Defining, Measuring and Tracking Disease Modification in Schizophrenia

Some Lessons from Medicine

Shitij Kapur
Institute of Psychiatry, King’s College London
Outline ..

• Schizophrenia
  – Is it a single “Disease”?  
  – What progresses and what does not  
  – Do we have markers of progression?

• Lessons from other illnesses
  – Multiple Sclerosis  
  – Rheumatoid Arthritis  
  – Dementia

• What does it mean for Schizophrenia
Schizophrenia is not a Disease

It is a mental disorder

Dorland’s Medical Dictionary

Disease: a definite pathological process having a characteristic set of signs and symptoms.

Disorder: a derangement or abnormality of function; a morbid physical or mental state.

What is a Mental/Psychiatric Disorder? From DSM-IV to DSM-V

Diagnostic Shifts During the Decade Following First Admission for Psychosis


FIGURE 2. Pattern of Shifts in Diagnosis for 432 Study Participants With First-Admission Psychosis at Baseline Who Received Diagnoses at All Four Assessment Points

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Year 10</th>
<th>Schizophrenia (N=210)</th>
<th>Bipolar Disorder (N=110)</th>
<th>Major Depression (N=48)</th>
<th>Substance-Induced Psychosis (N=29)</th>
<th>Other (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia (N=126)</td>
<td></td>
<td></td>
<td>6.2</td>
<td>4.5</td>
<td>6.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Schizophrenia (N=99)</td>
<td></td>
<td></td>
<td><strong>47.1</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bipolar disorder (N=5)</td>
<td></td>
<td></td>
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<tr>
<td>Major depression (N=3)</td>
<td></td>
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<tr>
<td>Substance-induced psychosis (N=1)</td>
<td></td>
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<tr>
<td>Other (N=5)</td>
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</tr>
</tbody>
</table>

14.3
Is there predictable decline?

- 21 studies, >5 years of follow up, ~2,000 patients, 1987 onwards
- 7-52% “Remission” (variously defined)
- 5-10% Suicide
- 34-70% with poor outcomes
- Symptoms fluctuate, negative symptoms most stable, but unclear if there is progression.
Cognition

- 31 Cross-sectional and 43 Longitudinal studies

- Cross-sectional studies, suggest deterioration with time

- Longitudinal studies, suggest no change with time

- Likely effect of selection bias
Brain Structures

Progressive Brain Change in Schizophrenia: A Prospective Longitudinal Study of First-Episode Schizophrenia
Nancy C. Andreasen, Peg Nopoulos, Vincent Magnotta, Ronald Pierson, Steven Ziebell, and Beng-Choon Ho

What Happens After the First Episode? A Review of Progressive Brain Changes in Chronically Ill Patients With Schizophrenia
Hilleke E. Hulshoff Pol and René S. Kahn

up to at least 20 years after their first symptoms. The extent of progressive brain tissue decrease in patients (−0.5% per year) is twice that of healthy controls (−0.2% per year).
Disease Modification

What can we learn from others?
Multiple Sclerosis

Fig 1. Kaplan-Meier analysis showing the probability of remaining exacerbation-free in the first 2 years of the study comparing 2 different doses of IFN-β to placebo.


Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group.
Multiple Sclerosis

### Table 1. FDA-Approved Disease-Modifying Therapies for Multiple Sclerosis.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Approved in US</th>
<th>Pregnancy Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingolimod (Gilenya)</td>
<td>0.5 mg</td>
<td>Oral</td>
<td>Daily</td>
<td>2010</td>
<td>C</td>
</tr>
<tr>
<td>Glatiramer acetate (Copaxone)</td>
<td>20 mg</td>
<td>SC</td>
<td>Daily</td>
<td>1996</td>
<td>B</td>
</tr>
<tr>
<td>IFNβ-1a (Avonex)</td>
<td>30 µg</td>
<td>IM</td>
<td>1× weekly</td>
<td>1996</td>
<td>C</td>
</tr>
<tr>
<td>IFNβ-1b (Betaseron)</td>
<td>0.25 mg</td>
<td>SC</td>
<td>Every other day</td>
<td>1993</td>
<td>C</td>
</tr>
<tr>
<td>IFNβ-1b (Extavia)</td>
<td>0.25 mg</td>
<td>SC</td>
<td>Every other day</td>
<td>2000</td>
<td>C</td>
</tr>
<tr>
<td>IFNβ-1a (Rebif)</td>
<td>22, 44 µg</td>
<td>SC</td>
<td>3× weekly</td>
<td>2002</td>
<td>C</td>
</tr>
<tr>
<td>Mitoxantrone (Novantrone)</td>
<td>12 mg/m²</td>
<td>IV</td>
<td>Every 3 months</td>
<td>2000</td>
<td>D</td>
</tr>
<tr>
<td>Natalizumab (Tysabri)</td>
<td>300 mg</td>
<td>IV</td>
<td>Monthly</td>
<td>2004/2006</td>
<td>C</td>
</tr>
</tbody>
</table>

**Abbreviations:** IM, intramuscular; IV, intravenous; SC, subcutaneous; US, United States.

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**Biogen multiple sclerosis drug Tecfidera wins European approval**

**BY BILL BERKROT**

Mon, Feb 3, 2014 - 02:29pm GMT
Clinical Improvement

Functional Improvement

Biomarker Improvement

Rheumatoid Arthritis

- Symptomatic Rx with NSAIDs and Steroids

- Disease Modifying Anti-Rheumatic Drugs (DMARDs)
  - Hydroxychloroquine (Plaquinil)
  - Leflunomide (Arava)
  - Cyclosporine (Neoral)
  - Sulfasalzine (Azulfidine)
  - Methotrexate (Rheumatrex, Trexall)
  - Azathioprine (Imuran)
  - Cyclophosphamide (Cytoxan)
  - Biologics (Actemra, Cimzia, Enbrel, Humira, Simponi)
ACR .. Clinical Rating Score

HAQ .. Patient Reported Disability Index

mTSS .. Radiological Erosion Score
Indications for DM drugs ..

Humira for RA
Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.

Cortisone for RA .. Per month

<table>
<thead>
<tr>
<th>Sams Club</th>
<th>$18.37</th>
<th>with discount</th>
</tr>
</thead>
</table>

Humira for RA .. Per Month

<table>
<thead>
<tr>
<th>Sams Club</th>
<th>$5,291.51</th>
<th>with discount</th>
</tr>
</thead>
</table>
Lessons for Schizophrenia

- The regulatory distinction between symptomatic control and “disease modification” is becoming clearer.

- Most recent DM approvals are based on a troika of:
  - Improving clinical symptoms
  - & Improvement in functional disability
  - & Related improvement in a mediating pathophysiological marker.

- In the absence of a mediating marker biomarker the burden-of-proof is higher and the pathway uncharted.
## Modification Options in Schizophrenia

<table>
<thead>
<tr>
<th>Define and Measure</th>
<th>Evidence of Progression</th>
<th>Biomarker</th>
<th>Clinical Relevance</th>
<th>Timeline 2-5 year study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotic TRS</td>
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<td></td>
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<tr>
<td>Cognitive Decline</td>
<td></td>
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<tr>
<td>Negative Symptoms</td>
<td></td>
<td></td>
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<tr>
<td>Structure Brain Decline</td>
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</tbody>
</table>

*Is it progression or selection?
A hypothetical “modifying” Scenario

- **Objective** – to decrease the progression to TRS [Currently at 20% at Y2] and gray matter decline [1% at Y2] in patients treated with standard atypical antipsychotics with the addition of Marmite.

- **DBRCT** – patients with FE – followed for 2 years.
  - Group 1: Receives TAU + Marmite + Yearly MRI
  - Group 2: Receives TAU + Placebo + Yearly MRI

- **Outcome Variables**
  - Primary – % with failure of two antipsychotics
  - Secondary – Functional Outcome as measured on SOFI
  - Supportive - Decrease GM decline

- With 400 patients, followed for 2 years, you will have the power to demonstrate that you have **modified the course** if we can show that:
  - A) a decrease in TRS from 20% to 10%
  - B) associated with functional improvement;
  - C) change in gray matter loss from 1% to 0.6%;
  - D) that the two [GM and TRS] are correlated (r > 0.4).

* Howes et al. BJP 2012
What’s needed ..

• Which patient subgroup within Schizophrenia?

• Progression of which particular symptom domain?

• What is the underlying biomarker that mediates and is modifiable?
What if there are no reliable biomarkers?

Symptomatic Treatment

Disease Modification

Defining and labeling disease-modifying treatments for Alzheimer’s disease

Jeffrey L. Cummings

Alzheimer’s & Dementia
Volume 5, Issue 5, September 2009, Pages 406-418