First-episode psychosis and schizophrenia

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Disclosures

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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 prevention 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
Overview

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 clinical trials
   • Prodromal phase
   • Acute psychosis
   • Post-psychotic/chronic phase
E. Summary: psychiatric jeopardy
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

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

  – N=404

• Results
  – Team-based, multi-component NAVIGATE improved primary outcome variable (QoL) more than CC
  – Effects were better for those with shorter DUP (median 74 weeks)

Neuroleptic strategy study (NeSSy)

- **Effectiveness study**
  - Double randomization*
  - Six pairs of SGA-FGA

- **Outcome variable**
  - Generic *patient-rated* quality of life scale (SF-36)
  - Area under the curve analysis*

- **Results**
  - SGA 85.1 points versus FGA 79.9 points (p=0.01)
  - No difference in Clinical Global Impression scale

*Novel design

Open dialogue

• What is it?
  – A Finnish treatment approach
  – Network meetings
  – Old wine in new bottles?

• Does it work in the US?
  – Gordon feasibility study
    • N=16 patients

• Can I use it with my patients?
  – Collaborative atmosphere
  – Judicious use of antipsychotics

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
    • Omega-3 fatty acids
• Tertiary prevention – minimize disability
  – Relapse prevention
    • Antipsychotics clear effective

2McGlashan TH. Schizophr Bull 2012;38:902.
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
RAISE – baseline cardiovascular risk

**Prevalence**

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

*HbA$_1$c based

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

Correll CU et al. JAMA Psychiatry 2014;71:1350.
Smoking cessation myths

- Tobacco use is self-medication
- Patients with schizophrenia are not interested in quitting
- Quitting destabilizes patients psychiatrically
- Smoking cessation is a lower priority problem

Do you know what to do if a patient with schizophrenia wants to quit smoking? Do you know what to prescribe? Do you think Chantix is safe?

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

Premature mortality in schizophrenia

- US national cohort 2001 to 2007
- N=1,138,853
- Results
  - **All-cause SMR 3.7** (95% CI, 3.7-3.7)
  - **Cardiovascular disease**
    - Highest mortality rate
    - 403.2/100,000 person-years
    - SMR 3.6 (95% CI, 3.5-3.6)
  - **Cancer mortality**
    - Lung cancer had highest mortality rate
    - 74.8/100,000 person-years
    - SMR 2.4 (95% CI, 2.4-2.5)
  - Particularly elevated SMR COPD (9.9) and influenza/pneumonia (7.0)
  - Accidental deaths twice as common as suicides
  - Notable cause of death was alcohol and other drug (nonsuicidal): 95.2/100,000 person-years

Olsson M et al. JAMA Psychiatry 2015 (in press).

Most of excess mortality in schizophrenia is due to natural causes.*
Possible BENCHMARK

80% glucose monitoring (40% lipid monitoring)

# New clinical trials

<table>
<thead>
<tr>
<th>GOALS</th>
<th>KEY QUESTION</th>
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<tbody>
<tr>
<td><strong>Prodromal Phase</strong></td>
<td>Prevent psychosis&lt;br&gt;Prevent schizophrenia?</td>
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<tr>
<td><strong>Acute Psychosis</strong></td>
<td>Keep DUP short&lt;br&gt;Achieve initial response and early positive symptoms remission</td>
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<tr>
<td><strong>Post-psychotic Phase</strong></td>
<td>Achieve sustained remission&lt;br&gt;Recovery and QOL&lt;br&gt;Prevent morbidity</td>
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PRODROMAL PHASE
DSM-5 Attenuated Psychosis Syndrome*

A. Characteristic symptoms

   *Attenuated positive symptoms with insight*

B. Frequency/currency

   *Once per week in past month*

C. Progression

D. Distress/disability/treatment seeking

E. Symptoms not better explained by

   *Depression, mania, substance use, ADD, ...*

F. Never had frank psychosis

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*Section III

Putatively prodromal
Clinical high-risk (HR) state for psychosis
At-risk mental state (ARMS)
Ultra-high-risk state (UHR)

www.dsm5.org
Early warning signs of psychosis

Fact Sheet: Early Warning Signs of Psychosis

Typically, a person will show changes in his or her behaviors before psychosis develops. The list below includes several warning signs of psychosis.

- Worrisome drop in grades or job performance
- New trouble thinking clearly or concentrating
- Suspiciousness, paranoid ideas or uneasiness with others
- Withdrawing socially, spending a lot more time alone than usual
- Unusual, overly intense new ideas, strange feelings or having no feelings at all
- Decline in self-care or personal hygiene
- Difficulty telling reality from fantasy
- Confused speech or trouble communicating

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 well²

PLEIOTROPIC

BROAD SYNDROME OF MENTAL DISTRESS

REVIEWS:

¹Fusar-Poli P. Arch Gen Psychiatry 2012;69:220.
Indicated prevention trial: follow-up

12 weeks fish oil
700 mg EPA
480 mg DHA

ω-3 FA
10%

Placebo
40%

N=71
6.7 years

Axis I disorder:
PUFA 52.9%
Placebo 82.9%

Early intervention guidance

IEPA=International Early Psychosis Association

• Treat syndromes (e.g., depression)¹
• Benign interventions to delay conversion²
  • Omega-3 fatty acids (requires replication); NAC?
  • Integrated psychological interventions (EDIPPP)³
• Antipsychotics only if DSM-IV diagnosis or special circumstances¹
  • Rapid deterioration
  • Severe risk of suicide
  • Aggression
• Note: do not treat for pseudo-ADD with stimulants⁴

¹Br J Psychiatry Suppl. 2005 Aug;48:s120.
²van der Gaag et al. Schizophr Res 2013;149:56.
³McFarlane et al. Schizophr Bull 2015;41:30.
Early psychosis field – lessons learned

• Need for subtyping of CHR subjects
  – Clinical subtyping to reduce heterogeneity\(^1\)
    • Brief limited psychotic symptoms (BLIPS): higher risk
    • Attenuated psychotic symptoms (APS)
      – 19% transition risk over 2 years
    • Genetic risk and deterioration (GRD): very low risk
    • Deconstruct CHR back into original components\(^2\)
      – Need for biological markers\(^3\)
      – Need for transdiagnostic approach
• Need for population health systems\(^4\)
  – Complex rather than complicated responses
• IEPA is looking beyond psychosis
  – Early Intervention in Mental Health

IEPA = International Early Psychosis Association
\(^1\)Fusar-Poli P et al. JAMA Psychiatry. 2016;73:113-120.
\(^3\)Bedi G et al. npj Schizophrenia 2015 (online)
ACUTE PSYCHOSIS

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

- Sepp Herberger
Etiology and pathophysiology

• Cannabis
  – Cannabis as component cause\(^1\)
    • Population-attributable fraction from skunk: 24%
  – Complex gene-environment interaction\(^2\)
  – Adolescent cannabis use predicts psychosis\(^3\)
    • Symptoms are subclinical
    • No evidence for reverse causation

• Celiac disease\(^4\)

• Autoantibodies
  – NMDA: false positive findings in schizophrenia\(^5\)
  – Autoimmune encephalitis in postpartum psychosis\(^6\)
  – Antibodies to surface dopamine-2 receptors\(^7\)

\(^4\)Delichatsios HK et al. NEJM 2016;374:1875-83.
\(^5\)de Witte LD et al. JAMA Psychiatry 201572:731-3.
\(^7\)Pathmanandavel K et al. Biol Psychiatry 2015;77:537-47.
New FDA drug approvals

• Cariprazine\textsuperscript{1}
  – 3\textsuperscript{rd} Partial D\textsubscript{2/3} agonist
• Pimavanserin\textsuperscript{2}
  – Approved for psychosis in Parkinson’s disease
  – 5-HT2A inverse receptor agonist (\textit{not} D\textsubscript{2} blocker)
• Of interest
  – ITI-007 (Intra-Cellular Therapies) published phase II trial\textsuperscript{3}
  – Encenicline (Forum) failed phase III trial

\textsuperscript{1}Citrome L. Clin Schizophr Relat Psychoses 2016;10:109-19.
Post-Psychotic Phase
Chronic phase

Nach dem Spiel ist vor dem Spiel.
- Sepp Herberger
Antipsychotic for relapse prevention

• 50 years of evidence
  • 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)

1Leucht S. Lancet 2012;379(9831):2063.
2Wunderink L et al. JAMA Psychiatry 2013;70:913.

“The benefit of maintenance drug treatment is relapse prevention, not comprehensive treatment of schizophrenia.”
-Wilhelm 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)
LAI antipsychotics for FEP

Offer routinely as first-line maintenance choice

LAI make non-adherence transparent and reduce family burden.

Carpenter WT and Buchanan RW. JAMA Psychiatry 2015;72:745 [editorial].
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.
Treatment for refractory psychosis

• Standard should be a clozapine monotherapy trial
  – Early use of clozapine\(^1\)
  – For limited response to clozapine you are “skating on thin ice”\(^2\)
    • Clozapine plus amisulpride or quetiapine
    • Clozapine plus valproate or lithium
    • ECT augmentation\(^3\)

• Antipsychotic combination treatment
  – Probably very limited if any benefit for most
  – Clozapine is preferred over polypharmacy\(^4\)
  – Polypharmacy can often be reduced\(^5\)

• ECT alone as maintenance treatment?

Clozapine news

• Effectiveness
  – Meta-analyses differ\textsuperscript{1,2}
  – Best outcome variable\textsuperscript{3}

• Safety
  – Diabetes, hyperlipidemia, intestinal obstruction\textsuperscript{4}
  – Safe for benign ethnic neutropenia\textsuperscript{5}

• Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program\textsuperscript{6}
  – Goal was to increase clozapine use
  – Replaces multiple registries
  – Absolute neutrophil count only
  – Different cut-offs for benign ethnic neutropenia
  – Implementation difficulties persist

\textsuperscript{3}McEvoy JP. JAMA Psychiatry. 2016 (in press).
\textsuperscript{6}https://www.clozapinerems.com/CpmgClozapineUI/home.u
Certify NOW for the Clozapine REMS Program!

Marder SR. Am J Psychiatry 2016;173:103
Antipsychotic safety

• Antipsychotics\(^1\)
  – Swedish database study
  – About 20,000 patients with schizophrenia in Sweden
  – Decreases mortality
    • HR 0.59; 95% CI, 0.49-0.70 (moderate exposure)
    • HR 0.75; 95% CI, 0.63-0.89 (high exposure)

• Concomitant benzodiazepine\(^2\)
  – Retrospective Medicaid database study
  – Almost 20,000 patients with schizophrenia
  – 20% were prescribed a benzodiazepine
  – Increased mortality
    • HR = 1.48; 95% CI, 1.15-1.91
    • HR = 3.08; 95% CI, 2.63-3.61 (if no antipsychotic)

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\(^4\)
- Cariprazine\(^5\)

Treatment for cognition

• Nicotinic system
  – Alpha-7 nicotinic acetylcholine receptor agonists
  – Encenicline positive phase II, FAILES phase III
  – Nelonicline (ABT-126) positive phase II
    • “Fell short of significance on the MCCB composite score”
    • Significant treatment-by-smoking interaction

• Estrogen
  – Selective estrogen receptor modulators

MCCB = MATRICS Consensus Cognitive Battery
Raloxifene add-on in schizophrenia

- Women with schizophrenia\(^1\)
- Raloxifene (brand name Evista)
  - Selective estrogen receptor modulator (SERM)\(^2\)
  - FDA-approved for breast cancer prevention and osteoporosis
  - Possible pro-cognitive benefit in schizophrenia\(^3\)
- Kulkarni trial\(^4\)
  - Women with refractory schizophrenia
  - Broad efficacy across several domains
  - No improvement in cognition

STRIDE study

- Stride = PREMIER lifestyle interventions with DASH diet
- Multi-site RCT in community settings and integrated health plan in Pacific Northwest
- 6 month weekly group intervention and 6 month monthly maintenance
- Inclusion criteria:
  - BMI had to be at least 27
  - Had to take antipsychotic
- N=200 randomized
  - Mean age 47
  - Mean BMI 38.3
  - 72% female
  - 29% schizophrenia spectrum

- Intervention participants
  - Lost 4.4 kg more than controls in first 6 months
  - Lost 2.6 kg more than controls over 12 months
  - Had lower fasting glucose after 12 months
  - Had fewer medical hospitalizations (6.7% vs. 18.8%)
- Open questions
  - Implementation challenges
  - Best maintenance treatment

Weight loss is possible for patients with SMI

CHANGE trial

- Randomized, pragmatic trial to reduce 10-year risk of cardiovascular disease
- Interventions
  - 12-month individual, manualized life-style coaching
  - Care coordination
- Outcome
  - N=428
  - No effects of either intervention compared to treatment as usual
- Do we need structural change?

CHANGE = ?
# Acronym Jeopardy

<table>
<thead>
<tr>
<th>Prodrome</th>
<th>Cohorts</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>APS</td>
<td>SOHO</td>
<td>RAISE</td>
</tr>
<tr>
<td>IEPA</td>
<td>STEP</td>
<td>EUFEST</td>
</tr>
<tr>
<td>CHR</td>
<td>PAFIP</td>
<td>CHANGE</td>
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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

*Rosenheck RA et al. Psychiatr Serv. 2016 (in press).*
The long view

You need to be

“The man in the arena.”
Thank you!

John Umstead Hospital, Butner, NC, ca. 1995