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Affective Disorders and their Treatment

AFFECTIVE DISORDERS AND MANKIND

- 1000 – 985 BC The madness of the king Saul (The Old Testament) - severe depression, BAP?
- 4th. century BC Hippocrates: Melancholy (black bile), mania (yellow bile)
- 150 BC Aretaeus of Cappadocia: Melancholy linked to mania
- 1899 Kraepelin: Manio-depressive psychosis x schizophrenia
- 1953 Kleist, Leonhard: Unipolar x bipolar disorder
- 1990 Goodwin, Akiskal: Bipolar spectrum
- 2013 DSM V – separation bipolar x unipolar

Classification of Affective Disorders

Classification Criteria for Affective Disorders:

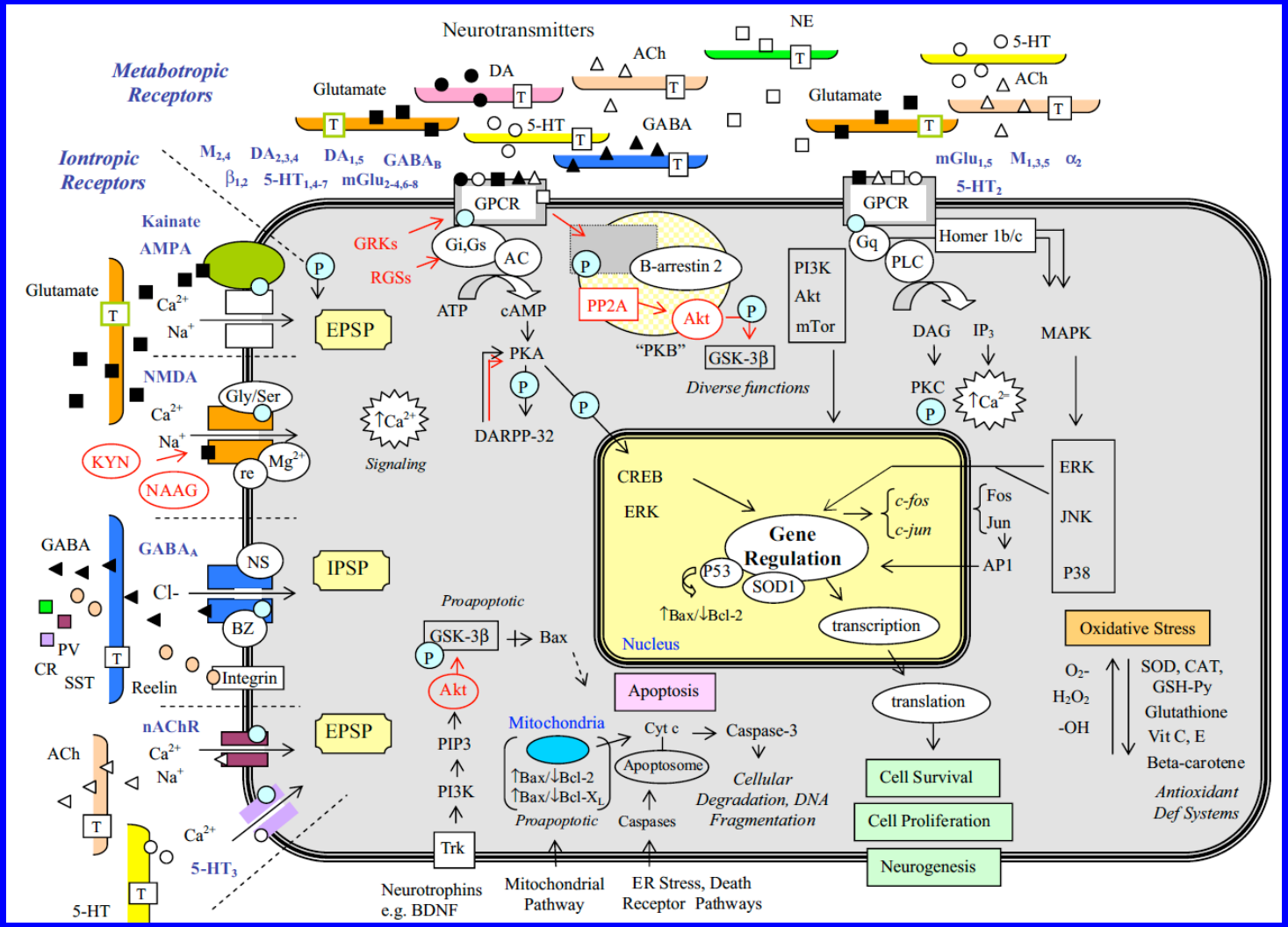
- **Cause – primary, secondary**
- **Polarity – bipolar, unipolar**
- **Intensity – mild, moderate or severe**
- **Quality – psychotic, non-psychotic**
- **Length – short-term fluctuations in mood (brief recurrent depressive disorder), long-term decline in mood (dysthymia)**

manic episode	depressive episode
• hypomania	• mild
• mania	• moderate
• mania with psychotic symptoms	• severe
	• severe with psychotic symptoms

Etiopathogenesis of affective disorders

Biological factors	• genetic factors • biochemical changes (5HT, D, Na, Glu) • changes in immunity (CRP, Il^{1,6}, TNF-alfa) • psychoendocrinologic changes - HPA • disruption of biorhythms • structural and functional changes in CNS • Mitochondrial dysfunction • Oxidative a nitrosative stress (antioxidants, lipid peroxidation) • Neurogenesis
Psychosocial factors	• adverse life events • life style

Depression – biologically very complex disorder



Lieberman et al., Pharmacol. Rev. 60:358-403, 2009

Etiopathogenesis of affective disorders

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Psychosocial factors	• adverse life events • life style

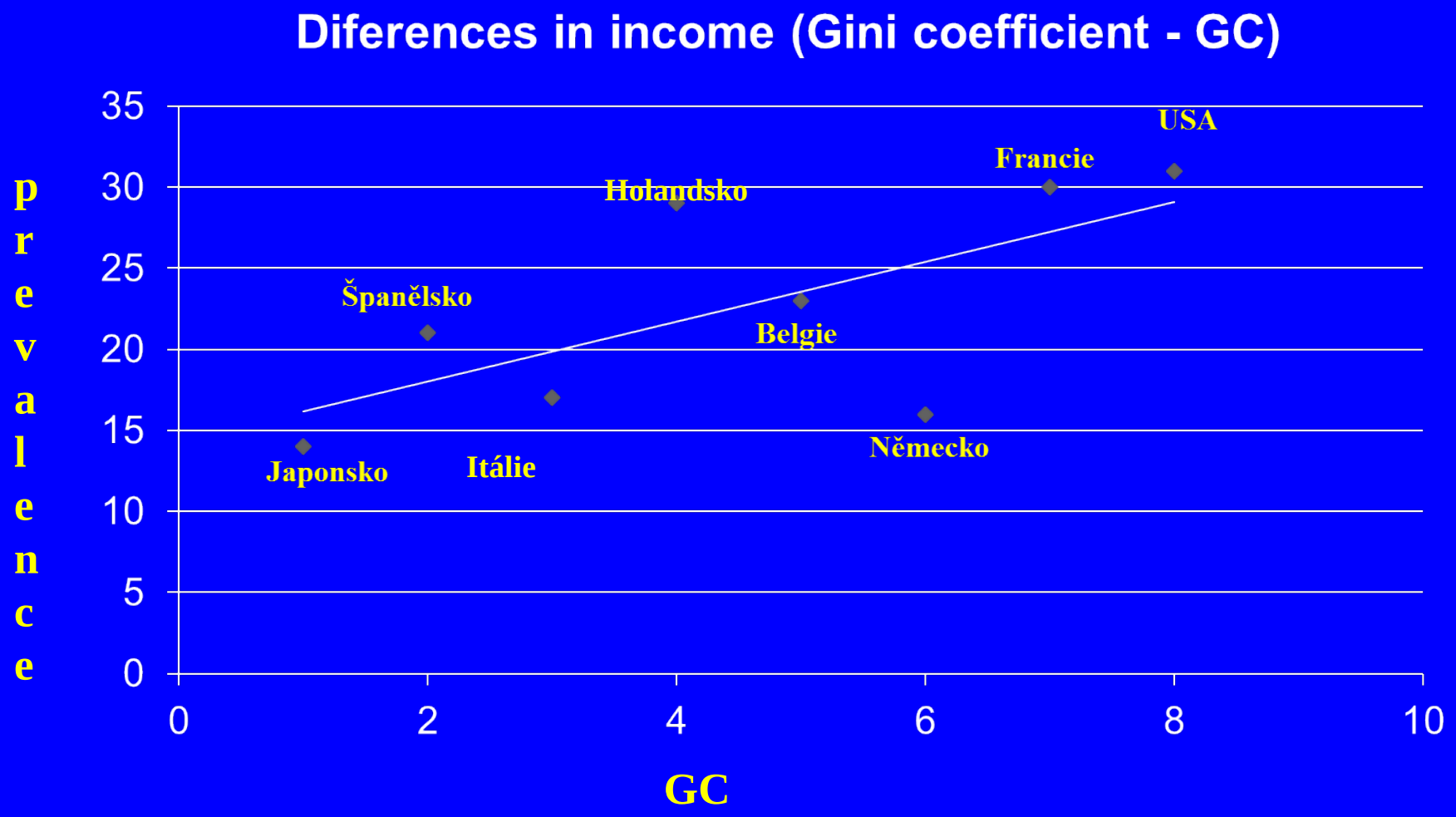
ECONOMIC CRISIS IN SPAIN
primary care

Mental disorder	2006	2010
Major depression	28,9	47,5
Minor depression	6,4	8,6
Dysthymia	14,6	25,1
GAD	11,7	19,7
Somatoform disorder	14,8	21,4
Panic disorder	9,7	15,7
Alcohol abuse	1,4	6,2
Alcohol dependency	0,2	2,7

$p < 0,001$

Gili et al., 2012

LIFETIME PREVALENCE OF DEPRESSION



Hidaka 2012

LIFE TIME PREVALENCE (%)
NCS

	Total	Men	Women
Affective disorders	17.1	12.7	21.7
Anxiety disorders	24.9	19.2	30.5
Dependencies	26.6	35.4	17.9
Non-affective psychoses	0.7	0.6	0.8
Mental disorders	48.0	48.7	47.3

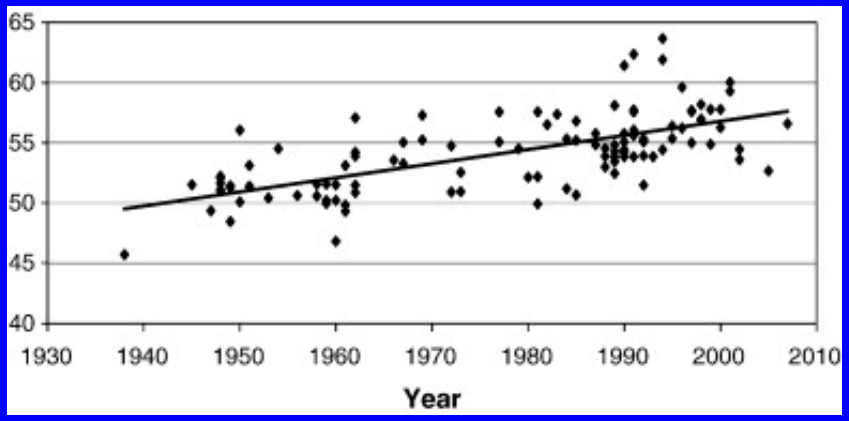
Kessler, 1994

LIFE TIME PREVALENCE – NCS-R

MENTAL DISORDERS USA	%	Age of onset (median)
Affective disorders	**20.8**	**30**
Anxiety disorders	**28.8**	**11**
Dependencies	**14.6**	**20**
Behavioral disorders	**24.8**	**11**
Mental disorders	**46.4**	**14**

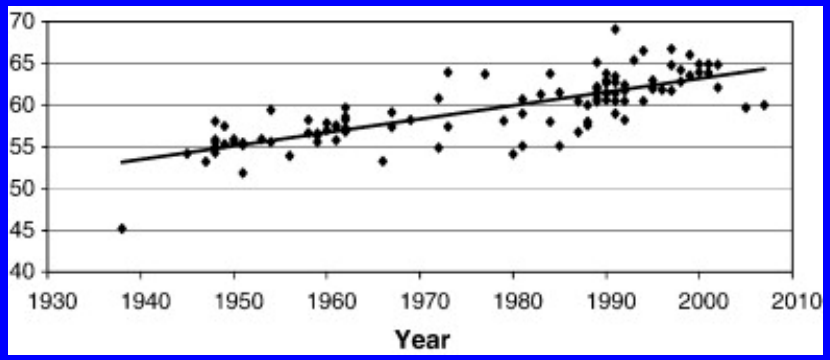
Kessler et al., 2005

US college students, 1938–2007

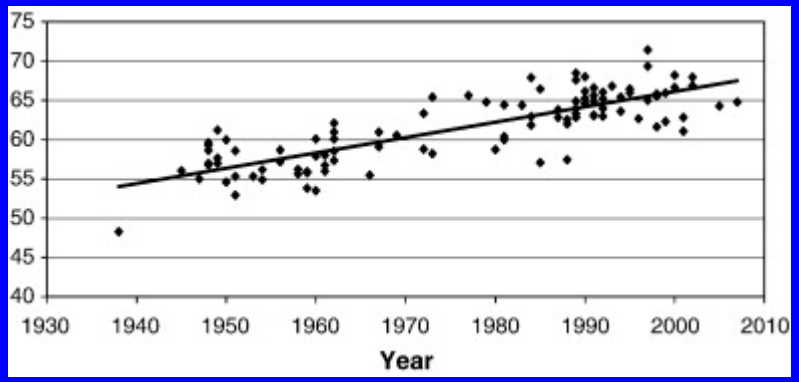


MMPI Depression (D) scale scores

metaanalysis
n=63 706



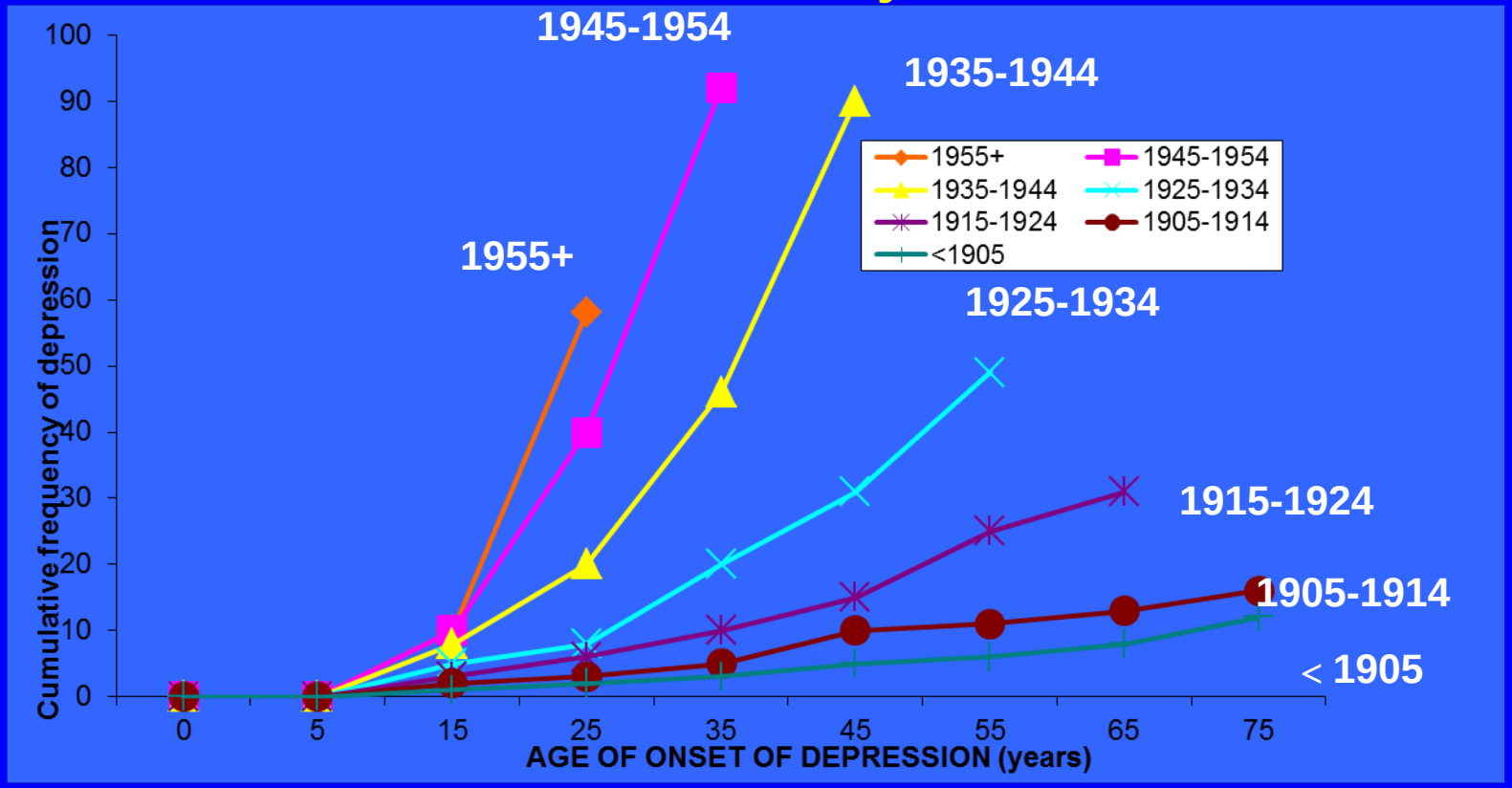
MMPI Psychopathic Deviation (Pd) scale scores



MMPI Hypomania (Ma) scale scores

Twenge et al., 2010

Cumulative frequency of depression according to the decade of birth and the age at the start of the disease
ECA study



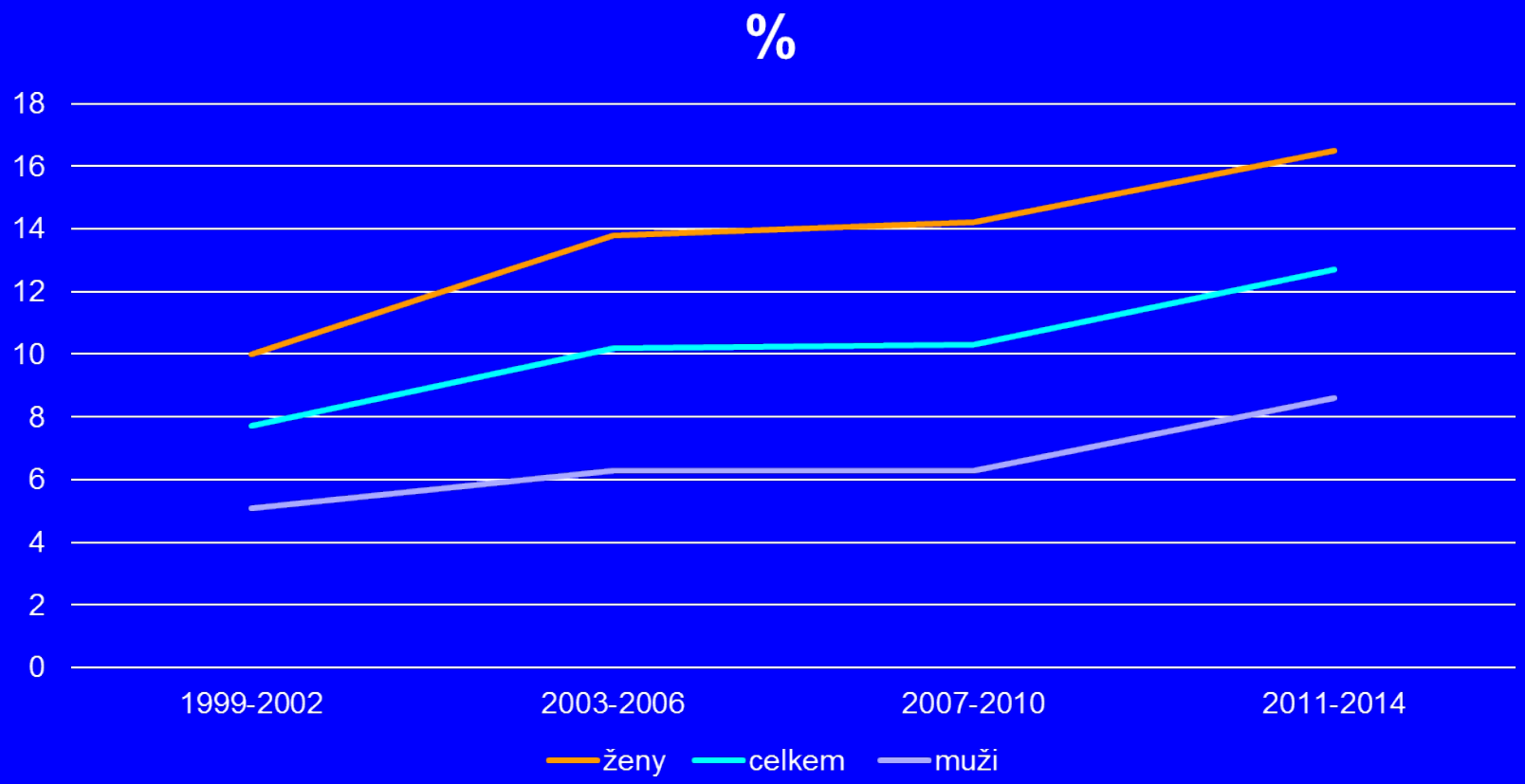
Wittchen et al., 1994

ONE-YEAR PREVALENCE OF DEPRESSIVE DISORDER

	1991-2	2001-2	P<
Number	42,862	43,093	
Total	3.33	7.06	0.001
Men	2.74	4.88	0.001
Women	3.88	9.06	0.001
18 – 29	5.99	9.98	0.001
30 – 44	3.86	7.32	0.001
45 +	1.32	5.54	0.001

Compton et al., 2006

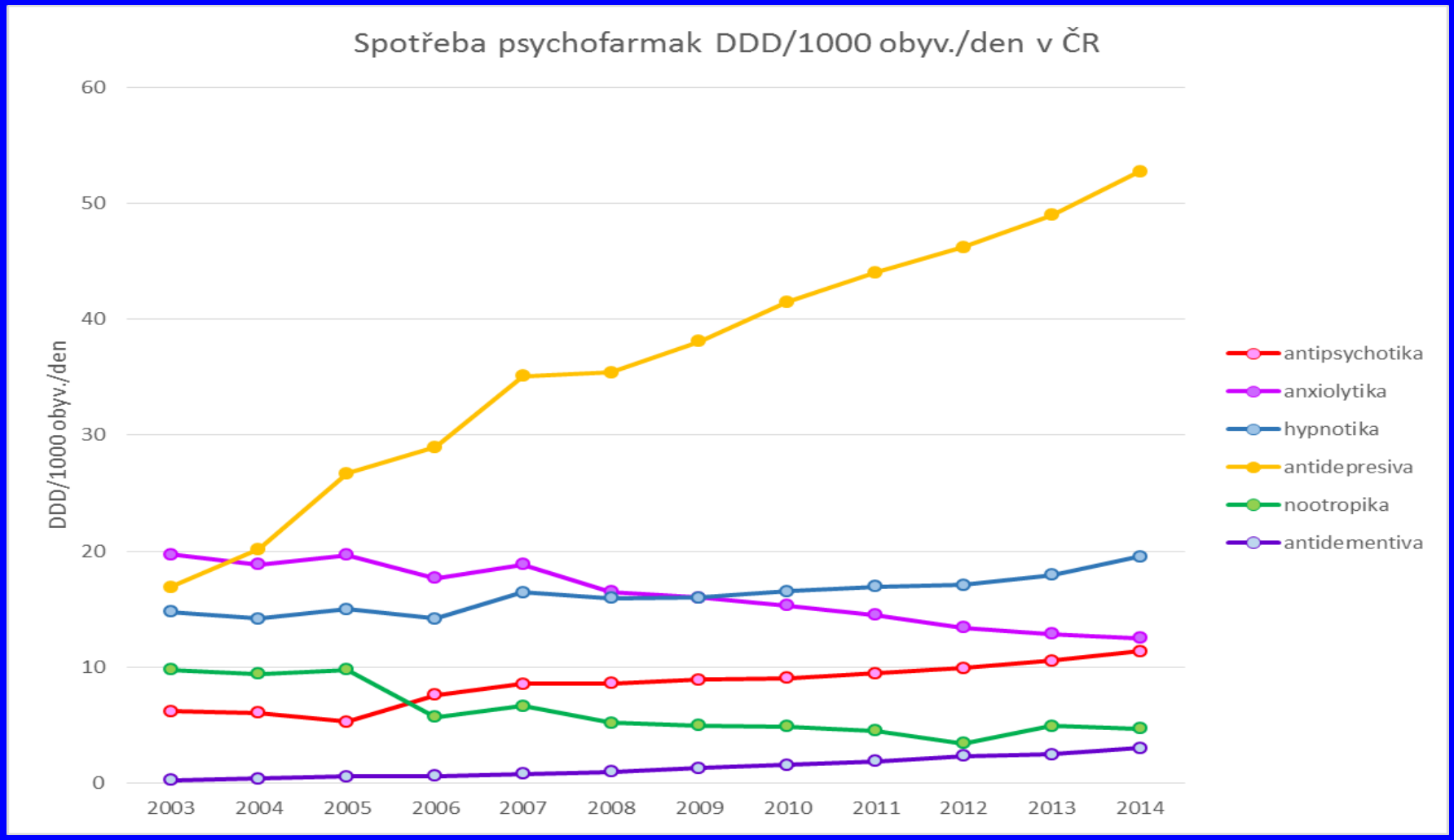
TRENDS OF CONSUMPTION OF ANTIDEPRESSANTS IN PERSONS OLDER THAN 12 YEARS IN THE USA



NCHS Data 2017

CONSUMPTION OF PSYCHOTROPIC DRUGS

DDD/1000 inhabitants/day



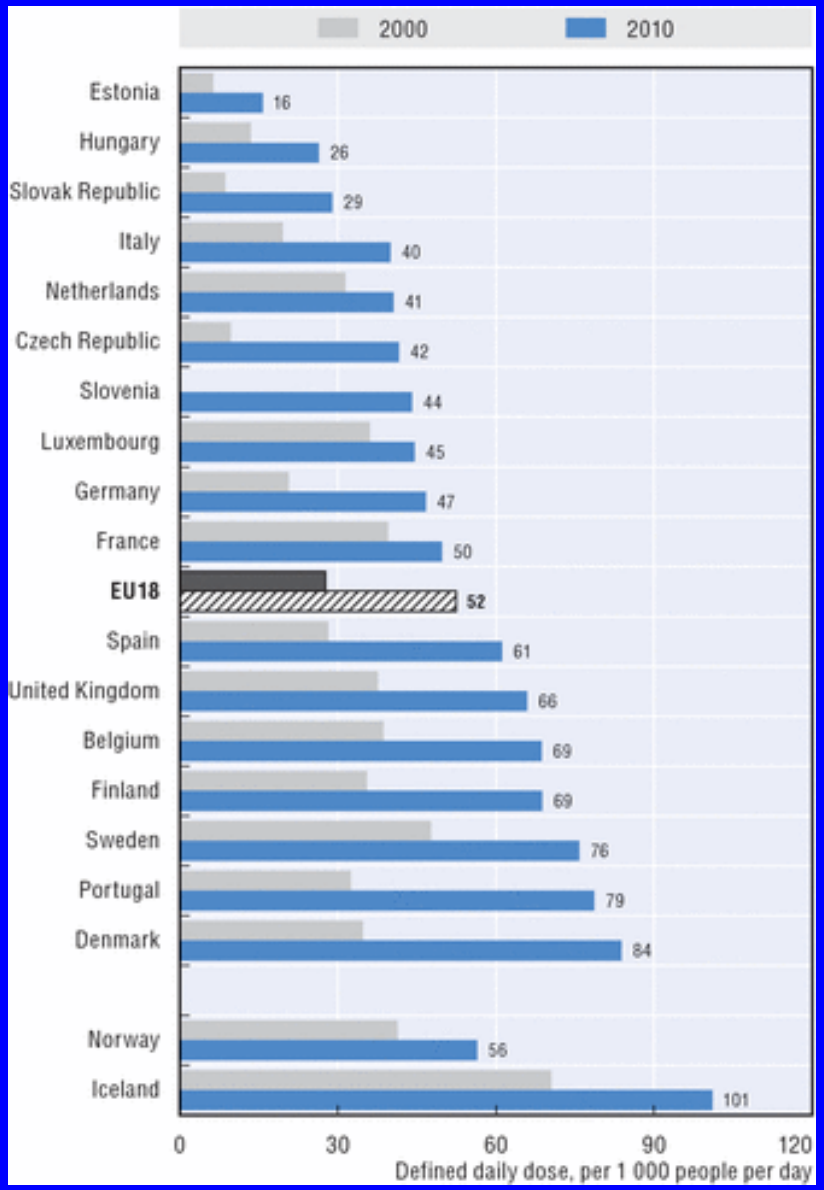
SÚKL, AISLP 2015

CZECH POPULATION 2014 (N=1028)

Drug	Occasionally (%)	Regularly (%)	Total
Anxiolytics	13	5	18
Antidepressants	6	5	11
Hypnotics	13	3	16

Raboch a Ptáček, 2015

ANTIDEPRESSANTS CONSUMPTION (DDD/1000/year) 2000 and 2010



OECD 2012

SUBGROUPS AT RISK

- AFFECTIVE DISORDER IN THE FAMILY (SUICIDE)
- LONELINESS, OLDER AGE
- FEMALE GENDER (POSTPARTUM PERIOD, PERIMENOPAUSE)
- ADVERSE LIFE EVENTS (DIVORCE, “EMPTY NEST“, JOB LOSS, BEREAVEMENT …)
- ABUSE OF ADDICTIVE SUBSTANCES
- LIFE STYLE
- SERIOUS PHYSICAL CONDITION (CARDIOVASCULAR, …)

ONE-YEAR PREVALENCE OF DEPRESSION

	%
General population	5.8
Chronically ill	9.4
Cancer patients	33
Patients with Parkinson's disease	39
Patients after MI	45
Patients after stroke	47

WPA 1997

PLUTARCH (40 – 125)

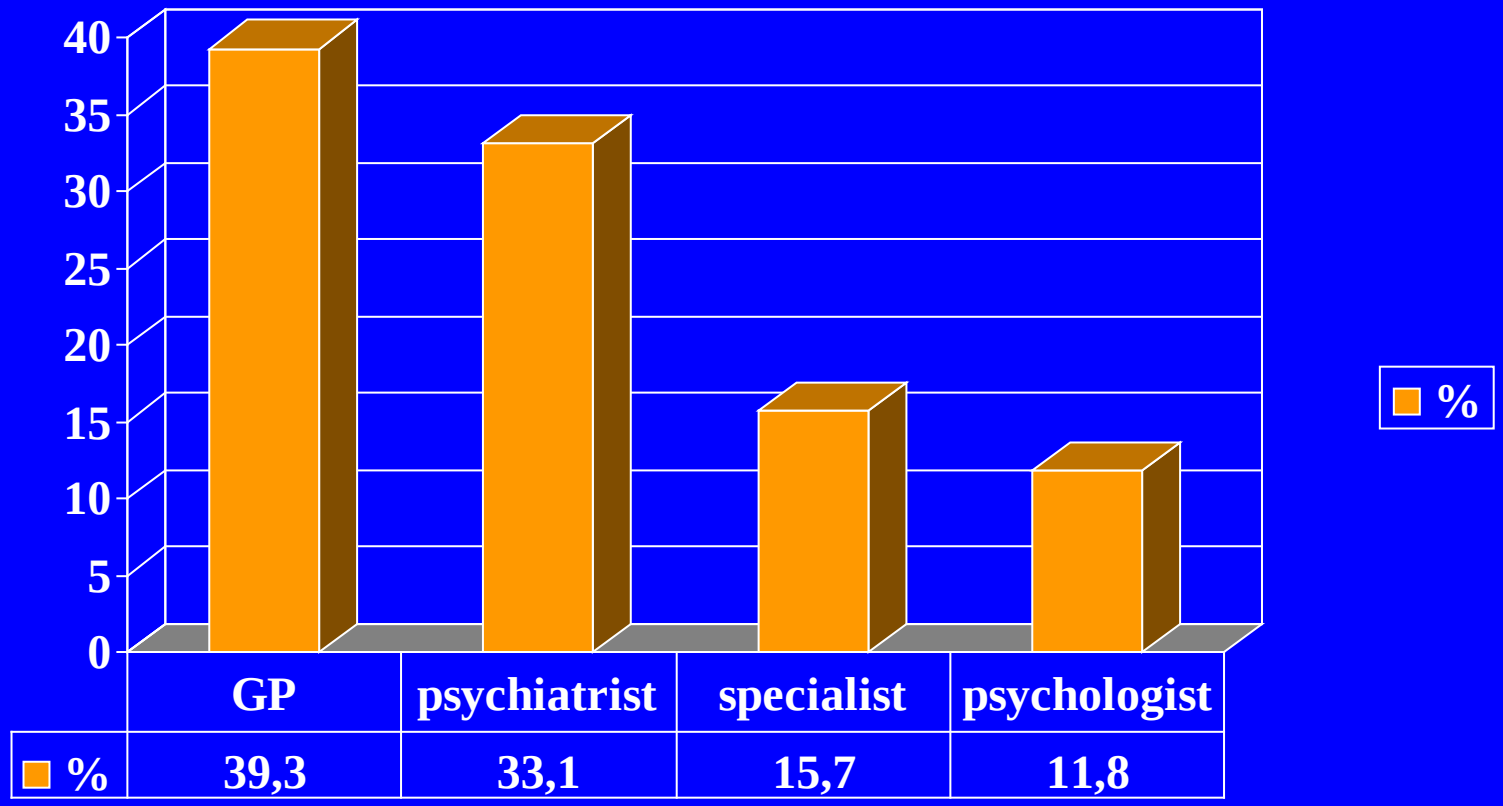
He looks like a man haunted by the wrath of gods ... he drives away physicians and his friends who try to comfort him ... "Leave me alone, so that I can endure my punishment.“

OBSTACLES IN IDENTIFYING DEPRESSION

- STIGMA
- TIME PRESSURE
- TRAINING IN MENTAL DISORDERS
- “TACIT AGREEMENT“
- COMORBID SOMATIC DISEASE

WPA, 1997

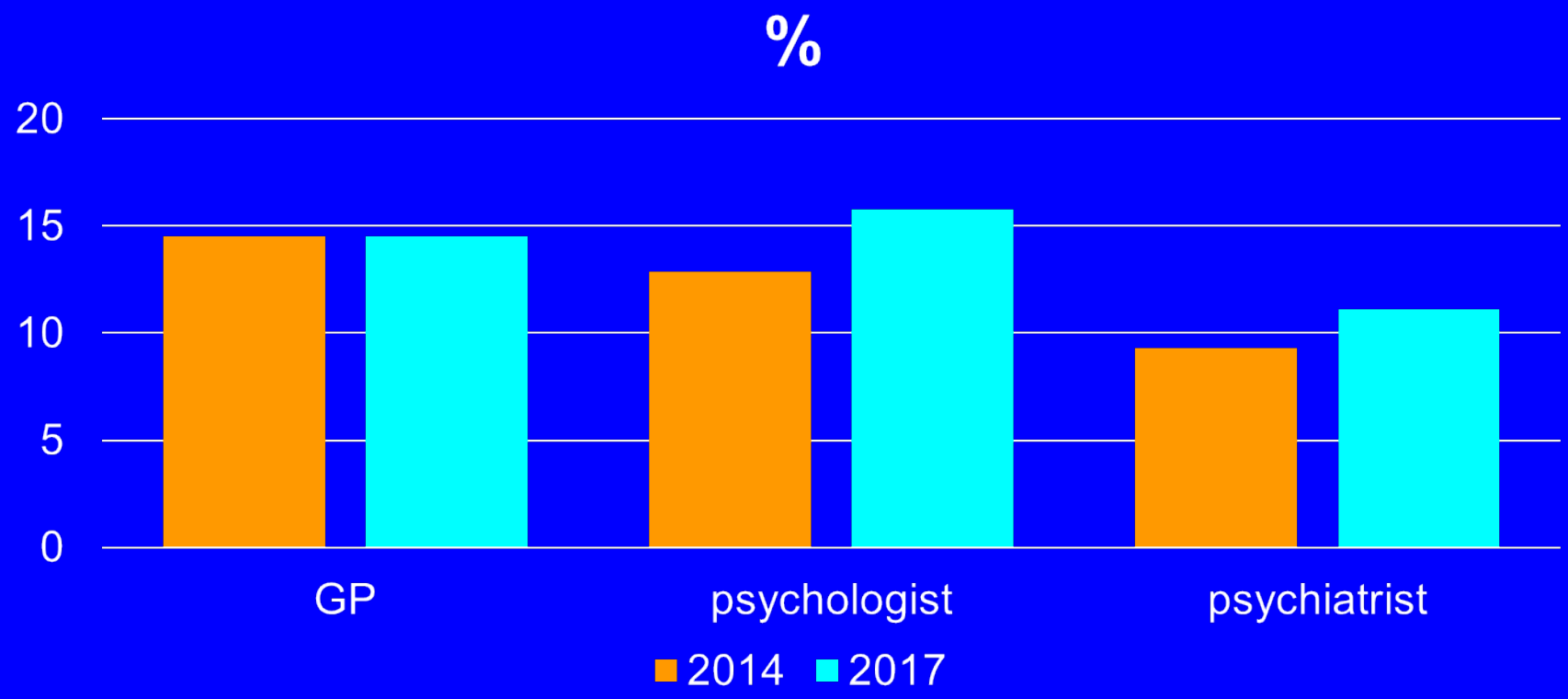
67.3 % “SOUGHT HELP“
mostly from non-physicians 81.3 %



	GP	psychiatrist	specialist	psychologist
%	39,3	33,1	15,7	11,8

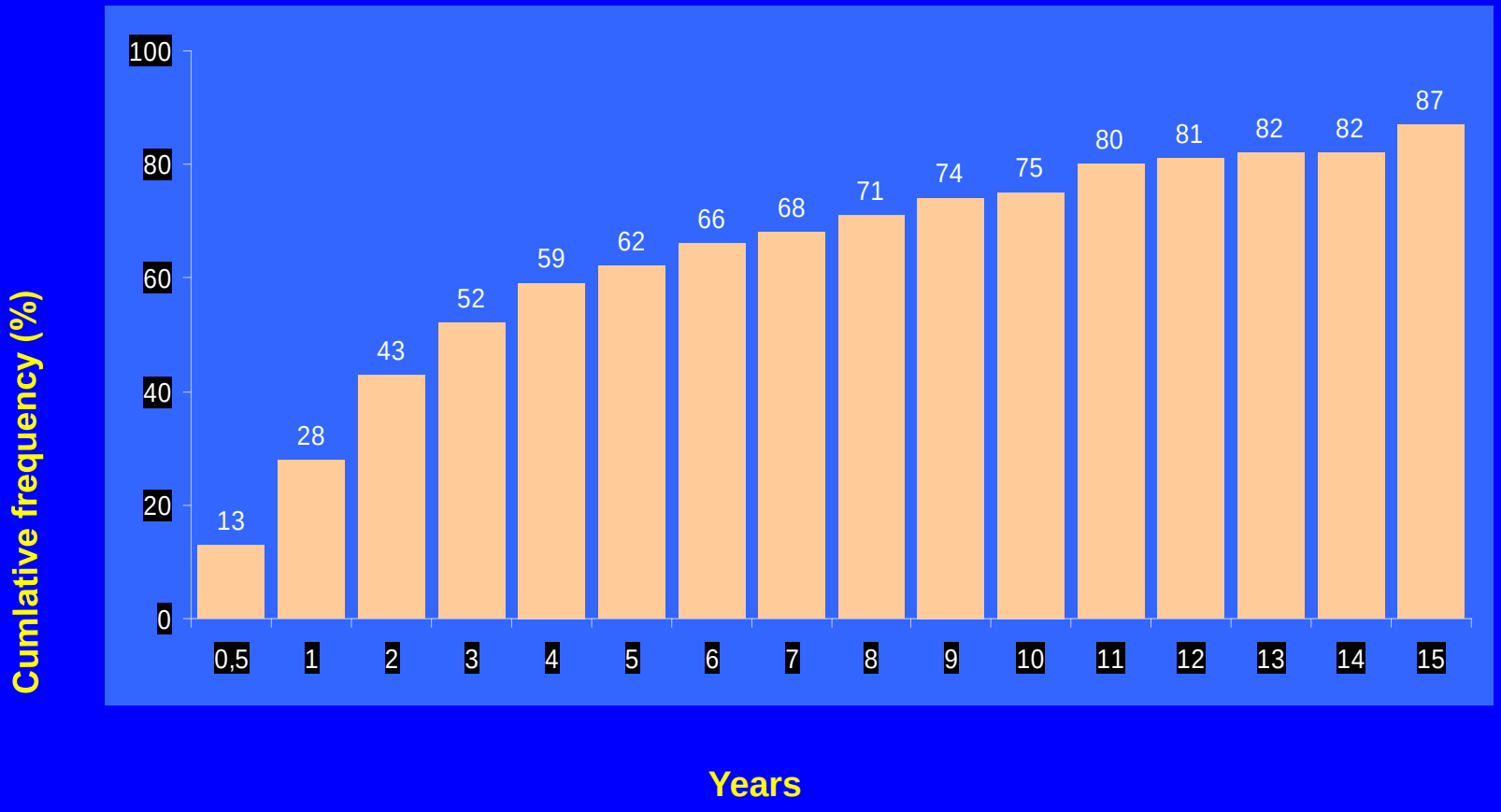
Vaněk, Raboch, Vaněk, 2000

FIRST CONSULTATION FOR PSYCHIC PROBLEMS



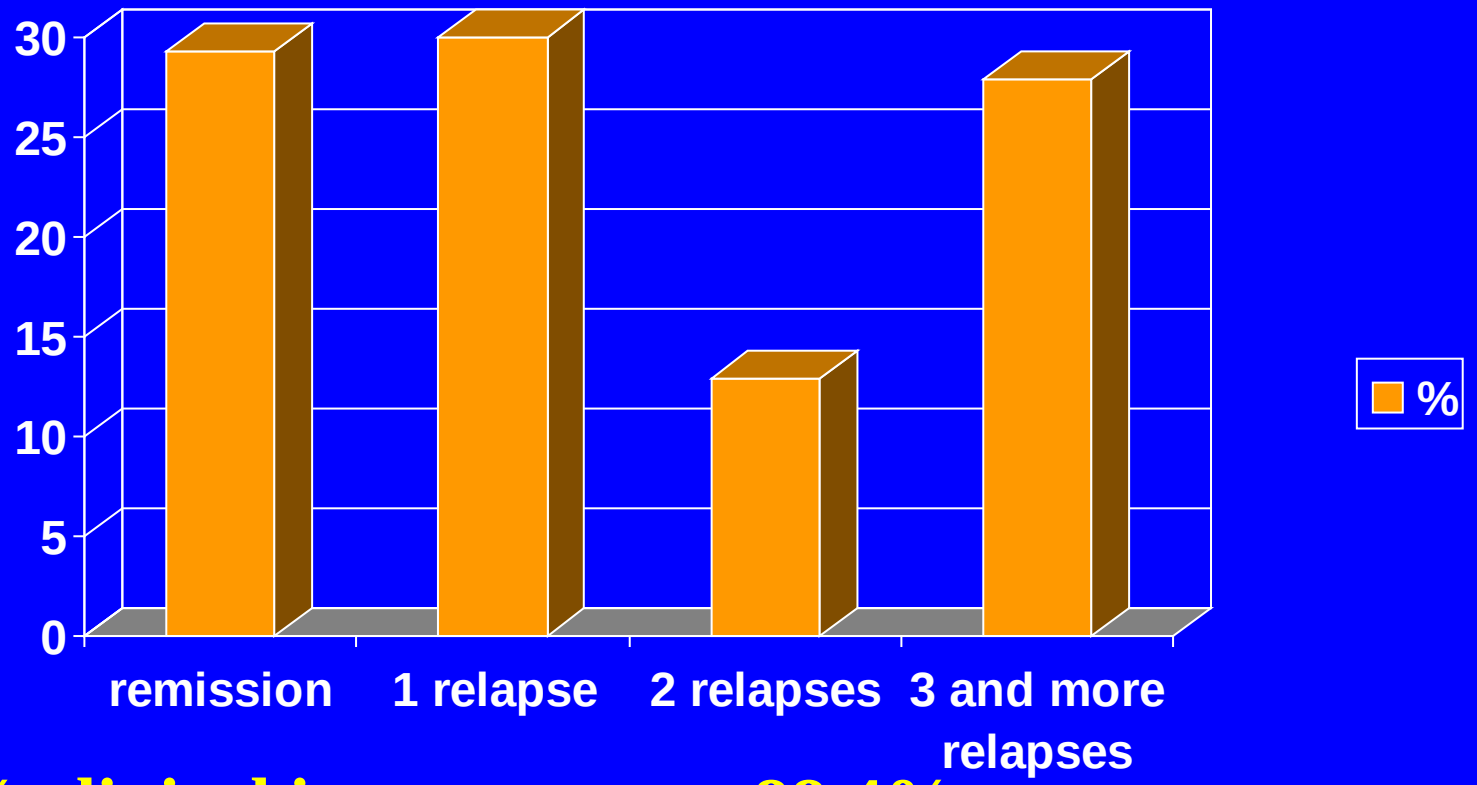
Raboch a Ptáček, 2017

CUMULATIVE FREQUENCY OF RELAPSES OF DEPRESSION (378 patients with depressive disorder)



Rothschild, A. J., et al.,1999

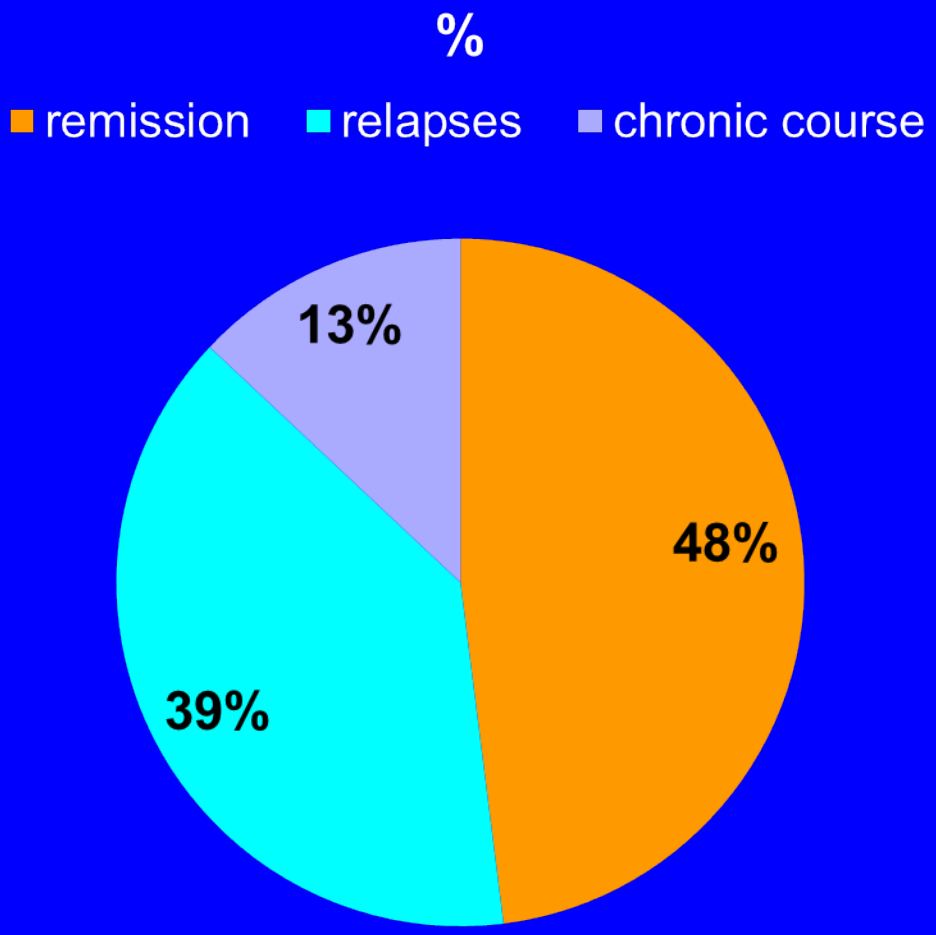
Long-term course of depressive disorder
163 patients monitored for 5 years



98.8% clinical improvement, 88.4% full remission, median 11 months

Holma et al., 2008

LONG-TERM COURSE OF DEPRESSIVE DISORDER



Steinert et al., 2014

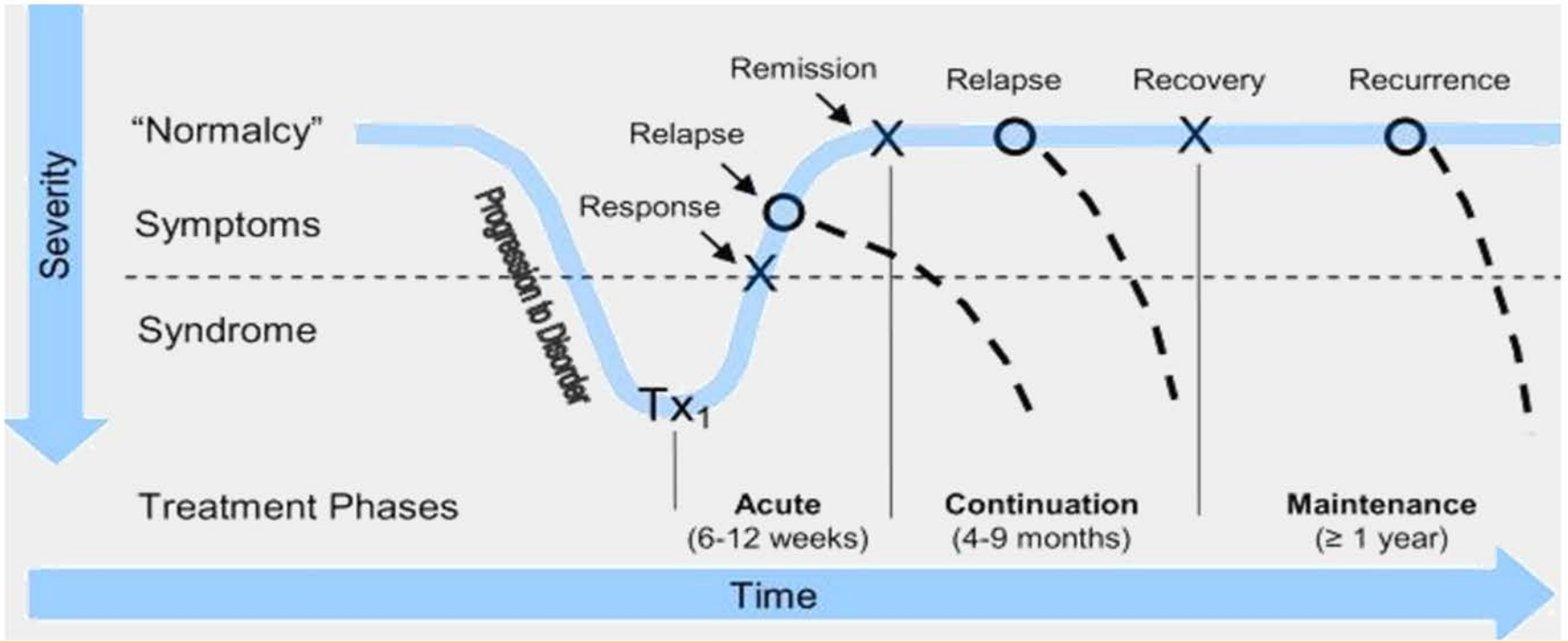
FACTORS INFLUENCING THE COURSE OF DEPRESSION

- GENETIC RISK
- AGE AT THE START OF DEPRESSION (<25, 60<)
- FEMALE GENDER
- NUMBER OF PREVIOUS EPISODES AND THEIR INTENSITY
- COMORBIDITY
- PSYCHOSOCIAL SITUATION (PARTNER)
- BIOLOGICAL FACTORS SLEEP PATTERN, HPA ACTIVITY, GENETIC FACTORS

TREATMENT IN 21st CENTURY

COMPLEX
EVIDENCE BASED
MEASUREMENT
BASED
PERSONALISED

PHASES OF DEPRESSION TREATMENT



Response = reduction >50% symptoms	**Remission = few, if any, symptoms of depression**
Recovery = Long lasting full remission of symptoms and return to previous functioning	

Rush AJ et al., 2006

DEPRESSION ACUTE TREATMENT OPTIONS

- PSYCHOTHERAPY (CBT, IP, PST,)
- ANTIDEPRESSANTS
- OTHER BIOLOGICAL METHODS
  - ECT
  - rTMS
  - PHOTOTHERAPY
  - SLEEP DEPRIVATION
  - AEROBIC EXERCISE
  - VNS, DBS, LNC, tDCS

Psychotherapy

- Basic treatment approach
  - in patients with mild to moderate depression
  - presence of psychosocial stressors, intrapsychic conflicts, interpersonal difficulties
  - comorbidity with personality disorder

- Patient's wish is also important

Forms of psychotherapy

- **Supportive psychotherapy - increases patient´s adherence**
- Part of the treatment of each patient, it is performed by the attending physician (listening, sympathy, support and encouragement, realistic goals
- Informing the patient (and his immediate family) about the therapy and the expected progress

EFFECTIVE PSYCHOTHERAPEUTIC METHODS

Psychotherapy	Main principles	Number of sessions	Notes
Problem-solving therapy	Identifying problems and developing the ability to solve them	4 – 6	Suitable for primary care
Cognitive Therapy	Identifying negative thoughts and replacing them with more rational approaches	12 – 16	Combination with behavioural therapy
Behavioural Therapy	Identification of inappropriate behaviours and replacing them with more suitable patterns	8 – 12	Combination with behavioural therapy
Interpersonal therapy	Identification of the main personal traits and problems, solutions to some of them	12 – 16	The combination of CBT and dynamic therapy

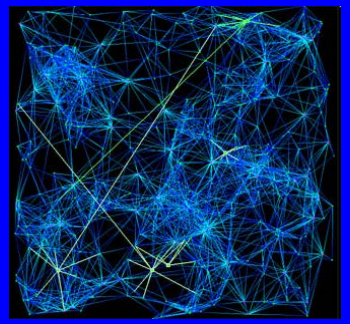
ASSUMED EFFECTS OF ANTIDEPRESSANTS

Reuptake blockade **Influence on receptors**

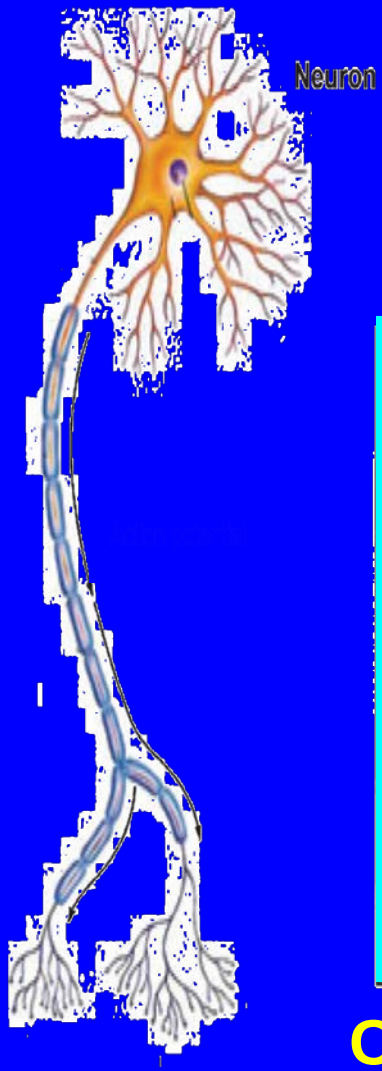
Skupina Lék	Na	S	D	Ach	a1	H1	S1	S2	S3	MT1/2
SSRI	0	+++	0	0	0	0	0	0	0	0
TCA	++	++	0	++	-	-	0	-	0	0
SARI	0	+	0	0	--	-	0	--	0	0
SNRI	+	++	+/-	0	0	0	0	0	0	0
NDRI	+/-	0	++	0	0	0	0	0	0	0
NaSSA	+/-	0	0	0	0	--	-	-	-	0
MASSA	0	0	0	0	0	0	0	-	0	+
SMRI	0	++	0	0	0	0	++ /-	0	-	0

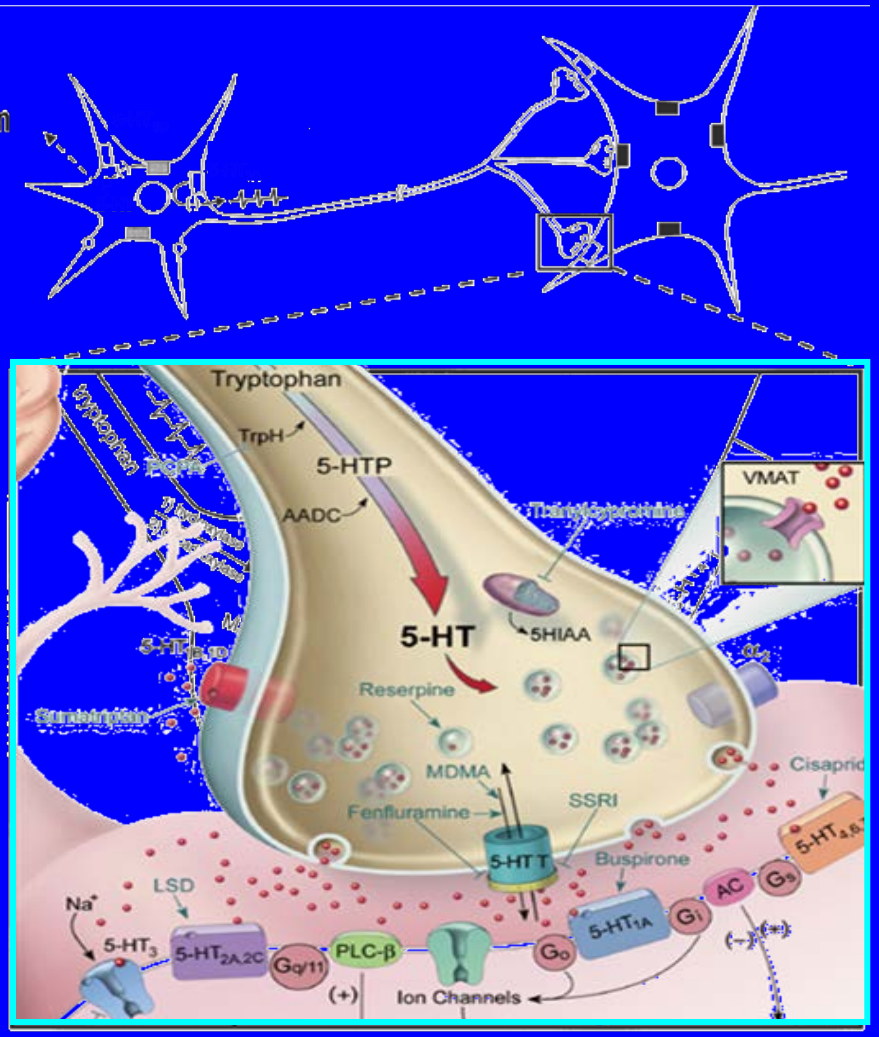
Schatzberg 2005, Stahl 2005, Fornaro 2010, Sanchez 2015

Neurotransmitter Systems



Network





Communication between Neurons

ACUTE TREATMENT OF SSRI
STIMULATION OF POSTSYNAPTIC RECEPTORS

Effects
adverse desirable

SEROTONINERGIC SYSTEM	EFFECT
5 HT1	ANTIDEPRESSANT EFFECT
5HT2	ANXIETY, INSOMNIA, SEXUAL PROBLEMS
5HT3	GIT, LOSS OF APPETITE

AMERICAN PSYCHIATRIC ASSOCIATION

- ANTIDEPRESSANTS REPRESENT A FIRST LINE OF TREATMENT FOR MODERATE OR SEVERE DEPRESSION
- THE EFFECTIVENESS OF VARIOUS ANTIDEPRESSANTS IS ESSENTIALLY IDENTICAL (50 – 70 %)
- THE CHOICE OF THE DRUG IS MADE BASED ON ITS SIDE EFFECTS, SAFETY, TOLERABILITY, FORMER BENEFICIAL EFFECT IN THE PATIENT OR HIS/HER RELATIVES, THE PATIENT'S WISH AND THE COST OF THE DRUG

APA, 2000

Side effects of selected antidepressants

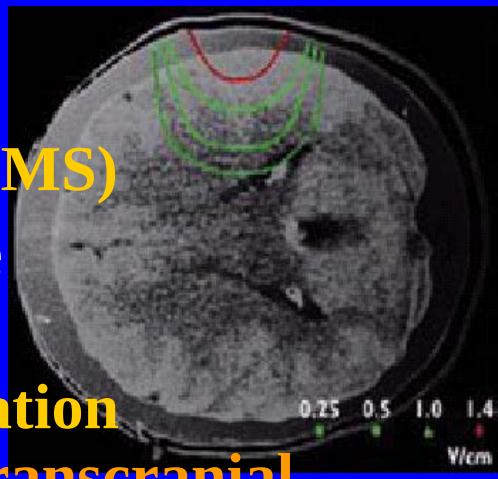
Substance	GIT	Sedaction	Insomnie/ agitation	Sexual dysfunction	Weight increase	Lethality in overdose
Citalopram	++	-	++	++	-	Low
Escitalopram	++	-	++	++	-	Low
Fluoxetine	++	?	+	?	?	Low
Sertraline	++	-	++	++	-	Low
Venlafaxine	++	-	++	++	-	Low
Amitriptyline	-	+++	-	+	+++	High
Clomipramine	+	+	+	++	++	Medium
Dosulepin	-	++	-	+	+	High
Bupropion	+	-	+	-	-	Low
Trazodone	+	++	-	++	+	Low
Mirtazapine	-	++	-	-	++	Low
Moklobemide	+	-	+	-	-	Low
Agomelatine	+	-	-	-	-	Low

Other biological treatments

- **Electroconvulsive therapy (ECT)**
  - **Remission in 85-95% of patients, more effective than psychotropic drugs, faster onset of action**
  - **Need for continued and prophylactic AT treatment**

Chronobiologic treatment

- **Phototherapy - exposure of intense white light for half an hour to two hours, preferably in the morning, especially in seasonal affective disorders**
- **Sleep deprivation or sleep shift**



- **Repetitive transcranial magnetic stimulation (rTMS)**
  - **Comparable effectiveness with ECT in some indications**
- **Vagal stimulation (VNS), deep brain stimulation (DBS), limbic neurosurgery (LNC), tDCS - transcranial direct-current stimulation**

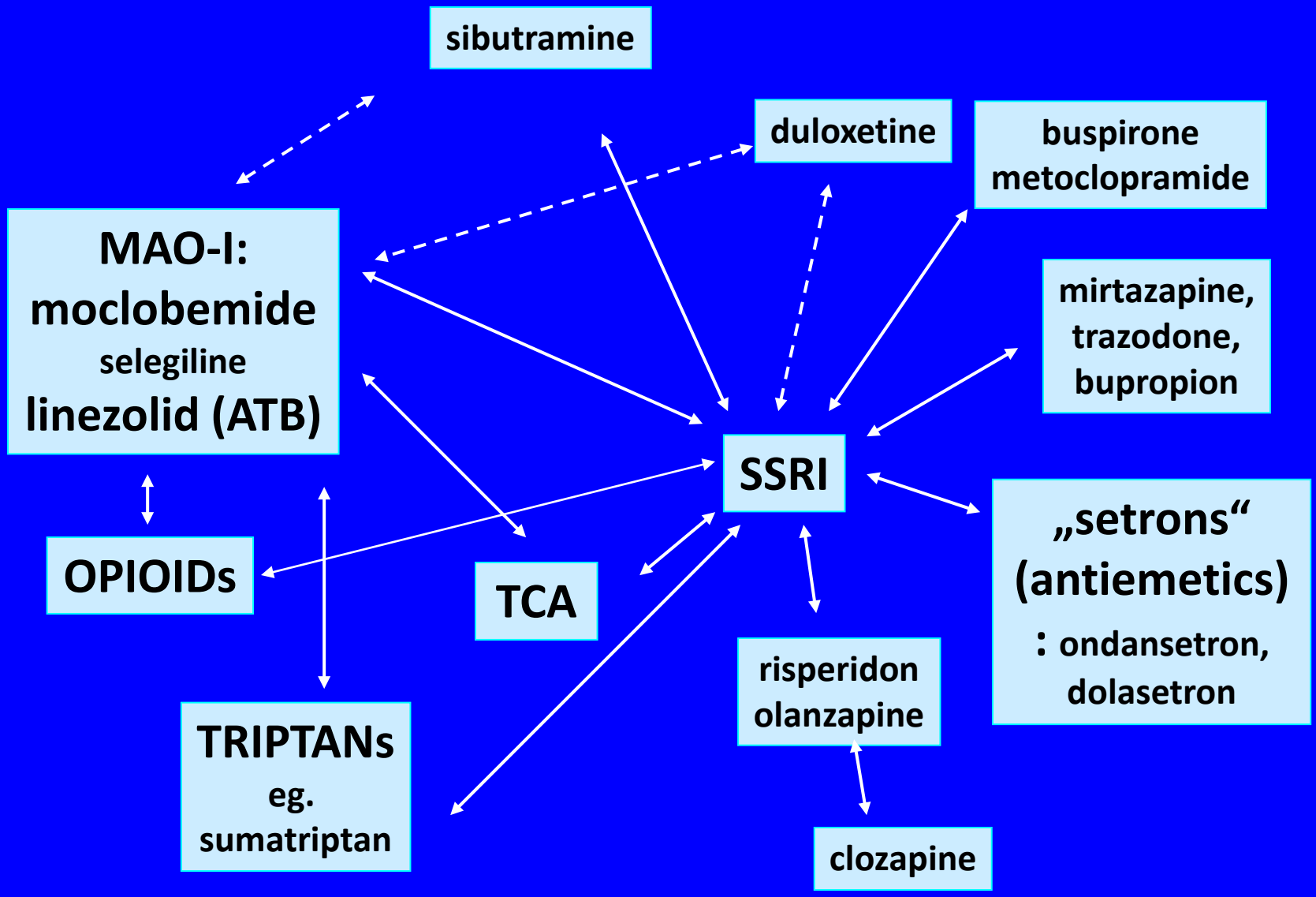
MEASUREMENT BASED CARE RATING SCALES

Depression	**Hamilton Rating Scale for Depression** **Montgomery-Asberg Depression Rating Scale** **Beck Depression Inventory**	**HAM-D** **MADRS** **DBI**
Mania	**Young Mania Rating Scale**	**YMRS**
Functional Measures	**Sheehan Disability Scale**	**SDS**
Quality of Life	**Quality of Life Enjoyment and Satisfaction Questionnaire**	**Q-LES-Q**

COMPLICATION OF SSRI ACUTE TREATMENT

- SEROTONIN SYNDROME
- FAILURE OF TREATMENT
- SUICIDAL BEHAVIOUR

Serotonine syndrome



Serotonine syndrome

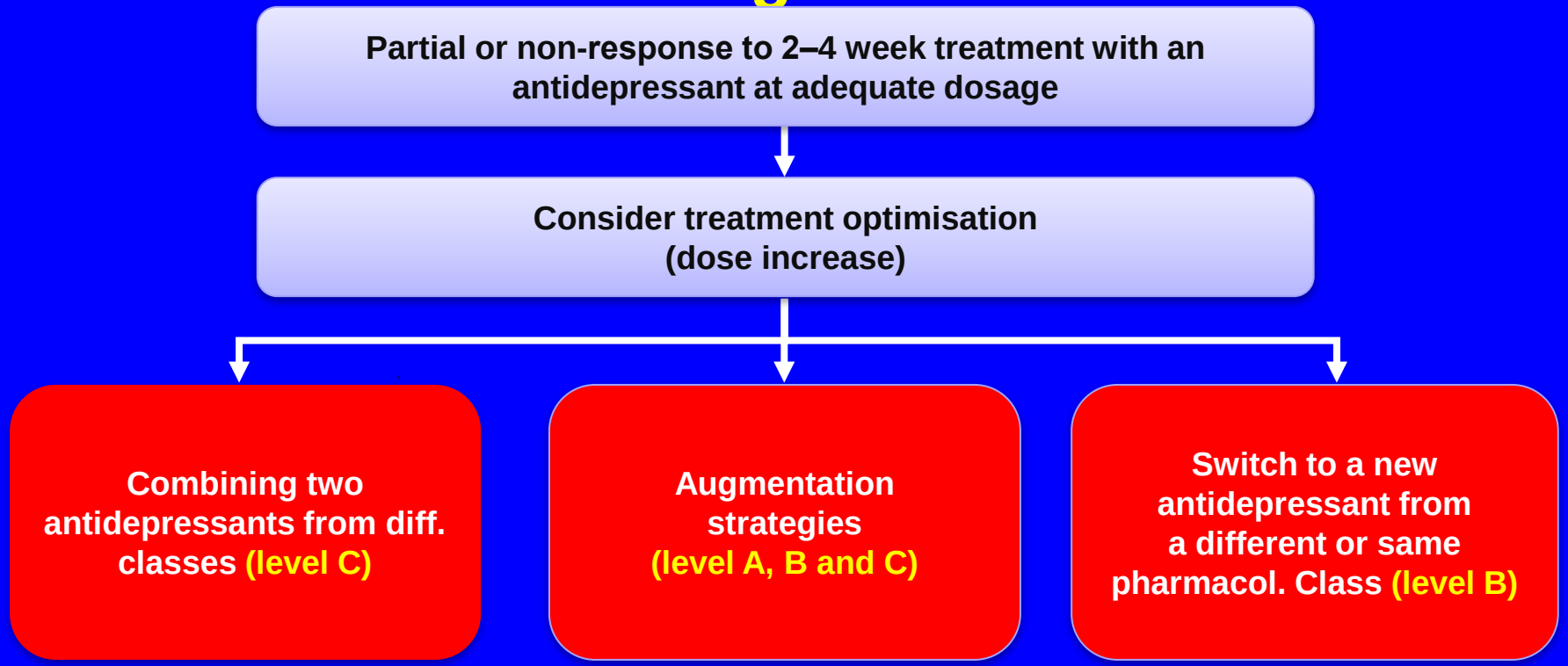
Rare, but life-threatening

- **Signs and symptoms:**
  - **Impairment of psychic functions: Agitation, confusion, mania**
  - **Impairment of autonomous functions: Sweatening, diarrhea, fever + chills**
  - **Impairment of neuromuscular functions: Hyperreflexia, movement incoordination, myoclonus, tremor**
- **Diagnosis: 3 of above mentioned symptoms**
- **Discontinuation of the serotoninergic drugs**
- **When suspected: Transport to intensive care unit**

FAILURE OF TREATMENT

- NO POSITIVE RESPONSE TO TREATMENT WITHIN 4-6 WEEKS
- RIGHT DIAGNOSIS?
- COMPLIANCE
- MAXIMISING THE DOSE
- CHANGE OF ANTIDEPRESSANTS
- COMBINATION
- POTENTIATION OF THE ANTIDEPRESSANT ACTION (LITHIUM, T3, STIMULANTS, ESTROGENS, ...)

Treatment strategies for depression: WFSBP guidelines



Adapted from Bauer et al 2013, World Federation of Societies of Biological Psychiatry (WFSBP)

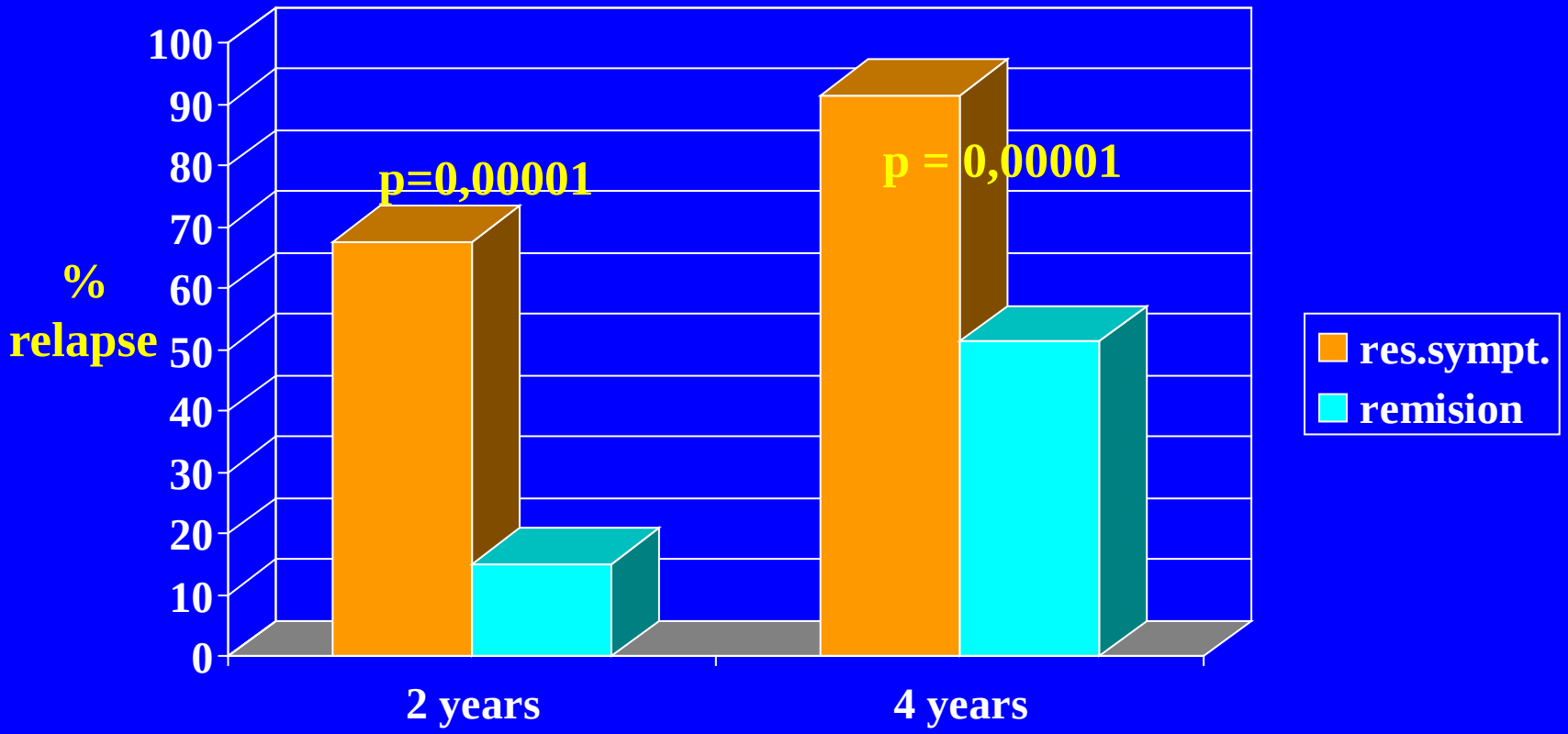
RESIDUAL SYMPTOMS

- Fatigue
- Loss of libido
- Sleep Disorders
- Psychic and somatic anxiety
- Subdepression
- Loss of weight

N=114, monitoring for 3 years

Karp et al., 2004

RESIDUAL SYMPTOMS – A NEGATIVE PROGNOSTIC FACTOR

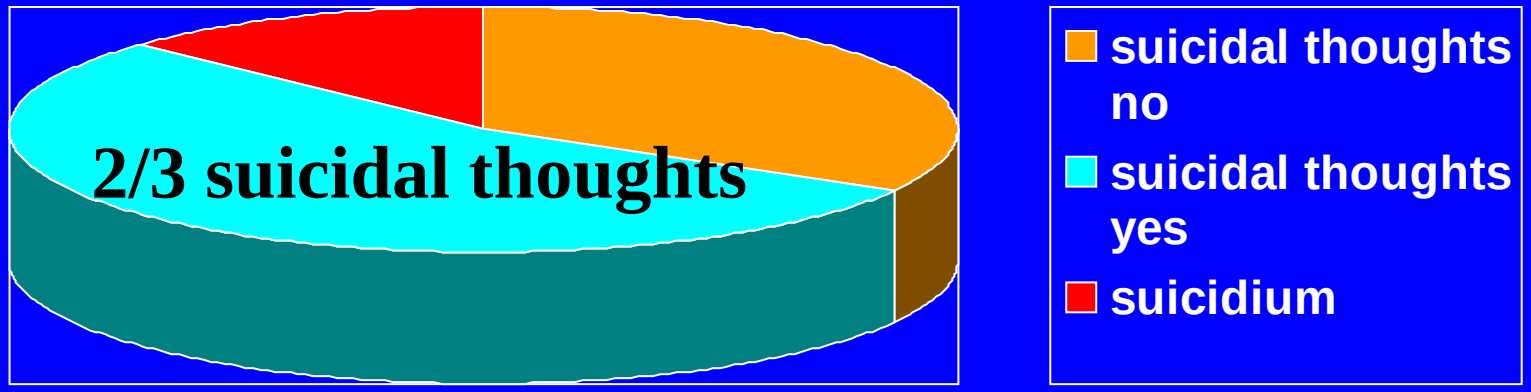


186/139 patients with major depressive episode
Naturalistic study

Pintor et al., 2003, 2004

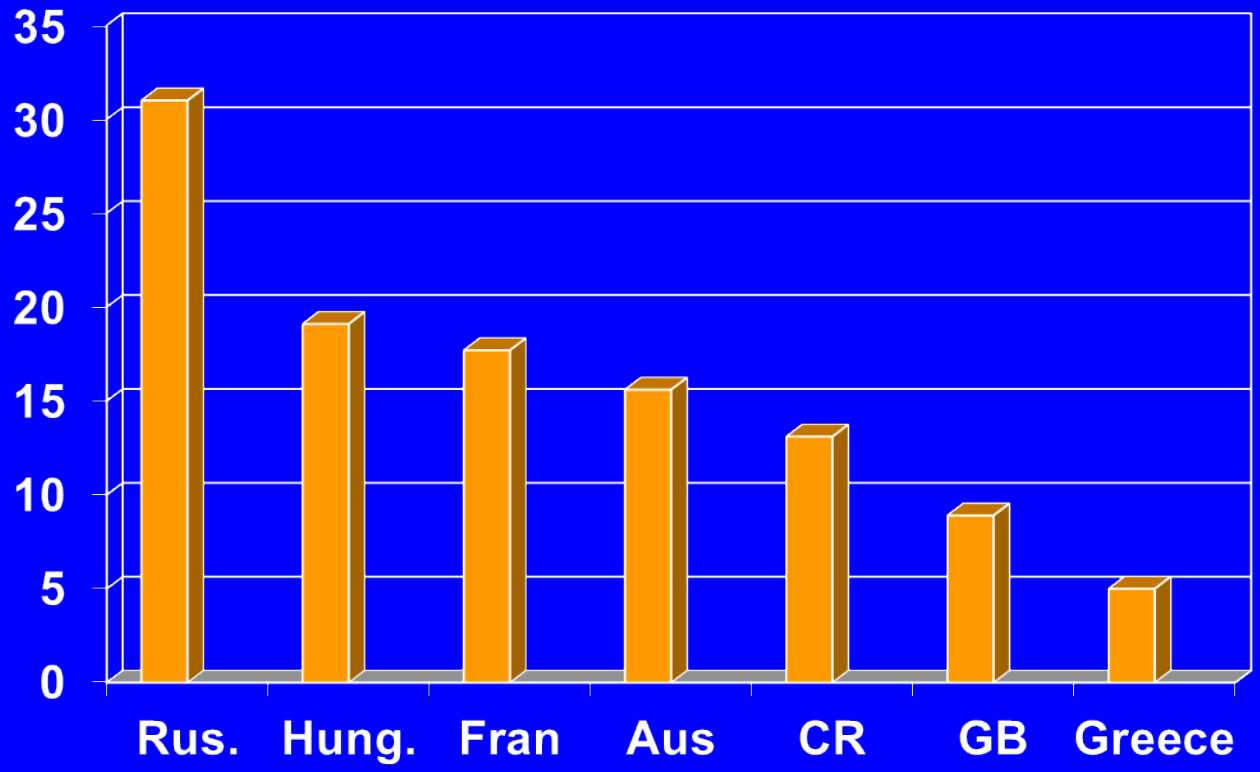
LONG-TERM COURSE OF DEPRESSION

7 – 15 % commits suicide



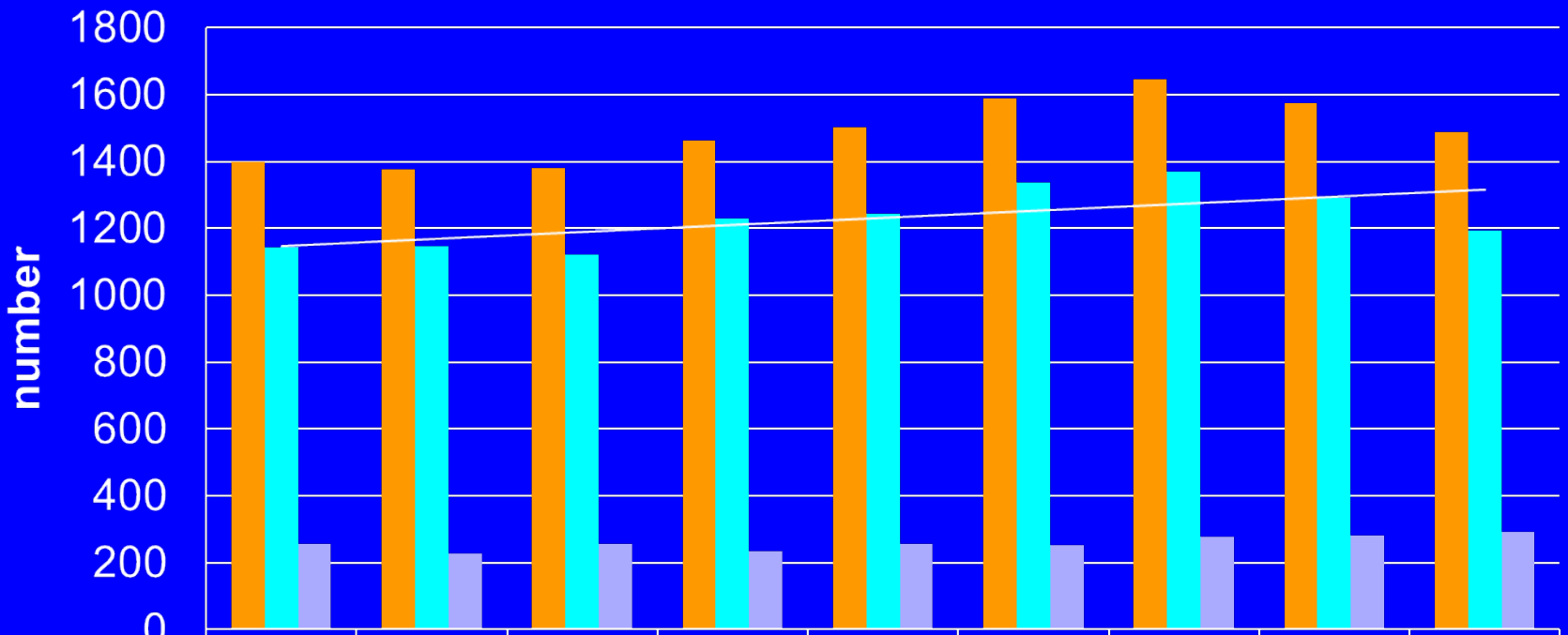
Keller and Sadock, 1991

NUMBER OF COMPLETED SUICIDES/100 000/YEAR



WHO 2018

Suicides/year CR



	2006	2007	2008	2009	2010	2011	2012	2013	2014
total	1400	1375	1379	1464	1502	1589	1647	1573	1488
men	1142	1147	1123	1230	1245	1337	1370	1291	1195
women	258	228	256	234	257	252	277	282	293

ČSÚ 2016

RISK OF SUICIDES ACCORDING TO DIAGNOSES

Disorder	Relative risk, SMR	Suicide rate, %/year	Lifetime risk %
Bipolar disorder	28	0,39	23,4
Severe depression	21	0,29	17,4
Mixed substance abuse	20	0,28	16,8
Severe anxiety disorder	11	0,15	9,0
Moderate depression	9	0,13	7,8
Schizophrenia	9	0,12	7,2
Personality disorder	7	0,10	6,0
Cancer	2	0,03	1,8
General population	1	0,014	0,8

Tondo et al., 2003

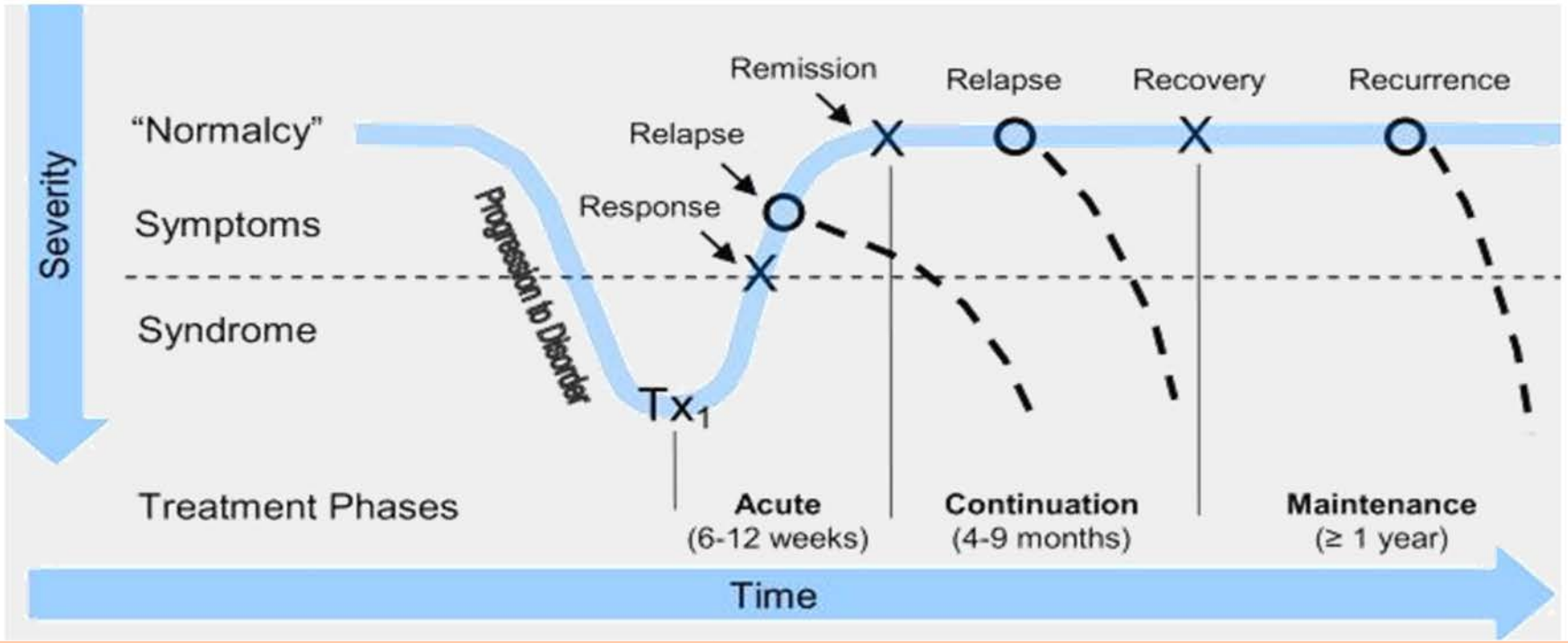
SUICIDAL BEHAVIOUR DURING ACUTE TREATMENT OF DEPRESSION

- ANTIDEPRESSANT EFFECT - 2 - 4 WEEKS
- ACTIVATING EFFECT - 1 - 2 WEEKS, ANXIETY
- FREQUENT VISITS, THE POSSIBILITY OF TELEPHONE CONSULTATION, CONTACT WITH RELATIVES

SUICIDAL PATIENT

- DO YOU EVER FEEL THAT LIFE IS NOT WORTH LIVING?
- DO YOU THINK ABOUT DEATH?
- DO YOU WANT TO DIE?
- DO YOU CONSIDER HURTING YOURSELF?
- DO YOU HAVE A PLAN?
- WHAT HELPED YOU NOT TO CARRY OUT THAT PLAN?

PHASES OF DEPRESSION TREATMENT



Response = reduction >50% symptoms	**Remission = few, if any, symptoms of depression**
Recovery = Long lasting full remission of symptoms and return to previous functioning	

Rush AJ et al., 2006

Indication for maintenance treatment with antidepressants

First depressive episode - no indication

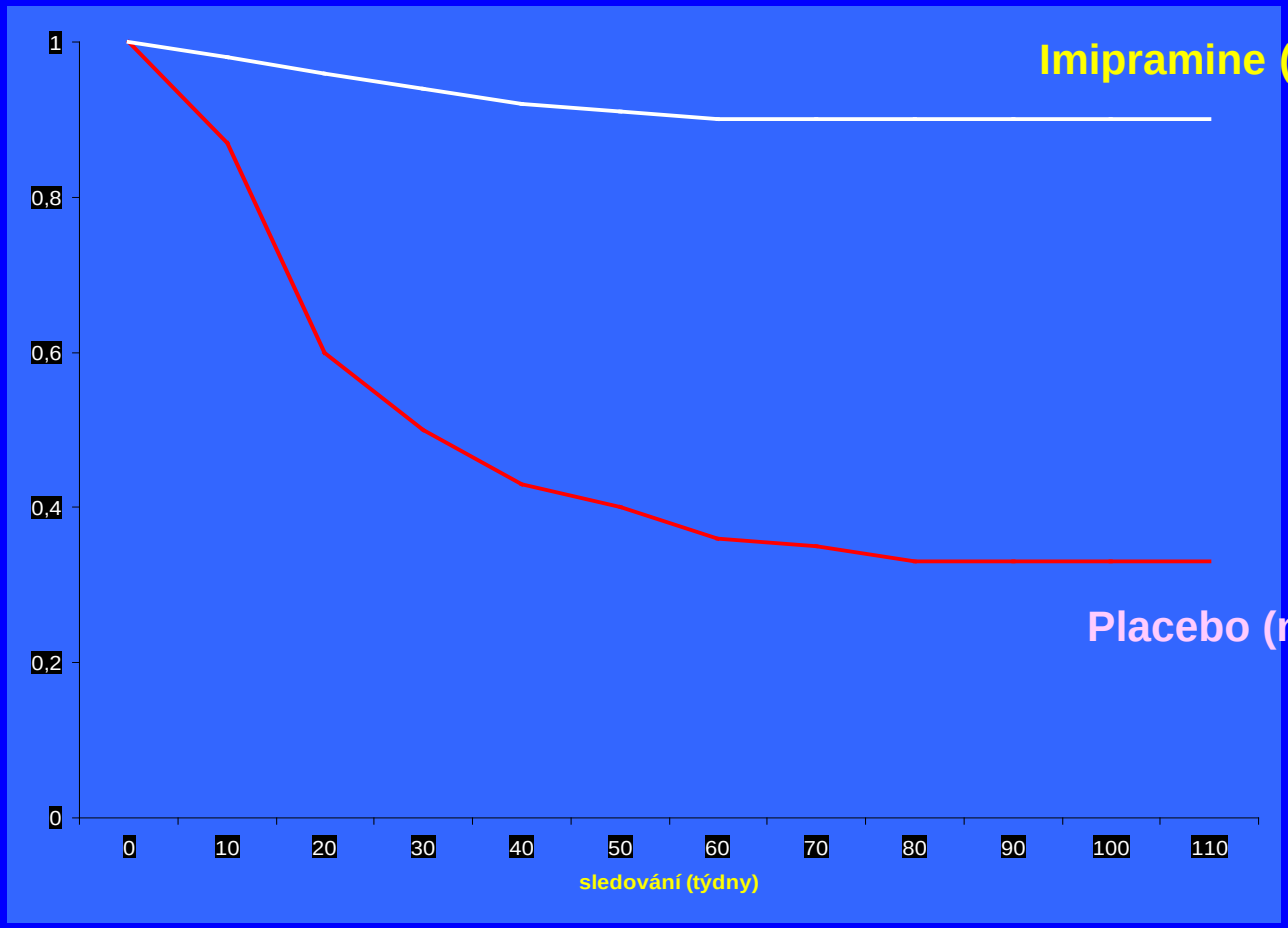
Two depressive episodes during the past 5 years and the following risk factors:

- Late onset (after the age of 60 years)
- Early onset (before the age of 30 years)
- Short interval between episodes
- Rapid development of episode
- Genetic risk of affective disorders
- Co-morbidity (anxiety disorders, dysthymia, overuse of alcohol or other addictive substances)
- Great intensity of depression, including suicidality
- Difficulties in the continuation treatment (residual symptoms)
- Difficulties in the restoration of working abilities and psychosocial functioning

Three depressive episodes during the past 5 years

Kasper a Lehofer, 2007, Raboch 2011

RESUTLTS OF MAINTENANCE TREATMENT WITH IMIPRAMINE IN 4. AND 5. YEARS IN COMPARISON WITH PLACEBO



The difference between the groups is statistically significant, p<0.006

Kupfer, D.J., et al., 1992

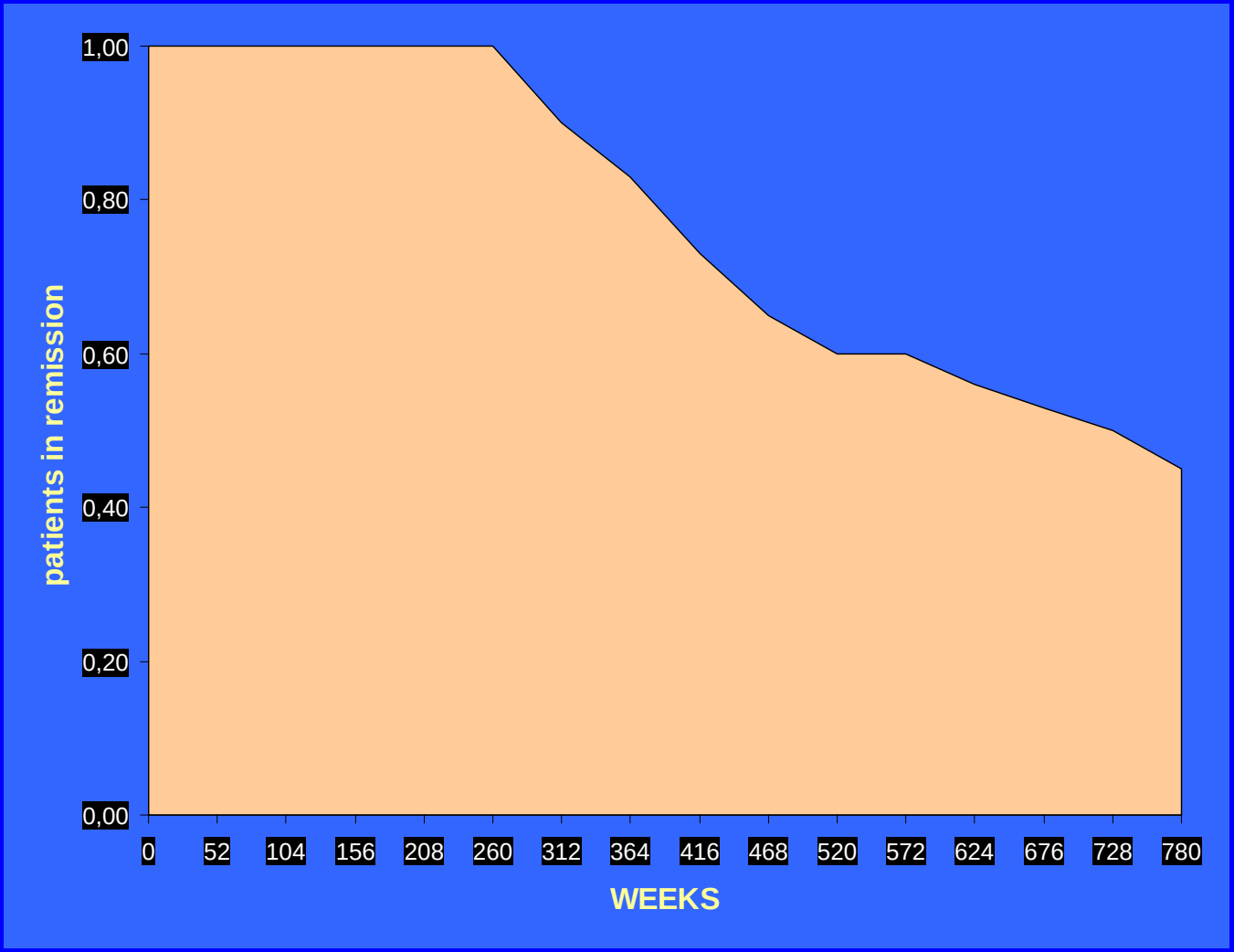
The inhibitory effects of modern antidepressants on cytochrome P450 (CYP) at usual doses

Drug	2C9	2D6	3A4
Fluoxetine	++	++++	++
Sertraline	++	+	++
Citalopram	0	+	0
Escitalopram	0	0	0
Venlafaxine	0	0	0
Bupropion	0	+++	0
Mirtazapine	0	0	0

0 insignificant, + mild, ++ moderate, +++significant, ++++ high

DeVane, 2004

Recurrences in 105 patients with major depression after 5 years-remission



Mueller, T.I., et al., 1999

F31 Bipolar affective disorder

- **Bipolar affective disorder**: Alternating manic and depressive episodes or, as the case may be, the state of remission (i.e. the state without signs of affective disorder)
- **Epidemiology**: Lifetime prevalence of bipolar disorder is 1% with no gender differences with the average onset of the disorder between 20 to 30 years
- High **comorbidity** with abuse of alcohol and drugs and somatic diseases (obesity, diabetes, cardiovascular and endocrine diseases)
- **Suicidality** in bipolar disorder is around 19%

F31 Bipolar affective disorder - bipolar depression

Treatment:

- **Biological methods prevail, but also psychotherapy**
- **In the acute phase (manic and depressive), to begin with mood stabilizers (lithium, valproate, olanzapine, risperidon, quetiapine, aripiprazol, ziprasidon, asenapin, paloperidol, lamotrigine)**
- **In complicated cases combinations of drugs or ECT**
- **From antidepressants, combinations with SSRIs are preferred**
- **With the onset of remission, continuation therapy is introduced (for at least 4 months) - the lowest effective level of mood stabilizers**

CANMAT 2012

COMPLIANCE

- **RATE OF ADHERENCE TO THE PRESCRIBED REGIMEN**
- **STRATEGIES FOR IMPROVING**
  - **PATIENT – PHYSICIAN RELATIONSHIP**
  - **EDUCATION (RELATIVES AND OTHERS)**
  - **ADEQUATE PHARMACOTHERAPY**

Haddad, 2000

THANK YOU FOR YOUR ATTENTION