Relapse Prevention In Schizophrenia

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Relapse Prevention In Schizophrenia

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Declaration

- Janssen Group
- Eli Lilly
- Astra Zeneca
- Nicholas Piramal-Rosch
- Sun Pharma- India

- Consultant
- Advisor
- Drug trial coordinator
- Research Investigator
- Reviewer
- Speaker
- Educational Groups
Relapse in schizophrenia: Current issues

- Nature of relapse
- What causes Relapse
- How to minimize
- What is beyond relapse prevention in improving outcome
Relapse: ‘Life is never the same again’

• Expected in 70% patients after First episode
• 70% of patients show an incomplete remission after first episode
• This includes Cognitive decline (in 55%)
• persistence of negative symptoms (in 41%),
• often associated with Social disabilities,
• Social Decline and a worsened QOL.
• Risk of relapse after an episode remained increased throughout the life.
Outcome-Recent Studies, Early Intervention

- Kobayashi T, 2004: 55
- Harrow M, 2005: 40
- Rosen K, 2005: 16
- Armenteros JL, 2006, Typicals: 72
- Armenteros JL, 2006-meta-analysis: 55
- Malla A, 2006: 53
- Grawe RW, 2006: 82
- Saeedi H, 2007: 78
- Harvey CA, 2007: 62
- Chabannes JP, 2008, No Relapse: 10
- Emsley R, 2008: 64 and 20.4

Chabannes JP, 2008, No Relapse
Armenteros JL, 2006, Typicals
Armenteros JL, 2006-meta-analysis
Malla A, 2006
Grawe RW, 2006
Saeedi H, 2007
Harvey CA, 2007
Chabannes JP, 2008, No Relapse
Cumulative Recovery Rate in First episode schizophrenia: Robinsons et al, JCP 2006

Symptom Remission, Social Functioning, Full Recovery

Year 3, Year 4, Year 5, Year 6
Schizophrenia Relapse rates
Survival Analysis of optimal NL dose and real world rehospitalization risk for multiepisodic NL responsive schizophrenia

Cost of Relapse in Schizophrenia
By Peter J. Weiden and Mark Oltson
Relapse: when and how it Occurs

- Side Effects
- Lack of efficacy
- Psychosocial stress
- Interrupted availability

With no Adherence
- Attitude- like/dislike
- Acceptance- personal Choice
- Lack of information, education

With partial adherence

With Complete Adherence
- Nature of illness
- Loss of efficacy of APD
- Life events
Concept of patient responsiveness is a continuum rather than dichotomy of response & nonresponse.
Relapse

Relapse is one of the outcome criteria

Underlying Neurobiology is poorly understood

Fairly Common irrespective and independent of nature, age of onset, treatment given, monitoring

What relapses: positive symptoms, depression, and suicide, lack of self-care, competency

Not relapsed does not mean good functioning. Non-relapsing patients do have disability, dysfunction and poor QOL.
The patient $\rightarrow$ The illness $\rightarrow$ The treatment

All of these components $\leftarrow$ The environment and family
Determinants of Relapse
Risk factors
Possible Mechanisms

Time to Remission

- Mean
- Median

- First episode
- Second episode
- Third episode

0 20 40 60 80 100 120 140

mean median
Protective Factors:

personal resource, good premorbid adjustment, a positive self concept & a competent social network
Effectiveness of intervention for Schizophrenia: Relapse rate

- Chlorpromazine + family Intervention: % Relapse after 1 year - Maximum 23, % of Relapse after One year 2
- Chlorpromazine: % Relapse after 1 year - Maximum 25, % of Relapse after One year 20
- Placebo: % Relapse after 1 year - Maximum 55

References:
First-episode schizophrenia versus chronic schizophrenia treated with risperidone (2)

Clinical Global Impression (CGI)

- First episode (n=161)
- Acute exacerbation, chronic (n=905)

Days of treatment

Mean CGI severity

*p<0.05

Rüther E, Klauder A. WCP, Hamburg, August 1999
Efficacy and effectiveness of Antipsychotic Medications: Annual Relapse Rate

- Placebo: 70
- Medication efficacy: 23
- Medication Effectiveness: 45

Annual Relapse Rate
Effectiveness of Antipsychotic Drugs in Schizophrenia

(Lieberman et al., 2005)
Cognitive behavior Therapy for residual symptoms in Schizophrenia Patients in Community
( Dickerson & Lehman, 2005)
Combining Medication and Family Education in Schizophrenia; Relapse Rates

% of patients relapsed

- Placebo: 70%
- Medication: 45%
- Medication + Family Therapy: 20%
Relapse rate in 2 years with Oral Vs LA Depot APD combined with psychosocial intervention, Schoolar et al, 2006

Months of treatment, N=5- each Group

Proportion surviving

Fluphenazine Decanoate
Fluphenazine Hydrochloride

0 0.2 0.4 0.6 0.8 1 1.2

0 3 6 9 12 15 18 21

Proportion surviving
Schizophrenia PORT
Current practices

% patients with Conformant Treatment

- Antipsychotic: 28%
- Antidepressants: 45%
- Psychological Intervention: 43%
- Family Intervention: 10%
- Vocational Intervention: 22%
Are Antipsychotics superior to psycho-social & cognitive behavioural therapies in relapse prevention of schizophrenia?

- Evidence is equivocal

Thus, there is a clear case for integrated and comprehensive therapy right from the day of the first contact; irrespective of the clinical settings; situations and alliances.
Antipsychotic Response is a function of 5HT2a & D2 blocking Ratio

D2 Receptor blocking % in Frontal Lobe

- Dysphoric response, No antipsychotic response: 95%
- Good positive symptom response: 85%
- Persistent Antipsychotic response: 65%
- Antipsychotic response: 40%
- Antidepressant response: 20%
Genetics - Examples

• An example of how a genetic predisposition for schizophrenia can be triggered by environmental influences can be seen in a research study taken from Biological Psychiatry, Volume 57:
  – Indicates that people who had multiple copies of a version of the COMT gene and who smoked marijuana had a 1,000% increase in their risk of developing schizophrenia

• Another example from the British Journal of Psychiatry:
  – Indicates that adopted children with high genetic/biological risk for schizophrenia (their mother had schizophrenia) had an 86% lower rate of developing schizophrenia raised in a healthy vs. a dysfunctional family.
  – Only 6% of the children developed schizophrenia in the healthy family.
  – 37% of the children of the dysfunctional families developed schizophrenia

(as cited on www.schizophrenia.com).
Why does comorbidity develop??
Why is Medication Not Sufficient?

• Neurodevelopmental dysfunction
• Subtle neurocognitive deficits from early childhood
• Diffuse system disruption
• Timing of first exacerbation disrupts adult socialization
• Residual primary and secondary negative symptoms
Impact of Non-Adherence

- ↓ Remission\(^1\)
- ↑ Relapse\(^2\)
- ↑ Hospitalization\(^3,4\)
- ↓ Functional outcomes\(^4\)

Non-adherence Associated with Poorer Functional Outcomes (n=1906)\(^4\)

- Substance use: Non-Adherent (n=376) vs. Adherent (n=1530)
  - p<0.001
- Hospitalized
  - Non-Adherent: 21.5%, Adherent: 14.1%
- Victim of crime
  - Non-Adherent: 15.1%, Adherent: 7.8%
- Violent
  - Non-Adherent: 10.8%, Adherent: 4.8%
- Emergency psych service use
  - Non-Adherent: 10%, Adherent: 6%
- Arrested
  - Non-Adherent: 8.4%, Adherent: 3.5%

References:
2. Robinson et al. Arch Gen Psychiatry 1999;56:241-7
Negotiating Medications

- Attitude, acceptance, Belief, culture
- Team efforts, Education, Monitoring, Reinforcing Compliance as answer
- Nature of illness, Medication Effect & Side effects
Expressed emotion and psychiatric relapse: a meta-analysis.
Community-Based Treatment of Schizophrenia and Other Severe Mental Disorders: Treatment Outcomes
cumulative relapse/rehospitalization rates during 18 to 24 months in randomized controlled trials of long-term family intervention for schizophrenia.
Specialized programs for relapse prevention are more effective in identifying prodromal episodes before frank relapse.

‘A Program for Relapse Prevention in Schizophrenia: A Controlled Study’

Marvin I. Herz, et al
Arch Gen Psychiatry. 2000;57:277-283.
Nature of Illness as Determinants of Relapse
Biological mechanisms of relapse may not become fully elucidated before the mechanisms of the schizophrenic pathophysiology are clarified.

- low serotonergic and high dopaminergic neurotransmission are associated with a relapse,

- possibly high noradrenergic neurotransmission plays a role in short-term relapses.

- Role of Certain cytokines, which have rarely been studied to date, seem to have an even higher impact on schizophrenic relapse.
Biological studies and Relapse

Week following haloperidol withdrawal model, likelihood ratio  \( p < 0.0005 \)
Biological studies and Relapse

Week following haloperidol withdrawal model, likelihood ratio p < 0.0005
Relevance of Neuro-cognitive deficits for functional outcome in schizophrenia
Can Neurocognitive Functioning Be Improved with Psychosocial Interventions?

Strategies for reducing Cognitive Demands
Stress-diathesis model forms the theoretical context of Risk-Vulnerability hypothesis.

Developmental and stress-related changes of neurotrophic factor gene expression in an animal model of schizophrenia.

Vulnerability/stress model of schizophrenic relapse: a longitudinal study;
Acta Psychiatrica Scandinavica Volume 89 Issue s382, 58-64, 1994

K. H. Nuechterlein
Maximizing outcome and preventing relapse: The necessary steps

- Support & Monitoring
- Early Intervention, Hospitalization and discharge
- Optimize Antipsychotic and Cognitive enhancers
- Intensive psychosocial intervention
- Work on acceptability and attitude
- Family education and family therapy
- Early detection and optimizing treatment
- Specific Suicide prevention program & strict monitoring for risk
- Early Discharge with high quality care plan
- Intensive patient and family education, monitor acceptability
What can a psychiatrist do?
Program based Intervention for psychosis: Advantages and Caution

- Much better than Treatment as usual
- Response, Recovery, outcome, Functioning & quality of life is better
- Relapse is less,
- Disability and morbidity due to side effect is reduced
- Caution: Continuity of care is clinical and ethical issue

- Discharging patients out of program is likely to compromise quality of care.
- Caution: discharge if remission has persisted for more than 5-7 years &
- subject has become over 40 years of age
- family is nor dysfunctional
- Genetic loading is not very high
- Low risk for suicide
Research needs for Relapse Prevention
Most Important ones:

• Biological Markers for
  – Course of psychosis
  – Responders Vs Non-responders
  – Endophenotypes of side effects of medications
  – Antipsychotic response

• Determinants of ‘Insight’ and ‘awareness’

• Biological pathways for Cognitive dysfunction

• Markers for stress response in psychosis
Summary:
Relapse Can be effectively minimized

- Relapse is common and main issue in outcome
- It is part of biological nature of illness, mostly in first 5-7 years
- Treatment barriers and risk factors for relapse needs to be identified and dealt with.
- Early Intervention, Education, Enhancing Compliance, Qualitative assessments, Safety of medication, Optimization of treatments are necessary
- Optimum Dose and adequate duration is a must.
- Program based Comprehensive and multidisciplinary treatment needs to be managed