Towards developing more effective mental health interventions in youth: a research perspective

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Disclosures:

- I have no financial relationships with pharmaceutical companies or other competing interests
- I work at the NIMH/NIH, but the views here presented should not be construed as official statements of the NIMH/NIH

Aims

- To review critically recent treatment research in youth mental health

- To discuss approaches to developing more targeted and pathogenesis-driven treatments

Clinicaltrials.gov: N=40,970 trials in 2007-2010

(Califf et al., JAMA 2012)

- N=3,537 (8.3%) in cardiology
  - 10.5% in youth (<18 y)
- N=3,695 (9.8%) in mental health
  - 17.9% in youth
  - 69% (U.S.), 21% (Europe), 11% (Asia)
  - 66% parallel, 10% cross-over, 3.5% factorial
  - 80% randomized; 40% open-label
  - 60% with N≤100

Psychosocial interventions for youth mental health

Interventions:	To treat:
• Psychoeducation & support	Depression
• Behavioral therapies	Conduct disorders, ADHD, autism
• Cognitive-behavioral therapies	Anxiety, depression, OCD, eating disorders
• Psychodynamic therapy	Anxiety, depression, personality disorders
• Inter-personal therapy	Depression

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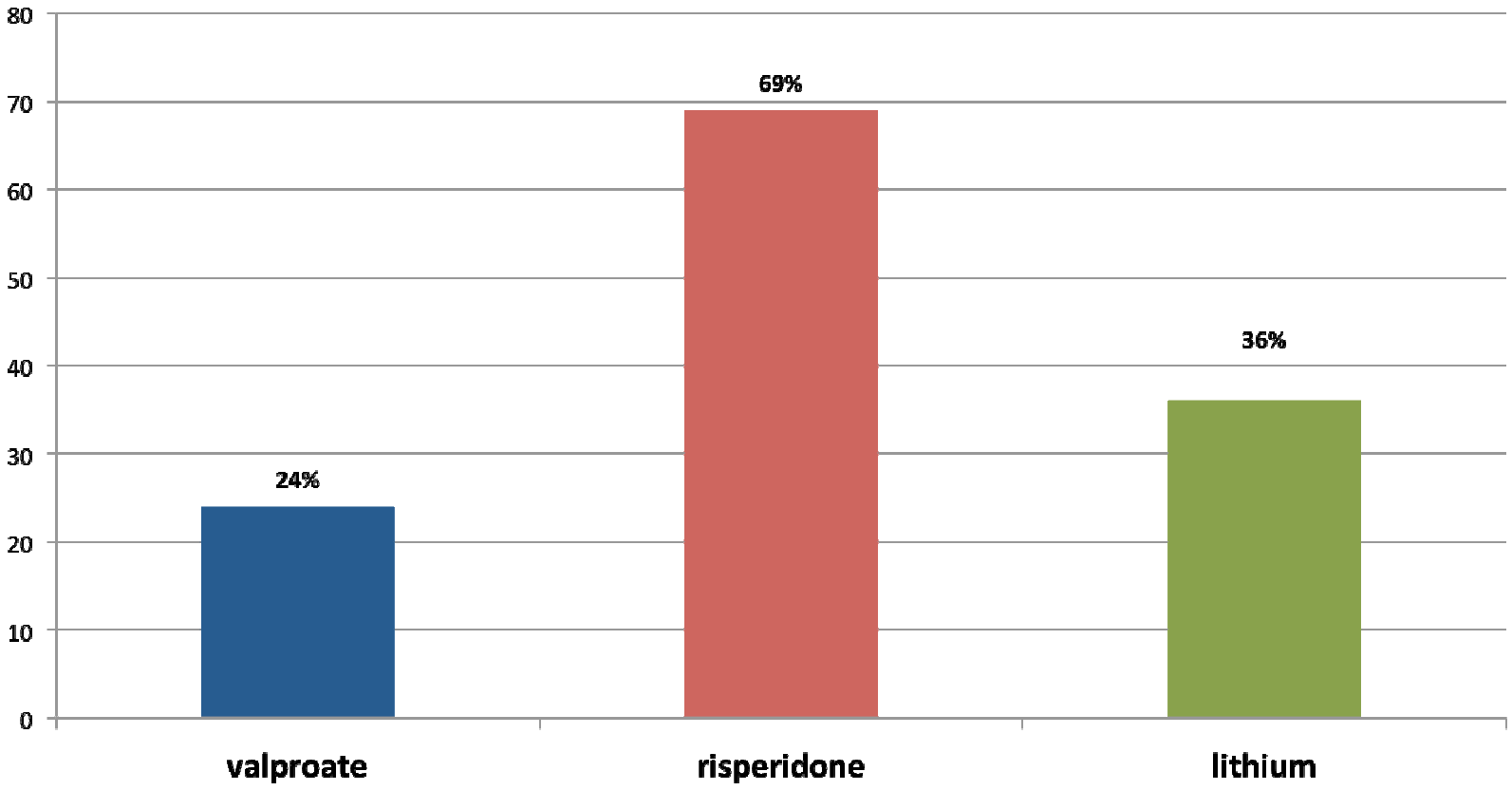
Psychopharmacology in youth

Medications:	To treat:
• Stimulants	ADHD
• SSRI antidepressants	Depression, OCD, anxiety
• Antipsychotics	Psychosis, mania, aggression
• Mood stabilizers	Bipolar, aggression

Response rate in the Treatment of Early Age Mania (TEAM) (N=279) (Geller et al., 2012)



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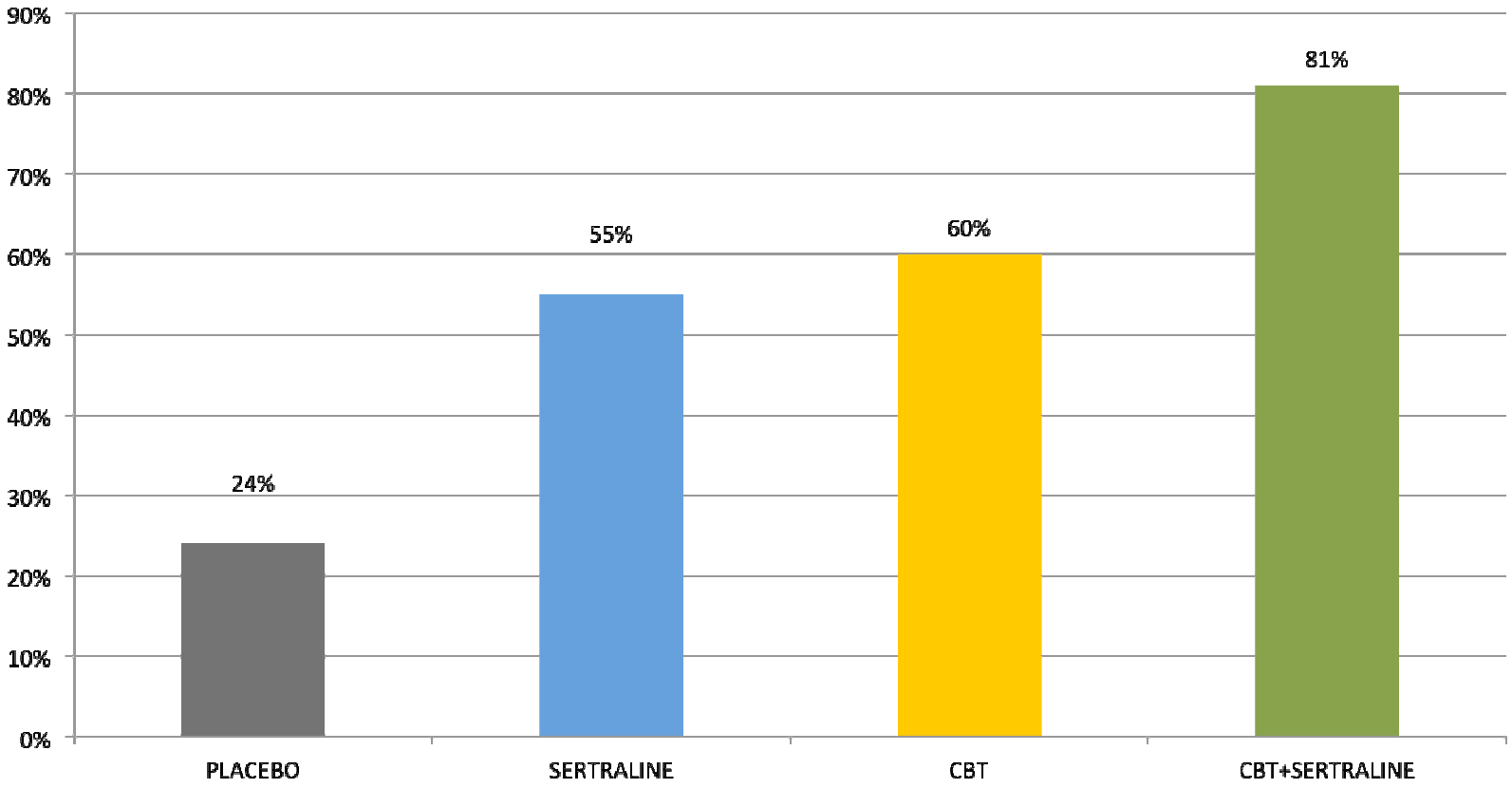
CBT, sertraline, and their combination in youth with anxiety disorders (N=488) (Walkup et al., N Engl J Med. **2008)**



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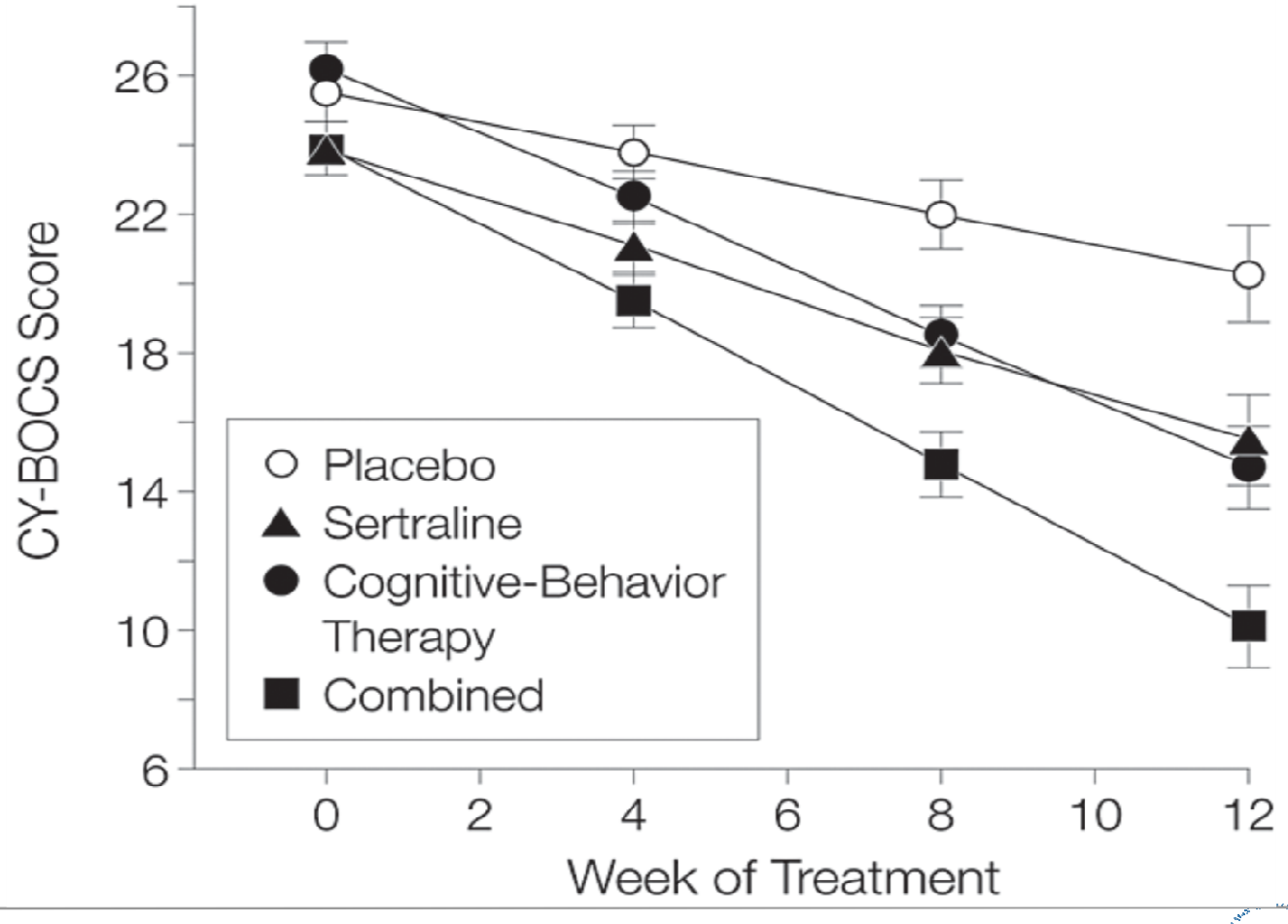
The Pediatric OCD Treatment Study (POTS)

POTS Team, JAMA. 2004



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Preferred treatment modalities

Psychotherapy	Pharmacotherapy	Combination
• Anxiety disorders • PTSD • OCD • Autism spectrum • Milder depression • Mild Tourette • High risk for psychosis	• Acute psychosis • Bipolar mania • Severe aggression • Severe depression • Severe ADHD • Severe Tourette	• Severe anxiety, • Severe OCD • Depression resistant to monotherapy • ADHD comorbidities

Clinical trials: limitations and concerns

- Many trials are inconclusive
- Questionable nosological targets
- External validity
- Efficiency
- Transparency and conflict of interest
- Globalization and outsourcing
- Need for innovation
- Funding

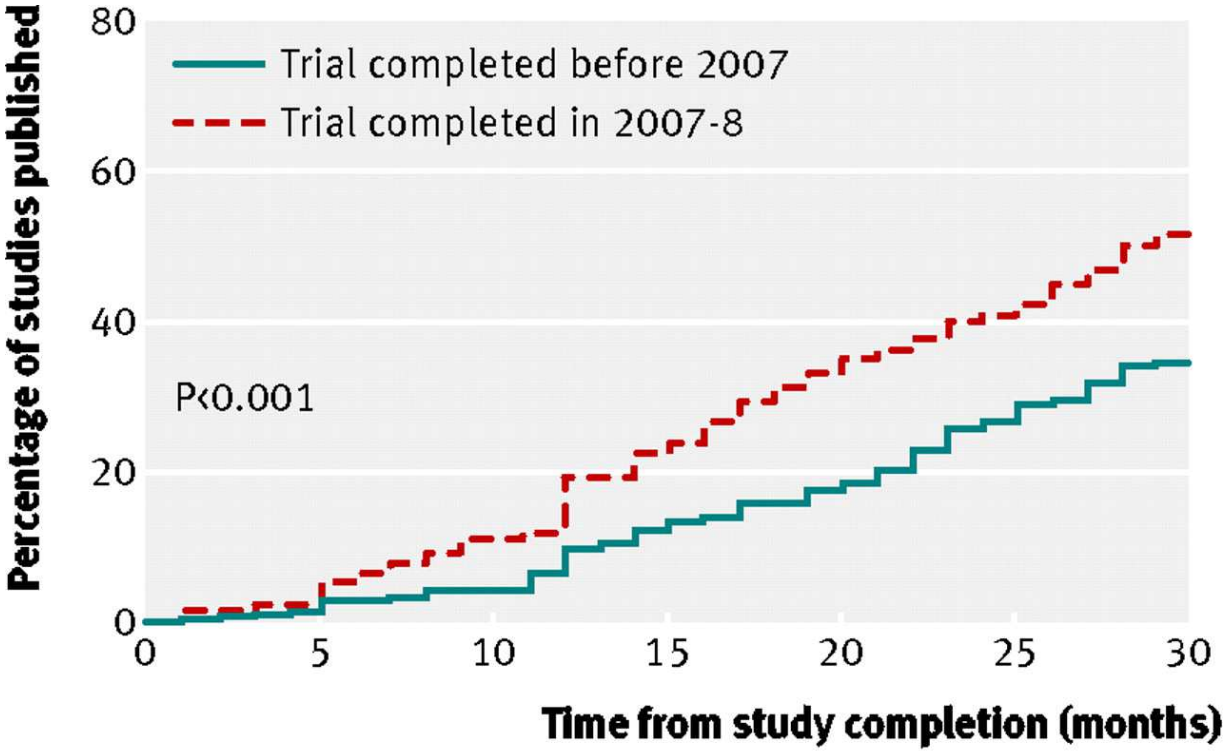
Inconclusive results

- Interventions often have a small effect size
  - Need for large N; most studies are underpowered
  - Results are difficult to replicate
- Psychiatric disorders are broad and heterogeneous categories
- No biological marker of treatment response
  - “Soft” outcomes, symptom-based, prone to high experimental error, high placebo effect

Clinical trials: how efficient?

- Time consuming
  - Average 5 years
  - Slow starting
  - Highly regulated
  - Slow recruitment
- Expensive
  - E.g., TADS (2004): $39,000/pt
- Not always informative
  - How to interpret negative findings? (“failed trials”?)
  - Some trials are not published….

Cumulative percentage of studies published in peer reviewed biomedical journal indexed by Medline during 30 months after trial completion among NIH funded clinical trials registered within ClinicalTrials.gov



No of unpublished studies						
Trial completed before 2007						
269	264	259	235	221	197	175
Trial completed in 2007-8						
366	356	324	282	244	215	176

Ross J S et al. BMJ 2012;344:bmj.d7292

BMJ

Need for innovation and translational research

- Many advances in neuroscience...but still few clinical applications
- How to build a rational, targeted treatment development in child psychiatry:
  - Focus on mechanism
  - Experimental medicine model
  - Rare disease models

Emphasis on:

- Understanding the pathogenesis and mechanisms of psychopathology
- Targeting domains of brain function relevant to psychopathology across parallel units of analysis (genes, molecules, cells, circuits, behavior, etc.)
- Treatment development using experimental medicine methods:
  - Pathogenesis-derived target
  - Documentation of target engagement
  - Dose-response relationship
  - Proof-of-concept studies for efficacy signal

Target of an intervention

- The hypothesized mechanism by which the intervention is supposed to produce the therapeutic effect

- Target engagement by the treatment must be measurable

Target can be at different levels

Levels of target:	Measures of engagement:
• Molecular	• RNA expression, protein synthesis
• Cellular	• Receptor, neurogenesis
• Neural circuit	• fMRI, EEG. MEG
• Physiology	• Cortisol, autonomic functions
• Behavioral	• Executive functions, attention bias
• Clinical	• Anhedonia, irritability/anger
• Health care organization	• Integration of services, collaborative care

Targeted drug development: fragile X syndrome

≥200 CGG triplets at promoter of FMR1 gene on chromosome X

→ silencing of the gene

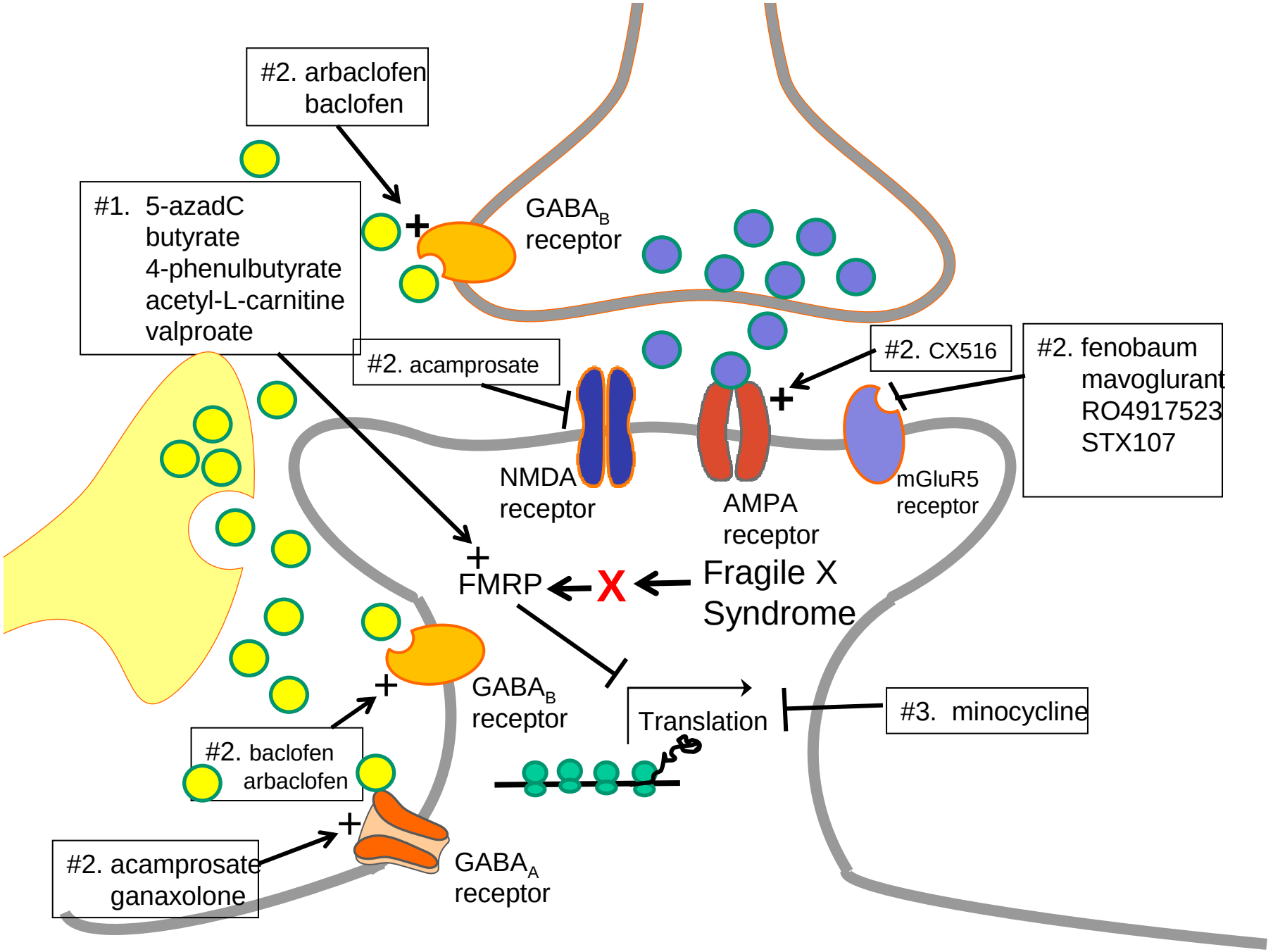
→ lack of FMRP (which is a translational repressor)

→increased protein synthesis

→ more mGluR1 and mGluR5

→ dysregulation in glutamatergic transmission

→clinical signs & symptoms


#2. arbaclofen
baclofen
#1. 5-azadC
butyrate
4-phenulbutyrate
acetyl-L-carnitine
valproate
GABA$_B$
receptor
#2. acamprosate
#2. CX516
#2. fenobaum
mavoglurant
RO4917523
STX107
NMDA
receptor
AMPA
receptor
mGluR5
receptor
FMRP
X
Fragile X
Syndrome
GABA$_B$
receptor
Translation
#3. minocycline
#2. baclofen
arbaclofen
#2. acamprosate
ganaxolone
GABA$_A$
receptor

Funding for treatment development

- NIH
  - NIMH
  - NICHD
  - National Center for Advancing Translational Sciences (NCATS)
- Industry
- Private foundations

A recent NIMH contract

- *New Experimental Medicine Studies: Fast-Fail Trials in Autism Spectrum Disorders (FAST-AS).*

For early treatment development in autism

The need for comparative effectiveness research

- Comparing alternative treatments
  - ADHD, depression, OCD, anxiety, etc

How to:

- Contain cost? Improve efficiency?
- Increase validity (generalizability)?
- Interpret negative findings?

Practical Clinical Trials

- Large simple trials addressing one main question of clinical relevance in practice settings using large sample (hundreds/thousands)

- Questions:
  - What is the need for practical trials in adolescent psychiatry?
  - Which are the best platforms for these trials?

Randomized practical clinical trials in 2000-2014

- Antidepressant meds: 10 trials, none with N≥1,000
  Total 4,206 patients

- Hypertensive meds: 46 trials, 72% had N≥1,000
  Total 208,014 patients

Practice research networks

- Which type of practical trials can be conducted in these networks?
- Can help increase efficiency (faster recruitment, lower cost) and validity (greater representativeness)?
- How to integrate research into practice?
  - Issues of motivating clinicians, minimizing burden, fostering feasibility

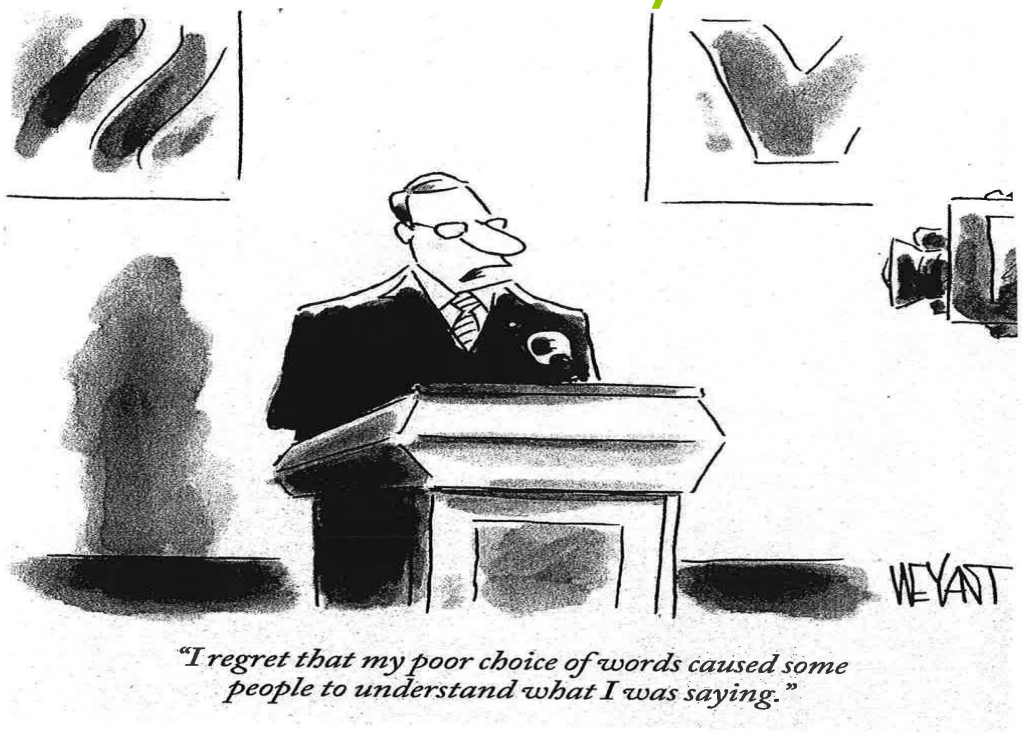
Funding for comparative effectiveness

- Patient Centered Outcomes Research Institute (PCORI)
- NIMH
- U.S. Agency of Healthcare Research and Quality
- Industry

Conclusions

- There is a need for innovation and greater efficiency in clinical research
- Neuroscience offers the prospect of a more targeted, mechanism-driven treatment development
- There is also a role for practical trials in practice settings to inform evidence-based care

Thank you


WEYANT
"I regret that my poor choice of words caused some people to understand what I was saying."