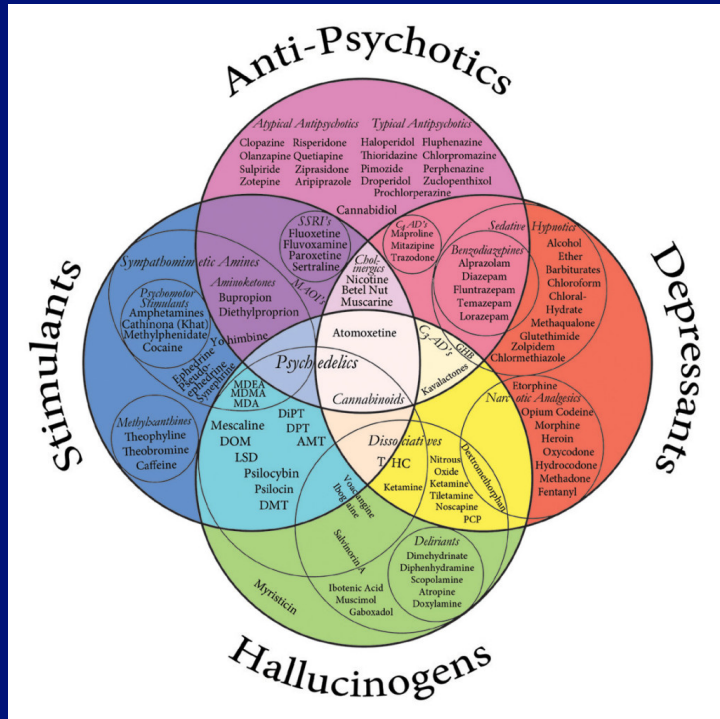


Introdução à Psicofarmacologia



Editorial

A Neuroscience-Based Nomenclature (NbN) for Psychotropic Agents

Alan Frazer, Pierre Blier

Int J Neuropsychopharmac 2016

Department of Pharmacology, University of Texas Health Science Center at San Antonio, San Antonio, Texas (Dr Frazer); Departments of Psychiatry and Cellular & Molecular Medicine, University of Ottawa, Ottawa, Canada (Dr Blier).

<http://nbnomenclature.org/>

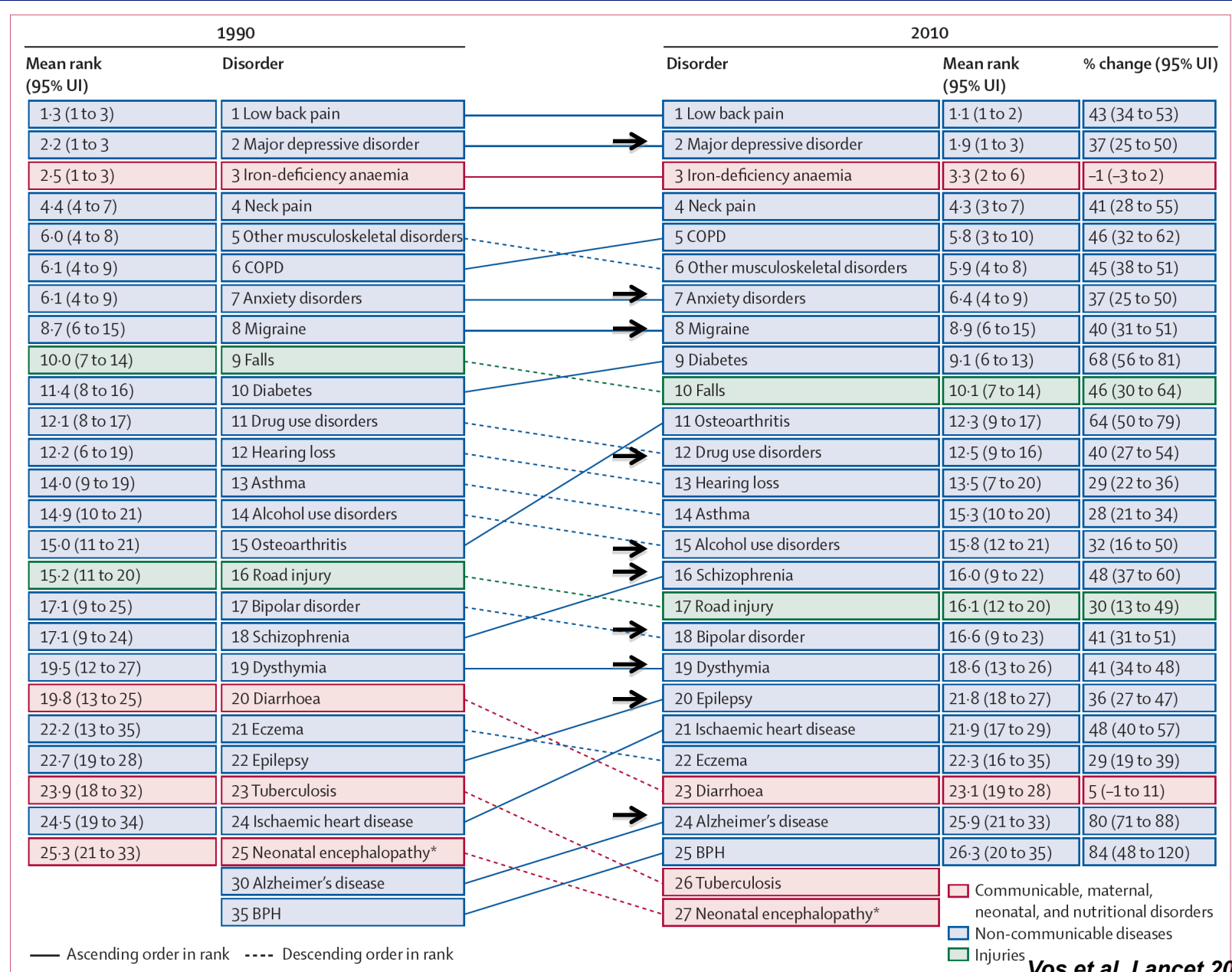
Antipsicóticos

Antidepressivos e estabilizadores do humor

Ansiolíticos e hipnóticos

Drogas de abuso (psicoestimulantes,
alucinógenos, etc.)

Transtornos neuropsiquiátricos: uma das principais causas de prejuízo à vida normal da população (Global years lived with disability, YLGs)



Depressão é a maior causa de incapacitação no mundo, diz OMS

Fotolia



Número de pessoas com depressão chegou, em 2015, a 322 milhões

DA AFP

30/03/2017 19h29

Folha de São Paulo

Grupo de drogas muito importante

2003: 12 das 50 drogas mais
prescritas eram
psicofármacos

Epidemiology of Psychotropic Drug Use in Rio de Janeiro, Brazil: Gaps in Mental Illness Treatments

Maria Ines Quintana^{1*}, Sergio B. Andreoli^{2,3}, Fernanda G. Moreira¹, Wagner S. Ribeiro¹, Marcelo M. Feijo¹, Rodrigo A. Bressan¹, Evandro S. F. Coutinho⁴, Jair J. Mari¹

¹ Federal University of São Paulo – Paulista Medical School, São Paulo, Brazil, ² Federal University of São Paulo – Paulista Medical School - Psychiatry Department, São Paulo, Brazil, ³ Santos Catholic University, Santos, Brazil, ⁴ National School of Public Health – Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

Drogas psicotrópicas
são das mais
empregadas pela
população
2013

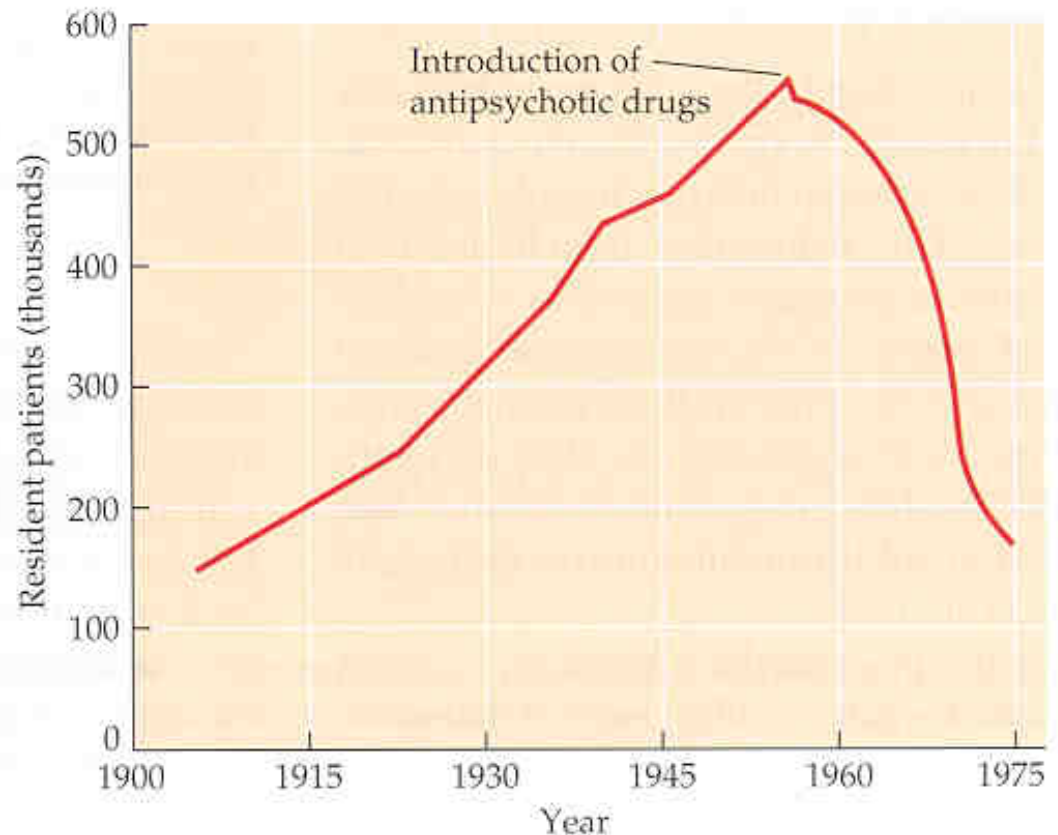
	Total (%)	Male (%)	Female (%)
All psychotropic drugs	6.55	3.19	9.13
Antidepressive	2.78	1.08	4.08
1 st generation	0.59	0.41	0.74
2 nd generation	2.36	0.67	3.65
Tranquilizers	1.61	1.04	2.04
Anoretics	1.65	0.80	2.30
Mood stabilizers	1.24	0.67	1.67
Antipsychotics	1.05	0.80	1.26
Typical	0.96	0.80	1.09
Atypical	0.09	0	0.17

Prevalence use (last month, > 15 years old)

A psicofarmacologia revolucionou a Psiquiatria a partir da década de 50



(B)



Esquizofrenia



Esquizofrenia

Sintomas positivos:

Alucinações

Idéias delirantes

Inadequação afetiva

Pensamento desorganizado

Sintomas negativos:

Embotamento afetivo

Falta de iniciativa

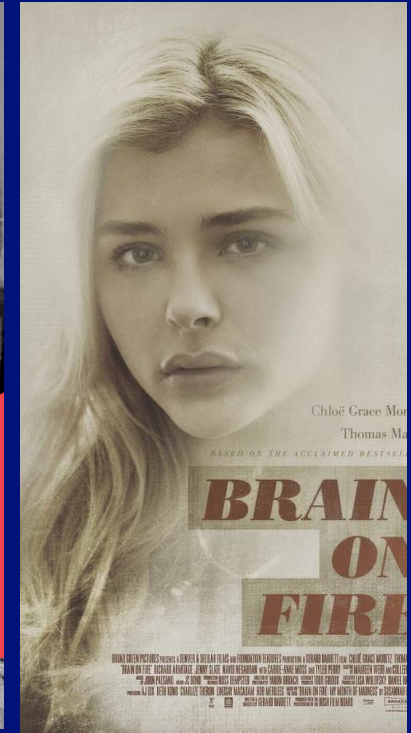
Pobreza de linguagem

Isolamento emocional

Sintomas cognitivos

Sintomas afetivos

Psicoses no cinema



David Helfgott
(do filme “Shine”)

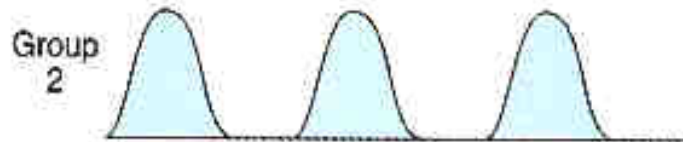
Anti-NMDA receptor encephalitis

Esquizofrenia: evolução



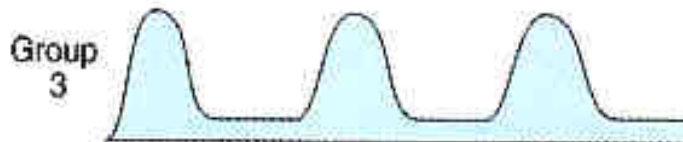
One episode only – no impairment

22%



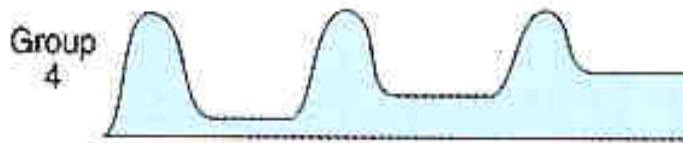
Several episodes with no or minimal impairment

35%



Impairment after the first episode with subsequent exacerbation and no return to normality

8%



Impairment increasing with each of several episodes and no return to normality

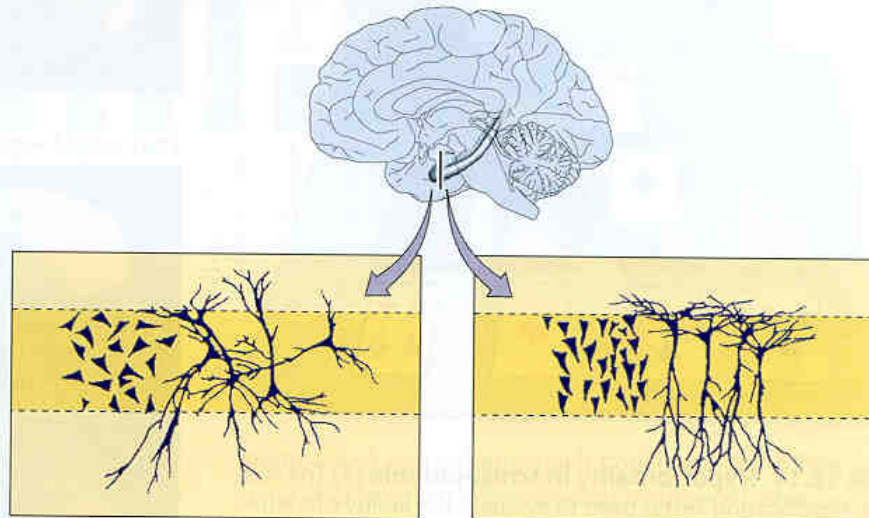
35%

Esquizofrenia: alterações morfológicas

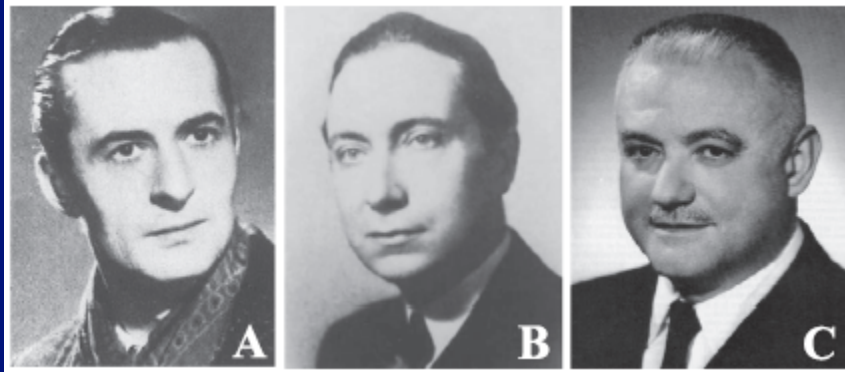
(A) Patient with schizophrenia



(B) Normal control



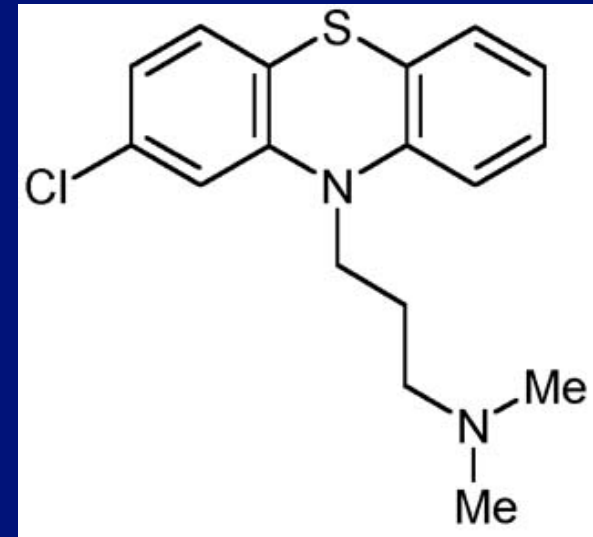
Antipsicóticos: Descoberta das propriedades antipsicóticas da clorpromazina



Henry
Laborit
(1951)

Jean
Delay

Pierre
Deniker

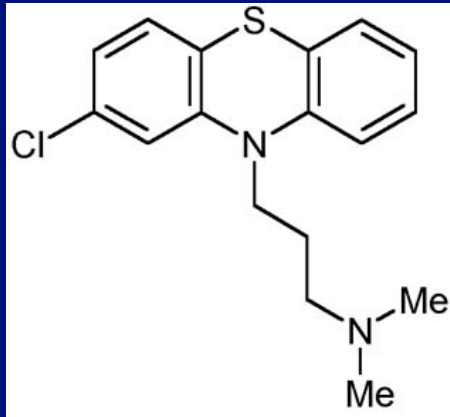


Clorpromazina (~ Prometazina)
Paul Charpentier (1950)
Simone Courvoisier

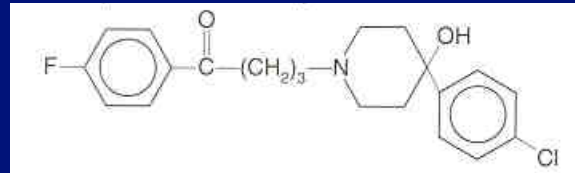
“Thus, a century and a half after Pinel physically liberated the alieneds, the French psychiatrists freed patients once more, this time by means of a pharmacological tool.”

Lopez-Munoz et al. (2004) Progr. Neuropsychopharmacol. Biol. Psychiatry

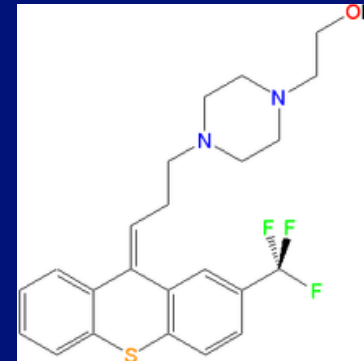
Antipsicóticos de Primeira Geração (Neurolépticos)



Fenotiazinas
Clorpromazina
Flufenazina



Butirofenonas
Haloperidol



Tioxantenos
Flupentixol

Etc...

{ Ataráticos
Tranqüilizantes Maiores
Neurolépticos
“Antischizophrenics”
Antipsicóticos

What's in a name?

The evolution of the nomenclature of antipsychotic drugs

Caroline King, MD; Lakshmi N.P. Voruganti, MD, MSc

In 1989, Deniker¹⁰ himself reminisced (p. 256) as follows:

[The] Americans were horrified — think of it: it was a matter of defining a group of drugs by their adverse effects — and they preferred such terms as “tranquilizers”, later on using the expression “major tranquilizers” and finally using the expression “antipsychotic.”

J Psychiatry Neurosci 2002;27(3):168-75.

Antipsicóticos e dopamina: a hipótese clássica

Acta pharmacol. et toxicol. 1963, 20, 140–144.

From the Department of Pharmacology, University
of Göteborg, Göteborg, Sweden

Effect of Chlorpromazine or Haloperidol on Formation of 3-Methoxytyramine and Normetanephrine in Mouse Brain

By

Arvid Carlsson and Margit Lindqvist

(Received June 13, 1963)

The effect is, it is suggested, due to a compensatory activation of monoaminergic neurons after **blockade of monoaminergic receptors.**

reduced by neuroleptic drugs. Carlsson and Lindqvist⁴ found that these drugs increase dopamine turnover and suggested this was secondary to **blockade of the dopamine receptor.**

Crow, 1980

On the basis of this and further neuropharmacological research with haloperidol and chlorpromazine, Carlsson and Lindqvist, in 1963, founded their seminal hypothesis that the **blockade of dopamine receptors** was responsible for the clinical effects of antipsychotic drugs (48). Only 12 years later,

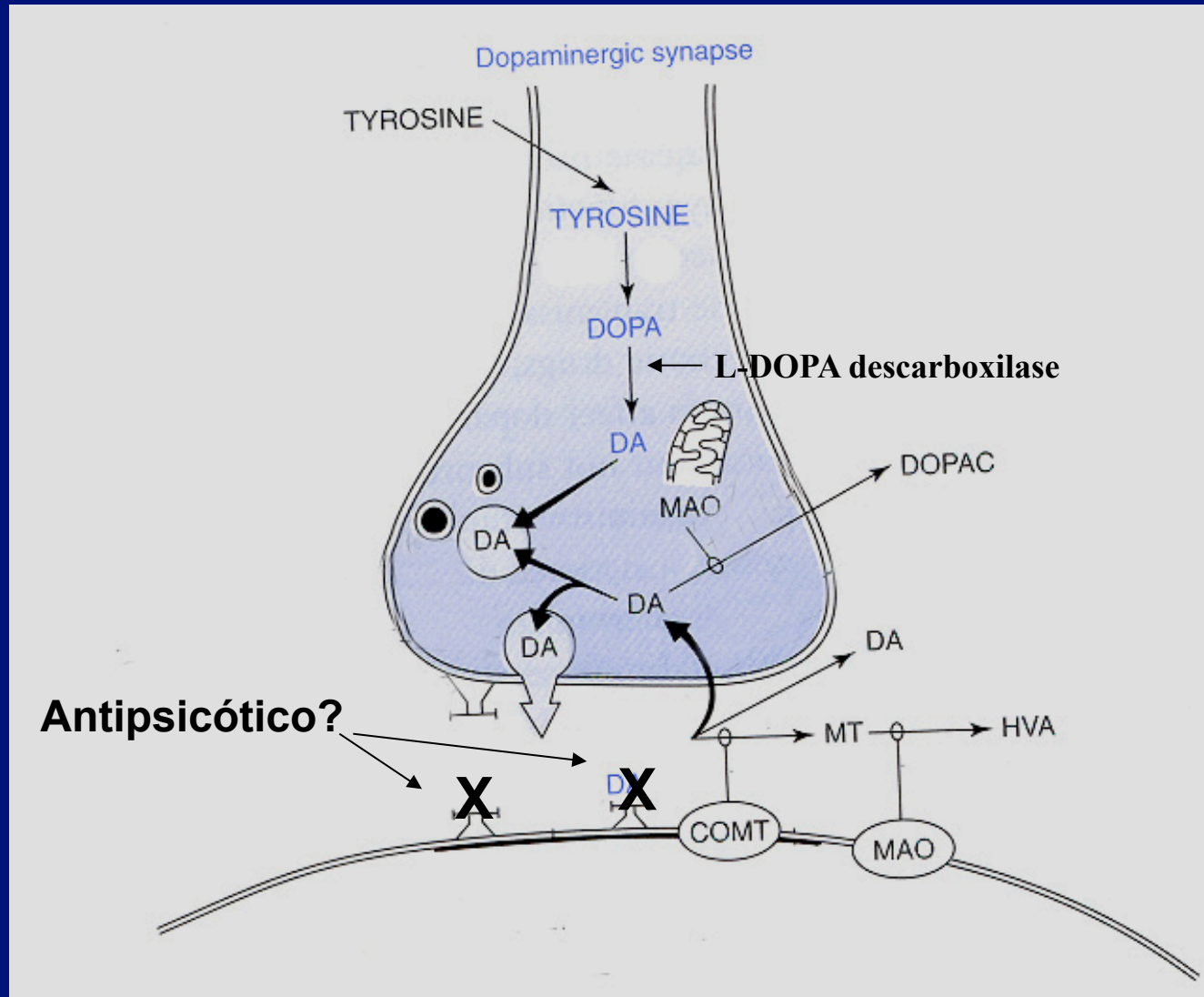
Lehmann & Bann, 1997



NATURE|Vol 447|24 May 2007

**"I won the Nobel Prize
40 years after my
discovery. Einstein
won one some 20
years after his. So I
guess my work was
twice as complicated."
— Arvid Carlsson**

Sinapse dopaminérgica



Mecanismo de ação dos Antipsicóticos



Antagonismo de receptor D2 de Dopamina



Drogas que intensificam Dopamina



Induzem psicoses



Hipótese dopaminérgica da Esquizofrenia!

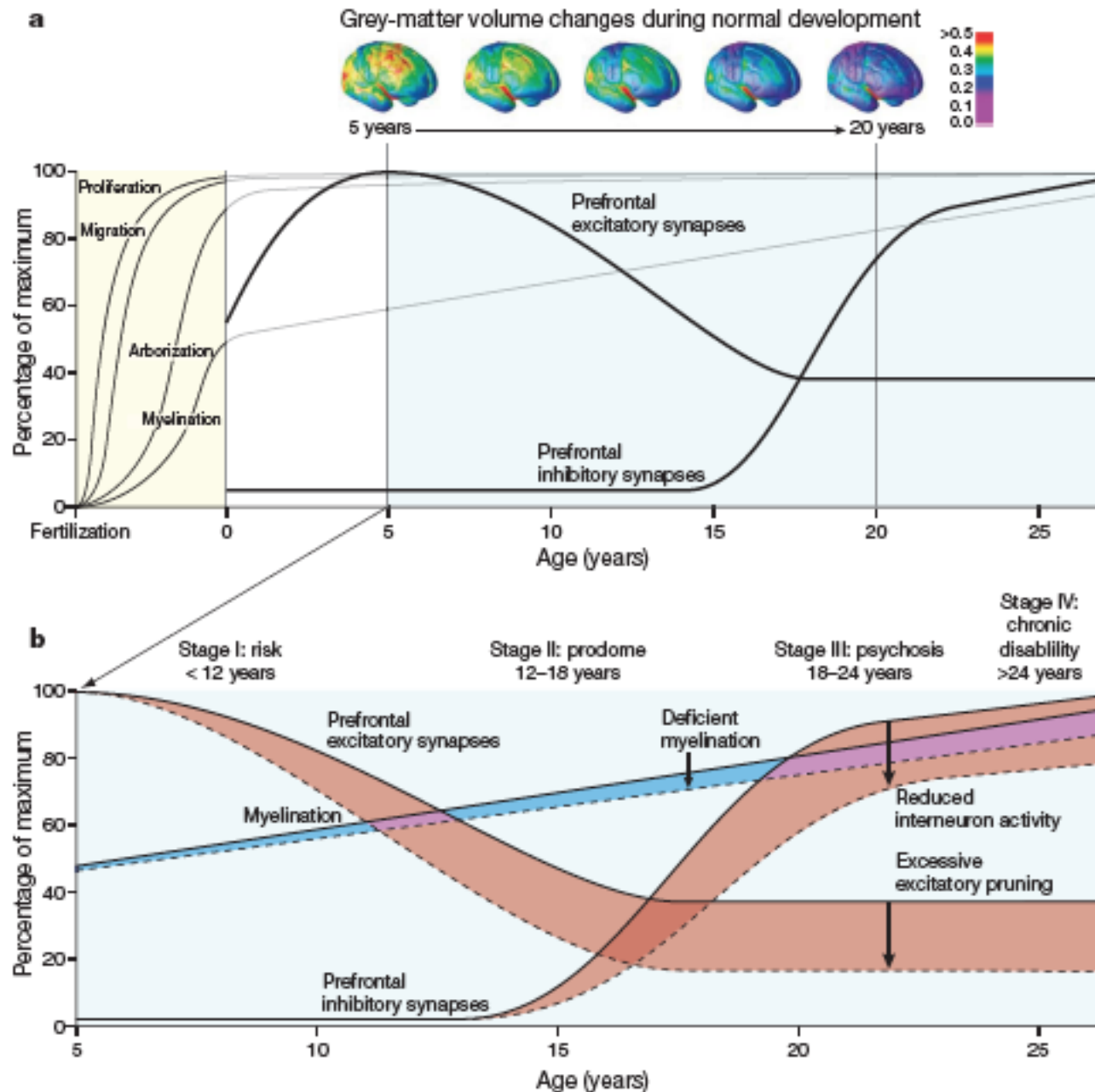
A esquizofrenia é um transtorno de neurodesenvolvimento

Rethinking schizophrenia

Thomas R. Insel¹

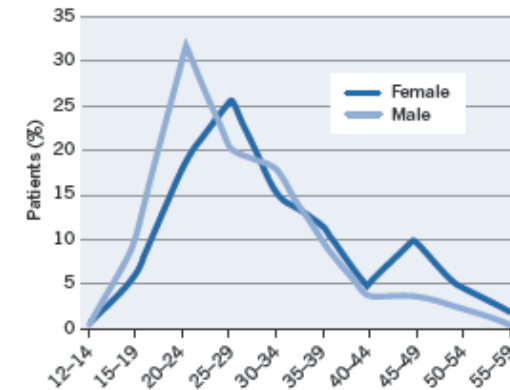
Nature 2010

Possíveis alterações de neurodesenvolvimento na esquizofrenia



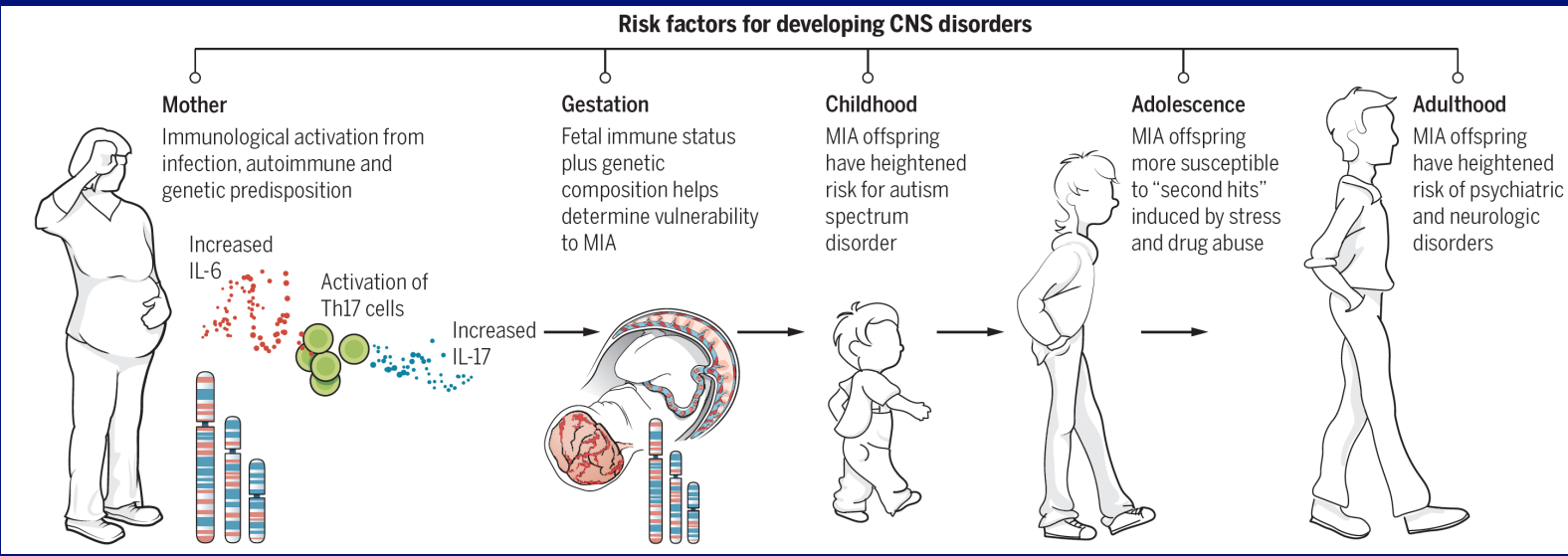
ACCENT ON YOUTH

Distribution of age at first admission for schizophrenia in males and females.

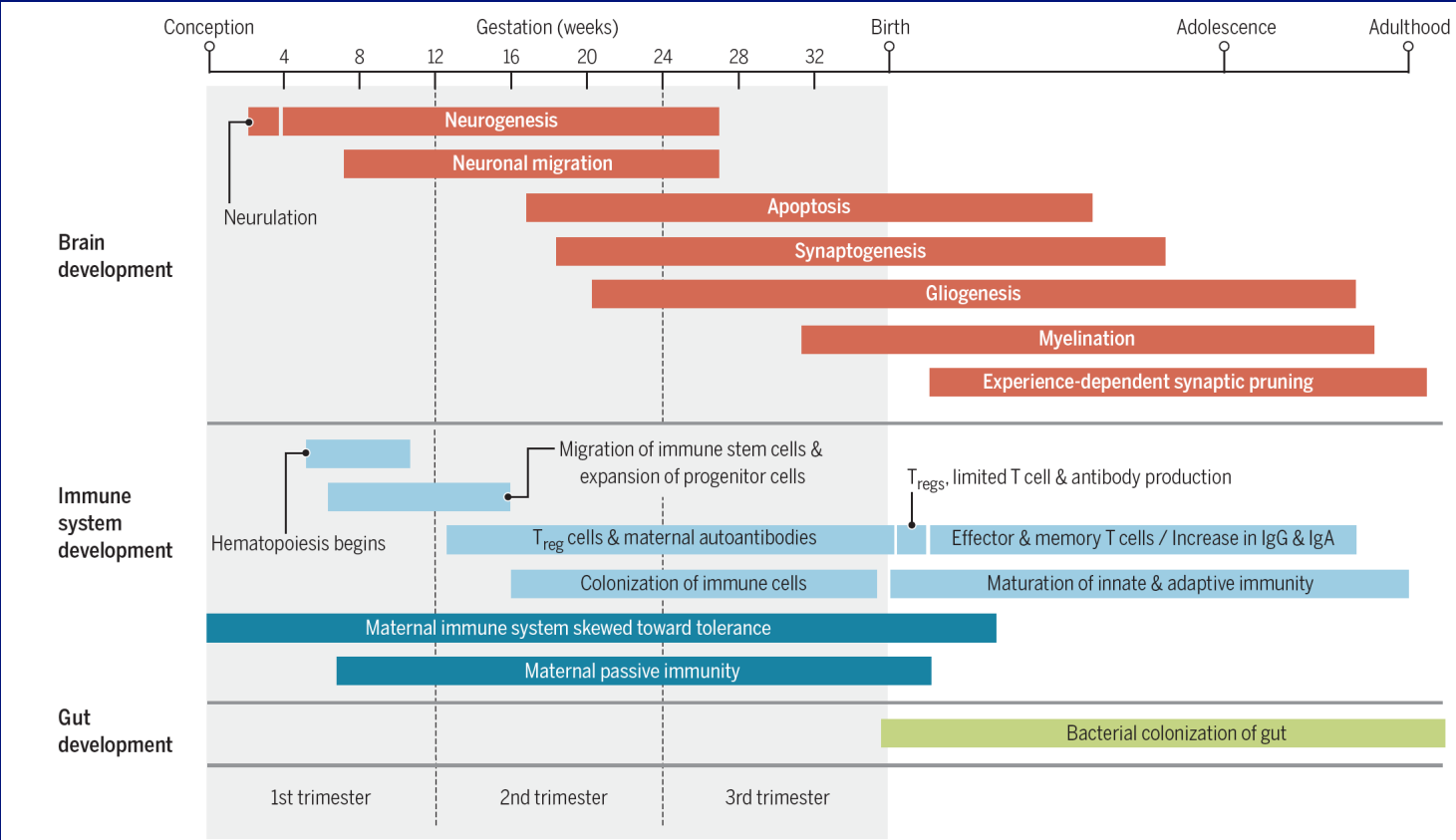


Doobs D, Nature 2010

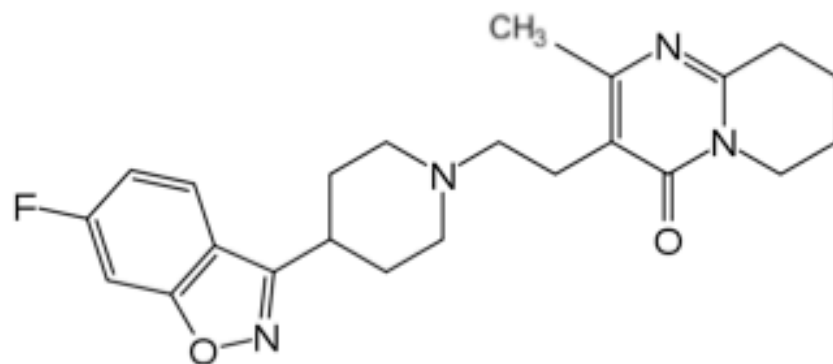
Estes et al.,
Science 353:772,
2016



Esquizofrenia:
uma doença de
neurodesenvol-
vimento
influenciada por
ativação do
sistema imune?



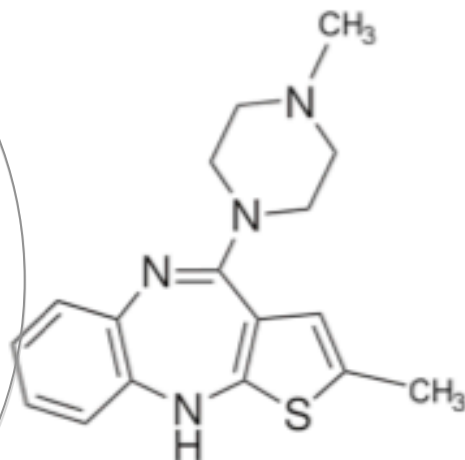
Antipsicóticos de Segunda Geração (“atípicos”)



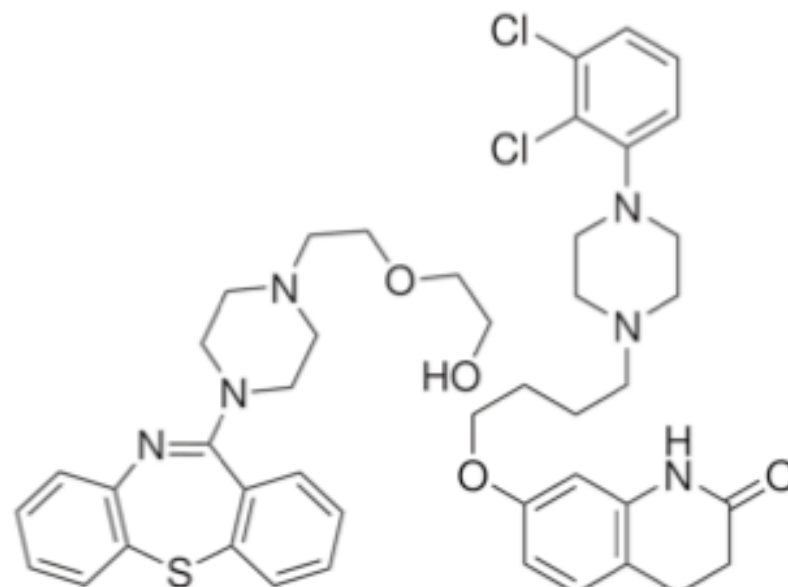
Risperidona



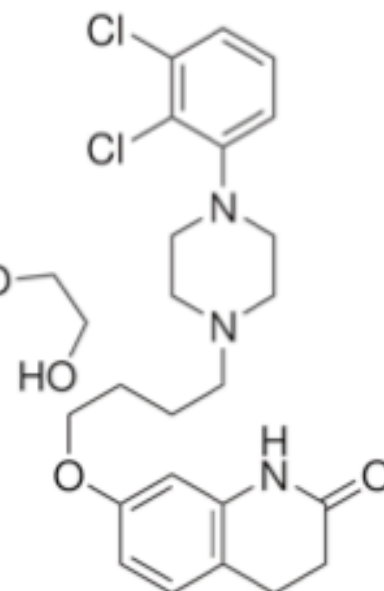
Clozapina



Olanzapina

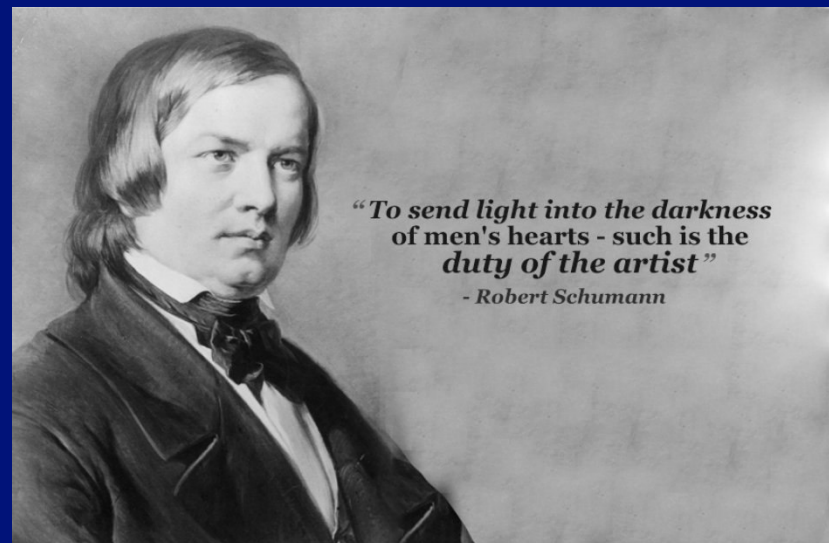
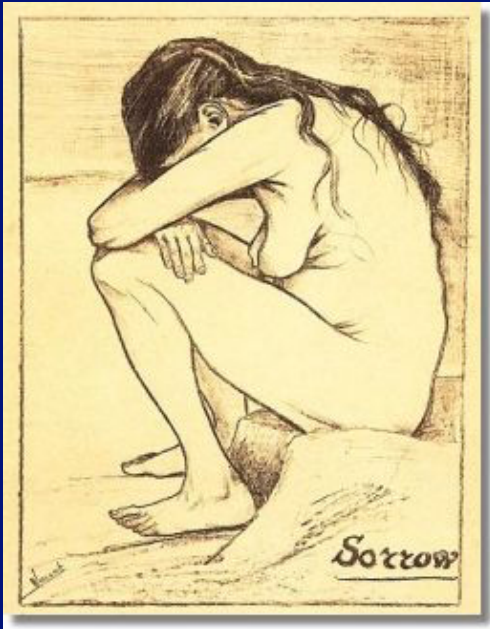
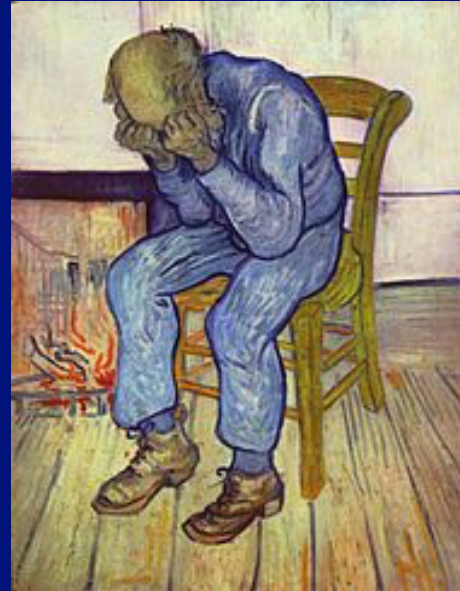


Quetiapina



Aripiprazole

Transtornos Afetivos



Classificação dos Distúrbios Afetivos

- Transtornos Depressivos

 - Depressão Maior

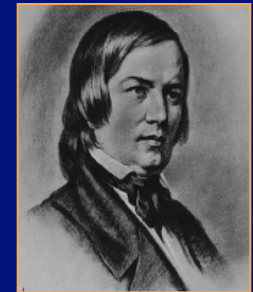
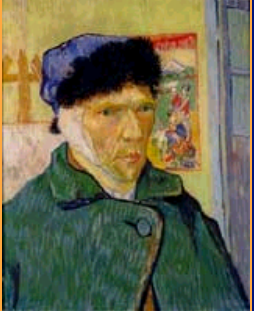


melancólica (40-
60% hosp.)

 - Distímia (transtorno depressivo persistente)

 - Tipos não-específicos

- Transtornos bipolares



Distúrbios Afetivos

Epidemiologia

- *Em um dado momento*

13-20% da população: algum sintoma depressivo

2-3% da população hospitalizada ou seriamente prejudicada por distúrbio afetivo

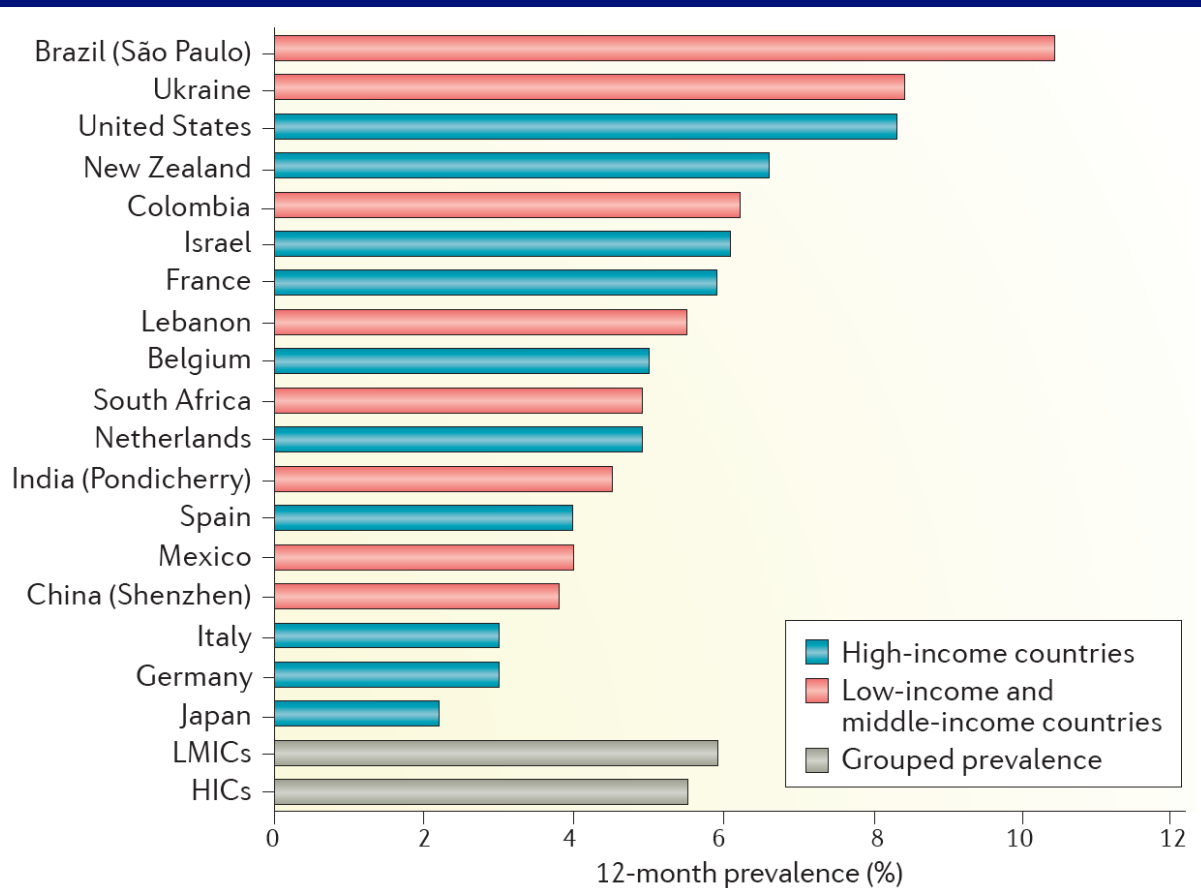
- *Risco durante a vida*

Distúrbio depressivo maior: 8,3% ♀ > ♂

Distúrbio bipolar: < 1,0% ♀ = ♂

Relato de paciente com depressão

“Eu duvido completamente de minha habilidade de fazer qualquer coisa bem. Parece que minha mente está lentificada ao ponto de se tornar virtualmente inútil... Eu estou com que assombrado... com a desesperança mais intensa. Outras pessoas dizem: É só temporário, isto passará, você irá melhorar, mas, naturalmente, eles não têm a mínima idéia de como me sinto, embora tenham certeza disto. Se eu não posso sentir, me mover, pensar ou me importar, qual o sentido de tudo?”.



- An individual will show five (or more) of the following symptoms, which should be present during the same 2-week period nearly every day and should represent a change from previous functioning:
 - Depressed mood*
 - Markedly diminished interest or pleasure in all, or almost all, activities*
 - Considerable weight loss when not dieting, weight gain, or decrease or increase in appetite
 - Insomnia or hypersomnia
 - Psychomotor agitation or retardation
 - Fatigue or loss of energy
 - Feelings of worthlessness, or excessive or inappropriate guilt, which might be delusional; that is, not merely self-reproach or guilt about being sick
 - Diminished ability to think or concentrate, or indecisiveness
 - Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan; the individual has made a suicide attempt or a specific plan for committing suicide
- The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning
- The episode is not attributable to the physiological effects of a substance or to another medical condition
- The occurrence of the episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder or other psychotic disorders
- The individual has never had a manic episode or a hypomanic episode

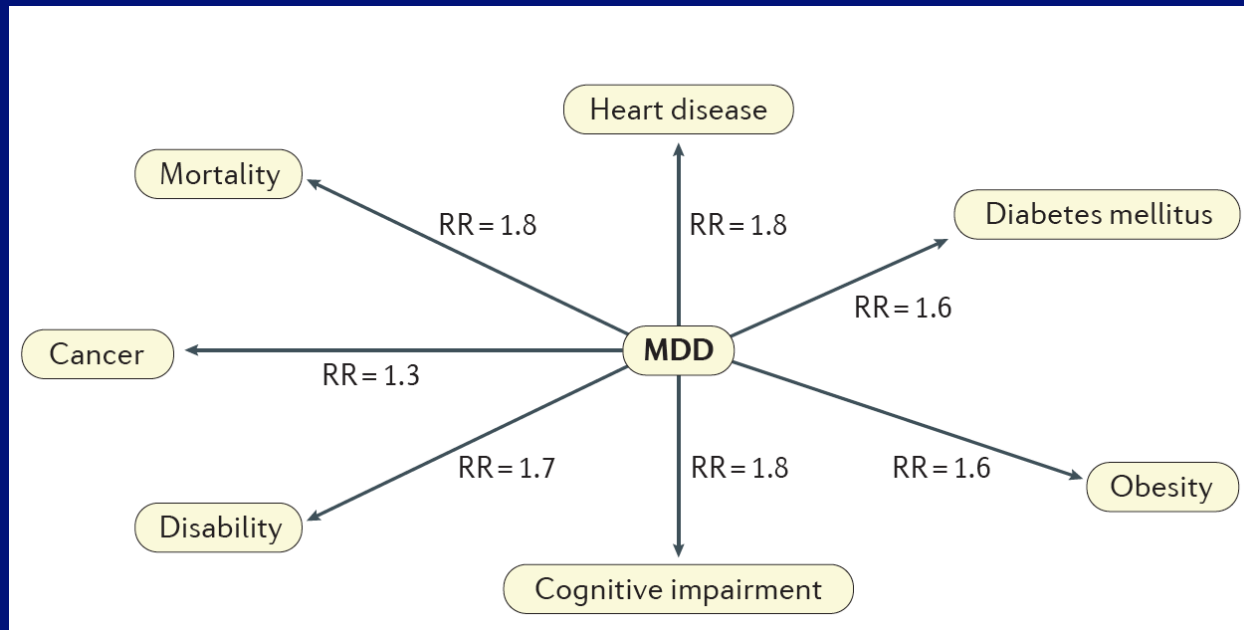
Specifiers of major depressive disorder (MDD) according to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders 5th edition¹) are:

- Severity
- With anxious distress
- With mixed features
- With melancholic features
- With psychotic features
- With peripartum onset
- With seasonal pattern

*Depressed mood and/or diminished interest or pleasure must be evident for a diagnosis.

Depressão maior: alta prevalência, sem diferença entre países desenvolvidos e em desenvolvimento (mas vejam o Brasil)

Aumento de risco de co-morbidades



USA: perda de 27,2 dias de trabalho por ano

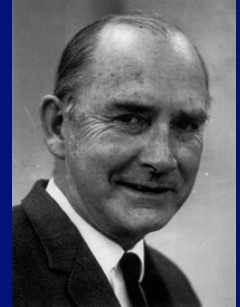
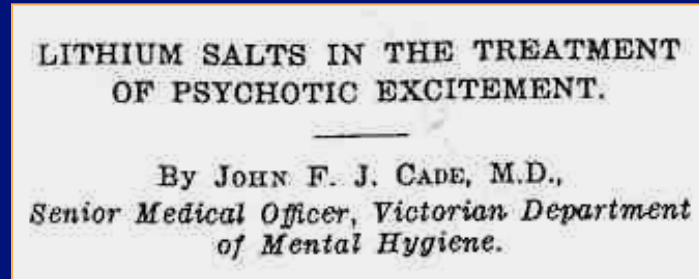
Mortalidade em depressão maior: aumenta 1,8 x

Perda de vida estimada: homens: 10,6 anos
mulheres: 7,2 anos

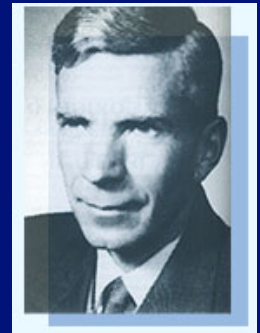
Risco de suicídio: 20 x maior

História das descobertas das drogas usadas em distúrbios afetivos

1949- Cade: **lítio**

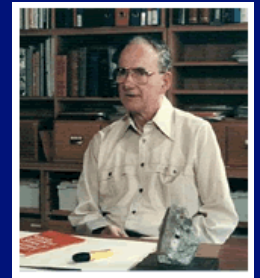


1952- Selikoff et al: iproniazida em tuberculose
Zeller et al.: iproniazida **inibe a MAO**



1957- Kuhn: **imipramina**
Kline: IMAO em depressão

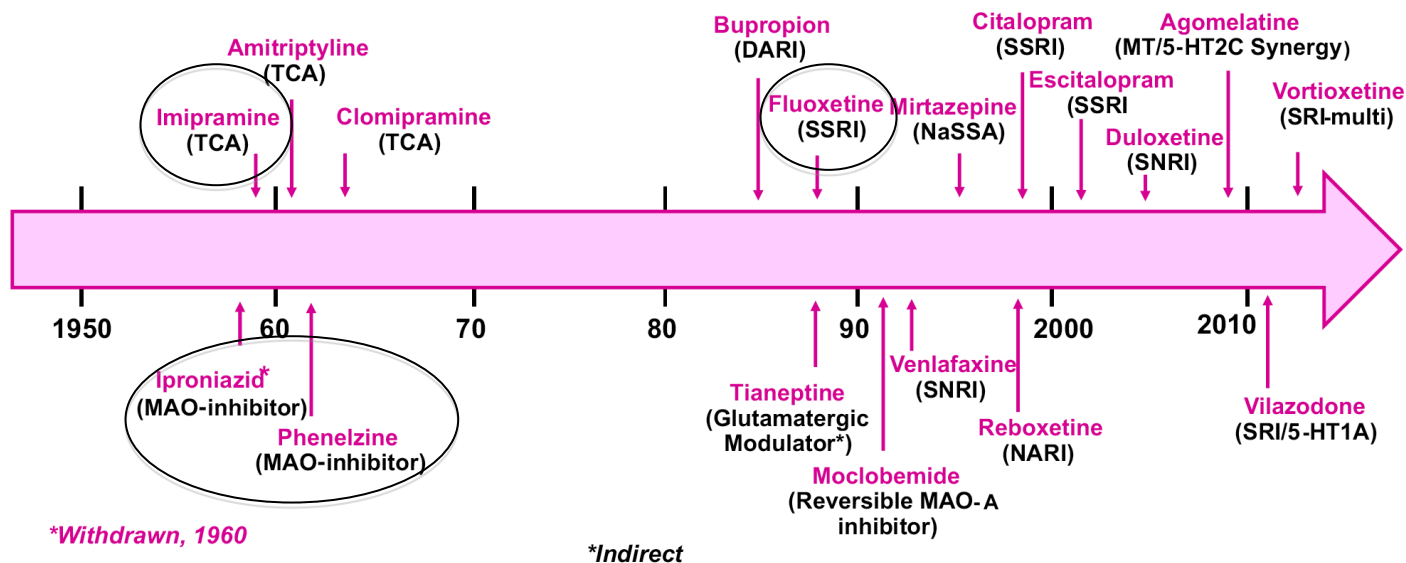
1959- Schou: lítio efetivo clinicamente



1964- Axelrod et al.: Antidepressivos inibem recaptação de monoaminas

Tratamento Farmacológico da depressão

Major depression



✓ “Antidepressivos”: tricíclicos (primeira geração)

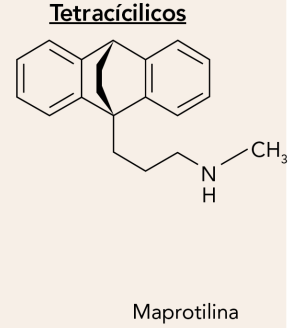
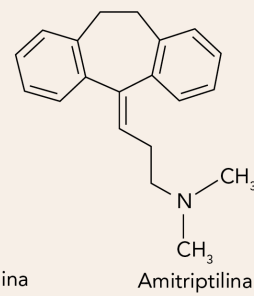
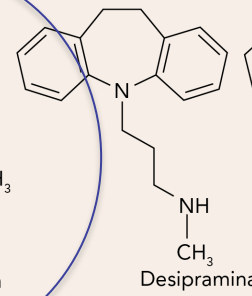
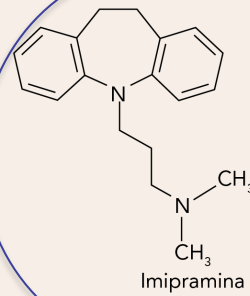
segunda geração (ISRS etc.)

terceira geração?

Inibidores da MAO

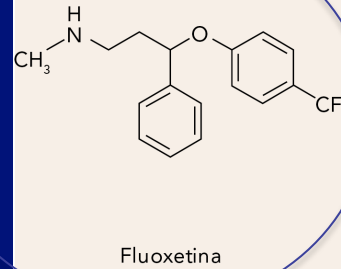
Classificação dos antidepressivos (histórica)

Antidepressivos tricíclicos

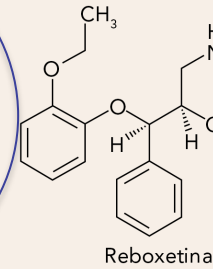


Antidepressivos de segunda geração

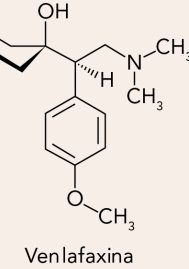
SSRI



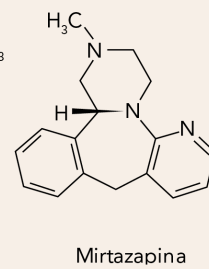
NSRI



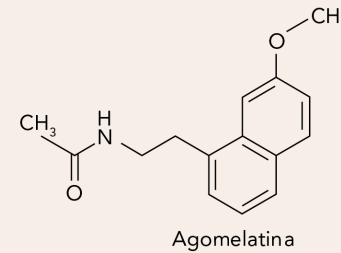
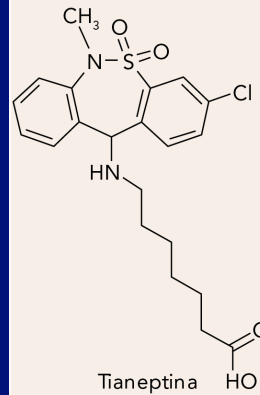
SNRI



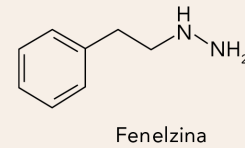
Antagonista de receptores monoaminérgicos



Antidepressivos de terceira geração



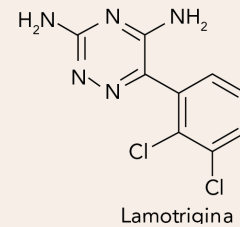
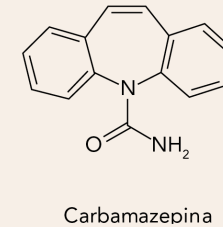
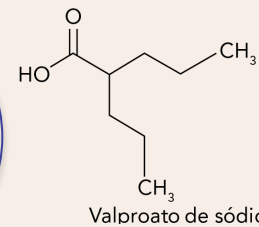
Inibidores da MAO



Estabilizadores do humor



Carbonato de lítio



Mecanismo de ação da imipramina: inibição de recaptação neuronal de noradrenalina e serotonina

Inhibition of Uptake of Tritiated-noradrenaline
in the Intact Rat Brain by Imipramine and
Structurally Related Compounds

NATURE December 26, 1964 VOL. 204

J. Glowinski, J. Axelrod

The ability of imipramine to prevent the rebinding of noradrenaline by cerebral tissues may be a mechanism for the antidepressant action of this drug. Such an action of the drug would allow more free physiologically active noradrenaline liberated from the central sympathetic neurones to react with the central adrenergic receptors.

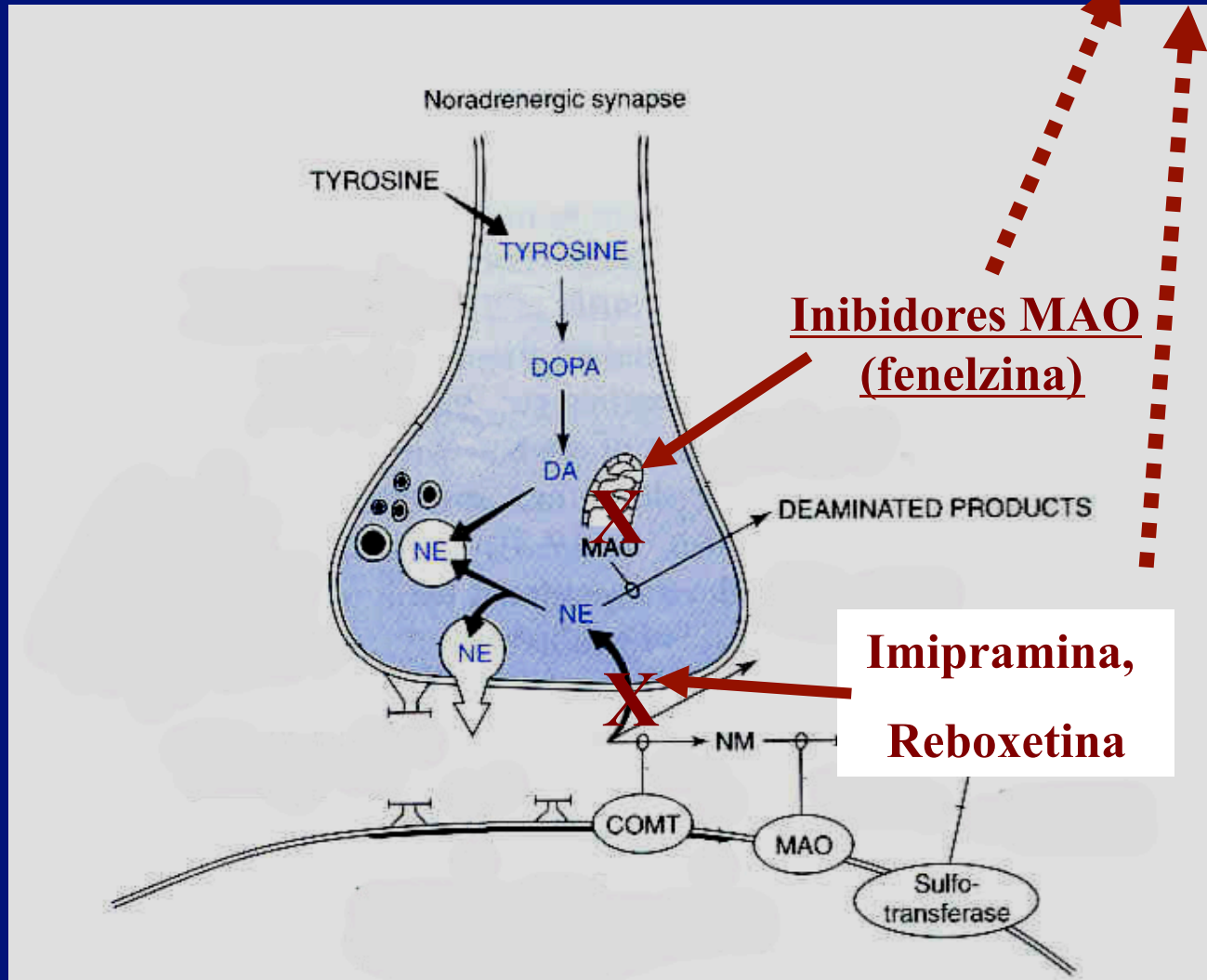
"for their discoveries concerning the humoral transmitters in the nerve terminals and the mechanism for their storage, release and inactivation"

<u>Treatment</u> <u>(mg/kg)</u>	<u>Clinical</u> <u>Antidepressant</u> <u>action</u>	<u>% Control</u> <u>Value</u>
Imipramine (20)	Yes	63*
Desmethyl- imipramine (20)	Yes	64*
Amitriptyline (10)	Yes	77*
Compound II (20)	No	99
Chlor- promazine (40)	No	91

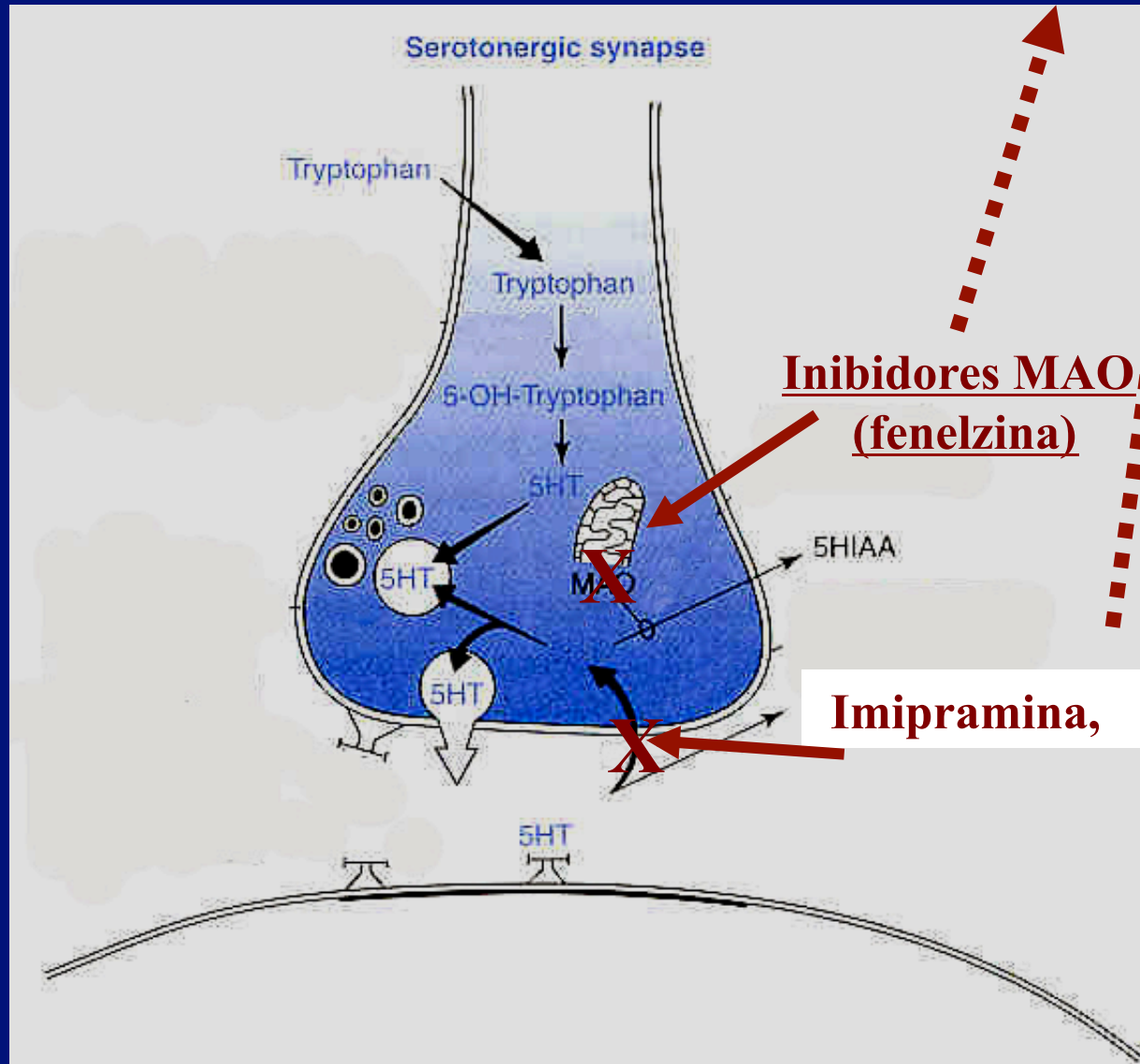


Sinapse noradrenérgica

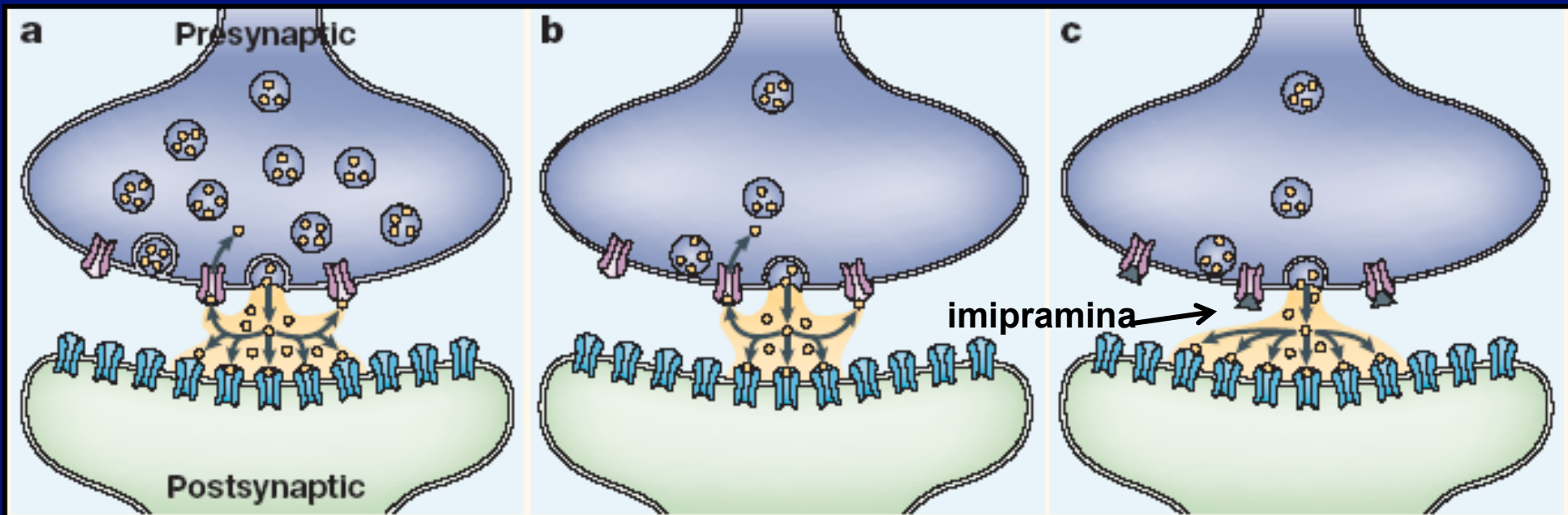
Efeito antidepressivo



Sinapse serotonérgica **Efeito antidepressivo**



Hipótese Monoaminérgica Clássica da Depressão



Castrén, 2005

↓ **Noradrenalina**
Schildkraut e Kety, 1965

e

↓ **Serotonina**
Lapin e Oxenkrug, 1969

no SNC

Porquê aumentar a neurotransmissão mediada por noradrenalina e/ou serotonina melhoraria a depressão?

Depressão é um quadro multifatorial, mas exposição a estressores tem papel importante

Fatores de desenvolvimento (abuso infantil, perda precoce dos pais)

Eventos negativos na vida (stress)

Genes (SERT, tryptophan hydroylase-2, 5-HT1AR, MAO-A, COMT, DBH, CREB, CRHM2, CRH1R, 5-HT2R, GR, MR, BDNF, ?)



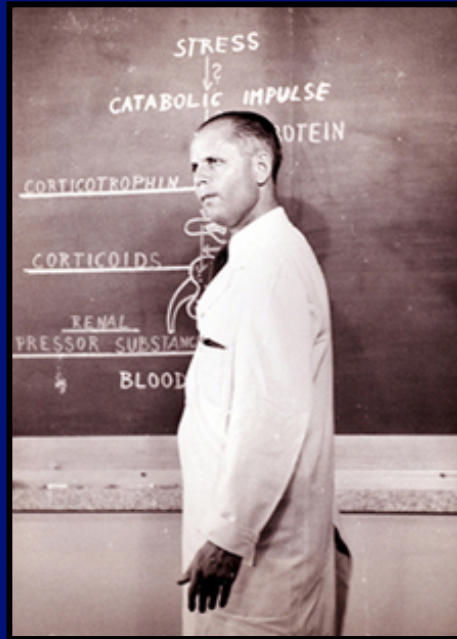
Como o estresse facilita
o aparecimento da
depressão?

Para sobreviver
precisamos lidar
com situações
aversivas



94 Masaccio, Adão e Eva expulsos do Paraíso, c. 1427,
205 x 90 cm

Síndrome Geral de Adaptação ou Estresse ?



H. Selye

A Syndrome produced by Diverse Nocuous Agents

EXPERIMENTS on rats show that if the organism is severely damaged by acute non-specific nocuous agents such as exposure to cold, surgical injury, production of spinal shock (transcision of the cord), excessive muscular exercise, or intoxications with sublethal doses of diverse drugs (adrenaline, atropine, morphine, formaldehyde, etc.), a typical syndrome appears, the symptoms of which are independent of the nature of the damaging agent or the pharmacological type of the drug employed, and represent rather a response to damage as such.

Selye, 1936. Nature, 138, 32.

Estresse: Ameaça real ou potencial à homeostasia



General adaptation syndrome

Alarm reaction
Resistance stage
Exhaustation

Alostase (estabilidade através da mudança)

Ameaça à estabilidade



Estado alostático



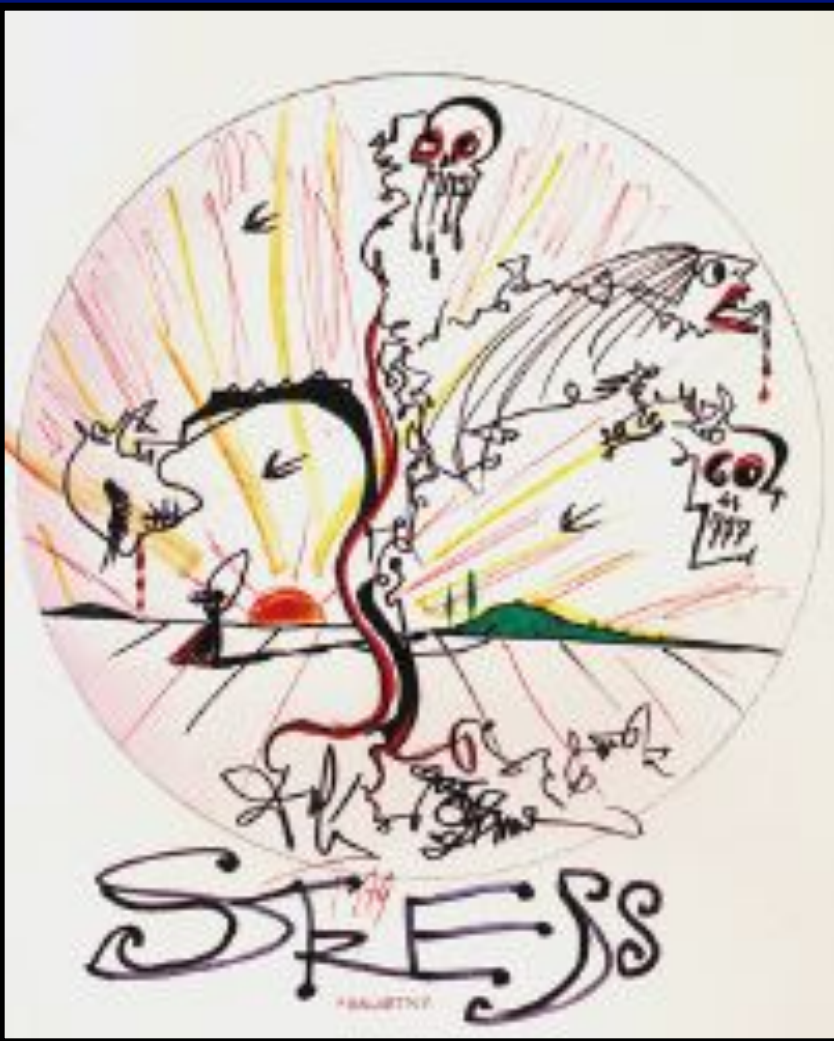
Sobre-carga
alostática

Adaptação

Maladaptação

B. McEwen

Depressão: falha nos mecanismos de adaptação ao estresse?



Salvador Dali para Selye, Monaco, 1979.

Fatores genéticos parecem alterar a sensibilidade individual ao efeito indutor de depressão de eventos estressantes (Kendler et al. Am J Psychiat 152,833, 1995)

Probabilidade mensal de início de crise de depressão

	Sem exposição a evento estressante	Com exposição a evento estressante
Baixo risco genético	0,5%	1,1%
Alto risco genético	6,2%	14,6%

A maior parte dos modelos animais de depressão envolve exposição a estressores (Willner 1989)

I. Modelos sem simulação

1. Reversão da reserpina
2. Comportamento de espera

II. Modelos de estresse

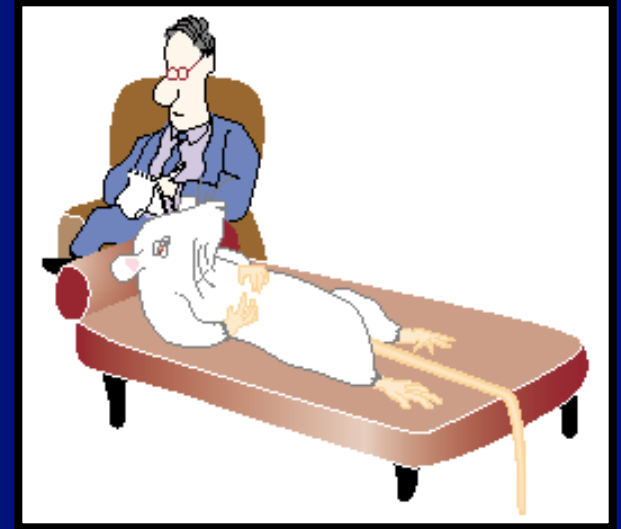
1. Desamparo aprendido
2. Nado forçado
3. Falha de adaptação ao estresse
4. Estresse crônico suave

III. Modelos de separação

1. Modelos em primatas
2. Isolamento social em ratos

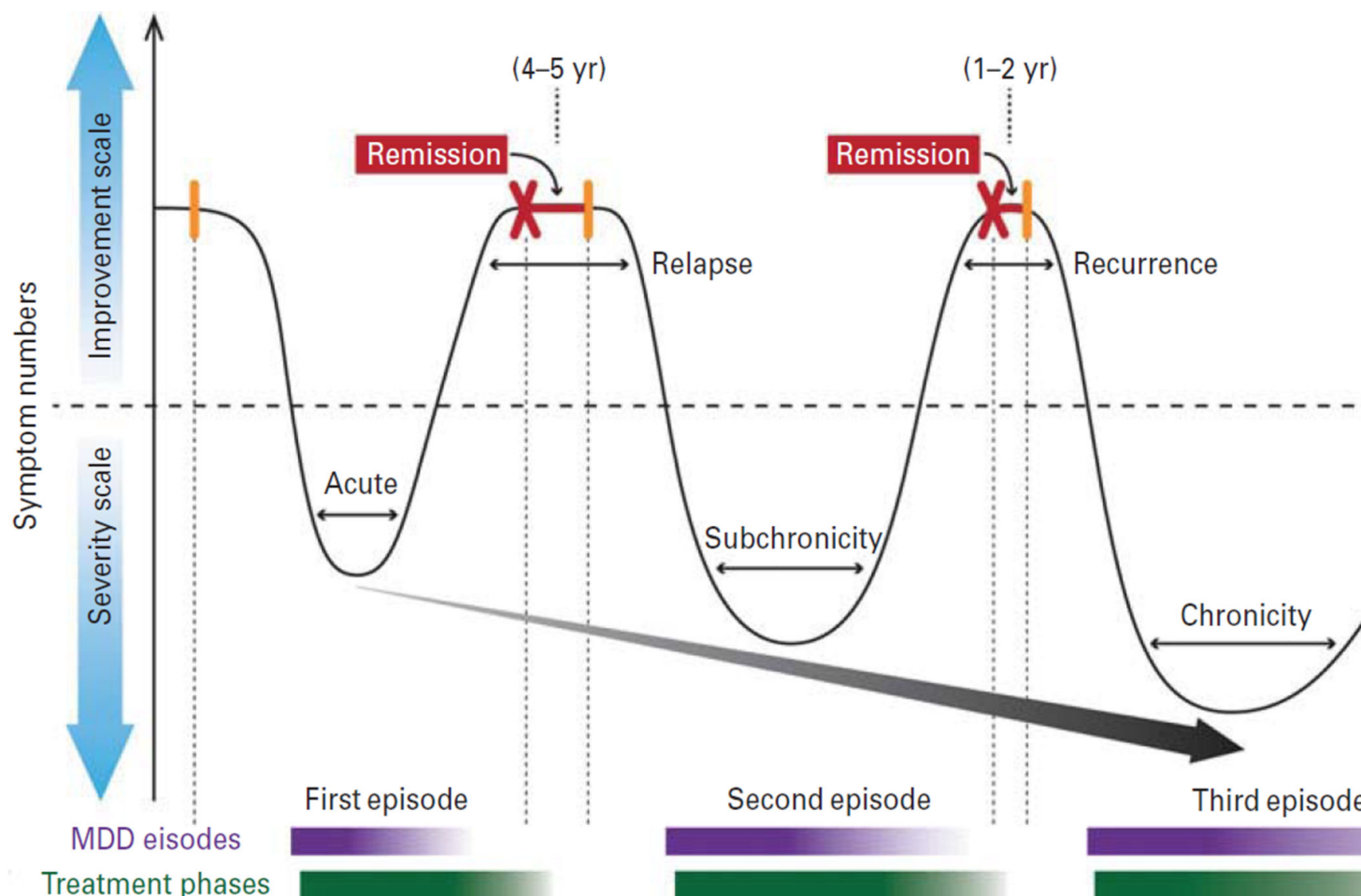
IV. Modelos de dano cerebral

1. Bulbectomia olfatória



Cryan et al., 2002

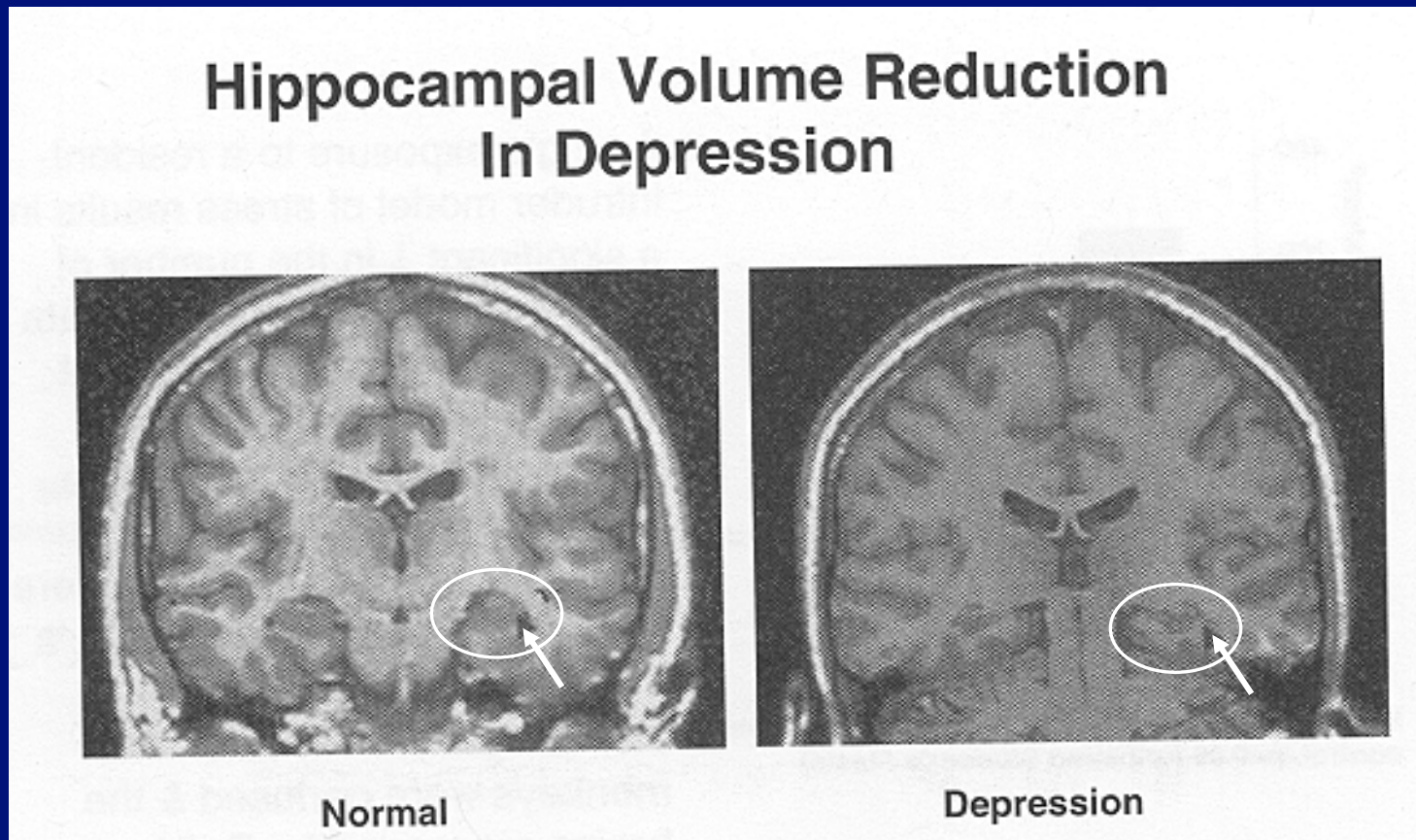
Cr terios de Valida  o:
validade de face
validade farmacol gica
validade de constructo



“Sensibilização” dos episódios depressivos

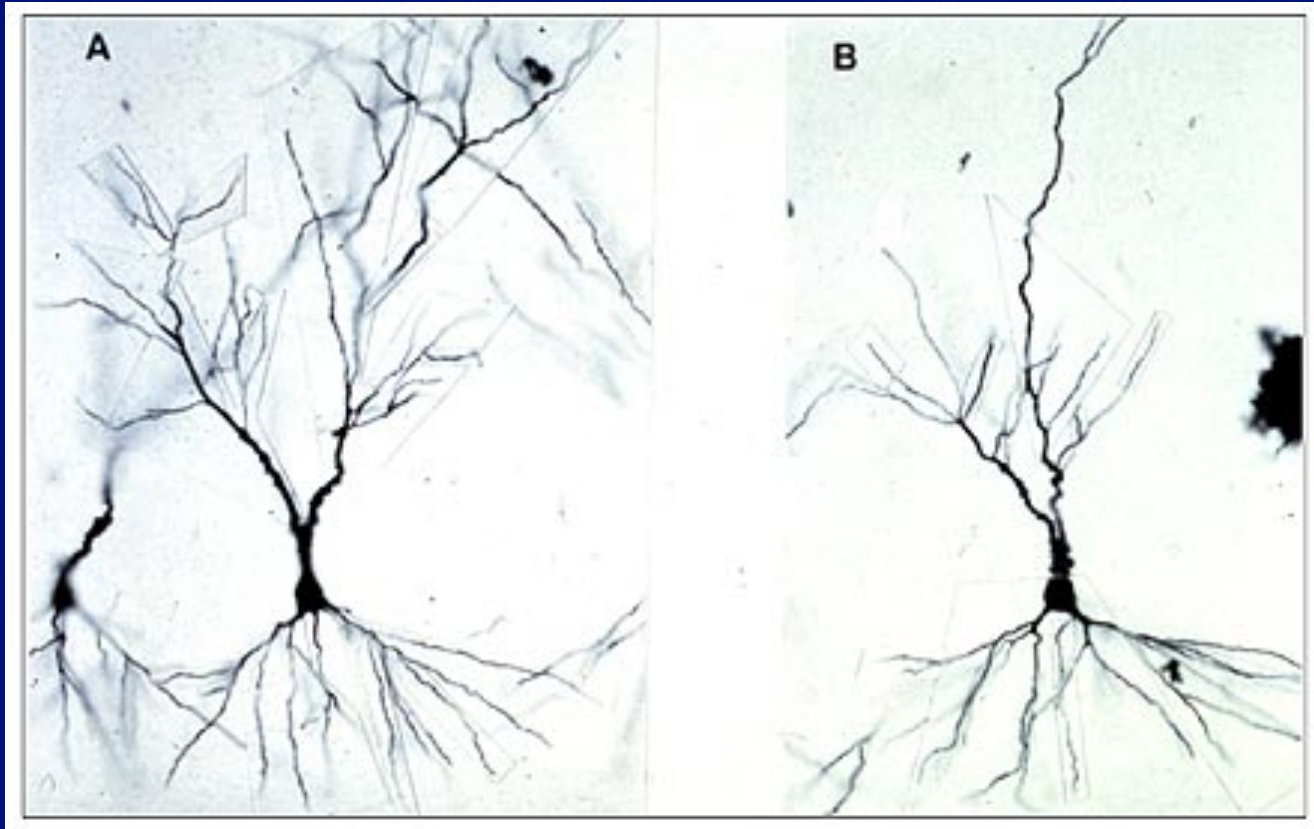
Como o estresse favoreceria a depressão: envolvimento de mecanismos neuroplásticos

(Pode existir diminuição do volume do hipocampo em pacientes com depressão)



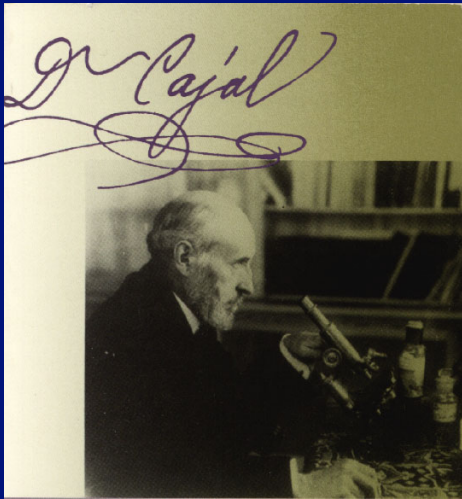
Gurvits et al., Biol Psych 40:1091, 1996, Bremer et al., Am J Psychiatry 2004, Sheline et al., 1996

Mecanismos: remodelamento de células piramidais do hipocampo após exposição a estressores?



Controle

Estressado



“In the adult centers the nerve paths are something fixed, ended and immutable. Everything may die, nothing may be regenerated.”

Santiago Ramon y Cajal (1913)

Autoradiographic and Histological Evidence of Postnatal Hippocampal Neurogenesis in Rats ¹

JOSEPH ALTMAN AND GOPAL D. DAS

Psychophysiological Laboratory, Massachusetts Institute of Technology, Cambridge, Massachusetts

ABSTRACT In the autoradiograms of young rats injected with thymidine- H^3 many of the granule cells of the dentate gyrus were found labeled. The number of labeled cells declined rapidly with increased age at the time of injection. Histological studies showed the presence in young rats of a large germinal matrix of mitotic cells in the ependymal and subependymal layers of the third and lateral ventricles. The areal

J. Comp. Neurol., 124: 319-336 (1965)

A descoberta da
neurogênese em cérebro de
adultos

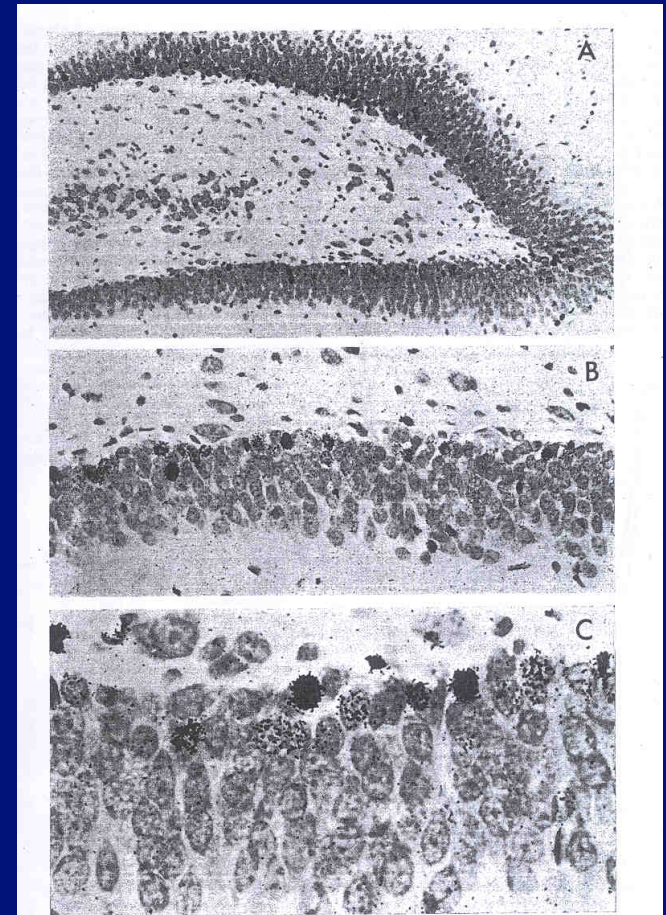


Fig. 1 Low and high power microphotographs of autoradiograms from the area of the dentate gyrus of the hippocampus in a rat injected with thymidine- H^3 at the age of ten days and killed two months after the injection. Note labeling of granule cells, predominantly in the internal border (basal surface) of the granular layer. A, 100 $\times$; B, 256 $\times$; C, 640 $\times$.

Neurogênese em humanos e roedores adultos (Borsini et al., 2015): regiões subventricular e subgranular do giro denteado

No rato ≈ 3.000 novas células por dia no giro denteado

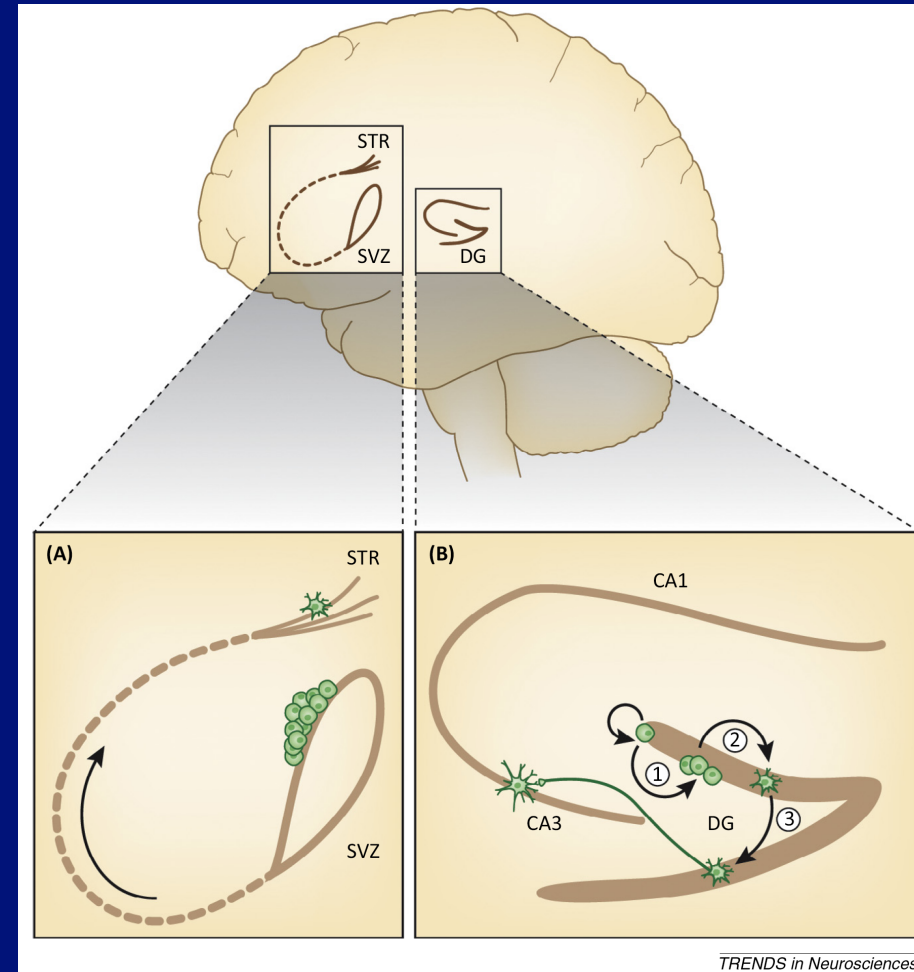
80% morrem no 1o. mês

20% sobrevivem

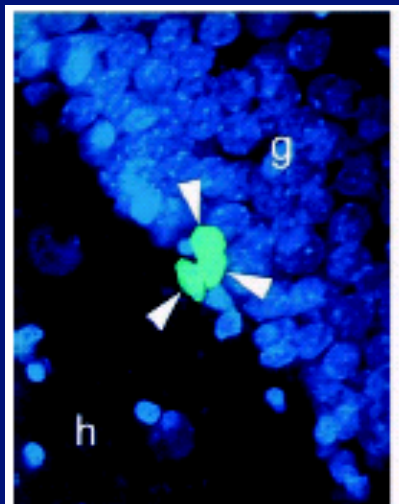
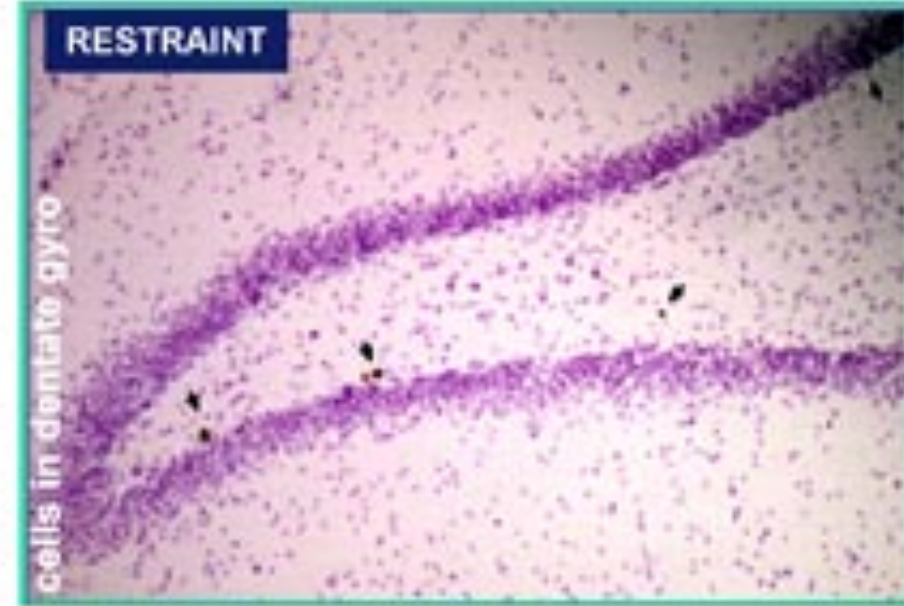
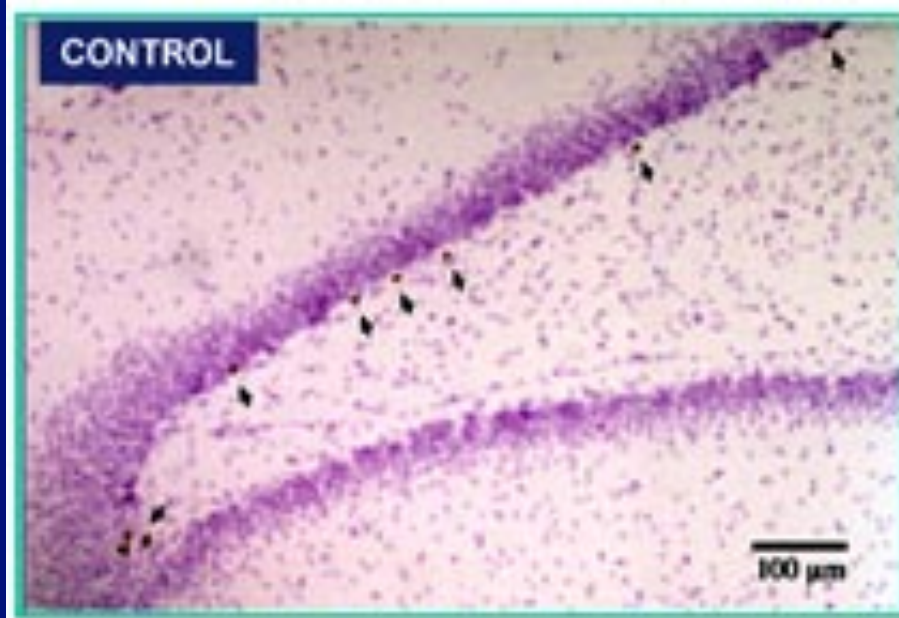
70% viram neurônios

30% viram astrócitos ou oligodendróglia

Em humanos ≈ 700 novos neurônios por dia no giro denteado



Estresse de imobilização diminui neurogênese no giro denteado do hipocampo

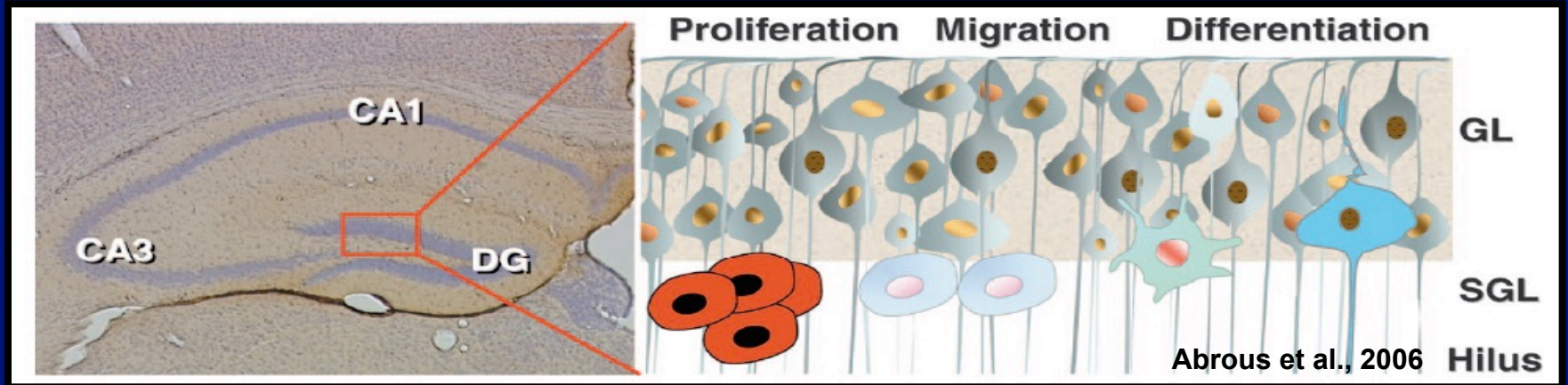


Controle

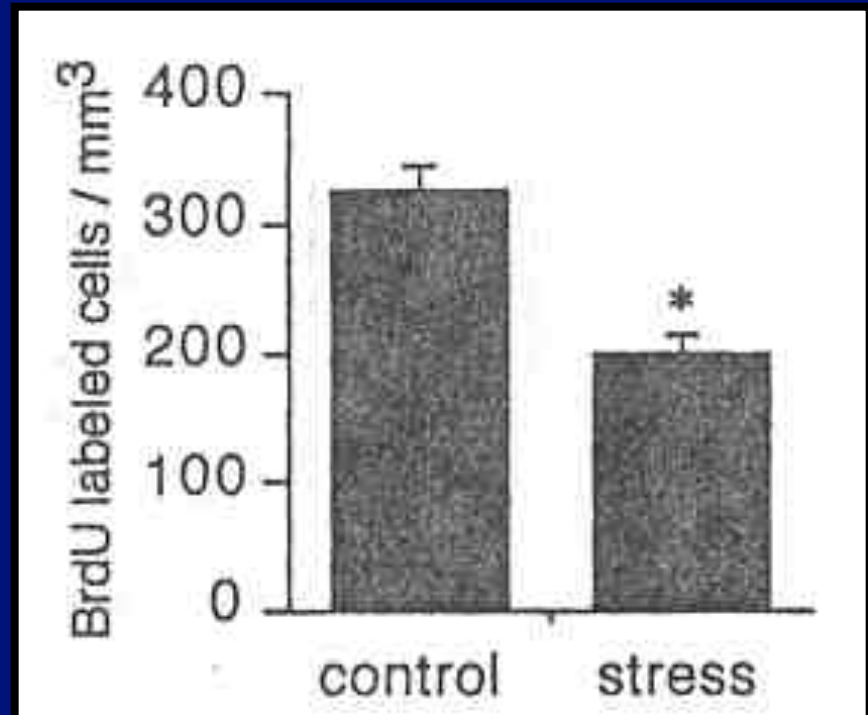
Estressado

Novos neurônios
no giro denteado
marcados por
BrdU

Estresse psicossocial reduz a neurogênese no giro denteado do hipocampo



Participação de glicocorticóides e de glutamato (Cameron et al., 1998)



Gould et al., 1998

Vários fatores interefrem na neurogênese hipocampal

Adult neurogenesis: a substrate for experience-dependent change

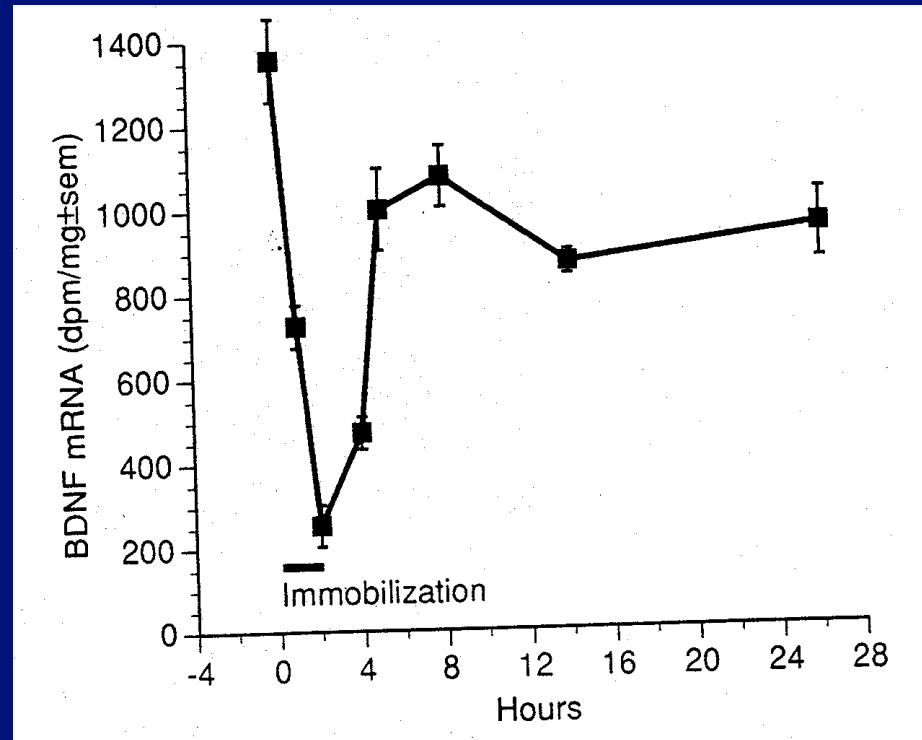
Maya Opendak and Elizabeth Gould

TICS 2015

	Stimulus	Adult neurogenesis	Cognitive performance	Anxiety-like behavior	References
Negative	Stress	↓	↓	↑	5,8,82,83
	High fat diet/obesity	↓	↓	↑	84,85
Positive	Physical exercise	↑	↑	↓	18,19,21,22,39
	Sexual experience	↑	↑	↓	36,86,87
	Enriched environment (EE)	↑	↑	↓	89,90
	Intracranial self-stimulation	↑	↑	?	91,92
Mixed	Parenting	↓	↑	↓	34,35,88,93
	Stress + physical exercise	=	=	=	74,75,94
	Stress + sexual experience	=	=	?	76,95
	Stress + EE	=	=	=	96,97

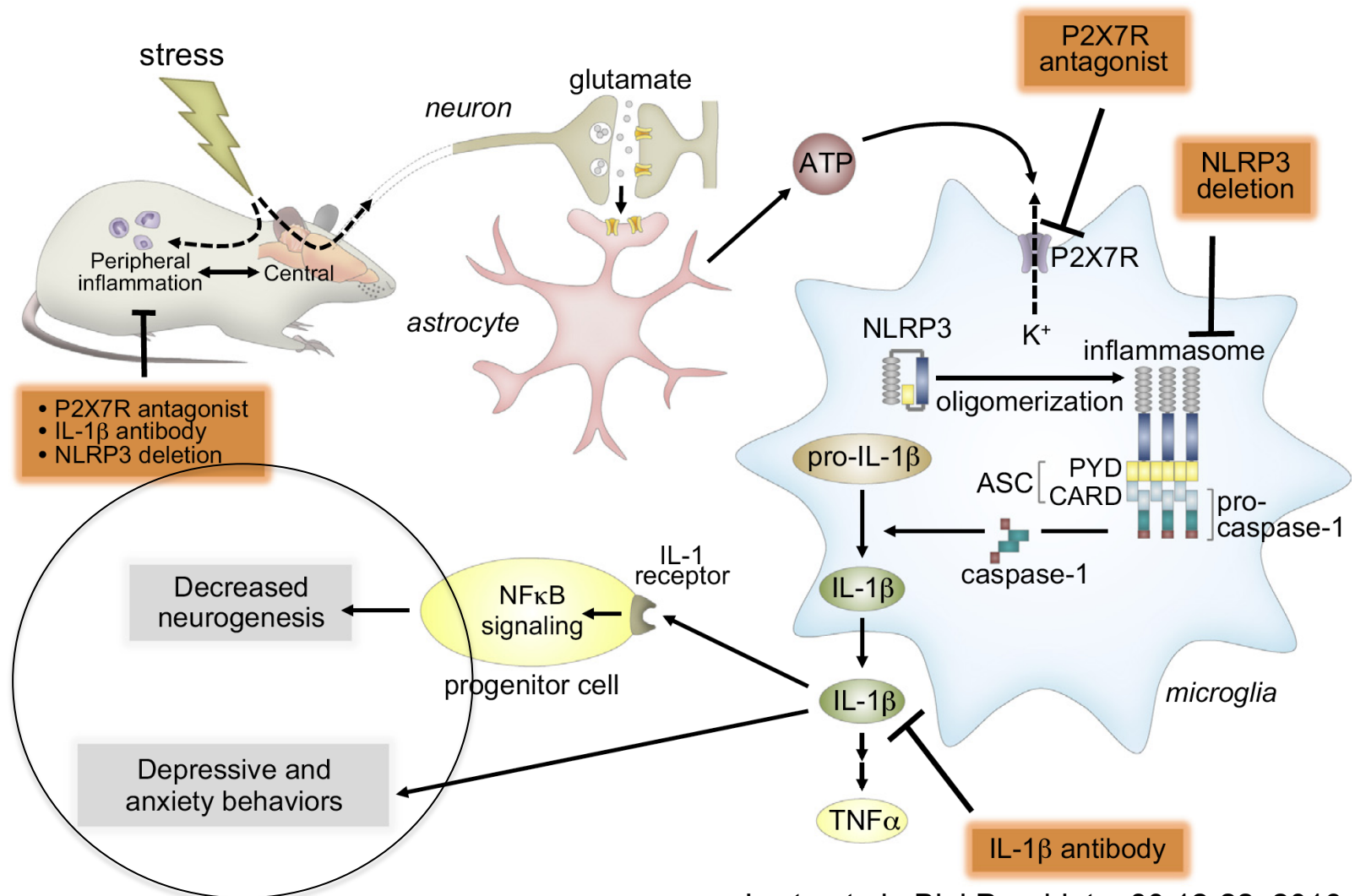
Como o estresse diminui a neurogênese e arborização dendrítica?

Estresse diminui a expressão da neurotrofina derivada do cérebro (Brain-derived neurotrophic factor, BDNF) no hipocampo

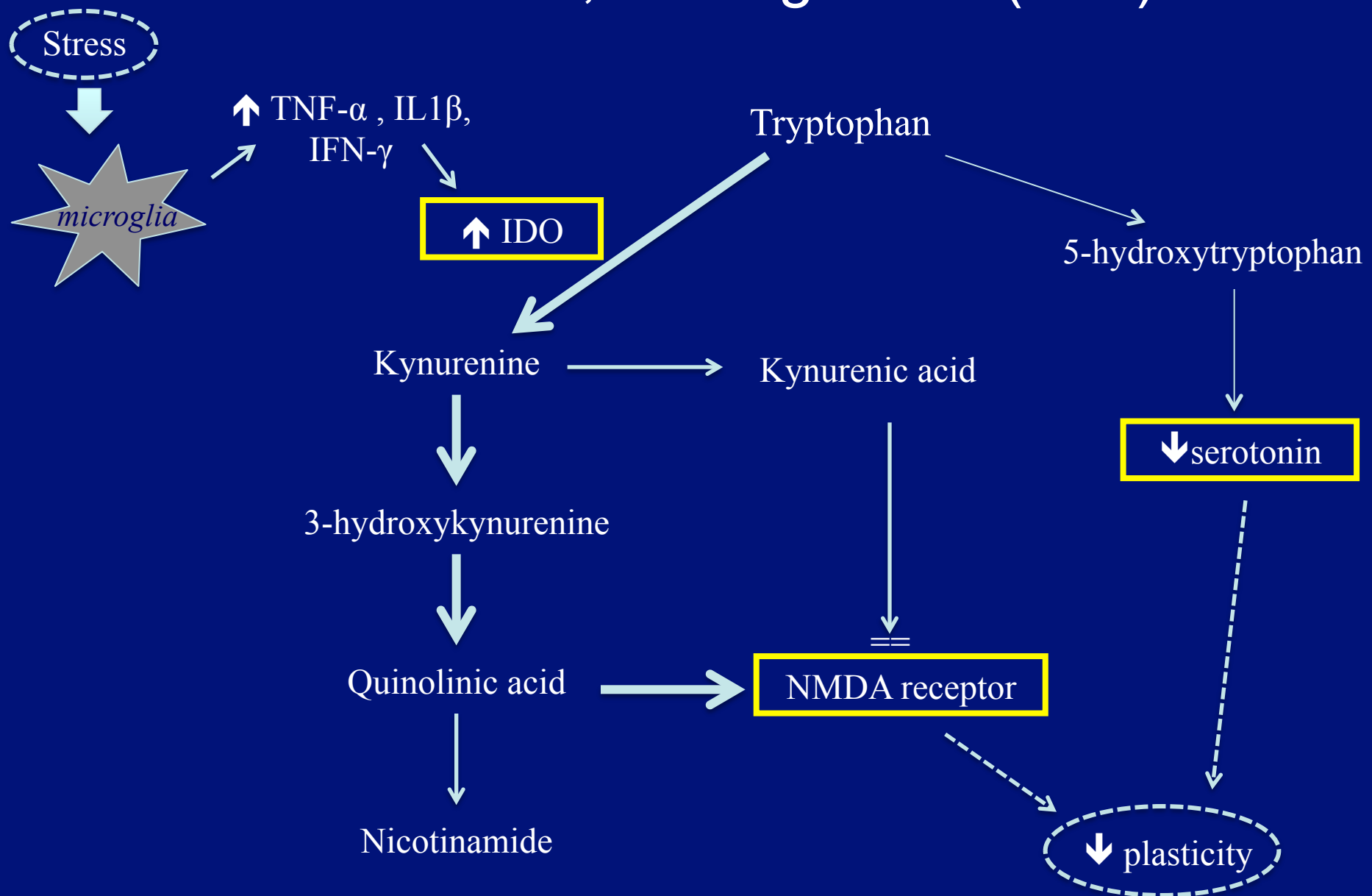


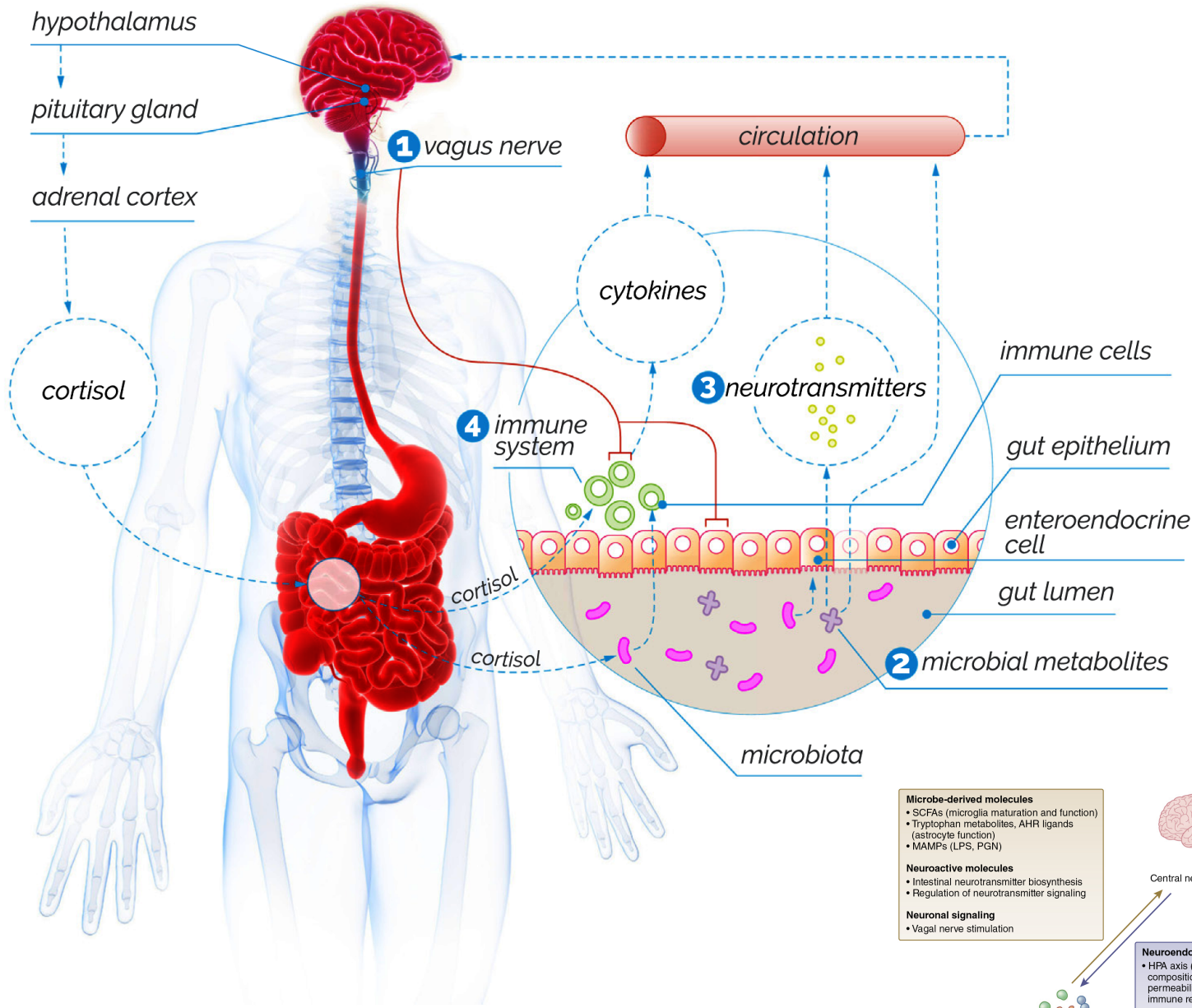
Como o estresse diminui a neurogênese e arborização dendrítica?

Possível papel de mecanismos inflamatórios/imunológicos



Hipótese inflamatória da depressão: papel da indolamina 2,3 dioxigenase (IDO)





AO eixo intestino-cérebro: a **microbiota** também pode ter papel no desenvolvimento de transtornos neuropsiquiátricos

More Than a Gut Feeling: The Implications of the Gut Microbiota in Psychiatry

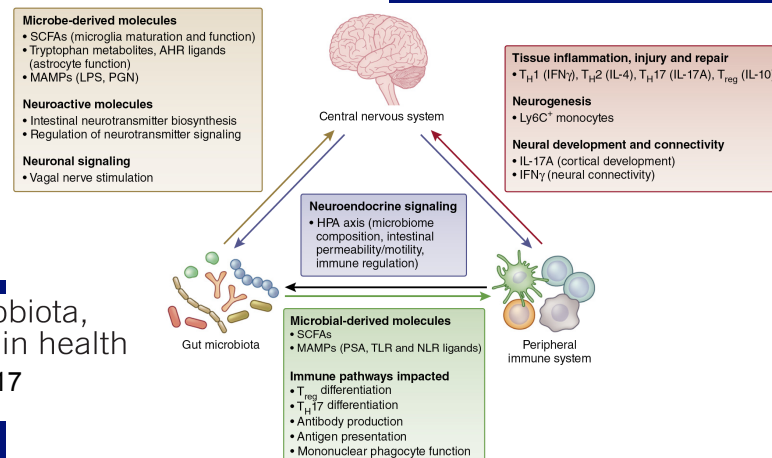
Pochu Ho and David A. Ross

Biol Psychiat 2017

Interactions between the microbiota, immune and nervous systems in health and disease

Thomas C Fung, Christine A Olson & Elaine Y Hsiao

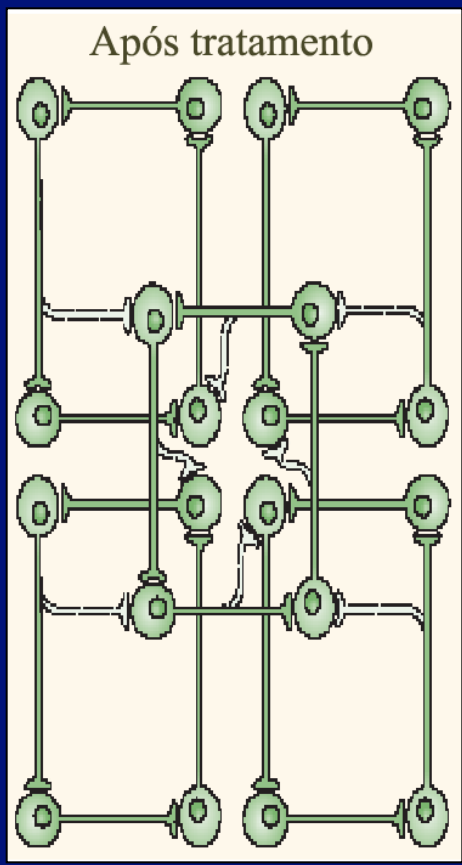
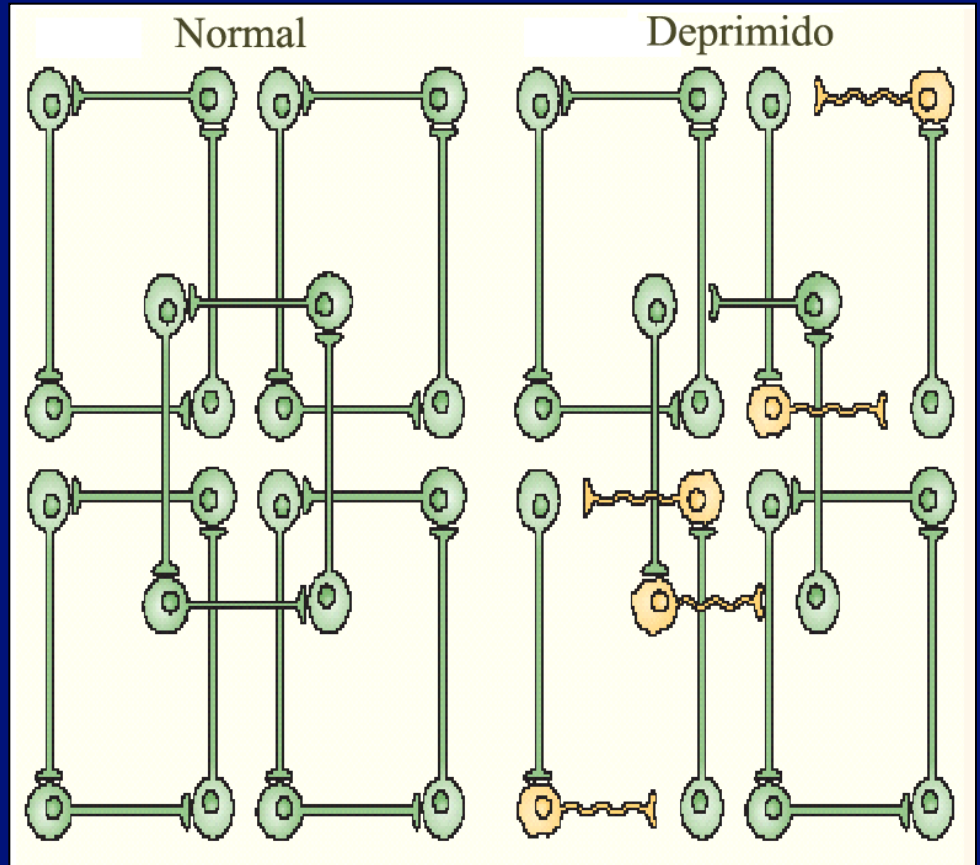
Nature Neurosc 2017



A hipótese de “redes neurais” da depressão



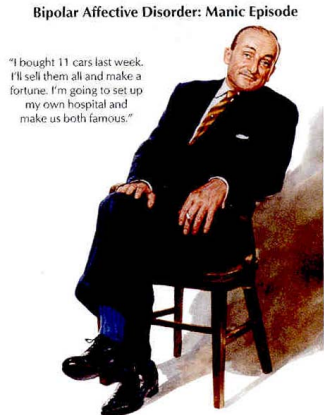
Castren
2007



E. Castren, 2005

Estresse → ↑ **Glutamato**, ↑ **glicocorticóides**,
outros fatores (↑ NO, neuroinflamação, ↓ BDNF)

↑ **Antidepressivos**
(↑ serotonina, ↑ noradrenalina)



Transtorno Afetivo Bipolar

“No princípio, quando estou me sentindo “alto”, é tremendo...as idéias são rápidas...como estrelas cadentes que você segue até outras aparecerem...toda a timidez desaparece, as palavras e gestos apropriados estão subitamente lá...pessoas e coisas desinteressantes se tornam intensamente interessantes. A sensualidade se espalha, o desejo de seduzir e ser seduzido é irresistível. Sua mente é infundida com um senso inacreditável de poder, onipotência, bem estar, euforia...você pode fazer qualquer coisa”

Transtorno bipolar: crise de mania



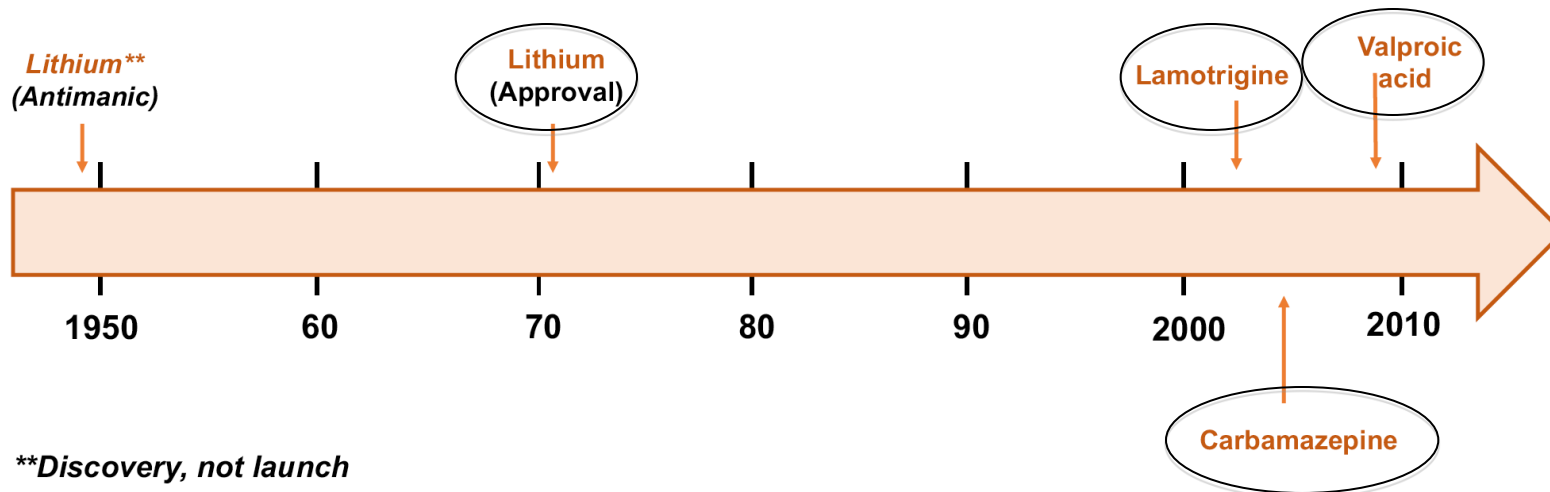
Lilly: The Bipolar Experience

“Estabilizadores do humor”

Lítio: Mecanismo de ação desconhecido

Alternativas: anticonvulsivantes (ácido valpróico, carbamazepina, lamotrigina)

Bipolar disorder*



*Several antipsychotics shown in Figure 1 have been authorised for the treatment of bipolar disorder - see Table 1

Transtornos ansiedade

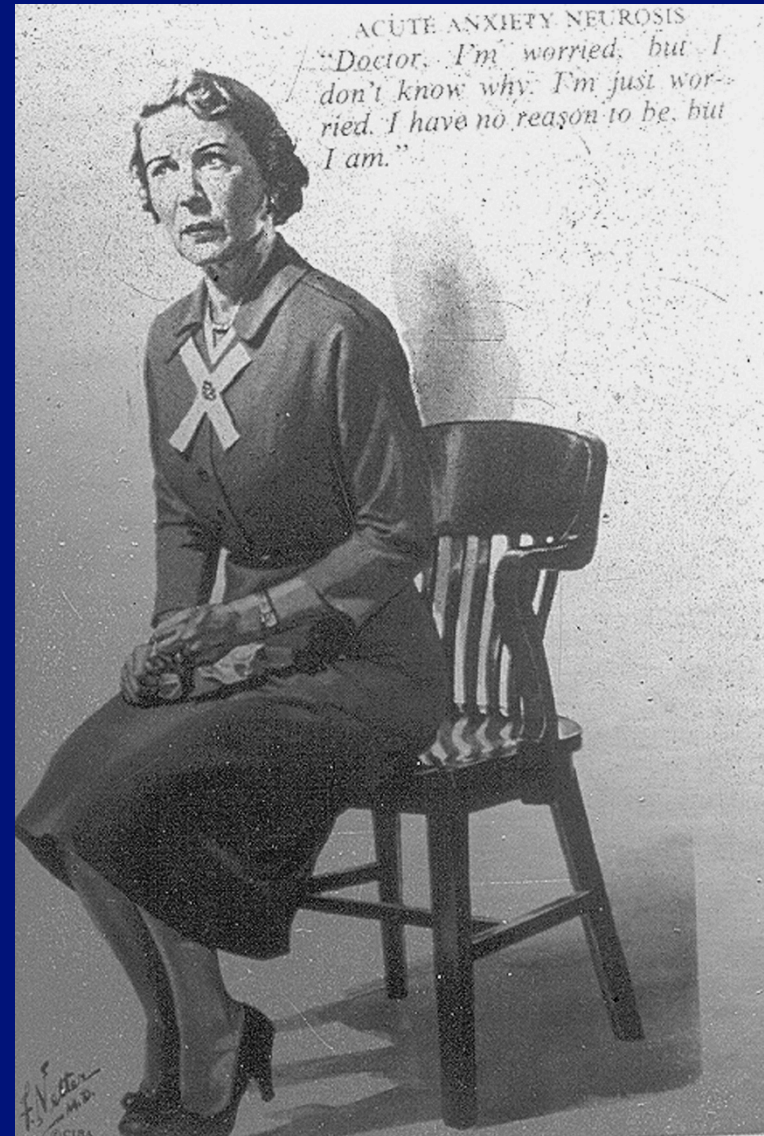
El hombre primitivo vivió
en el Paleolítico,
en el Mesolítico
y en el Neolítico...



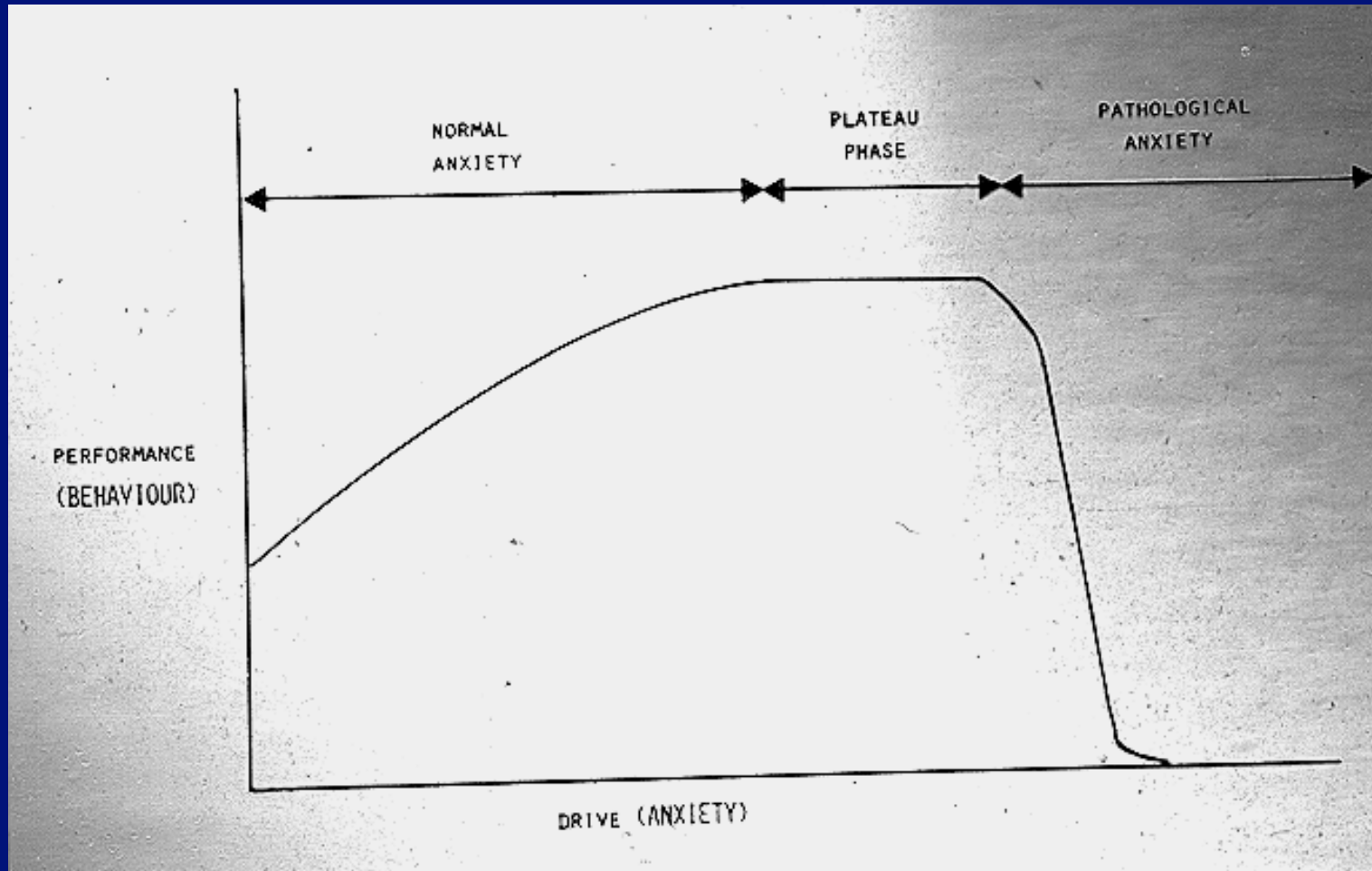
y el actual en
el Ansiolítico.

Dave LaMorda

ACUTE ANXIETY NEUROSIS
"Doctor, I'm worried, but I
don't know why. I'm just wor-
ried. I have no reason to be, but
I am."



Ansiedade normal versus patológica



Transtornos primários de ansiedade (DSM IV)

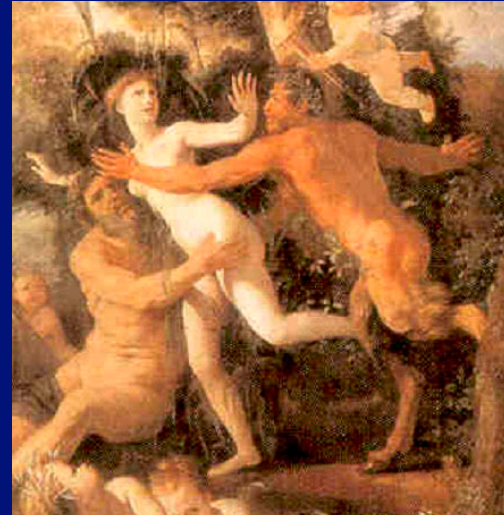
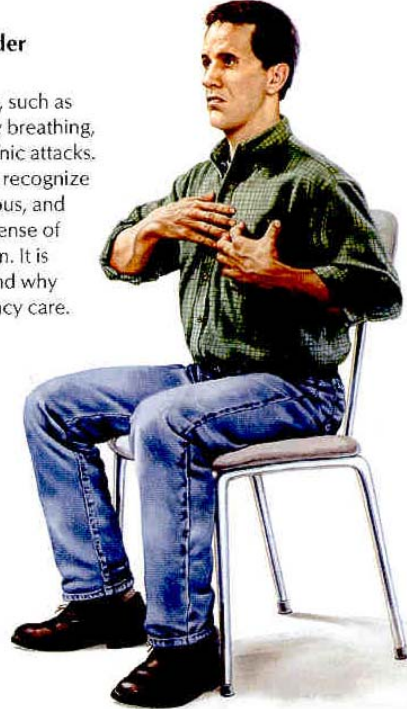
Anxiety State

"Doctor, I'm worried,
but I don't know why.
I'm just worried.
I have no reason
to be, but I am."



Panic Disorder

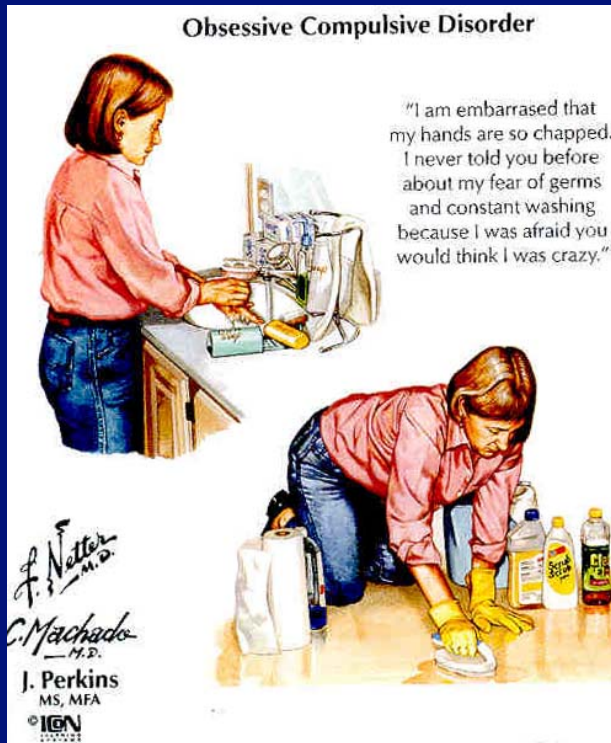
Somatic symptoms, such as
chest pain or difficulty breathing,
are the hallmark of panic attacks.
Patients often do not recognize
that they are anxious, and
have a very real sense of
impending doom. It is
easy to understand why
they seek emergency care.



Pânico

Ansiedade generalizada

Transtornos primários de ansiedade (DSM IV)



**(Transtorno
obsessivo-
compulsivo)**



Fobias: simples

**Social (ansiedade
social)**

Transtornos primários de ansiedade (DSM IV): outros

- (Estresse pós-traumático)
- Estresse agudo
- Agorafobia sem T. de pânico
- Ansiedade devido a condição médica geral
- Ansiedade induzido por substâncias químicas
- Ansiedade atípica

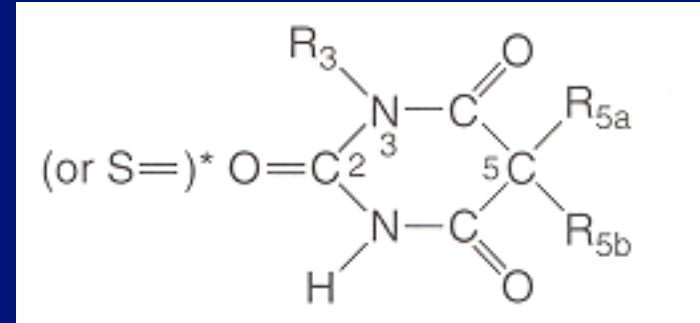


História dos ansiolíticos

- Etanol

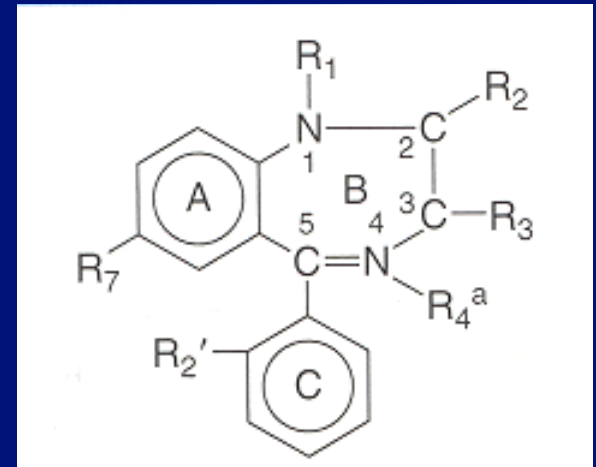
- Barbituratos - início do séc. XX

fenobarbital pentobarbital



- Benzodiazepínicos - década de 1960

clordiazepóxido	clorazepato
oxazepam	diazepam
bromazepam	midazolam



- Buspirona e antidepressivos- década de 1980

Transtornos de ansiedade (DSM IV)

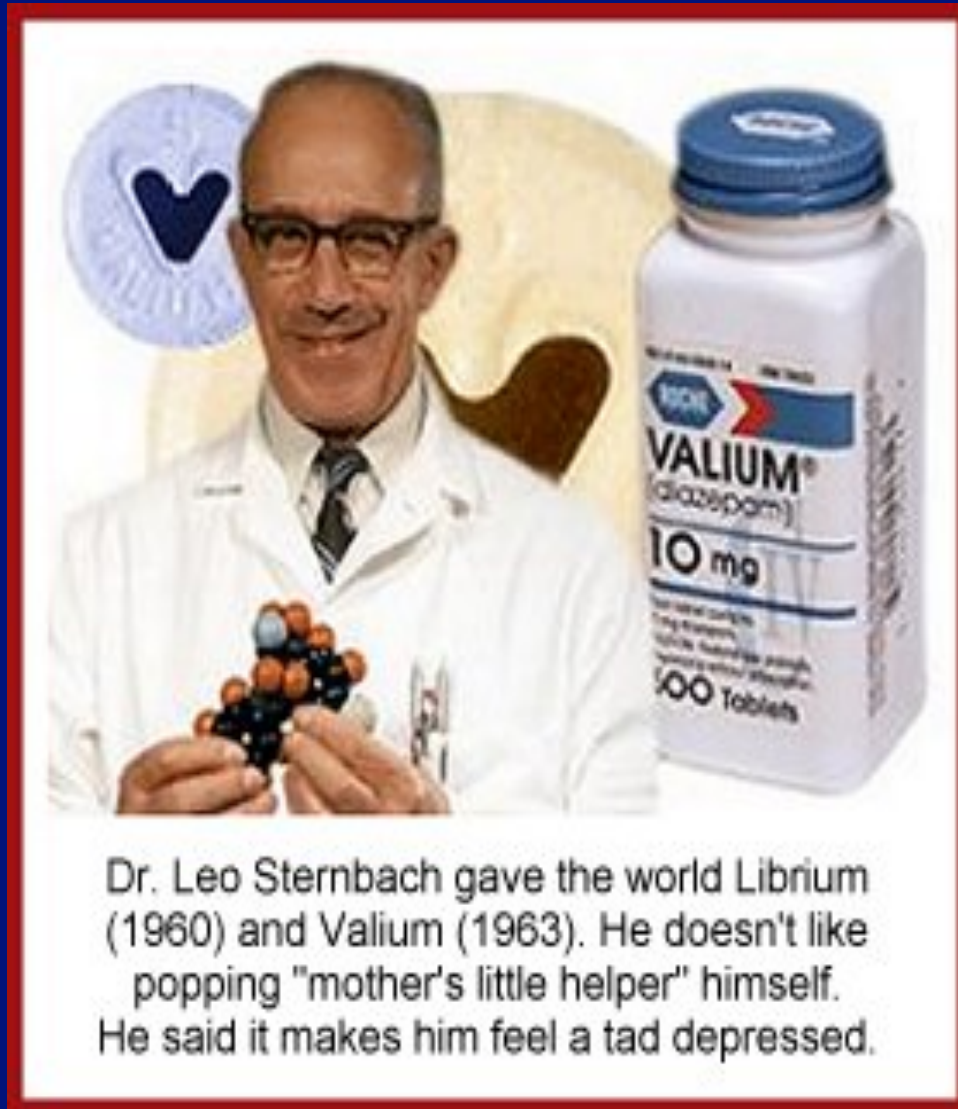
- Ansiedade generalizada
- Pânico
- T. obsessivo-compulsivo
- Estresse pós-traumático
- Ansiedade (fobia) social
- Agorafobia sem T. de pânico
- Fobia simples
- Ansiedade devido a condição médica geral
- Ansiedade induzido por substâncias químicas
- Ansiedade atípica

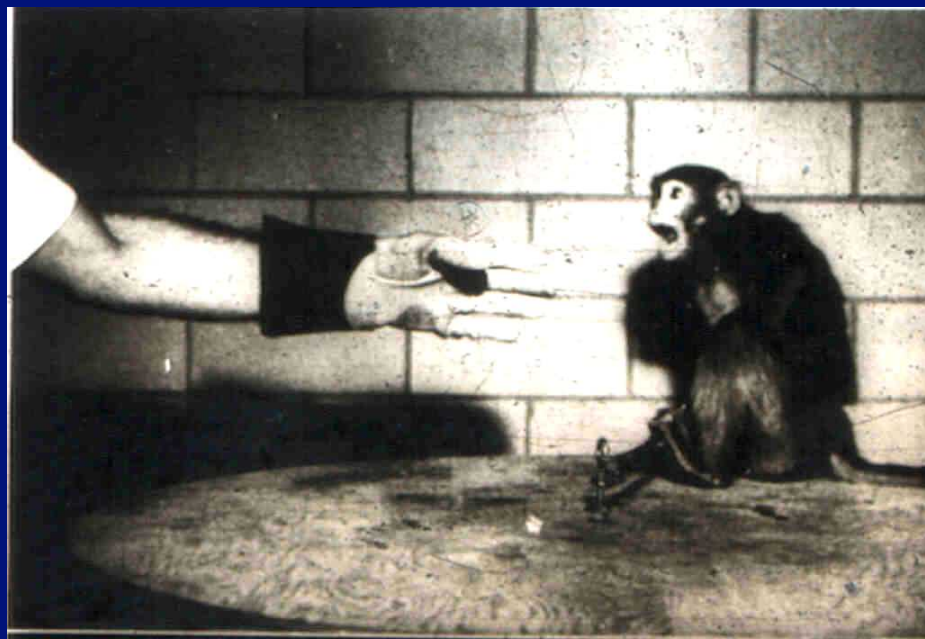
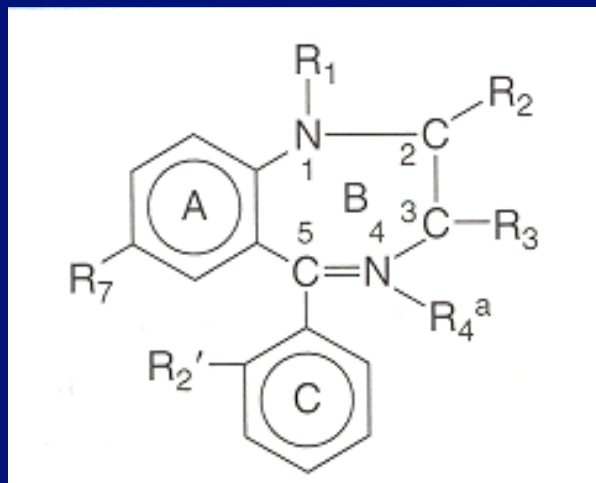
BZD

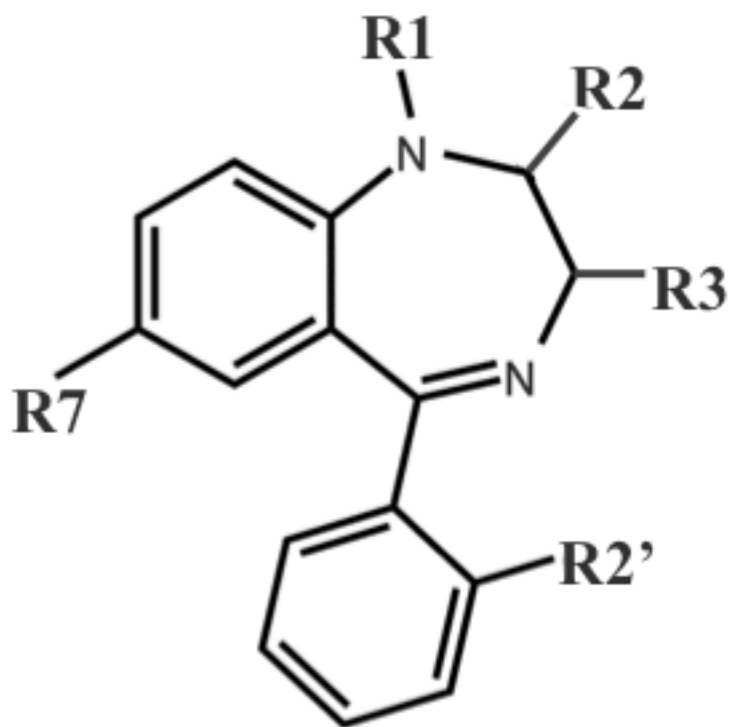
**Antidepressivo 2ª
geração**

?

Descoberta dos benzodiazepínicos







Estrutura Química dos Benzodiazepínicos

	R1	R2	R3	R7	R2'
Diazepam	-CH ₃	=O	-H	-Cl	-H
Clorazepato	-H	=O	-COO ⁻	-Cl	-H
Clordiazepóxido	-	-NHCH ₃	-H	-Cl	-H
Oxazepam	-H	=O	-OH	-Cl	-H
Lorazepam	-H	=O	-OH	-Cl	-Cl
Alprazolam	Anel triazolo		-H	-Cl	-H
Triazolam	Anel triazolo		-H	-Cl	-Cl
Midazolam	Anel imidazo		-H	-Cl	-F
Flumazenil	Anel imidazo		-H	-F	=O em C5 e CH ₃ em N4 (sem anel)

Efeitos dos benzodiazepínicos



Ansiolíticos



Hipnóticos



Anticonvulsivantes

Outros: relaxamento muscular central, amnésia anterógrada, tolerância, dependência, prejuízo psicomotor, interação com depressores SNC (ex. etanol)

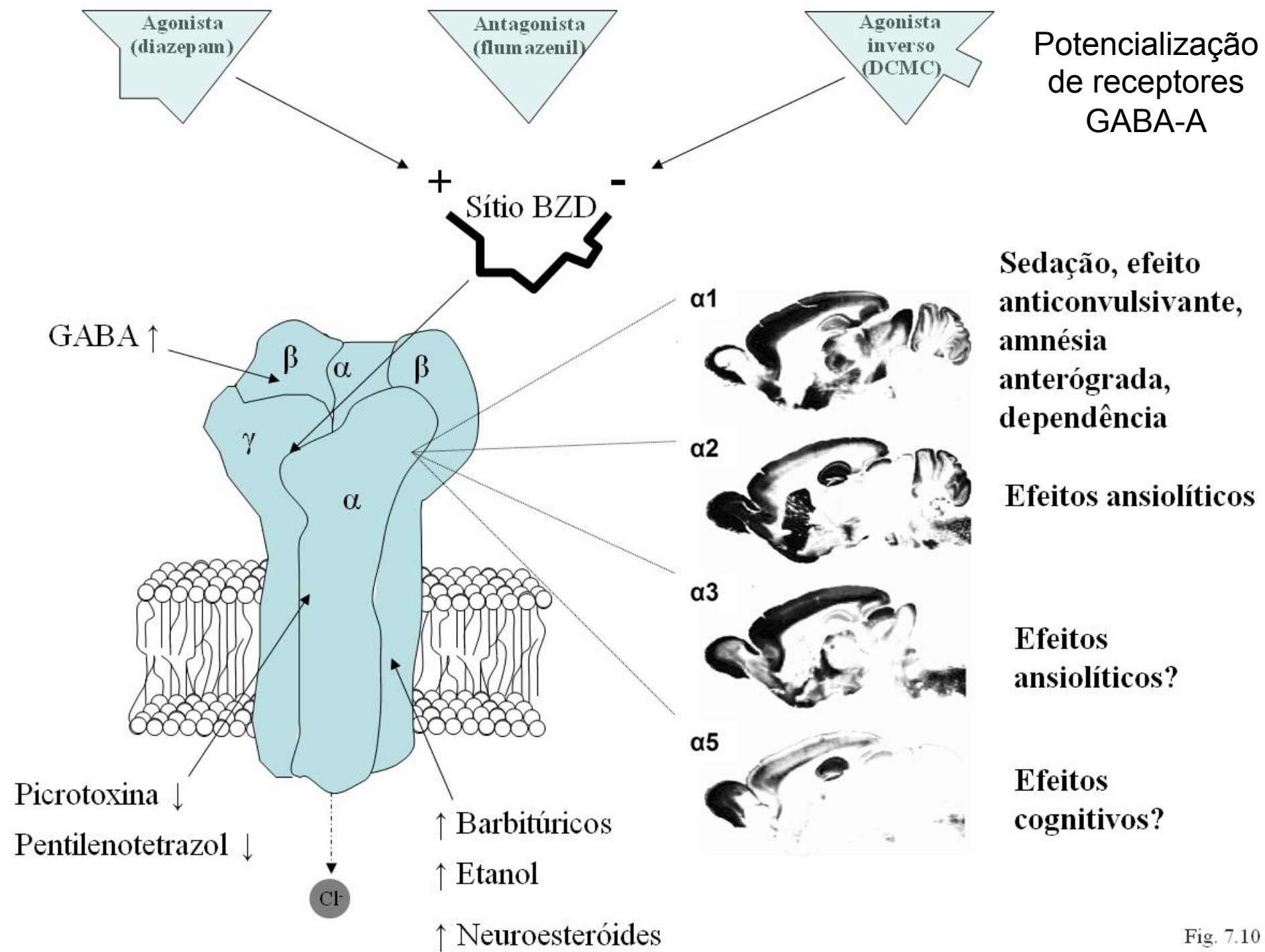


Fig. 7.10