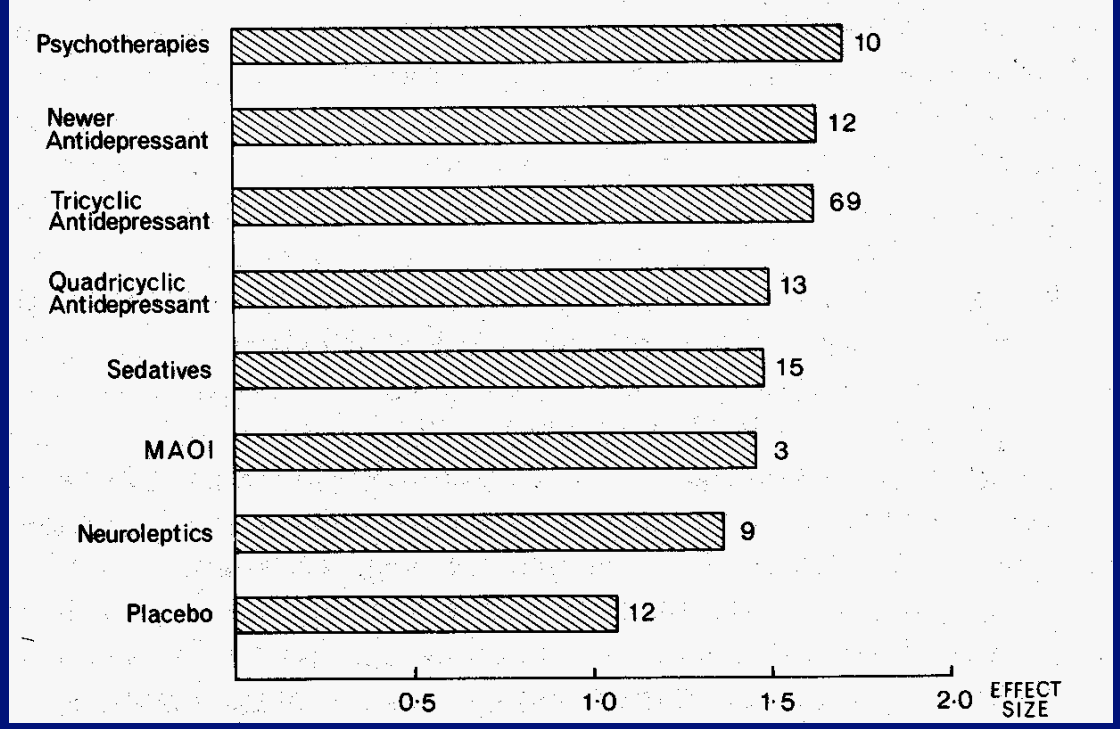
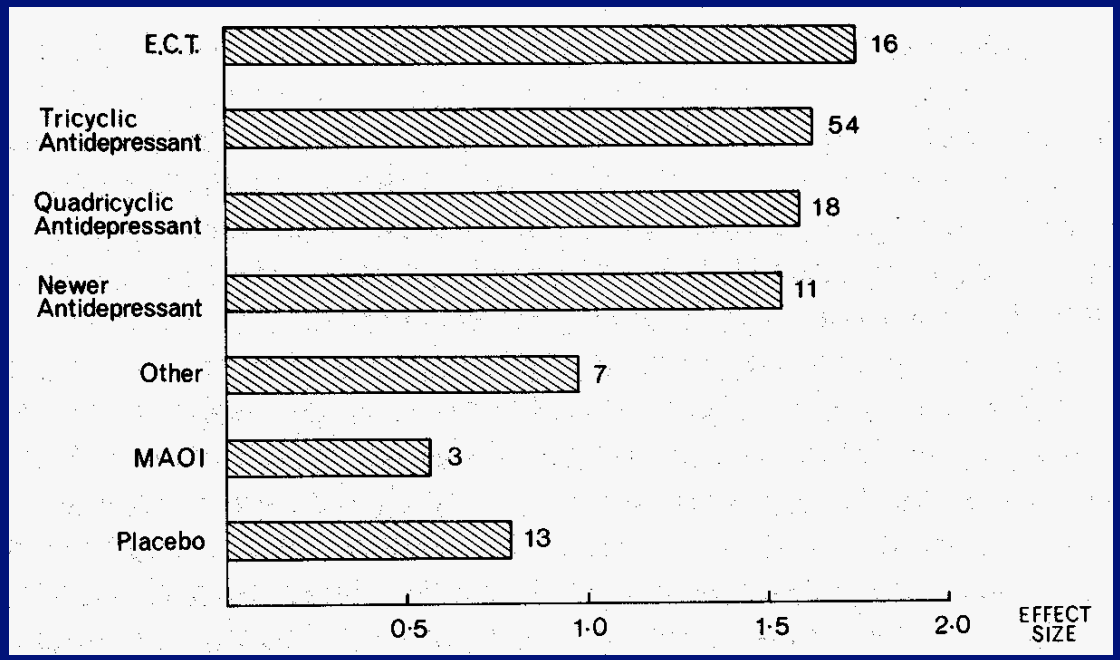


Depressão "neurótica"



Depressão Maior

Eficácia dos ISRS vs. placebo na depressão maior (131 trials, >27000 pacientes)

Equivaleu a uma melhora de 2,25 pontos na Hamilton depression de 17 itens (varia de 0 a 52 pontos)

(diferença média padronizada de 0,26, menor que o critério mínimo de 0,5)

Critérios para diferença média padronizada:

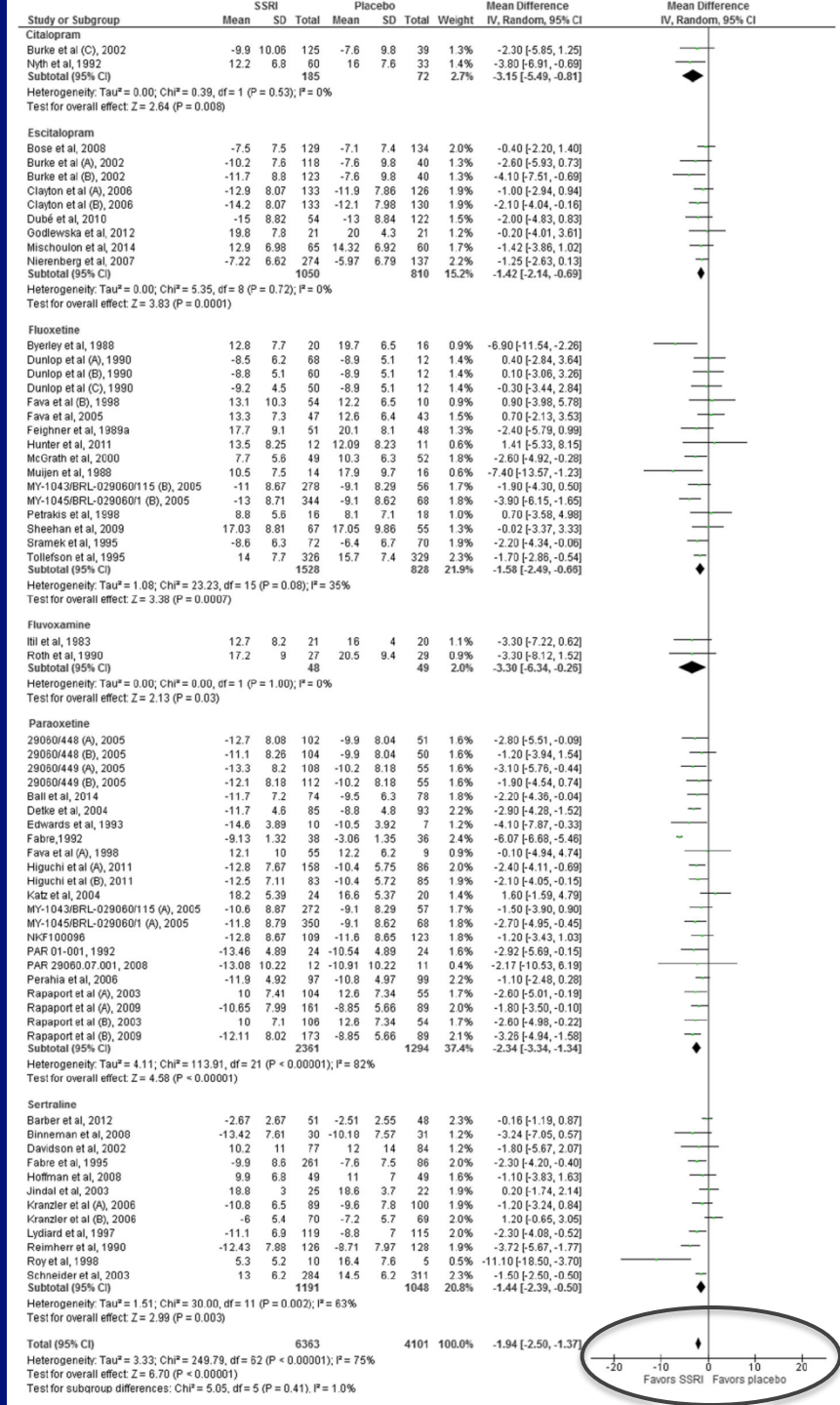
0,2: efeito pequeno

O,5: efeito moderado

0,8: efeito grande

Nenhum estudo utilizou placebo ativo: alto risco de bias

Jakobsen *et al. BMC Psychiatry* (2017) 17:58
DOI 10.1186/s12888-016-1173-2



Jakobsen et al. BMC Psychiatry (2017) 17:58
DOI 10.1186/s12888-016-1173-2

BMC Psychiatry

RESEARCH ARTICLE Open Access

Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis

Janus Christian Jakobsen[1,2*], Kiran Kumar Katakam[1], Anne Schou[1], Signe Gade Hellmuth[1], Sandra Elkjær Stallknecht[1], Katja Leth-Møller[1], Maria Iversen[1], Marianne Bjørnø Banke[1], Iggiannguaq Juhl Petersen[1], Sarah Louise Klingenberg[1], Jesper Krogh[3], Sebastian Elgaard Ebert[1], Anne Timm[1], Jane Lindschou[1] and Christian Gluud[1]

Conclusions

SSRIs versus placebo seem to have statistically significant effects on depressive symptoms, but the clinical significance of these effects seems questionable and all trials were at high risk of bias. Furthermore, SSRIs versus placebo significantly increase the risk of both serious and non-serious adverse events. Our results show that the harmful effects of SSRIs versus placebo for major depressive disorder seem to outweigh any potentially small beneficial effects.

Meanwhile more effective and less costly treatments were marginalised. The success of the SSRIs pushed older tricyclic antidepressants out of the market. This is a problem because SSRIs have never been shown to work for the depressions associated with a greatly increased risk of suicide (melancholia). The nervous states that SSRIs do treat are not associated with increased risk of suicide.[11] The focus on SSRIs also coincided with the abandonment of the pursuit of research into established biological disturbances linked to melancholia (raised cortisol); the SSRIs are ineffective in mood disorders with raised cortisol.[12]

Over two decades later, the number of antidepressant prescriptions a year is slightly more than the number of people in the Western world. Most (nine out of 10) prescriptions are for patients who faced difficulties on stopping, equating to about a tenth of the population.[13 14] These patients are often advised to continue treatment because their difficulties indicate they need ongoing treatment, just as a person with diabetes needs insulin.

Serotonin and depression
The marketing of a myth

Editorial BMJ 2015
David Healy

Mas….

DOI: 10.1017/neu.2017.23

ACTA NEUROPSYCHIATRICA

Commentary

Multiple possible inaccuracies cast doubt on a recent report suggesting selective serotonin reuptake inhibitors to be toxic and ineffective

Hieronymus F, Lisinski A, Näslund J, Eriksson E. Multiple possible inaccuracies cast doubt on a recent report suggesting selective serotonin reuptake inhibitors to be toxic and ineffective.

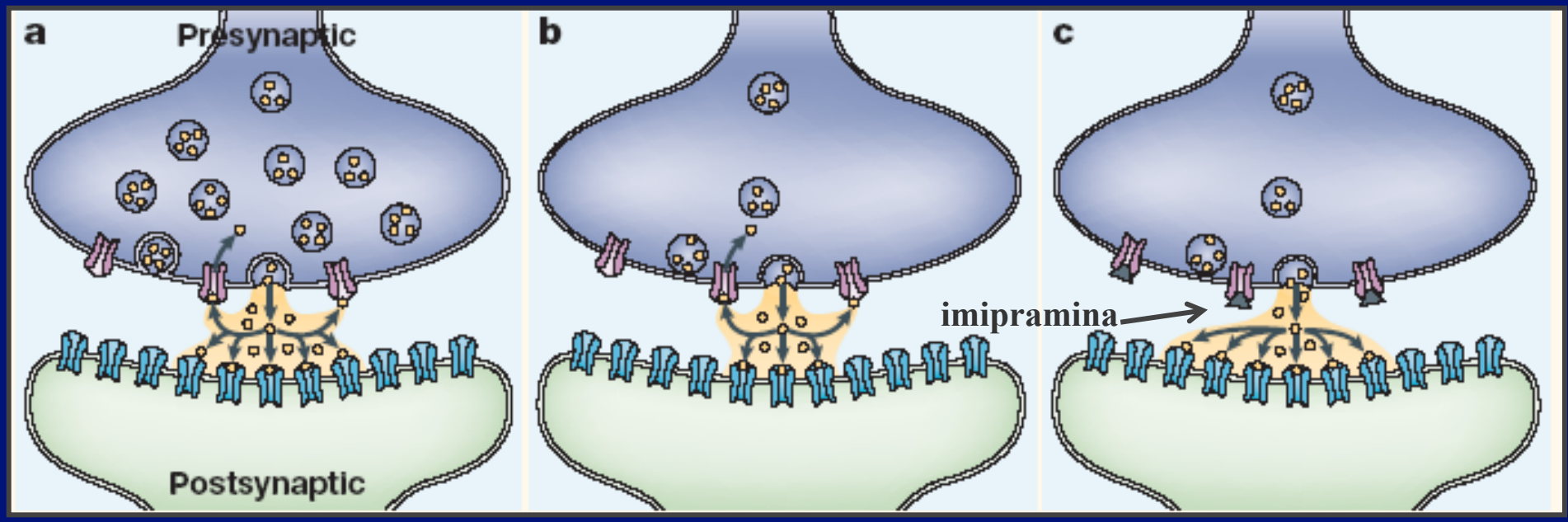
Fredrik Hieronymus, Alexander Lisinski, Jakob Näslund, Elias Eriksson

Department of Pharmacology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

According to a systematic review on the use of selective serotonin reuptake inhibitors (SSRIs) in adult depression that was recently published in BMC Psychiatry, the results of which have been widely disseminated in lay media, these drugs increase the risk for serious adverse events (SAEs) while

Using their paper to propagate the image of the SSRIs as generally toxic and ineffective is hence misleading.

Hipótese Monoaminérgica Clássica da Depressão

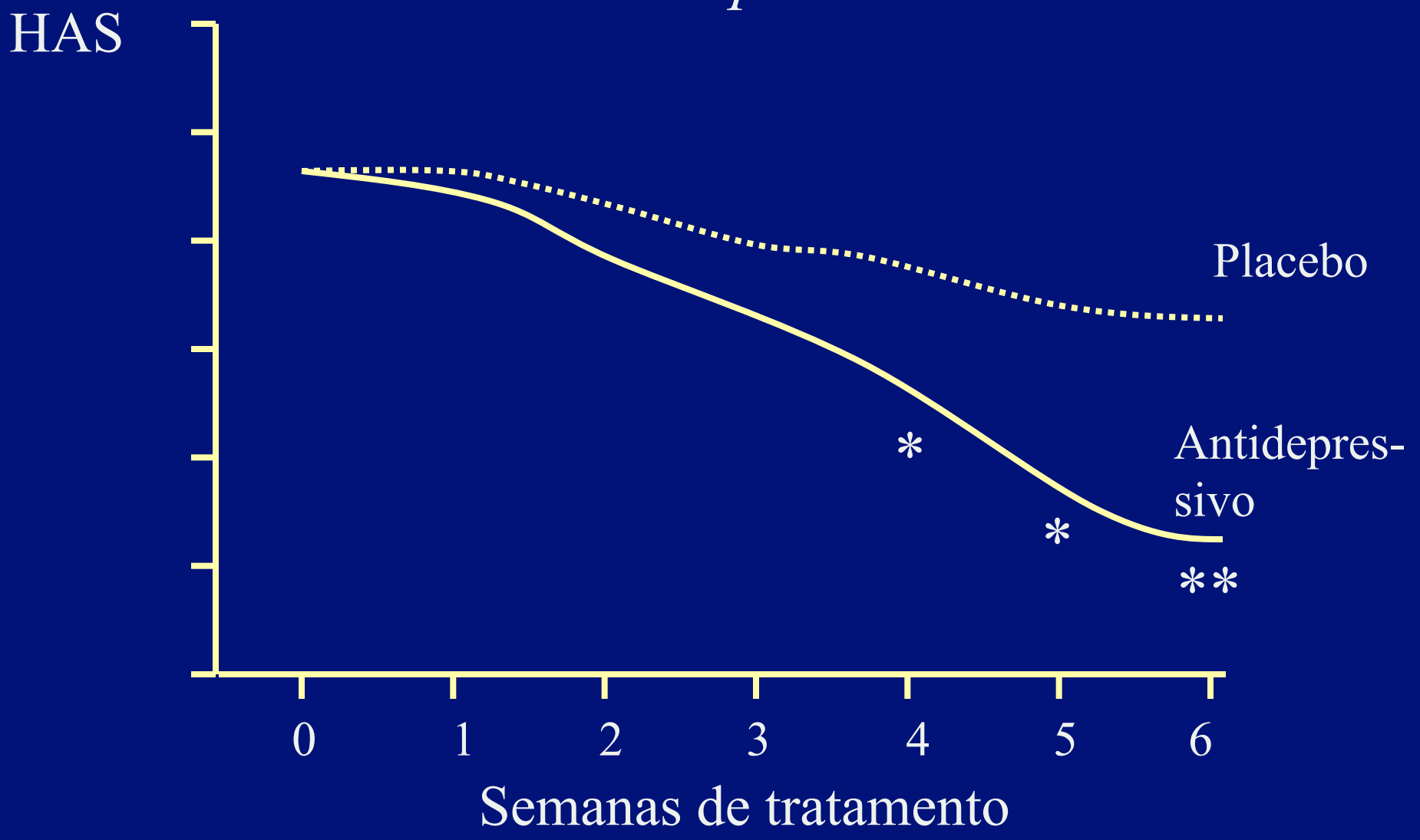


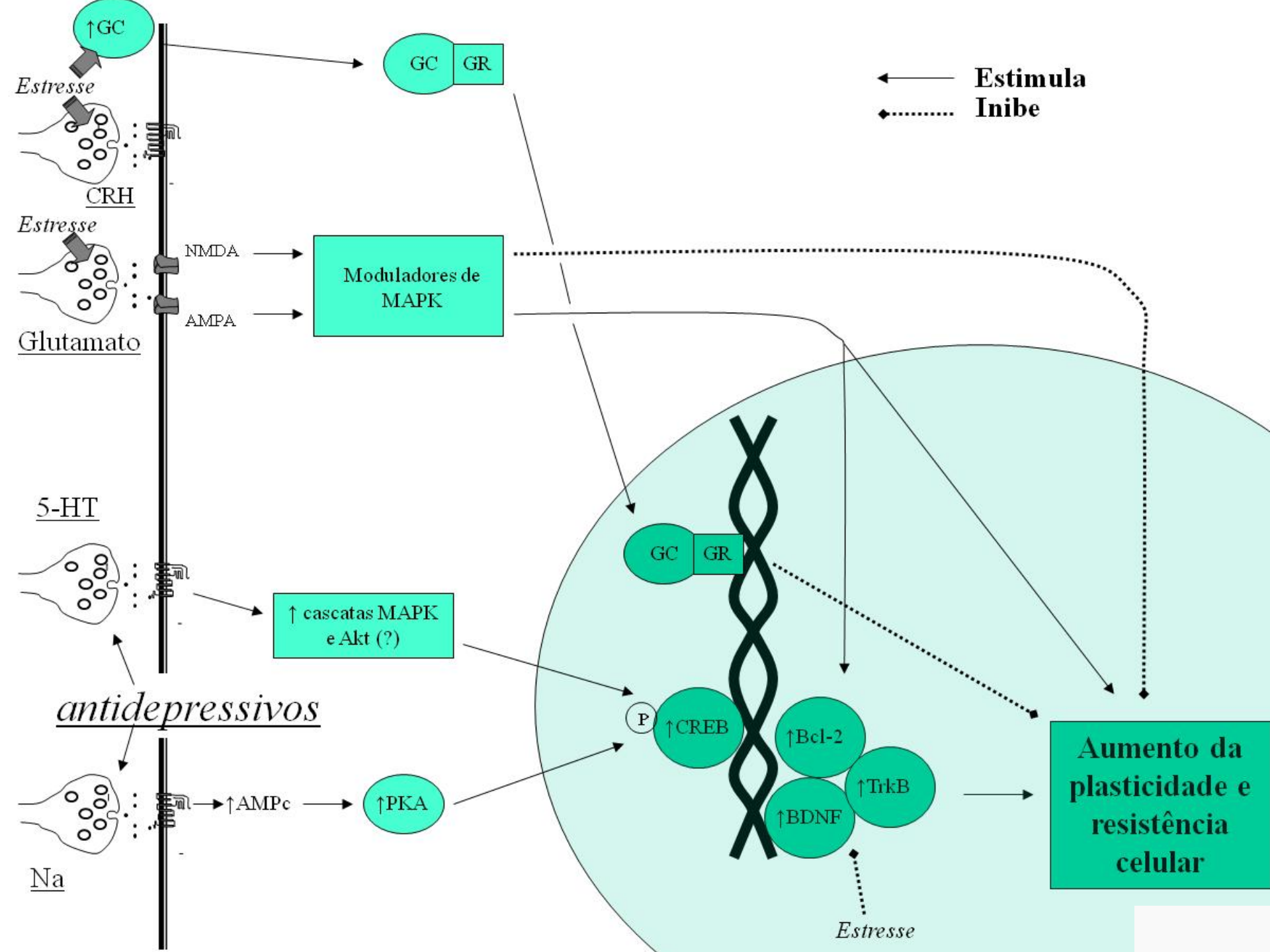
Castrén, 2005

↓ **Noradrenalina** (Schildkraut e Kety, 1965) **e** ↓ **Serotonina** (Lapin e Oxenkrug, 1969)

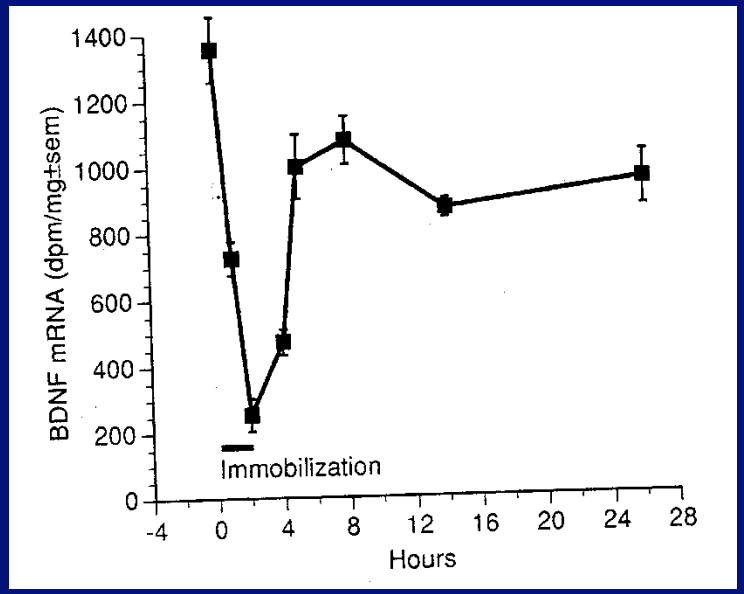
no SNC

Problema: Latência para o aparecimento do efeito de antidepressivos

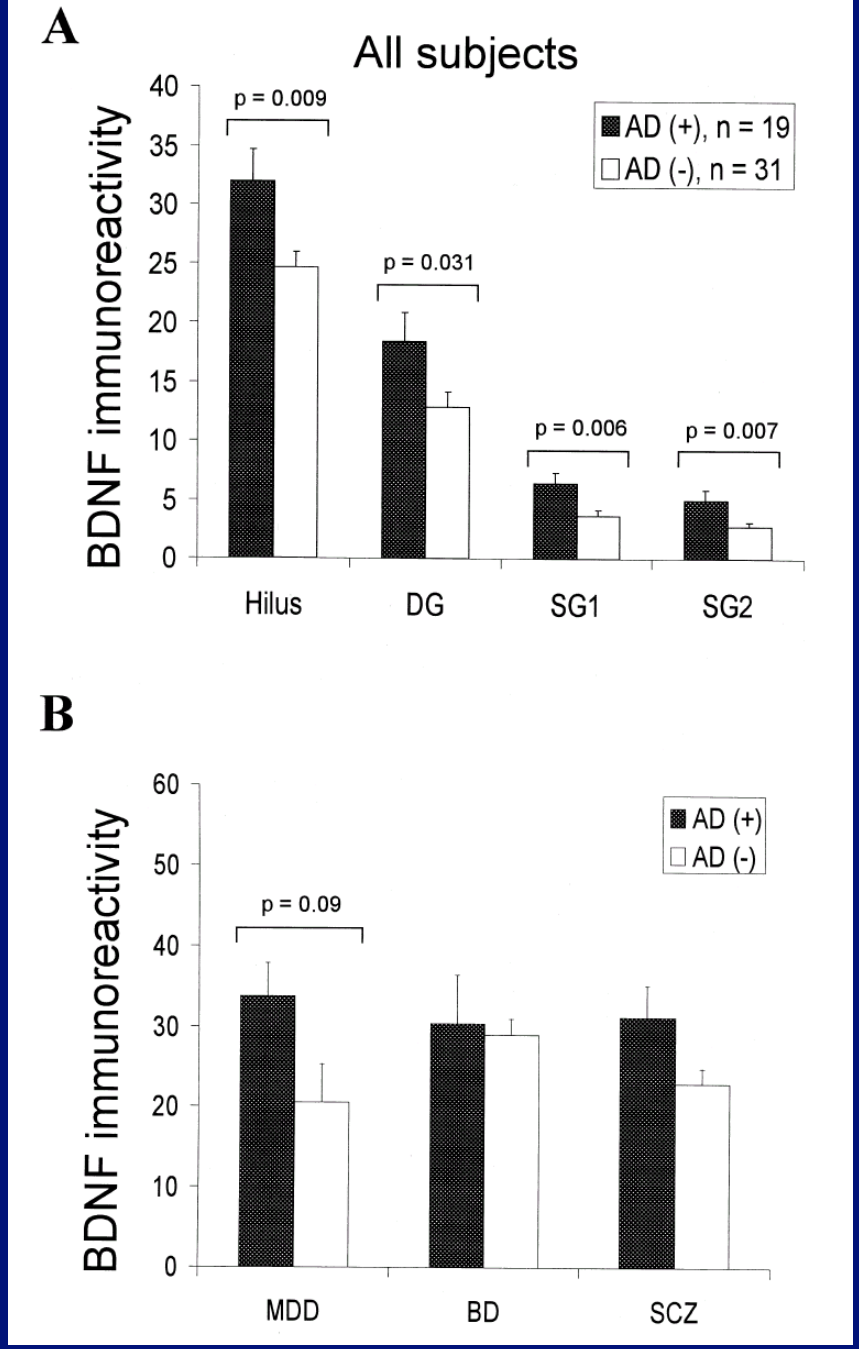



↑GC
Estresse
GC
GR
Estimula
Inibe
CRH
Estresse
NMDA
Moduladores de MAPK
AMPA
Glutamato
5-HT
↑ cascatas MAPK e Akt (?)
GC
GR
antidepressivos
P
↑CREB
↑Bcl-2
↑TrkB
↑BDNF
Aumento da plasticidade e resistência celular
↑AMPc
↑PKA
Na
Estresse

Antidepressivo crônico aumenta o BDNF hipocampal

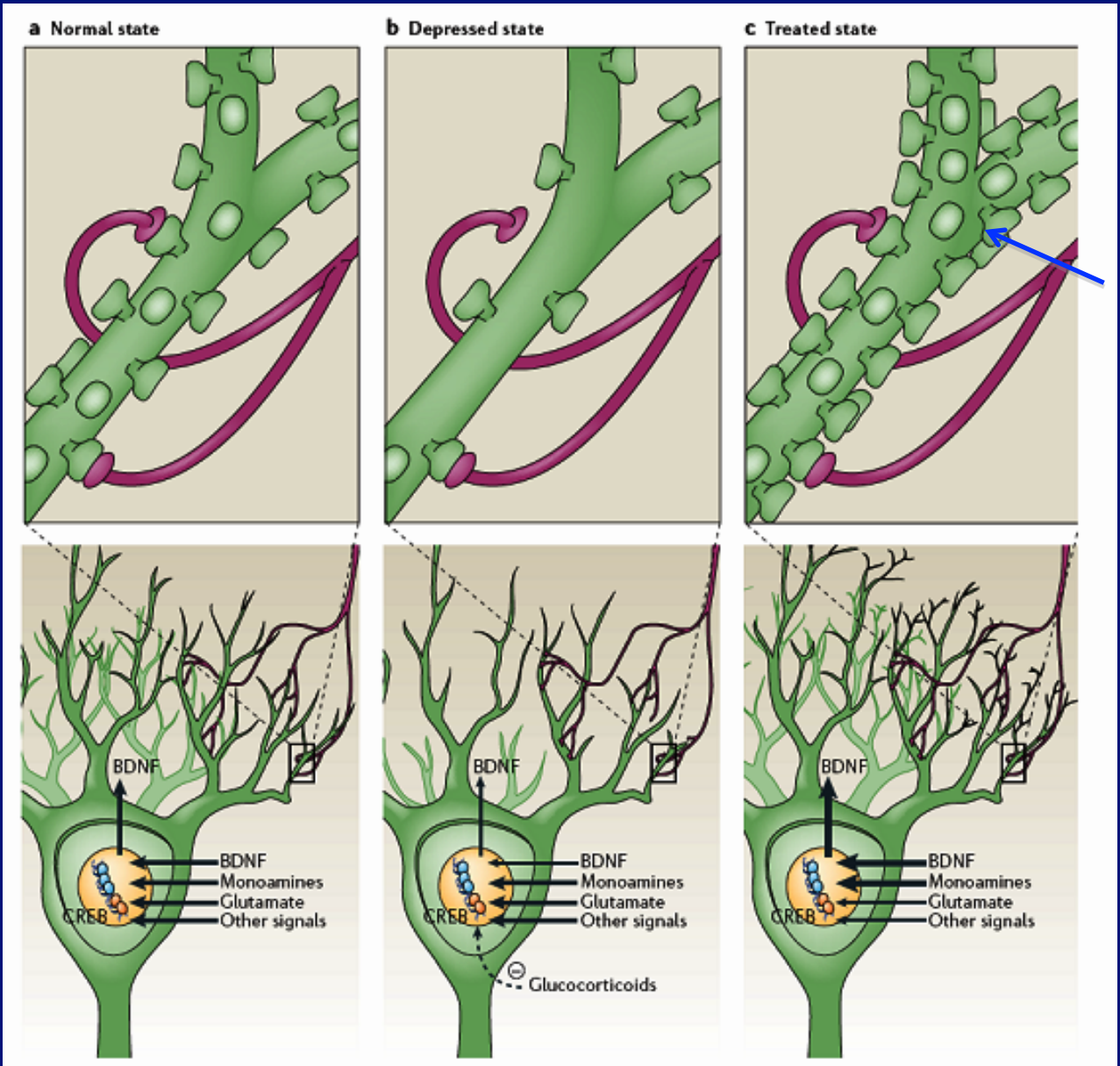


Estresse diminui a expressão de BDNF no hipocampo



Smith et al., Ann NY Acad Sc, 1995; Chen et al., Biol Psychiatry 50:260-265, 2001

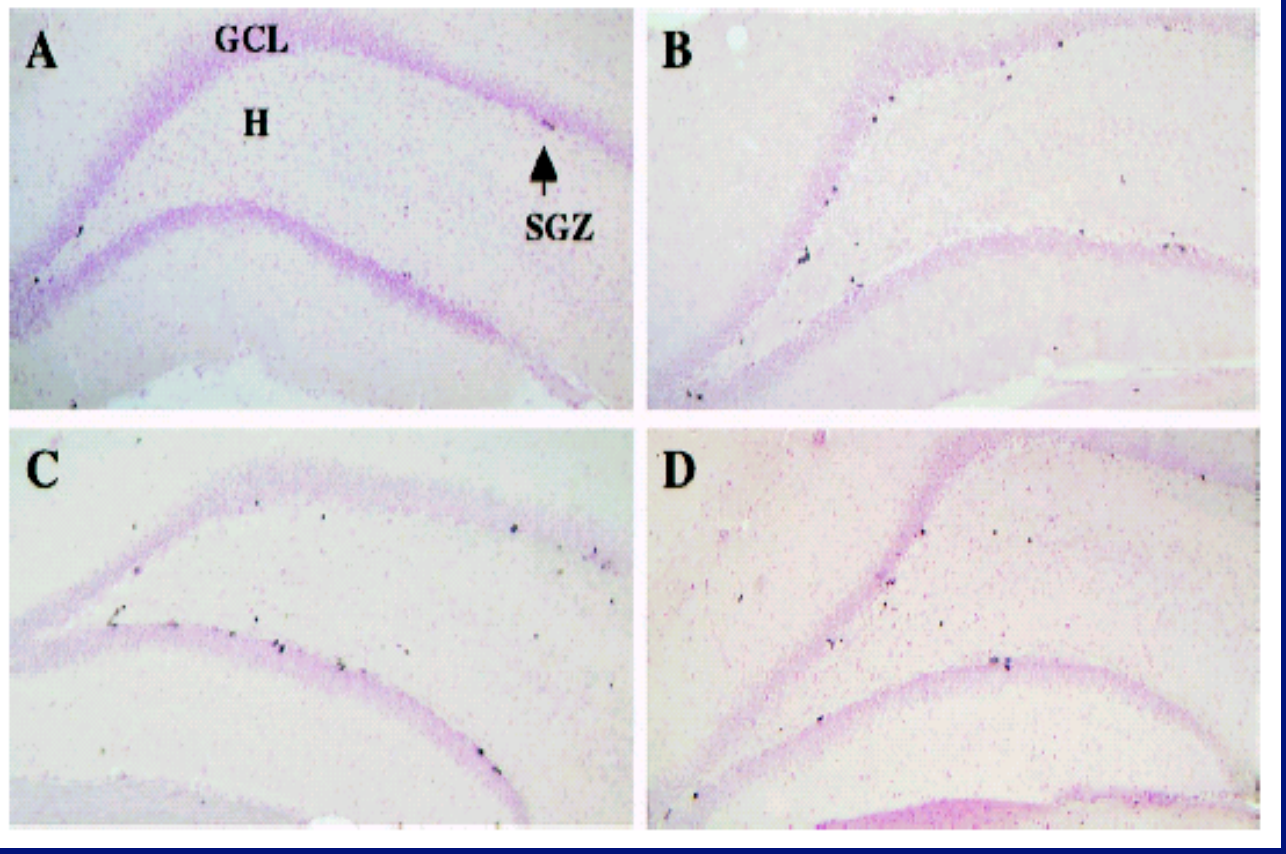
Antidepressivos revertem o “remodelamento” sináptico via aumento de BDNF



The Journal of Neuroscience, December 15, 2000, 20(24):9104–9110

Chronic Antidepressant Treatment Increases Neurogenesis in Adult Rat Hippocampus

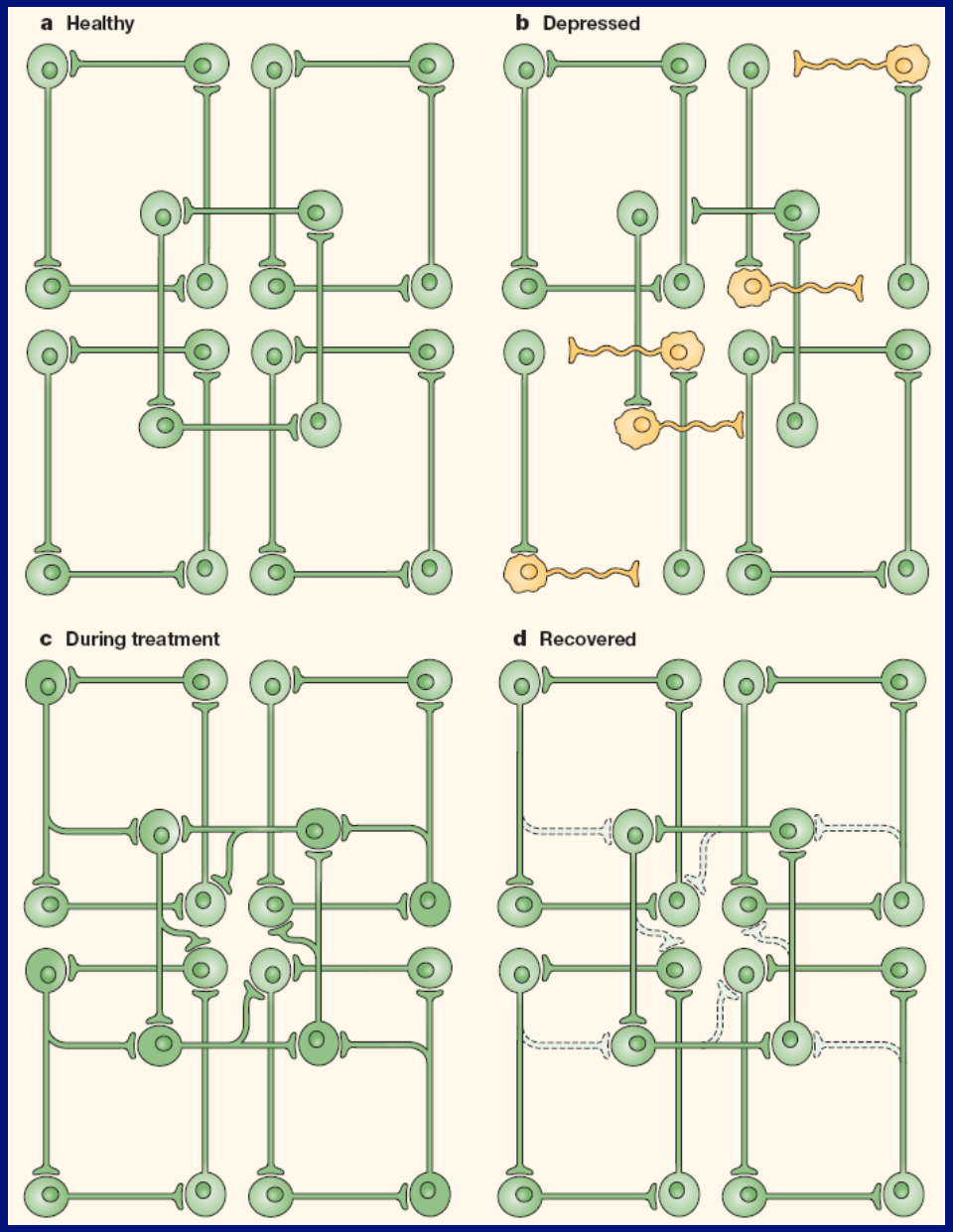
Jessica E. Malberg, Amelia J. Eisch, Eric J. Nestler, and Ronald S. Duman



Antidepressivos aumentam a neurogênese

A: Veículo, B: Tranilcipromine, C: ECS, D: Fluoxetina

A hipótese de "rede neural" da depressão

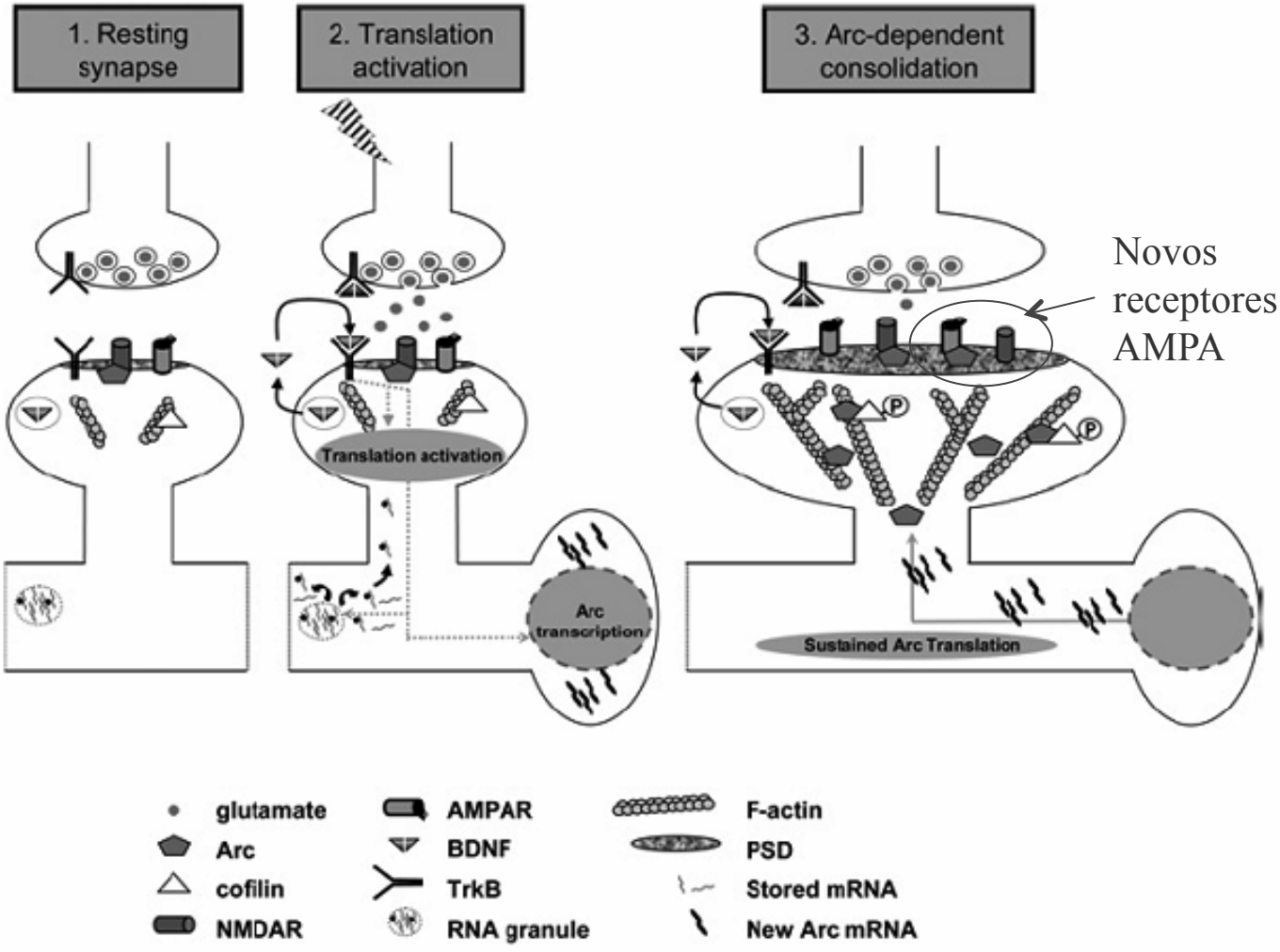


Castren 2007

Antidepressivos não aumentariam o humor diretamente, mas teriam efeito neuroplástico positivo via, por ex., aumento de BDNF

Brain-derived neurotrophic factor and control of synaptic consolidation in the adult brain

J. Soulé, E. Messaoudi and C.R. Bramham[1] 2006



Neurotrofinas como o BDNF servem para otimação, dependente de atividade, de contatos sinápticos via inserção de receptores AMPA

Consequências dessa hipótese:

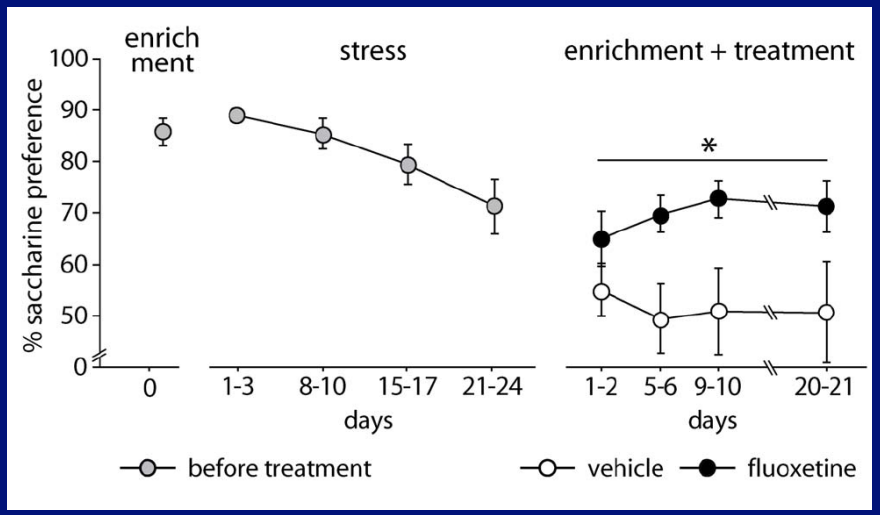
Antidepressivos teriam efeito permissivo, favorecendo a neuroplasticidade e permitindo ao meio ambiente reorganizar a rede neural alterada (importância da psicoterapia)

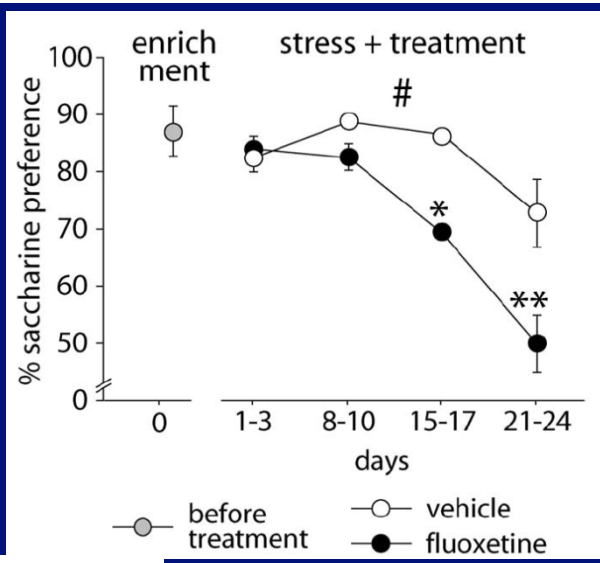
Efeito anti-anedônico da fluoxetina dependeu do ambiente

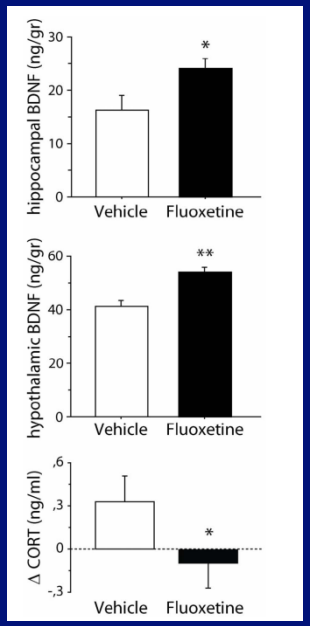
OPEN ACCESS Freely available online PLOS ONE

Antidepressant Treatment Outcome Depends on the Quality of the Living Environment: A Pre-Clinical Investigation in Mice

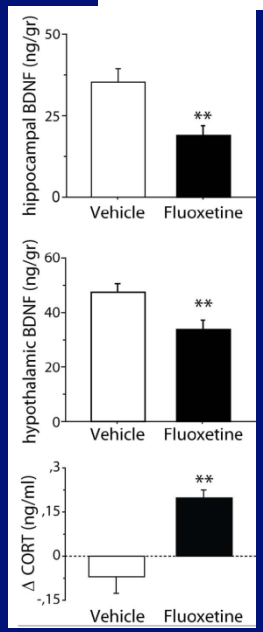
Igor Branchi[1,2*], Sara Santarelli[1], Sara Capoccia[1], Silvia Poggini[1], Ivana D'Andrea[3], Francesca Cirulli[1], Enrico Alleva[1]







Fluoxetina (10mg/kg, 21 dias) após período de estresse repetido variável (24 dias) administrada em ambiente enriquecido



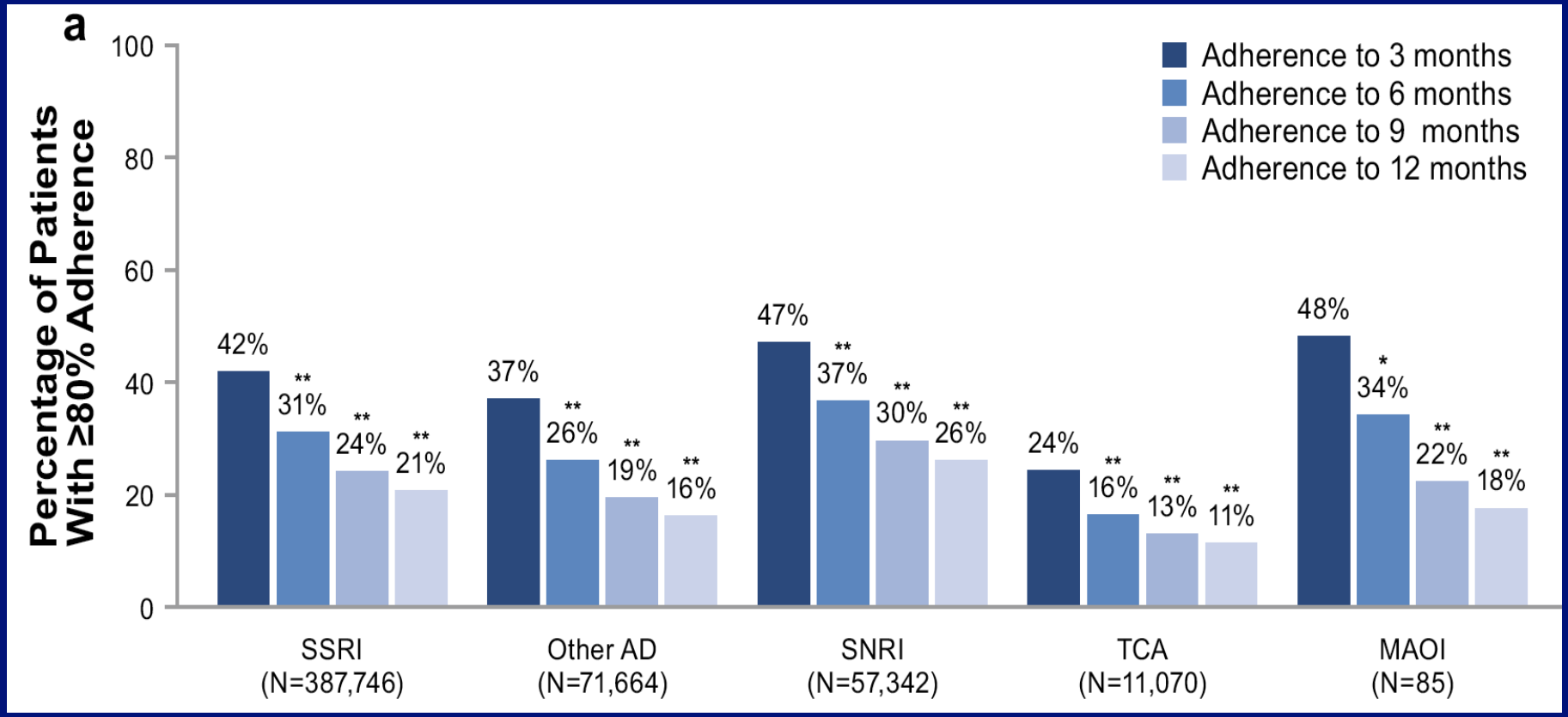
Fluoxetina durante período de estresse (24 dias) administrada após exposição a ambiente enriquecido

Aderência a diferentes grupos de antidepressivos dos 3 aos 12 meses de tratamento

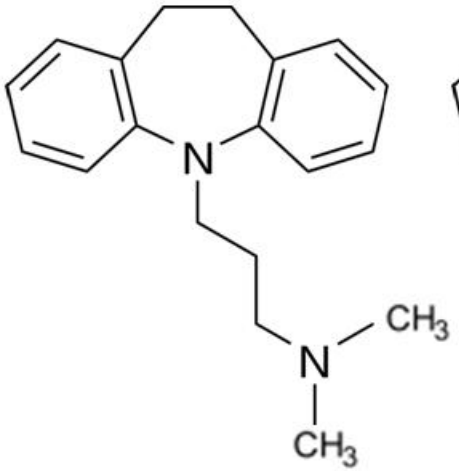
Adherence and Persistence Across Antidepressant Therapeutic Classes: A Retrospective Claims Analysis Among Insured US Patients with Major Depressive Disorder (MDD)

Katelyn R. Keyloun[1] · Ryan N. Hansen[2] · Zsolt Hepp[1] · Patrick Gillard[1] · Michael E. Thase[3] · Emily Beth Devine[2]

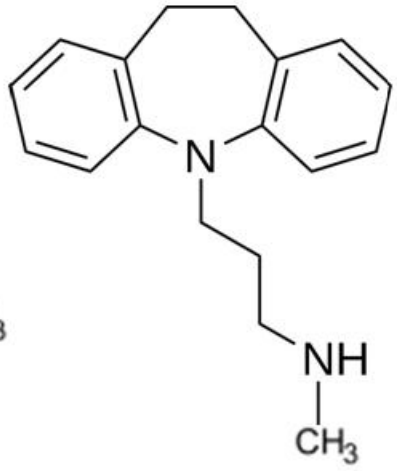
CNS Drugs 2017



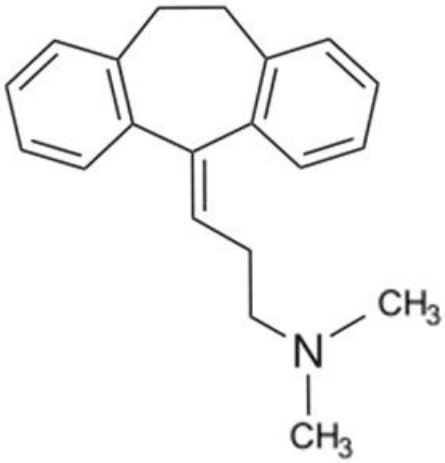
Antidepressivos tricíclicos



Imipramina

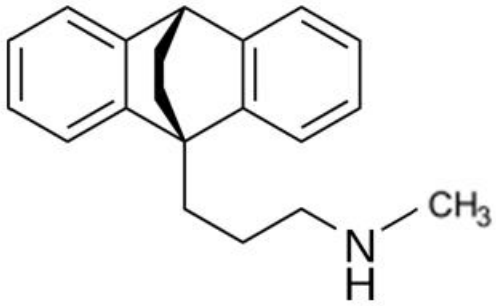


Desipramina



Amitriptilina

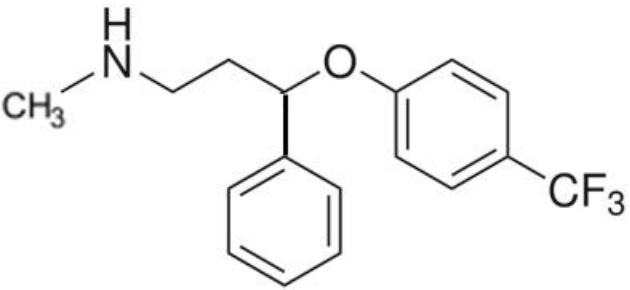
Tetracíclicos



Maprotilina

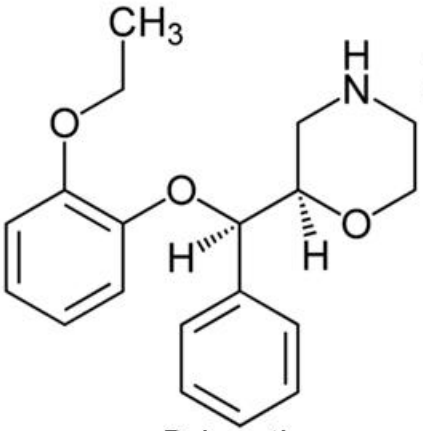
Antidepressivos de segunda geração

SSRI



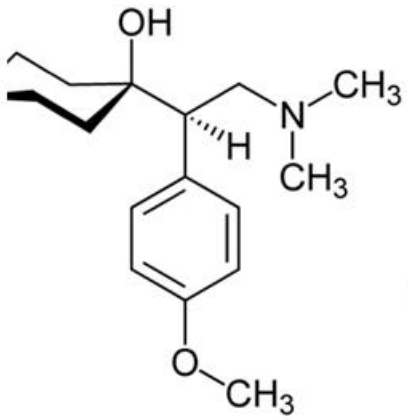
Fluoxetina

NSRI



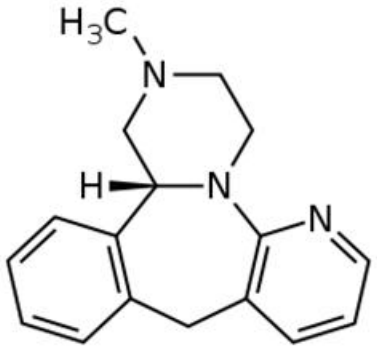
Reboxetina

SNRI



Venlafaxina

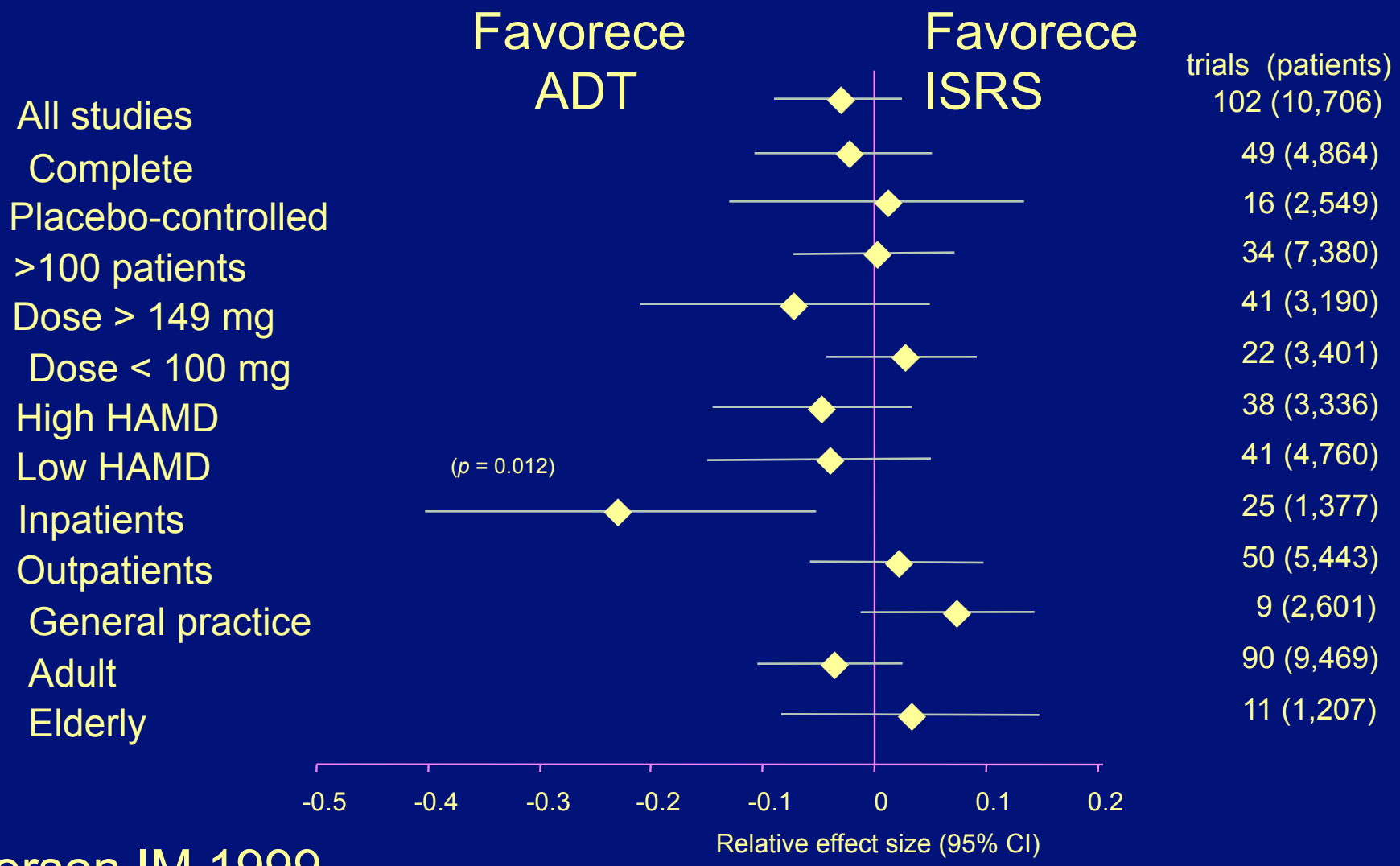
Antagonista de receptores monoaminérgicos



Mirtazapina

Fig. 6.10

Comparação antidepressivos tricíclicos vs. ISRS



Anderson IM 1999

Valores de Ki (em nM) de antidepressivos tricíclicos

Antidepressivo	Muscarínico	H_1	α_1
Imipramina	91	11	91
Amitriptilina	18	1,1	27
Clomipramina	37	31,2	39
Desipramina	196	110	130

Efeitos anticolinérgi-cos

Sedação, ganho de peso

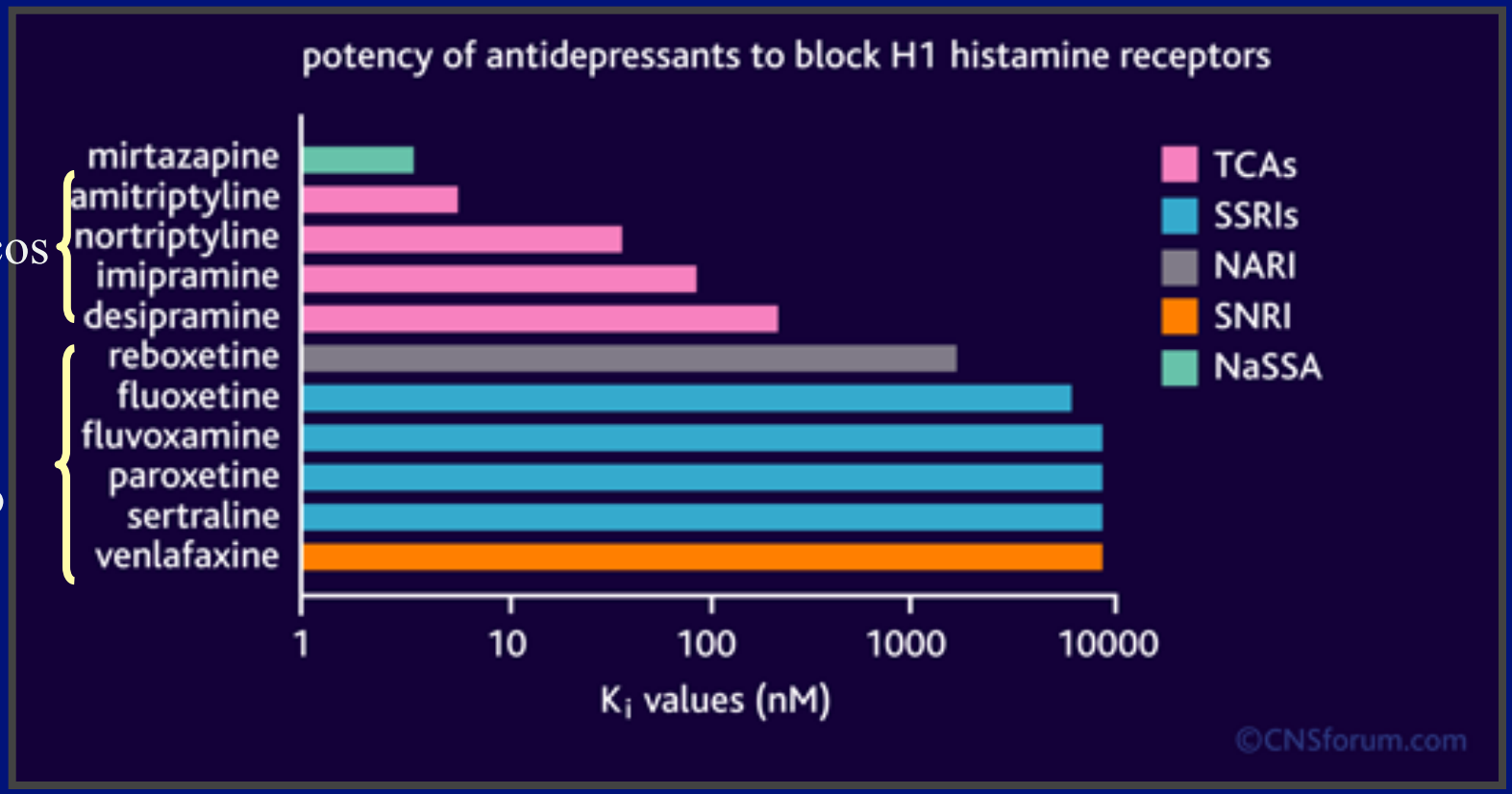
Hipotens ão postural

$$Ki = \frac{IC50}{1 + [L]/Kd}$$

Efeitos colaterais de antidepressivos: afinidade (Ki em nM) por receptores histamínicos (H1)

tricíclicos

2ª. geração

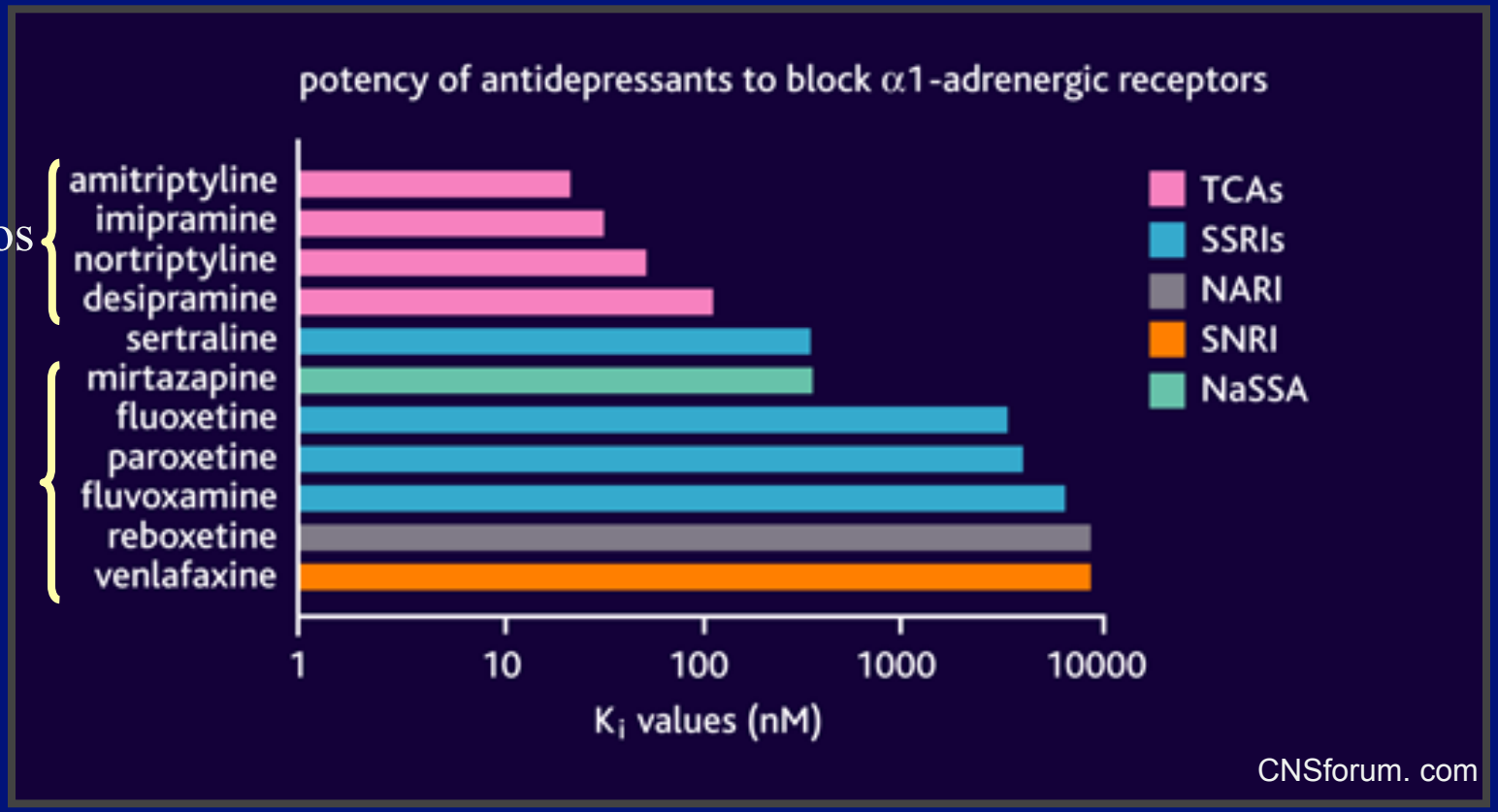


Conseqüências: sedação, ganho de peso

Efeitos colaterais de antidepressivos: afinidade (Ki em nM) por receptores alfa-1 adrenérgicos

tricíclicos

2ª. geração

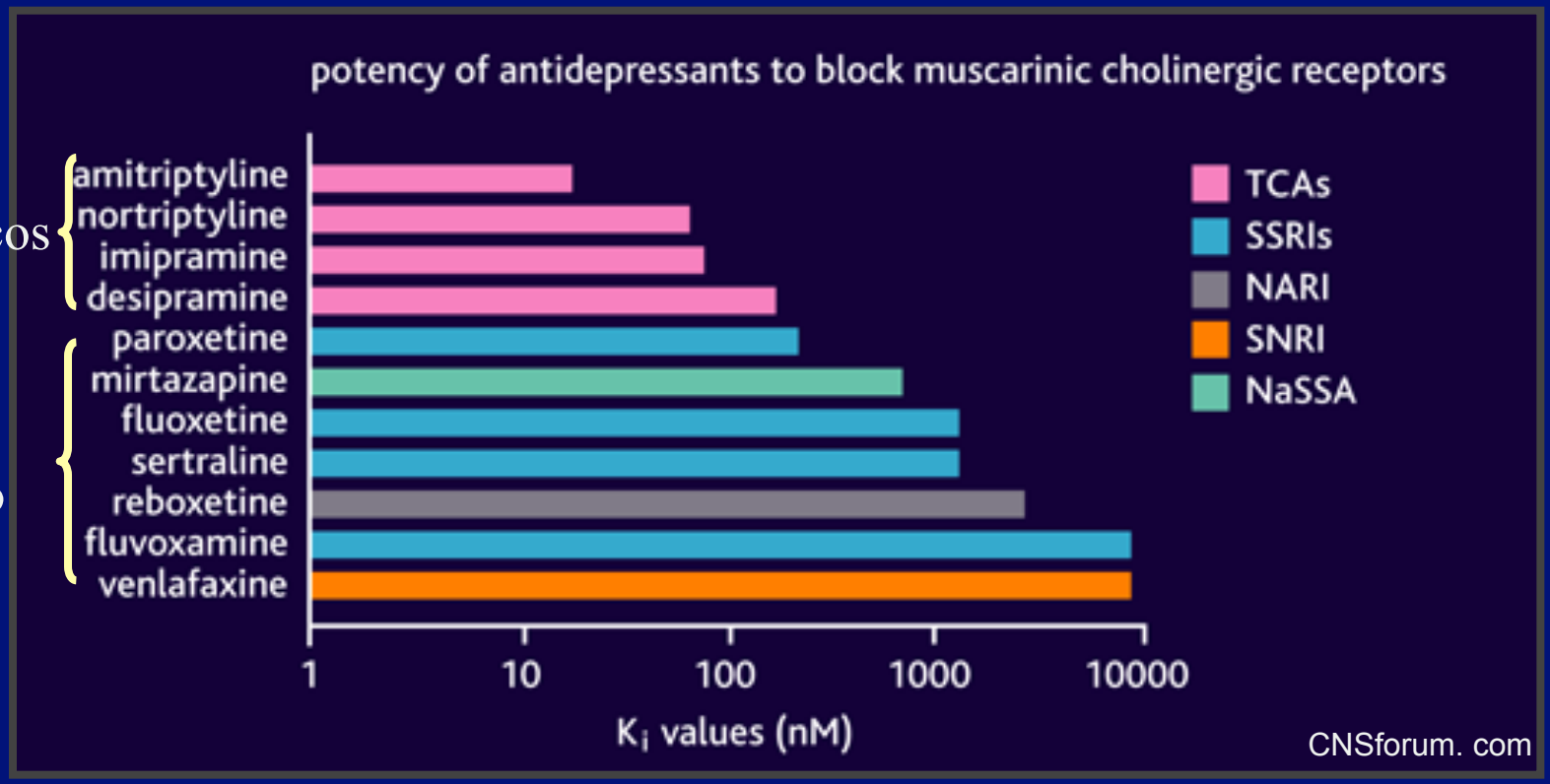


Conseqüências: hipotensão postural, dificuldades de ejaculação

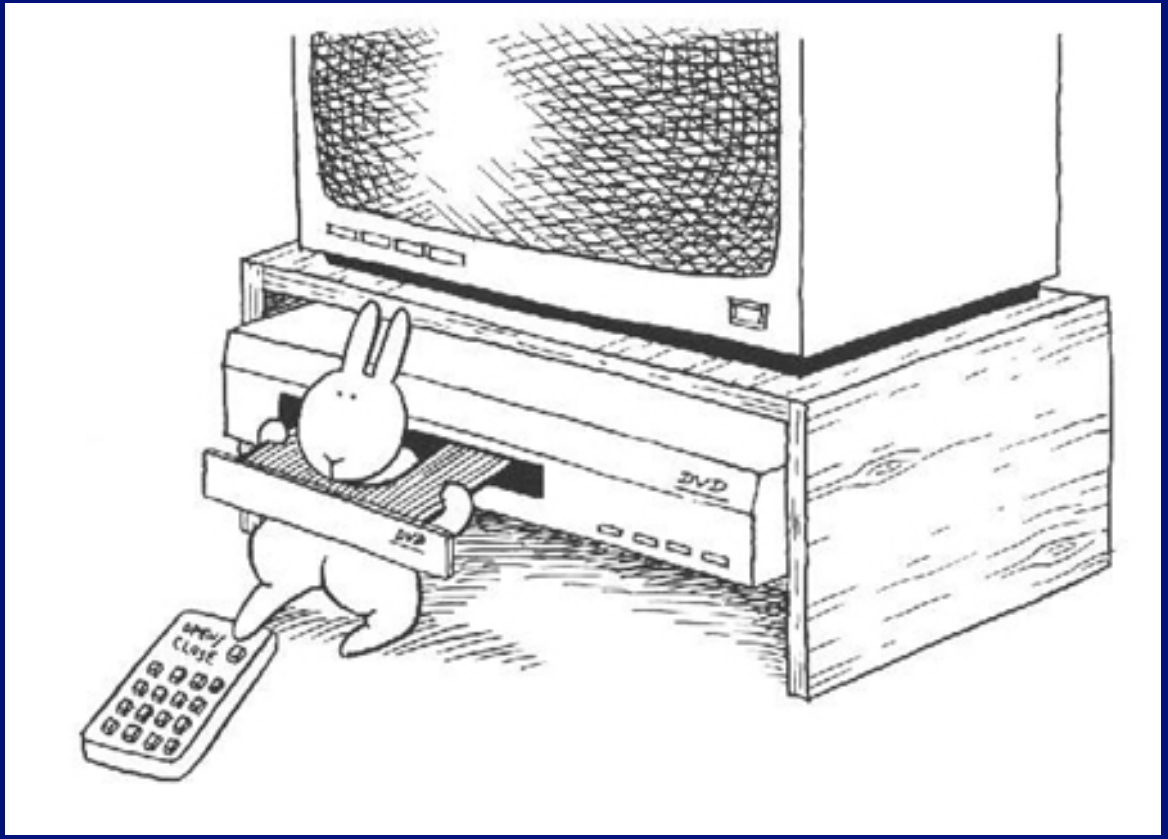
Efeitos colaterais de antidepressivos: afinidade (Ki em nM) por receptores muscarínicos

tricíclicos

2ª. geração



Consequências: boca seca, constipação, visão borrada, retenção urinária



Risco de suicídio e antidepressivos tricíclicos

Antidepressivos tricíclicos: diminuição da condução cardíaca em concentrações tóxicas *(ex. 5 a 6 x dose máxima diária de imipramina pode ser fatal)*

	Capacidade de alteração na condução cardíaca em conc. tóxicas
Imipramina	Sim
Amitriptilina	Sim
Desipramina	Sim
Maprotilina	Sim
Amoxapina	Baixa
Mianserina	Baixa
Trazodona	Baixa
Fluoxetina	Baixa
Bupropiona	Baixa
Alprazolam	Ausenta

Mortalidade por antidepressivos: mortality/self poisoning

Table 1
Risk of fatality from mood disorder medication overdose

Medication	Relative Toxicity Index
TCAs	
Lowest risk: amitriptyline	1.0
Highest risk: doxepin	2.6
Average of 7 studied TCAs	1.6
SNRIs	
Venlafaxine	0.29
NaSSA	
Mirtazapine	0.22
SSRIs	
Lowest risk: fluvoxamine	0
Highest risk: citalopram	0.12
Average of 5 studied SSRIs	0.06

Abbreviation: NaSSA, noradernergic and specific serotonergic antidepressant.

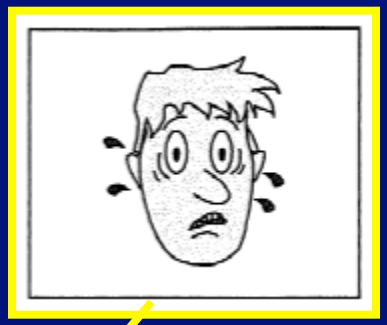
Data from Hawton K, Bergen H, Simkin S, et al. Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose. Br J Psychiatry 2010;196:354–8.

Efeitos adversos ISRSs (ex. Fluoxetina)

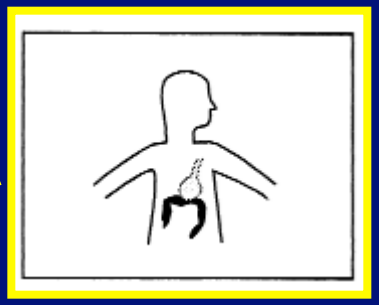
Agitação (13%)

Náusea/vômitos (20-30%)

Ansiedade (12%)

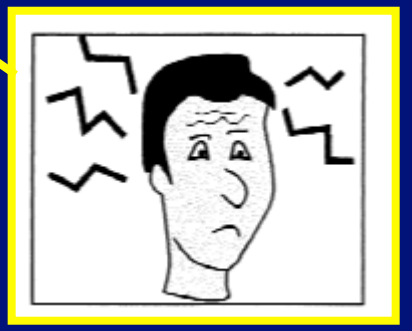


Diarréia (12%)



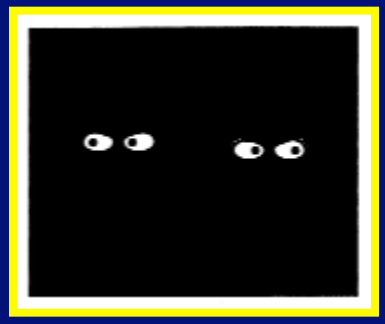
Insônia (9-26%)

Dor de cabeça (16,6%)



Interação de drogas (inibição isoenzimas citocromo P450))

Disfunção sexual



Suicídio(?)

Modificado de Stahl 1998

Incidência de efeitos adversos colaterais é variável entre os antidepressivos (pacientes podem, eventualmente, se beneficiar de troca da prescrição)

Table 2
Antidepressant side-effect frequency %

Drug	Diarrhea	Dizziness	Headache	Insomnia	Nausea
Bupropion	8.7	12.5	27.2	11–40	9–24
Citalopram	8	Up to 14	Up to 18	Up to 15	21
Duloxetine	7–13	6–17	NR	8–16	11
Escitalopram	6–14	4–7	24	7–14	15–18
Fluoxetine	12	2–11	16.6	9–26	20–30
Fluvoxamine	NR	NR	14.5	NR	22.2
Mirtazapine	8.8	12	12	8	↑ Appetite 17
Paroxetine	18	4–6	17–27	Up to 24	26
Sertraline	13–24	6–17	25	12–28	13–30
Venlafaxine	5.5	11–24	25–38	14–24	22–58

Abbreviation: NR, not reported.

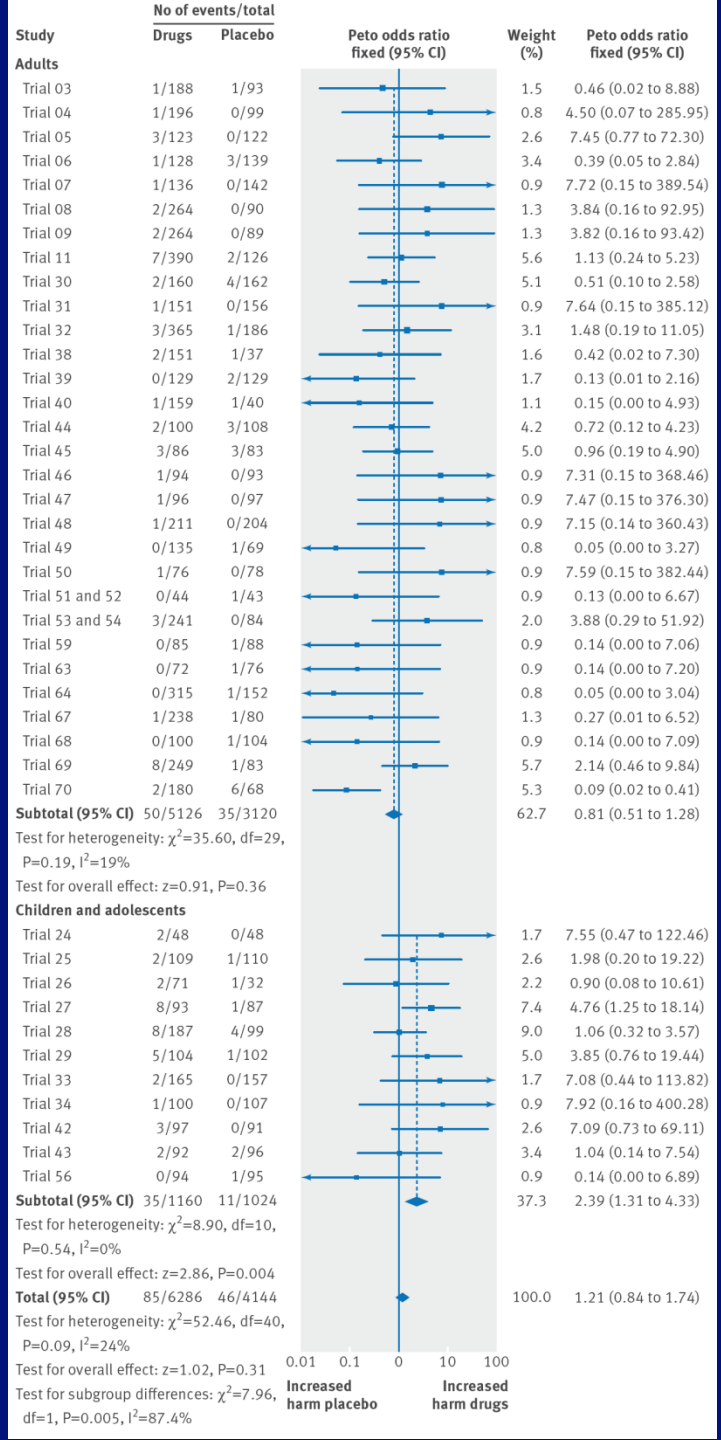
Data from Hansen RA, Gartlehner G, Lohr KN, et al. Efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder. Ann Intern Med 2005;143(6):415–26.

Outros efeitos: aumento de risco de suicídio em adultos jovens, adolescentes e crianças?

Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports

Brit Med J 2016

Tarang Sharma,[1,2] Louise Schow Guski,[1,2] Nanna Freund,[1,2] Peter C Gøtzsche[1,2]



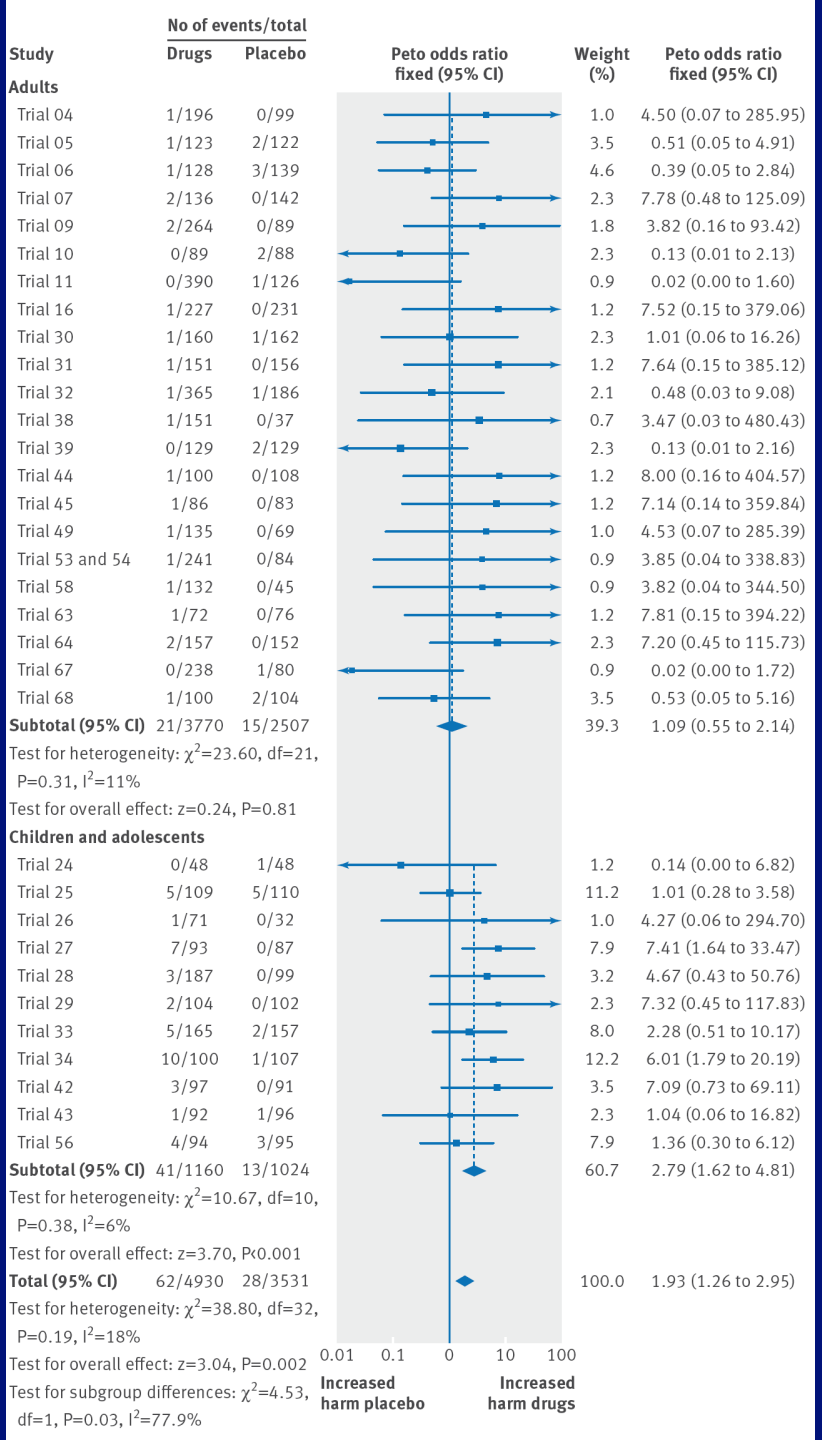
Study	No of events/total: Drugs	Placebo	Peto odds ratio fixed (95% CI)	Weight (%)	Peto odds ratio fixed (95% CI)
Adults					
Trial 03	1/188	1/93		1.5	0.46 (0.02 to 8.88)
Trial 04	1/196	0/99		0.8	4.50 (0.07 to 285.95)
Trial 05	3/123	0/122		2.6	7.45 (0.77 to 72.30)
Trial 06	1/128	3/139		3.4	0.39 (0.05 to 2.84)
Trial 07	1/136	0/142		0.9	7.72 (0.15 to 389.54)
Trial 08	2/264	0/90		1.3	3.84 (0.16 to 92.95)
Trial 09	2/264	0/89		1.3	3.82 (0.16 to 93.42)
Trial 11	7/390	2/126		5.6	1.13 (0.24 to 5.23)
Trial 30	2/160	4/162		5.1	0.51 (0.10 to 2.58)
Trial 31	1/151	0/156		0.9	7.64 (0.15 to 385.12)
Trial 32	3/365	1/186		3.1	1.48 (0.19 to 11.05)
Trial 38	2/151	1/37		1.6	0.42 (0.02 to 7.30)
Trial 39	0/129	2/129		1.7	0.13 (0.01 to 2.16)
Trial 40	1/159	1/40		1.1	0.15 (0.00 to 4.93)
Trial 44	2/100	3/108		4.2	0.72 (0.12 to 4.23)
Trial 45	3/86	3/83		5.0	0.96 (0.19 to 4.90)
Trial 46	1/94	0/93		0.9	7.31 (0.15 to 368.46)
Trial 47	1/96	0/97		0.9	7.47 (0.15 to 376.30)
Trial 48	1/211	0/204		0.9	7.15 (0.14 to 360.43)
Trial 49	0/135	1/69		0.8	0.05 (0.00 to 3.27)
Trial 50	1/76	0/78		0.9	7.59 (0.15 to 382.44)
Trial 51 and 52	0/44	1/43		0.9	0.13 (0.00 to 6.67)
Trial 53 and 54	3/241	0/84		2.0	3.88 (0.29 to 51.92)
Trial 59	0/85	1/88		0.9	0.14 (0.00 to 7.06)
Trial 63	0/72	1/76		0.9	0.14 (0.00 to 7.20)
Trial 64	0/315	1/152		0.8	0.05 (0.00 to 3.04)
Trial 67	1/238	1/80		1.3	0.27 (0.01 to 6.52)
Trial 68	0/100	1/104		0.9	0.14 (0.00 to 7.09)
Trial 69	8/249	1/83		5.7	2.14 (0.46 to 9.84)
Trial 70	2/180	6/68		5.3	0.09 (0.02 to 0.41)
Subtotal (95% CI)	50/5126	35/3120		62.7	0.81 (0.51 to 1.28)
Test for heterogeneity: χ^2=35.60, df=29, P=0.19, I^2=19%					
Test for overall effect: z=0.91, P=0.36					
Children and adolescents					
Trial 24	2/48	0/48		1.7	7.55 (0.47 to 122.46)
Trial 25	2/109	1/110		2.6	1.98 (0.20 to 19.22)
Trial 26	2/71	1/32		2.2	0.90 (0.08 to 10.61)
Trial 27	8/93	1/87		7.4	4.76 (1.25 to 18.14)
Trial 28	8/187	4/99		9.0	1.06 (0.32 to 3.57)
Trial 29	5/104	1/102		5.0	3.85 (0.76 to 19.44)
Trial 33	2/165	0/157		1.7	7.08 (0.44 to 113.82)
Trial 34	1/100	0/107		0.9	7.92 (0.16 to 400.28)
Trial 42	3/97	0/91		2.6	7.09 (0.73 to 69.11)
Trial 43	2/92	2/96		3.4	1.04 (0.14 to 7.54)
Trial 56	0/94	1/95		0.9	0.14 (0.00 to 6.89)
Subtotal (95% CI)	35/1160	11/1024		37.3	2.39 (1.31 to 4.33)
Test for heterogeneity: χ^2=8.90, df=10, P=0.54, I^2=0%					
Test for overall effect: z=2.86, P=0.004					
Total (95% CI)	85/6286	46/4144		100.0	1.21 (0.84 to 1.74)
Test for heterogeneity: χ^2=52.46, df=40, P=0.09, I^2=24%					
Test for overall effect: z=1.02, P=0.31					
Test for subgroup differences: χ^2=7.96, df=1, P=0.005, I^2=87.4%					

Outros efeitos: aumento de comportamento agressivo em adultos jovens, adolescentes e crianças?

Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports

Brit Med J 2016

Tarang Sharma,[1,2] Louise Schow Guski,[1,2] Nanna Freund,[1,2] Peter C Gøtzsche[1,2]



Incidência (%) de disfunção sexual com ISRSs

Efeito adverso	Método de coleta	Fluoxe-tina	Paroxe-tina	Sertra-lina	Fluvo-xamina
Disfunção Sexual (qualquer sintoma)	Queixa espontânea	20	22	16	
	Questionamento sistemático	54	65	56	59
Disfunção erétil/ dificuldades de lubrificação vaginal	Questionamento sistemático	16	35	16	10
Retardo do orgasmo ou ejaculação	Questionamento sistemático	34	48	37	31

Ferguson JMJ Clin Psych 2011

Neuropsychopharmacology (2011) 36, 1837–1847
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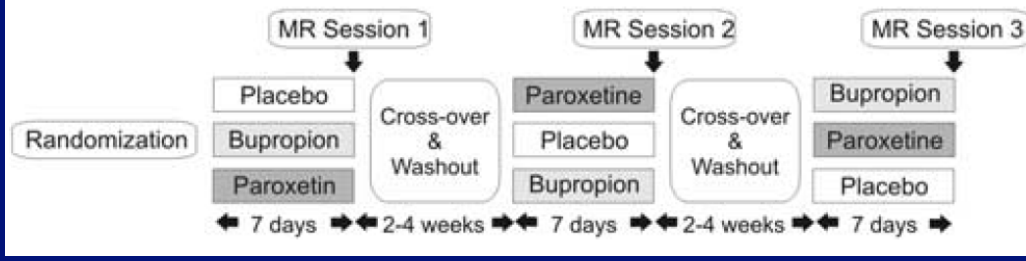
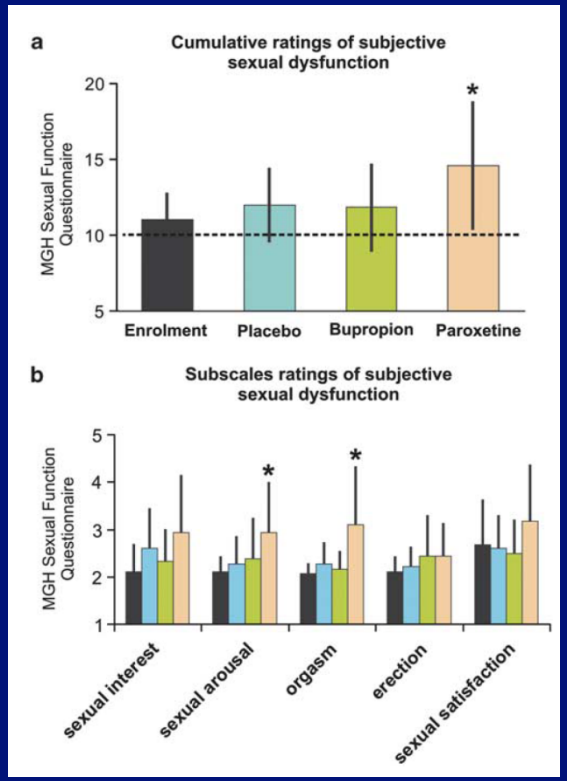
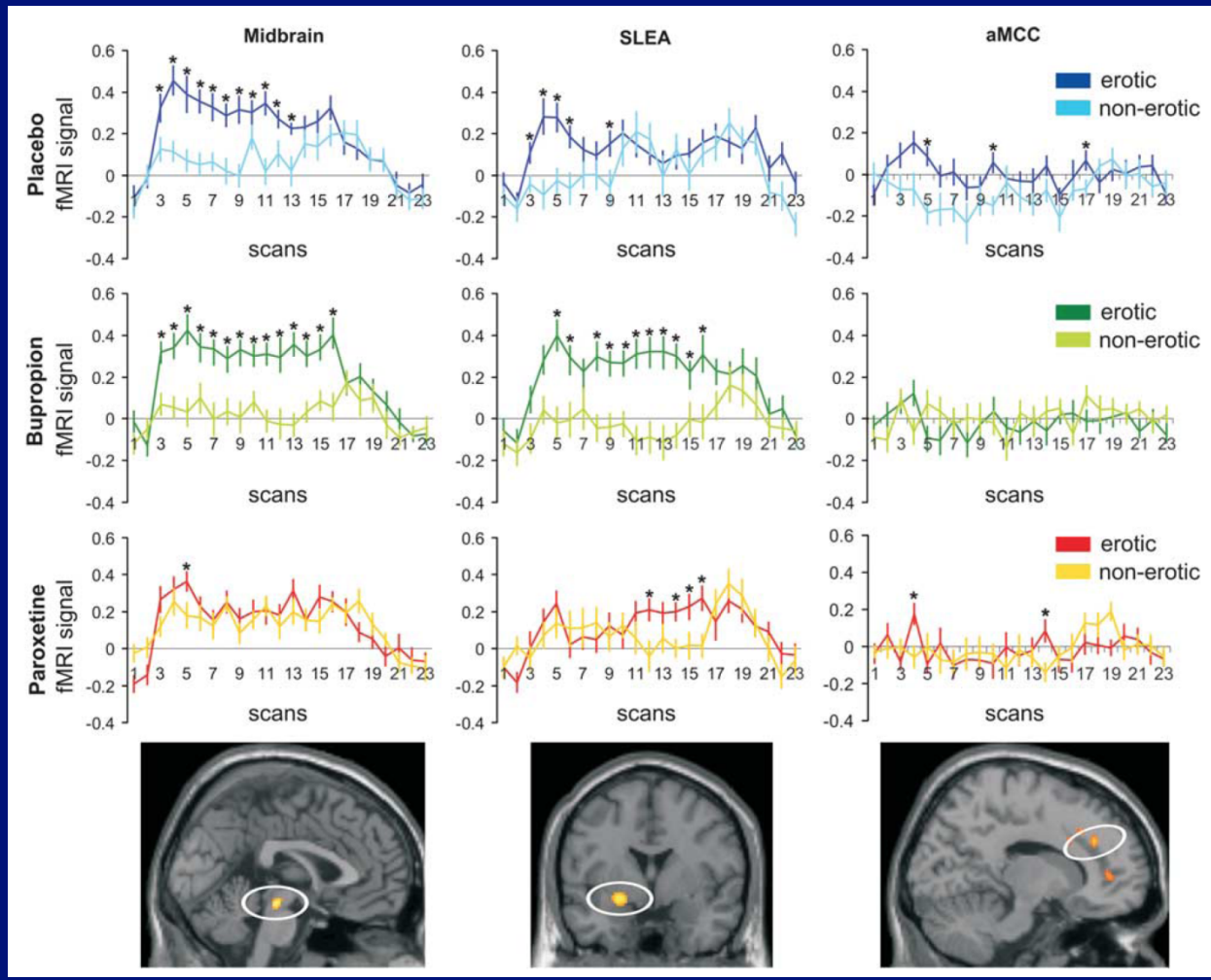
www.neuropsychopharmacology.org

Neural Correlates of Antidepressant-Related Sexual Dysfunction: A Placebo-Controlled fMRI Study on Healthy Males Under Subchronic Paroxetine and Bupropion

Birgit Abler*[,1,4], Angela Seeringer[2,4], Antonie Hartmann[1], Georg Grön[1], Coraline Metzger[3], Martin Walter[3] and Julia Stingl[2]







Paroxetina diminui ativação de áreas encefálicas por filme erótico

Efeitos adversos ISRSs

Custos aproximados de alguns antidepressivos (Reais-2011) tratamento mensal

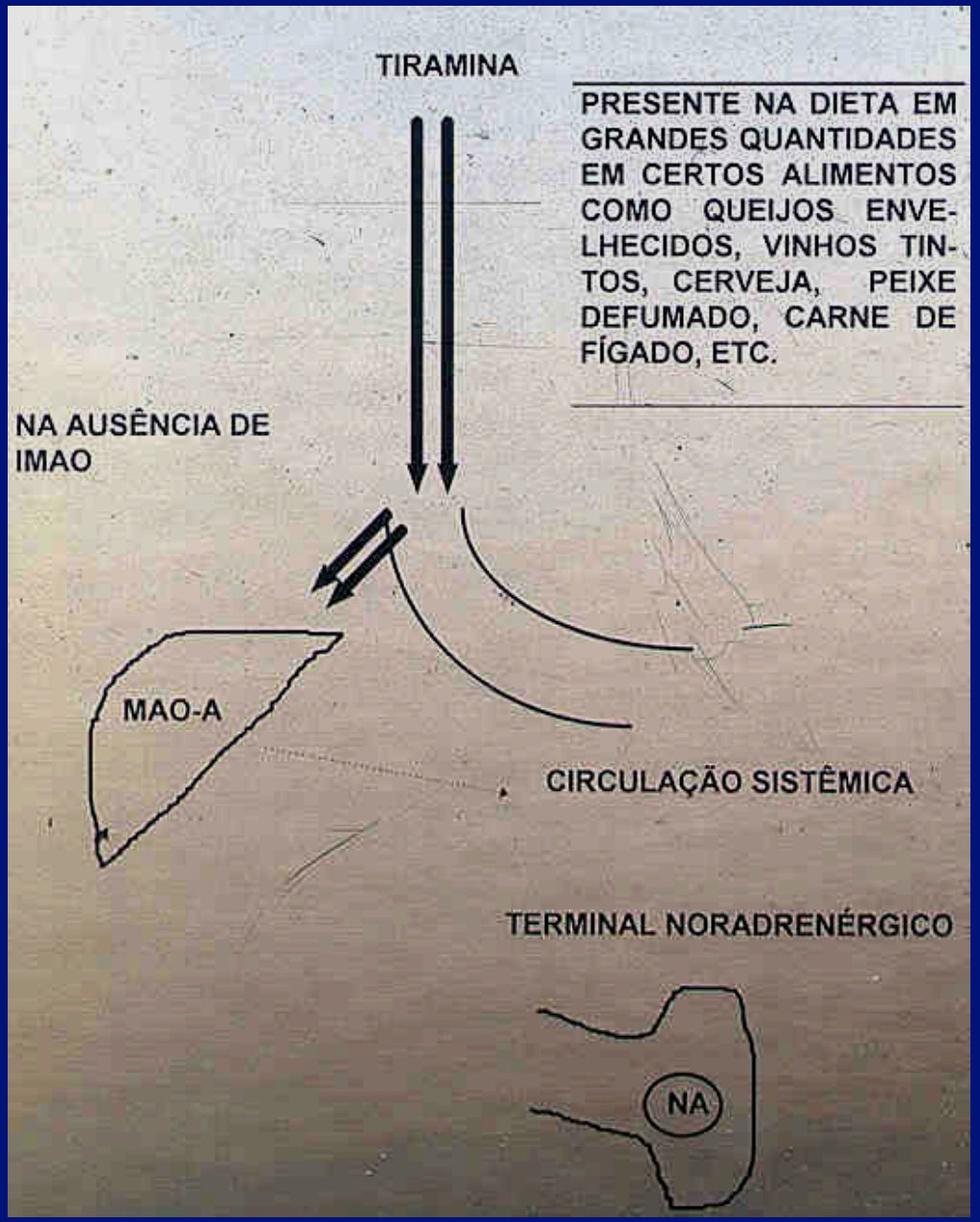
Imipramina	Genérico	23,00
Fluoxetina	Genérico	28,00
	Prozac	65,00
Escitalopram	Genérico	60,00
	Lexapro	165,00
desvenlafaxina	Pristiq	128,00
duloxetina	Cymbalta	168,00

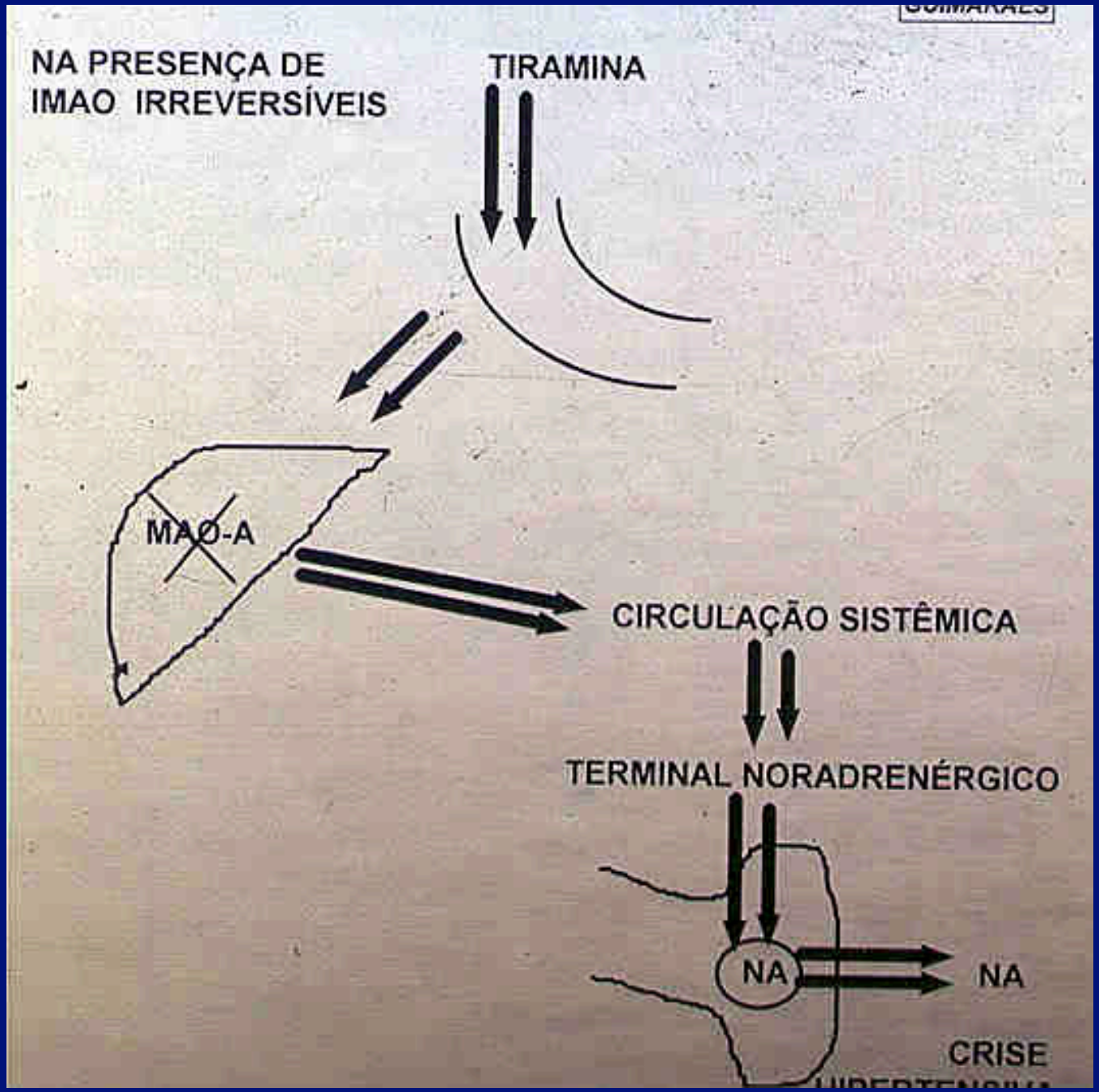
Duloxetina: 3a. “best selling drug” nos USA em 2012 (aproximadamente 1,3 bilhões/dólares)

Citation: Cipriani A, Koesters M, Furukawa TA, Nosè M, Purgato M, Omori IM, Trespidi C, Barbui C. Duloxetine versus other anti-depressive agents for depression. *Cochrane Database of Systematic Reviews* 2012, Issue 10. Art. No.: CD006533. DOI:

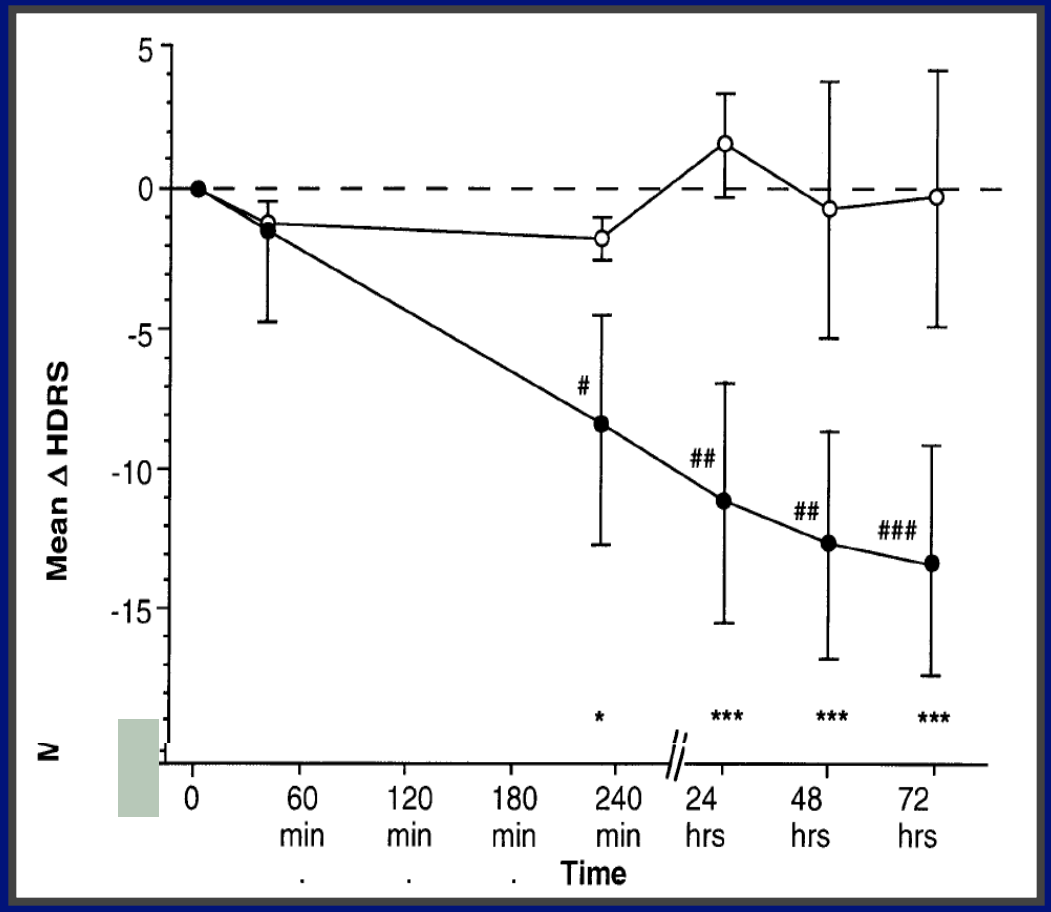
Duloxetine versus other antidepressive agents for depression

Although pharmacological and psychological interventions are both effective for major depression, antidepressant drugs remain the mainstay of treatment in moderate to severe major depression. During the last 20 years, newer compounds (such as selective serotonin reuptake inhibitors and dual action agents such as serotonin noradrenalin reuptake inhibitors) have progressively become the most commonly prescribed antidepressants. Duloxetine hydrochloride, one of the most recent antidepressants introduced in the market, is a selective serotonin noradrenergic reuptake inhibitor for oral administration. In the present review we assessed the evidence for the efficacy, acceptability and tolerability of duloxetine in comparison with all other antidepressants in the acute-phase treatment of major depression. Sixteen randomised controlled trials (5735 participants) were included. Duloxetine was not more effective than some other new antidepressant agents in the acute-phase treatment of major depression, and it was less well tolerated than escitalopram and venlafaxine as more patients allocated to duloxetine withdrew treatment before study end. However, due to the limited number of studies per comparison these results should be interpreted with caution.


TIRAMINA
PRESENTE NA DIETA EM GRANDES QUANTIDADES EM CERTOS ALIMENTOS COMO QUEIJOS ENVELHECIDOS, VINHOS TINTOS, CERVEJA, PEIXE DEFUMADO, CARNE DE FÍGADO, ETC.
NA AUSÊNCIA DE IMAO
MAO-A
CIRCULAÇÃO SISTÊMICA
TERMINAL NORADRENÉRGICO
NA


NA PRESENÇA DE
IMAO IRREVERSÍVEIS
TIRAMINA
MAO-A
CIRCULAÇÃO SISTÊMICA
TERMINAL NORADRENÉRGICO
NA
NA
CRISE

Hipótese glutamatérgica: tratamento AGUDO com doses baixas de Ketamina induz efeito antidepressivo rápido em humanos Efeitos são dissociados dos efeitos psicotomiméticos, persistindo por até uma semana



Ketamina:

↓ função MNDA

↑ função AMPA

Berman et al., al. Biol. Psychiatry, 2000

Eficácia da ketamina (infusão repetida, até 6 x em duas semanas) em depressão resistente

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *Qatar Clinical Neuroscience Conference*

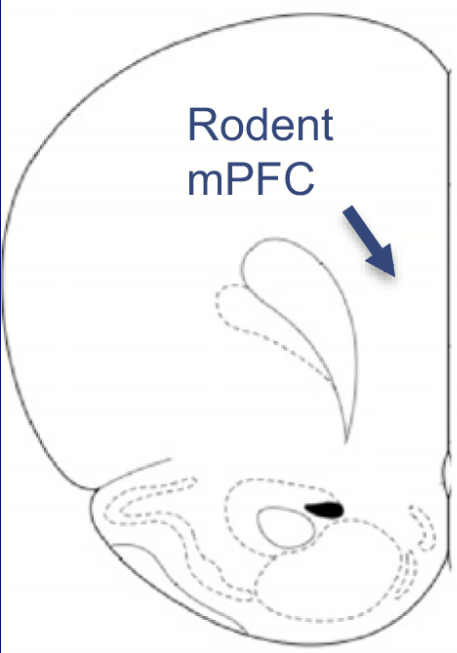
The promise of ketamine for treatment-resistant depression: current evidence and future directions

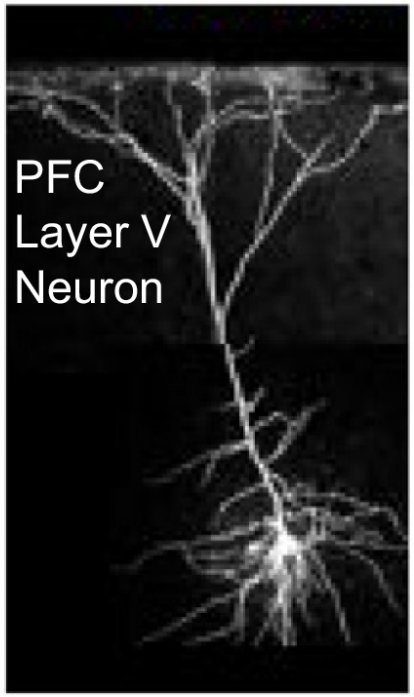
Kaitlin E. DeWilde,[1] Cara F. Levitch,[1] James W. Murrough,[1] Sanjay J. Mathew,[2] and Dan V. Iosifescu[1]

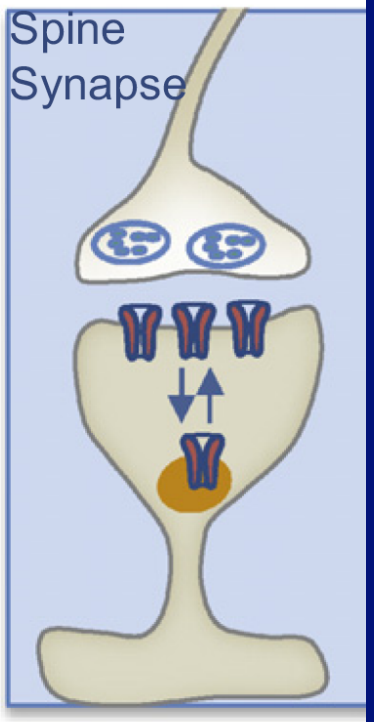
Table 2. Studies of repeated dose IV ketamine administration in patients with MDD

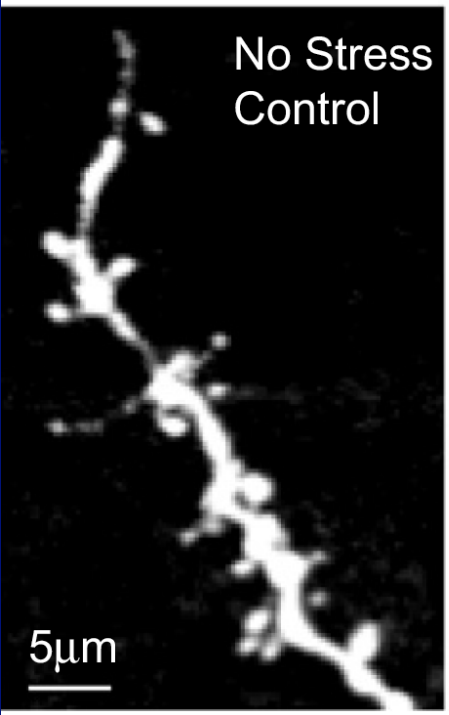
Study	Method	No. of patients (*n*)	Design	Treatment response[a] (%)
aan het Rot *et al.*[49]	IV	10	Open label	65%
Murrough *et al.*[16]	IV	24	Open label	70.8%
Diamond *et al.*[12]	IV	28	Open label	29%
Rasmussen *et al.*[50]	IV	10	Open label	80%
Segmiller *et al.*[51]	IV	6	Open label (esketamine)	50%

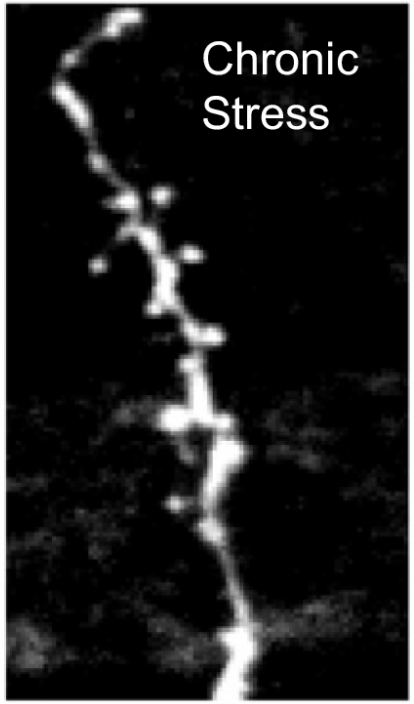
[a]Response is defined as ≥ 50% reduction in depressive symptoms (e.g., HAM-D or MADRS score) 24 h following IV ketamine.

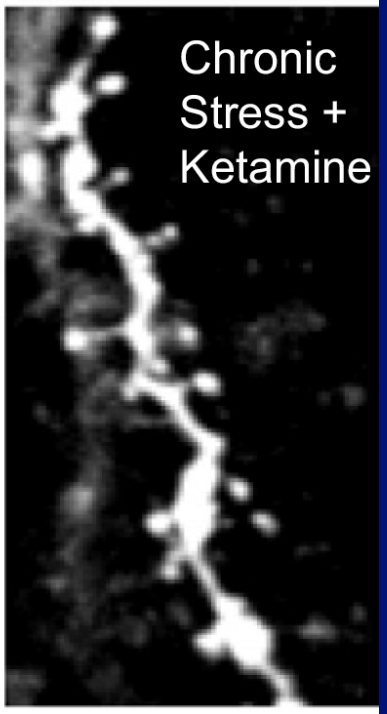










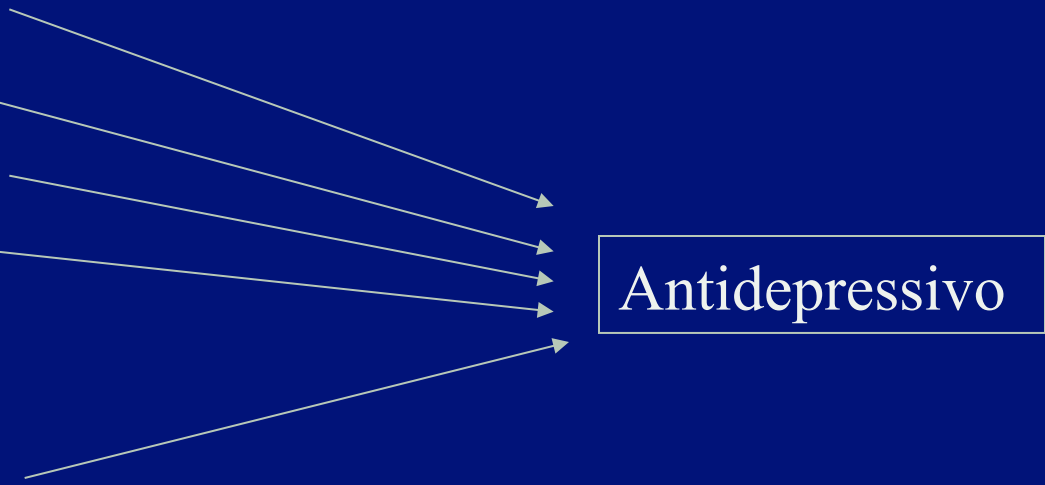


Stress diminui arborização dendrítica e número de espinhas dendríticas.
Efeito revertio por ketamine

Dwyer & Duman Biol Psych 2012

Antidepressivos, particularmente os inibidores seletivos de recaptação de serotonina, também são drogas de escolha no tratamento de vários transtornos de ansiedade

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



Antidepressivos aprovados para uso em transtornos não-afetivos

Transtornos não afetivo	**Antidepressivos aprovados (FDA)**
Ansiedade generalizada	Citalopram, escitalopram, paroxatina, venlafazina
TOC	Fluoxetina, fluvoxamina, paroxetina, sertralina
Pânico	Fluoxetina, paroxetina, sertralina, venlafaxina
Ansiedade generalizada	Duloxetina, escitalopram, paroxetina, venlafaxina
Ansiedade social	Fluvoxamina, paroxatina, sertralina, venlafaxina
PTSD	Paroxetina, Sertralina
Dor neuropática diabética	Duloxetina
Bulimia	Fluoxetina
T. disfórico pré-menstrual	Paroxetina, sertralina

Thronson et al. Med Clin North Am 2014

Tratamento de crise aguda de mania por lítio

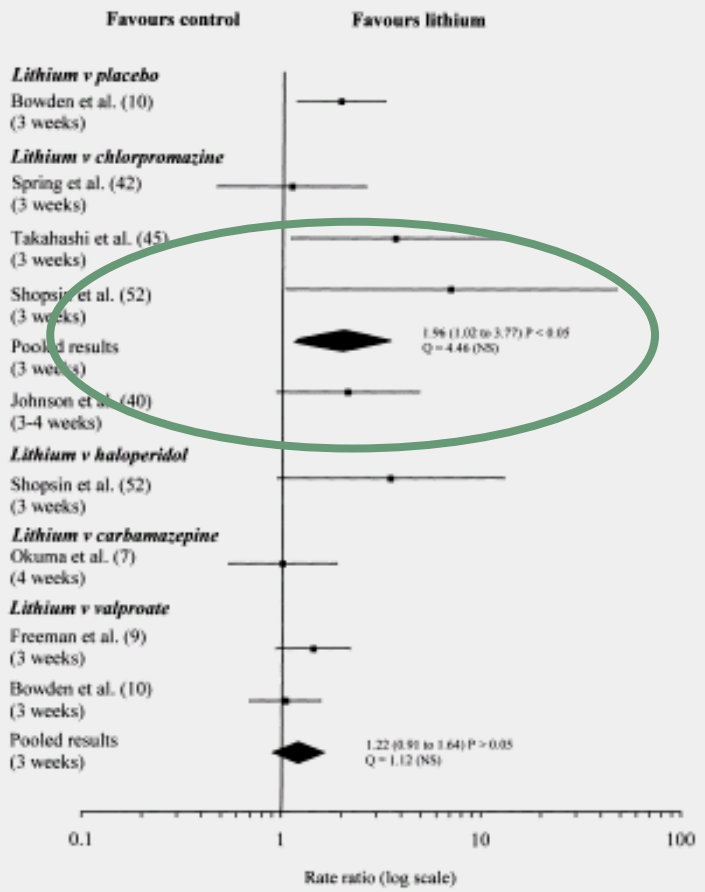
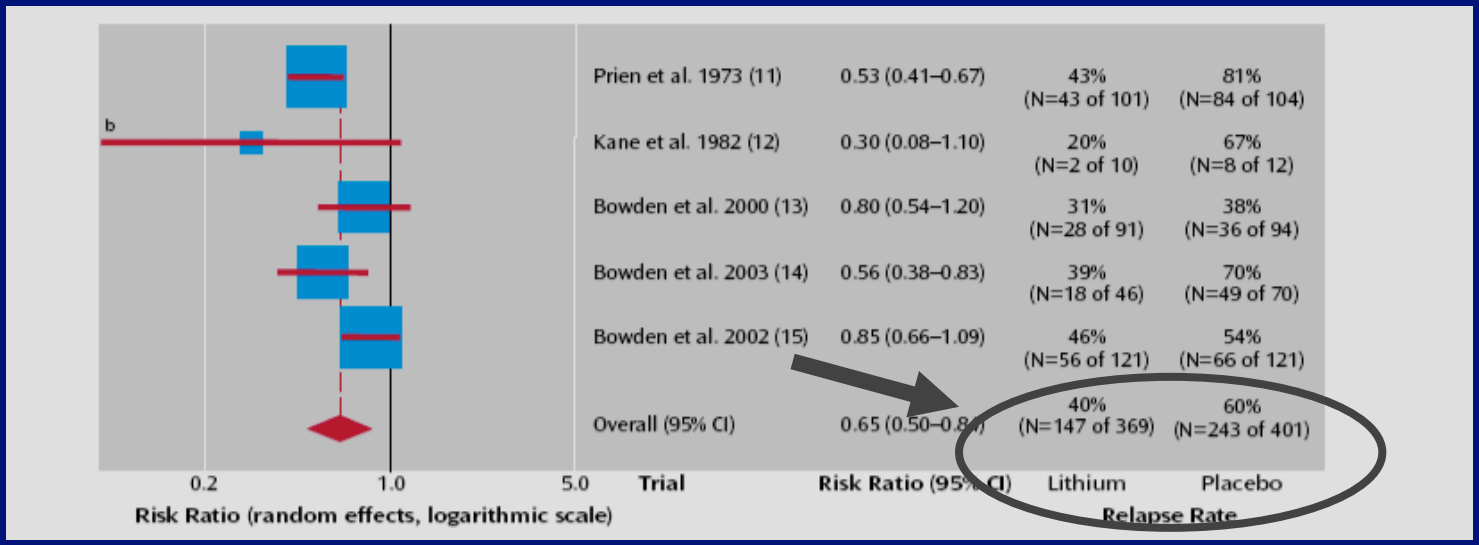
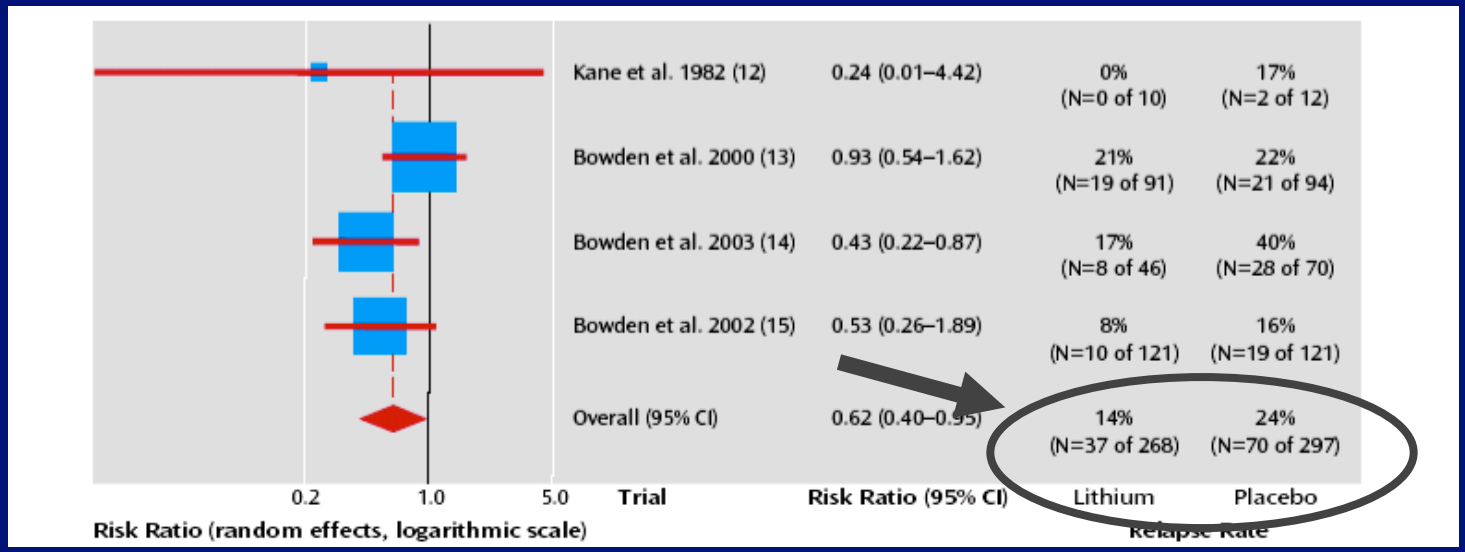


Fig. 2. Rate ratios (95% confidence intervals) for response with lithium and controls. Individual rate ratios (solid lines) are shown along with the pooled estimate of effect (black lozenges). Times of assessments are shown in parentheses.

Prevenção de recorrência por lítio



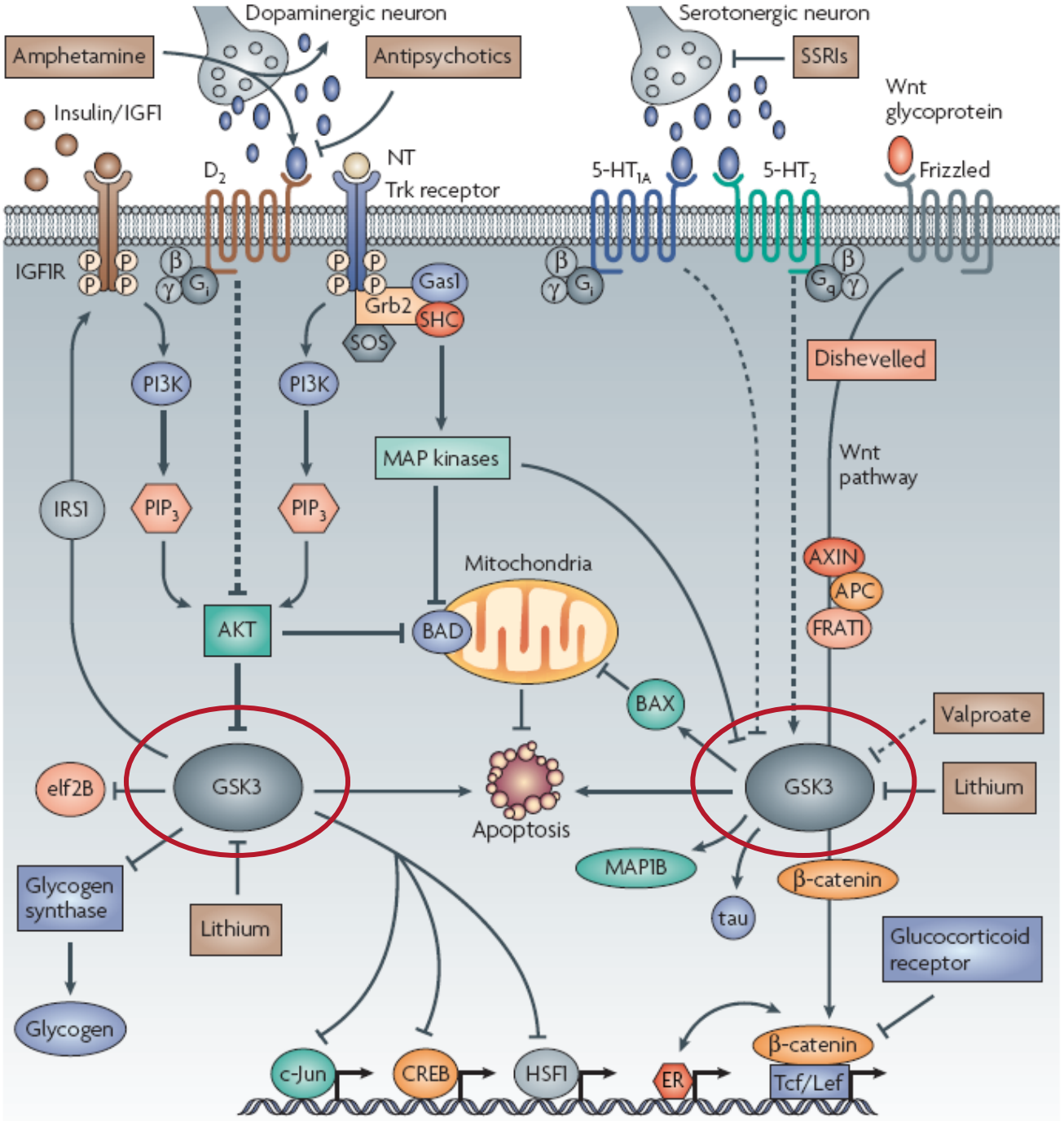
Prevenção de qualquer recorrência por lítio



Prevenção de recorrência de crise maníaca

Mecanismos propostos para os efeitos do Lítio

- bloqueia sinais comportamentais de supersensibilidade de receptores dopaminérgicos
- efeitos sobre Na e 5HT semelhantes aos antidepressivos
- inibe aumento de AMPc
- inibe a formação de fosfoinositóis (inibe PKC)
- altera cinética e distribuição de ions como sódio, potássio e magnésio
- altera proteínas-G (mantém em estado menos ativo)
- **alterações na expressão gênica** (c-fos, segundo mensageiros, neuropeptídeos, receptores de glicocorticóide, **fatores neuroprotetores**, ex β-cell lymphocyte protein-2, bcl-2)
- alterações em **"nodos" cruciais** envolvidos em relacionados a metabolismo energético, neuroplasticidade, neurogênese e sobrevivência neuronial (ex. GSK3)



Convergência de vias de sinalização em **"nodos" cruciais** (ex. glicogênio sintase quinase 3β) relacionados a metabolismo energético, neuroplasticidade, neurogênese e sobrevivência neuronial