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# Mood Symptoms as Comorbidity in Schizophrenia

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<https://ir.lib.uwo.ca/psychiatrypres/16>

# Mood symptoms as comorbidity in schizophrenia

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**Lecture.reginal.Mental.Health care.St.Thomas.**

# 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 in  
common  
21-80%

Prevalence

- 7 to 70%
- Wide range reflects how schizophrenia and depression was 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 & dysthymia

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

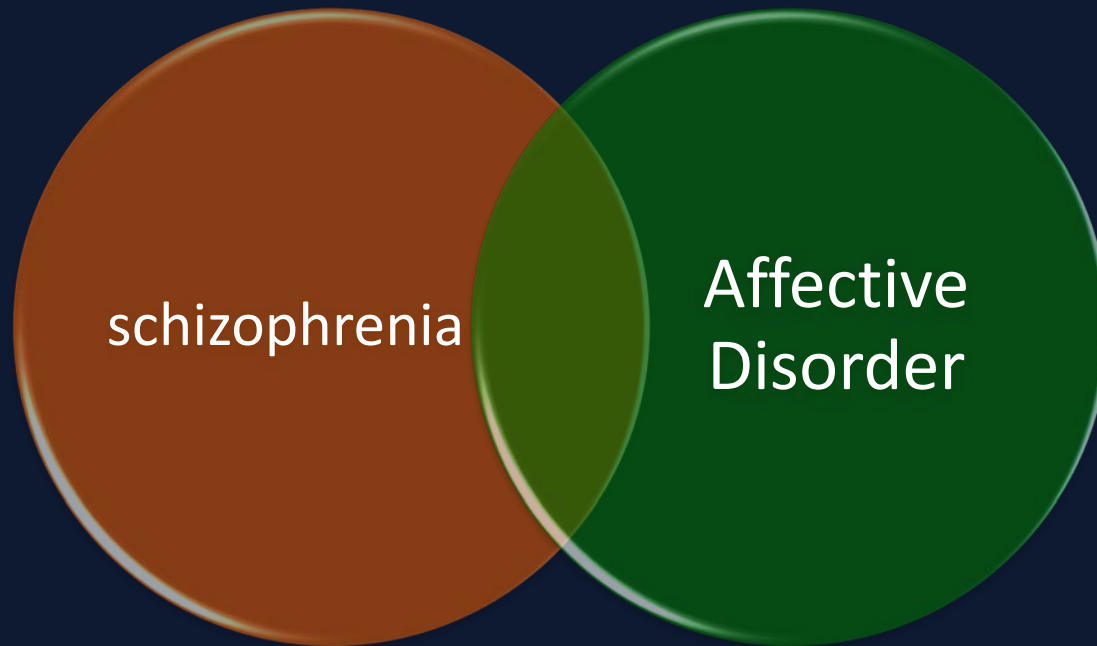
Longitudinal  
course



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

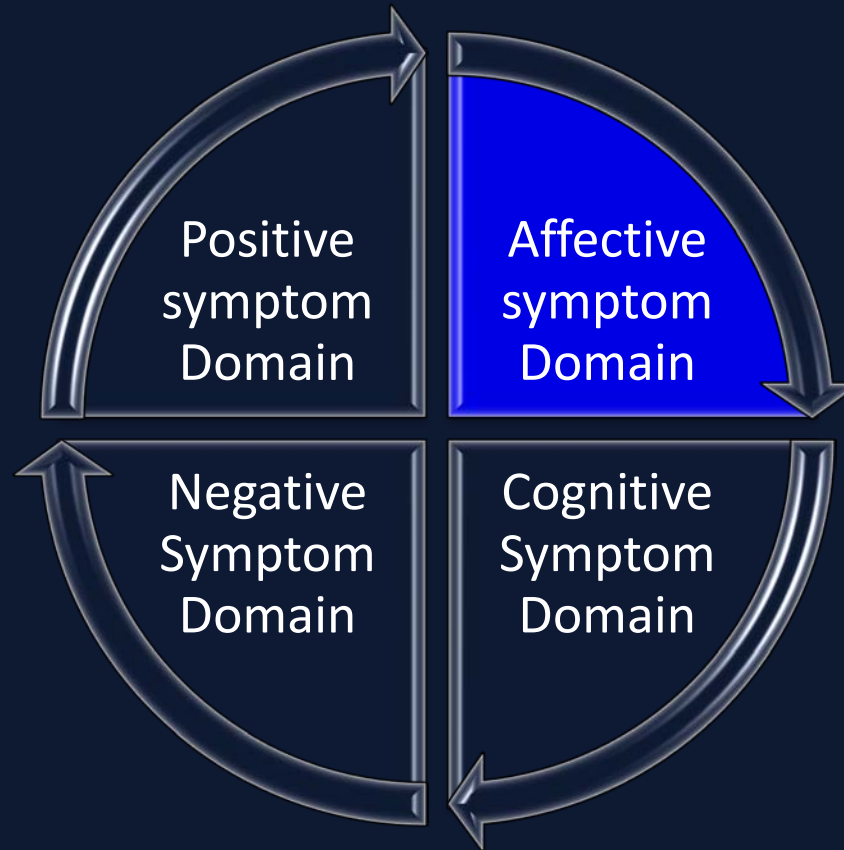
*“It is increasingly becoming clear that we can not distinguish satisfactorily between these two illness and this brings home the suspicion that our formulation of problem may be incorrect”*

*Kraepelin .E.*



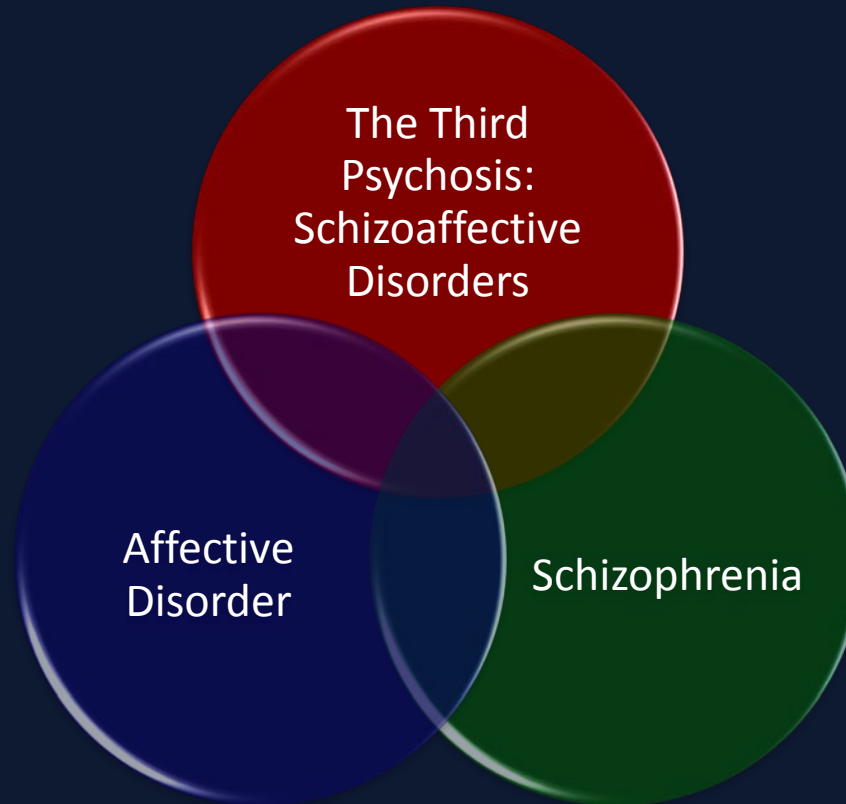
Historical Phenomenological and  
diagnostic dilemma

# 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

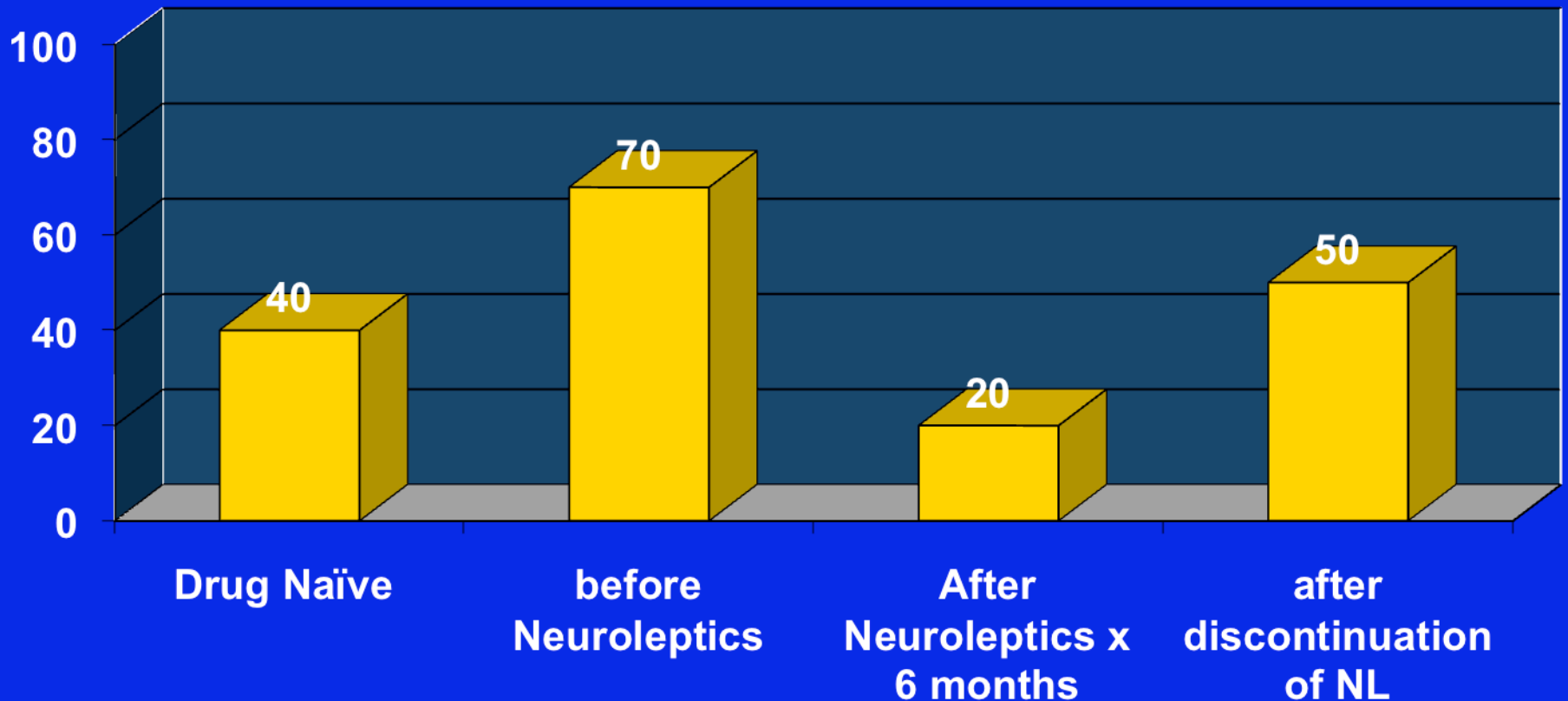
- Research on schizoaffective disorder has been marred by the variability of its definition.
- Further studies are however still necessary, especially with regard to the subtyping of the disorder and its pharmacological treatment.

# Are schizophrenia and affective disorder related? 2007

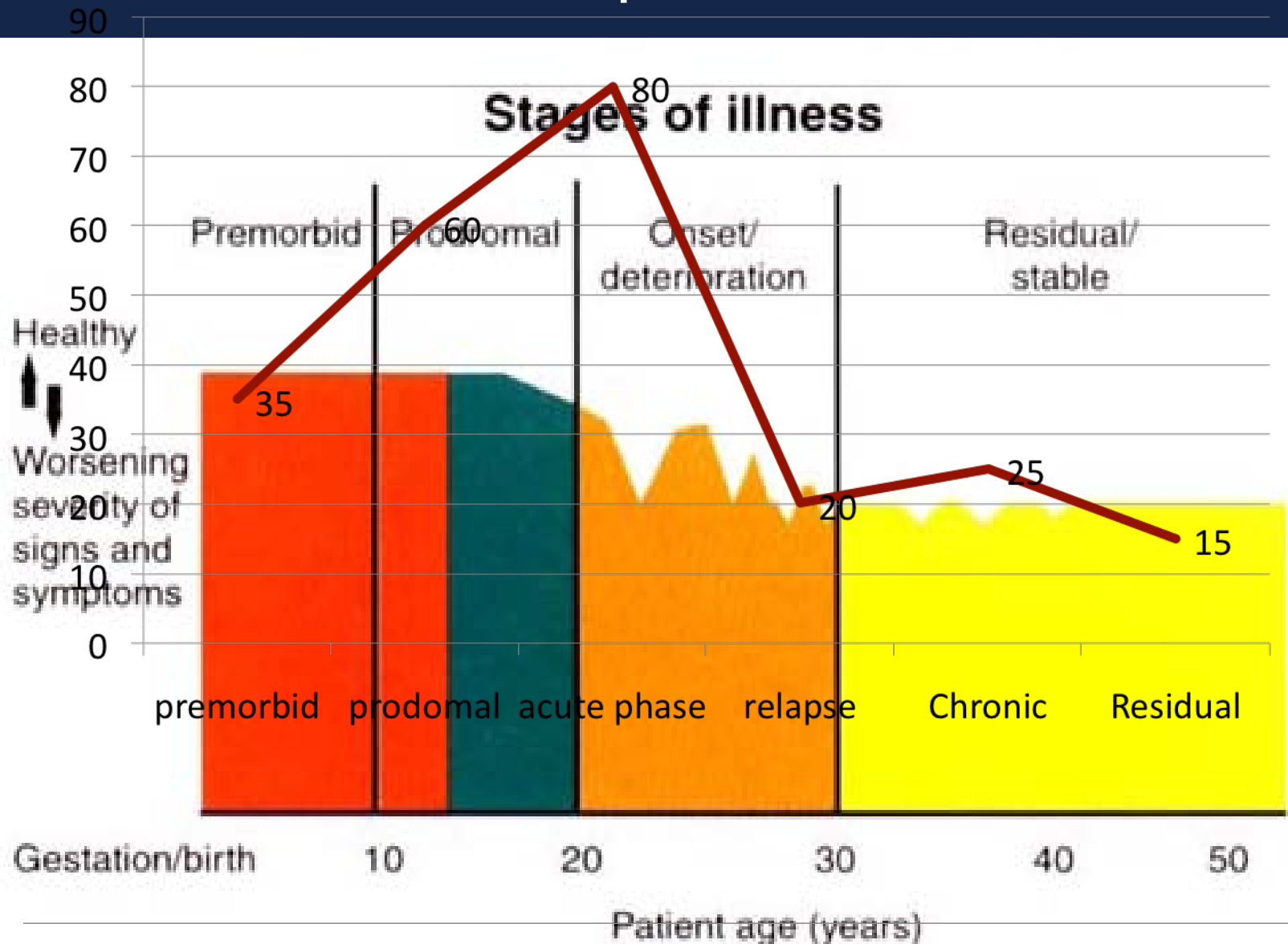
- The Kraepelinian view of psychoses may need modification.

# Best evidence of depression in Schizophrenia and Correlation with of Neuroleptics comes from epidemiology

( Johnson, 1981, Hirsch 1989, Hirsch 1973)

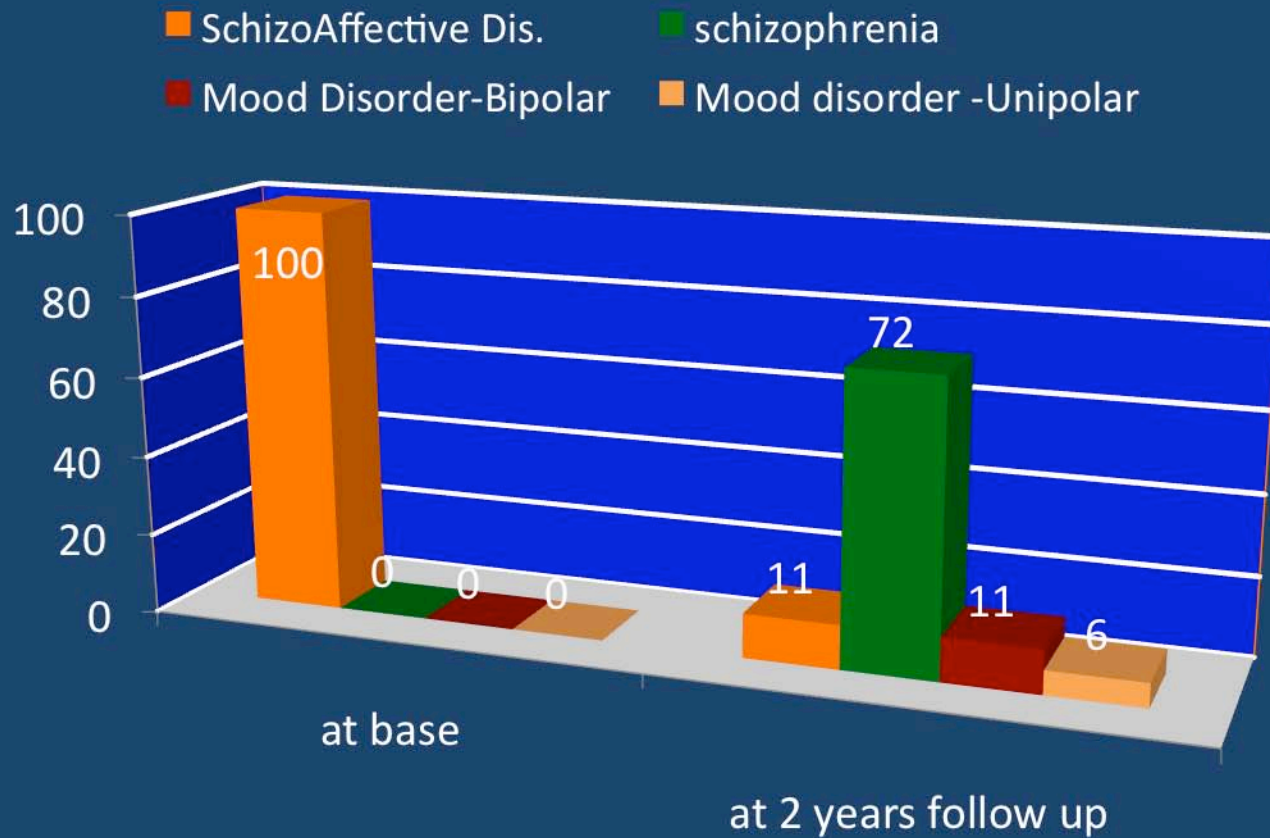


# Depression occurs across the course of schizophrenia



# 'Diagnostic Validity of Schizoaffective disorders'

Shrivastava A, Rao, S. IJP.1997



# Current Evidence

Population  
Prevalence

Related  
Symptom  
Cluster



Bipolar  
Spectrum



Depressive  
spectrum



Schizophrenia  
spectrum

Common neurobiological origin of  
'Severe' psychosis"

3-4%

Bipolar Disorder: type I

2%

Unipolar  
Depression with  
psychotic features

0.7-1.4%

Schizophrenia

0.5-0.7%

**Genotype**



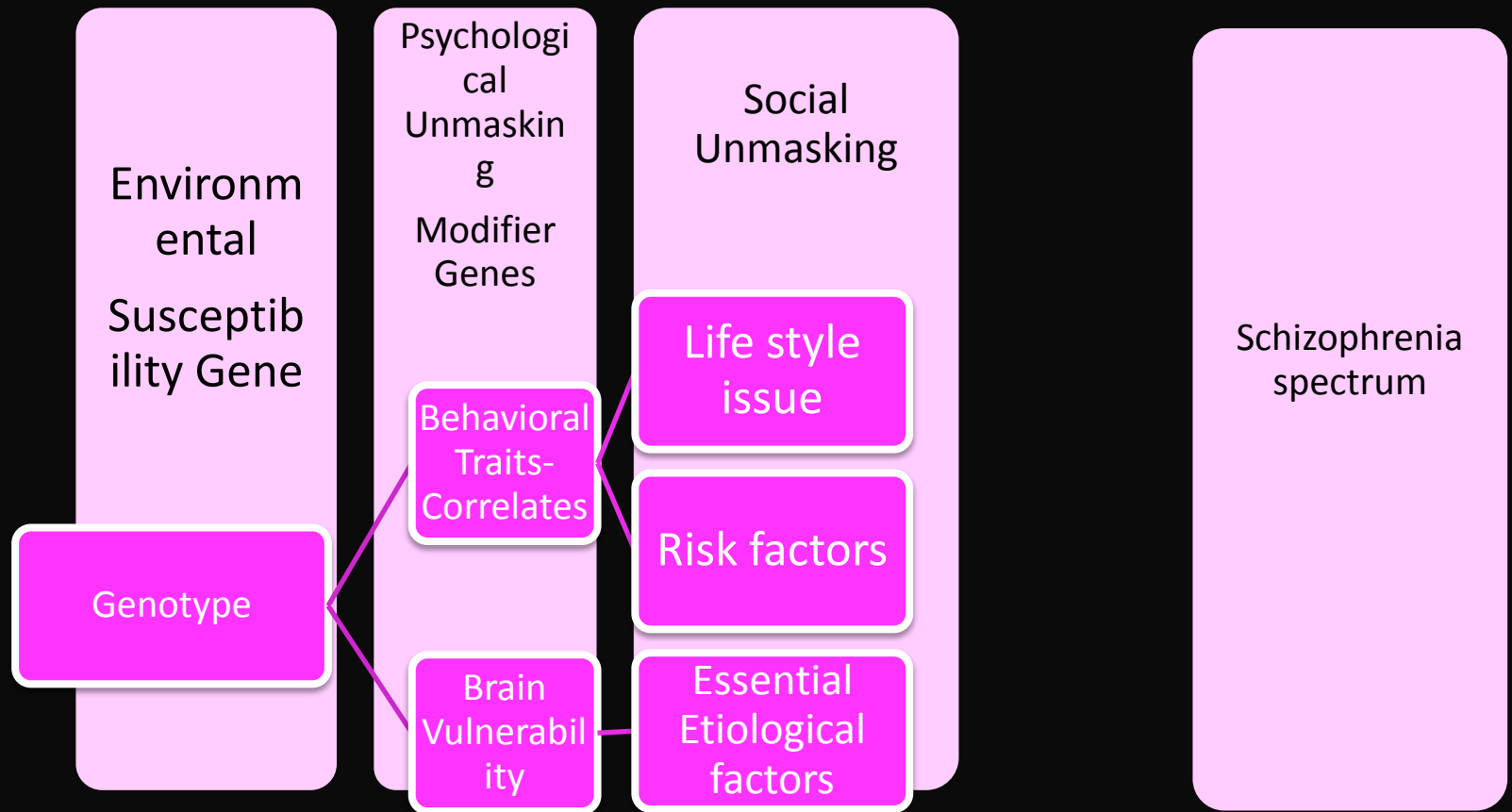
**Environmental  
unmasking**



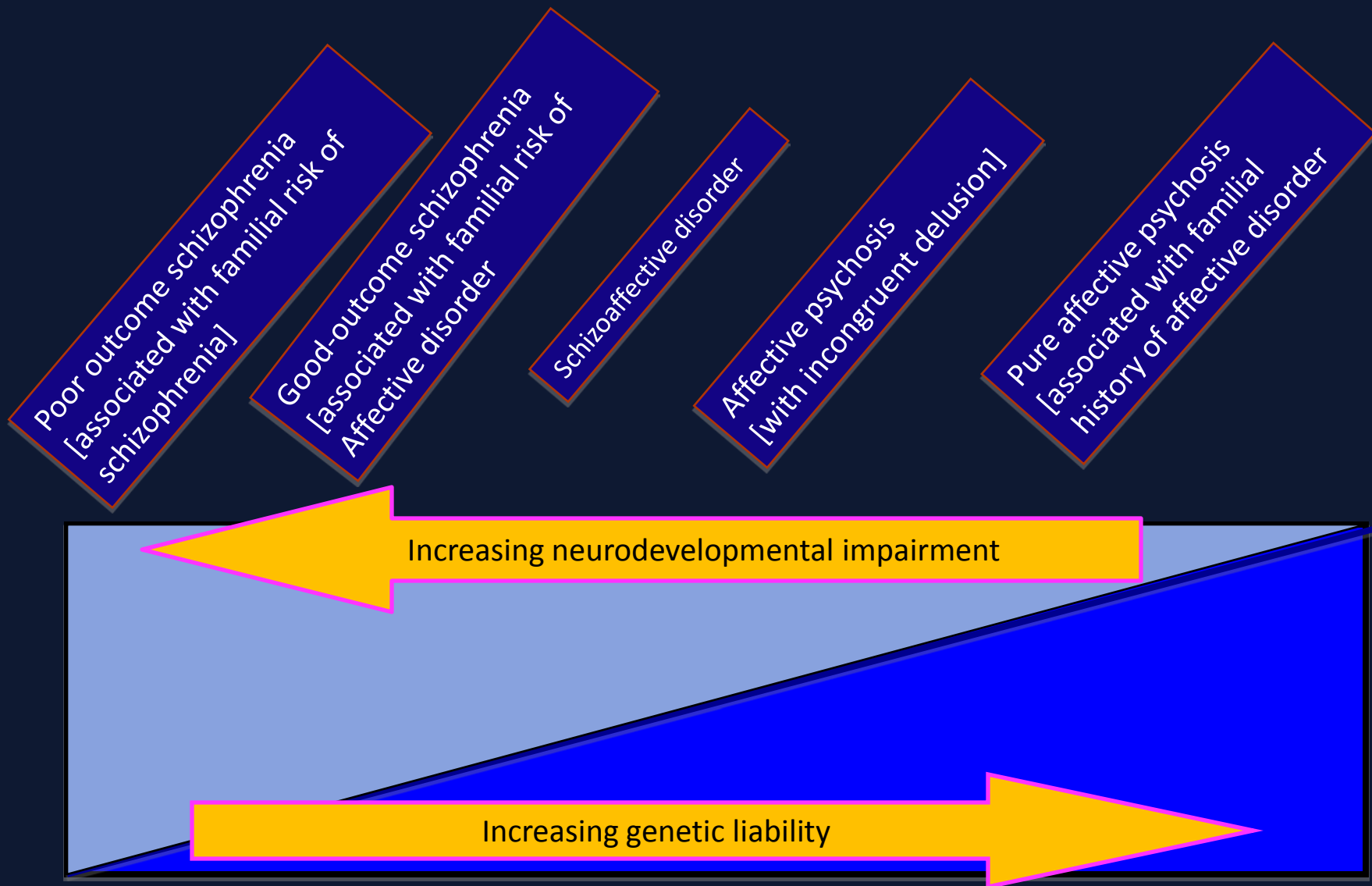
**Multiple  
disease  
phenotypes**



# An Endophenotype of Schizophrenia



# Continuum of genetic liability to psychotic illness



# 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. Nemeroffc 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

## Why does depression occur in schizophrenia: Neurobiology

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).

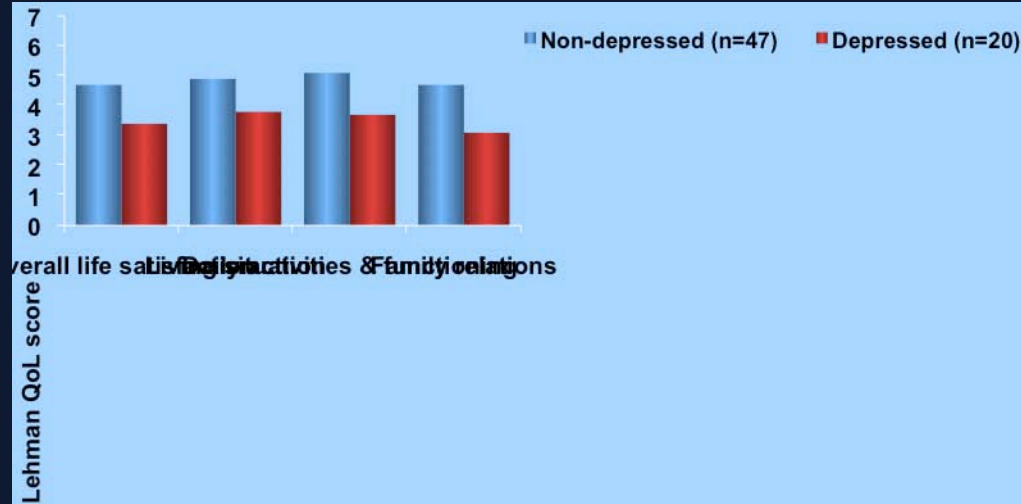








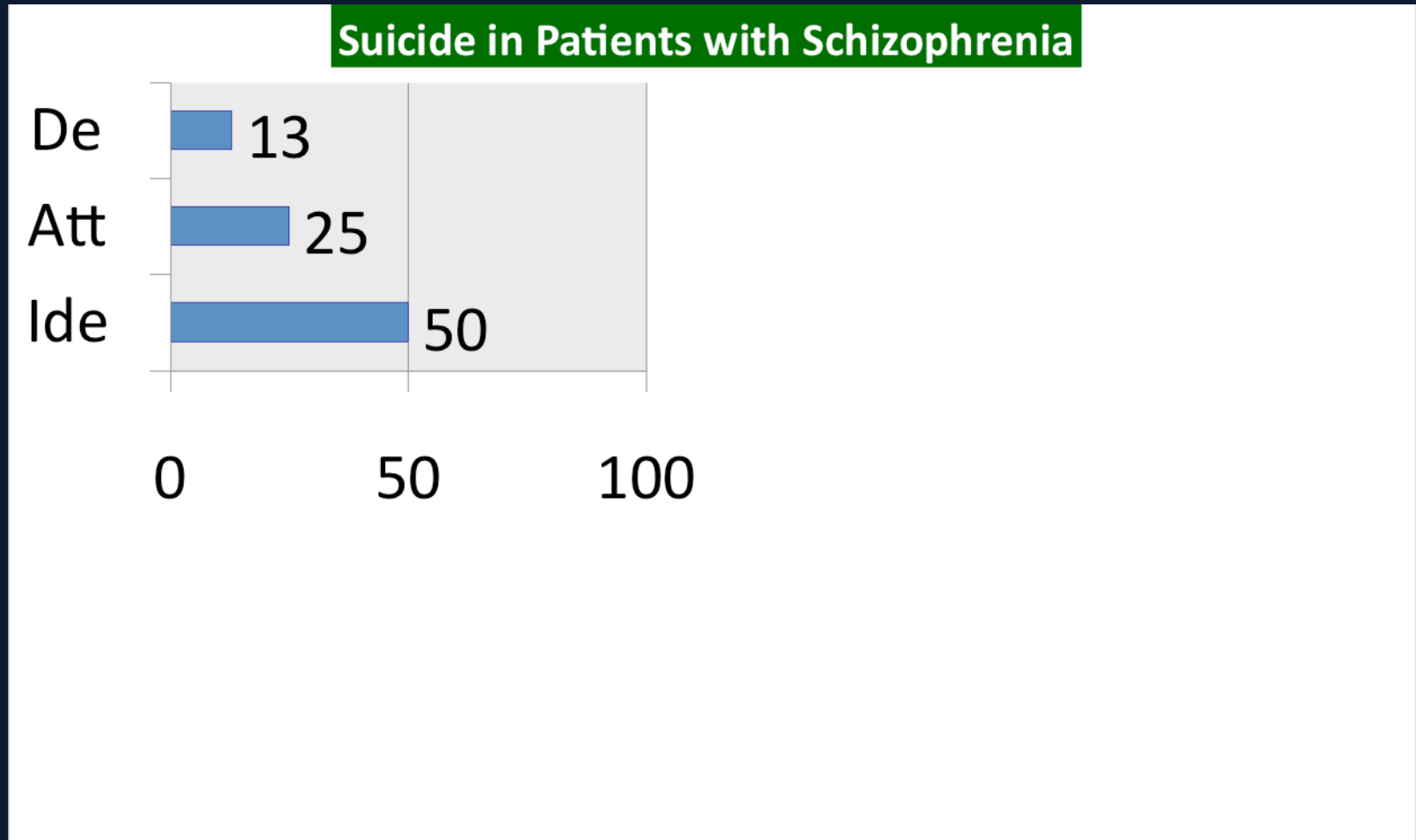
# Depression-suicide & Schizophrenia



- ↑ frequency & duration of hospitalization<sup>2</sup>
- ↑ risk of suicide<sup>3</sup>
- ↑ risk of relapse<sup>3</sup>
- ↑ impairment in social roles & relationships<sup>3</sup>
- ↑ unemployment<sup>4</sup>

# Burden of Illness of Comorbid Depression in Schizophrenia

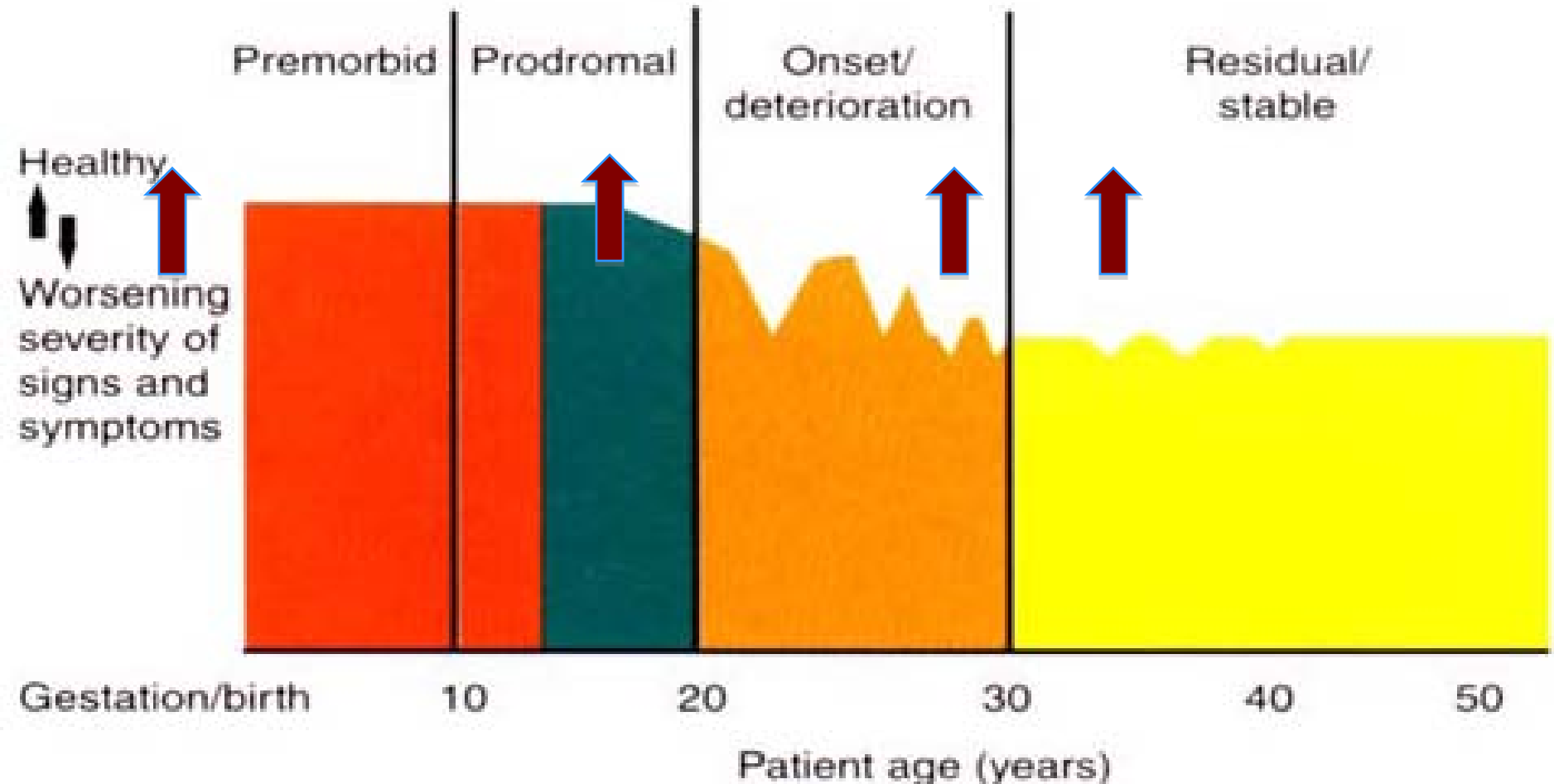
Depression in schizophrenia associated with lower QoL (n=67)<sup>1</sup>



# Treatment Choice and Phase of illness

## Natural history of schizophrenia

### Stages of illness





# Current evidence: Anti Depressant Drugs

Use of antidepressant drugs in schizophrenic patients with depression  
Encephale. 2006

- 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





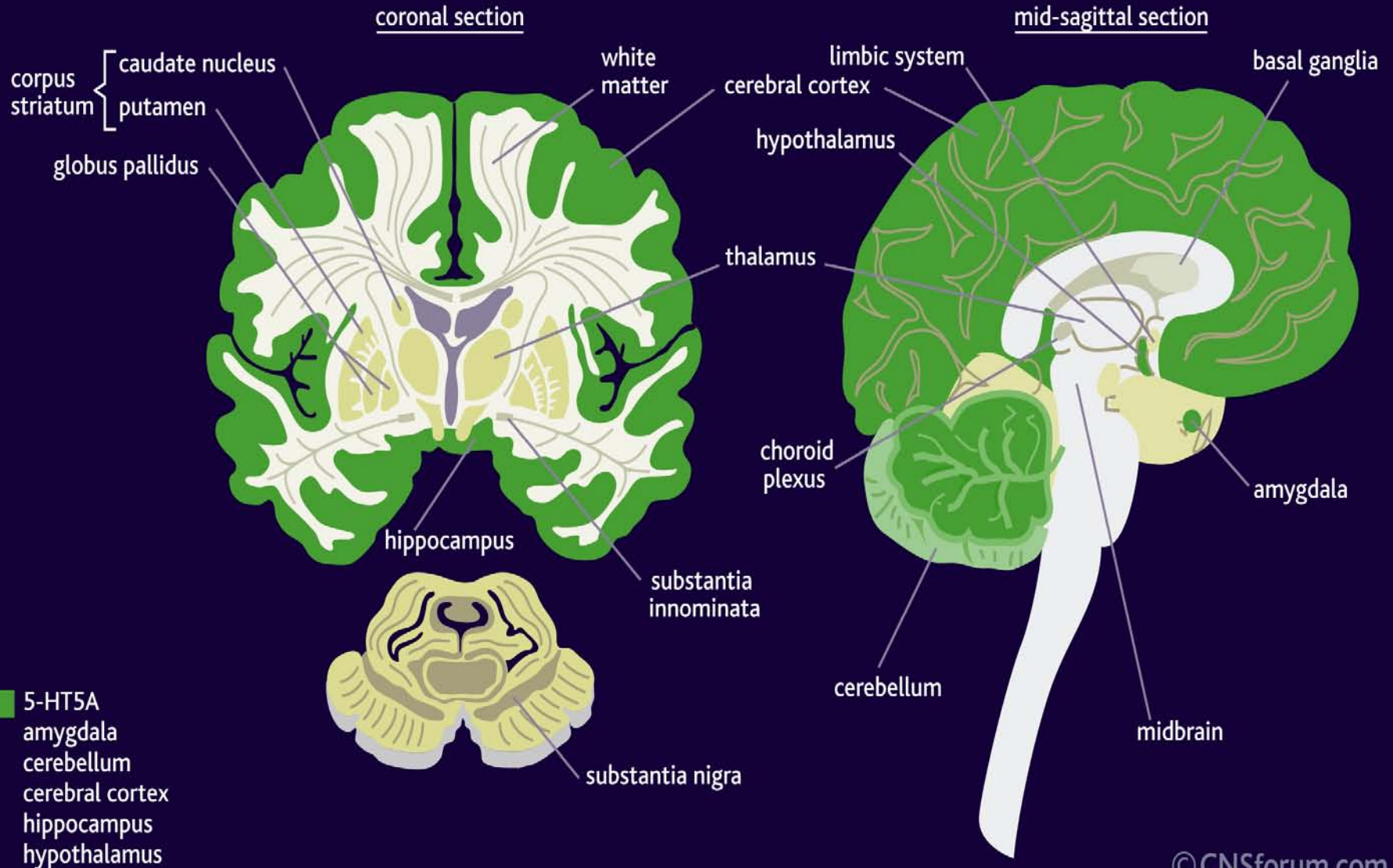
# Current evidence : Mood Stabilizers

- Lithium
- Carbamazepine
- Valproic acid
- Lamotrigine
- Topiramate
- 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



## Dopamine Deficit

## Serotonin Deficit

### Parkinson-like Symptoms

- slow reaction time
- anergia

### Anhedonia

- "pleasure center" dysfunction

### Depression & Craving

### OCD-like Symptoms

- obsessive thoughts
- compulsive behaviors

### Impulsivity

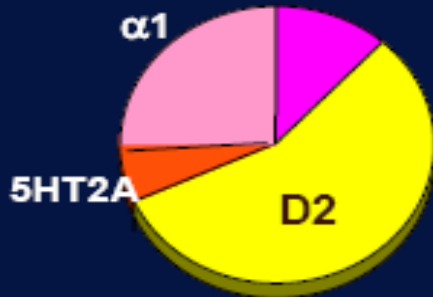
- suicide/aggression
- susceptibility to "cue triggers"

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

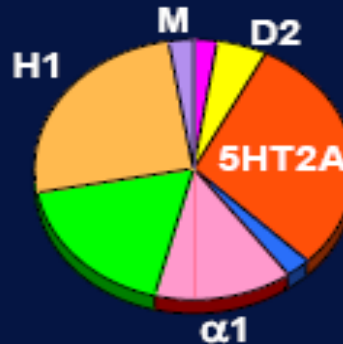
- decreased synaptic 5-HT
- decreased 5-HT cell activity
- decreased synaptic DA

## Comparative Receptor Binding Profiles

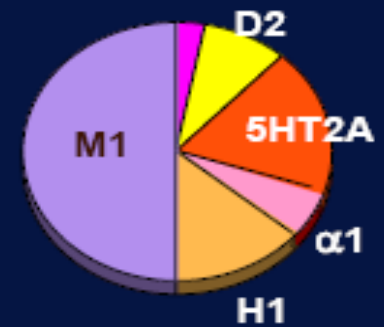
**Haloperidol**



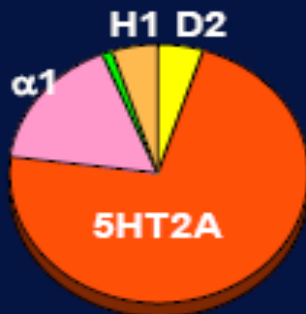
**Clozapine**



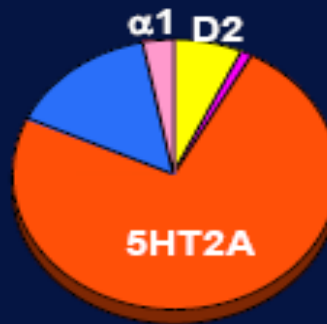
**Olanzapine**



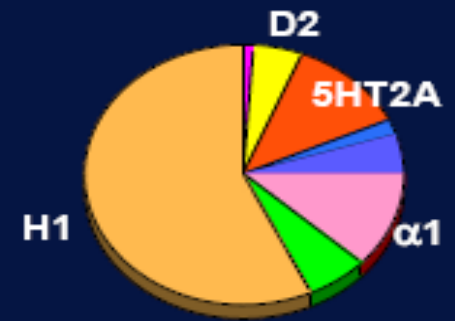
**Risperidone**



**Ziprasidone**



**Quetiapine**



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

## 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

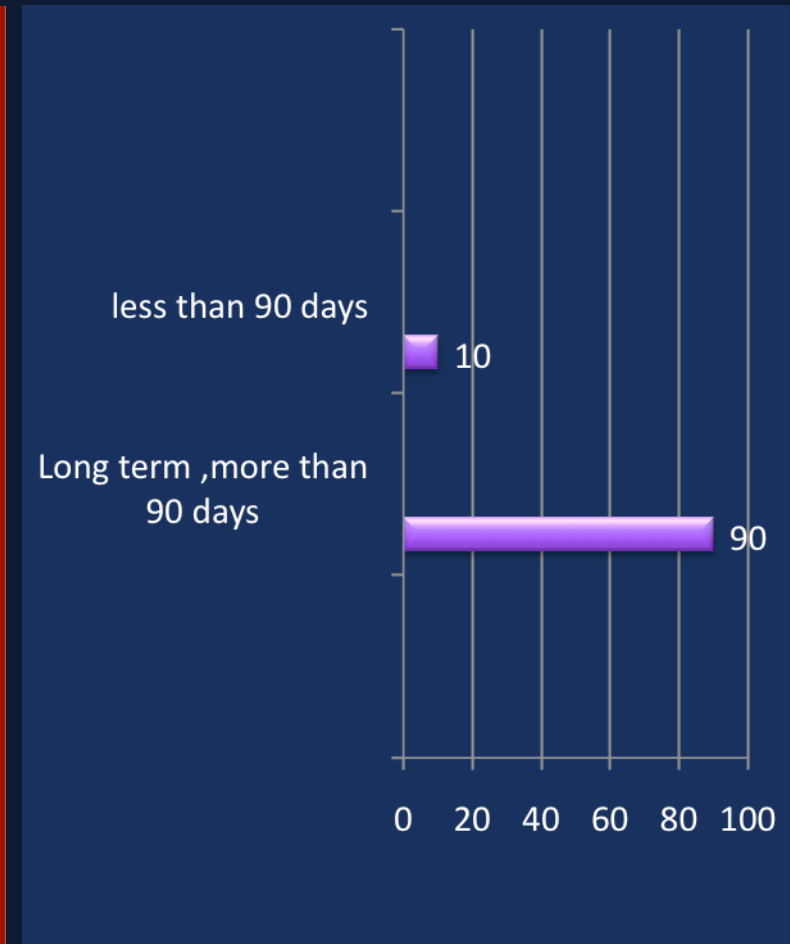
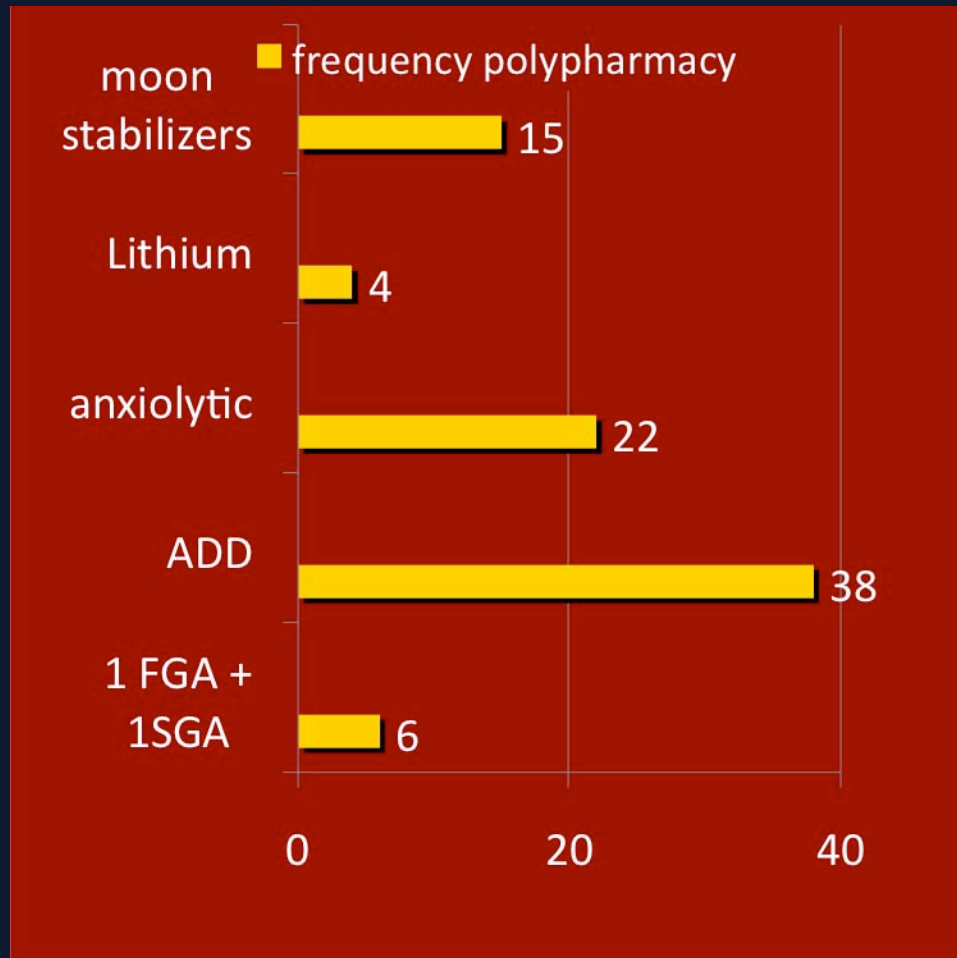
- Clozapine
- Olanzapine
- Aripiprazole
- Quetiapine
- Amisulpiride
- Ziprasidone
- Paliperidone
- Risperidone



Increasing efficacy



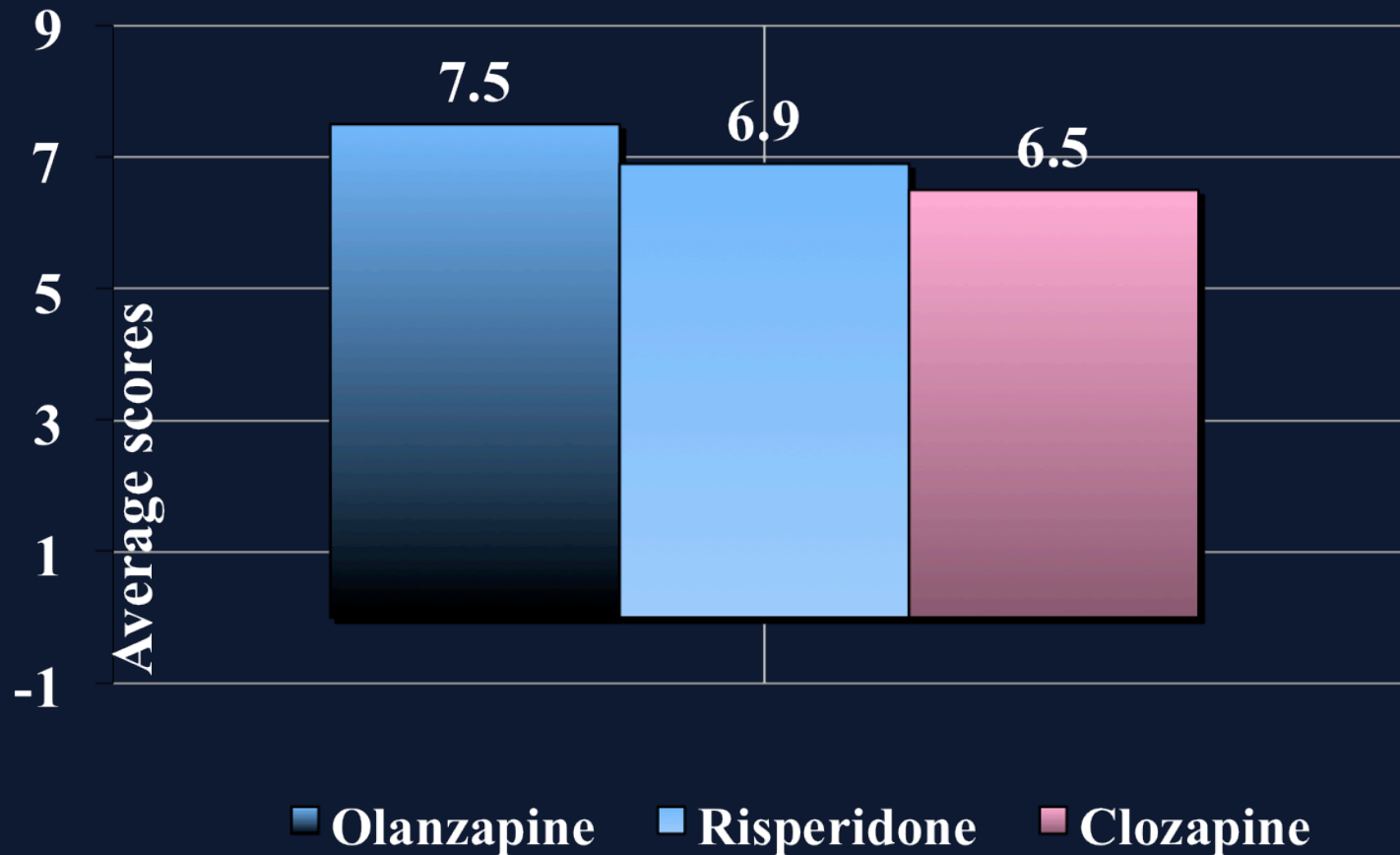
# CATIE outcome of Mood symptoms



# Does quetiapine have mood altering properties?

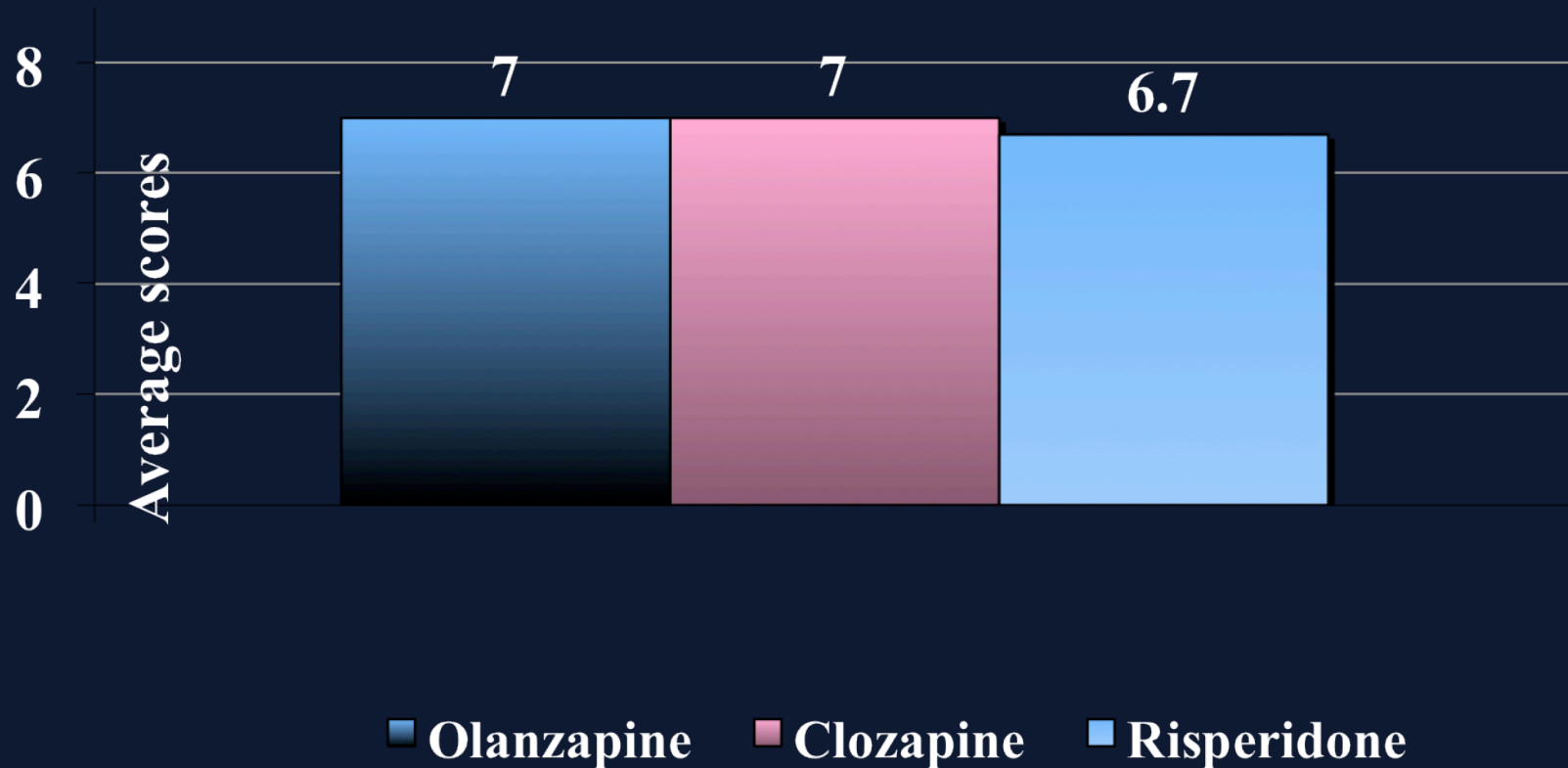
- The data indicate that a side-effect of quetiapine may be mood elevation.
- An ability to elevate mood while controlling psychoses would be helpful in the treatment of post-psychotic and bipolar depression.
- Its clinical importance in the control of manic episodes, for which atypical antipsychotics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

# Schizophrenia with associated complications: Dysphoria



McEvoy JP. Journal of Clinical Psychiatry 1999;60(11):1-80.

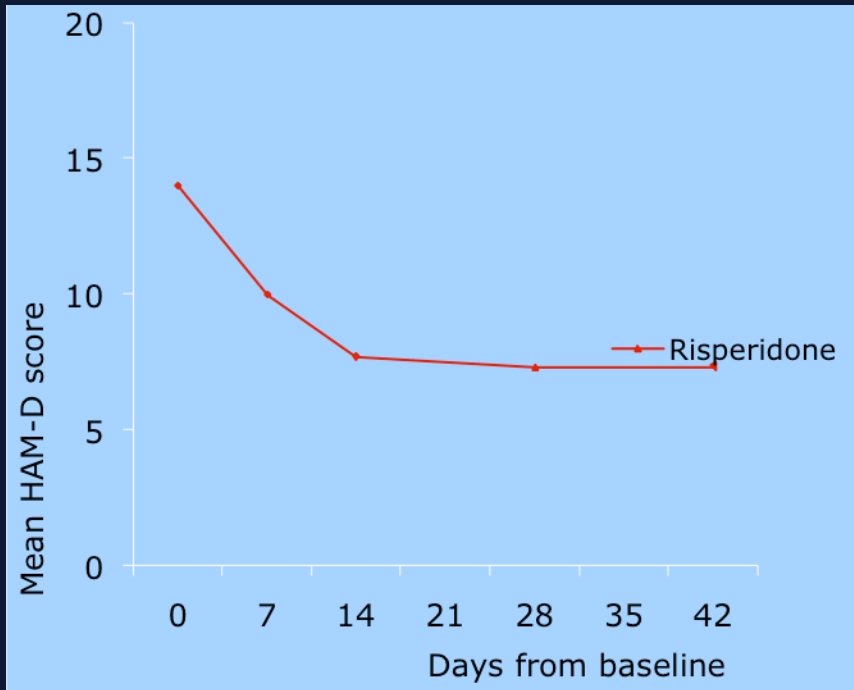
## Schizophrenia with associated complications: Suicidal behavior



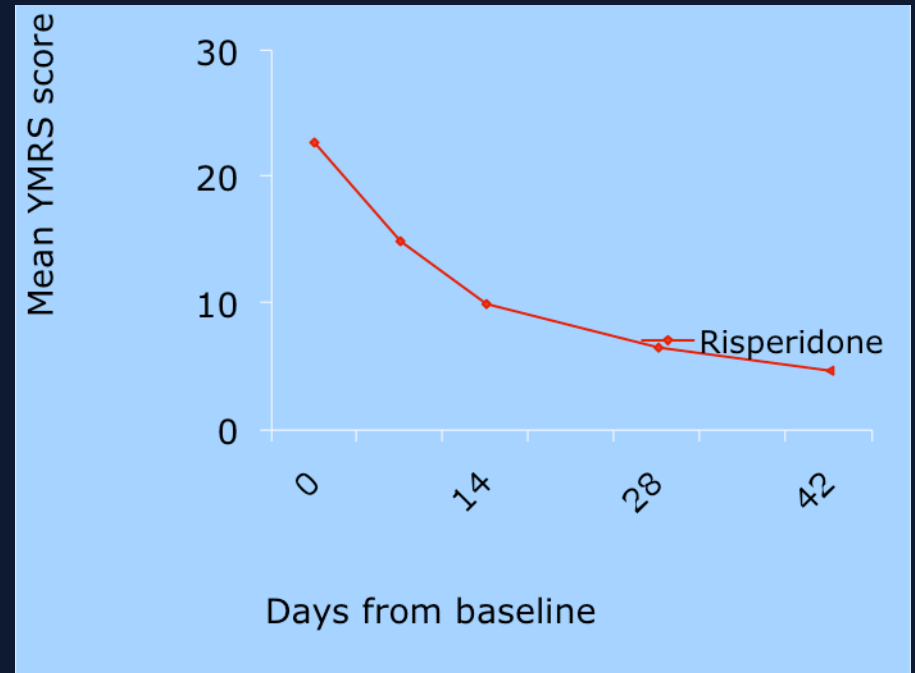
McEvoy JP. Journal of Clinical Psychiatry 1999;60(11):1-80.

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

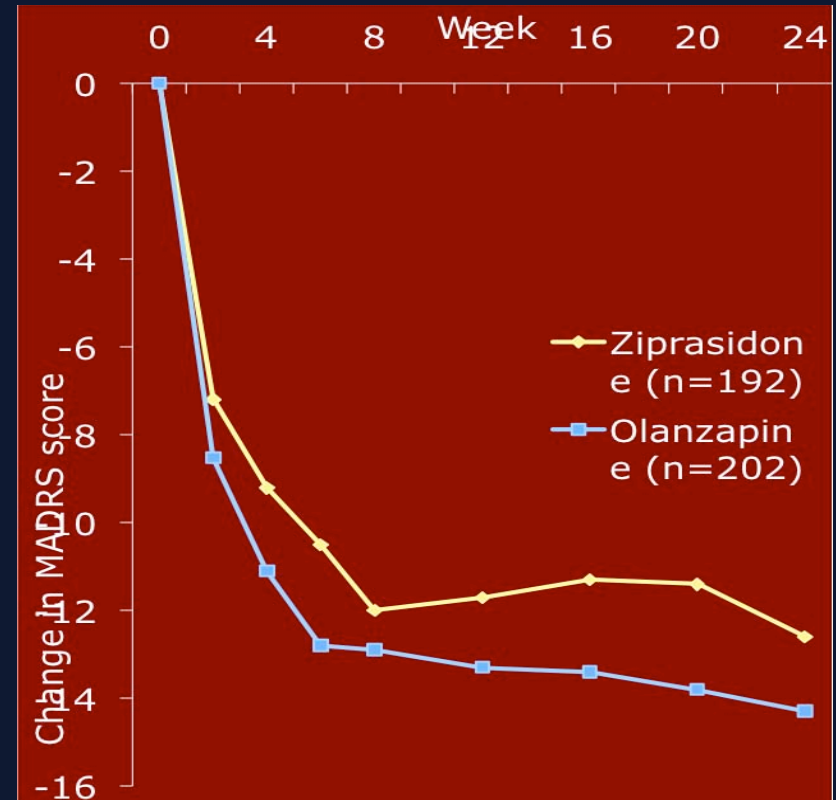
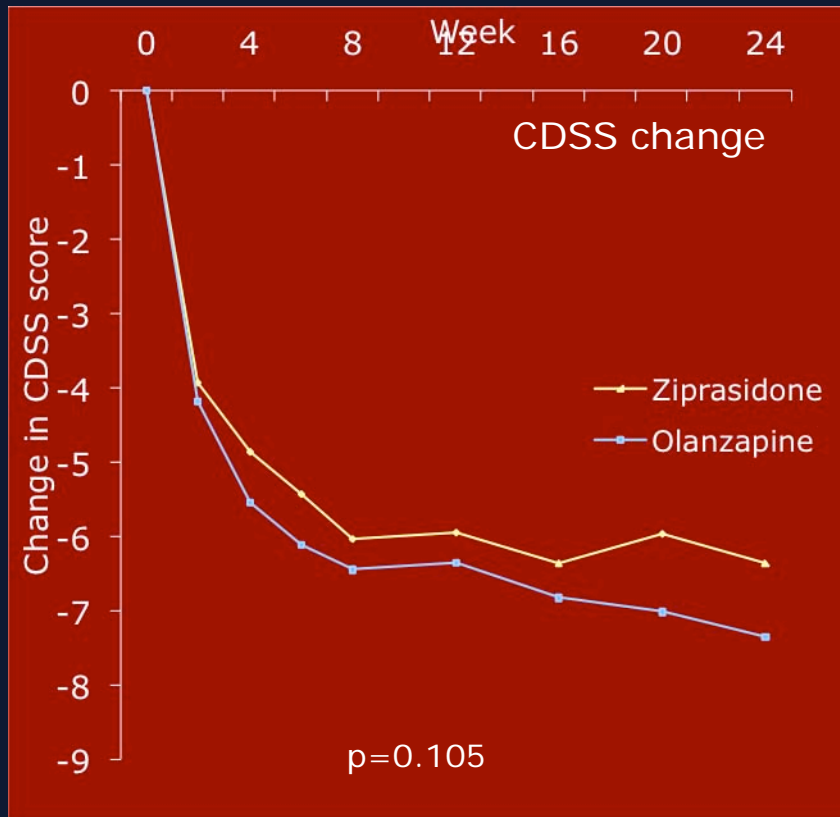
HAM-D change



YMRS change



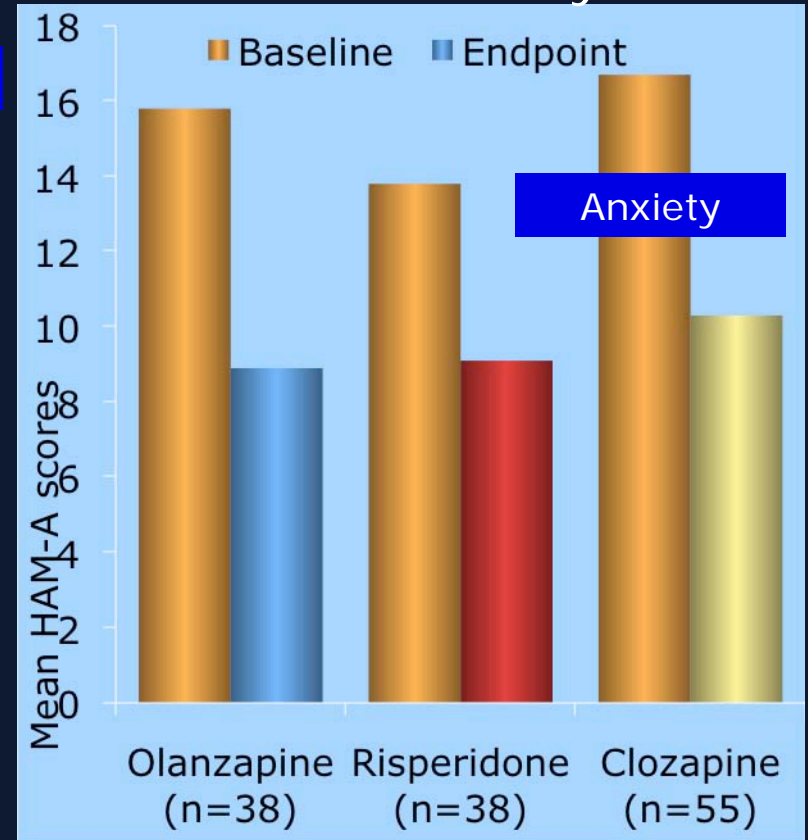
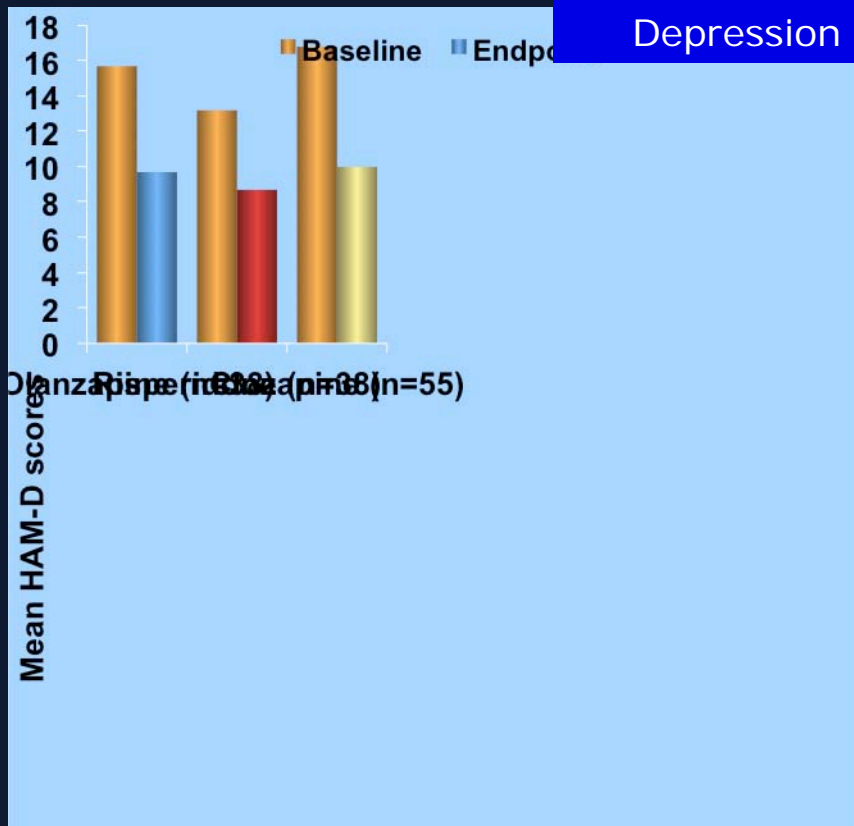
# 24-week, RCT in patients with schizophrenia or schizoaffective disorder with depressive symptoms (n=394)



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

# Atypical Antipsychotics: Improvement in Depressive Symptoms

12-week, naturalistic, observational study

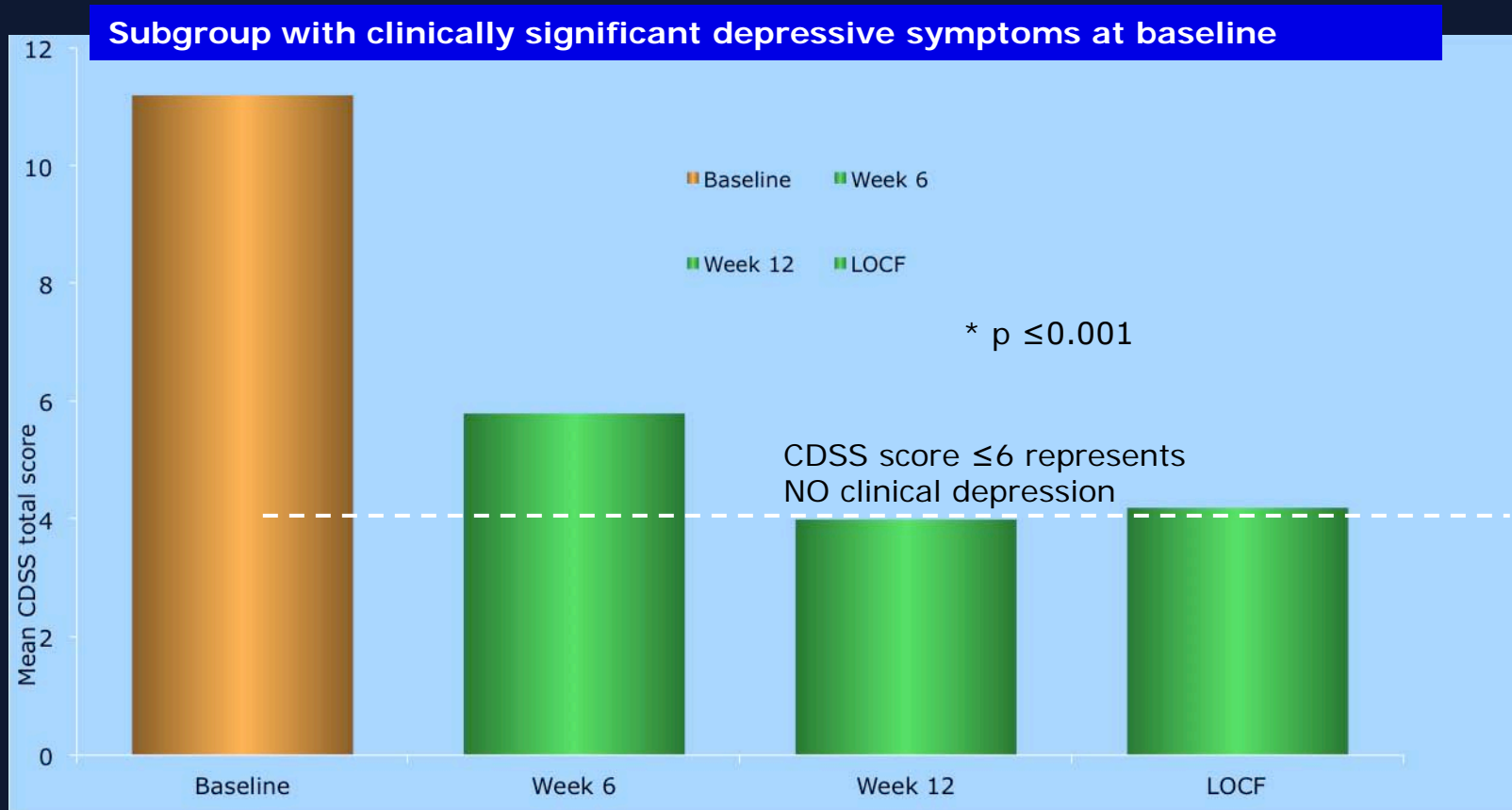


HAM-D: Hamilton Rating Scale for Depression;  
HAM-A: Hamilton Rating Scale for Anxiety

1. Strous et al. *Hum Psychopharm* 2006; 21:235-43.

# Quetiapine

## Switching Antipsychotics May Improve Depressive Symptoms



CDSS: Calgary Depression Scale for Schizophrenia



**SPECTRUM, 12-wk, open trial in  
patients with schizophrenia  
switched to quetiapine (n=509)**

# Current evidence : ECT

J ECT. 2006 Jun;22(2):127-32.

# 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<sup>2,3</sup>

- 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<sup>1</sup>**
  - **Social skills training**
  - **Cognitive remediation**
  - **Psychoeducational coping-oriented interventions with families & relatives**
  - **Cognitive behavioural therapy**

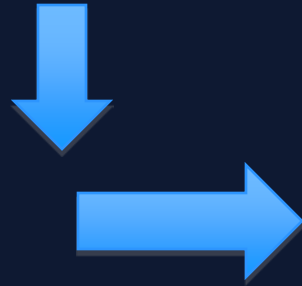
1. Pfammatter *et al.* *Schizophr Bull* 2006;32 Suppl 1:S64-80. 2. Jaeger *et al.* *Aust N Z J Psychiatry* 2006;40:452-61. 3. Lysaker *et al.* *J Rehabil Res Dev* 2005;42:673-82. 4. Pitschel-Walz *et al.* *J Clin Psychiatry* 2006;67:443-52.

# Comprehensive Treatment Programs

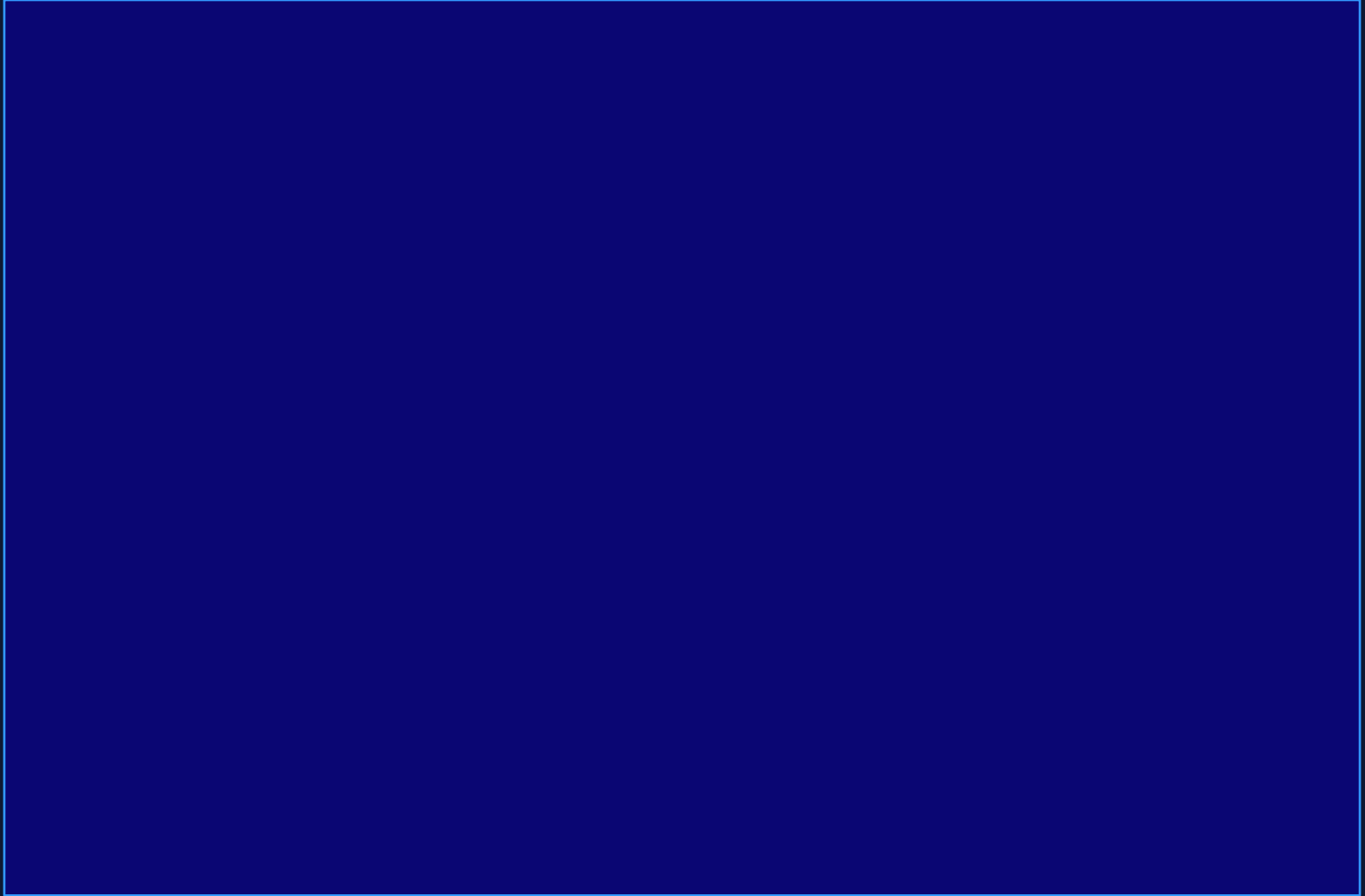
- Specialized early intervention approach can provide:<sup>1,2</sup>
  - ↑ short-term clinical and functional outcomes
  - ↑ retention in treatment
  - ↓ relapse rates
  - ↑ satisfaction with service delivery
  - ↑ greater family involvement
  - ↑ QoL

1. Malla *et al.* *Can J Psychiatry* 2005;50:881-91. 2. Harvey *et al.* *Can J Psychiatry* 2007;52:464-72.

# 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 mile stones 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.