ANTIDEPRESSZANSOK A PSZICHIATRIÁBAN

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2018.4.27

előadas, PTE Farmakológiai és Farmakoterapias Intezet

Gyógyszer és pszichoterápia kombináció, főleg ha antidepresszáns adása kockázatos

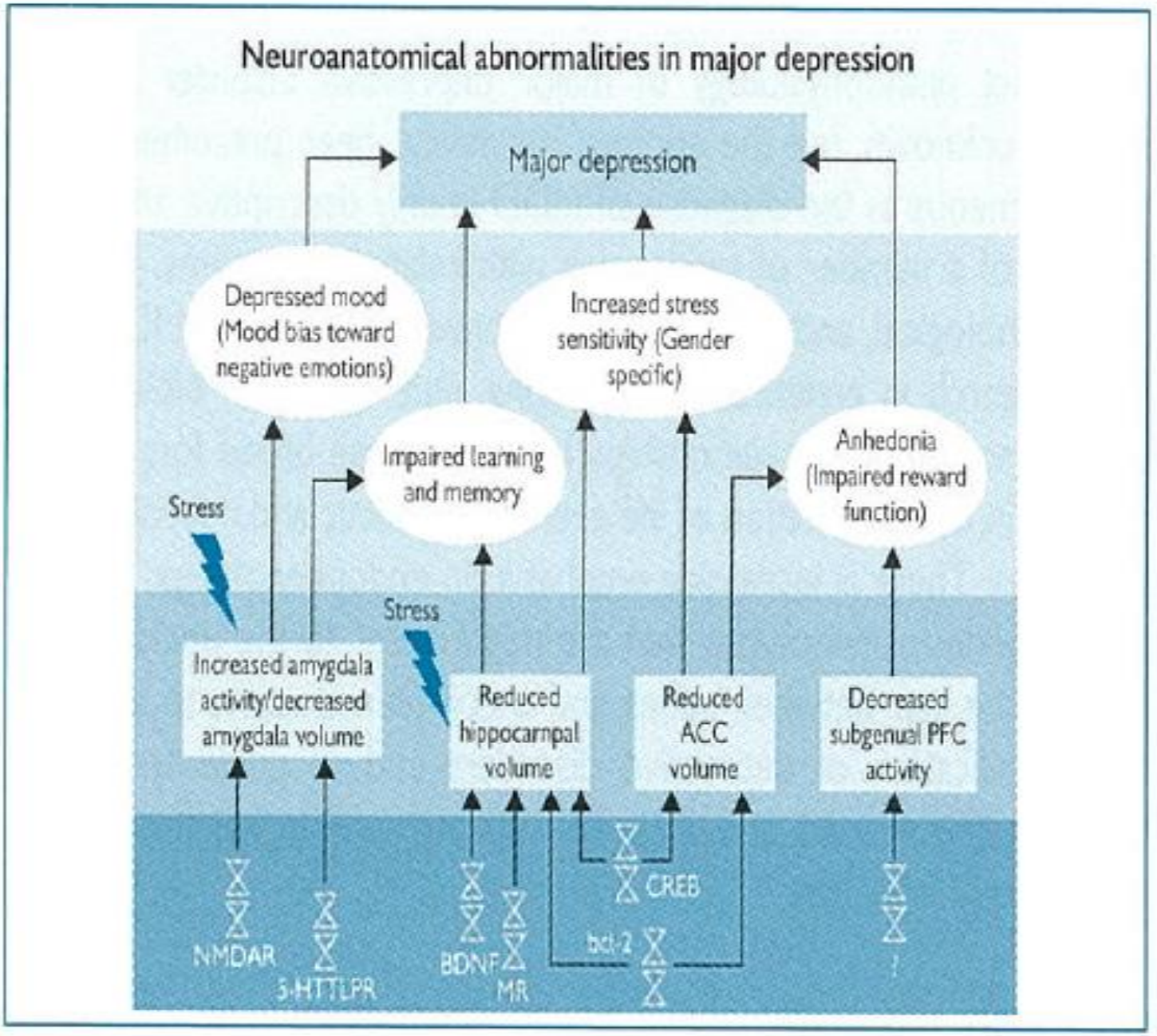
Szükség szerint anxiolitikum, alvásjavítás

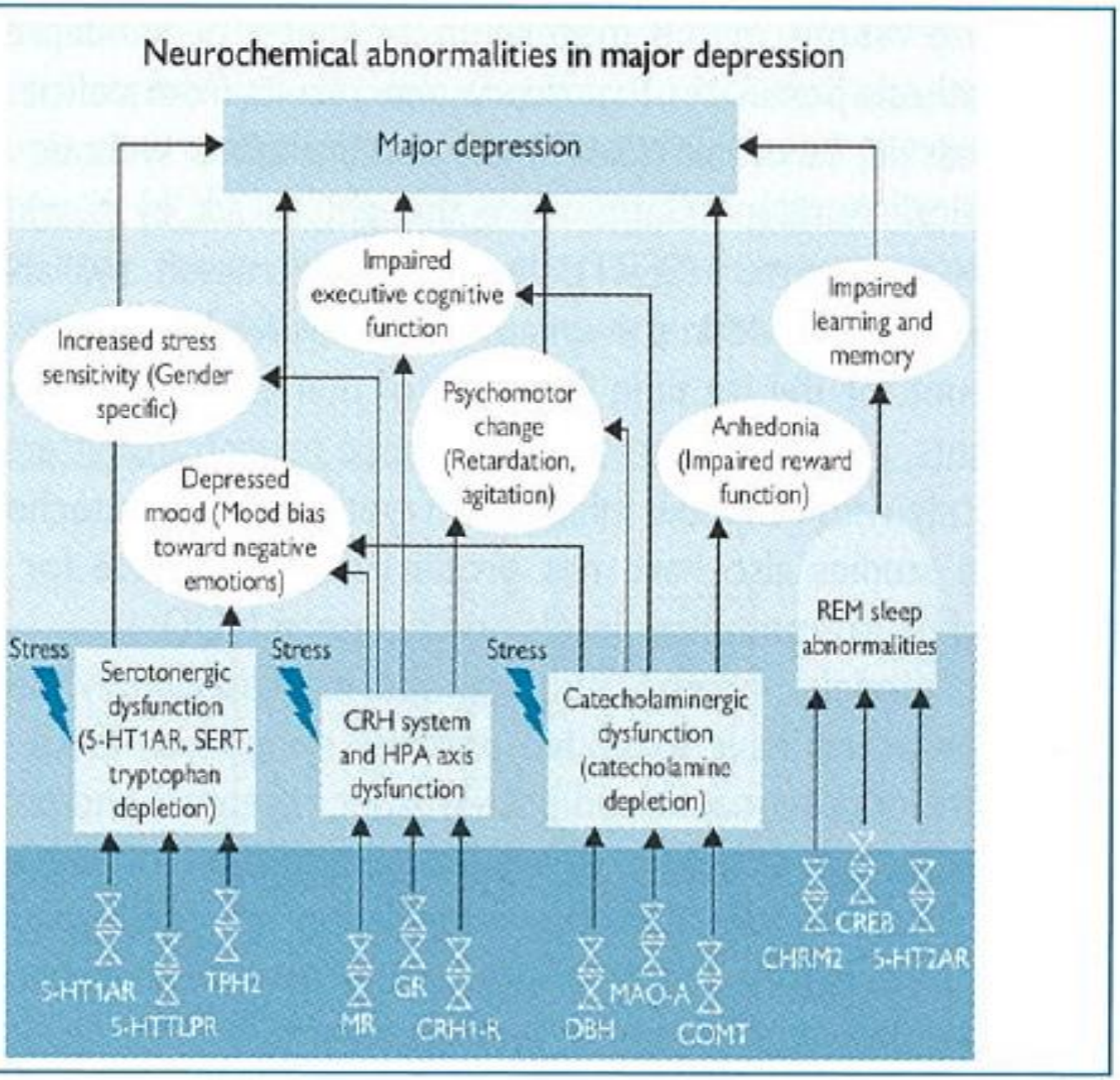
Antidepresszív szer, a választás sajátos szempontjai, augmentáció

Szupportív problémakezelés, ill. adott esetben célzottan pszichoterápia (kognitív, dinamikus, családterápia)

Pszichoedukáció

Different classes of antidepressants


Neuroanatomical abnormalities in major depression
Major depression
Depressed mood (Mood bias toward negative emotions)
Increased stress sensitivity (Gender specific)
Impaired learning and memory
Anhedonia (Impaired reward function)
Stress
Stress
Increased amygdala activity/decreased amygdala volume
Reduced hippocampal volume
Reduced ACC volume
Decreased subgenual PFC activity
CREB
bcl-2
NMDAR
5-HTTLPR
BDNF
MR
?


Neurochemical abnormalities in major depression
Major depression
Impaired executive cognitive function
Impaired learning and memory
Increased stress sensitivity (Gender specific)
Psychomotor change (Retardation, agitation)
Anhedonia (Impaired reward function)
Depressed mood (Mood bias toward negative emotions)
REM sleep abnormalities
Stress
Stress
Stress
Serotonergic dysfunction (5-HT1AR, SERT, tryptophan depletion)
CRH system and HPA axis dysfunction
Catecholaminergic dysfunction (catecholamine depletion)
5-HT1AR
5-HTTLPR
TPH2
MR
GR
CRH1-R
DBH
MAO-A
COMT
CHRM2
CREB
5-HT2AR


DEPRESSION
• Major depression
• Dysthymia
• Atypical depression
• Seasonal affective disorder (SAD)
• Premenstrual dysphoric disorder (PMDD)
A.D.A.M.

Antidepresszánsok hatásmechanizmusai

Az ismert antidepresszánsok a hatásukhoz szükséges szerotonin és/vagy noradrenalin/ dopamin, illetve újabb adatok szerint glutamát neuro-transzmisszió fokozását/módosítását/gátlását az alábbi mechanizmusok révén érik el (1-3 het delayed effect..) :

- Szerotonin- és/vagy noradrenalin-, ill. dopamin visszavétel gátlása
- MAO-bénítás
- Szintézis fokozása a prekurzorok által
- A poszt-szinaptikus receptorok működésének spec fokozása/gátlása
- A preszinaptikus (gátló) autoreceptorok antagonizálása
- Melatonin-receptor antagonizmus (biol ritmusok, HPA axis..)
- Glutamát-NMDA-receptor antagonizmus
- BDNF, (cAMP-CREB-BDNF) neuron-regeneráció…..

Milyen lenne egy ideális ANTIDEPRESSZIV szer?

- gyors hatáskezdet, mellékhatás nélkül
- Nem rontja a kognitív funkciókat
- Nincs hozzászokás, megvonási tünet
- Gyógyszerinterakciók - CYP450 lebontás - gyors-lassú metabolizálók, enzimindukció

Modern antidepresszansok

Klasszikus, tri és tetraciklusos szerek/imipramin.amotriptilin,clomipram

SSRI's: paroxetine, fluoxetine, sertraline, fluvoxamin, citalopram, eszcitalopram,

SNRI's, dual action venlafaxin, duloxetin, reboxetine….

SDA–buproprion (anhedonia, smoke) NA–atomoxetin (ADHD)

α2- antagonist + 5 HT2 antagonism: Remeron

5-HT reuptake inhibition + 5-HT2 antagonism: trazodone, nefazodone

RIMA – reverz.MAO inhibitor: moclobemide

Vortioxetin – „multimodalis" (ld kognitiv tuneteket is..)

Agomelatin – melatonin 1,2 rec.agonista; 5HT2c antag; ld anhedonia

Ketamin/eszketamin vizsgalatok igeretei?

First generation

MAOI RIMA

Phenelzine
Tranylcypromine
Selegiline patch
Moclobemide

TCA

Amitriptyline
Clomipramine
Nortriptyline
and others

Second generation

SSRI

Citalopram
Fluoxetine
Fluvoxamine
Paroxetine CR
Sertraline

ASRI

Escitalopram

NRI

Reboxetine

SNRI

Venlafaxine XR
Milnacipran
Duloxetine

NDM

Bupropion SR/XL

NaSSA

Mirtazapine

Third generation

Melatonergic

Agomelatine

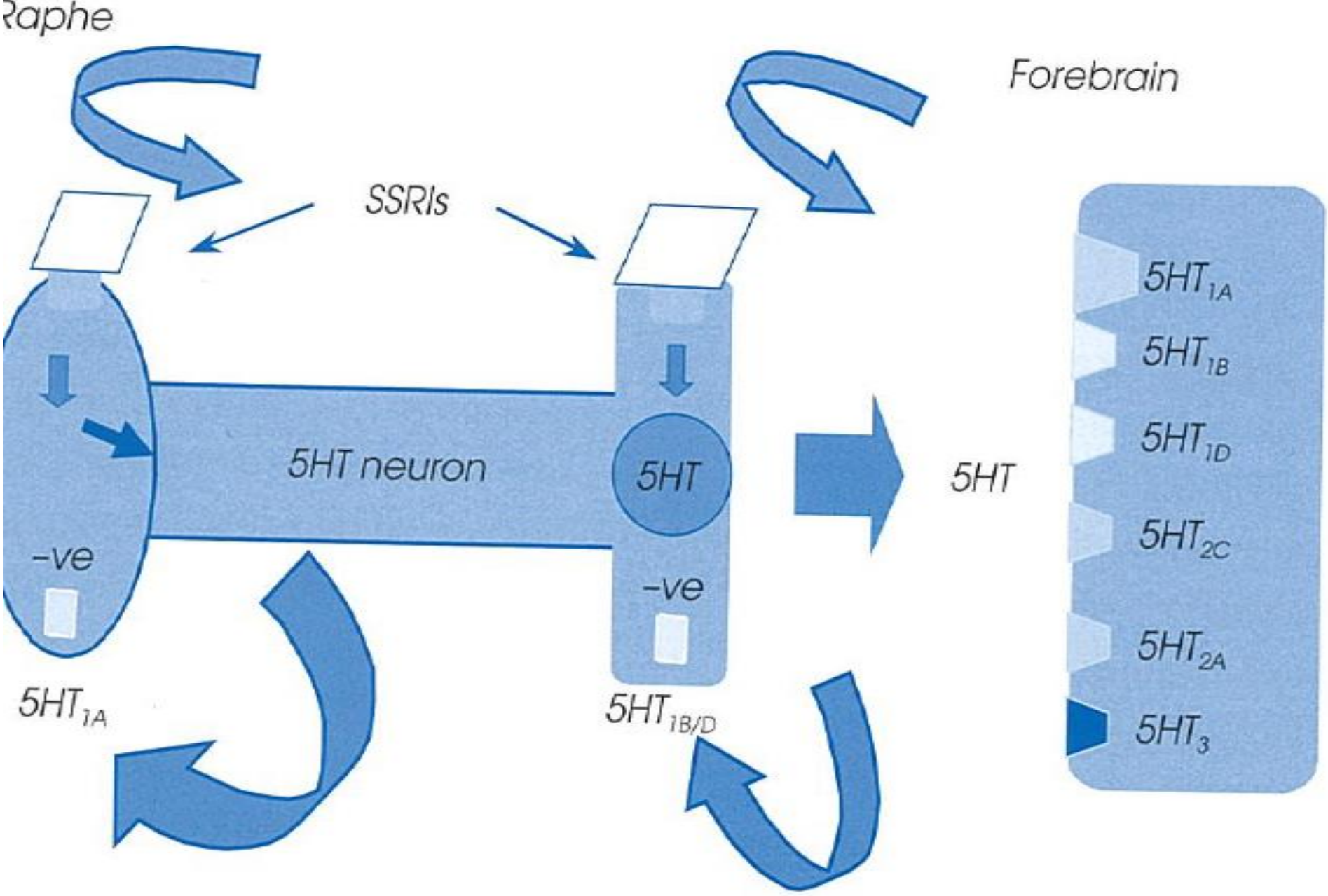
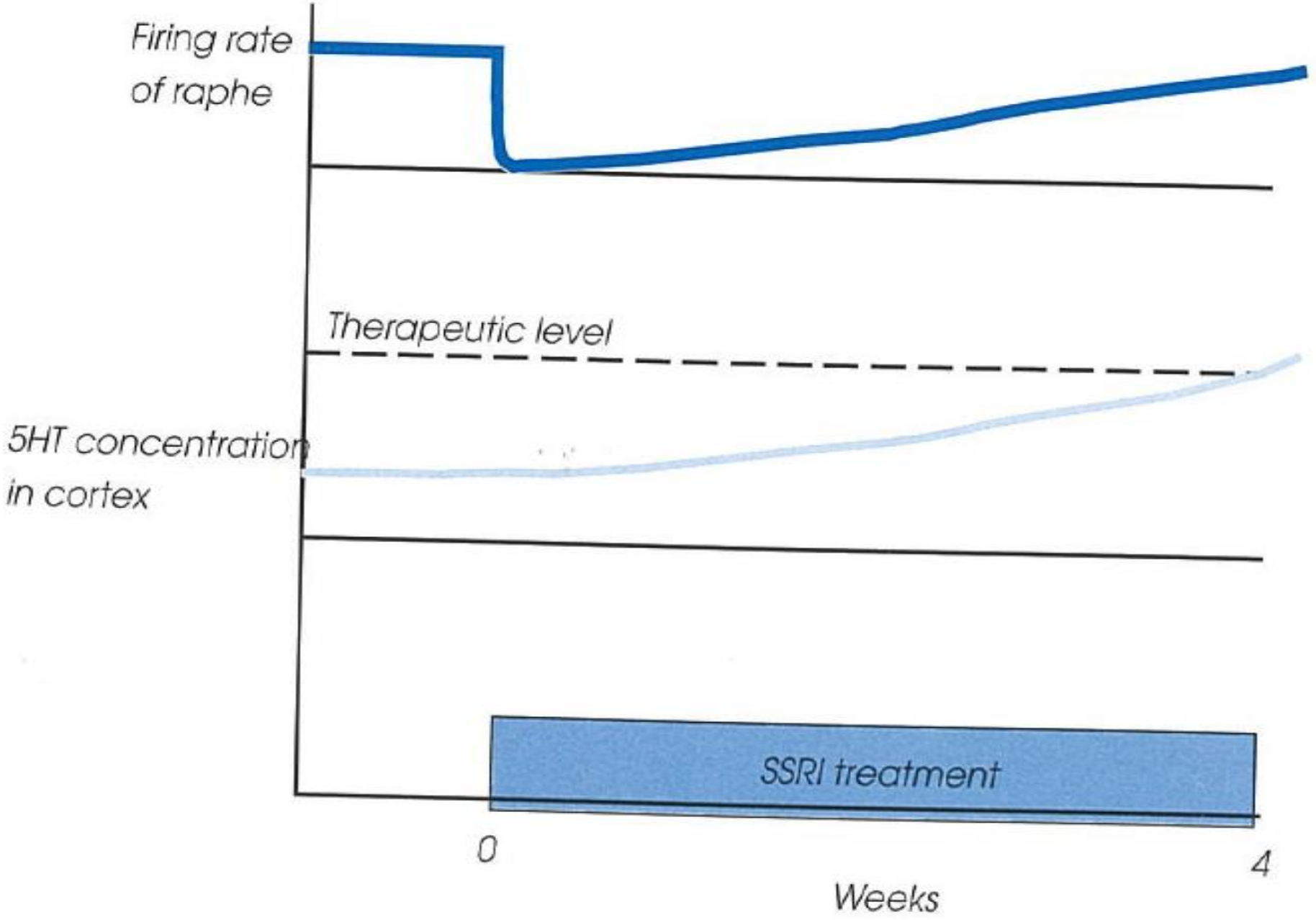
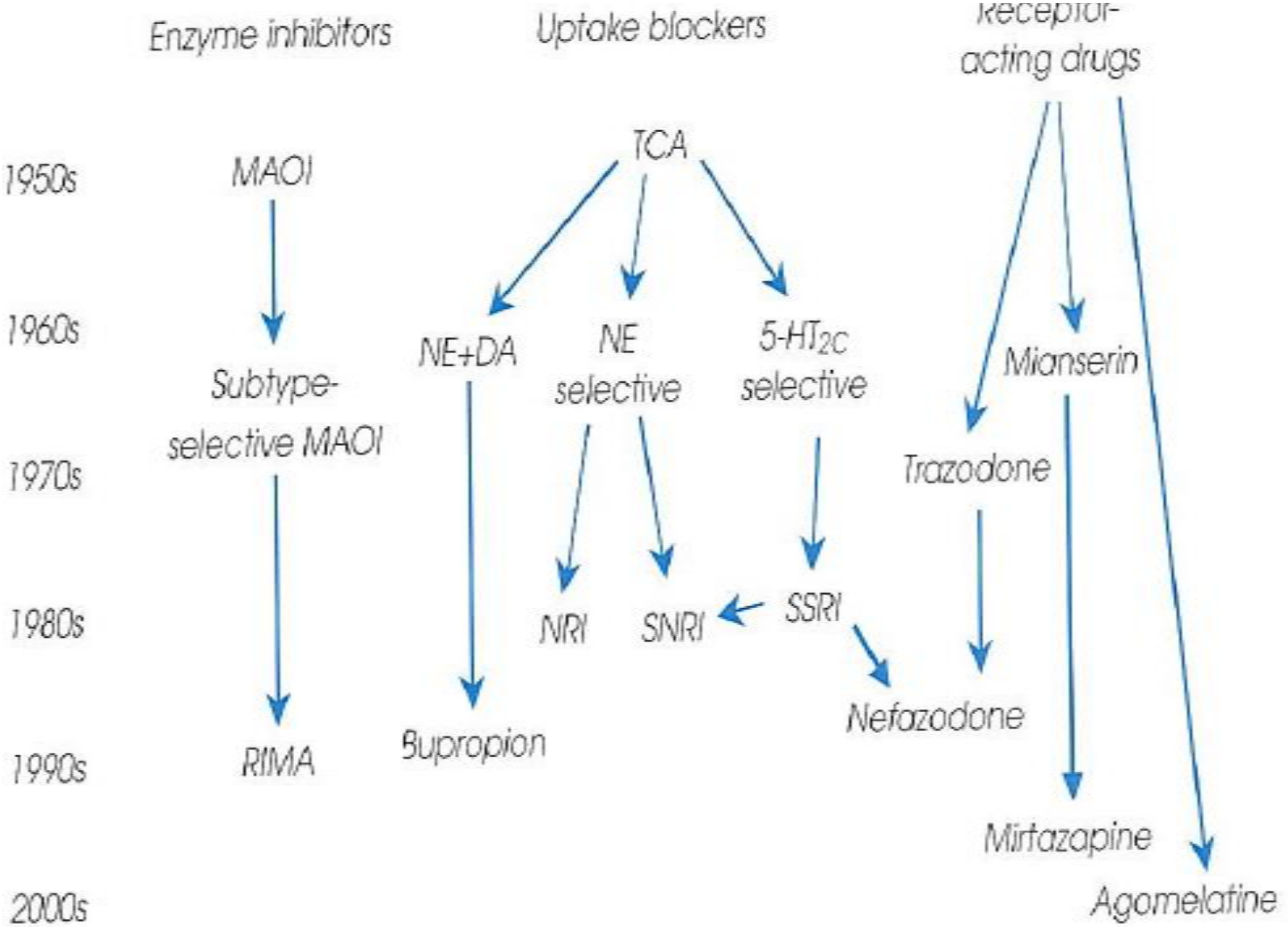


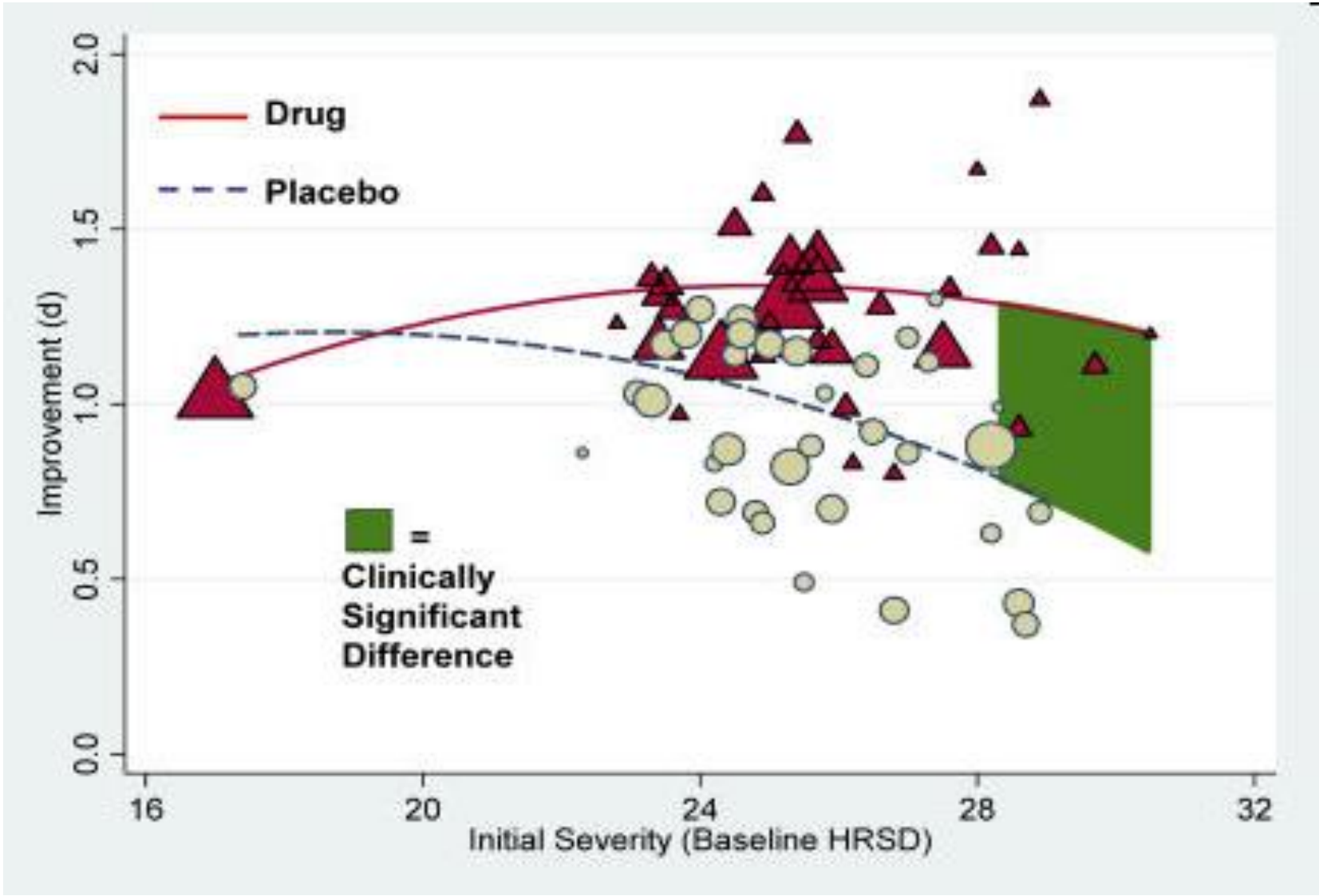
Figure 4.3 Serotonergic synapse: effect of uptake blockade.



gure 4.4 Time lag of SSRIs.


Enzyme inhibitors
Uptake blockers
Receptor-acting drugs
1950s
1960s
1970s
1980s
1990s
2000s
MAOI
TCA
Subtype-selective MAOI
NE+DA
NE selective
5-HT2C selective
Mianserin
Trazodone
NRI
SNRI
SSRI
Nefazodone
RIMA
Bupropion
Mirtazapine
Agomelatine

Mean Standardized Improvement as a Function of Initial Severity and Treatment Group



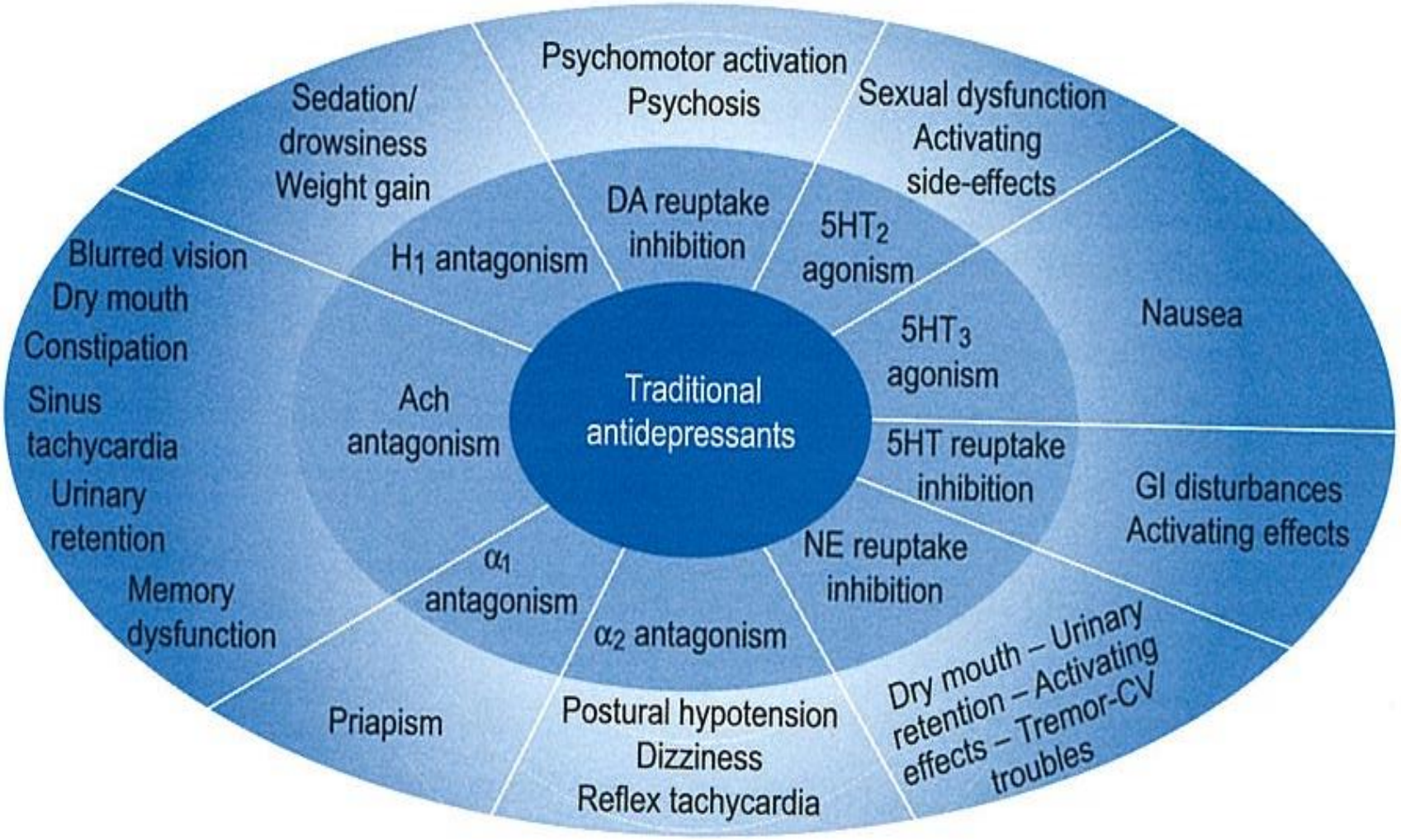


Figure 6.2 Antidepressant side-effects. Ach, acetylcholine; DA, dopamine. Adapted with permission from Richelson, 1993.

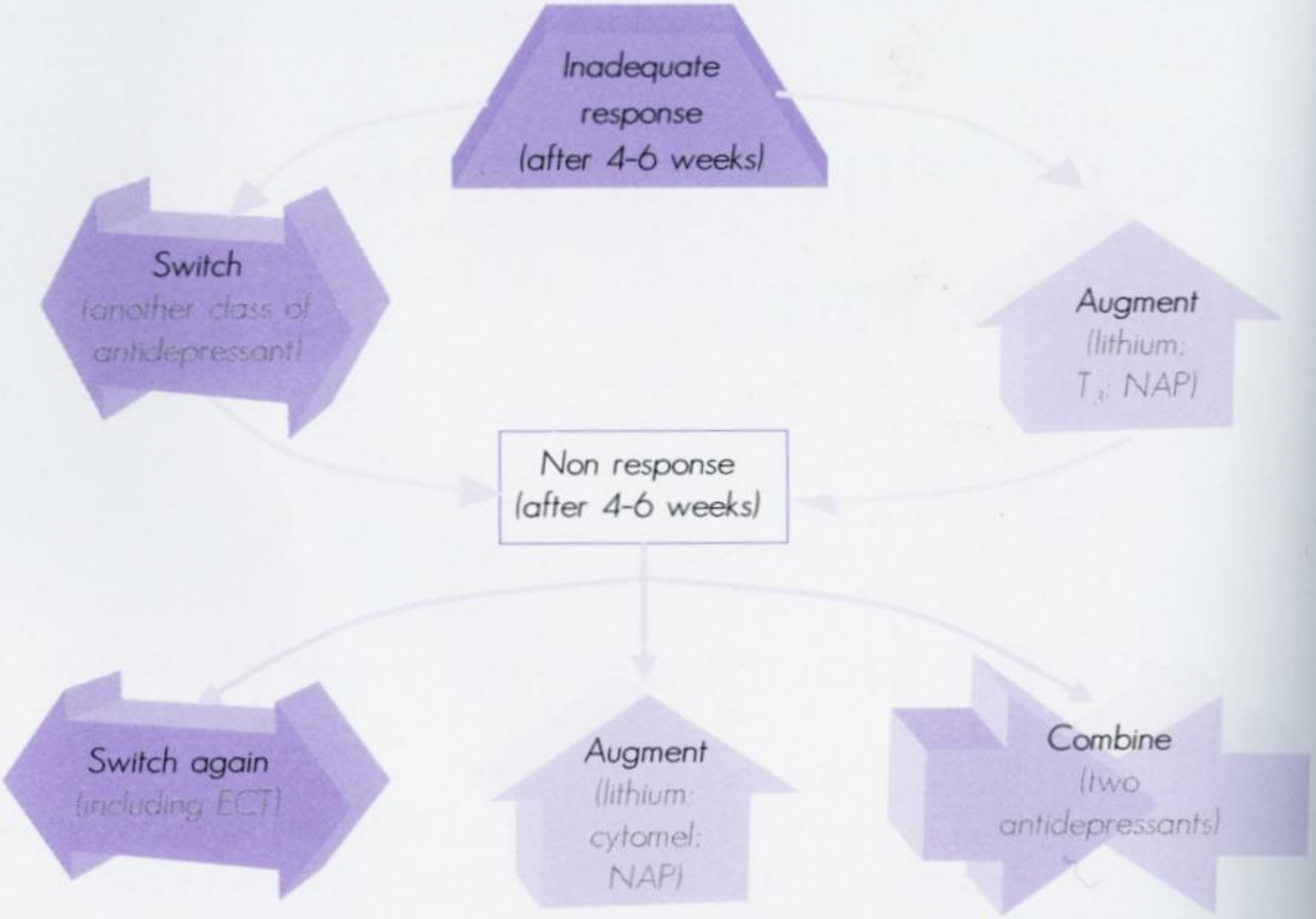

Inadequate response (after 4-6 weeks)
Switch (another class of antidepressant)
Augment (lithium; T_3; NAPI)
Non response (after 4-6 weeks)
Switch again (including ECT)
Augment (lithium; cytomel; NAPI)
Combine (two antidepressants)

Table 5.3 Recommendations for treatment of MDD

Therapeutic choice	*Recommendations*	*Evidence*
First	SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), agomelatine, bupropion and mirtazapine	Level 1
	Higher rates of remission have been reported with venlafaxine and particularly in severe depression with escitalopram	Level 1
Second	Among TCAs amitriptyline and clomipramine have greater efficacy than SSRIs in hospitalized depressed patients (safety and tolerability issues need to be considered)	Level 2
Third	Other TCAs and MAOIs (lower recommendation because of safety and tolerability issues)	Level 2

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

Andrea Cipriani, Toshi A Furukawa*, Georgia Salanti*, Anna Chaimani, Lauren Z Atkinson, Yusuke Ogawa, Stefan Leucht, Henricus G Ruhe, Erick H Turner, Julian P T Higgins, Matthias Egger, Nozomi Takeshima, Yu Hayasaka, Hissei Imai, Kiyomi Shinohara, Aran Tajika, John P A Ioannidis, John R Geddes

Summary

Background **Major depressive disorder is one of the most common, burdensome, and costly psychiatric disorders worldwide in adults. Pharmacological and non-pharmacological treatments are available; however, because of inadequate resources, antidepressants are used more frequently than psychological interventions. Prescription of these agents should be informed by the best available evidence. Therefore, we aimed to update and expand our previous work to compare and rank antidepressants for the acute treatment of adults with unipolar major depressive disorder.**

Methods **We did a systematic review and network meta-analysis. We searched Cochrane Central Register of Controlled Trials, CINAHL, Embase, LILACS database, MEDLINE, MEDLINE In-Process, PsycINFO, the websites of regulatory agencies, and international registers for published and unpublished, double-blind, randomised controlled trials from their inception to Jan 8, 2016. We included placebo-controlled and head-to-head trials of 21 antidepressants used for the acute treatment of adults (≥18 years old and of both sexes) with major depressive disorder diagnosed according to standard operationalised criteria. We excluded quasi-randomised trials and trials that were incomplete or included 20% or more of participants with bipolar disorder, psychotic depression, or treatment-resistant depression; or patients with a serious concomitant medical illness. We extracted data following a predefined hierarchy. In network meta-analysis, we used group-level data. We assessed the studies' risk of bias in accordance to the Cochrane Handbook for Systematic Reviews of Interventions, and certainty of evidence using the**

THE LANCET

Volume 391, No. 10128, p1357–1366, 7 April 2018

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

DOI: https://doi.org/10.1016/S0140-6736(17)32802-7

Cypriani, A. et al

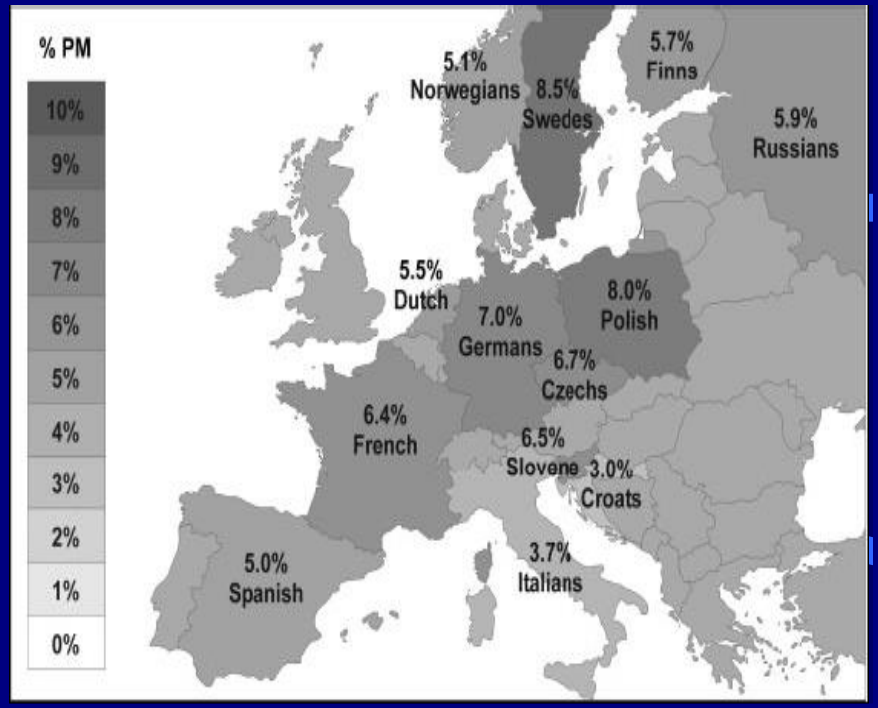
28 552 citations and of these included 522 trials comprising 116 477 participants

In head-to-head studies, **agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine** were more effective than other antidepressants (range of ORs 1·19–1·96),

For acceptability, **agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine** were more tolerable than other antidepressants (range of ORs 0·43–0·77),

Genetikai h

- Európában a PM fenotípus gyakorisága 3-8.5%,
- az UM fenotípusé 1-10% között változik
- Hazai adatok nem álltak rendelkezésre



150 főre tervezett egészséges önkéntesekből álló hazai népességmintában a variáns CYP2D6/CYP2C19 allélok megoszlásának és a genotípus-fenotípus korrelációjának vizsgálatát megkezdtük

Table 6.11 Pharmacokinetics of second and third generation antidepressants

Medication	*Biotransformation pathways*	*Half-life (hours)*	*Protein binding (%)*
Second generation			
Bupropion SR	Hydroxylation involves CYP2B6	21	84 (parent)
Citalopram and escitalopram	Demethylation in two steps involves CYP2C19, 2D6 and 3A4	37 (citalopram) 30 (escitalopram)	80
Duloxetine	Oxidation (involves CYP2D6 and 1A2), methylation and no active conjugation (sulfate and metabolite glucuronide)	9–19	>95 (parent)
Fluoxetine	Demethylation involves CYP2D6	96–144	95
Fluvoxamine	Demethylation and deamination involve CYP2D6 and 1A2	17–22	80
Mirtazapine	Demethylation and hydroxylation involve (parent) CYP2D6, 1A2 and 3A4	20–40	85 (parent)
Paroxetine	Oxidation and demethylation involve CYP2D6	24	95
Sertraline	Demethylation involves CYP3A4	25–26	98
Venlafaxine	O-demethylation involves IR/XR CYP2D6 and others	5–7 (parent) 11–13 (ODV)	27 (parent) 30 (ODV)
Third generation			
Agomelatine	Metabolism involves CYP1A2 and CYP2C9	1–2	95

ODV, O-desmethylvenlafaxine.

Table 8.5 Recommendations for investigational neuromodulation therapies

Recommendations	*Evidence*
• rTMS: preliminary evidence supports the efficacy of rTMS in non-psychotic and non-TRD populations	Level 2
• VNS received FDA approval as an adjunctive long-term treatment of TRD	Level 2
• DBS: preliminary results for TRD await replication under RCT conditions	Level 3
• Neurosurgical procedures including subcaudate tractotomy and anterior cingulotomy have support in TRD from case series only	Level 4

rTMS, repetitive transcranial magnetic stimulation; TRD, treatment-resistant depression; VNS, vagus nerve stimulation; FDA, Food and Drug Administration; DBS, deep brain stimulation; RCT, randomized controlled trial.

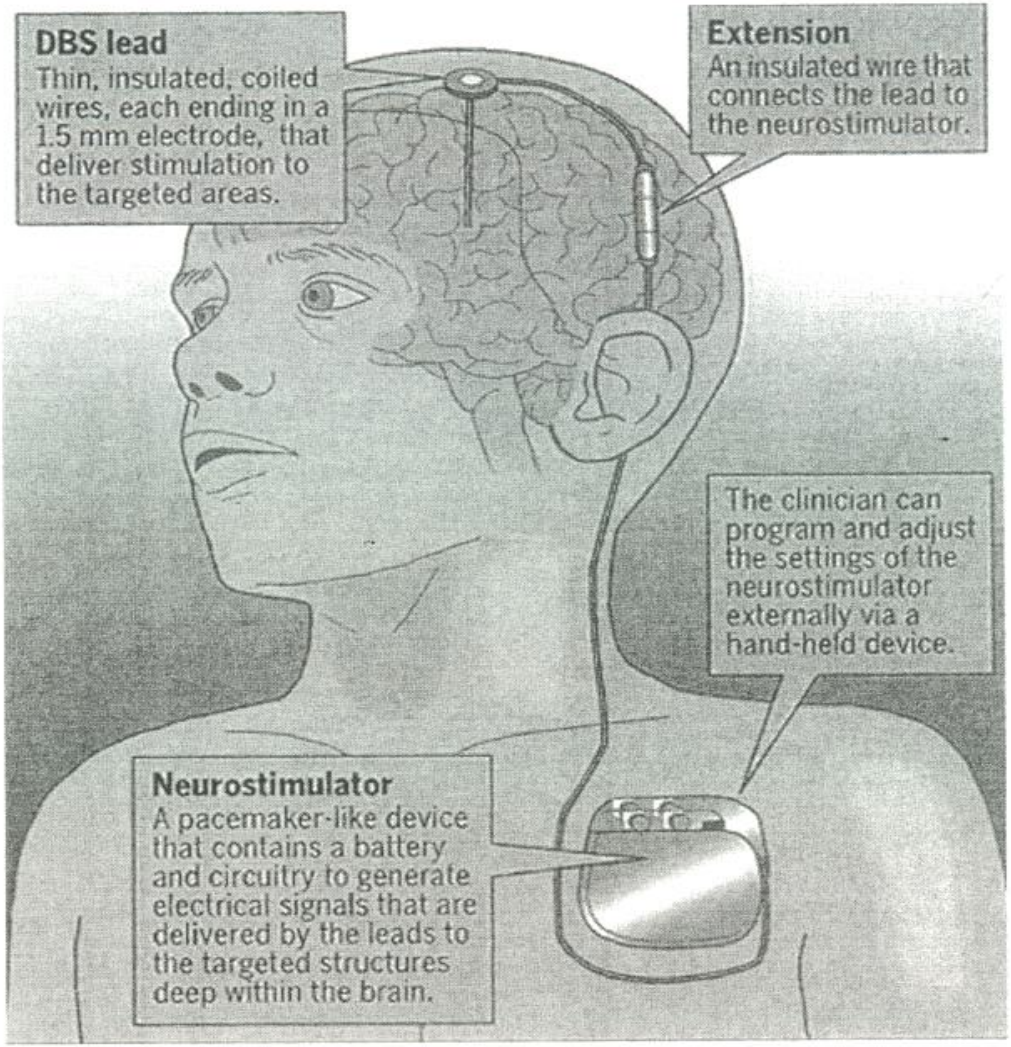


Figure 8.5 Deep brain stimulation electrodes inserted and connected to subclavicular pacemaker. The stimulator remains on all the time and batteries last 3–5 years.

- ECT….
- St.John’s wort, orbancfű Hypericum perforatum
- Omega3 zsirsav (EPA / DHA)
- Fizikai aktivitas
- Placebo, akupunktúra….
- Alvasmegvonas, fényterapia

- Ketamin (NMDA antag.)


Köszönöm a figyelmet!