MOOD DISORDERS

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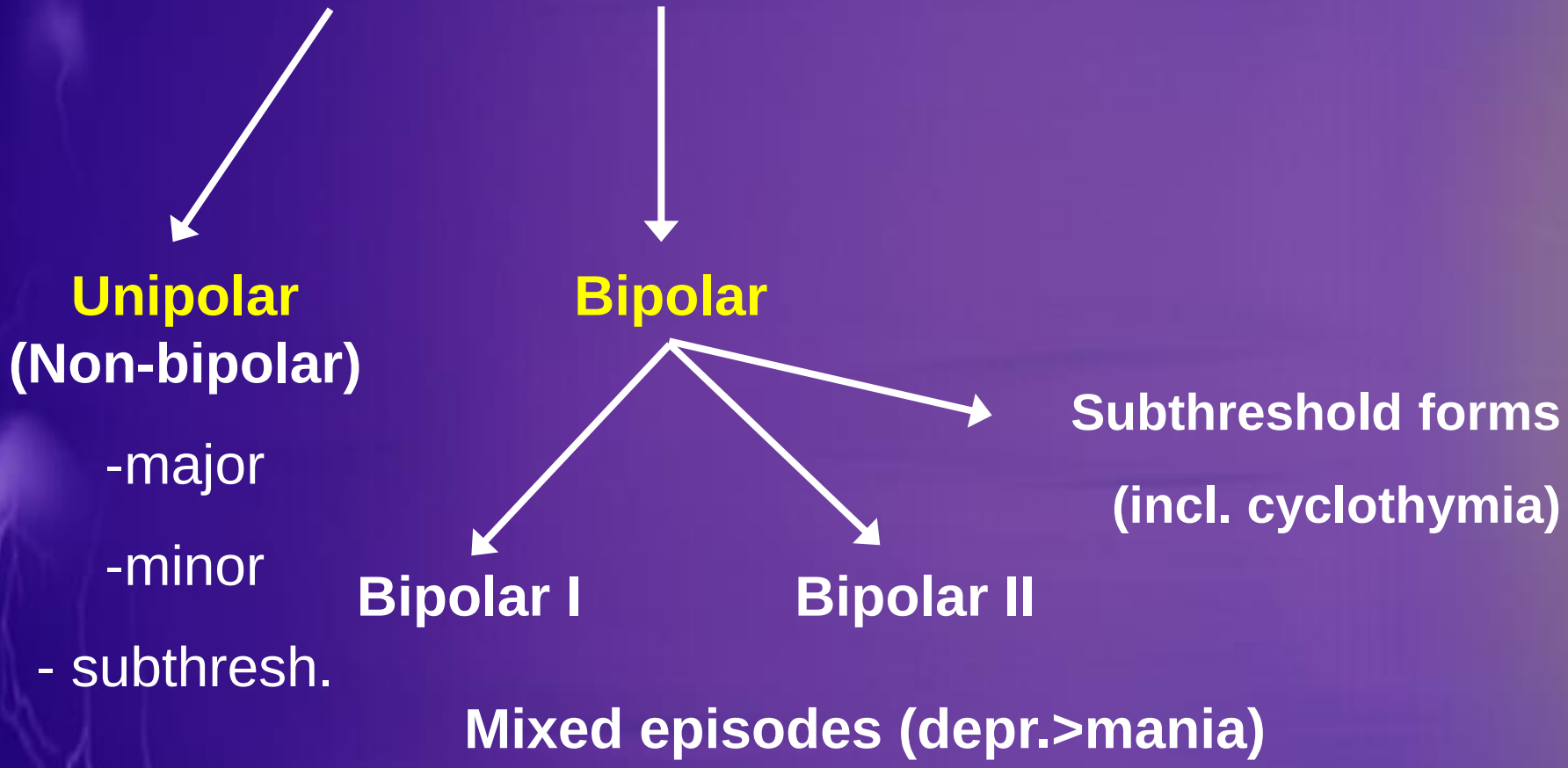
Heterogeneity of mood disorders

Clinical	Biological	Psychosocial
Polarity*	Genetics	Early negative life events
Severity	Biochemistry	Acute stressors
Periodicity	Brain morphology	Social support
Sex distribution	Electrophysiology	
Age of onset	Treatment response	
Comorbidity		

*Unipolar versus bipolar

Mood disorders. Clinical heterogeneity- Polarity



Clinical manifestations of mood (affective) disorders

MAJOR	Minor
• UNIPOLAR	
Unipol. maj. depr.	Minor depr.
Recurrent brief depr	Dysthymia
	Subs. sympt. depr.
• BIPOLAR	
Bipolar I	Min. bipol. disord.
Bipolar II	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 heterogenity of mood disorders

- Noon-familial (sporadic) cases (40-50%)

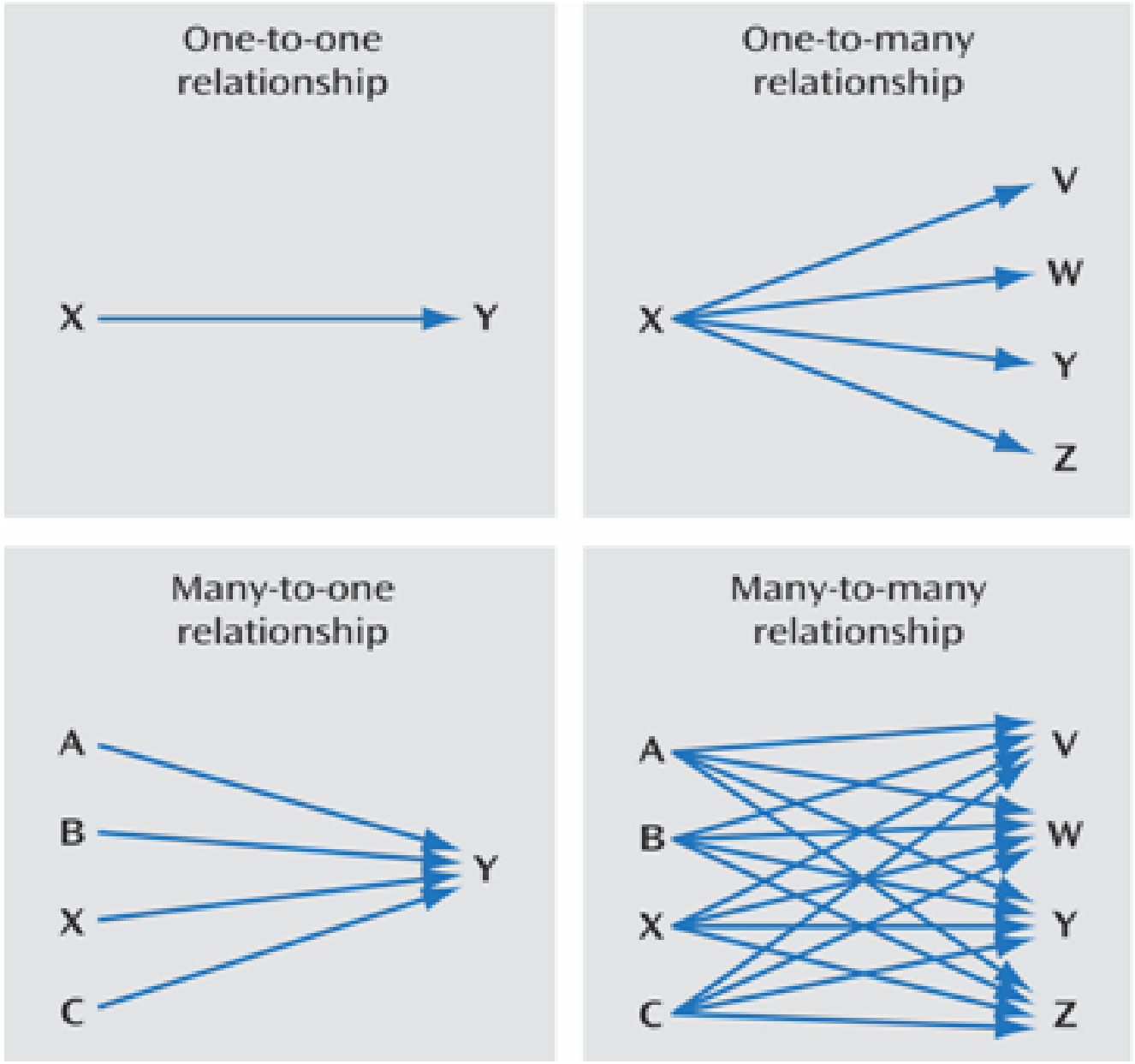
- Familial cases (50-60%)

  chromosomes:

  - X,18, 21, 5, 9,

    (TPH, 5-HT,NA, DA transporter etc)

Gene-phenotype relationships



Gén – fenotípus lehetséges kapcsolatai

A mentalis 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)
- Acethylcholine (?)

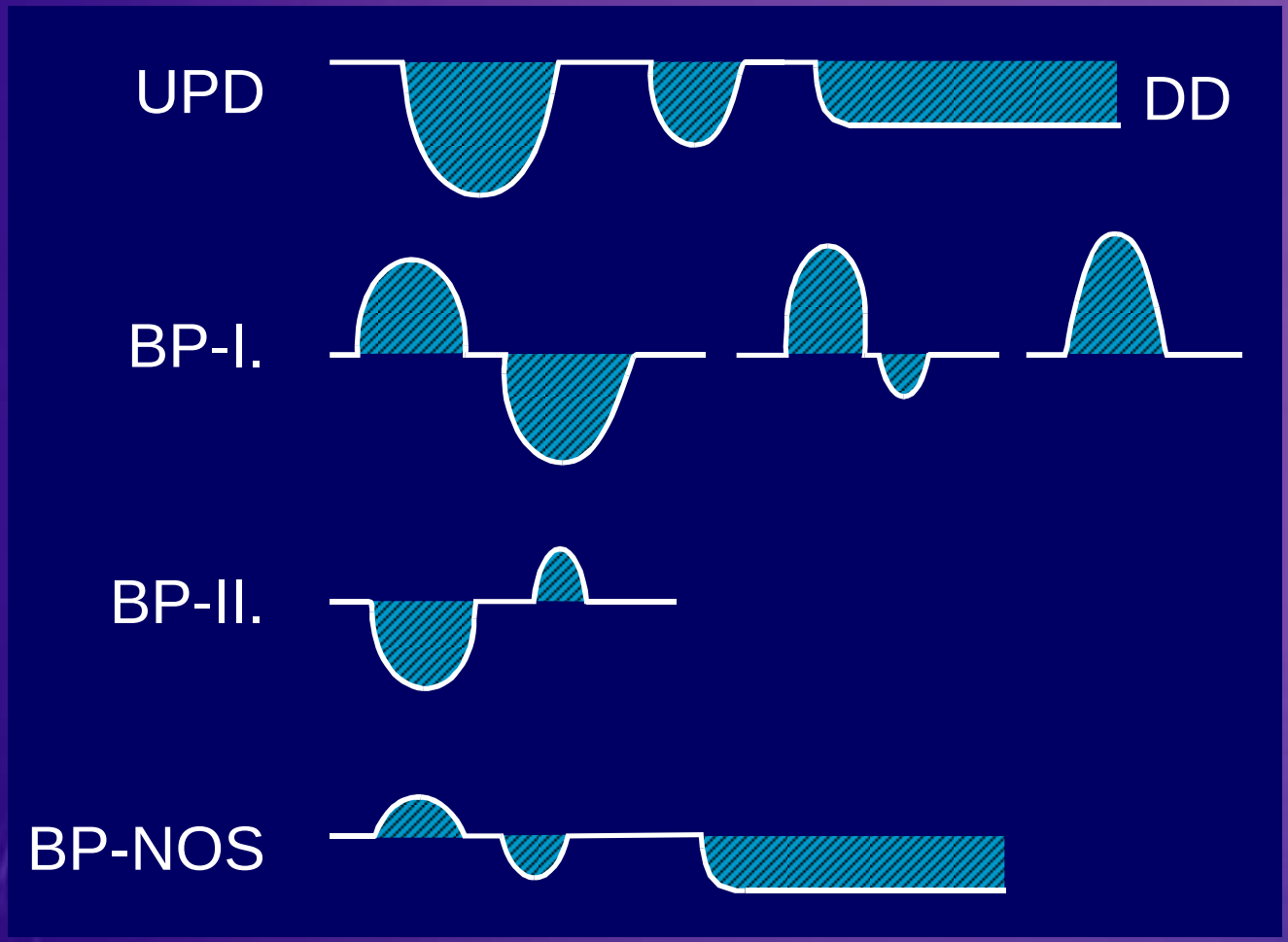
- MAO, COMT, TPH, 5-HT transporter (genetical polymorphism)
- Receptor function

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

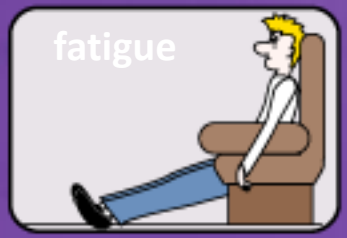
depressed mood

apathy/ loss of interest

one of these ***required***

weight/ appetite changes

sleep disturbances



worthlessness

executive dysfunction

suicidal ideation

four ***more*** *of these required*

Stahl, 2008

DSM-IV criteria of Major Depressive Episode - 2

B. The symptoms cause significant distress or funcional impairment

C. Possible casuses of substances or medical conditions are excluded

- (No grief-reaction – DSM-IV)

DSM-IV criteria of Dysthymic Disorder/Minor Depression

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

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

DSM-IV criteria of Mania

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

B. Three (or more) of the following (four or more if the mod is irritable):

1, Grandiosity, inflated self-esteem

2, Decreased need for sleep

3, More talkative, pressured speach

4, Flight of ideas, racing thoughts

5, Distractibility (reported or observed)

6, Psychomotor agitation

7, Excessive activities with negative consequences

C. Unequvivocal change in functining

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 remisson, 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 speach

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

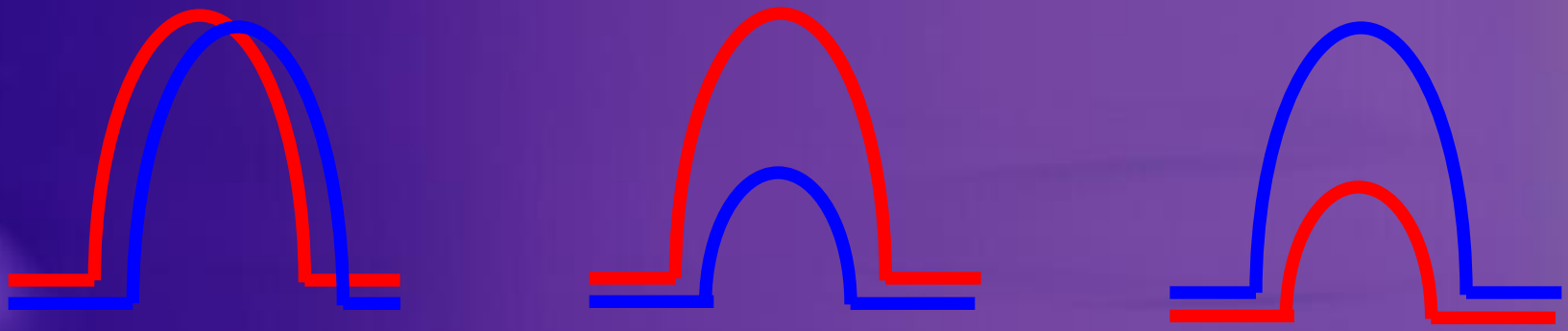
DSM-5 Major Depressive Episode „with mixed features" specifier - 2

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 physiologial 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

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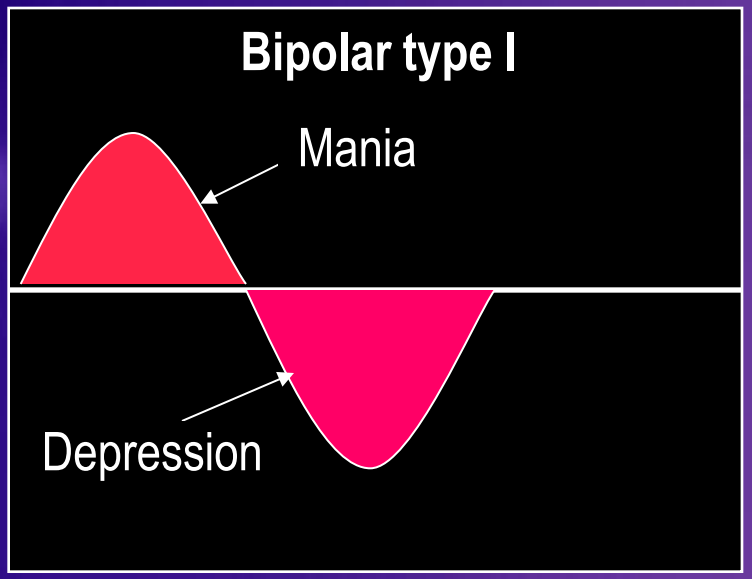
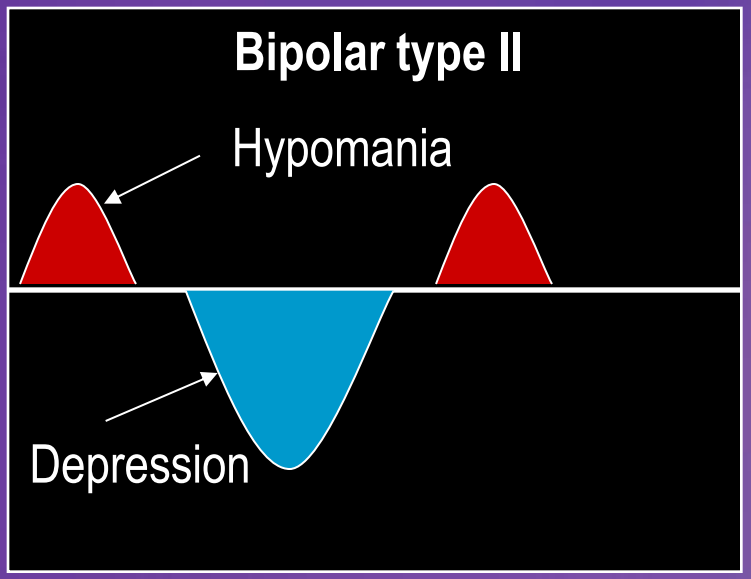
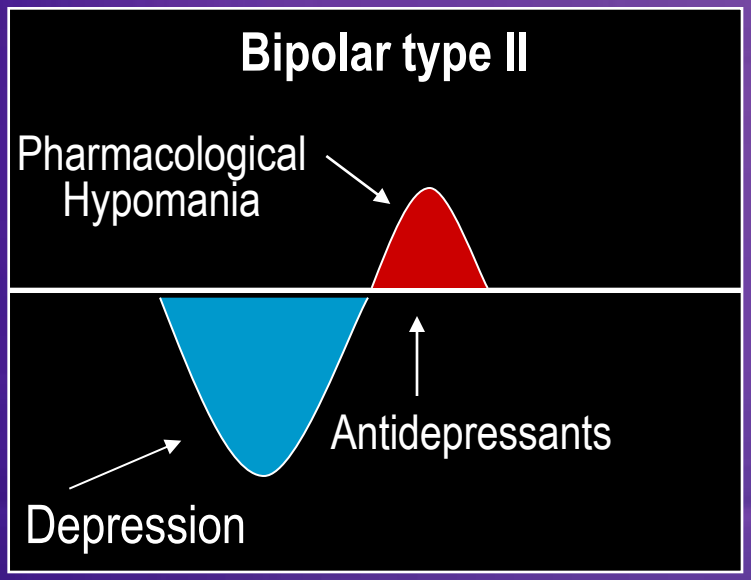
- Unipolar major depression
  - single episode
  - recurrent
- Bipolar I disorder
  - major depression + mania
  - minor depression + mania
- Bipolar II disorder
  - major depression + hypomania

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
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• Ten Have et al. 2002	CIDI-DSM-IIIR	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

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

Szádóczky 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:

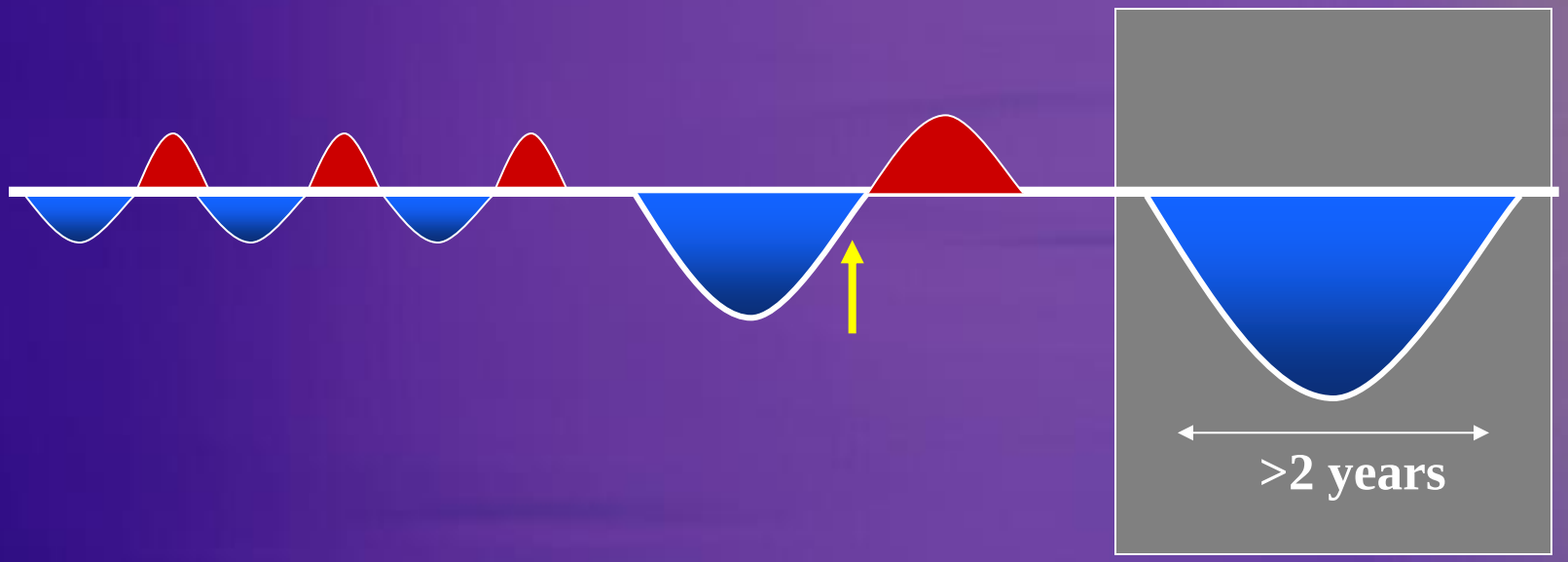
  10 - 15 % and 5 - 7 %

- 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



Hantouche, 2004

Unipolar – Bipolar conversion

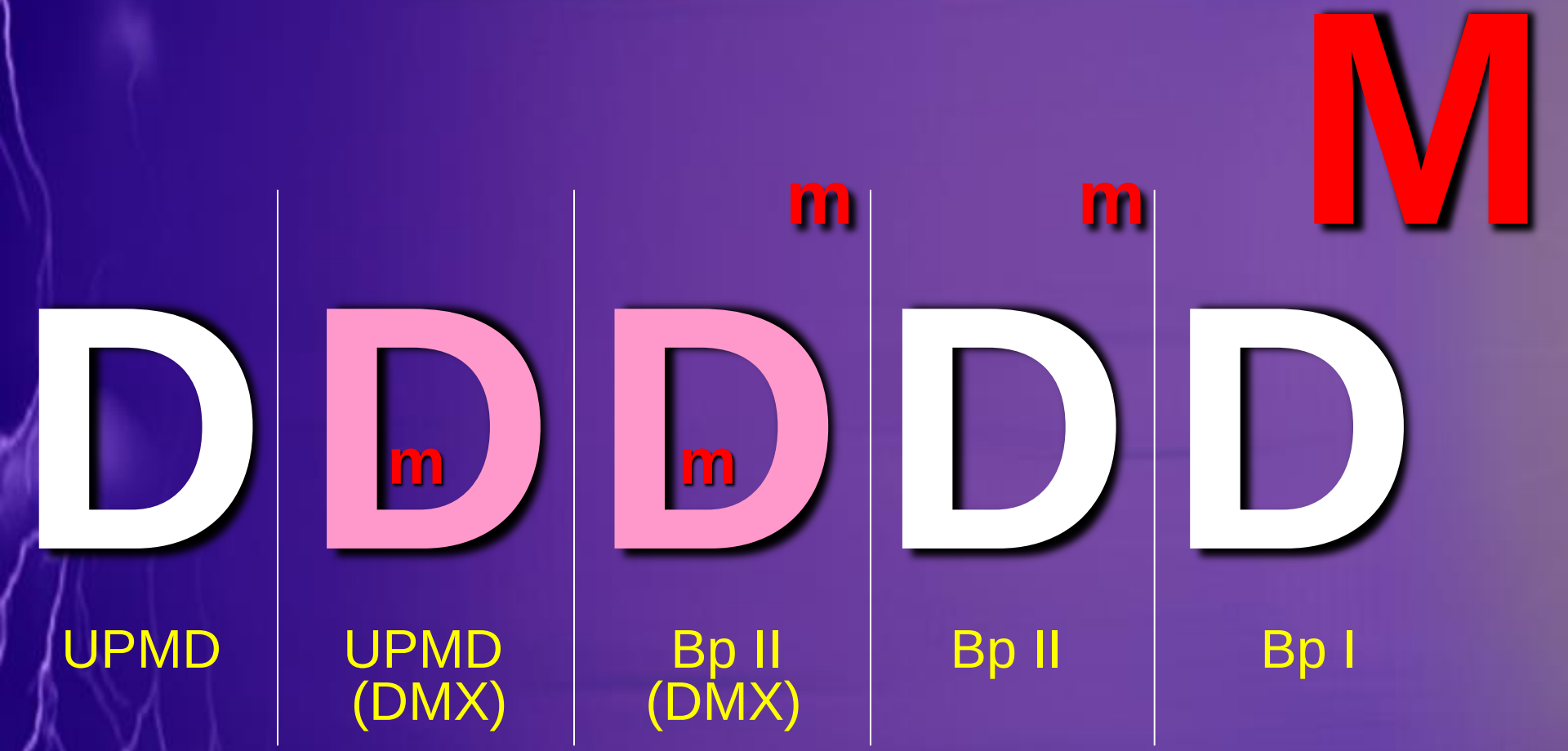
- 12.5 – 46 % of „unipolar” major depressives become Bipolar I or II during the 5 -15 year follow-up
- Predictors: early onset, severe depr., psychotic features, retardation, bipolar FH, cyclothymia/mood-energy lability

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)

Rihmer, 2004

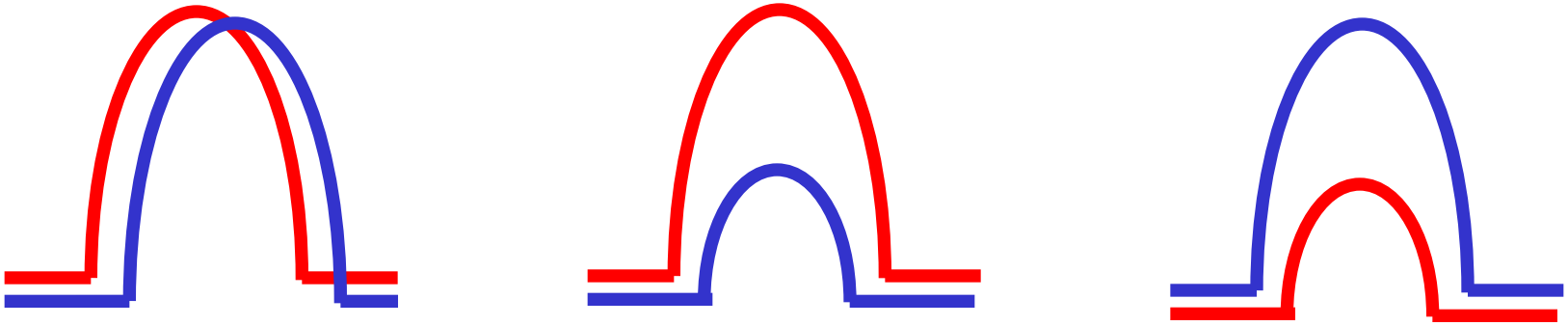
Depression and mania are both successive and simultaneous conditions (true)



Agitated depression

Rihmer, 2004

The three clinical phenotypes of overlapping affective episodes



Mixed affective episode

Dysphoric mania

Mixed (bipolar) depression

Rihmer, 2005

Pure vs comorbid mood disorders

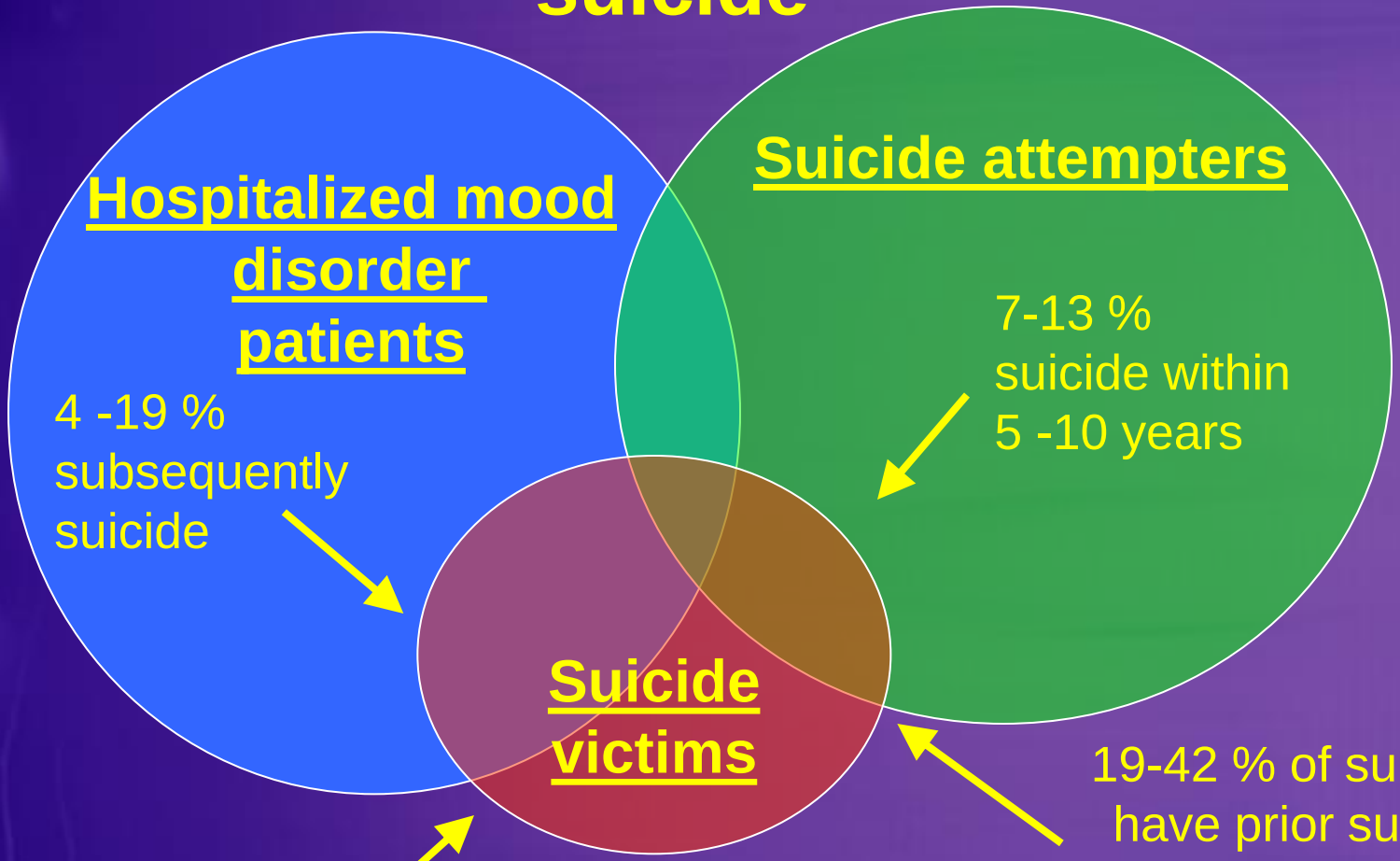
- Pure mood disorder (i.e. mood disorders without comorbid Axis I disorders) is relatively rare (30-40 %)
- The most frequent Axis I comorbid disorders in mood disorders are:
  - Anxiety disorders (30-60 %)
  - Substance use disorders (25-70 %)

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)
- Succesfull acute/long-term treatment of mood disorders significantly reduces the suicide mortality

Rihmer et al, Curr Opin Psychiat, 2002, 15: 83-87

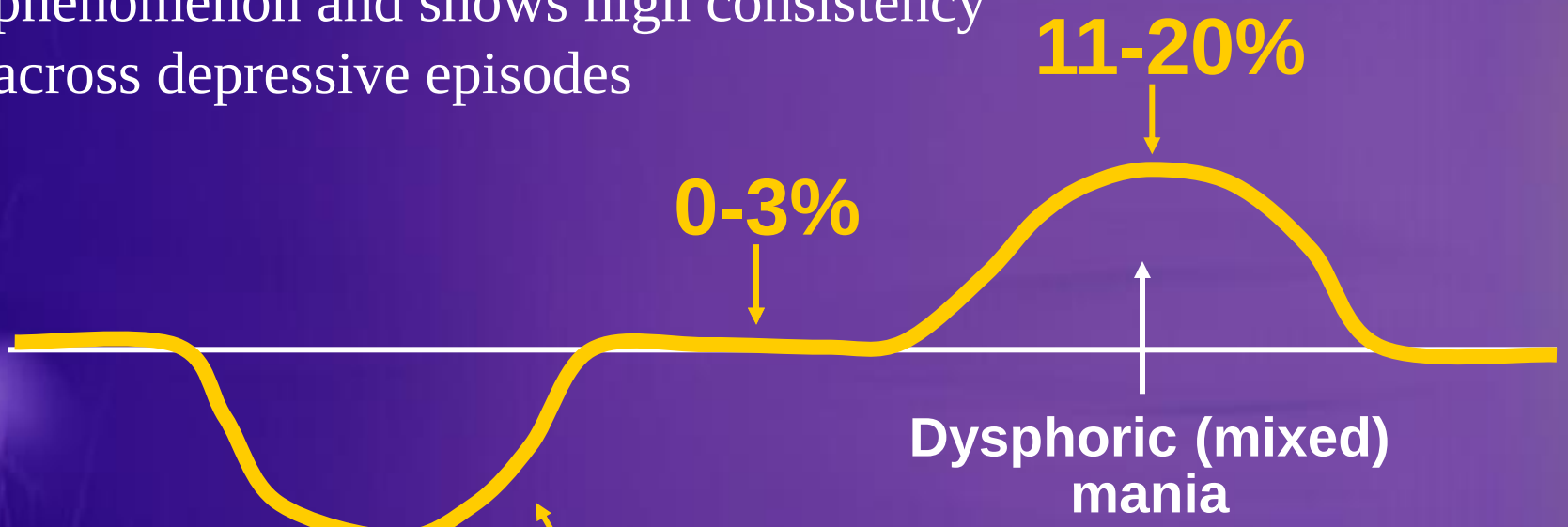
Major mood disorder, suicide attempt and suicide



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 vistims 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

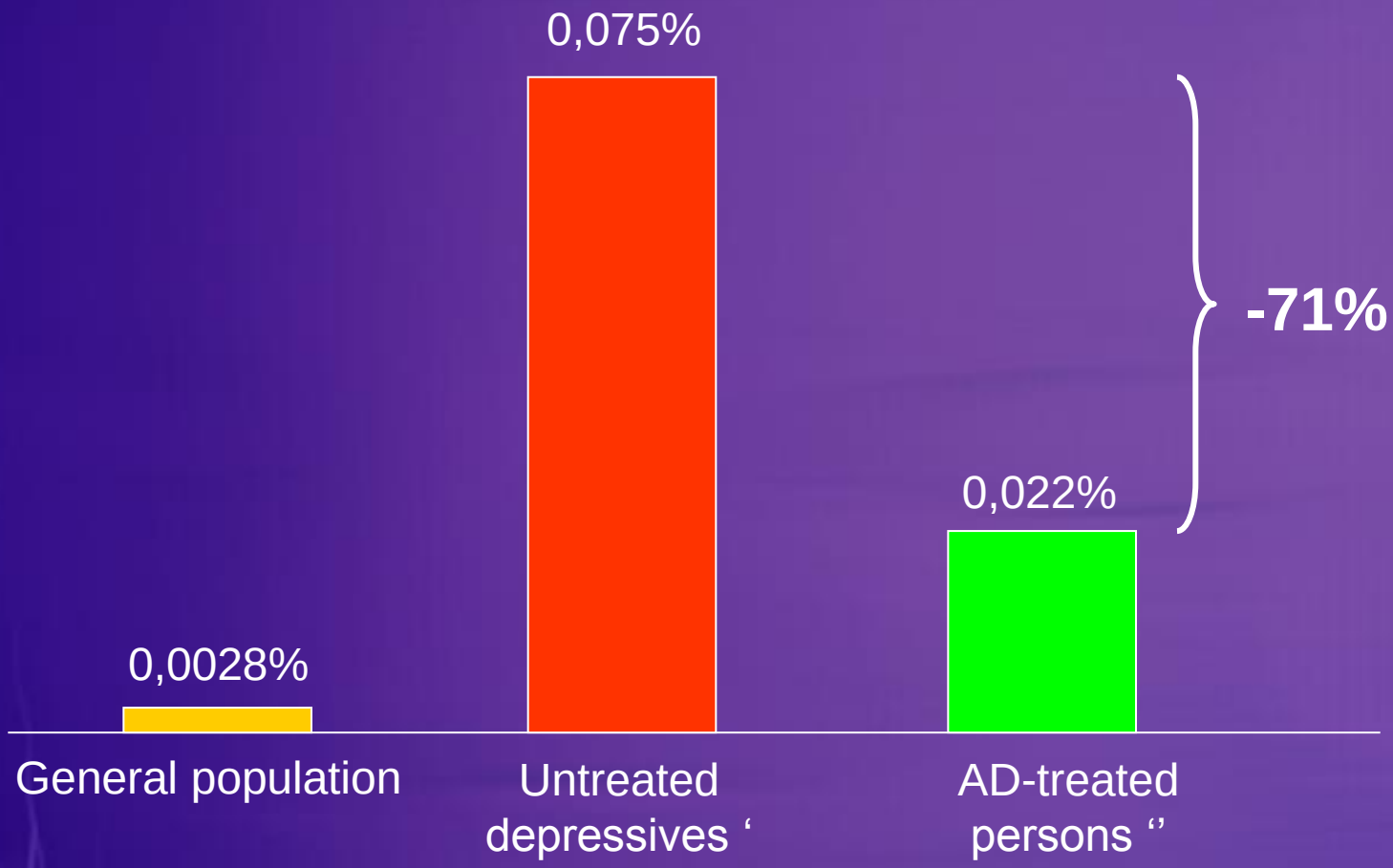
The yearly risk of completed suicide

- 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,

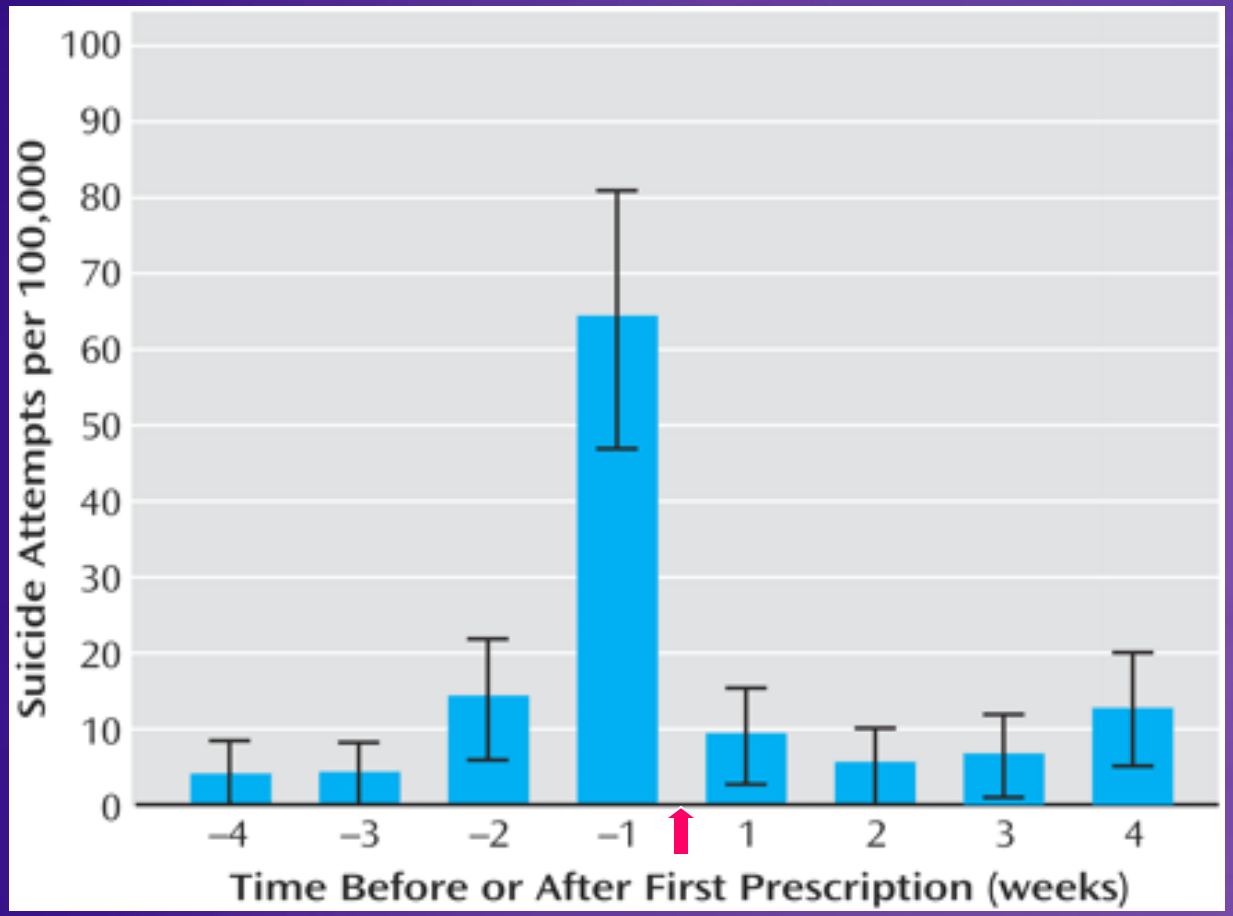


Figure 5. Rates of Suicide Attempts During the 4 Weeks Before and 4 Weeks After Initial Antidepressant Prescription[a]

[a]Bars indicate 95% confidence intervals.

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

Biological basis of mental disorders

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

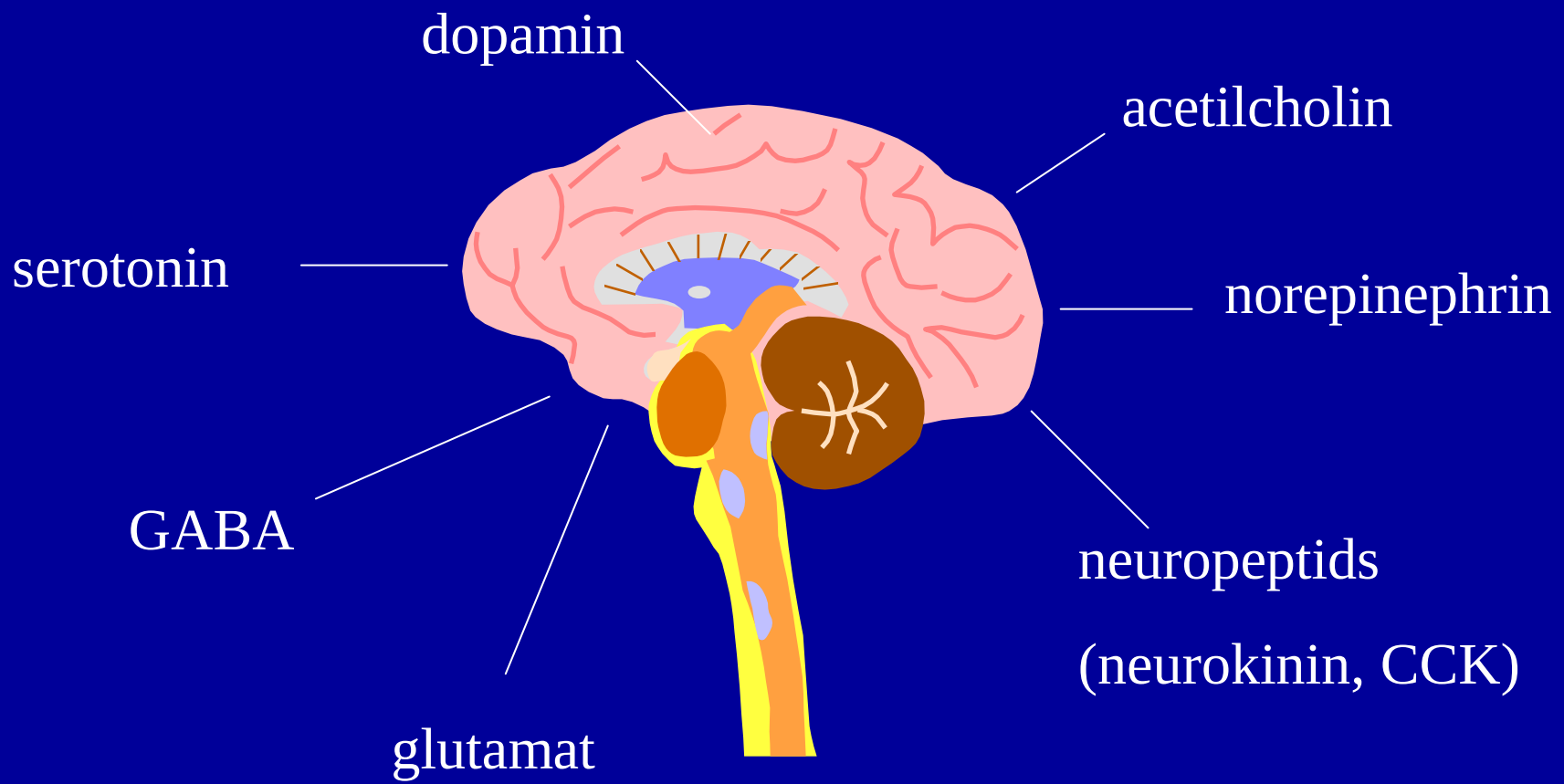
  Mood diasorders: serotonin, noradre-nalin, dopamine

  Schizophrenia: dopamine, glutamate

  Anxiety disorders: GABA, serotonin

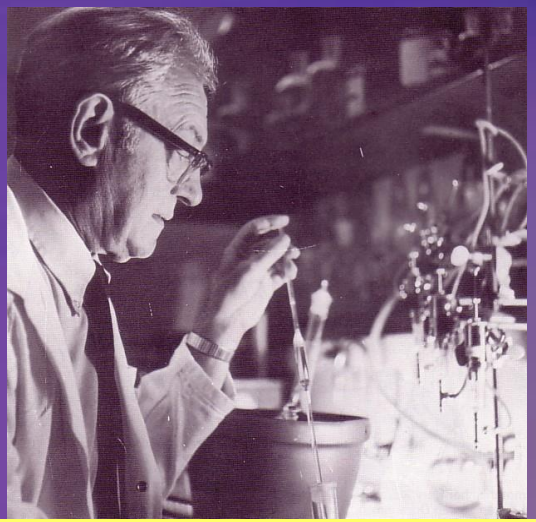
  Alzheimer disease: acethylcoline

NEUROTRANSMITTER SYSTEMS, RALATED TO PSYCHIATRIC DISORDERS

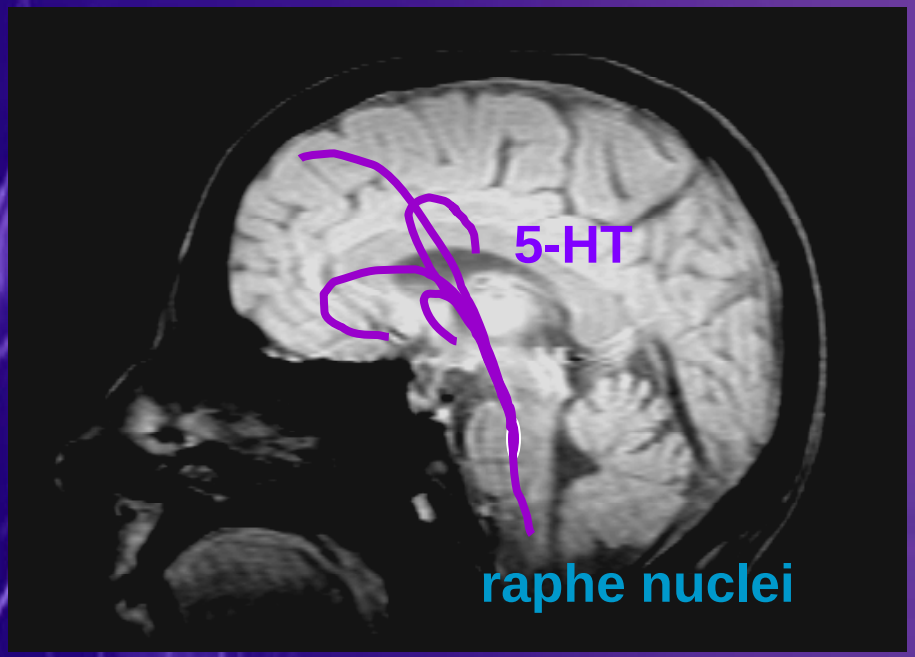


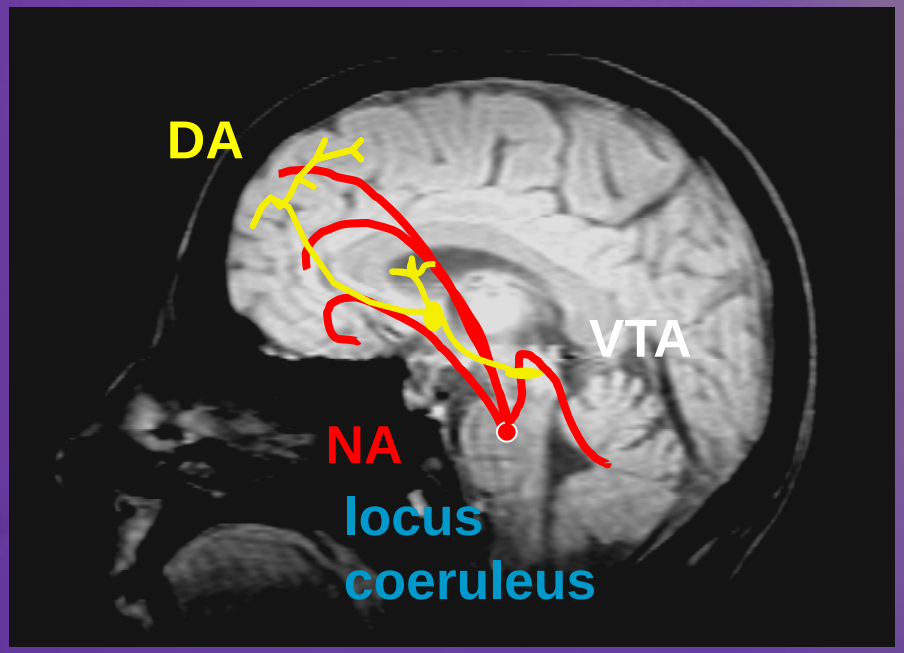
Reuptake inhibition, receptor (ant)agonism

and antidepressive/antimanic action



Julius Axelrod (1912-2004)





serotoninergic system

Noradrenergic/dopaminergic system

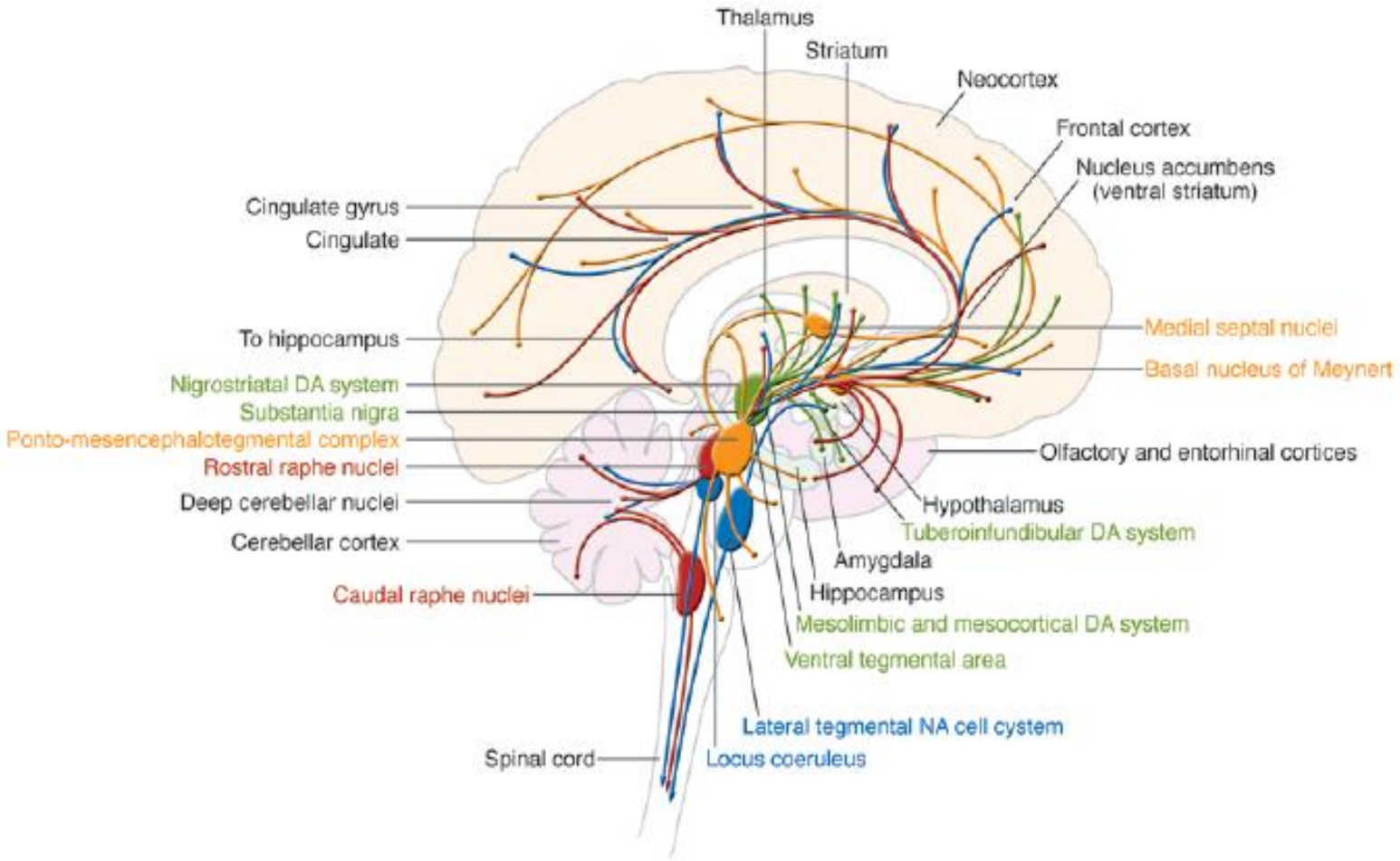
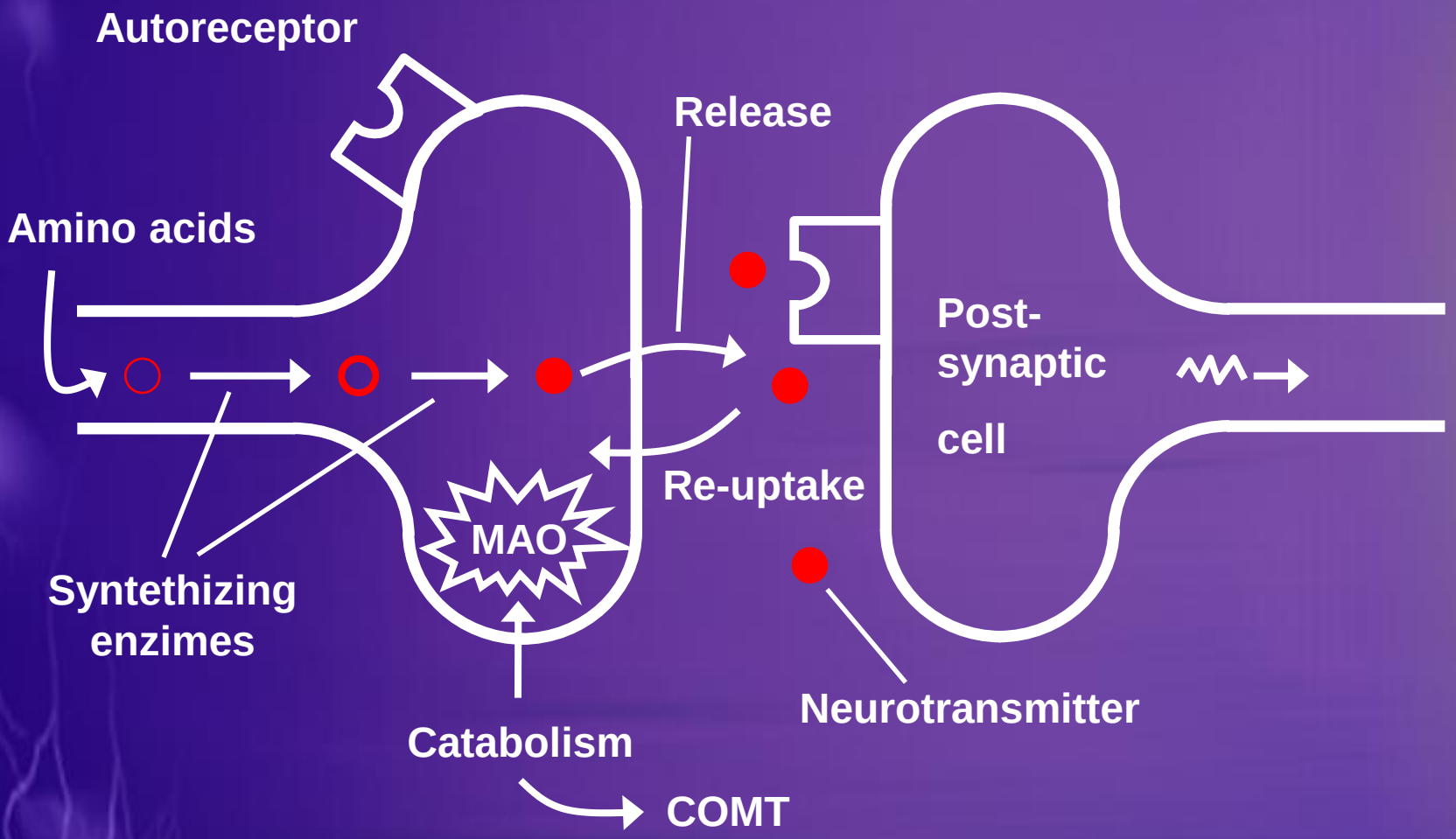


Figure 1
Locations of the monoaminergic nuclei within the brain as well as the projections from these nuclei throughout the brain. Nuclei as well as their projections are color coded: yellow, cholinergic; green, dopaminergic; blue, noradrenergic; red, serotonergic.

Neurotransmission in the CNS



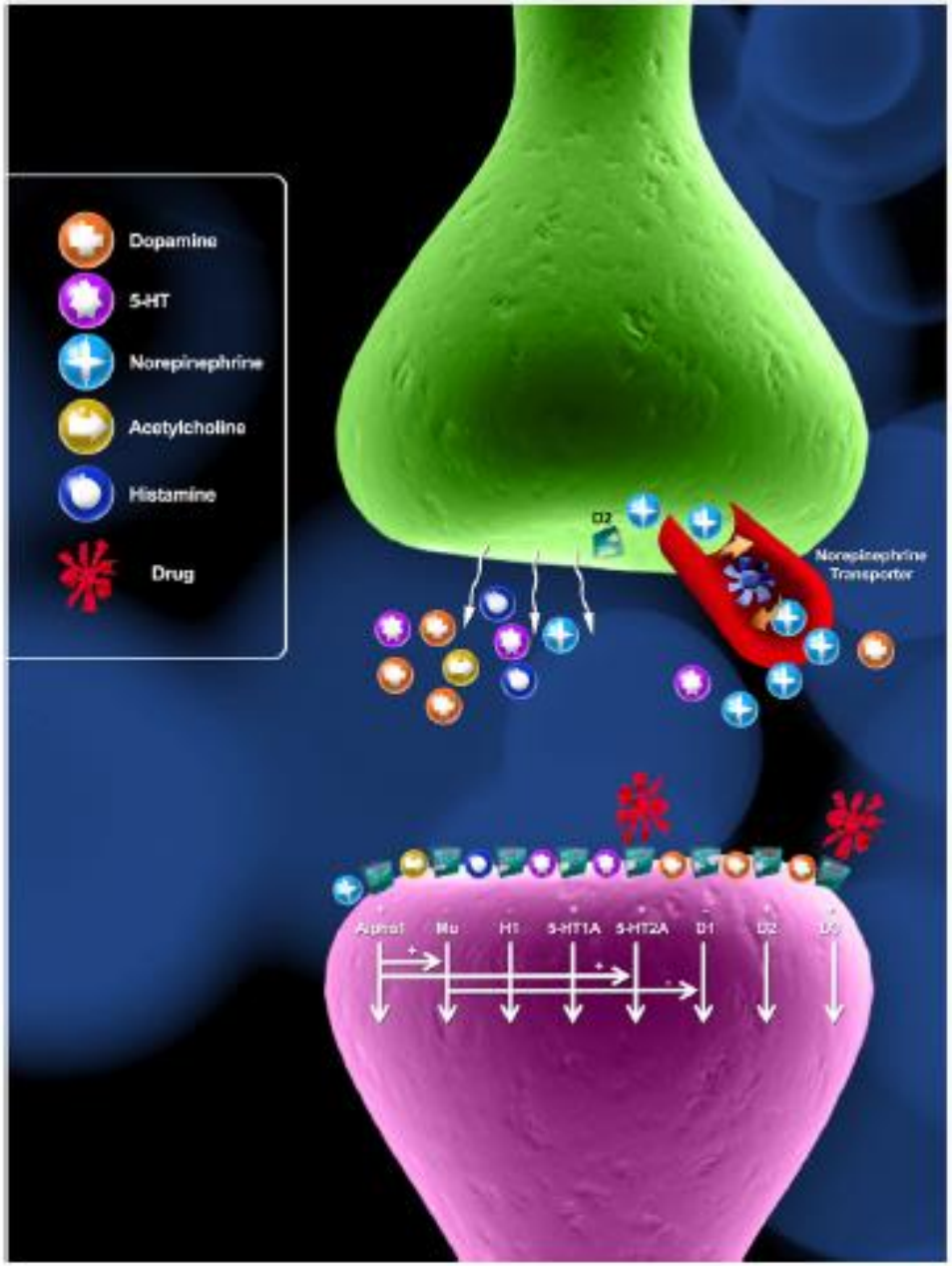
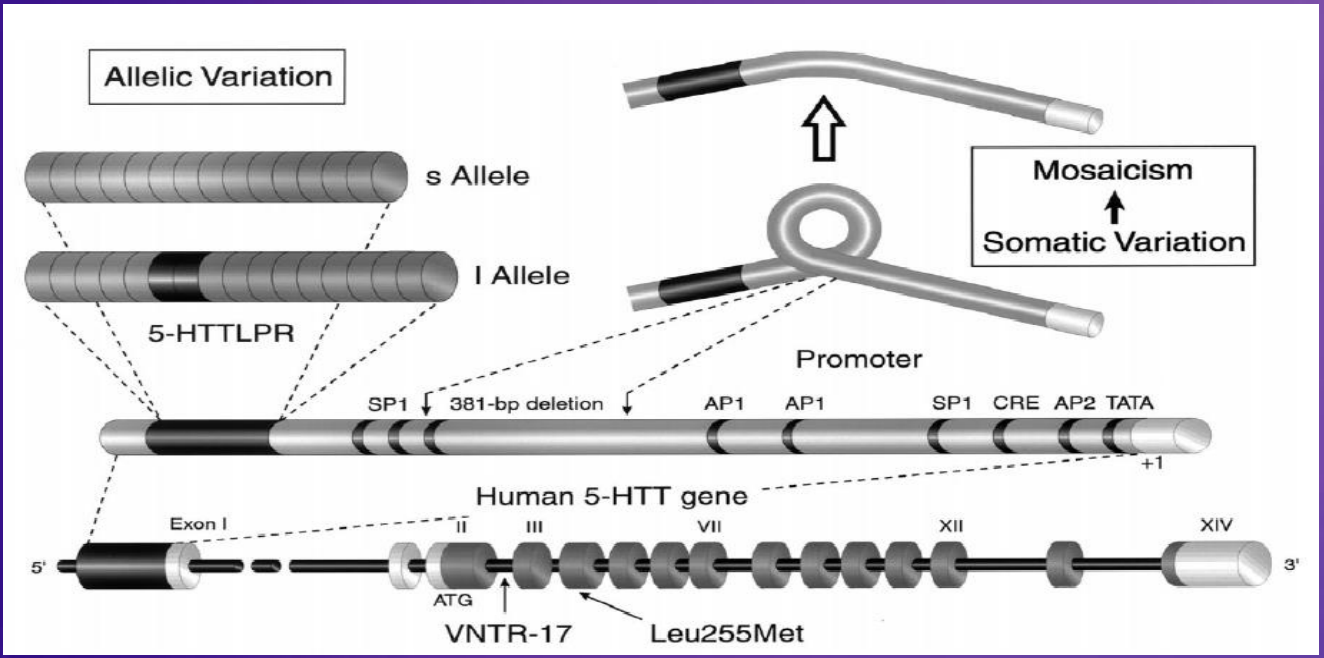


Fig. 3. Events at the synaptic level, related to the antidepressant effect in bipolar depression.

Serotonin transporter gene (5HTTLPR)

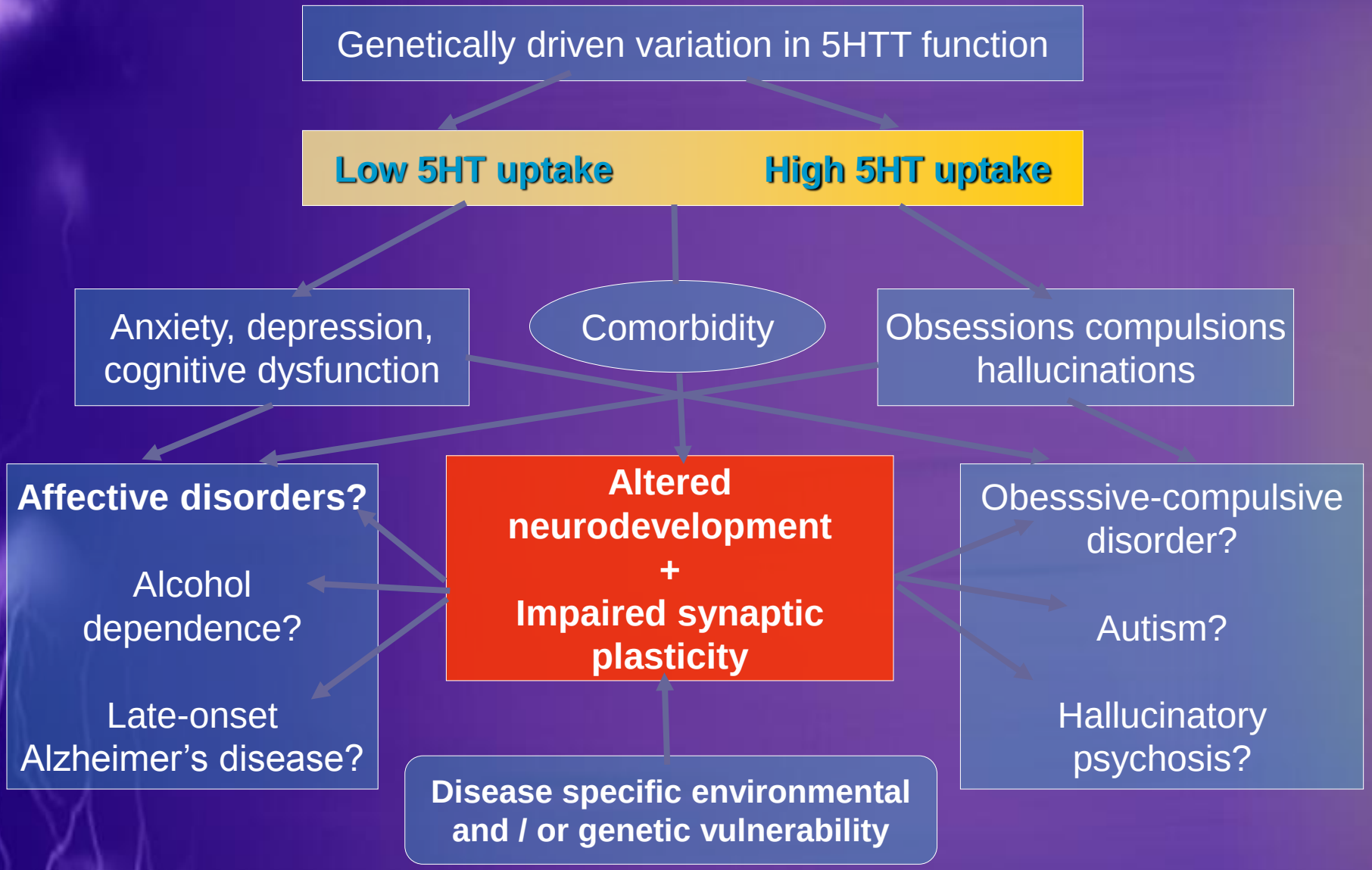
- SERT gene (SLC6A4): 17q11.1-q12
- Functional polymorphism in promoter
- s and l alleles



Lesch KP. J Affect Disord, 2001; 62: 57-76.

5HTTLPR

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



Lesch & Mössner R.(1998) Biological Psychiatry, 44: 179-192.

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

Striatum
emotional memory, drive

Hypothalamus
sleep, appetite, energy, libido

Prefrontal cortex
emotional & cognitive aspects of depression

Ventral tegmental area
reward, fear, motivation

Amygdala
processing of emotion

Hippocampus
long-term memory

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 dedpletion: 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.

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%,bipolars	25	28	33

Szádóczky et al. J.Aff.Dis. 1998,50:153-162
Szádóczky 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
• Szádóczky 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 (depen-dence)
- 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

Rihmer, Curr Opin Psychiat, 2007; 20: 17-22.

Tereatment of mood disorders

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

Pharmacotherapy of mood disorders

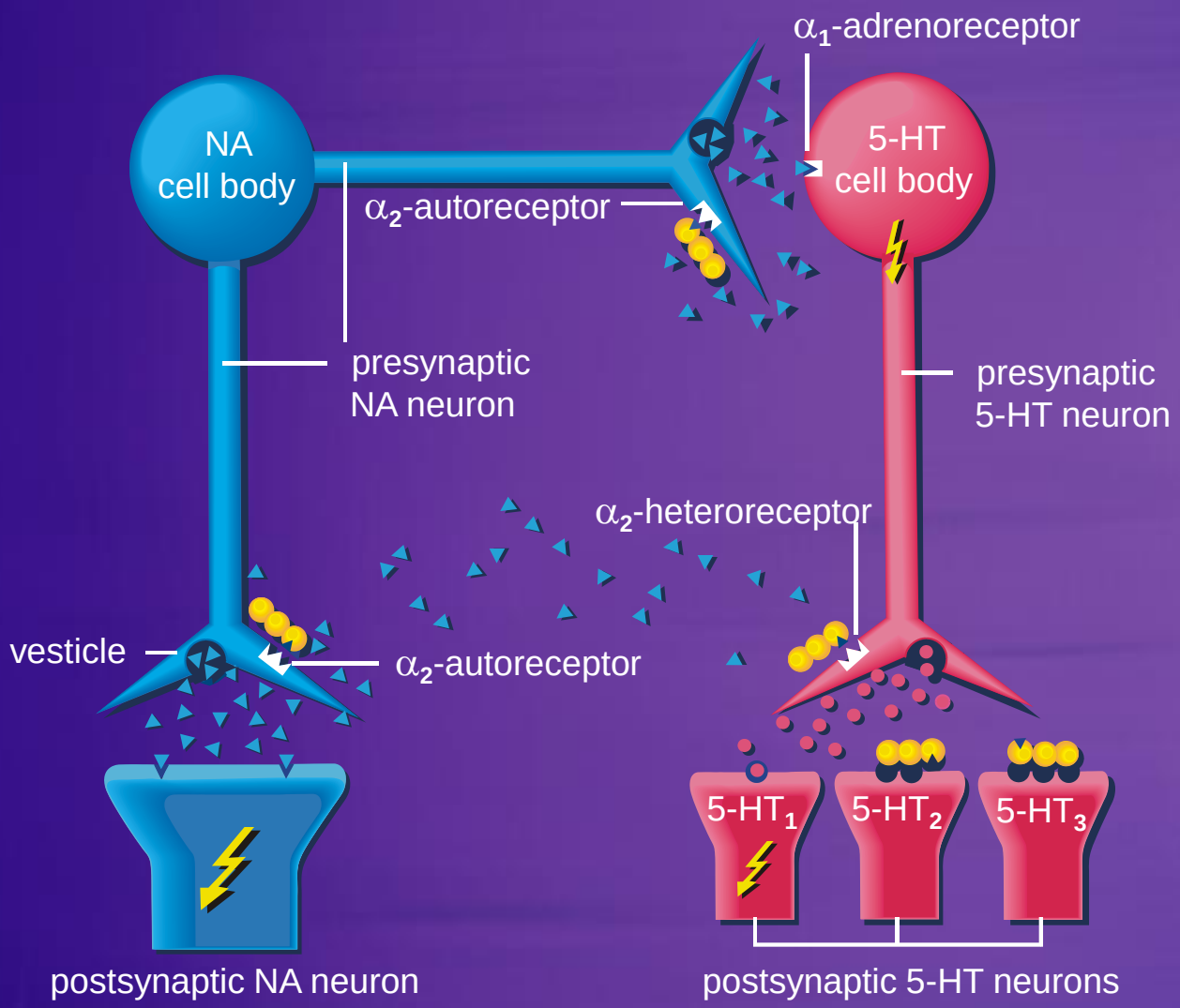
- Pharmacoterapy of depression
  momotherapy with ADs (uniolar depr.)
  combination of ADs and ANXLs, APs,
  mood stabilizers
- Pharmacotherapy of mania
  APs
  Mood stabilizers (Li, VPA, CBZ, LTG)
- Long-term treatment of mood disorders
  (mood stabilizers)

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, tranylcipro-mine/moclobemide)

Mirtazapine – Mechanism of action



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)
- Inncrease the dose in non/patrial 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 respodenrs 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%

O'Donovan et al, J Affect Disord. 2008; 107: 293-298.

Most frequent cause of antidepressant resistance in major depression

Unrecognized bipolar disorder

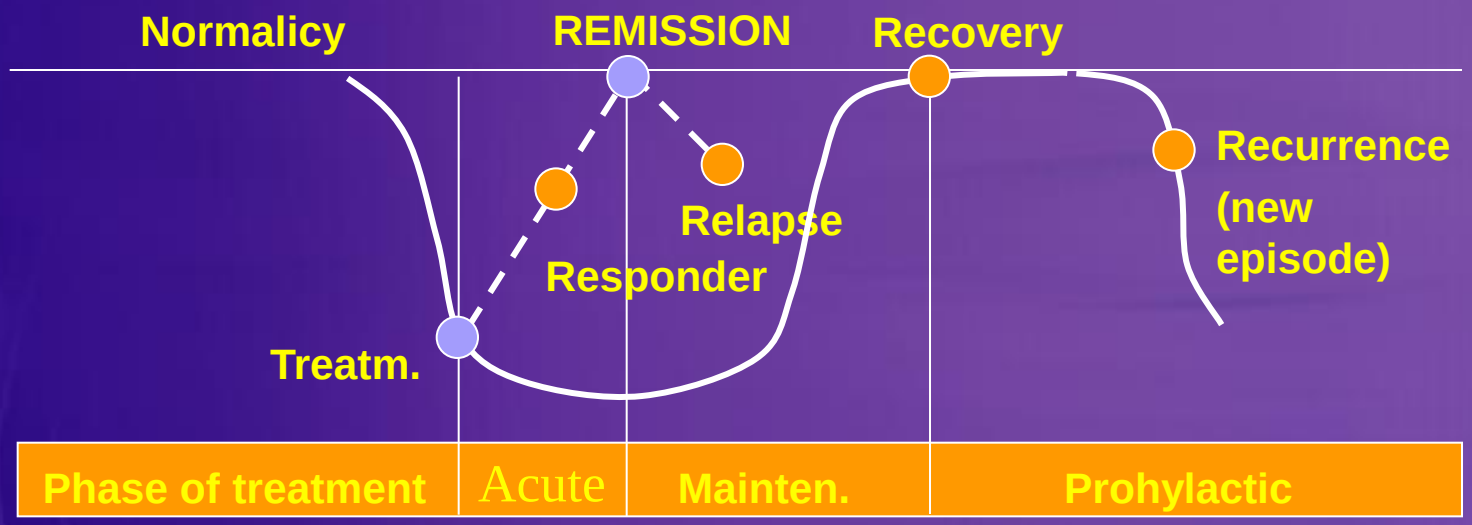
Inoue et al, J Affect Disord, 2006; 95: 61-67.

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

Pharmacotherapy of hypomania/mania

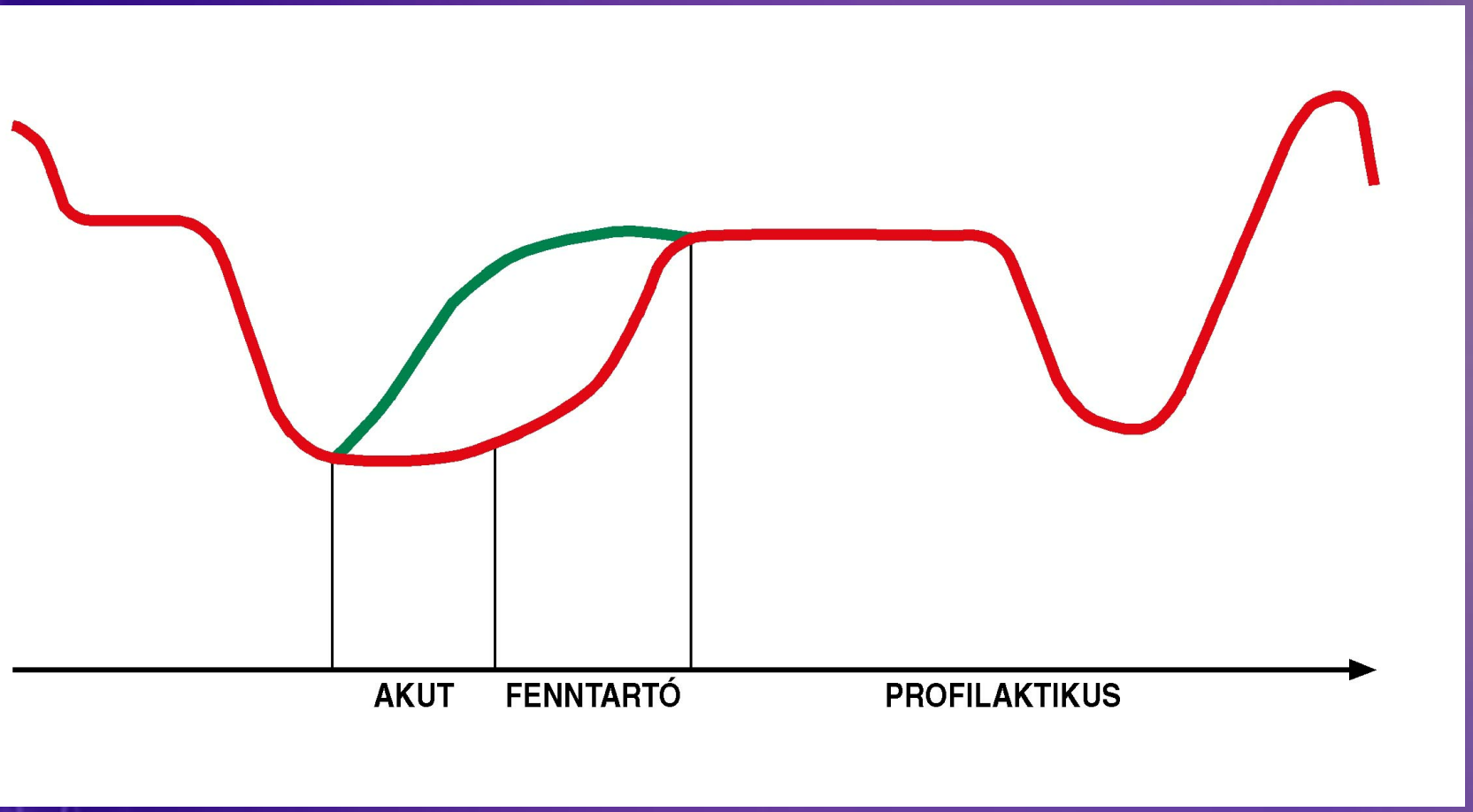
- Mood stabilizers (Li, VPA, CBZ)
- Antipsychotics (atypicals)
- Anxiolytics (clonazepam, alprazolam)

Treatment phases of unipolar major depression



Kupfer, 1991 után módosítva

A HOSSZÚTÁVÚ KEZELÉS FÁZISAI



Kupfer (1991) után, módosítva