

MOOD DISORDERS

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2017

Heterogeneity of mood disorders



Clinical

Polarity*
Severity
Periodicity
Sex distribution
Age of onset
Comorbidity



Biological

Genetics
Biochemistry
Brain morphology
Electrophysiology
Treatment response

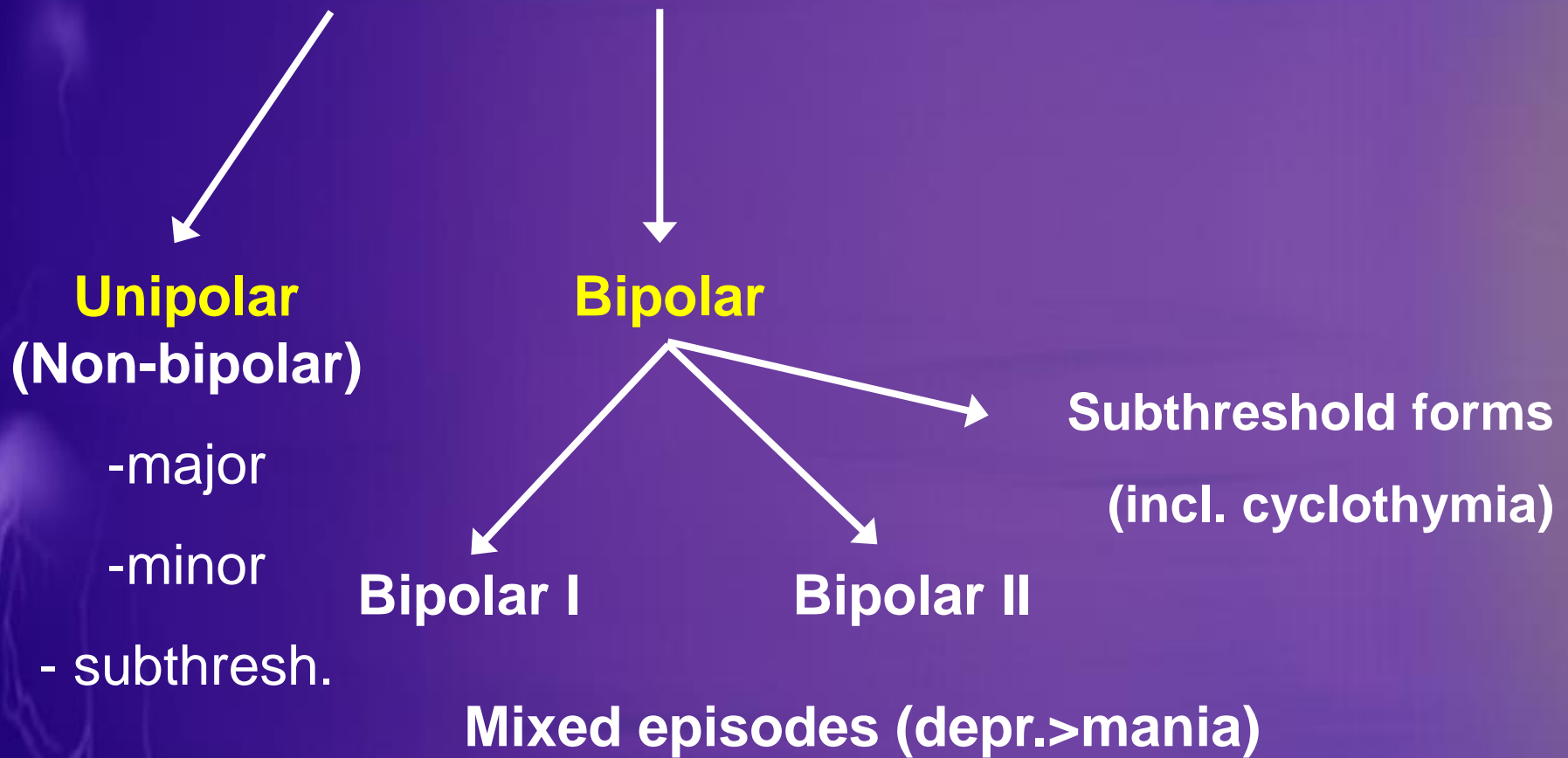


Psychosocial

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

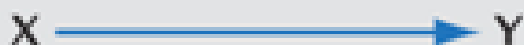
- Major depressive episode
 - nonmenalIncholic
 - melancholic-nonpsychotic
 - melancholic-psychotic
 - mood-congurent features
 - mood-incongurent features
 - catatonic
-

Genetical heterogeneity of mood disorders

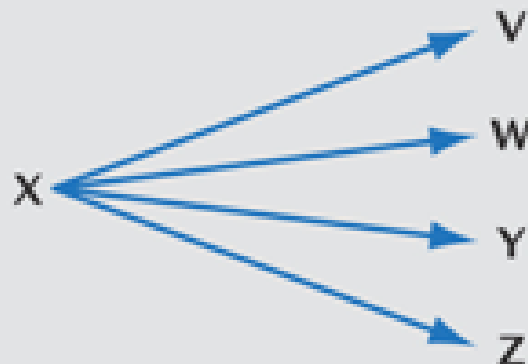
- Non-familial (sporadic) cases (40-50%)
 - Familial cases (50-60%)
chromosomes:
 - X, 18, 21, 5, 9,
(TPH, 5-HT, NA, DA transporter
etc)
-

Gene-phenotype relationships

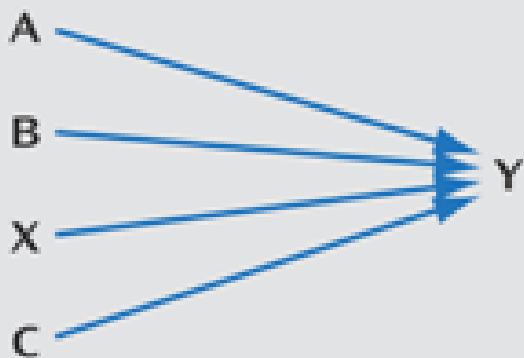
One-to-one relationship



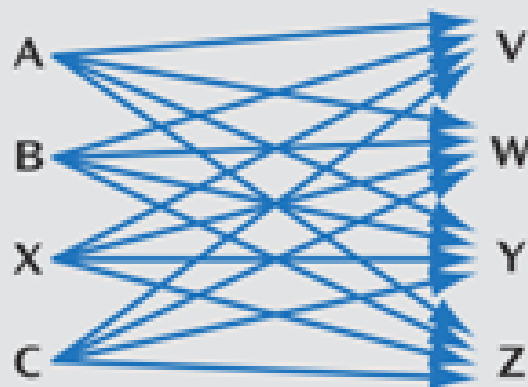
One-to-many relationship



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

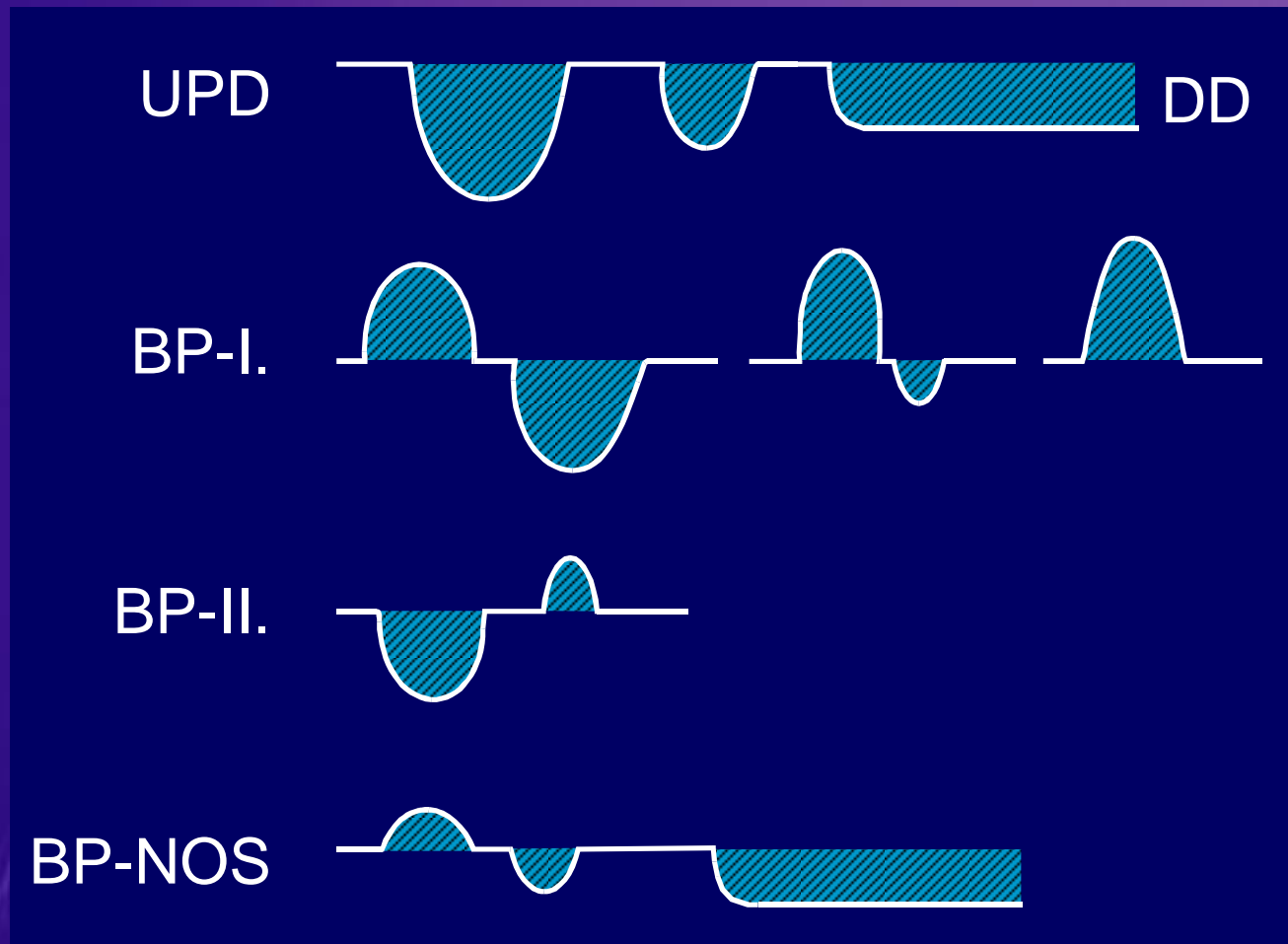
- Serotonin (5-HT)
 - Noradrenaline (NA)
 - Dopamine (DA)
 - Acetylcholine (?)

 - 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 (appetite)
 - 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

Symptom Dimensions of a Major Depressive Episode



depressed mood



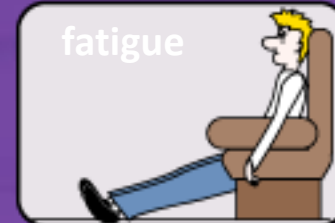
apathy/
loss of interest

one of these
required

weight/
appetite changes



sleep
disturbances



four
more of
these
required



worthlessness



executive
dysfunction



suicidal ideation

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

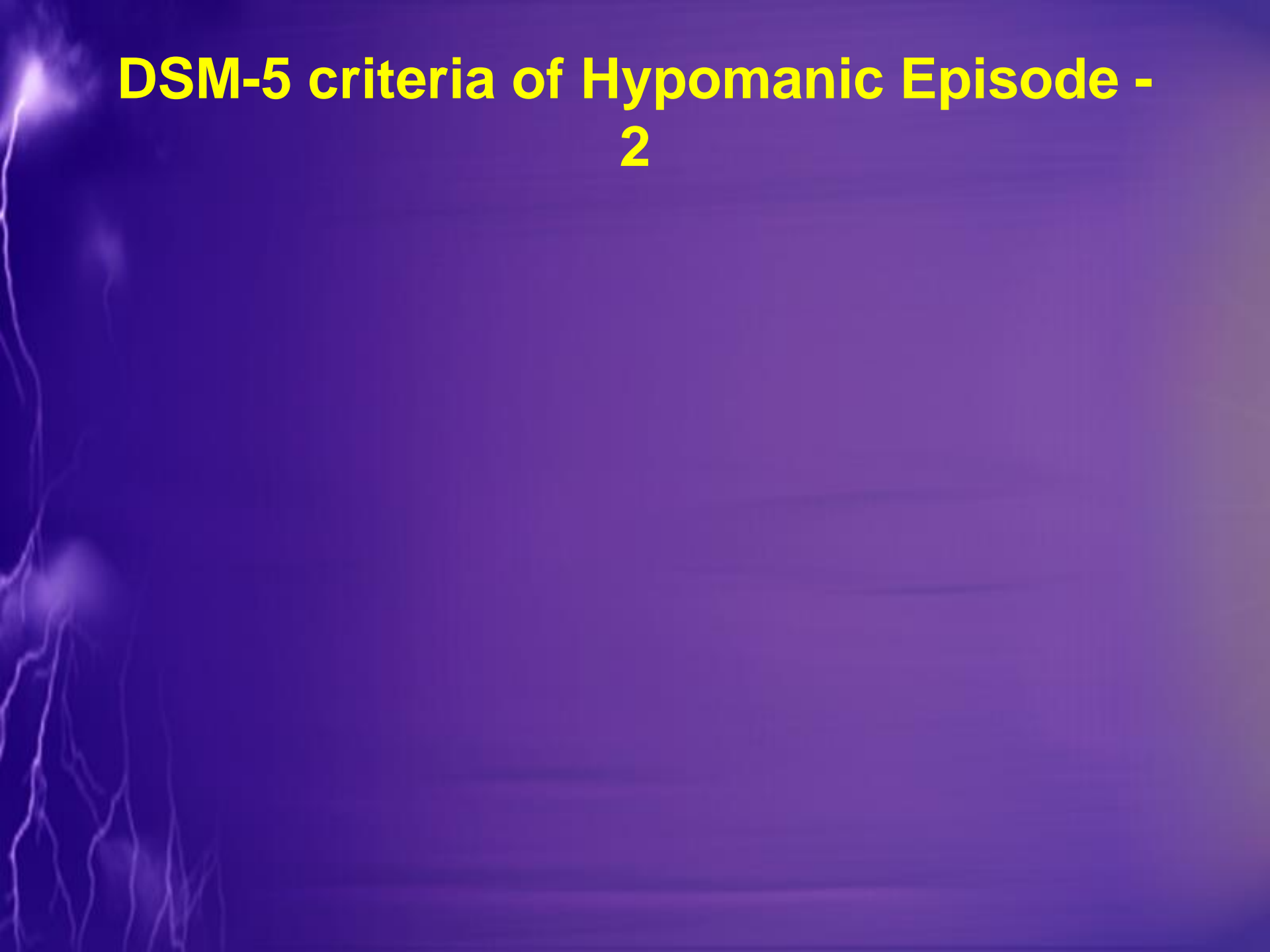
DSM-IV criteria of Mania

- 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



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

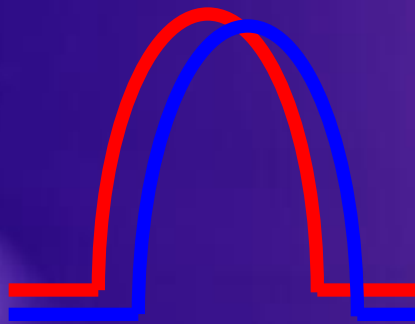
A, At least 3 of the following manic/hypomanic symptoms

- 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

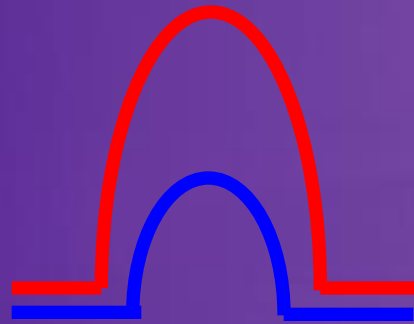
DSM-5 Major Depressive Episode „with mixed features” specifier - 2

- 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,...)

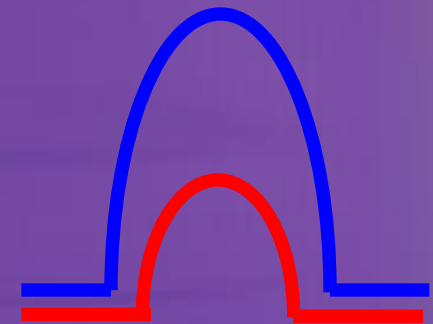
The three clinical phenotypes of overlapping affective episodes (DSM-IV)



Mixed
affective
episode



Dysphoric
mania



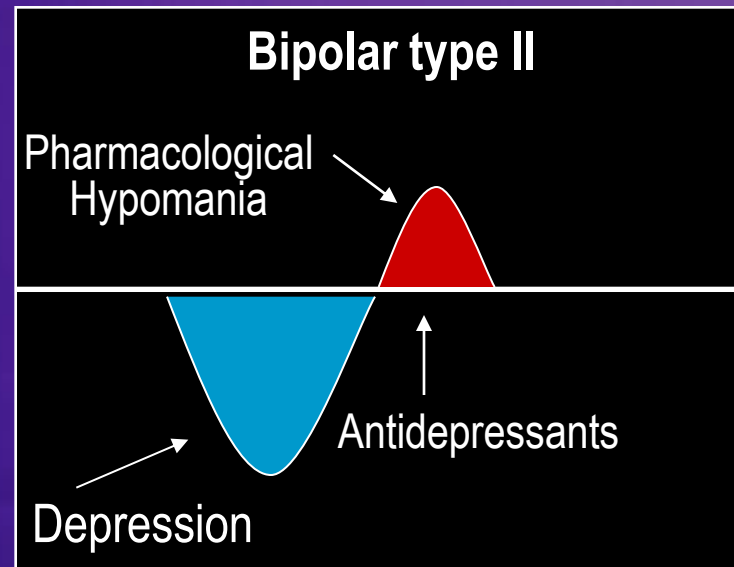
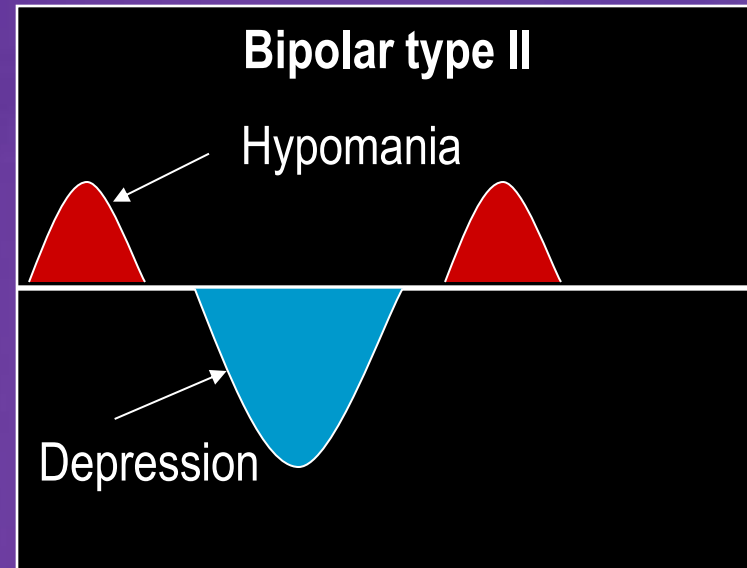
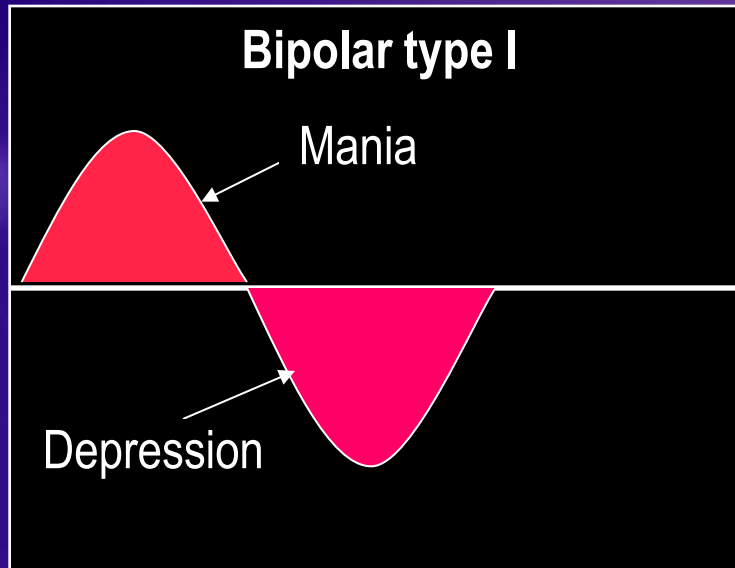
Mixed
(bipolar)
depression

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



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

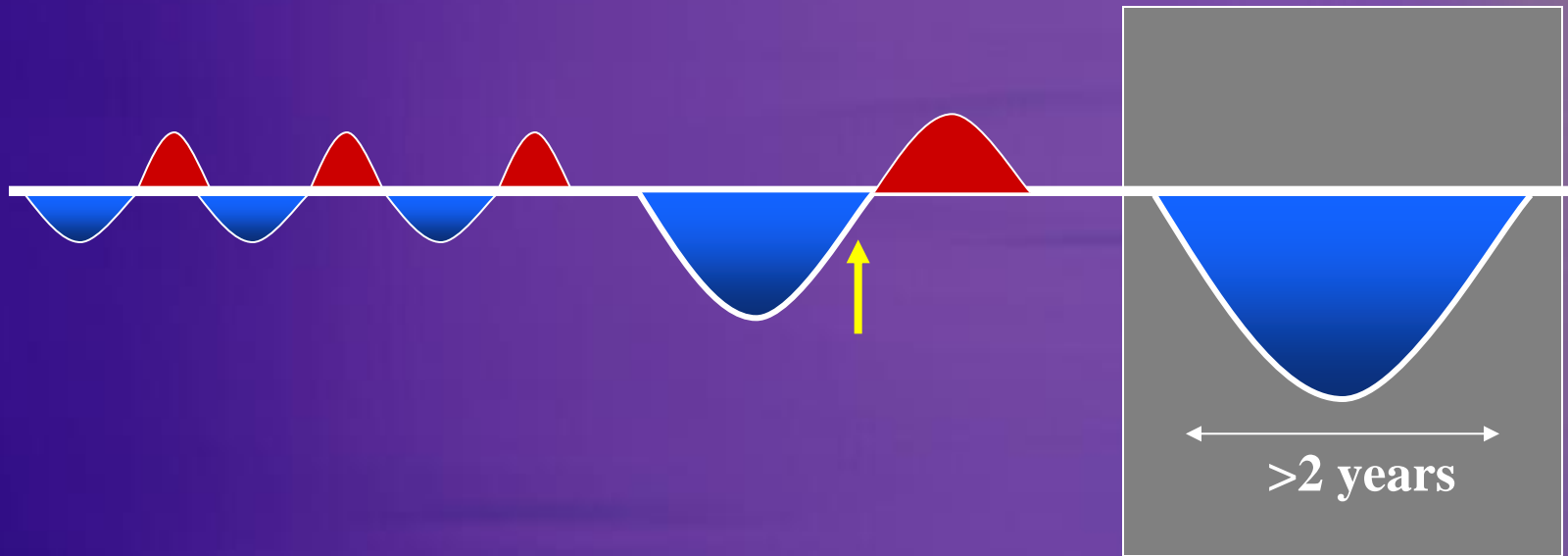
The point prevalence of major depression in primary care: 8 – 10 %

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.

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

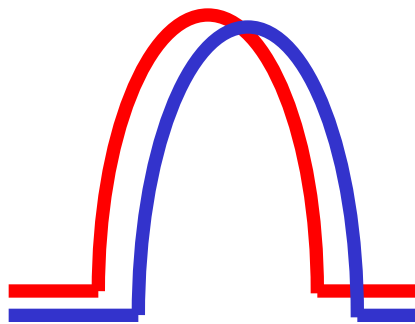
D

Bp I

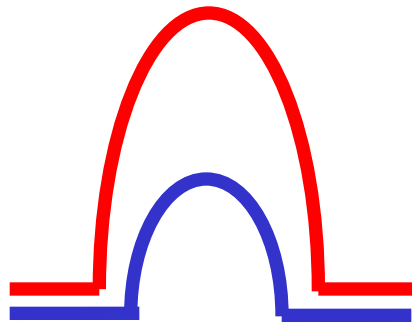
M

Agitated depression

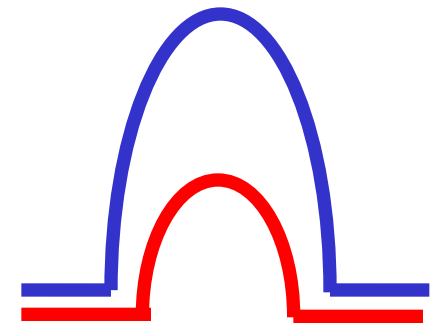
The three clinical phenotypes of overlapping affective episodes



Mixed
affective
episode



Dysphoric
mania



Mixed
(bipolar)
depression

Rihmer, 2005

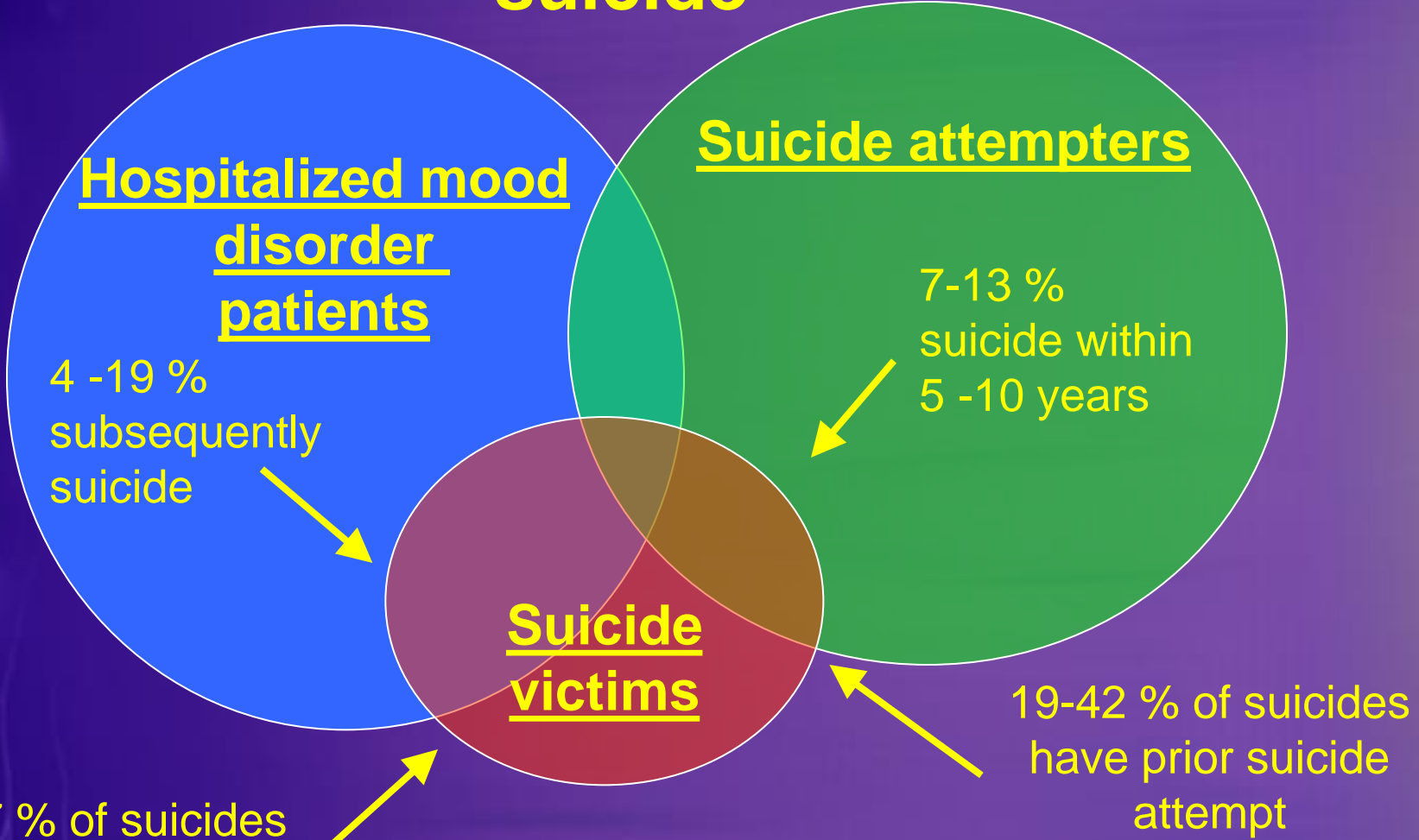
Pure vs comorbid mood disorders

- 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

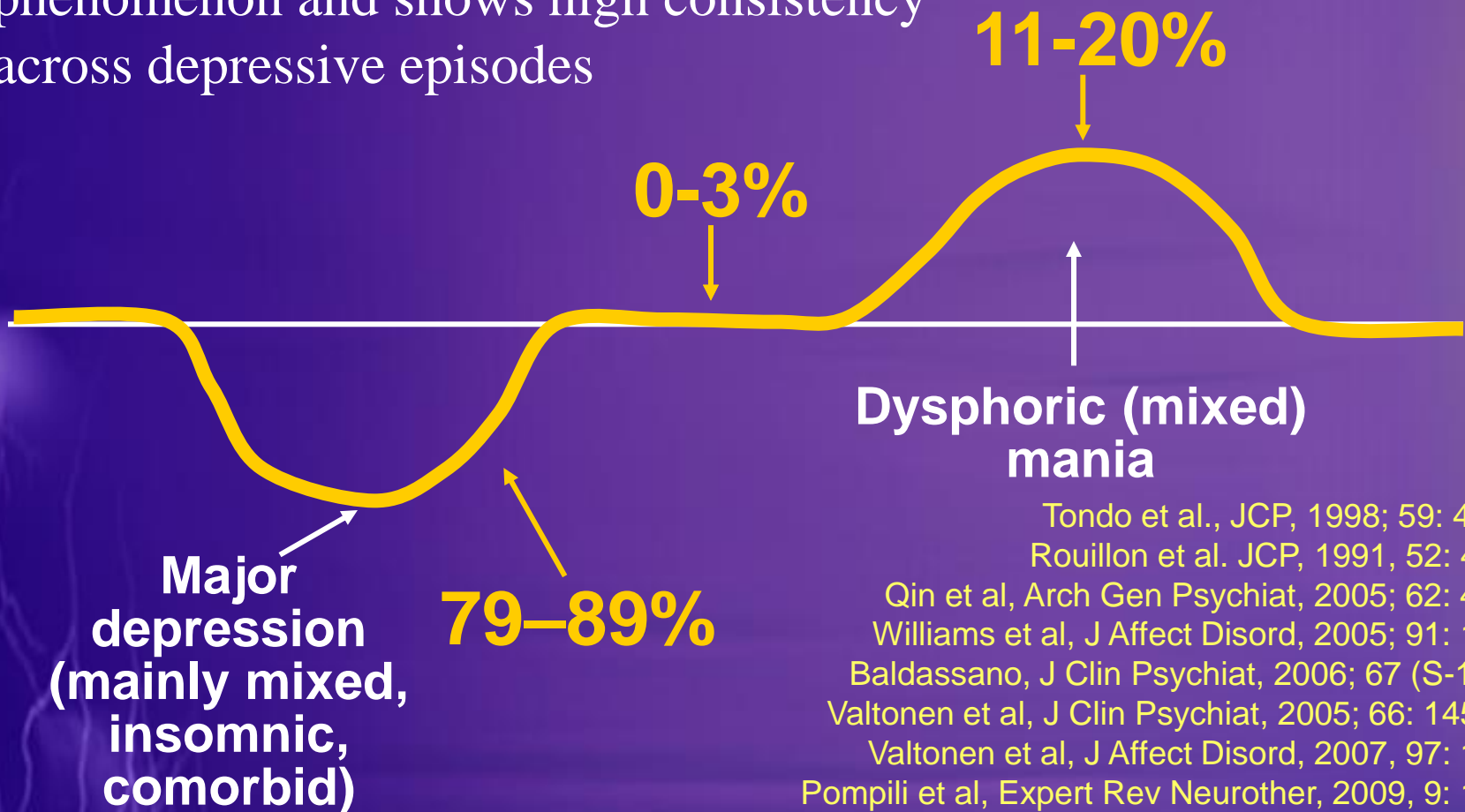


45-87 % of suicides have current major mood disorder (mostly untreated)

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 %)

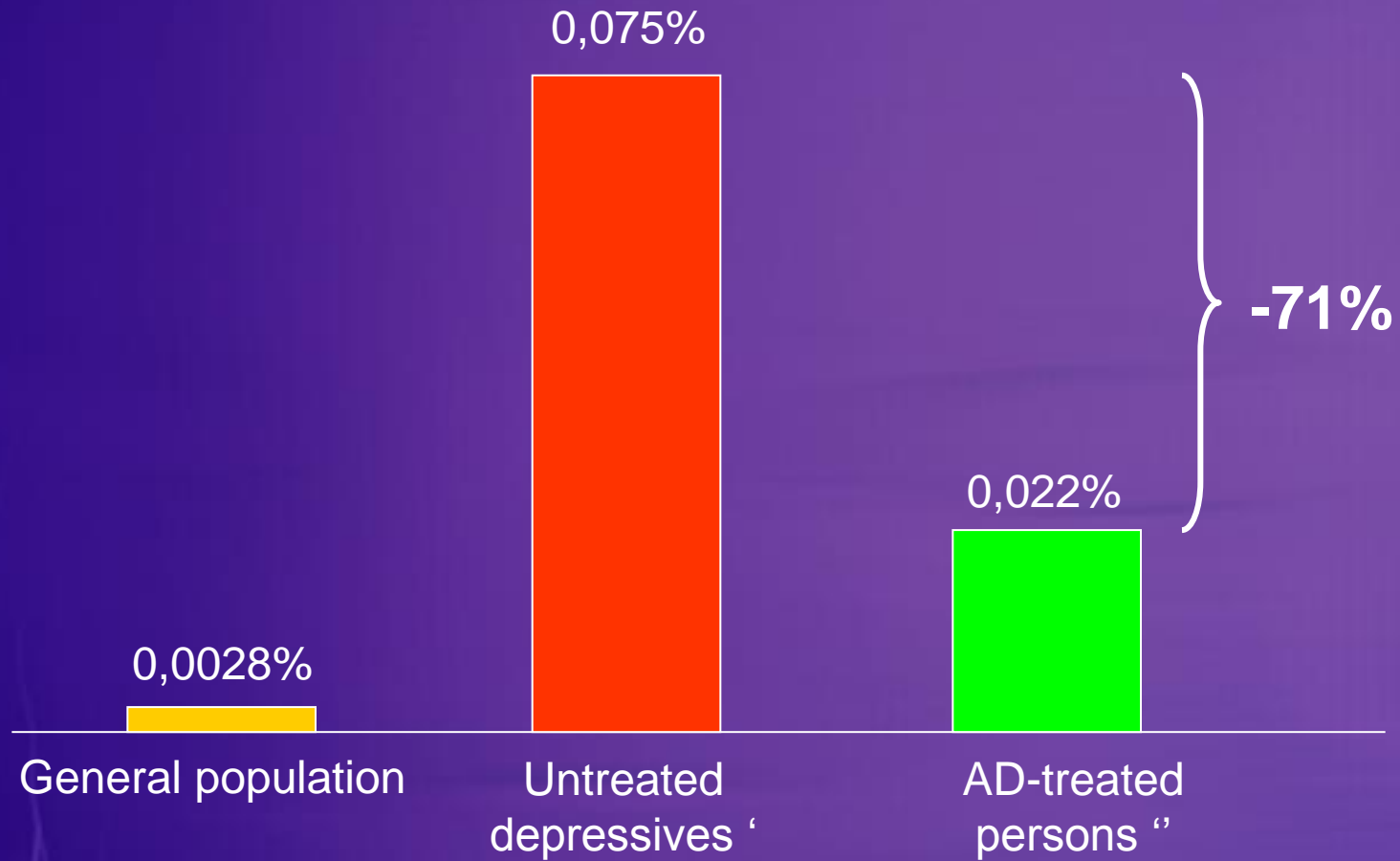
Untreated depressives vs gen. population: 27 X

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,

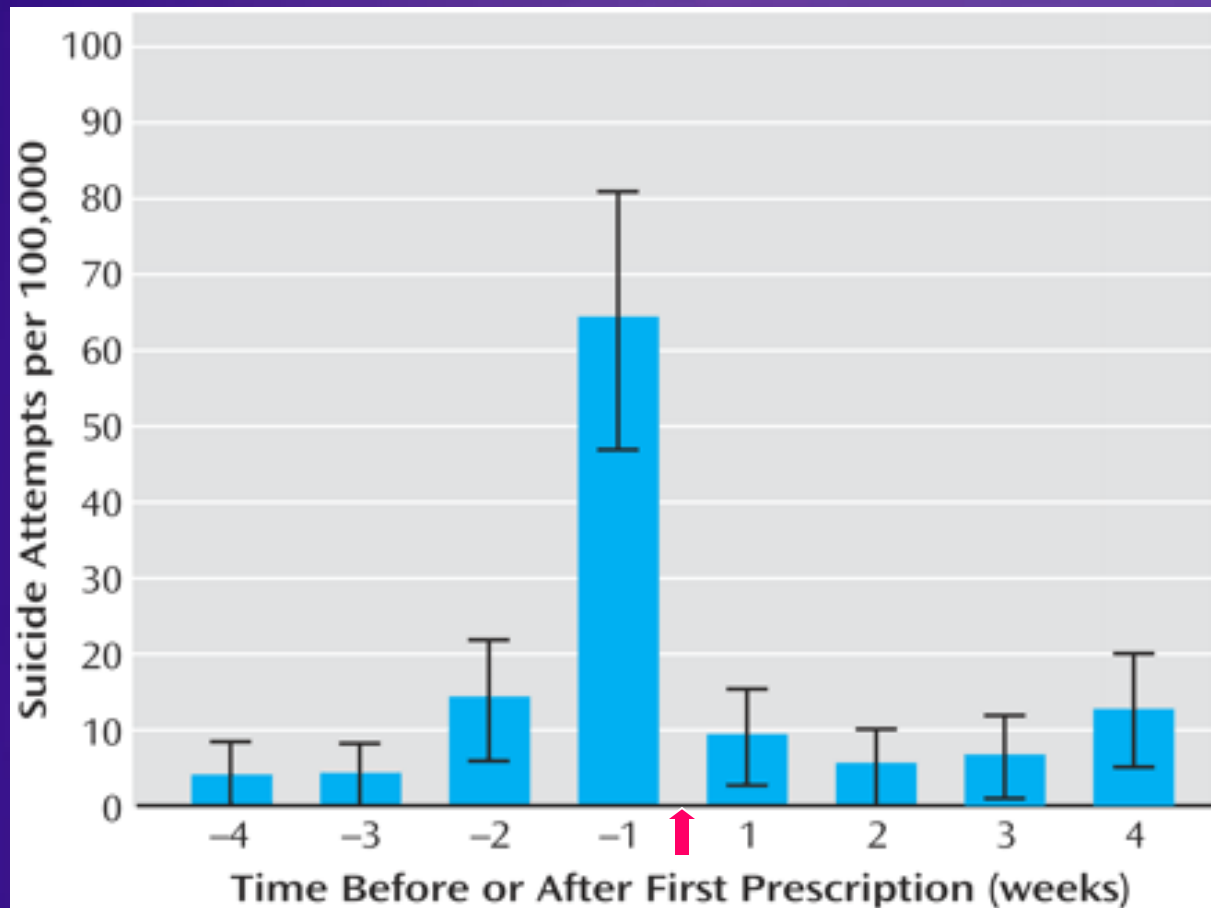


Figure 5. Rates of Suicide Attempts During the 4 Weeks Before and 4 Weeks After Initial Antidepressant Prescription^a

^aBars indicate 95% confidence intervals.

Biological basis of mental disorders

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

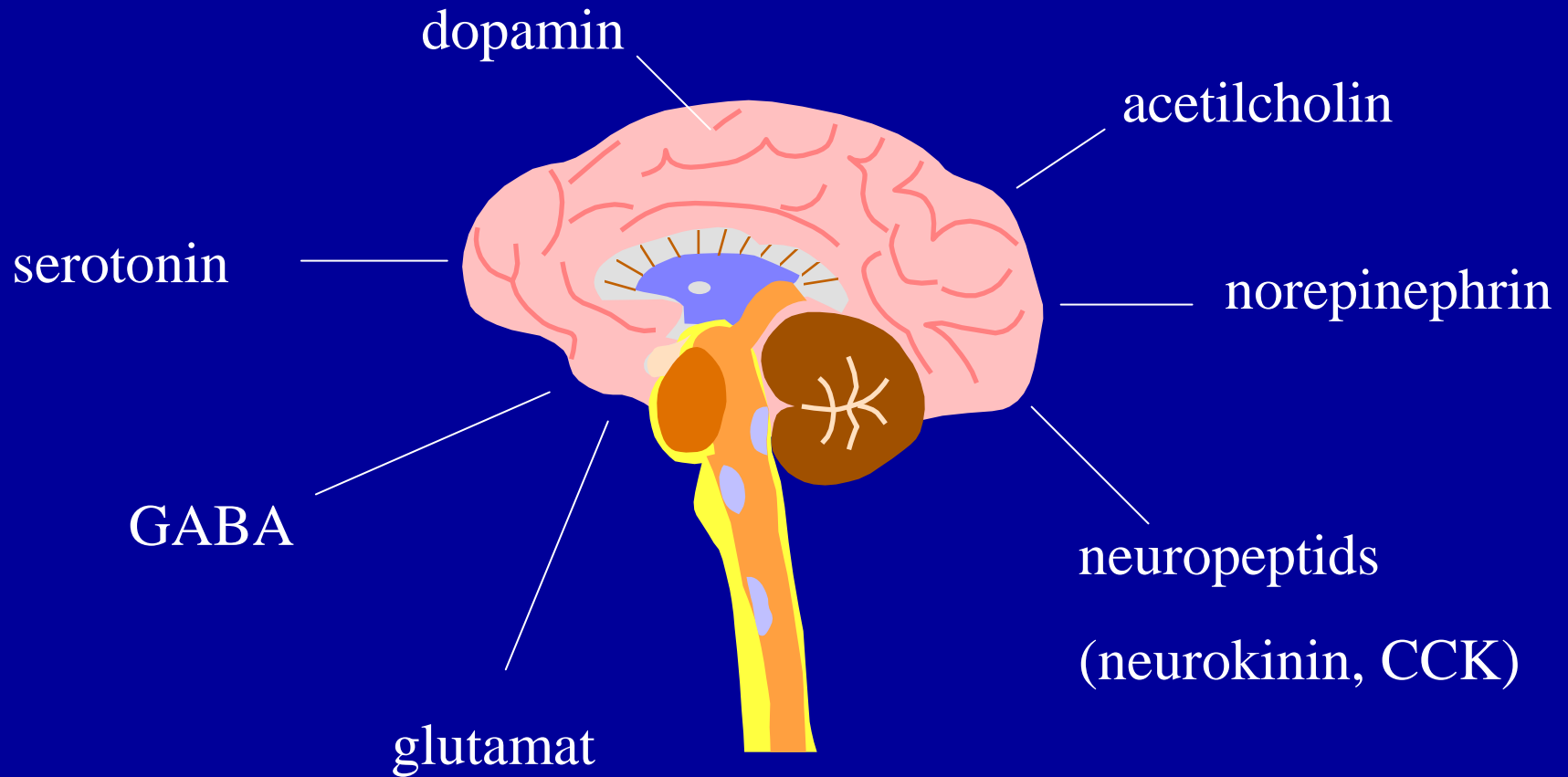
Mood disorders: serotonin, noradrenalin, dopamine

Schizophrenia: dopamine, glutamate

Anxiety disorders: GABA, serotonin

Alzheimer disease: acetylcholine

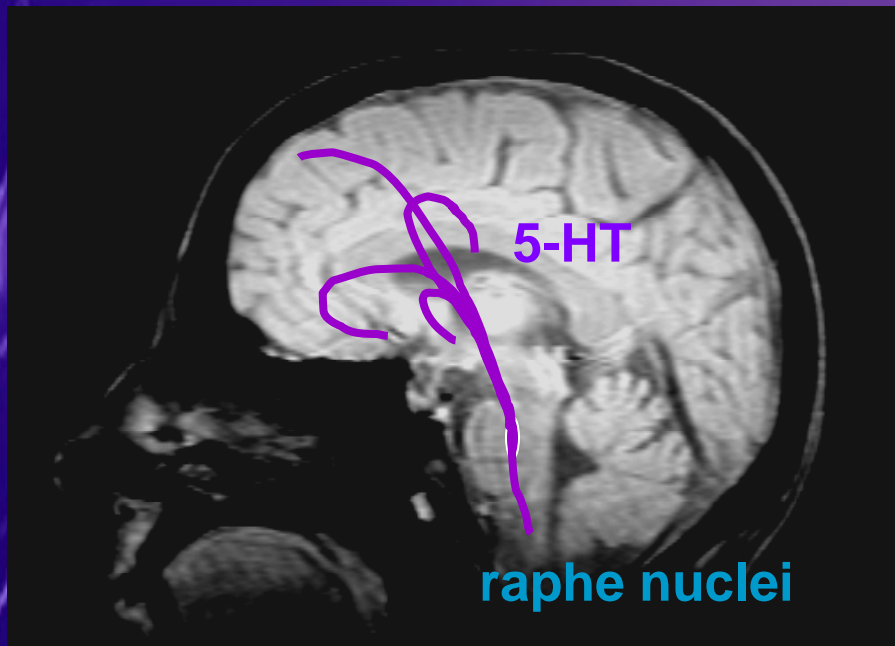
NEUROTRANSMITTER SYSTEMS, RELATED TO PSYCHIATRIC DISORDERS



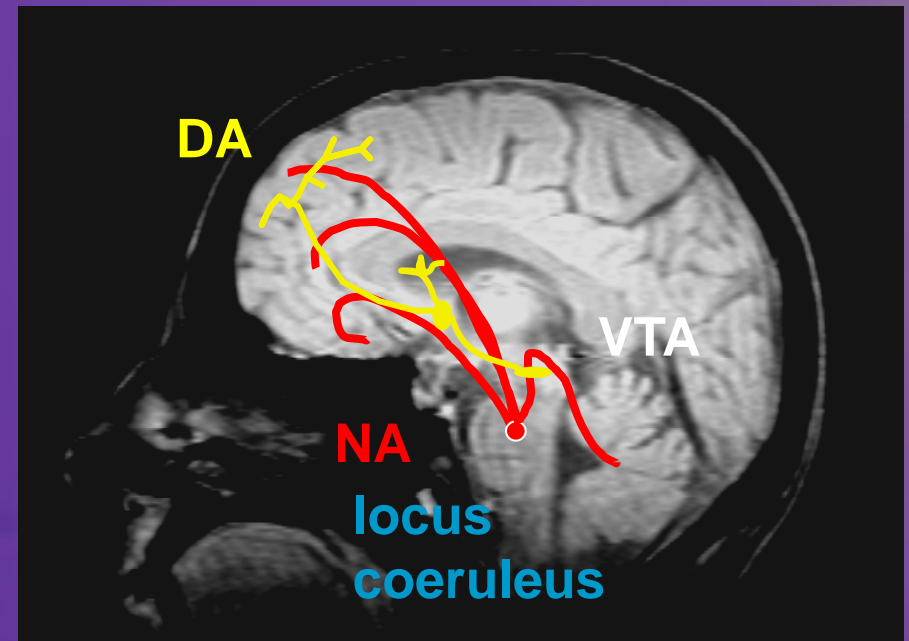
**Reuptake inhibition, receptor (ant)agonism
and antidepressive/antimanic action**



Julius Axelrod (1912-2004)



serotonergic system



Noradrenergic/dopaminergic system

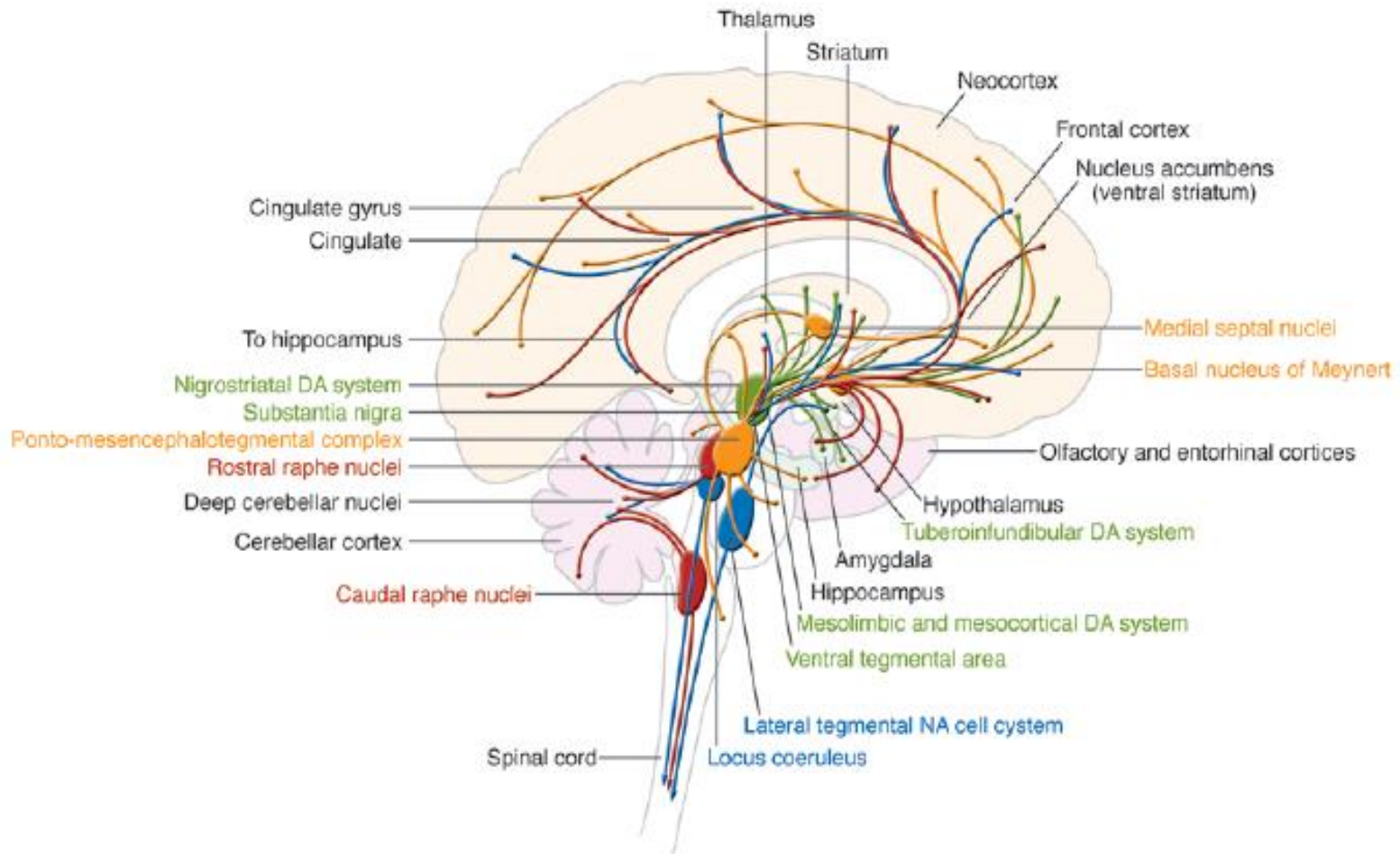
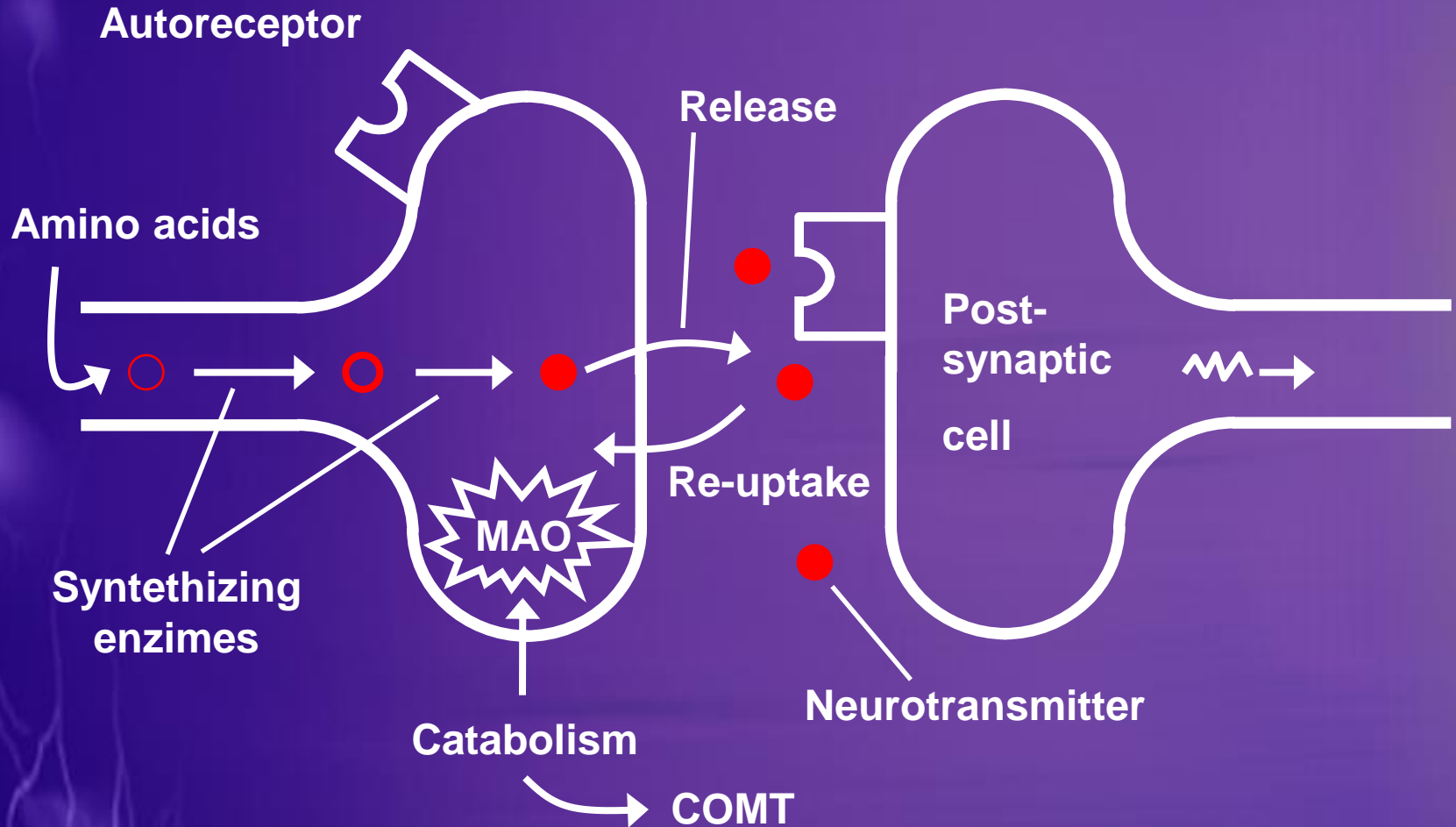


Figure 1

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



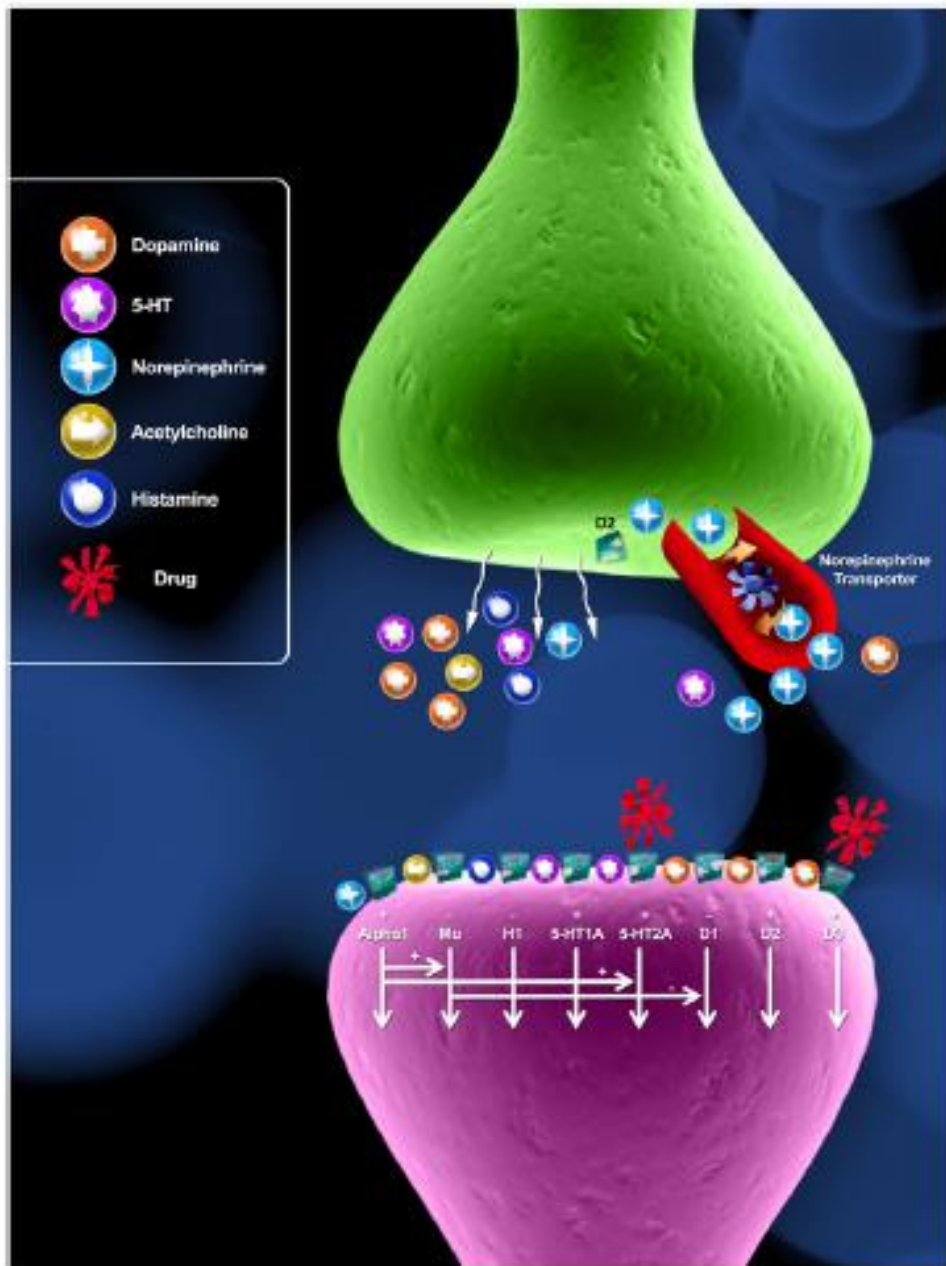
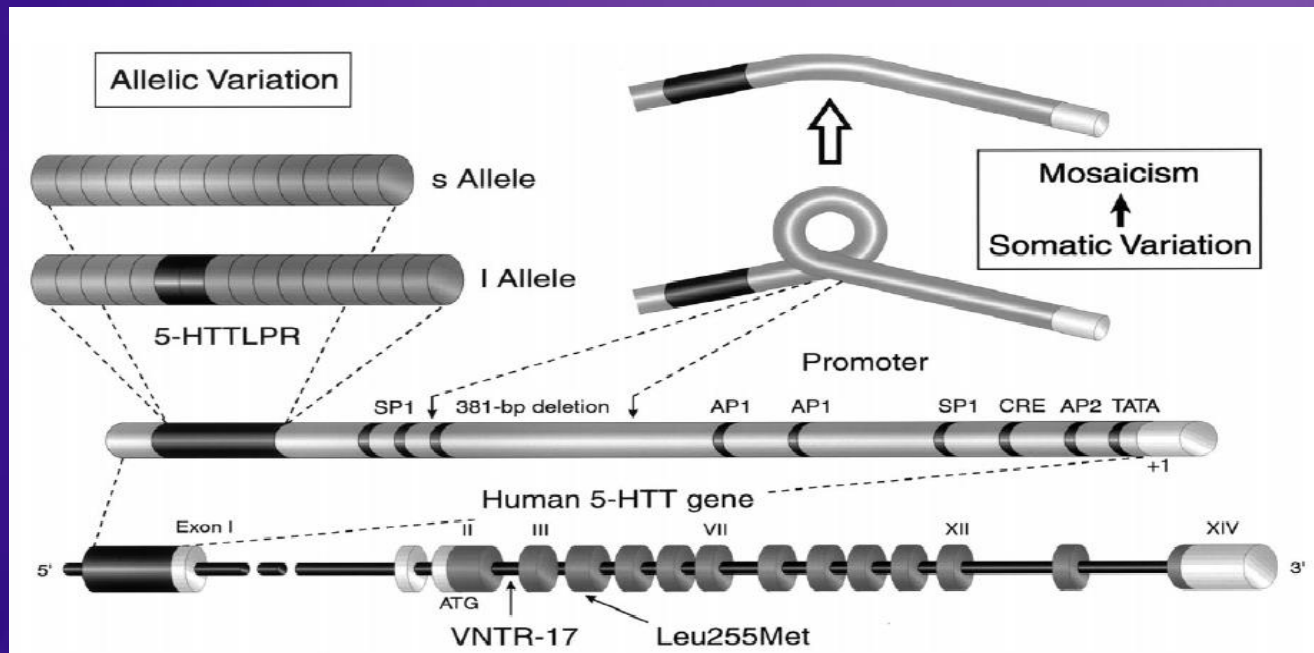


Fig. 3. Events at the synaptic level, related to the antidepressant effect in bipolar depression.

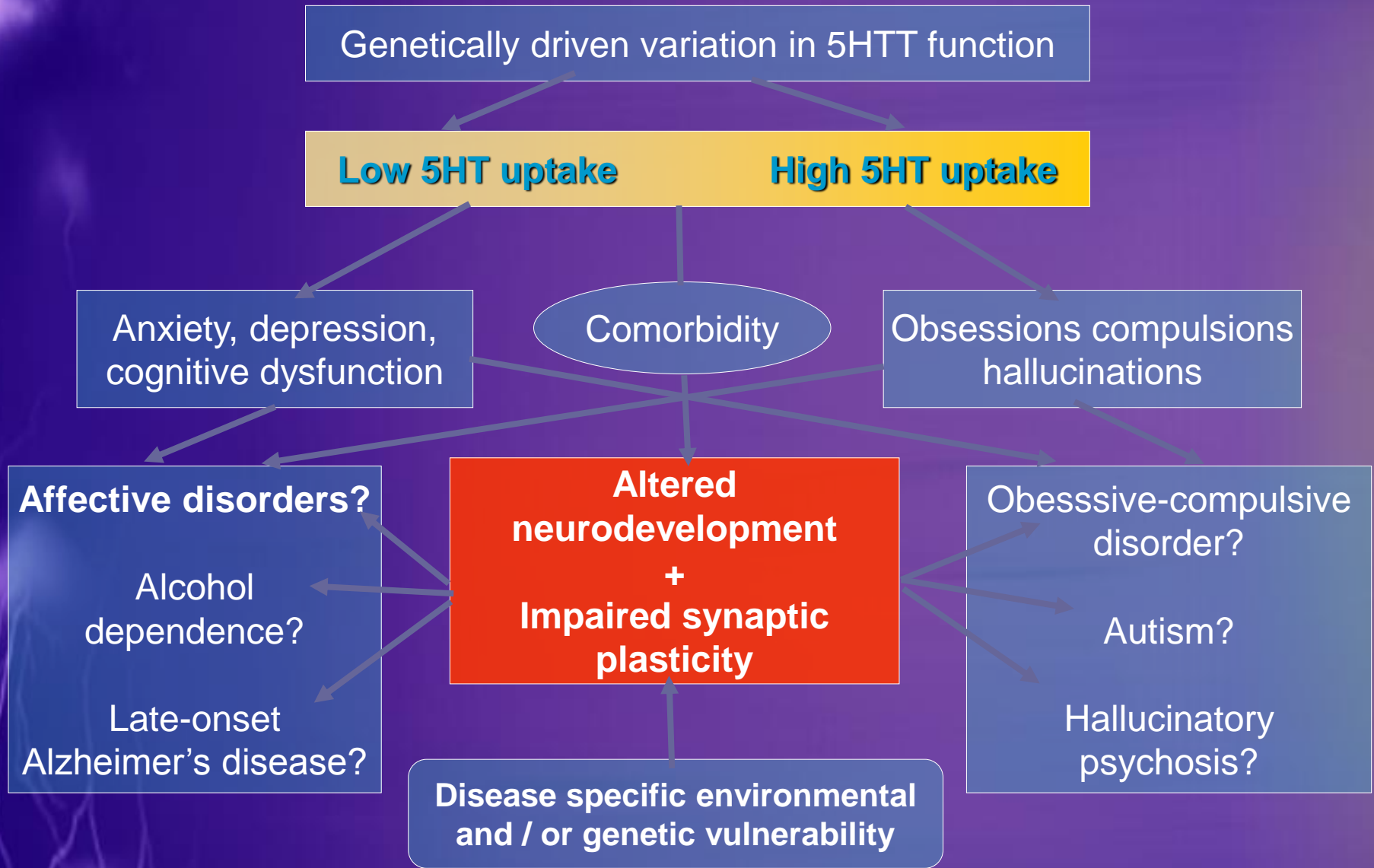
Serotonin transporter gene (5HTTLPR)

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



5HTTLPR

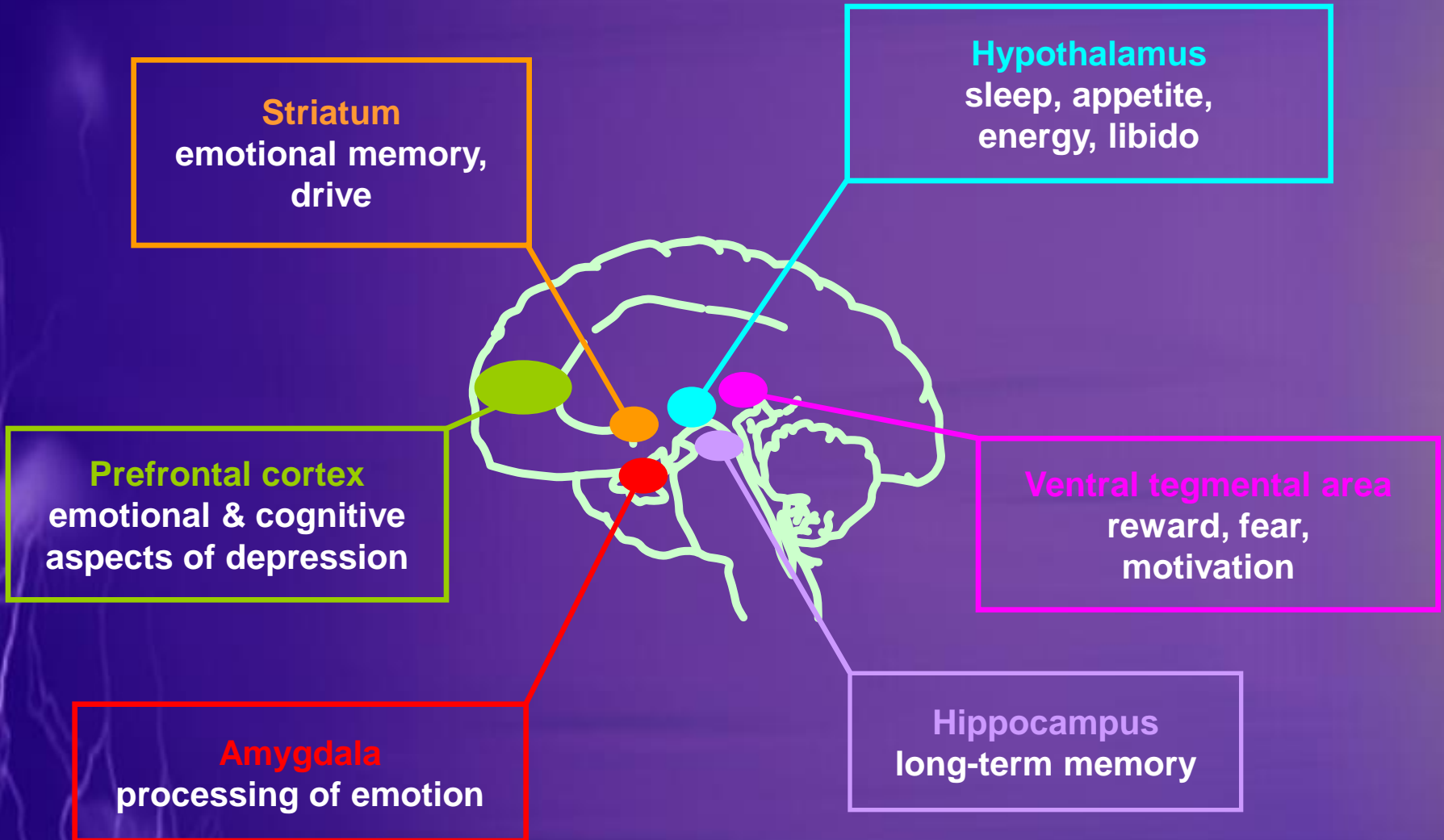
- Associated with
 - Affective disorders (major depression, bipolar disorders, subthreshold depr, DE, CT, IRR, ANX temperament)
 - Suicidal behaviour
 - Poor response to SSRIs, AD-induced switches
 - Psychological traits related to neuroticism and responsivity to stress
 - Anxiety disorders, migraine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

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%,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 (- 80%)
- 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

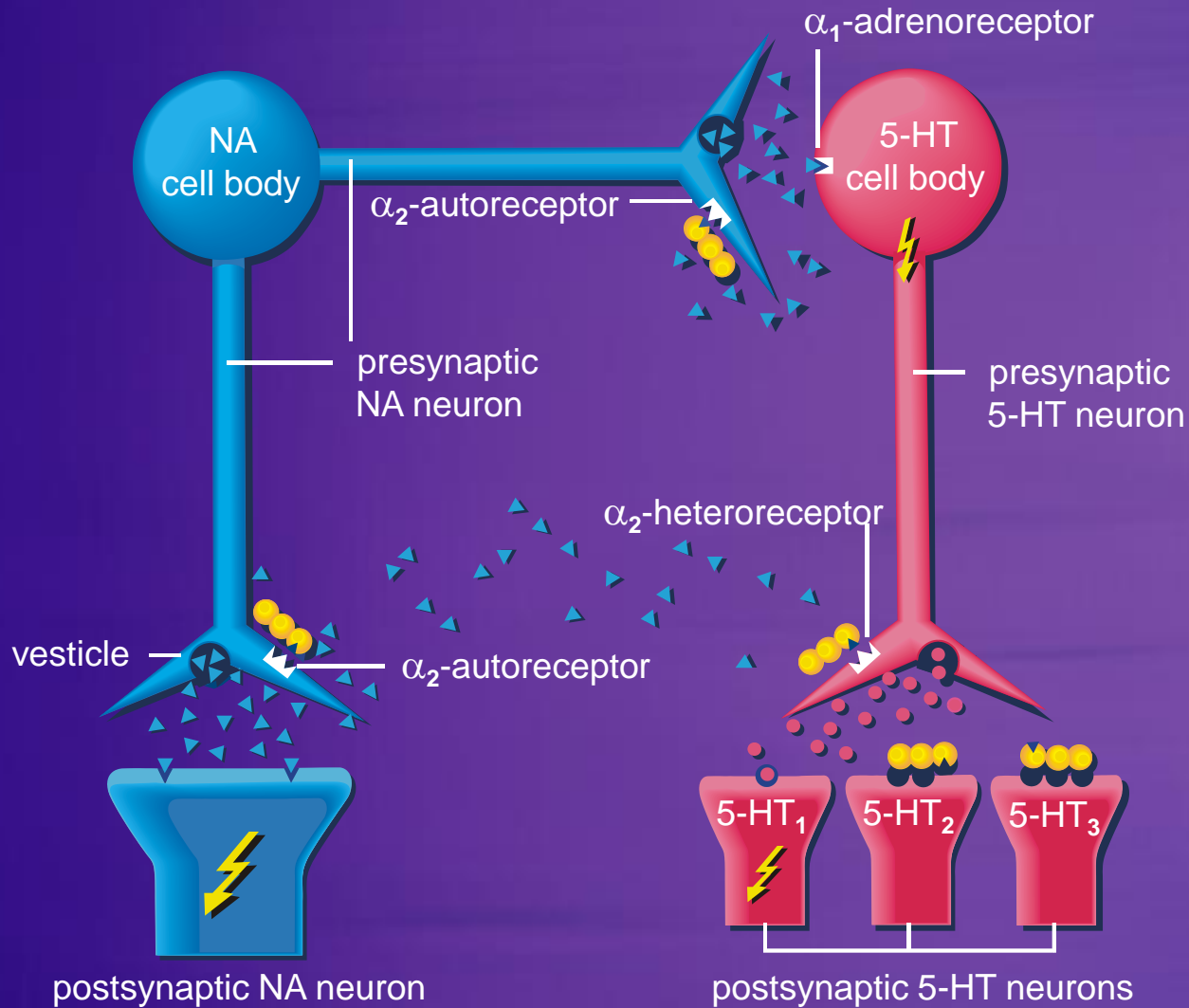
Pharmacotherapy of mood disorders

- 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) DD
 - NA+DA (bupropion)
- Multimodal AD (vortioxetine)
- 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

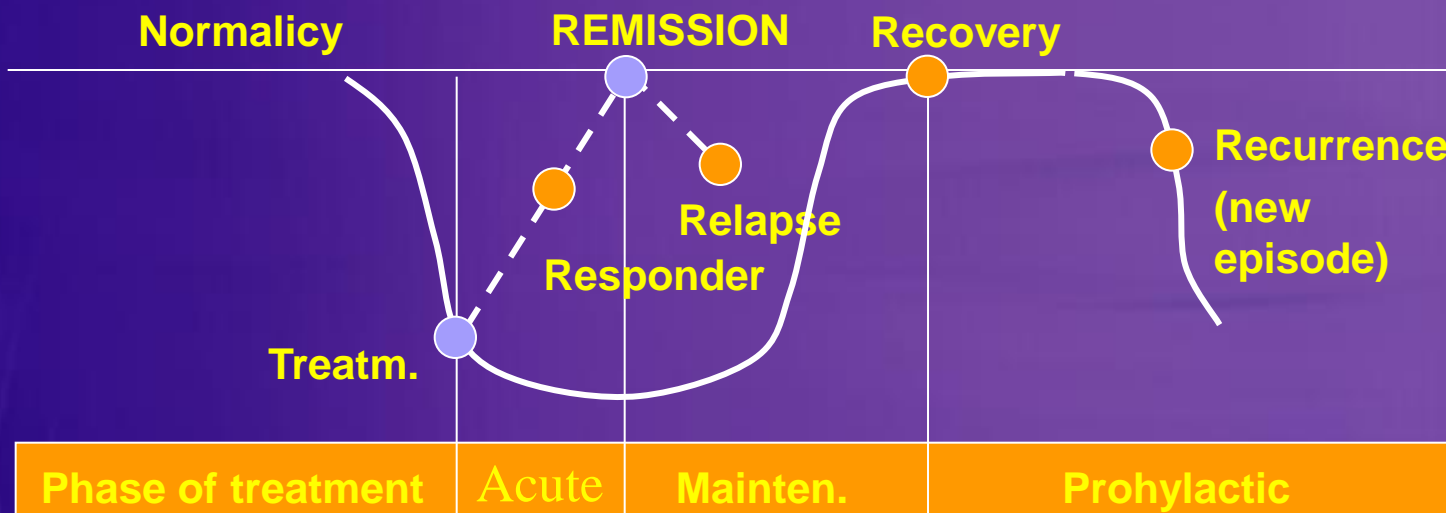
Inoue et al, J Affect Disord,
2006; 95: 61-67.

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

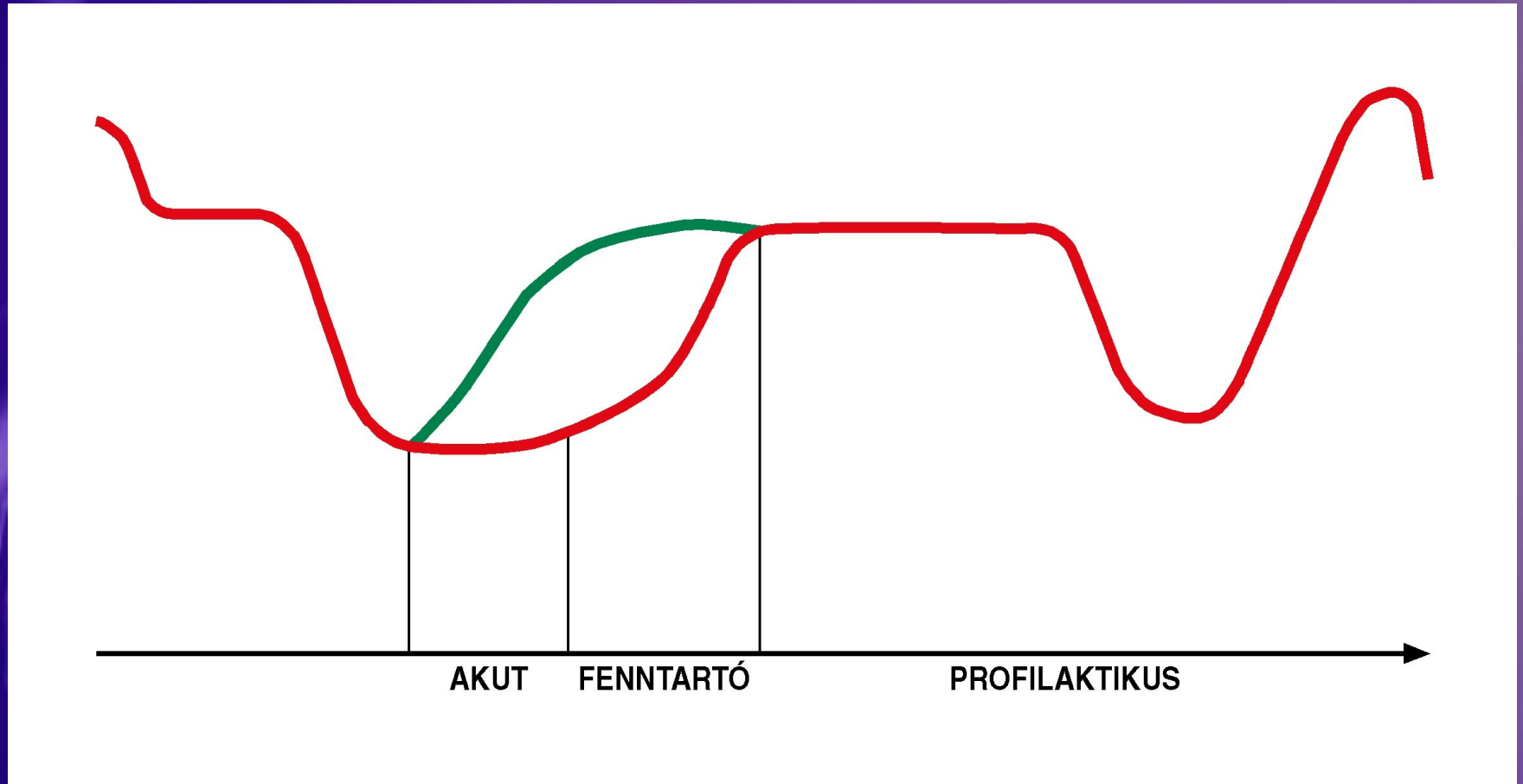
Pharmacotherapy of hypomania/mania

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

Treatment phases of unipolar major depression



A HOSSZÚTÁVÚ KEZELÉS FÁZISAI



Kupfer (1991) után, módosítva