

High-quality care in the outpatient setting

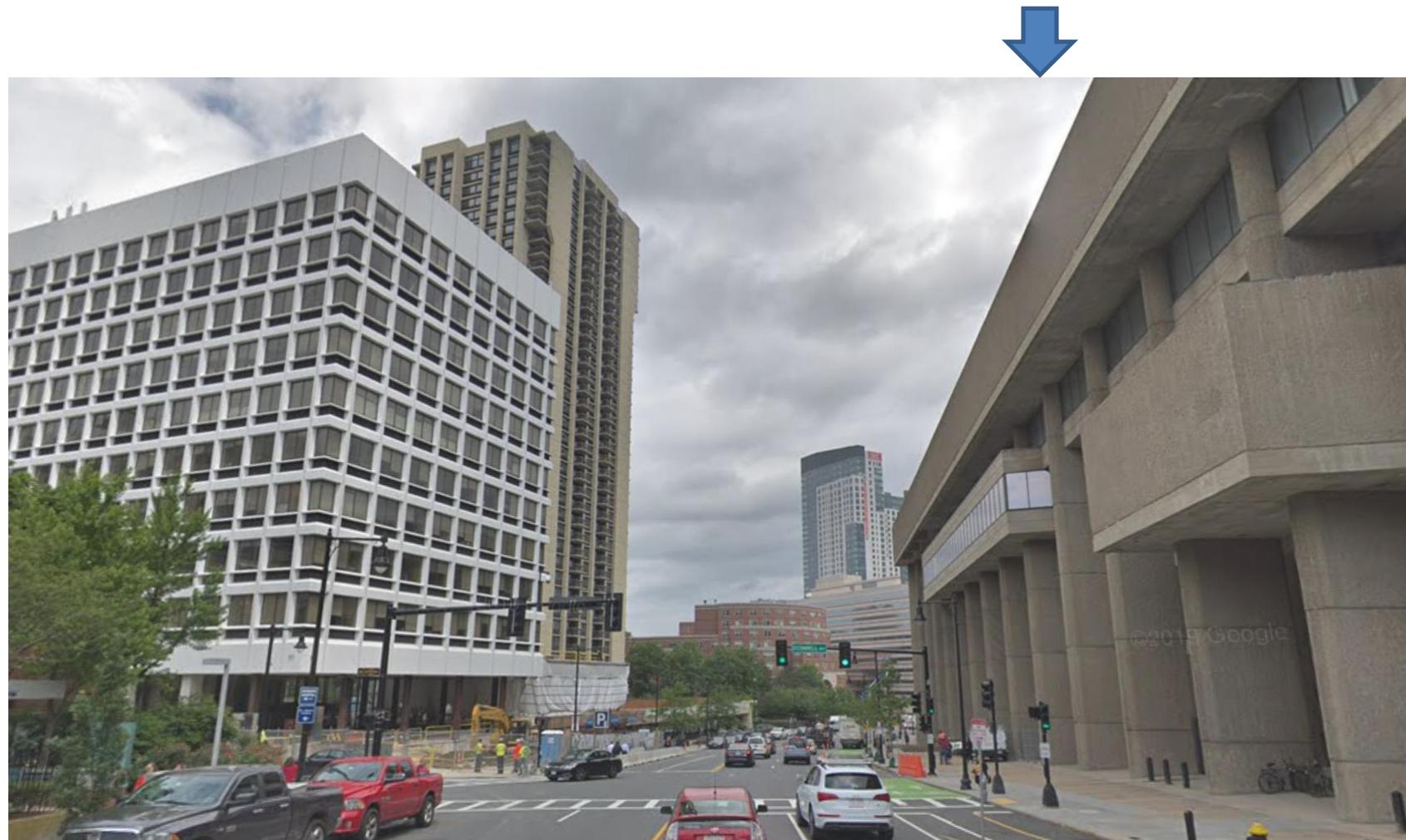
Schizophrenia and Bipolar Depression Institutional
Preceptorship

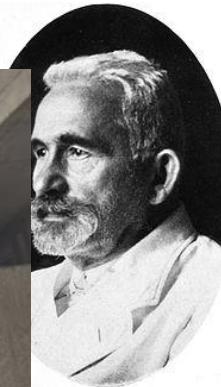
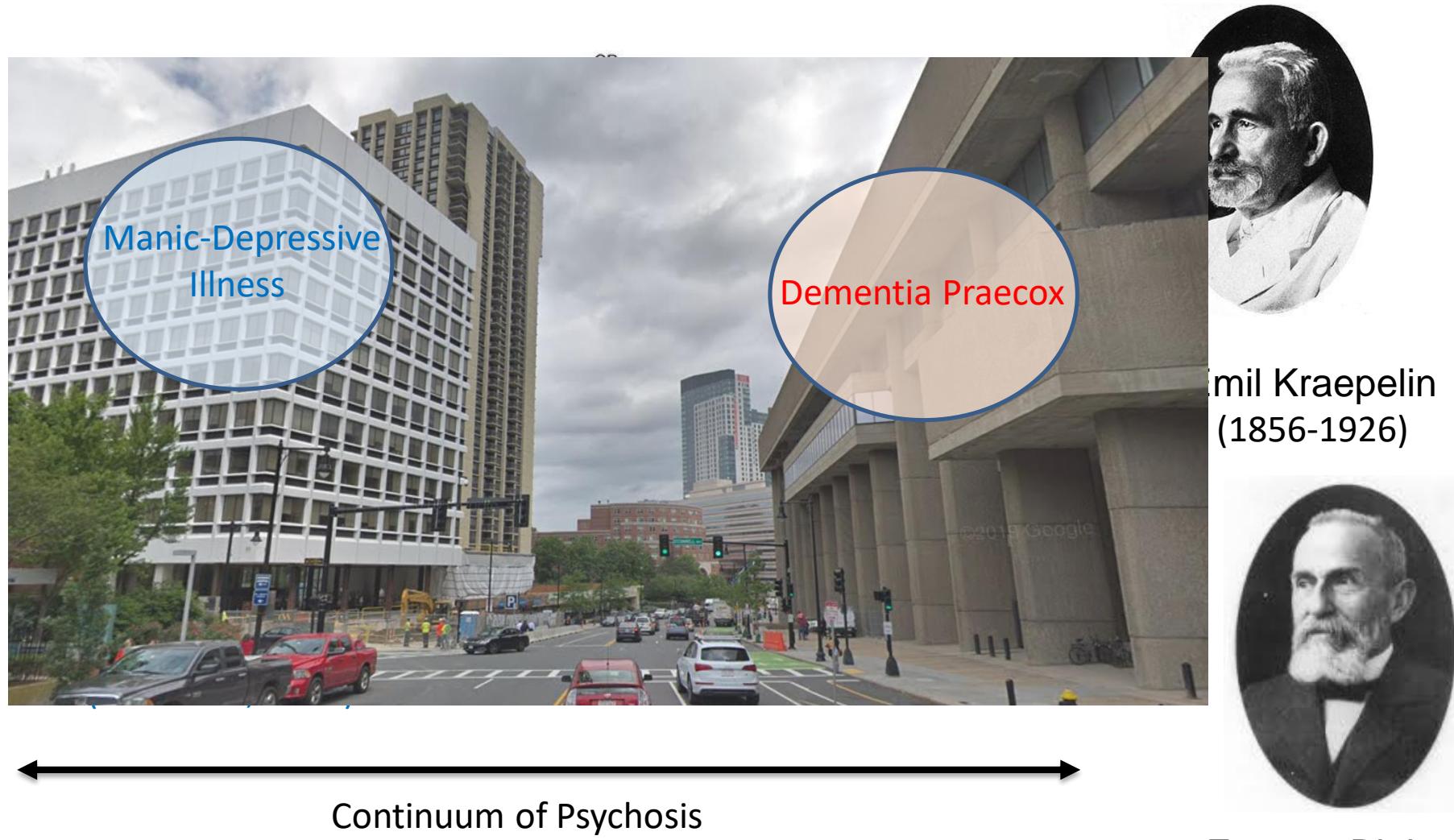
December 4, 2020

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Massachusetts General Hospital
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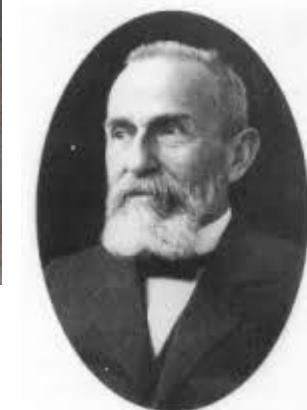


Erich Lindemann Mental Health Center

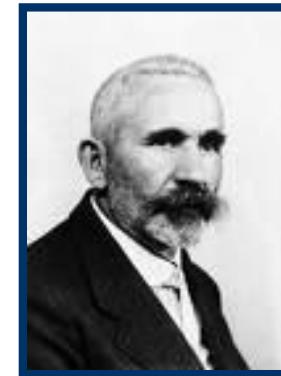
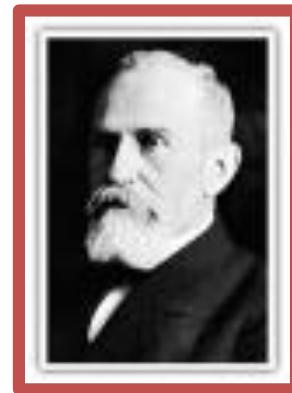




Emil Kraepelin
(1856-1926)



Eugene Bluler
(1857-1939)

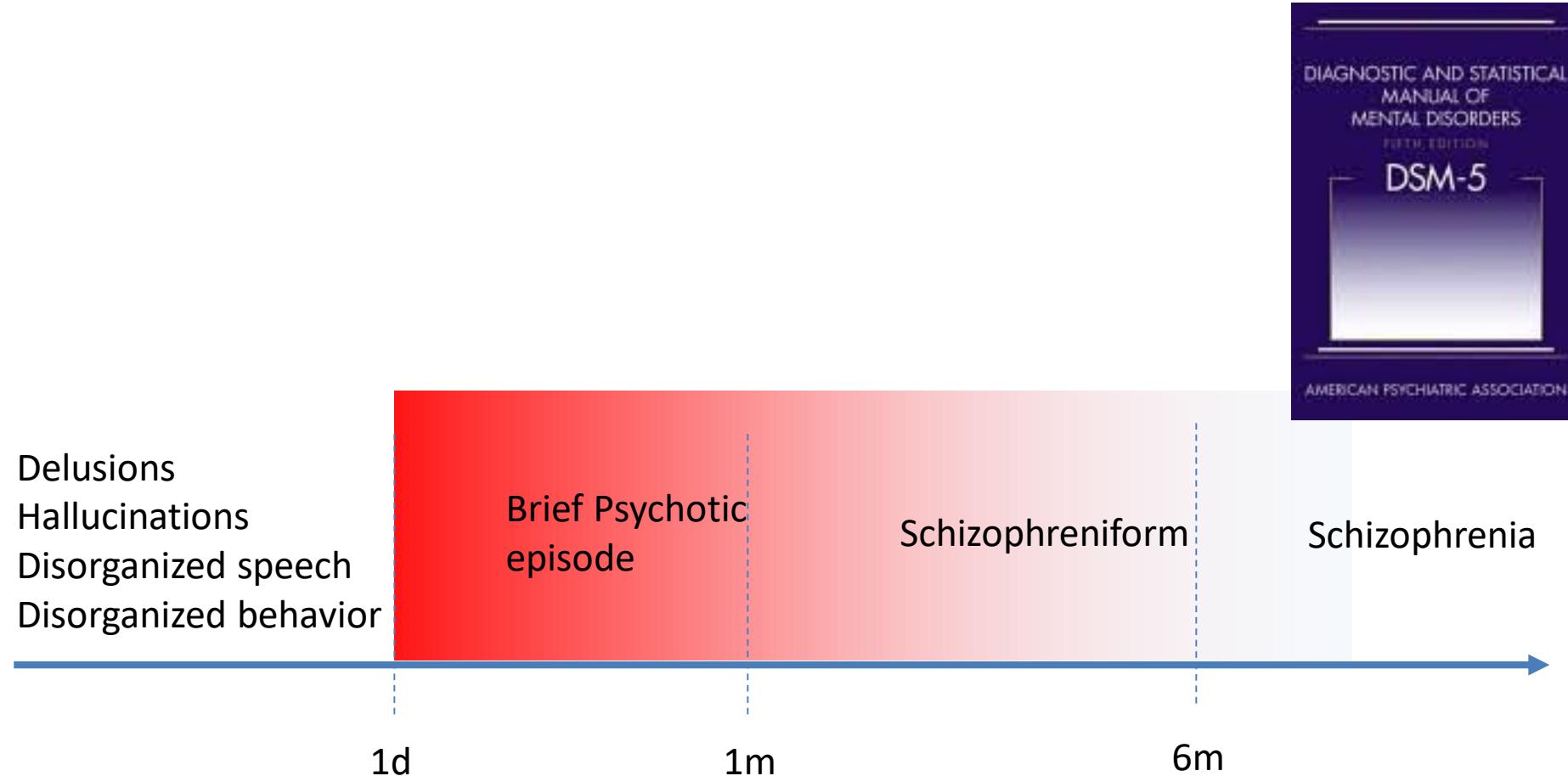


Fleishman M. Psychiatr Serv. 2003;54:142.

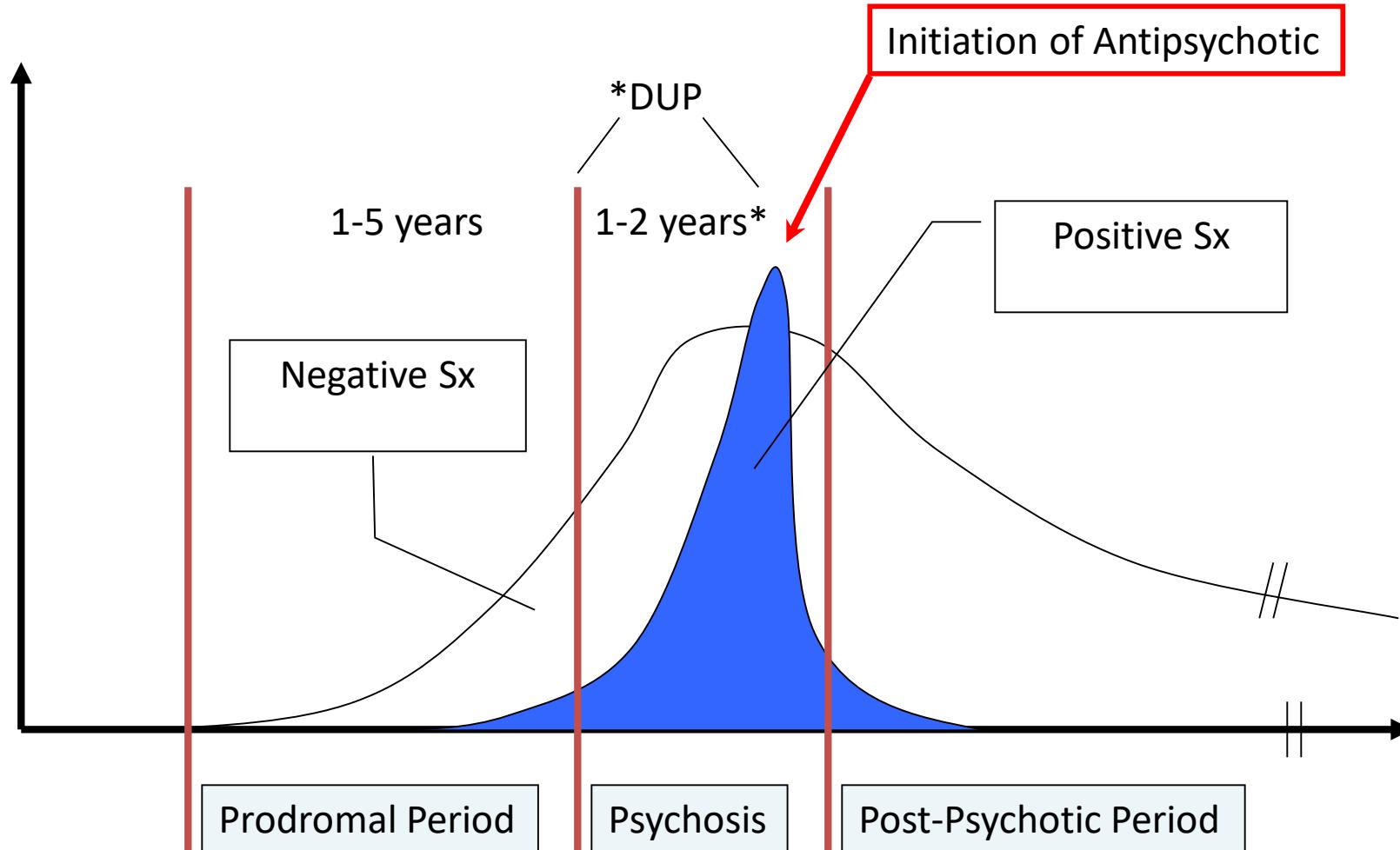
Symptoms of Schizophrenia

- Positive Symptoms
 - Hallucinations
 - Delusions
 - Thought (speech) disorganization
 - Grossly disorganized or catatonic behavior
- Negative Symptoms
 - Apathy
 - Anhedonia
 - Blunted affect
 - Social isolation
- Cognitive symptoms
 - Executive dysfunction
 - Memory impairment
 - Attention deficit
 - ...

Time Course of Diagnoses



Phases of the Illness



PREVENTION ORIENTATION

Prevention in schizophrenia¹

- Primary prevention
 - Universal prevention
 - Whole population
 - Selective prevention
 - More susceptible subgroup, still symptom free
- Secondary prevention – “early intervention”
 - Indicated prevention
 - Already showing signs of illness
- Tertiary prevention
 - Improving quality of life by reducing disability

Treatment
TIMING²

¹Brown AS and McGrath JJ. Schizophr Bull 2011;37:257.

²McGlashan TH. Schizophr Bull 2012;38:902.

Clinical staging in psychiatry

STAGE	Definition	Clinical features
0	Asymptomatic subjects	Not help seeking No symptoms but risk
1a	“Help-seeking” subjects with symptoms	Non-specific anxiety/depression Mild-to-moderate severity
1b	“Attenuated syndromes”	More specific syndromes incl. mixed At least moderate severity
2	Discrete disorders	Discrete depr/manic/psych/mixed sy Moderate-to-severe symptoms
3	Recurrent or persistent disorder	Incomplete remission Recurrent episodes
4	Severe, persistent and unremitting illness	Chronic deteriorating No remission for 2 years

Staging model of treatment

- Rational for staging:
 - Avoid progression to disease stages where only amelioration is possible
 - Better response to treatments in early stages
- Principles:
 - Early intervention to treat patients as early as possible in the disease course
 - Phase-specific care that tailors the interventions to the patient's needs
 - Stepped-up care that adjusts treatment intensity based on response
 - Integrated medical-psychiatric care to avoid medical comorbidities from treatment

HIGH QUALITY HEALTH-CARE

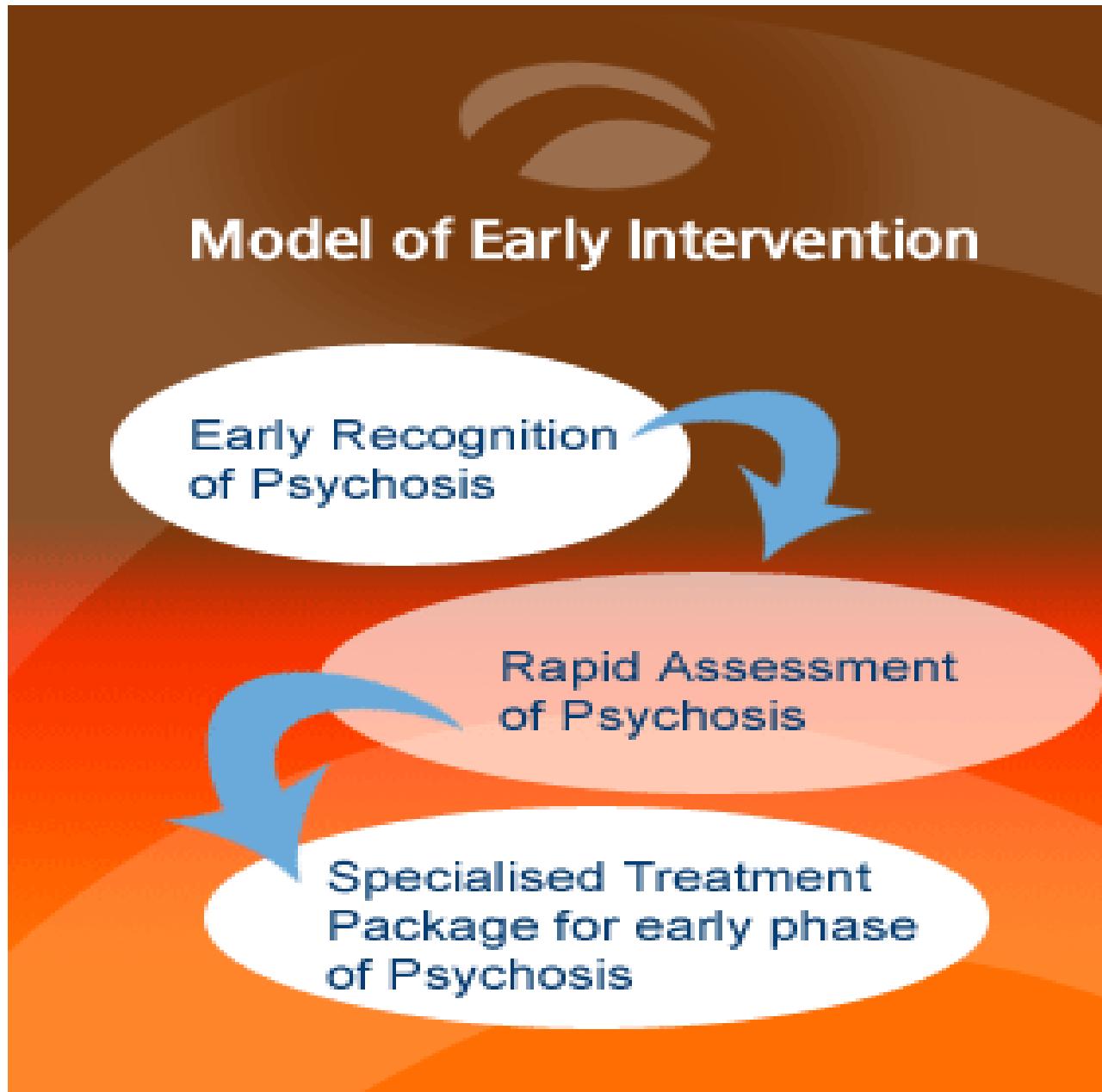
High quality health-care

6 aims for improvement

- 1) **Timely**
- 2) **Effective**
- 3) **Safe**
- 4) Patient-centered
- 5) Efficient
- 6) Equitable

Crossing the Quality Chasm: A New Health System for the 21st Century.
Institute of Medicine 2001.

Timely



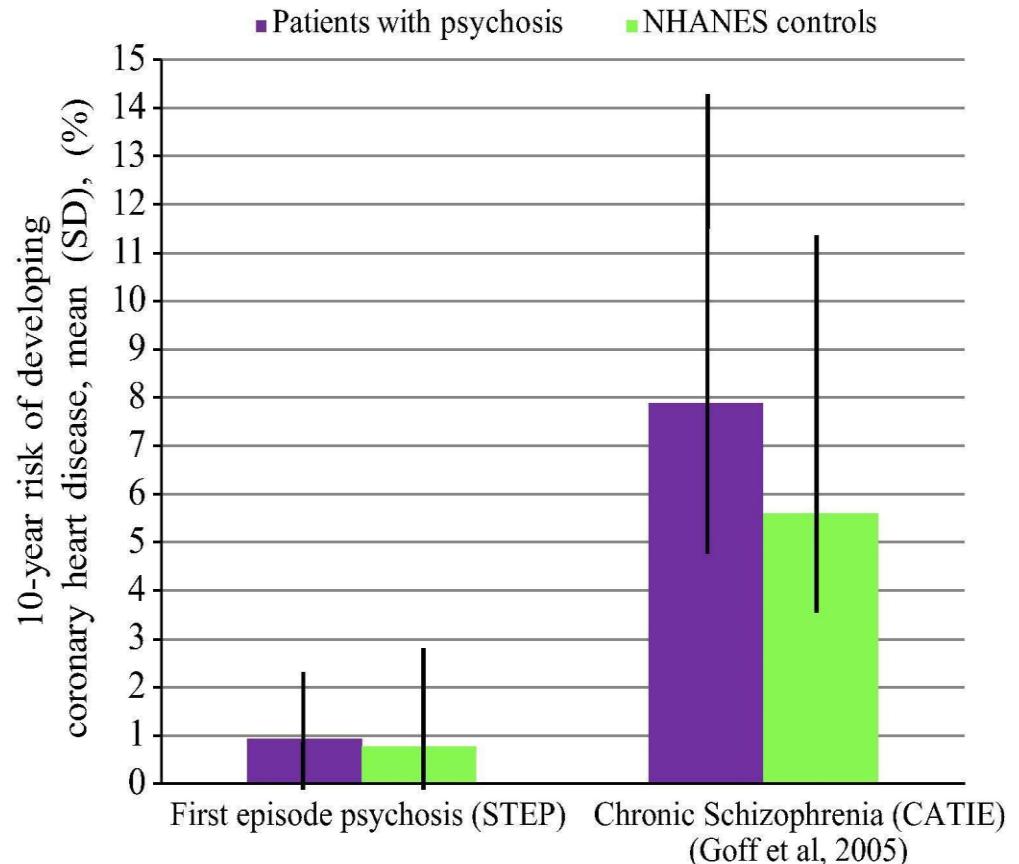
When do you start treatment? ASAP

- Minimize Duration of Untreated Psychosis (DUP)
- Early intervention is associated with:
 - Improved clinical outcomes at baseline¹, 2 years² and 5 years³
 - Fewer suicide plans or attempts: 4% vs 17%
- Long DUP is associated with¹:
 - poor treatment response
 - worse functional outcome
 - worse quality of life
 - increased social toxicity: disrupted development
- Long DUP significantly increases the odds of not achieving remission

1. Melle et al. Arch Gen Psych 2004;143-150.
2. Melle et al. Arch Gen Psych 2008;634-640.
3. Larsen et al. Psychol Med 2011;1461-1469.

“Critical period” for cardiovascular risk prevention

STEP = Specialized Treatment Early in Psychosis



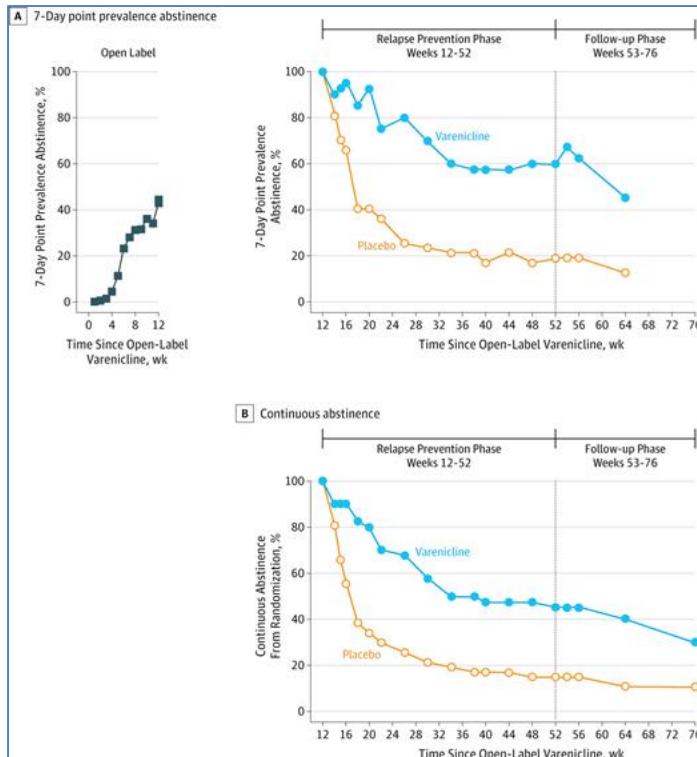
Phutane VH et al. *Schizophr Res* 2011;127:257
 Foley DL and Morley KI. *Arch Gen Psychiatry* 2011;68:609.
 Myles N et al. *J Clin Psychiatry* 2012;73:468.

**SMOKING
IN FES**

58.9%

Varenicline

EFFICACY



SAFETY

Article

Varenicline, Smoking Cessation, and Neuropsychiatric Adverse Events

Robert D. Gibbons, Ph.D.

J. John Mann, M.D.

Objective: In 2009, the U.S. Food and Drug Administration issued a black box warning for varenicline regarding neuropsychiatric events. The authors used data from randomized controlled trials and from a large Department of Defense (DOD) observational study to assess the efficacy and safety of varenicline.

Method: The authors reanalyzed data from the 17 placebo-controlled randomized controlled trials ($N=8,027$) of varenicline conducted by Pfizer, using complete intent-to-treat person-level longitudinal data to assess smoking abstinence and reports of suicidal thoughts and behavior, depression, aggression/agitation, and nausea and to compare effects in patients with ($N=1,004$) and without ($N=7,023$) psychiatric disorders. The authors also analyzed a large DOD data set to compare acute (30-day and 60-day) rates of neuropsychiatric adverse events in patients receiving varenicline or nicotine replacement therapy ($N=35,800$) and to assess reports of anxiety, mood, and psychotic symptoms and disorders, other mental disorders, and suicide attempt.

Results: In the randomized controlled trials, varenicline increased the risk of nausea (odds ratio=3.69, 95% CI=3.03–4.48) but not rates of suicidal events, depression, or aggression/agitation. It significantly increased the abstinence rate, by 124% compared with placebo and 22% compared with bupropion. Having a current or past psychiatric illness increased the risk of neuropsychiatric events equally in treated and placebo patients. In the DOD study, after propensity score matching, the overall rate of neuropsychiatric disorders was significantly lower for varenicline than for nicotine replacement therapy (2.28% compared with 3.16%).

Conclusions: This analysis revealed no evidence that varenicline is associated with adverse neuropsychiatric events. The evidence supports the superior efficacy of varenicline relative to both placebo and bupropion, indicating considerable benefit without evidence of risk of serious neuropsychiatric adverse events, in individuals with and without a recent history of a psychiatric disorder.

(*Am J Psychiatry* 2013; 170:1460–1467)

¹Evins AE et al. *JAMA* 2014;311:145.

²Gibbons RD and Mann JJ. *Am J Psychiatry* 2013;170:1460.

³Evins AE. *Am J Psychiatry* 2013;170:1385. (Editorial)

Effective

Effective treatment

- Comprehensive
 - Medications
 - Psychological treatments:
 - CBT
 - Cognitive Remediation
 - IMR
 - “Novel”
- Stepped-up care
 - Treatment intensity adjusted based on response: augmentation strategies

PORT Guidelines¹, 2 meta-analyses^{2,3}:

- Specialized Psychopharmacology
- Cognitive Behavioral Therapy
- Assertive Community Treatment
- Supportive Employment
- Family Based Treatment
- Dual Diagnosis Treatment
- Weight Management

1.PORT Guidelines, 2009 2.Addington et al. Psych Services 2013;452-457. 3. Jimenez et al. Schizophr Bull 2011;619-630.

CBT for schizophrenia

- Evidence-based treatment for residual psychosis (NICE recommended since 2009!)^{1,2}
 - Assumptions
 - Psychosis on a continuum with normal experience
 - 5% general population reports subclinical psychosis³
 - Stress-vulnerability hypothesis
 - Mind and senses as fallible
 - Delusions are not necessarily fixed beliefs
- CBT for negative symptoms⁴
- Future: D-cycloserine augmentation

¹Turner DT et al. Am J Psychiatry 2014;171:523. [Meta-analysis](#)

²Burns AM et al. Psychiatr Serv 2014 (in press). [Meta-analysis](#)

³van Os J et al. Psychol Med 2009;39:179.

⁴Perivoliotis D and Cather C. J Clin Psychol 2009;65:815.

Cognitive remediation

- Antipsychotics
 - Limited benefit for cognition¹
 - EUFEST ES 0.33 to 0.56
 - Might have cost
- Cognitive remediation
 - Makes use of **neuroplasticity**
 - Targets **systems, not symptoms**
 - Uses different approaches
 - Rehearsal learning (“drills”)
 - Compensatory strategies
 - Computer-based learning
- Meta-analysis²
- Critique
 - Needs to be combined with rehabilitation
 - Improvement in performance does not generalize
 - Patient selection critical (e.g., age)

“Brain remediation”
Cognitive training
Cognitive rehabilitation
Cognitive remediation

ES 0.45

¹Davidson M et al. Am J Psychiatry 2009;166:675.

²Wykes T et al. Am J Psychiatry 2011;168:472.

³Keshavan MS et al. Am J Psychiatry 2014;171:510. REVIEW

IMR is a curriculum that consists of:

- A series of weekly sessions
- A combination of motivational, educational, and cognitive-behavioral techniques
- Main focus on developing personalized strategies for managing psychiatric symptoms
- Collaborative environment with patients
- Provides information, strategies, and skills patients can use to further their own recovery





IMR principles

- Patients are asked to do homework on a weekly basis
- Families are included if desired
- Educational Handout Topics:
 - Recovery strategies
 - Practical facts about mental illness
 - The stress vulnerability model and treatment strategies
 - Building social support
 - Reducing relapses
 - Using medication effectively
 - Coping with stress and coping with problems and symptoms



- ❖ **FTC IMR Groups**
 - ❖ Curriculum Length: 12 weeks
 - ❖ Session Length: 1 Hour
 - ❖ Tuesdays 11:30am – 12:30pm

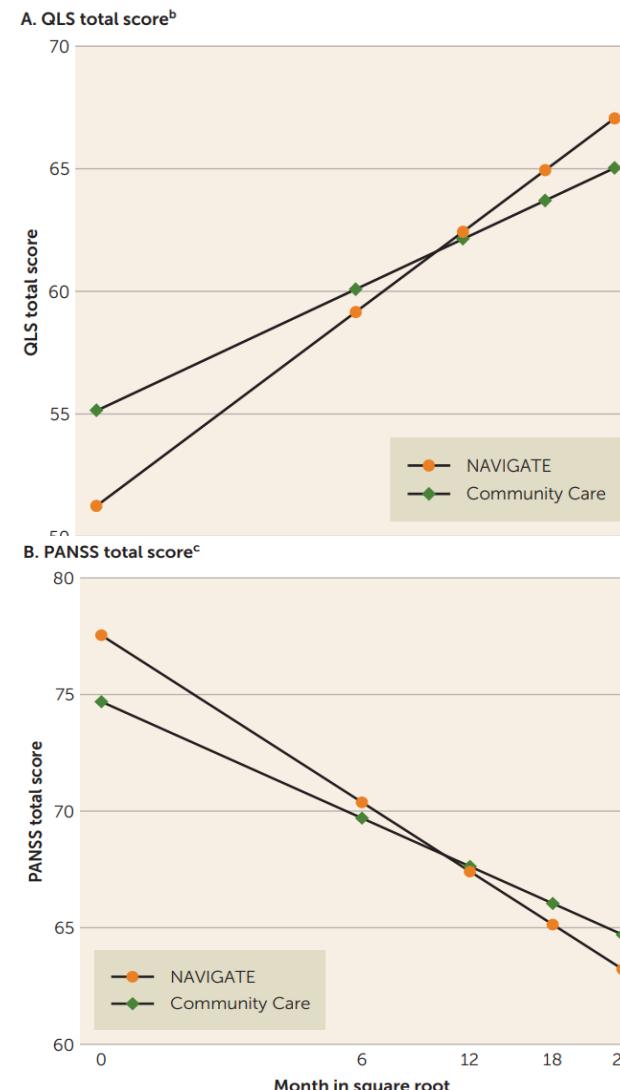
Target Population:

Young Clozapine/Olanzapine patients between the ages of 18-30 with a diagnosis of schizophrenia



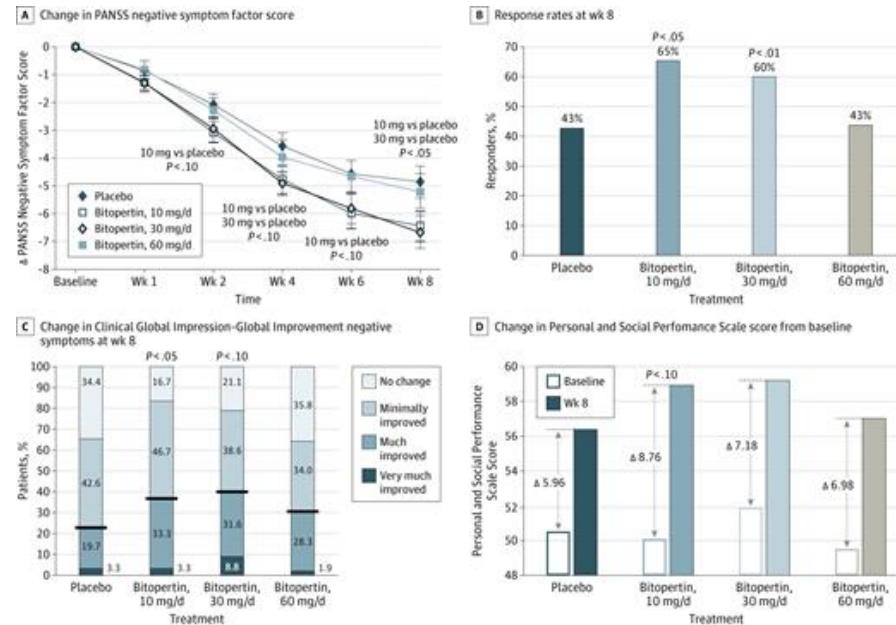
NAVIGATE Model

- NIMH RAISE initiative:
- Comprehensive tx vs. usual care
- Comprehensive tx (NAVIGATE model):
 - Med management, individual therapy, family psycho-ed, supp employment/ed
- Outcomes:
 - Time in treatment, functioning, QLS, PANSS, depression, hospitalizations



Glucine reuptake inhibitors

Bitopertin¹



Good news

Bad news²

- Negative symptoms
- “Area of therapeutic need”
- Glycine reuptake inhibitors
 - NMDA **hypofunction**
 - Glycine as allosteric modulator (agonist)

¹Umbricht D et al. JAMA Psychiatry 2014;71:637.

²Goff DC. JAMA Psychiatry 2014;71:621. Editorial: 2 negative phase III trials.

SAFE

Morbidity and Mortality

- Schizophrenia is associated with a 20 year decrease in life expectancy¹ and a 4 fold increase in mortality²
- Premature mortality is due to cardiovascular dz, respiratory dz, infections and cancers³
- Even in FEP, cardiac and metabolic abnormalities are present early on⁴
- Related to underlying illness, unhealthy lifestyle, antipsychotic meds, inadequate medical care

1. Druss et al. Med Care 2011;599-604. 2. Revier et al. J Nerv Ment Dis 2015;379-386. 3. Olfson et al. JAMA Psychiatry 2015;1172-1181. 4. Correll et al. JAMA Psychiatry 2014;1350-1363.

Monitoring guidelines

CAMESA GUIDELINE

Evidence-Based Recommendations for Monitoring Safety of Second Generation Antipsychotics in Children and Youth

Tamara Pringsheim, Constadina Panagiotopoulos, Jana Davidson, and Josephine Ho
for the CAMESA guideline group

The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) Guideline Project

Table 4. A practical tool for metabolic monitoring of children & youth treated with second-generation antipsychotics

Parameter	Pre-treatment Baseline	1 month	2 month	3 month	6 month	9 month	12 month
Assessment date							
Height (cm) ¹							
Height percentile							
Weight (kg) ¹							
Weight percentile							
BMI: (kg/m ²) ¹							
BMI percentile							
Waist circumference (At the level of the umbilicus) ²							
Waist circumference percentile							
Blood pressure (mm/Hg) ³							
Blood pressure percentile							
Neurological examination ⁴	<input type="checkbox"/> completed						
Laboratory evaluations:	Normal values						
Fasting plasma glucose	≤ 6.1 mmol/L ⁵	NR	NR				NR
Fasting insulin ⁶	≤ 100 pmol/L ⁷	NR	NR				NR
Fasting total cholesterol	< 5.2 mmol/L	NR	NR				NR
Fasting LDL-C	< 3.35 mmol/L	NR	NR				NR
Fasting HDL-C	≥ 1.05 mmol/L	NR	NR				NR
Fasting triglycerides	< 1.5 mmol/L	NR	NR				NR
AST		NR	NR	NR			NR
ALT		NR	NR	NR			NR
TSH (Quetiapine ONLY)		NR	NR	NR	NR	NR	NR
Prolactin ⁸		NR	NR	NR	NR	NR	NR
Other (e.g. Amylase, A1C, OGTT etc.) ⁹							
Physician Initials: →							

1 To determine height, weight and BMI percentiles, use age and sex specific growth charts at <http://www.cdc.gov/growthcharts/>.

2 To determine age and sex specific percentiles, go to http://www.idf.org/webdata/docs/Mets_definition_children.pdf (pages 18-19).

3 To determine age and sex specific percentiles, go to <http://pediatrics.appublications.org/cgi/content/full/114/2/S2/555>.

4 Tools available for monitoring extrapyramidal symptoms include: Abnormal Involuntary Movement Scale (AIMS), Simpson Angus Scale, Extrapyramidal Symptom Rating Scale, Barnes Akathisia Rating Scale.

5 For FPG values of 5.6-6.0 mmol/L, consideration should be given to performing an oral glucose tolerance test (OGTT).

6 Note that this assessment is NOT recommended for aripiprazole or ziprasidone, but IS appropriate for all other SGAs.

7 For fasting insulin levels >100pmol/L, consideration should be given to performing an OGTT. Normal reference range may vary between centres.

8 Assessment of prolactin levels should be completed according to protocol except when the patient is displaying clinical symptoms of hyperprolactinemia (i.e. menstrual irregularity, gynecomastia, or galactorrhea), in which case more frequent monitoring may be warranted. Please also note that risperidone has the greatest effect on prolactin.

9 It is recommended that amylase levels be monitored in case where the patient presents with clinical symptoms of pancreatitis (i.e. abdominal pain, nausea, vomiting).

NR = not recommended

Antipsychotics and Weight Gain

- Children (and all antipsychotic naïve pts) are particularly prone to weight gain
- Naturalistic study: At 12 weeks, antipsychotic naïve youth gained¹:
 - 4.4 kg on aripiprazole
 - 5.3 kg on risperidone
 - 6.1 kg on quetiapine
 - 8.5 kg on olanzapine

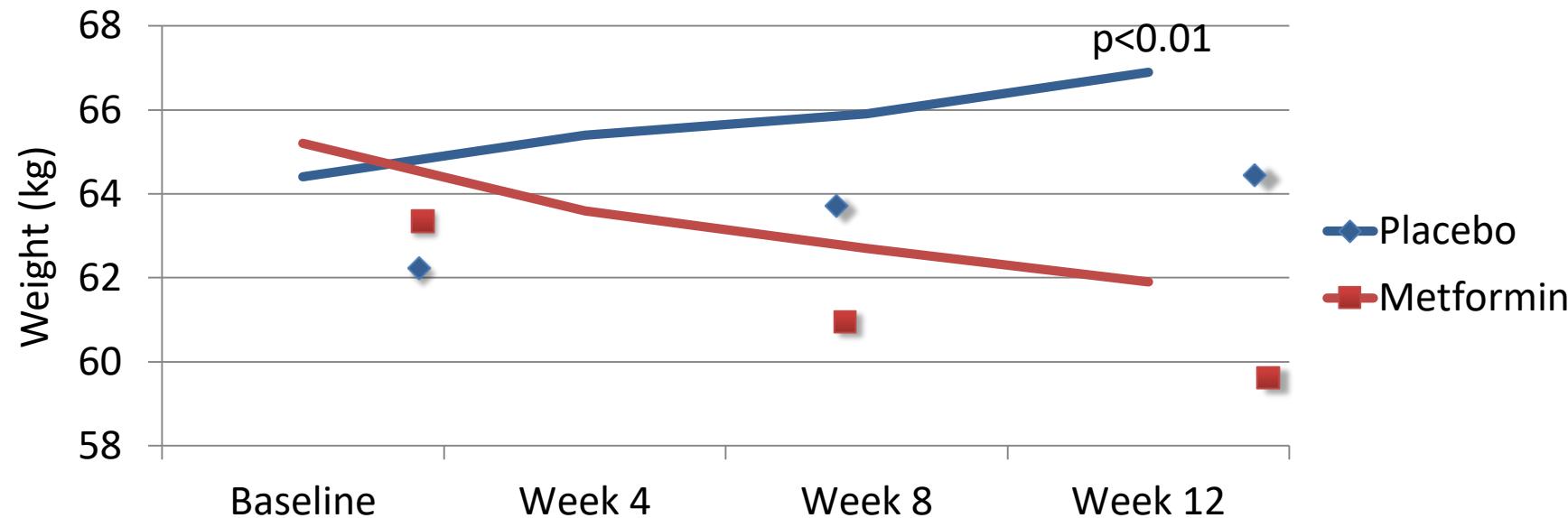


Monitoring

- Baseline:
 - BMI
 - Fasting glucose, lipids, BP
 - Family history of obesity, DM, CVD, HTN
- BMI: check at 4, 8, 12 weeks, every 3 months after
- Fasting glucose, lipids, BP: check at 3 months, then annually if normal
- Intervene for abnormalities!

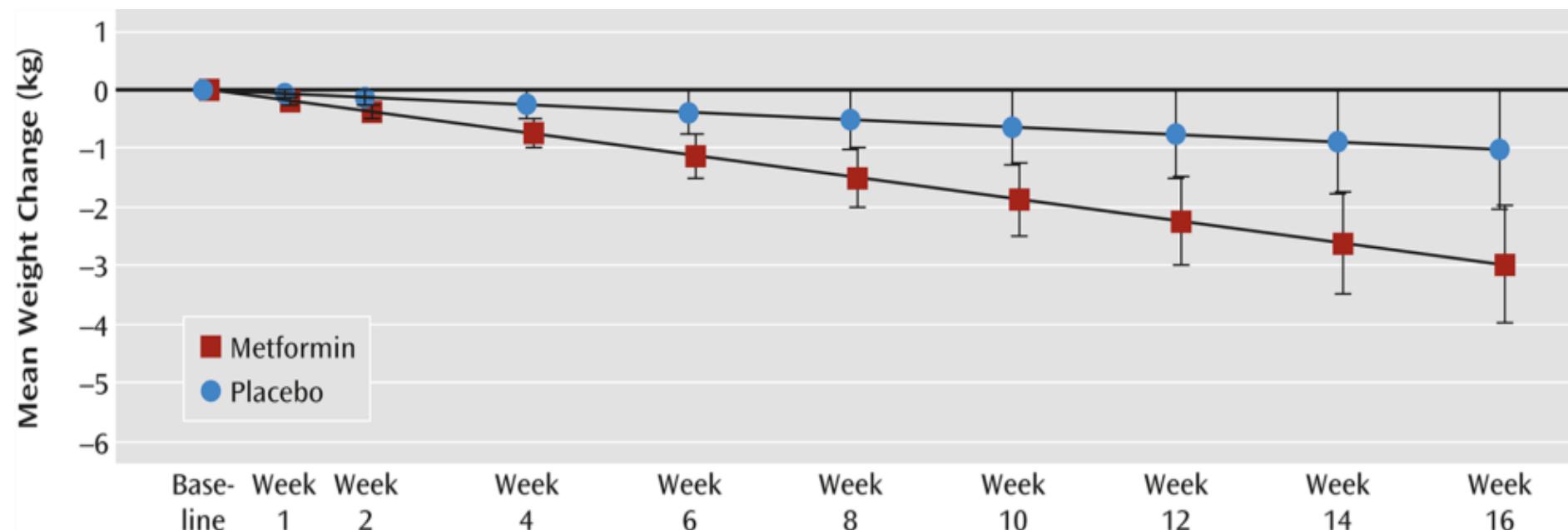
Metformin in Schizophrenia

- First episode patients, n=72
- Metformin 500 mg BID
- Weight loss (3.3 kg) & improved insulin sensitivity



Metformin

- N=148 patients with schizophrenia¹
- Randomized to metformin 1,000 mg BID or placebo
- All patients received diet and exercise counseling



Treatment principles

- **Recovery orientation**
 - Patient-centered care
 - Patient/peer involvement in disease management
 - *Holistic care (mens sana in corpore sano)*
- **Prevention orientation**
 - Timely care
 - Staging
 - *Medical prevention part of psychiatric care*
- **High-quality medical care**
 - Effective care
 - Safe care
 - *Integrated medical-psychiatric care*

Thank you!