First-episode psychosis and schizophrenia

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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 28.1
Subjective Well-being 57
Function 45.4
Symptoms 60.3

*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\(^1\)
  – 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

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

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
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

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): 664–673. [AESOP cohort]
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%

*HbA1c 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\(^4\)

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

• Maybe should focus on screening ... \(^5\)

\(^4\)Nicole GE et al. JAMA Psychiatry. 2018;75(8):788-796.
Safe medical care: screening

Possible BENCHMARK

80% glucose monitoring (40% lipid monitoring)

New FDA drug approvals

• 2017: Valbenazine¹
  – Approved for tardive dyskinesia (TD)
  – VMAT-2 inhibitor
• 2017: Deutetrabenazine²
  – Approved for Huntington’s disease and TD
  – VMAT-2 inhibitor
• 2017: Proteus sensor for aripiprazole
• 2017: Aripiprazole lauroxil long-acting injectable
  – 2-month dosage
  – New initiation regimen
• 2017: SC risperidone long-acting injectable

# 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>Haloperidol decanoate [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>Fluphenazine decanoate [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>Risperidone microspheres [RISPERDAL CONSTA]</td>
<td>12.5mg, 25 mg, 37.5 mg, 50 mg</td>
<td>12.5-50 mg every 2 weeks</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>Risperidone long-acting suspension [PERSERIS]</td>
<td>TBD</td>
<td>Monthly injection</td>
<td>For subcutaneous use</td>
</tr>
<tr>
<td>Paliperidone palmitate [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>[INVEGA TRINZA]</td>
<td>273 mg, 410 mg, 546 mg, 819 mg</td>
<td>273-819 mg every 3 months</td>
<td>No overlap with oral antipsychotic (higher initiation doses) Monitor for 3 hours of observation for post-injection delirium/sedation syndrome (PDSS)* 300 mg monthly corresponds to 10 mg/d oral</td>
</tr>
<tr>
<td>Olanzapine pamoate [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 (PDSS)* 300 mg monthly corresponds to 10 mg/d oral</td>
</tr>
<tr>
<td>Aripiprazole monohydrate [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>Aripiprazole lauroxil [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 AI-NCM, for initiation under FDA review 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
## New stage-based insights

<table>
<thead>
<tr>
<th>Phase</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 early positive symptoms remission</td>
<td>Problem: early non-response (positive Sx)</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 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 then 2\%\(^3\))

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
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?
- 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\(^5,6\)

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

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

- Sepp Herberger
Substance-induced psychosis

• Danish population-based registry study
  – 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?

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 risk

• Indications
  – Non-response at therapeutic doses
  – Uncertain drug adherence
  – Suboptimal tolerability
  – Pharmacokinetic drug-drug interactions


1Melkote R et al. Schizophr Res. 2018 (in press). [CATIE sample]
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

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\(^2\)

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 evidence¹
  - 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


“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)
Early 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
• Conclusions
  – High relapse rate in good-prognosis cases that is reduced with treatment
  – Duration of treatment did not protect against relapse
  – Cannabis use disorder diagnosis associated with relapse¹

PAFIP = Programa Asistencial de Fases Iniciales de Psicosis
¹Bowtell M et al. Schizophr Res. 2018;195:231-236.
Late antipsychotic discontinuation

• Finish cohort study
  – 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

Kahn RS. Am J Psychiatry. 2018;175(8):712-713. [Editorial]
Assessment of adherence

- No gold standard
  - Multiple sources
- Assess attitude and adherence

- Common errors
  - Overconfidence
  - Underappreciating partial adherence
  - Underappreciating lack of persistence over time

5Misdrahi D et al. Schizophr Res. 2018;193:114-118.
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

\(^1\)Tiihonen J et al. JAMA Psychiatry. 2017 Jul 1;74(7):686-693.
\(^2\)Subotnik KL et al. JAMA Psychiatry. 2015(8);72:822-9.
\(^3\)Buckley PF et al. Psychiatr Serv. 2016(12);67:1370-72.
\(^4\)Taipale H et al. Schizophr Res. 2017 (in press).
Not everyone gets better with first-line antipsychotics

• Move to clozapine\textsuperscript{1}
  – Refractoriness
  – Aggression and self-injury

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

\textsuperscript{1}Warnez S and Alessi-Severini S. BMC Psychiatry. 2014;14:102.
\textsuperscript{3}Tiihonen J et al. JAMA Psychiatry. 2017;74(7):686-93.
Clozapine news

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

• Safety
  – Diabetes, hyperlipidemia, intestinal obstruction,\(^3\) aspiration pneumonia
  – 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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NASMHDP = National Association of State Mental Health Program Directors
\(^2\)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
Treatment for negative symptoms

• Meta-analysis¹
  – No clinically significant improvement
• Rasagiline²
  – MAO-B inhibitor approved for Parkinson’s disease
  – Small RTC with benefit for avolition
• CBT for negative symptoms³
• Still waiting for glycine reuptake inhibitor
  – Bitopertin story (FlashLyte and DayLyte studies)⁴
• Cariprazine⁵
• L-methylfolate⁶

Treatment for CIAS
CIAS = Cognitive Impairment Associated with Schizophrenia

• Avoid adding insult to injury
  – Reduce anticholinergic burden
  – Quit smoking!1
• Consider cognitive training if available2
• Numerous pharmacological strategies including enhancing glutamatergic activity, cholinesterase inhibitors, and stimulants have failed3
• 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 II4,5

Keeping patients alive

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

• Example of illness self-management RTC
  – TTIM study\textsuperscript{3}
  – Better diabetes control after 60-week intervention

\textsuperscript{3}Sajatovic M et al. Psychiatr Serv. 2017 Sep 1;68(9):883-890.

HOME = Health Outcomes Management and Evaluation
TTIM = Targeted Training in Illness Management
Exercise for schizophrenia patients

• The challenge
  – Cardiovascular morbidity and mortality in SMI patients
  – Sedentary life-style associated with poor cognition

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

• Challenges
  – Implementation: supported exercise
  – Maintaining gains: sustaining exercise
  – Mobile interventions starting to show promise

Smoking cessation

• Address smoking in schizophrenia
  – Cardiovascular and cancer mortality\(^1\)
  – Cognitive benefits from quitting\(^2\)
    • Improved processing speed (digit symbol coding)

• Smoking cessation principles\(^3\)

• Varenicline
  – Efficacy: EAGLES trial\(^4\)
  – Safety: removal of black box warning\(^5\)

\(^1\)Olfson M et al. JAMA Psychiatry 2015;72(12):1172-81.
\(^3\)Cather C et al. CNS Drugs. 2017;31(6):471-81.
## Acronym Jeopardy

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<tr>
<th>Prodrome</th>
<th>Cohorts</th>
<th>Treatment</th>
</tr>
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<td>NAPLS</td>
<td>SOHO</td>
<td>OPTiMiSE</td>
</tr>
<tr>
<td>IEPA</td>
<td>RAISE</td>
<td>EAGLES</td>
</tr>
<tr>
<td>CHR</td>
<td>PEPP</td>
<td>TTIM</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
  – 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
• Deficits must be realistically assessed and supported
• Medical prevention must be part of psychiatric treatment

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

**Perfect is the enemy of good.**


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