First-episode psychosis and schizophrenia

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Disclosures

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• Avanir – Research grant
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• Janssen – Consultant (Advisory Board)
• Global Medical Education – Honoraria (CME speaker and content developer)
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• UpToDate – Royalties, honoraria (content developer and editor)
Erich Lindemann Mental Health Center

Erich Lindemann
1900-1974
Chief of Psychiatry MGH 1955-1965
Learning objectives

At the completion of this talk, participants will be able to

– Discuss which three **broad treatment principles** are critical for the optimal treatment of schizophrenia
– Give examples for **stage-based treatment goals** in schizophrenia
– Select patients who should be offered **long-acting injectable antipsychotics**

Erich Lindemann Mental Health Center

Erich Lindemann – Chief of Psychiatry at MGH 1955-1965
Outline

A. Background: a brief history of psychiatry
B. Broad treatment principles
   • Recovery orientation
   • Prevention principles
   • High-quality medical care
C. New FDA drug approvals
D. New stage-based insights
   • Prodromal phase
   • Acute psychosis
   • Post-psychotic/chronic phase
E. Summary: psychiatric jeopardy
Fleishman M. Psychiatr Serv. 2003;54:142.
Myth of “natural history”

- TB as social disease
- Holy grail of modern medicine: molecular basis of disease
- “Desocialization” of scientific inquiry
- “Structural violence”
  - Structural – built-in
  - Violence – causing injury
- Health disparities

Social interventions have greater impact on outcomes than molecular advances.

Broad treatment principles

• Recovery orientation
  – Patient-centered care*
  – Patient/peer involvement in disease management
  – Holistic care (mens sana in corpore sano; no medical health without psychiatric health)

• Prevention orientation
  – Timely care*
  – Staging
  – Medical prevention part of psychiatric care

• High-quality medical care
  – Effective care*
  – Safe care*
  – Integrated medical-psychiatric care

*Based on Institute of Medicine’s 6 Aims (2001)
RECOVERY ORIENTATION
SOHO* – positive psychiatry

SOHO = Schizophrenia Outpatients Health Outcomes study

*N=392 never-treated patients

Percent

RAISE trial

RAISE = Recovery After an Initial Schizophrenia Episode

• Goal
  – Develop early-intervention system in real world of fragmented US healthcare system
• NAVIGATE
  – Cluster randomization of 34 clinics in 21 states of NAVIGATE versus community care (CC)
  – Core services: family education, resilience training, supported employment/education, medications\(^1\)
  – N=404
• Results
  – Team-based, multi-component NAVIGATE improved primary outcome variable (QoL) more than CC\(^2\)
  – Effects were better for those with shorter DUP (median 74 weeks)\(^3\)
  – Improved QOL if more perceived autonomy support\(^4\)

QoL = Quality of Life

Psychotherapies

- Supportive psychotherapy
- Social skills training
- Resilience training\(^1\)
- Cognitive-behavioral therapy for negative symptoms\(^2\)
- Recovery-oriented cognitive therapy (CT-R)\(^3,4\)
- MOtiVation and Enhancement (MOVE) Training\(^5\)

PREVENTION
PRINCIPLES
Prevention in psychiatry

• Medical prevention in schizophrenia
• 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 – minimize disability
  – Relapse prevention


Mental health starts with physical health\(^1\)
Indicated prevention: the Amminger trial

12 weeks fish oil
700 mg EPA
480 mg DHA

N=71
6.7 years
Axis I disorder:
PUFA 52.9%
Placebo 82.9%

Amminger GP et al. Arch Gen Psychiatry 2010;67(2):146-54.
Staging model of treatment

• Rational for staging
  – Avoid progression to disease stages where only amelioration is possible
  – Better response to treatments in early stages
  – Earlier treatments are less aggressive

• 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 care that adjusts treatment intensity based on response
HIGH-QUALITY MEDICAL CARE
“However beautiful the strategy*, you should occasionally look at the results.**”

-Sir Winston Churchill

* = what your clinic does
** = how your patient is doing

RAISE – baseline cardiovascular risk

- **N= 394**
- **Age**
  - Mean age 24 (15 to 40)
- **Diagnosis**
  - FES spectrum
- **Treatment history**
  - Mean 46 days

**Prevalence**

- Diabetes*: 3%
- Prediabetes*: 15%
- Metabolic syndrome: 13%
- Hypertension: 10%
- Prehypertension: 40%
- Dyslipidemia: 57%
- Smoking: 51%
- Overweight: 48%

*HbA$_{1c}$ based

Schizophrenia and diabetes

- Diabetes risk
  - Increased at illness onset
  - Risk increases once antipsychotics introduced
- “Inherent” diabetes risk versus social determinants of health debate
- Maybe should focus on screening ...  

4Mangurian C et al. JAMA Psychiatry. 2017;74(7);761-2. [Letter]

Diabetes is a disease that often shows itself in families in which insanity prevails.
- Sir Henry Maudsley, 1879
Safe medical care: screening

**Possible BENCHMARK**

80% glucose monitoring (40% lipid monitoring)

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

Tamara Pringsheim, Constandina 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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-treatment Baseline</th>
<th>1 month</th>
<th>2 month</th>
<th>3 month</th>
<th>6 month</th>
<th>9 month</th>
<th>12 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
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<td>Weight (kg)</td>
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<tr>
<td>Height (cm)</td>
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<tr>
<td>Weight percentile</td>
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<tr>
<td>Height percentile</td>
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<tr>
<td>Waist circumference (%)</td>
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<td>Blood pressure (mmHg)</td>
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<td></td>
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<tr>
<td>Blood pressure percentile</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

---

Possible BENCHMARK

80% glucose monitoring (40% lipid monitoring)

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**Morrato EH et al. JAMA Psychiatry. 2016;73(7):721-30.**


New FDA drug approvals

- 2015: Cariprazine\(^1\)
  - 3\(^{rd}\) Partial D\(_{2/3}\) agonist
- 2016: Pimavanserin\(^2\)
  - Approved for psychosis in Parkinson’s disease
  - 5-HT2A inverse receptor agonist (not D\(_2\) blocker)
- 2017: Valbenazine\(^3\)
  - Approved for tardive dyskinesia
  - VMAT-2 inhibitor
- 2017: Deutetrabenazine\(^4\)
  - Approved for Huntington’s disease
  - VMAT-2 inhibitor
- 2017: Aripiprazole lauroxil
  - 2-month dosage long-acting injectable antipsychotic

# LAIs comparison

<table>
<thead>
<tr>
<th></th>
<th>Dosing interval</th>
<th>Loading dose option</th>
<th>Oral dose overlap</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAL DEC</td>
<td>Q 4 weeks</td>
<td>Yes</td>
<td>Recommended</td>
<td>Gluteal/deltoid</td>
</tr>
<tr>
<td>FLU DEC</td>
<td>Q 2-4 weeks</td>
<td>(Not established)</td>
<td>Recommended</td>
<td>Gluteal/deltoid</td>
</tr>
<tr>
<td>LAI risperidone</td>
<td>Q 2 weeks</td>
<td>NO!</td>
<td>3 weeks</td>
<td>Gluteal/deltoid</td>
</tr>
<tr>
<td>LAI paliperidone*</td>
<td>Q 4 weeks</td>
<td>Yes</td>
<td>Not needed</td>
<td>Deltoid loading</td>
</tr>
<tr>
<td>LAI olanzapine</td>
<td>Q 2-4 weeks</td>
<td>Yes</td>
<td>Not needed</td>
<td>Gluteal</td>
</tr>
<tr>
<td>LAI aripiprazole**</td>
<td>Q 4-8 weeks</td>
<td>No</td>
<td>2-3 weeks</td>
<td>Gluteal</td>
</tr>
</tbody>
</table>

*Also available as every 3 month preparation

**Available as every 4, 6 or 8 week preparation

Based on:
# New stage-based insights

<table>
<thead>
<tr>
<th></th>
<th>GOALS</th>
<th>KEY QUESTION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prodromal Phase</strong></td>
<td>Prevent psychosis</td>
<td>Treat with antipsychotic?</td>
</tr>
<tr>
<td></td>
<td>Prevent schizophrenia?</td>
<td></td>
</tr>
<tr>
<td><strong>Acute Psychosis</strong></td>
<td>Keep DUP short</td>
<td>Which antipsychotic?</td>
</tr>
<tr>
<td></td>
<td>Achieve initial response and</td>
<td>Problem: early non-response (positive Sx)</td>
</tr>
<tr>
<td></td>
<td>early positive symptoms remission</td>
<td></td>
</tr>
<tr>
<td><strong>Post-psychotic Phase</strong></td>
<td>Achieve sustained remission</td>
<td>Treat for how long?</td>
</tr>
<tr>
<td></td>
<td>Recovery and QOL</td>
<td>Problems: early relapse and residual Sx (adherence); risk-benefit</td>
</tr>
<tr>
<td></td>
<td>Prevent morbidity</td>
<td></td>
</tr>
</tbody>
</table>
PRODROMAL PHASE
**Prodromal schizophrenia**

- Prodrome can only be diagnosed in **retrospect**
  - Transition risk for putatively prodromal patients not 100%\(^1\)
    - 18% after 6 months
    - 22% after 1 year
    - 29% after 2 years
    - 36% after 3 years
  - Majority will not convert ("false-positive")
  - "Probably at risk, but certainly ill"
    - Help-seeking and not well\(^2\)

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**PLEIOTROPIC**

**BROAD SYNDROME OF MENTAL DISTRESS**

**REVIEWS:**

\(^1\)Fusar-Poli P. Arch Gen Psychiatry 2012;69:220.

Transition risk prediction

• Challenge of identifying high-risk patients for selective or indicated prevention
  – Well-established in medicine (e.g., Framingham risk score)

• Two risk predictors:
  – NAPLS-2 sample\(^1\): http://riskcalc.org:3838/napls/
    • Need neurocognitive data and data from SIPS interview
  – South London and Maudsley NHS Foundation Trust\(^2\): http://www.psychosis-risk.net

• Limits of clinical approach
• Risk prediction only if preventive intervention

NAPLS = North American Prodrome Longitudinal Study
Clinical high-risk (CHR) state

- Construct validity tested in population-based sample (PEPP Montreal)
- Nine symptoms represent APSPS*
  1. Suspiciousness or odd ideas of reference – 44%
  2. Odd/bizarre ideas (not delusional) – 33%
  3. Odd, unusual or eccentric behavior
  4. Unusual perceptual experiences (not clearly psychotic)
  5. Disorganized or odd speech
  6. Inappropriate affect
  7. Hallucinations (subthreshold)
  8. Delusions (subthreshold)
  9. Passivity experiences
- 68% endorsed at least one APSPS (retrospectively)
- Nota bene: most endorsed symptoms were non-specific!

*Expert agreement
APSPS = attenuated positive or subthreshold psychotic symptoms
Omega-3 fatty acids for indicated prevention

STUDY DESIGN
• Ultra-high risk patients
• Intervention: omega-3 PUFA x 6 months
• All participants received Cognitive Behavioral Case Management

RESULTS
• N=304 randomized
• ¼ lost to follow-up
• 6-month transition rates (CAARMS):
  – Placebo 5.1% (=15)
  – PUFA 6.7% (=17)
• 12-month transition rates:
  – Placebo 11.2%
  – PUFA 11.5%
• No effect of adherence (40%)!

Early intervention CHR guidance

IEPA=International Early Psychosis Association¹
EPA = European Psychiatric Association²

- Assess and treat syndromes (anxiety, depression)
- Benign interventions to delay conversion¹,²
  - CBT should be first-line treatment
  - Integrated psychological interventions (EDIPPP)³
  - Omega-3 fatty acids might be ineffective; NAC?
- Use of antipsychotics
  - Low-dose second-generation antipsychotic
  - If severe symptomatology
  - Not long-term for primarily preventive purpose
- Note: do not treat for pseudo-ADD with stimulants⁴,⁵

¹Br J Psychiatry Suppl. 2005 Aug;48:s120.
³McFarlane et al. Schizophr Bull 2015;41:30.
ACUTE PSYCHOSIS

“Der Ball ist rund und das Spiel dauert 90 Minuten.”

- Sepp Herberger
Should you switch antipsychotics?

OPTiMiSE = Optimization of Treatment and Management of Schizophrenia in Europe

- Good overall remission rate after 10 weeks of treatment – 2/3 of patients
- Most respond completely in four weeks to amisulpride
- No benefit from switching to olanzapine
- Some benefit from switching to clozapine but not as good as responders

Preliminary results presented at EPA 2017, Florence
Antipsychotic switching

- Meta-analysis of 1416 patients\(^1\)
- Two strategies of discontinuation
  - Immediate
  - Gradual
- No differences in any clinical outcome
- Chose strategy based on patient need
  - Immediate: simple
  - Gradual: risk of stalled cross-taper and polypharmacy
- In a pilot RTC, no differences with either strategy for switch to clozapine\(^2\)

\(^1\)Takeuchi H et al. Schizophr Bull. 2017 (in press).
Post-Psychotic Phase
Chronic phase

Nach dem Spiel ist vor dem Spiel.
- Sepp Herberger
Schizophrenia is a relapsing-remitting illness with accrued disability over time.
Cost of relapse in schizophrenia

• Relapse has psychosocial toxicity
  – Loss of job
  – Derailed education
  – Criminal problems
  – Suicide
  – Loss of reputation

• Relapse might be biologically harmful\(^1\)
  – Emergent treatment non-response in 16%

• Sustained remission is basis for accrued treatment benefits over time

Prevention in psychiatry

• Primary prevention
• Secondary prevention – “early intervention”
• Tertiary prevention – minimize disability

Relapse prevention as key goal of schizophrenia care
Rationale for treatment

Treatment as prevention
Antipsychotic for relapse prevention

• 50 years of evidence\(^1\)
  • Meta-analysis of N=6493
  • Median follow-up 26 weeks
• Antipsychotics reduce 1-year relapse rate
  • Drug 27% versus placebo 64%
  • RR 0.40 [95% CI 0.33-0.49]
  • No effect of: number of episodes; length of stability; FGA vs. SGA; abrupt vs. gradual withdrawal
• Limitations
  – Limited view of schizophrenia (recovery!)
  • Long-term cost-benefit (function)\(^2\)

\(^1\)Leucht S. Lancet. 2012;379(9831):2063.

“The benefit of maintenance drug treatment is relapse prevention, not comprehensive treatment of schizophrenia.”

-William Carpenter 2001

“It suggests the disquieting conclusion that the benefits of active neuroleptics in reducing relapse may exact a price in occupational terms.”

-Timothy Crow (1980s)
Antipsychotic discontinuation

• Spanish cohort study (PAFIP)
  – Naturalistic, with 3-year follow-up

• Eligibility
  – Stable symptomatic and functional recovery after first episode of psychosis

• Results
  – Discontinuation group: 31/46 = 68%
    • Mean time to relapse: 209 days (most in first 6 months)
    • Signs of relapse: unreliable (too abrupt = within one month)
    • Possible predictors: DUP, psychosis, family history, living with family
  – Control group: 7/22 = 32%
    • Fairly high relapse rate

• Conclusion
  – High relapse rate in good-prognosis cases that is reduced with treatment

PAFIP = Programa Asistencial de Fases Iniciales de Psicosis
See also: Landolt K et al. Schizophr Res. 2016;172:145-51.
Assessment of adherence

• No gold standard\(^1\)
  – Multiple sources

• Assess attitude and adherence

• Common errors
  – Overconfidence\(^2\)
  – Underappreciating partial adherence\(^3,4\)
  – Underappreciating lack of persistence over time\(^5\)

\(^5\)Misdrahi D et al. Schizophr Res. 2017 (in press).
LAI antipsychotics for FEP

Offer routinely as first-line maintenance choice

LAI make non-adherence transparent and reduce family burden.

PROACTIVE

PROACTIVE = Preventing Relapse Oral Antipsychotics Compared to Injectables Evaluation Efficacy

• Multi-site randomized trial
  – Masked assessments
  – Long duration (30 months)
• N=305
• LAI risperidone versus physician choice oral SGA
• No benefit of LAI risperidone for relapse/rehospitalization
• Biweekly monitoring and flexibility with oral antipsychotics in unselected patients removes possible LAI benefit

Clinical trials methodology

• LAIs are at least as effective as oral antipsychotics in treatment of psychotic disorders\(^1\)
  
• Meta-analysis of RTCs do not show reduced relapse with LAIs compared to oral antipsychotics\(^2\)
  
  • Older trials of FGA LAIs showed advantage

• Advantage of depot formulations in study designs other than RTC\(^3,4\)

• Double-blind trial not goal-standard?\(^5\)

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Long-acting injectable (LAI) antipsychotic medications

- Real-world effectiveness\(^1\)
  - Greatest differential effects if started in hospital on patients who have relapsed because of non-compliance
  - Reasonable for first-episode patients\(^2\)
- Can be used as risk mitigation strategy\(^3\)
- Allows for shared decision-making based on facts
  - Makes non-adherence transparent
- Avoids family conflict
- Best if part of comprehensive care program
  - Part of repertoire
  - Frequent clinical contact as psychosocial relapse prevention\(^4\)
- No panacea ...

\(^1\)Tiihonen J et al. JAMA Psychiatry. 2017 (in press).
Antipsychotics and cortical thinning

“Little evidence was found to support a negative long-term effect of initial or maintenance antipsychotic treatment on outcomes, compared with withholding treatment.”

Not everyone gets better with first-line antipsychotics

• Move to clozapine\(^1\)
  – Refractoriness
  – Aggression and self-injury

• Risks of not prescribing clozapine
  – Accruing psychosocial toxicity
  – “End-stage” brain disease with poor function
  – Polypharmacy
  – Higher mortality\(^4\)

Clozapine news

• Effectiveness
  – Excellent for relapse prevention\(^1\)
  – Clozapine augmentation strategies are limited\(^2\)

• Safety
  – Diabetes, hyperlipidemia, intestinal obstruction\(^3\)
  – Safe for benign ethnic neutropenia\(^4\)

• Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program\(^5\)
  – Goal was to increase clozapine use
  – Replaces multiple registries
  – Absolute neutrophil count only
  – Different cut-offs for benign ethnic neutropenia

• NASMHDP report: Clozapine underutilization: addressing the barriers\(^6\)

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\(^2\)Correll CU et al. JAMA Psychiatry. 2017;74(7):675-84.
\(^5\)https://www.clozapinerems.com/CpmgClozapineUI/home.u
\(^6\)http://www.nasmhpd.org/sites/default/files/Assessment%201_Clozapine%20Underutilization.pdf
Certify NOW for the Clozapine REMS Program!
Treatment for negative symptoms

• Meta-analysis\(^1\)
  – No clinically significant improvement
• Rasagiline\(^2\)
  – MAO-B inhibitor approved for Parkinson’s disease
  – Small RTC with benefit for avolition
• CBT for negative symptoms\(^3\)
• Still waiting for glycine reuptake inhibitor
  – Bitopertin story (FlashLyte and DayLyte studies)\(^4\)
• Cariprazine\(^5\)
• L-methylfolate\(^6\)

Treatment for CIAS

CIAS = Cognitive Impairment Associated with Schizophrenia

• Avoid adding insult to injury
  – Reduce anticholinergic burden
• Consider cognitive training if available¹
• Multiple pharmacological strategies including enhancing glutamatergic activity, cholinesterase inhibitors, and stimulants have failed to improve cognitive functioning²
• Recent failures include alpha-7 receptor nicotinic agonists like encenicline (EVP-6124) in phase III and bradanicline (TC-1659) in phase II
  – Maybe nelonicline (ABT-126) positive (?) phase II³

Keeping patients alive

• Example of med-psych integration RTC
  – HOME study\(^1,2\)
  – Improved quality of care (not clinical outcome...)

• Example of illness self-management RTC
  – TTIM study\(^3\)
  – Better diabetes control after 60-week intervention

HOME = Health Outcomes Management and Evaluation
TTIM = Targeted Training in Illness Management

\(^3\)Sajatovic M et al. Psychiatr Serv. 2017 (in press).
Pharmacotherapy for smoking cessation

• Address smoking in schizophrenia
  – Cardiovascular and cancer mortality\(^1\)

• Smoking cessation principles\(^2\)

• Varenicline
  – Efficacy: EAGLES trial\(^3\)
  – Safety: removal of black box warning\(^4\)

\(^1\)Olfson M et al. JAMA Psychiatry 2015;72(12):1172-81.
\(^3\)Anthenelli RM et al. Lancet. 2016;387(10037):2507-20. [EAGLES = ?]
# Acronym Jeopardy

Capture! Shock! Excite! Clinical trial acronyms and the "branding" of clinical research.

<table>
<thead>
<tr>
<th>Prodrome</th>
<th>Cohorts</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>APS</td>
<td>SOHO</td>
<td>OPTiMiSE</td>
</tr>
<tr>
<td>IEPA</td>
<td>RAISE</td>
<td>EAGLES</td>
</tr>
<tr>
<td>CHR</td>
<td>PAFIP</td>
<td>TTIM</td>
</tr>
</tbody>
</table>

The right treatment, at the right intensity, at the right time, in the right place

• Right treatment
  – Effective care = evidence-based*
    • Comprehensive care
      – Medications
      – Psychological treatments and rehabilitation
    – Safe care = integrated and population-based
• Right intensity
  – Stepped care
    • Treatment intensity adjusted based on response
• Right time
  – Timely care = without delay*
  – Phase-specific care
• Right place
  – Patient-centered = humane care*
  – Continuum of care
    • Includes asylum

*Based on Institute of Medicine’s 6 Aims (2001)
Sequential antipsychotic trials

- **Select**
  - Lowest-risk choice
  - Patient preference
    - LAI acceptable?
  - Cost*
  - Early ancillary medical prevention
    - Behavioral interventions
    - Adjunctive metformin
- **Monitor**
  - Clinical response
  - Follow antipsychotic monitoring guidelines
- **Adjust**
  - Switch antipsychotics
    - Early use of clozapine for refractory patients
    - Clozapine over polypharmacy
  - Add psychological treatments and group behavioral interventions
  - Treat medical morbidities

The long view and whose job is it?

You need to be “The man in the arena.”

Thank you!

John Umstead Hospital, Butner, NC, ca. 1995