Early Detection & Intervention for Psychotic Disorders: Is it ready for “prime time”?

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Disclosure

• Does not accept any personal financial remuneration for consulting, speaking or research from pharmaceutical, biotechnology or medical device companies.

• Receives funding n medication supplies for investigator-initiated research from Denovo, Taisho, Pfizer, Sunovion, and Genentech, and company sponsored phase II, III and IV studies from Alkermes, Allergan and Boehringer Ingelheim, which does not contribute to his compensation.

• Consultant or advisory board member of Intracellular Therapies, Lilly, Pierre Fabre, Karuna, Sage, Takeda, Pear Therapeutics and Psychogenics for which he receives no remuneration.

• Paid consultant for Bracket, a clinical research services organization, and holds a patent from Repligen that yields no royalties.
End Stage of Schizophrenia (Dementia Praecox)

E. Kraepelin 1919
Etiologic & Pathophysiologic Hypotheses of Schizophrenia

• Genetic
• Dopamine
• Glutamate
• Autoimmune
• Infectious Pathogen
• Neurodevelopmental
Natural History of Schizophrenia

Stages of Illness

Healthy

Worsening Severity of Signs and Symptoms

Genes
Trauma

Gestation/Birth 10
Puberty 20

Premorbid Prodromal Onset/Progression

First Break

Deterioration

Chronic/Residual

No Sxs Early Sx Psychotic Sxs

Years 10 20 30 40 50

Negative Symptoms Cognitive Deficits Functional Impairment

Columbia Psychiatry
Gray Matter Volume Changes in the Course of Schizophrenia
Pathophysiology and Neuropathology of Schizophrenia

adapted from Glantz and Lewis
Neurodevelopmental Versus Neurodegenerative
Neurodevelopmental
Doomed from the womb!

Versus

Neurodegenerative
Disease Modification?

Are Antipsychotic Drugs
Symptom Improving Or Disease Modifying
Antipsychotic Drugs:

What they can do
- Suppress symptoms
- Prevent recurrence
- Side effects
- Prevent progression?

What they can’t do
- Refractory psychotic sxs
- Negative symptoms
- Cognitive symptoms
Regression of Excessive Gray Matter Density Change on Number of Hospitalizations in Patients

N=96.
P=.03.
van Haren NEM et al. Neuropsychopharmacology. 2007 Feb 28; [Epub ahead of print]
Regression of Excessive Gray Matter Density Change on Cumulative Clozapine Intake (mg/y) During Scan-Interval

N=58.  
P=.02.

van Haren NEM et al. Neuropsychopharmacology. 2007 Feb 28; [Epub ahead of print]
Neurodevelopmental
*Doomed from the womb!*

Versus

Neurodegenerative
*Disease Modification?*

Duration of Untreated Illness

Recurrent Psychotic Episodes
Treatment Intervention in Psychosis (TIPS) Study

• Test feasibility and impact of reducing DUP on outcomes

• Comparison of intensive and comprehensive early detection (Denmark, Sweden) with usual detection (Norway). Treatment was equivalent.

• Median DUP in intensive regions reduced from 26 to 5 weeks; in usual region median DUP was 16 weeks

• 5 & 10 year outcomes better in intensive regions

The “Recovery After an Initial Schizophrenia Episode” initiative seeks to alter the trajectory and prognosis of schizophrenia through aggressive treatment with coordinated specialty care in the early stages of illness.

NIMH 2008
Principles & Elements of Optimized FEP Intervention

• Goals
  – Facilitate Symptom Remission and Recovery
  – Prevent progression of illness
  – Limit disability

• Method
  – Coordinated Specialty Care
    • Medical Management and Psychopharmacology
    • Psychoeducation
    • Case Management
    • Rehabilitation
    • Substance Abuse Treatment
    • Suicide prevention
  – Individualized Care Plan
  – Shared Decision Making
Each patient’s odds of remission increased by 1.55 times (CI: 1.31, 1.83; p<0.0001) each month in f/u to month 6 and remained stable.

Global Function score increased by 0.96 points (CI: 0.60, 1.32, p<0.0001) every month.

Dixon et al 2014
Early Detection and Intervention

For Psychotic Disorders (Schizophrenia and Affective Psychoses) is Ready for Prime Time and Should Be the Standard of Care
Natural History of Schizophrenia

“An Ounce of Prevention is Worth a Pound of Cure”

Ben Franklin

Stages of Illness

Premorbid Onset/Progression

Deterioration

Puberty

Chronic/Residual End-Stage

Healthy

Worsening Severity of Signs and Symptoms

Gestation/Birth

10

Puberty

20

Years

No Sxs

Early Sx

Psychotic Sxs

Psychotic Sxs

Negative Sxs

Cognitive Sxs

Prevention of Progression

Help-seeking individuals with functional and psychosocial complaints

Not at risk

Assessment

At-risk subgroups

BLIP

APS

UPS

BS

GRD

Active treatment or monitoring

FEP treatment

Transition to psychosis

Final assessment/discharge

Fusar-Poli et al., 2013
# Utility of Criteria to Diagnose Disease

<table>
<thead>
<tr>
<th></th>
<th>Diagnosis = Negative</th>
<th>Diagnosis = Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Result = Positive</strong></td>
<td>False Positive</td>
<td>True Positive</td>
</tr>
<tr>
<td><strong>Positive</strong> Predictive Value: TP/(TP+FP)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Test Result = Negative** | True Negative | False Negative |
| **Negative** Predictive Value: TN/(TN+FN) |

| **Specificity:** | TN/(TN + FP) |
| **Sensitivity:** | TP/(TP + FN) |
## Comparison of Risk Calculations

<table>
<thead>
<tr>
<th>Risk Calculator</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Columbia</td>
<td>40%</td>
<td>85%</td>
<td>55%</td>
<td>77%</td>
</tr>
<tr>
<td>NAPLS</td>
<td>35%</td>
<td>91%</td>
<td>39%</td>
<td>90%</td>
</tr>
<tr>
<td>Framingham</td>
<td>39%</td>
<td>89%</td>
<td>13%</td>
<td>97%</td>
</tr>
<tr>
<td>Mammography (50-69 yo)</td>
<td>~90%</td>
<td>~90-95%</td>
<td>60-80%</td>
<td>99%</td>
</tr>
<tr>
<td>Prostate Specific Antigen (4ng/ml)</td>
<td>21%</td>
<td>91%</td>
<td>30%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Girgis et al 2018
DSM V/APS Criteria

a) Characteristic symptoms: At least one of the following is present in attenuated form with intact reality testing but of sufficient severity and/or frequency that it is not discounted or ignored
   i. Delusions
   ii. Hallucinations
   iii. Disorganized speech

b) Frequency/currency: Symptom or symptoms meeting criteria A must be present in the past month and occur at an average frequency of at least once per week in the past month

c) Progression: Symptoms meeting criteria A must have begun or worsened in the past year

d) Distress/disability/treatment seeking: Symptoms meeting criterion A are sufficiently distressing and disabling to the patient and/or parent/guardian/others to lead them to seek help

e) Symptoms meeting criterion A are not better explained by any other DSM-V diagnosis, including substance-related disorders

f) Clinical criteria for any DSM-V frank psychotic disorder have never been met
Therapeutic Interventions to Prevent Psychosis

- Randomized, unblinded comparison of risperidone+therapy vs TAU (McGorry et al 2003)
- Randomized unblinded comparison of cognitive behavioral therapy (Morrison et al 2004)
- Randomized, double blind comparison of olanzapine vs PBO (McGlashan et al 2006)
- Randomized double blind comparison of omega-3- fatty acid vs PBO (Amminger et al 2010)
- Glutamate Modifying Drugs (Javitt, Girgis, Lieberman, Schobel, Small 2015, 2018, 2019)
Key Limitations for Early Intervention in the Prodromal Phase

♦ Diagnostic criteria lack specificity and precision

• Unclear what is the best modality and treatment.
Anatomic Areas of Pathology for Biomarker Development in Schizophrenia

Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium

Molecular Psychiatry (2016) 21, 547–553
The Hippocampal Complex

- Ant. cingulate
- Post. cingulate
- Orbitofrontal
- Amygdala
- Striatum

Subregions of the hippocampus:
- CA1, CA3
- DG
- SUB
- EC
Hippocampal Biomarker for Psychosis

Adapted from Schobel, Small et al 2013
Correlation Between CBV and Atrophy
The importance of high resolution

Schobel et al. 2013
Changes associated with emergence of psychosis

Hypermetabolism ‘propagates’

HIPP contracts

Schobel et al 2013
Glutamate Dysregulation Precipitates Psychosis
MR Spectroscopy In Schizophrenia

Frontal Cortical Gray
ROI

[Graph showing NAA, Cre, Cho, tGLX peaks]
Glutamate Dysregulation Precipitates Psychosis

Rationale for Glu Targeted Rxs

- NMDA allosteric modulators: Glycine, D-Serine, GlyT inhibitors
- Glutamate modulators: Gabapentin, Pregabalin, NAC, Benzoate
- mGlu-Receptor 2,3,5 modulators
- AMPA potentiators
Human CBV phenotype replicated in rodent model

Adapted from Schobel, Moore, Small et al
mGluR 2/3 agonist protects against the metabolic and structural changes produced by repeated ketamine

Schobel et al 2013
Pathogenesis of SCZ

Lieberman et al Mol Psych. 2018
Pathogenesis of SCZ and AD

Lieberman et al Mol Psych. 2018
Regenerative Drugs that Restore and Enhance Neural Connectivity

BDNF, ERKs, Bcl-2

Downregulation of PKC isozymes

Adapted from H. Manji
Natural History of Schizophrenia
Rationale for Early Detection and Intervention

Stages of Illness

Premorbid
Prodrome
Onset/Progression
Chronic/Residual
End-Stage

Healthy

Worsening
Severity of
Signs and
Symptoms

No Sxs
Early Sx
First Break
Prevention of Onset & Progression

Gestation/Birth 10 20 30 40 50 Years

Puberty 20

Years

Conclusions

• Schizophrenia is a progressive disorder that evolves from a neurodevelopmental diathesis

• Clinical and biological measures can identify people at risk for scz and related psychotic disorders

• Disease modification is possible by limiting the duration of untreated illness and prevention of psychotic relapses using APD’s

• Early detection and intervention indicated for first episode psychosis and possible for prodromal stage with improved criteria and possibly glutamate modulating drugs