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Special Challenges: Bipolar and Epilepsy

Challenges in Study Design:
What Needs to be Done to Move Things Along

Industry Perspective Discussants

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Disclosures

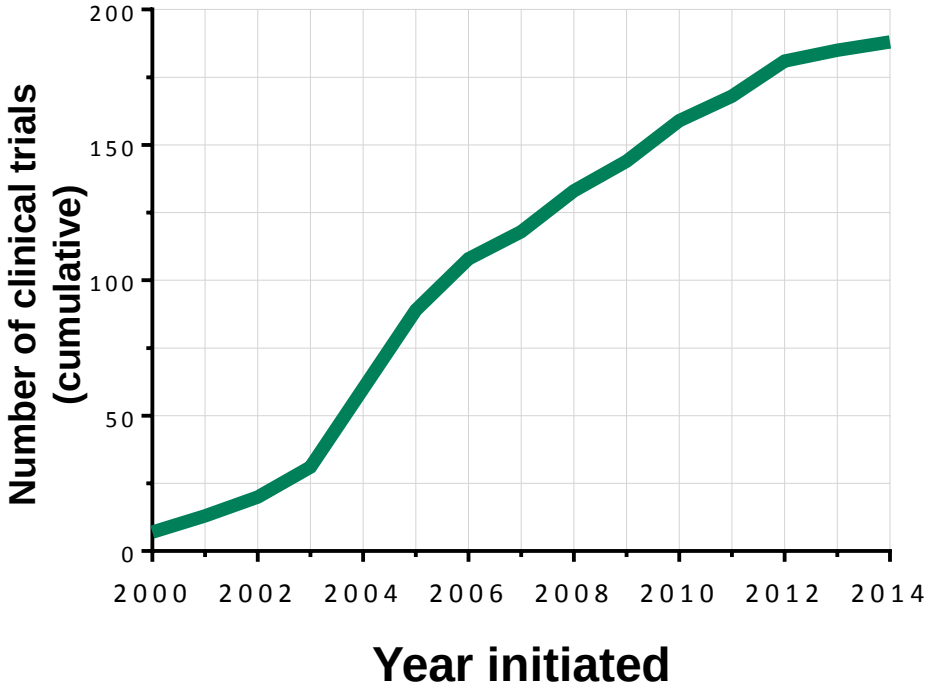
- Discussants are employees of Sunovion Pharmaceuticals

Cognitive endpoints are infrequent in bipolar disorder trials

ClinicalTrials.gov

Condition = "bipolar"
Sponsor = "Industry"
Phase = 2 or 3

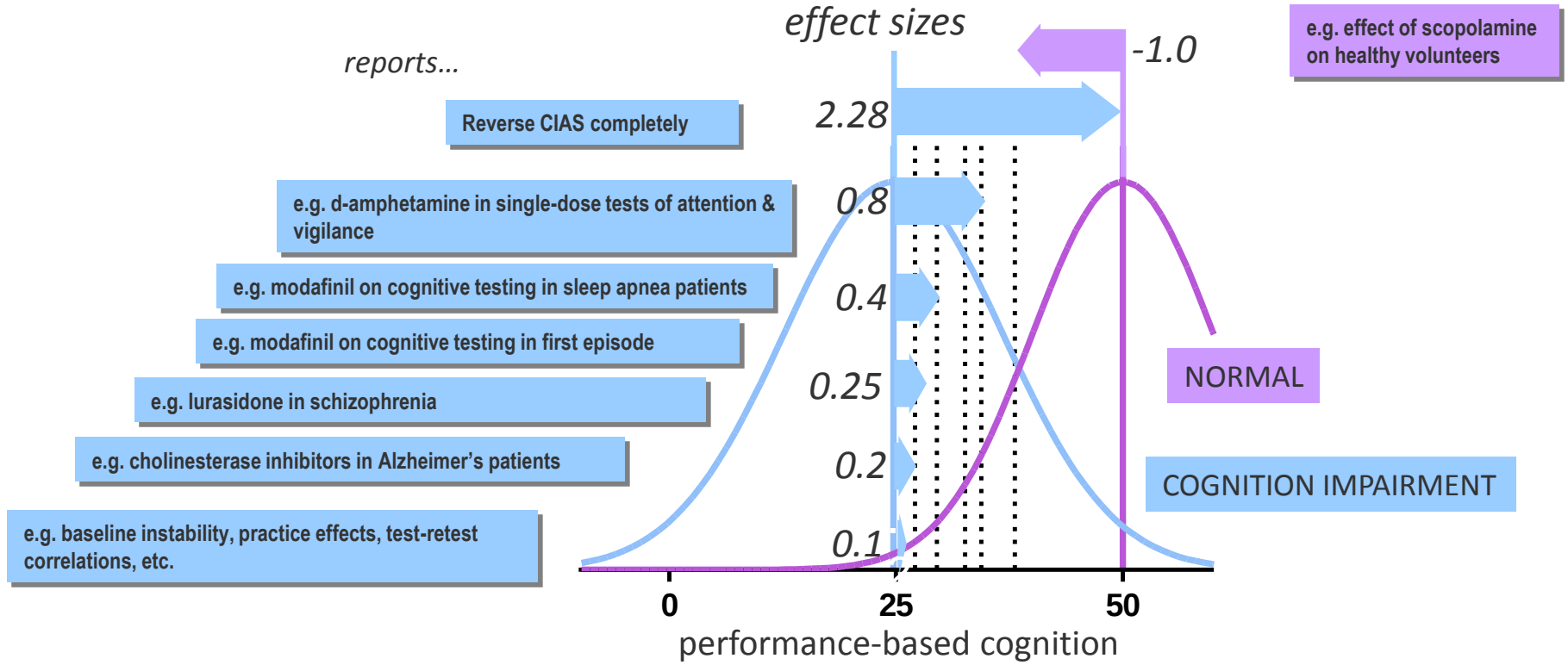
188 clinical trials



Drug	Trials
quetiapine	27
aripiprazole	26
ziprasidone	14
asenapine	12
risperidone	12
lurasidone	11
olanzapine	10
valproate	9
lamotragine	9
cariprazine	6
ramelteon	5
armodafinil	5
topiramate	5
licarbazepine	5

- only 7 trials reported with neurocognitive endpoints (asenapine, ziprasidone, and EPO)
  - only as secondary endpoints

The magnitudes of cognitive improvements are small relative to impairment, regardless of disorder or treatment

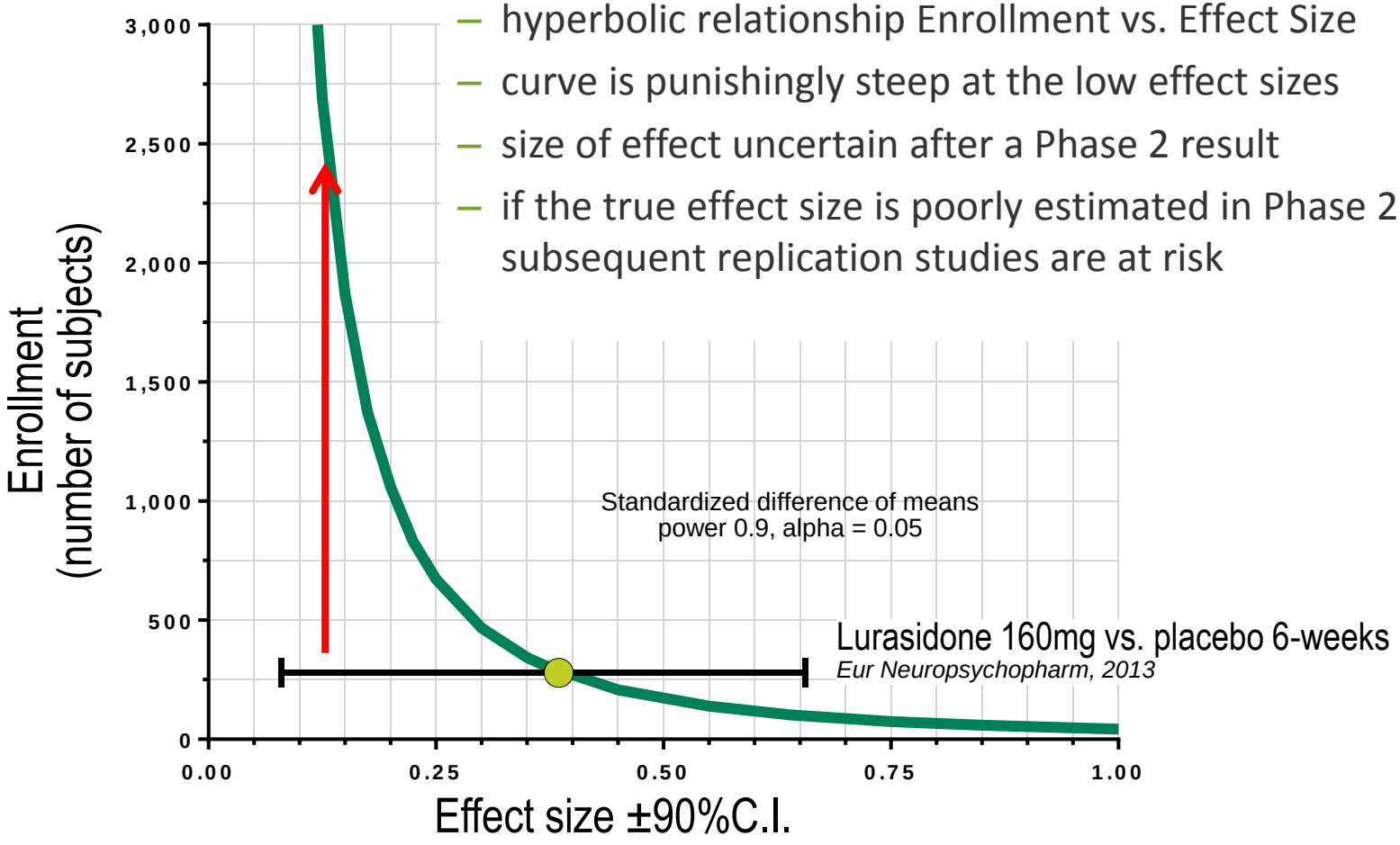


- magnitude of effect sizes reported for cognitive improvements is always small
- attempts to *improve* cognition are much smaller than the *impairments*
- the consequences of small and uncertain effect sizes is evident in the (*large*) scale and (*high*) risk of industry-sponsored clinical development

Replication is a challenge for registering cognition drugs – confidence around underlying effect size

Replication challenge

- hyperbolic relationship Enrollment vs. Effect Size
- curve is punishingly steep at the low effect sizes
- size of effect uncertain after a Phase 2 result
- if the true effect size is poorly estimated in Phase 2 studies, the subsequent replication studies are at risk



Industry perspective on challenges – developing treatments for cognitive impairment

- Very large investments have failed even in the face of
  - plausible mechanism or evidence for preclinical behavioral effects, preclinical validation in animal models
  - favorable clinical checkpoints of target engagement confirmation in man, modulation of cognitive impairment biomarkers/ neuroimaging
  - safety demonstrated in Phase I studies
  - positive initial POCs
- Replication is a unique challenge to industry
  - uncertainty around small effect sizes elevates statistical risk
  - economic consequences of all-or-nothing investments
- Regulatory pathway/requirements for cognitive endpoints and indication in bipolar disorder need to be better defined
- HCP and payer acceptance is somewhat unclear

Searching For New Procognitive Agents In Bipolar Disorder: What Are We Looking For?

- Preclinical requirements (2-4 years)
  - good discovery science/MOA
  - drug-like characteristics attuned to CNS
  - safety toxicology
  - preclinical biomarkers of target engagement
- Phase 1 approach (1-2 years)
  - early tolerability/safety demonstrated in NHV/patients
  - preliminary therapeutic dose range (including min/max dose)
  - translational biomarkers (qEEG, ERPs, fMRI, PET, PSG)
- Phase 2 transitions (~2.5 years)
  - initial open-label study demonstrating "signal" (2a)
  - POC study – fairly rigorous demonstration of effect vs control (2b)
  - dose ranging studies (2b/3)

Searching For New Procognitive Agents In Bipolar Disorder: What Are We Looking For?

- Phase 3 and beyond (3+ years)
  - confirmatory trials to clearly and consistently demonstrate both statistically and clinically relevant effects
  - secondary endpoints showing effects on multiple domains of outcome (eg employment, educational, interpersonal), quality of life, cost-effectiveness
- Cognitive remediation approaches
- Will payers support such an agent based on clinical trial evidence and “real world” effectiveness?
  - restrictions on use (eg ”fail first”/eligible populations/duration of therapy etc)
- Assessment of response to treatment/clinical dilemmas

Searching for New Procognitive Agents in Bipolar Disorder

- Registration study design?
  - guidance document/academic consensus publication
  - cognitive test battery; pencil and paper vs electronic
    - cognitive endpoints-- composite or specific domain(s)
  - functional co-primary assessment
  - validated translations for international use
  - study duration
- Cognitive/functional impairment at baseline?
  - Change from premorbid level of cognitive functioning
  - severity cut-off
  - how to control practice effects
- Stable vs symptomatic patients?
  - criteria for stability (eg time since stabilized; severity thresholds for depressive/manic sx)
    - can acutely symptomatic (depressed/manic) populations be utilized?
    - treatment-resistant patients

What Are The Implications of This Statement?

- “Cognitive impairment is also seen with affective disorder, but, here, it tends to be episodic over time, with return to a relatively normal baseline between episodes, in keeping with the periodicity of these disorders”.

Laughren T. FDA Perspective on the DSM-5 approach to classification of “cognitive” disorders. J Neuropsychiatry Clin Neurosci 2011; 23:126-131