et al, 2000

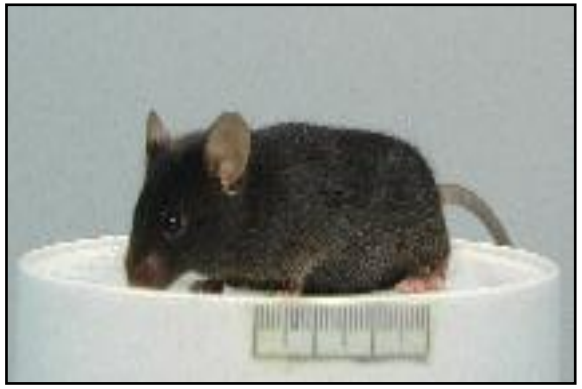
Animal models in Psychiatry



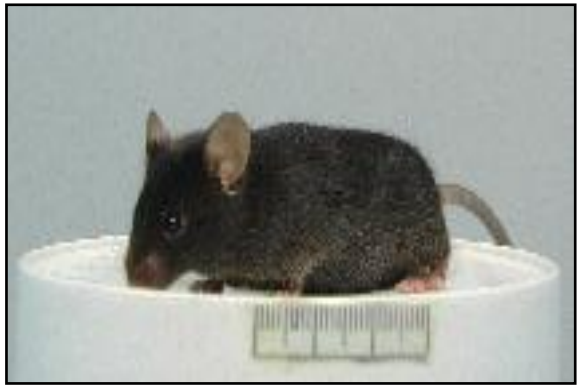
- Healthy mouse



- Manic mouse

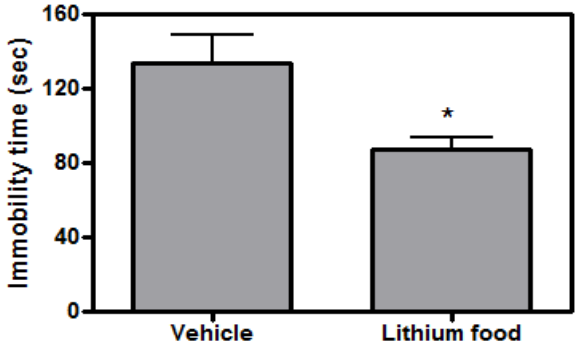


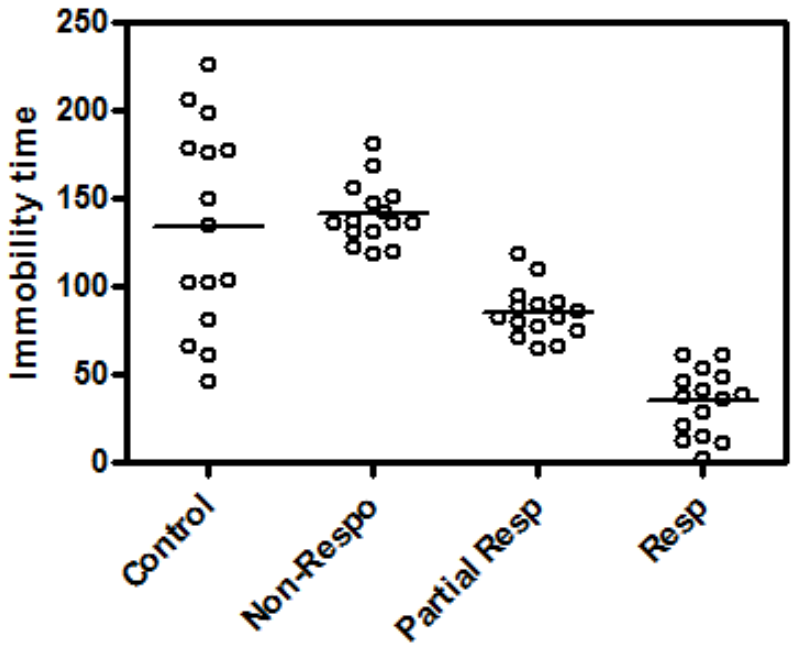
- Depressed mouse



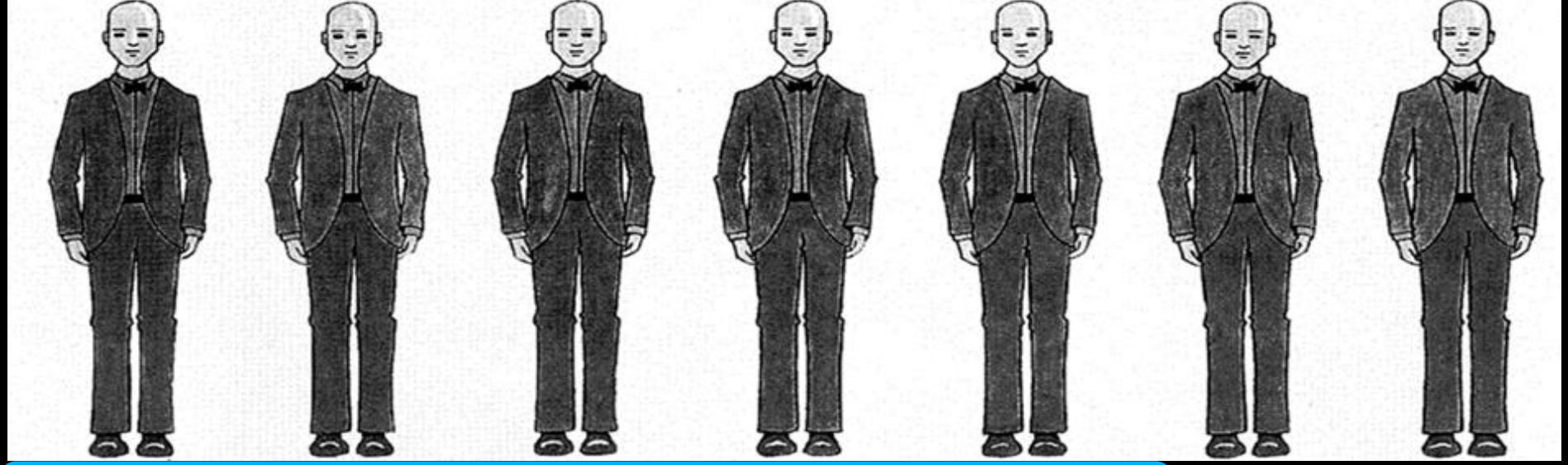
- Schizophrenic mouse

Variability of treatment response in mice





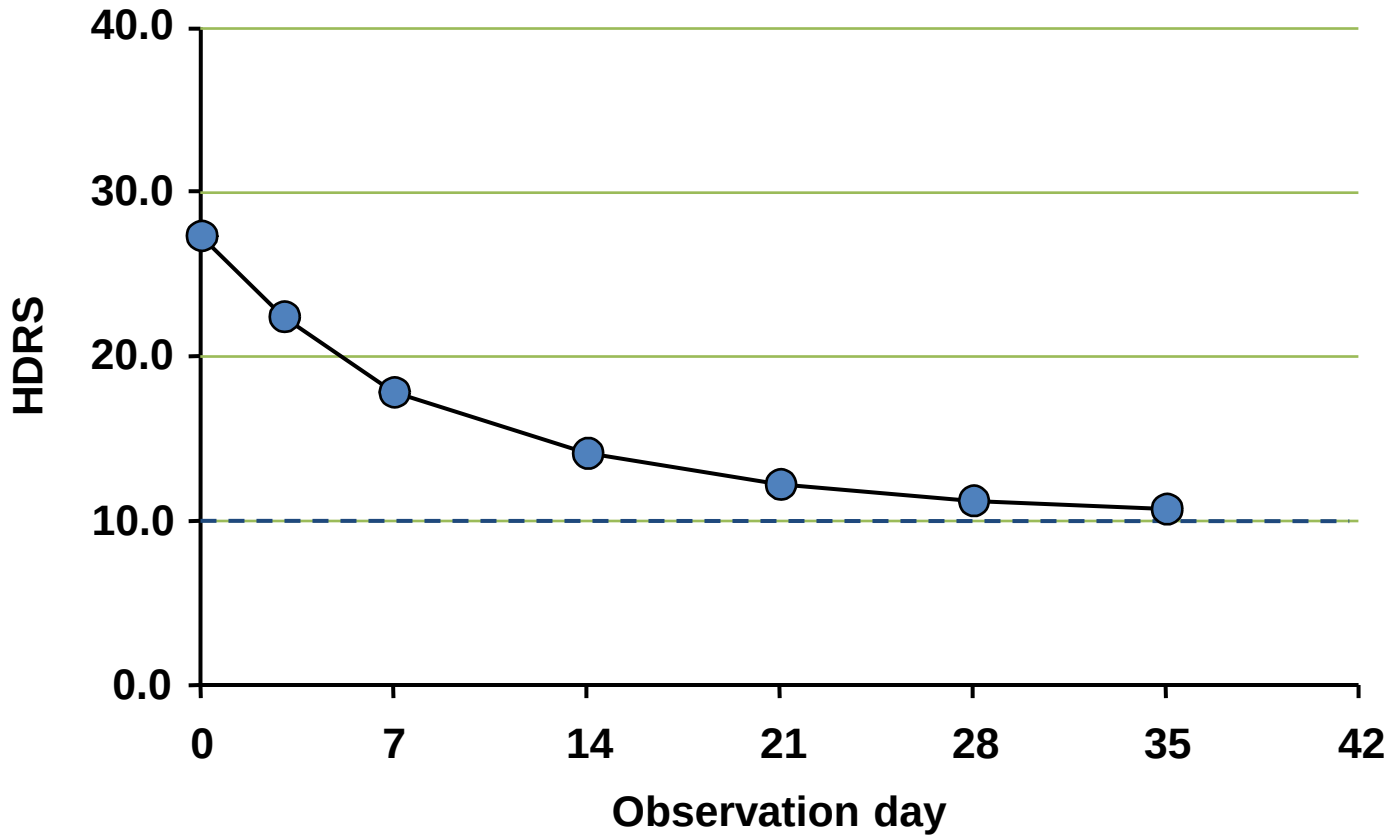
For example: chronic lithium treatment to ICR mice has antidepressant-like effects in the FST (at the group level) but analysis of individual response clearly distinguished between responders and non-responders



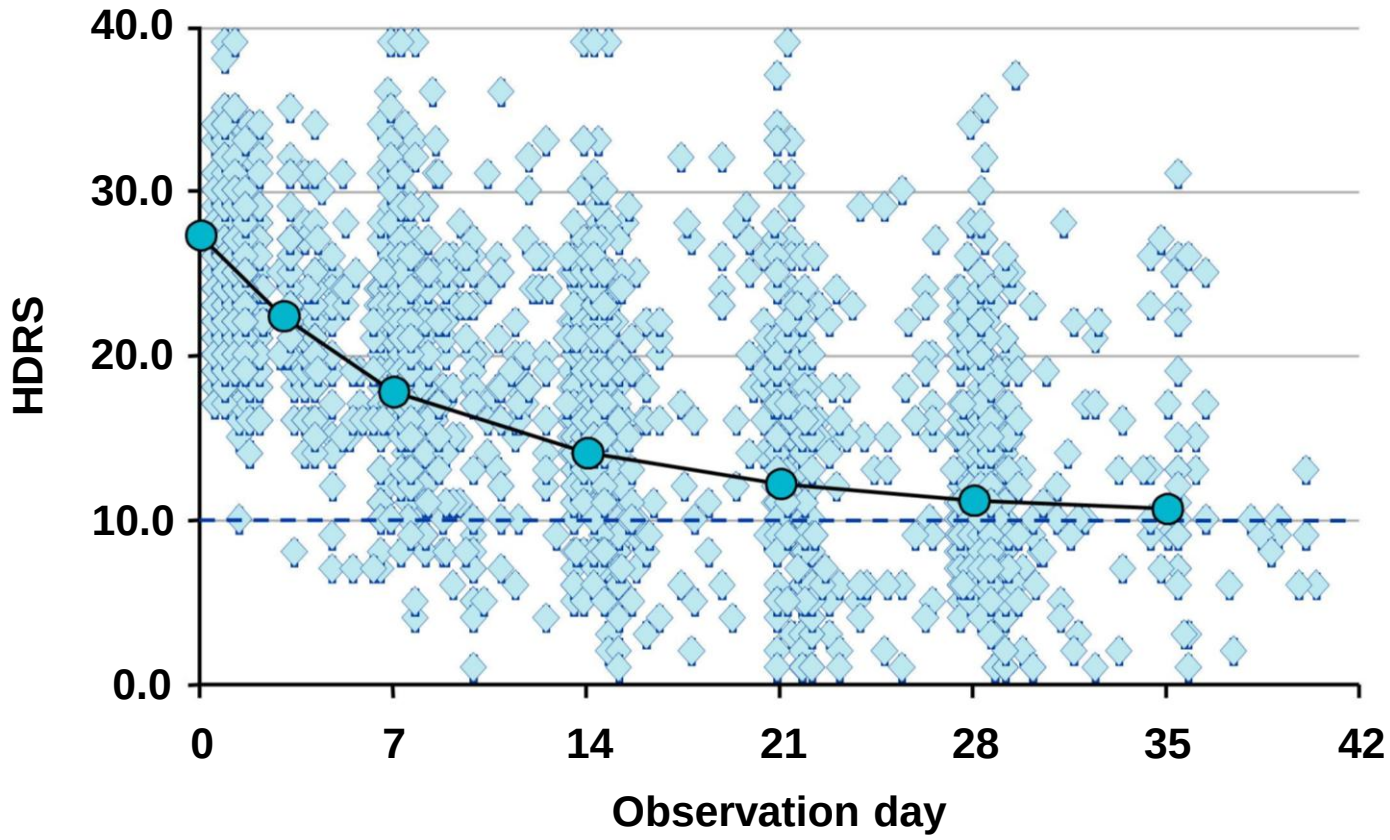
Patients in clinical trials versus patients in clinical practice...

...same treatment?

Clinical trials show mean values, not individual data



Clinical trials show mean values, not individual data



Pragmatic trials

The NEW ENGLAND JOURNAL of MEDICINE

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Maintenance or Discontinuation of Antidepressants in Primary Care

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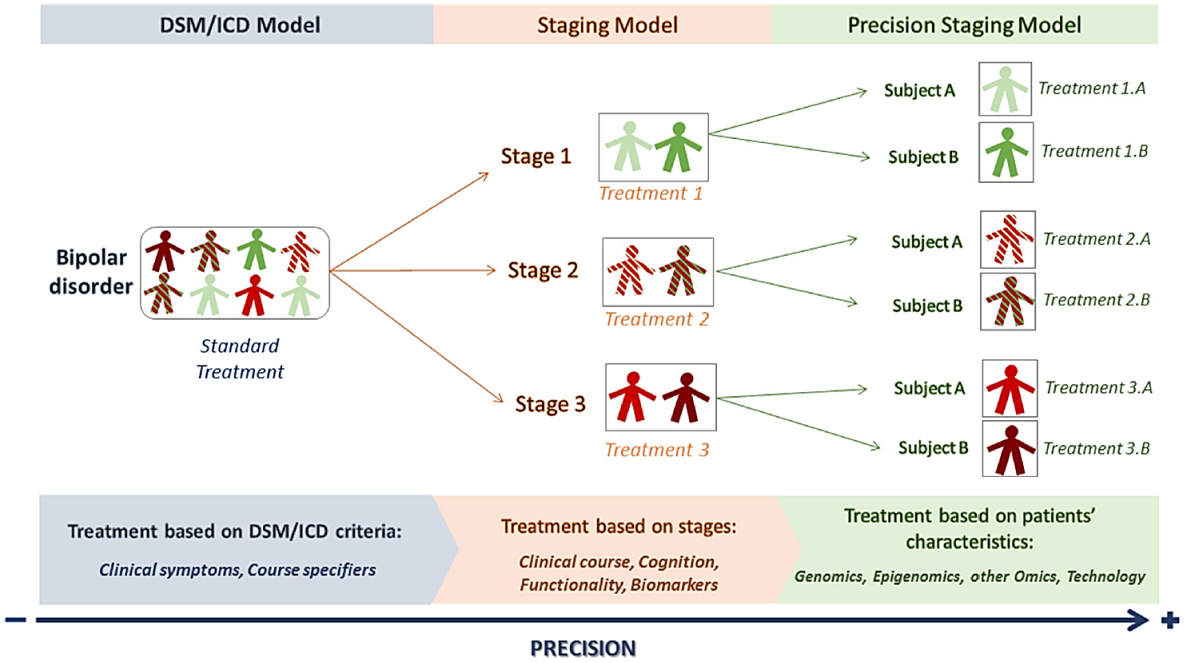
Precision Psychiatry

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Rev Psiquiatr Salud Ment (Barc.). 2015;xxx(xx):xxx–xxx

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EDITORIAL

Personalized medicine applied to mental health: Precision psychiatry☆

La medicina personalizada aplicada a la salud mental: la psiquiatría de precisión

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I remember it as if it were today, although many years have passed now. That skinny, simple woman, who had to leave school at the age of 12 to help her mother, who was supporting the family because the father had lost his job; those were hard times. An almost illiterate woman, yes, but intelligent. She presented rapid cycling bipolar disorder type II, with cycles that were very hard to stabilize. Until one day it happened. A year before, a new drug had been brought onto the market, it was only indicated for schizophrenia, although its mechanism of action suggested potential antidepressant effects. We started with a low dose, but noticed a change immediately. Six months later, the patient was able to remain stable for longer periods of time than ever in the past seven years. Then, after thanking me for having stabilized her after innumerable attempts with so many different medications, she asked me that question: "Thank you doctor, but why you did not ... pills from the beginning?"

Personalized medicine ...

It is much more important to know the genetic lineage of a neoplasm than its location. In psychiatry we still have subjective diagnoses, not completely reliable[1] and much less valid, and we still prescribe by trial and error: a drug that cures one patient does not work well with another, but there is no way of foreseeing what will happen before we try it. Our knowledge about the aethiopathogenesis of mental diseases, despite the remarkable progress made, continues to be "top to bottom" instead of being "from the bottom up", or what we popularly call "to begin building a house from the roof." The drugs available at the moment are the result of the discovery of the ... psychiatric disorders, but ... clinical observ...

Vieta, *Revista Psiquiatr Salud Ment*, 2015

Precision medicine in contrast to the “one-size-fits-all”

The problem: drugs do not always work

Antidepressants (SSRIs)	38% failure
Asthma drugs	40% failure
Diabetes drugs	43% failure
Arthritis drugs	50% failure
Alzheimer's drugs	70% failure
Cancer drugs	75% failure

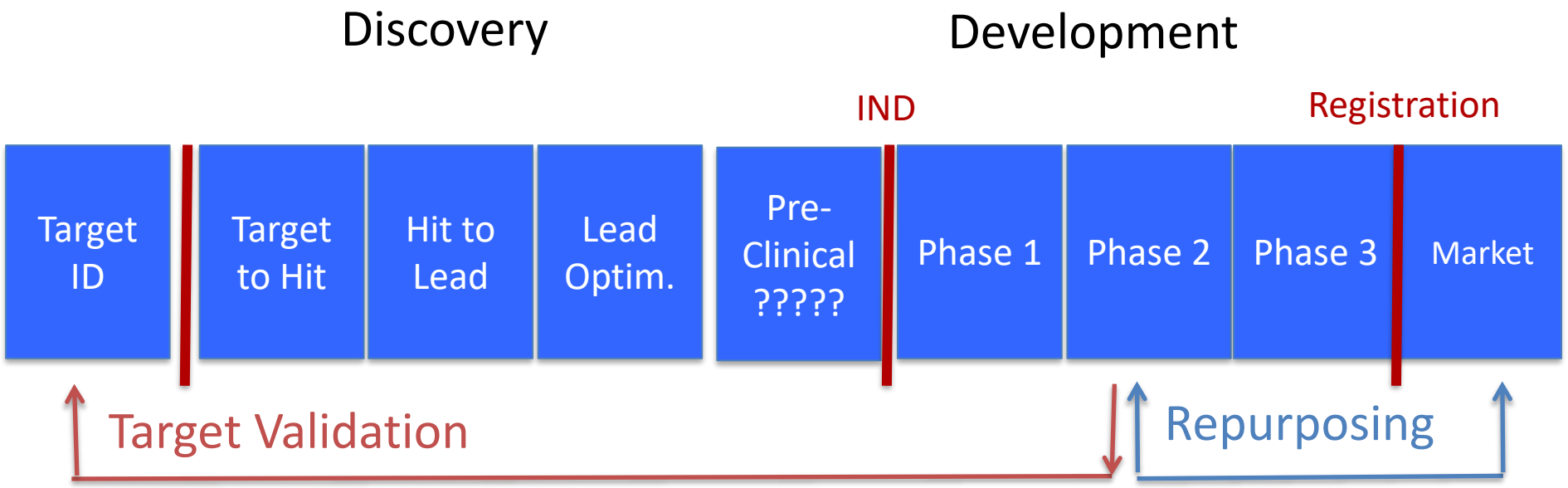
90% of drugs work in 30%–50% of individuals

Table 1. Response rates of patients to a major drug for a selected group of therapeutic areas[1]

Therapeutic area	Efficacy rate (%)
Alzheimer's	30
Analgesics (Cox-2)	80
Asthma	60
Cardiac Arrythmias	60
Depression (SSRI)	62
Diabetes	57
HCV	47
Incontinence	40
Migraine (acute)	52
Migraine (prophylaxis)	50
Oncology	25
Osteoporosis	48
Rheumatoid arthritis	50
Schizophrenia	60

Spear BB, Heath-Chiozzi M, Huff J. Trends Mol Med 2001;7(5):201-204

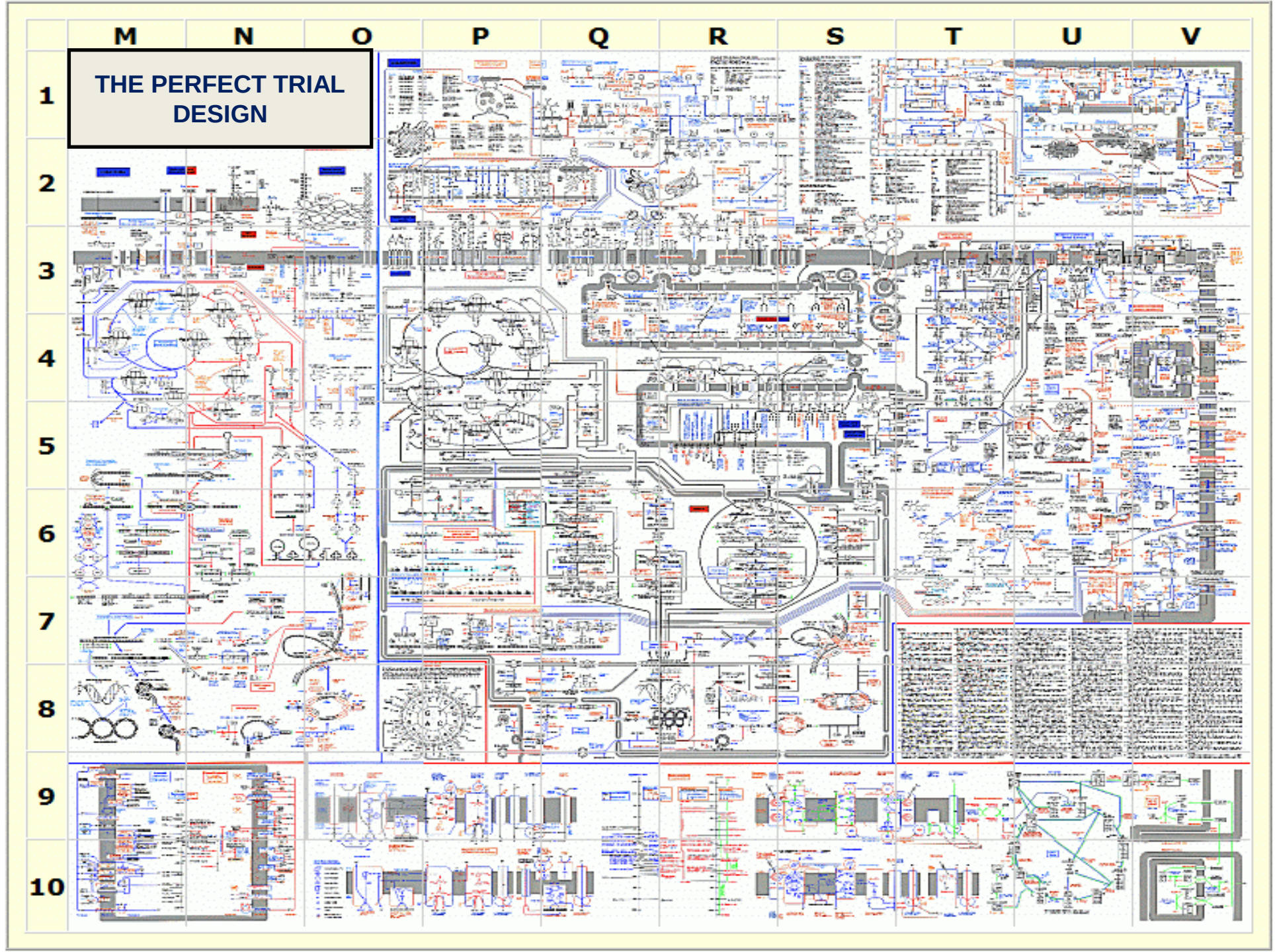
Transforming Treatment Development



Astute clinical observation
Stratified patient groups
Adaptive designs

Move quickly into humans (pre-clinical is not predictive)
Is the target engaged by the drug? (At what dose is the drug penetrating BBB?)
Fast fail is success

THE PERFECT TRIAL DESIGN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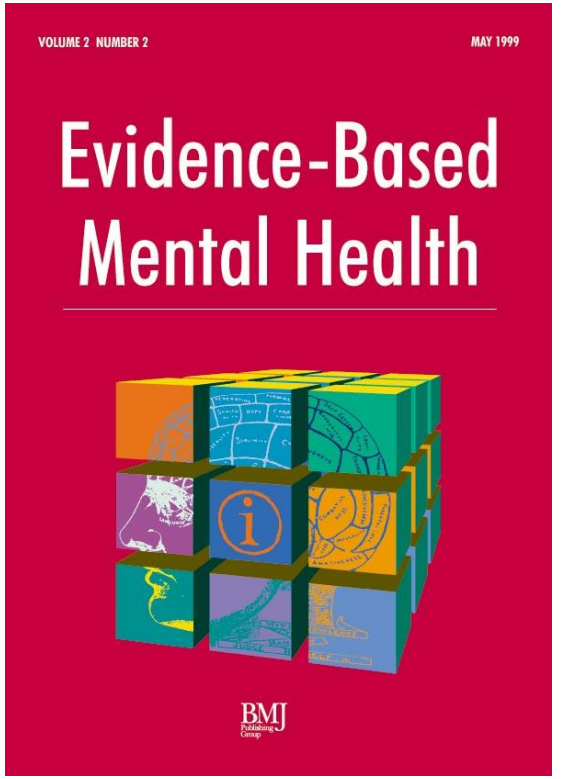
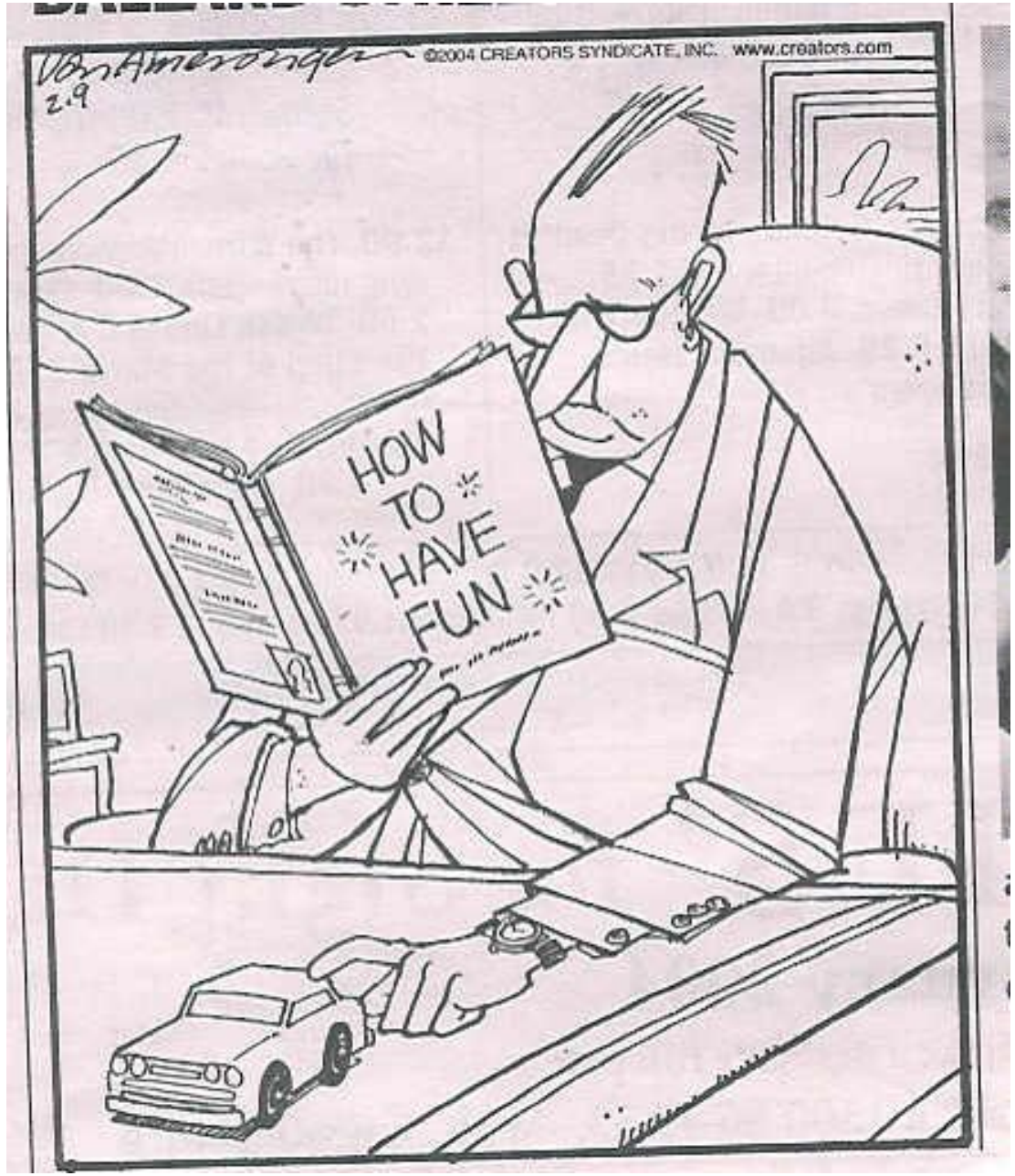
THE PERFECT TRIAL DESIGN

Good mentors or scientific evidence?



Maybe both…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