# Report on ISCTM Consensus Meeting on Clinical Assessment of Response to Treatment of Cognitive Impairment in Schizophrenia

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**ISCTM, October 7, 2014**

# Financial Disclosures

## Past 3 Years

Consultant/Ad Board/Service Provider for: Abbvie, Akebia, Amgen, Asubio, AviNeuro/ChemRar, Biogen Idec, BiolineRx, Biomarin, Boehringer-Ingelheim, Eli Lilly, EnVivo/FORUM, GW Pharmaceuticals, Lundbeck, Merck, Minerva Neuroscience Inc., Mitsubishi, Novartis, Otsuka, Pfizer, Roche, Shire, Takeda, Targacept

Research Funding: NIMH, Singapore Medical Research Council, Columbia University Foundation for Mental Hygiene, GlaxoSmithKline, PsychoGenics, Novartis, Brain Plasticity Institute

Investment: Founder of NeuroCog Trials, Inc., which provides rater training, data quality assurance and consultation to several pharmaceutical companies and other consortia. Investor in Sengenix, Inc. but do not do any work related to this company.

Royalties: Brief Assessment of Cognition in Schizophrenia (BACS), MATRICS Consensus Cognitive Battery (MCCB), Virtual Reality Functional Capacity Assessment Tool (VRFCAT)

# Background

- There are currently no treatments approved for the treatment of cognitive impairment in schizophrenia (CIAS)
- Significant ongoing treatment development holds promise for an approved drug for CIAS before the end of this decade

# Background

- The assessment of cognition in patients with schizophrenia is not a standard component of education in psychiatry
- When treatments for CIAS become available, it will be essential for treating psychiatrists and others involved in prescribing medications to evaluate whether their patients are responsive to treatment
- Yet there are many challenges to the evaluation of treatment response for CIAS

# Aims of the Meeting

- To reach consensus on:
  - 1) methods for monitoring response to procognitive medications and interventions for patients with schizophrenia;
  - 2) the necessary tools and training to conduct this assessment in the clinic setting; and
  - 3) approaches to prescribing procognitive medications and interventions in the clinic

# Steering Committee

- George Haig, co-chair
- Richard Keefe, co-chair
- Steve Marder
- Phil Harvey
- Eduardo Dunayevich
- Ilise Lombardo
- Alice Medalia
- Michael Davidson

# Survey Methods

- Survey questions were developed by the Steering Committee and sent to 46 experts in schizophrenia, cognition, clinical trials, community psychiatry, and drug development
- Thirty-four (73%) respondents completed the survey.
- A small number of questions were not clearly understood based on comments from the experts and their data were disregarded
- Several questions revealed existing consensus and were not discussed further.
- Most questions revealed significant disagreement or divergence of opinions, and were the focus of discussion at this meeting

# Discussion Process

- A group of 23 academic and industry experts in cognition, schizophrenia, community psychiatry, and drug development were selected from the pool of 46 experts who completed the survey and invited to participate as panelists at the consensus meeting
- The consensus meeting was open to 70 audience participants who were interested in the discussion

# Panelists

| | |
|---|---|
| Chris Bowie, PhD | Queens University, Toronto |
| Robert Buchanan, MD | University of Maryland |
| Dragana Bugarski-Kirola, MD | Roche |
| William Carpenter, MD | University of Maryland |
| John Csernansky, MD | Northwestern Univ Feinberg School of Medicine |
| Pedro Dago, MD | Northwestern Univ Feinberg School of Medicine |
| Eduardo Dunayevich, MD | Amgen |
| Dante Durand, MD | University of Miami |
| Fred Frese, PhD | Northeast Ohio Medical University |
| Donald Goff, MD | Nathan Kline Institute |
| Jim Gold, PhD | University of Maryland, Baltimore |
| George Haig, PharmD | AbbVie |
| Christine Hooker, PhD | Harvard University |

# Panelists

| | |
|---|---|
| Richard Keefe, PhD | Duke University Medical Center |
| Alex Kopelowicz, MD | Semel Institute for Neuroscience |
| Tony Loebel, MD | Sunovion |
| Stephen Marder, MD | Semel Institute at UCLA |
| Susan McGurk, PhD | Dartmouth Medical School |
| Alice Medalia, PhD | Columbia University |
| Lewis Opler, MD, PhD | Columbia University Medical Center |
| Amy Pinkham, PhD | Southern Methodist University |
| Robert Stern, MD | Essex County Hospital Center |

# Meeting Structure and Process

- Brief description, including pros and cons, of several cognitive assessment methods to ground panelists in their understanding of relevant tools
- Very brief presentations where speakers were asked to argue on opposing sides of an issue or question, followed by extensive discussion by all panelists
- All of the questions that were discussed and debated during the conference were posed to the panelists for a final vote, and their responses were recorded with an audience response system
- Included in the voting process was a rank ordering of preferred method for assessing cognition in the office setting
- The audience participants were asked to record their responses on paper and were collected following the meeting

# Methods of Assessment

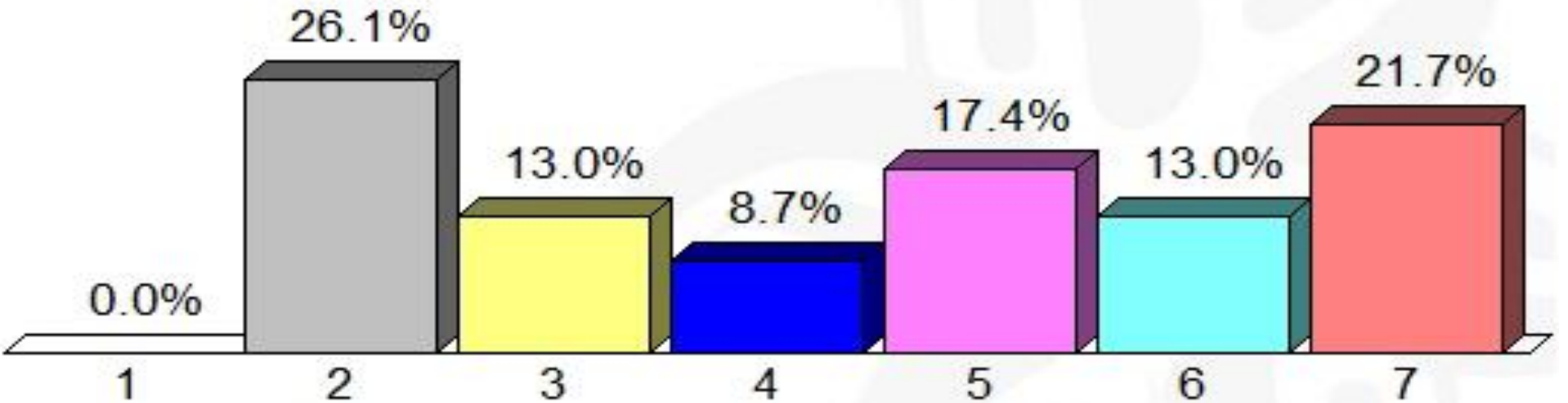
- Comprehensive cognitive performance assessment (1-2 hours)
- Brief cognitive performance assessment
  - 15-30 mins; 10 mins; 5 mins
- Interview-based measures of cognition
- Interview-based assessment of real-world functioning
- Performance-based measures of functional capacity

# Conclusions

- Both cognition and functioning are important in the evaluation of efficacy for a cognitive-enhancing treatment
- No consensus was reached on whether the impracticality of formal assessments of cognition outweighs their validity for monitoring treatment in clinical practice
- Strong consensus that clinicians can assess response if they have frequent contact with the patient and that patient interviews alone are not sufficient
- The role of informants is important, but depends upon the frequency of contact between patient and clinicians
- There was no consensus on the best methods for assessing treatment response, although brief performance-based cognitive assessments, interview-based assessments, and performance-based measures of functional capacity were viewed as slightly more favorable

# Importance of Monitoring Response to Procognitive Medications and Interventions

The impracticality of formal assessments of cognition outweighs their validity for monitoring treatment in clinical practice

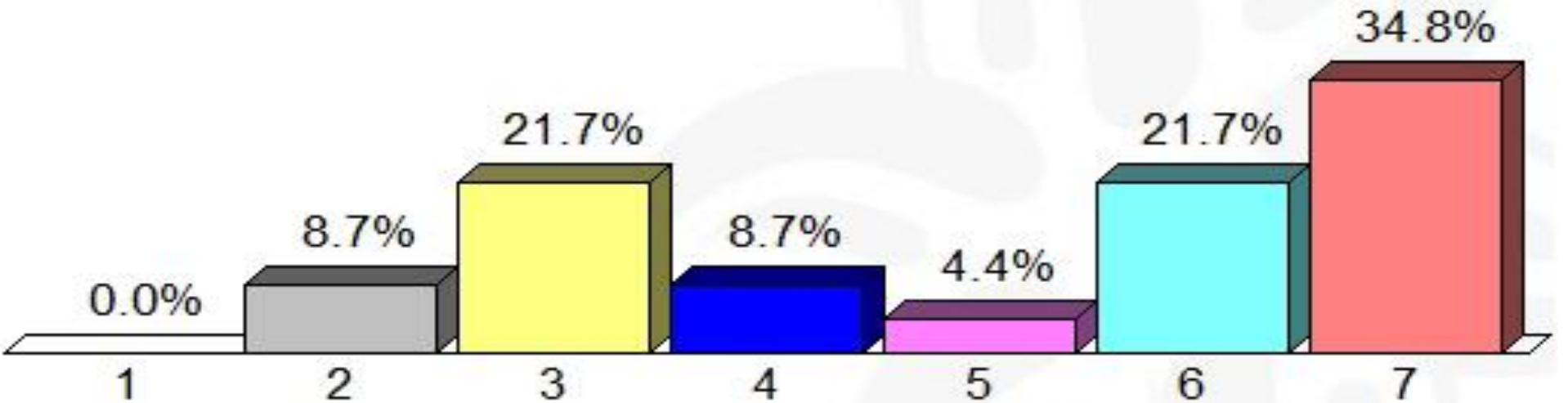



Mean: 4.4

Slide: 6

# Inputs Needed for Interview-Based Methods

## 1. Patient interviews are sufficient to assess response

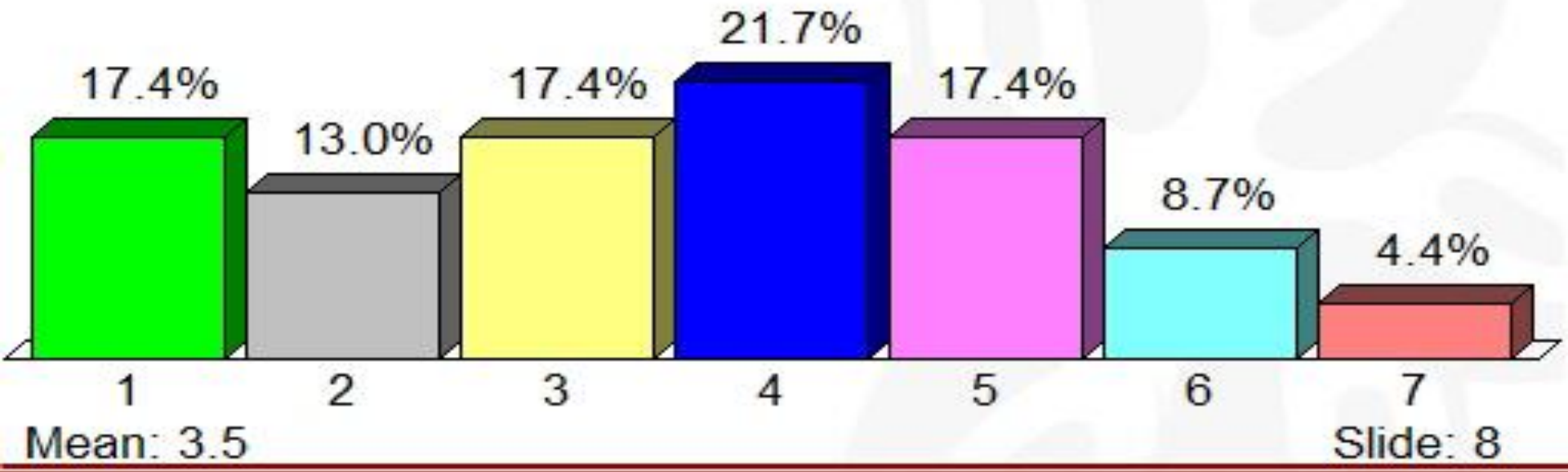



Mean: 5.1

Slide: 7

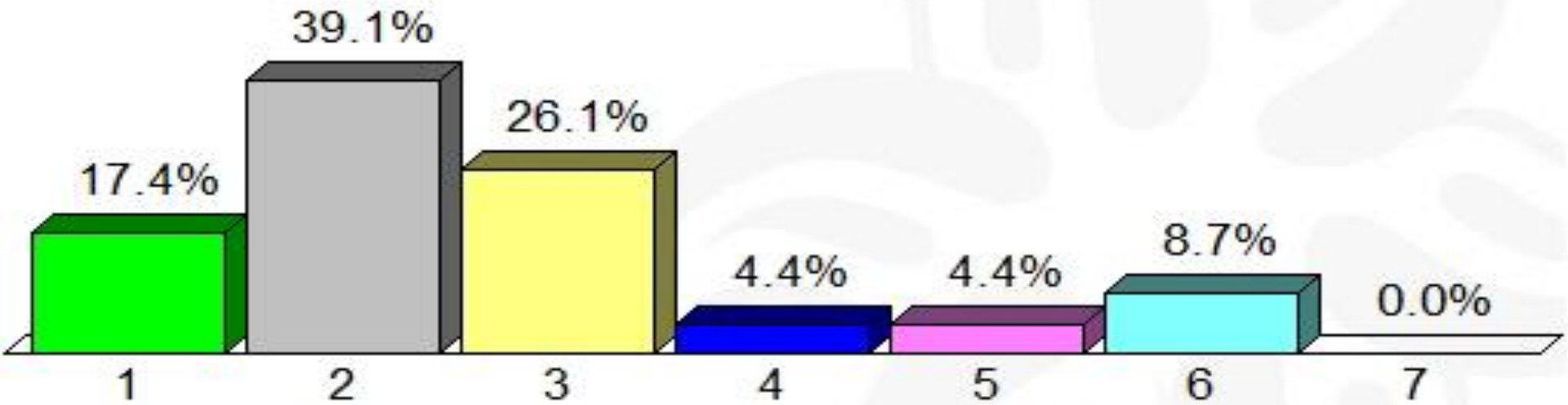
# Inputs Needed for Interview-Based Methods

2. Informants (caregiver/family/employer) are vital to the assessment of response



# Inputs Needed for Interview-Based Methods

3. A high-contact clinician can determine response based on regular examinations

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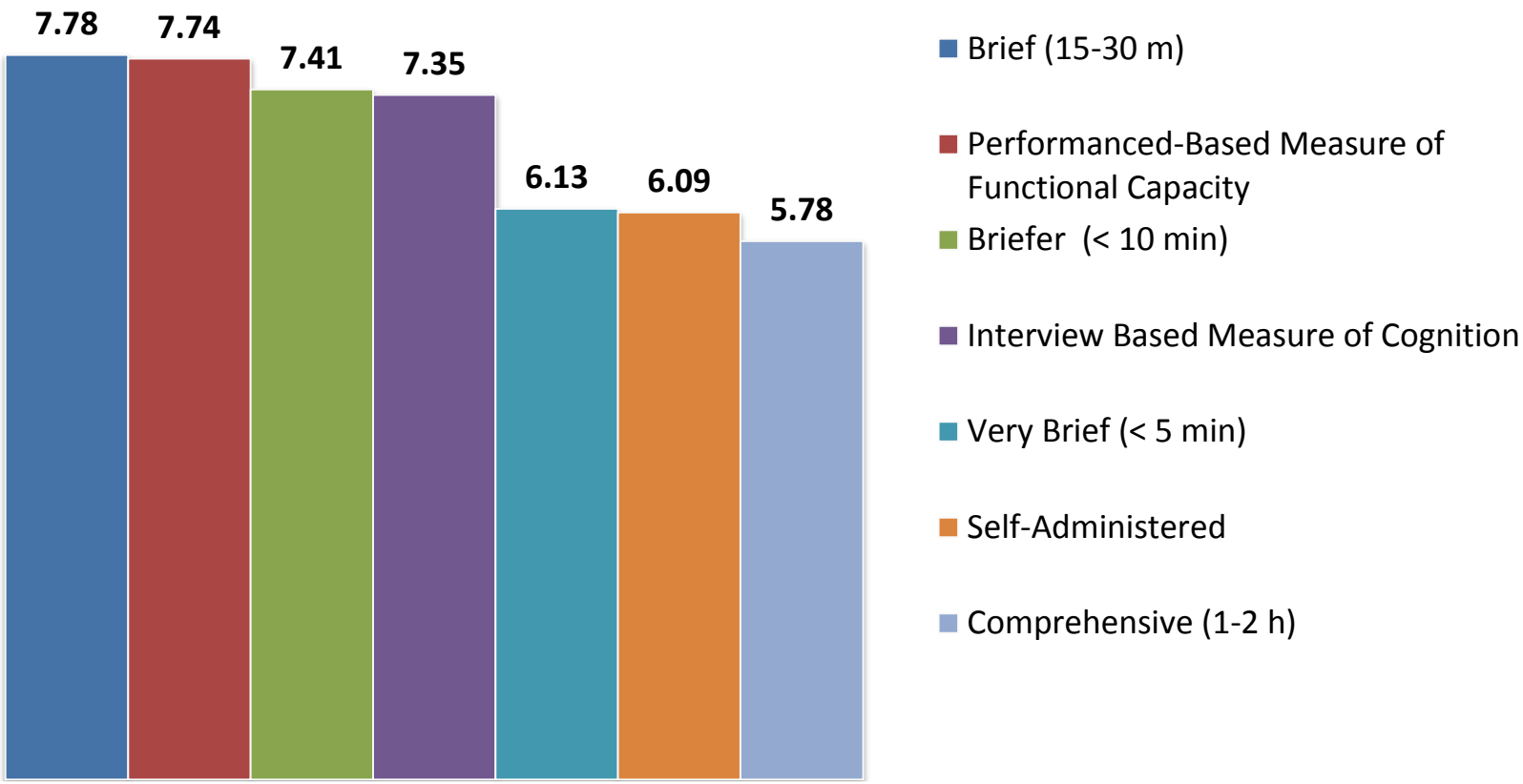
# Weighted Evaluation of Assessment Methods



# Conclusions: Patient Selection

- There was clear consensus that age and duration of illness should not be a consideration in patient selection for procognitive treatments. However, if resources are limited the participants viewed younger and less chronic patients as a priority.
- Which patients receive treatment should not depend upon their baseline level of cognitive impairment or their opportunity to improve functionally.

# Conclusions: Positive Symptom Concerns

- Treatment can be initiated in a patient population that is likely to respond to treatment, with or without the presence of low-moderate or relatively unstable positive symptoms
- Procognitive medications need not be discontinued during periods of acute exacerbation of psychosis.

# Conclusions: Cognitive Remediation

- Cognitive remediation is likely to facilitate and potentially enhance a drug treatment benefit.
- However, cognitive remediation should not be required for drug treatment to be initiated
- Drug companies and other developers of procognitive medications should study the additive benefits of cognitive remediation and other nonpharmacological treatments in the development of procognitive medications, and data should be published or included in product labeling

# SUPPORTIVE DATA SLIDES

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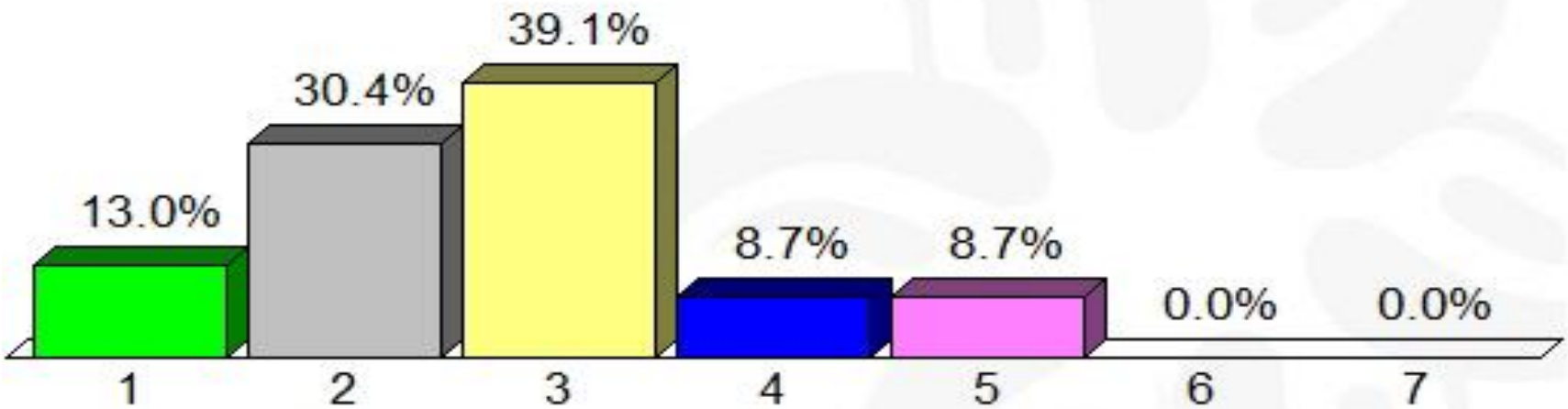
# Definition of Treatment Response

1. Efficacy is defined as improvement in cognition




Mean: 2.7

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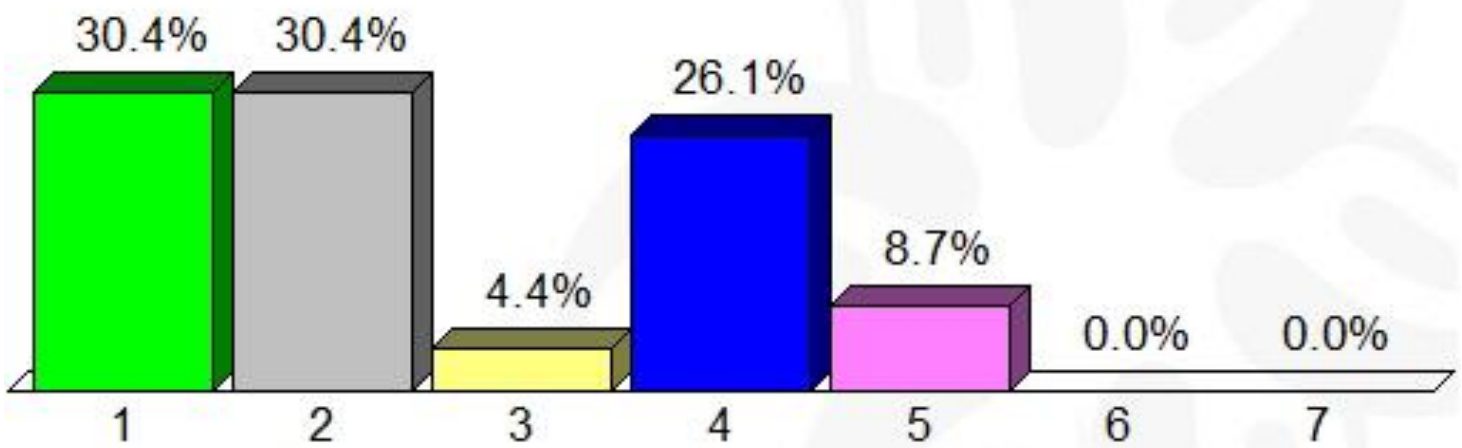
# Definition of Treatment Response

## 2. Efficacy is defined as functional improvement




Mean: 2.5

Slide: 4

# Comprehensive Batteries (Keefe)

- Many different domains of cognitive impairment in schizophrenia
  - MATRICS group chose 7 of them for a *clinical trials battery*
- Patients with schizophrenia vary greatly in their profile and severity of their cognitive impairment
- What aspect of cognition is improving (or getting worse!) with treatment is tremendously important clinical information
- Clinical response is difficult to detect and depends heavily on the test-retest reliability of the measure
  - 90% Reliable Change Index of MCCB composite score with test-retest reliability of .90 is 10 points!
- Sensitive assessment needs to be broad and deep

# Validated Brief Assessments (Gold)

- <u>30 minute tools:</u>
  - RBANS
  - BACS
- <u>10-15 minute tools—none have RCIs:</u>
  - BNA,  Fervaha, 2014: LNS + Dig Sym
  - BCATS, Hurford, (2011):TMTB, Fluency, Dig Sym
  - BCA, Velligan (2004):Fluency, TMTA+B,HVLT
- “If you sacrifice reliability for testing time, the consequence is that even larger changes will be needed to be considered beyond chance, and that won’t happen very often, so even a drug with significant benefits will look like a failure.”

# Functional Capacity Measures (Bowie)

1. Mediate the cognition – functioning relationship

1. Easy to administer, well tolerated

1. Very good psychometric properties (comparable to cognition)

1. Superior to cognition for predicting independent living and work

1. Indirect relationship to cognitive change

1. Issues with cultural adaptability?*

1. Intrapersonal, Interpersonal, and Extrapersonal factors limit the relationship with actual community functioning

1. No direct assessment of work*

# Community Functioning (Harvey)

- Domains of Community Functioning
  - Social
  - Vocational/Productive
  - Residential/Self Care
- Assessment Strategies
  - Self Report
  - Informants/Observers/Clinician
  - Record/Archives

# Patient/Care-giver/Staff assessment (Marder)

- Strengths
  - Describes functioning in real world
  - Cognition and functional capacity measures are only weakly related to real world functioning
  - Data from SCoRS and other instruments indicates Care-giver information is valuable – perhaps more than pt information
  - Patients may appreciate changes in cognition that do not translate to functioning
- Limitations
  - Other informants may not be available
  - Informants may have agendas
  - Patients – and others – can not reliably compare their cognition with that of others.

# Formal Assessments Are Necessary (Hooker)

- Self-report susceptible to <u>bias</u>
- Formal assessment is <u>objective</u>
  - Performance assessment more reliable
  - Standardized criteria for cognitive improvement
  - Sensitive to cognitive change
- Tests measure different cognitive processes
  - target & assess specific neurocognitive systems
- Feasible
  - Web-based tools

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## Why test?

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When you **test yourself** and **build your brain profile**, you contribute to brain research.

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Of Mice and Man-sized Unicorns: In Defense of Large Sample Science Earlier this year, Button et al. published an excellent article highlighting the need for greater statistical power in ...

Hormones and Being Overweight – Research Study at Massachusetts General Hospital I wanted to pass this along to anyone who is interested.  My colleagues at Massachusetts General Hospital are looking for ...

## Brain tests

### What You Value

4354 brains

This test looks at how much you prefer to invest in the present, future, yourself, or other people.

Estimated time to complete: 12 minutes

Go!

### Personality and Emotion

5511 brains

This test looks at three different aspects of your daily emotions and personality.

Estimated time to complete: 15 minutes

Go!

### Matching Faces In Photographs

9144 brains

These tests look at how good you are at matching two photographs of the same person

Estimated time to complete: 20 minutes

Go!

### Famous Faces

38508 brains

Face recognition can be surprisingly difficult - can you identify famous people from their faces?

Estimated time to complete: 5 minutes

Go!

## Your profile

### Brain Profile


Click "Go!" next to any of the tests to the left to get started!

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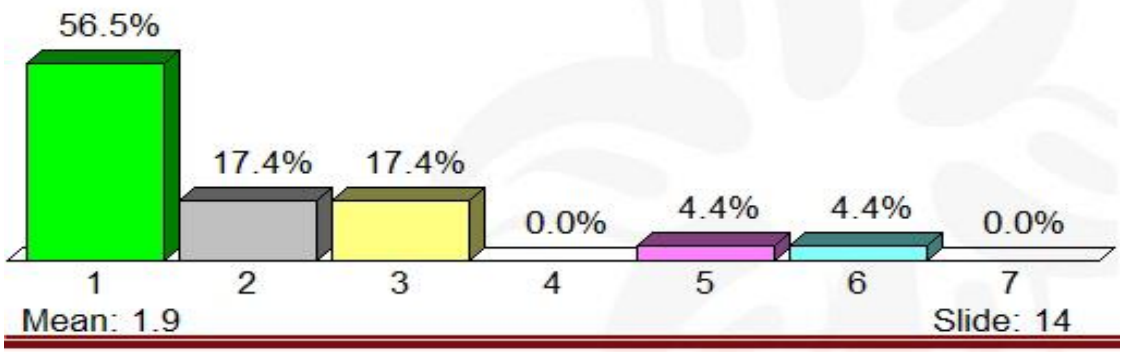
## Age and Chronicity of Disease

1. Treatment of cognitive impairment in clinical practice should be initiated independent of a patient's age and chronicity.




Mean: 1.9

Slide: 14

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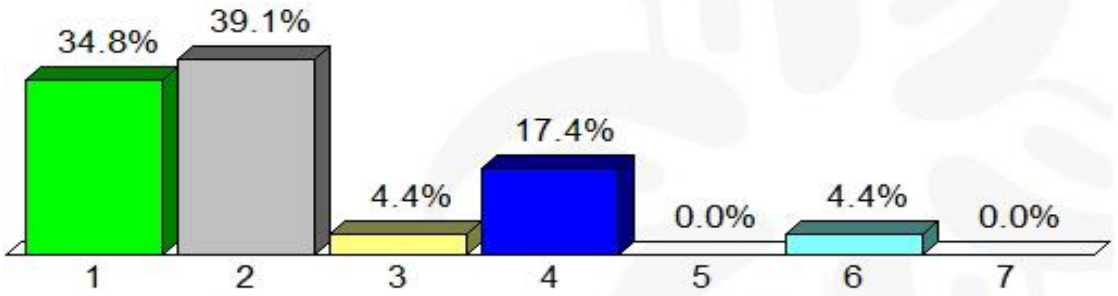
## Age and Chronicity of Disease

2. If age and chronicity are considered, should treatment of cognitive impairment in clinical practice focus on younger, less chronic patients or older, more chronic patients?




Mean: 2.2

Slide: 15

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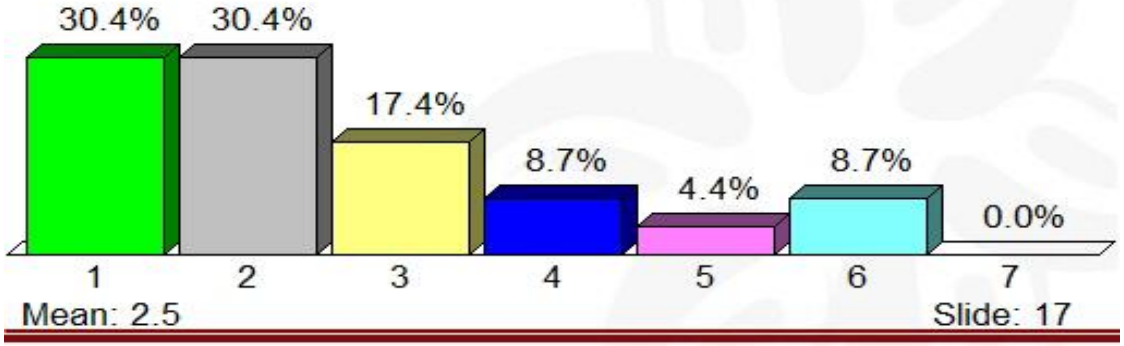
## Baseline Level of Cognitive Impairment

1. Treatment of cognitive impairment in clinical practice should be initiated independent of a patient's level of cognitive impairment.



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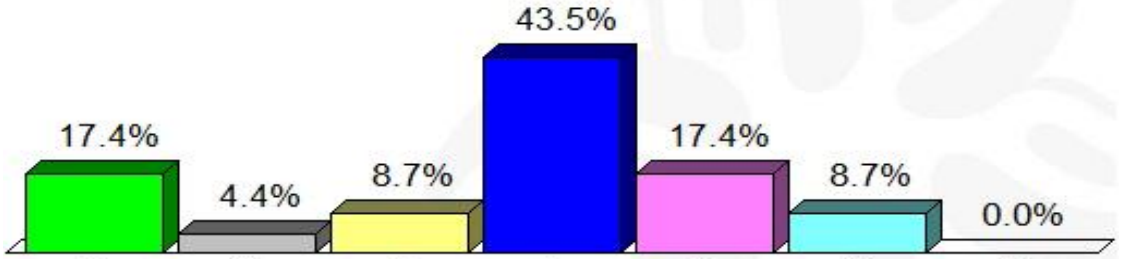
## Baseline Level of Cognitive Impairment

2. If baseline level of cognitive impairment is considered, should treatment of cognitive impairment in clinical practice focus on less impaired patients or more impaired patients?




Mean: 3.7

Slide: 18

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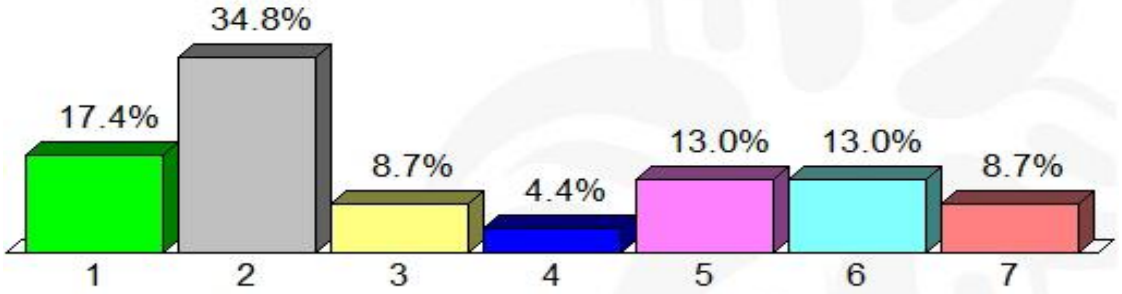
## Baseline Level of Everyday Functioning

1. Treatment of cognitive impairment in clinical practice should be initiated independent of a patient's baseline level of everyday functioning.




Mean: 3.3

Slide: 20

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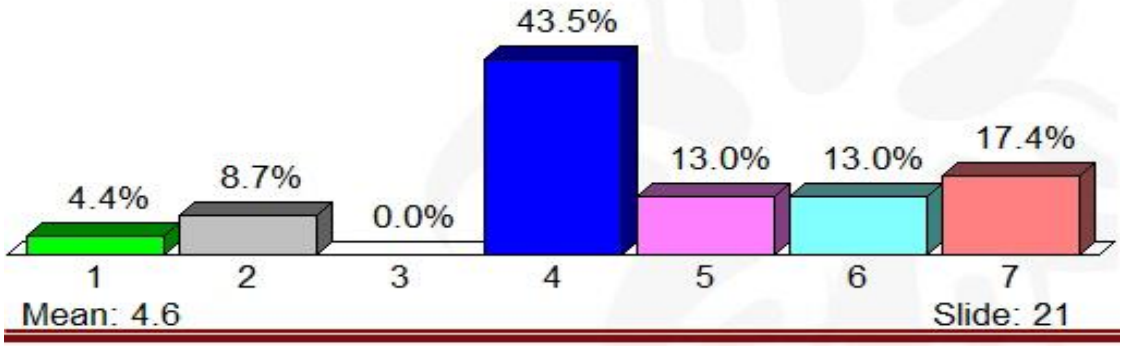
## Baseline Level of Everyday Functioning

2. If baseline level of functioning is considered, should treatment of cognitive impairment in clinical practice focus on patients with lower or higher levels of everyday functioning?




Mean: 4.6

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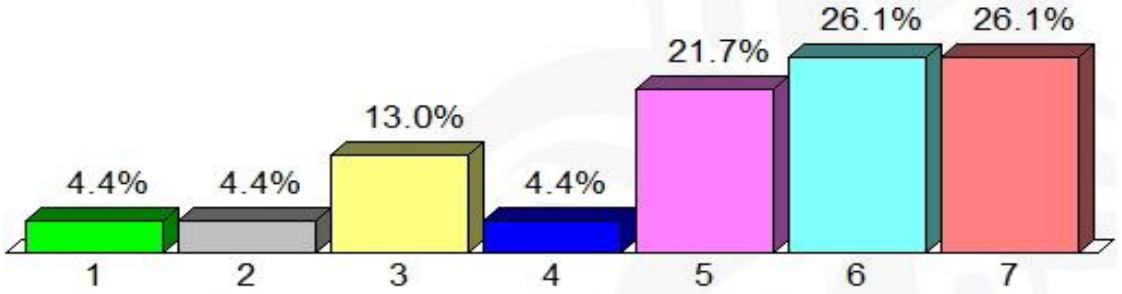
## Level of Positive Symptoms

1. Should medication treatment of cognitive impairment be restricted to patients whose positive symptoms are stable and low to moderate or be used in the broader population?




Mean: 5.2

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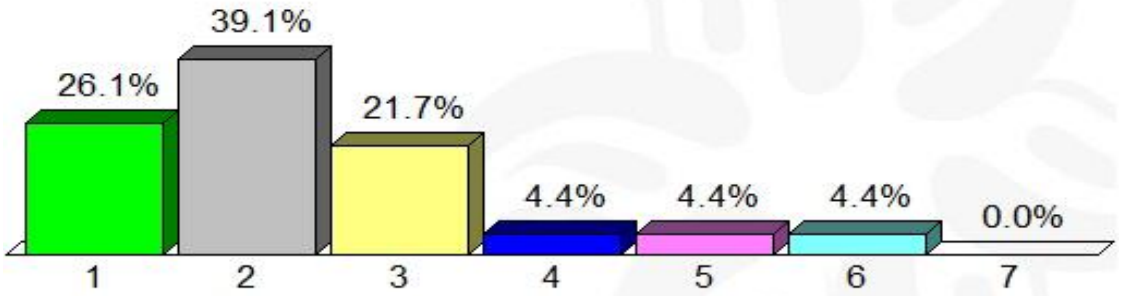
## Use of Procognitive Medications with Non-Pharmacological Treatments

1. Cognitive remediation is likely to provide substantial benefits when using medications

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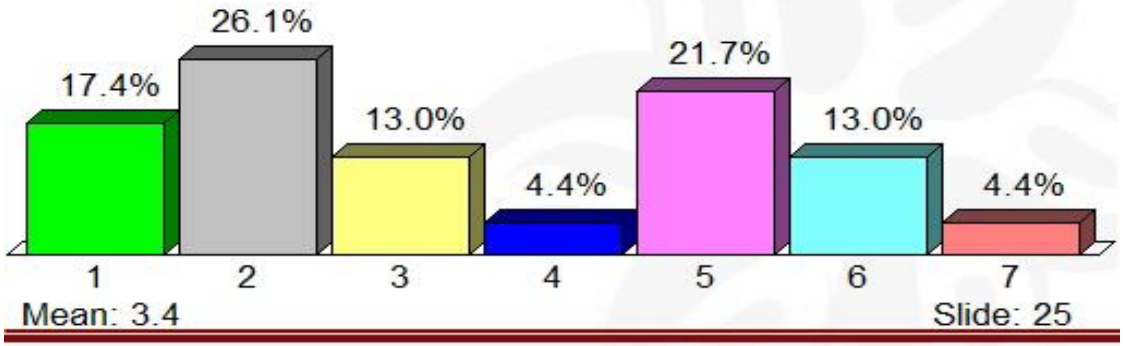
## Use of Procognitive Medications with Non-Pharmacological Treatments

2. Non-pharmacological treatments are an essential component of cognitive enhancement



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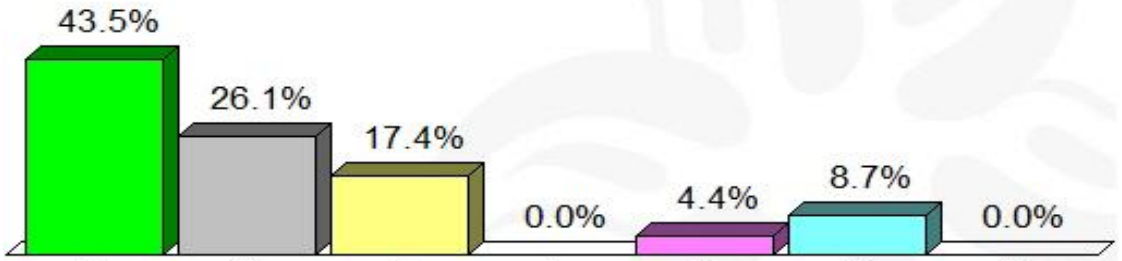
Use of Procognitive Medications with Non-Pharmacological Treatments

3. Requiring the addition of cognitive remediation to a prescription for a precognitive medication would discourage the use of these medications




Mean: 2.2

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