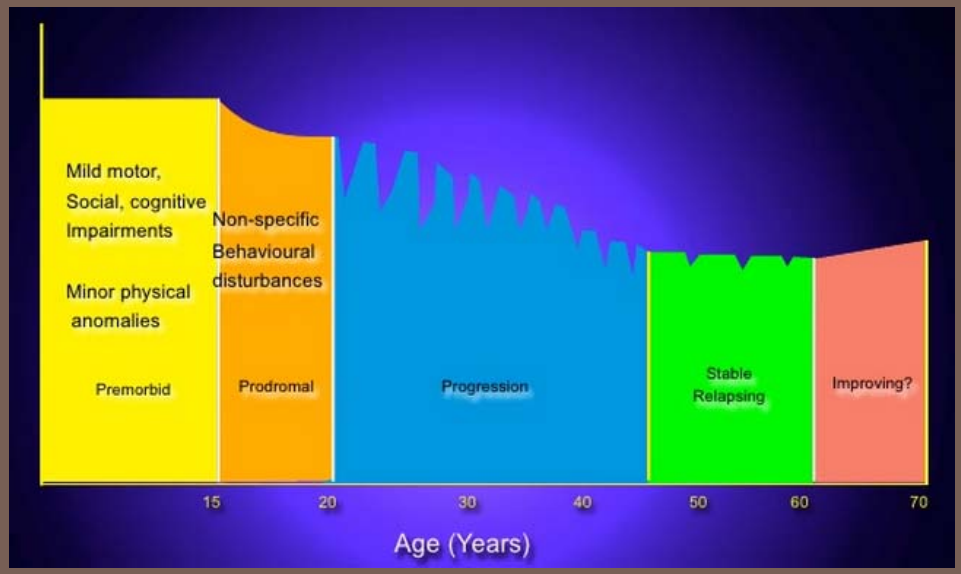


SCHIZOPHRENIA: ALL PHASES OF THE ILLNESS

Manote Lotrakul

Aug 2015

Outline

- Diagnostic criteria
- Clinical features
- Treatments

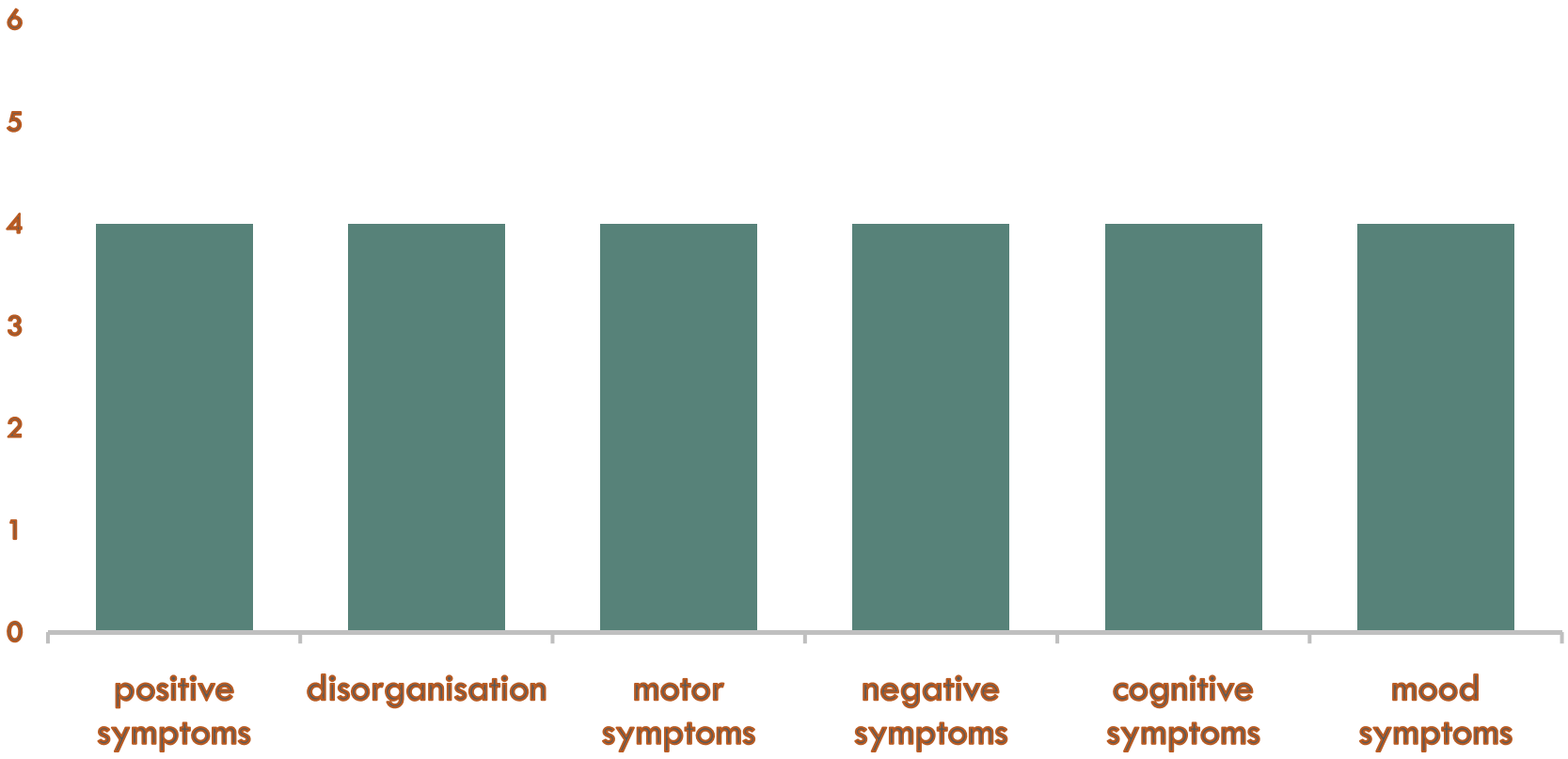
DSM-5 : Schizophrenia

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period
At least one of these must be (1), (2), or (3):
1. Delusions.
2. Hallucinations.
3. Disorganized speech
4. Grossly disorganized or catatonic behavior.
5. Negative symptoms

DSM IV Schizophrenia subtypes

- ~~Paranoid type~~
- ~~Disorganized type~~
- ~~Catatonic type~~
- ~~Undifferentiated type~~
- ~~Residual type~~

Schizophrenic disorders are characterized by a diverse set of signs and symptoms



Psychopathology differentially expressed across patients and through the course of the illness

Positive Symptoms

- Impaired reality testing and include delusions, hallucinations, and other reality distortions
- Persecutory delusions and delusions of reference are most frequent
- Threatening or accusatory voices speaking to the person are more common
- Dopaminergic mesolimbic hyperactivity underlies positive symptoms, which are most responsive to antipsychotic medications

Disorganization of thinking and behavior

- Formal thought disorder, eg.
  - Circumstantiality
  - Tangentiality
  - Incoherence

- Long-held beliefs that formal thought disorder is specific for schizophrenia and present in all persons with the disorder
- Neither of these claims has held up as loosening of association is observed in a minority of persons with schizophrenia and is not uncommon in mania

ความเชื่อ

ที่ข้าพเจ้าเชื่อ

ประยุกต์ ศรีเมือง

สงวนลิขสิทธิ์ 50.

เขาคงเชื่อว่าผมเป็นผู้รู้เขาจึงหายกังวลเมื่อธรรมชาติพร้อม ผมผลักละเอียดกว่าเขา ผมเชื่อว่าผมรู้มากกว่าคนอื่นเพราะมีโอกาสผลักละเอียดถี่ธรรมชาติอยากรู้ รู้เท่าใดก็ไม่ผลักแล้วแต่โอกาส ธรรมชาติพร้อมธรรมชาติพร้อมผลักละเอียดธรรมชาติพร้อมโอกาสมาก โอกาสพร้อมถี่อยากธรรมชาติพร้อมฉันใช่ไหม ผลักละเอียดไม่มาก โอกาสเรียนรู้ประสบการณ์พร้อม ธรรมชาติพร้อมโอกาสไม่มาก โอกาสผลักละเอียดมาก ผิวพรรณโอกาสไม่มาก ผิวพรรณโอกาสมาก หุ่นโอกาสไม่มาก หุ่นโอกาสมาก ไม่ให้โอกาสผมธรรมชาติผลักแล้วคุณจะธรรมชาติผลักได้อย่างไร

โอกาสผลักละเอียดห่าง โอกาสพร้อมกว่า โอกาสพร้อมไม่มาก หายกังวลใช่ไหมที่มีโอกาสร่วมพร้อมผู้รู้ ผิวพรรณโอกาสมาก หุ่นโอกาสมาก ประสบการณ์พร้อมมาก ประสบการณ์พร้อมไม่มาก อยากพร้อมละเอียดให้โอกาสเรียนรู้ธรรมชาติพร้อมละเอียดห่าง

หายกังวลที่รู้มากกว่าคนอื่น ไม่กังวลใช่ไหมที่พร้อมคนรู้มาก รู้สึกกังวลที่พร้อมคนผลักหย่าบ ฉันเป็นผู้รู้มาก รู้สึกกังวลที่พร้อมคนรู้ไม่มาก โอกาสประสบการณ์ผลักถี่ ผมเป็นคนรู้มาก ท่านเป็นคนรู้มากแล้ว (บุคคลที่สูงกว่าโสดาบัน) ธรรมชาติอยากพร้อม ฉันเชื่อว่าฉันผู้รู้มาก

Motor symptoms and catatonia

- **Catatonic syndrome:** stupor or excitement, echolalia, echopraxia, automatic obedience, waxy flexibility, and extreme negativism
- Infrequent as presentations of schizophrenia in recent decades
- Catatonia may not be part of the core psychopathology of schizophrenia

Negative symptoms

- Involve a blunting or loss of a range of affective and conative functions
  - Impairments in affective experience and expression
  - Alogia (poverty of speech)
  - Anhedonia (inability to experience pleasure)
  - Avolition (lack of initiative),
  - Apathy (lack of interest)
  - Reduced social drive
- Primary and secondary negative symptoms (neuroleptics, depression)

Cognitive symptoms

- Highly prevalent in patients with schizophrenia, although to varying degrees
- Modest improvements in the course of antipsychotic treatment
- A similar pattern of lesser severity is present in non-psychotic relatives
- A strong predictor of **poor social and vocational outcome** with impairments in social cognition being particularly potent predictors

Neurocognitive function in schizophrenia

- After the onset of illness cognitive function is relatively stable overtime
- In a review of 15 studies, follow-up ranged from 1-15 years, patients' cognitive deficit remain relatively stable, with no evidence for either decline or improvement

Social Cognition

- Ability to perceive and understand relevant social cues:
  - Facial expression & voice tone
  - Hints and indirect suggestions
  - Social/cultural norms (e.g., difference between a co-worker and friend)
  - Rules of personal disclosure (i.e., gradually increase level of disclosure, matched to other person's level)

When do the cognitive impairment emerge?

- Precursors to the cognitive deficits are evident relatively early
- These develop gradually and that they are found in corresponding form and approximately the same degree in the prodromal phase, as in remission
- The psychotic symptoms exacerbate the neurocognitive deficits somewhat during the acute phase

Clinical implications of neuropsychological deficits

- Cognitive deficits underlie adaptive behavior deficits which medications cannot improve
- Improvement in cognition may improve social skills, work skills, etc;

Etiology of Schizophrenia

Contemporary models of schizophrenia

- Schizoprenia is a neurocognitive disorder, with the various signs and symptoms reflecting the downstream effects of a more fundamental cognitive deficit

- Schizoprenias is neurodevelopmental disorder

Neurodevelopmental model

- Supposes in schizophrenia the presence of “silent lesion” in the brain, mostly in the parts, important for the development of integration (frontal, parietal and temporal)

- Caused by different factors (genetic, inborn, infection, trauma...) during very early development of the brain in prenatal or early postnatal period of life

Neurodevelopmental Model

- It does not interfere too much with the basic brain functioning in early years

- Expresses itself in the time, when the subject is stressed by demands of growing needs for integration, during formative years in adolescence and young adulthood

The mechanisms and phenotype of schizophrenia

- Multiple cumulative hits
- May affect brain development and connectivity at multiple stages, with young adulthood being most critical
- When sufficient hits accumulate, the phenotype appears
- The phenotype is defined by a impairment in some basic cognitive process

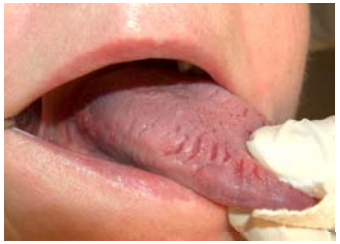
Summary of evidence for the neurodevelopmental hypothesis of schizophrenia

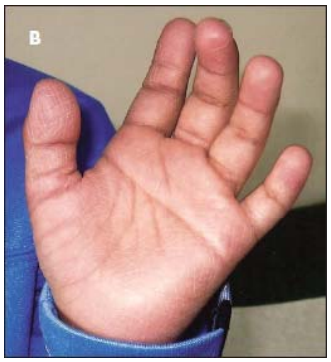
Prenatal or perinatal risk factors		
Obstetric complications	↑	++
Low birthweight	↑	++
In-utero infection	↑	++
Developmental trajectory		
Motor delay	↑	++
Social alterations	↑	++
Cognitive impairments	↑	++
Brain structural alterations		
Ventricular enlargement	↑	++
Grey matter reductions	↑	++
White matter disruption	↑	+

++=found in meta-analysis. += found in well controlled studies.

Evidence for neurodevelopmental encephalopathy

- **Increased frequency of minor physical anomalies**
  - **enlarged ventricles**
  - **very fine hair**
  - **covered epicanthus**
  - **low seated ears**
  - **furrowed tongue**
  - **curved 5th finger**
  - **single palmar crease**
  - **webbed toes**
  - **3rd toe longer than 2nd**

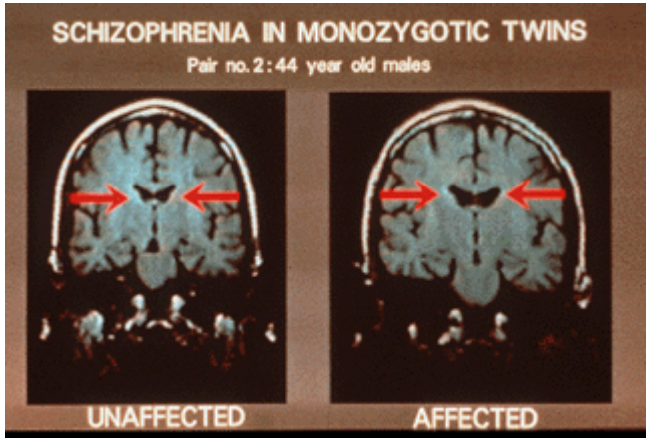


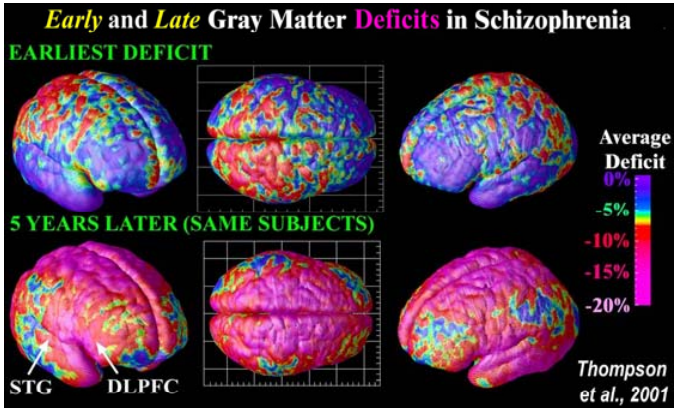


Schizophrenia is associated with structural changes in the brain

Gray matter volume loss

- Larger ventricles than healthy controls
  - lateral ventricle: 80% of the studies,
  - third ventricle: 73% of the studies
- Reduced frontal lobes volume: 59% of the studies
- Reduction in the volume of the temporal lobes- the medial temporal lobe : 74% of the study

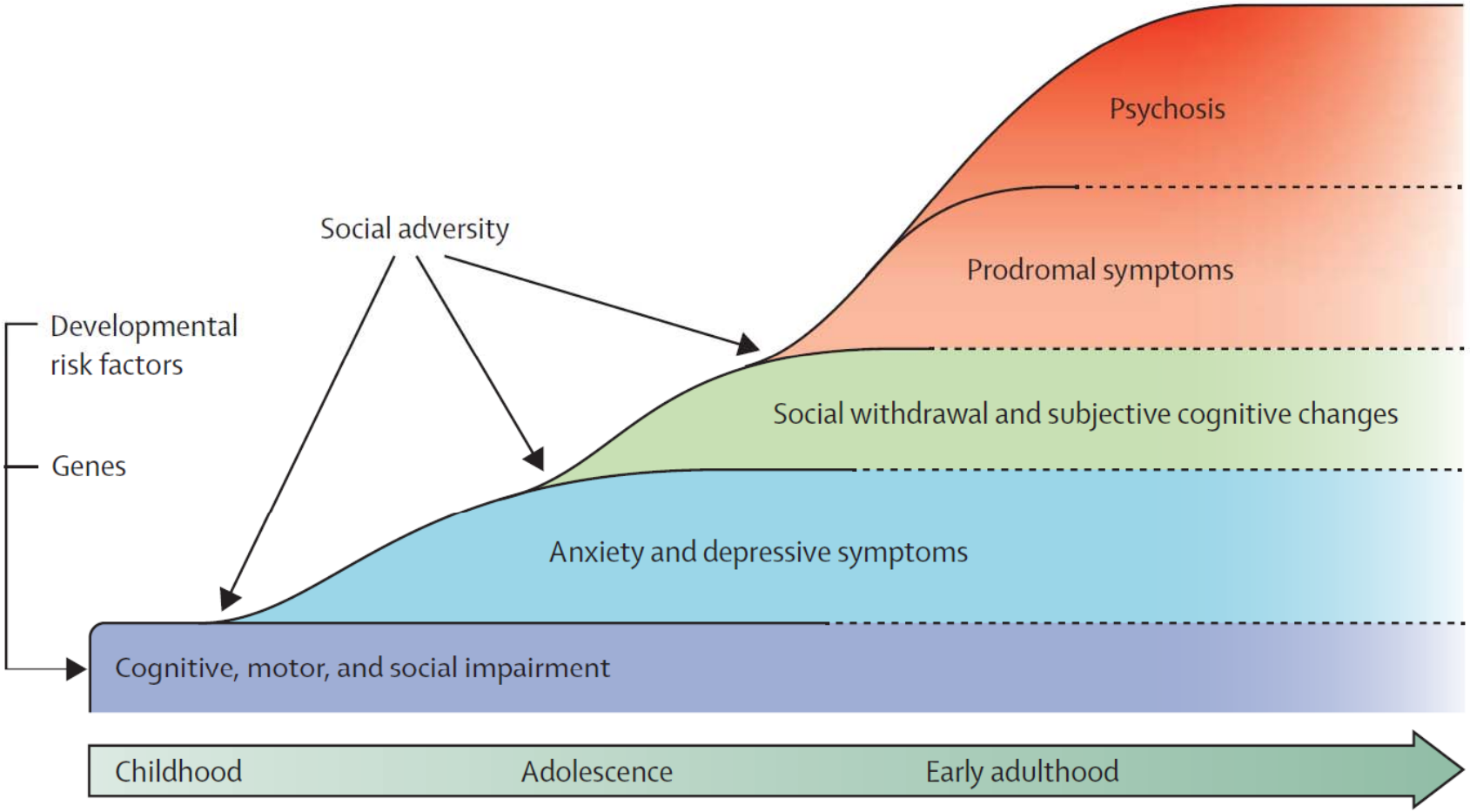




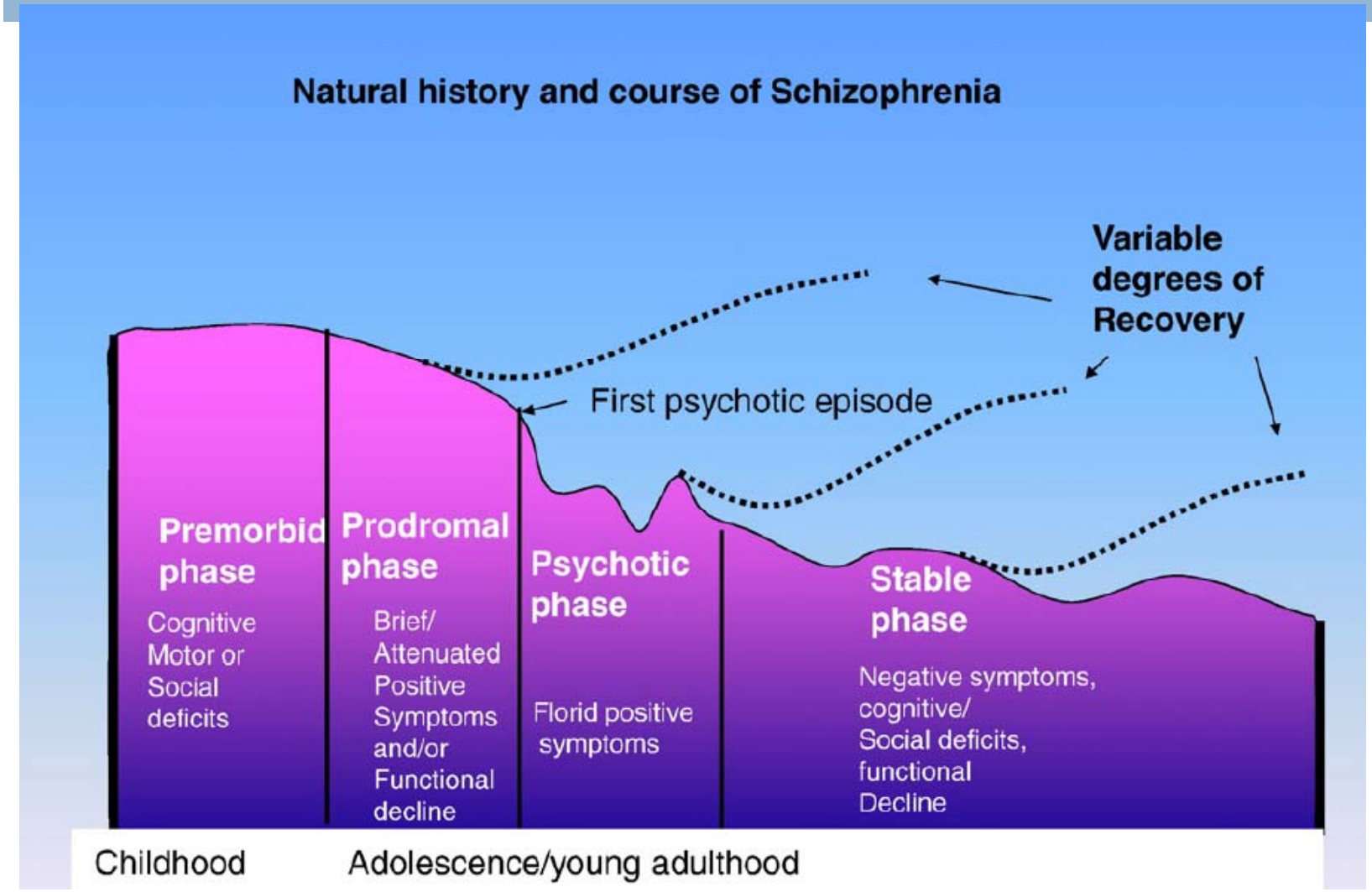
What do we know about structural changes in the brain of patients with schizophrenia

- Progressive volume loss seems most pronounced in the frontal and temporal areas
- Progressive brain tissue loss in schizophrenia is, during a 20-year time period, found to be approximately twice that found in healthy people due to normal ageing
- Changes in the brain take place before the clinical symptoms emerge

The trajectory to schizophrenia showing the evolution of symptoms



Onset and Course



Prodromal phase

- Prodromal or at-risk or ultra high-risk states for psychosis
- Defined by duration of time, starting with the onset of decline in the baseline level of functioning and ending at the time when the criteria for a schizophrenia spectrum diagnosis are met
- The prodrome may last from months to years, with a mean of ~5 years

Prodromal phase

- **“at-risk mental state” (ARMS):**
  - Decline in cognitive and overall function, increased social isolation, difficulties with attention, decreased personal hygiene, and a change in emotions with some flattening of affect
  - Attenuated positive symptoms:(APS): low-grade positive psychotic symptoms
  - Brief limited intermittent psychotic symptoms (BLIPS): brief bursts of frank psychotic symptoms
- Individuals commonly exhibit more serious APS that remain subpsychotic in terms of frequency, duration and intensity (skepticism)

Prodromal phase

Problem

- Prodrome can only be diagnosed in retrospect

- Transition risk for at-risk mental state ARMS not 100%
  - 18% after 6 months
  - 22% after 1 year
  - 29% after 2 years
  - 36% after 3 years

Fusar-Poli P. Arch Gen Psychiatry 2012;69:220.

The initial psychotic episode

- The onset typically occurs between the ages of 15 to 45 years with 5–7 years later in females
- Individuals with an early age of onset (< 20 years) and a very early-onset (< 13 years) manifest worse premorbid function, more severe negative and disorganization symptoms, greater cognitive deficits, and inferior overall prognosis

Salience dysregulation

- Normal dopamine transmission has a role in predicting novel rewards and in marking and responding to motivationally salient stimuli

Salience dysregulation and the dopaminergic system

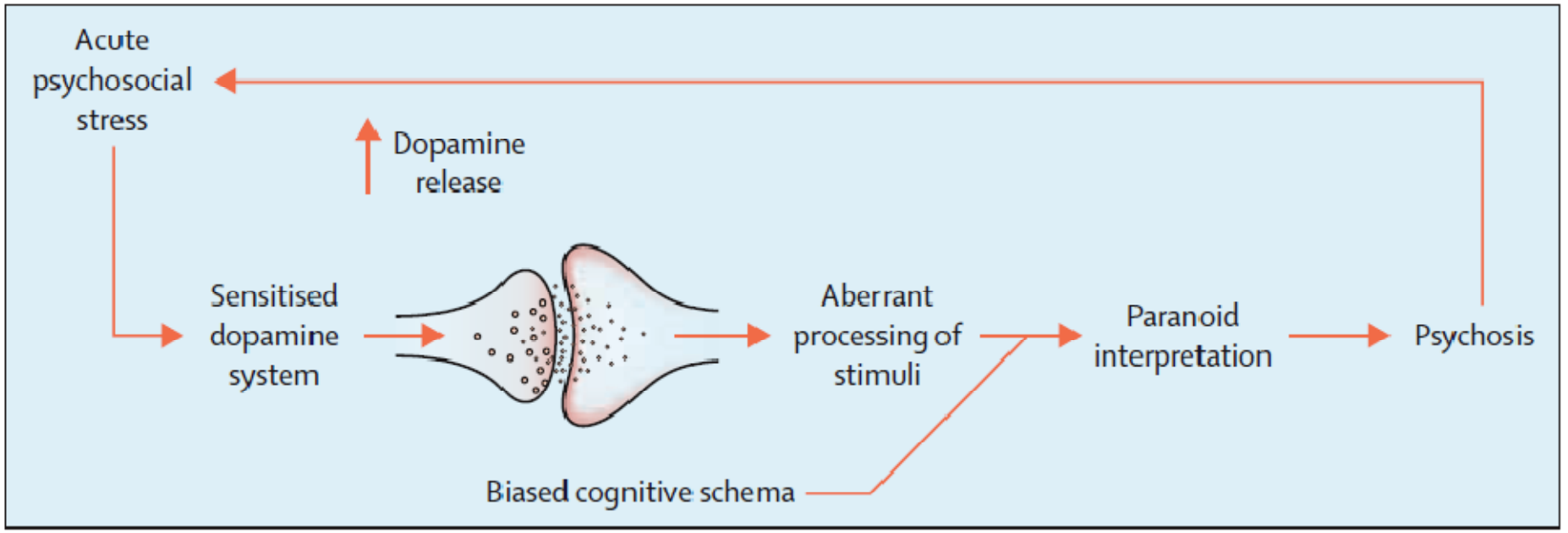
- **Salience** : a high-order mental process that allows certain objects to attract the spotlight, thus being incorporated into thoughts and behaviors (relevance assignment)
- The abnormal firing of dopamine neurons and the abnormal release of dopamine leads to an aberrant assignment of salience to innocuous stimuli

Salience	Type	Definition	Ex. of adaptive salience	Ex. of aberrant salience
	Visual (perceptive)	Automatic and/or subliminal process of bottom-up visual discrimination by which certain stimuli stand out in the perceptive field and attract attention	A human form is more ''salient'' (relevant) than an amorphous form. The colour red is more ''salient'' than grey	Selective attention towards the pen that the person speaking has in his pocket
	Emotional	Process of categorising reality affectively, by which the most memorable stimuli, which direct our attention and favour certain behavioural responses, are designated as such on the basis of experience and learning	A gun is more ''salient'' than a pencil. A familiar song is more ''salient'' than a background noise	The pen is a potential threat (it can record, could be a weapon) and produces a fearful reaction
	Social	Application of the previous process to social cognition, that is to say: the process by which importance is given to certain social cues, inferring certain mental states from these cues (emotions, ideas or intentions)	Pointing or winking gestures are more ''salient'' than an insignificant movement	Speaker's casual gesture (touching the pen) transmits vital information: threat or death

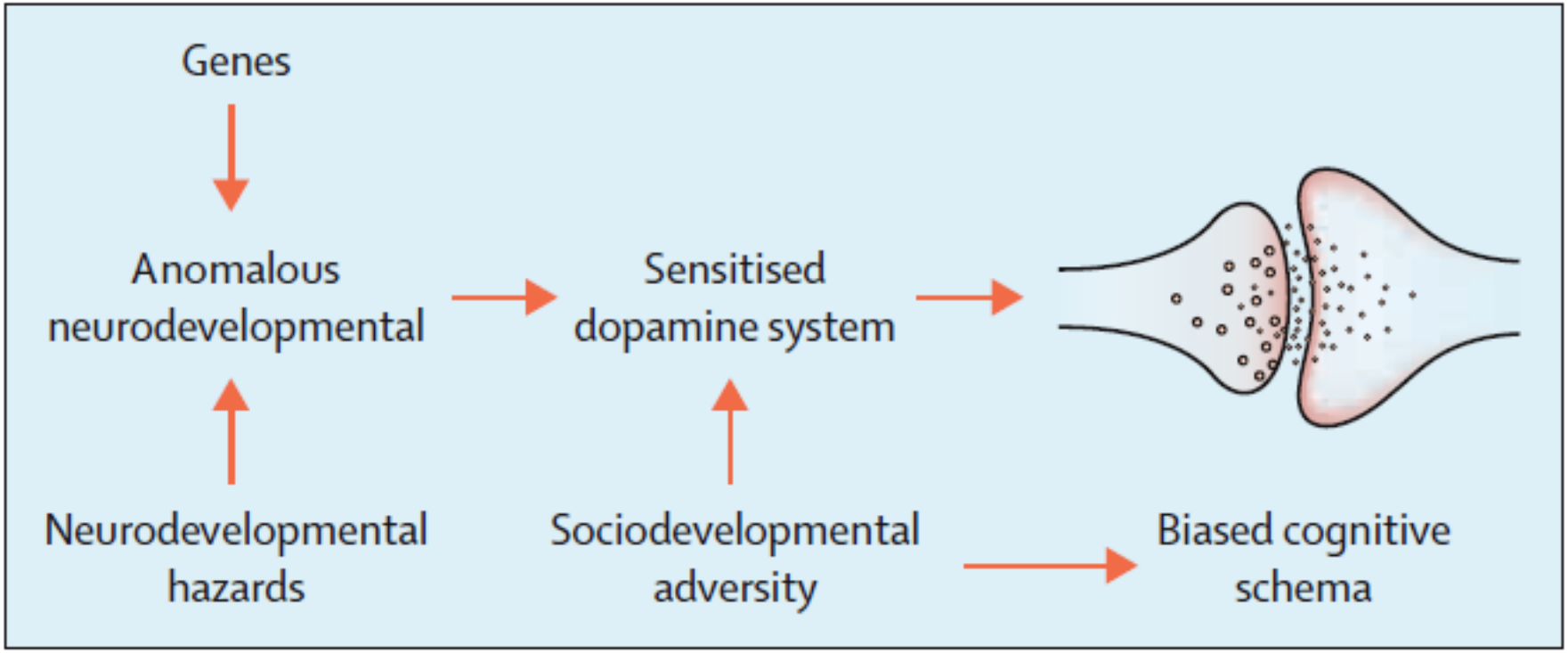
Salience dysregulation and the dopaminergic system

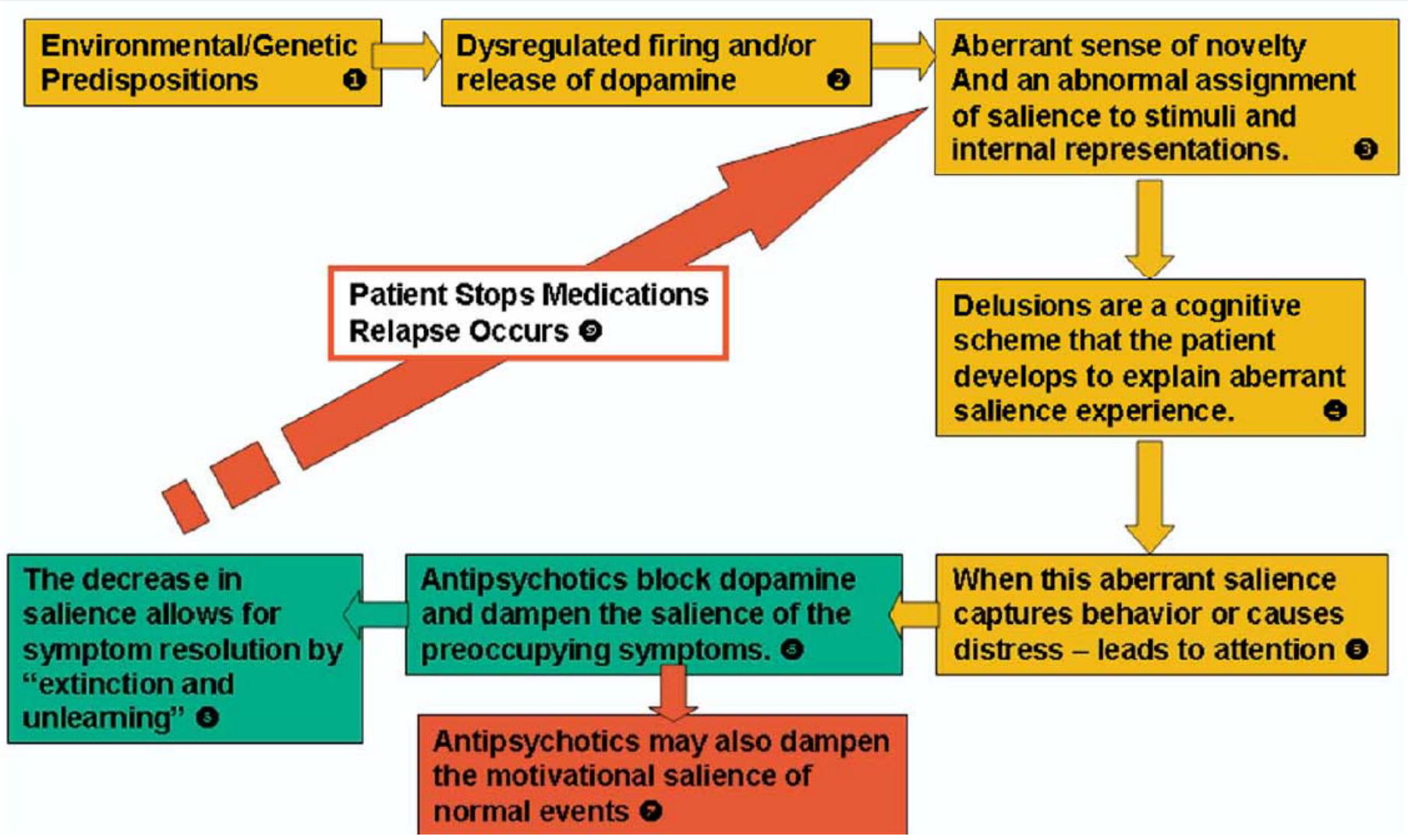
- The abnormal firing of dopamine neurons and the abnormal release of dopamine leads to an aberrant assignment of salience to innocuous stimuli

Model of the onset of psychosis showing the interaction between acute stress, dopamine dysfunction, and biased cognitive schema



The effect of neurodevelopmental risk factors for psychosis on the dopamine system and cognitive schema

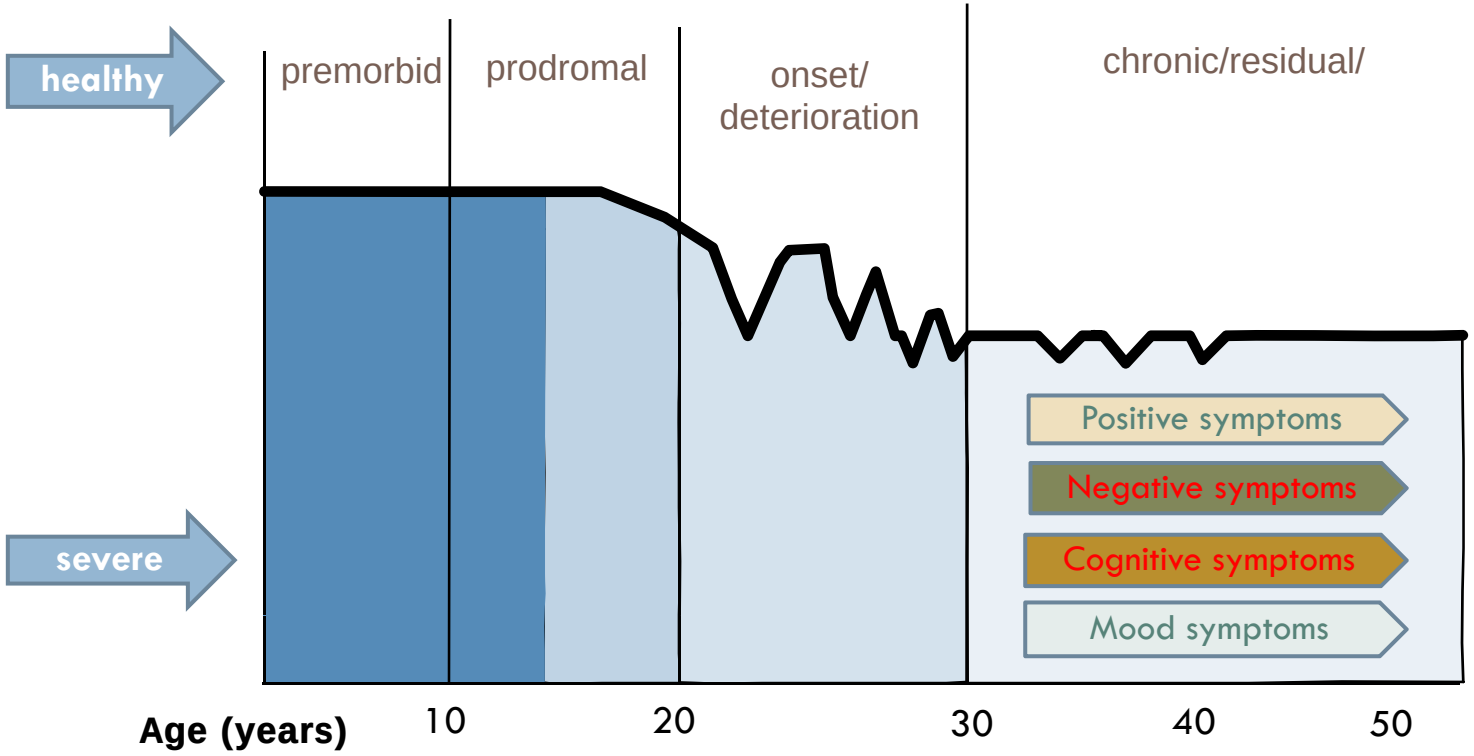



Environmental/Genetic Predispositions 1
Dysregulated firing and/or release of dopamine 2
Aberrant sense of novelty And an abnormal assignment of salience to stimuli and internal representations. 3
Delusions are a cognitive scheme that the patient develops to explain aberrant salience experience. 4
When this aberrant salience captures behavior or causes distress – leads to attention 5
Antipsychotics block dopamine and dampen the salience of the preoccupying symptoms. 6
The decrease in salience allows for symptom resolution by "extinction and unlearning" 8
Antipsychotics may also dampen the motivational salience of normal events 7
Patient Stops Medications Relapse Occurs 9

Salience dysregulation

- The disappearance of delusions and hallucinations is a dynamic process wherein antipsychotics block dopamine and thereby lessen the salience of the concerns, the patient works through their symptoms toward a psychological resolution
- Only with time, and only in some, via the mediation of new learning and plasticity, is there a complete resolution of symptoms

Chronicity and recovery



Chronicity and recovery

- Decline in function is most pronounced in the first 3-5 years after a first episode of psychosis
- The extent of deterioration appears to be related, in part, to the duration of untreated psychosis
- The best predictor of poorer functioning in the long term was poor functioning in the first 3 years post-diagnosis

Duration of Untreated Psychosis (DUP)

- Prolonged DUP
  - Poorer response
  - Worse outcome
- Social toxicity
  - Stigmatization
  - Loss of job
  - Interrupted schooling
  - Loss of friendships
  - Loss of family support
  - Criminal record
  - Accidental death
  - Accidental homicide

Chronicity and recovery

- Following this, a plateau is frequently reached, characterized by either remission or chronicity

- Following this, the illness stabilizes and, although there may be subsequent exacerbations, there is generally no further consistent illness-driven decline in functioning and increase in residual symptoms.

Phase-specific treatment

- **Prodrome**
- **Acute phase**
  - Lost contact with reality
- **Stabilization phase**
  - patient is recovering functionality and adjusting to an increasingly more demanding environment
- **Stable phase (or maintenance phase)**
  - Stable but the medication is in process

Acute phase

Treatment goals

- Prevent harm to self or others
- Control disturbed behavior
- Reduce severity of psychosis
- Develop an alliance with the patient and family
- Formulate short- and long-term treatment plans

Indications for hospitalization

- Pose a serious threat of harm to self or others
- Unable to care for self, needing constant supervision
- General medical or psychiatric problems that make outpatient treatment unsafe or ineffective

Environmental Adaptations

- Establish rapport with the patient, minimize the use of multiple interviewers whenever possible.
- If possible, perform the assessment in a structured, simple environment with minimal extraneous noise and stimuli.
  - Employ clear, simple communication.
  - Employ restraints only when necessary to prevent aggressive behavior toward self and others.
  - With acutely agitated patients, assessments should be conducted with the interviewer closest to the door (for interviewer safety).

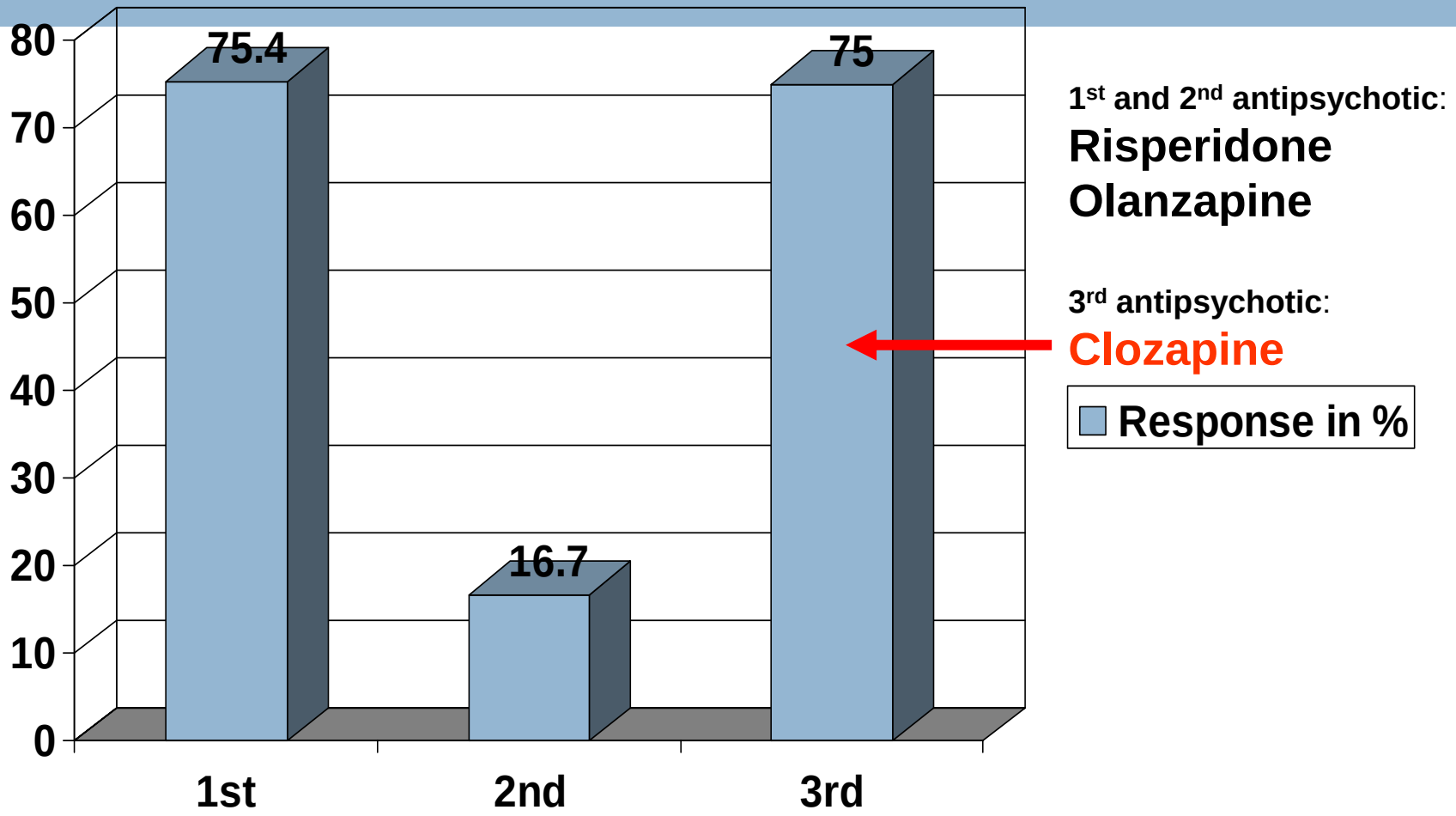
First-episode schizophrenia

- Antipsychotics should be used with care due to the higher risk of EPS
- The first-line use of both first-generation (FGA) and second generation (SGA) antipsychotic medication at the lower end of the standard dose range
- Benzodiazepines may be used to relieve distress, insomnia and behavioral disturbances secondary to psychosis while antipsychotic medication takes effect

First-episode schizophrenia

- FGAs and SGAs are effective in reducing psychotic symptoms and in general no differences between drugs could be detected
- No differences in efficacy among the SGAs, but clozapine was superior to all other antipsychotic agents in treatment-resistant schizophrenia
- Clozapine, olanzapine and risperidone were better than FGAs with medium to small effect sizes

Early use of clozapine



Agid O et al. J Clin Psychiatry 2011;72:1439.

ECT in acute phase

- ECT in combination with antipsychotic medications may be considered for patients with severe psychotic symptoms that have not responded to treatment with antipsychotic agents.
- The greatest therapeutic benefits appear to occur when ECT is administered concomitantly with antipsychotic medications.
- A trial of clozapine will generally be indicated before acute treatment with ECT.
- ECT may also be beneficial if comorbid depressive symptoms are resistant to treat or if features such as suicidal ideation and behaviors.

Stabilization phase

Treatment goals

- Sustain symptom remission or control,
- Reduce the stress on patient
- Decrease the probability of relapse
- Enhance adaptation to life in the community
- Continually reduce symptoms and consolidate their remission
- Promote the recovery process

Stabilization phase: Psychosocial interventions

- Psychotherapeutic interventions remain supportive but may be less structured and directive than in the acute phase
- Actively involve family members in the treatment process
- Education about the course and outcome of the illness and about factors that influence the course and outcome
- Self-management (e.g., how to cope with side effects) and symptom self-management (e.g., how to identify early warning signs of relapse)

Stable phase: Antipsychotic medications

- Taking the same medication and dose for the next 6 months
- Premature lowering of dose or discontinuation of medication during this phase may lead to a relatively rapid relapse

Stable phase: Antipsychotic medications

- After in remission antipsychotics should be maintained for a minimum of 2 years

- Clozapine for treatment-resistant schizophrenia

Psychological therapies

- Family intervention :
  - communication skills
  - problem solving
  - psychoeducation

- Should be offered to all individuals especially where there are persistent symptoms or a high risk of relapse

- 10 sessions over a 3-month period should be considered the minimum effective dose.

Stable phase

Treatment goals

- Maintain symptom remission or management.
- Preserve or improve functionality and quality of life.
- Carry out continued follow-up of treatment side effects.
- Monitoring and improving medication adherence

Stable phase: Antipsychotic medications

- Without maintenance treatment, 60%–70% of patients relapse within 1 year, and almost 90% relapse within 2 years.
- Antipsychotic drugs used at a dose that minimizes side effects but is still in the effective range of a particular drug
- **Indefinite maintenance medication** is recommended for patients who have had multiple prior episodes or two episodes within 5 years
- Early intervention using supportive therapeutic techniques and increasing medication as indicated can be very helpful in reducing the likelihood of relapse and hospitalization

Multiple episode schizophrenia (relapse)

- The most common contributors are antipsychotic medication non-adherence, substance use and stressful life events
- Antipsychotics should be guided by the patient's previous experience of symptom response and side effects, the presence of comorbid medical conditions, and potential interactions with other prescribed medications
- The dose may be titrated as quickly as tolerated to the target therapeutic dose

Stable phase: Psychosocial interventions

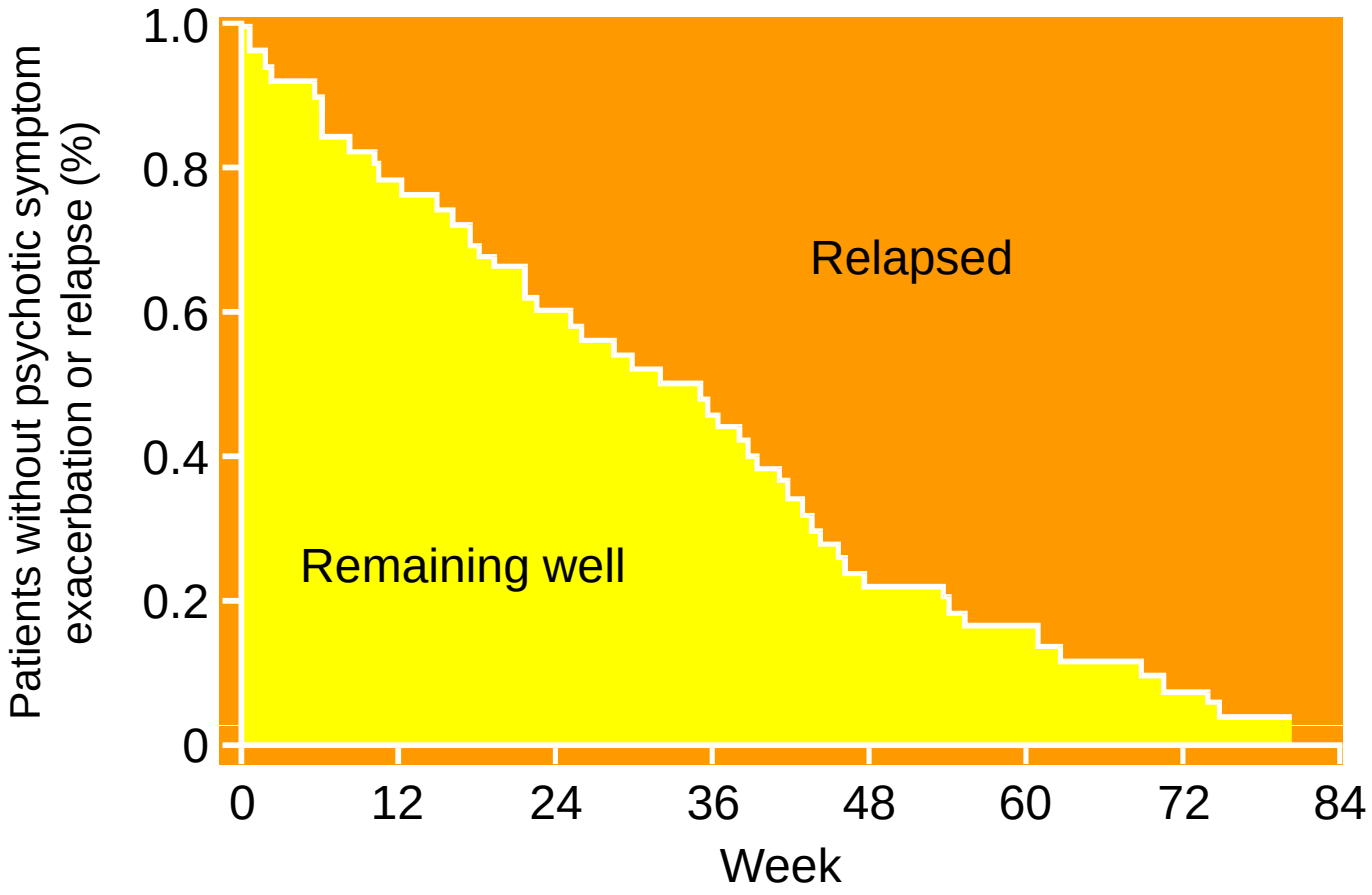
- Supportive psychotherapy for problem solving is recommended given that it significantly reduces relapses and boosts social and occupational function
- Re-education in terms of basic daily life skills, social skills training
- Cognitive rehabilitation
- provide occupational support to patients who are moderately or mildly disabled
- Provide education aimed at the patient and his/her family to increase knowledge on the first signs of relapse.

Psychological therapies

- A Individual CBT should be offered to all individuals diagnosed with schizophrenia whose symptoms have not adequately responded to antipsychotic medication and where persisting symptoms and/or depression are being experienced

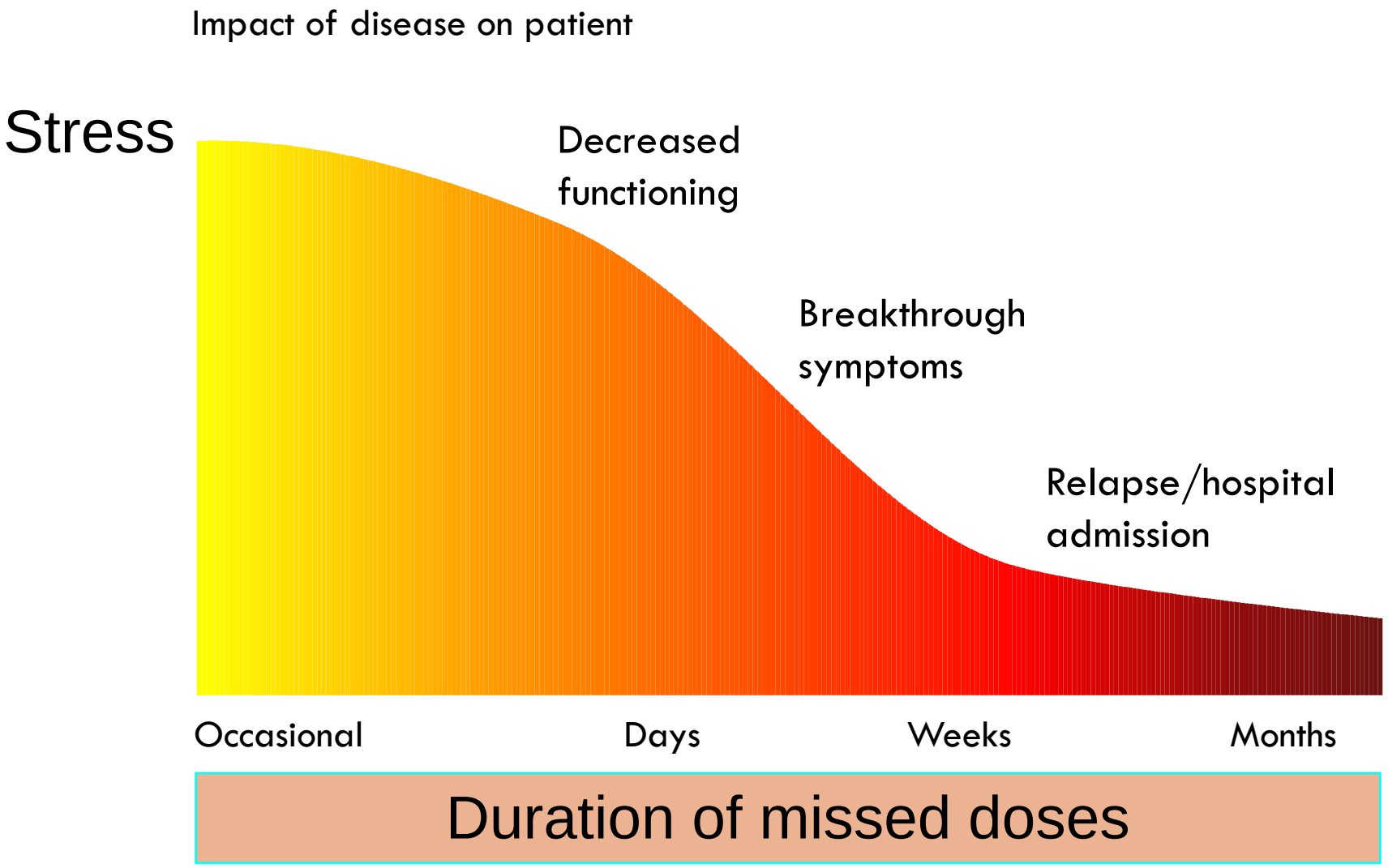
- CBTp can be started during the initial phase, the acute phase or recovery phase including inpatient settings

Stopping medication: relapse is almost inevitable

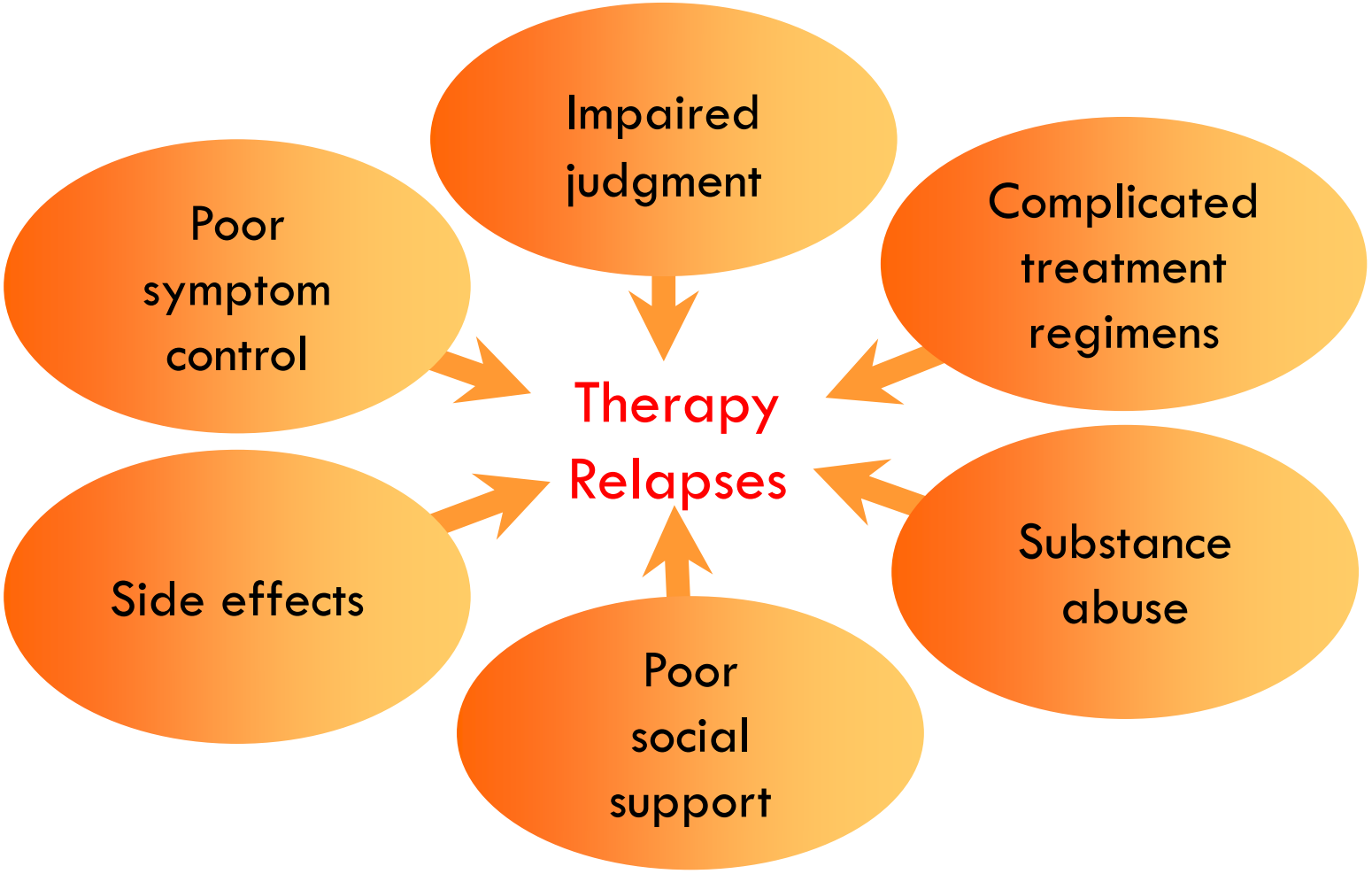


Gitlin M, et al. Am J Psychiatry 2001;158:1835–42

What is the impact of partial compliance?



Why do schizophrenia patients stop taking medication?



Conclusions

- The disorder is characterized by an admixture of positive, negative, cognitive, and mood symptoms
- The severity of different symptoms varies across patients and through the course of the illness
- Interventions should be adjusted to the stage of the illness
- Treatment adherence is one of the most important issues in illness management