Manejo farmacológico de los SPCD: oportunidades y riesgos

Reunión de primavera grupo de demencias de la SEGG
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21 de abril de 2012

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Centre Sociosanitari
JESÚS-TORTOSA

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT

SIZE OF TREATMENT EFFECT

	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care

Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit is not recommended is not indicated should not be performed/ administered/ other is not useful/ beneficial/ effective	COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B			

Premisas en el abordaje de los SCPD

- Identificación del problema con descripción del síntoma diana.
- Descartar otras posibles causas (delirium…)
- Identificar desencadenantes ambientales o del entorno
- Impacto en el paciente o cuidadores (gravedad)
- INICIAR MEDIDAS NO FARMACOLÓGICAS.

SCPD Y DOLOR: ANALGESIA

Un manejo eficaz contra el dolor puede jugar un lugar importante en el tratamiento de la agitación y puede ayudar a reducir medicación psicotropa.

Valorar y **tratar** eficazmente **el dolor** como **prevención** de la agitación y agresividad. Mejora la agitación, la agresividad, el dolor y no afecta la situación funcional ni cognitiva.

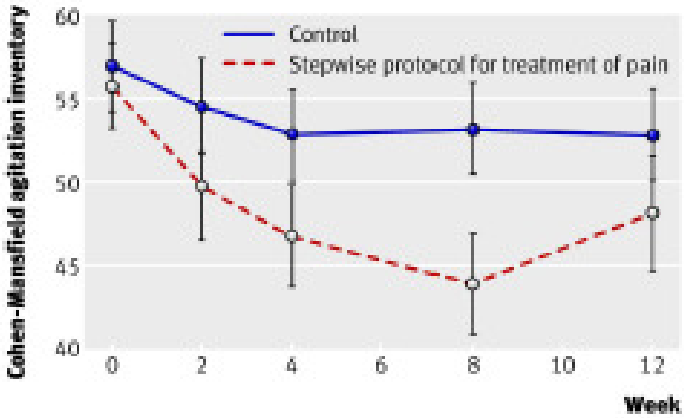
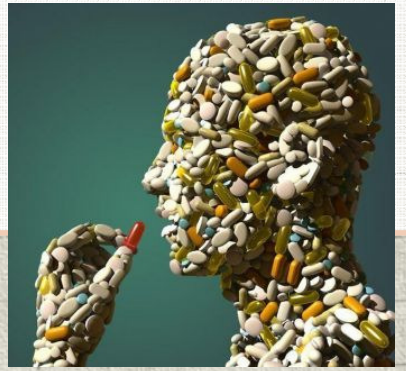


Fig 2 Cohen-Mansfield agitation inventory scores, with 95% confidence intervals, over study period

Husebo B. et al. Efficacy of treating pain to reduce behavioral distrubances In residents of nursing homes with dementia: cluster randomised clinical trial. BMJ 2011; 343:d4065

Manejo farmacológico de los SCPD

- Anticolinesterásicos y Memantina
- Neurolépticos
- Antidepresivos
- Estabilizadores del humor
- Otras alternativas



IACE y Memantina

Hipótesis colinérgica y trastornos de conducta

Tratamiento de primera línea en E.A leve-moderada

(grado A, nivel 1)

Antagonista NMDA y reduce la excitotoxicidad mediada por glutamato

Eficacia en fases moderadas-grave, en monoterapia o combinada IACE (grado B, nivel 1). Buena tolerancia y perfil de seguridad

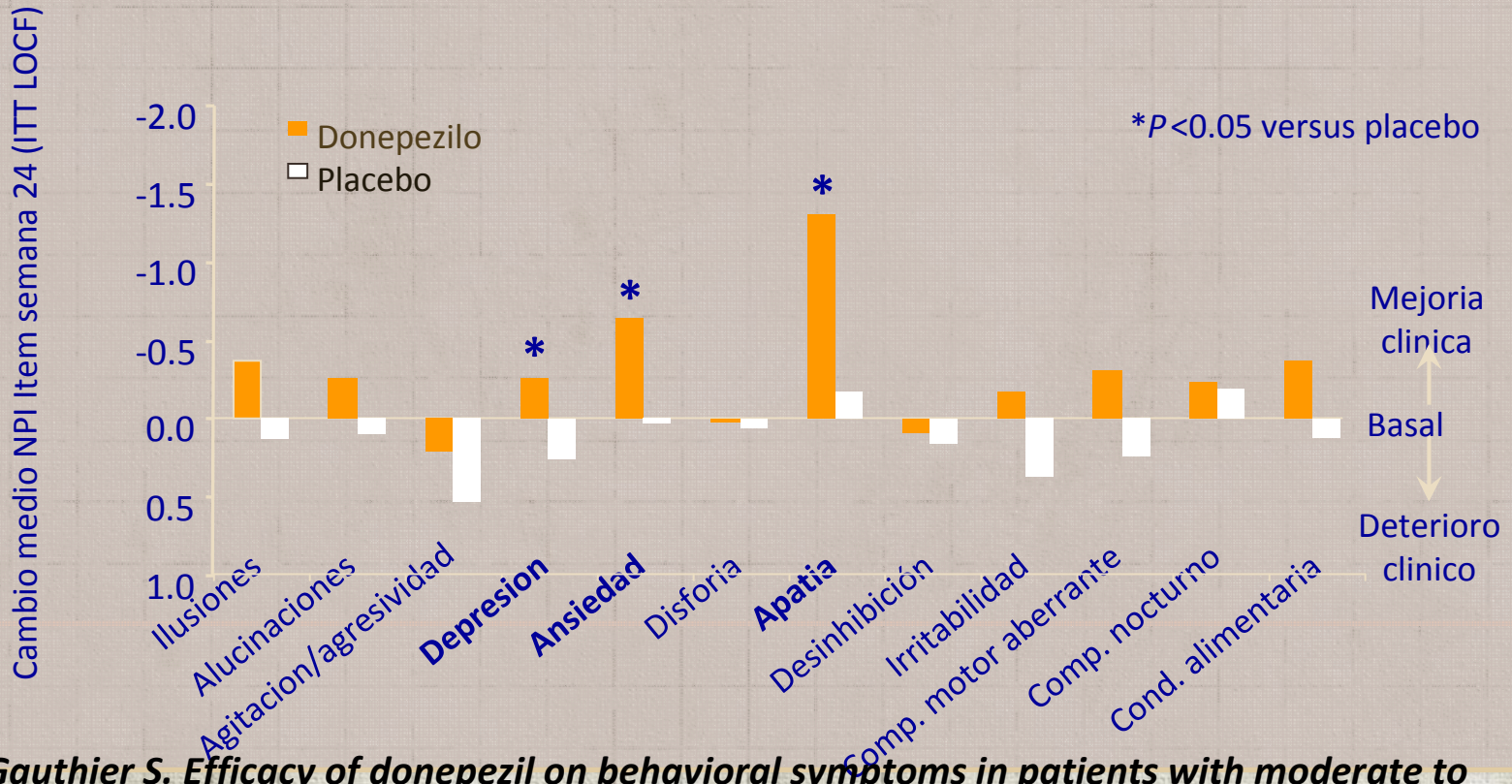
↓↓ Intensidad o suprime algunos SCPD

↓↓ medicación psicotropa

Prevención de incidencia de nuevos SCPD

Donepezilo

Estudio DC en 290 EA modera-grave: se objetivó una mejoría de la puntuación del NPI y de forma específica en tres dominios: APATÍA, ANSIEDAD Y DEPRESIÓN.



Gauthier S. Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer´s disease. Int Psychogeriatr 2002; 14: 389-404

Donepezilo

Agrupando el NPI por síntomas, fue **superior** al placebo en **síntomas psicóticos, agitación, humor**, pero no en desinhibición, euforia, conducta motora aberrante o alteración del ritmo noche-vigilia.

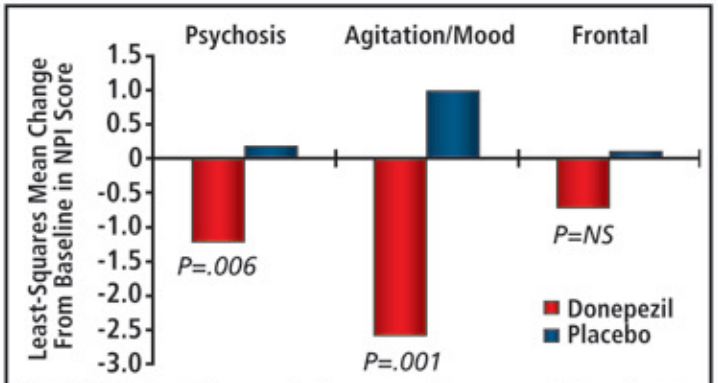


FIGURE 2. Effect of donepezil on combined NPI scores* for various classes of neuropsychiatric symptoms in patients with moderate to severe Alzheimer's disease[16]

*Change in scores between baseline and week 24 (last observation carried forward) are shown.

†Psychosis characterized by delusions, hallucinations, appetite/eating change.

‡Agitation/mood characterized by agitation/aggression, depression/dysphoria, anxiety, apathy/indifference, irritability/lability.

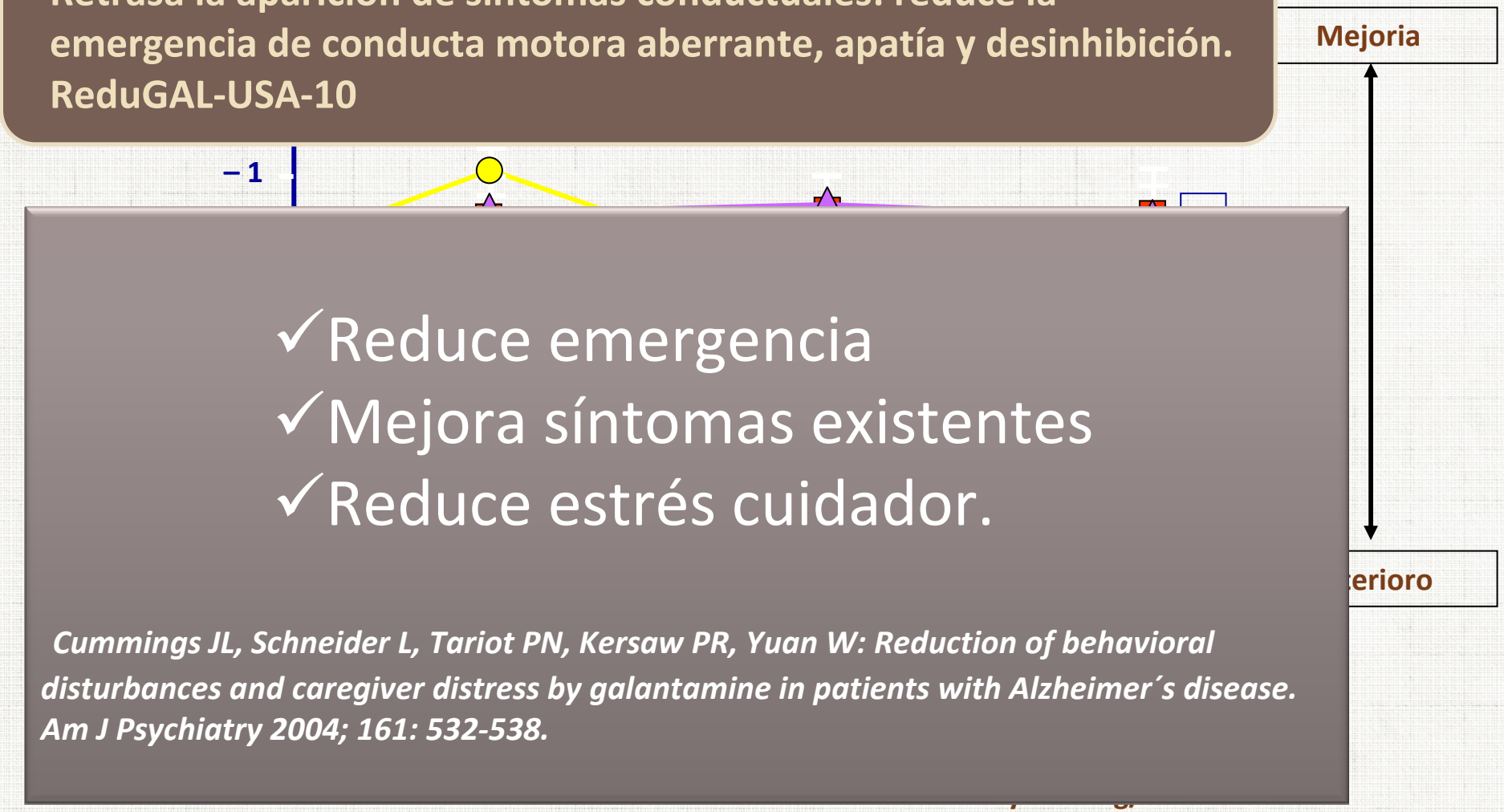
§Frontal characterized by disinhibition, elation/euphoria, aberrant motor behavior, nighttime behavior.

NPI=Neuropsychiatric Inventory; NS=not significant.

Cummings JL. *CNS Spectr.* Vol 10, No 11 (Suppl 18). 2005.

Galantamina

Retrasa la aparición de síntomas conductuales: reduce la emergencia de conducta motora aberrante, apatía y desinhibición. ReduGAL-USA-10



- ✓Reduce emergencia
- ✓Mejora síntomas existentes
- ✓Reduce estrés cuidador.

Cummings JL, Schneider L, Tariot PN, Kersaw PR, Yuan W: Reduction of behavioral disturbances and caregiver distress by galantamine in patients with Alzheimer´s disease. Am J Psychiatry 2004; 161: 532-538.

Tariot et al. Neurology 2000; 54: 2269-2276

RIVASTIGMINA

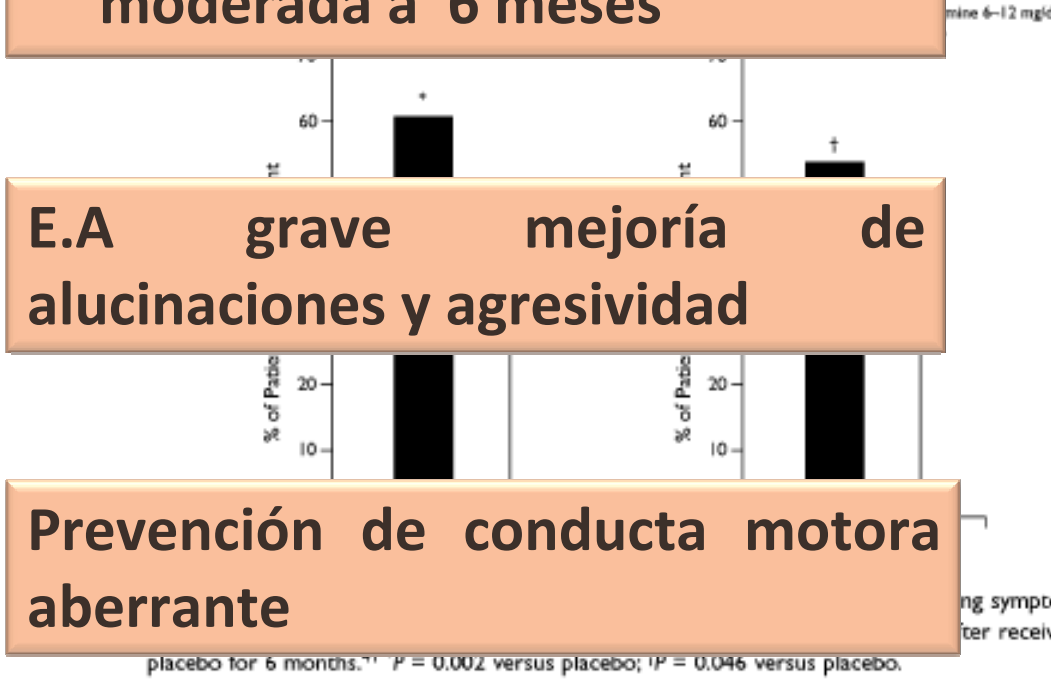
Metanálisis de 3 EDC a 6 meses en 1840 pacientes con EA leva a moderada.

En estudio abiertos a 6 y 12 meses con EA grave (n=113)

Mejoría de síntomas en EA leve-moderada a 6 meses

E.A grave mejoría de alucinaciones y agresividad

Prevención de conducta motora aberrante



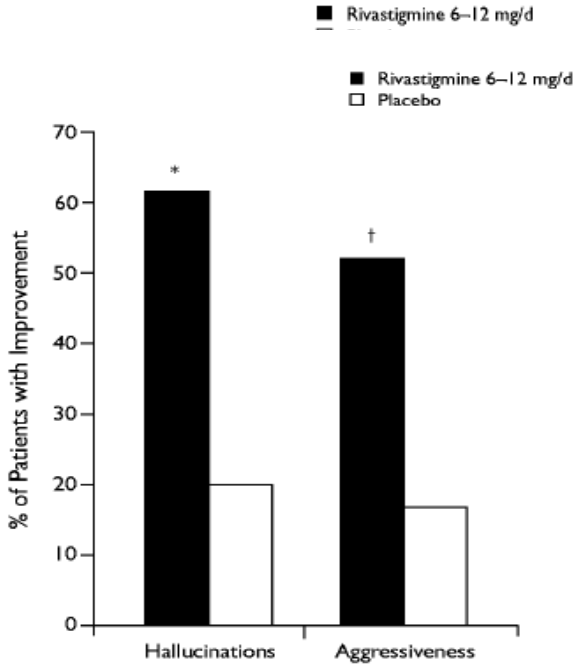


Figure 3. Proportions of patients with advanced Alzheimer's disease and symptoms of hallucinations and aggressiveness at study entry who showed improvement in these symptoms after receiving rivastigmine or placebo for 6 months.[41] Logistic regression analysis: *P = 0.039; †P = 0.030.

Finkel SI. Effects of rivastigmine on Behavioral and Psychological Sym
Clinical Therapeutics 2004, 26: 980-990.

Rivastigmina

En demencia r
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PCD en 173

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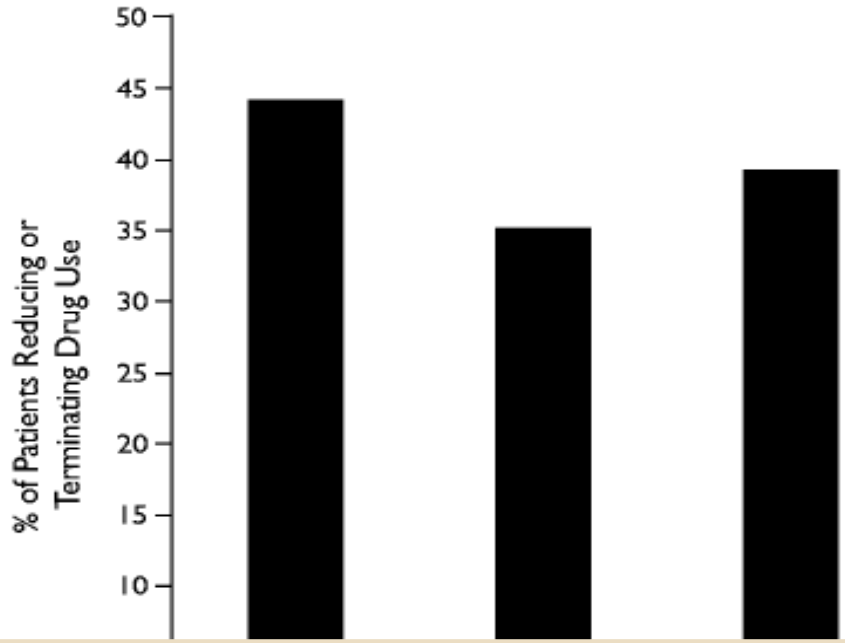

Se asocia con la reducción o retirada de medicación psicotropa

cnotic medications in nursing home patients receiving rivastigmine for 12 months.[52]

Cummings JL, Koumaras B, Chen M,
Effects of rivastigmine treatment on r
a 26-week, multicenter, open-label study. Am J Geriatr Pharmacother 2005; 3 (3): 137-48.

to severe problable Alzheimer´s disease.

RIVASTIGMINA

Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease (Review)

Rolinski M, Fox C, Maidment I, McShane R

THE COCHRANE COLLABORATION®

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¿Hay diferencias entre los distintos IACE?

Review: 02- The Efficacy of chEls (Donepezil, Rivastigmine and Galantamine) on BPSD in AD. A Meta-Analysis.
Comparison: 01 ChEls vs placebo (Fixed Effect Model):
Outcome: 01 Change in total NPI score from baseline:

Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	Weight %	WMD (fixed) 95% CI
01 Combined ChEls vs placebo of 9 included studies: 3 Studies Did Not Report Full Data.						
Tariot 2000	508	−0.10 (13.36)	262	2.00 (11.84)	24.84	−2.10 [−3.95, −0.25]
Feldmen 2001	121	−4.65 (17.76)	126	1.00 (17.52)	4.37	−5.65 [−10.05, −1.25]
Rockwood 2001	261	−0.40 (10.66)	125	0.50 (11.29)	15.13	−0.90 [−3.26, 1.46]
Tariot 2001	103	−2.30 (14.50)	105	−4.90 (14.70)	5.37	2.60 [−1.37, 6.57]
Winblad 2001	136	0.59 (13.76)	138	1.72 (12.23)	8.89	−1.13 [−4.21, 1.95]
Holmes 2004	41	−2.90 (8.96)	55	3.30 (13.36)	4.23	−6.20 [−10.67, −1.73]
Winblad 2006	128	−3.80 (15.20)	120	−2.10 (15.80)	5.67	−1.70 [−5.56, 2.16]
Howard 2007	104	3.56 (15.90)	97	3.78 (16.70)	4.15	−0.22 [−4.73, 4.29]
Winblad 2007	263	−2.30 (13.40)	281	−1.70 (15.70)	14.11	−0.60 [−3.05, 1.85]
Winblad 2007a	253	−2.20 (14.10)	281	−1.70 (15.70)	13.24	−0.50 [−3.03, 2.03]
Subtotal (95% CI)	1918		1590		100.00	−1.38 [−2.30, −0.46]
Test for heterogeneity: Chi² = 13.85, df = 9 (p = 0.13), I² = 35.0%						
Test for overall effect: Z = 2.95 (P = 0.003)						
Total (95% CI)	1918		1590		100.00	−1.38 [−2.30, −0.46]
Test for heterogeneity: Chi² = 13.85, df = 9 (P = 0.13), I² = 35.0%						
Test for overall effect: Z = 2.95 (P = 0.003)						

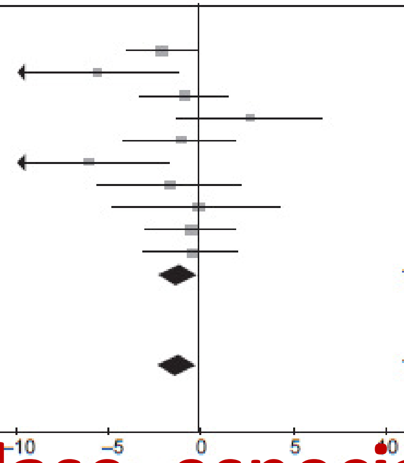
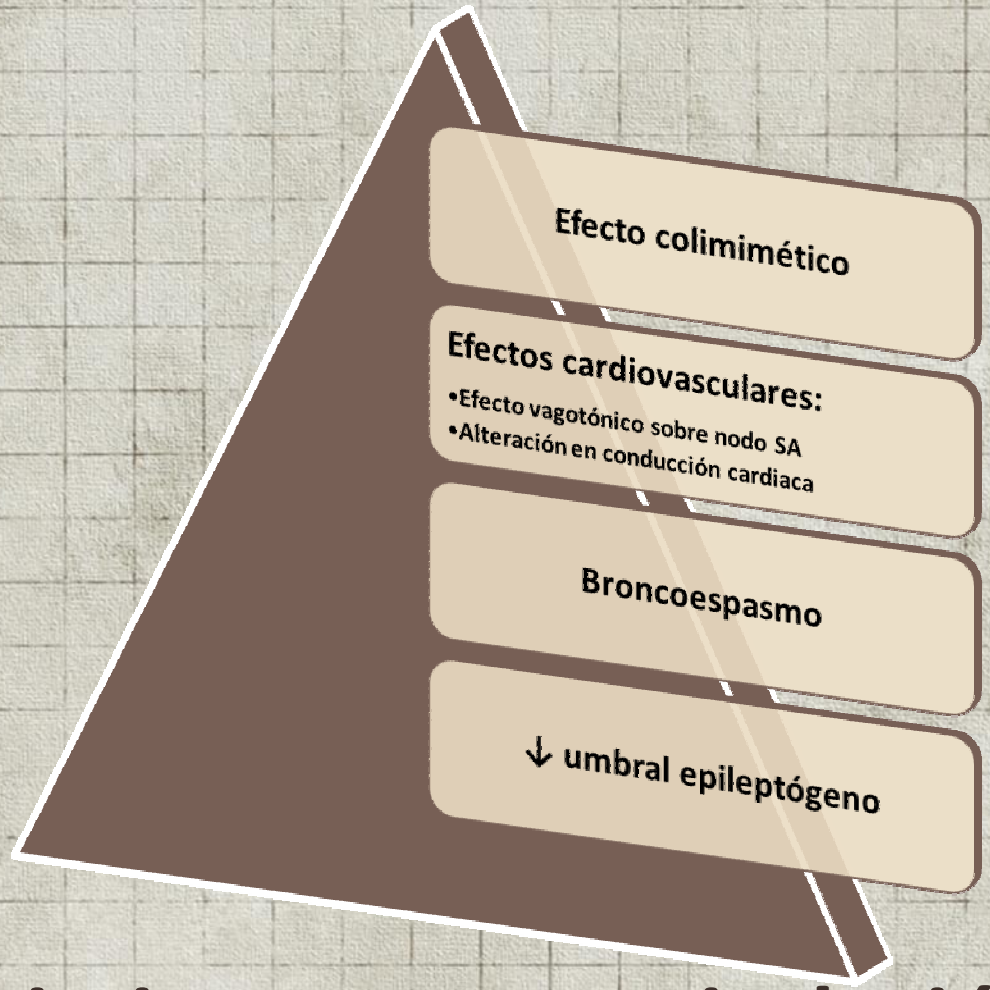


Figure 1 The effects of ChEls on BPSD among patients with mild to severe AD.

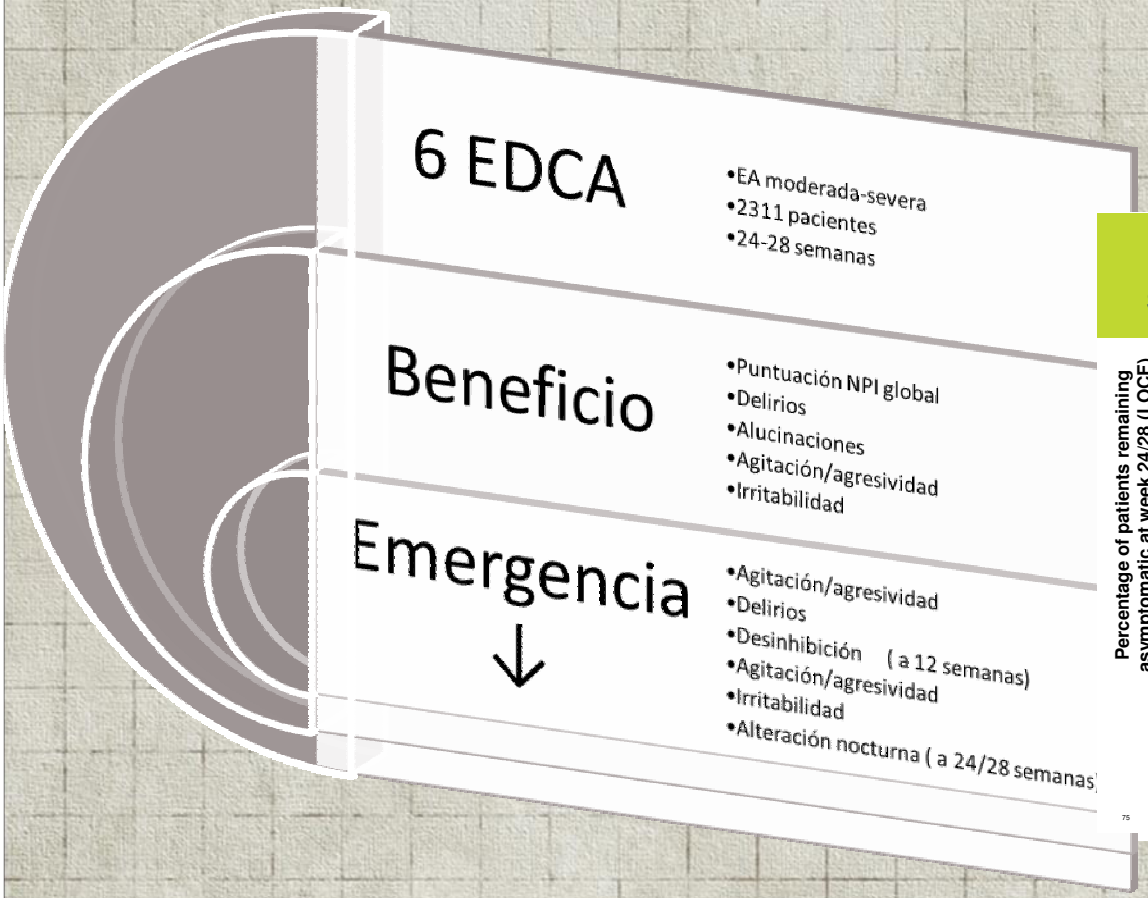
Efecto beneficioso de clase, especialmente en demencias leve - moderada

IACE: efectos adversos

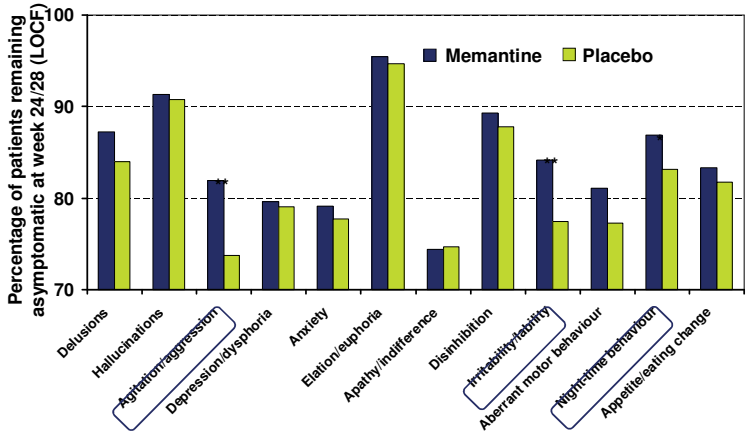


- Se minimizan con una titulación lenta.

Memantina



Memantine prevents behavioural symptoms in asymptomatic AD patients



*p=0.05; **p<0.01

Gauthier et al. Int J Geriatr Psychiatry 2008; 23: 537–545

Gauthier: Improvenmt in behavioural symptoms in patients with moderate to severe Alzheimer´s disease by memantine: a pooled data analysis. Int J Geriatr Psychiatry 2008;23:537-45.

IACE + Memantina

Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I; Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomised controlled trail. JAMA 2004; 291 (3):317-24.

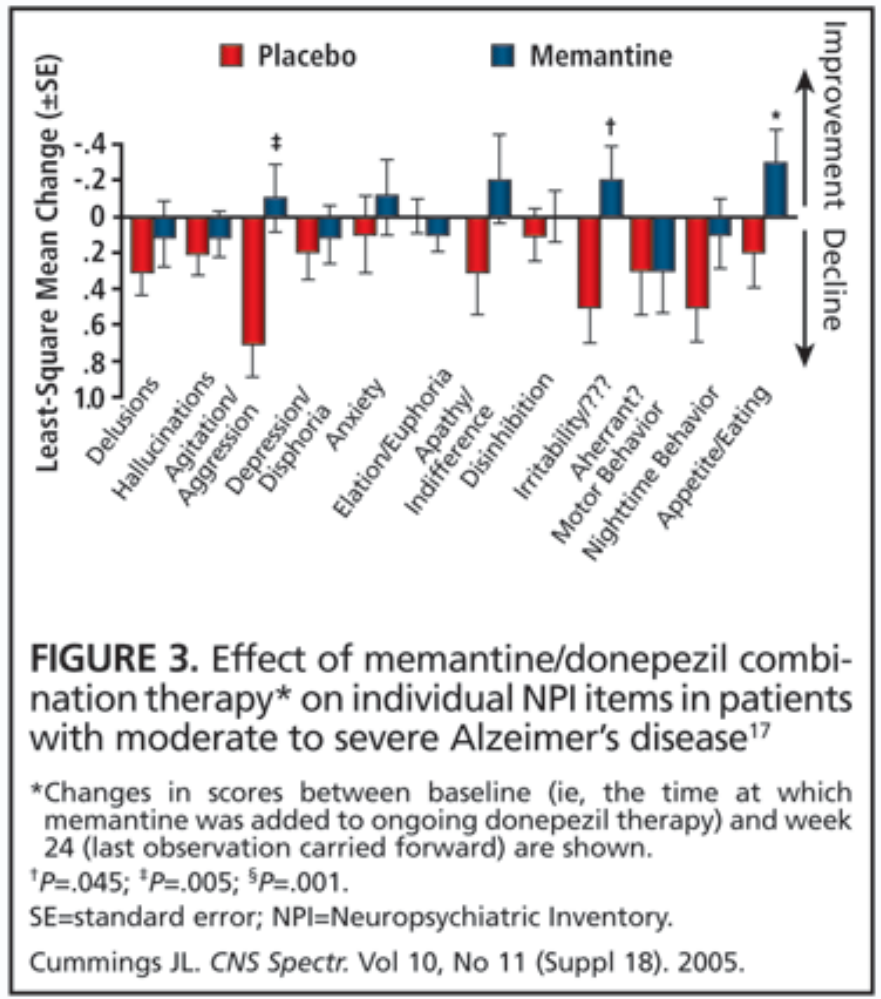


FIGURE 3. Effect of memantine/donepezil combination therapy* on individual NPI items in patients with moderate to severe Alzeimer's disease[17]

*Changes in scores between baseline (ie, the time at which memantine was added to ongoing donepezil therapy) and week 24 (last observation carried forward) are shown.

†P=.045; ‡P=.005; §P=.001.

SE=standard error; NPI=Neuropsychiatric Inventory.

Cummings JL. *CNS Spectr.* Vol 10, No 11 (Suppl 18). 2005.

- Efecto beneficioso en **agitación**, **irritabilidad** y **conducta alimentaria**.
- Disminuye la sobrecarga del cuidador
- ↑ probabilidad de permanecer asintomáticos a la 24 semana en **agitación**, **agresión**, **irritabilidad** y **conducta nocturna** que sólo donepezilo

Cummings, Neurology 2006.

IACE + Memantina

- ✓ La adición de la memantina al IACE retrasa la institucionalización (x 3,4)
- ✓ No se asoció con la mortalidad.

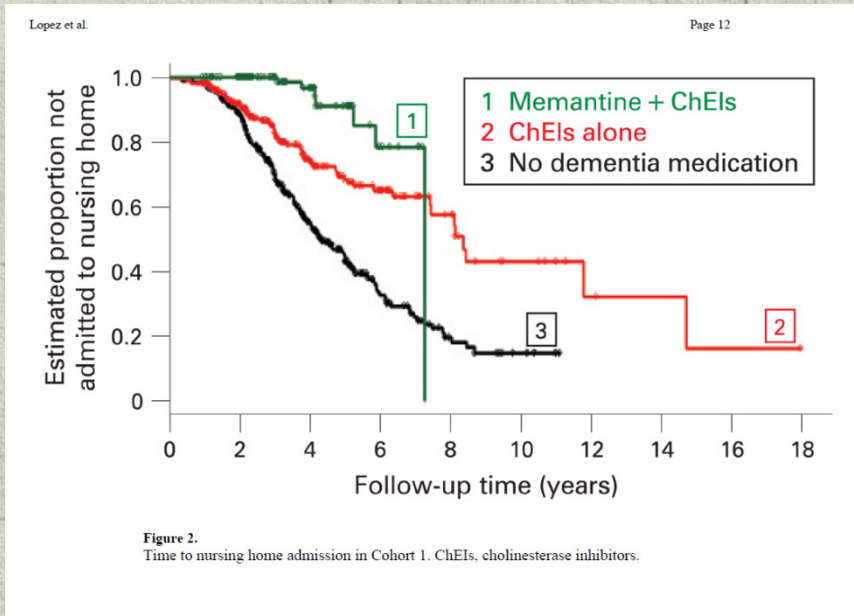


Figure 2.
Time to nursing home admission in Cohort 1. ChEIs, cholinesterase inhibitors.

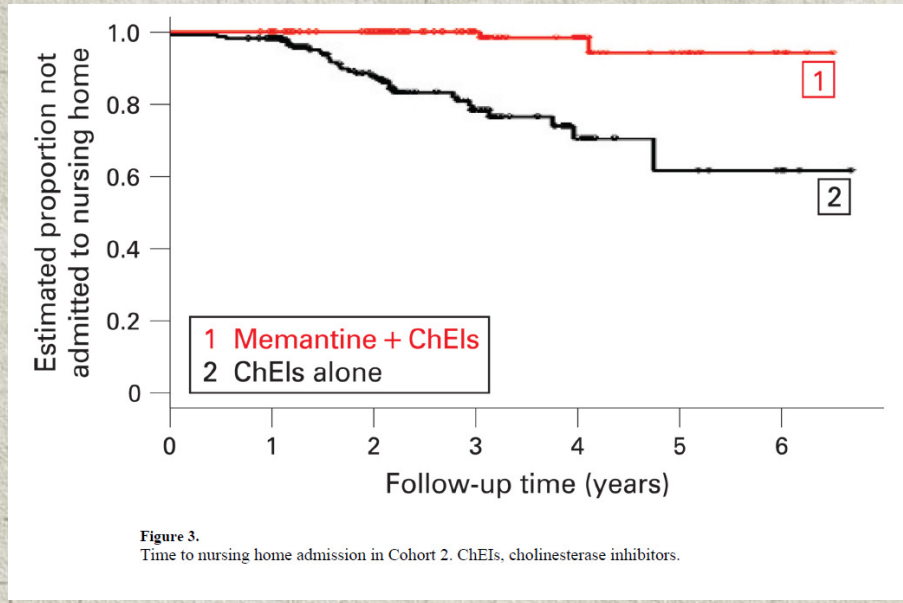


Figure 3.
Time to nursing home admission in Cohort 2. ChEIs, cholinesterase inhibitors.

Lopez OL, Becker JT, Wahed AS, Saxton J, Sweet RA, Wolk DA et al.
Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease.
J Neurol Neurosurg Psychiatry 2009; 80:600-607.

IACE + Memantina

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Donepezil and Memantine for Moderate-to-Severe Alzheimer's Disease

Robert Howard, M.D., Rupert McShane, F.R.C.Psych., James Lindesay, D.M., Craig Ritchie, M.D., Ph.D., Ashley Baldwin, M.R.C.Psych., Robert Barber, M.D., Alistair Burns, F.R.C.Psych., Tom Dening, F.R.C.Psych., David Findlay, M.B., Ch.B., Clive Holmes, Ph.D., Alan Hughes, M.B., Ch.B., Robin Jacoby, D.M., Rob Jones, M.B., Ch.B., Roy Jones, M.B., Ian McKeith, F.Med.Sc., Ajay Macharouthu, M.R.C.Psych., John O'Brien, D.M., Peter Passmore, M.D., Bart Sheehan, M.D., Edmund Juszczak, M.Sc., Cornelius Katona, M.D., Robert Hills, D.Phil., Martin Knapp, Ph.D., Clive Ballard, M.D., Richard Brown, Ph.D., Sube Banerjee, M.D., Caroline Onions, P.G.Dip., Mary Griffin, R.G.N., Jessica Adams, B.Sc., Richard Gray, M.Sc., Tony Johnson, Ph.D., Peter Bentham, M.B., Ch.B., and Patrick Phillips, Ph.D.

ABSTRACT

BACKGROUND

Clinical trials have shown the benefits of cholinesterase inhibitors for the treatment of mild-to-moderate Alzheimer's disease. It is not known whether treatment benefits continue after the progression to moderate-to-severe disease.

METHODS

We assigned 295 community-dwelling patients who had been treated with donepezil for at least 3 months and who had moderate or severe Alzheimer's disease (a score of 5 to 13 on the Standardized Mini–Mental State Examination [SMMSE, on which scores range from 0 to 30, with higher scores indicating better cognitive function]) to continue donepezil, discontinue donepezil, discontinue donepezil and start memantine, or continue donepezil and start memantine. Patients received the study treatment for 52 weeks. The coprimary outcomes were scores on the SMMSE and on the Bristol Activities of Daily Living Scale (BADLS, on which scores range from 0 to 60, with higher scores indicating greater impairment). The minimum clinically important differences were 1.4 points on the SMMSE and 3.5 points on the BADLS.

RESULTS

Patients assigned to continue donepezil, as compared with those assigned to discontinue donepezil, had a score on the SMMSE that was higher by an average of 1.9 points (95% confidence interval [CI], 1.3 to 2.5) and a score on the BADLS that was lower (indicating less impairment) by 3.0 points (95% CI, 1.8 to 4.3) (P<0.001 for both comparisons). Patients assigned to receive memantine, as compared with those assigned to receive memantine placebo, had a score on the SMMSE that was an average of 1.2 points higher (95% CI, 0.6 to 1.8; P<0.001) and a score on the BADLS that was 1.5 points lower (95% CI, 0.3 to 2.8; P=0.02). The efficacy of donepezil and of memantine did not differ significantly in the presence or absence of the other. There were no significant benefits of the combination of donepezil and memantine over donepezil alone.

CONCLUSIONS

In patients with moderate or severe Alzheimer's disease, continued treatment with donepezil was associated with cognitive benefits that exceeded the minimum clinically important difference and with significant functional benefits over the course of 12 months. (Funded by the U.K. Medical Research Council and the U.K. Alzheimer's Society; Current Controlled Trials number, ISRCTN49545035.)

Cognitivo y funcional (Resultado principal)

Beneficio con donepezilo o memantina en monoterapia vs placebo.

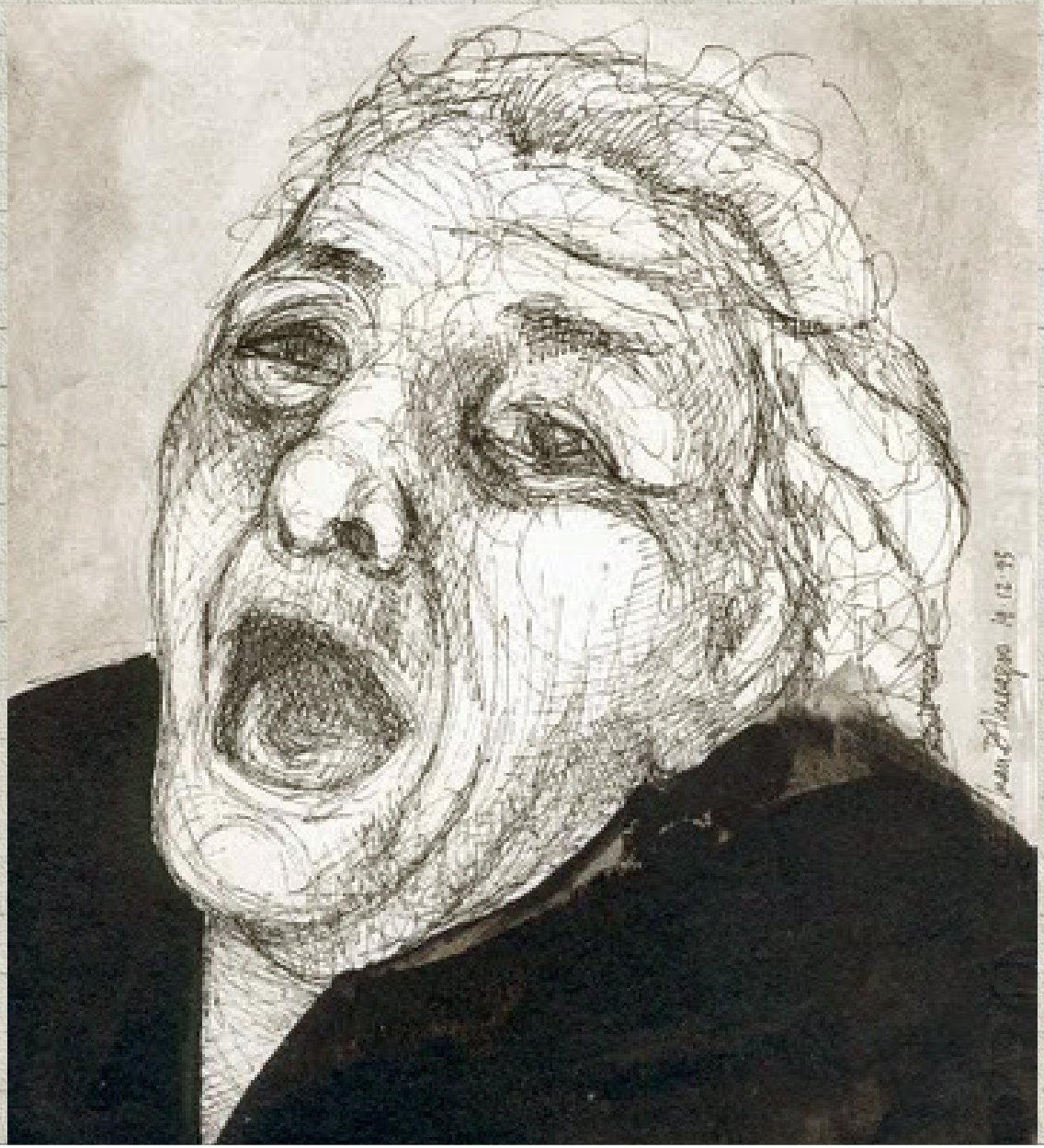
La terapia combinada no fue más eficaz que la monoterapia.

En la conducta (resultado secundario)

Únicamente los grupos tratados con **memantina** (mono o combinada) mostraron mejoría significativa en el NPI (escala de conducta) vs placebo.

La monoterapia con memantina mostró una diferencia significativa de 4,0 puntos (p=0,002). *No ocurrió con donepezilo.*

ANTIPSICÓTICOS



ANTIPSICÓTICOS Y SINTOMAS PSICÓTICOS

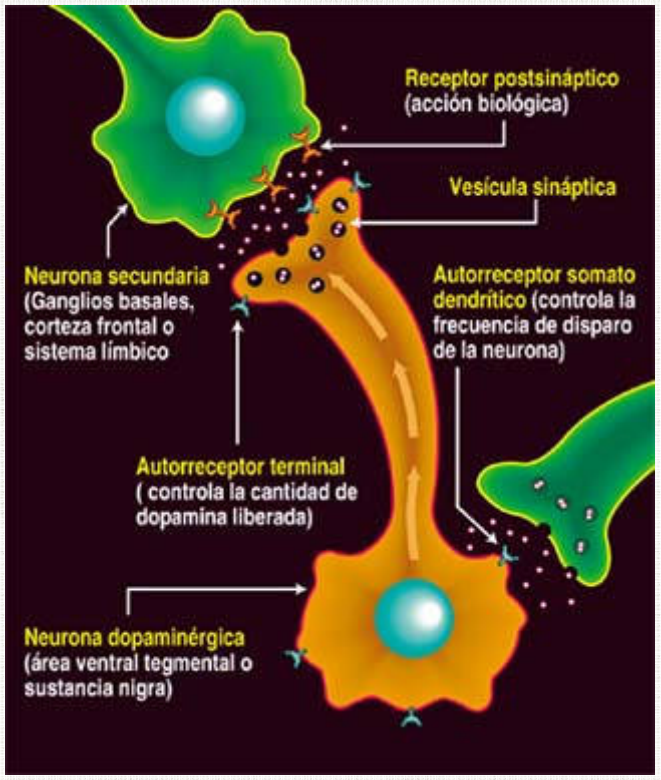
Los síntomas psicóticos son la causa de mayor distrés del cuidador

La presencia de síntomas psicóticos acelera la progresión de la enfermedad (cognitivo y funcional) y afecta a la calidad de vida.

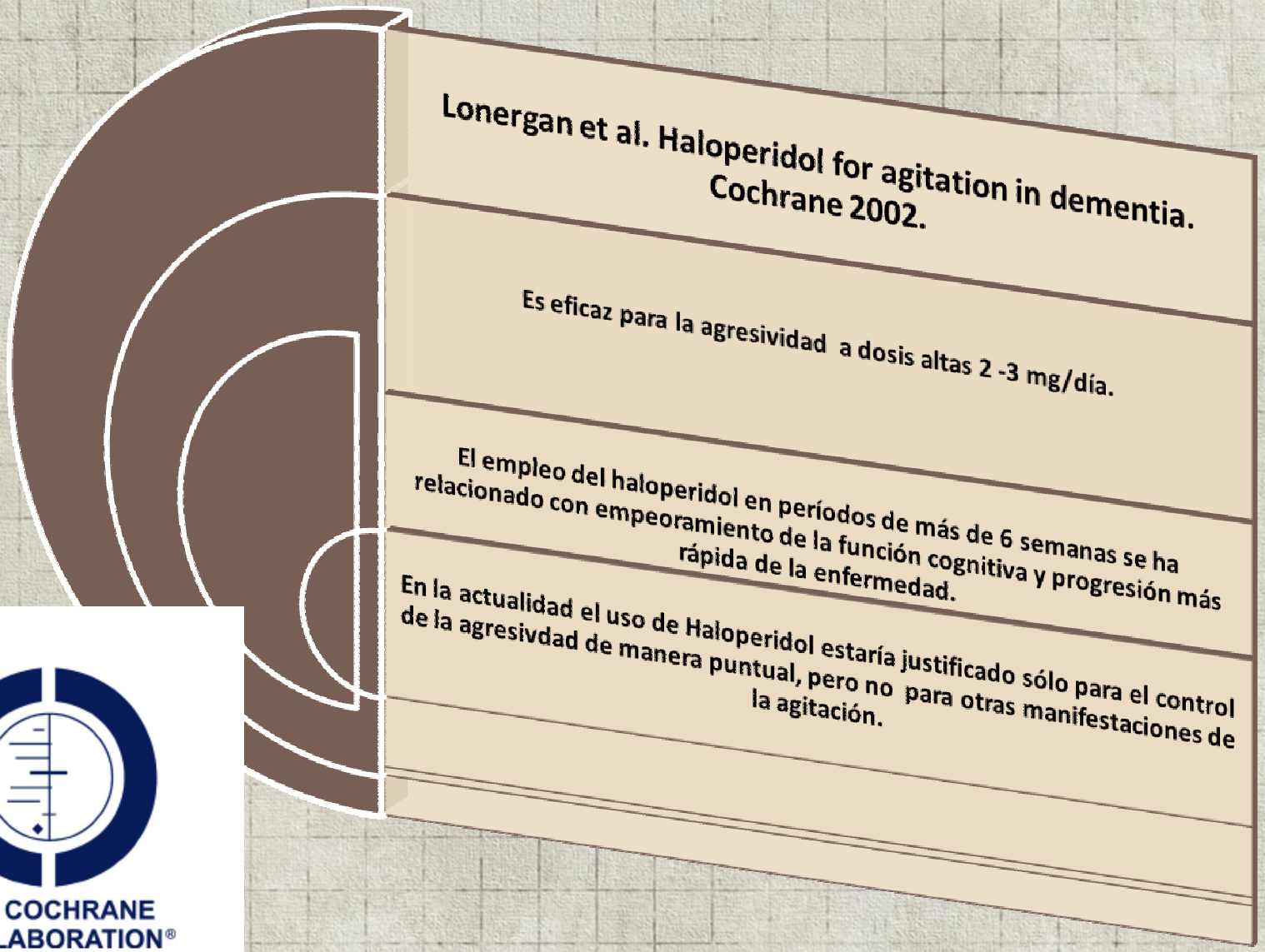
Síntomas psicóticos predicen la institucionalización

Los antipsicóticos han sido los fármacos más usados para los síntomas psicóticos, comportamientos violentos y hostilidad

Mecanismo de acción es el bloqueo de los R dopaminérgicos del sistema límbico y ganglios basales. Aumento de dopamina en el SNC.

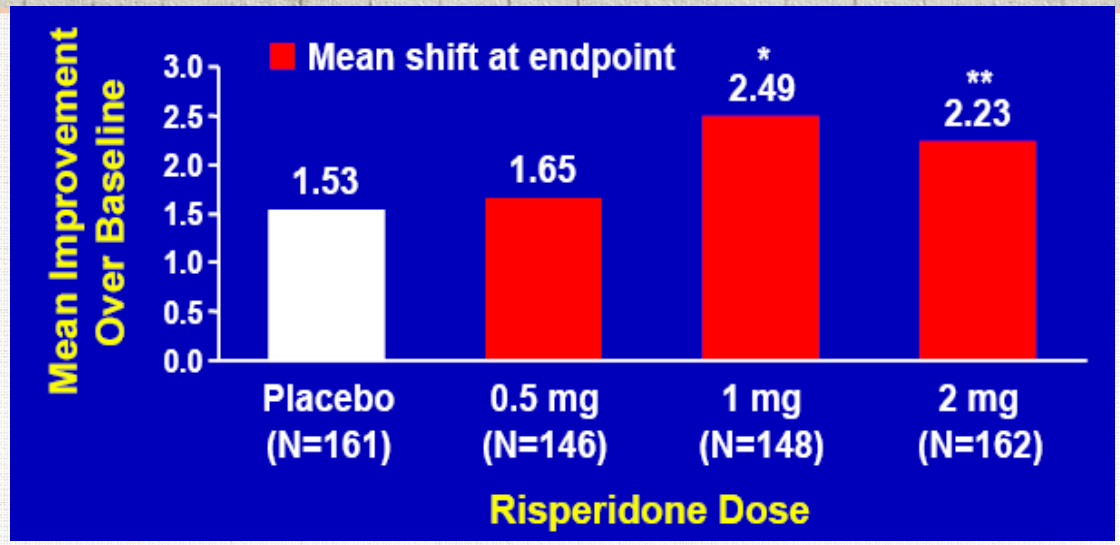


ANTIPSICÓTICOS TÍPICOS



THE COCHRANE COLLABORATION®

RISPERIDONA



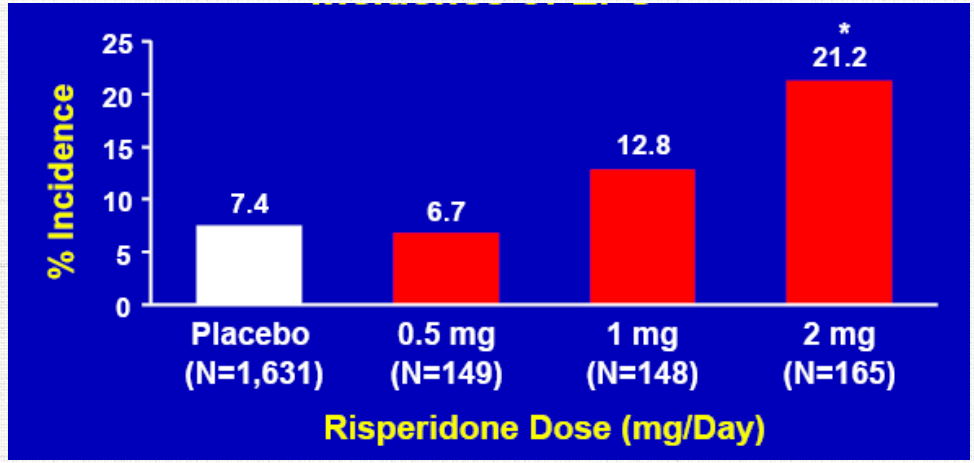
- RCT doble ciego
- N=625 pacientes NH
- Edad media: 82.7 años
- 12 semanas de estudio
- EA, DV o mixta con SCPD.
  >30% de mejoría

THE JOURNAL OF CLINICAL PSYCHIATRY

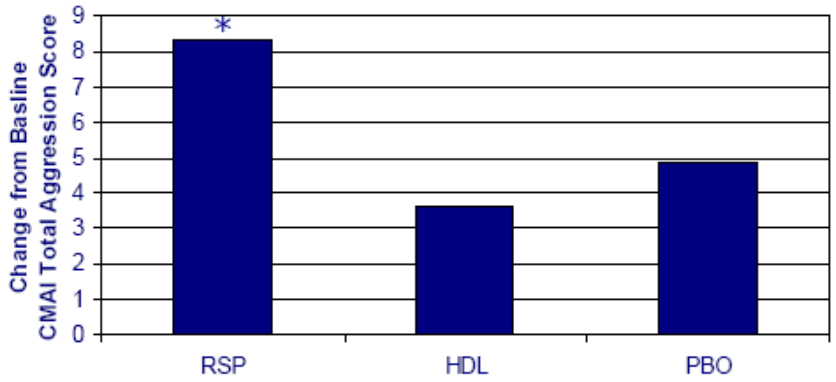
Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group.

Katz IR et al. J Clin Psychiatry. 1999 (Feb);60 (2):107-115.

Incidencia de síntomas extrapiramidales



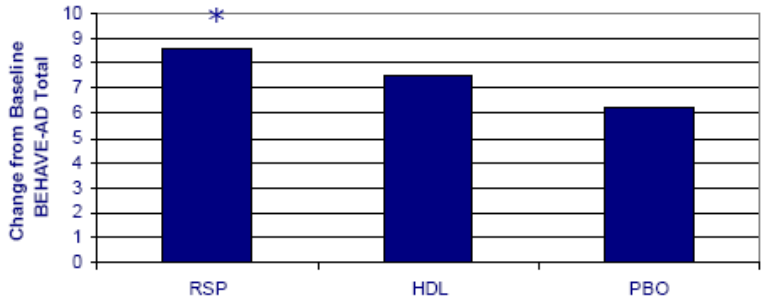
RISPERIDONA vs HALOPERIDOL



* RSP vs PBO significantly different, $p < .02$; RSP vs HDL significantly different, $p < .02$; De Deyn et al., *Neurology,* 1999.

Risperidona vs Haloperidol

- **RCT doble ciego**
- **N=344 pacientes con demencia**
- **Dosis: 0.5-4 mg/dia**
  - **Media: RSP 1.1 mg /HDL 1.2 mg**
- **La severidad de EPS fue similar con placebo y sig menor que con haloperidol.**
- **Reducción >30% en los SCPD**

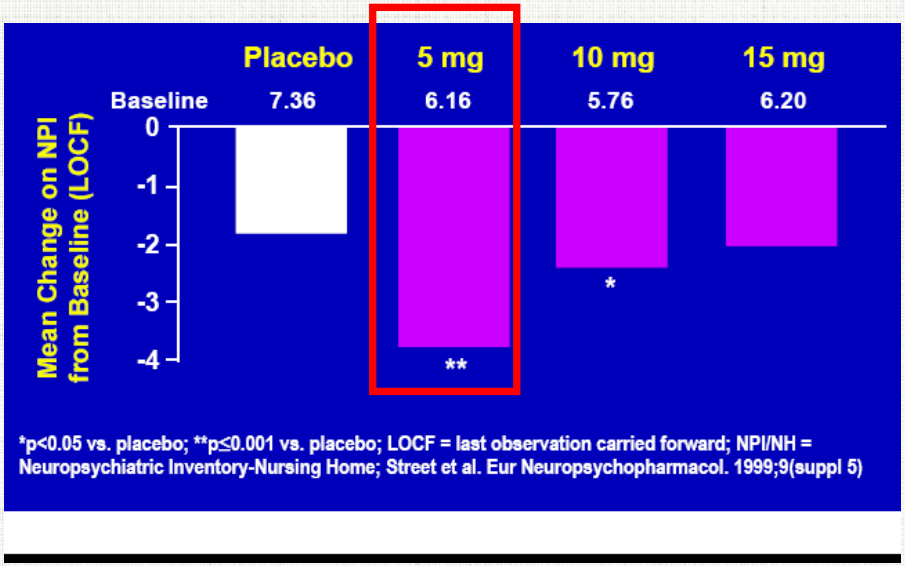


* RSP vs PBO significantly different, $p < .05$; De Deyn et al., *Neurology,* 1999.

NEUROLOGY

De Deyn PP, Rabheru K, Rasmunssen A, Bocksberger JP, Dautzenberg PLJ, Eriksson S et al.
A randomized, double blind trial of risperidone, placebo and haloperidol for behavioural symptoms of dementia.
Neurology, 1999, 53:946-955

OLANZAPINA

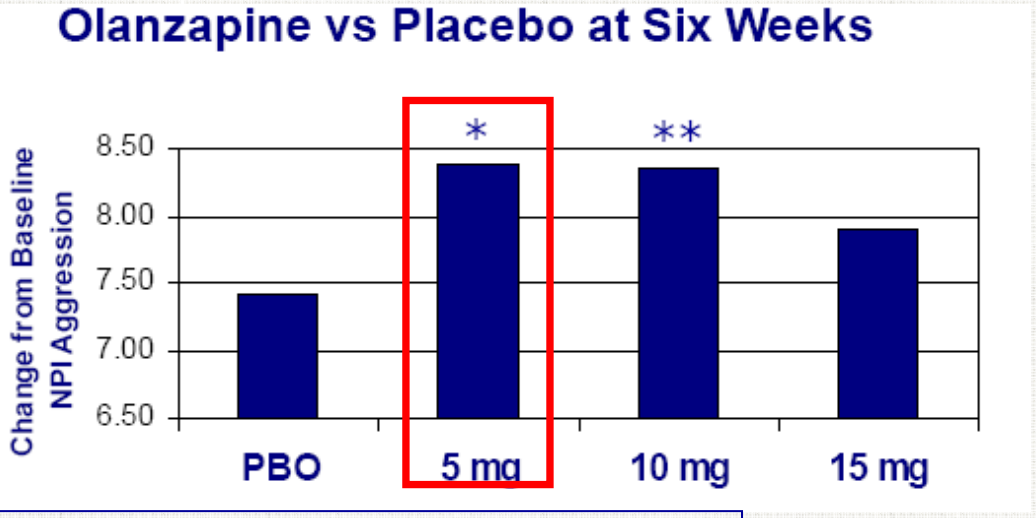


Delirios y alucinaciones

Presentación IM útil en agitación aguda √

- RCT doble ciego multicentrico
- N=206 residentes NH, EA DV
- 6 semanas
- Dosis bajas de olanzapina (5-10mg) mejoraron los SCPD frente a placebo.

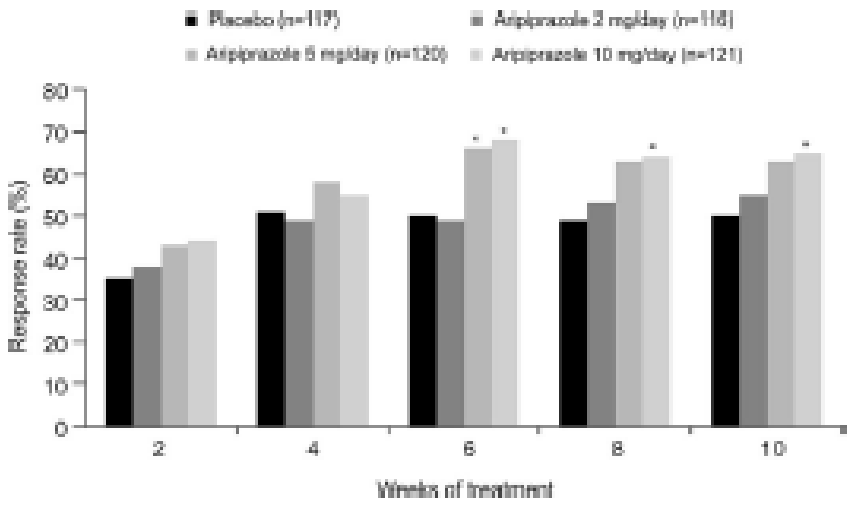
(-7.6 vs -3.7 [*P*<.001] y 6.1 vs -3.7 [*P* = .006]).



Olanzapine Treatment of Psychotic and Behavioral Symptoms in Patients With Alzheimer Disease in Nursing Care Facilities
Street et al. Arch Gen Psychiatry. 2000;57:968-976

ARIPIPRAZOL

FIGURE 2. Response Rate Based on the NPI-NH Psychosis Score (LOCF)



*p ≤0.05 versus placebo [CMH general association test]. Response defined as ≥50% decrease from baseline. NPI-NH, Neuropsychiatric Inventory–Nursing Home version Psychosis Subscale; LOCF, last observation carried forward; CMH, Cochran–Mantel–Haenszel.

- EDCC a tres dosis fijas vs placebo.
- 487 pacientes NH
- Demencia + psicosis
- Eficacia en el tratamiento de síntomas psicóticos y agitación a dosis de 10 mg, algunos con 5 mg/día con una buena tolerancia.

Similar eficacia que la risperidona en el tratamiento de la agresividad

Mintzer JE,Tune LE, Breder CD, Swanink R, Marcus RN,McQuade RD et al.
Aripiprazole for the treatment of psychoses in institutionalized patients with Alzheimer dementia: a multicenter, randomized, double-blind, placebo-controlled assessment of three fixed doses. Am J Geriatrc Psych 2007; 15:918-31

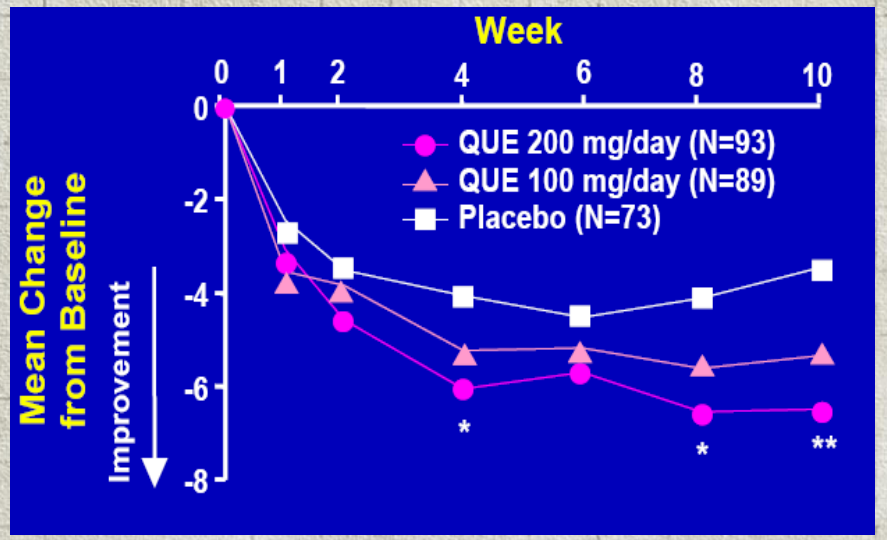
QUETIAPINA

QUETIAPINA: STAR TRIAL

- Doble ciego
- Quetiapina a dosis 100-200 mg vs placebo

Dosis flexible 25mg-200mg (175-225mg)

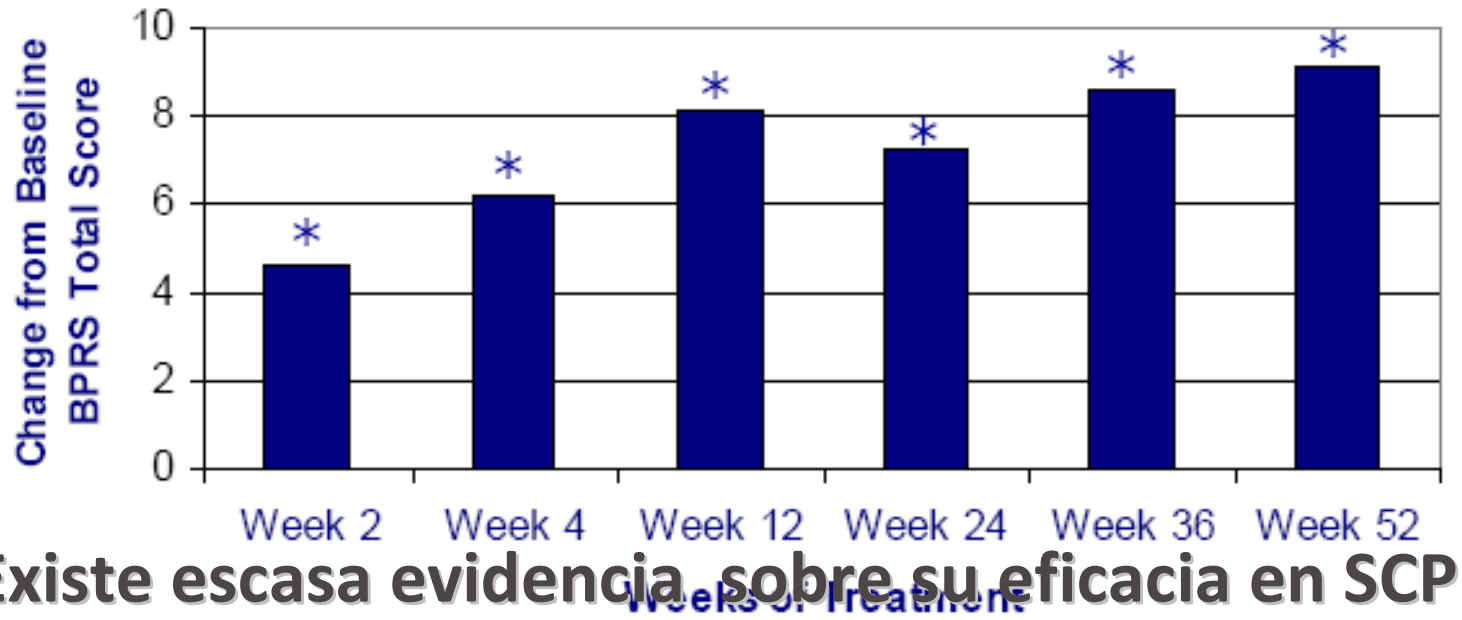
- Edad media 83 años, 333 institucionalizados
- MMSE : 5-6
- 10 semanas
- **Agitación**
- Más sedación:
  - 31% somnolencia,
  - 17% mareo
  - 15% hipotensión postural



Dosis de 200 mg/día era más eficaces que placebo
para el control de la agitación,
Menor efecto de síntomas extrapiramidales
No incremento del riesgo de ECV y con una incidencia de efectos adversos baja

QUETIAPINA

- Escaso riesgo de efectos extrapiramidales.
- Buena tolerancia a dosis 150 mg/día*



Existe escasa evidencia sobre su eficacia en SCPD

**Long-Term use of quetiapine in elderly patients with psychotic disorders Tariot PN et al.*

Clin Ther. 2000 Sep;22(9):1068-84

***Ballard C, Margallo-Lana M, Juszczak E, et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. BMJ 2005; 330:874*

¿Son todos los antipsicóticos atípicos igual de eficaces?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 12, 2006 VOL. 355 NO. 15

Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease

Lon S. Schneider, M.D., Pierre N. Tariot, M.D., Karen S. Dagerman, M.S., Sonia M. Davis, Dr.P.H., John K. Hsiao, M.D., M. Saleem Ismail, M.D., Barry D. Lebowitz, Ph.D., Constantine G. Lyketsos, M.D., M.H.S., J. Michael Ryan, M.D., T. Scott Stroup, M.D., David L. Sultzer, M.D., Daniel Weintraub, M.D., and Jeffrey A. Lieberman, M.D., for the CATIE-AD Study Group*

Table 2. Medication Doses and Outcomes in the Intention-to-Treat Sample.*

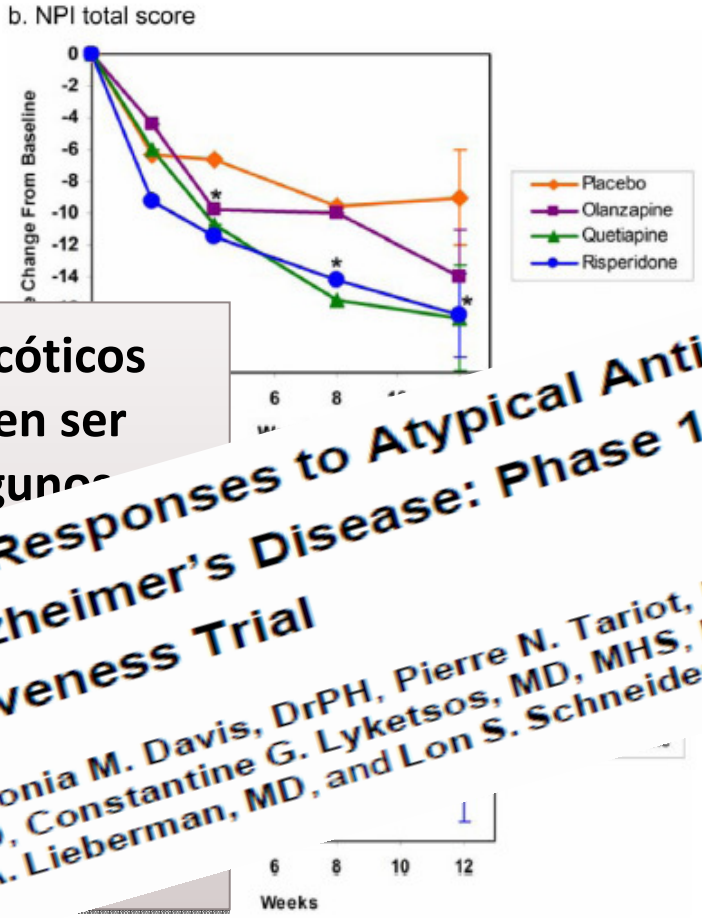
Dose and Outcome	Olanzapine Group (N=99)	Quetiapine Group (N=94)	Risperidone Group (N=84)	Placebo Group (N=139)	P Value (Overall Comparison)†
Discontinuation of treatment for any reason — no. of patients (%)	79 (80)	77 (82)	65 (77)	118 (85)	
Discontinuation of treatment because of lack of efficacy — no. of patients (%)	39 (39)	50 (53)	37 (44)	97 (70)	
Kaplan–Meier estimate of time to discontinuation — wk					0.002†

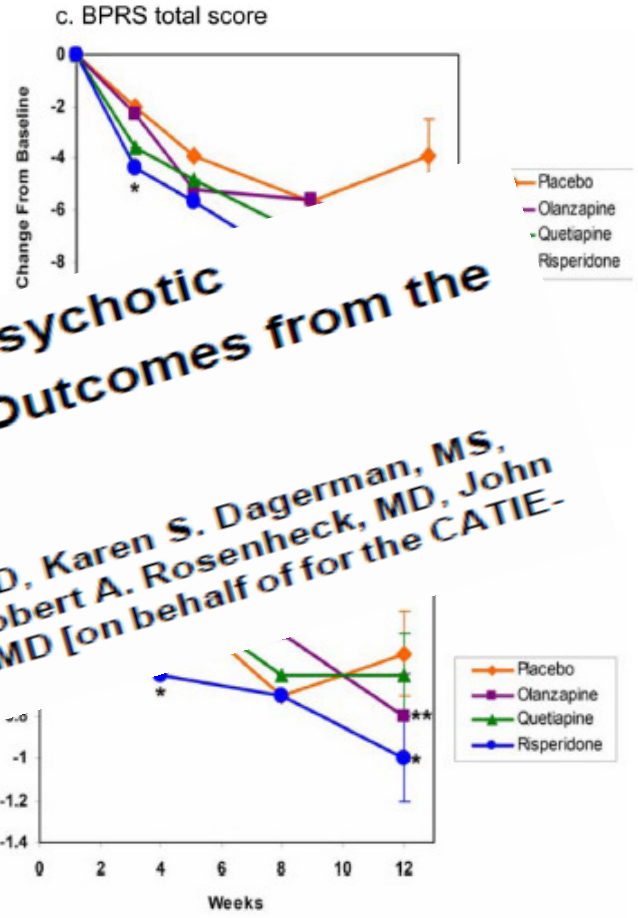
Dose and Outcome	Olanzapine Group (N=99)	Quetiapine Group (N=94)	Risperidone Group (N=84)	Placebo Group (N=139)	P Value (Overall Comparison)†
Discontinuation of treatment because of intolerability, adverse events, or death — no. of patients (%)	24 (24)	15 (16)	15 (18)	7 (5)	
Kaplan–Meier estimate of time to discontinuation — wk**					0.009†
25th percentile	13.7	29.4	20.1	?	

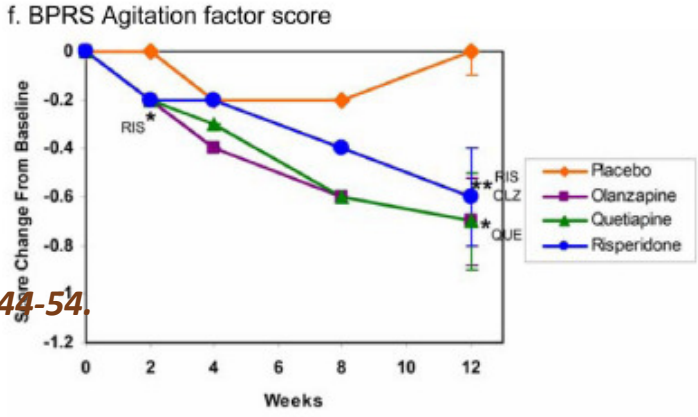
Algunos antipsicóticos atípicos pueden ser eficaces en algunos síntomas

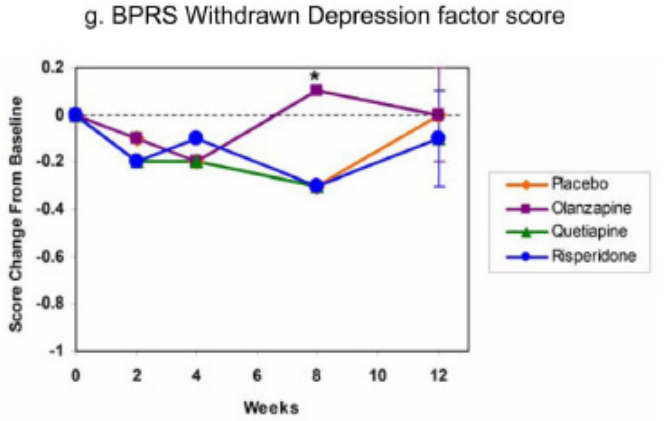
Clinical Symptom Responses to Atypical Antipsychotic Medications in Alzheimer's Disease: Phase 1 Outcomes from the CATIE-AD Effectiveness Trial

David L. Sultzer, MD, Sonia M. Davis, DrPH, Pierre N. Tariot, MD, Karen S. Dagerman, MS, Barry D. Lebowitz, PhD, Constantine G. Lyketsos, MD, MHS, Robert A. Rosenheck, MD, John K. Hsiao, MD, Jeffrey A. Lieberman, MD, and Lon S. Schneider, MD [on behalf of for the CATIE-AD Study Group]









Am J Psychiatry 2008; 165: 844-54.

Efectividad de los fármacos antipsicóticos atípicos para el tratamiento de la agresividad y la psicosis en la enfermedad de Alzheimer

Ballard C, Waite J

THE COCHRANE COLLABORATION®

Revisión Cochrane traducida. En: *La biblioteca Cochrane Plus*, 2008 Nº1. Oxford: Update Software Ltd.

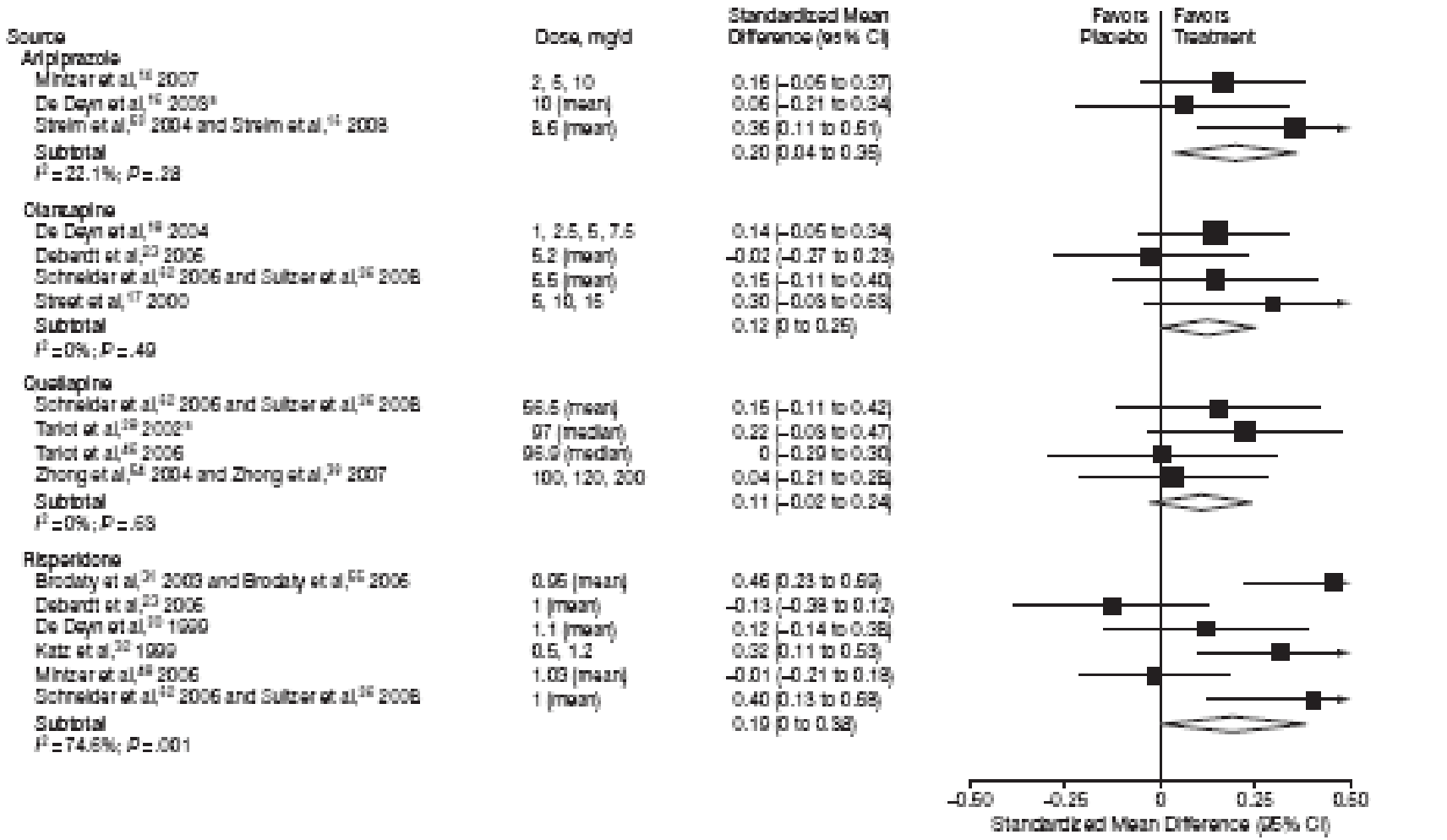
1. La evidencia sugiere que la risperidona y la olanzapina son útiles con moderada eficacia para reducir la agresividad y que la risperidona reduce la psicosis
2. Pero ambas se asocian con eventos adversos graves cerebrovasculares y síntomas extrapiramidales y no deberían usarse en forma sistemática para a menos que hubiera un riesgo marcado o perturbación severa.

JAMA, February 2, 2005—Vol 293, No. 5

Pharmacological Treatment of Neuropsychiatric Symptoms of Dementia

Beneficios con risperidona y olanzapina en 4/7 ensayos
No estudios de clozapina ni quetiapina
para esta indicación en el momento del análisis

Figure 1. Controlled Trials of Patients Taking Atypical Antipsychotic Medications vs Placebo

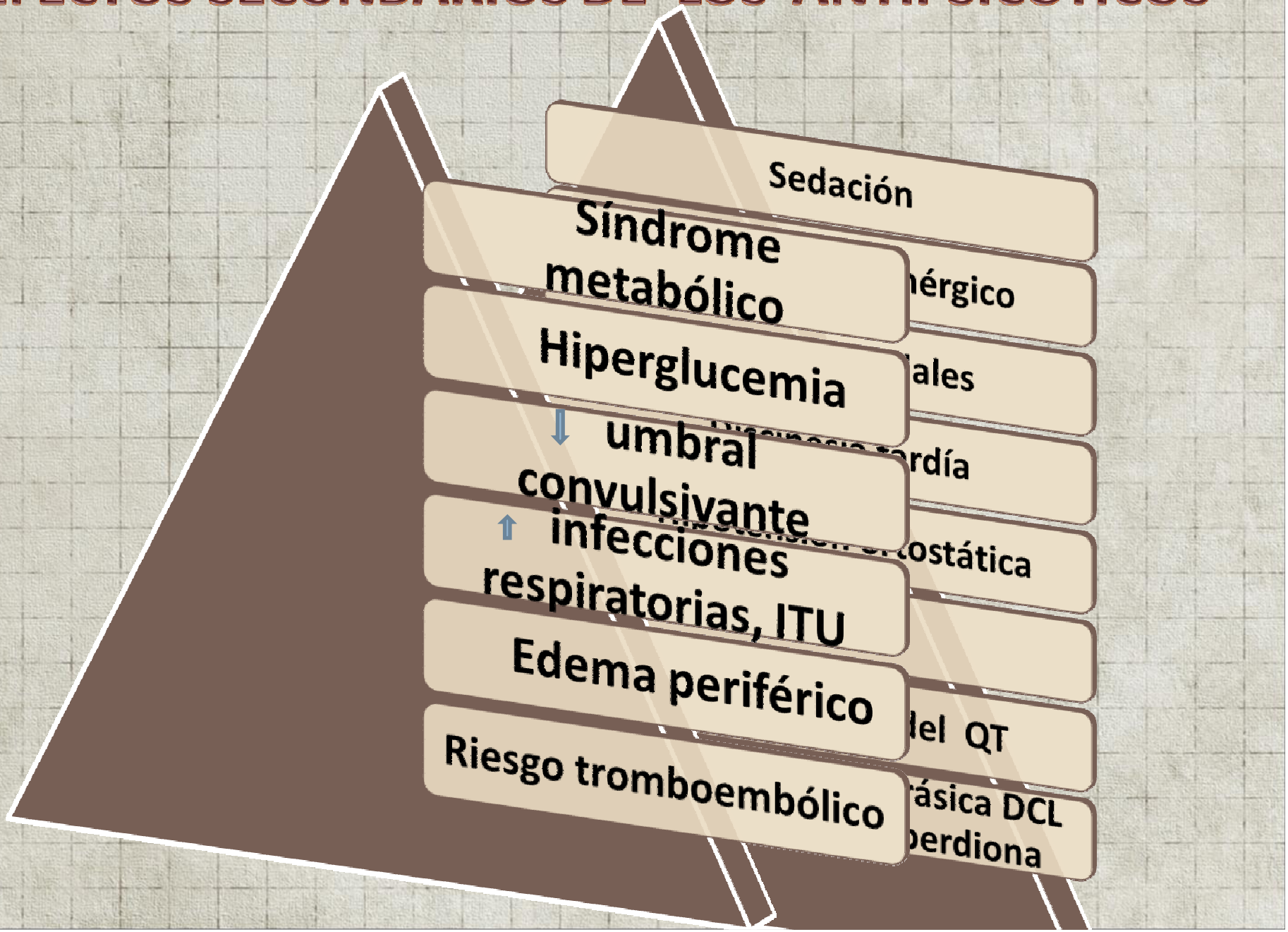


Total global scores are presented and include the symptoms of delusion, hallucination, dysphoria, anxiety, agitation or aggression, euphoria, disinhibition, irritability, apathy, aberrant motor activity, and behavioral disturbances. Weights are from a random-effects analysis. The size of the data markers is proportional to the sample size of the trial.

[a]The data used for this study were abstracted from the meta-analysis by Schneider et al.[16]

Maher A et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-Label uses in adults. A sysmtematic Review and meta-analysis. JAMA,2011;206,12: 1359-69

EFECTOS SECUNDARIOS DE LOS ANTIPSICÓTICOS



BMJ

Cite this as: *BMJ* 2010;341:c4245
doi:10.1136/bmj.c4245

RESEARCH

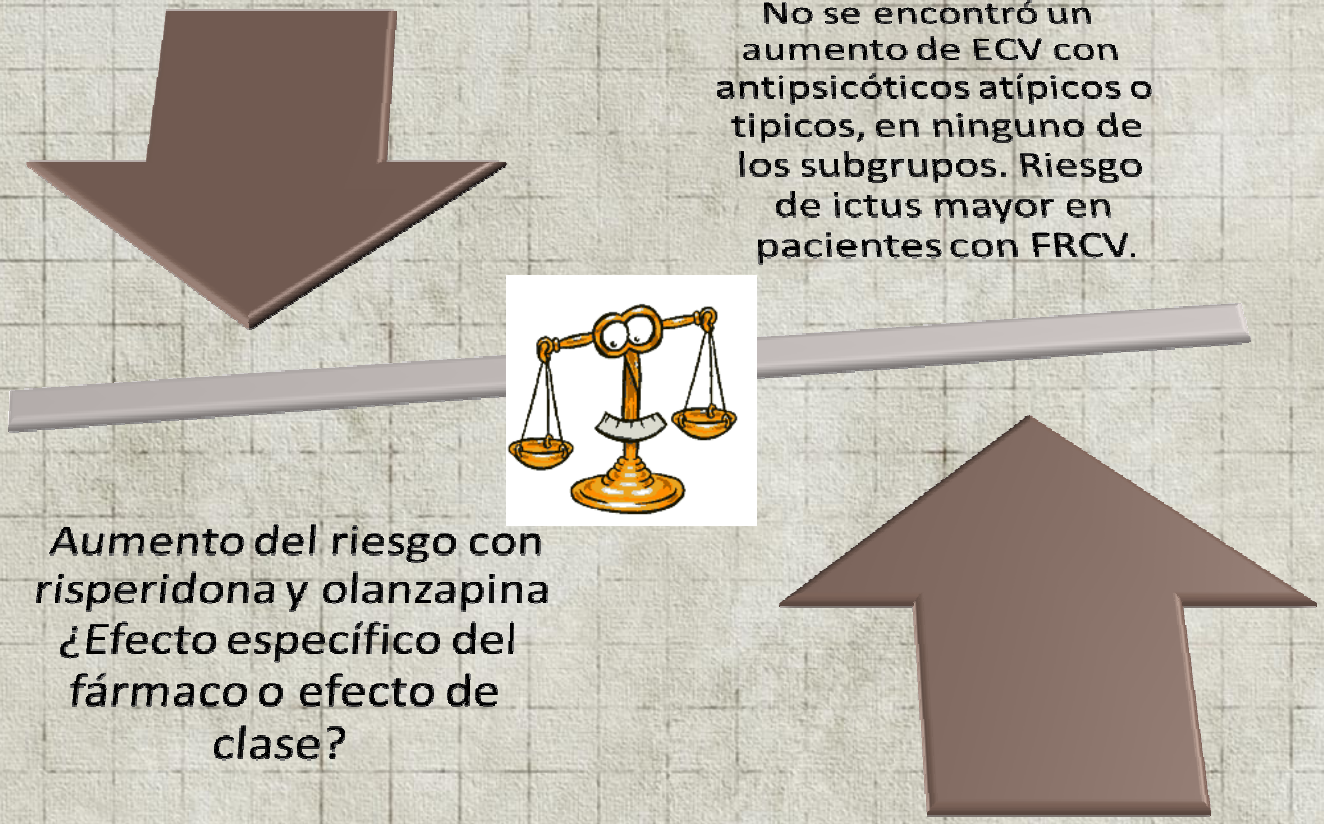
Antipsychotic drugs and risk of venous thromboembolism: nested case-control study

Chris Parker, medical statistician,[1] Carol Coupland, associate professor in medical statistics,[2] Julia Hippisley-Cox, professor of clinical epidemiology and general practice[2]

✓ **Existe una asociación entre el uso de antipsicóticos y el riesgo de Enfermedad Tromboembólica en una población extensa de AP.**

✓**El aumento del riesgo es mayor entre los pacientes con inicio reciente y con antipsicóticos atípicos**

RIESGO DE ACV



No se encontró un aumento de ECV con antipsicóticos atípicos o tipicos, en ninguno de los subgrupos. Riesgo de ictus mayor en pacientes con FRCV.

Aumento del riesgo con *risperidona* y olanzapina ¿Efecto específico del fármaco o efecto de clase?

Schneider. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis Of randomized, placebo-contorlled trial. Am J Geriatr Psych 2006;14: 191-210.

Gill et al. Atypical antipsychotic drugs and Risk of ischaemic stroke: population based restrspective cohort study. BMJ 2005;330:445.

Table 1. Adverse Events Associated With Use of Atypical Antipsychotic Medications Compared With Placebo in Elderly Patients With Dementia

	No. of Studies	Placebo		Atypical Antipsychotic Drugs		Pooled OR (95% CI)
		No. of Adverse Events	Sample Size	No. of Adverse Events	Sample Size	
Cardiovascular event[a]						
Aripiprazole	1	12	121	42	366	1.20 [0.58-2.55
Olanzapine	5	9	440	40	778	2.30 [1.08-5.61
Quetiapine	3	15	254	29	366	1.10 [0.53-2.30
Risperidone	6	34	1010	119	1767	2.10 [1.38-3.22
Cerebrovascular accident						
Aripiprazole	3	2	253	2	340	0.70 [0.05-10.4
Olanzapine	2	4	232	6	278	1.50 [0.33-7.44
Quetiapine	2	6	241	3	185	0.70 [0.10-3.08
Risperidone	4	8	753	24	1099	3.12 [1.32-8.21
Increased appetite or weight increase						
Aripiprazole	2	10	223	23	472	1.00 [0.44-2.40
Olanzapine	3	6	326	34	482	4.70 [1.87-14.1
Quetiapine	1	4	142	5	94	1.90 [0.40-10.0
Risperidone	2	5	236	14	281	3.40 [1.08-12.7
Anticholinergic events						
Olanzapine	1	12	90	60	178	3.30 [1.62-7.17
Sedation						
Aripiprazole	4	22	374	116	706	2.60 [1.57-4.64
Olanzapine	5	25	440	158	778	4.60 [2.87-7.66
Quetiapine	4	18	353	84	446	5.20 [2.93-9.61
Risperidone	6	102	922	265	1260	2.30 [1.79-3.06
Extrapyramidal symptoms						
Aripiprazole	4	16	374	39	706	1.30 [0.68-2.57
Olanzapine	1	2	142	18	100	15.20 [3.50-138.
Quetiapine	3	9	254	18	366	1.20 [0.46-3.08
Risperidone	5	31	916	130	1561	3.00 [1.96-4.70
Urinary tract symptoms						
Aripiprazole	3	44	348	115	603	1.40 [0.92-2.09
Olanzapine	1	1	94	19	204	9.50 [1.47-401.
Quetiapine	2	12	191	44	332	2.40 [1.16-5.15
Risperidone	4	71	666	164	1060	1.60 [1.13-2.13

Abbreviation: OR, odds ratio.
[a]Category excludes patients who experienced cerebrovascular accident.

RIESGO DE MORTALIDAD

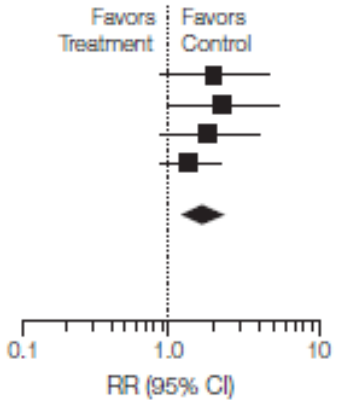
Risk of Death With Atypical Antipsychotic Drug Treatment for Dementia

Meta-analysis of Randomized Placebo-Controlled Trials

Figure 4. Deaths Based on Total Drug and Placebo Exposures Pooled by Drug

Drug	Death: Treatment, No. of Events/ Total No.	Death: Placebo, No. of Events/ Total No.	RR (95% CI) (Random-Effects Model)
Aripiprazole	21/95	6/54	1.99 (0.86-4.62)
Olanzapine	31/217	6/97	2.31 (1.00-5.35)
Quetiapine	21/58	7/36	1.86 (0.88-3.93)
Risperidone	45/201	22/133	1.35 (0.85-2.14)
Overall	118/571	41/320	1.65 (1.19-2.29)

Test for Heterogeneity $\chi^2_3 = 1.63$, $I^2 = 0\%$ ($P = .65$)
Test for Overall Effect $z = 3.01$ ($P = .003$)



chotic drugs (eg, haloperidol and thioridazine) and have been considered preferred treatments for these behavioral disturbances associated with dementia.[2,3] Reasons for this preference include emerging clinical trials evidence,[4-8] perceived relative safety advantages compared with older antipsychotic drugs and other medications, the opinions of expert clinicians, and ex-

dence interval [CI], 1.06-2.23; $P = .02$; and risk difference was 0.01; 95% CI, 0.004-0.02; $P = .01$). Sensitivity analyses did not show evidence for differential risks for individual drugs, severity, sample selection, or diagnosis.

Conclusions Atypical antipsychotic drugs may be associated with a small increased risk for death compared with placebo. This risk should be considered within the context of medical need for the drugs, efficacy evidence, medical comorbidity, and the efficacy and safety of alternatives. Individual patient analyses modeling survival and causes of death are needed.

JAMA. 2005;294:1934-1943 www.jama.com

For editorial comment see p 1963.

Author Affiliations are listed at the end of this article. **Corresponding Author:** Lon S. Schneider, MD, MS, Department of Psychiatry and the Behavioral Sciences, Keck School of Medicine, University of Southern California, 1510 San Pablo St, HCC 600, Los Angeles, CA 90033 (lschneid@usc.edu).

- Mortalidad fármaco 3.5% vs placebo 2.3%
- Riesgo de muerte era 1.5 veces más.
-

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk of Death in Elderly Users of Conventional vs. Atypical Antipsychotic Medications

Philip S. Wang, M.D., Dr.P.H., Sebastian Schneeweiss, M.D., Jerry Avorn, M.D., Michael A. Fischer, M.D., Helen Mogun, M.S., Daniel H. Solomon, M and M. Alan Brookhart, Ph.D.

ABSTRACT

BACKGROUND

Recently, the Food and Drug Administration (FDA) issued an advisory sta ical antipsychotic medications increase mortality among elderly patients. advisory did not apply to conventional antipsychotic medications; the with these older agents is not known.

METHODS

We conducted a retrospective cohort study involving 22,890 patients 65 older who had drug insurance benefits in Pennsylvania and who began re ventional or atypical antipsychotic medication between 1994 and 2003. An tality rates and Cox proportional-hazards models were used to compare th within 180 days, less than 40 days, 40 to 79 days, and 80 to 180 days afte of therapy with an antipsychotic medication. We controlled for potential variables with the use of traditional multivariate Cox models, propensity-score adjustme

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in risk occurred soon after therapy was initiated and with higher dosages of convention-

Table 2. Relative Risk of Death within 180 Days after Beginning Therapy with Conventional as Compared with Atypical Antipsychotic Medications.*

Model	Hazard Ratio (95% CI)
Unadjusted analysis	1.51 (1.43–1.59)
Adjusted analysis†	
Use of any conventional APM	1.37 (1.27–1.49)
Low dose of conventional APM (<median)	1.14 (1.04–1.26)
High dose of conventional APM (>median)	1.73 (1.57–1.90)
Adjusted analysis of death†	
<40 Days after beginning therapy	1.56 (1.37–1.78)
40–79 Days after beginning therapy	1.37 (1.19–1.59)
80–180 Days after beginning therapy	1.27 (1.14–1.41)
Adjusted analysis of patient subgroups†	
With dementia	1.29 (1.15–1.45)
Without dementia	1.45 (1.30–1.63)
In a nursing home	1.26 (1.08–1.47)
Not in a nursing home	1.42 (1.29–1.56)

* APM denotes antipsychotic medication, and CI confidence interval.
† Hazard ratios were adjusted for calendar year, age, sex, race, the presence or absence of cardiac arrhythmias, cerebrovascular disease, congestive heart failure, diabetes, myocardial infarction, other ischemic heart disease, other cardiovascular disorders, cancer, HIV infection, dementia, delirium, mood disorders, psychotic disorders, other psychiatric disorders, and the use or nonuse of other psychiatric medications, total number of medications used, hospitalizations, and nursing home stays.

22890 pacientes > 65 años que iniciaron tratamiento con antipsicóticos. Cuatro cohortes (0-40, 40-80, 80-180, >180 días).

Los neurolépticos convencionales tienen un 37% más de mortalidad (dosis-dependiente) a corto plazo que los atípicos. OR: 1.27-1.56

Annals of Internal Medicine | ARTICLE

Antipsychotic Drug Use and Mortality in Older Adults with Dementia

Sudeep S. Gill, MD, MSc; Susan E. Bronskill, PhD; Sharon-Lise T. Normand, PhD; Geoffrey M. Anderson, MD, PhD; Kathy Sykora, MSc; Kelvin Lam, MSc; Chaim M. Bell, MD, PhD; Philip E. Lee, MD; Hadas D. Fischer, MD; Nathan Herrmann, MD; Jerry H. Gurwitz, MD; and Paula A. Rochon, MD, MPH

Background: Antipsychotic drugs are widely used to manage behavioral and psychological symptoms in dementia despite concerns about their safety.

Objective: To examine the association between treatment with antipsychotics (both conventional and atypical) and all-cause mortality.

Design: Population-based, retrospective cohort study.

Setting: Ontario, Canada.

Patients: Older adults with dementia who were followed between 1 April 1997 and 31 March 2003.

Measurements: The risk for death was determined at 30, 60, 120, and 180 days after the initial dispensing of antipsychotic medication. Two pairwise comparisons were made: atypical versus no antipsychotic use and conventional versus atypical antipsychotic use. Groups were stratified by place of residence (community or long-term care). Propensity score matching was used to adjust for differences in baseline health status.

Results: A total of 27 259 matched pairs were identified. New use of atypical antipsychotics was associated with a statistically significant increase in the risk for death at 30 days compared with nonuse in both the community-dwelling cohort (adjusted hazard ratio, 1.31 [95% CI, 1.02 to 1.70]; absolute risk difference, 0.2 percentage point) and the long-term care cohort (adjusted hazard ratio, 1.55 [CI, 1.15 to 2.07]; absolute risk difference, 1.2 percentage points). Excess risk seemed to persist to 180 days, but unequal rates of censoring over time may have affected these results. Relative to atypical antipsychotic use, conventional antipsychotic use was associated with a higher risk for death at all time points. Sensitivity analysis revealed that unmeasured confounders that increase the risk for death could diminish or eliminate the observed associations.

Limitations: Information on causes of death was not available. Many patients did not continue their initial treatments after 1 month of therapy. Unmeasured confounders could affect associations.

Conclusions: Atypical antipsychotic use is associated with an increased risk for death compared with nonuse among older adults with dementia. The risk for death may be greater with conventional antipsychotics than with atypical antipsychotics.

- Predisposición a arrtimias x Prolongación QT
- Aumento de broncoaspiración y asfixia por sedación
- Relación con TEP
- Riesgo de ACV

¿Persiste el aumento de riesgo de mortalidad en tratamientos a largo plazo con neurolépticos?

Lancet Neurol 2009; 8: 151-57

- ✓**Hay un aumento de la mortalidad en pacientes tratados con antipsicóticos a los 12 meses SCPD (Supervivencia 77% placebo vs 70% tto); más marcados a 24 (71% vs 46%)-36meses.**
- ✓**Risperidona 67%; haloperidol 26%**
- ✓**Aunque los resultados no pueden generalizarse a otros atípicos, apuntan a la necesidad de alternativas más seguras para el tratamiento de los SCPD.**

¿ Hay diferencias en la mortalidad entre los diferentes antipsicóticos?

HALOPERIDOL
- **En los primeros 30 días**
- RR=3,2 dosis> 1 mg/día
- RR=1.5; =< 1 mg/dia

RISPERIDONA
- RR=1,6 dosis > 1 mg/día
- RR= 1.1 ; =< 1 mg/día

OLANZAPINA
- RR=1,5 dosis >2,5mg/día
- RR=1, =< 2,5 mg

QUETIAPINA
- > < 50 mg/día: no mayor mortalidad

Las dosis habituales se asocian a una mayor mortalidad a corto plazo excepto para la quetiapina.

Todas las dosis de HL asociadas a mayor riesgo

No aumento del riesgo de mortalidad pasados los 30 días.

Rossom et al. Are all commonly prescribed antipsychotics associated with greater mortality In elderly male veterans with dementia? JAGS 2010;58:1027-1034.

¿ Hay diferencias en la mortalidad entre los diferentes neurolépticos?

Article

Risk of Mortality Among Individual Antipsychotics in Patients With Dementia

Helen C. Kales, M.D.

Hyungjin Myra Kim, Sc.D.

Kara Zivin, Ph.D.

Marcia Valenstein, M.D., M.S.

Lisa S. Seyfried, M.D., M.S.

Claire Chiang, Ph.D.

Francesca Cunningham, Pharm.D.

Lon S. Schneider, M.D., M.S.

Frederic C. Blow, Ph.D.

Objective: The use of antipsychotics to treat the behavioral symptoms of dementia is associated with greater mortality. The authors examined the mortality risk of individual agents to augment the limited information on individual antipsychotic risk.

Method: The authors conducted a retrospective cohort study using national data from the U.S. Department of Veterans Affairs (fiscal years 1999–2008) for dementia patients age 65 and older who began outpatient treatment with an antipsychotic (risperidone, olanzapine, quetiapine, or haloperidol) or valproic acid and its derivatives (as a nonantipsychotic comparison). The total sample included 33,604 patients, and individual drug groups were compared for 180-day mortality rates. The authors analyzed the data using multivariate models and propensity adjustments.

Results: In covariate-adjusted intent-to-treat analyses, haloperidol was associated with the highest mortality rates (relative risk=1.54, 95% confidence interval [CI]=1.38–1.73) followed by risperidone (reference), olanzapine (relative risk=0.99, 95% CI=0.89–1.10), valproic acid and its derivatives (relative risk=0.91, 95% CI=0.78–1.06), and quetiapine (relative risk=0.73, 95% CI=0.67–0.80). Propensity-stratified and propensity-weighted models as well as analyses controlling for site of care and medication dosage revealed similar patterns. The mortality risk with haloperidol was highest in the first 30 days but decreased significantly and sharply thereafter. Among the other agents, mortality risk differences were most significant in the first 120 days and declined in the subsequent 60 days during follow-up.

Conclusions: There may be differences in mortality risks among individual antipsychotic agents used for treating patients with dementia. The use of valproic acid and its derivatives as alternative agents to address the neuropsychiatric symptoms of dementia may carry associated risks as well.

(Am J Psychiatry 2012; 169:71–79)

Estudio retrospectivo de cohortes de > 65 años

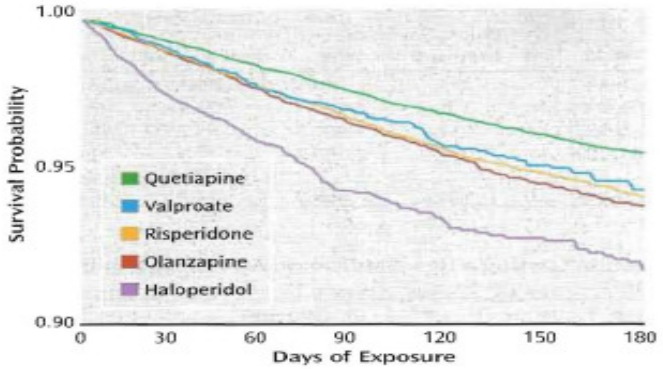
Inicio antipsicóticos o ácido valproico en demencias (33.604 pacientes).

Seguimiento a 180 días.

La mortalidad fue 1,5 veces más alta en los primeros 120 días que en los sucesivos para todos los fármacos excepto el haloperidol.

El mayor riesgo de mortalidad con el haloperidol es mayor en los pirmeros 30 días: RR= 2,24 que en el grupo de risperidona de 150-180 días.

FIGURE 1. Covariate-Adjusted Survival Function by Days of Exposure in a Study of Mortality Risk Among Individual Antipsychotics



RECOMENDACIONES

Quetiapina es una alternativa a dosis de inicio de 25 mg/noche hasta 75 mg/12h.

Escasa evidencia de eficacia en Demencia.

Risperidona a dosis máximas de 1 mg día también es eficaz, pero dosis más altas se asocian con aumento de efectos adversos.

Única con la indicación en España.

Olanzapina dosis de inicio de 2.5 mg hasta 5 mg/12h.

Al menos efecto modesto en SCPD en EA y DV.

Efecto extrapiramidal bajo a estas dosis

Aripiprazol 5-10 mg/día

Escaso efecto

Extrapiramidal y bajo riesgo cerebrovascular

SÓLO EN PACIENTES CON SCPD GRAVES NO OTRA ALTERNATIVA INFORMAR FAMILIA RIESGOS

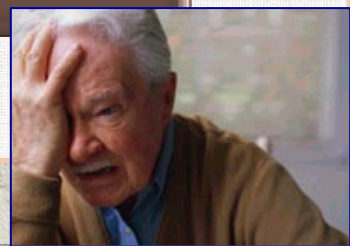
Y REVISAR

ANTIDEPRESIVOS

- Depresión
- Agitación y psicosis
- Insomnio
- Ansiedad
- Hipersexualidad

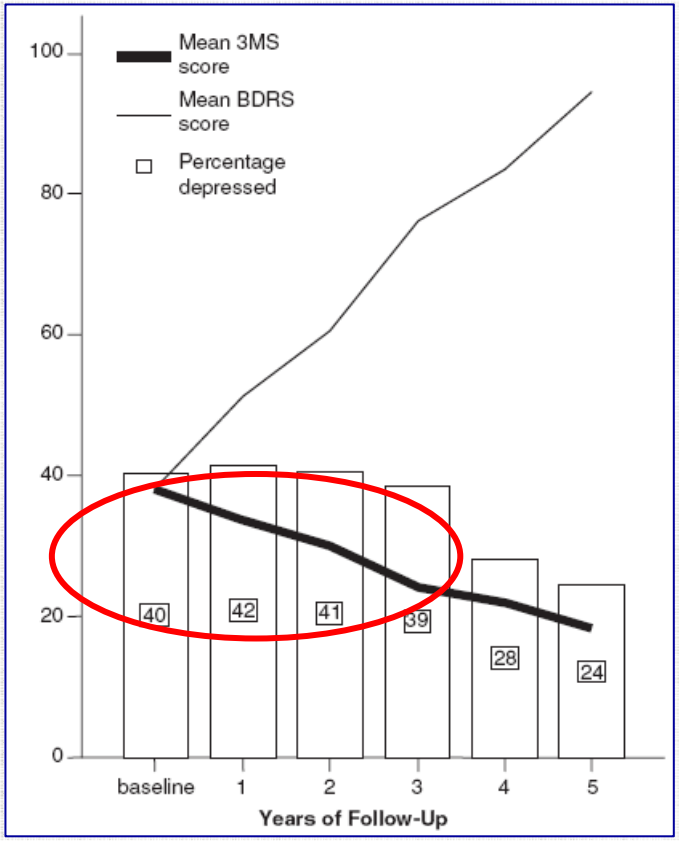
Antidepresivos: depresión y demencia

- Los ancianos deprimidos tienen un mayor riesgo de desarrollar demencia
- Si no es tratada puede acelerar el deterioro cognitivo: indicado ISRS si síntomas de la esfera afectiva.
- Dx difícil: confusión con otros síntomas de demencia (apatía, trastornos del sueño y retracción social)
- Si duda: un ensayo terapéutico con AD la única estrategia diagnóstica
- Peor respuesta que población general: ¿Otros mecanismos neurobiológicos?



Antidepresivos: depresión y demencia

- Prevalencia de depresión: 40% en los tres primeros años, decrece con el tiempo.
- El deterioro funcional puede preceder a la aparición de los síntomas depresivos en pacientes con probable EA, más que el cognitivo.

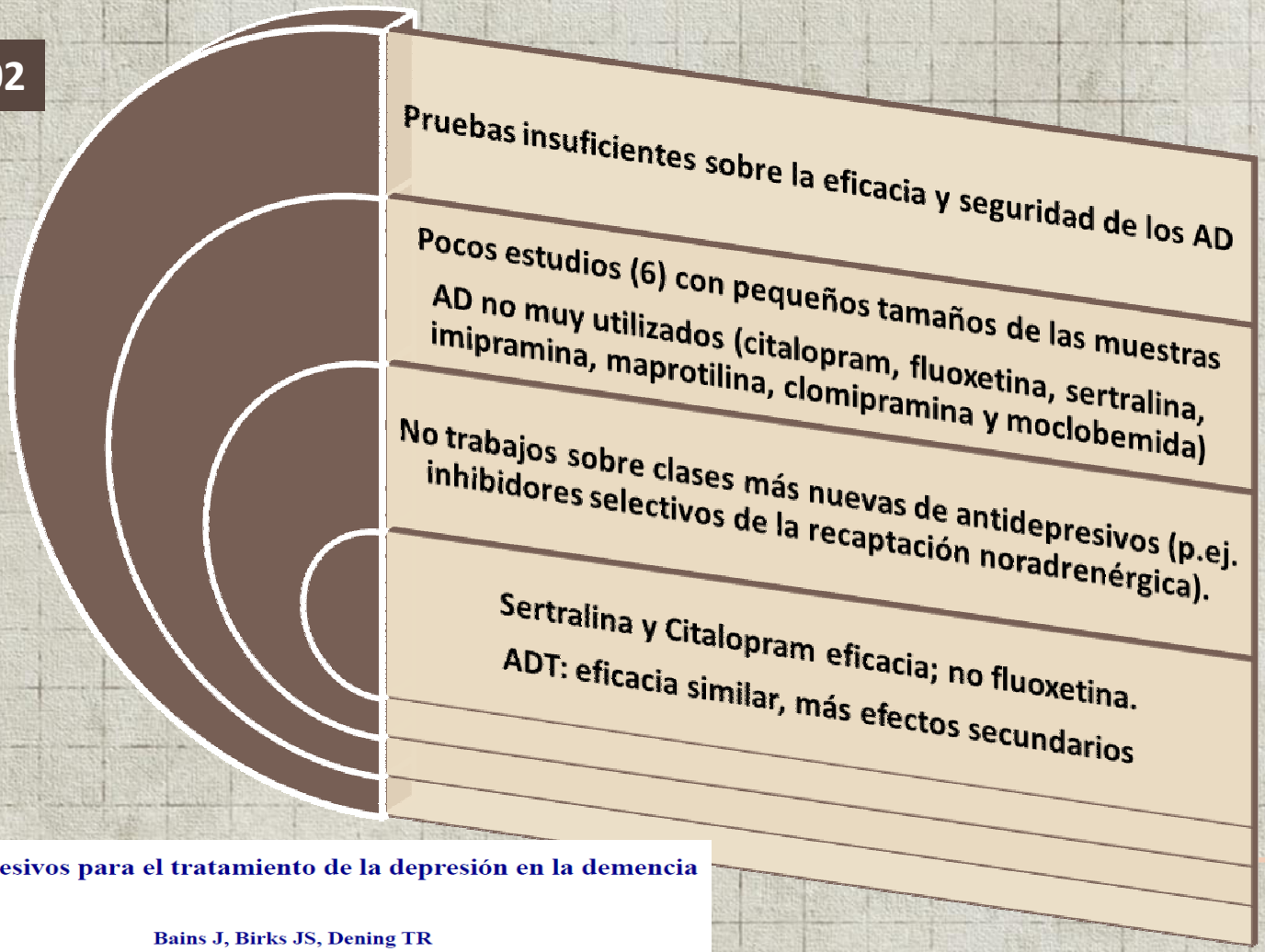


536 pacientes seguidos durante 14 años.

Depressive symptoms in Alzheimer disease: natural course and temporal relation to function and cognitive status.
Holtzer R et al. J Am Geriatr Soc 2005; 53:2083-2089

¿Qué evidencia hay para el uso de antidepresivos en el tratamiento de la depresión en la demencia?

2002



Antidepresivos para el tratamiento de la depresión en la demencia

Bains J, Birks JS, Dening TR

Reproducción de una revisión Cochrane, traducida y publicada en *La Biblioteca Cochrane Plus,* 2008, Número 2

THE COCHRANE COLLABORATION®

Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial

Sube Banerjee, Jennifer Hellier, Michael Dewey, Renee Romeo, Clive Ballard, Robert Baldwin, Peter Bentham, Chris Fox, Clive Holmes, Cornelius Katona, Martin Knapp, Claire Lawton, James Lindesay, Gill Livingston, Niall McCrae, Esme Moniz-Cook, Joanna Murray, Shirley Nurock, Martin Orrell, John O'Brien, Michaela Poppe, Alan Thomas, Rebecca Walwyn, Kenneth Wilson, Alistair Burns

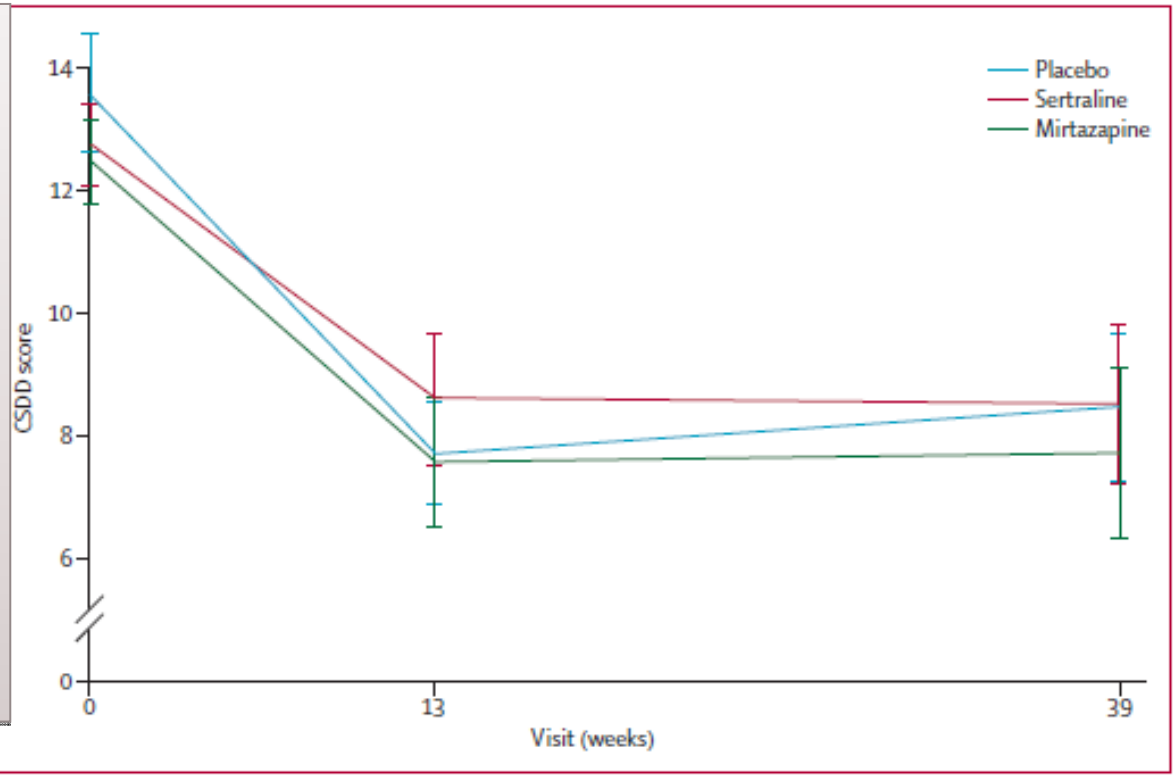
Summary

Background Depression is common in dementia but the evidence base for appropriate drug treatment is sparse and equivocal. We aimed to assess efficacy and safety of two of the most commonly prescribed drugs, sertraline and mirtazapine, compared with placebo.

Lancet 2011; 378: 403–11
Published Online
July 18, 2011
DOI:10.1016/S0140

- ✓326 pacientes de Psicogeriatría D+D
- ✓No beneficio sobre placebo.
- ✓Necesidad de pensar alternativas no farmacológicas

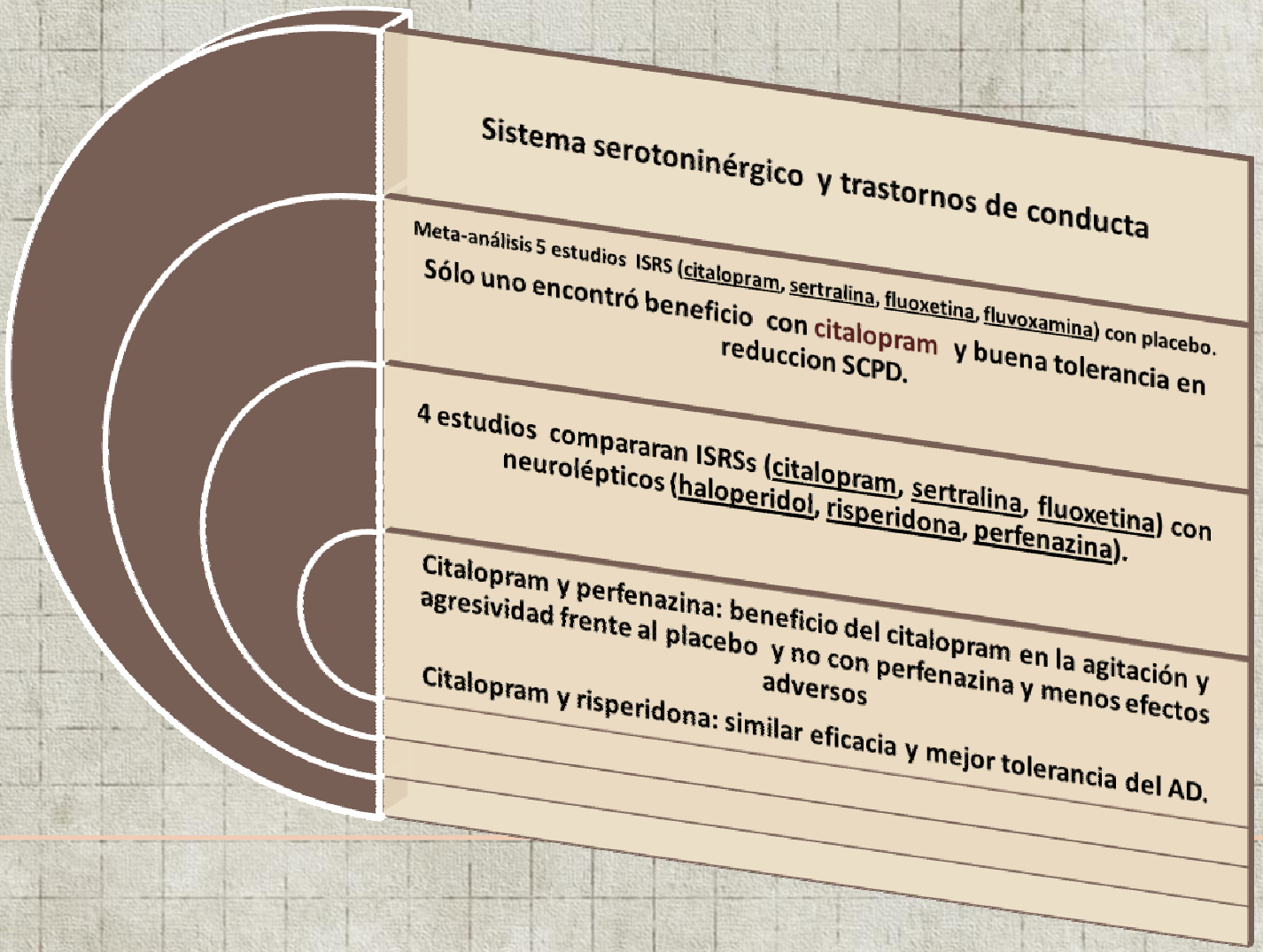
- ✓Actitud expectante en 13 semanas (43% mejoría placebo)
- ✓No descarta uso de AD en casos de gravedad o persistencia
- ✓No extensibles a otros AD.



Antidepresivos para la agitación y la psicosis en la demencia.

Seitz DP, Adunuri N, Gill SS, et al.

2011



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Archives of Gerontology and Geriatrics 47 (2008) 207–215
www.elsevier.com/locate/archger

Trazodone for Alzheimer's disease: A naturalistic follow-up study

Secundino López-Pousa [a,b,*], Josep Garre-Olmo [a], Joan Vilalta-Franch [a,b], Antoni Turon-Estrada [b], Imma Pericot-Nierga [b]

[a] *Research Unit, Institut d'Assistència Sanitària, Hospital Santa Caterina, Parc Hospitalari Martí i Julià, C/Dr. Castany s/n, 17190 Salt, Girona, Spain*
[b] *Memory and Dementia Assessment Unit, Institut d'Assistència Sanitària, Hospital Santa Caterina, Parc Hospitalari Martí i Julià, C/Dr. Castany s/n, 17190 Salt, Girona, Spain*

Received 7 February 2007; received in revised form 12 July 2007; accepted 23 July 2007
Available online 25 September 2007

Abstract

This study intended to provide a patient profile for trazodone (a triazolopyridine-derivative of phenylpiperazine) prescription in everyday clinical practice in patients with Alzheimer's disease (AD), and to describe clinical evaluation and the impact on caregiver burden at a 6-month follow-up. A naturalistic, prospective and observational study was performed, with a 6-month follow-up in 396 patients with probable AD, according to the NINCDS-ARDRA criteria. At the baseline and at the 6-month visit, patients were administered the Neuropsychiatric Inventory (NPI) to determine their Behavioral and Psychological Symptoms of Dementia (BPSD), and the Zarit Burden Interview (ZBI) to assess the impact on caregiver burden. Trazodone was prescribed for 6.1% of patients. With respect to the baseline visit, the untreated group showed an increased global NPI score (3.1 points; 95% CI = 1.9–4.2; $p = 0.001$) and ZBI score (2.2 points; 95% CI = 0.9–3.4; $p = 0.001$). At 6 months, the global NPI and ZBI scores remained unchanged for the treated group. The treated group showed a significant reduction in the NPI irritability subscale score (2.1 points; 95% CI = 0.4–3.7; $p = 0.015$). In the clinical practice, trazodone treatment was prescribed for patients with irritability, agitation and disinhibition. After 6 months, patients treated with trazodone exhibited no increase in BPSD frequency or severity, nor was an increase noted in the caregiver burden.

Keywords: AD; Trazodone; Behavioral disturbance; Geriatric psychopharmacology

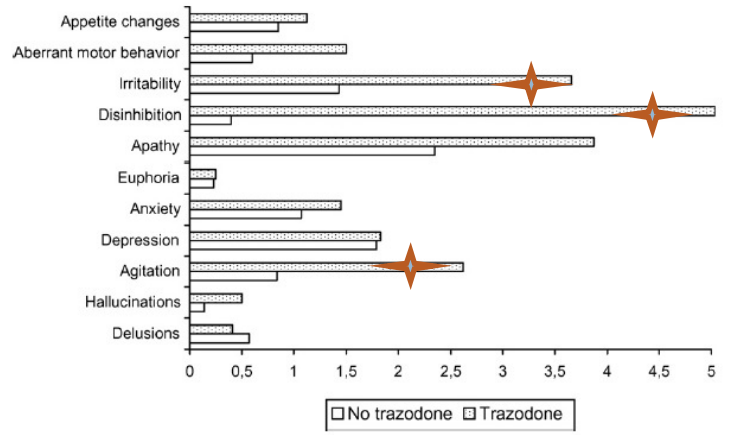
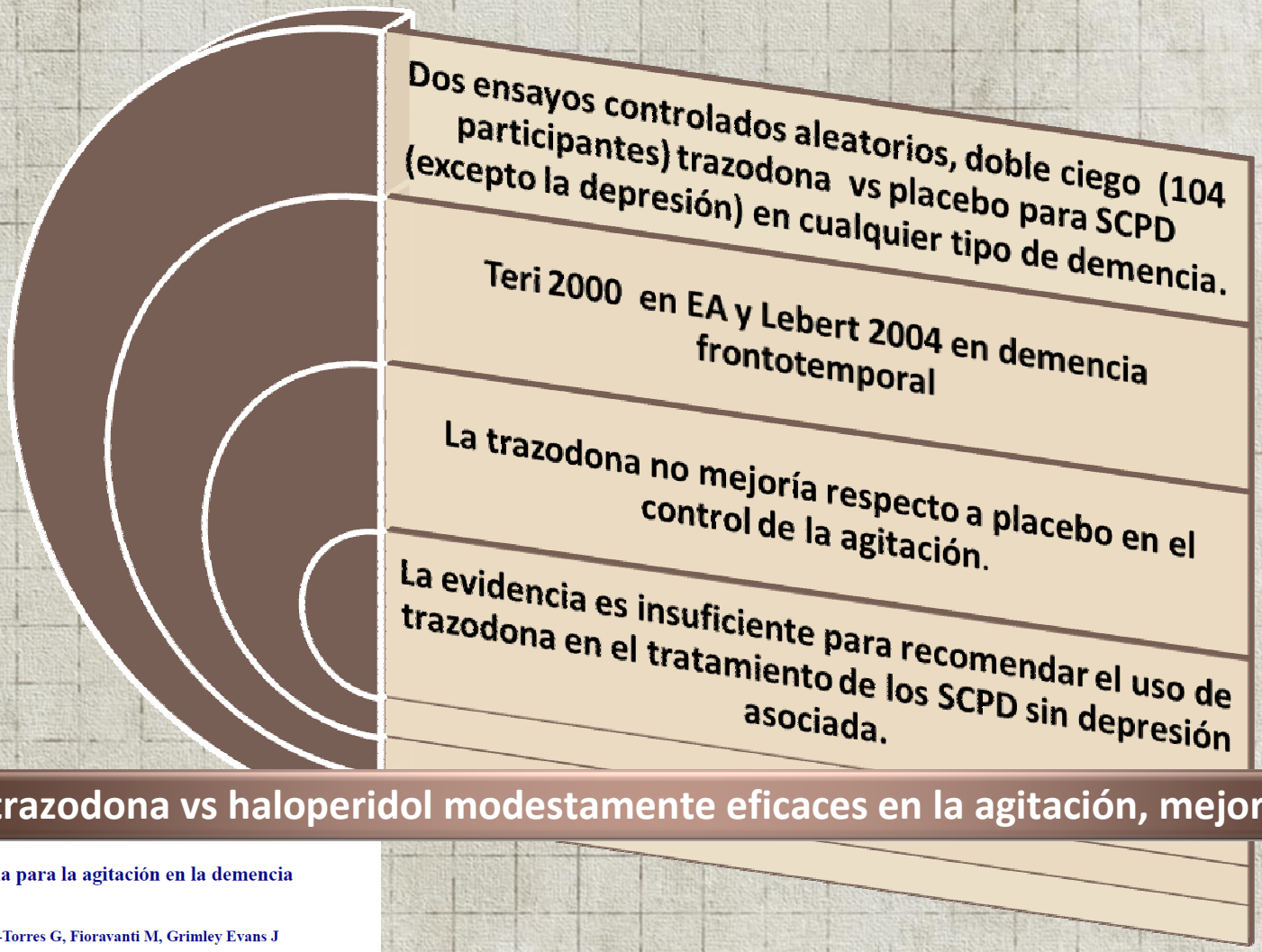


Fig. 1. Mean baseline score for the NPI subscales in the trazodone-treated group and the untreated group.

TRAZODONA PARA LA AGITACIÓN EN LA DEMENCIA

2004



EDCA trazodona vs haloperidol modestamente eficaces en la agitación, mejor tolerada

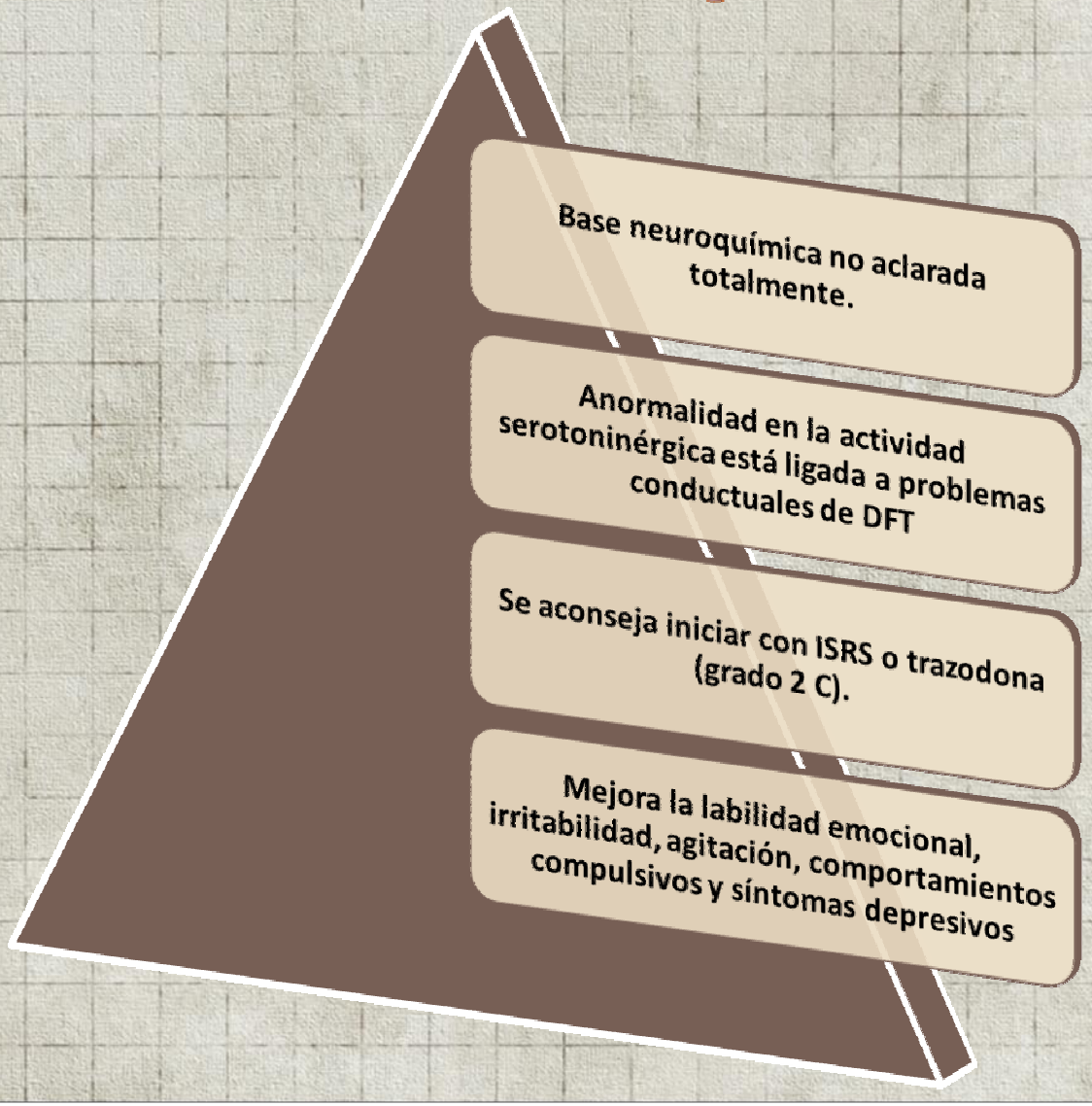
Trazodona para la agitación en la demencia

Martinon-Torres G, Fioravanti M, Grimley Evans J

Reproducción de una revisión Cochrane, traducida y publicada en *La Biblioteca Cochrane Plus,* 2008, Número 2

THE COCHRANE COLLABORATION®

ISRS en demencia frontotemporal



Entonces ¿Cuándo suspendemos los ISRS?

BMJ

BMJ 2012;344:e1566 doi: 10.1136/bmj.e1566 (Published 9 March 2012)

RESEARCH

Discontinuation of antidepressants in people with dementia and neuropsychiatric symptoms (DESEP study): double blind, randomised, parallel group, placebo controlled trial

Sverre Bergh *researcher*[1], Geir Selbæk *head of research department*[1 2], Knut Engedal *professor*[1 2 3]

[1]Centre for Old Age Psychiatric Research, Innlandet Hospital Trust, N-2312 Ottestad, Norway ; [2]Norwegian Centre for Dementia Research, Oslo University Hospital, Oslo, Norway ; [3]University of Oslo, Oslo

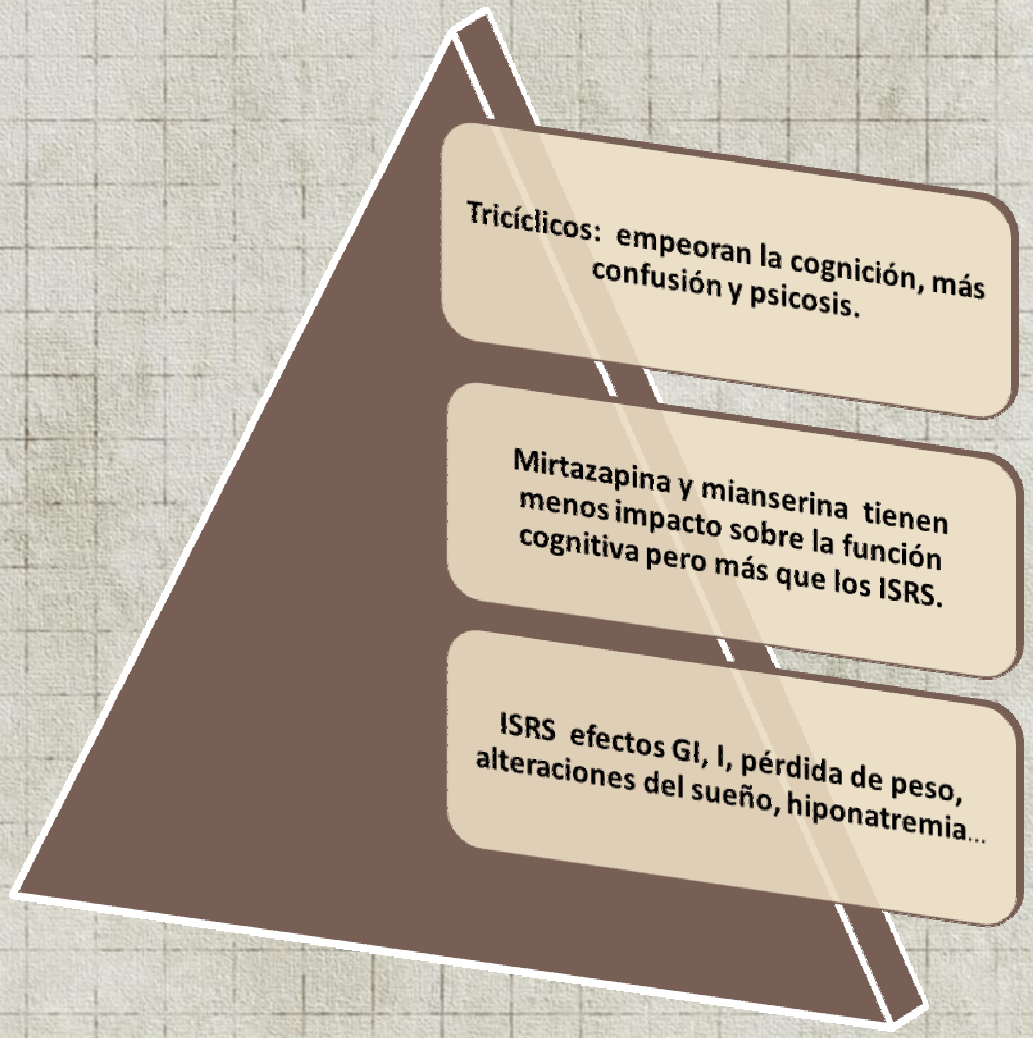
128 pacientes de NH
EA o DV y SCPD (no depresión)
Escitalopram, citalopram, sertralina, paroxetina
Seguimiento a 13 y 25 semanas.

La suspensión del AD llevó a aumento de síntomas depresivos.

Más pacientes del grupo de STOP Interrumpieron el estudio por aparición deSCPD

La mayoría del grupo STOP fue Bien tolerado. MONITORIZAR!!!

Antidepresivos: efectos adversos



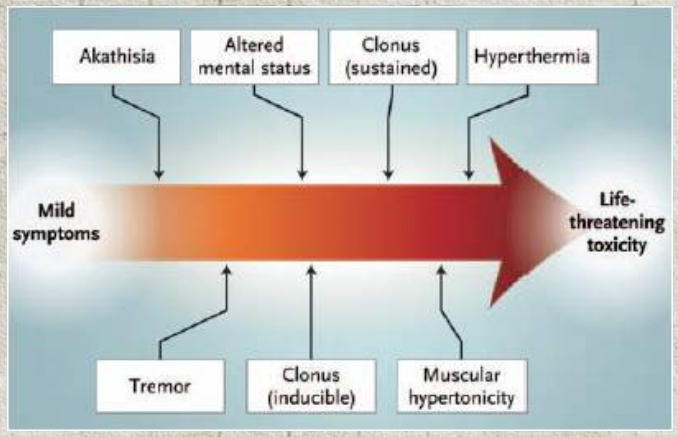
Toxicidad Serotoninérgica

Definición

- **Toxicidad Serotoninérgica:**
  Conjunto de manifestaciones autonómicas, neuromusculares y alteraciones del estado mental, que ocurren como resultado de un aumento de la concentración intrasináptica de la 5-HT en el SNC y receptores periféricos.

- **Concentración-dependiente: se puede presentar tras la ingesta terapéutica de un solo fármaco, por sobredosis de un fármaco, o con más frecuencia por el uso de 2 o más fármacos con efecto serotoninérgico.**

Espectro clínico



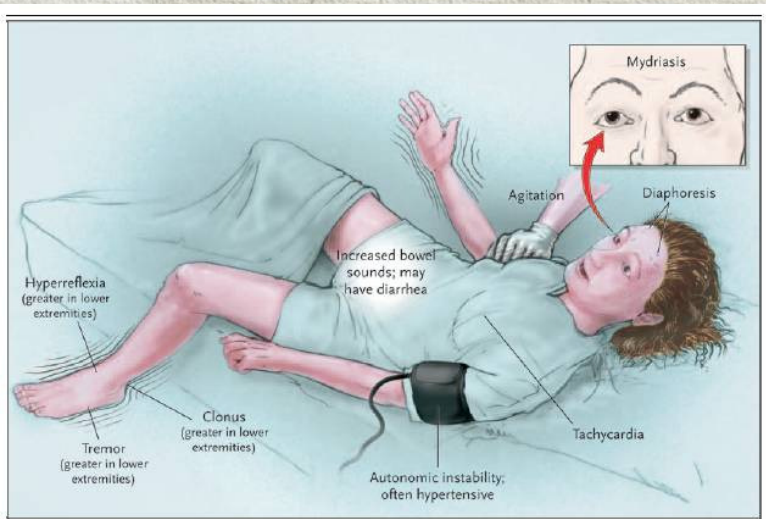


Figure 2. Findings in a Patient with Moderately Severe Serotonin Syndrome.
Hyperkinetic neuromuscular findings of tremor or clonus and hyperreflexia should lead the clinician to consider the diagnosis of the serotonin syndrome.

Table 1 Mechanisms of common drugs that influence serotonin syndrome

5-HT Synthesis	5-HT Release	Inhibit 5-HT Uptake	Inhibit 5-HT Metabolism	Postsynaptic Receptor Stimulation
L-tryptophan 5-hydroxytryptophan	Amphetamines and derivatives dextramphetamine metamphetamine fenfluramine dexfenfluramine phenteramine MDMA (ecstasy) Cocaine Reserpine Tetrabenazine Levodopa MAOIs phenelzine tranylcypromine isocarboxazide selegiline meclobemide	SSRIs fluoxetine paroxetine sertraline fluvoxamine citalopram Trazadone Nefazadone Venlafaxine TCAs amitriptylline imipramine clomipramine doxepin desipramine Bupropion Dextromethorphan Tramadol Meperidine Sibutramine Cocaine St. John's wort Amphetamine and derivatives	MAOIs phenelzine tranylcypromine isocarboxazide selegiline meclobemide St. John's wort	Buspirone 5HT1 agonists sumatriptan zolmitriptan naratriptan rizatriptan Lithium Carbamazepine

ANTICOMICIALES

- Pobre control de impulsos, desinhibición
- Labilidad emocional o afectividad inapropiada
- Episodios de agresión física perseverante
- Sexualidad inapropiada
- Apatía
- Lenguaje soez

Carbamacepina

Tariot, 1998

- CBZ superior a placebo en el tratamiento de la agitación y la agresividad.
- Efectos secundarios significativamente superiores (ataxia y desorientación)

Olin, 2001

- Estudio realizado en pacientes agitados resistentes al tratamiento con antipsicótcos.
- Carbamazepina no superior a placebo.
- Buena tolerancia

No hay evidencia suficente
Para apoyar el beneficio
De CBZ en SCPD

Valproato para la agitación en la demencia.

Lonergan et al. Revisión Cochrane traducida 2008.

Estudios de Porsteinsson, Tariot, Sival.

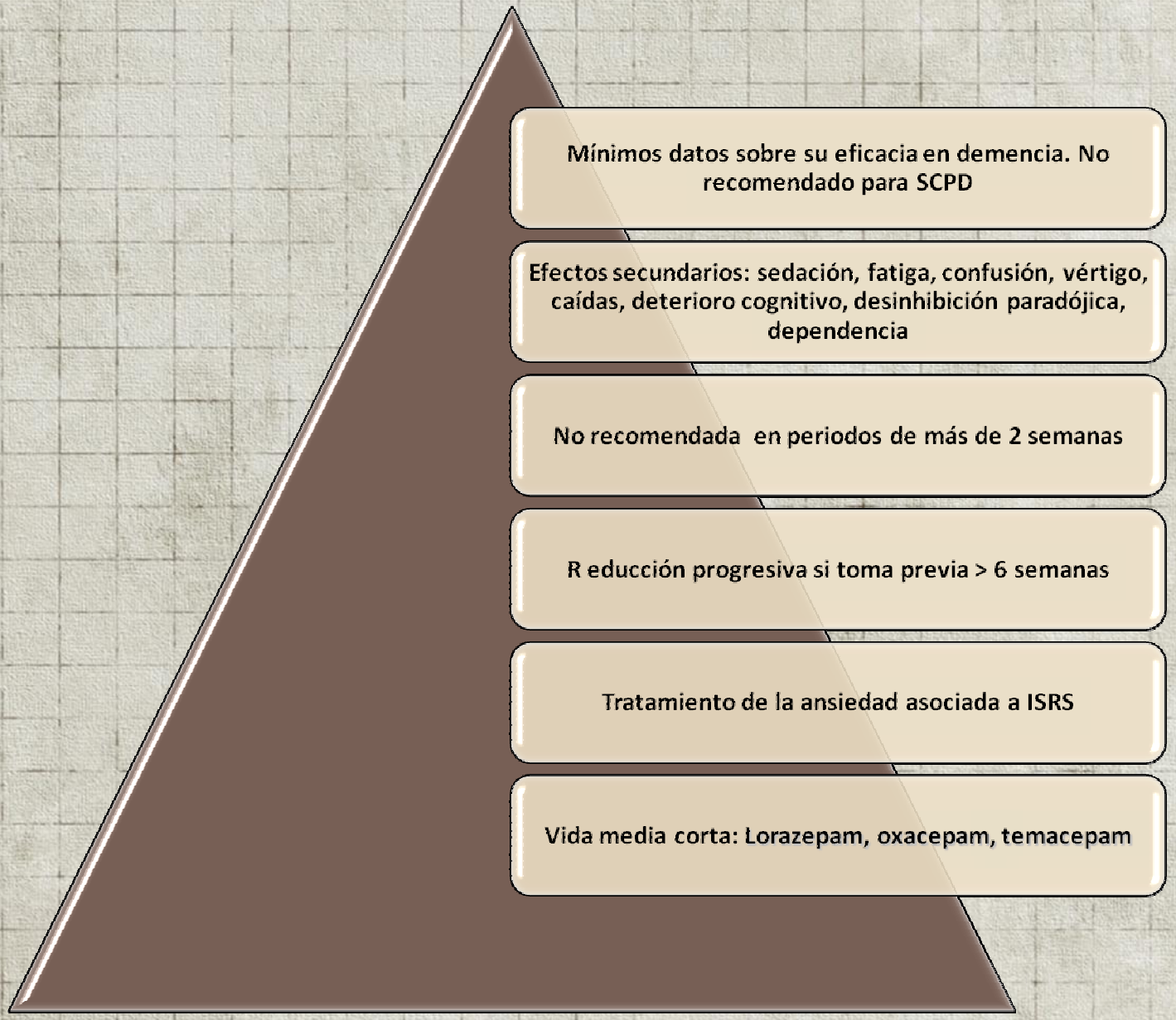
Dosis bajas no es eficaz para tratar la agitación y con dosis altas, tasa inaceptable de efectos adversos.

Las preparaciones de valproato no pueden recomendarse para el tratamiento de la agitación de la demencia

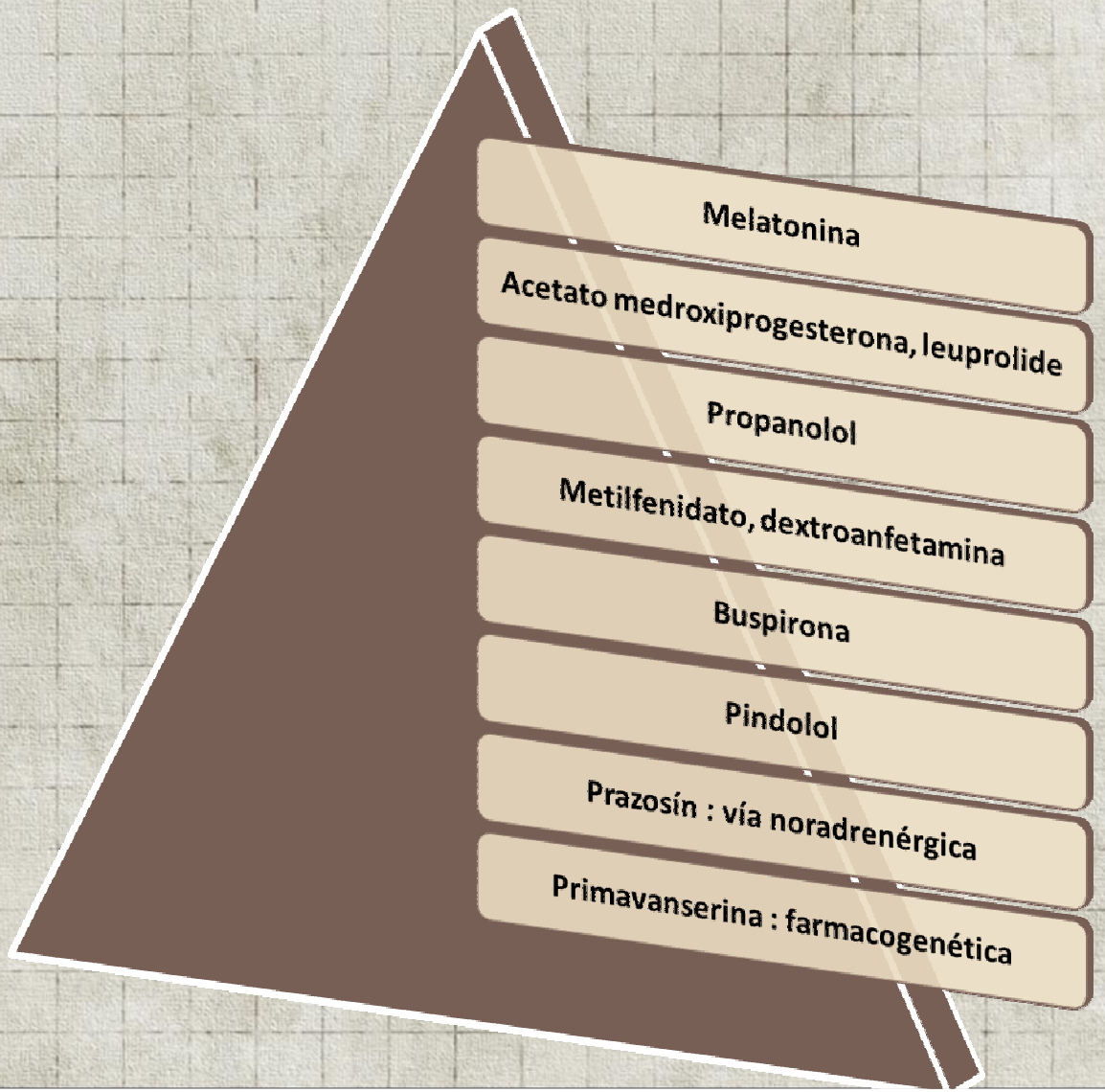
Otros anticomiciales

- Gabapentina, lamotrigina, pregabalina o topiramato
- Serie de casos y estudios abiertos: algunos resultados prometedores pero tienen que ser contrastados.
- La gabapentina es bien tolerado en ancianos
- Se ha descrito algún caso de empeoramiento brusco al prescribirlo en pacientes con demenica por cuerpos de Lewy.
- La oxcarbamazepina : sólo un EDCC con resultados positivos para el control de la agitación y agresividad en demencia

BENZODIACEPINAS



OTROS FÁRMACOS…



CONCLUSIONES

✓El tratamiento de SPCD es un reto . Cambios en las pautas en últimos años

✓ El manejo no farmacológico es el primer escalón del tratamiento

✓Descartar causas orgánicas, dolor

✓Se aconseja el tratamiento específico con IACE y/o Memantina

✓En presencia de trastorno afectivo o ansiedad o si agitación y contraindicación de memantina: ISRS

✓Psicosis o agitación grave o aguda: con sufrimiento, un antipsicótico explicando riesgo/beneficio, titulación lenta y mínima dosis

✓Monitorizar la aparición de efectos adversos e intentar reducir dosis

✓Si ineficaz: estabilizador del humor

✓Para síntomas refractarios: otros fármacos.


A pesar de ausencia de alternativas más seguras y eficaces es inaceptable el nihilismo terapéutico