# Development of treatments for Cognitive Impairment associated with Bipolar and Epilepsy

Co-Chairs: Gary Sachs, Sophia Frangou

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# Agenda

| | | |
|---|---|---|
| 8:15 10 m | Defining the Problem & Session Overview | Gary Sachs |
| 8:25 20 m | Cognition in Bipolar Disorder: Research and Clinical Implications | Sophia Frangou |
| 8:45 15 m | Discussion | |
| 9:00 20 m | Neurocognitive Dysfunction In Bipolar Disorder: Methodology for Intervention Studies | Kate Burdick |
| 9:20 15 m | Discussion | |
| 9:35 15 m | Break | |
| 9:50 20 m | Methodological challenges developing treatment for Cognitive impairment associated with Epilepsy | Kim Meador |
| 10:10 15 m | Discussion | |
| 10:25 20 m | Industry Perspective 1: Challenges in Study Design<br>What needs to be done to move this along | Tony Loebel |
| 10:45 15 m | Discussion | |
| 11:00 20 m | Perspective: Industry perspective 2 | Robert Goldman |
| 11:20 30 m | Discussion | |
| 11:50 10 m | Summary | Gary Sachs |

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# Gary Sachs

## Declaration of Conflicts of Interest:

(within the last two years, last updated 9.21.2014)

- Grants/ research support: NIMH
- Advisory Board and Consulting fees: Abbott labs, AstraZeneca, Forest labs, Janssen, Merck, Otsuka, Sunovion, Takeda
- Employee: Bracket, Massachusetts General Hospital, Private Practice: Collaborative Care Initiative (Founder and Owner)
- Shares in: Amyris, AthenaHealth, ExpressScripts, McKesson, Oracle
- Expert Testimony

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# Cognitive impairment associated with …

Methodological Challenges

- Target
- Eligibility
- Outcomes

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# Cognitive impairment associated with other CNS disorders (Bipolar and Epilepsy)

- Is this an entity or entities that might be amenable to treatment?
- What interventions are proposed or imagined as targeting an indication in this area?
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# Before reaching the Future

The episode (seizure) ≠ The Illness

Cognitive impairment associated with many chronic conditions like Bipolar and Epilepsy) is variable and complex.

Primary Illness Progression

-Well state- Prodrome, Illness onset, Variable course (during treatment "well states" alternate with recurrent episodes), Treatment effects

Cognitive impairment

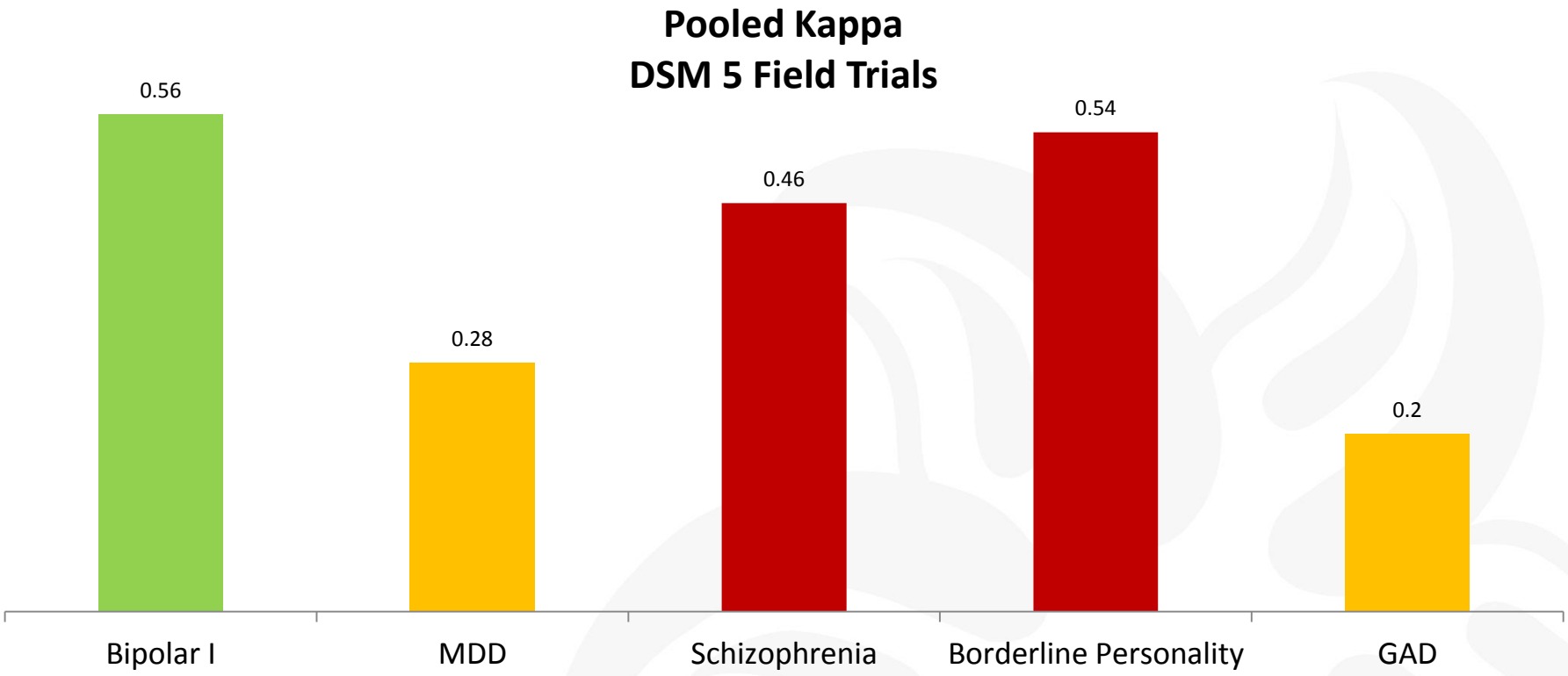
-State / Trait

-Static / dynamic

## Common challenges

- Why?
- What?
- Who?
- How?

# Reliability of Psychiatric diagnoses




## Opportunity: Maximize chance of success

by prioritizing disorders that can be diagnosed with high reliability.

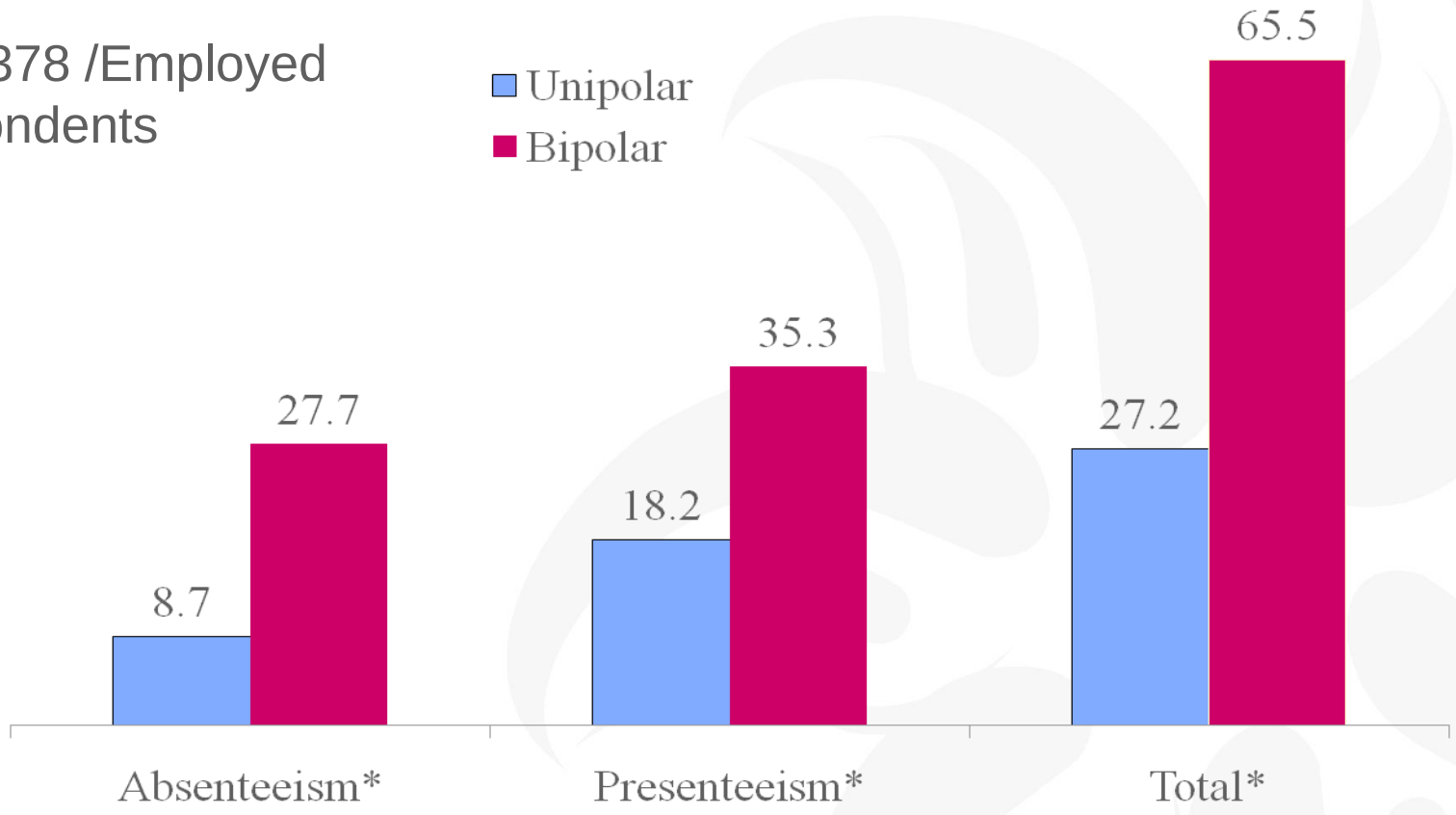
*Adapted from Regier DA, et al. Am J Psychiatry 2013;170:59-70.* 10.1176/appi.ajp.2012.12070999

# Workplace Impact: Measurable Need

## National Comorbidity Survey

### Days lost /yr

N= 3378 /Employed respondents




*p=0.05 Kessler et al. Am J Psychiatry. 2006; 163(9): 1561-1568

BIPOLAR DISORDERS
AN INTERNATIONAL JOURNAL OF PSYCHIATRY AND NEUROSCIENCES

Bipolar Disorders 2014: 16: 159–171



BIPOLAR DISORDERS

Original Article

# 12-month longitudinal cognitive functioning in patients recently diagnosed with bipolar disorder

Torres IJ, Kozicky J, Popuri S, Bond DJ, Honer WG, Lam RW, Yatham LN. 12-month longitudinal cognitive functioning in patients recently diagnosed with bipolar disorder.
Bipolar Disord 2014: 16: 159–171. © 2013 John Wiley & Sons A/S.
Published by John Wiley & Sons Ltd.

Ivan J Torres[a,b], Jan Kozicky[a], Swetha Popuri[a], David J Bond[a], William G Honer[a,b], Raymond W Lam[a] and Lakshmi N Yatham[a]

**Objectives**: Although cognitive deficits are observed in the early stages of bipolar disorder, the longitudinal course of neuropsychological functioning during this period is unknown. Such knowledge could provide etiologic clues into the cognitive deficits associated with the illness, and could inform early treatment interventions. The purpose of the present study was to evaluate cognitive change in bipolar disorder in the first year after the initial manic episode.

**Methods**: From an initial pool of 65 newly diagnosed patients with bipolar disorder (within three months of the end of the first manic or mixed episode) and 36 demographically similar healthy participants, 42 patients [mean age 22.9 years, standard deviation (SD) = 4.0] and 23 healthy participants [mean age 22.9 years (SD = 4.9)] completed baseline, six-month, and one-year neuropsychological assessments of multiple domains including processing speed, attention, verbal and nonverbal memory, working memory, and executive function. Patients also received clinical assessments, including mood ratings.

**Results**: Although patients showed consistently poorer cognitive performance than healthy individuals in most cognitive domains, patients showed a linear improvement over time in processing speed ($p = 0.008$) and executive function ($p = 0.004$) relative to the comparison group. Among patients, those without a history of alcohol/substance abuse or who were taken off an antipsychotic treatment during the study showed better improvement.

**Conclusions:** The early course of cognitive functioning in bipolar disorder is likely influenced by multiple factors. Nevertheless, patients with bipolar disorder showed select cognitive improvements in the first year after resolution of their initial manic episode. Several clinical variables were associated with better recovery, including absence of substance abuse and discontinuation of antipsychotic treatment during the study. These and other factors require further investigation to better understand their contributions to longitudinal cognitive functioning in early bipolar disorder.

# Many variables impact cognition

-Eligibility criteria
-Stage of illness
-Concurrent medication
Self-administered psychoactives
-Testing conditions
-Co-occurring conditions
-Attrition

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# Longitudinal Study

## Following First manic or mixed episode

Clinical and medication variables for patients who completed all time points (n = 42)

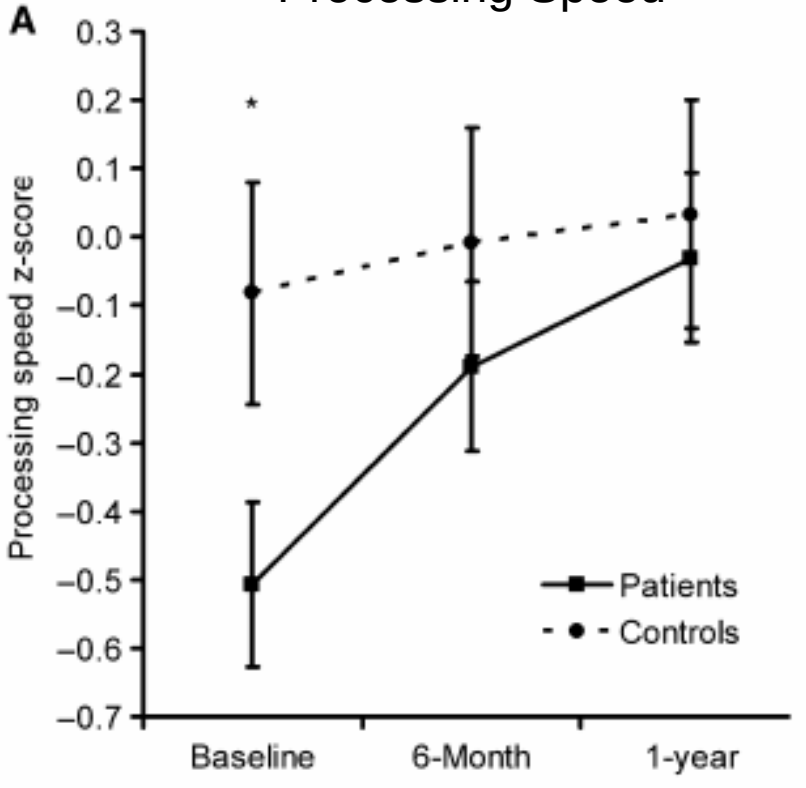
| | Baseline | Six months | One year |
|---|---|---|---|
| Psychiatric rating scales, mean (SD) | | | |
| PANSS–Positive score | 7.8 (1.5) | 7.2 (1.0) | 7.3 (1.9) |
| Brief Psychiatric Rating Scale | 23.1 (5.9) | 20.1 (3.1) | 19.7 (3.8) |
| Young Mania Rating Scale[a] | 1.3 (3.2) | 1.0 (3.2) | 1.5 (4.4) |
| Hamilton Depression Rating Scale–29 item[a] | 7.3 (7.5) | 4.9 (5.7) | 3.0 (5.2) |
| Medications, n (%) | | | |
| *Mood stabilizers* | 38 (91) | 37 (90) | 34 (83) |
| Lithium | 18 (43) | 17 (41) | 15 (37) |
| Divalproex | 22 (52) | 20 (49) | 20 (49) |
| Lamotrigine | 1 (2) | 1 (2) | 1 (2) |
| *Atypical antipsychotic agents* | 34 (81) | 27 (66) | 22 (54) |
| Olanzapine | 7 (17) | 6 (15) | 7 (17) |
| Quetiapine | 11 (26) | 12 (29) | 9 (22) |
| Risperidone | 19 (45) | 9 (22) | 6 (15) |

**Are these Mood ratings realistic?**

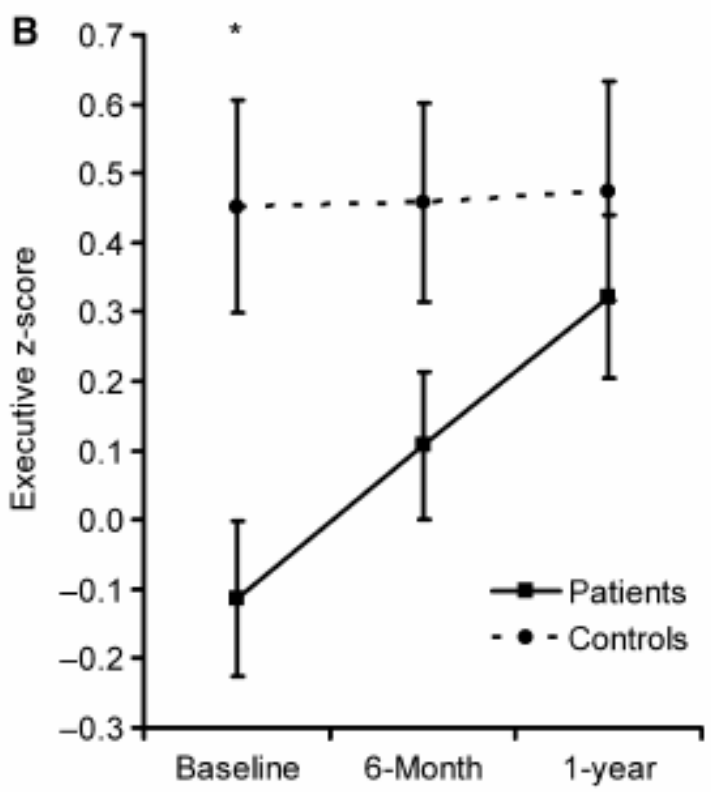
[a]For 40% of the sessions, mood ratings were obtained on the day of cognitive testing; for 55% of sessions, within three days of testing; for 77%, within two weeks of testing; and for 91%, within one month of testing.

Torres et al. 12-month longitudinal cognitive functioning in patients recently diagnosed with bipolar disorder. Bipolar Disorders 2014

Processing Speed

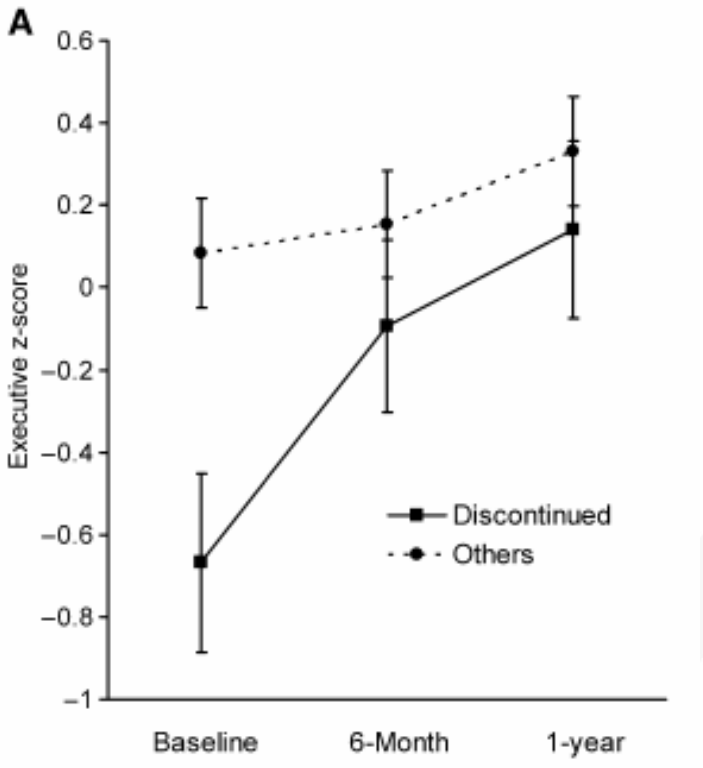



Executive Function

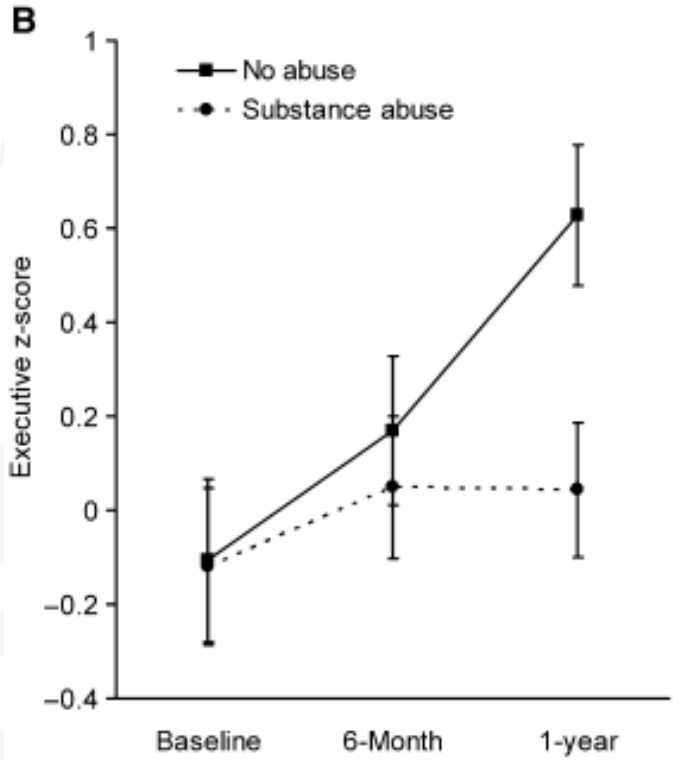


# Longitudinal cognitive functioning varies for different subgroups.

Subjects who **discontinued antipsychotic** treatment during the study versus those who did not




Subjects with **substance abuse history** versus no such history



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**Watch this space!**

The Future