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Introduction to Schizophrenia

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What is schizophrenia?

- The term schizophrenia describes a mental disorder characterized by disorganized thought processes, disrupted perceptions and diminished or exaggerated emotional responses. Schizophrenia can affect an individual's thoughts, emotions, mood and behaviour; disturbances in mood are referred to as affective symptoms.
- The range and course of symptoms experienced vary greatly among individuals, personal circumstances and cultural settings.
- Symptoms that reflect abnormal psychological phenomena are often referred to as 'positive'.
- Symptoms that describe loss of emotional expression or motivation are termed 'negative'.
- Cognitive functions, such as concentration, memory and planning, are almost always impaired in people with schizophrenia, and this can reduce insight into their condition.

Positive Symptoms

- Hallucinations
  - Any perceptions by any of the 5 senses that are not related to actual external stimuli
  - Auditory (75%) and visual (49%) are most common
- Delusions
  - Firmly held, but untrue, beliefs that arise from disturbed thinking rather than perception (eg, paranoid delusions, delusions of grandeur)
- Disorganised behaviour/speech
  - Poor hygiene, odd or socially unacceptable behaviours
- Catatonic behaviours
  - Motor immobility and unresponsiveness
  - Excessive motor activity
  - Peculiarities of voluntary movements

Negative Symptoms

- Blunted or flattened affect
- Alogia
  - Decreased amount or fluency of speech
- Avolition
  - Decreased will to initiate activity
- Anhedonia
  - Inability to experience pleasure
- Asociality
  - Withdrawal from normal social contact

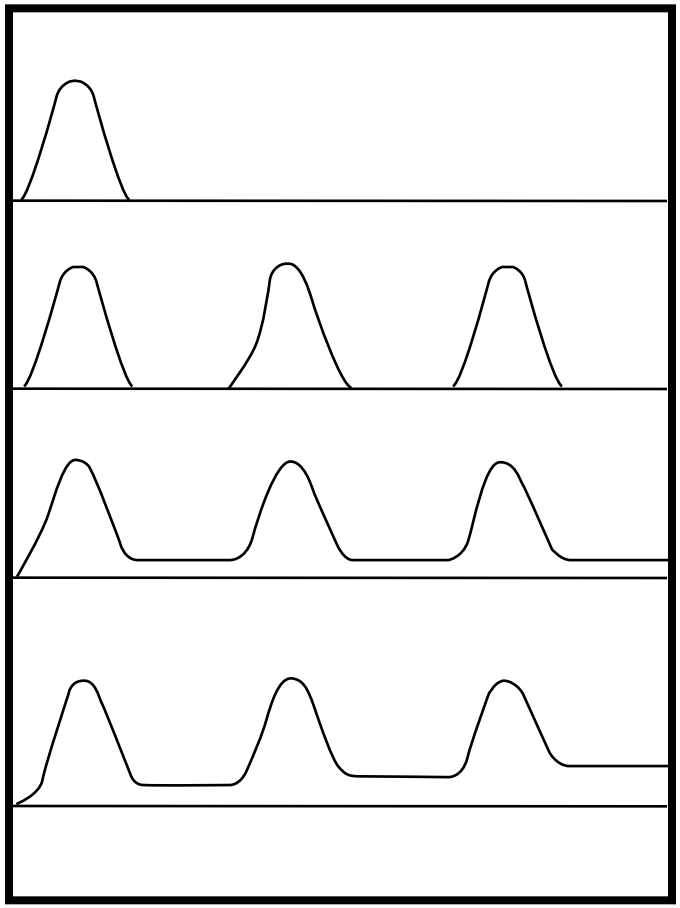
Cognitive Symptoms

- Disorganised thoughts or speech
  - Speech slips off track onto unrelated ideas
  - Incoherent speech
  - Answer to questions may be unrelated
  - Bizarre explanations are given for things or events
- Impaired attention
- Impaired memory and executive function
  - Difficulty with problem solving
- Lack of insight
  - Patients do not see a need for treatment

Mood Disturbances

- Dysphoria
  - Emotional state marked by anxiety, depression, and restlessness
- Depression
- Euphoria
  - Elevated mood, to an excessive degree and not linked to events
- Hostility/aggression
- Suicidality
  - Intention of taking one's own life
- Anxiety
- Hopelessness
- Agitation

Course of Schizophrenia



Course Type	% of Patients (N=102)
One episode with no impairment	13%
Several episodes with no or minimal impairment	30%
Impairment after the first episode with occasional exacerbations of symptoms. No return to normality	10%
Impairment increasing with each exacerbation of symptoms. No return to normality	47%

Shepherd M et al. *Psychol Med Monogr.* 1989;15(suppl 1):1-46.

Prevalence

- Schizophrenia has a global lifetime prevalence of 0.3% to 1.6%; median of 0.95%[a]
- Overall rate is similar across genders and cultures, mean onset in women is later[b]

[a]Kessler RC et al. *Biol Psychiatry.* 2005;58(8):668-676.

[b]Castle E et al. *Br J Psychiatry.* 1991;159:790-794.

Diagnosis and Assessment

Background on diagnostic systems

- The International Statistical Classification of Diseases, 10th revision (ICD-10) is a coding of diseases and signs, symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases, as classified by the World Health Organization (WHO)

- The US currently utilises the *Diagnostic and Statistical Manual,* 5th revision (DSM-5)

DSM 5

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):
   1. Delusions.
   2. Hallucinations.
   3. Disorganized speech (e.g. frequent derailment or incoherence).
   4. Grossly disorganized or catatonic behavior.
   5. Negative symptoms (i.e., diminished emotional expression or avolition).

B. For a significant of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior of the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).

C. Coninuous signs of the disturbance persist for at least 6 months.

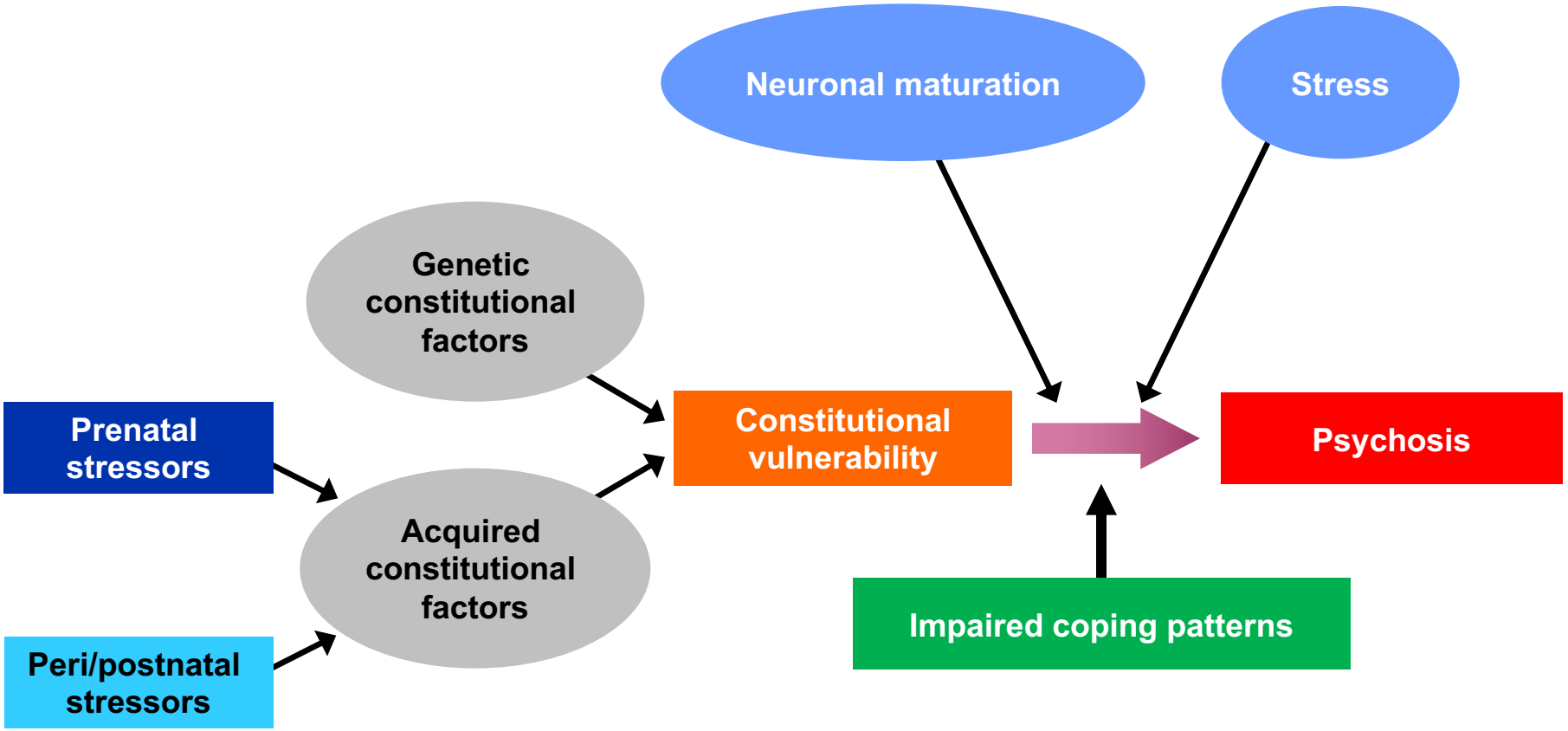
D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.

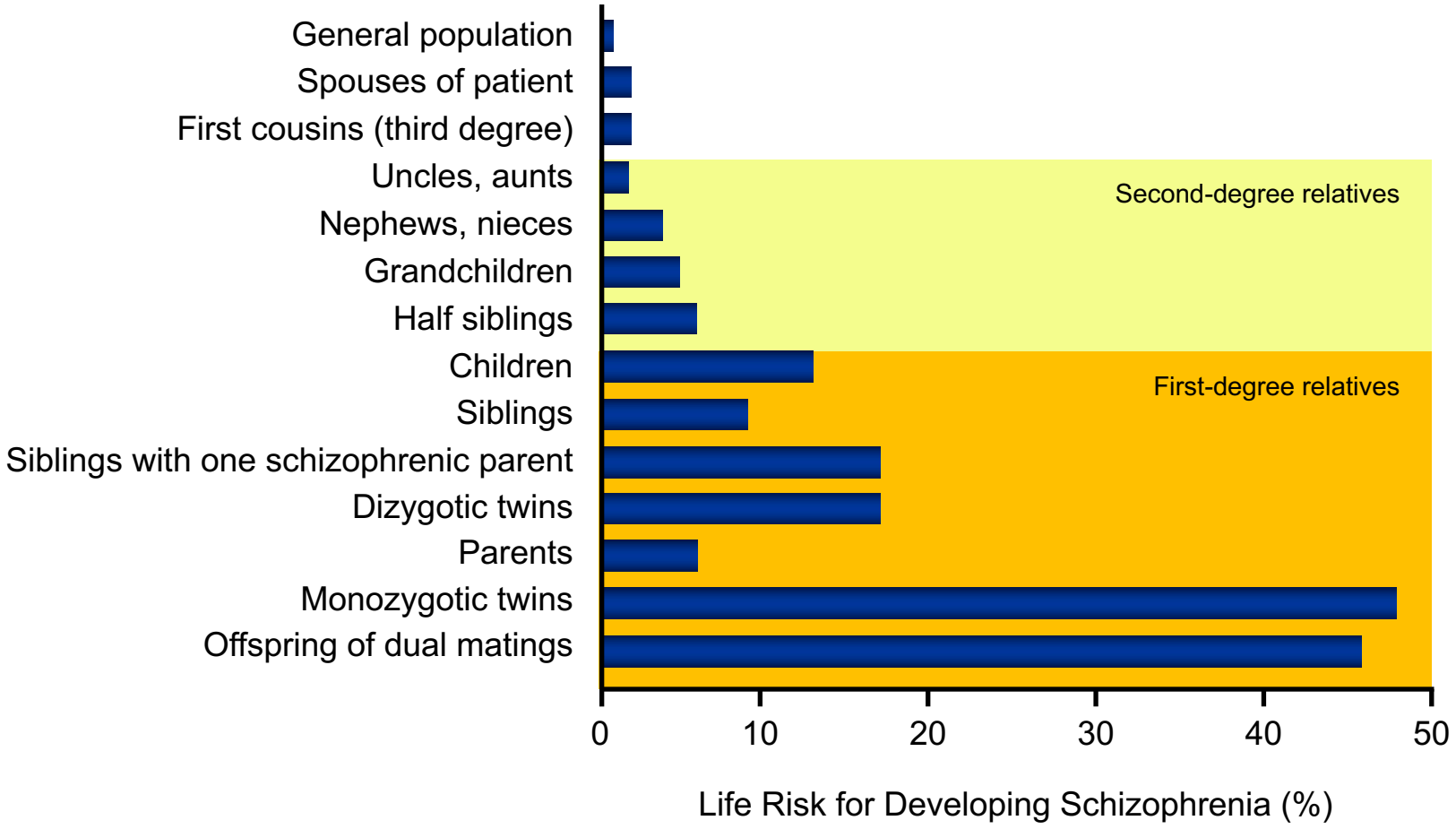
F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).

Causes of Schizophrenia

Vulnerability-Stress-Coping Model



Lifetime Risk of Developing Schizophrenia Is Increased In Relatives



Gottesman I et al. *Schizophrenia Genesis: the Origin of Madness*. New York, Oxford: WH Freeman;1991:203.

Current Dopamine Hypothesis of Schizophrenia

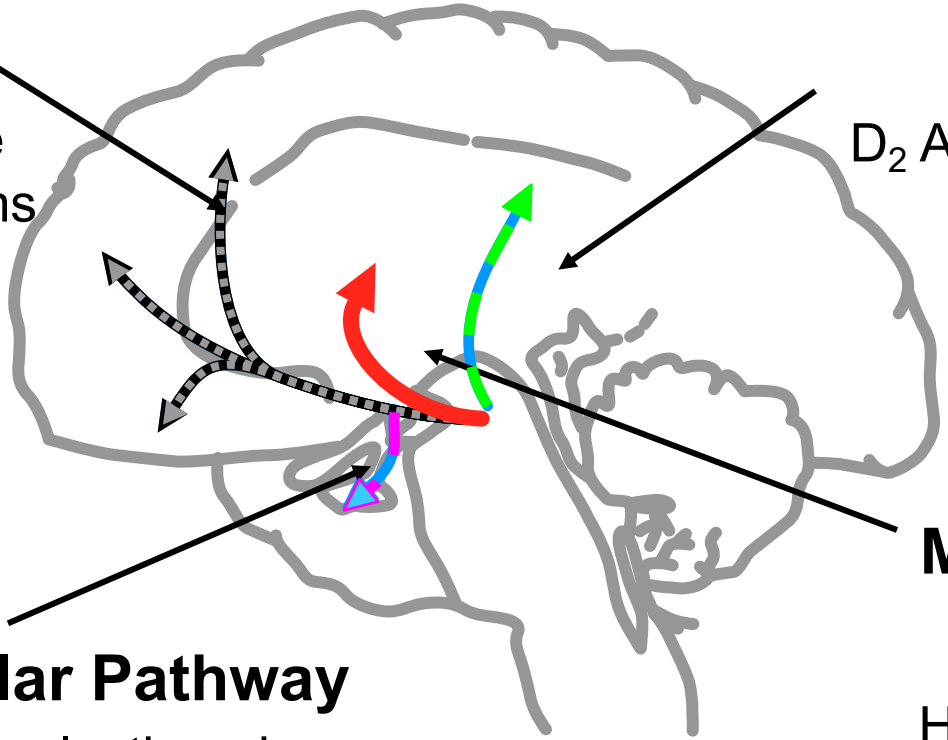
Dopaminergic Pathways in the Brain

Mesocortical Pathway

Hypoactivity: Negative and Cognitive Symptoms

Nigrostriatal Pathway

D_2 Antagonist: EPS



Tuberoinfundibular Pathway

D_2 Antagonist: Hyperprolactinemia

Mesolimbic Pathway

Hyperactivity: Positive Symptoms

Carlsson. *Neuropsychopharmacology*. 1988;1:179; Carlsson. *Science*. 2001;294:1021.

Quality of Life (QoL) and Functional Outcomes

Impact on QoL and Functionality

- Substantial impairments in QoL
  - Schizophrenia: QoL more strongly related to levels of depression and negative symptoms[a,b]
  - Patients are dissatisfied with their QoL, even when remitted, mostly due to insight into illness and medication side effects[a,c]
- Unemployment is common among patients
  - >40% of patients with schizophrenia[d]
- Patients with mental illness are usually of low socioeconomic status
  - 65% of patients with schizophrenia earn <$35,000/year[d]

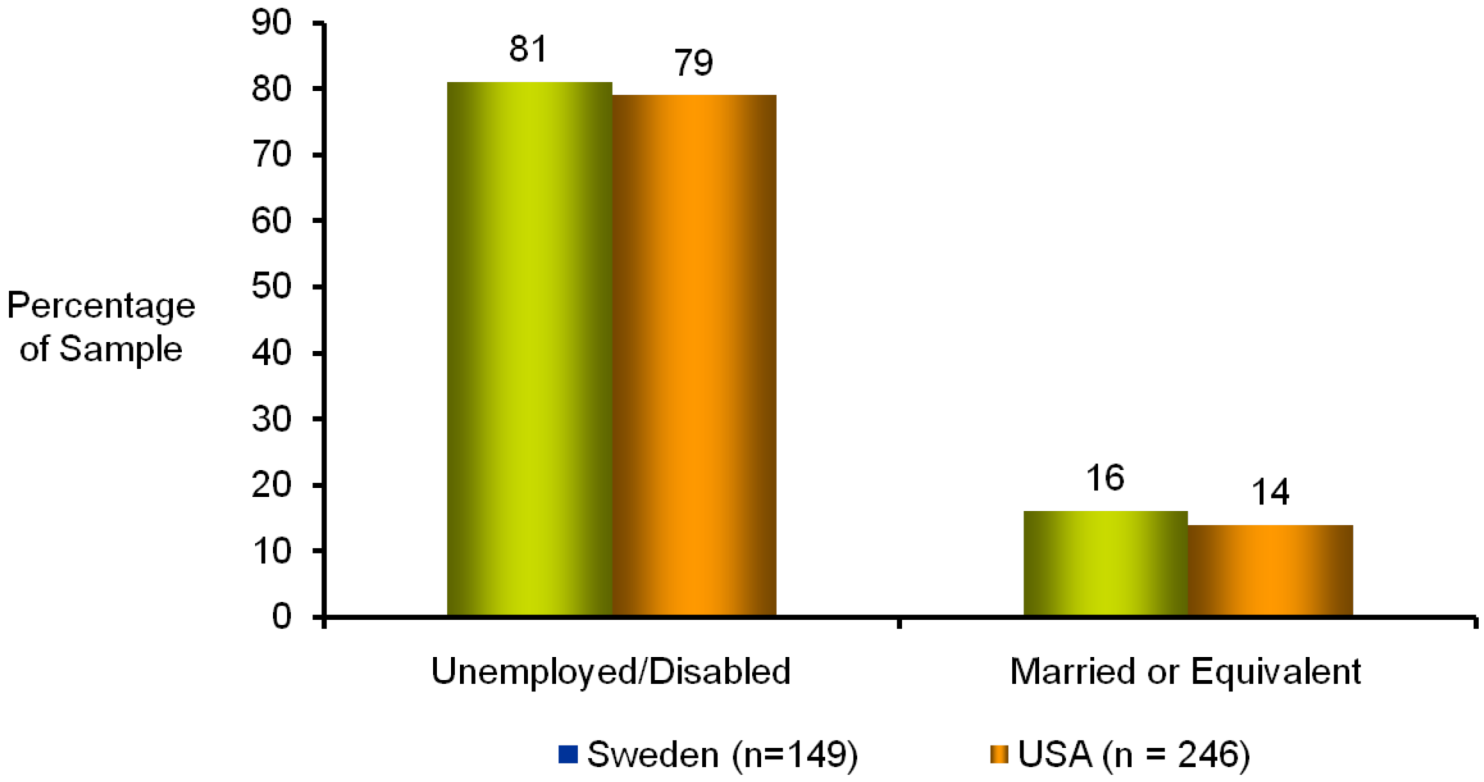
[a]Brissos S et al. *Psychiatry Res*. 2008;160(1):55-62.

[b]Fleischhacker WW et al. *Brit J Psychiatry*. 2005;187:131-136.

[c]Yen CF et al. *Bipolar Disord*. 2008;10(5):617-624.

[d]Schizophrenia: Public Attitudes, Private Needs. Conducted for NAMI by Harris Interactive, 2008.

Functional Outcomes in Schizophrenia



Harvey P et al. *Am J Psychiatry.* 2009; 166:821-827.

Burden of Illness

- Physical burden
  - Among neuropsychiatric conditions, schizophrenia ranks 3rd globally, in both gender of all ages, in the leading causes of years lived with disability[a]
- Economic burden[b]
  - Cost of illness estimates highlight a heavy societal burden (between 1.5%-3% of total national health care expenditures)
    - Total costs in Denmark in 1992 were €378 million
    - Total costs in France in 1992 were €2.7 billion
    - Total costs in Germany in 1995 were €4.6-9.2 billion
    - Total costs in UK in 1997 were €192.2 million
  - Generally, between 1/3 and 2/3 of total health care cost is for hospitalisation

[a]The World Health Report: 2001: Mental health: new understanding, new hope.
[b]Knapp M et al. *Schizophr Bull.* 2004;30(2):279-293.

Mortality Associated With Schizophrenia

- Life expectancy for patients with mental illness is substantially shorter than that of the general population[a]
  - 20% shorter (61 years vs 76 years)[b]
  - Mostly due to increased risk for cardiovascular disease[c]
  - Up to 10-fold greater risk for committing suicide vs general population[b]

[a]Fagiolini A, Goracci A. *J Clin Psychiatry*. 2009;70(suppl 3):22-29.

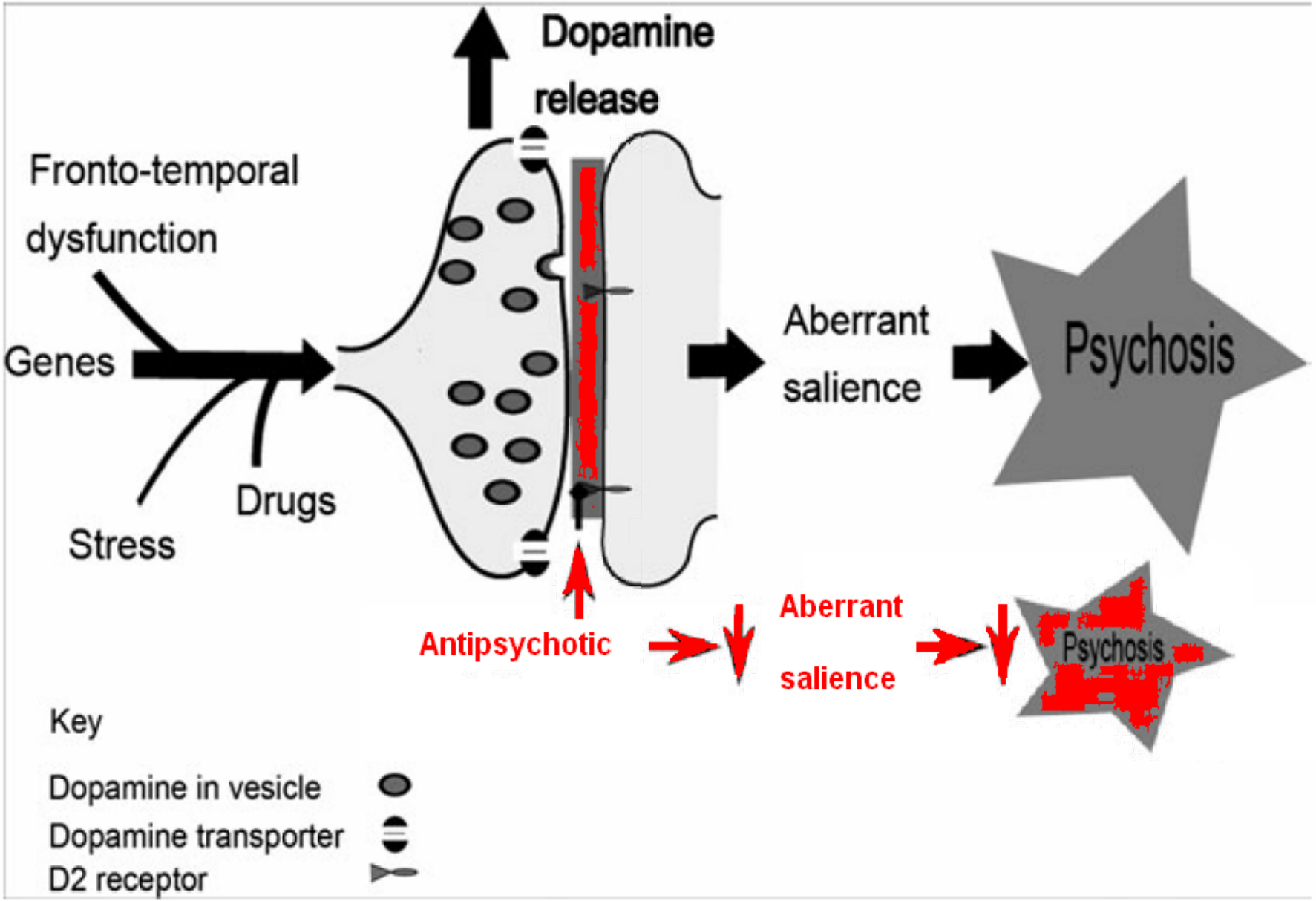
[b]Hennekens CH et al. *Am Heart J*. 2005;150:1115-1121.

[c]Fleischhacker WW et al. *J Clin Psychiatry*. 2008;69:514-519.

Treatment

General Treatment Recommendations

- Antipsychotics
  - Preferable monotherapy
- Duration:
  - First episode psychosis: 1-2 y
  - Multiple episodes: 3-5 y
  - After symptom remission: discontinuation attempt via slow taper
- Psychoeducation
- Specific psychosocial treatments
  - Cognitive behavioural therapy
  - Rehabilitation
  - Include caregivers



Howes and Kapur, Schizo Bull 2009

Commonly used antipsychotics

1st generation	2nd generation	3rd generation
Blonanserin	Amisulpride	Aripiprazole
Flupenthixol	Clozapine	Brexpiprazole
Fluphenazine	Lurasidone	Cariprazine
Haloperidol	Olanzapine	
Perphenazine	Paliperidone	
Sulpiride	Quetiapinee	
Zuclopenthixol	Risperidone	
	Ziprasidone	
	Zotepine	

Potential benefits and limitations of current antipsychotic medication

Benefits

- Reduction of positive symptoms
- Treatment of acute episodes
- Reduced risk of relapse
- Provision of stability and a platform for other treatments
- Reduction of aggression and hostility
- Reduced suicidal behaviour

Limitations

- Limited efficacy against negative symptoms
- Inadequate treatment of cognitive impairment
- Troubling side effects or tolerability issues
- Low acceptability to some patients
  - Poor adherence
  - Negative perceptions

Potential side effects of current antipsychotic medication

- Extrapyramidal symptoms
  - Slow, stiff movement and tremor (parkinsonism)
  - Abnormal muscle tone/muscle spasms (dystonia)
  - Involuntary movements (tardive dyskinesia)
  - Subjective experience of restlessness and restless movements (akathisia)
- Weight gain
- Metabolic disturbances
  - Changes in blood glucose levels
  - Increases in cholesterol and triglycerides
- Sedation
- A feeling of being ill-at-ease (dysphoria)
- Hormonal changes
- Sexual dysfunction
- Changes in the electrical activity of the heart (rare)
- Neuroleptic malignant syndrome (a rare but life-threatening neurological disorder)
- Agranulocytosis (very low levels of white blood cells, also life-threatening but rare)

Psychosocial treatments

- Psychoeducation
- Psychotherapy
  - Cognitive behavioural psychotherapy
  - Supportive psychotherapy
  - Family therapy
- Rehabilitation
  - Supported housing
  - Occupational therapy
  - Supported employment

Summary

Schizophrenia is a disorder with complex and varying psychopathological symptoms

It occurs with similar prevalence across cultural boundaries

Its etiology is unknown as yet

Both biological and environmental factors contribute to its pathophysiology

Strong leads from various fields of research point to an important involvement of CNS dopamine pathways

Its course and prognosis depend heavily on the provision of integrative pharmacological and psychosocial treatments