

MOOD DISORDERS

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Heterogeneity of mood disorders



Clinical

Polarity*
Severity
Periodicity
Sex distribution
Age of onset
Comorbidity



Biological

Genetics
Biochemistry
Brain morphology
Electrophysiology
Treatment response

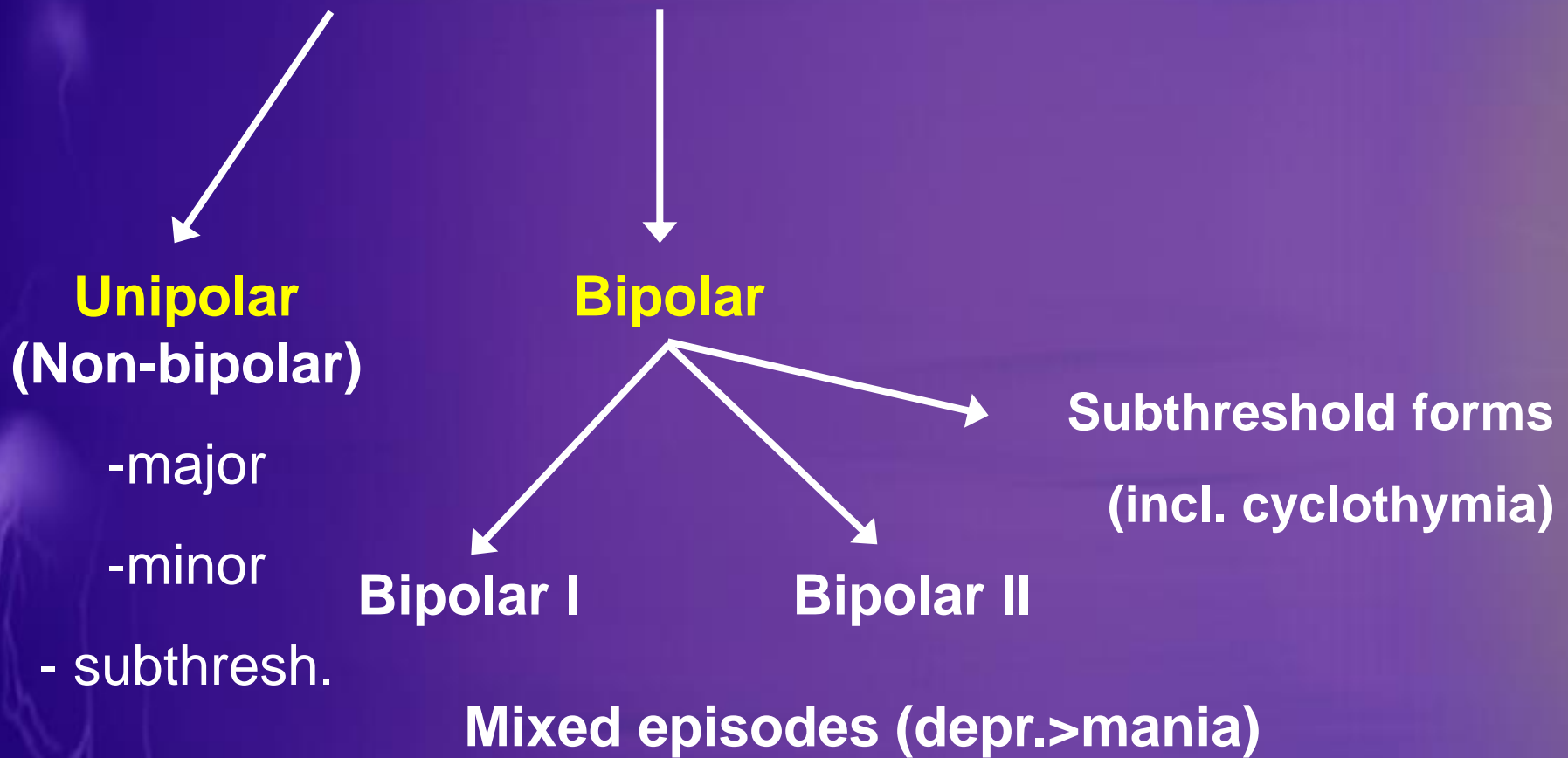


Psychosocial

Early negative life events
Acute stressors
Social support

*Unipolar versus bipolar

Mood disorders. Clinical heterogeneity- Polarity



Clinical manifestations of mood (affective) disorders

MAJOR

Minor

- UNIPOLAR

Unipol. maj. depr.

Recurrent brief depr

Minor depr.

Dysthymia

Subs. sympt. depr.

- BIPOLAR

Bipolar I

Bipolar II

Min. bipol. disord.

Cyclothymia

Clinical heterogeneity of mood disorders

-
- Primary vs Secondary
 - Unipolar vs Bipolar
 - Major vs Minor
 - Episodic vs Chronic
-

Different level of severity in major depression

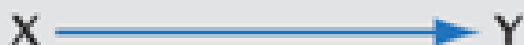
- Major depressive episode
 - nonmenalncholic
 - melancholic-nonpsychotic
 - melancholic-psychotic
 - mood-congurent features
 - mood-incongurent features
 - catatonic
-

Genetical heterogeneity of mood disorders

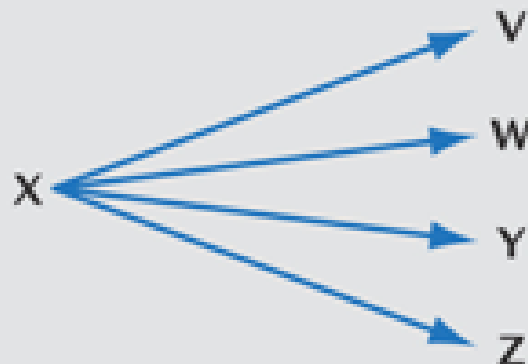
- Non-familial (sporadic) cases (40-50%)
 - Familial cases (50-60%)
chromosomes:
 - X, 18, 21, 5, 9,
(TPH, 5-HT, NA, DA transporter
etc)
-

Gene-phenotype relationships

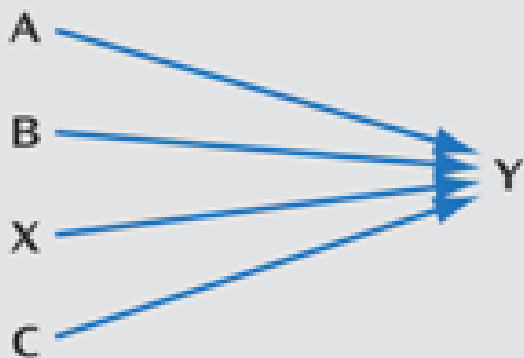
One-to-one relationship



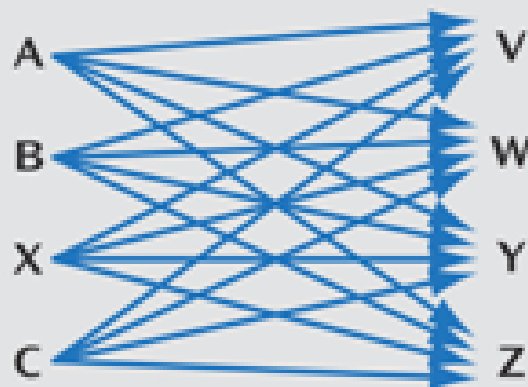
One-to-many relationship



Many-to-one relationship



Many-to-many relationship



**Gén –
fenotípus
lehetséges
kapcsolatai**

**A mentális
zavarokra
inkább a
'sok-sok'
modell illik**

**(Kendler,
*Am J
Psychiat*
162: 1243-
1252, 2005)**

Biochemical heterogeneity of mood disorders

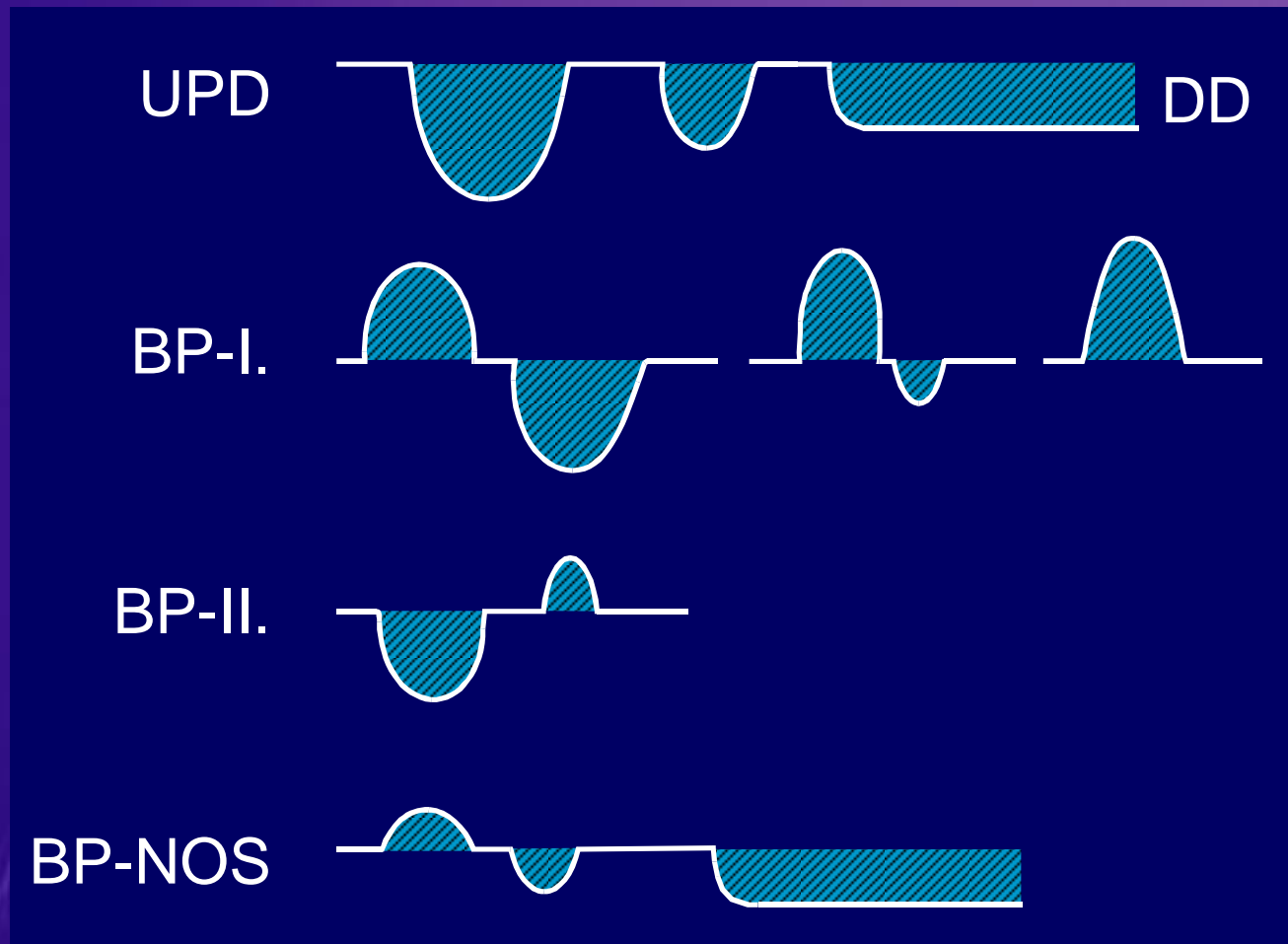
- Serotonin (5-HT)
 - Noradrenaline (NA)
 - Dopamine (DA)
 - Acetylcholine (?)

 - MAO, COMT, TPH, 5-HT transporter
(genetical polymorphism)
 - Receptor function
-

Psycho-social heterogeneity of mood disorders

- Early (childhood) negative life events
(predisposition)
 - Adulthood negative life events
(provocation)
 - Social support
(present, absent)
-

Unipolar – bipolar spectrum (syndromal forms)



DSM-5 criteria of Major Depressive Episode - 1

- A. Five (or more) of the following symptoms for at least two weeks:
- 1, DEPRESSED MOOD
 - 2, LOSS OF INTEREST/PLEASURE
 - 3, Significant weight loss or gain
 - 4, Insomnia or hypersomnia
 - 5, Psychomotor agitation or retardation
 - 6, Fatigue, loss of energy
 - 7, Worthlessness, guilt, self-blaming
 - 8, Diminished ability to think or concentrate
 - 9, Thoughts of death, suicidality

DSM-IV criteria of Major Depressive Episode - 2

- B. The symptoms cause significant distress or functional impairment
 - C. Possible causes of substances or medical conditions are excluded
-
- (No grief-reaction – DSM-IV)

DSM-IV criteria of Dysthymic Disorder/Minor Depression

- x Depressed mood for at least 2 yrs/wks+
- x Two (or more) of the following:
 - 1, Poor appetite or overeating
 - 2, Insomnia or hypersomnia
 - 3, Low energy or fatigue
 - 4, Low self-esteem
 - 5, Poor concentration/making decisions
 - 6, Feelings of hopelessness

Organic causes, grief-reaction is excluded, time criterion for DD: 2 years

DSM-IV criteria of Mania

- x Abnormally elevated/expansive/irritable mood for at least 1 week and:
- x Three (or more) of the following:
 - 1, Grandiosity
 - 2, Decreased need for sleep
 - 3, Talkative, pressured speech
 - 4, Flight of ideas, racing thoughts
 - 5, Distractibility
 - 6, Psychomotor agitation
 - 7, Excessive pleasurable activities
- x Markedly impaired functions/hospitalization

Organic causes excluded, time criterion: 1 week (or hospitalization)

DSM-5 criteria of Hypomanic Episode - 1

- A. Persistently elevated/expansive/irritable mood and abnormally increased activity or energy for at least 4 days and
- B. Three (or more) of the following (four or more if the mood is irritable):
 - 1, Grandiosity, inflated self-esteem
 - 2, Decreased need for sleep
 - 3, More talkative, pressured speech
 - 4, Flight of ideas, racing thoughts
 - 5, Distractibility (reported or observed)
 - 6, Psychomotor agitation
 - 7, Excessive activities with negative consequences
- C. Unequivocal change in functioning

A vertical lightning bolt strikes the left side of the slide, illuminating the dark purple background. The bolt is bright white and yellow at the top, with several smaller, branching strikes extending downwards.

DSM-5 criteria of Hypomanic Episode - 2

DSM-5 Specifiers for Depressive Disorders

With

- Anxious distress
- **Mixed features**
- Melancholic features
- Atypical features
- Catatonia
- Psychotic features
- Peripartum onset
- Seasonal pattern
- In partial/full remission, Mild/moderate/severe
- (With suicidal features) ?

DSM-5 Major Depressive Episode „with mixed features” specifier - 1

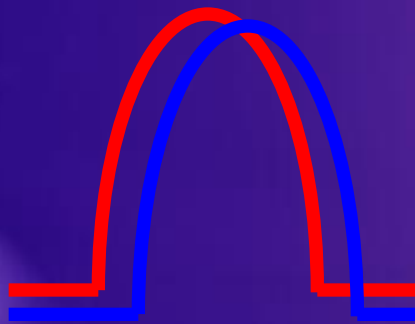
A, At least 3 of the following manic/hypomanic symptoms

- 1, Elevated, expansive mood
- 2, Inflated self-esteem or grandiosity
- 3, More talkative/pressured speech
- 4, Flight of ideas, racing thoughts (subjective)
- 5, Increased energy/goal-directed activity (socially, at work or school, or sexually)
- 6, Excessive involvement in activities that have painful consequences (money, buseniss, sexuality)
- 7, Decreased need of sleep

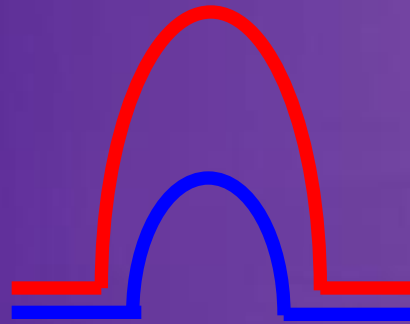
DSM-5 Major Depressive Episode „with mixed features” specifier - 2

- B, Mixed symptoms are observable by others
- C, When symptoms meet the full criteria for mania or hypomania the diagnosis should be bipolar I or II disorder
- D, The mixed symptoms are not attributable to the physiological effects of a substance (drug of abuse, medication,...)

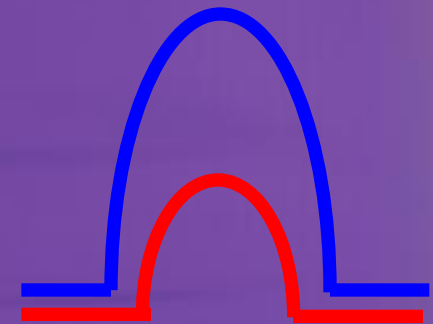
The three clinical phenotypes of overlapping affective episodes (DSM-IV)



Mixed
affective
episode



Dysphoric
mania



Mixed
(bipolar)
depression

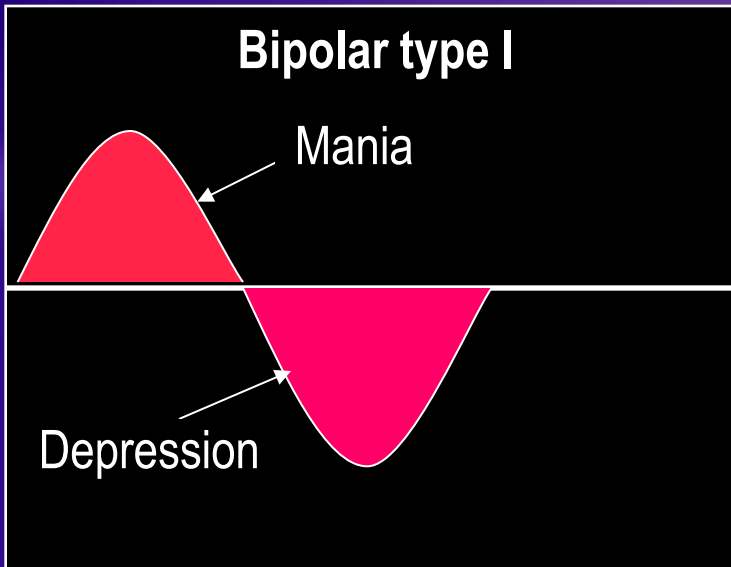
Rihmer, 2005

Most frequent clinical manifestations of major mood disorders

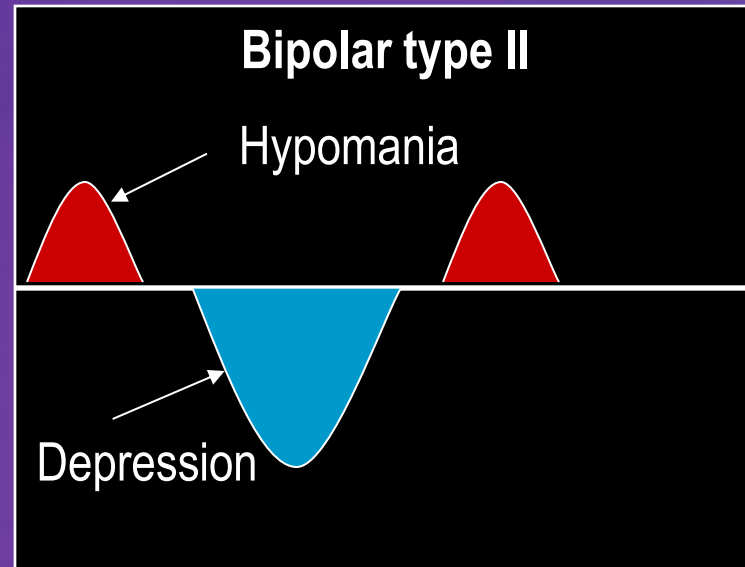
- Unipolar major depression
 - single episode
 - recurrent
 - Bipolar I disorder
 - major depression + mania
 - minor depression + mania
 - Bipolar II disorder
 - major depression + hypomania
-

Bipolar spectrum

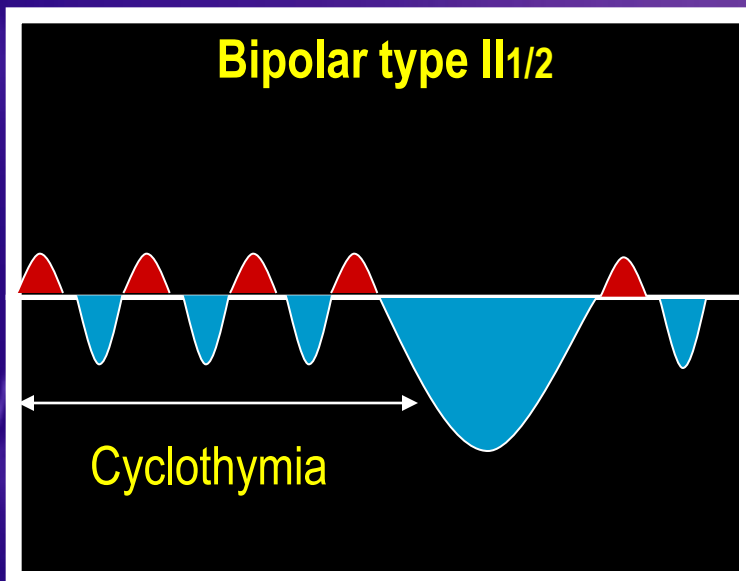
Bipolar type I



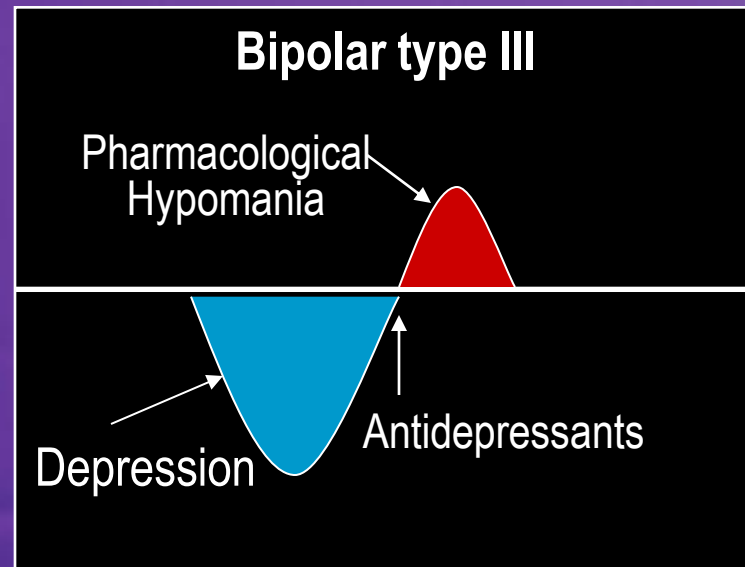
Bipolar type II



Bipolar type II/2



Bipolar type III



Lifetime Prevalences of Bipolar I, Bipolar II, and Unipolar Major Depression (%) in the Adult Population

Source	Diagnosis	BP-I	BP-II	UPMD	%BP
• Weissman et al. 1988	DIS- DSM-III	0,8	0,5	4,4	23
• Kessler et al. 1994	CIDI- DSM-III-R	1,6	0,2	15,8	10
• Szádóczy et al. 1998	DIS- DSM-III-R	3,0	2,0	15, 1	25
• Ten Have et al. 2002	CIDI- DSM-III-R	1,3	0,6	15,4	11
• Faravelli et al. 2004	MINI/FPI- DSM-IV	0,5	0,4	9,5	8
Merikangas et al.	DSM-IV	1.0	1.1		

BP-I: 0.8-3.0 %, BP-II: 0.2-2.0 %, UPMD: 4.4-15.8 %

Prevalences of DSM-III-R Major Mood Disorders (%) in the Adult Population of Hungary (N=2953, 18-64 yrs)

Diagnosis	Lifetime	1-year	1-month
• Major Depr. Dis.	15,1	7,1	2,6
• Bipolar Dis.	5,0	2,7	1,3
Bipolar I	3,0	1,1	0,5
Bipolar II	2,0	1,6	0,8

Szádóczy et al. J. Aff. Dis. 1998, 50:153-162
Szádóczy et al. Orv. Hetil. 2000, 141:17-22

Prevalence, recognition and adequate treatment of major depression in primary care

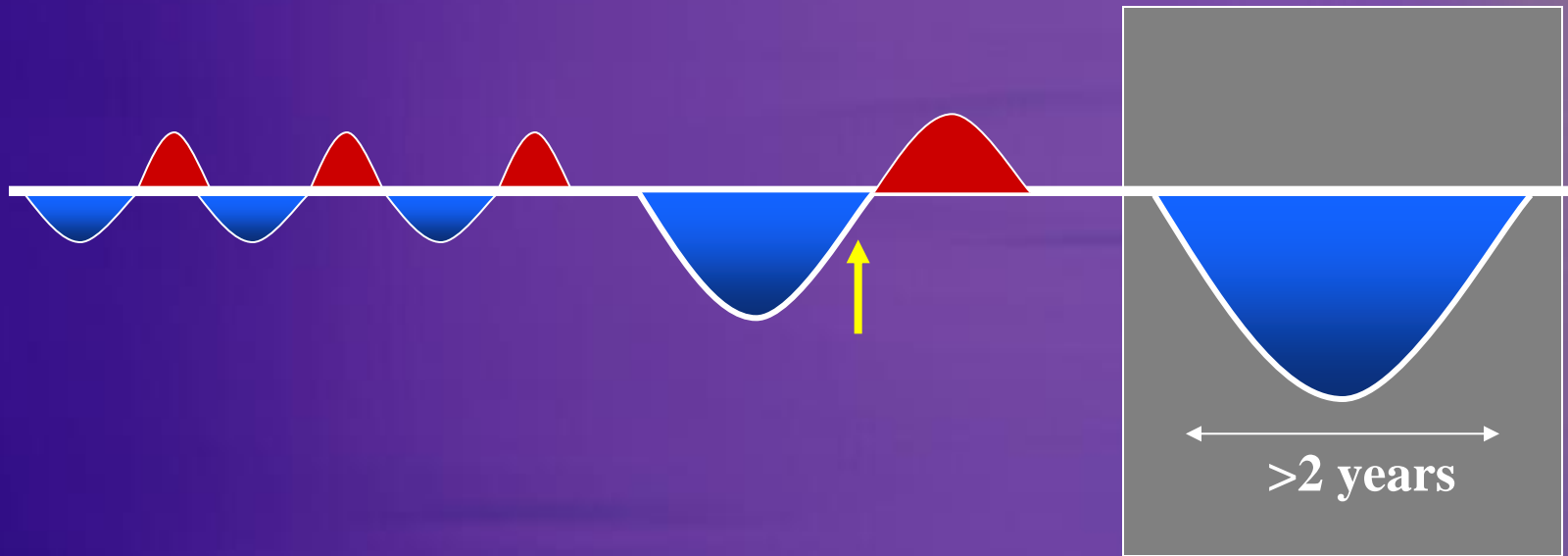
The point prevalence of major depression in primary care: 8 – 10 %

Recognition and **treatment** rate:

- 1991 and before:
10 - 15 % and **5 - 7 %**
- 1996 and after:
62 - 85 % and **33 - 50 %**

Lecrubier, Int J Psychiat Clin Pract, 2001; 5 (S-1) 3-10.
Berardi et al, Psychother Psychosom, 2005; 74: 225-230.

Evolution of bipolar disorder



Unipolar – Bipolar conversion

- 12.5 – 46 % of „unipolar” major depressives become Bipolar I or II during the 5 -15 year follow-up
- Predictors: early onset, severe depr., psychotic features, retardation, bipolar FH, cyclothymia/mood-energy lability

Akiskal et al, Arch Gen Psychiat, 1995, 52: 114-125.

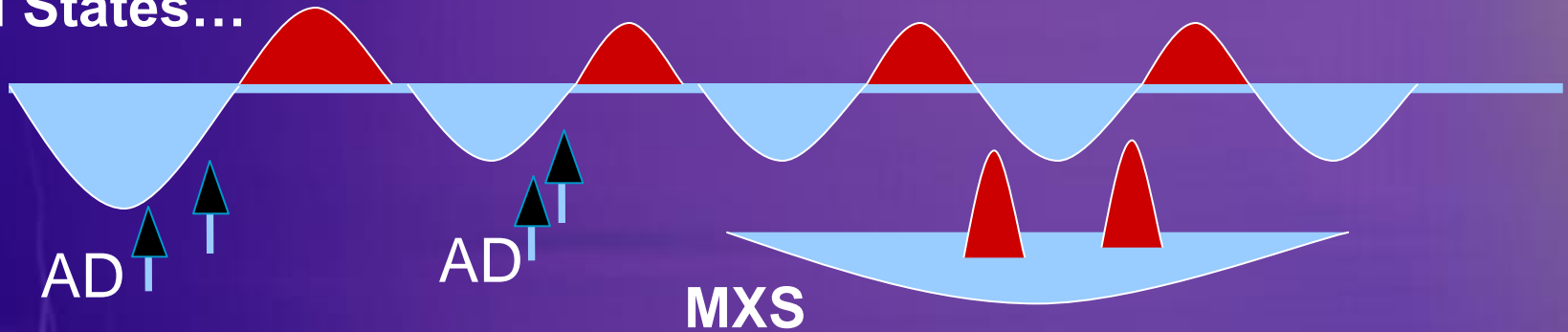
Goldberg et al, Amer J Psychiat, 2001, 158. 1265-1270.

Apparently Unipolars

Mood Switching considered as a “good response”



Chronic exposure to AD = Destabilisation, Rapid Cycling, Mixed States...



Adapted from A. Koukopoulos

Depression and mania are only successive conditions (false)

D

UPMD

D

Bp II

m

D

Bp I

M

Depression and mania are both successive and simultaneous conditions (true)

D

UPMD

D
m

UPMD
(DMX)

D
m

Bp II
(DMX)

D

Bp II

D

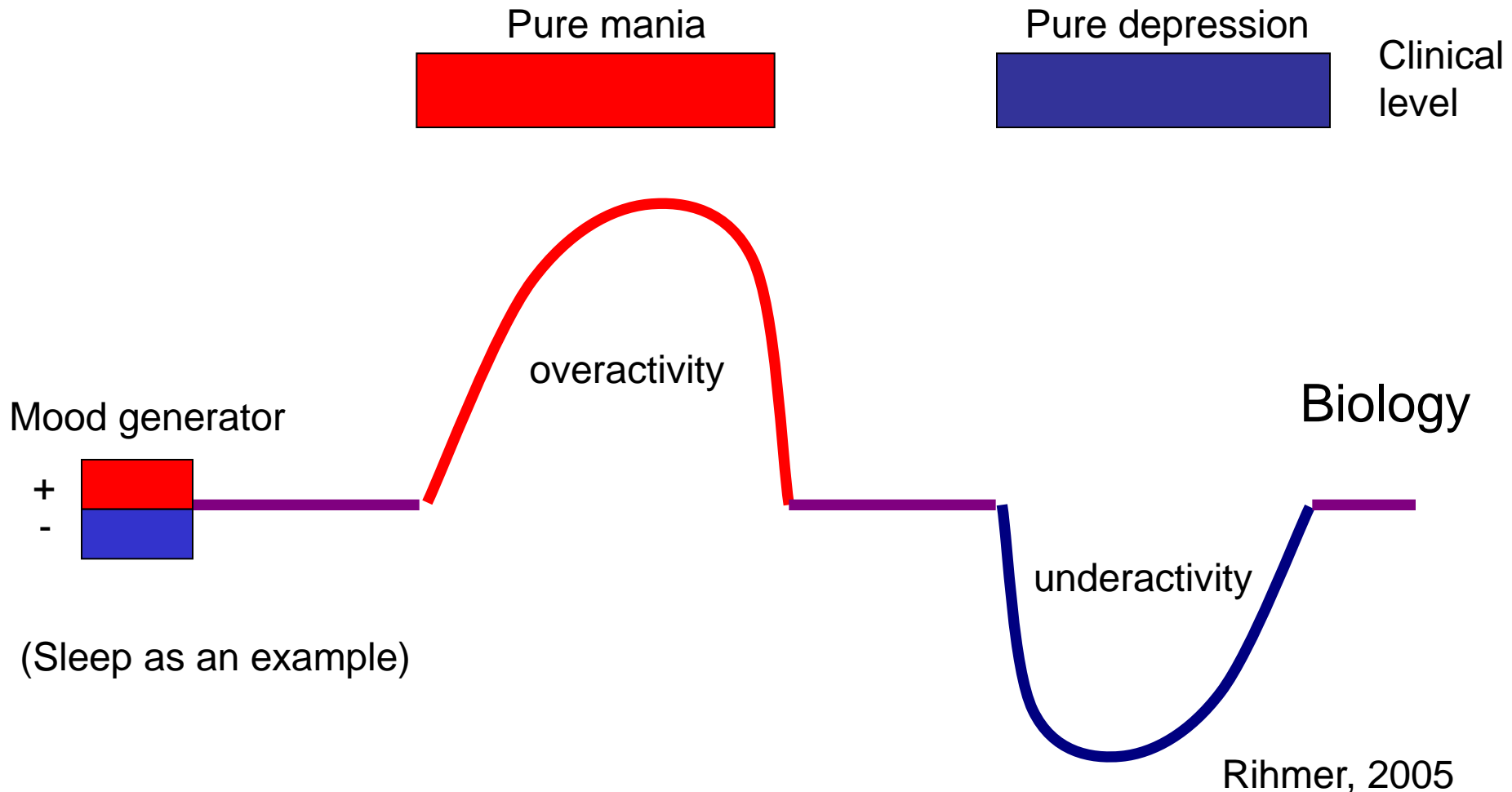
Bp I

M

Agitated depression

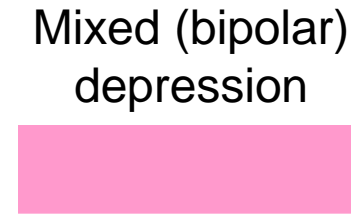
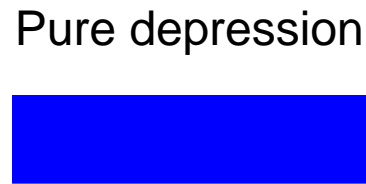
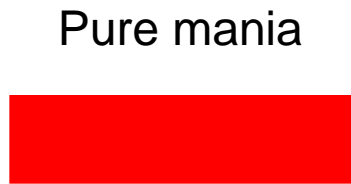
Traditional concept:

mania is an active and depression is a passive condition



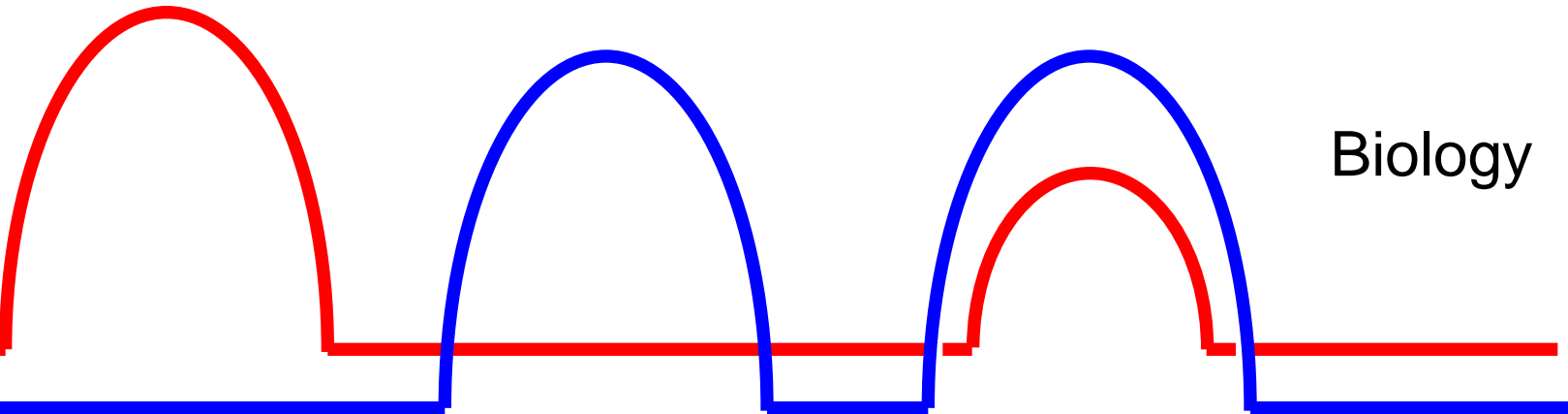
Current concept:

Both mania and depression are active processes that can occur both successively and simultaneously



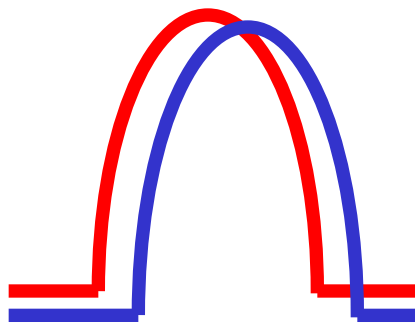
Clinical level

Generators of mood

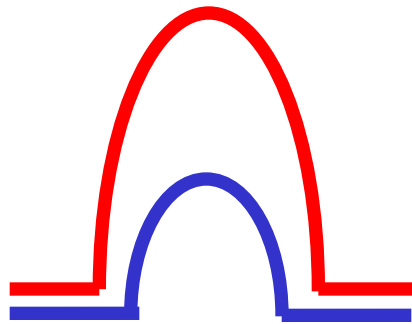


Rihmer, 2005

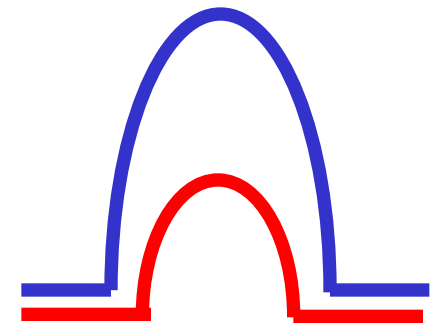
The three clinical phenotypes of overlapping affective episodes



Mixed
affective
episode



Dysphoric
mania



Mixed
(bipolar)
depression

Rihmer, 2005

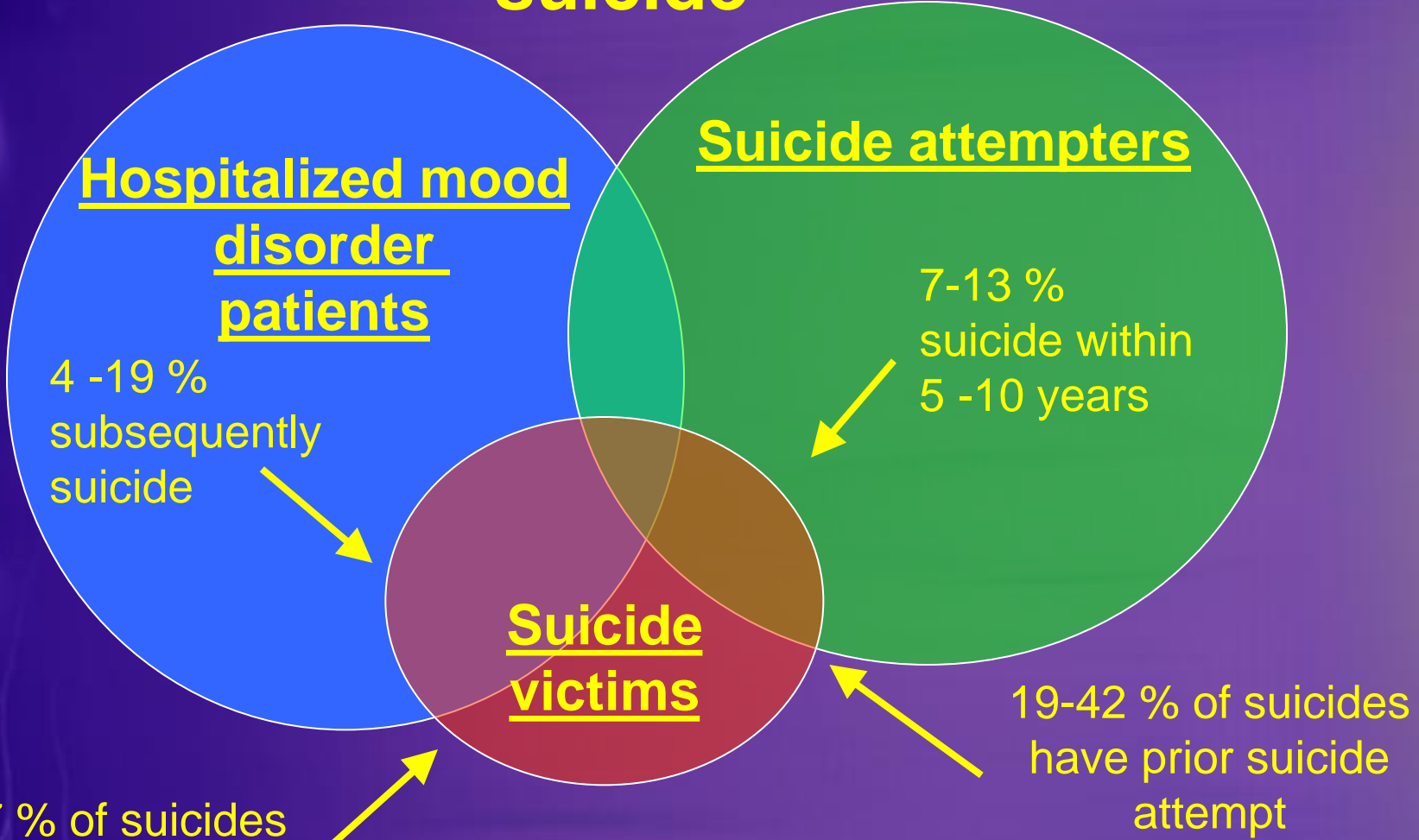
Pure vs comorbid mood disorders

- Pure mood disorder (i.e. mood disorders without comorbid Axis I disorders) is relatively rare (30-40 %)
 - The most frequent Axis I comorbid disorders in mood disorders are:
 - Anxiety disorders (30-60 %)
 - Substance use disorders (25-70 %)
-

Depression and suicide

- 60-75 % of suicide victims have (mostly untreated) major depression (UP or BP)
- 15-19 % of patients with major mood disorders subsequently suicide
- 35-65 % of patients with major mood disorders have prior suicide attempt(s)
- Successful acute/long-term treatment of mood disorders significantly reduces the suicide mortality

Major mood disorder, suicide attempt and suicide

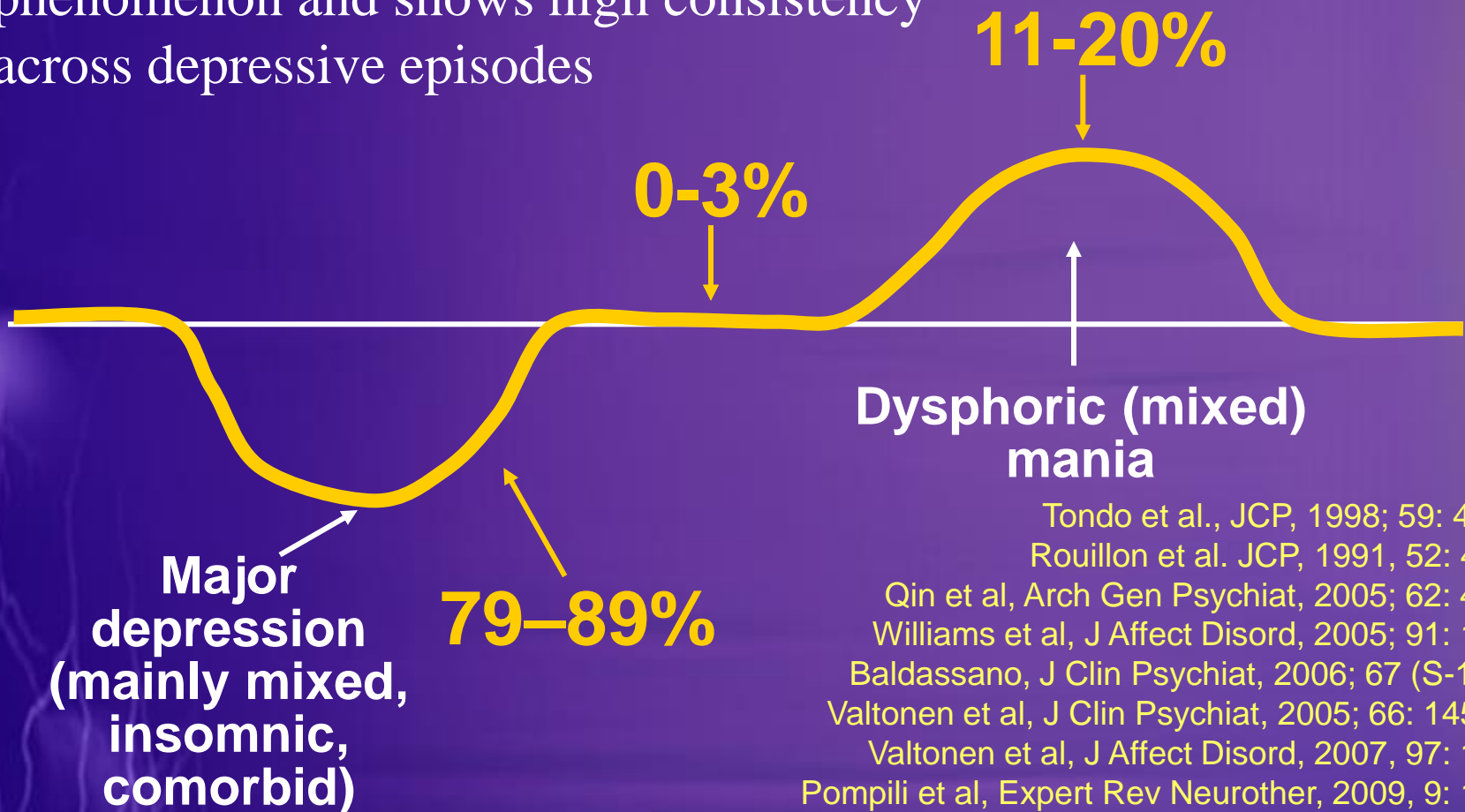


45-87 % of suicides have current major mood disorder (mostly untreated)

Avery and Winokur, Arch Gen Psychiat 1978; 35: 749-753
Bostwick and Pankratz, Amer J Psychiat 2000, 157: 1925-1932
Rihmer and Kiss, Bipol Disord 2002, 4:(Suppl.1), 21-25.
Suokas et al, Acta Psychiat Scand 2001,104: 117-121

When do major mood disorder patients commit or attempt suicide?

Suicidal behaviour in mood disorders is state-and severity dependent phenomenon and shows high consistency across depressive episodes



- Tondo et al., JCP, 1998; 59: 405-414.
- Rouillon et al. JCP, 1991, 52: 423-431.
- Qin et al, Arch Gen Psychiat, 2005; 62: 427-432.
- Williams et al, J Affect Disord, 2005; 91: 189-194.
- Baldassano, J Clin Psychiat, 2006; 67 (S-11): 8-11.
- Valtonen et al, J Clin Psychiat, 2005; 66: 1456-1462.
- Valtonen et al, J Affect Disord, 2007, 97: 101-107.
- Pompili et al, Expert Rev Neurother, 2009, 9: 109-136.
- Isometsa, Can J Psychiat, 2014; 59: 120-130.

Suicide risk factors

Primary suicide risk factors

Psychiatric disorder: major depression, schizophrenia, substance-use disorders

Secondary suicide risk factors

Early negative life events, acute psycho-social stressors, unemployment

Tertiary suicide risk factors

Male gender, old age, spring, morning

Pharmacological treatment and medical contact of depressed suicides

- The rate of appropriate antidepressant pharmacotherapy among currently depressed suicide victims is between 10 and 20 %
- Up to 60 % of suicide victims contact their GPs or psychiatrists 1-3 months before the suicide

Luoma et al, *Amer J Psychiat*, 2002; 159: 909-916.
Rihmer, *Curr Opin Psychiat*, 2007; 20: 17-22.

Suicidal behaviour in treated vs untreated mood disorder patients

The yearly risk of completed suicide

- General population 0.011 %
(USA, UK, Australia)
- Untreated depressives 0.298 %
- Patients on antidepressants 0.090 %
(USA, UK, Australia) (Risk reduction: 71 %)

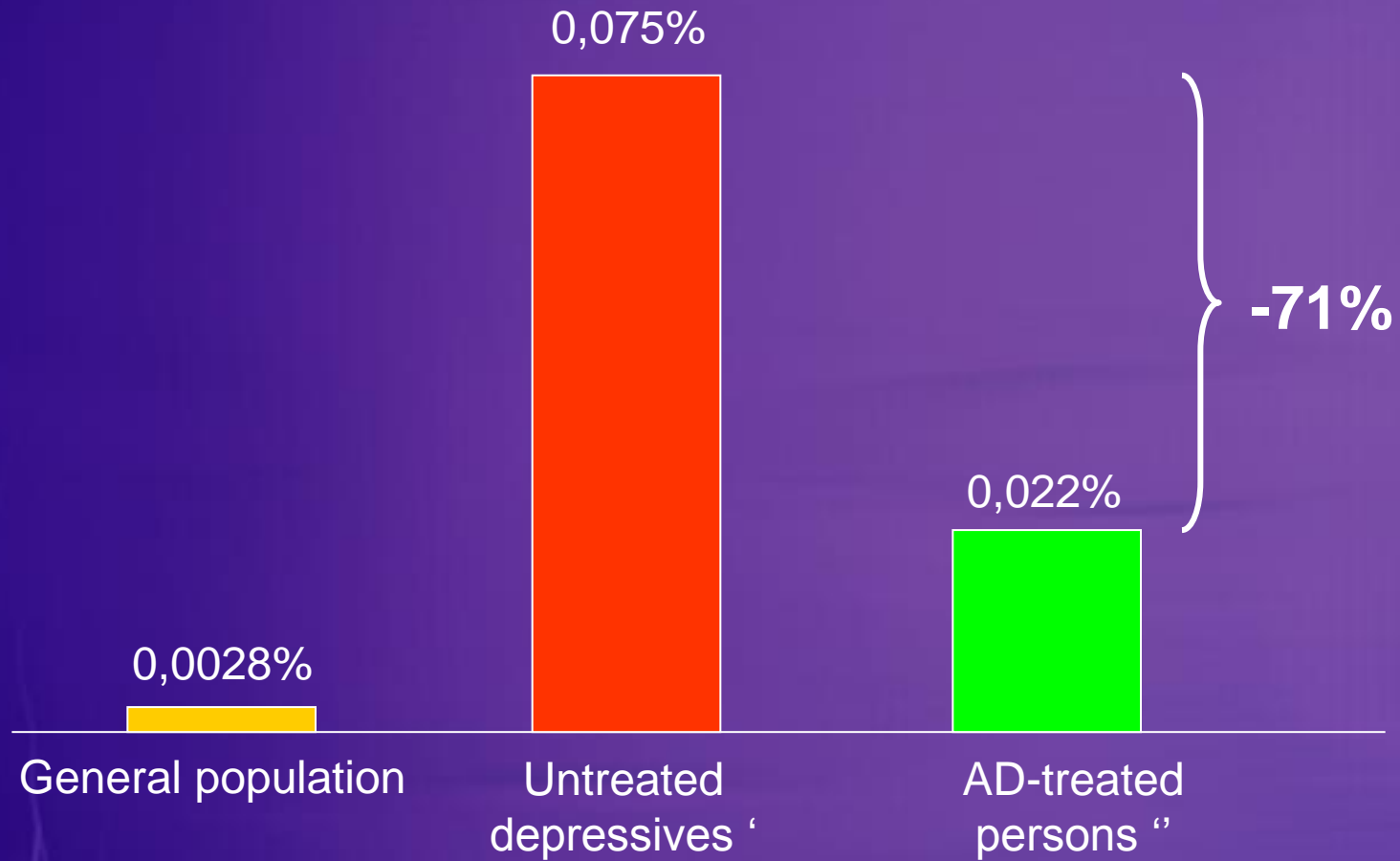
Untreated depressives vs gen. population: 27 X

Untreated depressives vs patients on ADs: 3 X

Patients on ADs vs gen. population: 8 X

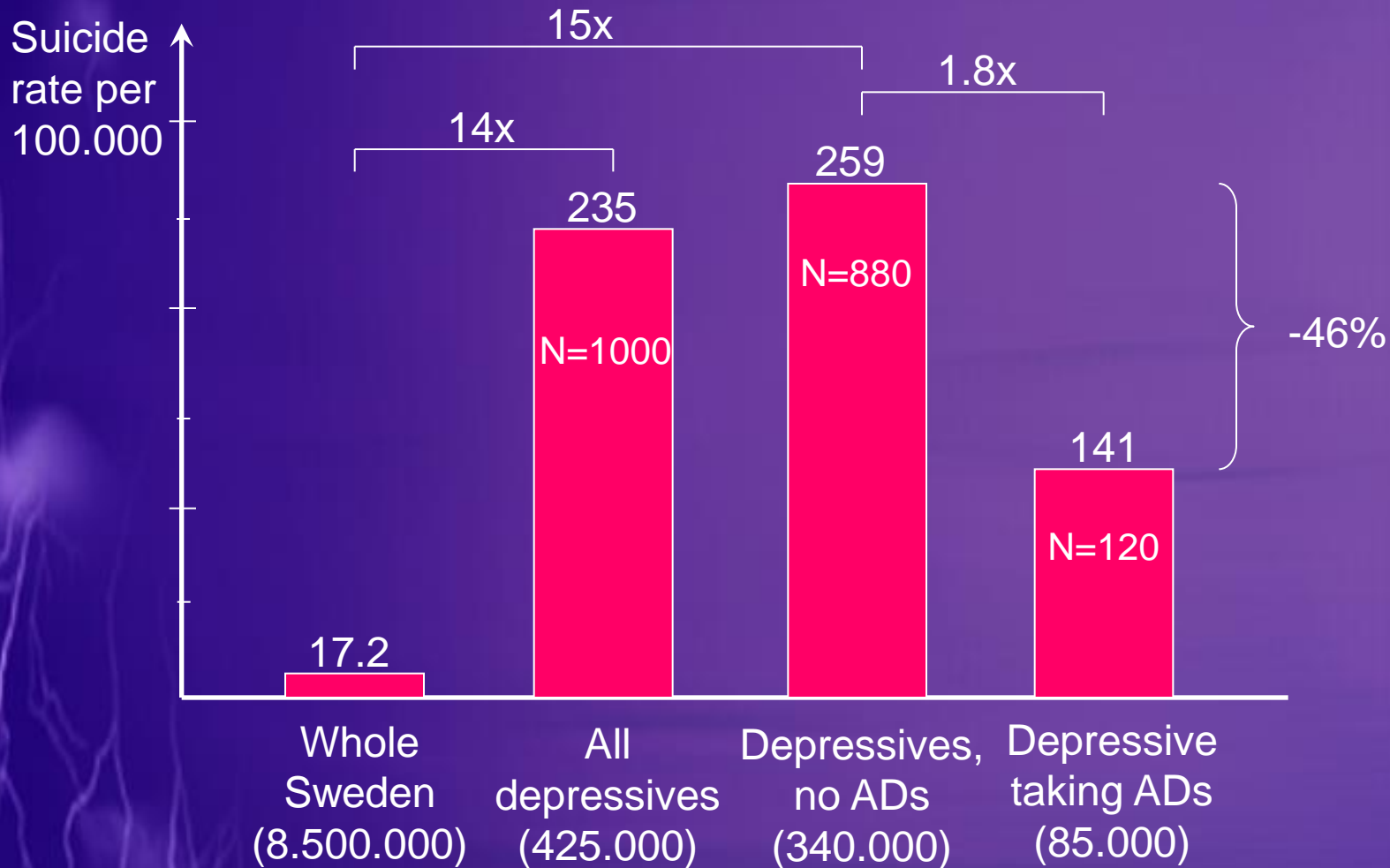
Simon et al, Amer J Psychiat, 2006, 163, 41-47.

3-month risk of suicide among AD-treated persons (USA, UK, Australia)



‘ Harris and Barraclough, 1997, ‘ Jick et al, 2004, Didham et al, 2005, Simon et al, 2006,

Estimated yearly suicide rates (per 100.000) of depressives with and without AD treatment in Sweden (1990-1991)



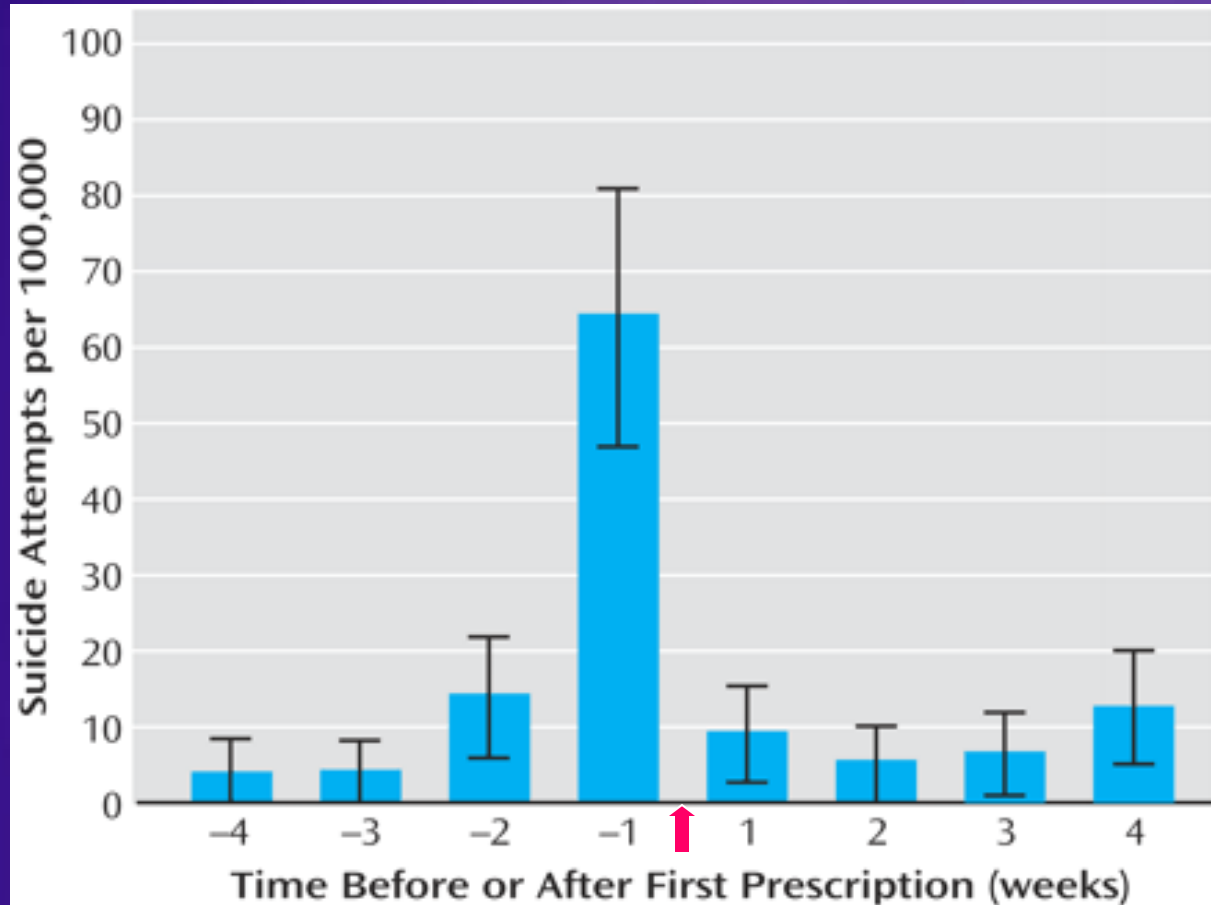


Figure 5. Rates of Suicide Attempts During the 4 Weeks Before and 4 Weeks After Initial Antidepressant Prescription^a

^aBars indicate 95% confidence intervals.

Biological basis of mental disorders

- Genetical predisposition
- Life events (early and current)
- Neurotransmitter vulnerability

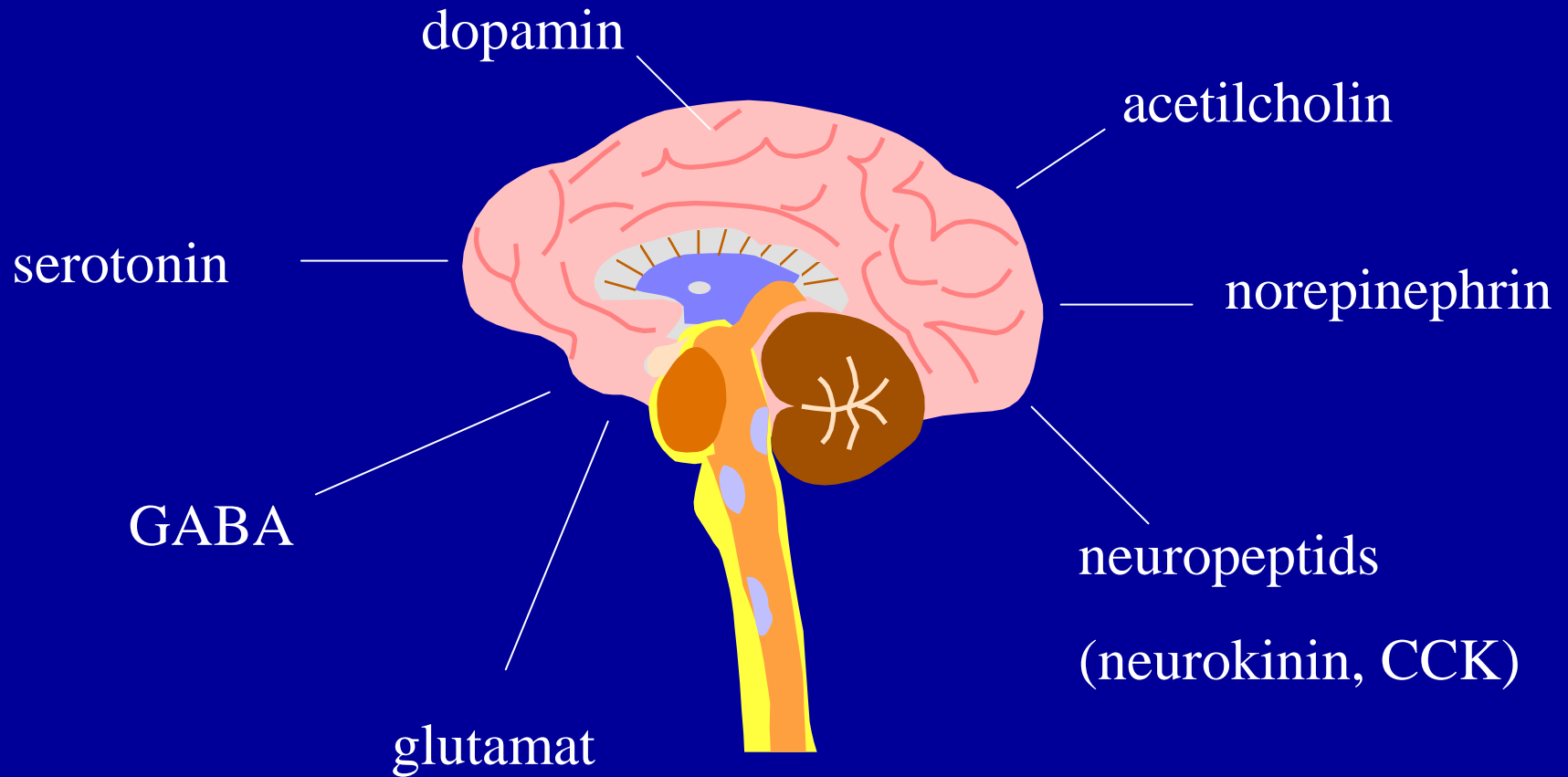
Mood disorders: serotonin, noradrenalin, dopamine

Schizophrenia: dopamine, glutamate

Anxiety disorders: GABA, serotonin

Alzheimer disease: acetylcholine

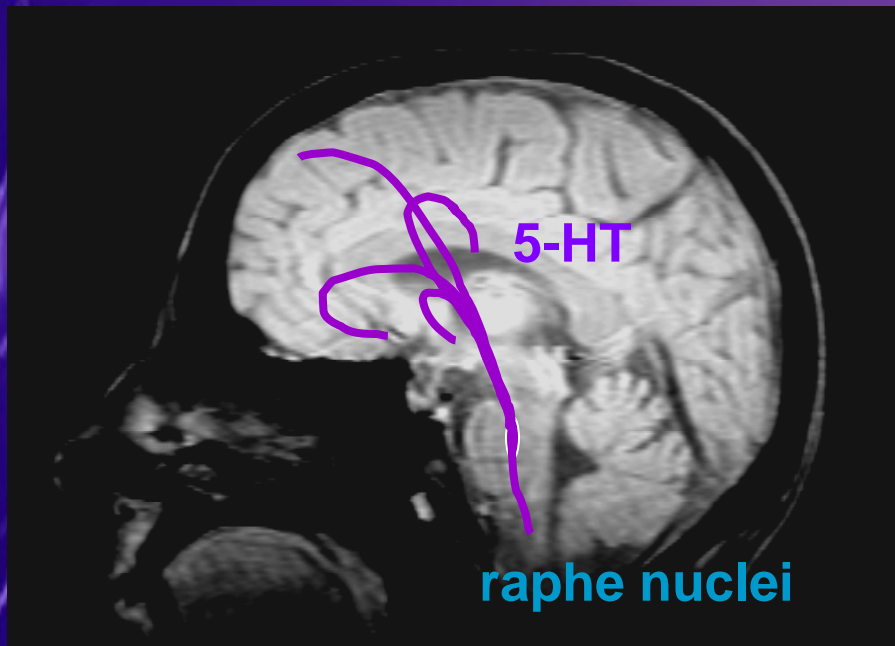
NEUROTRANSMITTER SYSTEMS, RELATED TO PSYCHIATRIC DISORDERS



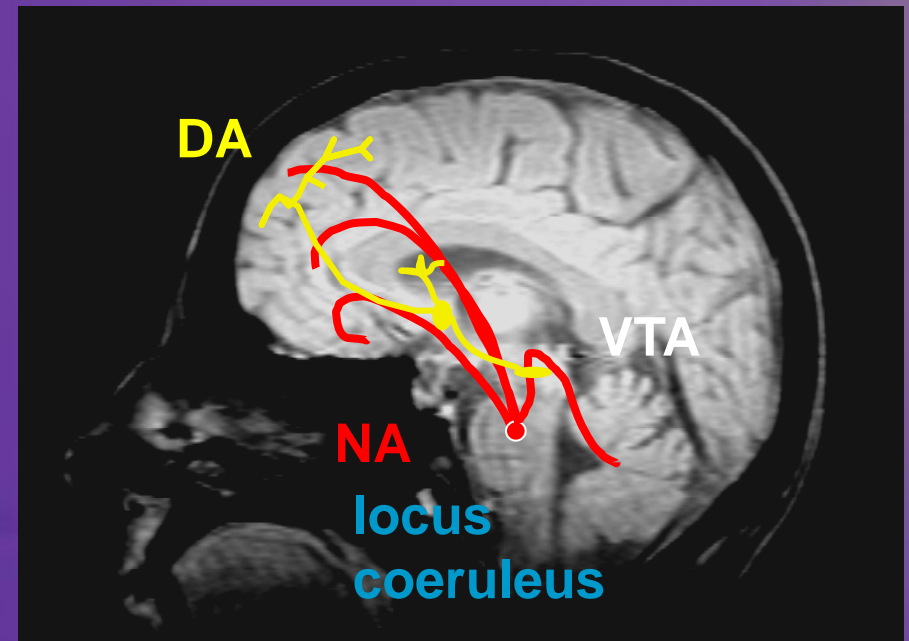
**Reuptake inhibition, receptor (ant)agonism
and antidepressive/antimanic action**



Julius Axelrod (1912-2004)



serotonergic system



Noradrenergic/dopaminergic system

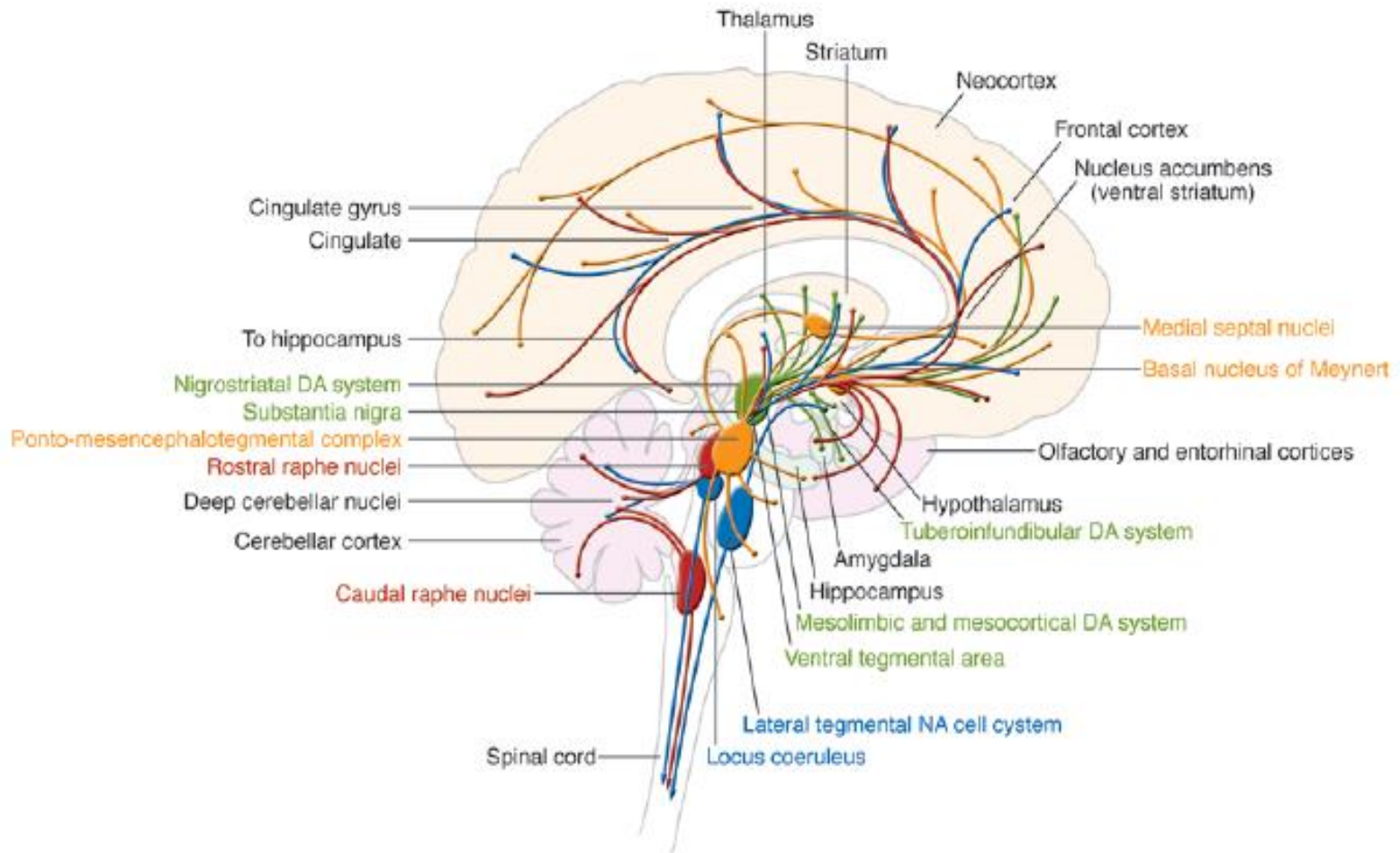
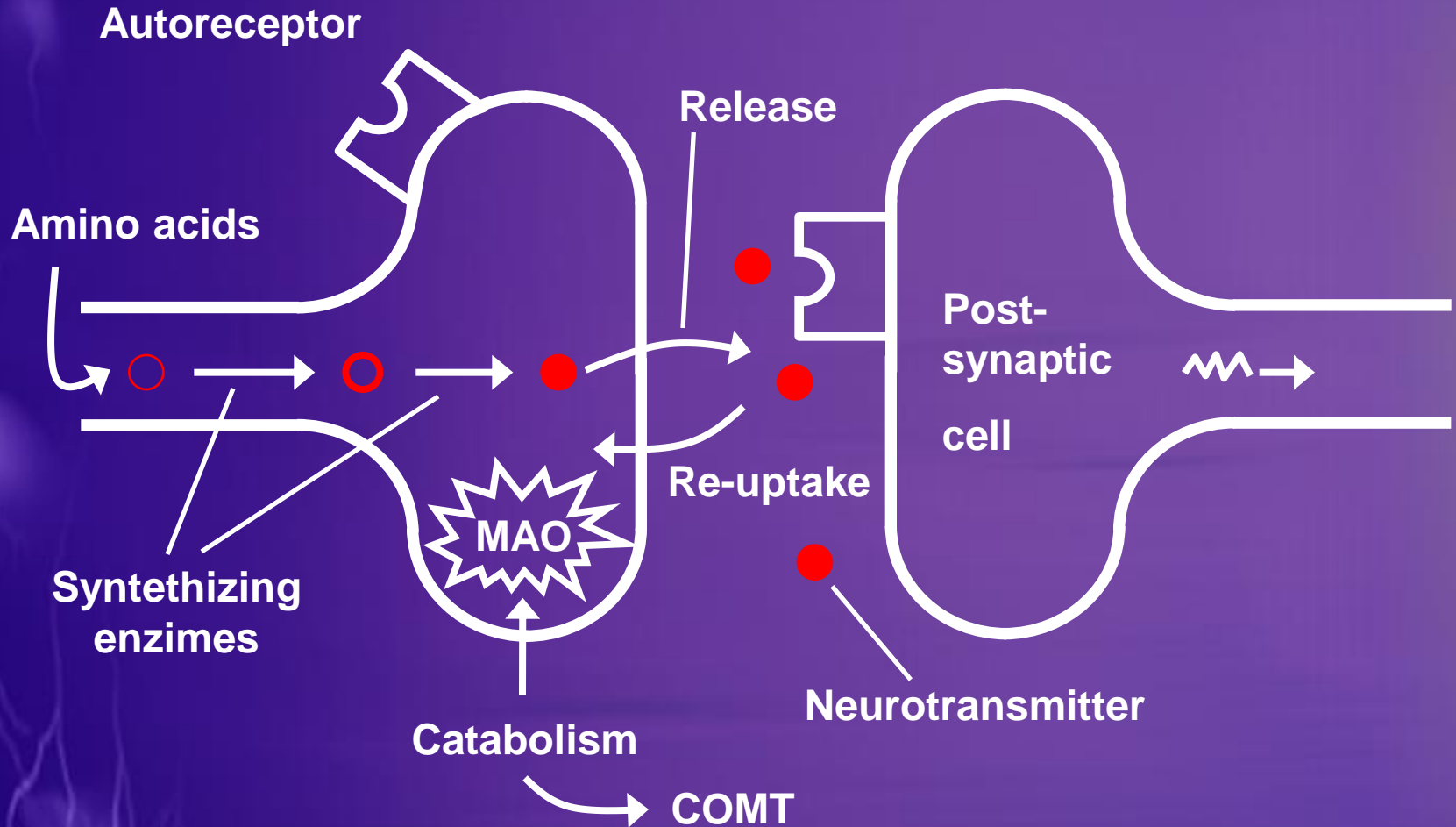


Figure 1

Locations of the monoaminergic nuclei within the brain as well as the projections from these nuclei throughout the brain. Nuclei as well as their projections are color coded: yellow, cholinergic; green, dopaminergic; blue, noradrenergic; red, serotonergic.

Neurotransmission in the CNS



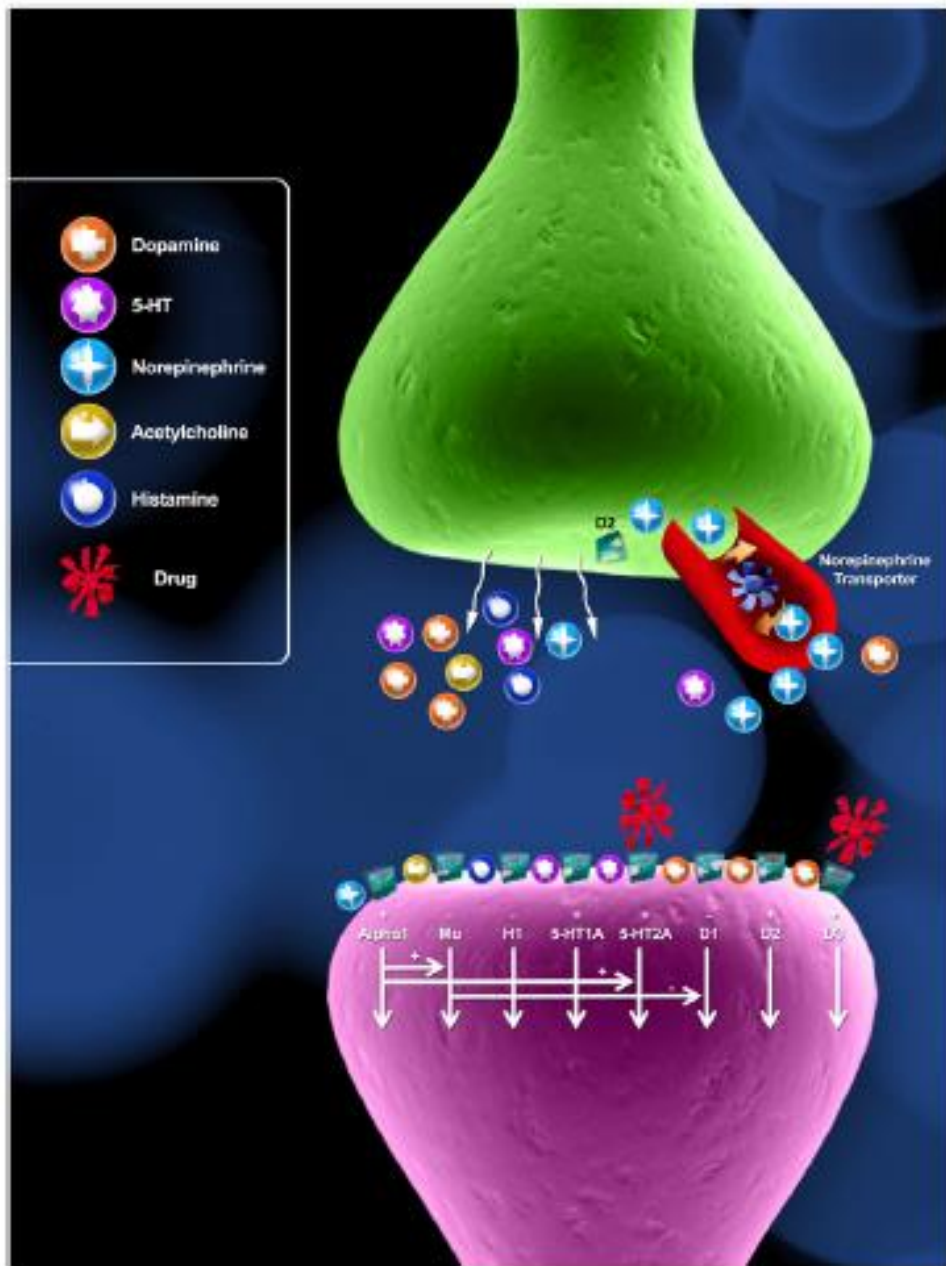
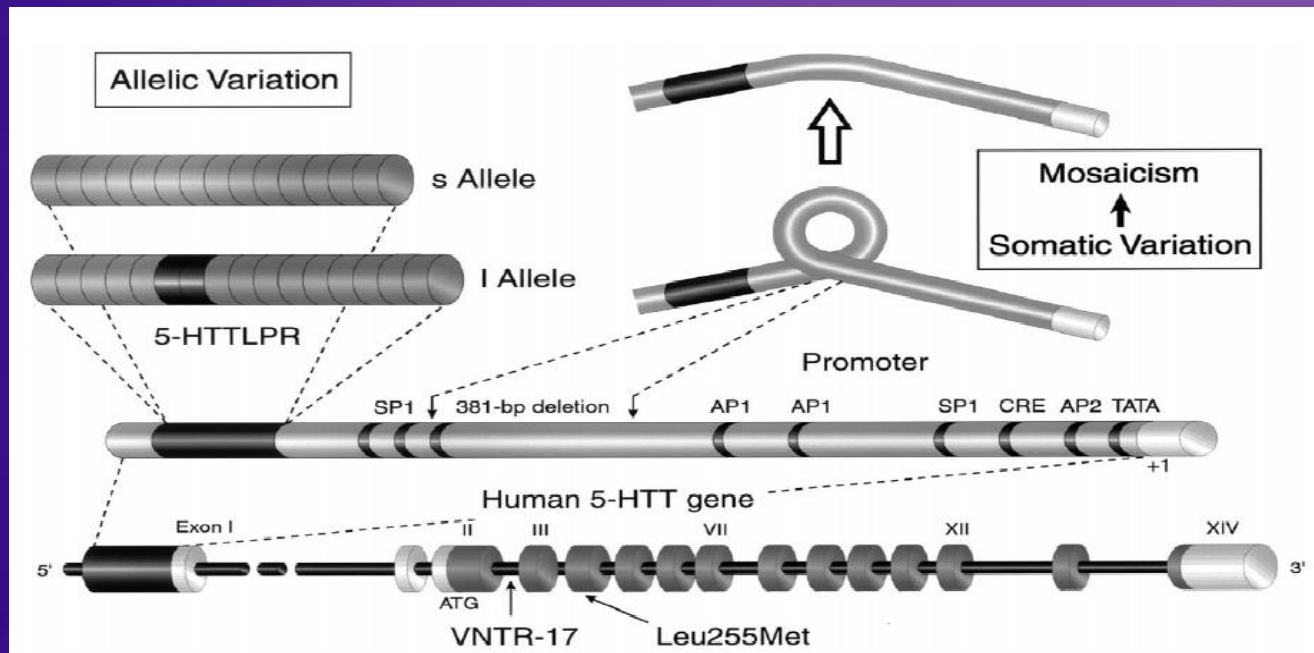


Fig. 3. Events at the synaptic level, related to the antidepressant effect in bipolar depression.

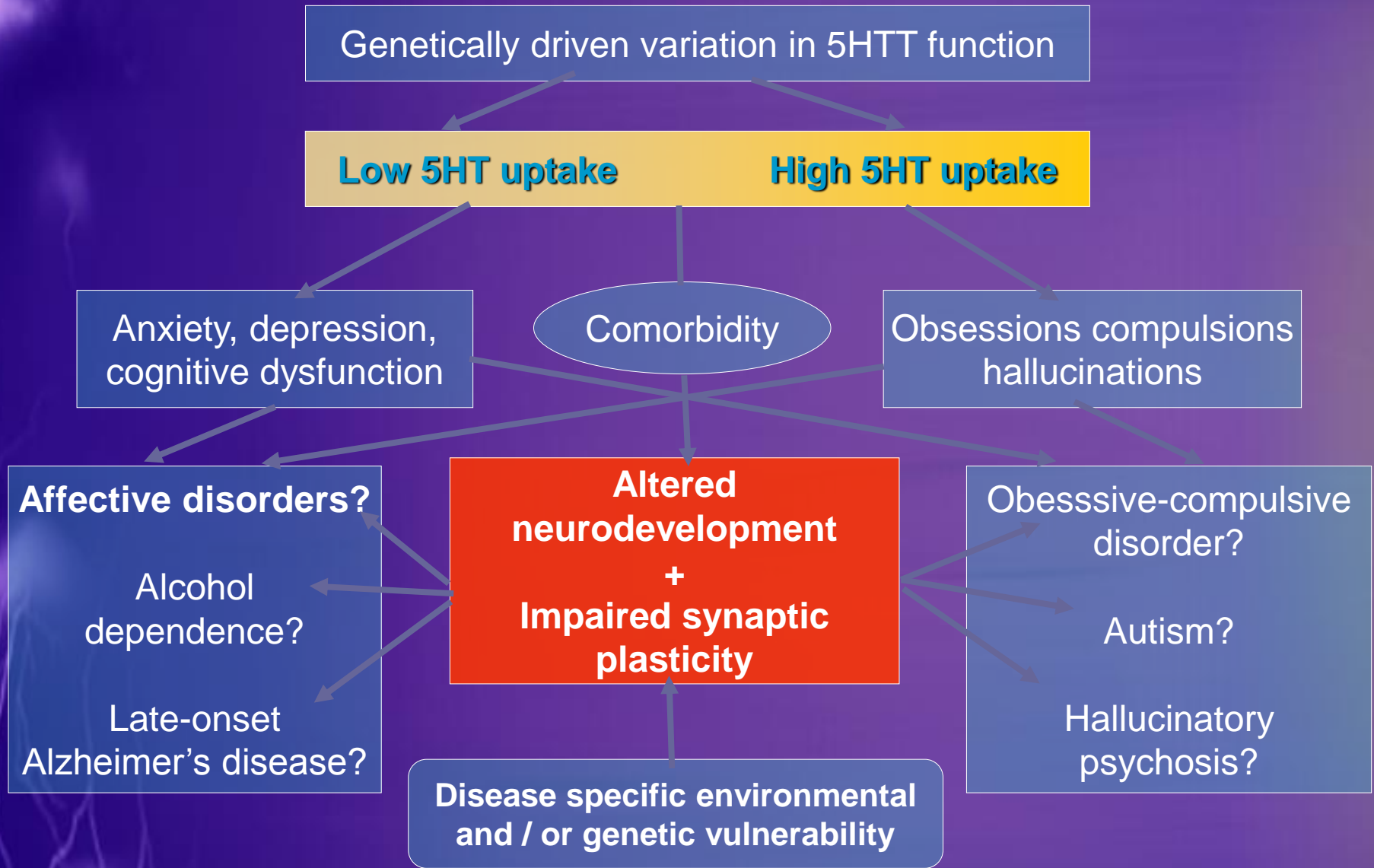
Serotonin transporter gene (5HTTLPR)

- SERT gene (SLC6A4): 17q11.1-q12
- Functional polymorphism in promoter
- **s and l alleles**



5HTTLPR

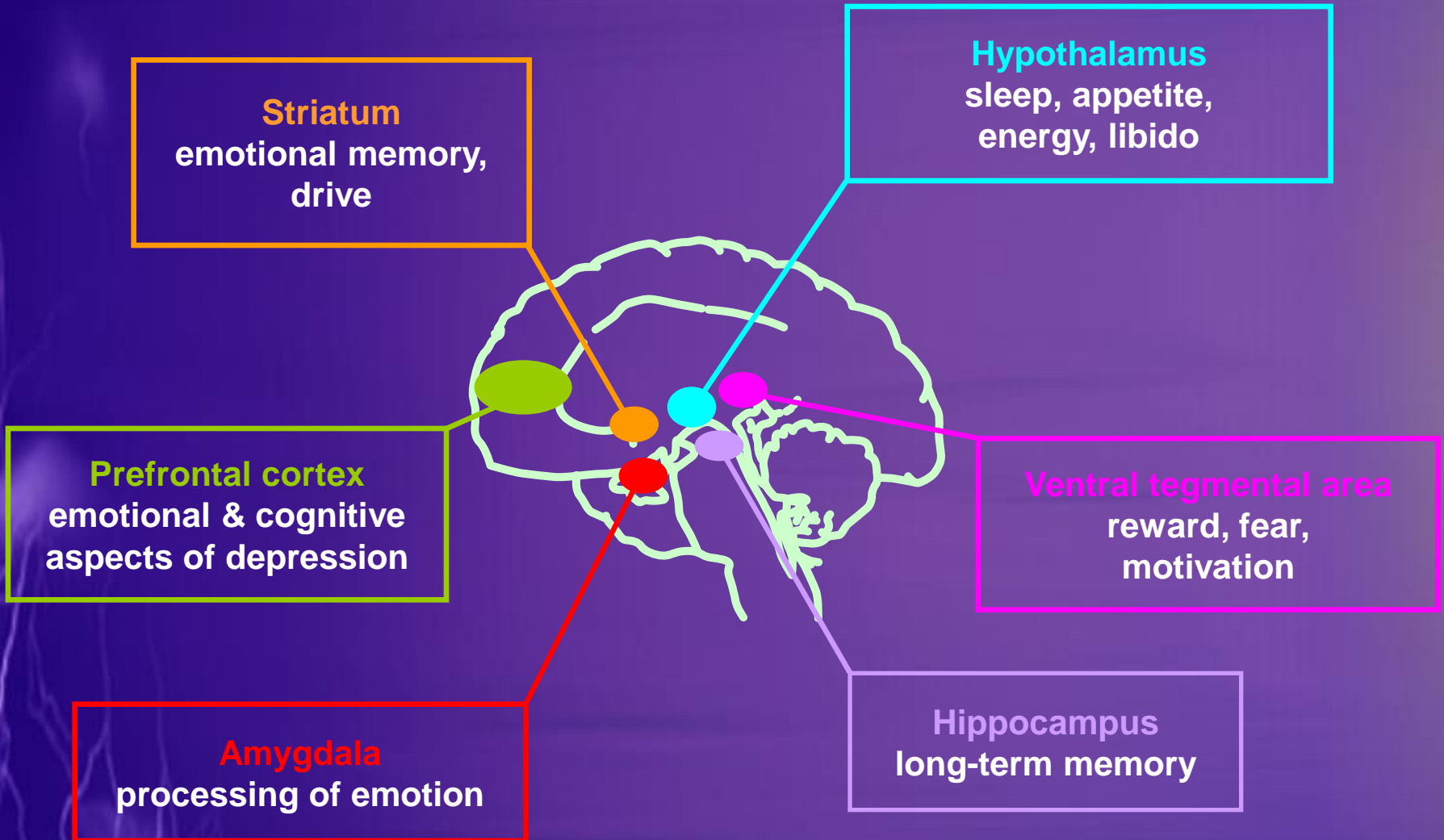
- Associated with
 - Affective disorders (major depression, bipolar disorders, subthreshold depr, DE, CT, IRR, ANX temperament)
 - Suicidal behaviour
 - Poor response to SSRIs, AD-induced switches
 - Psychological traits related to neuroticism and responsivity to stress
 - Anxiety disorders, migraine
 - Neurodevelopment



Biological/neuroendocrine changes/markers in depression

- Abnormal DST
 - Shortened REM-latency
 - Blunted TSH response to TRH
 - Reduced cortisol response to DMI
 - Decreased cellular immune function
 - 5-HT and DA/NA depletion
 - Brain imaging techniques (MRI,SPECT etc.)
-

Brain regions involved in depression



5-HT and DA/NA depletion in depression

- SSRI responders:
 - 5-HT depletion: relapse
 - DA/NA depletion: no change
- NRI responders:
 - 5-HT depletion: no change
 - DA/NA depletion: relapse

Delgado et al, Arch Gen Psychiat, 1994; 51: 865-874.

Spillman et al Psychopharmacology, 2001; 155: 123-127

Booig et al, J Affect Disord, 2005; 86: 305-311.

Delgado Primary Psychiatry, 2009; 16 (S-4), 8-15

Tokor et al, Isr J Psychiat Rel Sci, 2010; 47: 46-55.

Lifetime Prevalences of Bipolar I, Bipolar II, and Unipolar Major Depression (%) in the Adult Population

Source	Diagnosis	BP-I	BP-II	UPMD	%BP
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Bipolar II	2,0	1,6	0,8
% ,bipolars	25	28	33

Szádóczy et al. J.Aff.Dis. 1998,50:153-162

Szádóczy et al. Orv.Hetil. 2000,141:17-22

Prevalence of Bipolar (I+II) Disorders in Primary Care

Source, country	Diagnosis	Point prev. (%)
• Spitzer et al. 1994, USA n=1000,	PRIME-MD DSM-III	1,0
• Szádóczy et al. 1998, Hungary n=301	DIS DSM-III-R	1,3
• Ansseau et al. 2004, Belgium n=2316	PRIME-MD DSM-IV	1,9

Complications of untreated major mood disorders

- Suicidal behaviour
 - Secondary alcohol/drog abuse (dependence)
 - Loss of productivity, disability, loss of job
 - Family breakdown, interpersonal conflicts
 - Increased somatic morbidity/mortality
 - Increased health-care costs
-

Depression and cardiac mortality (RR)

Cardiac disease	Depression	Cardiac-death	IHD-death
• no	no	1,0	1,0
• no	minor	1,6	1,4
• no	major	3,8	5,1
• yes	no	3,4	4,5
• yes	minor	5,1	8,5
• yes	major	10,5	17,7

Penninx et al, Arch Gen Psychiat 2001,58:221-.

Successful acute and long-term treatment of mood disorders

- Significantly reduces the suicide mortality and morbidity
 - Reduces the development of secondary substance-use disorders
 - Reduces the cardiovascular morbidity and mortality
 - Reduces the cost of health care
-

Treatment of mood disorders

- Biological treatments
 - pharmacotherapy
 - sleep-deprivation
 - light therapy (winter depression)
 - ECT
 - TMS, DBS, VNS (?)
- Non-biological treatments
 - psychoeducation
 - supportive psychotherapy
 - specific psychotherapies
 - CBT
- Combination of biological/nonbiological treatments

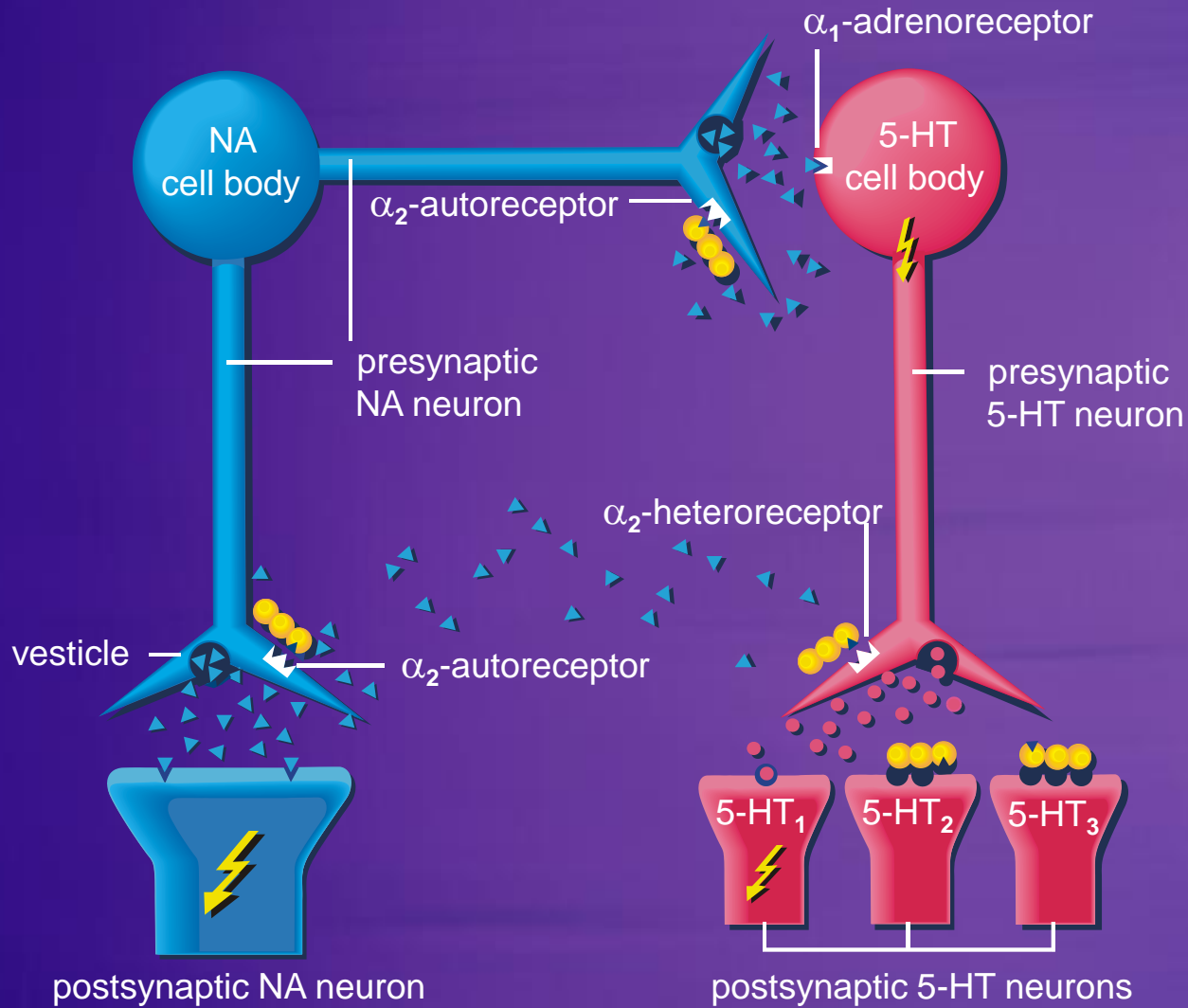
Pharmacotherapy of mood disorders

- Pharmacotherapy of depression
 - monotherapy with ADs (unipolar depr.)
 - combination of ADs and ANXLs, APs, mood stabilizers
- Pharmacotherapy of mania
 - APs
 - Mood stabilizers (Li, VPA, CBZ, LTG)
- Long-term treatment of mood disorders (mood stabilizers)

Classification of antidepressants

- First-generation reuptake-inhibitors
 - tri/tetracyclic ADS (impir., amitript., clompir., maprot. etc)
- SSRIs (flox., fluvox., sertr., citalpor., paroxetin, escitalopram.)
- Dual action ADs
 - 5-HT+NA (venlafaxine, mirtazapine, duloxetine)
 - NA+DA (bupropion)
- MAO inhibitors/RIMA (phenelzine, tranylcipromine/moclobemide)

Mirtazapine – Mechanism of action



▼ noradrenaline

● serotonin

●●● mirtazapine



Selection of antidepressants

- Personal and family history of drug-treated depression (same response)
- Clinical picture
 - agitated/suicidal/winter depression: mainly SSRIs
 - retarded, anhedonic depression: mainly NA-DAergic antidepressants
 - depressive mixed state: MS/AP+AD
 - psychotic depression: ADs + APs

Niculescu and Akiskal, *Molec Psychiat* 2001, 6: 263-266.

Ferguson et al, *Int Clin Psychopharmacol*, 2002, 17: 45-51.

Recommendations for AD pharmacotherapy (1)

- Appropriate dose
- Appropriate duration (min. 2-3-4 weeks)
- Increase the dose in non/partial responders
- Augmentation of the effect in non/partial responders (Li, VPA, CBZ, APs, folic acid, L-thyroxin)
- Change the medication after 4-5 weeks in nonresponders – long term treatment in responders if needed (2 or more episodes)

Recommendations for AD pharmacotherapy (2)

- Mood stabilizers (+ ADs) in all bipolar depressives
- Atypical antipsychotics (+ ADs) in psychotic depression
- Anxiolytics (+ADs) in depression with comorbid anxiety/anxiety disorders

Antidepressant monotherapy in bipolar depression: The major source of treatment resistance/destabilization

- Akiskal and Mallya, Psychopharmacol Bull, 1987; 23: 68-73.
- Sharma, J Affect Disord, 2001; 64: 99-106.
- Shi et al, J Affect Disord, 2004; 82: 373-383
- Sharma et al, J Affect Disord, 2005; 84: 251-257.
- El-Mallakh et al, J Affect Disord, 2005; 84: 267-272.
- Inoue et al, J Affect Disord, 2006; 95: 61-67.
- Woo et al, Int J Psychiat Clin Pract, 2008; 12: 142-146.
- O'Donovan et al, J Affect Disord, 2008; 107: 293-298.

Antidepressant monotherapy in pre-bipolar and unipolar depression

	Pre-bipolar n=17	Unipolar n=17
Response to ADs		
full response	41%	82%
partial response	18%	18%
nonresponse	41%	0%
Treatment emerg. symptoms		
sleep loss	47%	0%
rage	24%	0%
agitation	65%	0%
mood lability	47%	12%
suicidality	18%	0%
psychomotor activation	47%	0%
mixed symptoms	47%	6%
FH of suicide	65%	6%

Most frequent cause of antidepressant resistance in major depression

Unrecognized bipolar disorder

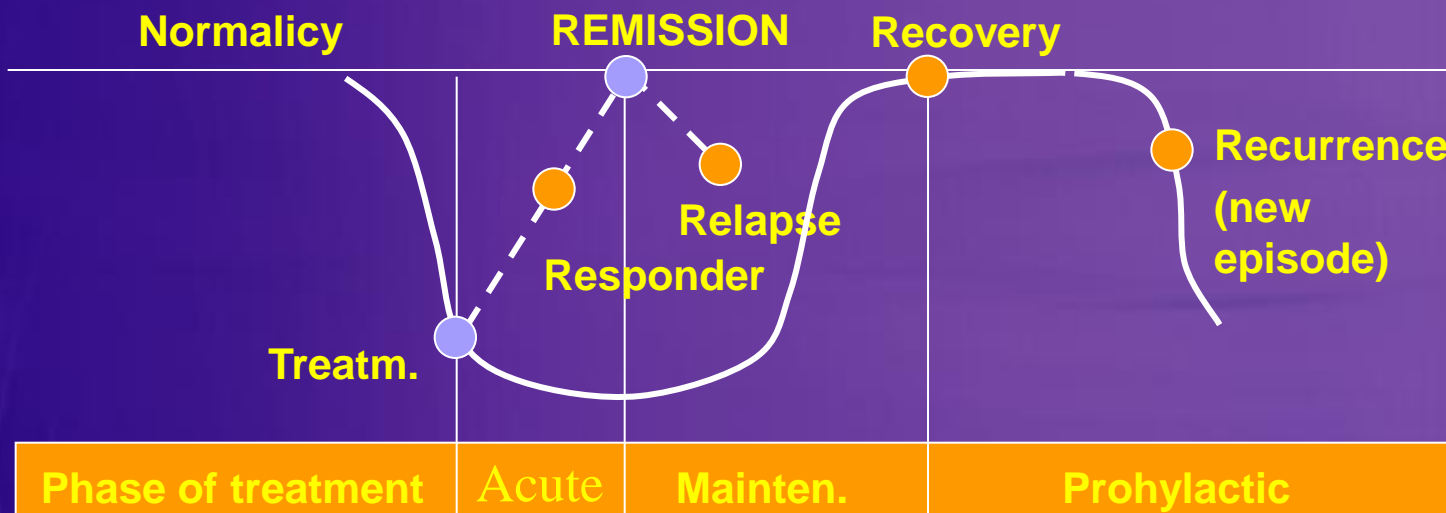
Inoue et al, J Affect Disord,
2006; 95: 61-67.

Woo et al, Int J Psychiat Clin Pract,
2008, 12: 142-146.

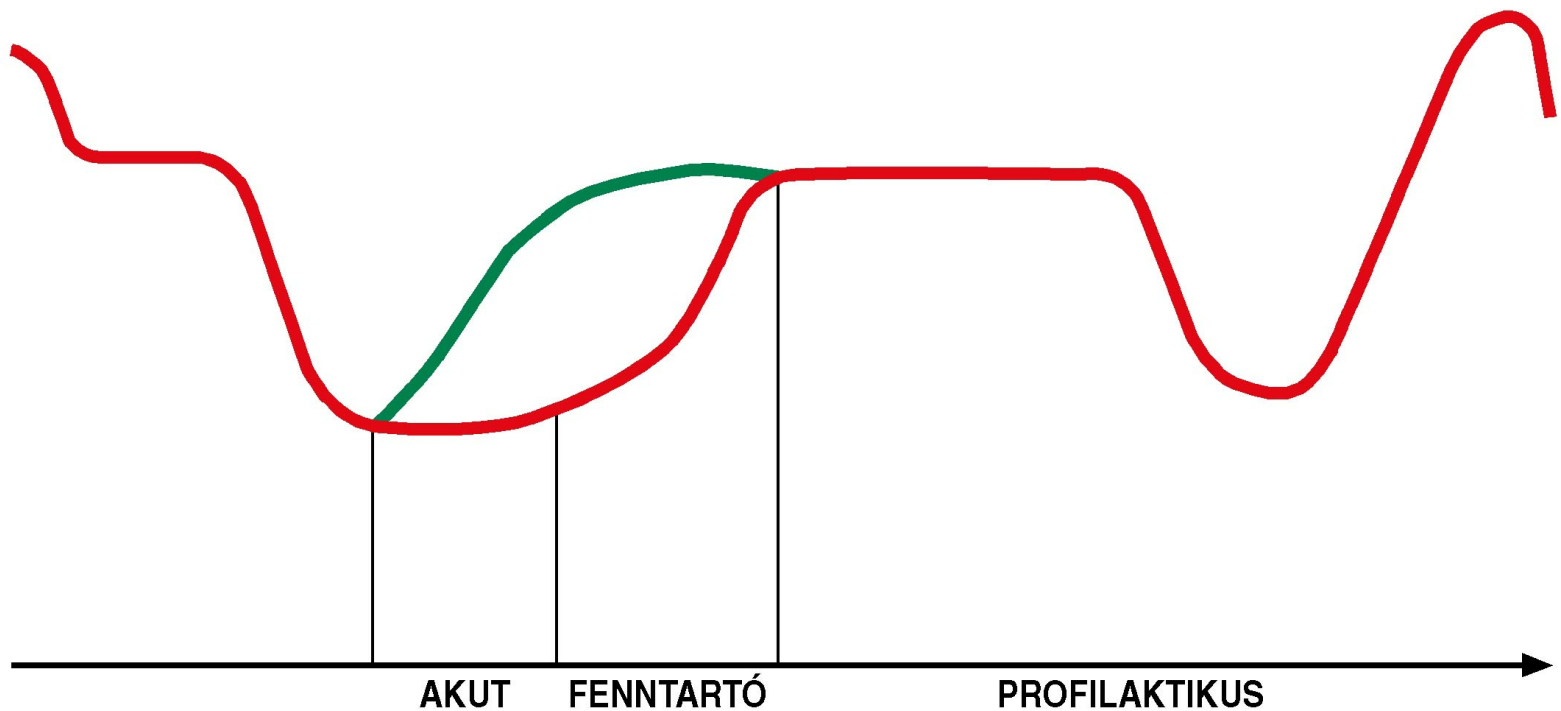
Pharmacotherapy of hypomania/mania

- Mood stabilizers (Li, VPA, CBZ)
- Antipsychotics (atypicals)
- Anxiolytics (clonazepam, alprazolam)

Treatment phases of unipolar major depression



A HOSSZÚTÁVÚ KEZELÉS FÁZISAI



Kupfer (1991) után, módosítva