

Disease Modification in Schizophrenia: Overview of the Issues

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Need for a New Treatment Paradigm in Schizophrenia

Sixty years after approval for the first neuroleptic, and 20 years after introduction of 5HT₂/D₂ atypicals, treatment of schizophrenia is characterised by

- 35% of patients experience “good” and 25% “poor” outcome; only 35% report a “functional recovery”
- Over 33% of patients experience relapse of psychotic symptoms
- 16% do not remit from an episode
- 15% experience an episode with affective psychotic symptoms that start on average 6 years after diagnosis
- 10% commit suicide
- 20% experience “persistent” negative symptoms even after a “good outcome”
- Over 70% discontinue medication within 18 months

Obviously, current treatment strategies in schizophrenia have provided suboptimal benefit, and there is a need to consider new treatment paradigms

Need for a New Treatment Paradigm in Schizophrenia (ii)

Current paradigm in schizophrenia treatment, and antipsychotic development do not target arresting deterioration at the beginning of the disease

- Initial 2-5 years of the clinical phase represent period of maximum vulnerability to effects of disease
- No biological target research ongoing that considers targeting disease related worsening at the onset
- Lessons from AD research and other illnesses with significant disability need to focus disease modifying therapies very early in disease
- Major issues that need to be considered include:
 - Progression of disease in schizophrenia
 - Homogeneity of diagnosis/course of disease,
 - Identification of early subjects at risk of progression
 - Target variables/symptoms
 - Design of trials/regulatory perspective
- Meeting today represents only the beginning of a discussion on this issue, not the end, the beginning of the end or even the end of the beginning

Complexities in Designing Disease Modifying Trials in Schizophrenia

Prior to designing trials and therapies to modify disease progression in schizophrenia, it is imperative to address key fundamental questions

- Is there disease progression in schizophrenia?
- Does the disease progress in every patient?
- Are there cohorts who progress and those who don't?
- Is the progression due to genetic factors: is poor outcome determined by other factors such as age of onset, gender, environment, duration of untreated psychosis, treatment, "expressed emotion", family structure, etc.?
- What symptom domains, if any, progress in schizophrenia?
- Are there biological/neuroanatomical correlates of progression?
- What outcomes could be assessed to evaluate disease progression?
- What patient types should be evaluated in such trials?

Is There Disease Progression in Schizophrenia?

- Schizophrenia is heterogeneous in presentation, and may represent different disease processes with varied outcomes
- Impossible to define usual course of progression in patients who maybe heterogeneous in etiology, pathophysiology, and phenomenology
- Observation of clinical decline varies between cohorts, and maybe influenced by patient intake, country, methods, type of treatment, periods of follow-up, and lack of knowledge of premorbid status
- Despite evidence of inheritance, no strong candidate genes, or significant risk factors identified
- Post-mortem findings (lack of gliosis, inclusion bodies, evidence of neuronal death, apoptosis, etc.) do not fit usual model of degenerative disease

Changes in Viewing Schizophrenia as a Progressive Disease

- Kraepelin (1899) described “Dementia Praecox” “serious ...and only partially reversible damage to the cerebral cortex ..., 75% of cases reach higher grades of dementia and sink deeper and deeper”
- View not shared by Bleuler who considered “group of schizophrenias” (SCZ) as “splitting of the mind”; several outcomes possible, recovery and not just a progressively deteriorating one,
- Jasper considered SCZ as a biological brain disorder but focused on phenomenology
- Pneumoencephalographic studies (1920-1950) indicated ventricular enlargement in SCZ, with increase over time
- Johnstone (1976)/Weinberger (1978) used CT to demonstrate increased ventricular size compared to controls; not correlated with duration of illness or treatment

Changes in Viewing Schizophrenia as a Progressive Disease II

- Major findings in favor of progression include; lateral ventricular enlargement , grey matter reductions, reduced white matter integrity, regional volume reductions, developmental abnormalities
 - Many findings already evident in first episode patients (ventricular enlargement, hippocampal reduction) while others appear later (temporal lobe, amygdala)
- Dominant view before 1990s was that SCZ had an inherited component that led to altered neurodevelopment

“Synaptic pruning”, fixed lesion from early neonatal life, impairment of neuronal migration, genetic influences over neural development, considered as explanations
- Unlikely that abnormal brain development in children (<6 years) contributes to brain findings in patients as cranial volume in patients is not smaller
- Up to 10 year MRI follow-up indicates progressive volume loss in gray matter and increase in lateral ventricles with more pronounced changes in patients with poor outcome(Van Haren et al,2008), severe negative symptoms (Saijjo et al,2001), and cognitive deterioration(Gur et al, 1998)

Clinical Outcomes During Long-term Follow-Up

- Ram et al. (1992): 7 long term follow-back studies (5-30 years) and 13 prospective studies (1-5 years)
 - “Good” outcome (almost complete remission): 28%
 - “Moderate” outcome (partial remission): 50%
 - “Poor” outcome (chronic psychosis): 22%
- Hegarty et al. (1994): 100 years of outcome literature “improved” (after 5.6 years): 40%
- Eaton et al. 1991: (early onset cases)
 - “Good” outcomes: 10-64%
 - “Poor” (chronic psychosis): 10-40%
- Wiersma et al. (1998): 15 years follow-up
 - 3 years follow-up results
 - “Complete” remission: 35 %
 - “Partial” remission: 35 %
 - Chronic psychosis: 24%
 - Suicide: 6 %
 - 15 years follow-up
 - “Complete” remission: 27 %
 - “Partial” remission: 50 % (negative syndrome)
 - Chronic psychosis: 11%
 - Unknown: 12 %
 - Suicide: 12 %
- Longer follow-up not necessarily reflected in worse outcomes

Natural Course of Schizophrenic Disorders

Course of non-affective functional psychosis over 15 years (n = 82)

Course	n (%)
One episode followed by complete remission	10 (12.2)
Two or more episodes followed by complete remission	12 (14.6)
One episode followed by partial remission (anxiety/depression)	5 (6.1)
Two or more episodes followed by partial remission (anxiety/depression)	9 (11.0)
One episode followed by negative syndrome	3 (3.7)
Two or more episodes followed by negative syndrome	24 (29.3)
Chronic psychotic all the time (one episode)	9 (11.0)
Course unknown (refused or untraceable)	10 (12.2)

Chronicity of psychosis: No remission or partial remission (negative symptoms)

Course of psychotic episodes	Persisting psychotic symptoms (%)	Negative symptoms (%)
First episode (n = 82)	12	15
Second episode (n = 49)	8	25
Third episode (n = 27)	19	22
Fourth episode (n = 15)	27	20

Schizophrenia: Course

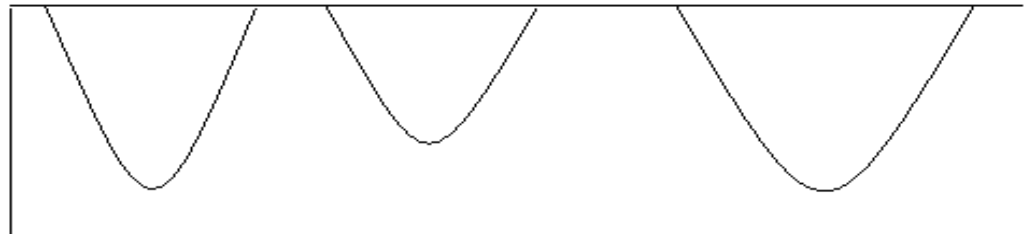
Group 1

15% have only a single episode of illness with no subsequent impairment



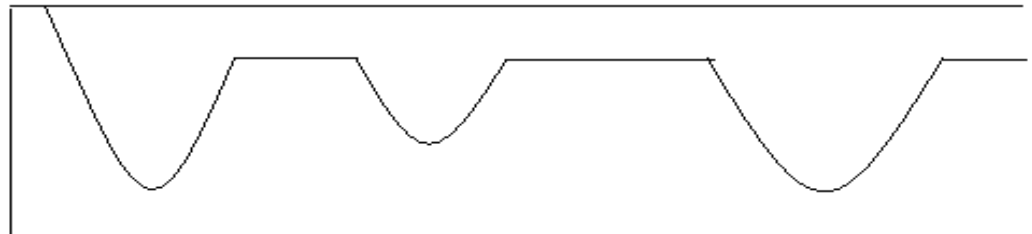
Group 2

25% have repeated episodes of illness with no impairment between episodes



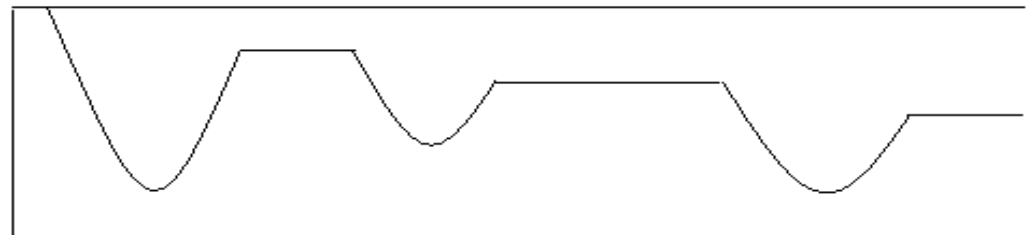
Group 3

30% have repeated episodes of illness with some impairment between episodes



Group 4

30% have repeated episodes of illness with gradually declining impairment between episodes



Findings From Studies in Early Patients

- Meta-analysis (Menezes et al, 2006) of 37 prospective studies involving 4100 First Episode Patients with mean follow-up of 36 months indicated :
 - “Good” outcome: 31 %
 - “Intermediate” outcome: 42 %
 - “Poor” outcome: 30 %
 - Longer studies had lower rates for “good “, higher “rates for “intermediate” outcomes, and a slight increase for “poor outcomes”; higher rates for re-admission and relapse
- Follow-up studies in “Ultra-high Risk”/ “At Risk Mental State”(Wood et al, 2008) indicate:
 - No lateral ventricle/amygdala enlargement in UHR subjects: no difference in hippocampal volume and cognition (paired associate/visuospatial learning) between UHR-P and UHR-NP subjects in cross-sectional studies
 - Higher rate of change in right pre-frontal region/decline in visuospatial memory, verbal fluency, and attentional switching noted in UHR-P but not in UHR-NP subjects: suggests faster grey matter retraction in pre-psychotic subjects during transition to psychosis

Selecting Outcome Measures for Disease Modifying Trials

Currently, there is no scientific/regulatory consensus on the concept of disease progression in schizophrenia, its etiology, pathophysiology, pathological markers, or its long-term course

However, there is agreement that the disease leads to:

- Relapses (over 80% of patients) and hospitalizations (60%)
 - Break-through symptoms (60%), inter-episode impairment (60%),
 - Significant negative symptoms (60%), functional decline(60%) and measurable cognitive deterioration (60%)
 - Suicidality (>50%)
- Consensus that the period of maximum change is the first 2-5 years from diagnoses
 - Repeat episodes are linked with worse prognoses
 - Brain changes are more prominent in more chronic and severe patients
 - Outcome measures for disease progression need to focus on these core deficits observed in schizophrenics

These measures have been well-evaluated and have face and construct validity for schizophrenia

Selecting Outcome Measures for Disease Modifying Trials(ii)

There is a need to differentiate symptomatic benefits from disease modifying benefits

- Based on heterogeneity in course, randomized start/ withdrawal design, or changes in slopes is unlikely to define disease modifying effect
- Attributes necessary for disease modifying effect should include significant:
 - Reduction in relapses (no more than 1; not only time to failure) over study length
 - Reduction in break-through symptoms (PANSS)
 - No worsening of negative symptoms compared with baseline
 - Less functional decline and measurable cognitive deterioration
 - Improvement in suicidality
 - Attenuation of brain changes
- Need to define composite measure that could include 2-3 of above, and determine weights of each component

Patient selection and overall design for Disease Modifying Trials in schizophrenia

Study design, outcome measures, length of treatment/follow-up is contingent on the cohort of patients that would be evaluated

- Chronic psychotic patients (> 5 years of psychosis)
 - Worsened positive and negative symptoms, impaired cognition, functional disabilities
- First episode patients (< 1 year after diagnosis)
 - Responders/remitters, ability to function in community, cognition not significantly impaired
- Ultra-high risk patients (displaying “need for care”, attenuated psychotic symptoms, brief intermittent psychotic symptoms, recent functional decline)
 - Conversion to psychosis low, many revert to normalcy
- Ideal population would consist of remitted first episode patients whose first episode was well characterized (Psychosis/MRI/Cognition/Functioning)
 - Would ensure schizophrenia diagnosis, treatment responsiveness, reduce likelihood of brain changes due to prior antipsychotic medication
 - All patients must be treated with atypical antipsychotics to reduce potential effects on atrophy
 - Select patients with changes in pre-frontal cortex structure and function
- Overall design
 - Randomised placebo controlled, parallel group add-on to standard of care
 - Duration of treatment 2-3 years

Next Steps

- Further impetus to understand the pathophysiology of brain degeneration in schizophrenia myelin-related dysfunction
- Develop analytic techniques that detect small changes in right pre-frontal cortex
- Need data on fMRI changes during cognitive tasks
- Develop cognitive tasks that discern very small changes in pre-frontal cortical tasks such as visuospatial memory, attentional switching
- Need more data on UHR-P/UHR-NP/FES subjects longitudinally
- Develop composite measures that could be used in disease progression trials
- Need Academia/Industry/Regulatory Partnership