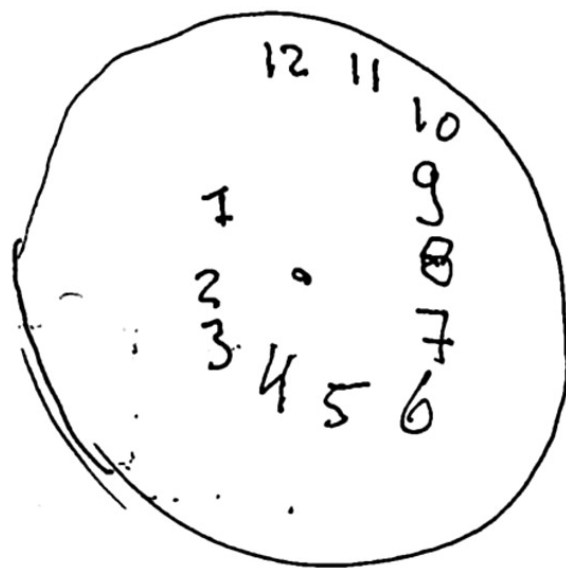
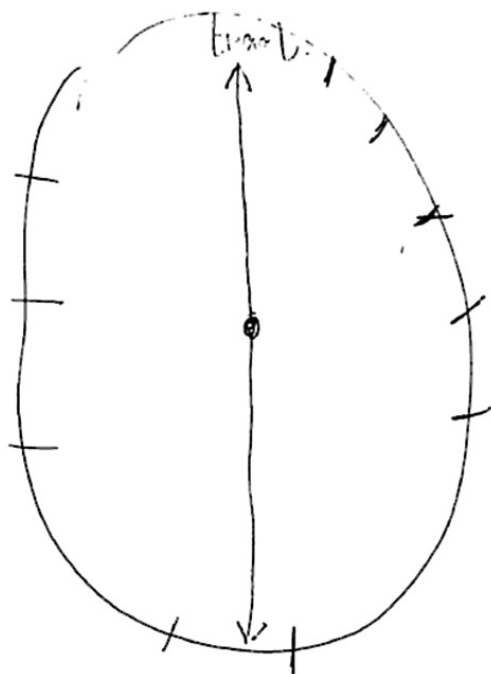
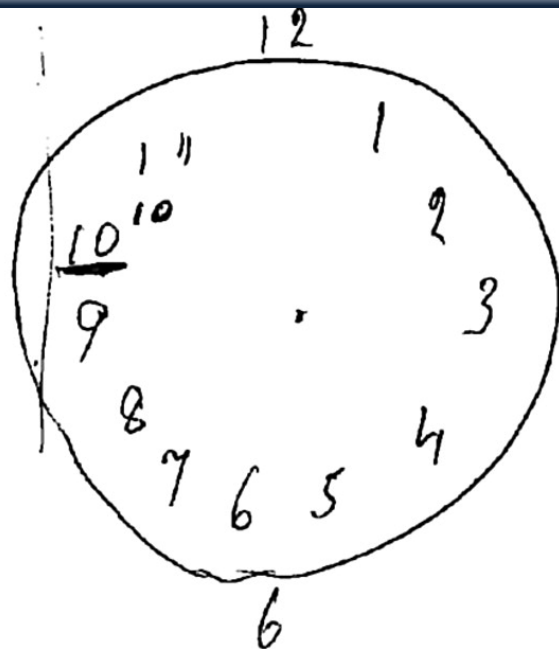
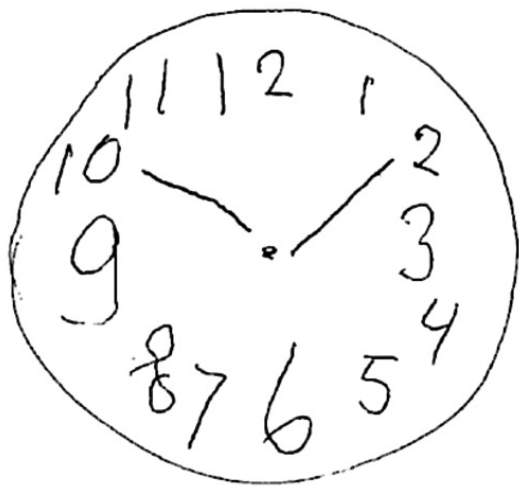


Universidade de São Paulo
Faculdade de Medicina de Ribeirão Preto
Departamento de Farmacologia

Farmacologia das Doenças Neurodegenerativas

Profa. Alline Campos

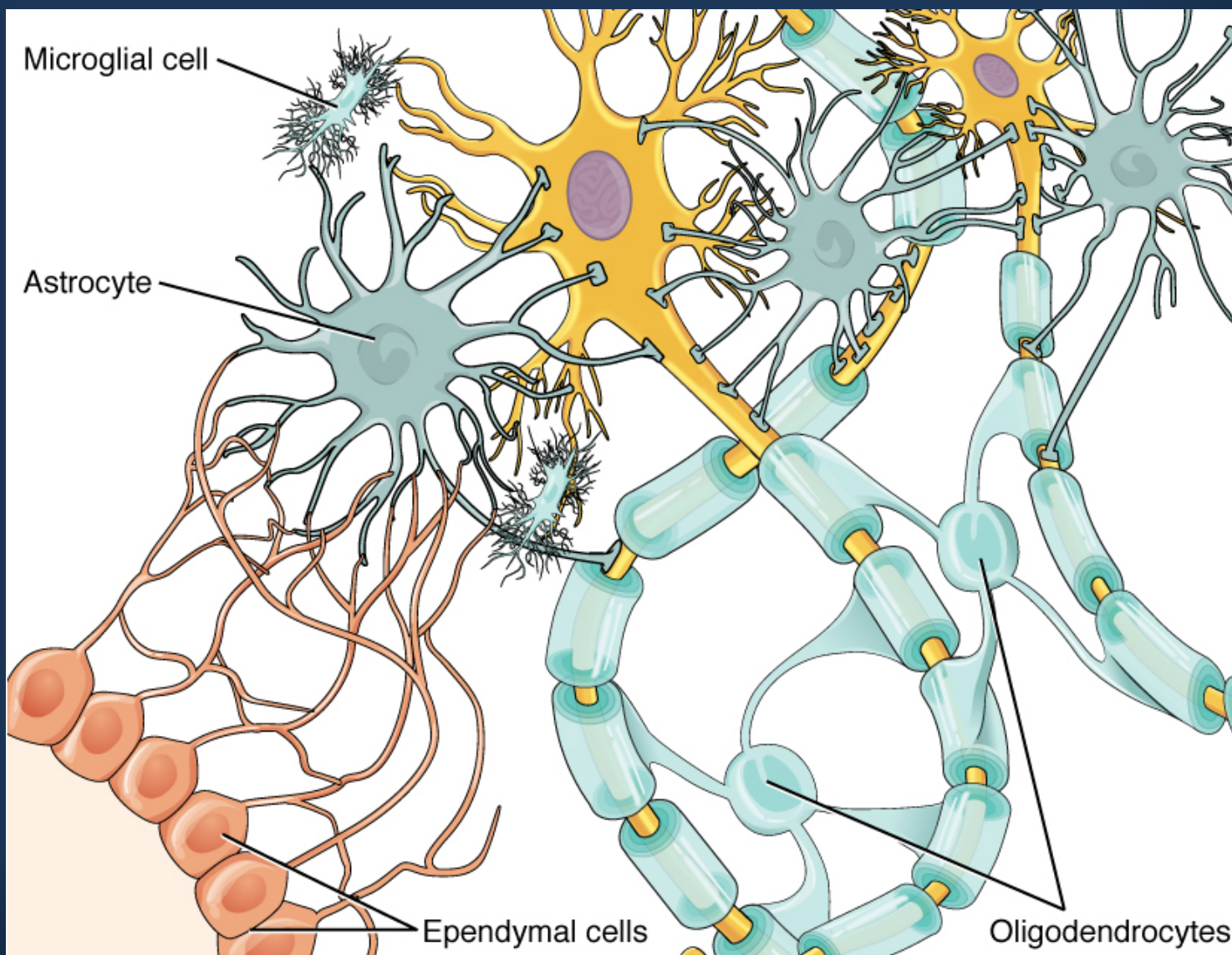


Doenças Neurodegenerativas

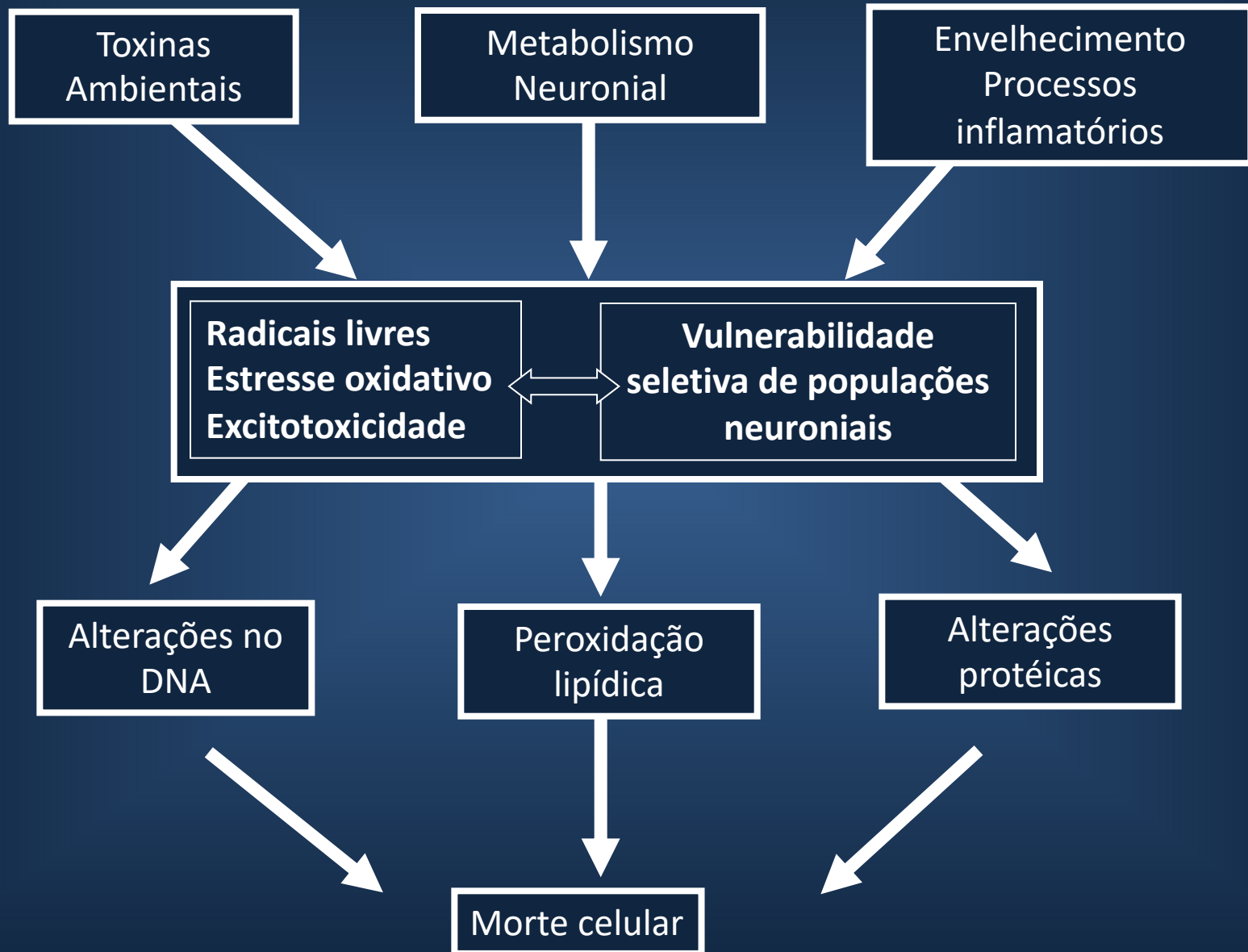


Doenças caracterizadas pela perda progressiva e irreversível de neurônios no sistema nervoso (as vezes em regiões específicas) .

Doenças Neurodegenerativas além do neurônio



Como ocorre a neurodegeneração e por quê?



Doenças Neurodegenerativas

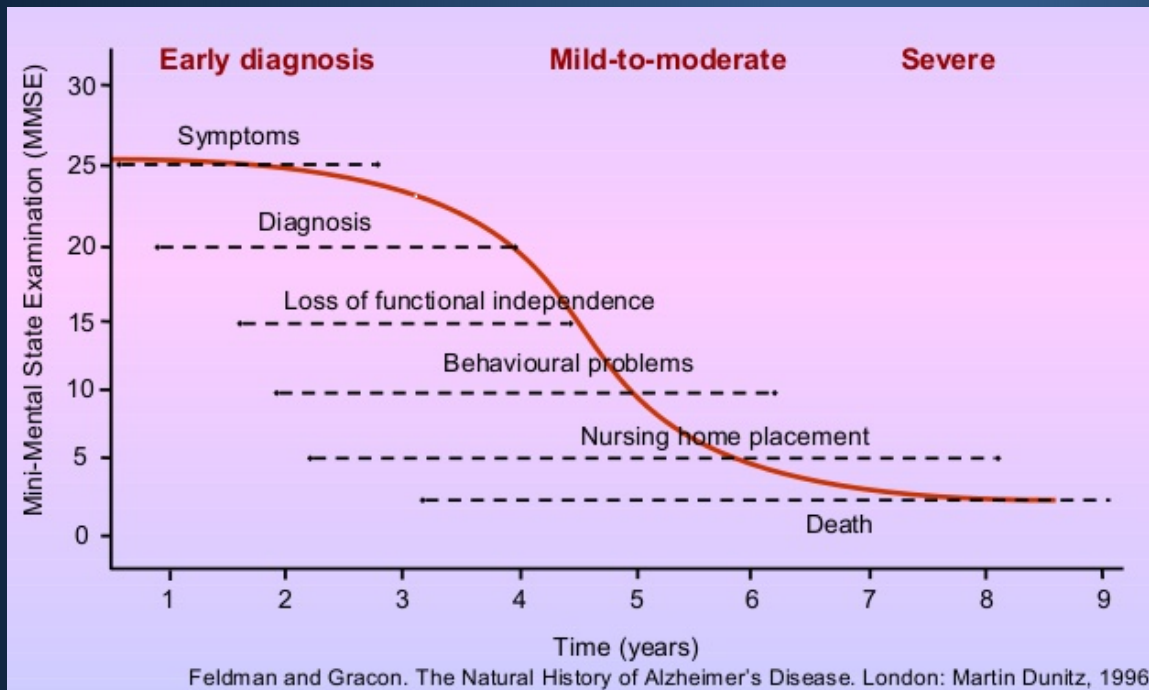
Não há tratamentos disponíveis que evitem de modo relevante a evolução da neurodegeneração ou evoluem para cura.

Qualidade de vida

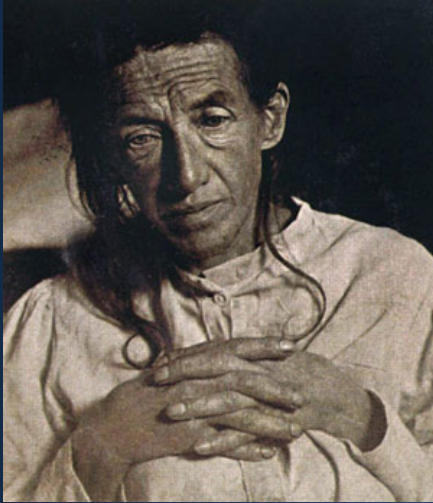
Mortalidade vs Morbidade

Doença de Alzheimer

- 8 a 15% da população mundial com mais de 65 anos;
- 70% do conjunto das doenças que afetam a população geriátrica.



Doença de Alzheimer



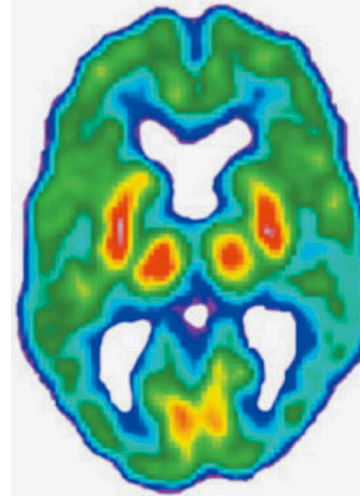
Auguste Deter

1906: Alois Alzheimer “enfermidade específica do córtex cerebral”

“He set a new standard for understanding neurodegenerative disorders by establishing a close clinical relationship with his patients and using new scientific tools to determine how symptoms related to physical brain changes.”

- Atrofia do córtex cerebral, hipocampo, amígdala
- Redução dos lobos frontal, parietal e temporal

Redução do metabolismo de glicose



Atrofia cortical



Alterações neuroanatômicas

MINI-EXAME DO ESTADO MENTAL

(Folstein, Folstein & McHugh, 1.975)

Paciente: _____

Data da Avaliação: ____/____/____ Avaliador: _____

ORIENTAÇÃO

- Dia da semana (1 ponto)()
- Dia do mês (1 ponto)()
- Mês (1 ponto)()
- Ano (1 ponto)()
- Hora aproximada (1 ponto)()
- Local específico (apartamento ou setor) (1 ponto)()
- Instituição (residência, hospital, clínica) (1 ponto)()
- Bairro ou rua próxima (1 ponto)()
- Cidade (1 ponto)()
- Estado (1 ponto)()

MEMÓRIA IMEDIATA

- Fale 3 palavras não relacionadas. Posteriormente pergunte ao paciente pelas 3 palavras. Dê 1 ponto para cada resposta correta()
Depois repita as palavras e certifique-se de que o paciente as aprendeu, pois mais adiante você irá perguntá-las novamente.

ATENÇÃO E CÁLCULO

- (100 - 7) sucessivos, 5 vezes sucessivamente (1 ponto para cada cálculo correto)()
(alternativamente, soletrar MUNDO de trás para frente)

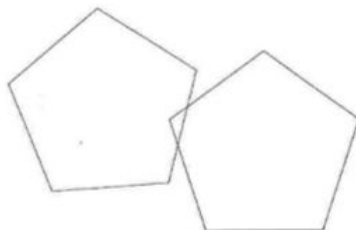
EVOCAÇÃO

- Pergunte pelas 3 palavras ditas anteriormente (1 ponto por palavra)()

LINGUAGEM

- Nomear um relógio e uma caneta (2 pontos)()
- Repetir "nem aqui, nem ali, nem lá" (1 ponto)()
- Comando: "pegue este papel com a mão direita dobre ao meio e coloque no chão (3 pts)()
- Ler e obedecer: "feche os olhos" (1 ponto)()
- Escrever uma frase (1 ponto)()
- Copiar um desenho (1 ponto)()

ESCORE: (____/30)





Normal
Score 10



Mild
Cognitive
Impairment
(Numbers error
and
placement
of hands)
Score 8



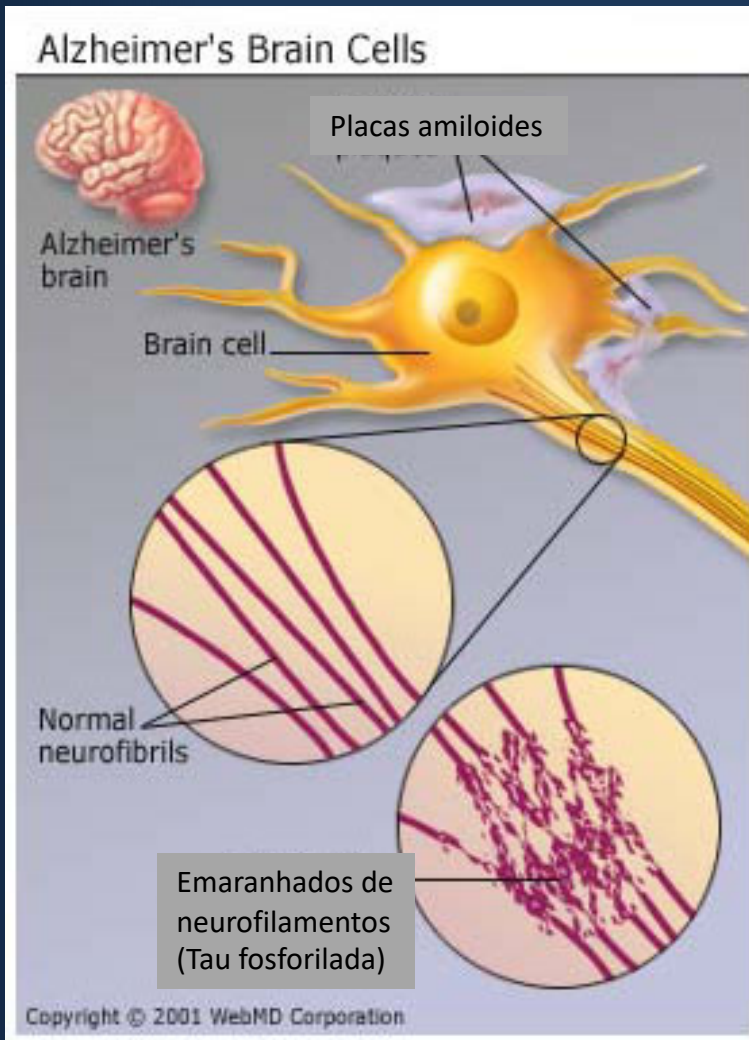
Moderate
Cognitive
Impairment
Score 4



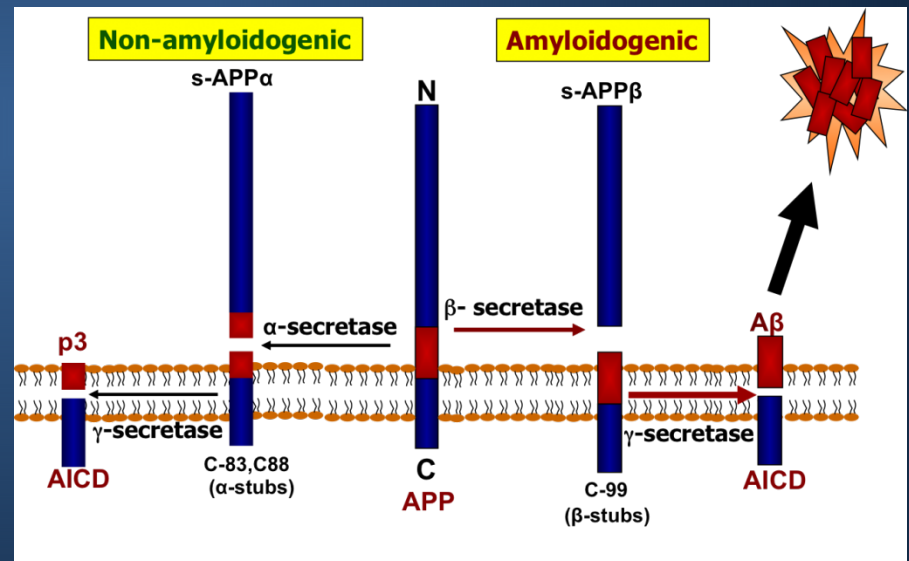
Severe
Cognitive
Impairment

Doença de Alzheimer

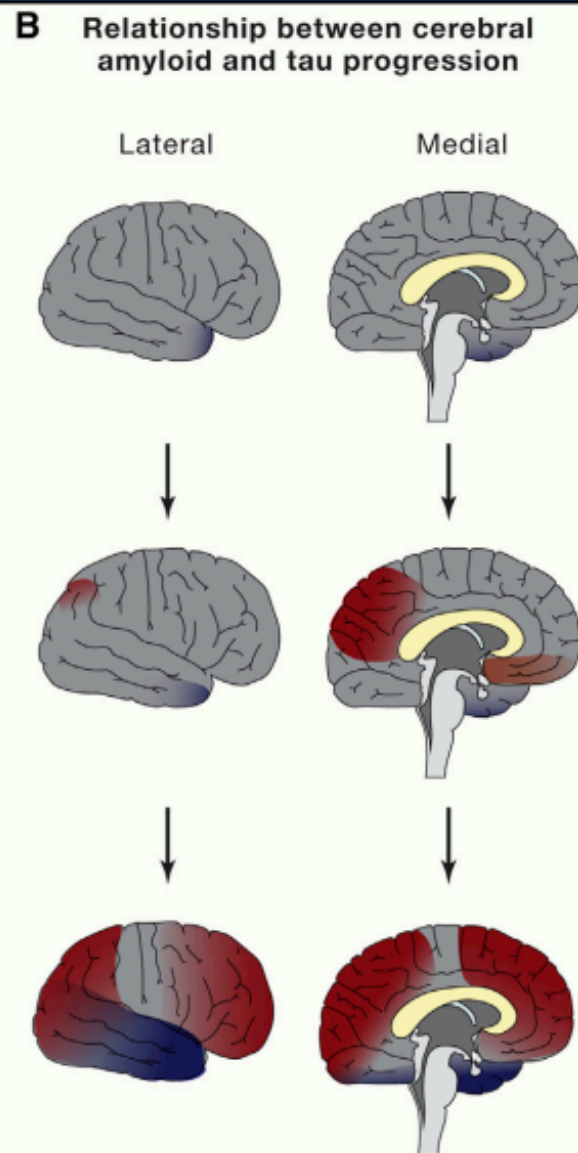
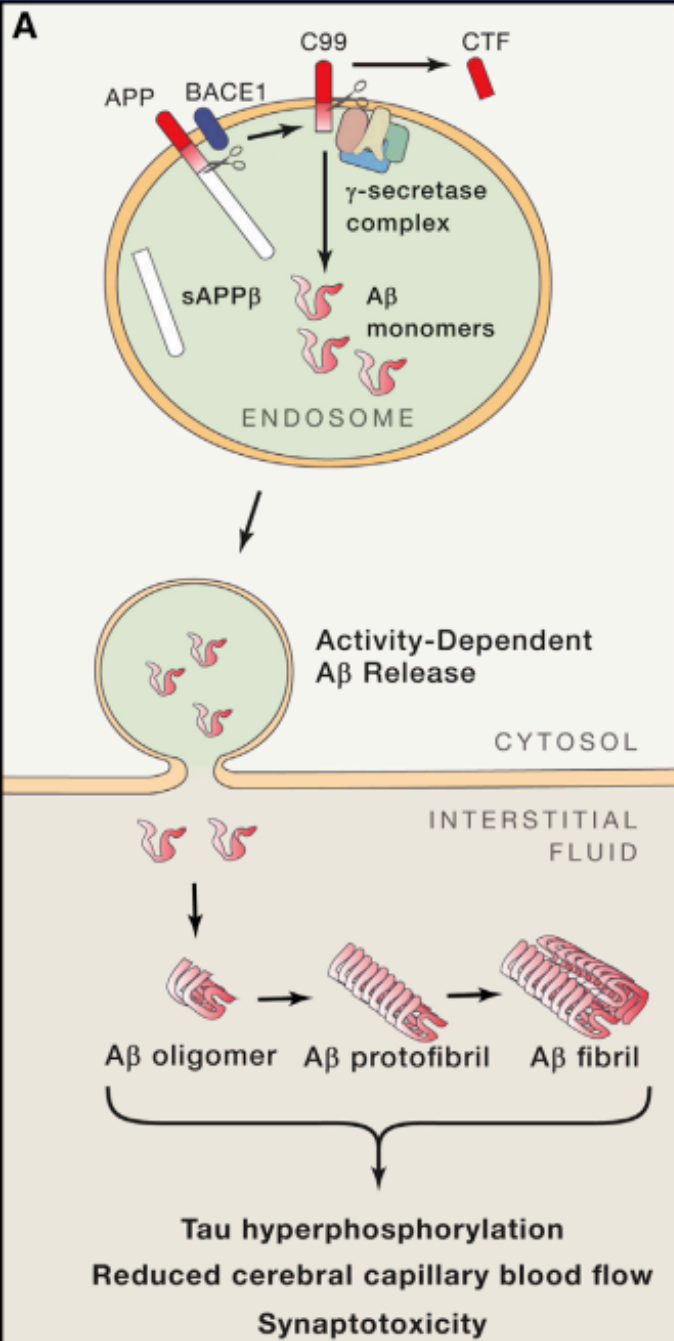
Fisiopatologia



- Emaranhados de neurofilamentos (Proteína Tau-microtúbulos) → hiperfosforilação
- Placas de proteína β -amilóide → APP (amyloid beta precursor protein- super expressão) → Balanço alpha e beta secretases.



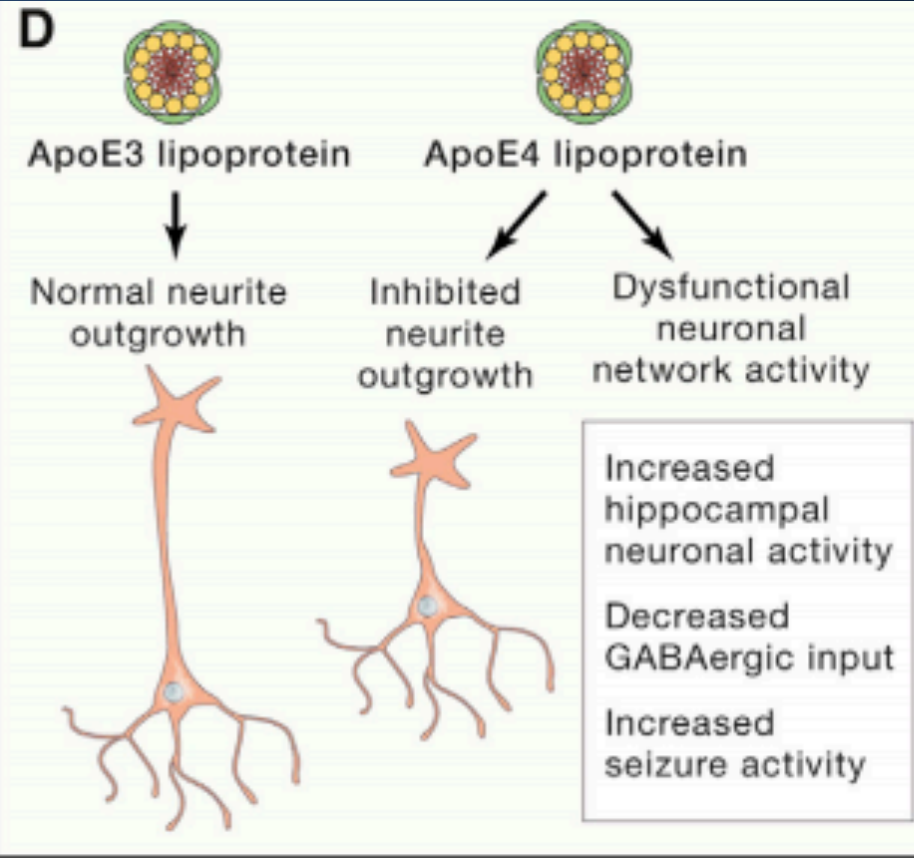
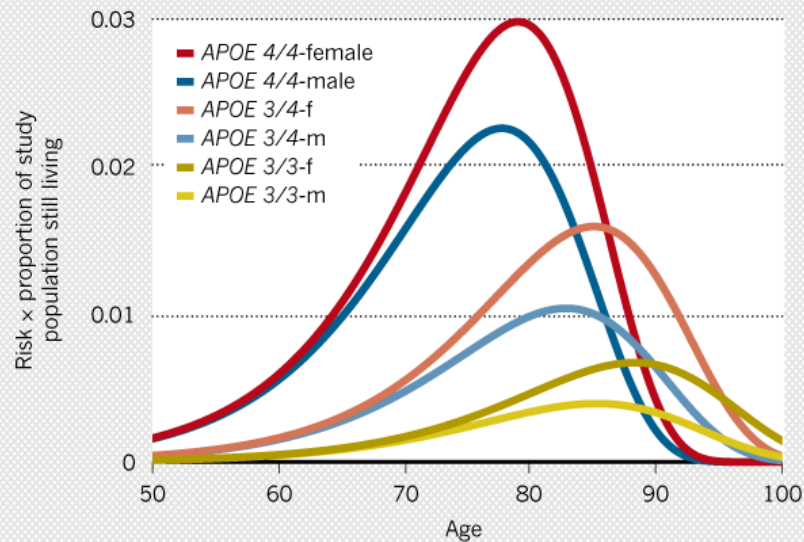
- Alelo APOE $\epsilon 4$ (múltiplas hipóteses): 76% dos casos.



Alelo APOE $\epsilon 4$

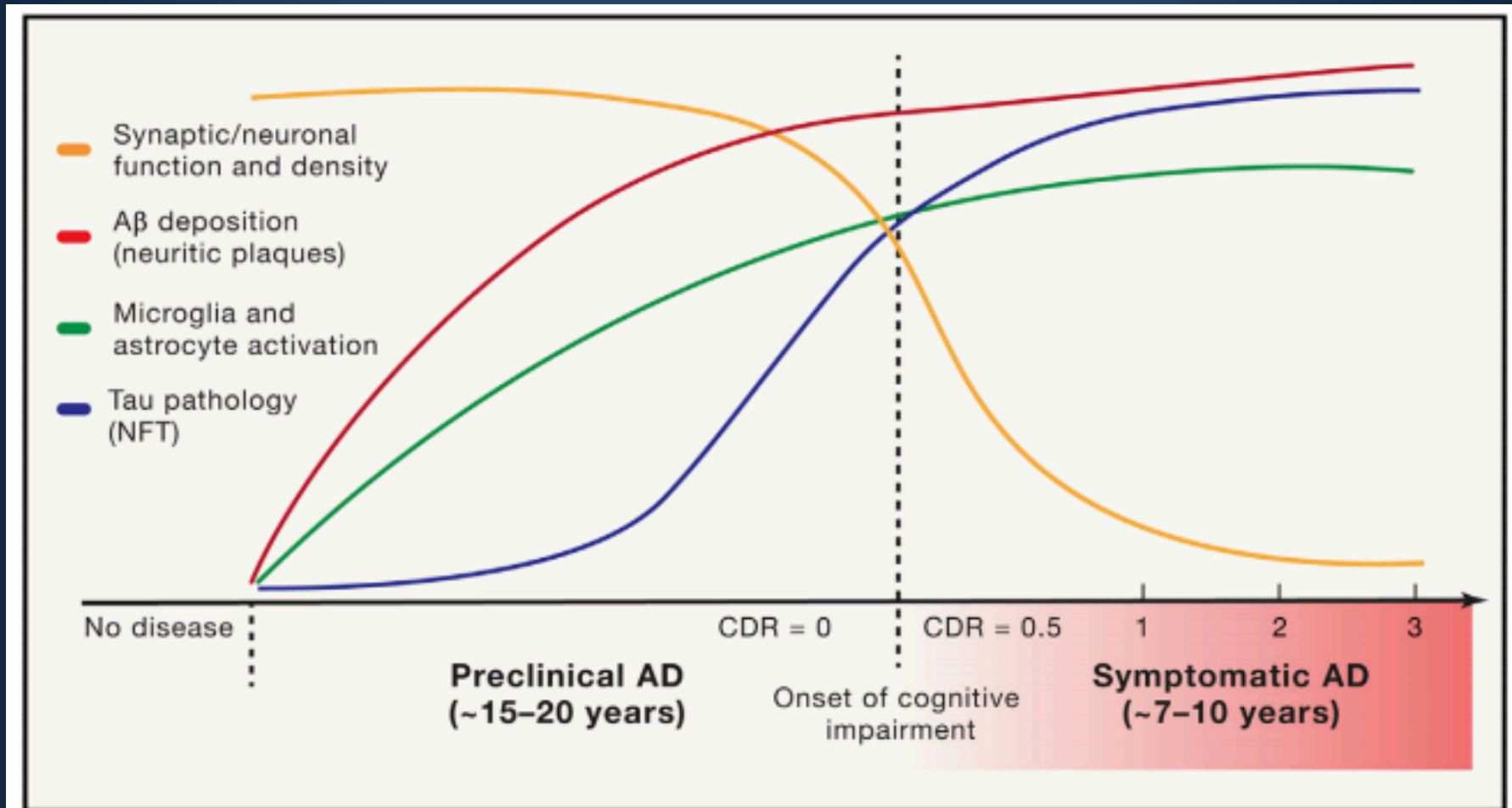
RISKY INHERITANCE

People who carry the gene variant *APOE4* tend to develop Alzheimer's at a younger age than those with two copies of *APOE3*.



Doença de Alzheimer

A deposição e formação da proteína Beta-amilóide e dos emaranhados de neurofilamentos estão diretamente correlacionados com a severidade de DA.



Doença de Alzheimer

Característica: perda de neurônios colinérgicos?

THE LANCET, DECEMBER 25, 1976

Letters to the Editor

SELECTIVE LOSS OF CENTRAL CHOLINERGIC NEURONS IN ALZHEIMER'S DISEASE

THE LANCET, OCTOBER 15, 1977

CHOLINE IN ALZHEIMER'S DISEASE

Department of Perinatal Medicine,
Yale-New Haven Hospital,
New Haven, Connecticut, U.S.A.

Perinatal Intensive Care Unit,
Women's College Hospital,
Toronto, Canada

THOMAS G. MATTHEWS
ZYGMENT M. WILCZEK

ANDREW T. SHENNAN

TABLE I—CHOLINE ACETYLASE (μ mol/h/g WET WEIGHT)

Brain area	Controls (mean $\pm$ S.E.M.) (10)	Alzheimer's			
		A	B	C	% of control (mean)
Hippocampus	0.7 $\pm$ 0.2	0.06	0.05	0.06	8.1
Amygdala	2.0 $\pm$ 0.4	0.08	0.3	0.2	9.6
Parietal cortex	0.5 $\pm$ 0.1	0.15	0.1	0.07	21.0
Sensory cortex	1.0 $\pm$ 0.1	0.03	0.1	0.08	7.0
Occipital cortex	0.5 $\pm$ 0.1	0.05	0.1	0.1	16.6
Frontal cortex	0.7 $\pm$ 0.1	0.2	0.4	0.1	33.3

Níveis de AchE!

VALUES FOR NEOCORTICAL BIOCHEMICAL MARKERS (IN % OF CONTROL VALUES) IN TWO CASES OF PRESENILE DEMENTIA WITHOUT HISTOLOGICAL EVIDENCE OF ALZHEIMER'S DISEASE

Cholinergic system		G.A.B.A. system	
Choline uptake	Choline acetyltransferase activity	G.A.B.A. uptake	Glutamate decarboxylase activity
85 36 (76-124*; n=7)	92 36 (56-144*; n=11)	84 90 (75-125†; n=9)	92 81 (61-139*; n=8)

Alterações não observadas em pacientes com outros tipos de demência senil

Doença de Alzheimer e a neurotransmissão colinérgica: abordagem farmacológica

J Neural Transm (1986) 67: 275–285

Journal of
Neural Transmission

© by Springer-Verlag 1986

Short Notes

Physostigmine Restores ^3H -Acetylcholine Efflux from Alzheimer Brain Slices to Normal Level

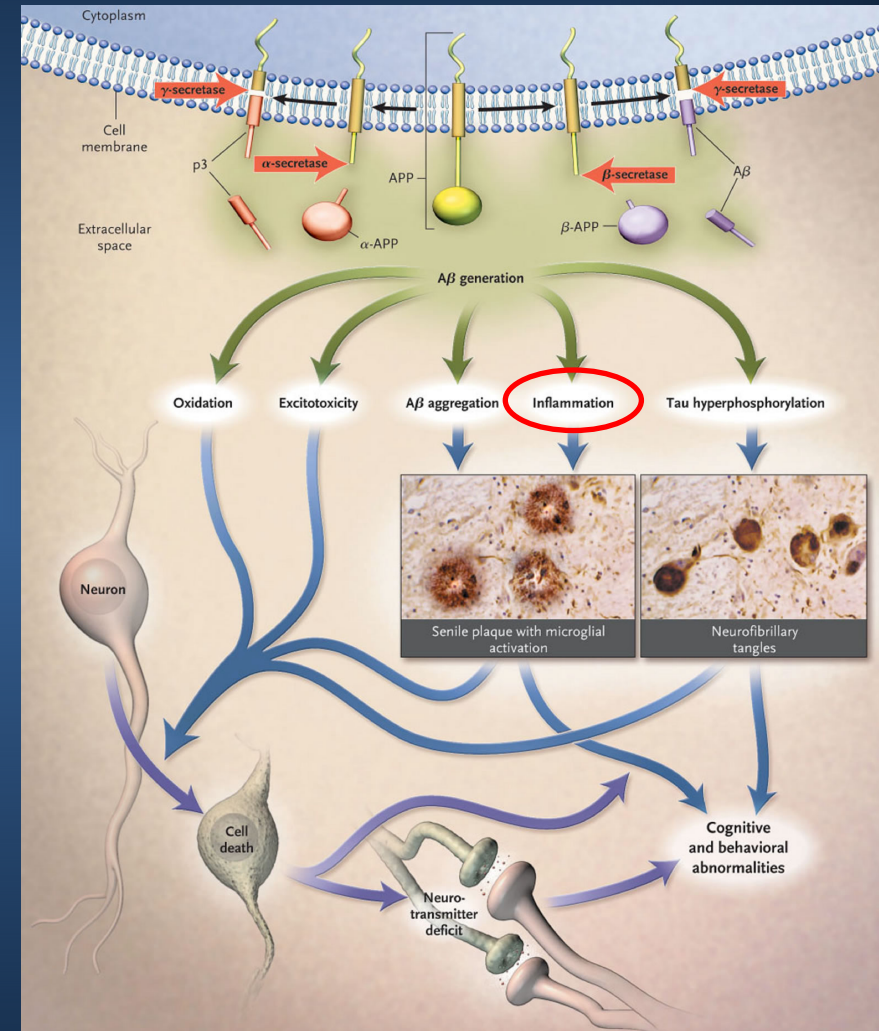
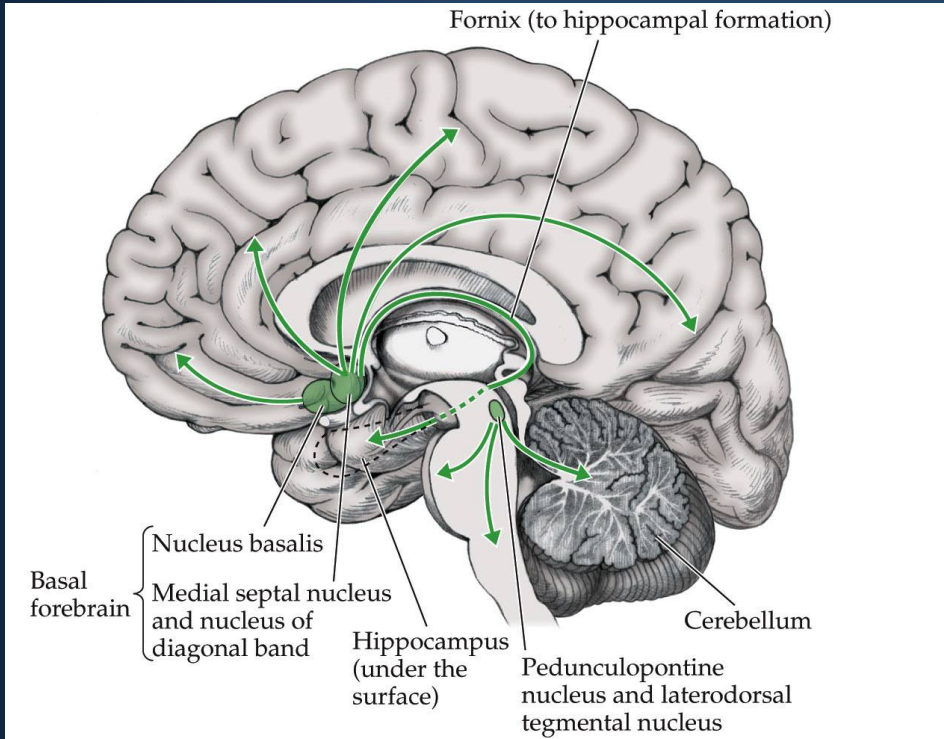
Lena Nilsson¹, Agneta Nordberg¹, J. Hardy²,
P. Wester², and B. Winblad³

Table 3. *Effect of physostigmine 10^{-5} and 10^{-4} M on ^3H release from control and AD/SDAT brain slices at 20 minutes (pmol/g wet weight $\times$ minutes)*

	Physo- stigmine	Basal	35 mM K ⁺	Evoked release
Control				
n=3	—	25.9 $\pm$ 2.2	40.9 $\pm$ 4.1	14.9 $\pm$ 1.9
n=5	10^{-5} M	28.6 $\pm$ 8.9	41.0 $\pm$ 7.9	12.3 $\pm$ 2.8
n=4	10^{-4} M	12.2 $\pm$ 2.4**	21.4 $\pm$ 3.5*	9.2 $\pm$ 2.3
AD/SDAT				
n=3	—	34.3 $\pm$ 2.9	37.4 $\pm$ 4.9	3.4 $\pm$ 2.0
n=3	10^{-5} M	25.1 $\pm$ 7.0	34.0 $\pm$ 9.5	8.9 $\pm$ 3.2
n=3	10^{-4} M	19.2 $\pm$ 3.6*	34.6 $\pm$ 3.1	15.4 $\pm$ 0.7**

Doença de Alzheimer e a neurotransmissão colinérgica: mecanismos neurobiológicos.

Projeções colinérgicas para o córtex e hipocampo, áreas relacionadas com cognição

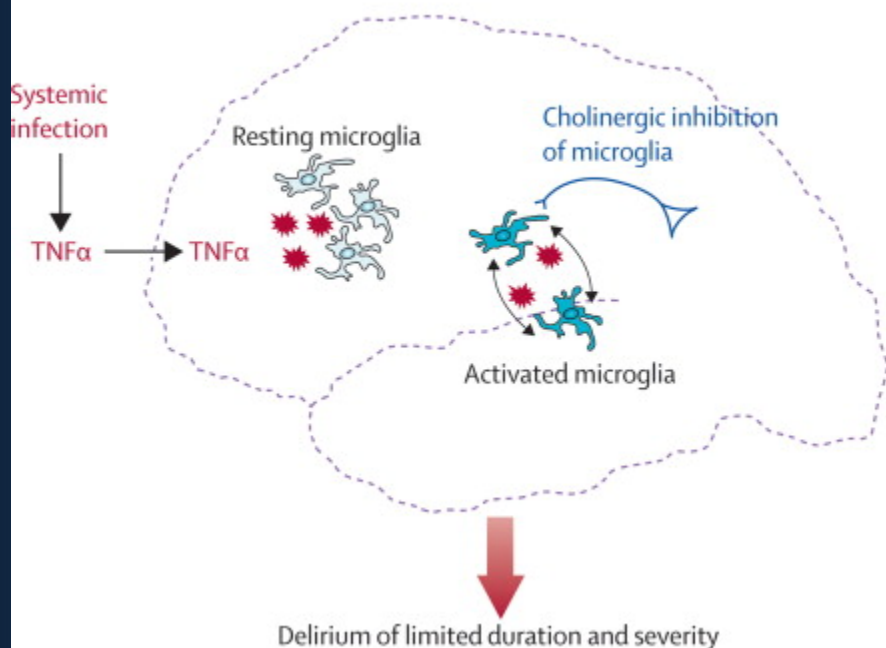


Neurotransmissão colinérgica: eventos plásticos no SNC

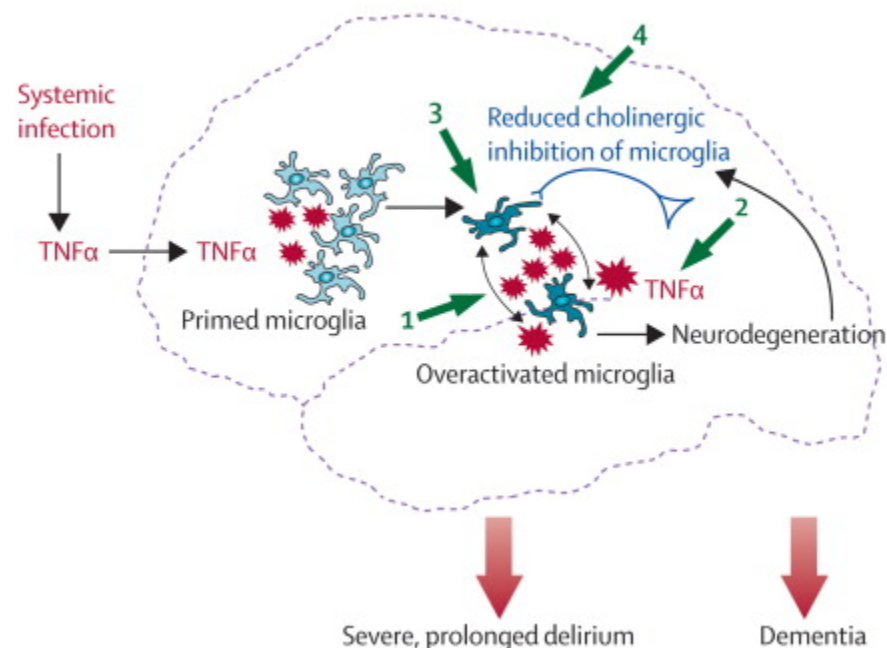
Doença de Alzheimer e a neurotransmissão colinérgica: mecanismo?

Papel inibitório da neurotransmissão colinérgica sobre a ativação da micróglia

A Normal situation



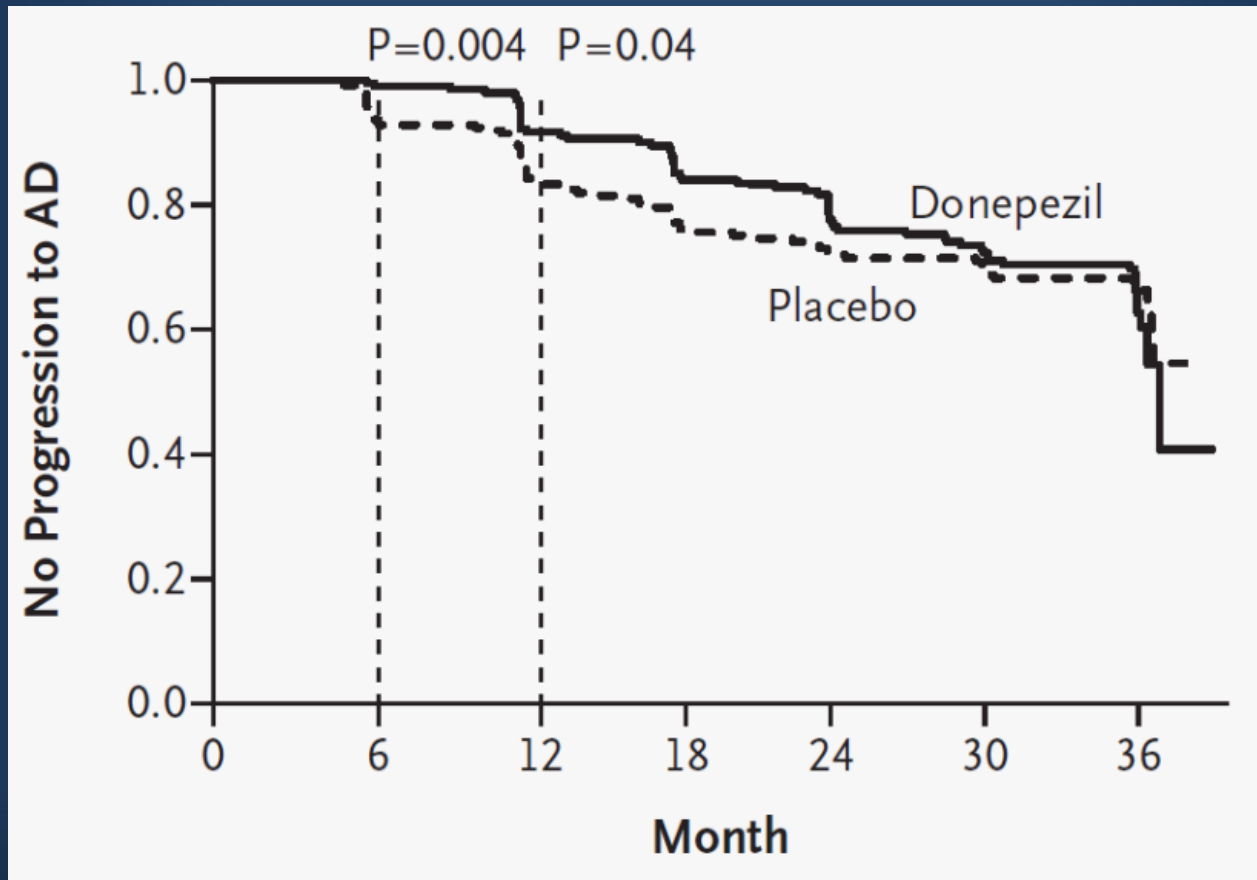
B Old age, incipient neurodegenerative disease, or anticholinergic drug treatment



Doença de Alzheimer

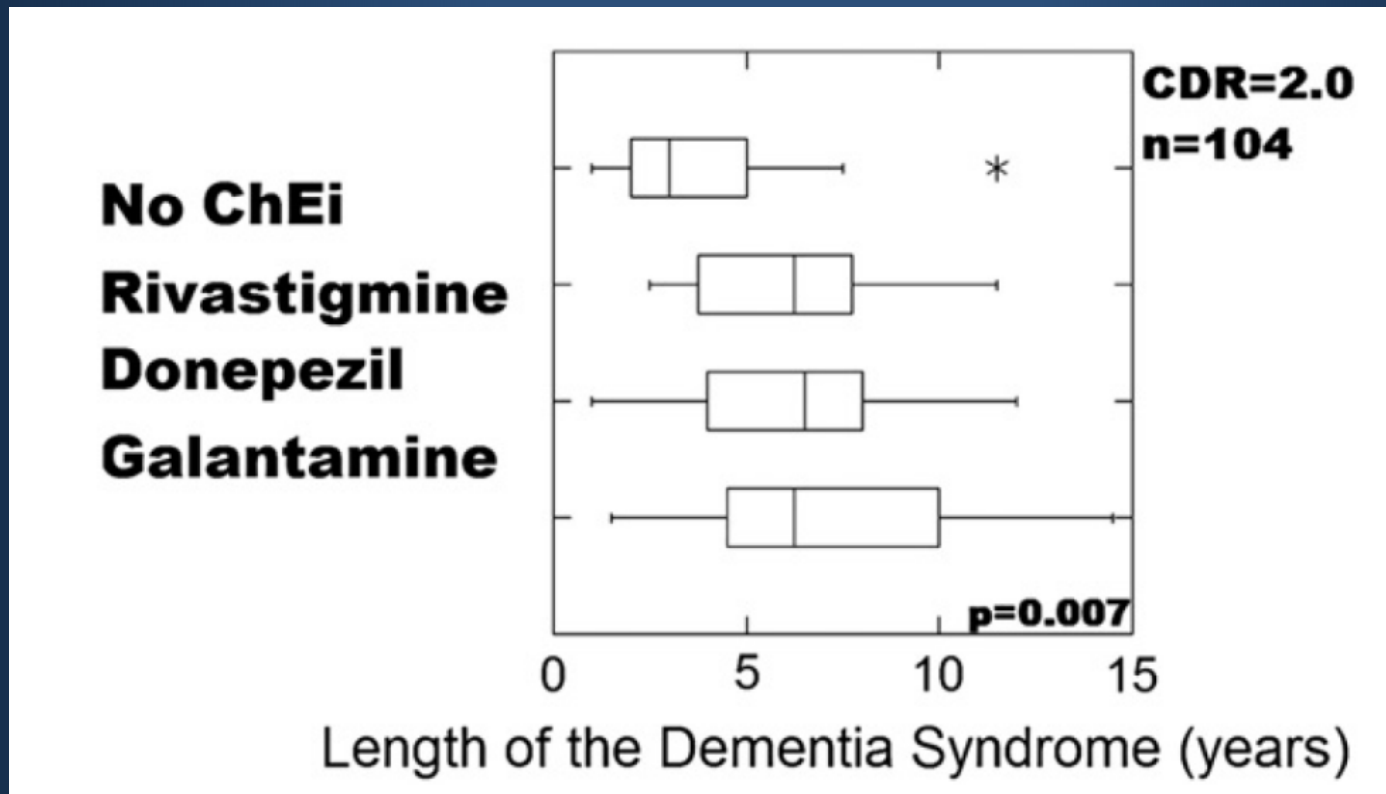
Abordagem farmacológica (aprovados na década de 90)

Inibidores da AchE:



Doença de Alzheimer

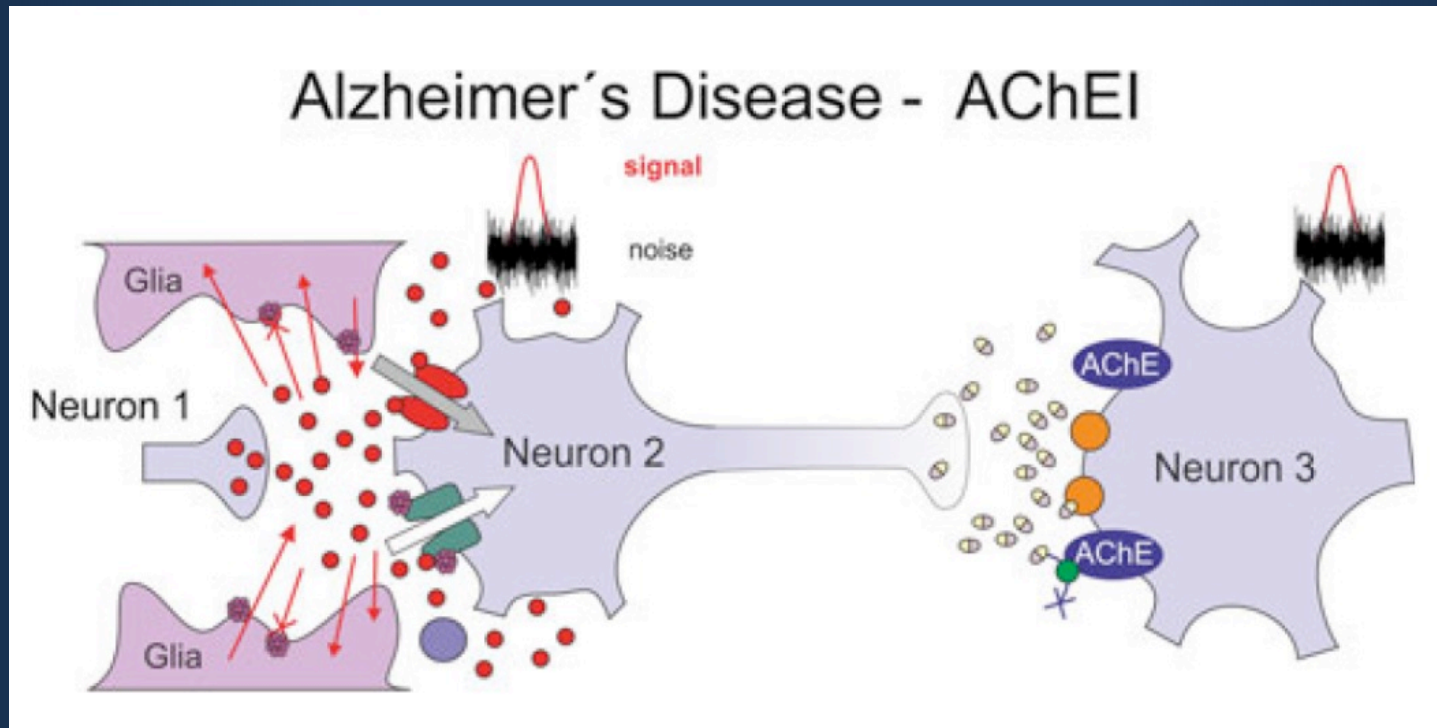
- Abordagem farmacológica
- Inibidores da AchE aumentam a sobrevida dos pacientes



Doença de Alzheimer

Abordagem farmacológica

Inibidores da AchE: Mecanismo de ação



Doença de Alzheimer

Abordagem farmacológica

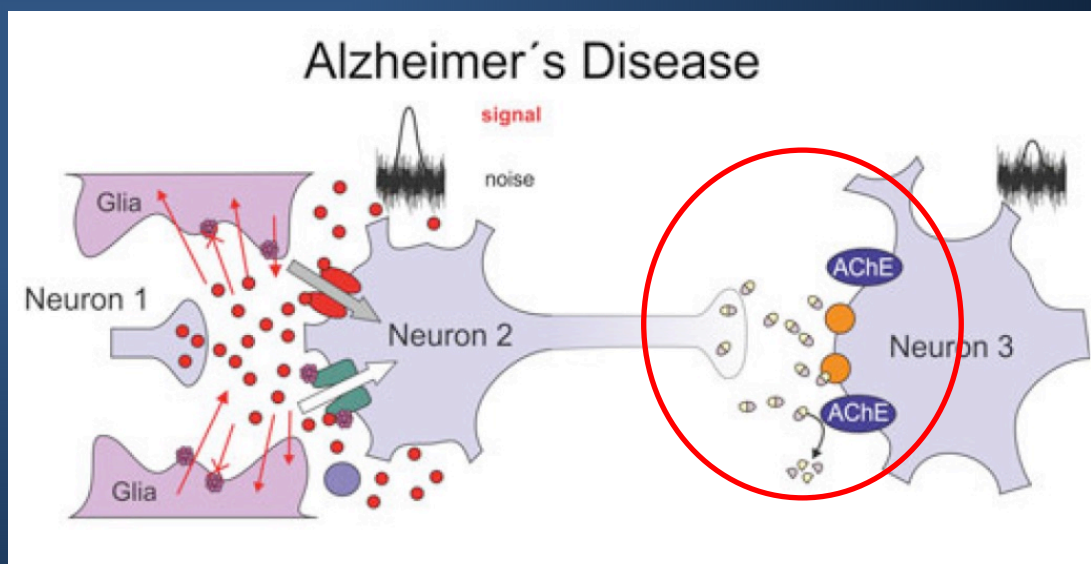
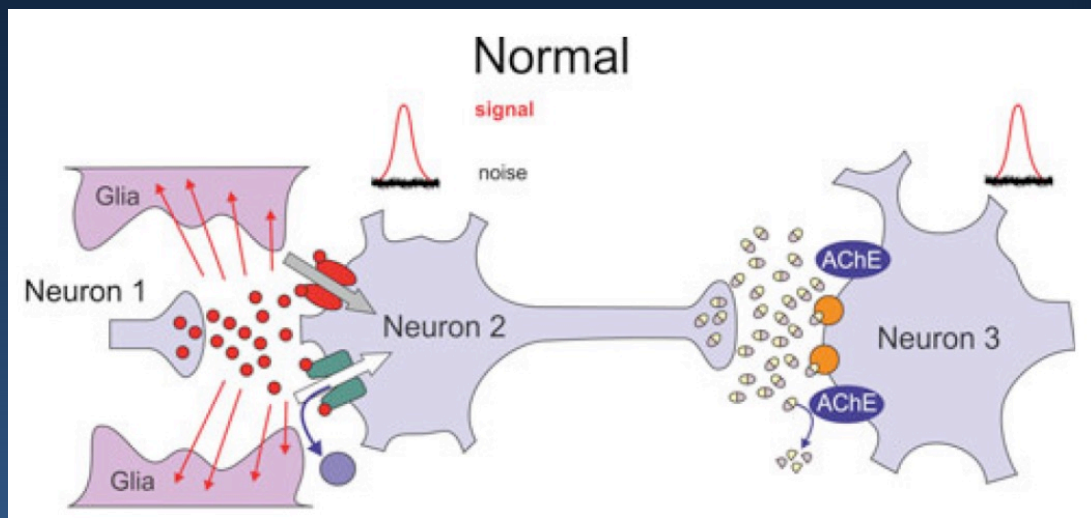
Inibidores da AchE:

- Tacrina: AchE e BuChE → Não competitivo
- Donepezil: AchE → Não competitivo
- Rivastigmina: AchE e BuChE → Não competitivo
- Galantamina: AchE e BuChE → Competitivo e age em receptores nicotínicos.

Doença de Alzheimer

Envolvimento da Neurotransmissão glutamatérgica

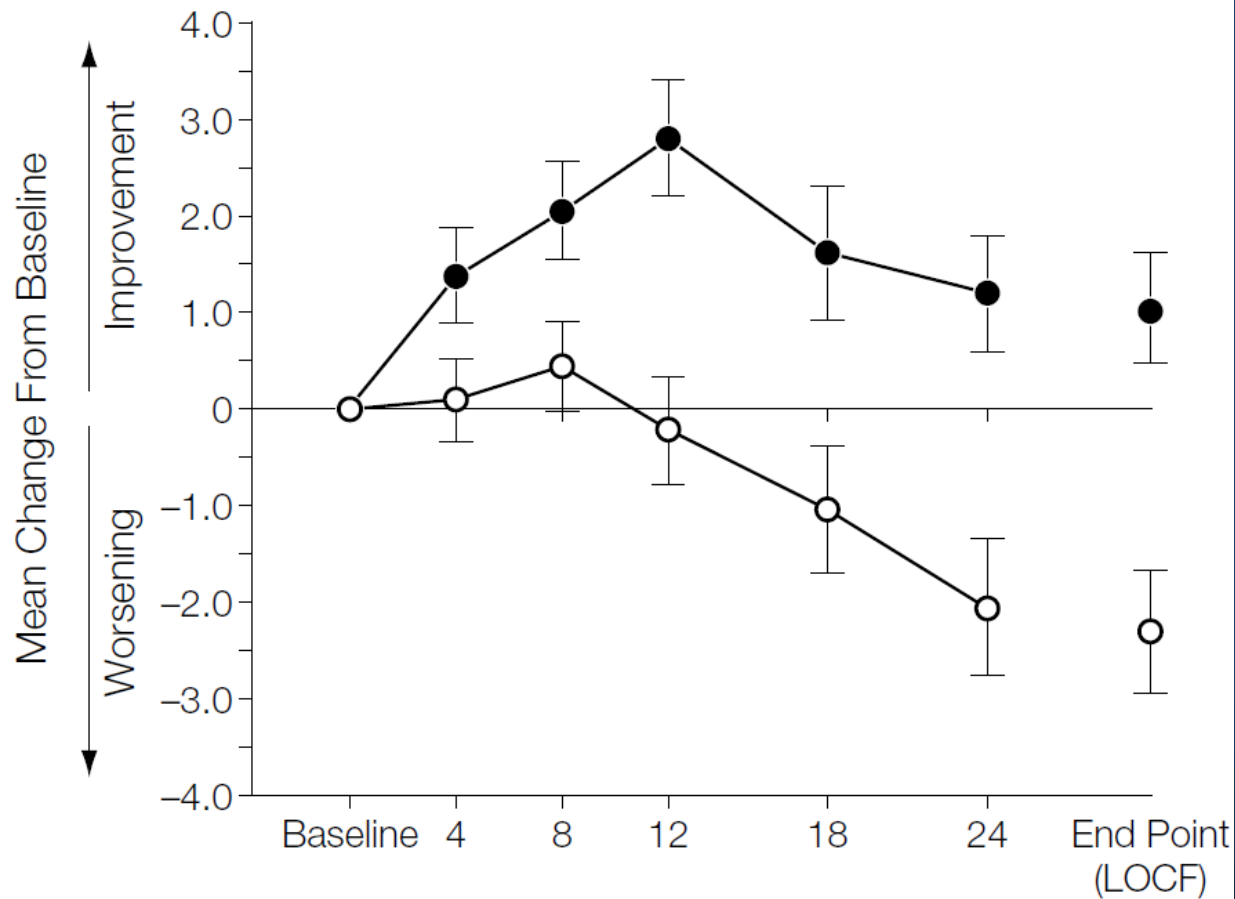
Abordagem farmacológica



Doença de Alzheimer

Abordagem farmacológica

A Memantina

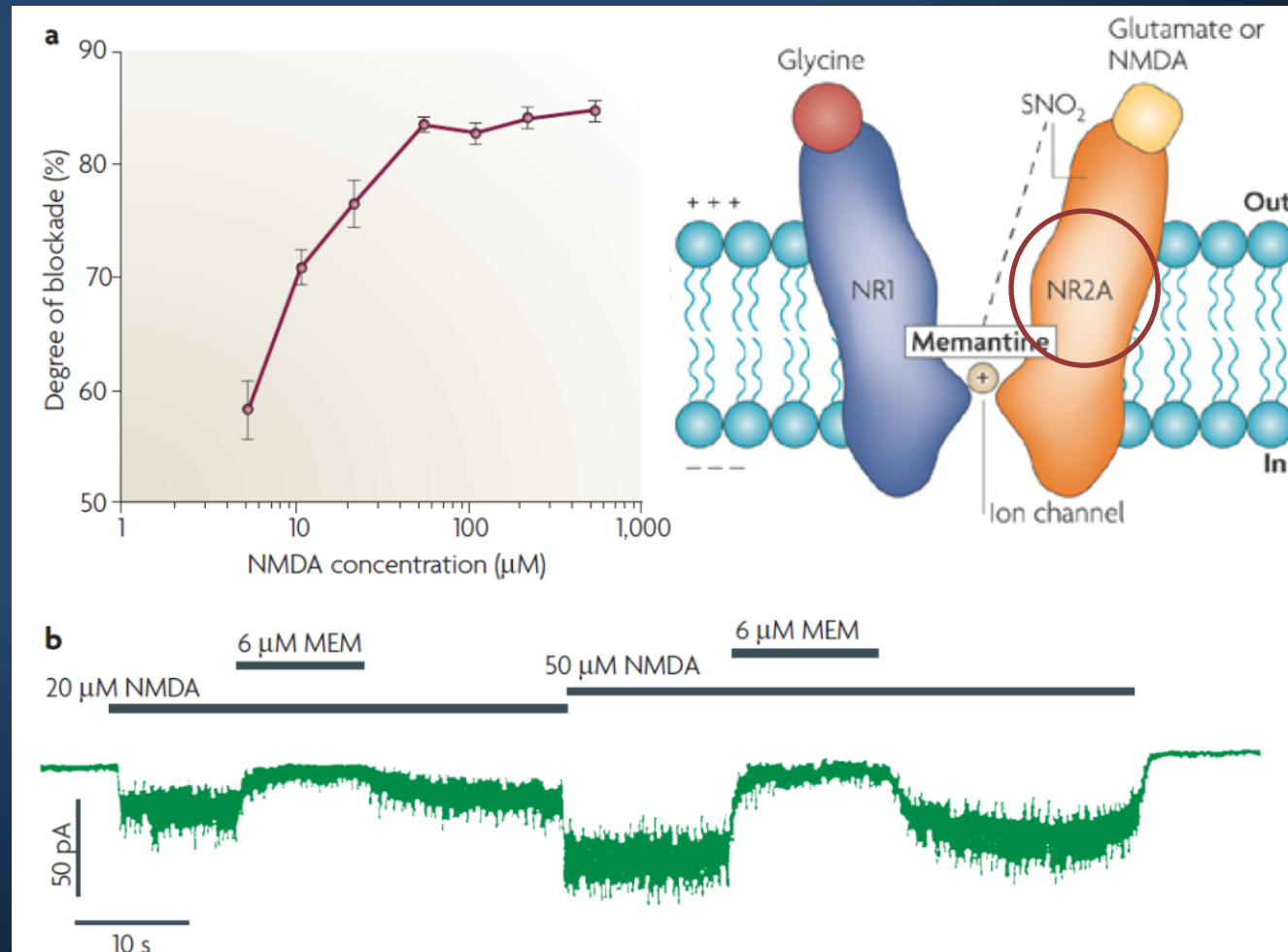


Doença de Alzheimer

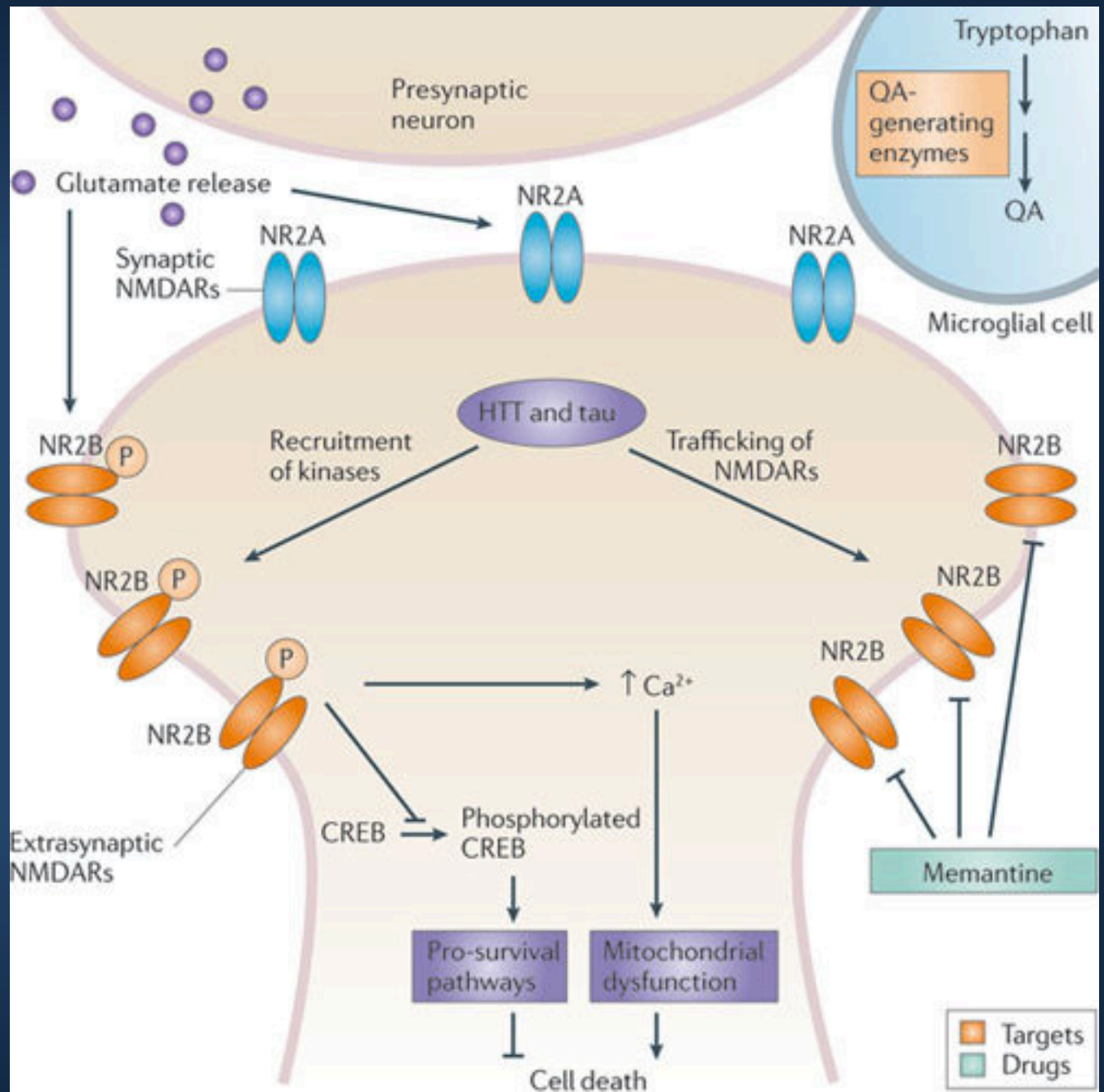
Abordagem farmacológica

Mecanismo de ação da Memantina: antagonista não competitivo de receptores NMDA

A intensidade do bloqueio do receptor NMDA pela memantina e a presença do agonista (glutamato).



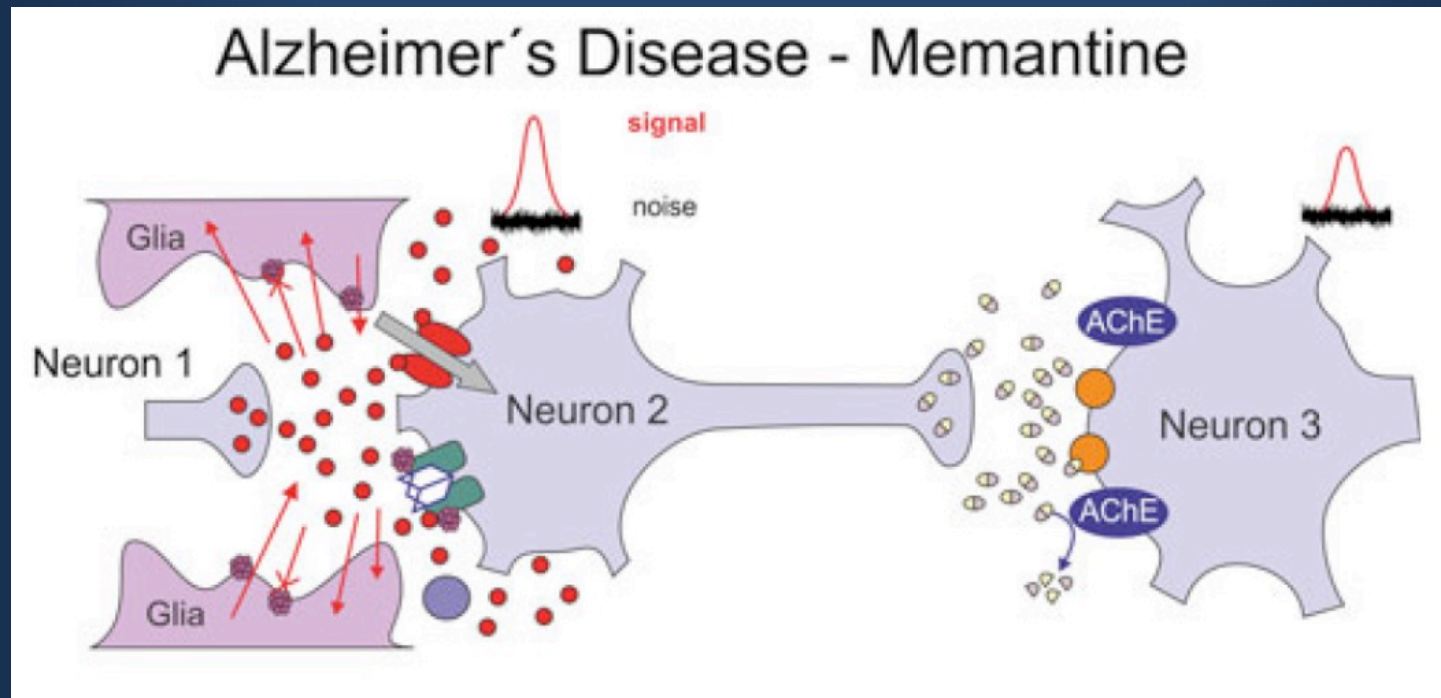
Mecanismo de ação
da Memantina:
Receptores extra-
sinapticos.



Doença de Alzheimer

Abordagem farmacológica

Mecanismo de ação da Memantina: antagonista não competitivo de receptores NMDA



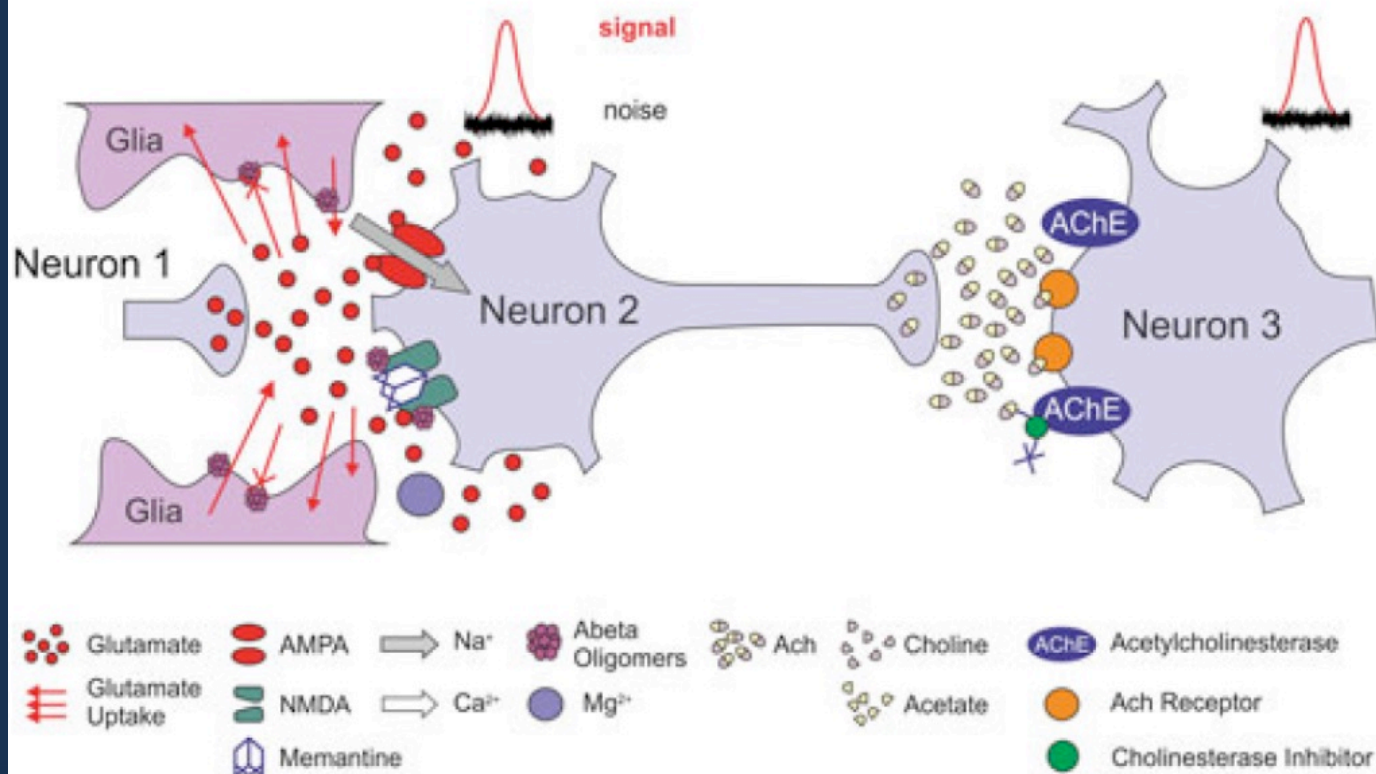
Bloqueio preferencial da atividade excessiva extra sináptica dos receptores NMDA

Doença de Alzheimer

Abordagem farmacológica

Combinação de tratamentos

Alzheimer's Disease - Memantine and AChEI



Doença de Alzheimer

Abordagem farmacológica

Como escolher o melhor tratamento?

Table 2. Efficacy of Cholinesterase Inhibitors and Memantine on the Behavioral Symptoms of Patients with Alzheimer's Disease: Results from Randomized, Placebo-Controlled Trials That Used the Neuropsychiatric Inventory Scale

Drug	Study Duration (mo)	Disease Stage	Baseline MMSE Score	Maximum Dosage (mg/day)	Mean Baseline NPI Score	
					Treatment Group	Placebo Group
Cholinesterase inhibitors						
Donepezil ⁴⁹	6 ^c	Mild to moderate	10–27	10	14.3	15.1
Galantamine ⁵³	5	Mild to moderate	10–22	16	12.4	11.0
				24	11.9	
Donepezil ⁴⁷	6	Moderate to severe	5–17	10	19.6	19.3
Donepezil ⁴³	6	Mild to severe; nursing home study	5–26	10	21.0	20.5
Donepezil ⁵⁷	6	Severe; nursing home study	1–10	10	19.0	19.6
Memantine						
Memantine ⁵⁸	6	Mild to moderate	10–22	20	11.5	12.2
Donepezil + memantine ⁵⁹	6	Moderate to severe	5–14	20	13.4	13.4
Memantine ⁶⁰	7	Moderate to severe	3–14	20	21.4	19.5

MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; SEM = standard error of the mean; NS = not statistically significantly different

Featured Article

Alzheimer's disease drug development pipeline: 2019

Jeffrey Cummings^{a, b}, Garam Lee^b, Aaron Ritter^b, Marwan Sabbagh^b, Kate Zhong^c

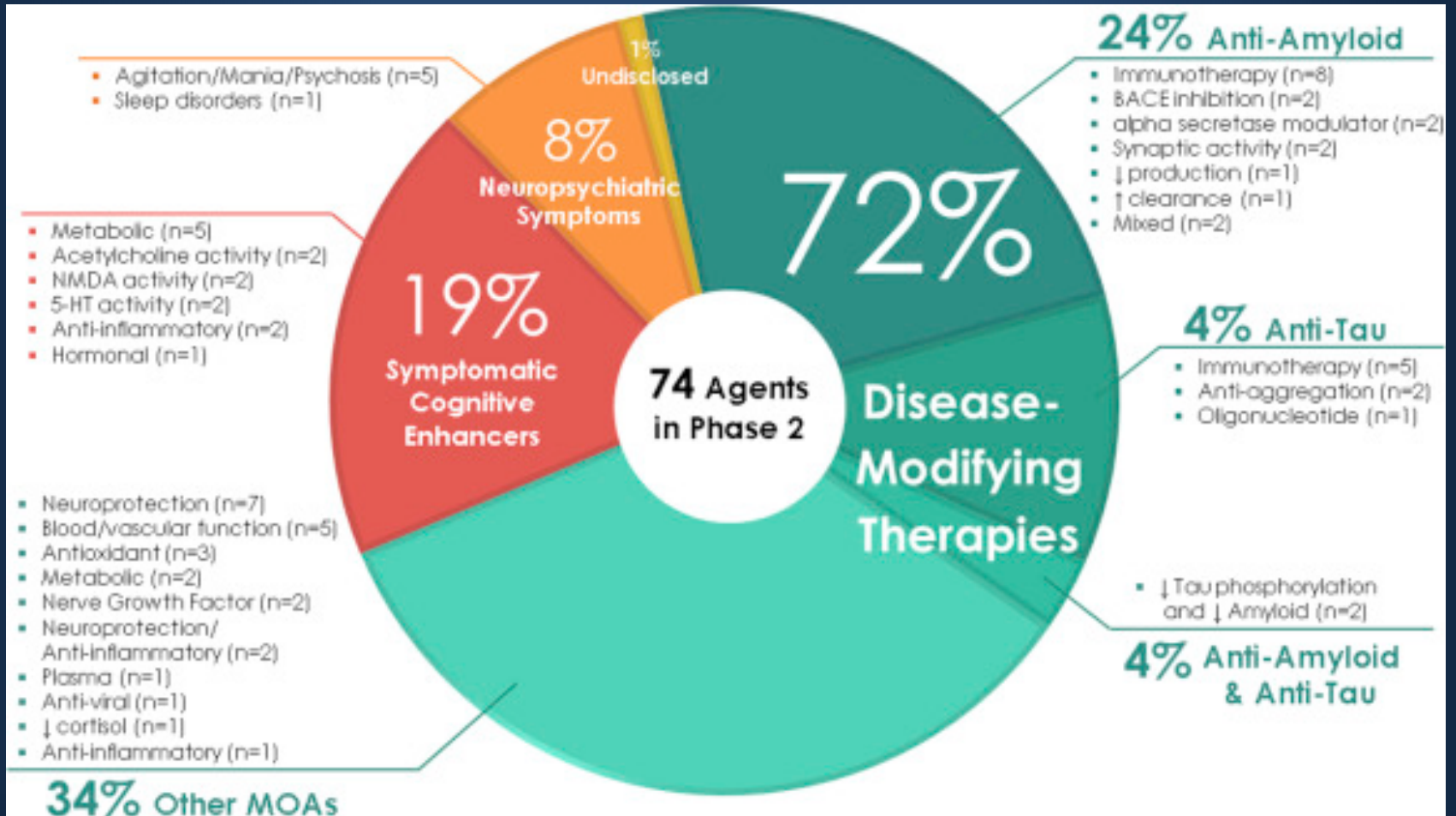
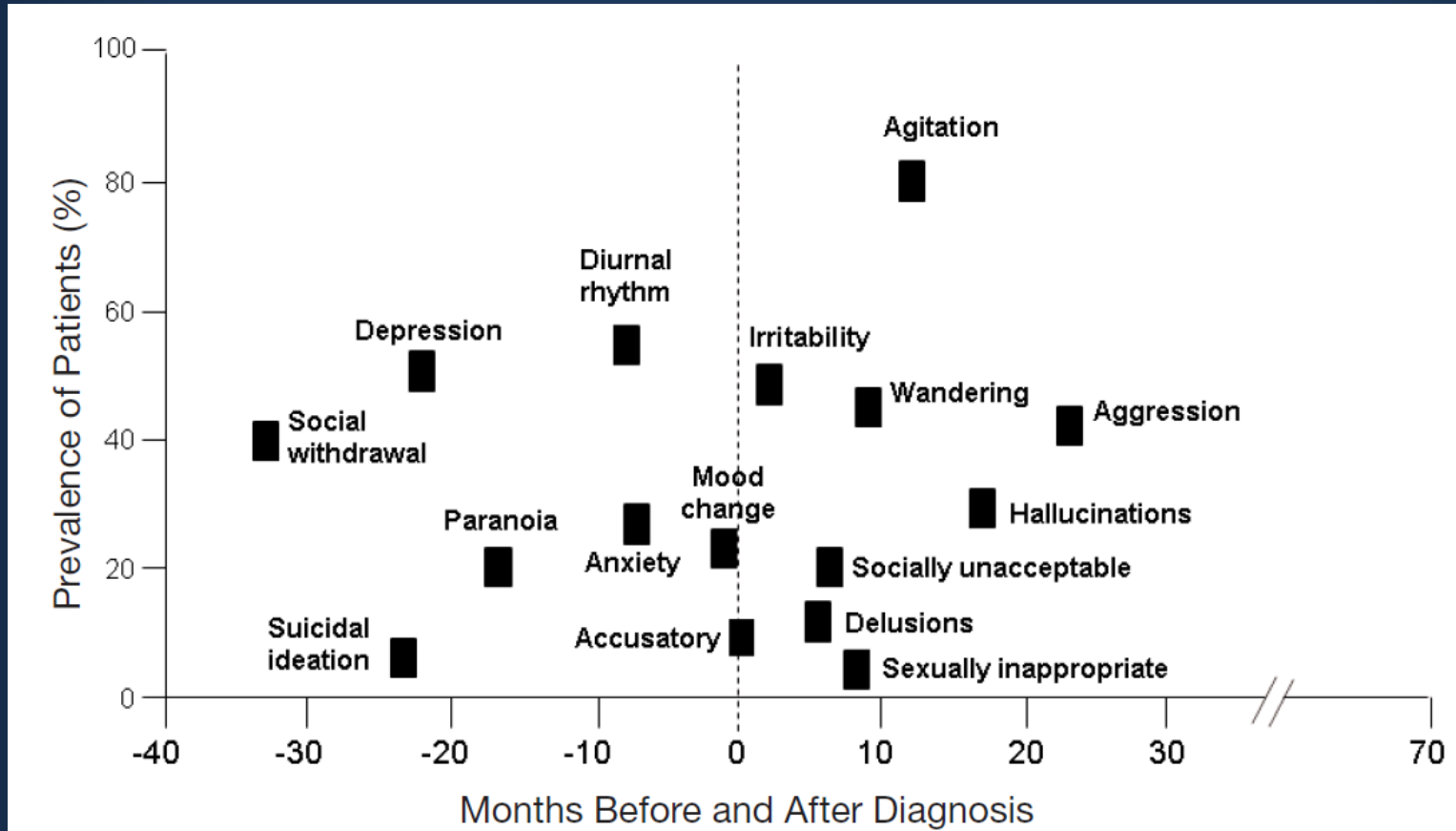


Table 1. Discontinued Phase 3 Disease-Modifying Drug Trials in AD, Excluding ChEI and Memantine Trials

Drug (Study Name)	Study Population	Target/Mechanism	Type of Molecule	Outcome	ClinicalTrials.gov NCT Identifier	Reference
Bapinezumab	Mild-to-moderate AD	Soluble and fibrillar A β	Monoclonal antibody	No effect on cognition or ADL	NCT00575055 NCT00574132	(Salloway et al., 2014)
Solanezumab (EXPEDITION-1, 2 and 3)	Mild-to-moderate AD; mild AD	Soluble monomeric A β	Monoclonal antibody	No effect on cognition or ADL	NCT00905372 NCT00904683	(Doody et al., 2014; Honig et al., 2018)
Crenezumab (CREAD-1/2)	very-mild-to-mild AD with amyloid positive biomarkers	Oligomeric, fibrillar and plaque-based A β	Monoclonal antibody	No effect on cognition or ADL on preliminary analysis	NCT03114657	
Aducanumab (ENGAGE; EMERGE)	Mild AD	Conformation-specific A β aggregates	Monoclonal Antibody	No change in rate of cognitive decline	NCT03639987	(Selkoe, 2019)
AN-1792	Mild-to-moderate AD	Active immunization	Full-length A β 42 immunogen	Trial halted due to development of meningoencephalitis in 4 patients	NCT00021723	
Semagacestat (IDENTITY-1/2)	Mild-to-moderate AD	γ -secretase inhibitor	Small molecule	No effect on cognition or ADL; increased risk of skin cancer	NCT01035138 NCT00594568	(Doody et al., 2013)
Tarenflurbil	Mild AD	γ -secretase modulator	Small molecule	No effect on cognition or ADL	NCT00105547	(Green et al., 2009)
CNP520 (Umibecestat) (API Generation)	Cognitively normal APOE ϵ 4/ ϵ 4 carriers	BACE1 inhibitor	Small molecule	Worse cognitive performance, weight loss	NCT03131453 NCT02565511	(Lopez Lopez et al., 2019)
Lanabecestat (AMARANTH; DAYBREAK-ALZ)	Very-mild-to-mild AD	BACE1 inhibitor	Small molecule	No effect on cognition or ADL	NCT02783573 NCT02245737	
Atabecestat	Preclinical AD; positive amyloid, normal cognition	BACE1 inhibitor	Small molecule	Worse performance on some cognitive tests; in some cases, prominent side effects	NCT02569398	(Henley et al., 2019)

Doença de Alzheimer

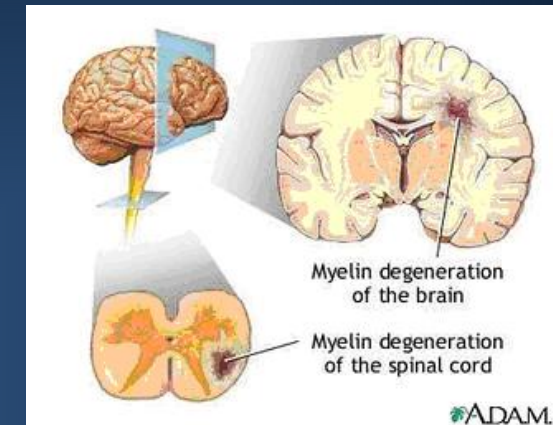
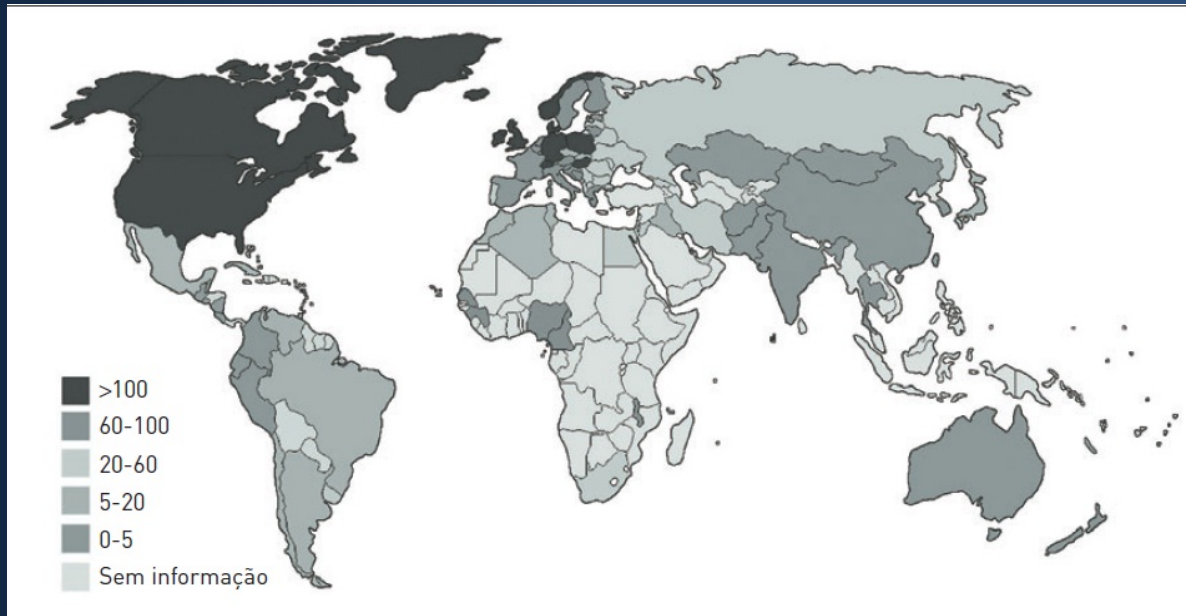
Outros sintomas além dos cognitivos: Síndrome Comportamental



- Antipsicóticos atípicos (aumentam risco de AVE- afinidade por receptores alpha-2 adrenérgicos e Muscarínicos do tipo 1- M1 ??);
- antidepressivos, carbamazepine.

Esclerose Múltipla

- A incidência mundial é de 2,5 milhões de pessoas;
- Brasil : prevalência média é de aproximadamente 15 casos/100.000 habitantes → Sul e Sudeste.



Causas?

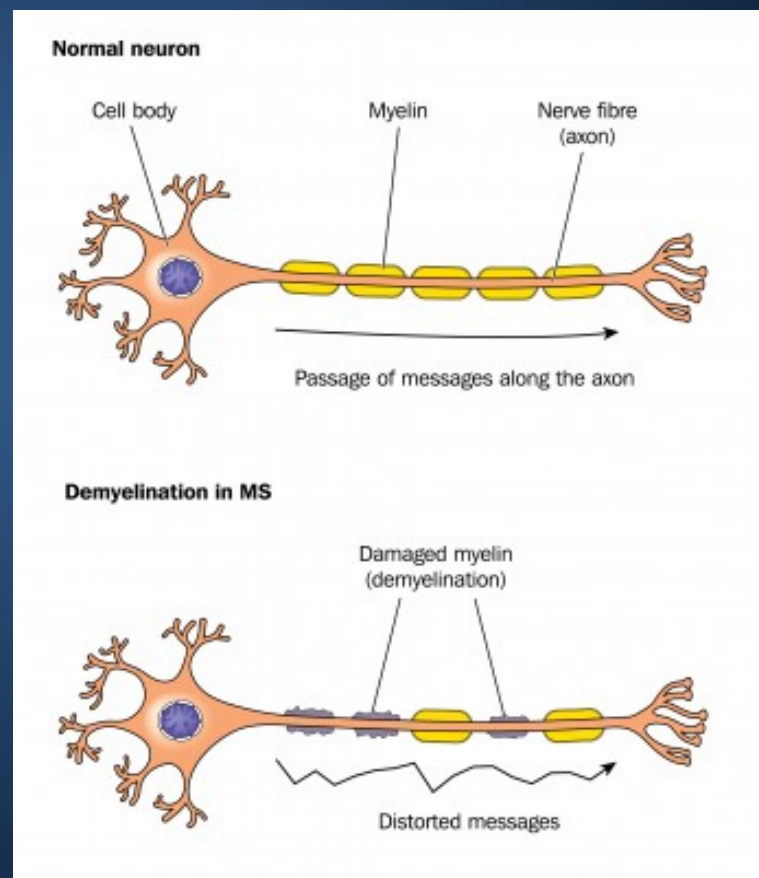
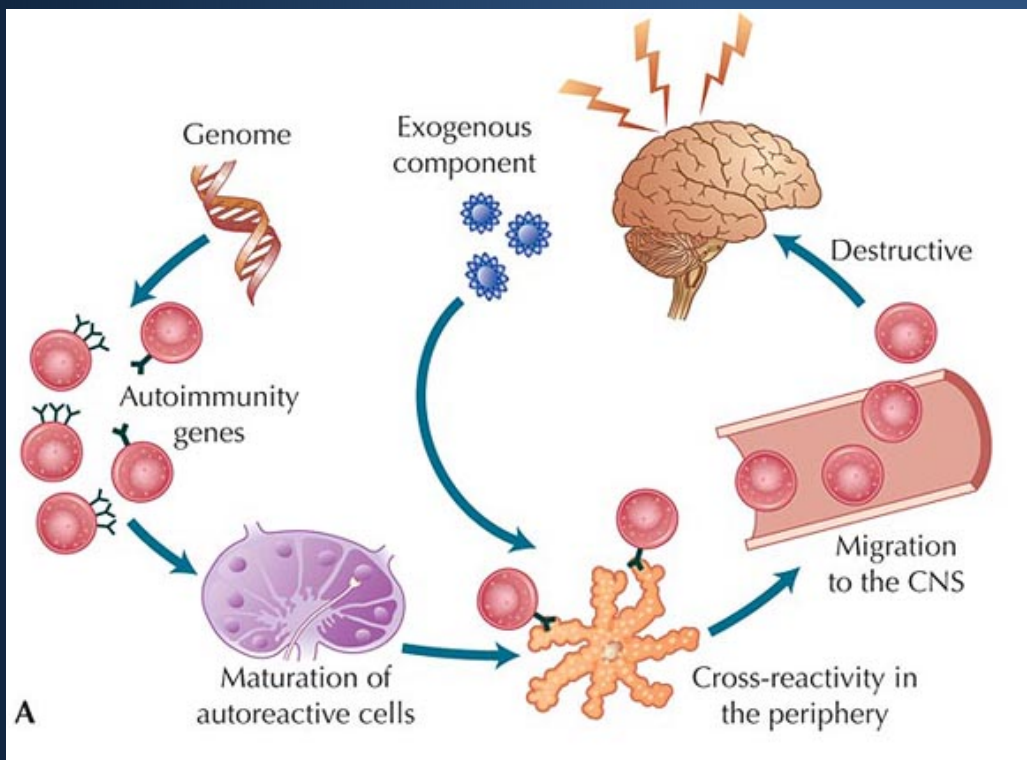
- Ambientais (climas mais frios), infecciosas (Sarampo, Clamidia, herpes virus, Epstein-Barr), genéticos.

Mais prevalente em mulheres e adultos jovens.

Esclerose Múltipla

- Doença autoimune

Produção de auto-anticorpos contra a mielina produzida pelos oligodendrócitos - ≠ Células de Schwann.



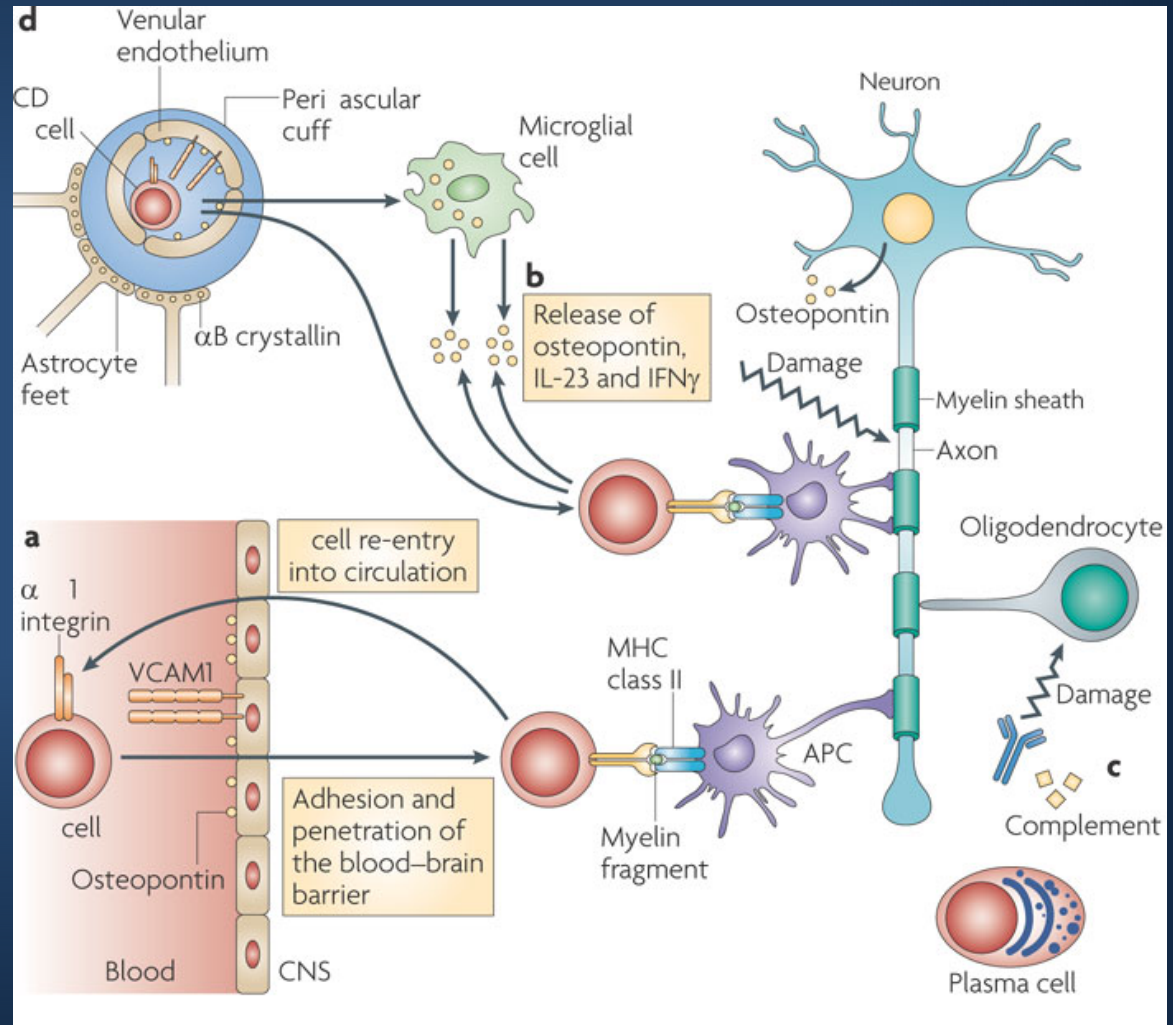
Esclerose Múltipla

Mecanismo: Imunidade inata e adaptativa

_Linfócitos T no SNC →
secretam citocinas + células
apresentadoras de antígenos
→ oligodendrócitos;

_Células B (plasmáticas)
produzem auto-anticorpos
(contra mielina);

_astrócitos → integridade
BHE.



Expressão de receptores de integrinas reconhecido pela BHE.

Esclerose Múltipla

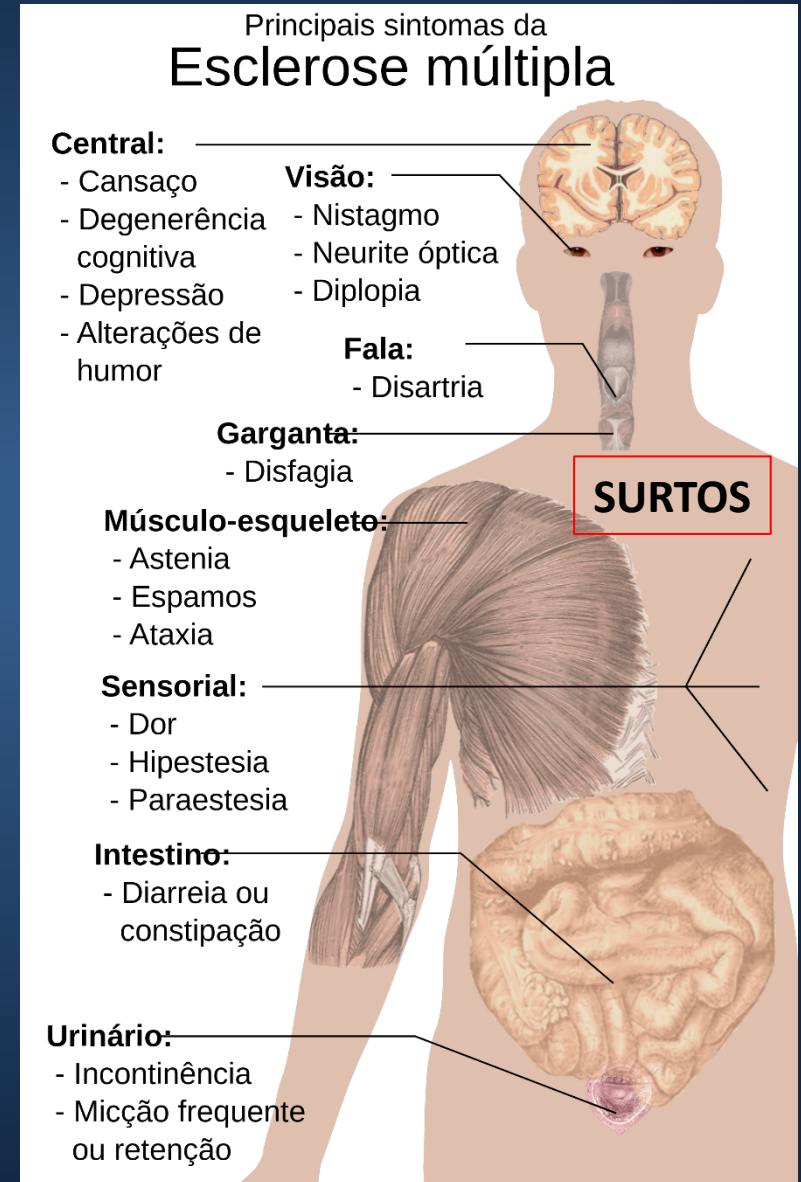
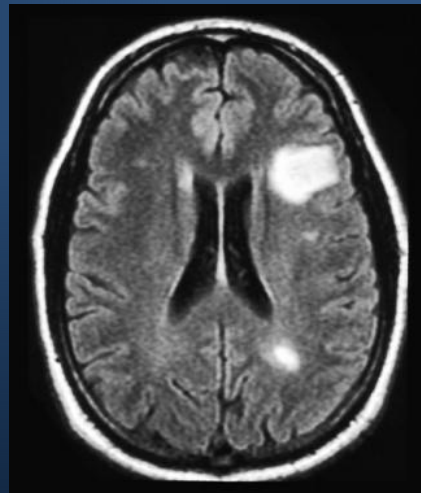
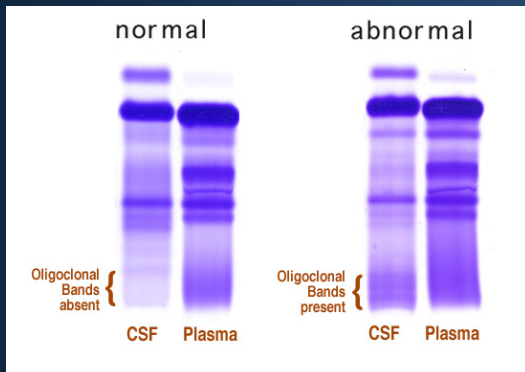
Sintomas

Similar a várias patologias →
Dificuldade no diagnóstico (testes sanguíneos)

Principais sinais para o diagnóstico:

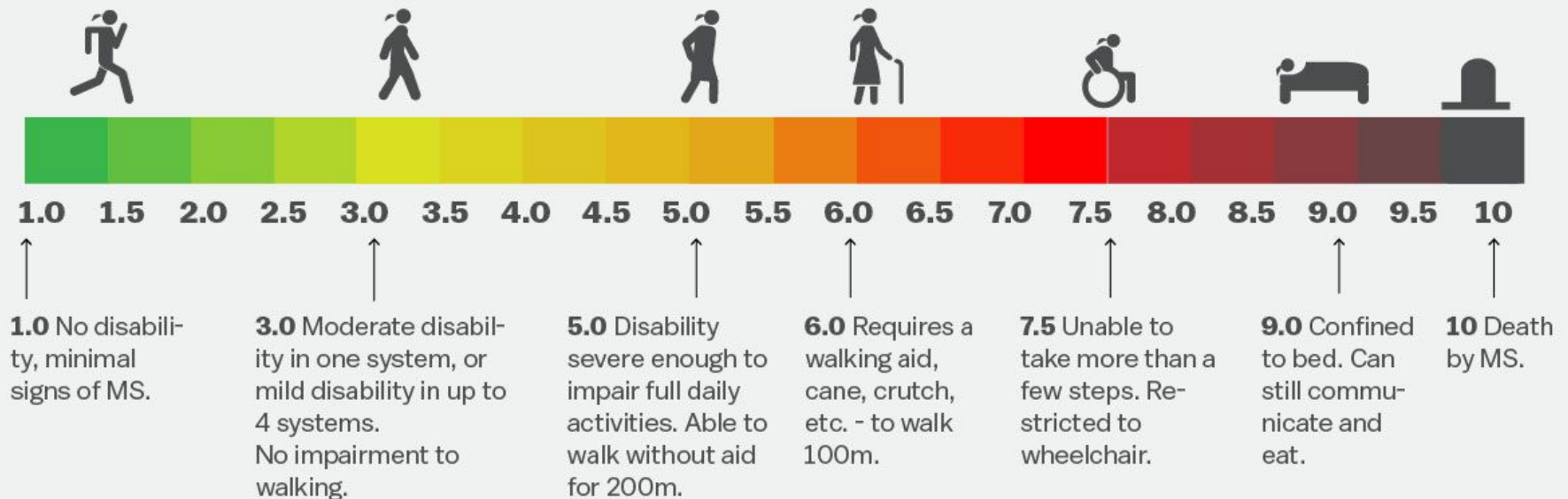
Bandas oligoclonais (LICOR);

Doença multifocal de substância branca no cérebro e na medula espinhal (Vistos através de exames de ressonância magnética)



How multiple sclerosis progresses

The Expanded Disability Status Scale (EDSS) is a method of quantifying disability in multiple sclerosis and monitoring changes over time. It is widely used in clinical trials and in the assessment of people with MS.

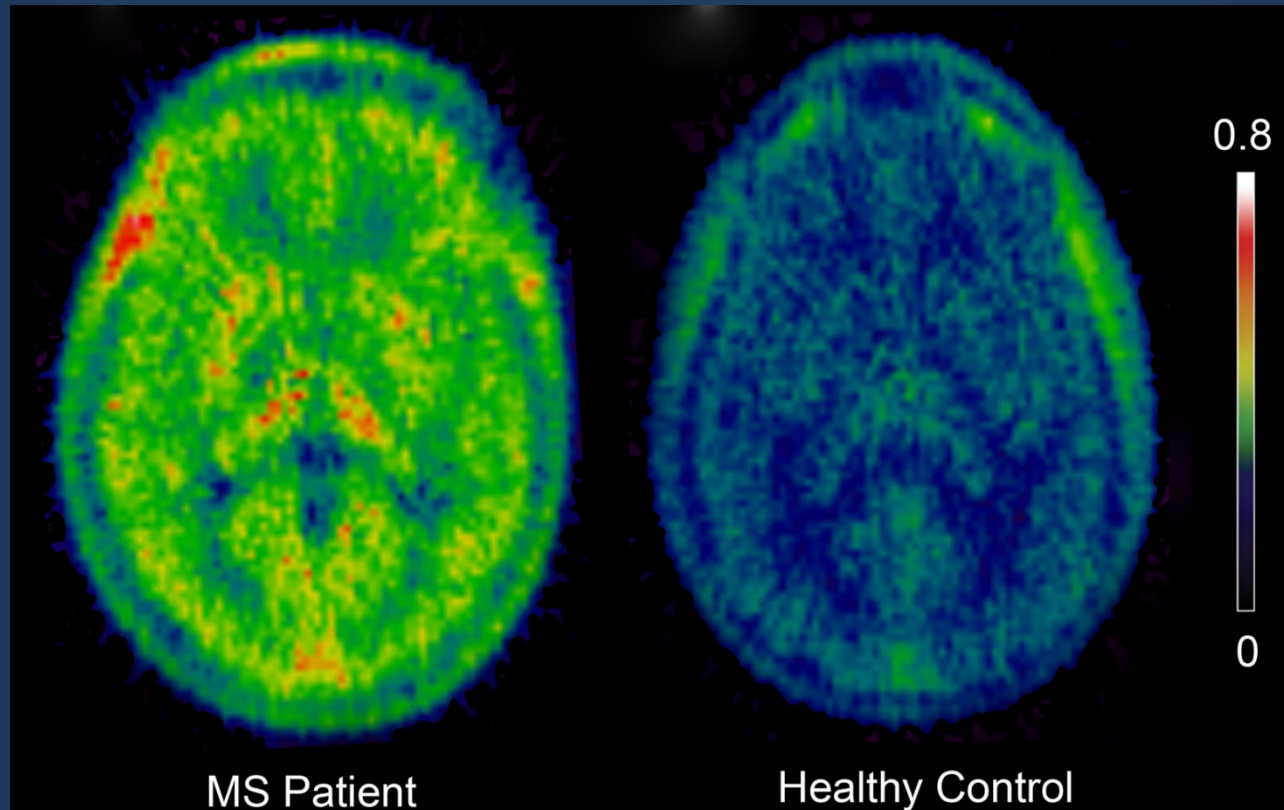


SOURCE: mstrust.org.uk

Vox

Esclerose Múltipla

Aumento da ativação da micróglia em pacientes com diagnóstico de esclerose múltipla



Detecção da proteína translocadora 18 kDa → relacionada com a produção de citocinas pró-inflamatórias e da ativação da micróglia

Sistema Nervoso Central “mais inflamado???”

Treat early



Disability

Disease
Onset

Treatment
at diagnosis

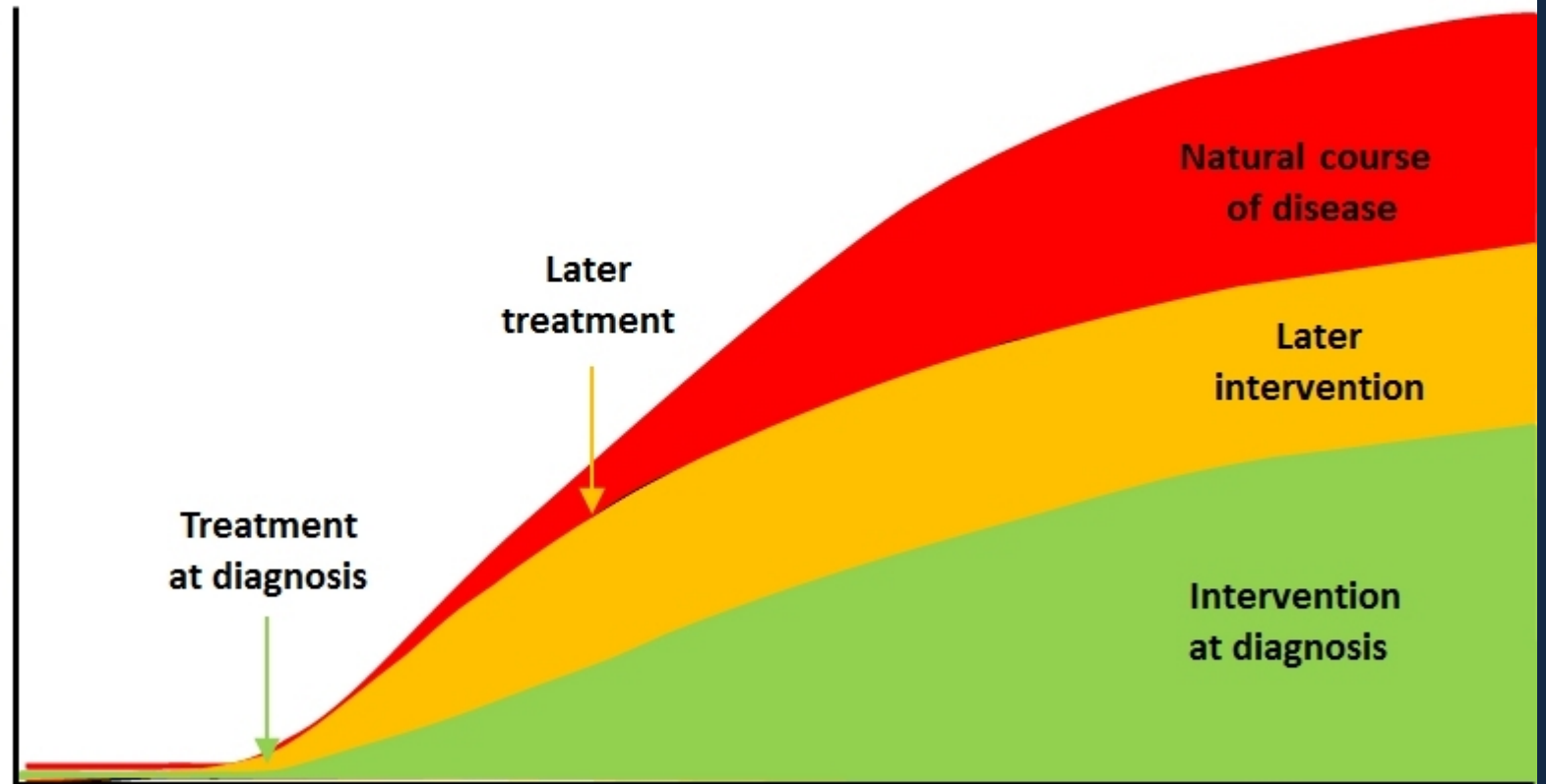
Later
treatment

Natural course
of disease

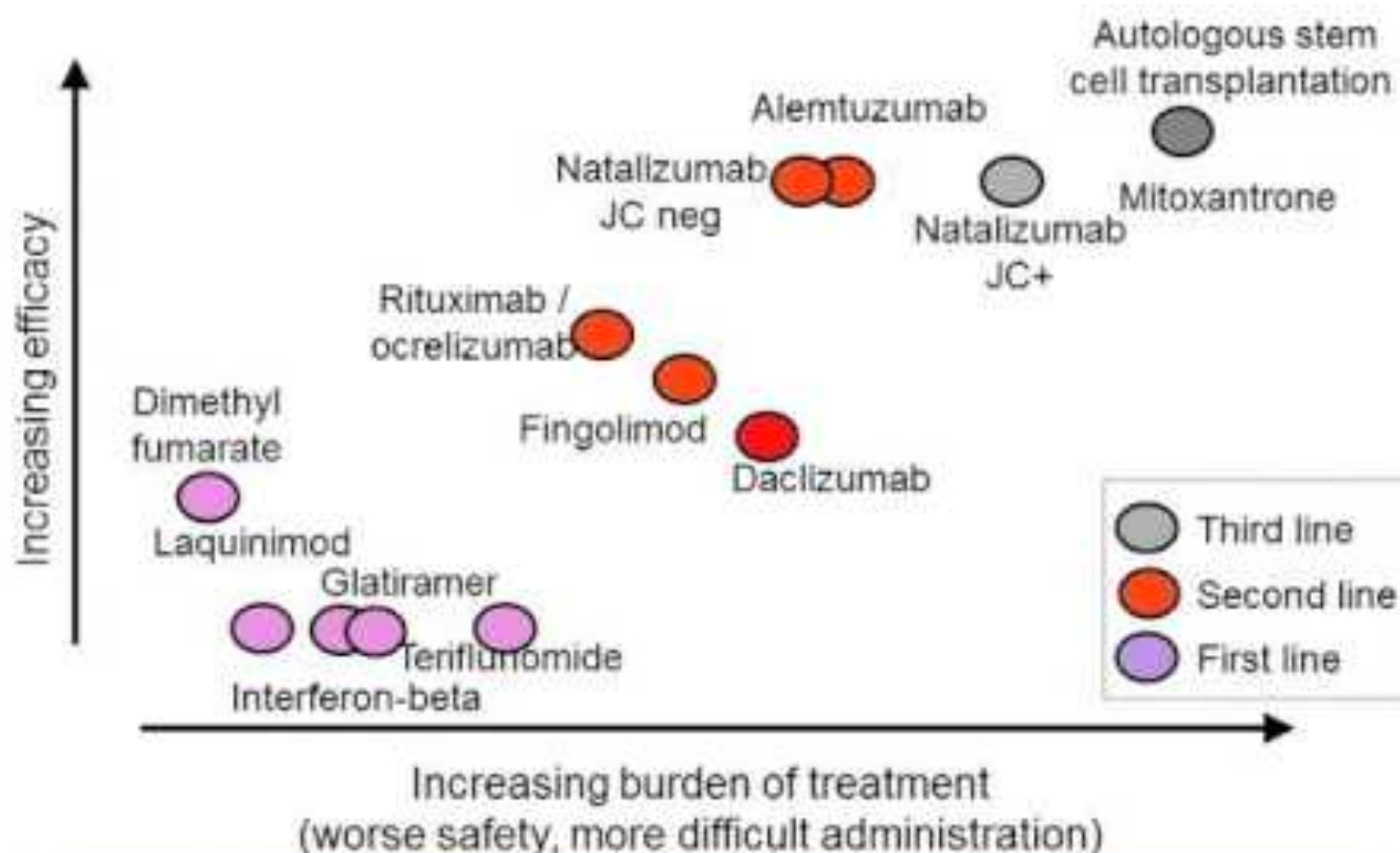
Later
intervention

Intervention
at diagnosis

Time



First, Second and Third Line Therapies



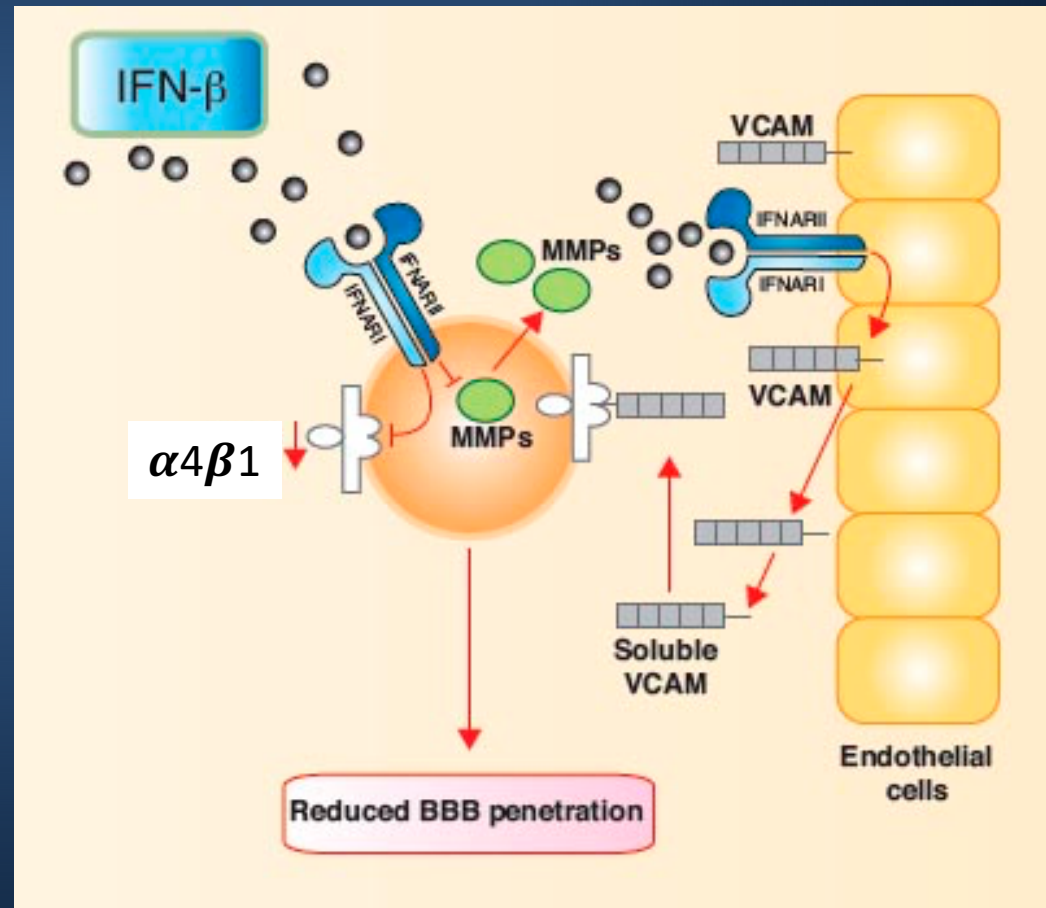
Esclerose Múltipla

Tratamentos farmacológicos (Primeira linha)

Interferon β -1a (Avonex[®] - I.M); Interferon β -1b (Betaseron[®]) (S.C)

Mecanismos:

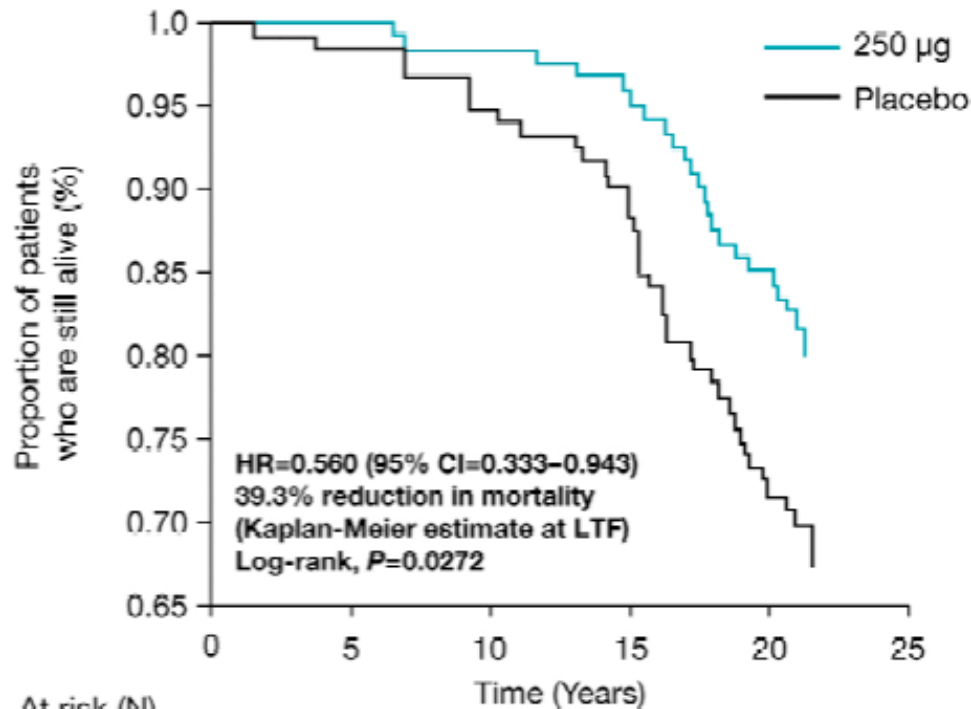
Inibição da diapedese e das das metaloproteinases (degradam matriz extracelular $\rightarrow$ quebra da BHE).



Esclerose Múltipla

Tratamentos farmacológicos (Primeira linha)

Interferon β -1a (Avonex[®]- I.M.); Interferon β -1b (Betaseron[®])
(S.C.)



At risk (N)					
IFN β -1b 250 μ g	124	124	121	117	103
Placebo	123	120	117	109	88

Varios efeitos adversos:
Necrose cutânea
Leucopenia
↓ função hepática

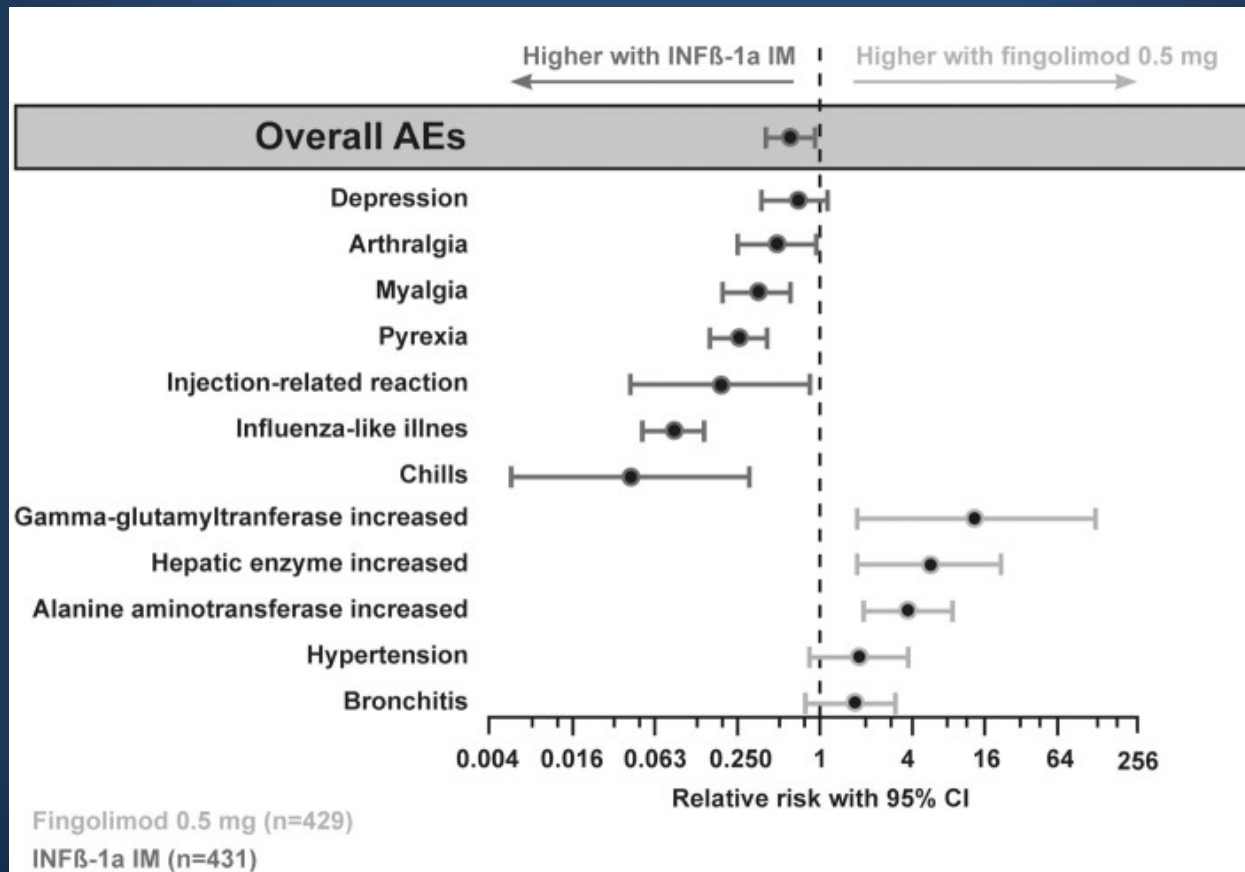
Risco de aparecimentos de transtornos neuropsiquiátricos.

Esclerose Múltipla

Interferon β -1a (Avonex[®]); Interferon β -1b (Betaseron[®]) (I.M.)

Efeitos adversos importantes

O tratamento crônico com IFN-alpha promove alterações de humor, fadiga, halucinações.



Esclerose Múltipla

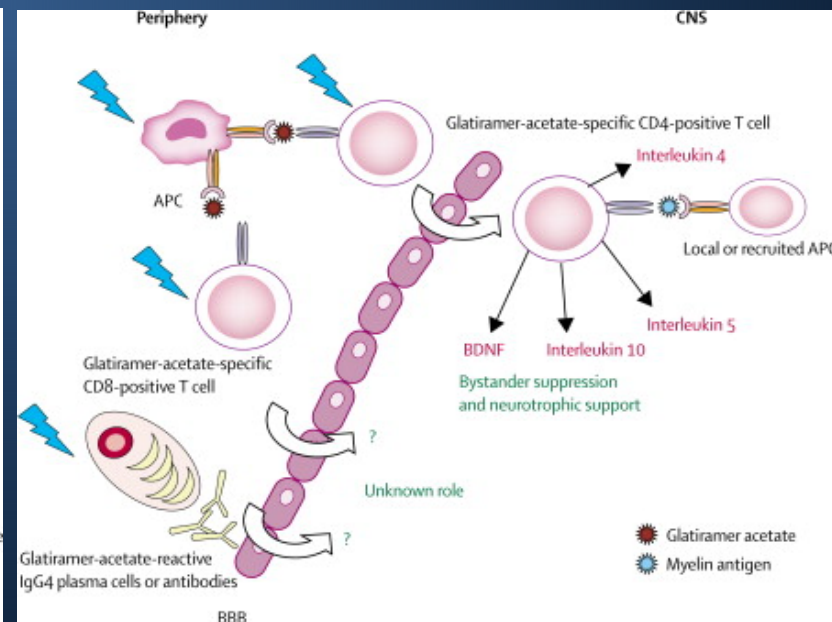
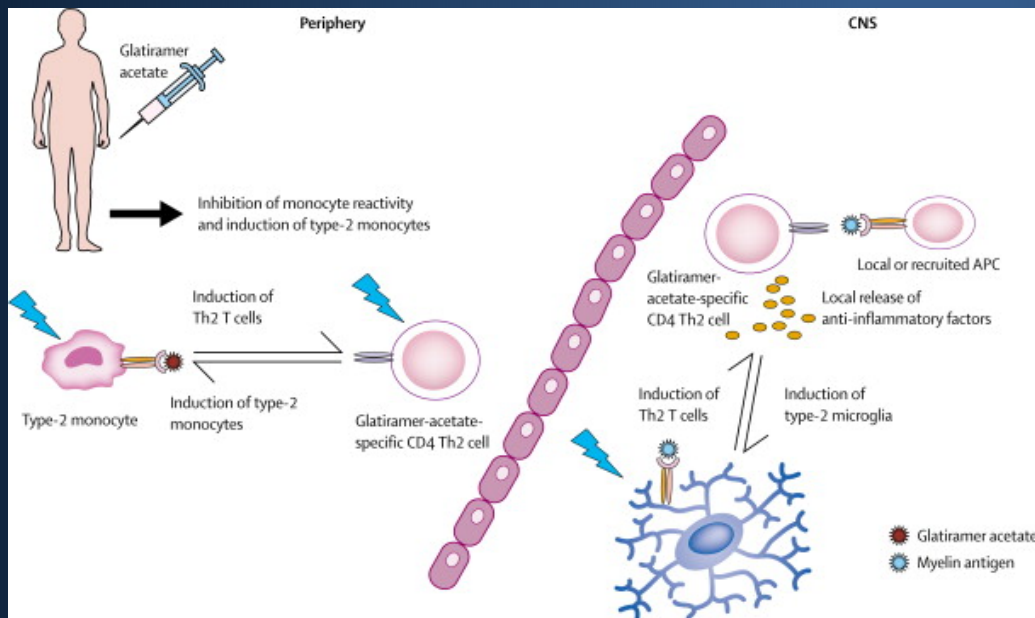
Acetato de glatirâmer (Copaxone®) S.C.

Mistura de polipeptídeos sintéticos (4aa, proteína básica de mielina)

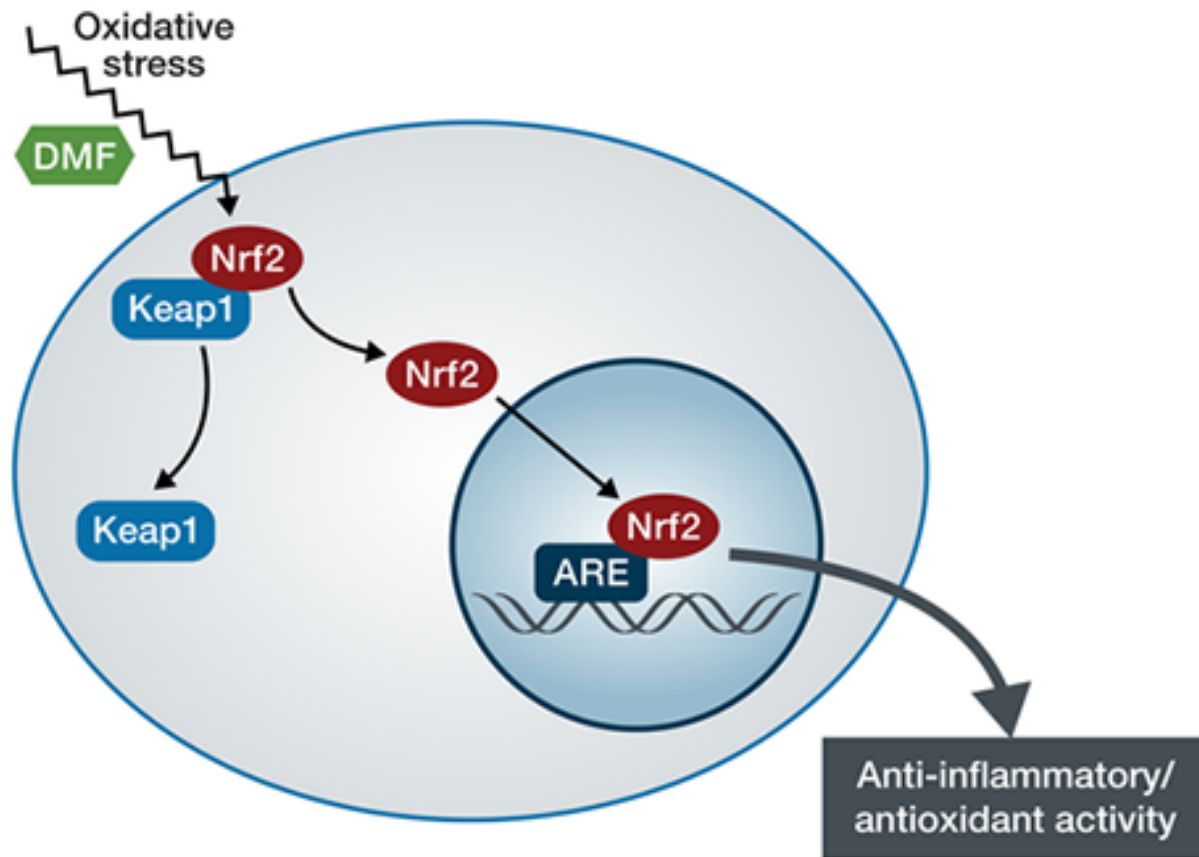
Compete com os fragmentos de mielina → MHC de classe II

Shift TH1 → Th2 (IL-10: anti-inflamatória)

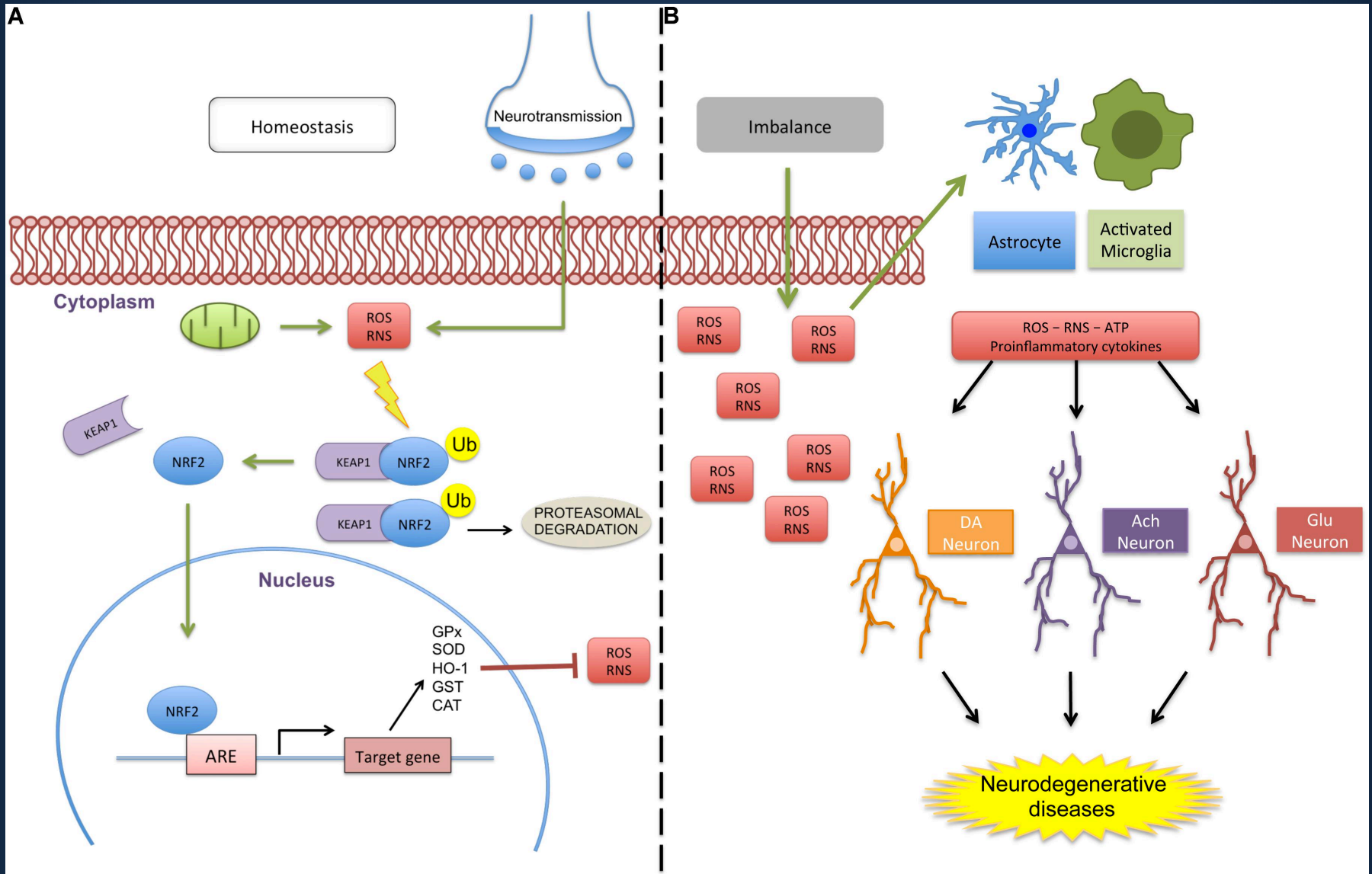
Produção de neurotrofinas neuroprotetoras → Fator neurotrófico do cérebro (BDNF)

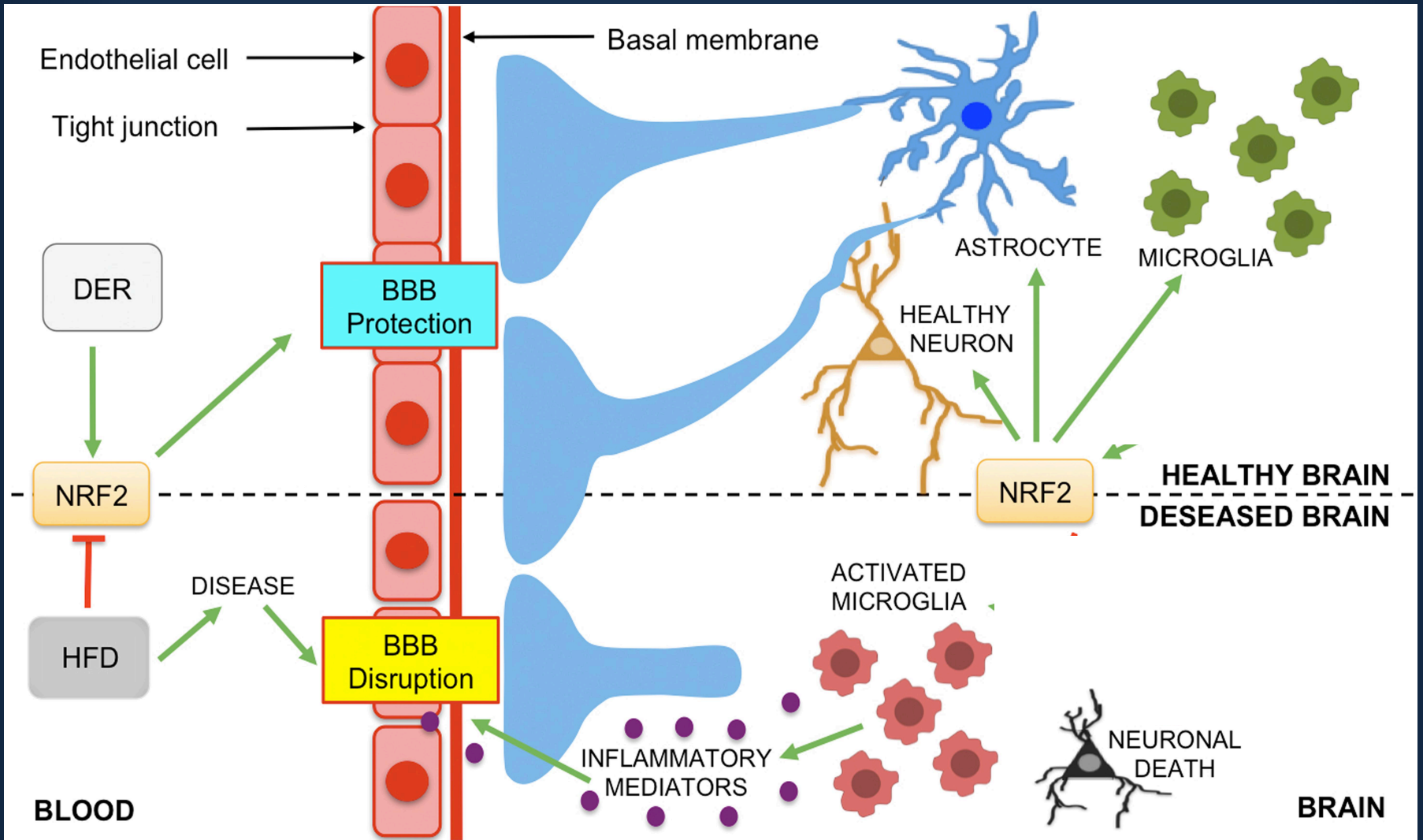


Dimethyl Fumarate Mechanism of Action



Dubey D, et al. *Expert Rev Neurother*. 2015;15:339-346.



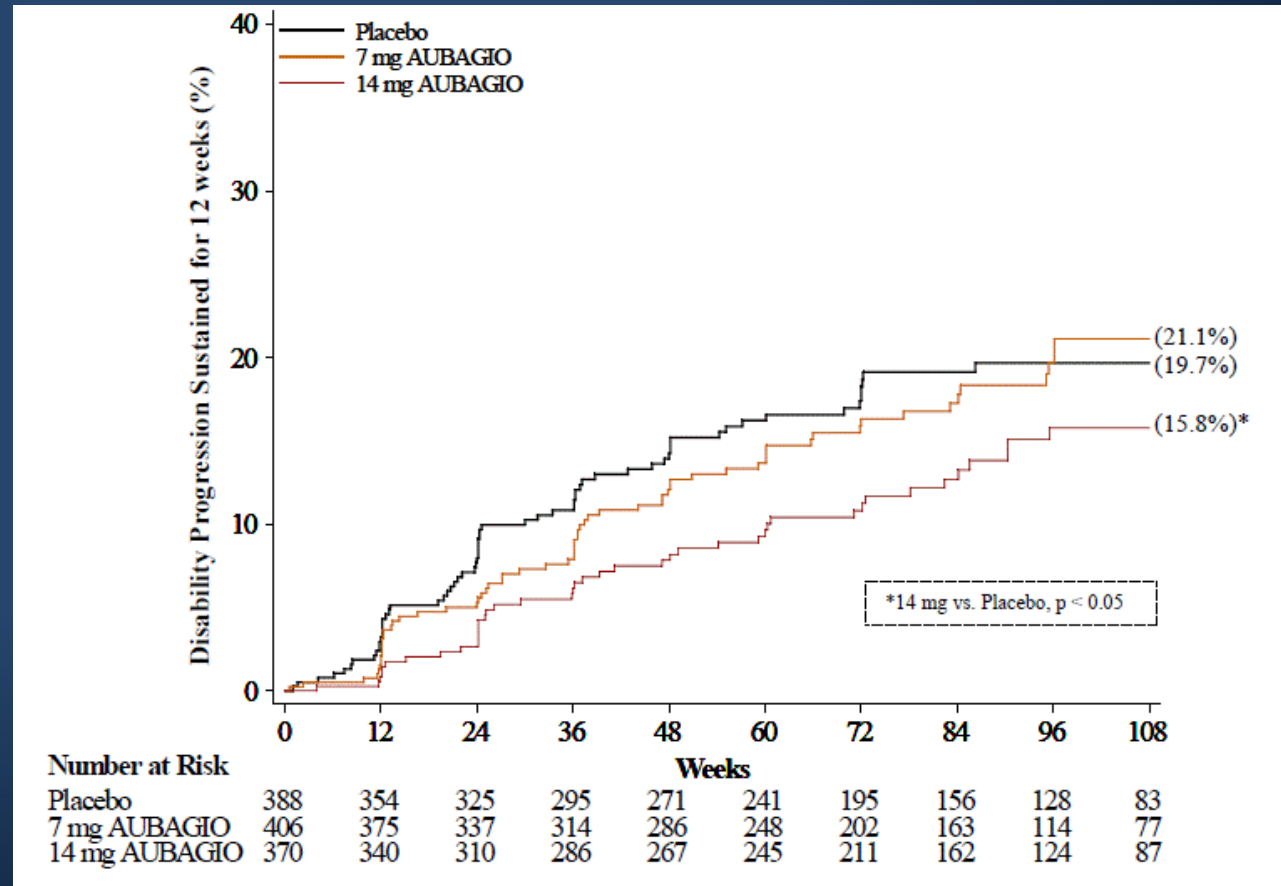


Esclerose Múltipla

Teriflunomida (Aubagio®) → V.O

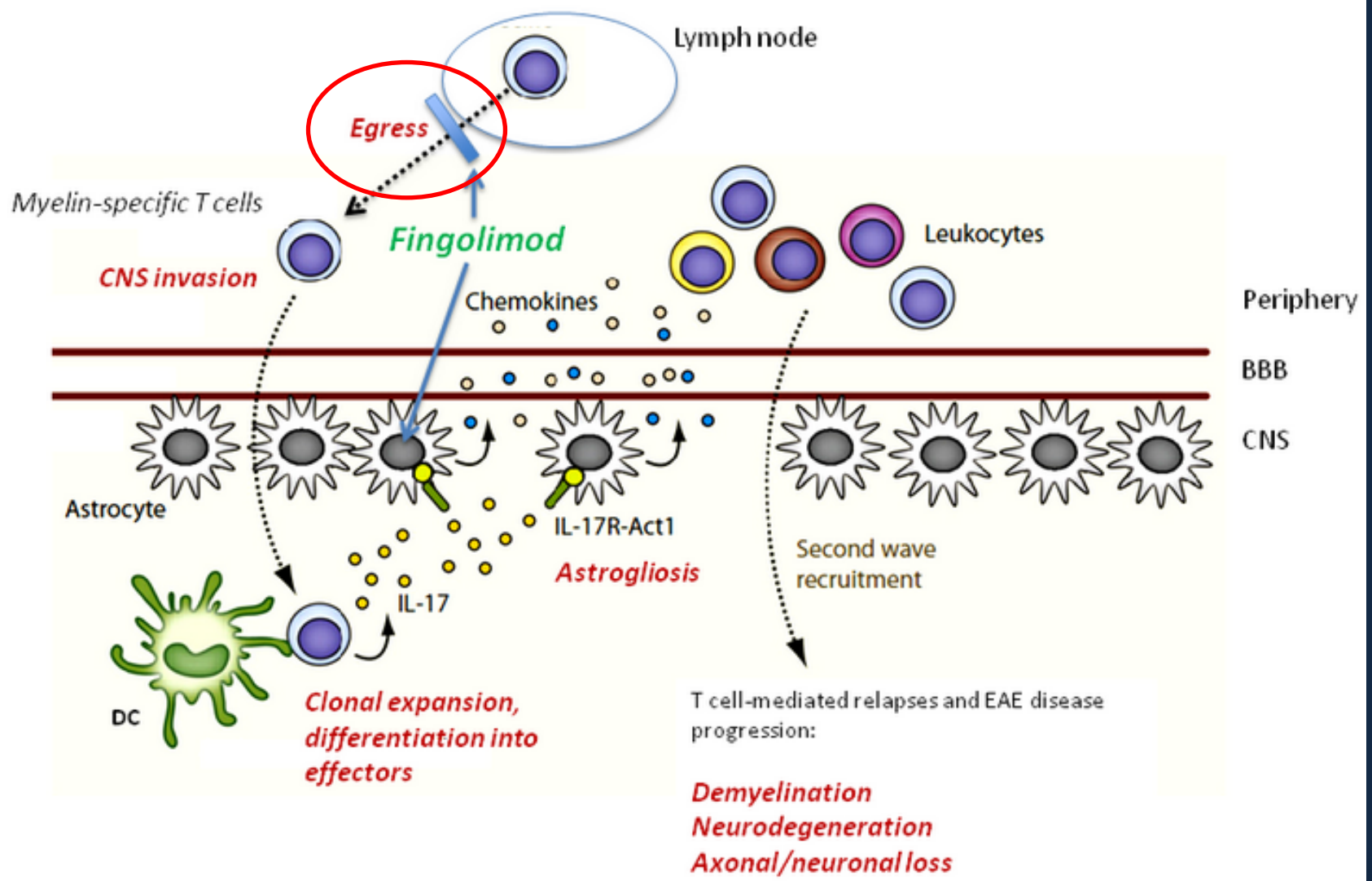
FDA: 2012

Inibe a proliferação
dos linfócitos →
menor dano ao SNC.

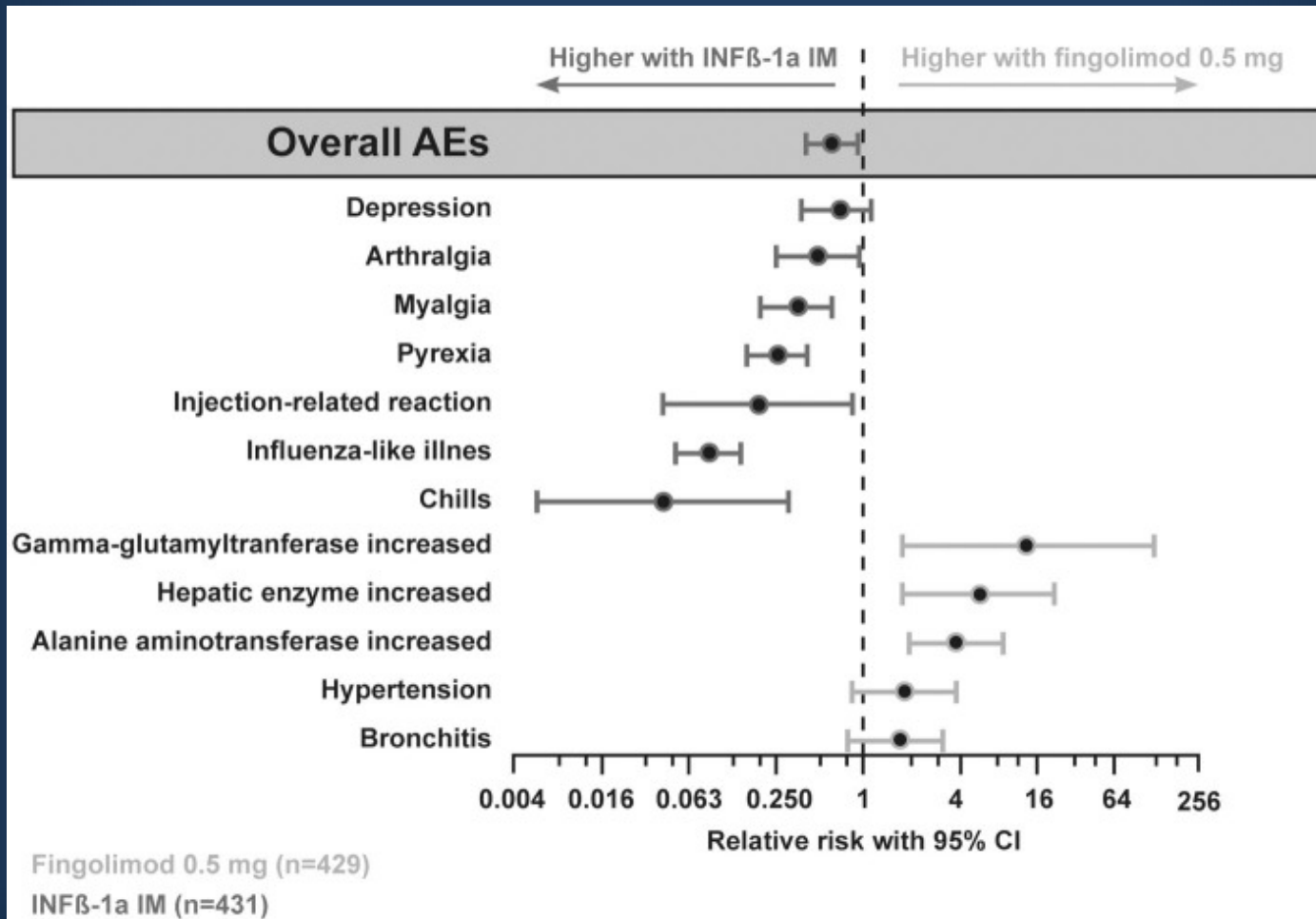


Esclerose Múltipla

Fingolimod – V.O



Esclerose Múltipla



Esclerose Múltipla (Remitente e Recorrente)

Tysabri®

“Segunda linha”

Anticorpo monoclonal humanizado

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL THERAPEUTICS

Natalizumab for Multiple Sclerosis

Richard M. Ransohoff, M.D.

Table 1 | **13-Month clinical endpoints in Study 1 (monotherapy study)**

Clinical endpoints	Tysabri, <i>n</i> = 627	Placebo, <i>n</i> = 315
Annualized relapse rate*	0.25	0.74
Percentage of patients remaining relapse-free	76%	53%

*Relative reduction = 66%.

Table 3 | **13-Month clinical endpoints in Study 2 (add-on study)**

Clinical endpoints	Tysabri plus Avonex, <i>n</i> = 589	Placebo plus Avonex, <i>n</i> = 582
Annualized relapse rate*	0.36	0.78
Percentage of patients remaining relapse-free	67%	46%

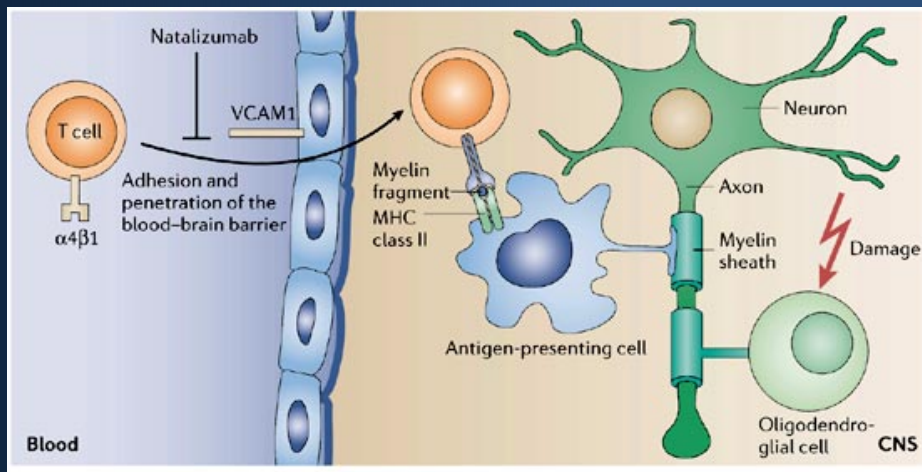
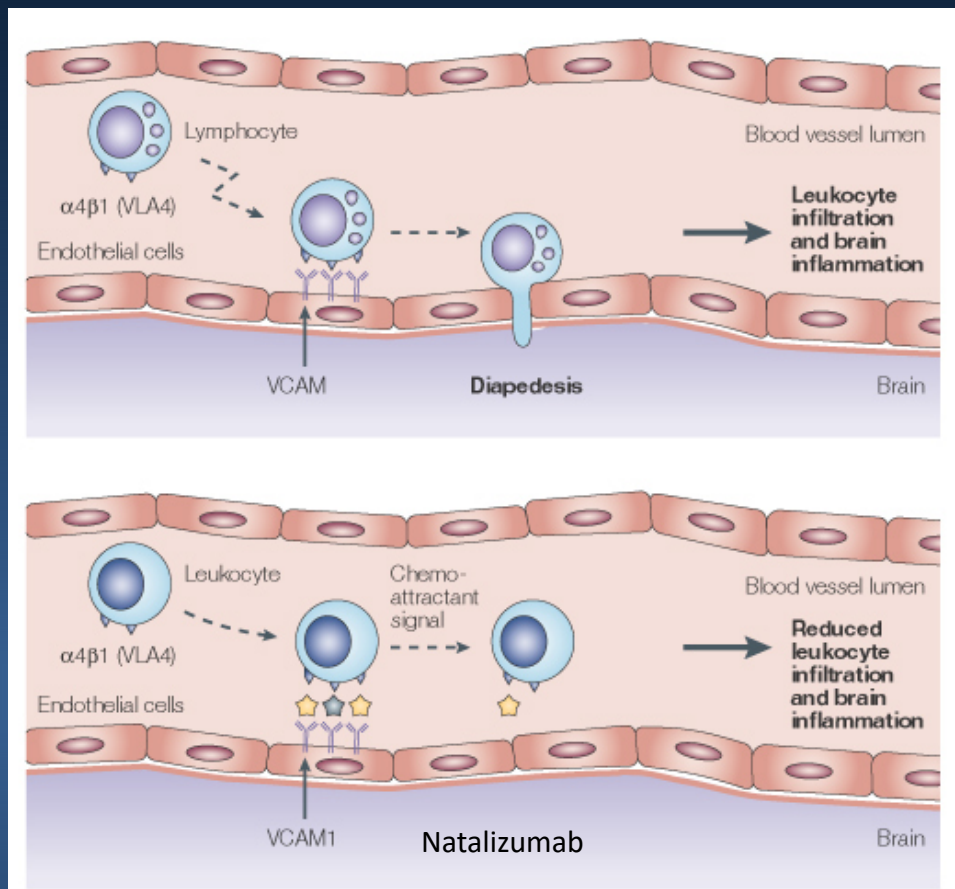
*Relative reduction = 54%.

Reduz a probabilidade de surtos e a progressão da incapacidade

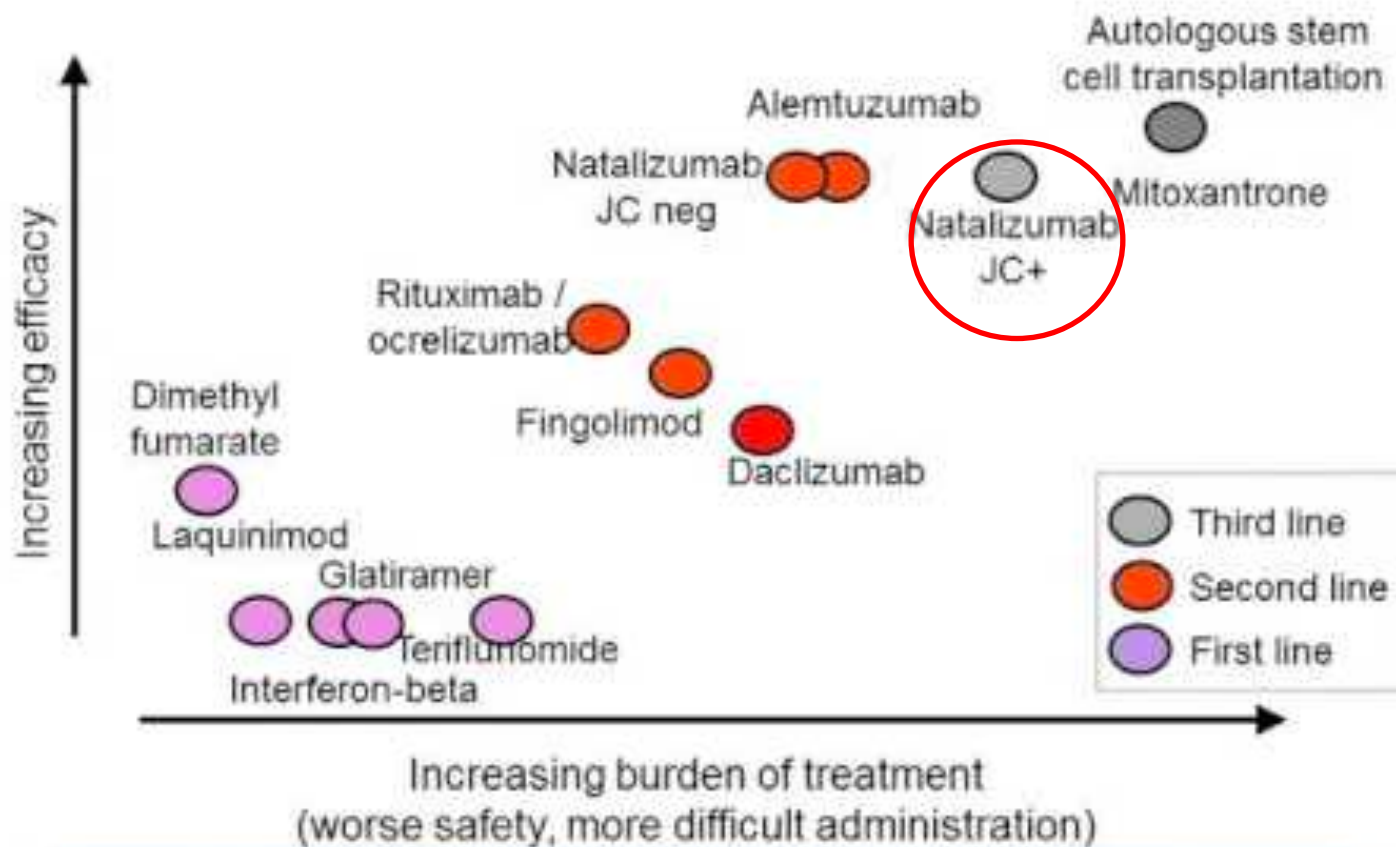
Esclerose Múltipla

Natalizumab → Mecanismo

Anticorpo contra os receptores de integrinas $\alpha 4\beta 1$
Inibe a adesão e a diapedese

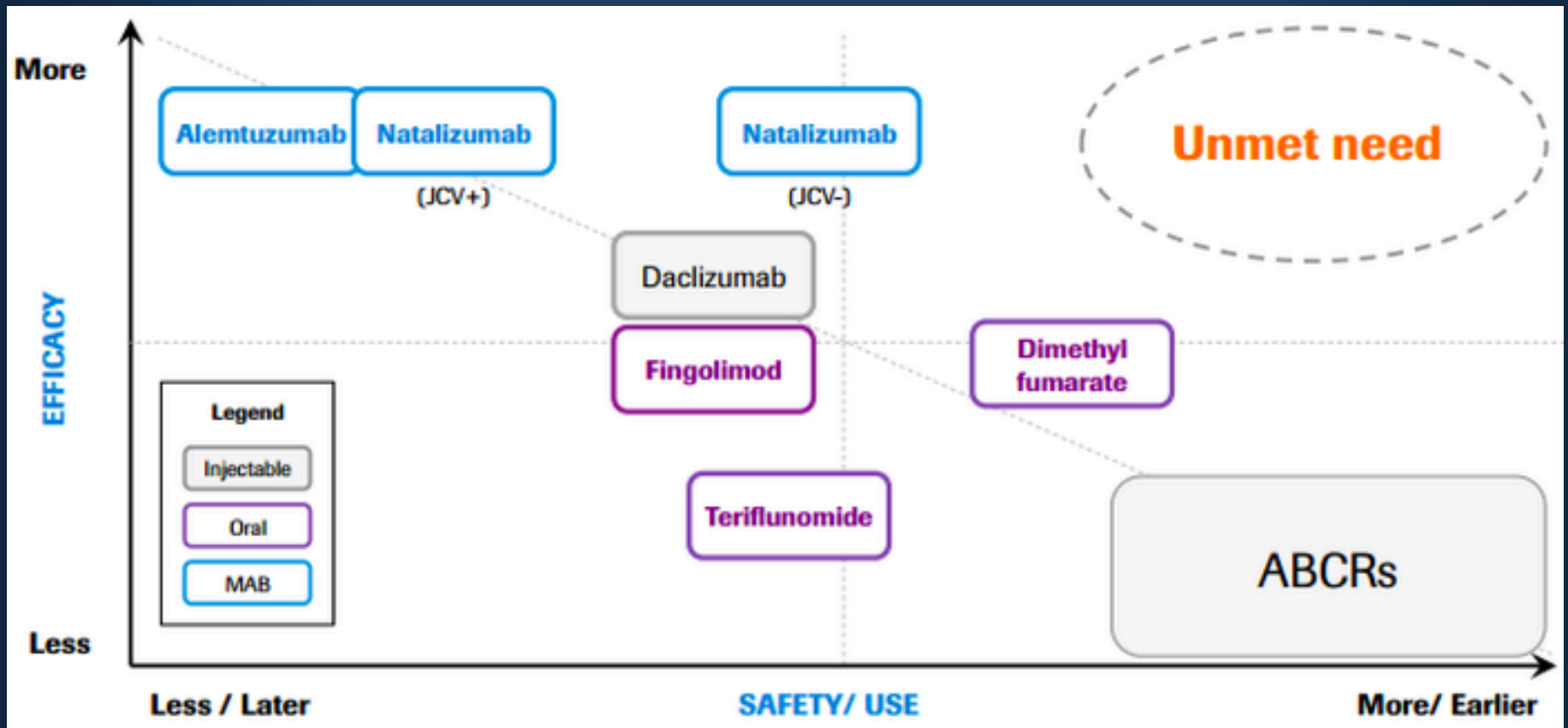


First, Second and Third Line Therapies



Modified from Hauser S. *Annals Neurology*. 2012;74:317-327

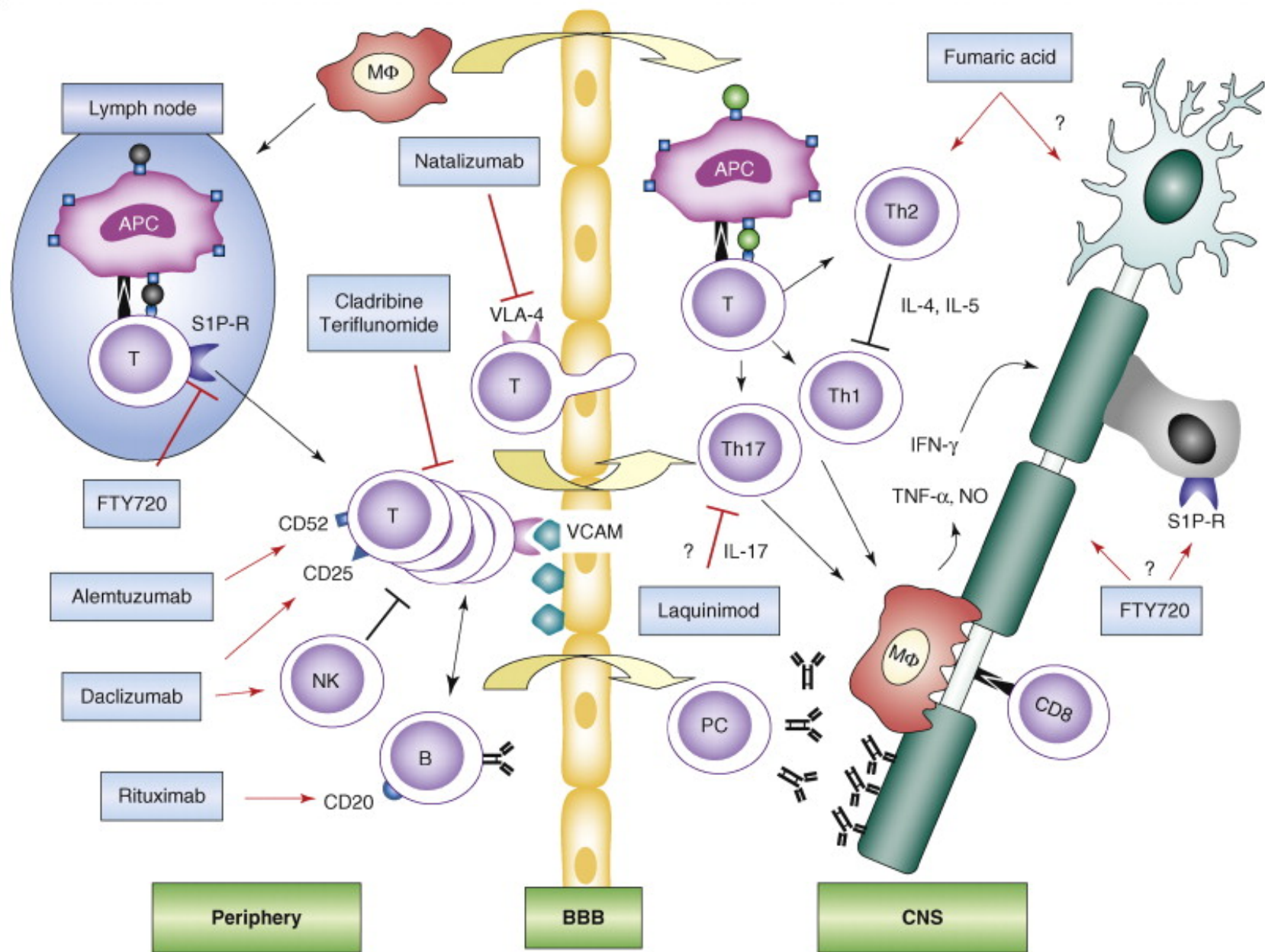
John Cunningham virus → Progressive Multifocal Leukoencephalopathy (PML)



ABCRs: Avonex, Betaseron, Copaxone

Table 1. FDA-Approved Agents for Treatment of MS

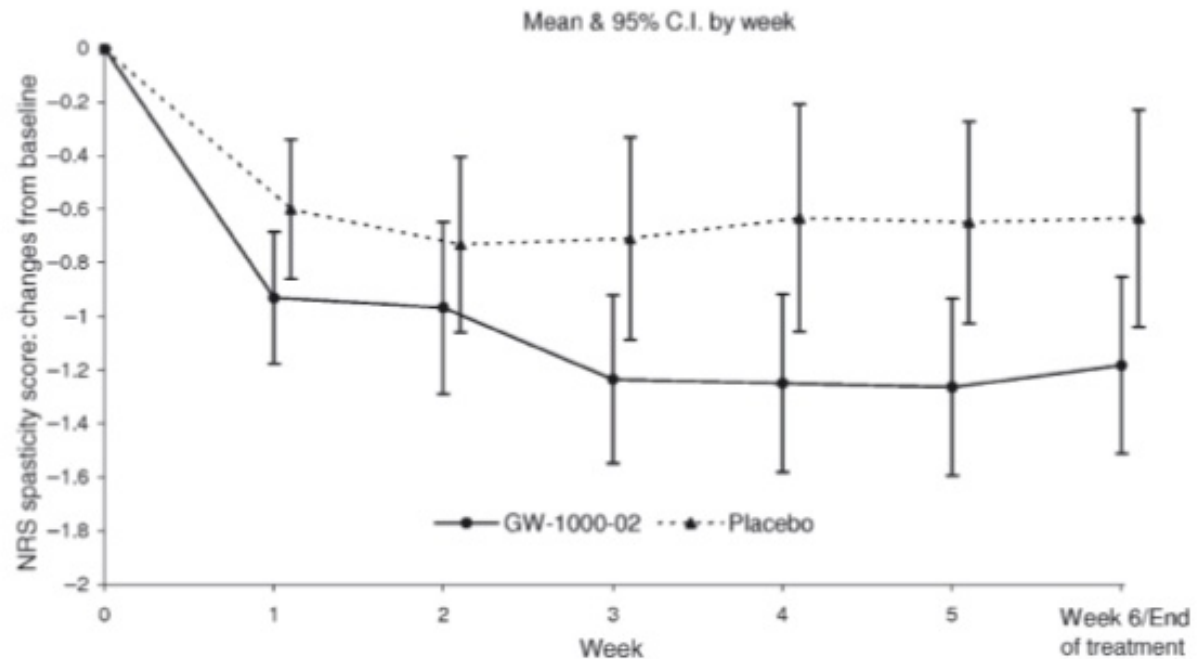
Drug (Brand)	Dosage	Route	Frequency	Mechanism of Action
Interferon beta-1a (Avonex)	30 mcg	IM	1× wk	Enhances immune cell activities; unknown in MS
Interferon beta-1a (Rebif)	<i>Initial:</i> 8.8 mcg; increase to <i>Target:</i> 22 mcg or 44 mcg	SC	3× wk	Enhances immune cell activities; unknown in MS
Interferon beta-1b (Betaseron)	<i>Initial:</i> 0.0625 mg; increase to <i>Target:</i> 0.25 mg (8 million units)	SC	Every other day	Enhances immune cell activities; unknown in MS
Glatiramer acetate (Copaxone)	20 mg	SC	Daily	Induces and activates T-lymphocyte suppressor cells
Mitoxantrone (Novantrone)	12 mg/m ²	IV	Every 3 mo	Immunosuppressant
Natalizumab (Tysabri)	300 mg	IV	Every 4 wk	Selective adhesion molecule inhibitor
Fingolimod (Gilenya)	0.5 mg	Oral	Daily	S1PR receptor modulator



Esclerose Múltipla

Tratamentos sintomáticos: Espasmos

Sativex® → 50% THC + 50% CBD

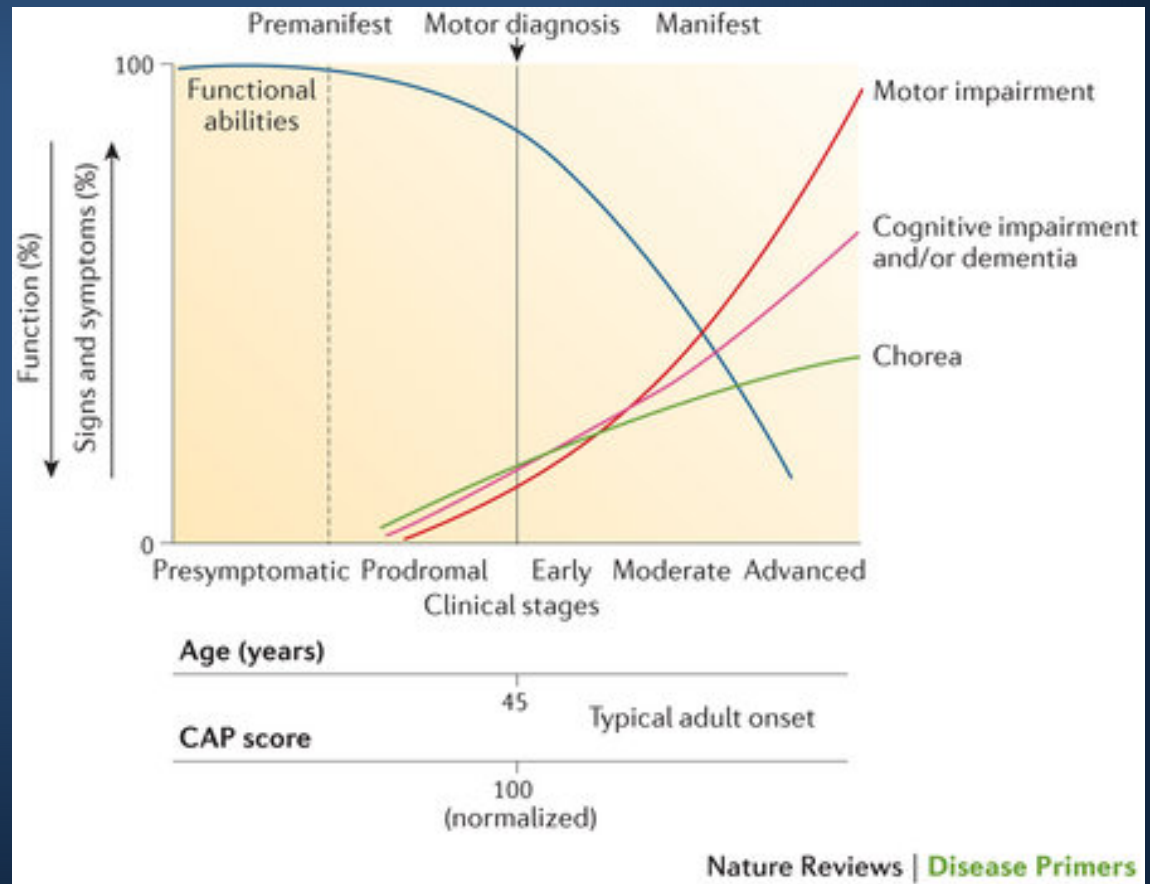
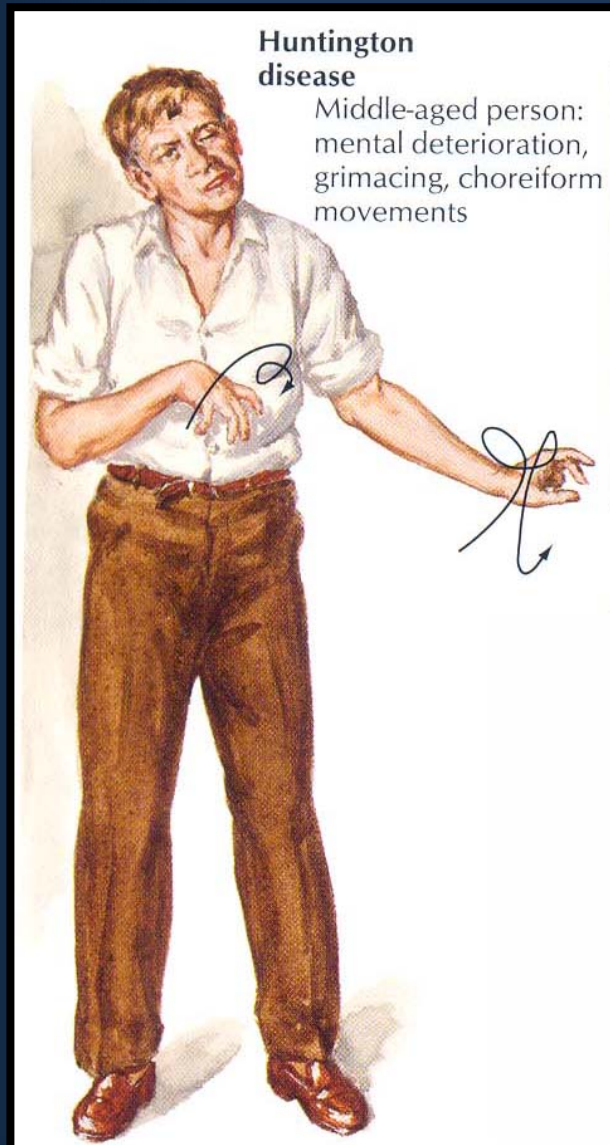


Uso aprovado: Reino Unido, Espanha, Canadá

Gabapentina (↓ glutamato terminais pre-sinápticos), Baclofen (GABA_B- nível medular),

Doença de Huntington

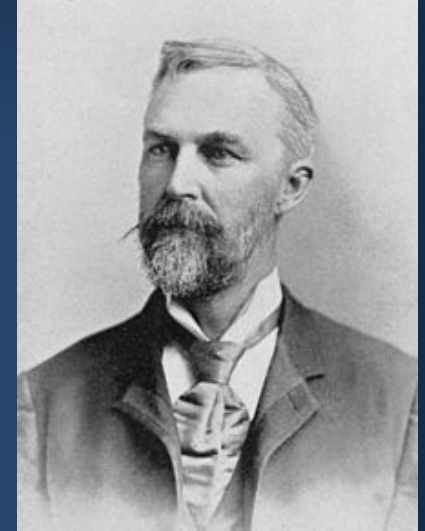
- Disfunções motoras (coreia)
- Prejuízo cognitivo (estágio avançado)
- Alterações emocionais
- Manifesta-se na vida adulta



Doença de Huntington

1860: Johan Christian Lund

1872: *On Chorea* (*Chorea* → *latim: grupo de dança, coral*)

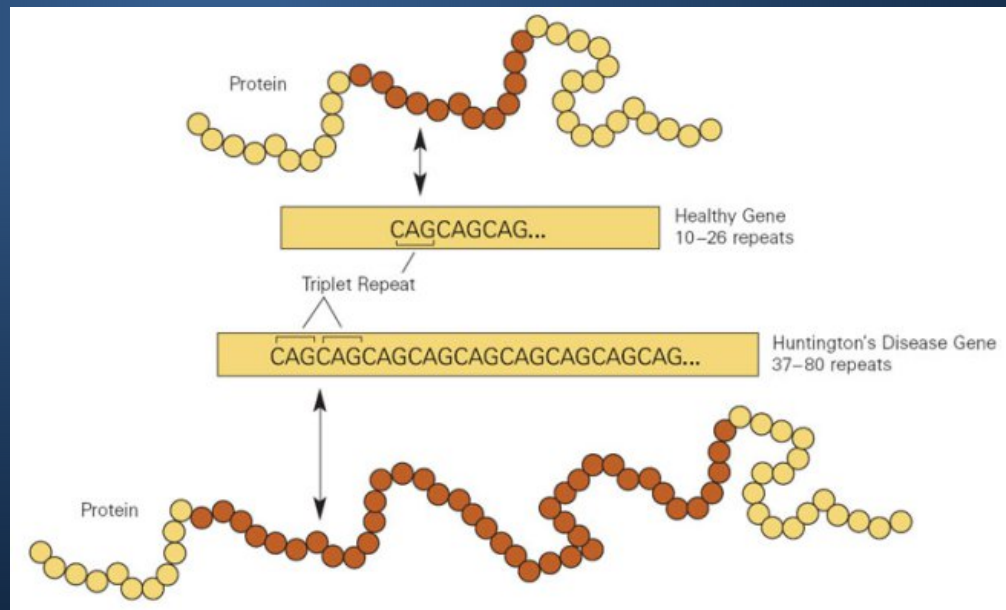


1993:

The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*. 1993;72:971–983.

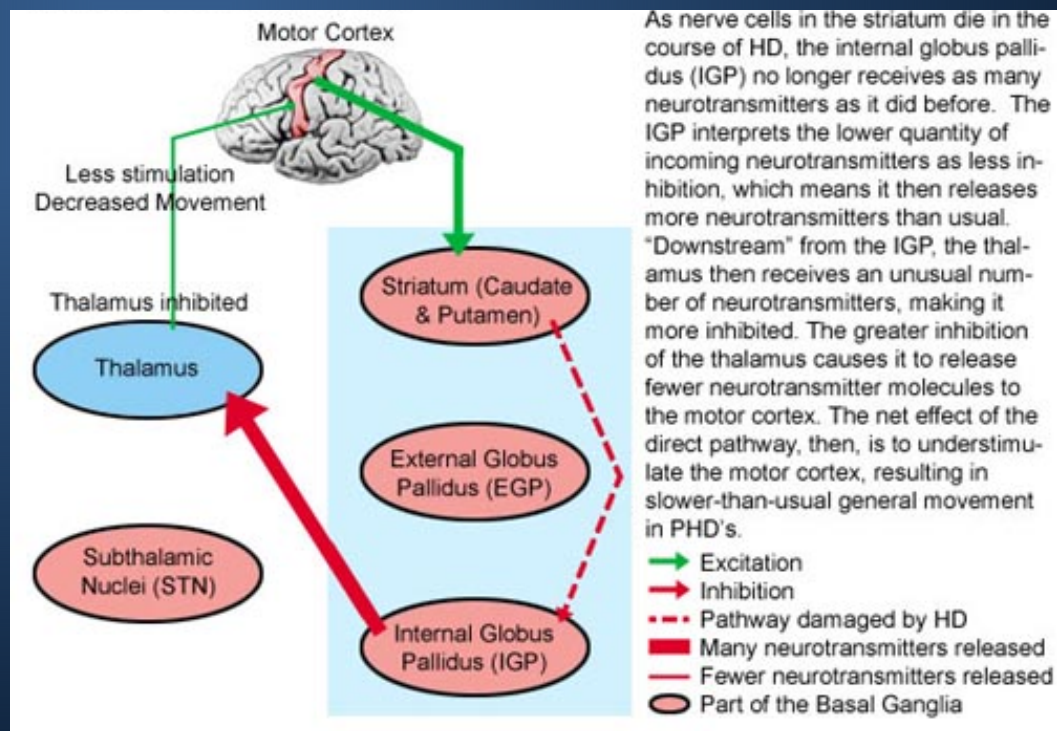
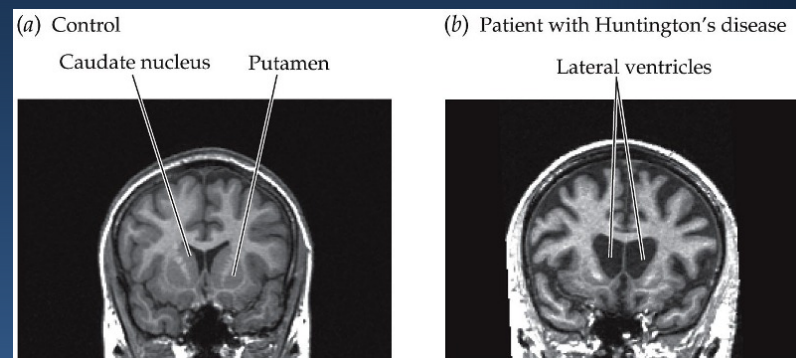
Doença de Huntington

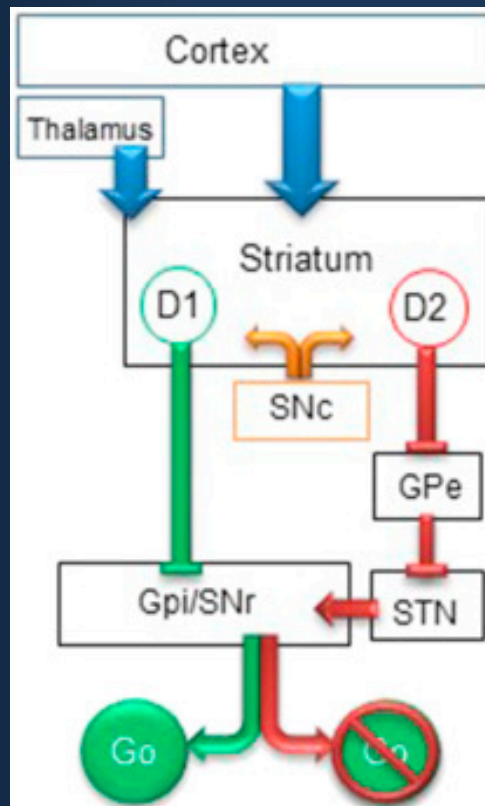
- 1993: Gene alterado codifica uma proteína (mutação IT15 → Huntingtina) que favorece apoptose e excitotoxicidade.
- Funções biológicas da huntingtina permanecem pouco conhecidas
- Fator Hereditário (antecipação: manifestação dos sintomas 20 anos → pai). Repetições CAG (triplets)



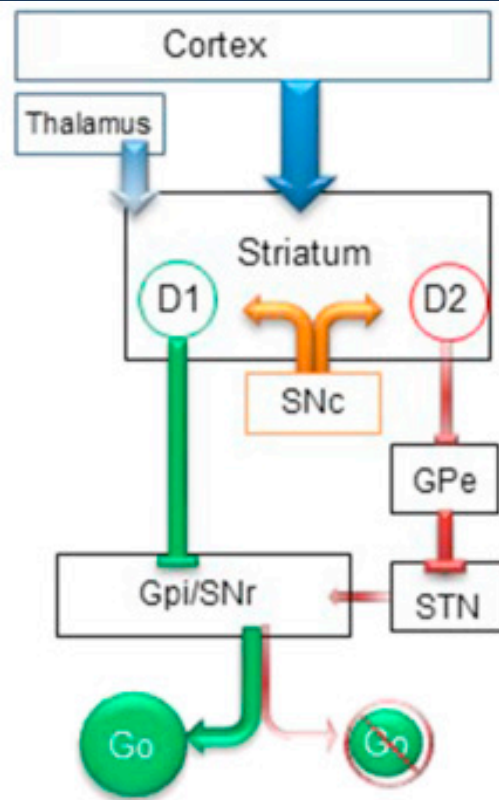
Doença de Huntington

- ↓ tamanho do núcleo caudado e do córtex cerebral.
- ↓ neurônios GABAérgicos estriatais → hiperatividade dopaminérgica.

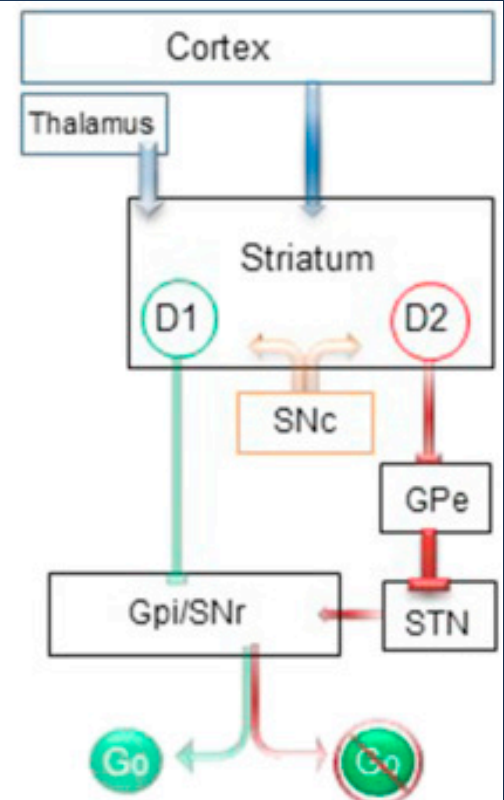




Normal

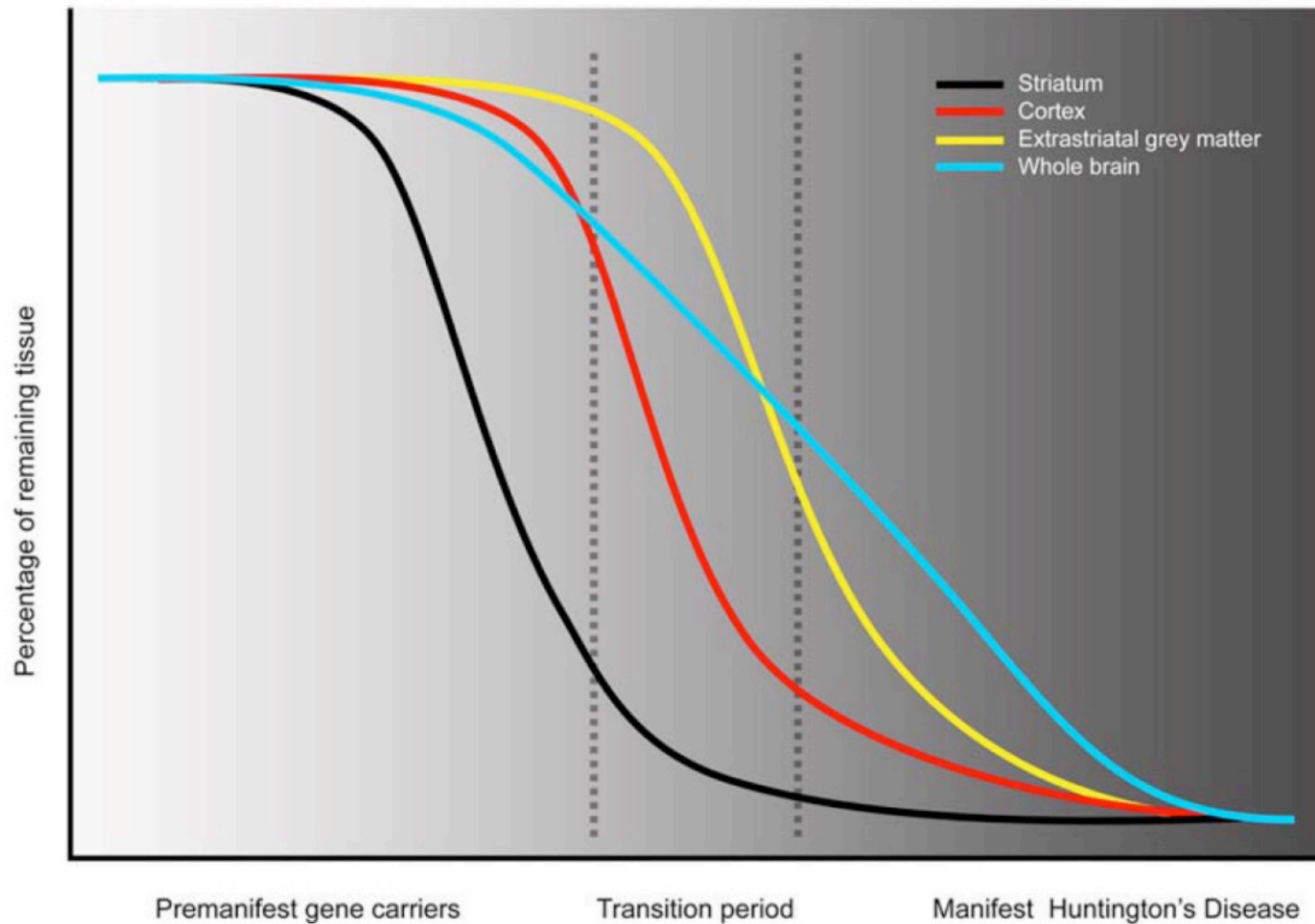


Early HD



Late HD

Doença de Huntington

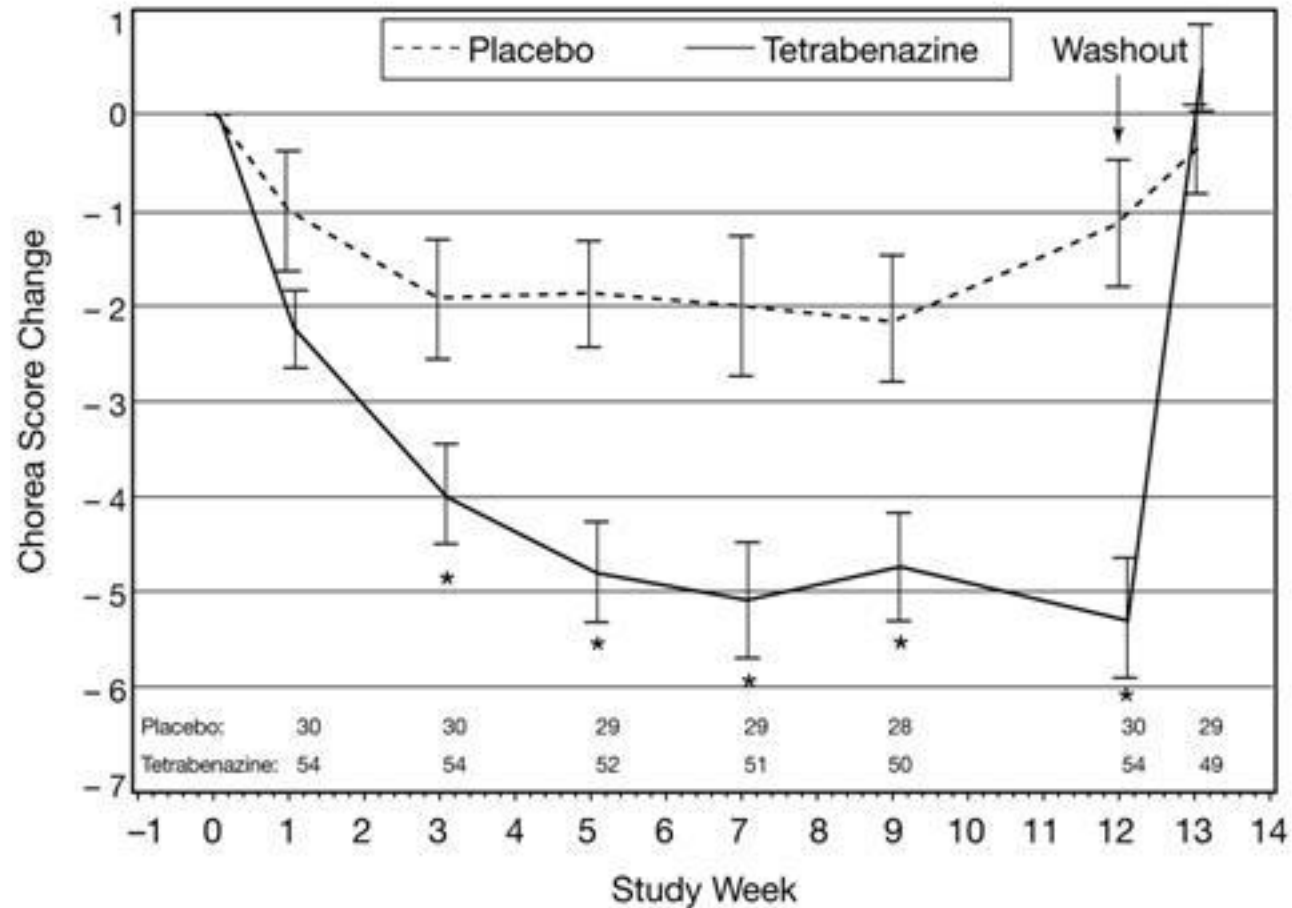


Doença de Huntington

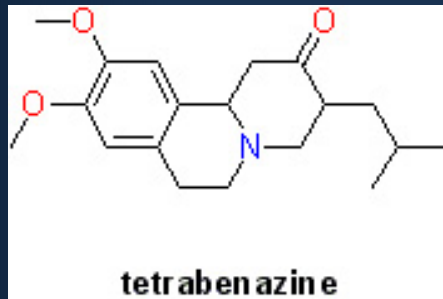
Tratamento

Não há cura, apenas a diminuição de alguns sintomas, tais como a Coreia.

Tetrabenazina

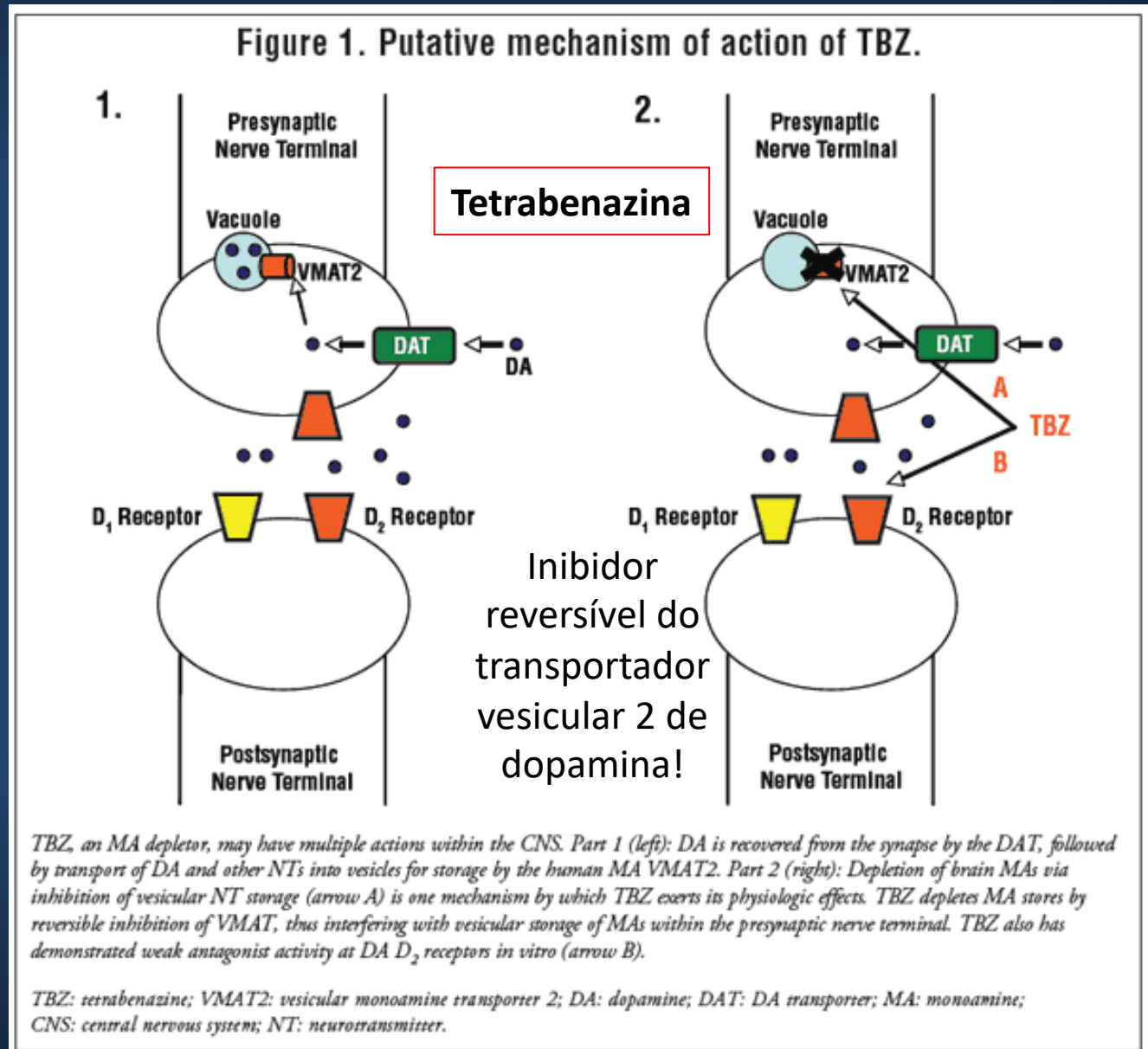


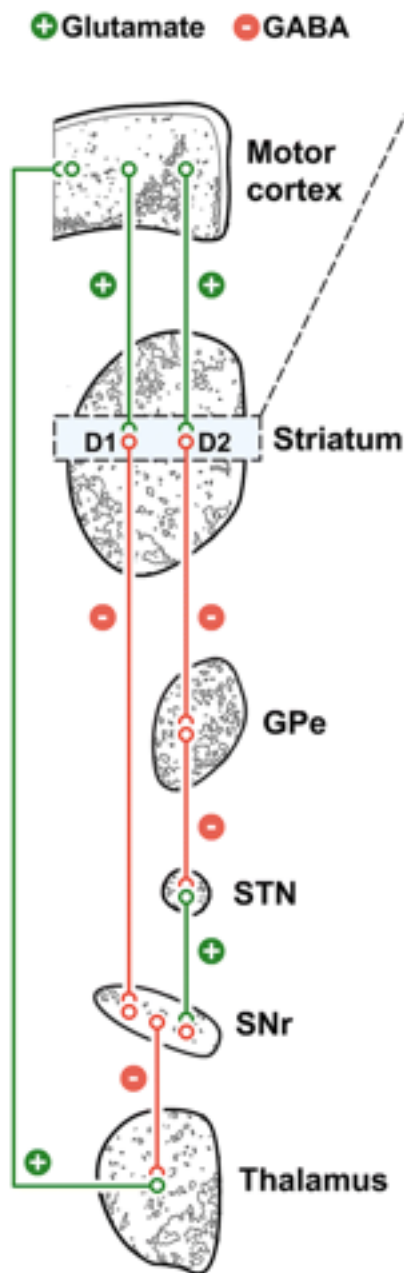
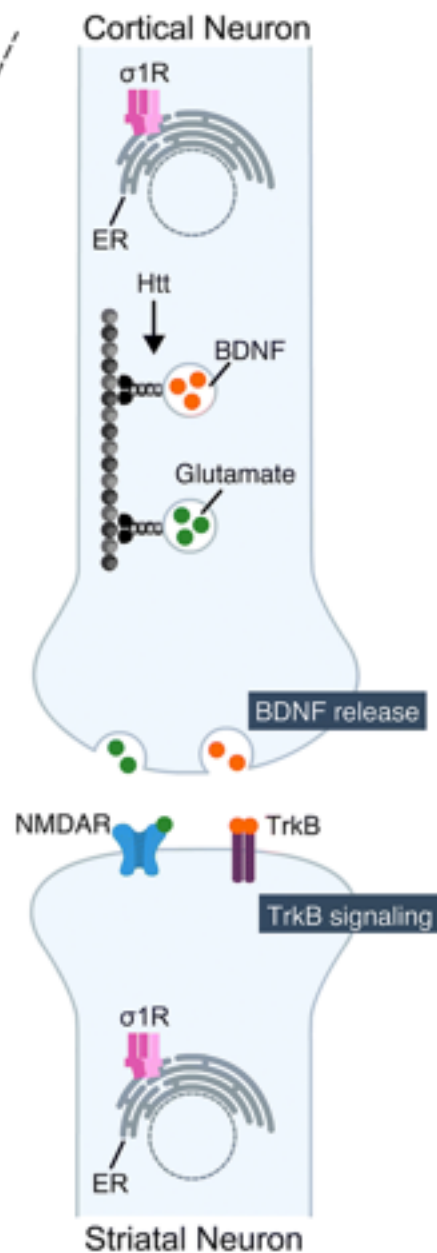
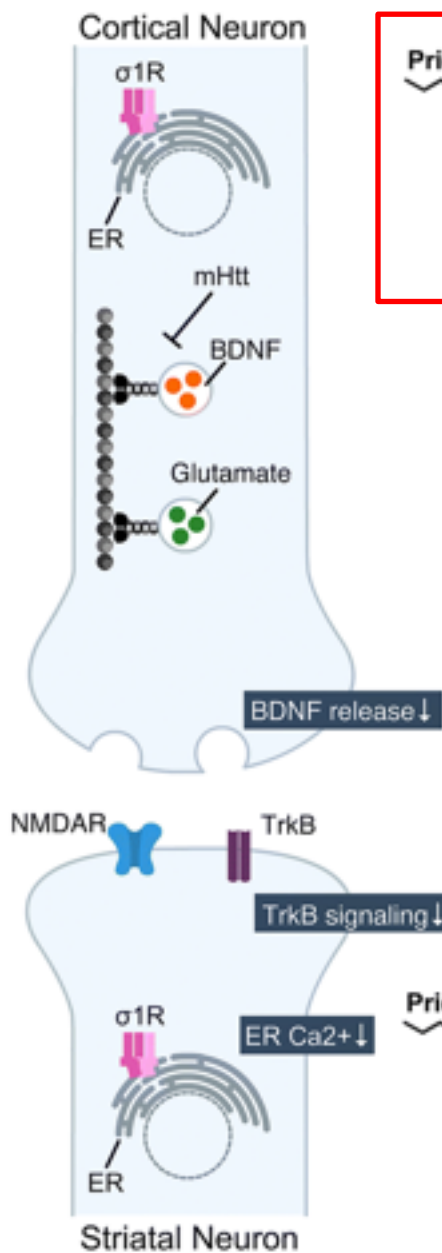
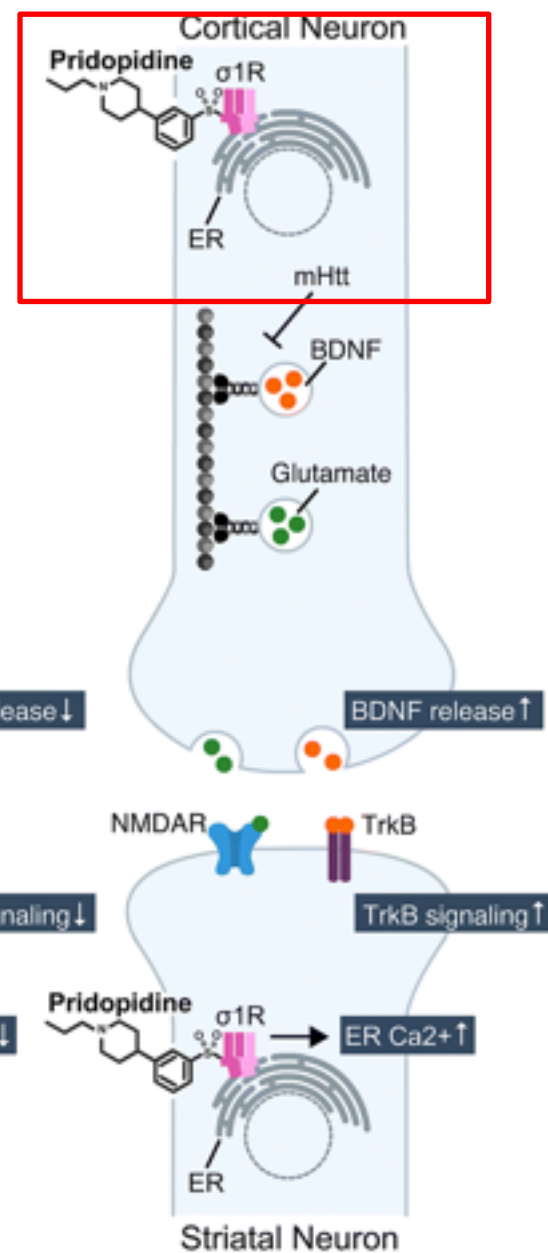
Doença de Huntington



Mecanismo de ação não está completamente elucidado.

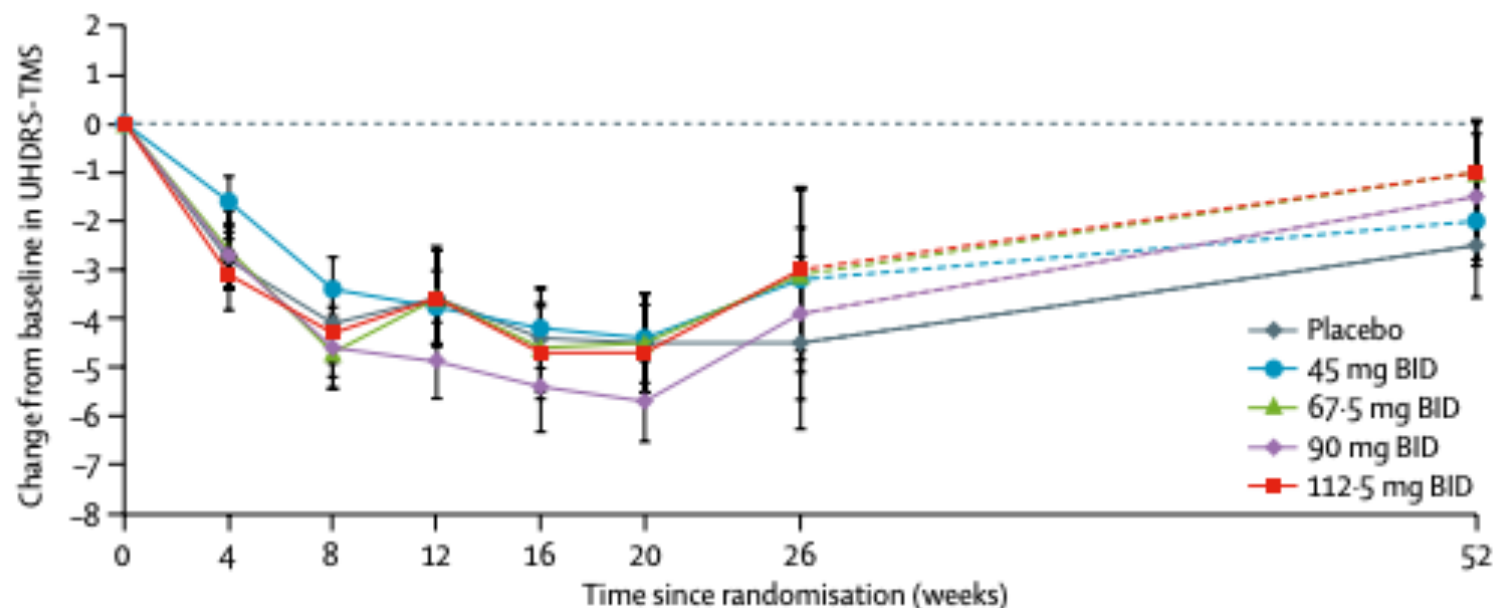
Efeitos colaterais
Hipotensão postural
e Depressão Grave (risco de suicídio)



A Motor Circuit**B Wild-type****C HD****D HD & Pridopidine**

Safety and efficacy of pridopidine in patients with Huntington's disease (PRIDE-HD): a phase 2, randomised, placebo-controlled, multicentre, dose-ranging study

Ralf Reilmann*, Andrew McGarry*, Igor D Grachev, Juha-Matti Savola, Beth Borowsky, Eli Eyal, Nicholas Gross, Douglas Langbehn, Robin Schubert, Anna Teige Wickenberg, Spyros Papapetropoulos, Michael Hayden, Ferdinando Squitieri, Karl Kieburtz, G Bernhard Landwehrmeyer, on behalf of the European Huntington's Disease Network and the Huntington Study Group investigators†



“Pridopidine did not improve the UHDRS-TMS at week 26 compared with placebo and, thus, the results of secondary or tertiary analyses in previous trials were not replicated. A potentially strong placebo effect needs to be ruled out in future studies.”

Table 1

Summary of clinical trials of pridopidine in Huntington Disease

	Scandinavian study³⁶	MermaiHD³⁷	HART³⁸
Study design	Double-blind, placebo-controlled	Double-blind, placebo-controlled	Double-blind, placebo-controlled
Study duration	4 weeks	26 weeks	12 weeks
Demographics	58 patients from Scandinavia	437 patients from Europe	228 patients from USA and Canada
Treatment groups	Pridopidine 50 mg/day Placebo	Pridopidine 45 mg/day Pridopidine 90 mg/day Placebo	Pridopidine 20 mg/day Pridopidine 45 mg/day Pridopidine 90 mg/day Placebo
Primary outcome	Change from baseline in weighted cognitive score based on Symbol Digit Modalities, verbal fluency, and Stroop (3 items) tests	Change from baseline to Week 26 in the mMS	Change from baseline to Week 12 in the mMS
Additional outcomes	Change in UHDRS motor scores Reitan Trail-Making Test A Leeds Sleep Evaluation Questionnaire HADS CGI-C	UHDRS-TMS UHDRS motor scale subscores UHDRS cognitive scales UHDRS functional score UHDRS independence scale HADS CGI-C CGI-I	UHDRS-TMS UHDRS motor scale subscores UHDRS cognitive scales UHDRS functional score HADS CGI-C
Results	No significant difference in change in weighted cognitive scores Significant improvement of gait in pridoipidine treated-patients Significant improvement of m-UHDRS scores but only in patients	No effect with pridoipidine 45 mg/day Trend toward improvement of the mMS with pridoipidine 90 mg/day (-0.99 ; $P=0.042$) Strongly significant improvement of the UHDRS-TMS ($P=0.004$) and the motor subscores of dystonia ($P=0.001$), hand movements ($P=0.015$), and equilibrium	No effect with pridoipidine 20 or 45 mg/day Trend toward improvement of the mMS (-1.2 ; $P=0.08$), UHDRS-TMS (-2.8 ; $P=0.04$) and motor subscores of hand movements and equilibrium with pridoipidine 90 mg/day

Doença de Huntington

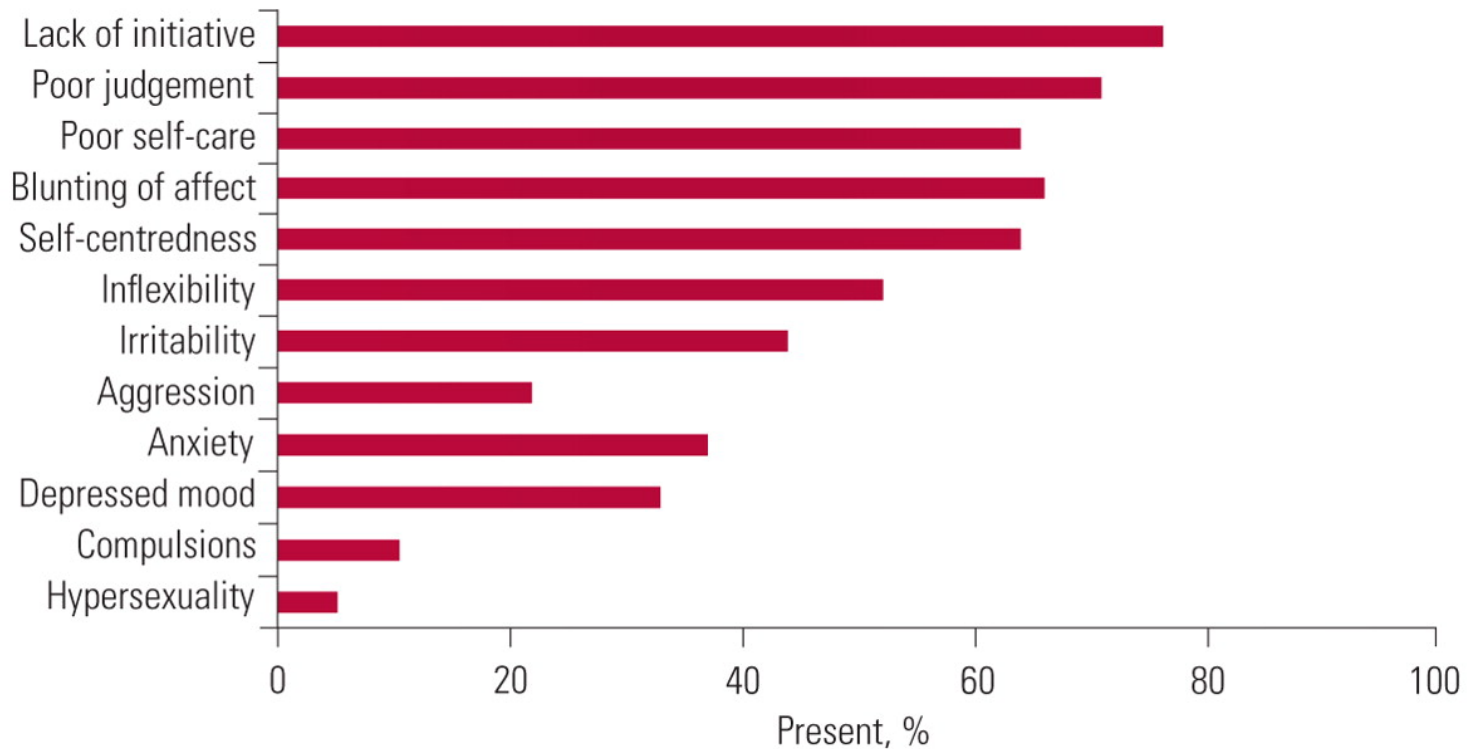


FIG 1 Frequency of behavioural changes in Huntington's disease (Craufurd 2002: p. 84. Reproduced with permission of Oxford University Press).

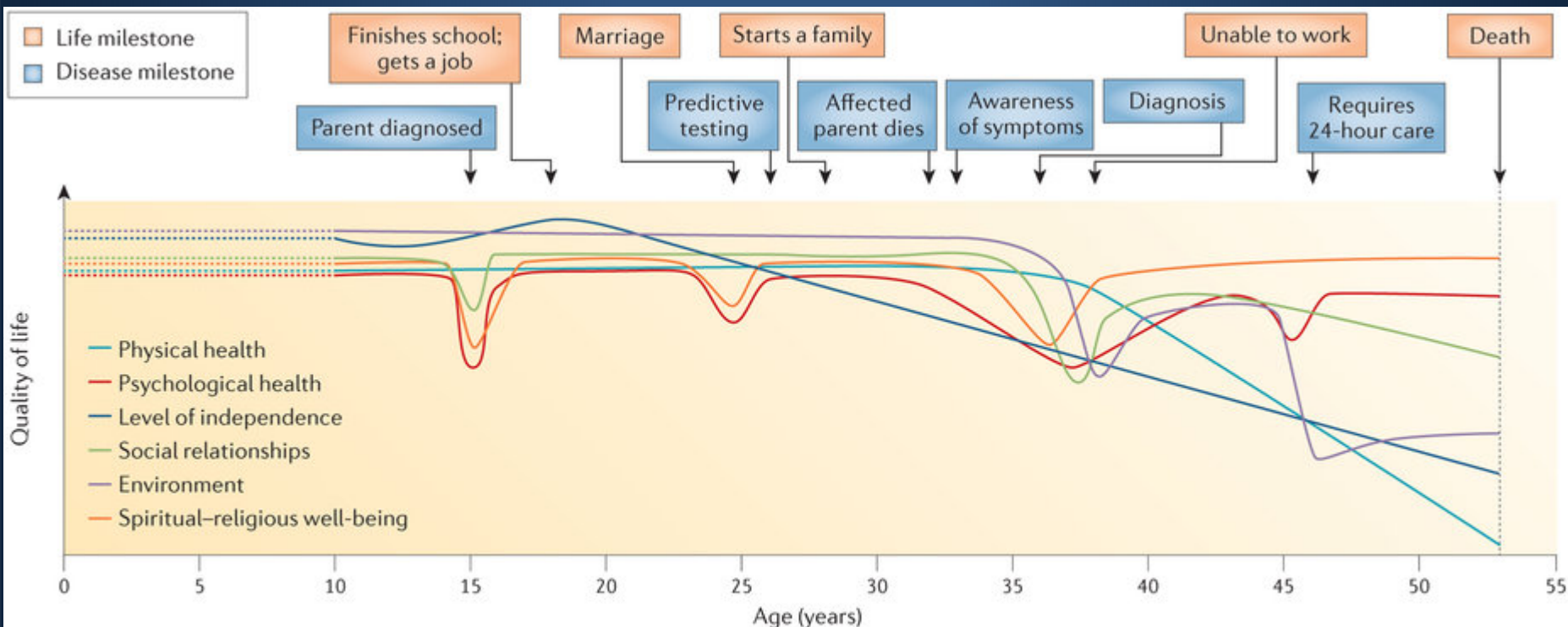
Outros tratamentos (Não são consenso)

Riluzole (glutamato), amantadina (glutamato), clozapine (antipsicóticos- Parkinsonismo), antidepressivos (monoaminas)

O papel de abordagens não farmacológicas

Prevenção de perdas cognitivas- atenção psicossocial

Estímulo a recuperação de autonomia nas atividades diárias- fisioterapia; terapia ocupacional



Paciente com D.Huntington

O papel de abordagens não farmacológicas

rough cut excerpt 8.2

Bibliografia

Goodman & Gilman, 11ª e 12ª Edições

Rang & Dale, 5ª e 6ª Edições.

Dúvidas: allinecampos@usp.br