

# **Adherence & relapse in Schizophrenia**

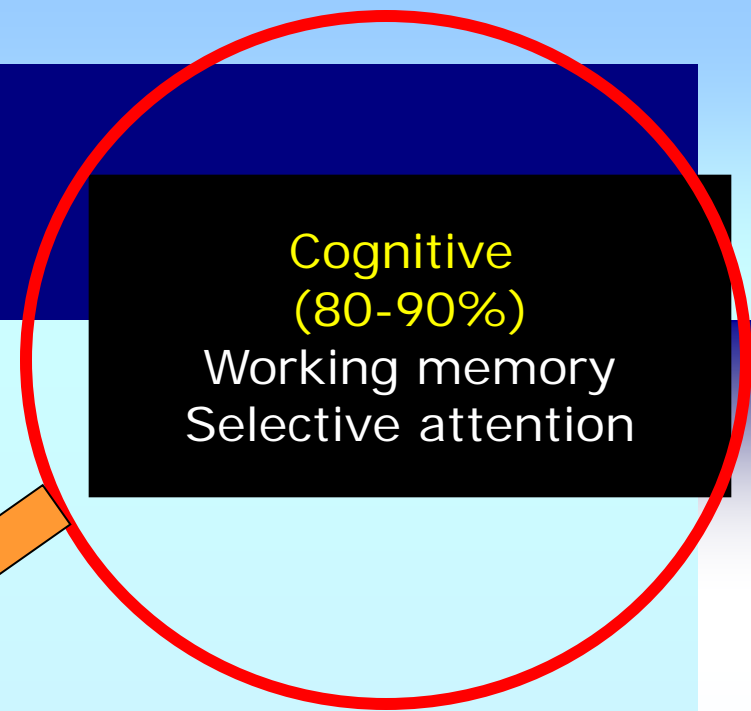
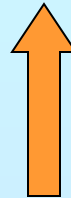
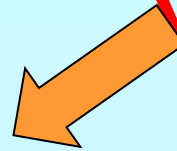
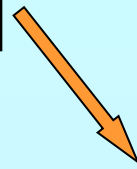
**Dr. S. Kalyanasundaram**  
**Bangalore**

**Positive symptoms**  
(40-50 %)  
Hallucinations  
Delusions  
Loose associations

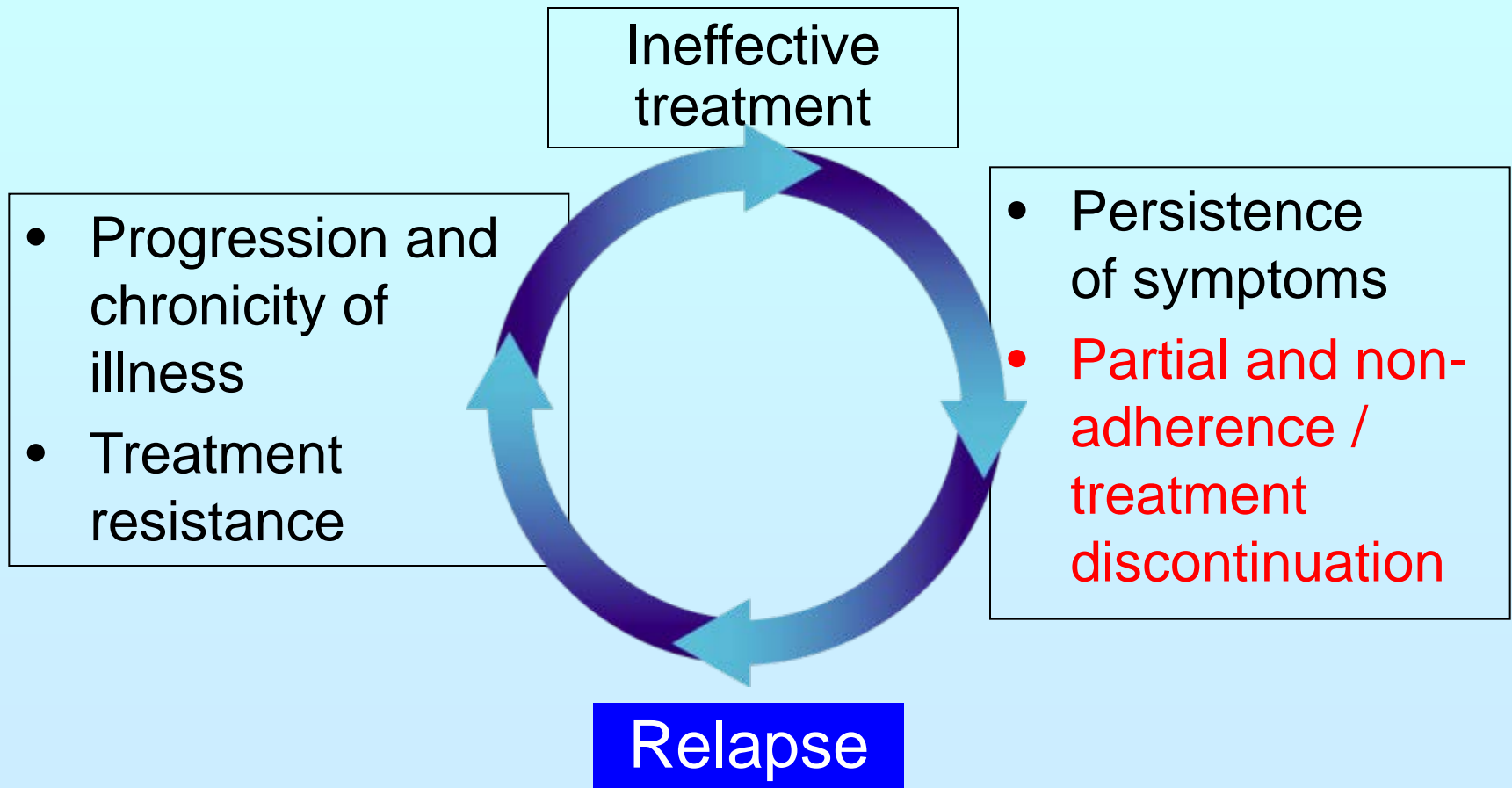
**Cognitive**  
(80-90%)  
Working memory  
Selective attention

Functional  
Impairment

**Negative symptoms**  
(60-70 %)  
Avolition  
Anhedonia  
Anergia  
Asociality  
Alogia



# Factors affecting the course and outcome of schizophrenia



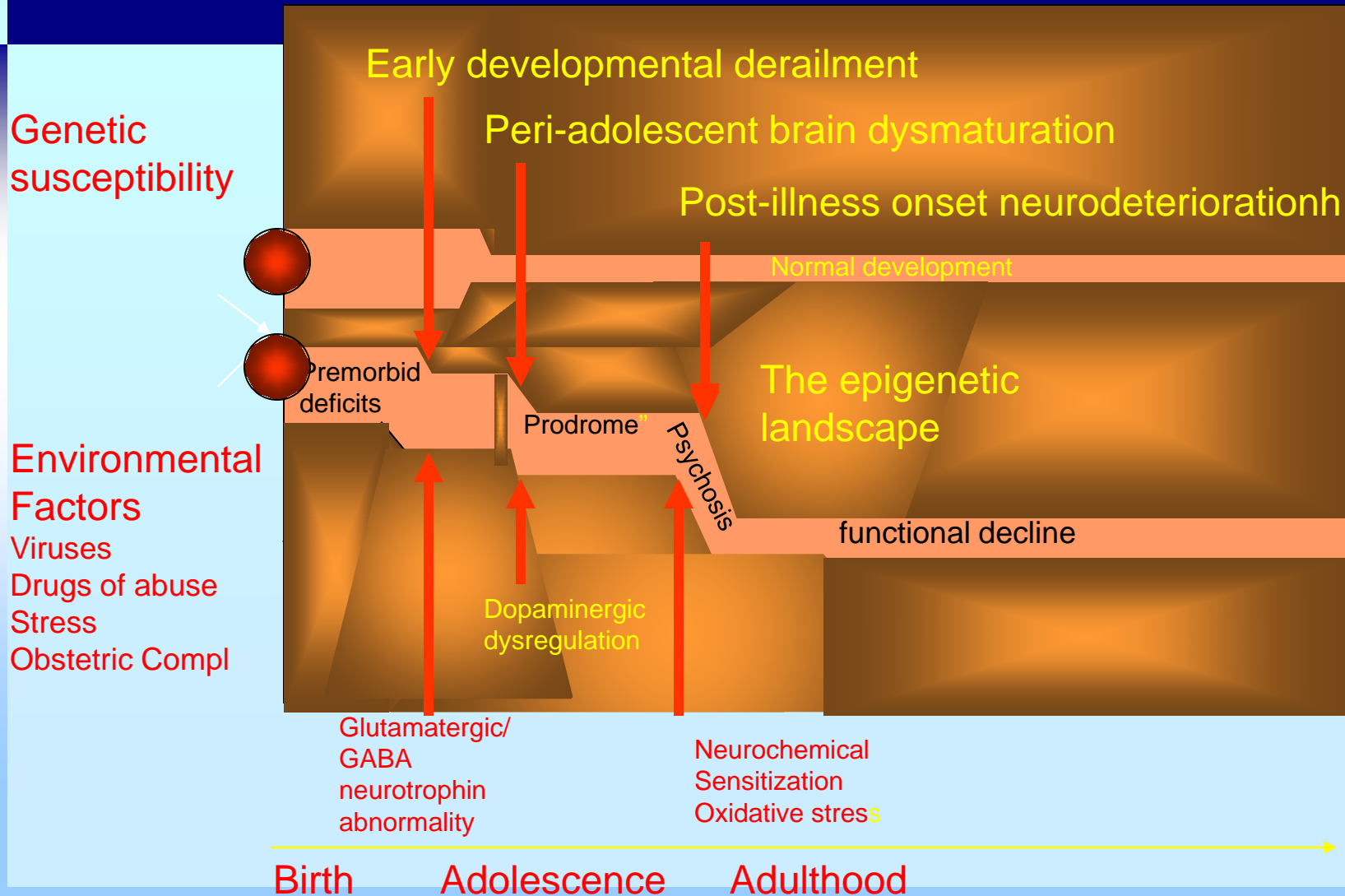
# Reality of patient outcomes in schizophrenia

- Long-term clinical outcomes are variable<sup>1</sup>
  - Only 10–15% of patients are free from further episodes
  - Majority of patients display exacerbations and experience clinical deterioration
  - 10–15% of patients remain chronically severely psychotic
- Early in the disease course, patients respond well to treatment but frequently relapse<sup>2</sup>
  - Associated with clinical deterioration
  - High level of distress and burden for carers<sup>3</sup>

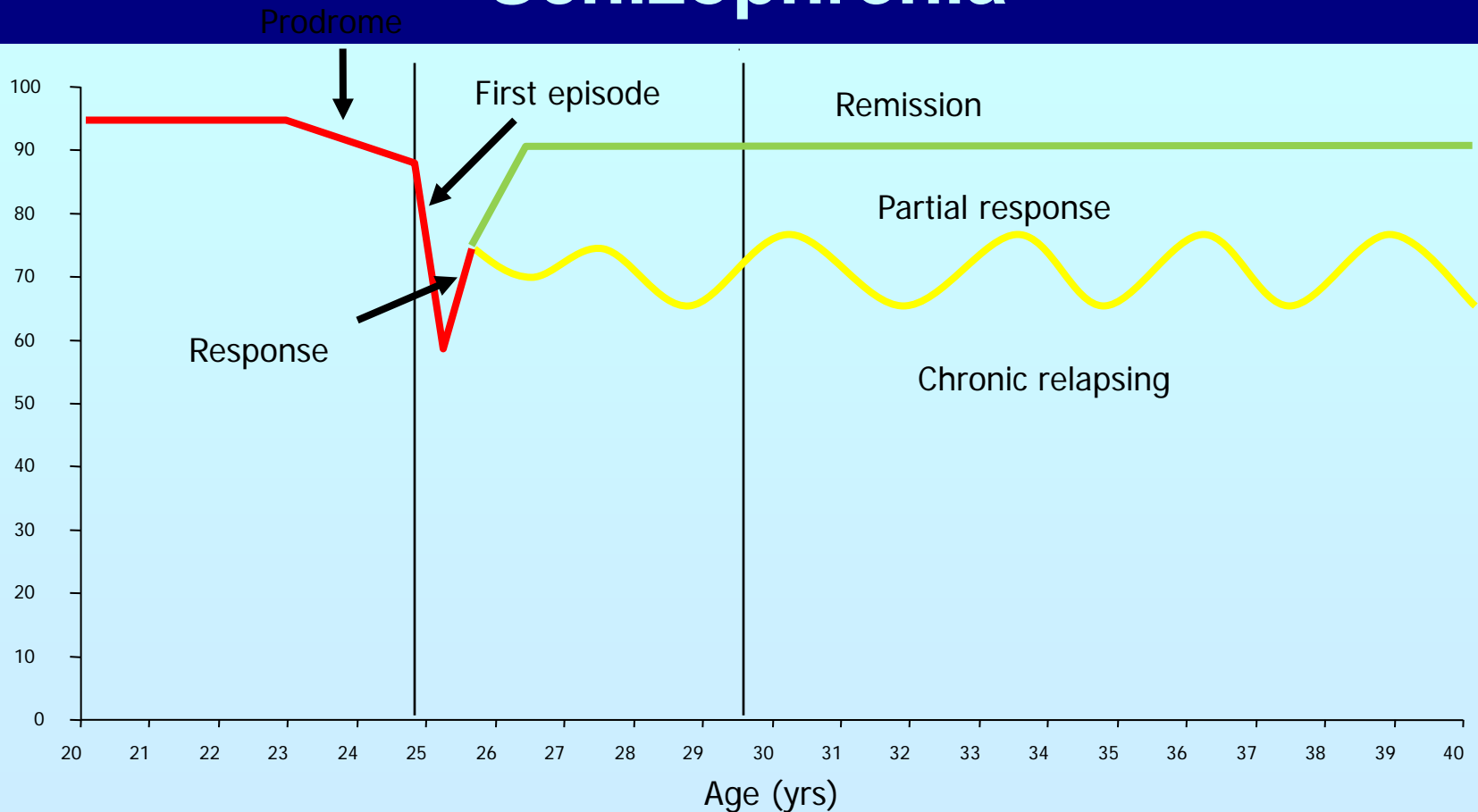
1. APA Practice Guidelines, 2004. [http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=Schizophrenia2ePG\\_05-15-06;](http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=Schizophrenia2ePG_05-15-06;)

2. Robinson et al. Arch Gen Psychiatry 1999;56:241–247; 3. Awad & Voruganti. Pharmacoeconomics 2008;26:149–162

# Pathophysiology of early phases of schizophrenia may involve a cascade of Sequential, cumulative events

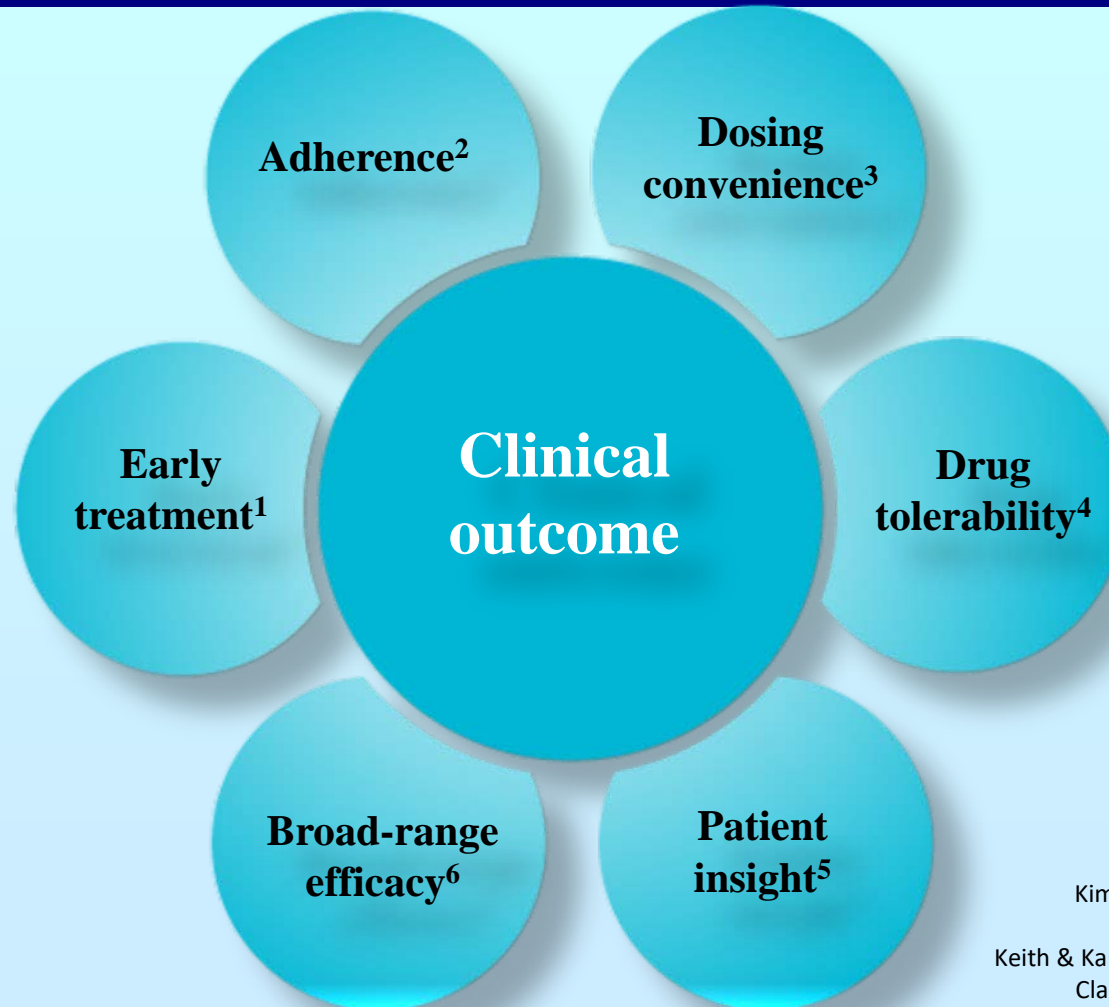


# Typical Disease Course in Schizophrenia



1. Birchwood M et al. Br J Psychiatry 1998;172 (S 33):53-9.
2. Breier et al. Am J Psychiatry 1994;151:20-26

# Factors Affecting Clinical Outcome Of Schizophrenia



Kim et al. Prog Neuropsychopharmacol Biol Psychiatry 2008;83:263–274

Keith & Kane. J Clin Psychiatry 2003;64:1308–1315

Claxton et al. Clin Ther 2001;23:1296–1310

Haddad & Sharma. CNS Drugs 2007;21:911–936

Dam et al. Nord J Psychiatry 2006;60:114–120

Weiden et al. J Clin Psychiatry 2007;68:1–48

# Non-adherence & consequences of relapse

Loss of self-esteem

Illness may become resistant to treatment

Potential danger to self and others

Loss of functional achievements

Increased cost of care

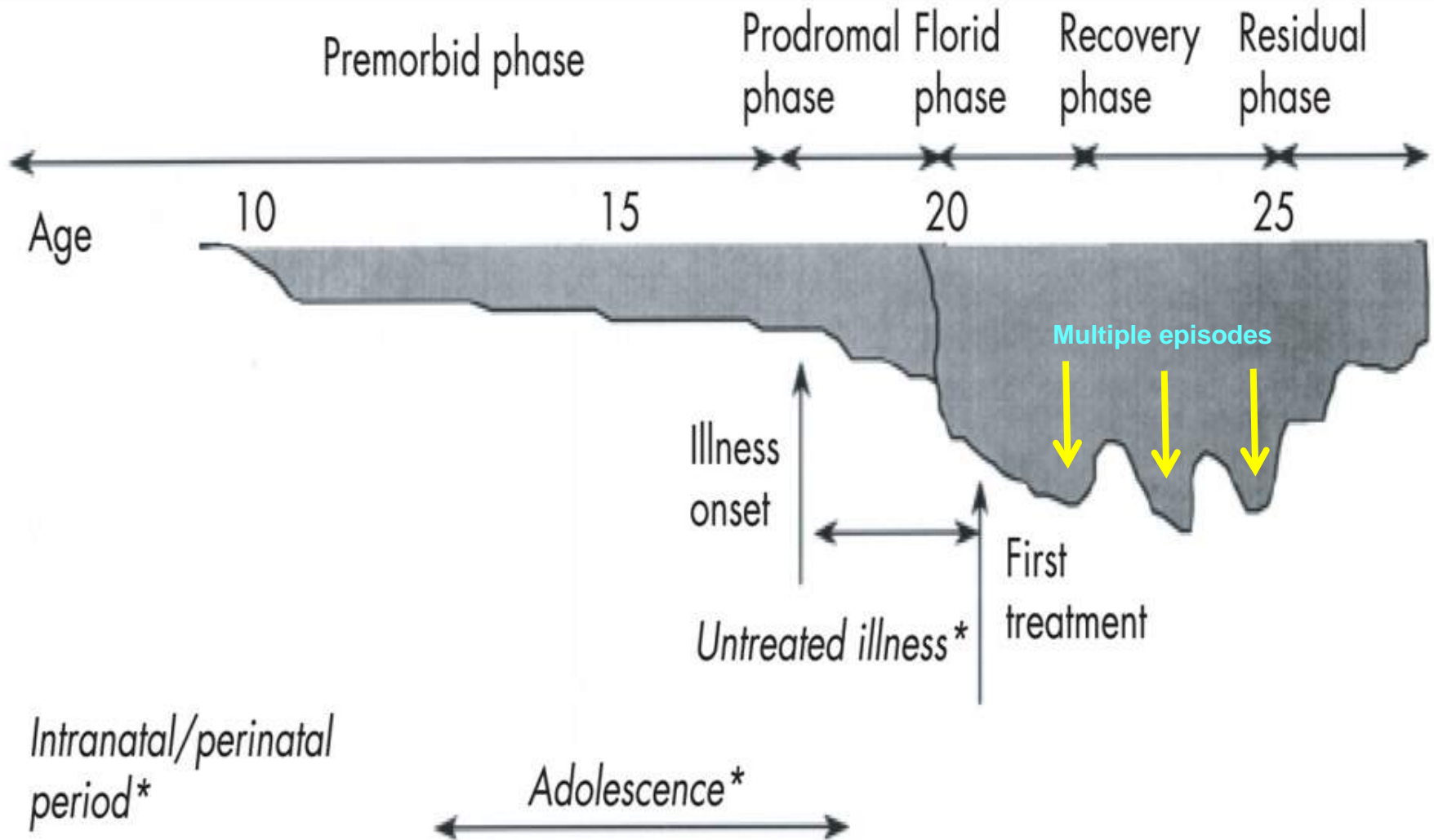
Harder to re-establish previous gains

Family burden and estrangement

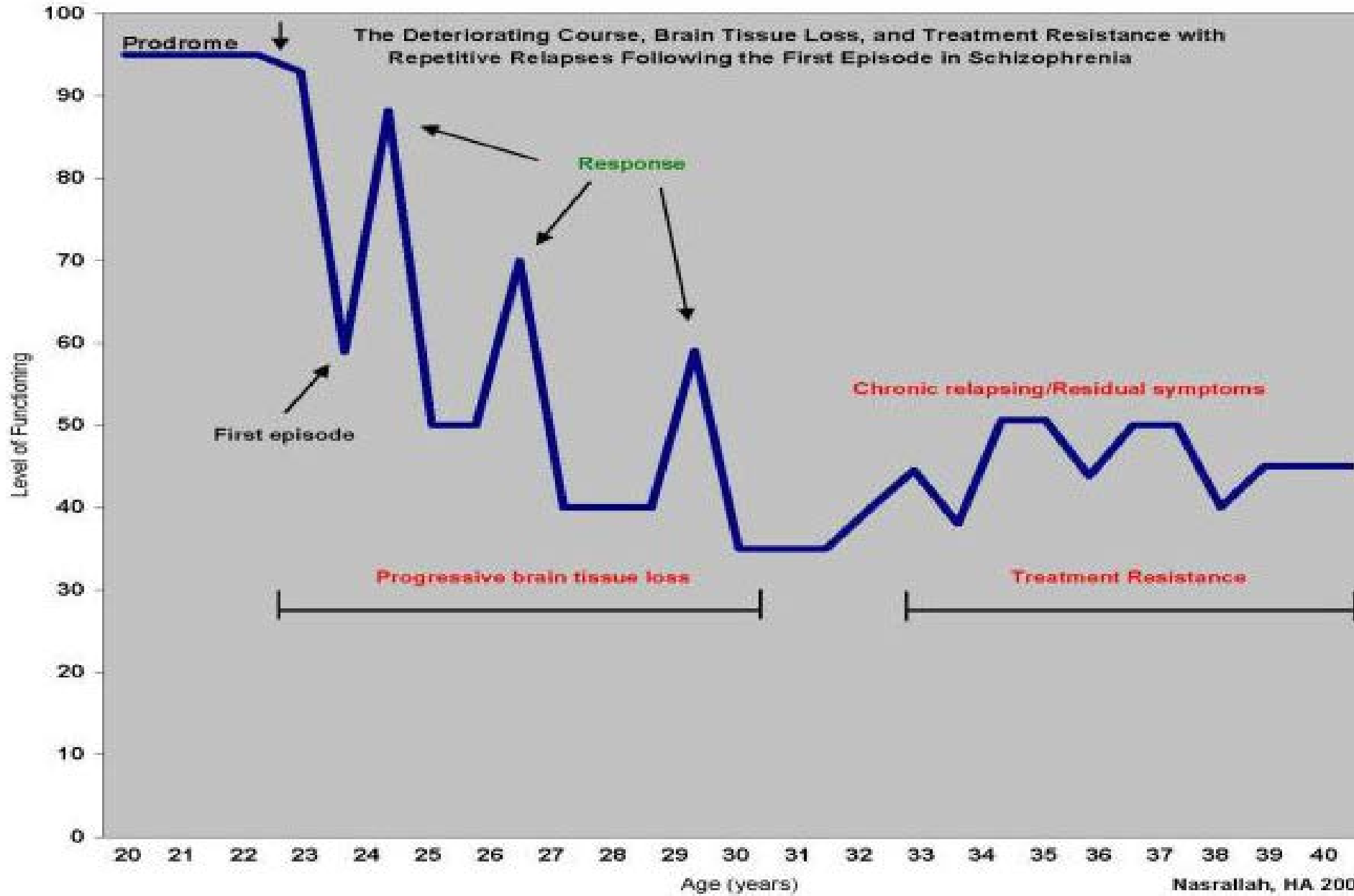
Potential neurobiological sequelae



# With every episode of relapse there is a decline of Psychosocial Functioning



# The Deteriorating Course, Brain Tissue Loss, and Treatment Resistance with Repetitive Relapses Following the First Episode in Schizophrenia



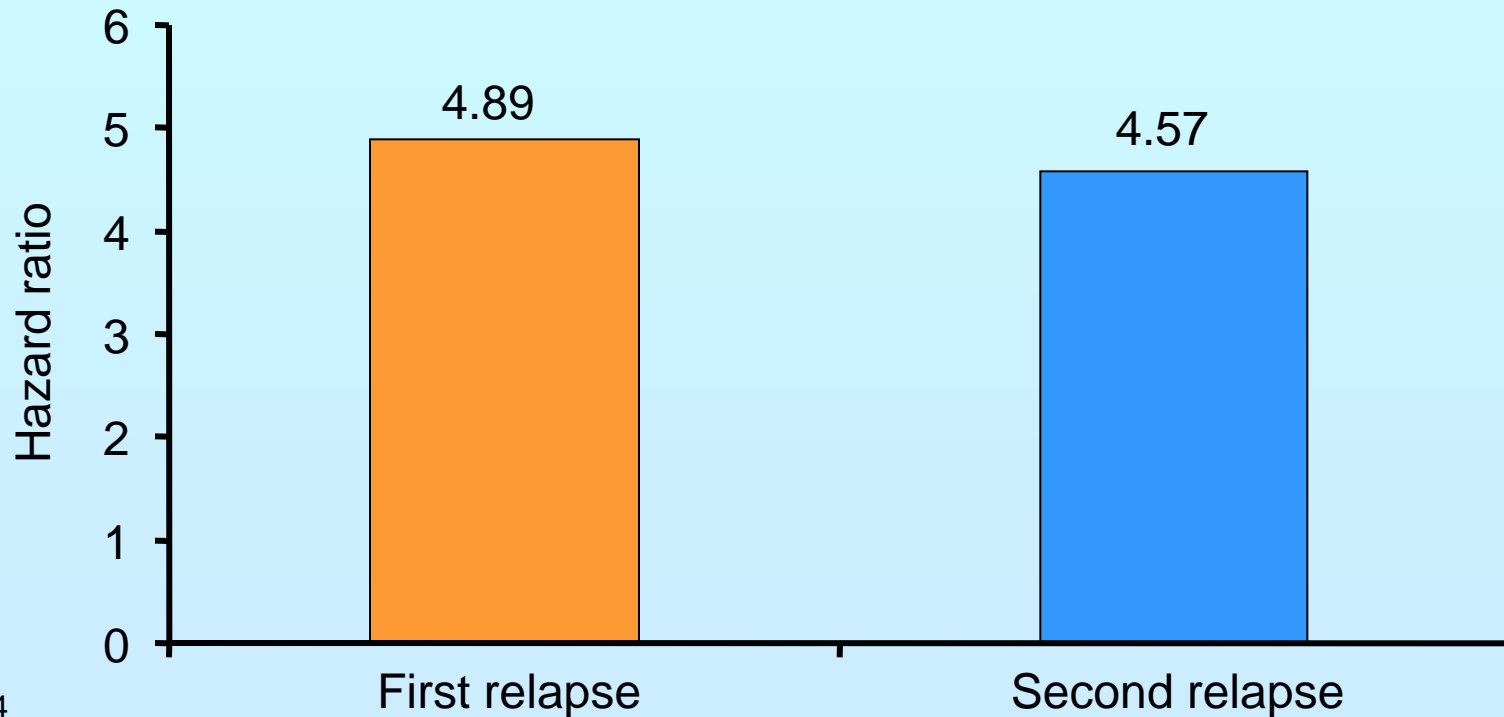
# Preventing relapse in schizophrenia

- Preventing relapse is a key goal highlighted in many international clinical guidelines<sup>1–3</sup>
- Medication discontinuation is one of the top predictors of relapse in schizophrenia<sup>4</sup>
  - Treatment discontinuation increases the relapse risk five-fold<sup>4</sup>
  - The chance of relapse is decreased if pharmacotherapy continues uninterrupted<sup>5</sup>
- Other risk factors include:<sup>3</sup>
  - Substance abuse, residual symptoms, poor insight

**Relapse prevention strategies should ensure periods of non-adherence to medication are minimized<sup>3</sup>**

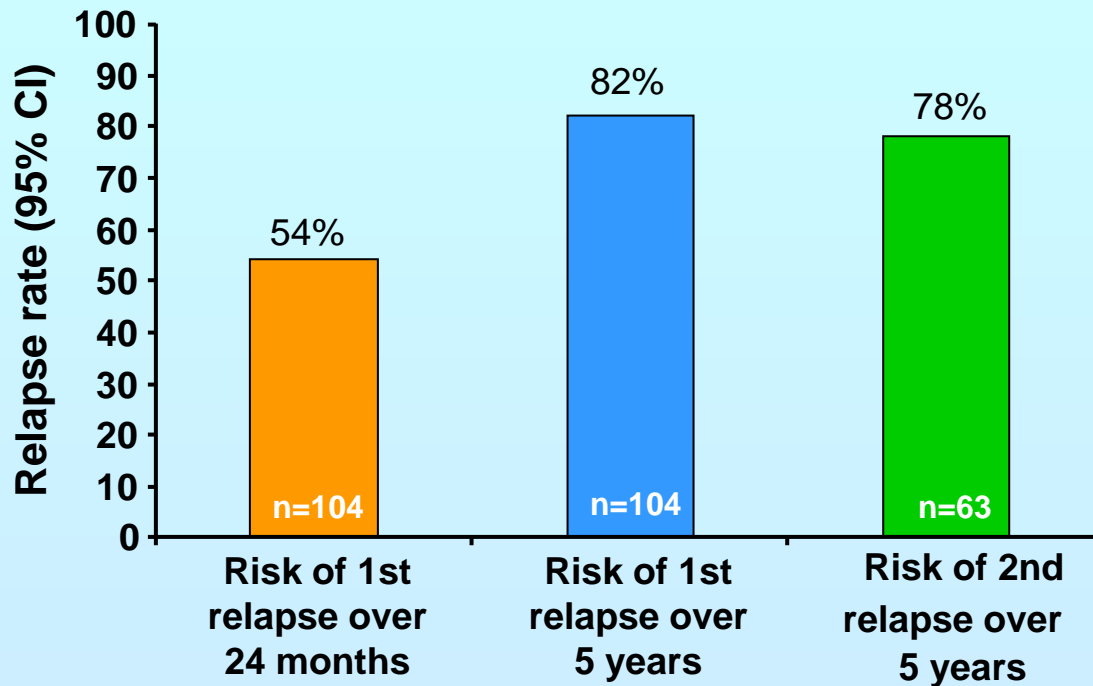
# Stopping medication is the most powerful predictor of relapse

Survival analysis: risk of a first or second relapse when **not** taking medication ~5 times greater than when taking it



n=104

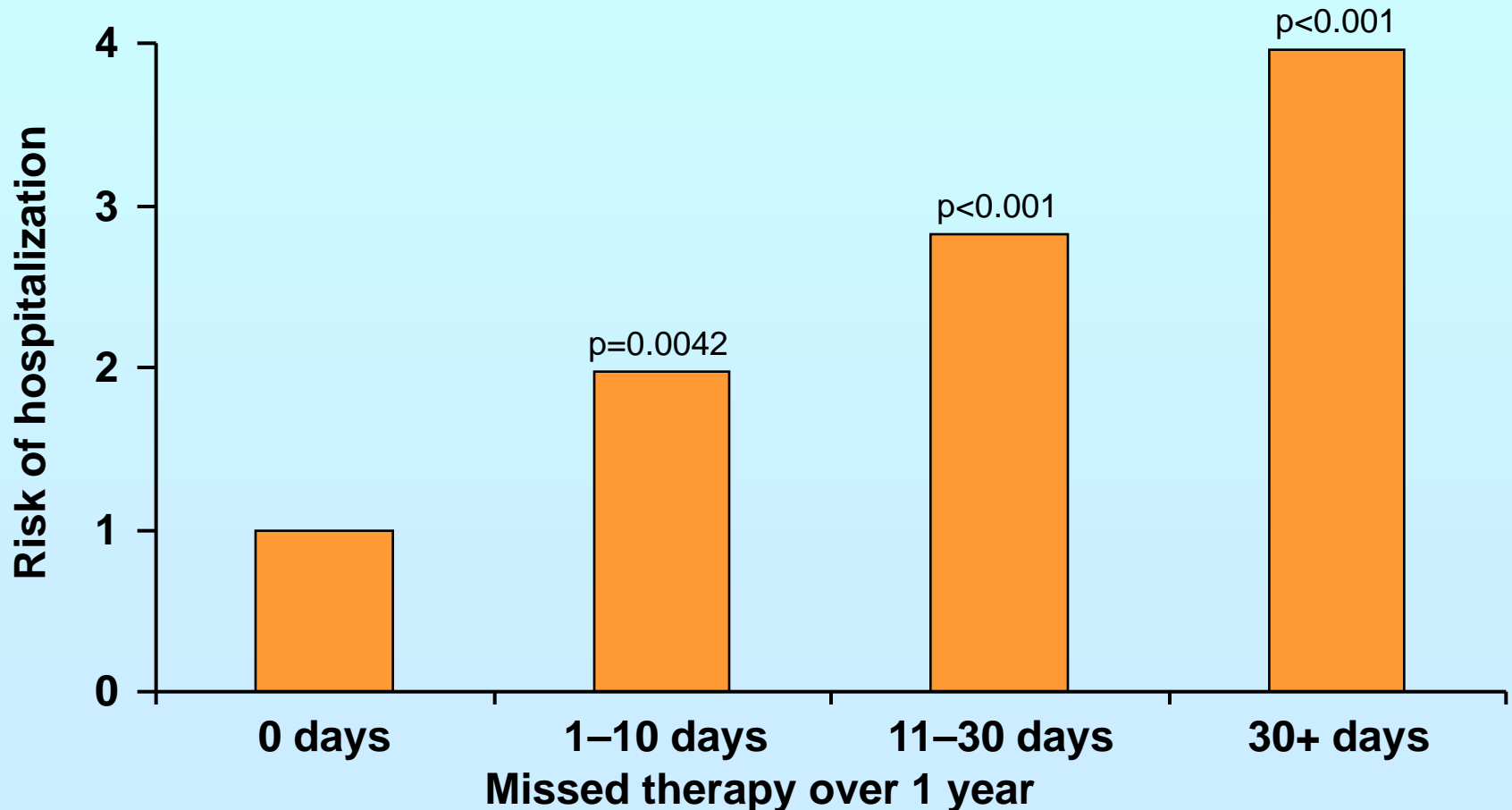
# First-episode patients are at high risk of relapse



**There is a high rate of relapse within 5 years after a first episode**

# Even 1–10 days therapy missed per year leads to an increased risk of hospitalization

Recent Californian Medicaid assessment (n>4000 patients)



p values given with 0 days as the referent

# Treatment Adherence

- A World Health Organization (WHO, 2003) report defined **treatment adherence** broadly as:
- The extent to which a person's behavior taking medication, following a diet, and/or executing lifestyle changes, corresponds with **agreed recommendations** from a healthcare provider”

# Categorizing non-adherence behaviors:

- (a) *Full non-adherence*, or complete noncompliance with all provider instructions;
- (b) *Selective non-adherence*, or compliance with some but not all instructions (e.g., taking only one of two prescribed medications)
- (c) *Intermittent adherence, or noncompliance*, but only during certain periods (e.g., not taking medications when abusing alcohol or drugs)
- (d) *Late adherence or, non-adherence or initial noncompliance followed by later adherence* (e.g., increased adherence over time due to improved insight into illness or specific intervention efforts), or vice versa
- (e) *Abuse, or taking more medication than prescribed* (e.g., attempts by patients to increase a medication's effectiveness by taking more of it)
- (f) *Behavioral non-adherence*, or lack of adherence to the non-medication aspects of treatments.

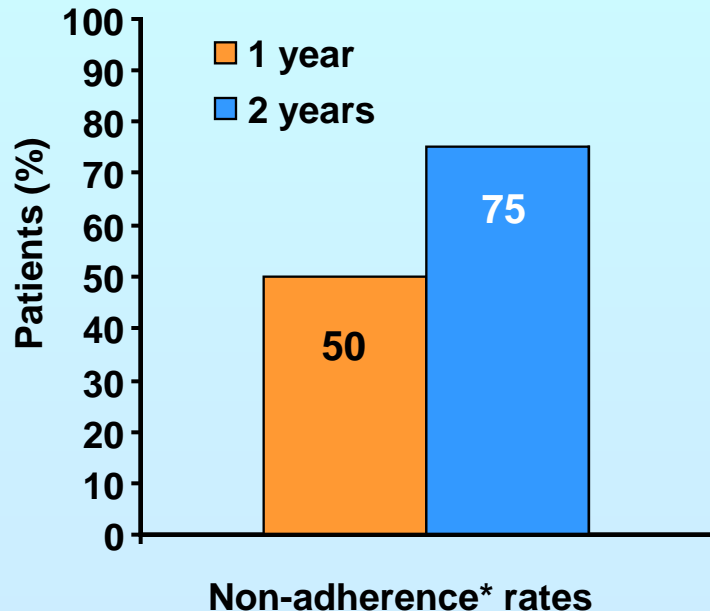


# Why is adherence still a challenge in patient care?

- Non-adherence is more common than treatment refusal or discontinuation
- Medications with improved safety and tolerability profiles have not improved adherence rates
- HCPs focus on difficult-to-treat patients on maintenance therapy
  - Patients who openly refuse or repeatedly discontinue treatment
- Lack of awareness of patients' non-adherence impacts prescribing behaviour and patient outcomes
- HCPs may not consider partial adherence a worthy issue
- **Partial adherence may be perceived as inevitable and unavoidable, by HCPs**

# Adherence rates in schizophrenia

## Non-adherence to maintenance antipsychotic therapy after discharge<sup>1†</sup>



\*Non-adherence <70% medication adherence in the previous week

†Antipsychotic medication includes oral FGAs and SGAs

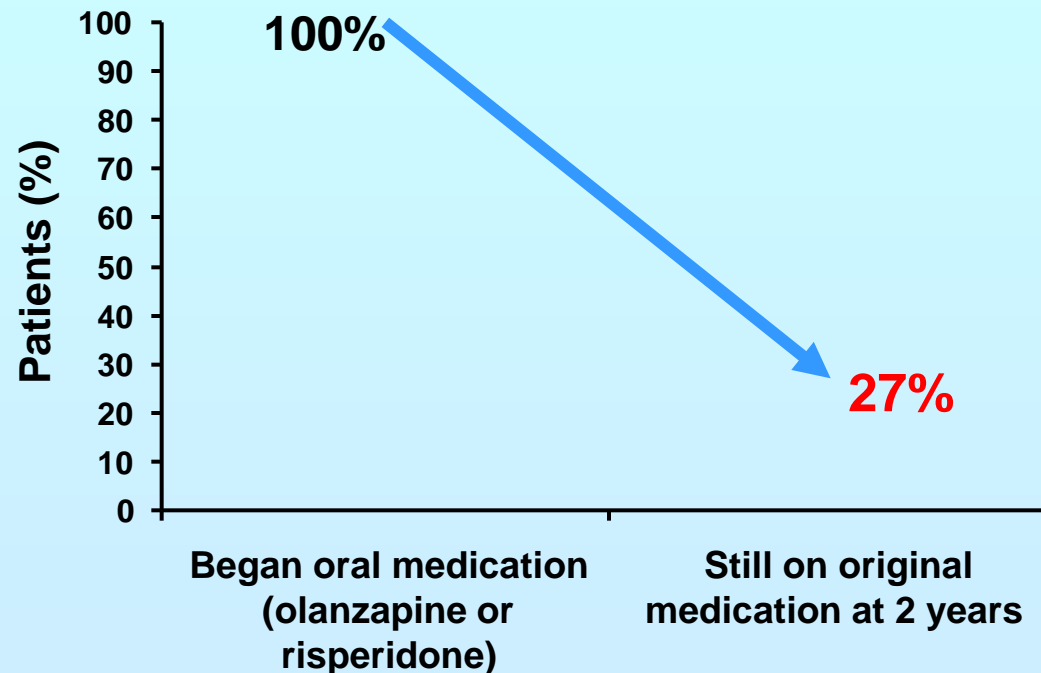
One year after discharge 50% of patients do not fully adhere to antipsychotic treatment<sup>1</sup>

Non-adherence with therapy is a major contributor to relapse, poor outcome, and high costs<sup>2</sup>

FGA, first-generation antipsychotic; SGA, second-generation antipsychotic

# Majority of patients who discontinue do so without medical supervision

Naturalistic study of patients at a Veterans Affairs Medical Center



n=495

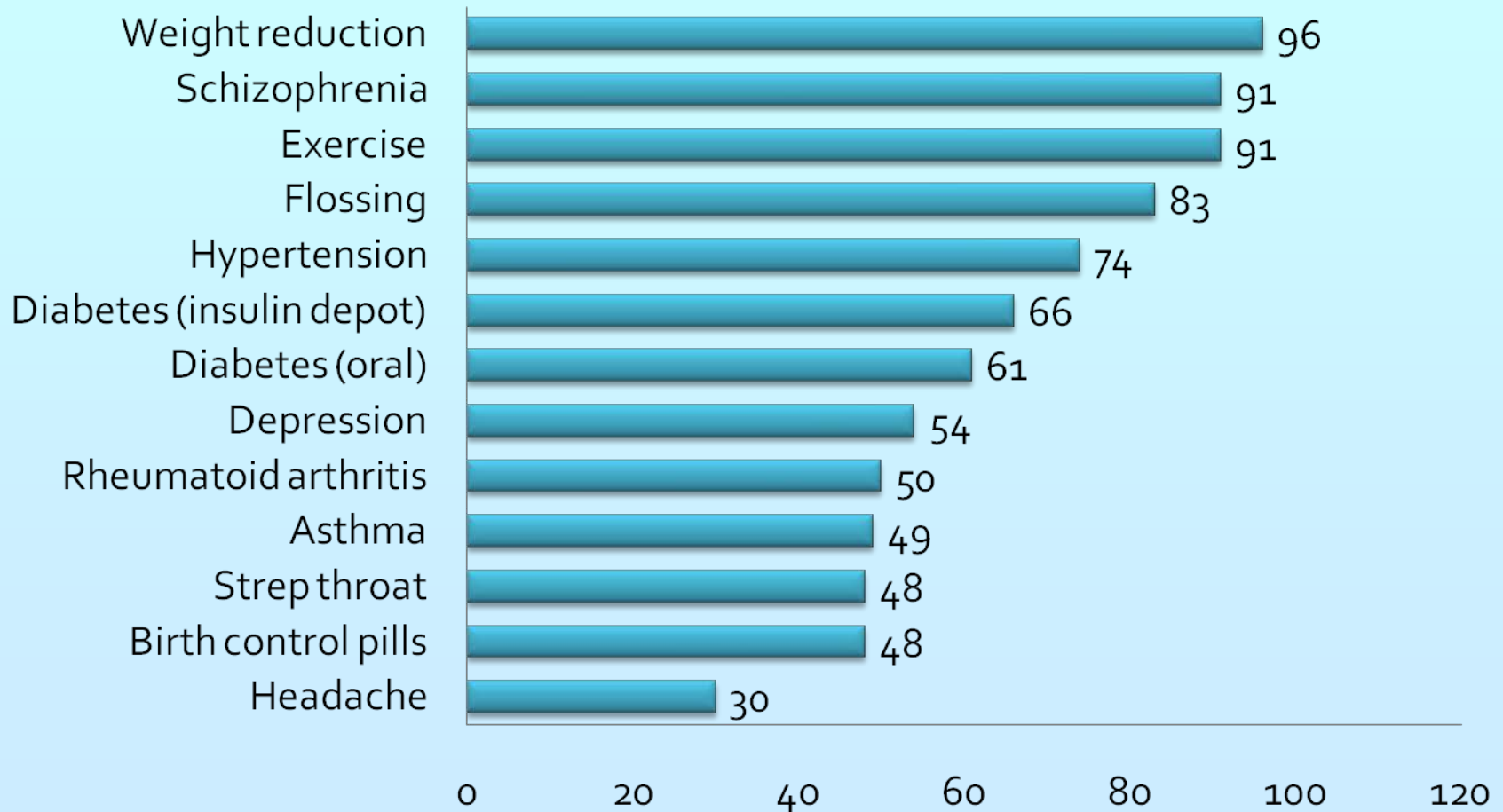
**48% of patients self-discontinued medication\***

\*Medication discontinuation defined as switch between antipsychotics, or self-discontinuation when a patient is without medication supply for longer than 1 month

# Why Poor Compliance is a Major Problem In Schizophrenia

- Denial of illness (anosognosia)
- Cognitive impairment
  - Memory functions
  - Executive [frontal] functions
- Negative symptoms
  - Lack of initiative
  - Lack of motivation
- Side effects of medications
- Chaotic lifestyle with substance abuse
- **Partial compliance is HUMAN NATURE !**  
[even in people with chronic pain !]

# Various Types of Non-Adherence



# Reasons for non-adherence can be complex

## Treatment-related

- Side effects
- Efficacy
- Lack of clinician awareness
- Complexity of regimen
- Poor therapeutic alliance
- Access to treatment
- Cost

## Psychological/social

- Stigma (of disease and medication)
- Environmental stressors
- Level of support from family/friends
- Irregular daily routine
- Substance abuse
- Religious beliefs

## Disease-related

- Poor insight
- Disease severity
- Cognitive impairment
- Motivational deficits

## Human nature

- Full adherence is difficult for anyone to maintain, eg exercise, diets
- Patient does not believe medication necessary once response achieved

# Factors affecting medication adherence

## Patient-related factors<sup>1</sup>

- **Lack of insight**
- **Attitudes and past behaviours**
- **Demographic factors**
- **Environmental factors**
- **Cognitive impairment**
- **Medication-related factors**

COMMON DENOMINATOR

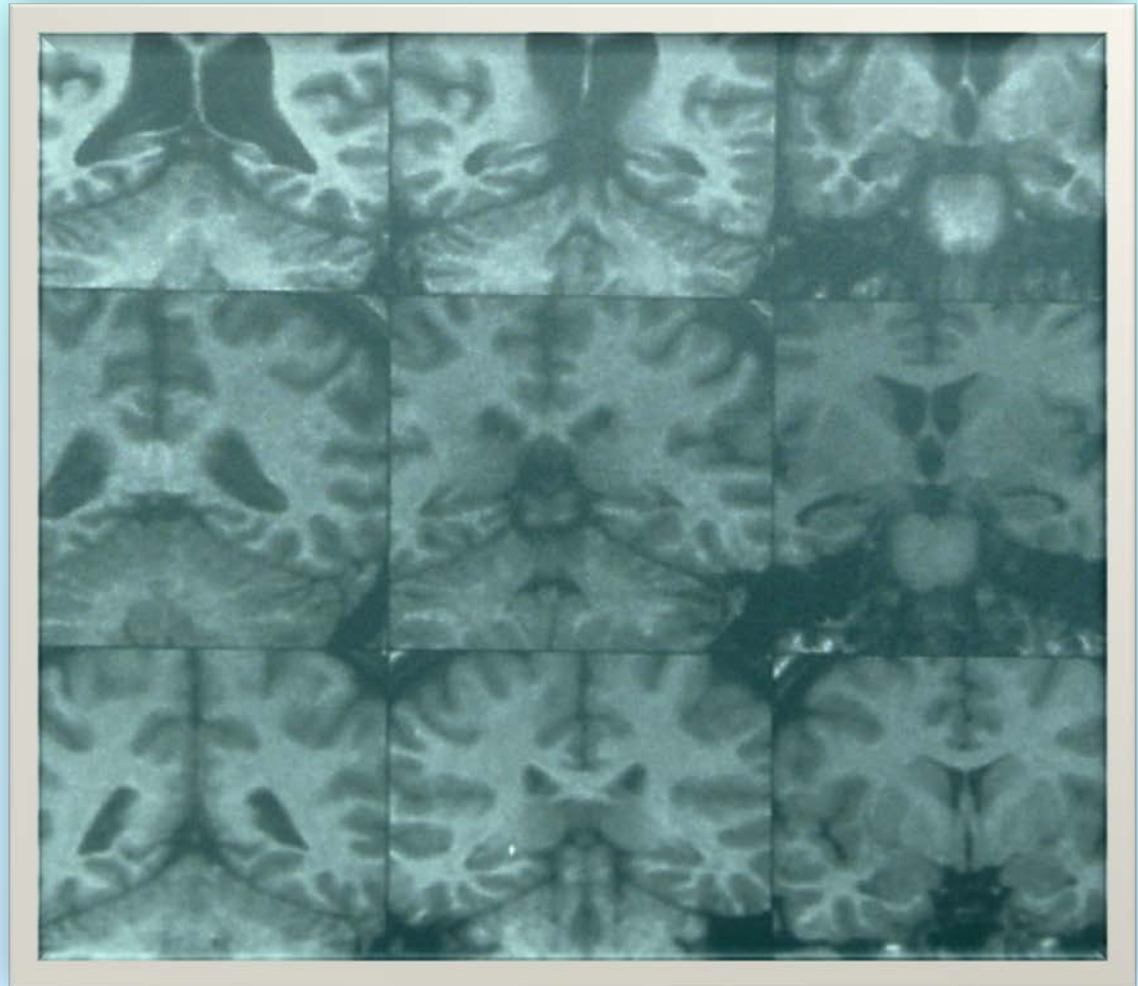
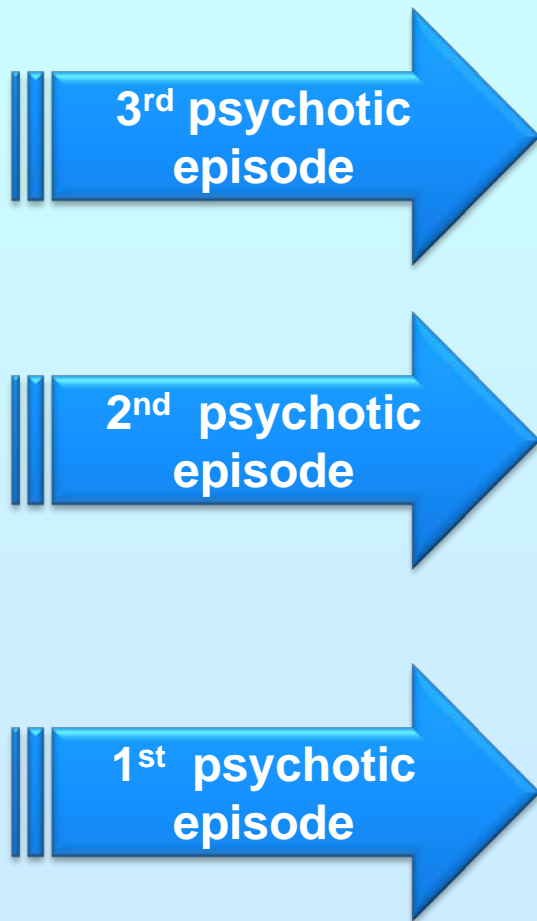
## Relationship factors<sup>1</sup>

- **Therapeutic alliance**
- **Family and social support**

## Factors related to the service delivery system

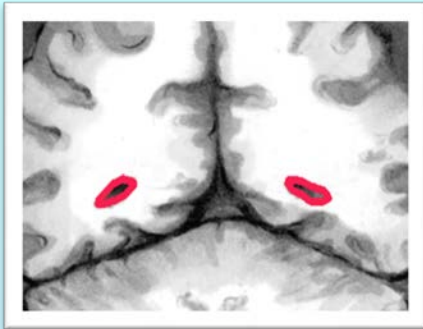
- **Inadequate discharge planning and aftercare<sup>1</sup>**
- **Dissatisfaction with level of information provided regarding medication (side effects, etc)<sup>2</sup>**
- **Lack of funding for necessary medications<sup>2</sup>**
- **Level of access to psychiatrists<sup>1</sup>**

# Progressive MRI changes over three relapses in a male with schizophrenia

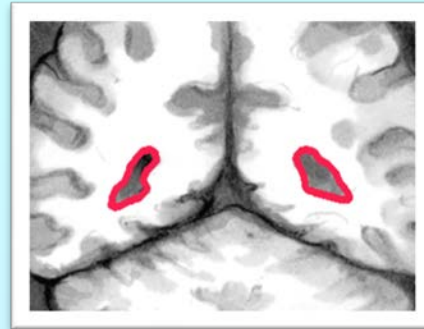




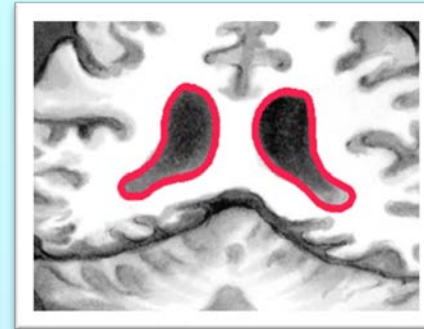
# MRI Schematic of Progression in Schizophrenia



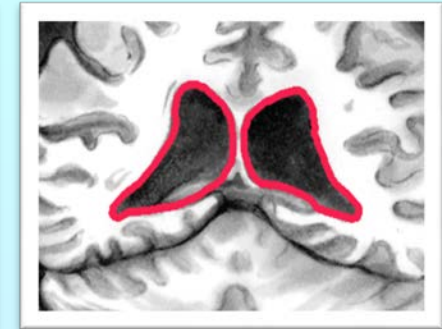
First Episode



Second Episode



Third Episode



Fourth Episode

- Ventricular enlargement associated with poor outcome patients
- Longer duration of treatment associated with less ventricular enlargement over time

# Which factor do you think has the greatest impact on medication non-adherence?

## Patients

## Carers

## Psychiatrists

1.

Effectiveness of AP treatment

Effectiveness of AP treatment

Insight

2.

Self-management of side effects

Insight

Side effects

3.

Insight

Support from carers

Negative expectations

6. Side effects

5. Effectiveness of AP treatment

# Patient centered outcomes: Attending to the R's

## Achieve

Recovery

Remission

Response

## Avoid

Relapse

Partial  
response

Refract-  
oriness

# Strategies to assess adherence

## DIRECT<sup>1</sup>

Observe intake  
of medication

Measuring plasma  
drug levels

Measuring a  
biological marker

## INDIRECT<sup>1</sup>

Patient self-report

Patient questionnaire

Patient diary

Pill counts

Prescription refill data

Electronic monitors

Scales eg DAI<sup>2</sup> MARS<sup>3</sup>

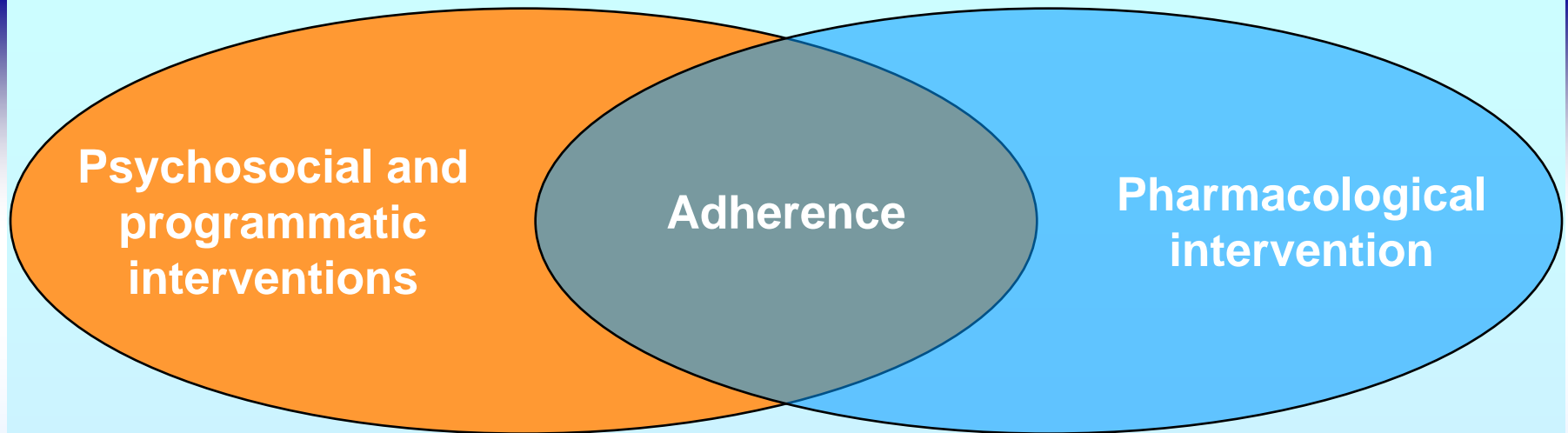
All methods are subject to inaccuracies

DAI, drug attitude inventory; MARS, medication adherence rating scale

1. Kane. CNS Spectr 2007;12(10 suppl 17):21–26;

2. Hogan et al. Psychol Med 1983;13:177–183; 3. Thompson et al. Schizophr Res 2000;42:241–247

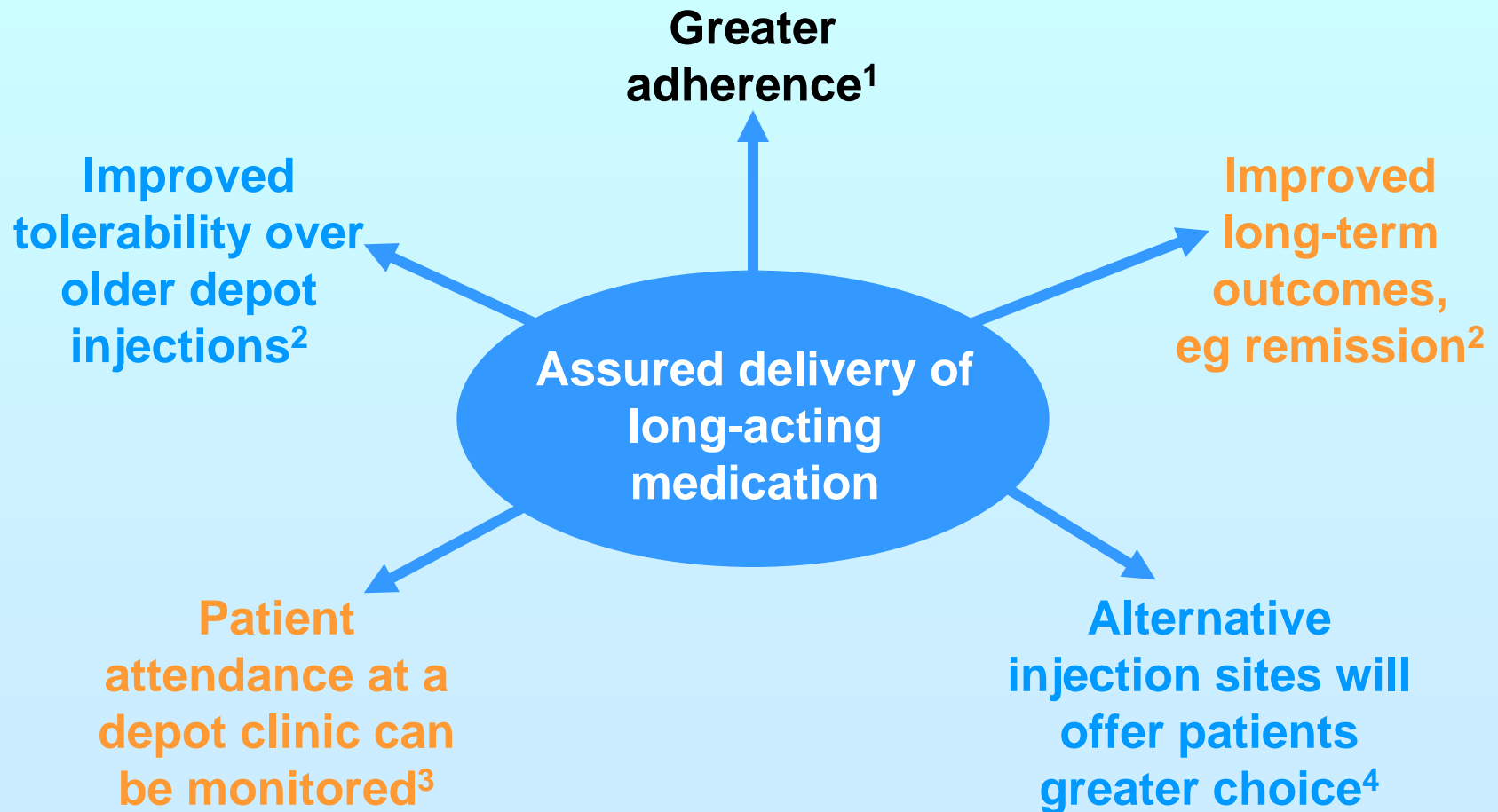
# Interventions to improve adherence



- Cognitive behavioural therapy
- Compliance therapy
- Cognitive adaptation
- More frequent and/or longer visits
- Patient/family psycho-education
- Symptom/side effect monitoring

- Dose correction to reduce side effects
- Simplified medication regimen
- First generation long-acting injectable antipsychotics
- Second-generation long-acting injectable antipsychotics

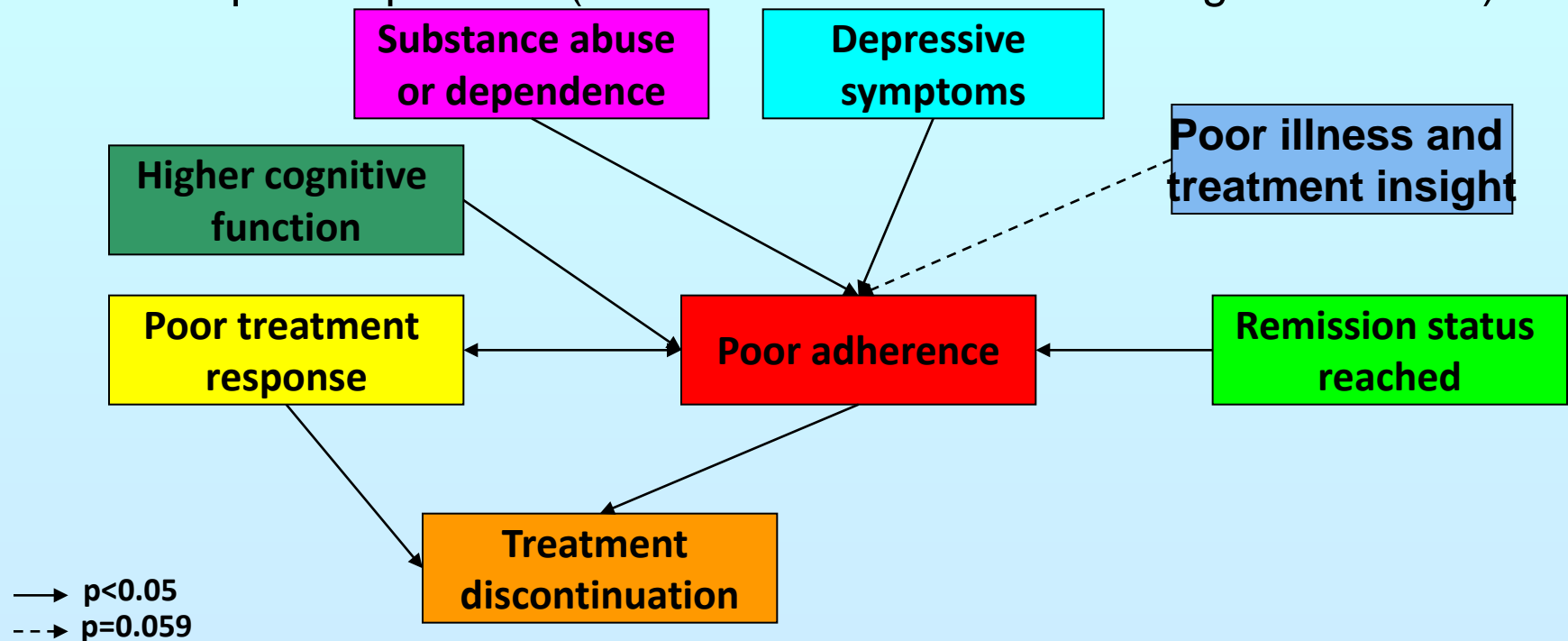
# Pharmacological approaches to improve adherence



# Factors associated with treatment discontinuation in first-episode patients

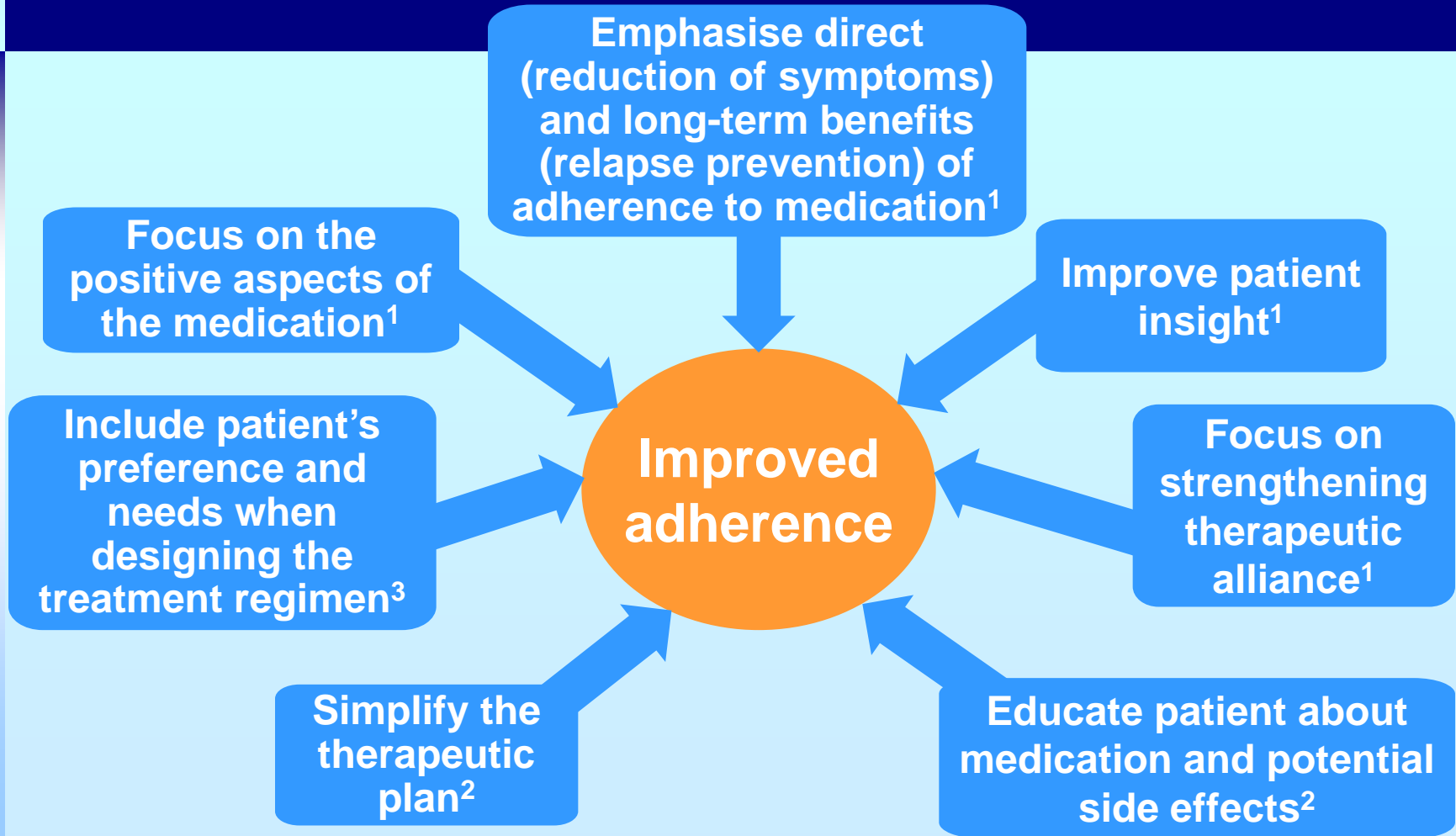
52-week multicentre study

400 first-episode patients (115 discontinued treatment against advice)



Treatment adherence and response appear to be mutually reinforcing

# How can attitudes to medication adherence be improved?

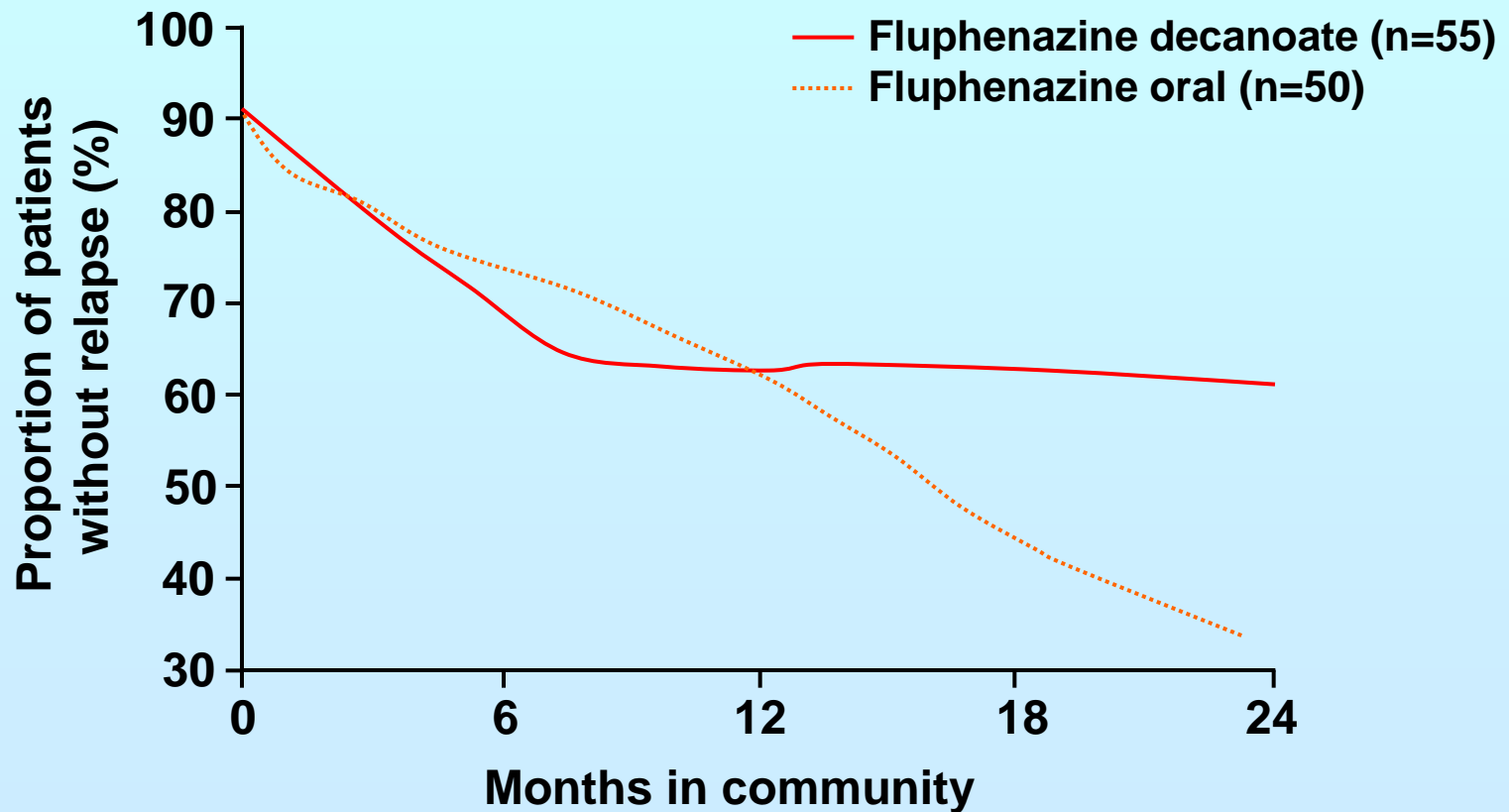


HCP, healthcare professional

1. Kikkert et al. Schizophr Bull 2006;32:786–794;
2. Charpentier et al. Encephale 2009;35:80–89;
3. NICE Clinical Practice Guidelines in Schizophrenia, CG82, March 2009



# Depot formulations may have advantages over their oral counterparts in long-term treatment



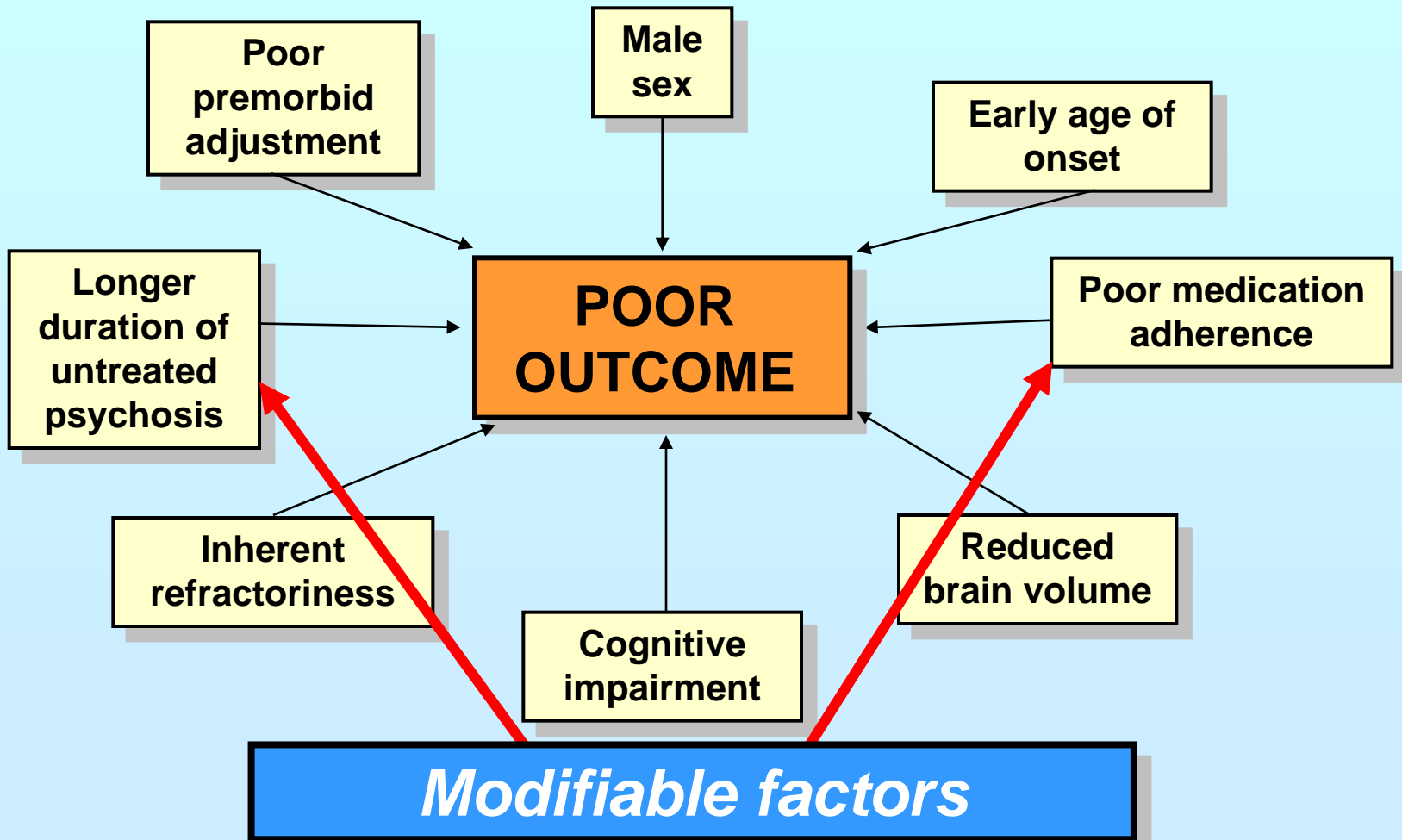
# What is the evidence for illness progression after relapse?

- Treatment response is better in first-episode than in multi-episode patients<sup>1</sup>
- 7-year follow-up study:<sup>2</sup>
  - 80% deteriorated
  - Degree of deterioration significantly correlated with the number of relapses
- 15-year follow-up study:<sup>3</sup>
  - Striking finding: one in six patients did not remit after each episode
- Preliminary study:<sup>4</sup>
  - Increased times to treatment response in succeeding episodes

# Partial/non-adherence in early schizophrenia

- Adherence problems are common in the early stages of schizophrenia<sup>1</sup>
- Partial/non-adherence rates are 59% within first year of starting treatment<sup>2</sup>
- Antipsychotic discontinuation is a strong predictor of relapse<sup>3</sup>
- Disease progression leads to deterioration of treatment response, particularly with oral antipsychotics<sup>4</sup>
- Each psychotic episode predisposes further episodes<sup>4</sup>
- Fewer relapses help improve long-term patient outcomes<sup>4</sup>
- Early detection and intervention are critical<sup>4</sup>

# Predictors of treatment outcome



# Other predictors of non-adherence to antipsychotic therapy in first-episode psychosis

- Lack of social and family support<sup>1</sup>
- Refusal of medication at the first offer of treatment<sup>1</sup>
- More likely to be single<sup>1</sup>
  - Consecutive first-episode patients (n=100) admitted to a specialized early intervention service
  - Medication adherence evaluated monthly for 6 months
- Substance abuse<sup>2</sup>
  - First-episode patients (n=400) included in a 52-week, randomized, double-blind, flexible-dose multicentre trial

# Relapse rates after antipsychotic discontinuation

Study	N	Time in remission	Discontinuation period	Relapse rate
Hogarty et al (1976) <sup>1</sup>	41	2 to 3 yr	12 mo	65%
Johnson (1976) <sup>2</sup>	23	1 to 2 yr	6 mo	53%
Dencker et al (1980) <sup>3</sup>	32	2 yr	24 mo	94%
Chueng (1981) <sup>4</sup>	13	3 to 5 yr	18 mo	62%
Johnson (1981) <sup>5</sup>	60	1 to 4 yr	18 mo	80%
Wistedt (1981) <sup>6</sup>	16	6 mo	12 mo	97%
Gitlin et al (2001) <sup>7</sup>	53	3 mo	24 mo	96%

yr, years; mo, months

1. Hogarty et al. Dis Nerv Syst 1976;37:494–500; 2. Johnson. Acta Psychiatr Scand 1976;53:298–301; 3. Dencker et al. Acta Psychiatr Scand Suppl 1980;279:64–76; 4. Cheung. Br J Psychiatry 1981;138:490–494; 5. Johnson. Acta Psychiatr Belg 1981;81:161–172; 6. Wistedt et al. Acta Psychiatr Scand 1981;64:65–84; 7. Gitlin et al. Am J Psychiatry 2001;158:1835–1842

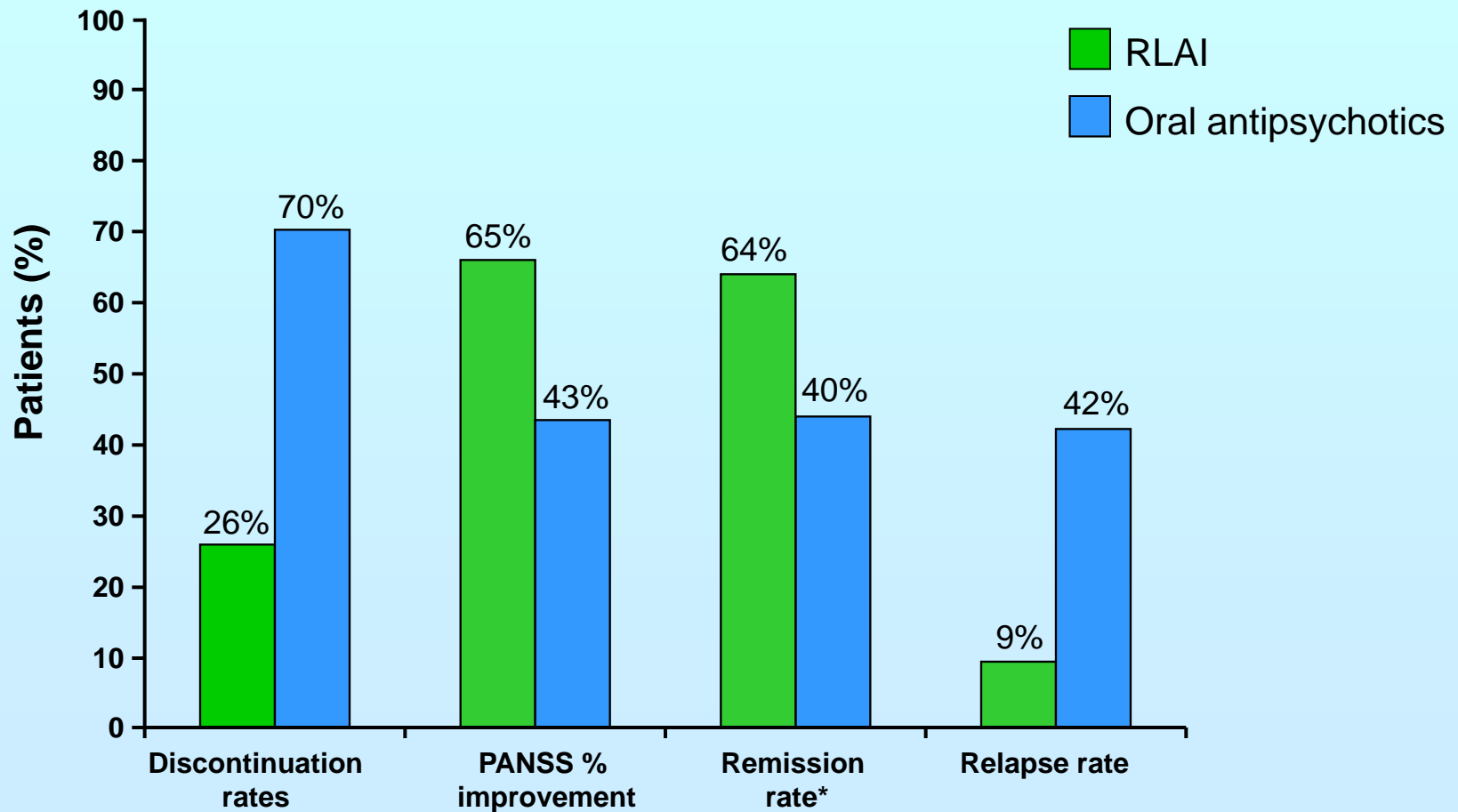
# Considerations for using LAIs in early schizophrenia

- The discontinuation rate in the CAFE study was 70% over 1 year<sup>1</sup>
- In the EUFEST study there was a 42% all-cause discontinuation rate among the 498 study patients over 1 year<sup>2</sup>
- Greater medication adherence is a predictor of remission status<sup>3</sup>
- Early treatment with APs in FEP decreases long-term morbidity<sup>4</sup>
- LAIs have the potential to reduce discontinuation rates<sup>2</sup>

LAI: long-acting injectable; CAFE, Comparison of Atypicals in First Episode; EUFEST, European First Episode Schizophrenia Trial; AP, antipsychotic; FEP, first-episode psychosis

1. McEvoy et al. *Am J Psychiatry* 2007;164:1050–1060; 2. Miller. *J Psychiatr Pract* 2008;14:289–300;  
3. Malla et al. *Psychol Med* 2006;36:649–658; 4. Wyatt et al. *Br J Psychiatry Suppl* 1998;172:77–83

# RLAI versus oral antipsychotics in early psychosis: *post hoc* comparison of two studies



n=50

\*Remission according to Andreasen et al. Am J Psychiatry 2005;162:441-449

RLAI, risperidone long-acting injectable; PANSS, Positive and Negative Syndrome Scale

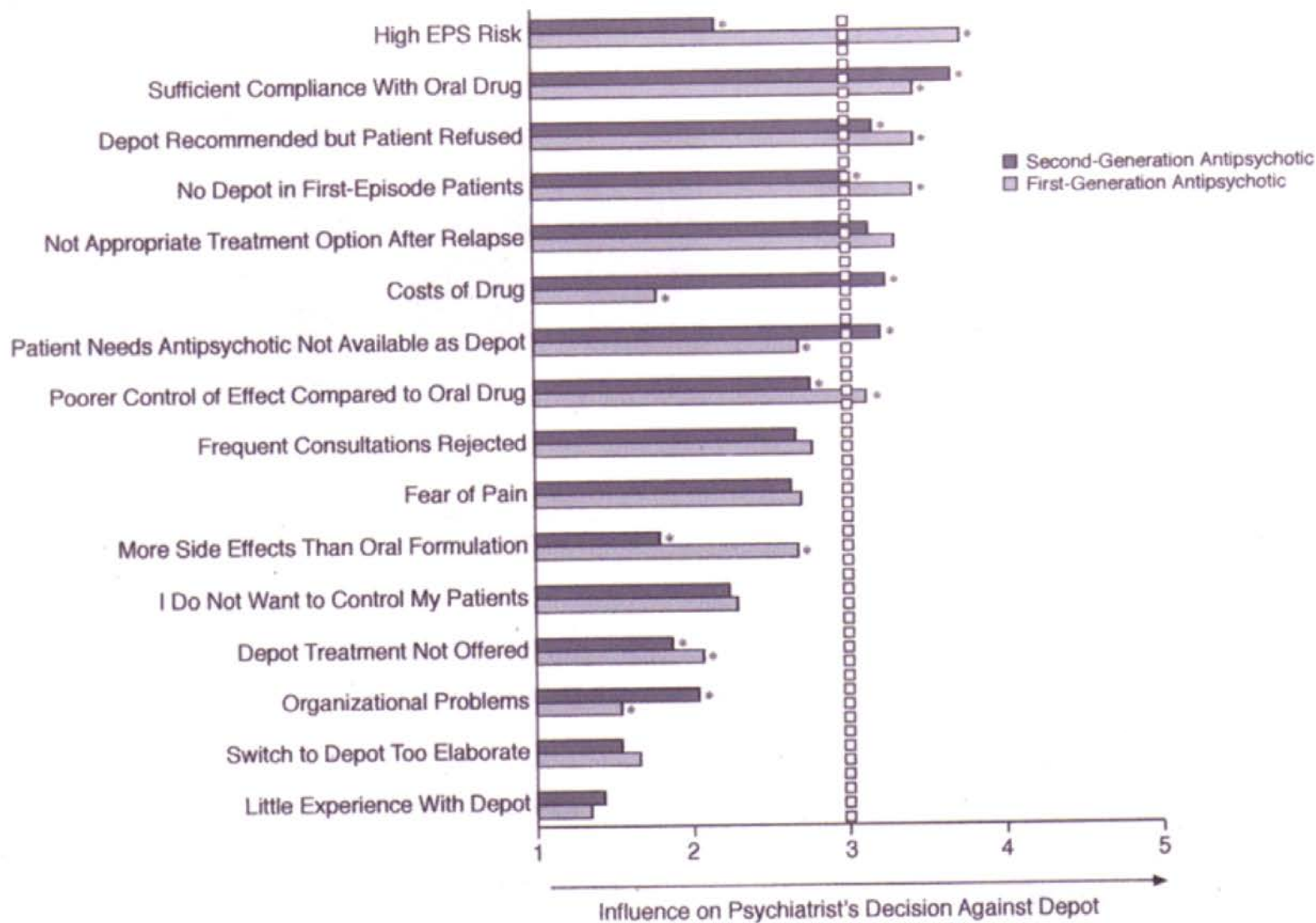


# Your experience in adherence

- What % of patients with schizophrenia would be non-adherent?
- What are the common reasons you encounter?
- How do you ensure adherence?
- How successful have you been?

The reasons they **do not prescribe** a first or second generation depot anti psychotic for their patients with Schizophrenia and Schizoaffective disorder

Figure 1. Mean Rating per Statement<sup>a-c</sup>



<sup>a</sup>Respondent Ns range from 224 to 237.

<sup>b</sup>Rating scale: very seldom = 1, seldom = 2, sometimes = 3, frequently = 4, very frequently = 5.

<sup>c</sup>Highlighted threshold of minimal mean rating score of 3 for potential impact on decision.

\*p < .001.

# 1. High risk EPS

- Risperidone Consta 0.6% to 0.7 % risk in long term study by Fleishhacker of > 700 pts.

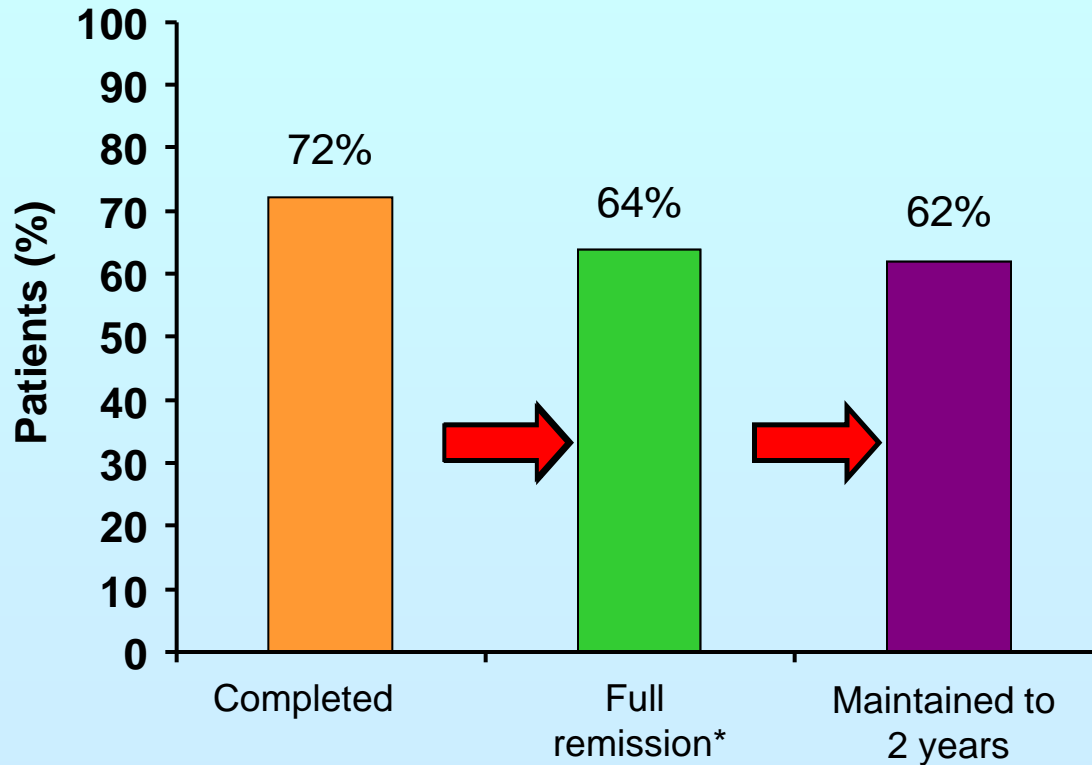
## 2. Sufficient compliance with oral meds.

- 25 % stop within 7 days
- 50 % stop within 1 year
- 80 % stop within 3 years

### **3. Depot recommended, but patients refused**

- Only 36% were ever offered

# 2-year outcomes with RLAI in early psychosis

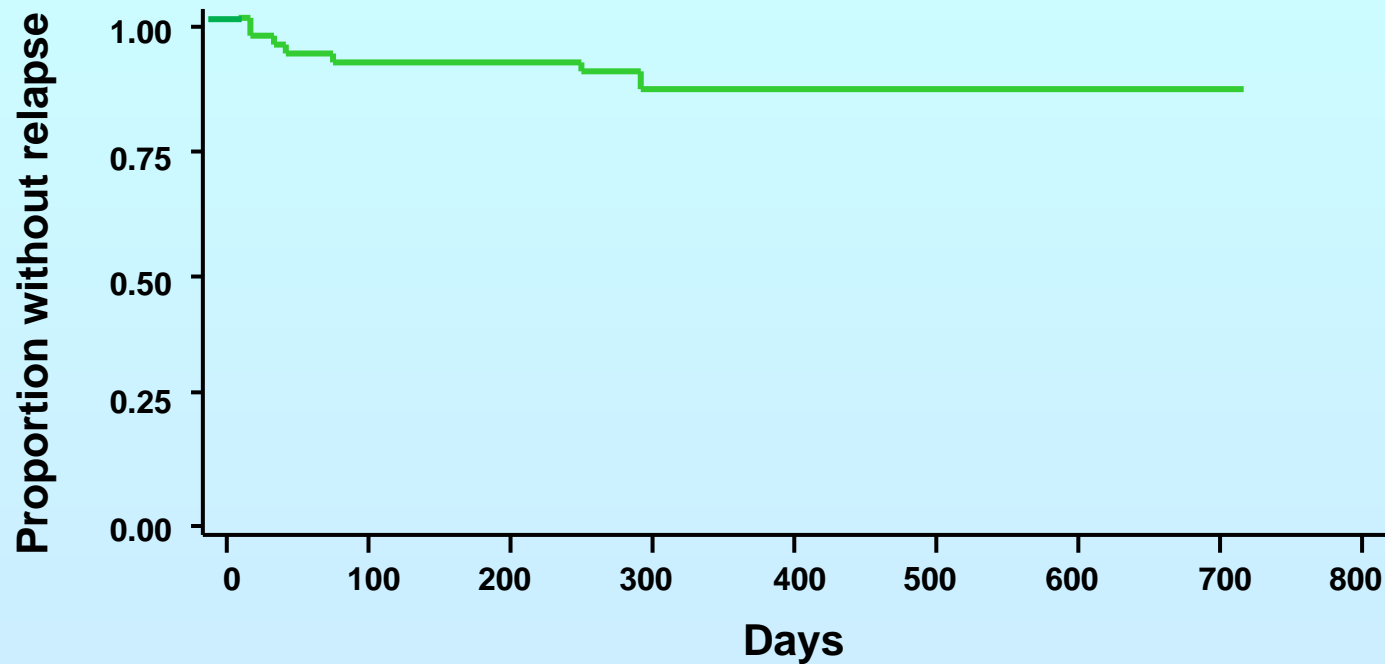


n=50

\*Remission according to Andreasen et al. Am J Psychiatry 2005;162:441-449

RLAI, risperidone long-acting injectable

# Relapse rates with RLAI over 2 years

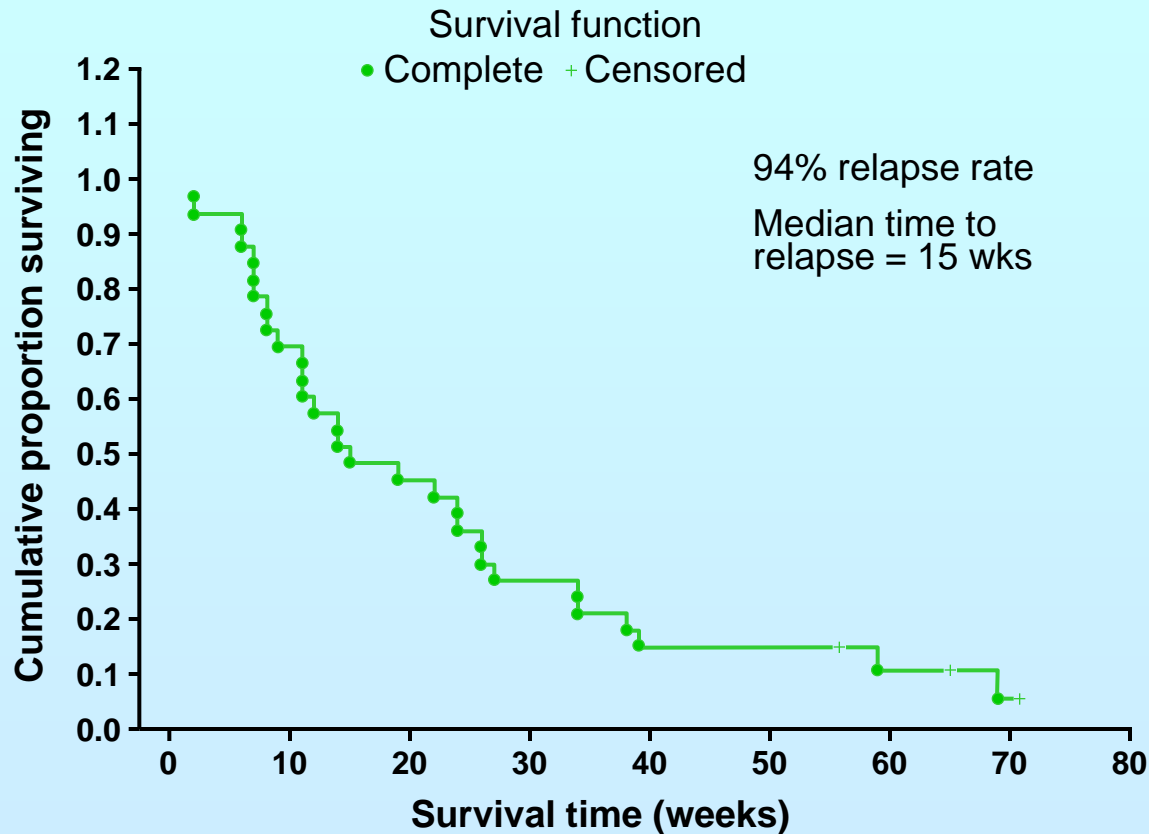


**Of the patients who responded, 4 relapsed  
No relapses in the second 12 months**

\*Relapse criteria defined according to Schooler et al. Am J Psychiatry 2005;162:947–953



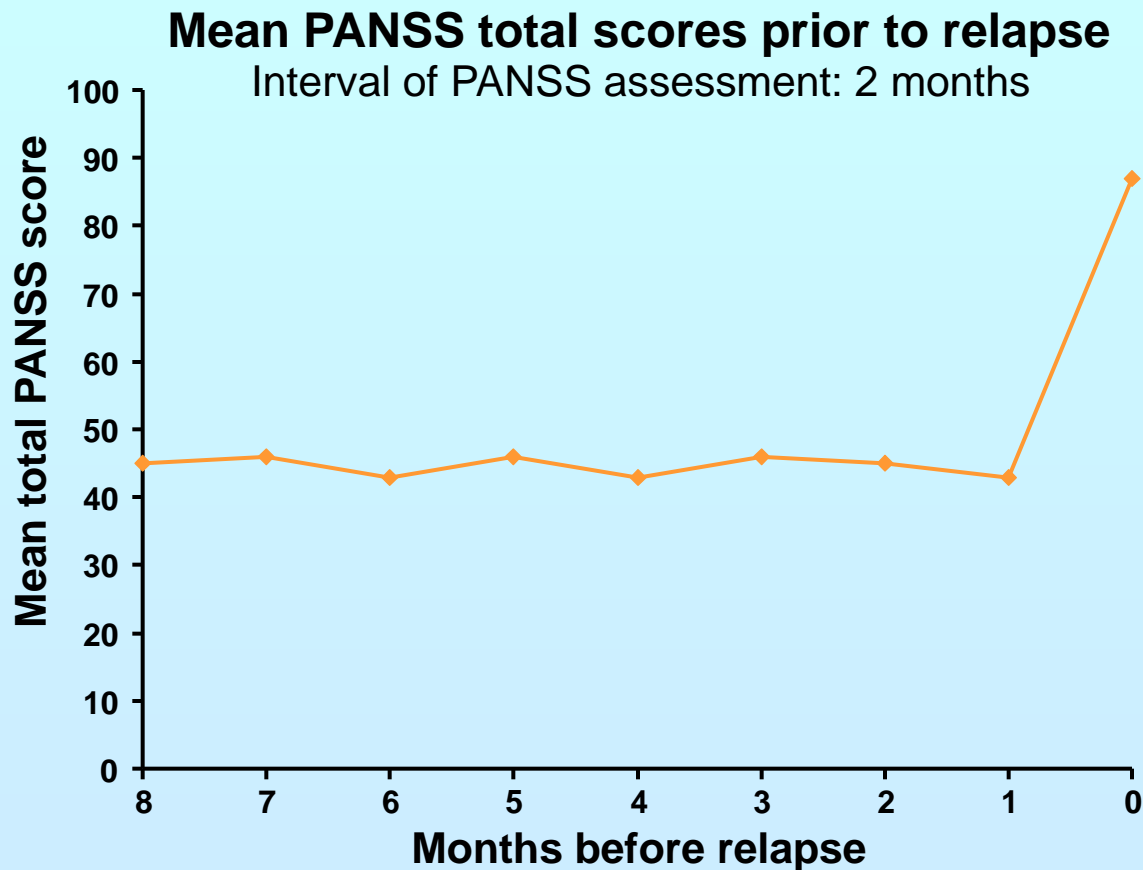
# Relapse after antipsychotic discontinuation in remitted subjects after 24-month continuous treatment



Patients with recent onset psychosis who achieved remission relapsed after stopping treatment with RLAI, therefore, treatment continuation should be considered

RLAI, risperidone long-acting injectable

# Relapses occur suddenly and without warning



n=26

**Mean PANSS score may not indicate whether a patient is at risk of relapse**

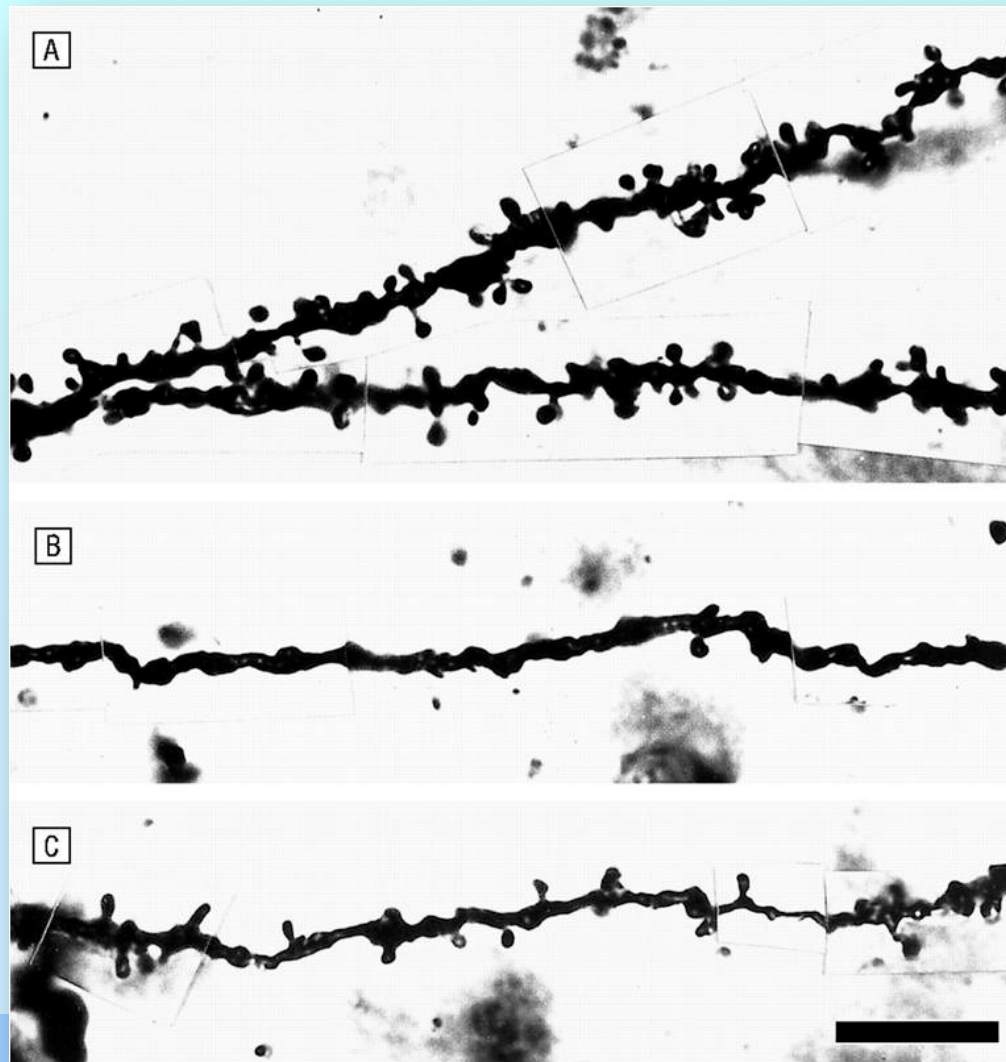
PANSS, Positive and Negative Syndrome Scale

**WHAT COMPONENTS OF  
BRAIN TISSUE ARE LOST  
IN SCHIZOPHRENIA  
DURING PSYCHOTIC  
RELAPSES??**

# Shrinkage of the Brain in Schizophrenia: It's in the Neuropil

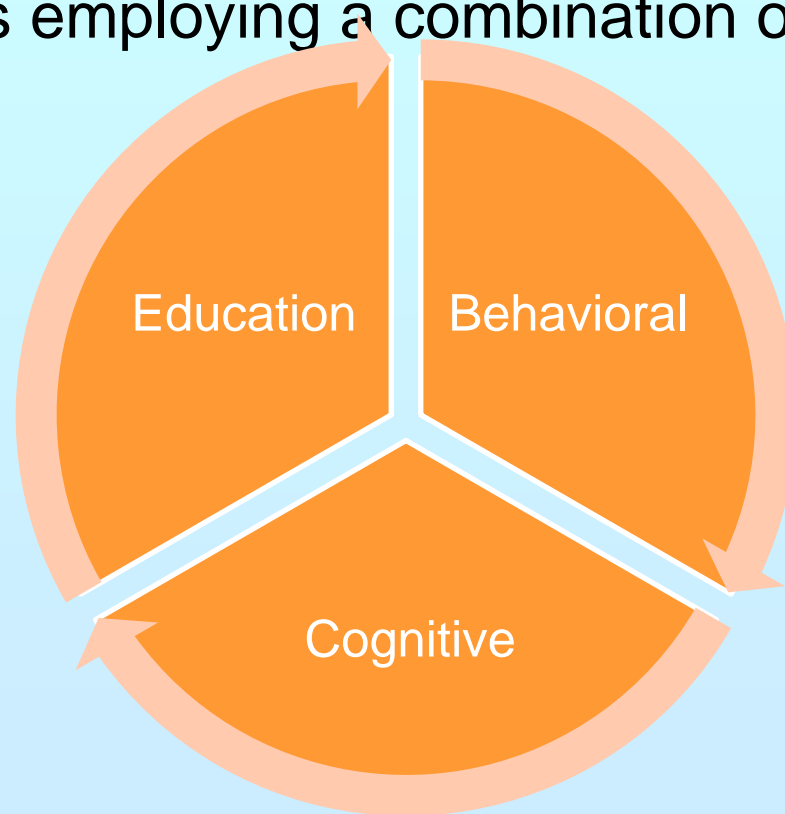
- ↓ dendrite length by 50%
- ↓ in the number and size of of dendritic spines
- ↓ in the size [contraction] of neurite extension
- ↓ in # of glial cells

**Brightfield photomicrographs illustrating Golgi-impregnated basilar dendrites and spines on dorsolateral prefrontal cortex layer 3 pyramidal neurons from normal control subject 390 (A) and 2 subjects with schizophrenia (subjects 410 [B] and 466 [C])**



# Combination of Strategies for effective outcome

- Greatest improvement in adherence was seen with interventions employing a combination of



# Psychosocial treatments promote functional recovery

## Social skills training

- Affects a number of dimensions important to recovery
- Broader effects on community functioning

## Cognitive behavioural therapy

- Effective at reducing severity of positive and negative symptoms
- Including some aspects of community functioning and QoL

## Cognitive remediation

- Integrates dimension-specific treatments to improve multiple targets (eg cognition and work)
- Consistent with a recovery model

## Social cognition training

- Individuals can improve performance on tasks measuring a range of social cognitive processes linked to successful social functioning (eg affect perception)

QoL, quality of life

# Psychosocial interventions

- The interventions effectively lower relapse rates, reduce expressed emotion and improve the outcome of patients with schizophrenia
- Psychosocial interventions that enhance medication compliance are of considerable public health importance, but no single approach is likely to work for all patients.
- According to Fenton (2000), new psychosocial interventions have been developed to target medication compliance, perhaps the single most important determinant of successful community tenure among patients with severe mental illness (SMI).



# Psycho education

- **Individual Psychoeducation**
- **Psychoeducation for parents and family**
- **Psychoeducation for caretakers**
  - The involvement of family members is crucial because studies consistently show that poor insight or lack of illness awareness is commonly associated with poor treatment adherence
  - Family psycho education program could be conducted on the ward, in the clinic or in the community, depending on need
- **Social Psychoeducation**

# Conclusions

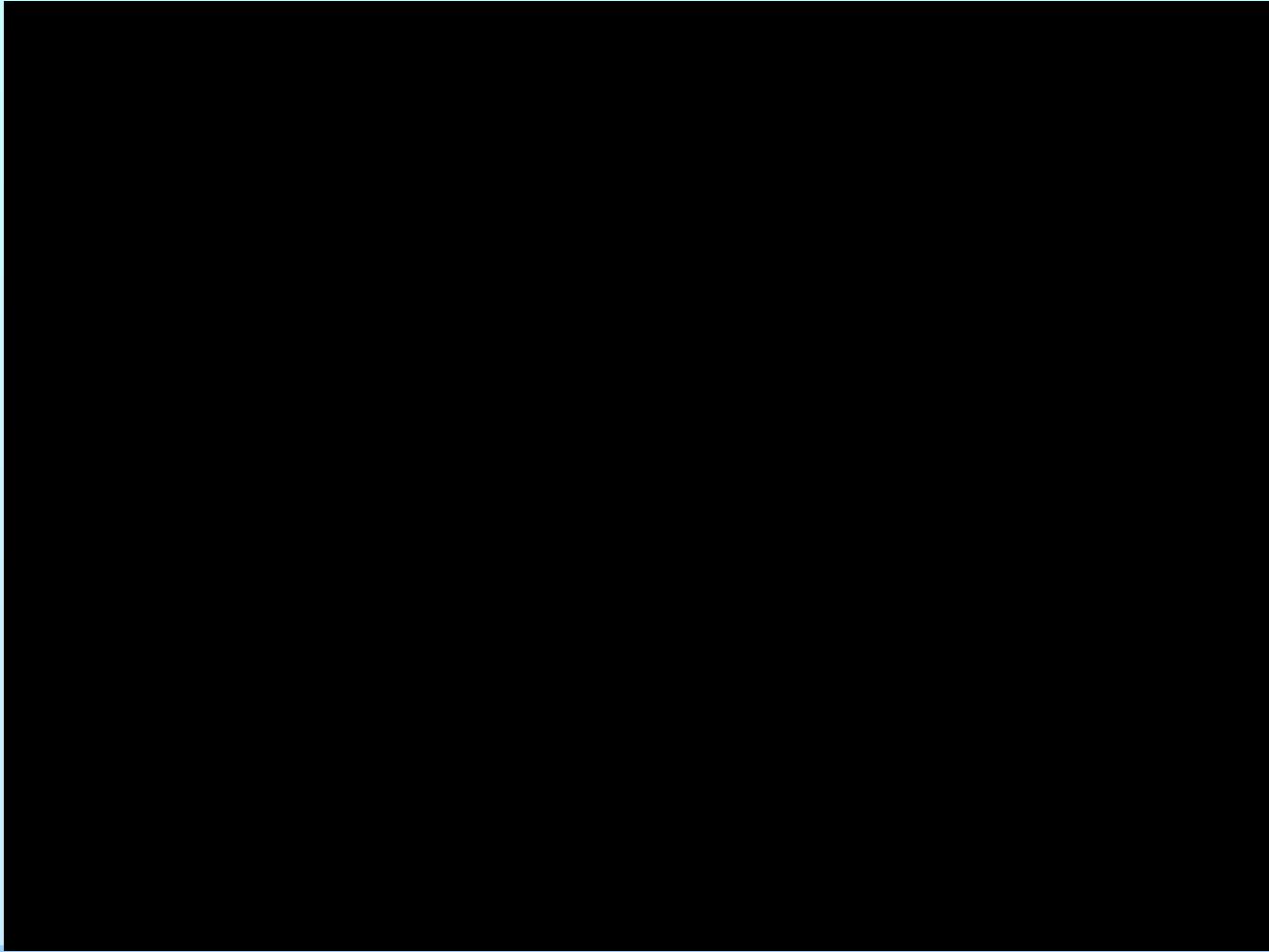
- Grey matter decreases progressively across the course of schizophrenia<sup>1</sup>
  - Progression of frontal tissue loss is related to the number of psychotic relapses<sup>2</sup>
- Poor adherence has been associated with a 10-fold increased risk of relapse<sup>3</sup>
  - Each successive relapse reduces the likelihood of full recovery to the baseline level of functioning<sup>4</sup>
- Appropriate intervention is important early in the disease course of schizophrenia, before the complications associated with chronicity become established<sup>4</sup>
- Psychiatrists seem to use injectable formulations of antipsychotics in a conservative way<sup>5</sup>
  - Most psychiatrists only introduce them after several episodes and for reasons of non-adherence to medication<sup>5</sup>
  - A recent consensus concluded that LAI antipsychotics could be used earlier in the course of the disease to promote adherence and prevent relapse<sup>4</sup>

LAI, long-acting injectable

# Key points

- Antipsychotic medication is critical in the prevention of relapse and rehospitalization.
- Rates of non-adherence are enormously high among patients taking antipsychotic medication.
- Long-acting formulations can be a very powerful strategy in helping to ensure that patients get the benefit of the medication they have been prescribed.
- Patients should be offered the option of LAI antipsychotic treatment and should understand the logistics and the potential benefits of the regimen.
- Communication strategies can be used to improve clinicians' dialogue with patients about LAI treatment

# A true story





**THANK YOU**

*Happy Dussehra*

*&*

*Deepavali*

*to you all*