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Mood Symptoms as Comorbidity in Schizophrenia

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Mood symptoms as comorbidity in schizophrenia

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Declaration

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

• Consultant
• Advisor
• Drug trial coordinator
• Research Investigator
• Reviewer
• Speaker
• Educational Groups
Depression in and within schizophrenia is common, with a prevalence ranging from 7 to 70%. The wide range reflects how schizophrenia and depression were diagnosed.
Epidemiology

ECA patients meeting DSM III criteria for schizophrenia were 14 to 28.5 times more likely to have a concurrent major depressive syndrome than general population.

In NCS, 59% of patients with schizophrenia met DSM III R criteria for major or minor depression.
Presentation and Nature of Depression as Syndrome in the clinical course

Co-existing co morbid depression & dysthiamia

- As major depressive episode
- As frank manic episode
- As mixed states
- As dysphoric states
- As masked depression or somatized
- As suicidality

Schizo-affective
Schizomanic
Schizo-obsessive
Schizophrenia spectrum
Major mood disorder
Bipolar disorder

Longitudinal course
“It is increasingly becoming clear that we cannot distinguish satisfactorily between these two illness and this brings home the suspicion that our formulation of problem may be incorrect”

Kraepelin E.
Affective symptoms as integral part of schizophrenia across its course
Emergence of new diagnosis: Jacob kasonin 1933

Clinical overlap of schizophrenia spectrum and bipolar spectrum disorder
Current issues on schizoaffective disorder

Encephale. 2005

- Research on schizoaffective disorder has been marred by the variability of its definition.
- Further studies are however still necessary, especially with regard to the subtyping of the disorder and its pharmacological treatment.
Are schizophrenia and affective disorder related? 2007

- The Kraepelinian view of psychoses may need modification.
Best evidence of depression in Schizophrenia and Correlation with Neuroleptics comes from epidemiology

Depression occurs across the course of schizophrenia.
‘Diagnostic Validity of Schizoaffective disorders’
Shrivastava A, Rao, S. IJP.1997
Current Evidence

Common neurobiological origin of ‘Severe’ psychosis

- Bipolar Disorder: type I
- Unipolar Depression with psychotic features
- Schizophrenia

Population Prevalence

- Bipolar Spectrum: 2%
- Depressive spectrum: 0.7-1.4%
- Schizophrenia spectrum: 0.5-0.7%
- Related Symptom Cluster: 3-4%
Genotype → Environmental unmasking → Multiple disease phenotypes
An Endophenotype of Schizophrenia

Environmetal Susceptibility Gene

Genotype

Psychological Unmasking Modifier Genes

Behavioral Traits-Correlates

Brain Vulnerability

Social Unmasking

Life style issue

Risk factors

Essential Etiological factors

Schizophrenia spectrum

15/03/2008
Continuum of genetic liability to psychotic illness

- Poor outcome schizophrenia (associated with familial risk of schizophrenia)
- Good-outcome schizophrenia (associated with familial risk of affective disorder)
- Schizoaffective disorder
- Affective psychosis (with incongruent delusion)
- Pure affective psychosis (associated with familial history of affective disorder)

Increasing neurodevelopmental impairment

Increasing genetic liability
Neuroendocrine:
Evidence for a neuromodulatory role for TRH

CSF thyrotropin-releasing hormone concentrations differ in patients with schizoaffective disorder from patients with schizophrenia or mood disorders,:

Charles B. Nemeroфф Journal of Psychiatric Research
Volume 35, Issue 5, September-October 2001,
Does schizoaffective disorder really exist? middle point of a continuum between SCH and MD.

_J Affect Disord_. 2008 Mar

Schizoaffective disorder merges schizophrenia and bipolar disorders as one disease-

**there is no schizoaffective disorder**

_Curr Opin Psychiatry_. 2007 Jul;

Schizoaffective disorders are psychotic mood disorders; there are no schizoaffective disorders.

_Psychiatry Res_. 2006 Aug
Insight
Depression
The Evidence
Depression in schizophrenia: MRI and PET findings. Biol Psychiatry. 1998

The high depression group had larger bilateral temporal lobe volumes and decreased laterality (left minus right of metabolism in the anterior cingulate).
- ↑ frequency & duration of hospitalization
- ↑ risk of suicide
- ↑ risk of relapse
- ↑ impairment in social roles & relationships
- ↑ unemployment
Burden of Illness of Comorbid Depression in Schizophrenia

Depression in schizophrenia associated with lower QoL (n=67)\textsuperscript{1}

Suicide in Patients with Schizophrenia

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\textsuperscript{1}
Treatment Choice and Phase of illness

Natural history of schizophrenia

Stages of illness

Premorbid | Prodromal | Onset/deterioration | Residual/stable

Healthy → Worsening severity of signs and symptoms → Onset/deterioration → Residual/stable

Gestation/birth | 10 | 20 | 30 | 40 | 50

Patient age (years)
The results provide weak evidence for the efficacy of antidepressants in patients with schizophrenia and depression.

the only SSRI tested in the treatment of depression in schizophrenic patients is sertraline.

In meta-analysis, No difference between the 2 treatment groups was demonstrated.
Current evidence: Mood Stabilizers

- Lithium
- Carbamezapine
- Valproic acid
- Lamotregene
- Toperamate
- Gabapentine
- Calcium channel blockers
Are atypical neuroleptics mood stabilisers?

- Are they effective beyond psychotic affective states?
- Are they effective against the depressive phase of bipolar disorder?
- Do they induce mania?
- Do they work in mixed states?
- Do they work in rapid cycling?
- Can they prevent suicide?
5 HT System in the Brain

Coronal section:
- corpus striatum
- caudate nucleus
- putamen
- globus pallidus
- hippocampus
- substantia innominata
- substantia nigra

Mid-sagittal section:
- limbic system
- cerebral cortex
- hypothalamus
- thalamus
- choroid plexus
- cerebellum
- midbrain
- amygdala
- basal ganglia

5-HT5A
- amygdala
- cerebellum
- cerebral cortex
- hippocampus
- hypothalamus

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Dopamine Deficit

- Parkinson-like Symptoms
  - slow reaction time
  - anergia
- Anhedonia
  - "pleasure center" dysfunction

Depression & Craving

- decreased synaptic DA
- altered DA transporter function
- postsynaptic receptor changes

Serotonin Deficit

- OCD-like Symptoms
  - obsessive thoughts
  - compulsive behaviors
- Impulsivity
  - suicide/aggression
  - susceptibility to "cue triggers"

- decreased synaptic 5-HT
- decreased 5-HT cell activity
- decreased synaptic DA
Comparative Receptor Binding Profiles

- **Haloperidol**: D2, 5HT2A, α1
- **Clozapine**: M, D2, 5HT2A, α1, H1
- **Olanzapine**: M1, 5HT2A, α1, H1
- **Risperidone**: H1, D2, 5HT2A, α1
- **Ziprasidone**: α1, D2, 5HT2A
- **Quetiapine**: D2, 5HT2A, H1, α1

Arndt J, Skarsfeldt T. Neuropsychopharmacology 1998; Goldstein et al.

*Depression in schizophrenia: perspective in era of ‘atypical antipsychotics’. Siris, S.G. AJP 2000; 157*
How do we explain?

Why do Atypical antipsychotics have Antidepressant action?
A: Regional distribution of 5-HT System in the Brain??

- Optimizing antipsychotic treatment and atypical antipsychotics prove to be most effective
- Adjunctive antidepressants may be useful for patients who are not acutely ill
- Careful longitudinal assessment is required to ensure identification of primary mood disorders
Relative Efficacy of AAPD for mood symptoms and suicidality in Schizophrenia

- Clozapine
- Olanzapine
- Aripiprazole
- Quetiapine
- Amisulpiride
- Ziprasidone
- Paliperidone
- Risperidone

Increasing efficacy
CATIE outcome of Mood symptoms

- Mood stabilizers: 15
- Lithium: 4
- Anxiolytic: 22
- ADD: 38
- 1 FGA + 1 SGA: 6

Less than 90 days: 10
Long term, more than 90 days: 90
Does quetiapine have mood altering properties?

- The data indicate that a side-effect of quetiapine may be mood elevation.
- An ability to elevate mood while controlling psychoses would be helpful in the treatment of post-psychotic and bipolar depression.
- Its clinical importance in the control of manic episodes, for which atypical antipsychotics are used increasingly, is uncertain.
Schizophrenia with associated complications: Dysphoria

Schizophrenia with associated complications:
Suicidal behavior

Average scores

Olanzapine  Clozapine  Risperidone

6-wk, open-label study in patients with schizoaffective disorder, bipolar type (n=102)

HAM-D change

YMRS change

24-week, RCT in patients with schizophrenia or schizoaffective disorder with depressive symptoms (n=394)

CDSS: Calgary Depression Scale for Schizophrenia
MADRS: Montgomery-Asberg Depression Rating Scale

CDSS change

Change in CDSS score

Week
0 4 8 12 16 20 24

CDSS change

Change in CDSS score

Week
0 4 8 12 16 20 24

Ziprasidone
Olanzapine

p=0.105

Change in MADRS score

Week
0 4 8 12 16 20 24

Ziprasidone (n=192)
Olanzapine (n=202)
Atypical Antipsychotics: Improvement in Depressive Symptoms

12-week, naturalistic, observational study

HAM-D: Hamilton Rating Scale for Depression; HAM-A: Hamilton Rating Scale for Anxiety

Switching Antipsychotics May Improve Depressive Symptoms

Quetiapine

CDSS: Calgary Depression Scale for Schizophrenia

SPECTRUM, 12-wk, open trial in patients with schizophrenia switched to quetiapine (n=509)
Current evidence: ECT

Role of Adjunctive Therapies for Mood Symptoms.

- **Schizoaffective disorder**
  - **Lithium:** little evidence of benefit for manic type
  - **Antidepressants:** Antipsychotic + AD equal or less effective than antipsychotic alone
  - **Anticonvulsants:** No evidence of benefit

Antidepressants\textsuperscript{2,3}

- Acutely: no advantage of antipsychotic + AD vs. antipsychotic alone
- Post-psychotic MDD: adjunctive AD may be useful

Optimizing antipsychotic treatment is likely a more effective strategy for mood symptoms

Psychosocial Interventions in Schizophrenia

- Proven effective adjuncts to pharmacotherapy\(^1\)
  - Social skills training
  - Cognitive remediation
  - Psychoeducational coping-oriented interventions with families & relatives
  - Cognitive behavioural therapy

Comprehensive Treatment Programs

- Specialized early intervention approach can provide:\textsuperscript{1,2}
  - $\uparrow$ short-term clinical and functional outcomes
  - $\uparrow$ retention in treatment
  - $\downarrow$ relapse rates
  - $\uparrow$ satisfaction with service delivery
  - $\uparrow$ greater family involvement
  - $\uparrow$ QoL

Future Classification of mental disorders: Hypothesis: From 1933 to 2008
Why does suicide occur in psychosis?
What is clinical relevance of this context?

Evidence for occurrence of depression before suicide attempt
1. Biological findings
2. Psychological theories
3. Epidemiological findings
4. Postmortem studies
5. Post-vention studies

There is evidence of depressed mood in 98% subjects who successfully kill themselves.
Prevention of Suicide in Psychotic Disorders: General principles and strategies.

Term ‘Discharge’ is a misnomer. It is actually ‘transfer of Care from Hospital to Community’. It is a dynamic Process.

It is just a milestones on Continuous spectrum of care

Review: Assessment, Outcome, Care Plan, Discharge Plan, Risk Management & Transfer of care

Documentation
Prevention of Suicide in Psychotic Disorders: General principles and strategies.
Prevention of Suicide in Psychotic Disorders: General principles and strategies.
Conclusions:
Schizoaffective disorders.
There are many unanswered questions

- Mood symptoms are common, responsive and severe.
- Schizoaffective disorder is a severe psychotic disorder with disability, burden and complications.
- Schizoaffective Disorder is an inconsistent condition and does not deserve an independent diagnosis.
- We are moving towards unitary theory for single-severe-psychotic-disorder, based on clinical and biological evidences.
- Treatment appears inadequate and unclear, but optimizing atypicals APD appears best option.
- Clozapine has a special efficacy.