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 **stage-based treatment goals** in schizophrenia
– Select patients who should be offered **long-acting injectable antipsychotics**

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
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

Subjective Well-being

Function

Symptoms

Asymptomatic* 18%

Percent

QoL**

*N=392 never-treated patients

*Schennach R et al. Schizophr Res. 2019 [Epub ahead of print].
**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)
  - Improved QOL if more perceived autonomy support

QoL = Quality of Life

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

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%!)

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
## Clinical staging in psychiatry

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

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\(^1\)
  – Risk increases once antipsychotics introduced\(^2,3\)
  – Insulin sensitivity decreases rapidly after second-generation antipsychotics are started\(^4\)
  – Subtype of schizophrenia\(^5\)

• “Inherent” diabetes risk versus social determinants of health debate

• Maybe should focus on screening ... \(^6\)

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Safe medical care: screening

Possible BENCHMARK

80% glucose monitoring
(40% lipid monitoring)

New FDA drug approvals

• 2017: Valbenazine\(^1\)
  – Approved for tardive dyskinesia (TD)
  – VMAT-2 inhibitor
• 2017: Deutetrabenazine\(^2\)
  – Approved for Huntington’s disease and TD
  – VMAT-2 inhibitor
• 2017: Proteus sensor for aripiprazole
• 2017: Aripiprazole lauroxil long-acting injectable
  – 2-month dosage
• 2018: Aripiprazole lauroxil long-acting injectable
  – New initiation regimen
• 2018: SC risperidone long-acting injectable
• 2019: NONE
  – Perhaps lumateperone – PDUFA date September 27, 2019

## Long-acting injectable antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose strengths</th>
<th>Dose (IM) &amp; Frequency</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haloperidol decanoate</strong> [HALDOL DECANOATE]</td>
<td>Vials 50mg/ml Vials 100mg/ml</td>
<td>50 - 200 mg monthly Other dose intervals are possible</td>
<td>Initiation: overlap with oral antipsychotic Loading dose strategy possible Maintenance dose equals 20 x oral dose</td>
</tr>
<tr>
<td><strong>Fluphenazine decanoate</strong> [PROLIXIN DECANOATE]</td>
<td>Vials 25mg/ml</td>
<td>6.25 - 25 mg every 2 weeks Other dose intervals are possible</td>
<td>Initiation: overlap with oral antipsychotic</td>
</tr>
<tr>
<td><strong>Risperidone microspheres</strong> [RISPERDAL CONSTA]</td>
<td>12.5mg, 25 mg, 37.5 mg, 50 mg</td>
<td>12.5-50 mg every 2 weeks Other dose intervals are possible</td>
<td>Initiation: 3 week overlap with oral antipsychotic Main release of drug occurs 3 weeks after injection 50 mg every two weeks corresponds to 4 mg/d oral [50 mg is highest IM dose]</td>
</tr>
<tr>
<td><strong>Risperidone long-acting suspension</strong> [PERSERIS]</td>
<td>90 mg, 120 mg</td>
<td>90 or 120 mg monthly subcutaneously</td>
<td>For subcutaneous use 90 mg corresponds to 3 mg/d oral 120 mg corresponds to 4 mg/d oral</td>
</tr>
<tr>
<td><strong>Paliperidone palmitate</strong> [INVEGA SUSTENNA]</td>
<td>39 mg, 78 mg, 117 mg, 156 mg, 234 mg</td>
<td>39-234 mg monthly</td>
<td>Loading dose of 234 mg [deltoid!] to initiate (no oral overlap needed), 2nd dose one week later, the monthly 156 mg monthly corresponds to 9 mg/d oral Every 3 months dose can be used after 4 months of monthly injections 546 mg corresponds to 9 mg/d oral</td>
</tr>
<tr>
<td><strong>[INVEGA TRINZA]</strong></td>
<td>273 mg, 410 mg, 546 mg, 819 mg</td>
<td>273-819 mg every 3 months</td>
<td></td>
</tr>
<tr>
<td><strong>Olanzapine pamoate</strong> [ZYPREXA RELVPEVV]</td>
<td>150 mg, 210 mg, 300 mg, 405 mg</td>
<td>150 or 300 mg every 2 weeks 405 mg monthly</td>
<td>No overlap with oral antipsychotic (higher initiation doses) Monitor for 3 hours of observation for post-injection delirium/sedation syndrome (PDDS)* 300 mg monthly corresponds to 10 mg/d oral</td>
</tr>
<tr>
<td><strong>Aripiprazole monohydrate</strong> [ABILIFY MAINTENA]</td>
<td>Vials 200 mg/ml</td>
<td>160mg- 400mg monthly</td>
<td>Initiation: 2 week overlap with oral antipsychotic 300 mg corresponds to 10 mg/d oral; 400 mg to 15 mg/d</td>
</tr>
<tr>
<td><strong>Aripiprazole lauroxil</strong> [ARISTADA]</td>
<td>441 mg, 662 mg, 882 mg, 1064 mg</td>
<td>441,662,882 mg every 4 weeks 882 mg every 6 weeks 1064 mg every 2 months</td>
<td>Initiation: 3 week overlap with oral antipsychotic or with initiation regimen Inject rapidly due to non-Newtonian fluid characteristics Only lowest dose of 441 mg dose can be given in deltoid 441 mg monthly corresponds to 10 mg/d oral 662 mg monthly or 1064 mg every two months corresponds to 15 mg/d oral 882 mg monthly corresponds to 20 mg/d oral (highest IM dose)</td>
</tr>
</tbody>
</table>

*Oral test dose required for all antipsychotic if patient has never been exposed to IM antipsychotic

*See REMS website for olanzapine pamoate
Typical course of schizophrenia

- **Prodrome**
- **Pre-psychotic phase**
- **Critical phase**
- **Chronic phase**
- **First episode**
- **Second episode**
- **Full recovery**
- **Partial recovery**
- **Stable disability**
## 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\(^2\)

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 in routine care
  – Low positive predictive value of positive symptoms (less than 2\%)\(^3\)
  – Risk predictors are only for patients *identified* for being at risk
  – Risk predictors are not for routine screening

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Early intervention CHR guidance

IEPA=International Early Psychosis Association\(^1\)
EPA = European Psychiatric Association\(^2\)

- Assess and treat syndromes (anxiety, depression)
- Benign interventions to delay conversion\(^1,2\)
  - CBT should be first-line treatment
  - Integrated psychological interventions (EDIPPP)\(^3\)
  - Omega-3 fatty acids ineffective;\(^4\) NAC?; minocycline?
- 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 stimulants\(^5,6,7\)

\(^1\)Br J Psychiatry Suppl. 2005 Aug;48:s120.
\(^3\)McFarlane et al. Schizophr Bull 2015;41:30.
\(^7\)Moran LV et al. NEJM. 2019;380(12):1128-38.
Cannabis guidance

• Clear down-sides
  – Component risk factor for 12% of schizophrenia
  – Increasingly potent THC products
  – Destabilizes early course schizophrenia via reduced adherence
  – Effects on cognition

• CBD oil (brand name Epidiolex) (Schedule V)
  – 2018 FDA-approved for Lennox-Gastaut and Dravet syndrome
  – Off-label prescribing
  – Minimal research regarding CBD

ACUTE PSYCHOSIS

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

- Sepp Herberger
Suicide prevention

- Mortality risk in early course schizophrenia
  - 12-month mortality rate comparable to being age 70\(^1\)
  - High-risk period for suicide
  - Substance-related deaths contribute significantly\(^2\)
- Participation in early psychosis programs reduces risk of premature death from suicide
  - PEPP program in greater London, Ontario\(^3\)
    - 75% reduced mortality risk in those in program compared to those who are not
    - Higher hospitalization rate for those in program
  - EASY program in Hong Kong\(^4\)
    - Reduced suicide risk in 12-year follow-up for those in program

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PEPP = Prevention and Early Intervention Program for Psychoses
EASY = Early Assessment Service for Young People with Psychosis
\(^2\)Reininghaus U et al. Schizophr Bull. 2015 May; 41(3): 664–73. [AESOP cohort]
\(^4\)Chan SKW et al. JAMA Psychiatry. 2018;75(5):458-64.
Substance-induced psychosis

- Danish population-based registry study\textsuperscript{1,2}
  - 20-year follow-up
  - N=6,778
  - Majority alcohol, cannabis, amphetamines
  - 32.2\% of patients converted to schizophrenia or bipolar disorder
    - Substantial differences in conversion rates between substances
      - Almost 50\% if cannabis-induced psychosis
    - Half converted within 3 years to schizophrenia
    - The younger the patient, the higher the conversion risk

- Implications
  - 50\% of cannabis induced psychosis will become schizophrenia
  - Longer-term follow-up and treatment needed to prevent schizophrenia?
  - Are we looking at increased incidence rates of schizophrenia?
- “…drug-precipitated disorder in highly vulnerable individuals”\textsuperscript{3,4}

\textsuperscript{2}Ghose S. Am J Psychiatry. 2018;175(4):303-4. [Editorial]
\textsuperscript{4}Tandon R and Shariff SM. Am J Psychiatry. 2019;176(9):683-4. [Editorial]
Antipsychotic choice

• **Efficacy**\(^1,2\)
  
  – Antipsychotics not equivalent
    
    • Clozapine ES 0.88
    
    • Olanzapine ES 0.59
    
    • Risperidone ES 0.56
  
  – Overall efficacy for rest
    
    • ES 0.33 to 0.50

• **Avoid haloperidol in first-episode patients**\(^3\)

• **Partial agonist antipsychotics**
  
  – No higher risk for psychiatric hospitalization when switching to aripiprazole\(^4\)

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\(^3\)Zhu Y et al. Lancet Psychiatry. 2017;4(9):649-705. [network meta-analysis]

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
- 56% responded in four weeks to amisulpride
- No added benefit from switching to olanzapine
- Some benefit from switching to clozapine (25%) but not as good as responders


Amisulpride
Olanzapine
Clozapine

DOUBLE BLIND

4 w
6 wks
12 wks

OPTiMiSE = Optimization of Treatment and Management of Schizophrenia in Europe
Post-Psychotic Phase
Chronic phase

Nach dem Spiel ist vor dem Spiel.
- Sepp Herberger
Premise

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

• Finish cohort study$^{1,2}$
  – N=8,719 first-episode patients, followed for 20 years
  – Three main findings
    • Antipsychotics reduce relapse risk
    • Risk of relapse increases with increased treatment duration
    • Lowest risk of death in continuously treated patients compared to untreated or minimally treated patients
  – Conclusion
    • Patients stabilized on antipsychotics for several years have a high relapse risk if antipsychotics are discontinued

• Unclear that diagnosis can be improved by discontinuing antipsychotics$^{3}$
  – Clear risks: higher mortality, reduced responsiveness after relapse

$^{2}$Kahn RS. Am J Psychiatry. 2018;175(8):712-713. [Editorial]
Deprescribing

• Classic study\(^1\)
  – Eliminating a second antipsychotic often possible
  – Successful switch in 2/3 of patients
• Recent meta-analysis\(^2\)
  – All-cause discontinuation favors staying: RR = 2.28, 95% CI = 1.50-3.46, P < 0.001
• Prioritize
  – TD risk: reduce cumulative antipsychotic dose and limit FGA use
  – Metabolic risk: eliminate high-risk antipsychotics
  – Cognition: anticholinergics
  – May want to keep clozapine plus aripiprazole\(^3\)
  – May want to keep antidepressant\(^4\)

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\(^2\)Matsui K et al. Schizophr Res. 2019 [Epub ahead of print].
\(^3\)Tiihonen J et al. JAMA Psychiatry. 2019 [Epub ahead of print].
\(^4\)Stroup TS et al. JAMA Psychiatry. 2019 [Epub ahead of print].

See also behavioral economics (nudging): Sacarny A et al. JAMA Psychiatry. 2018; 75(10):1003-11.
Long-acting injectable antipsychotic medications

- Relapse risk 20 to 30% lower for LAI compared to oral\(^1\)
- Shared decision-making should be based on facts
  - LAI gives real-time, accurate information about adherence
- Greatest benefit if started in hospital on patients who have relapsed because of non-compliance
- A reasonable strategy for patients experiencing a first psychotic episode\(^2\)
  - Avoids family conflict
- Best if employed as part of comprehensive care program
  - Maintaining frequent clinical contact may be a valid psychosocial relapse prevention treatment\(^3\)
- Can be life-saving\(^4\)
  - 30% lower risk LAI compared to oral antipsychotic
- Breakthrough symptoms (hospitalization) still high: 30% incidence\(^5\)

\(^3\)Buckley PF et al. Psychiatr Serv. 2016(12);67:1370-72.
https://www.thenationalcouncil.org/topics/long-acting-medications/
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\(^4\)

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Over 80% of refractory patients are refractory from the start.\(^2\)

Clozapine has real-world effectiveness for relapse prevention.\(^3\)

TDM – Potential benefits

• Informed decision regarding root causes of treatment complications
  – Poor response to antipsychotics (25% of patients)
    • Pseudo-refractoriness (non-adherence) vs. refractoriness*
  – Poor tolerability of antipsychotics (15% of patients)
    • Slow elimination vs. high drug sensitivity
• Identifies patients at higher relapse risk¹
• Indications
  – Non-response at therapeutic doses
  – Uncertain drug adherence
  – Suboptimal tolerability
  – Pharmacokinetic drug-drug interactions

¹Melkote R et al. Schizophr Res. 2018; 201:324-328. [CATIE sample]

*1 in 5 TRS patients may have non-detectable drug level.
Clozapine news

• Effectiveness
  – Excellent for relapse prevention\(^1\)
  – Clozapine augmentation strategies are limited\(^2\)
  – Clozapine plus aripiprazole prevents hospitalizations\(^3\)
  – Best clinical efficacy (cohort studies)\(^4\)

• Safety
  – Diabetes, hyperlipidemia, intestinal obstruction,\(^5\) aspiration pneumonia
  – Safe for benign ethnic neutropenia\(^6\)
  – Feasible to continue during chemotherapy\(^7\)

• Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program\(^8\)
  – Goal was to increase clozapine use
  – Replaces multiple registries
  – Absolute neutrophil count only
  – Different cut-offs for benign ethnic neutropenia

Clozapine underutilization

• Clozapine underused in London community settings¹
  – Point-prevalence of TRS: 56%
  – Never received clozapine: 52%

• NASMHDP report: Clozapine underutilization: addressing the barriers²,³

NASMHDP = National Association of State Mental Health Program Directors
¹Back K et al. J Psychopharmacol. 2019 [Epub ahead of print].
²http://www.nasmhpd.org/sites/default/files/Assessment%201_Clozapine%20Underutilization.pdf
Treatment for negative symptoms

- SSRI antidepressant\(^1\)
  - Efficacy seen in DECIFER trial for citalopram\(^2\)
  - ES 0.32 (DUP <18 weeks) and 0.52 (DUP >18 weeks)
- Rasagiline\(^3\)
  - MAO-B inhibitor approved for Parkinson’s disease
  - Small RTC with benefit for avolition
- CBT for negative symptoms\(^4\)
- Cariprazine\(^5\)
- L-methylfolate\(^6\)

\(^2\)Goff DC et al. Schizophr Res. 2019;208:331-337.
Treatment for CIAS
CIAS = Cognitive Impairment Associated with Schizophrenia

• Avoid adding insult to injury
  – Reduce anticholinergic burden
    • Short-term and long-term risks (10% of dementia cases)\(^1\)
  – Quit smoking!\(^2\)

• Consider cognitive training if available\(^3,4\)

• Psychopharmacology add-on strategies
  – Numerous pharmacological strategies including enhancing glutamatergic activity, cholinesterase inhibitors, cannabidiol, alpha-7 nicotinic agonists have failed
  – Missing: dopaminergic strategies (COMT inhibitors)\(^5\)

Beyond monitoring: need for action

• Physical health monitoring (screening) *alone* does not improve mortality

• Improving physical health through intervention\(^1\)
  – Psychiatric stability
  – Dietary and exercise interventions
  – Choice and duration of antipsychotic prescribing
  – Pharmacological support for smoking cessation
  – Screening for health conditions

• Correct (*standard*) medical treatment saves lives\(^2\)


Ward MC and Druss BG. JAMA Psychiatry. 2019;76(7):759-60. [JAMA Network Insights]
Keeping patients alive

• Iatrogenic morbidity¹
• Example of med-psych integration RTC
  – HOME study²,³
  – Improved quality of care (not clinical outcome...)
• Example of illness self-management RTC
  – TTIM study⁴
  – Better diabetes control after 60-week intervention
• Example of screening
  – Screening, Testing, Immunization, Risk-Reduction, Integrated Treatment (STIRR-IT)⁵
• Example of optimal cardiovascular care
  – Secondary prevention of myocardial infarction⁵

Exercise for schizophrenia patients

• The challenge
  – Cardiovascular morbidity and mortality in SMI patients
  – Sedentary life-style associated with poor cognition\(^1\)

• The simple solution
  – Exercise is “neuroprotective”
  – Exercise has broad effects on well-being\(^2\)
    • Improves global cognition\(^3\)
    • Key pathways: inflammatory pathways, BDNF (hippocampus)

• Challenges
  – Implementation: supported exercise
  – Maintaining gains: sustaining exercise
  – Mobile interventions starting to show promise\(^4\)

\(^1\)Hamer M et al. Psychol Med. 2009;39:3-11.
\(^3\)Firth J et al. Schizophr Bull. 2017;43:546-556.
Smoking cessation

• Prevalence remains high
  – 62% in a sample of research patients\textsuperscript{1}
  – Smoking affects, among other things, quality of life\textsuperscript{2}
• Address smoking in schizophrenia
  – Cardiovascular and cancer mortality\textsuperscript{3}
  – Cognitive benefits from quitting\textsuperscript{4}
    • Improved processing speed (digit symbol coding)
• Smoking cessation principles\textsuperscript{5}
• Varenicline
  – Efficacy: EAGLES trial\textsuperscript{6}
  – Safety: removal of black box warning\textsuperscript{7}

\textsuperscript{3}Olfson M et al. JAMA Psychiatry 2015;72(12):1172-81.
\textsuperscript{6}Anthenelli RM et al. Lancet. 2016;387(10037):2507-20. [EAGLES trial]
\textsuperscript{7}www.fda.gov/downloads/Drugs/DrugSafety/UCM532262.pdf
## 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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<tbody>
<tr>
<td>NAPLS</td>
<td>SOHO</td>
<td>OPTiMiSE</td>
</tr>
<tr>
<td>IEPA</td>
<td>RAISE</td>
<td>EAGLES</td>
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<tr>
<td>CHR</td>
<td>GROUP</td>
<td>DECIFER</td>
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</tbody>
</table>

How do we avoid poor outcomes?

• Poor outcomes so commonly observed in schizophrenia are likely best explained by:
  – Poor access to treatment
  – Late engagement in care
  – Poor engagement in ongoing care/poor adherence
  – Cumulative negative impact of substance abuse, medical/psychiatric comorbidities, and multiple social determinants of health

• Antipsychotic adherence to prevent relapse is a critical part of treatment
  – Increasing role of digital medicine unavoidable*

• Deficits must be realistically assessed and supported

• Medical prevention must be part of psychiatric treatment
  • 2018 WHO Guidelines for Management of physical health conditions in adults with severe mental disorders**

**https://www.who.int/mental_health/evidence/guidelines_physical_health_and_severe_mental_disorders/en/
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**

- **Step-up**
  - Switch antipsychotics
    - Early use of clozapine for refractory patients
    - Clozapine over polypharmacy
  - Add psychological treatments
  - Treat medical morbidities


It is not the critic who counts [...]. The credit belongs to the man who is actually in the arena [...].
President Theodore Roosevelt (1910)
„Die Medizin ist eine soziale Wissenschaft, und die Politik ist nichts weiter als Medizin im Großen.“

- Rudolf Virchow, 1821-1902
Thank you!

John Umstead Hospital, Butner, NC, ca. 1995