

Evidence-based Practices

Psychopharmacology for Recovery

Stephen R. Marder, M.D.

Professor , Department of Psychiatry

David Geffen School of Medicine at UCLA

Director, VISN 22 Mental Illness Research, Education and Clinical Center (MIRECC)

Los Angeles, California

Disclosure Information for Stephen R. Marder, MD

- Advisory board
 - AstraZeneca; Aventis; Bristol-Myers Squibb Company; Eli Lilly and Company; Janssen Pharmaceutica; Novartis; Otsuka America Pharmaceutical, Inc.; Solvay
- Honoraria
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- Speaker
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Recovery in Schizophrenia

- Definition of Recovery
- A new paradigm for designing treatments
- Improving physical health
- Addressing cognitive impairments

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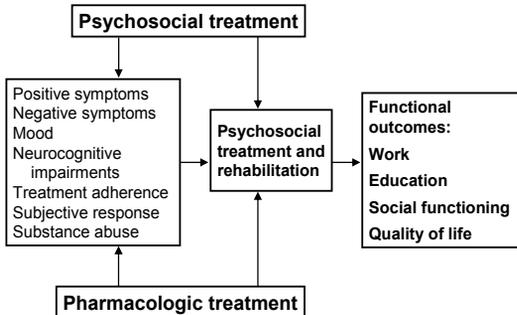
Recovery in schizophrenia

- Focuses on restoration of function rather than stabilization
- Patients are at the center of the process and are partners in setting goals and planning treatment
- Restores hope and optimism in the recovery process

Recovery in Schizophrenia

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Combining Pharmacologic and Psychosocial Intervention



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**Effective Psychosocial Treatments:
Schizophrenia PORT**

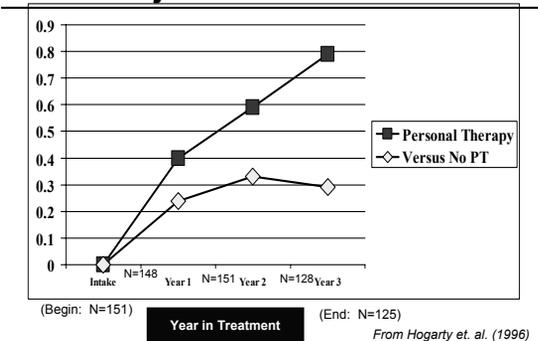
- Illness education
- Family interventions that provide education and support
- Supported employment
- Assertive community treatment
- Skills training
- Cognitive behaviorally oriented psychotherapy

PORT = Patient Outcomes Research Team.

**Trials Combining Medication With
Psychosocial Treatments (Both Controlled)**

	N	Medication (MED)	Psychosocial Treatment (PST)	Outcome	Result
Hogarty et al. (1973, 1974)	360	Chlorpromazine	Major role therapy	Relapse	>1 y: MED + ↑ PST
Hogarty et al. (1979)	105	Fluphenazine	Social therapy	Relapse	>1 y: MED + ↑ PST
Hogarty et al. (1986, 1991)	90	Fluphenazine	Family treatment, social skills training	Relapse, expressed emotion	1 y + 2 y: MED + ↑ PST
Schooler et al. (1997)	313	Fluphenazine	Psychoeducation vs family therapy	Rehospitalization symptoms	No difference between 2 PSTs
Marder et al. (1996)	80	Fluphenazine	Behavioral skills training, supportive group	Relapse, social adjustment	MED + PST adjustment ↑

**Cumulative Effect Sizes
Adjustment Outcomes**



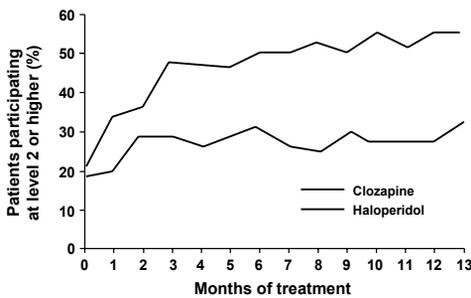
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Newer Antipsychotics and Quality of Life

- 1-year double-blind comparison of clozapine and haloperidol
- Clozapine-treated patients more likely to participate in psychosocial programs
- Participation in psychosocial treatment reduced symptoms and improved quality of life

Rosenheck et al. *Arch Gen Psychiatry*. 1998;55:618.

Comparison of Patients Assigned to Clozapine or Haloperidol Treatment With Participation in Psychosocial Treatment



Rosenheck et al. *Arch Gen Psychiatry*. 1998;55:618.

Controlled Studies of Social Skills Training (SST) in Schizophrenia

	Symptom Outcome	Relapse	Social Adjustment
Bellack (1984)	ST > CN	ST = CN	
Lieberman (1986)	SST > HH	SST = HH	SST > HH
Hogarty et al. (1986, 1991)	Groups =	Fam = Com ≥ SST = CN	Com ≥ Fam ≥ SST ≥ CN
Dobson (1995)	SST = MIL	SST = MIL	
Hayes (1995)	SST = DIS	SST = DIS	SST ≥ DIS
Marder et al. (1996)	SST = Sup	SST = Sup	SST > Sup

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MRRS II: Glynn, Marder et al

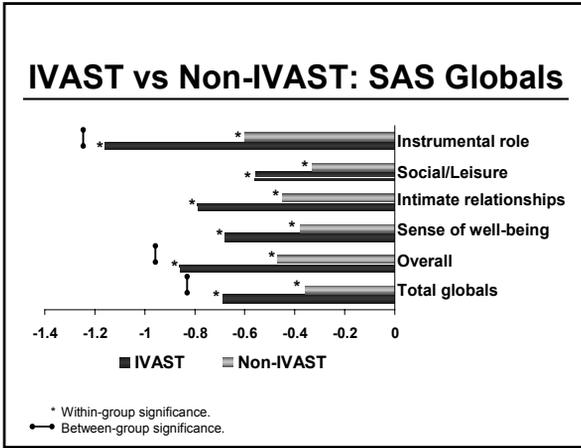
- 2-year study
- 2 (15 months educational/skills training groups ± IVAST) x 2 (haloperidol vs risperidone) design
- In vivo amplified skills training (IVAST)
 - Approximately 2 h/wk practicing group skills in community
- 62 outpatients with *DSM-IV* schizophrenia

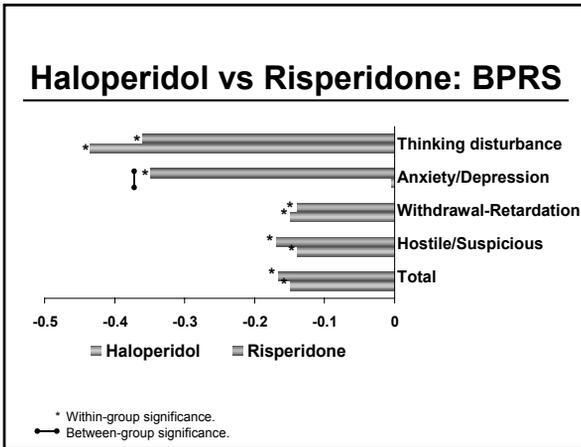
**Demographics:
Risperidone vs Haloperidol**

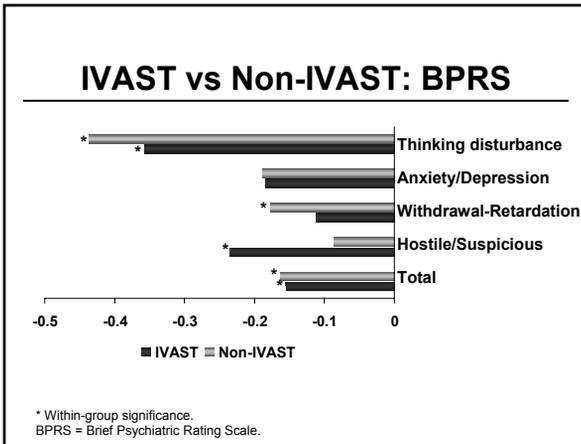
	Risperidone n = 32	Haloperidol n = 30
Age, y (± SD)	43.7 (9.2)	43.3 (8.4)
Age of onset, y (± SD)	25.3 (6.1)	24.7 (4.9)
Education, y (± SD)	12.9 (1.4)	12.7 (1.1)
% Male	87.9	96.7
% White	42.4	46.7
% Single	97.0	96.7

Overview of IVAST

- Overall goal is to improve generalization from clinic to community
 - Linked to clinical-based skills training
 - Support homework completion
 - Identify opportunities to use skills
 - Reinforce use of skills
 - Approximately 2 h/wk
 - Manualized (author, Karen Blair, MS)
- IVAST = in vivo amplified skills training.







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Summary from MRRS II Study

- Risperidone treatment was associated with reductions in anxiety and depression when compared with haloperidol
- IVAST with Behavioral Skills Training (BST) was associated with improvements in social adjustment when compared with BST alone
- Patients with fewer side effects and IVAST were more likely to continue with psychosocial treatments

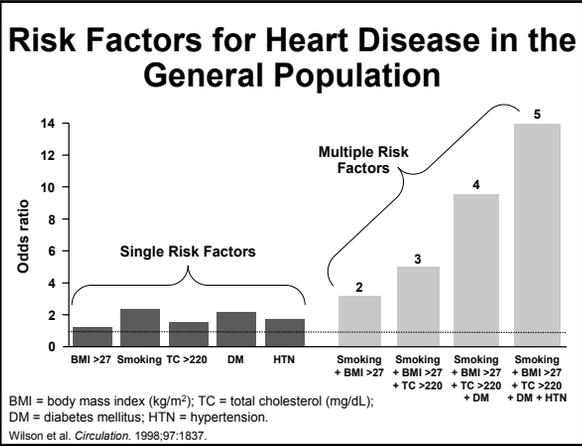
Recovery in Schizophrenia

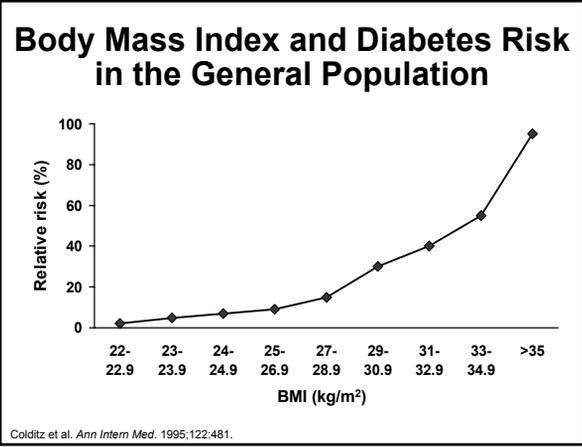
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Increased Mortality Associated With Schizophrenia

- Mortality: 1.6-2.6 times greater than nonschizophrenic population^{1,2}
- Life expectancy: 20% shorter than general population²
 - Average age of death 61 vs 76 years

1. Harris and Barraclough. *Br J Psychiatry*. 1998;173:11.
 2. Newman and Bland. *Can J Psychiatry*. 1991;36:239.
 3. Goff et al. *Med Clin North Am*. 2001;85:663.





Cardiovascular and Metabolic Risks

Heart attack

Diabetes

Peripheral vascular disease

Metabolic Syndrome
3 or more risk factors required for definition

Risk Factor	Defining Level
Abdominal obesity	Waist circumference >102 cm (>40 in) Men >88 cm (>35 in) Women
TG	≥150 mg/dL
HDL cholesterol	<40 mg/dL Men <50 mg/dL Women
Blood pressure	≥130/85 mm Hg
Fasting blood glucose	≥110 mg/dL

Insulin resistance

Atherosclerosis

Stroke

Acute coronary syndrome

Adapted from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486.

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Mount Sinai Consensus Conference on Antipsychotic Prescribing (October 17-18, 2002)

- Organizers: Susan Essock, Alexander Miller, Steve Marder, Scott Stroup, Catherine Craig, Ellen Weissman, Steven Shon. Schizophrenia experts: Jeffrey Lieberman, John Davis, Bob Buchanan, Nina Schooler, John Kane, Dan Casey, Nancy Covell, Donna Wirshing. Medical experts: Len Pogach, Bonnie Davis, Xavier Pi-Suney, J. Thomas Bigger, Steve Yevich, David Kleinberg, Alan Friedman.

Horizontal lines for notes.

Mount Sinai Conference on Medical Monitoring

- BMI: Should be monitored for all patients; Patient should be weighed at every visit for first 6 months after starting a new medication; Weight gain of 1 BMI unit should lead to consideration of changing patients to an agent with a lower weight gain liability. Diabetes: A baseline measure of glucose should be collected for all patients before starting a new antipsychotic; Patients who have significant risk factors for diabetes should have fasting glucose or HbA1c monitored 4 months after starting an antipsychotic and then yearly.

Horizontal lines for notes.

Mount Sinai Conference on Medical Monitoring (cont'd)

- Lipids: Psychiatrists should assure that treatment guidelines are followed for monitoring and treating abnormal lipids. Prolactin: The following questions should be asked yearly: Women should be asked about changes in menstruation, libido, and whether they have milk coming out of their breasts; Men should be asked about changes in libido and erectile and ejaculatory function.

Horizontal lines for notes.

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Recovery in Schizophrenia

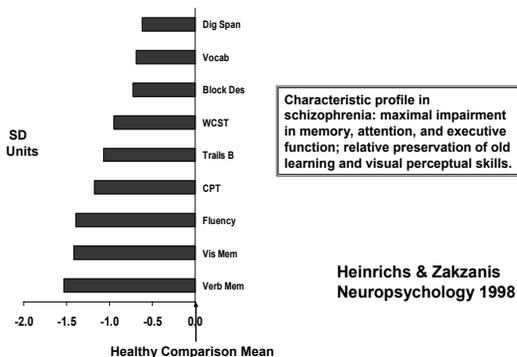
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**Cognition in Schizophrenia:
Core Feature of the Illness**

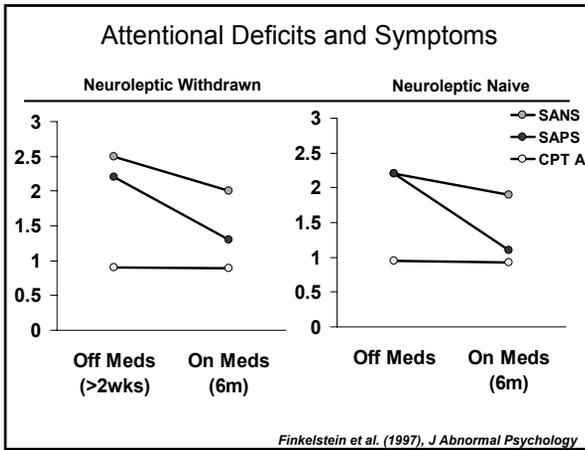
- Present before onset of clinical symptoms
- Seen in unaffected first-degree relatives
- Relatively stable across clinical state; life span
- Low cross sectional correlations w/ psychotic symptoms
- Discrepancy between clinical and cognitive effects of antipsychotic meds
- Schizophrenia profile of deficits (w/ variation)

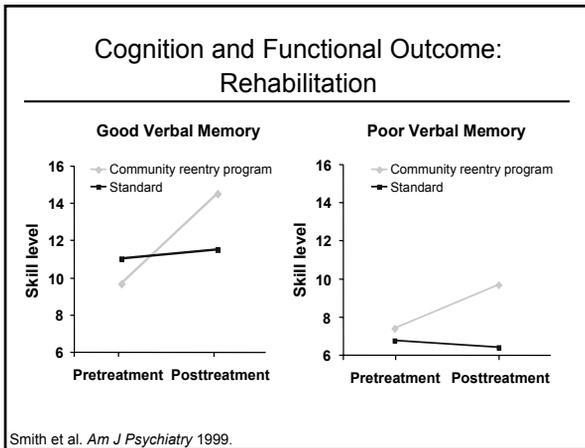
Magnitude of Cognitive Deficits in Schizophrenia

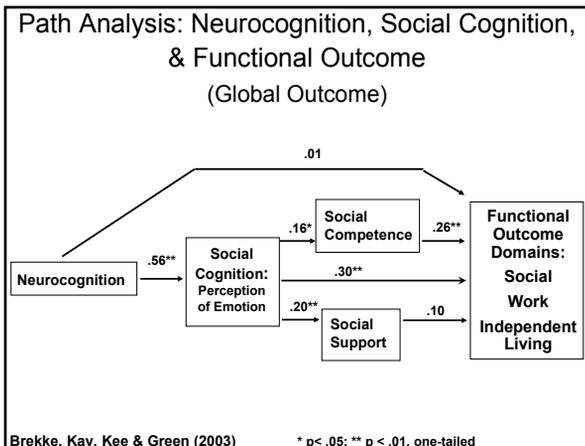
Meta-Analysis; 204 studies, 7420 patients and 5865 controls



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MATRICS: Measurement and Treatment
Research to Improve Cognition in Schizophrenia

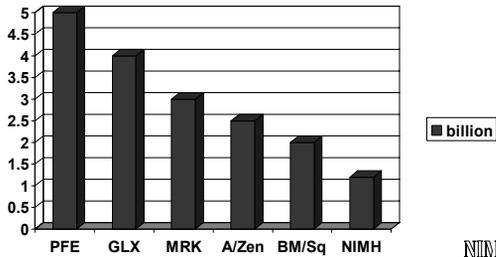
Steve Marder, M.D., P.I.
Michael Green, Ph.D., Co-P.I.

NIMH Project Officer: Wayne Fenton, M.D.
NIMH Division Director, DMDBA: Ellen Stover, Ph.D.

www.matrics.ucla.edu



Research Budget (billions): Top 5
Pharmaceutical Companies



MATRICS: Background and Rationale

- Increasing evidence that cognitive deficits are core features of schizophrenia
- Increasing support for relationships between cognition and functional outcome in schizophrenia
- Increasing research focus on the basic studies of neuropharmacology of cognition



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**MATRICS:
Objectives**

- Promote development of novel compounds to enhance cognition in schizophrenia

- Catalyze regulatory acceptance of cognition in schizophrenia as target for drug registration

- Focus economic research power of industry on neglected clinical target

- Identify lead compounds and support proof of concept trials for cognition in schizophrenia

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**MATRICS:
Deliverables**

- **Six Consensus-oriented conferences & papers: approximately 60-70 leading experts per conference**

- **Select NIMH / MATRICS consensus cognition battery for clinical trials**

- **Create database of potential lead compounds**

- **Lead to translational proof of concept trial**

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**NIMH-MATRICS Consensus Cognitive
Battery for Clinical Trials**

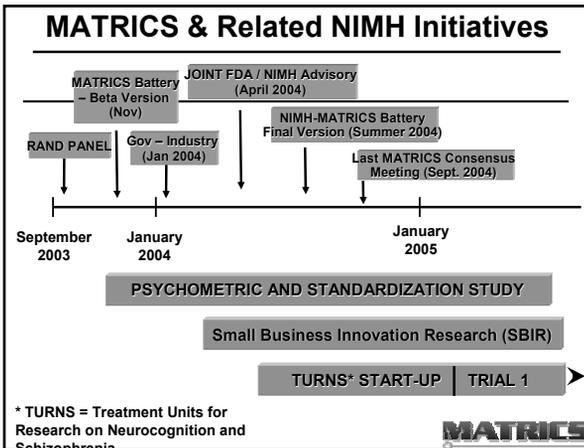
- 1) Working Memory
- 2) Attention/Vigilance
- 3) Verbal Memory and Learning
- 4) Visual Memory and Learning
- 5) Reasoning and Problem Solving
- 6) Speed of Processing
- 7) Social Cognition



MATRICS Ranking of Targets

Target	# of nominations
■ Alpha-7 nicotinic receptor agonists	31
■ D1 receptor agonists	30
■ AMPA glutamatergic receptor agonists	14
■ Alpha-2 adrenergic receptor agonists	14
■ NMDA glutamatergic receptor agonists	12
■ Metabotropic glutamate receptor agonists	12
■ Glycine reuptake inhibitors	8
■ M1 muscarinic receptor agonists	7
■ GABA A R subtype selective agonists	5

MATRICS



Summary

- Improving functional outcomes in schizophrenia requires attention to mediating factors, such as symptoms, treatment adherence, subjective response, and side effects
- These factors are affected by both psychosocial and pharmacologic interventions
- Psychiatrists should take responsibility for the health of their patients
