First-episode psychosis and schizophrenia

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UpToDate – Royalties
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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
Silo mentality
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

- Combined remission: 28.1%
- Subjective Well-being: 57%
- Function: 45.4%
- Symptoms: 60.3%

*N=392 never-treated patients

See book: Positive Psychiatry (Dilip V Jeste and Barton W. Palmer)
PREVENTION
PRINCIPLES
Prevention in psychiatry

- **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
    - Omega-3 fatty acids plus alpha-lipoic acid **NOT effective**

- **Medical prevention in schizophrenia**

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1 Brown AS and McGrath JJ. Schizophr Bull 2011;37:257.
2 McGlashan TH. Schizophr Bull 2012;38:902.
Indicated prevention trial

N=81
- 41 PUFA
- 40 placebo
Age 16.5 years

12 weeks fish oil
700 mg EPA
480 mg DHA

Figure 2. Kaplan-Meier estimates of the risk of transition from the at-risk state to psychotic disorder in patients assigned to ω-3 fatty acids or placebo (P=.007 by log-rank test).

Amminger GP et al. Arch Gen Psychiatry 2010;67:146.
“Critical period” for cardiovascular risk prevention

STEP = Specialized Treatment Early in Psychosis

Smoking in FES<sup>a</sup>
58.9%

Iatrogenic weight gain<sup>b</sup>
AP* reliably increase weight
*exception: ziprasidone

STEP
Phutane VH et al. Schizophr Res 2011;127:257
Foley DL and Morley KL. Arch Gen Psychiatry 2011;68:609.

<sup>b</sup>Tek C et al. Early Interv Psychiatry 2015 (in press).
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

Correll CU et al. JAMA Psychiatry 2014;71:1350.
Metformin in schizophrenia

• Wang trial\(^1\)
  – N=72; early course
  – 500 mg bid
    • Weight loss
    • Improved insulin sensitivity

• Meta-analysis\(^2\)
  – Metformin + lifestyle: 7.8 kg weight loss in 12 weeks

• Jarskog trial\(^3\)
  – N=148; chronic patients
  – 1000 mg bid
    • −2.0 kg (95% CI=−3.4 to −0.6; \(p=0.007\))
    • 17.3% lost > 5% (vs. 9.8% placebo)

Is it time to extend the early intervention paradigm for treating first-episode psychosis to encompass the body as well as the mind?


\(^1\)Wang M et al. Schizophr Res 2012;138:54.
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

Safe medical care

Medical morbidity and mortality gap
- Smoking
- Iatrogenic contribution
- Poor quality of medical care
  - Higher mortality after infections\textsuperscript{a}

New FDA drug approvals

• Brexpiprazole (REXULTI)
• Paliperidone palmitate (INVEGA TRINZA)

Possible future approvals
  – Encenicline (by FORUM Pharmaceuticals)
    • Alpha-7 nicotinic agonist
    • Positive phase II trial (d=0.257, P=0.034)\(^1\)
    • FDA Fast Track Designation for “Unmet Medical Need”
  – Cariprazine (by Gedeon Richter)
    • Partial D\(_{2/3}\) agonist

\(^1\)Keefe RSE et al. Neuropsychopharmacology 2015 (in press)
Brexpiprazole

• Brand name: REXULTI (0.25, 0.5, 1, 2, 3, 4 mg)
• FDA approval: July 2015
• Indications
  – Schizophrenia
  – Adjunctive therapy for major depressive disorder
• Structurally almost identical with aripiprazole
• Pharmacodynamics
  – Structurally similar to aripiprazole
• Pharmacokinetics
  – Dosing for schizophrenia
    • 1 mg/d x 4 days, then 2 mg/d; up to 4 mg/d (MAX)
  – Drug interactions via 3A4 and 2D6

Kane JM et al. Schizophr Res 2015;164:127. [BEACON]
LAI – 3-month paliperidone palmitate

• Brand name: INVEGA TRINZA (273, 410, 546, 819 mg)
• FDA approval: May 2015
• Indications
  – Schizophrenia
• Dosing
  – 3-month injection (4 times per year!)
  – Patient needs to be stabilized with INVEGA SUSTENNA (monthly paliperidone palmitate) for 4 months
  – Establish tolerability with oral paliperidone/risperidone before using LAI

New clinical trials

Based on Häfner, ABC Schizophreniestudie

Prodromal Period

Psychosis

Post-Psychotic Period

Initiation of Antipsychotic

Positive symptoms

Negative symptoms

Depression

Cognitive difficulties

* DUP

5 years

1-2 years*

Psychosis Threshold
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

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


*Section III
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**

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**REVIEWS:**

\(^1\)Fusar-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

Placebo

10%
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.
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%
  – Alcohol as confound\(^2\)

• Nicotine\(^3\)

• Autoantibodies
  – NMDA: false positive findings in schizophrenia\(^4\)
  – Autoimmune encephalitis in postpartum psychosis\(^5\)
  – Antibodies to surface dopamine-2 receptors\(^6\)

\(^1\)Di Forti M et al. Lancet Psychiatry 2015 (in press).
\(^4\)de Witte LD et al. JAMA Psychiatry 2015;72:731.
\(^6\)Pathmanandavel K et al. Biol Psychiatry 2015;77:537.
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)

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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.**”

-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)
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

Buckley PF et al. Schizophr Bull 2015;41:449.
A new landmark trial?¹

- Real-world 15-month trial
  - 444 adults with schizophrenia and recent incarceration
- Primary endpoint: treatment failure
  - Included arrest/incarceration
- LAI paliperidone versus oral antipsychotic
  - LAI paliperidone had longer time to treatment failure
    416 days vs. 226 days (P=.011)²

Basis for expanded label application by Janssen
(delayed relapse from LAI paliperidone compared to oral antipsychotics)

ACLAIMS
ACLAIMS = A Comparison of Long-acting Injectable Medications for Schizophrenia

- No panacea!
  - Patient will miss injections
  - 1/3 relapse rate in ACLAIMS

- Probably effective
  - Patient selection is key
  - Double-blind trial not goal-standard?\textsuperscript{a}

- Choice guided by side effects\textsuperscript{b}

\textsuperscript{b}Freudenreich O. Evid Based Ment Health. 2014;17:110.
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].
Treatment for refractory psychosis

- Clozapine
  - Early use of clozapine¹
  - CAVE: Clozapine/N-desmethylclozapine ratio correlates with working memory²
  - ECT augmentation³,⁴
- Return of the asylum⁵

⁵Sisti DA et al. JAMA 2015;313:243 [viewpoint].
Treatment for negative symptoms

• Meta-analysis\(^1\)
  – No clinically significant improvement
• Rasagiline (AZILECT)\(^2\)
  – MAO-B inhibitor approved for Parkinson’s disease
  – Small RTC with benefit for avolition
• Still waiting for glycine reuptake inhibitor
  – Bitopertin story\(^3\)

\(^1\)Fusar-Poli P et al. Schizophr Bull 2015;41:892.
\(^2\)Buchanan RW et al. Schizophr Bull 2015;41:900.
\(^3\)Goff DC. JAMA Psychiatry 2014;71:621.
Treatment for cognition

• Antipsychotics
  • Limited benefit for cognition\(^1\)
    • EUFEST ES 0.33 to 0.56
  • Might have cost
  • *Waiting for alpha-7 agonist*
• The magic of movement\(^2\)
• Cognitive remediation
  • Makes use of *neuroplasticity*
  • Targets *systems, not symptoms*
  • Uses different approaches
    • Rehearsal learning (“drills”)
    • Compensatory strategies
• Meta-analysis\(^3\)
• Critique
  • Needs to be combined with rehabilitation, e.g., supported employment\(^4\)

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\(^1\)Davidson M et al.  *Am J Psychiatry* 2009;166:675.
\(^2\)Sommer IE and Kahn RS.  *Schizophr Bull* 2015;41:776.
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

### Acronym Jeopardy

<table>
<thead>
<tr>
<th>Prodrome</th>
<th>Cohorts</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>APS</td>
<td>SOHO</td>
<td>ACLAIMS</td>
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<td>IEPA</td>
<td>STEP</td>
<td>VECTOR</td>
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<td>EDIPPP</td>
<td>RAISE</td>
<td>STRIDE</td>
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Sequential antipsychotic trials

- **Select**
  - Lowest-risk choice
  - Patient preference
    - LAI acceptable?
  - 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\(^a\)
  - Add psychological treatments and behavioral interventions
  - Treat medical morbidities


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

John Umstead Hospital, Butner, NC, ca. 1995