Neurolépticos y Demencia

Reunión del Grupo COGVAL
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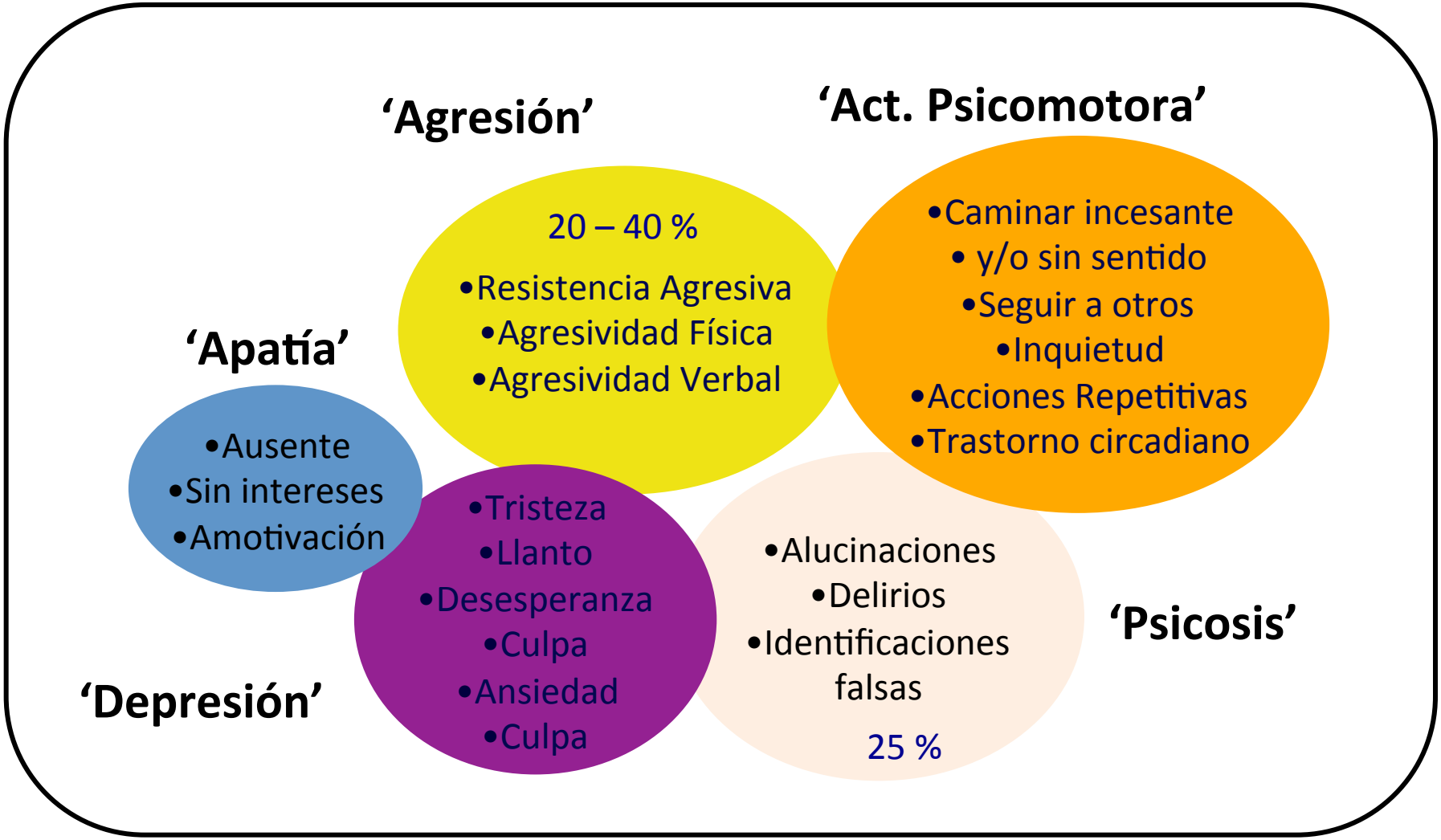
Dr Dº Joaquín Escudero Torrella
Servicio de Neurología
Área Clínica de Neurociencias
Consorcio Hospital General Universitario de Valencia

Clusters en los SPCD



Adaptado de McShane R, Int Psychogeriat 2000

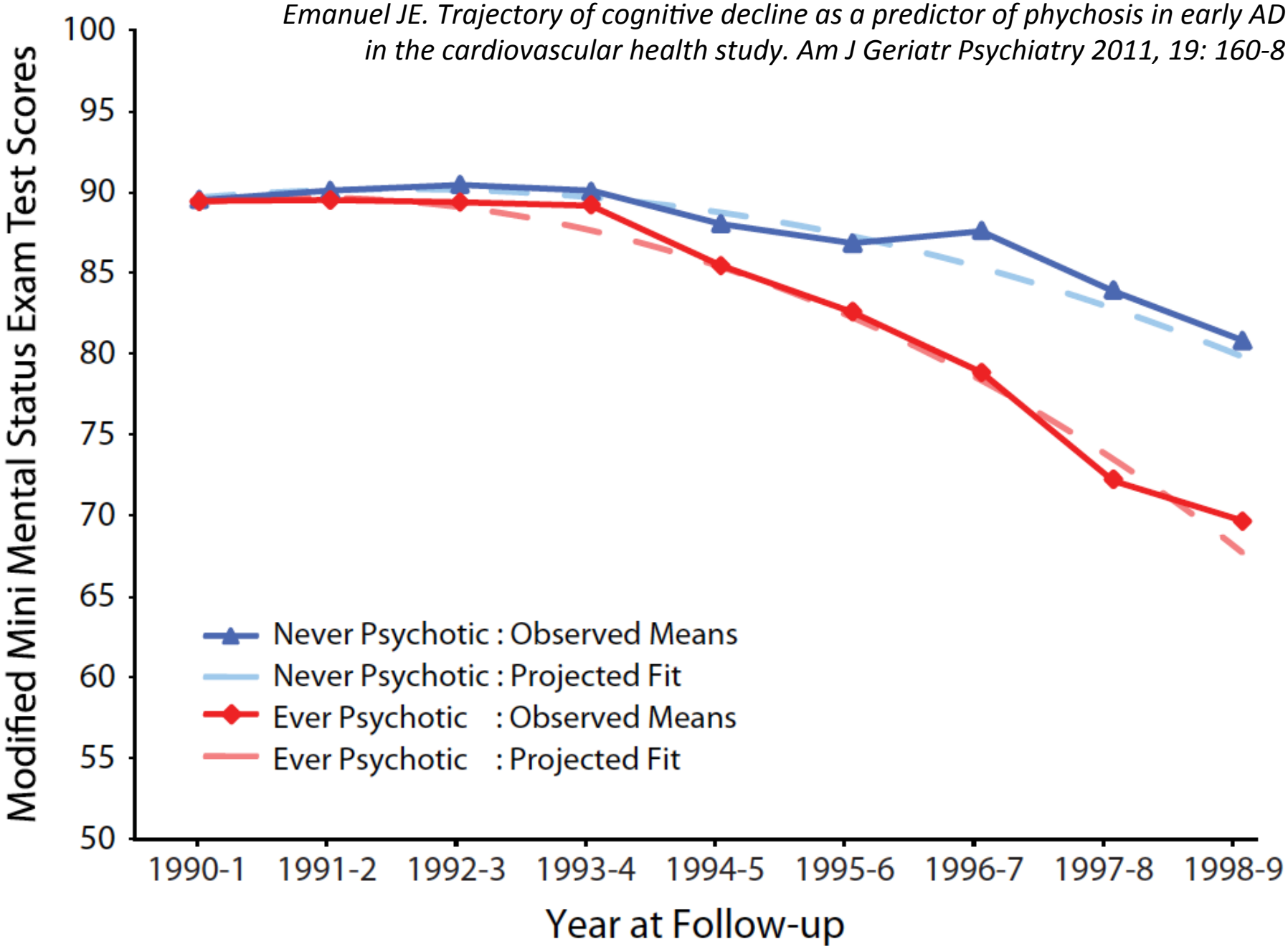
Neurobiología de los SPCDs

- Correlaciónes Neuroquímicas en SPCD
  - ↓ actividad ChAT en córtex temporal y frontal e Hiperactividad en pacientes con demencia
  - ↑ de receptores muscarínicos (M2 pre-sinápticos) en pacientes con psicosis y EA
  - ↓ receptores AMPA y NMDA en cortex frontal y temporal en FTD
- Correlaciones clínico-patológicas en SPCD
  - Psicosis ……. ↑ NFT en neocortex
  - Agitación …… ↑ NFT en córtex orbito-frontal
  - Apatia ……. ↑ NFT en cingulado anterior
  - Depresión…… hipo-metabolismo frontal
  - Reducción de Ach, GLU, DOP, NADr, SER…. (EA, DCLw…)
- No correlación clara entre
  - Mejoría o declinar cognitiva y SPCDs (salvo apatia y irritabilidad)

Psicosis en EA

- Prevalencia media 25 % (20 – 50)
  - Frecuencia baja en fase inicial, aumenta en moderada y severa
  - Es el segundo trastorno psicótico después de la esquizofrenia, y pronto será el primero….
- Se asocia con otros SPCDs (agresividad y agitación)
- Incremento de alteración funcional
- Mas distress familiar
- Mas índice de institucionalización
- Mayor mortalidad
- Mayor alteración cognitiva (estudios transversales) y más velocidad de declinar cognitivo
  - Incluso antes de aparecer la psicosis

Emanuel JE. Trajectory of cognitive decline as a predictor of phychosis in early AD in the cardiovascular health study. Am J Geriatr Psychiatry 2011, 19: 160-8



Psicosis en EA

- Reducción substancia gris cortex frontal (RM) y mas hipometabolismo córtex frontal bilateral y prefrontal (PET)
- Neuropatologia
  - Incremento de los Haces Neurofibrilares en Neocortex (excepto temporal), no relación con placas amiloideas
  - Mayor alteración sináptica
  - Reducción de niveles de AB1-40, sin alterar el AB1-42
- Neurotransmisores
  - Incremento receptores D3 en nucleo accumbens
  - Ratio incrementada de Acetilcolin-estearasa / 5HT2
- Mayor afectación de Regiones Neocorticales Frontales
  - Dorsolateral y prefrontal
- Hay cierta evidencia de agregación familiar

Tratamiento de los trastornos psicológicos y de la conducta

- Identificar los síntomas conductuales.
- Detectar posibles factores desencadenantes.
- Aplicar primero medidas no farmacológicas.
- Escoger el fármaco más adecuado a cada síntoma.
- Iniciar con dosis pequeñas y aumentar las dosis progresivamente.
- Vigilar estrechamente los efectos secundarios.
- Replantearse periódicamente la supresión o disminución del medicamento.
- Muy pocas evidencias científicas de los tratamientos
  - Basado mas en experiencias que en ECR
  - Salvo IACh, memantina, risperidona….

Medidas no farmacológicas

- Modificar el ambiente.
- Utilizar estimulaciones.
- Utilizar rutinas.
- Evaluar y eliminar los factores desencadenantes.
- Prestar información y apoyo al paciente y al cuidador.

Introducción

- Los SPCDs (psicosis, agresividad, agitación) son frecuentes en pacientes con demencia (15-50 %)
  - Condiciona mayor riesgo de muerte, institucionalización y peor pronóstico
- En Residencias el uso de neurolépticos es elevado (30-50 %)
- Se piensa que el uso de neurolépticos en estos pacientes conlleva un mayor riesgo de mortalidad (FDA black box, 2005)
  - Dificultades metodológicas (gravedad de los pacientes en institución, dosis utilizadas mas altas en residencias, etc..
- En general estos fármacos (SAP) no están autorizados en ficha técnica para su uso en esta patología (salvo la risperidona)
  - La FDA permite el off-label
  - No disponemos de regulación en la CV (algoritmos terapeúticos)
- Regulación en algunos países para reducir el uso continuado en demencia (3-6 meses) y se quiere reducir su uso a < 15 %
- Aunque no disponemos de muchas opciones terapeúticas para estos SPCDs (¿qué hacemos?)

Historia de los Neurolépticos

- En 1952 se descubre la Clorpromazina
- Se sintetizan diferentes neurolépticos de 1ª generación (FAP)
  - 51 productos de seis clases diferentes (fenotiazina, butiroferona, tioxantinas, dibenzoxazepinas, dihidroindolonas, difenilbutilpiperidinas)
  - largactil, tioridazina, haloperidol, loxapina, pimozide…..
  - De los cuales 12 todavía permanacen en activo
- En 1959 se sintetiza la clozapina
  - Sin efectos extrapiramidales, y por ello se le denominó “atípico”
  - Se comercializó en Europa en 1972, pero se retiró en 1974 por la agranulocitosis
  - Se reintrodujo como fármaco especial en 1989
- En 1993 se introducen nuevos neurolépticos de segunda generación (SAP)

Efectos de los (FGA)
Antipsicóticos de Primera Generación

- Efectos Bioquímicos
  - Antagonistas (+/- potentes) de los receptores D2 post-sinápticos
  - Según la potencia de dicho bloqueo (alta, media y baja)
  - Efectos anticolinérgicos, antiserotoninérgicos, antihistamínicos y antiadrenérgicos
- Bloqueo dopaminérgico en las vías mesolímbicas
  - Efecto sobre los síntomas + de la esquizofrenia
  - Bloqueo en vías meso-corticales (efectos cognitivos)
- Bloqueo Nigro-estriatal
  - Efectos extrapiramidales agudos (parkinsonismo, distonia, akatisia…)
  - A largo plazo produce discinesia tardia
- Bloqueo de la via tubero-infundibular
  - Aumento de PRL: amenorrea, galactorrea,etc..
- Otros bloqueos
  - Anticolinérgico (M1 muscarinico): estreñimiento, visión borrosa, retención urinaria, boca seca, sedación
  - Antihistamímico H1: sedación, aumento de peso
  - Alfa-adrenérgico: mareo, hipoTA ortostática, sedación

Historia de los Neurolépticos

- Los SGA se desarrollaron imitando a la clozapina, con mayor antagonismo serotoninérgico y menor dopaminérgico
  - Antagonismo D2 más específico (mesolimbico y mesocortical) frente a nigro-estriatal
  - Antagonismo 5HT2A reduce liberación glutamato en area tegmental ventral, y reducción de excitación de neuronas dopaminérgicas
- Grupo de antagonistas de la serotonina / dopamina
  - Olanzapina, Risperidona, Paliperidona, Quetiapina, Ziprasidona, Iloperidona, Arsenapine
- Agonista parcial de la dopamina y antagonista de la serotonina (aripiprazol).....TGA (tercera generación)
- Efectos no solo en síntomas +, sino también negativos, afectivos y cognitivos

TABLE 1 Currently Approved Atypical Antipsychotics

Drug	Date of Original FDA Approval[a]
Clozapine[b]	September 26,1989
Risperidone	December 29,1993
Olanzapine	September 30,1996
Quetiapine	September 27,1997
Ziprasidone	February 5, 2001
Aripiprazole	November 15, 2002
Paliperidone[c]	December 19, 2006
Iloperidone[c]	May 6, 2009
Asenapine[c]	August 13, 2009

FÁRMACO	LABORATORIO	mercado (España)
Clozapina	*Novartis*	1972
Risperidona	*Janssen*	1993
Sertindol	*Lundbeck*	1996
Olanzapina	*Eli Lilly*	1996
Quetiapina	*Astra Zeneca*	1997
Ziprasidona	*Pfizer*	2001
Amisulprida	*Sanofi Aventis*	(1988) 2002
Aripiprazol	*Bristol-Myers*	2002
Paliperidona	*Janssen*	2007

Antipsicóticos de Segunda Generación

Clozapina (dibenzodiazepina)

- Poca ocupación D2 (pocos Extrap.)
- 5HT2A, 5HT1C, adrenérgicos y colinérgicos
- Alta afinidad 5HT2A frente baja D2

Risperidona (benzisoxazole)

- Alta afinidad por 5HT2A y D2
- No efecto colinérgico, poco H1, potente alfa-adrenérgica
- Más Efectos Extrap. que otros SAP

Olanzapina (thiobenzodazepina)

- Mayor 5HT2 que D2
- Alta H1 y alfa-adrenergico

Quetiapina (dibenzothiazepina)

- Baja afinidad D2 (30 %)
- 5HT2, alfa-adrenergicos, histamina…

Ziprasidona (benzisothiazolyl piperacina)

- Mayor 5HT2 que D2 (mas que clozapina y olanzapina)
- Poco efecto adrenérgico e histamina

Aripiprazol (dihydroquinolinona)

- Antagonismo potente 5HT2A y agonismo parcial D2 (3º Generación)
- Alta afinidad D3, D4, 5HT2C, 5HT7, H1 y Alfa adrenérgico

Paliperidona

- Metabolito activo de la risperidona

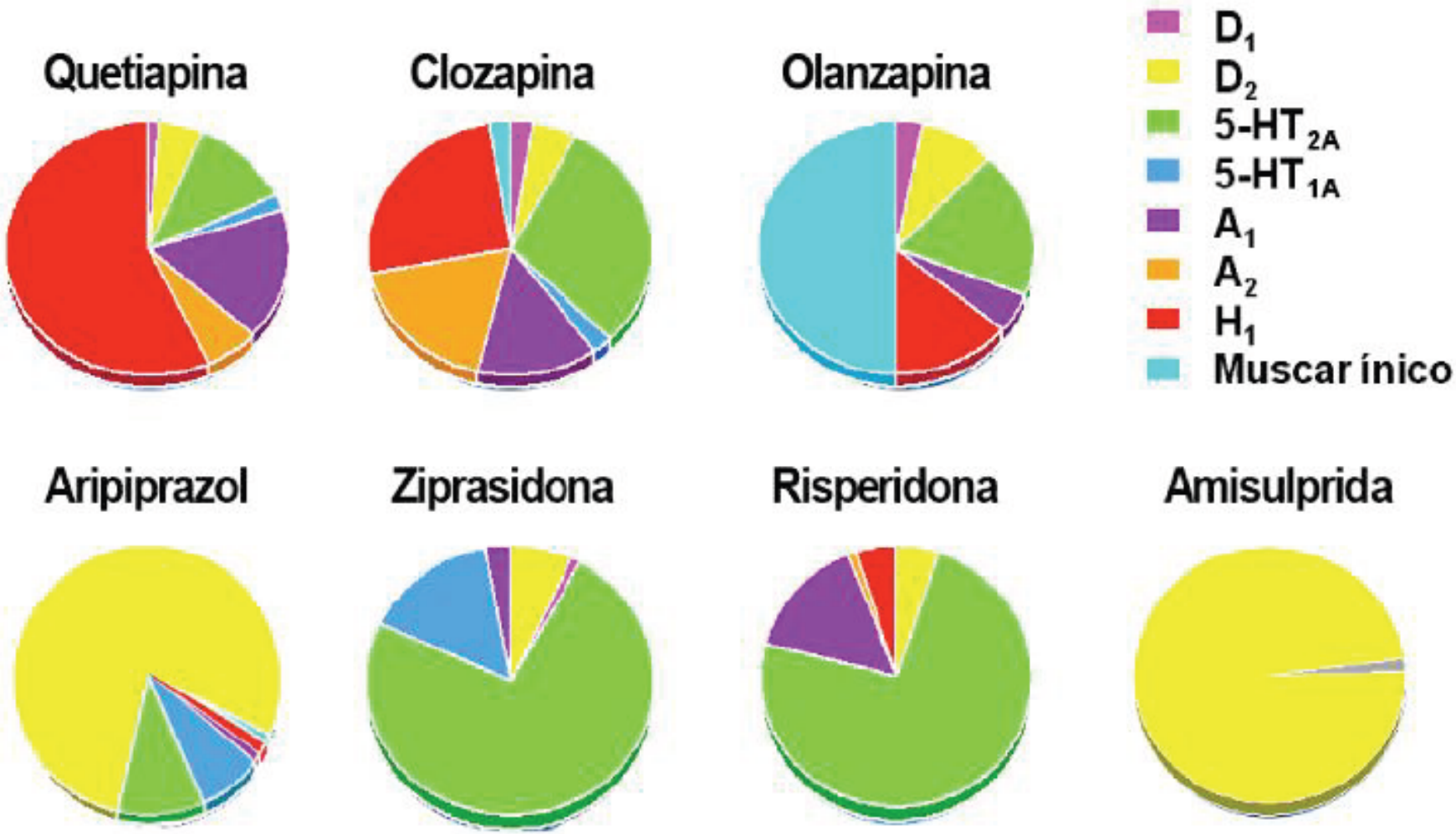
Iloperidona

- Antagonismo de 5HT2A y D2
- Alta afinidad adrenergica (HipoTA)

Arsenapina

- Antagonismo de 5HT2A y D2

Perfil de Receptores



Efectos 2º de los FGA

- Neurológicos
  - Extrapiramidales (parkinsonismo, temblor, akatisia, distonia… discinesia tardia)
  - Mayor cuanta mayor potencia de bloqueo (> 80 %)
  - A largo plazo hipersensibilidad de los D2
- Cardiológicos
  - Prolongación del QT y arritmias (ventricular, torsades de pointes…)
- Metabólicos (SGN > FGN)
  - Obesidad, aumento de peso
  - Elevación del colesterol y TGs
  - Resistencia a la insulina y diabetes
- Autonómicos
  - Disfunción autonómica (mareo, hipoTA; tquicardia…)

Efectos 2º de los FGA

- Gastrointestinales
  - Estreñimiento, nauseas, vómitos, boca seca
  - Colostasis (clorpromazina)
- Genito-urinarios
  - Retención urinaria, disfunción eréctil eyaculación retrograda….
- Endocrinológicos
  - Amenorrea, galactorrea, ginecomastia, reducción libido,
  - SIADH
- Dermatológicos
  - Fotosensibilidad, alergia cutánea
- Oftalmológicos
  - Visión borrosa, glaucoma de ángulo cerrado, cataratas, alteracion visión nocturna….

Efectos 2º de los SGA

Antipsicóticos de Segunda Generación

- Neurológicos
  - En general menor riesgo de EPS y DT frente a FGA (10 veces menos)
  - Clozapina y Quetiapina los que menos EPS (poco riesgo incluso dosis altas)
  - El resto incrementa el riesgo con la dosis (rara la distonía)
  - Clozapina riesgo de crisis epilépticas (dosis altas)
- Metabólicos
  - Aumento de peso, dislipemia, hiperglicemia
  - Riesgo alto (clozapina, olanzapina); Medio (risperidona, quetiapina), Bajo (ziprasidona, aripiprazol)
- Cardio-Vascular
  - Prolongación del QT (no suele ser clínicamente significativo). Sobre todo ziprasidona
  - Clozapina se ha relacionado con casos de miocarditis
- Autonómicos
  - HipoTA ortostática (Clozapina, risperidona, olanzapina y quetiapina)

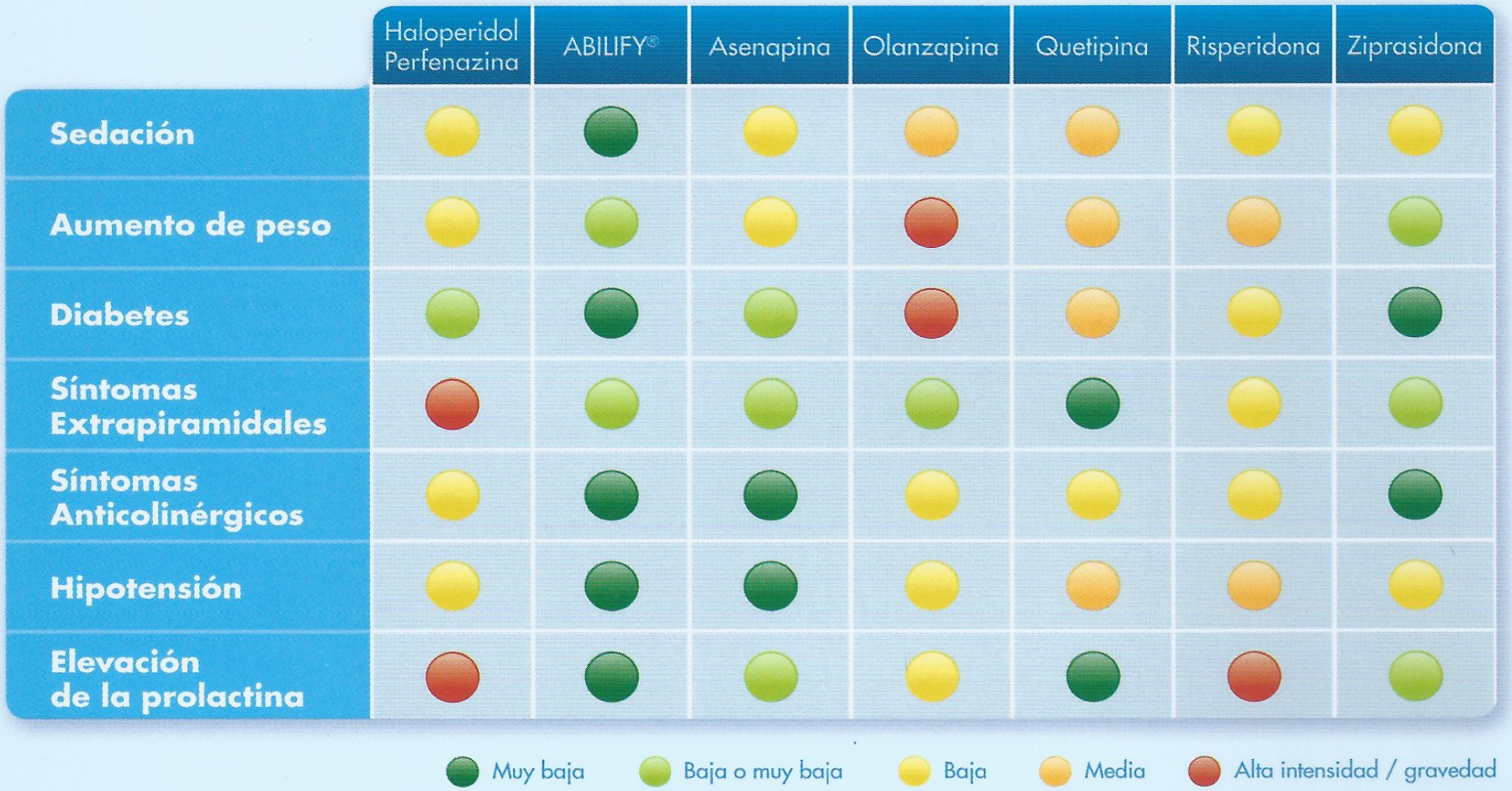
Efectos 2º de los SGA

- Gastrointestinal
  - Aumento de Enzimas hepaticas (inicio de olanzapina)
  - Estreñimiento (risperidona, olanzapina y quetiapina)
- Endocrinológicos
  - Hiperprolactinemia (risperidona)
- Hematológicos
  - Agranulocitosis (clozapina)
- Oftalmológicos
  - En animales (perros) ha aparecido cataratas con quetiapina, aunque no en humanos
  - Recomendado la revisión en pacientes en tratamiento

Aripiprazol (Abilify®)

- Antisicótico del grupo de la dihydroquinolinona
  - Descubierto en 1998 y aprobado por la FDA en 2002
- Mecanismo diferente que combina
  - Agonismo parcial D2 (D3, 5HT1) y Antagonismo potente 5HT2A
  - Por ello, también llamado de Tercera Generación
  - Menor actividad antagonista D2 en vias mesocortical, nigroestriada y tubero-infundibular (menos efectos secundarios)
  - Alta afinidad D3, D4, 5HT2C, 5HT7, H1 y Alfa adrenérgico
- Buena absorción (3-5 h CPM y BD del 87 %). Unión 99 % PP
- Metabolismo hepático (CBZ, ketoconazol, quinidina)
- Compr de 5,10, 15 mgr y solución oral (1 mgr(ml). Injectable (10 mgr) IM (máximo 3 al dia). Posología: 1 al dia
- Efectos secundarios:
  - cefalea, insomnio, agitación, ansiedad
  - No aumento PRL, no EPS

ABILIFY®, excelente perfil de tolerabilidad[12,13]



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BRIEF REPORT

Aripiprazole for the Treatment of Psychosis in Patients With Alzheimer's Disease

A Randomized, Placebo-Controlled Study

Peter De Deyn, MD, Dilip V. Jeste, MD,† Rene Swanink, MSc,‡ Dusan Kostic, PhD,§ Christopher Breder, MD,|| William H. Carson, MD,¶ and Taro Iwamoto, PhD‡*

Abstract: This study compared the efficacy, safety, and tolerability of aripiprazole, a novel antipsychotic, with placebo in patients with psychosis associated with Alzheimer's Disease (AD). This 10-week, double-blind, multicenter study randomized 208 outpatients (mean age, 81.5 years) with AD-associated psychosis to aripiprazole (n = 106) or placebo (n = 102). The initial aripiprazole dose of 2 mg/d was titrated upwards (5, 10, or 15 mg/d) according to efficacy and tolerability. Evaluations included Neuropsychiatric Inventory (NPI) Psychosis subscale and Brief Psychiatric Rating Scale (BPRS), adverse event (AE) reports, extrapyramidal symptoms (EPS) rating scales, and body weight. Overall, 172 patients (83%) completed the study. Mean aripiprazole dose at end point was 10.0 mg/d. The NPI Psychosis subscale score showed improvements in both groups (aripiprazole, −6.55; placebo, −5.52; $P = 0.17$ at end point). Aripiprazole-treated patients showed significantly greater improve-

years. AD is characterized by declining cognitive function, but is also associated with a high prevalence of psychotic symptoms[1] and behavioral disturbances.[2,3] Psychotic symptoms have been linked to increased cognitive and functional decline[4,5] and an increased likelihood of institutionalization[5] in patients with dementia.

Antipsychotics are the most studied treatment of psychosis, aggression, and agitation in elderly patients with dementia.[6,7] Safety and tolerability is a key aspect of treatment in the elderly due to their increased sensitivity to adverse events (AEs), making atypical antipsychotics a more attractive option than typicals.[6] Studies have shown that risperidone, olanzapine, and quetiapine can reduce psychotic symptoms and behavioral disturbances in patients with dementia.[8–14] However, the side-effect profiles of individual atypicals may impact on their overall effectiveness and ac-

N = 208 172 (83 %) completaron el estudio Pacientes no institucionalizados

TABLE 1. Mean Changes in Efficacy Measures From Baseline at Week 10 (LOCF)

		Placebo			Aripiprazole		
Efficacy Measure	**n**	**Mean Baseline**	**Mean Change**	**n**	**Mean Baseline**	**Mean Change**	***P***
NPI Psychosis*	100	12.12	−5.52	103	12.69	−6.55	0.169
NPI Total*	100	40.08	−9.75	103	39.82	−11.20	0.582
BPRS Psychosis†	93	5.25	−1.27	99	5.46	−1.93	0.029
BPRS Core†	97	11.68	−2.7	101	12.28	−3.9	0.042
BPRS Total†	95	43.42	−6.58	100	43.63	−8.53	0.153
CGI-S‡	100	4.84	−0.54	102	4.83	−0.69	0.345
CGI-I§	100	—	3.07	103	—	3.17	0.564
MMSE‖	86	14.13	0.53	94	14.35	−0.81	0.001

LOCF indicates last observation carried forward.

*NPI: 12-item, caregiver-based assessment. Item scores can be in the range 0–12; NPI Total score is in the range 0–144. NPI Psychosis subscale (delusions; hallucinations) score is in the range 0–24.

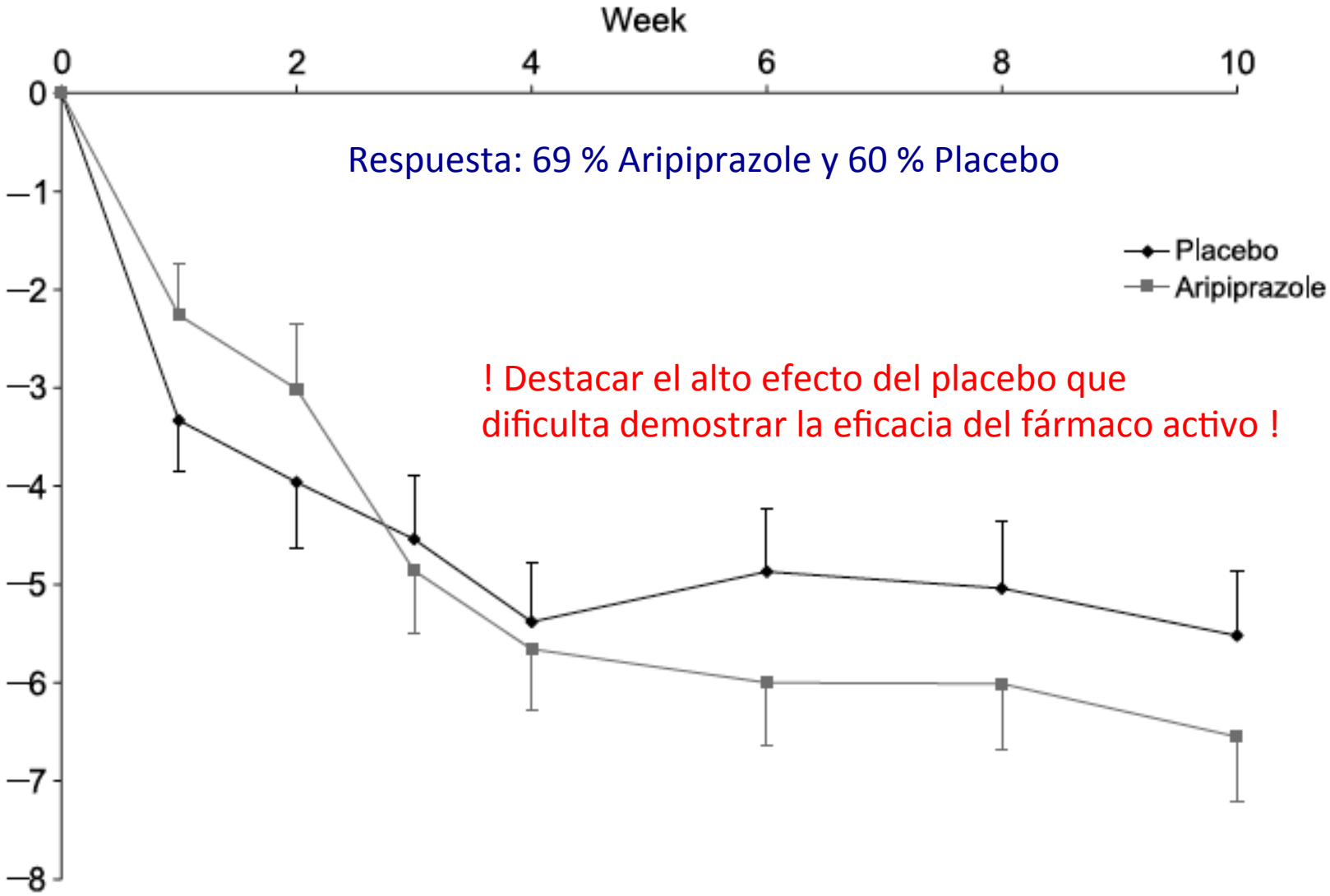
†BPRS: 18-item, physician-rated assessment. Each item is assessed on a 7-point severity scale. BPRS Total score is in the range 18–126. BPRS Core subscale consists of 4 items (conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content). BPRS Psychosis subscale consists of 2 items (hallucinatory behavior; unusual thought content).

‡CGI-S: illness severity, rated from 1 (normal) to 7 (extremely ill).

§CGI-I: change from baseline, rated from 1 (very much improved) to 7 (very much worse).

‖MMSE: 19-item assessment of cognition. MMSE total score can range from 0 (worst) to 30 (best); a positive score represents improvement.

4 fallecidos en el grupo activo



Mean baseline score: placebo, 12.1; aripiprazole, 12.3

FIGURE 1. Mean (±SE) change in NPI Psychosis subscale scores from baseline (LOCF analysis).

Aripiprazole for the Treatment of Psychoses in Institutionalized Patients With Alzheimer Dementia: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Assessment of Three Fixed Doses

Jacobo E. Mintzer, M.D., Larry E. Tune, M.D., Christopher D. Breder, M.D., Ph.D., René Swanink, M.S., Ronald N. Marcus, M.D., Robert D. McQuade, Ph.D., Andy Forbes, Ph.D.

Objective: *To assess the efficacy and safety of aripiprazole for psychosis associated with Alzheimer dementia (AD).* **Methods:** *In this double-blind, multicenter study, 487 institutionalized patients with psychosis associated with AD were randomized to placebo or aripiprazole, 2, 5 or 10 mg/day. Primary efficacy assessment was the mean change from baseline to week 10 on the Neuropsychiatric Inventory–Nursing Home (NPI-NH) version Psychosis Subscale score. Secondary measures included NPI-NH Total, Clinical Global Impression–Severity of Illness (CGI-S), Brief Psychiatric Rating Scale (BPRS) Core and Total, and the Cohen-Mansfield Agitation Inventory (CMAI) scores.* **Results:** *Aripiprazole 10 mg/day showed significantly greater improvements (mean change [2 x SD]) than placebo on the NPI-NH Psychosis Subscale (−6.87 [8.6] versus −5.13 [10.0]; $F = 6.29$, $df = 1, 422$, $p = 0.013$ by analysis of covariance [ANCOVA]); CGI-S (−0.72 [1.8] versus −0.46 [1.6]; $F = 4.68$, $df = 1, 419$, $p = 0.031$ [ANCOVA]); BPRS Total (−7.12 [18.4] versus −4.17 [21.6]; $F = 4.72$, $df = 1, 399$, $p = 0.030$ [ANCOVA]); BPRS Core (−3.07 [6.9] versus −1.74 [7.8]; $F = 7.30$, $df = 1, 407$, $p = 0.007$ [ANCOVA]); CMAI (−10.96 [22.6] versus −6.64 [28.6]; $F = 5.23$, $df = 1, 410$, $p = 0.023$ [ANCOVA]), and NPI-NH Psychosis response rate (65 versus 50%; $\chi^2 = 5.52$, $df = 1$,*

N = 487 pacientes de ellos 284 completaron 10 semanas

TABLE 1. Demographics and Baseline Clinical Characteristics, Randomized Sample

Variable	Placebo (N = 121)	Aripiprazole 2 mg/day (N = 118)	Aripiprazole 5 mg/day (N = 122)	Aripiprazole 10 mg/day (N = 126)
Mean age, years (range)	82.2 (56.0–96.0)	83.0 (62.0–95.0)	82.4 (60.0–97.0)	82.3 (56.0–94.0)
Female/male (%)	82/18	81/19	76/24	76/24
Race (%)[a]				
White	88	86	89	85
Black	6	7	4	7
Hispanic, Latino	2	6	2	5
Asian, Pacific Islander	4	2	3	3
Other	0	0	2	0
Mean weight, kg (range)	61.3 (35.1–98.0)	60.2 (39.2–101.7)	62.5 (38.7–118.8)	62.6 (29.3–108.0)
Mean age of AD symptom onset, years (range)	77.5 (49.0–93.0)	78.7 (56.0–92.0)	78.1 (55.0–93.0)	78.4 (52.0–94.0)
Mean age of psychosis symptoms onset, years (range)	79.8 (49.0–94.0)	80.8 (57.0–93.0)	80.3 (57.0–94.0)	80.1 (53.0–94.0)
Prominent symptom at onset (%)[a]				
Delusions	65	78	65	69
Hallucinations	11	6	12	9
Both	24	16	24	22

[a]Because of rounding, values may not add up to 100%.

TABLE 2. Discontinuation Rates

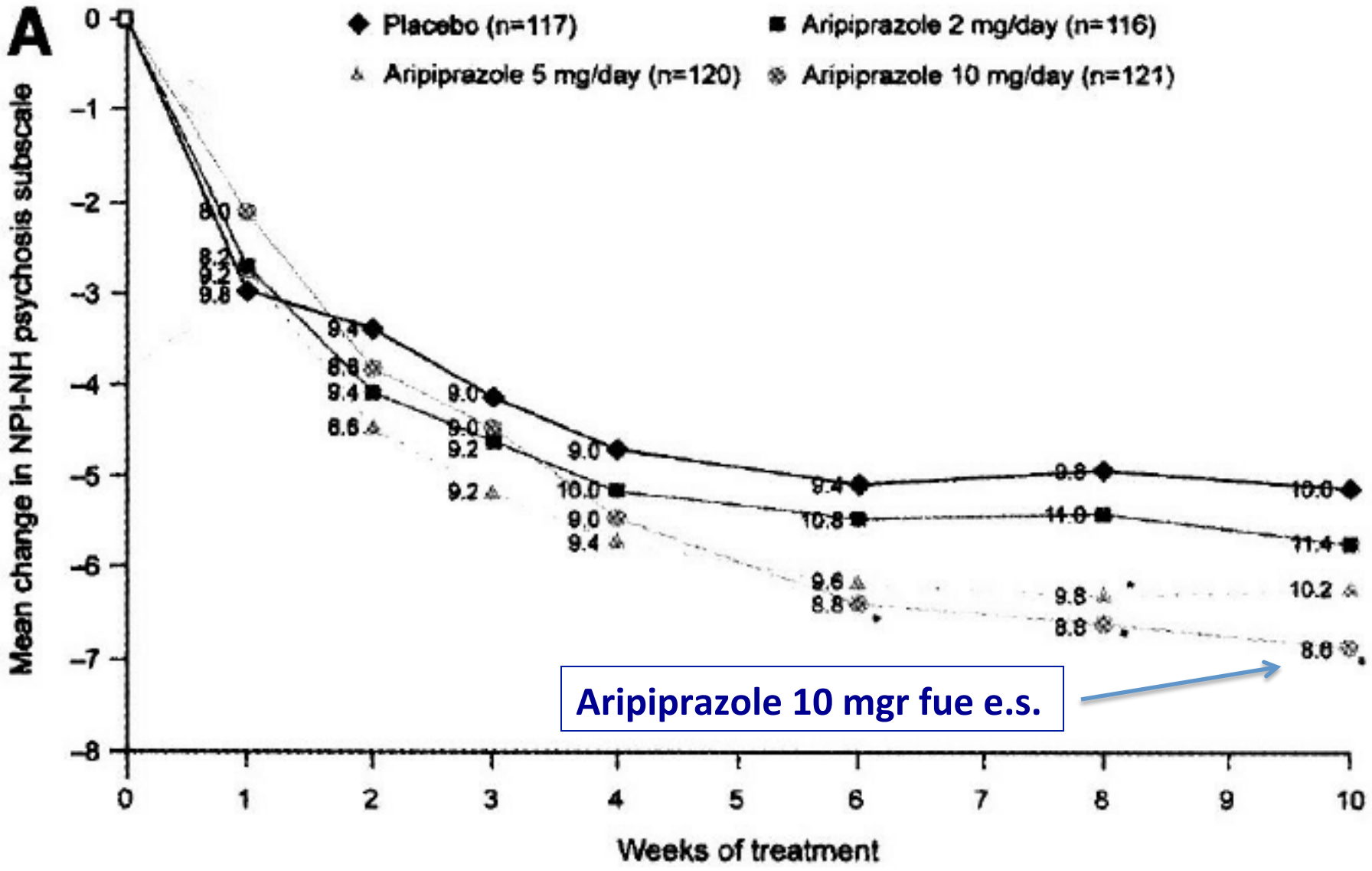
Patient Status	Placebo	Aripiprazole 2 mg/day	Aripiprazole 5 mg/day	Aripiprazole 10 mg/day
Randomized	121	118	122	126
Discontinued	56 (46)	41 (35)	49 (40)	57 (45)
Adverse event	16 (13)	9 (8)	22 (18)	31 (25)
Lack of efficacy/ response[a]	31 (26)	28 (24)	21 (17)	20 (16)
Other	9 (7)	4 (3)	6 (5)	6 (5)
Completed acute phase	65 (54)	77 (65)	73 (60)	69 (55)

Data are N (%).

[a]Lack of response defined as CGI-I ≥4 at week 6 or after; these patients had the option to enter an open-label continuation phase (to be reported elsewhere).

- 18 muertes (3 Plac, 4 en 2 mgr, 3 en 5 mgr, 8 en 10 mgr)
- 7 Ictus en el grupo activo y 0 en Placebo

Mean Change from Baseline in NPI-NH Psychosis Subscale Score



A Randomized, Double-Blind, Placebo-Controlled Tolerability Study of Intramuscular Aripiprazole in Acutely Agitated Patients With Alzheimer's, Vascular, or Mixed Dementia

Stephen A. Rappaport, MD, Ronald N. Marcus, MD, George Manos, PhD, Robert D. McQuade, PhD, and Dan A. Oren, MD

Objectives: To evaluate the tolerability of intramuscular (IM) aripiprazole in patients with agitation associated with dementia.

Design: A 24-hour, double-blind, placebo-controlled, randomized study.

Setting: Sixteen healthcare facilities in the United States.

Participants: A total of 129 patients with acute agitation associated with Alzheimer's, vascular or mixed dementia in healthcare facilities.

Intervention: Patients were randomized to IM aripiprazole (5 mg, 10 mg, or 15 mg) or IM placebo administered in divided doses 2 hours apart.

Measurements: Adverse events (AEs), Extrapyramidal Symptom Rating Scale, Sedation-Alertness Scale, and Negative Syndrome Scale–Excited Component (PEC) scores and Agitation-Calmness Evaluation Scale (ACES).

Results: There was greater incidence of AEs with IM aripiprazole (50% to 60%) than IM placebo (32.0%), but over 90% were mild or moderate in severity. The incidence of oversedation was low. PEC scores showed greater improvements in agitation with IM aripiprazole 10 mg and 15 mg compared with IM placebo.

Conclusion: A total of 10 mg or 15 mg of IM aripiprazole administered in divided doses was safe and well tolerated for treatment of agitation associated with Alzheimer's, vascular, or mixed dementia in long-term care. Preliminary analysis showed greater efficacy compared with IM placebo. **(J Am Med Dir Assoc 2009; 10: 21–27)**

Table 1. *Patient Demographics and Baseline Characteristics*

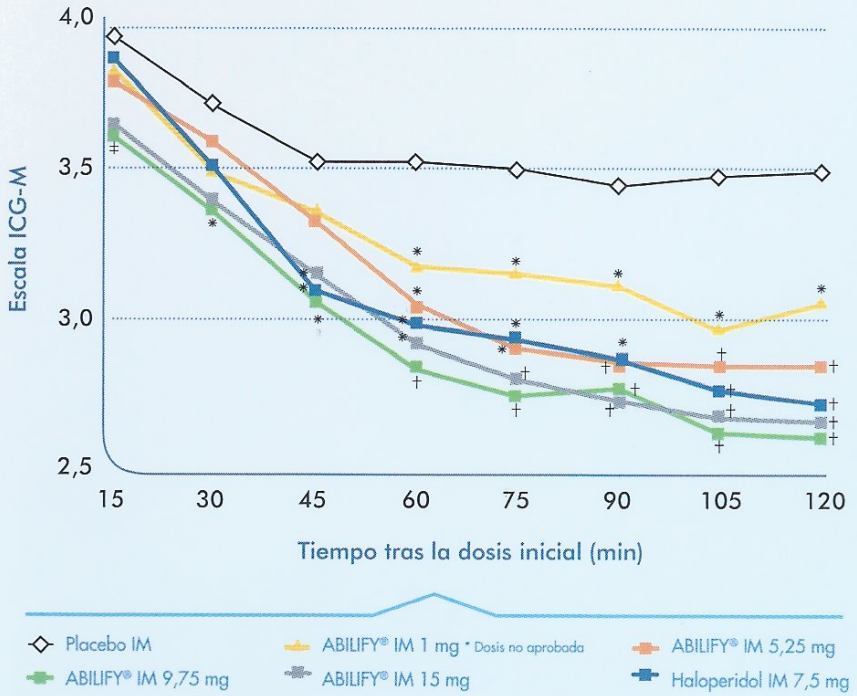
	IM Placebo (Total from 3 Cohorts)	IM Aripiprazole 5 mg (Cohort 1)	IM Aripiprazole 10 mg (Cohort 2)	IM Aripiprazole 15 mg (Cohort 3)	IM Aripiprazole (Total from 3 Cohorts)
N	26	12	78	13	103
Mean ± SD age, y	79.5 ± 7.8	80.2 ± 5.4	80.0 ± 10.3	79.9 ± 6.0	80.0 ± 9.3
Male/female, n (%)	10/16 (38/62)	4/8 (33/67)	28/50 (36/64)	4/9 (31/69)	36/67 (35/65)
Race, n (%)					
White	22 (85)	9 (75)	61 (78)	13 (100)	83 (81)
Black/African American	4 (15)	3 (25)	17 (22)	0	20 (19)
Ethnicity, n (%)					
Hispanic/Latino	6 (23)	3 (25)	6 (8)	1 (8)	10 (10)
Not Hispanic/Latino	20 (77)	9 (75)	72 (92)	12 (92)	93 (90)
Underlying diagnosis, n (%)					
Alzheimer's dementia	22 (85)	9 (75)	61 (78)	10 (77)	80 (78)
Mixed dementia	2 (8)	2 (17)	12 (15)	1 (8)	15 (15)
Vascular dementia	2 (8)	1 (8)	5 (6)	2 (15)	8 (8)
Mean ± SD age at diagnosis, y	75.7 ± 8.2	76.3 ± 4.6	76.3 ± 11.0	76.7 ± 6.5	76.4 ± 9.9
Mean ± SD PEC Total score	20.0 ± 3.7	21.7 ± 3.9	20.6 ± 3.7	20.8 ± 3.3	20.7 ± 3.7
Mean ± SD ACES score	2.0 ± 0.5	1.9 ± 0.5	2.1 ± 0.6	2.1 ± 0.8	2.1 ± 0.6
Mean ± SD CGI-S score	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.7	4.5 ± 0.9	4.4 ± 0.7

IM, intramuscular; PEC, Positive and Negative Syndrome Scale (PANSS) Excited Component; ACES, Agitation–Calmness Evaluation Scale; CGI-S, Clinical Global Impression–Severity of Illness; SD, standard deviation.

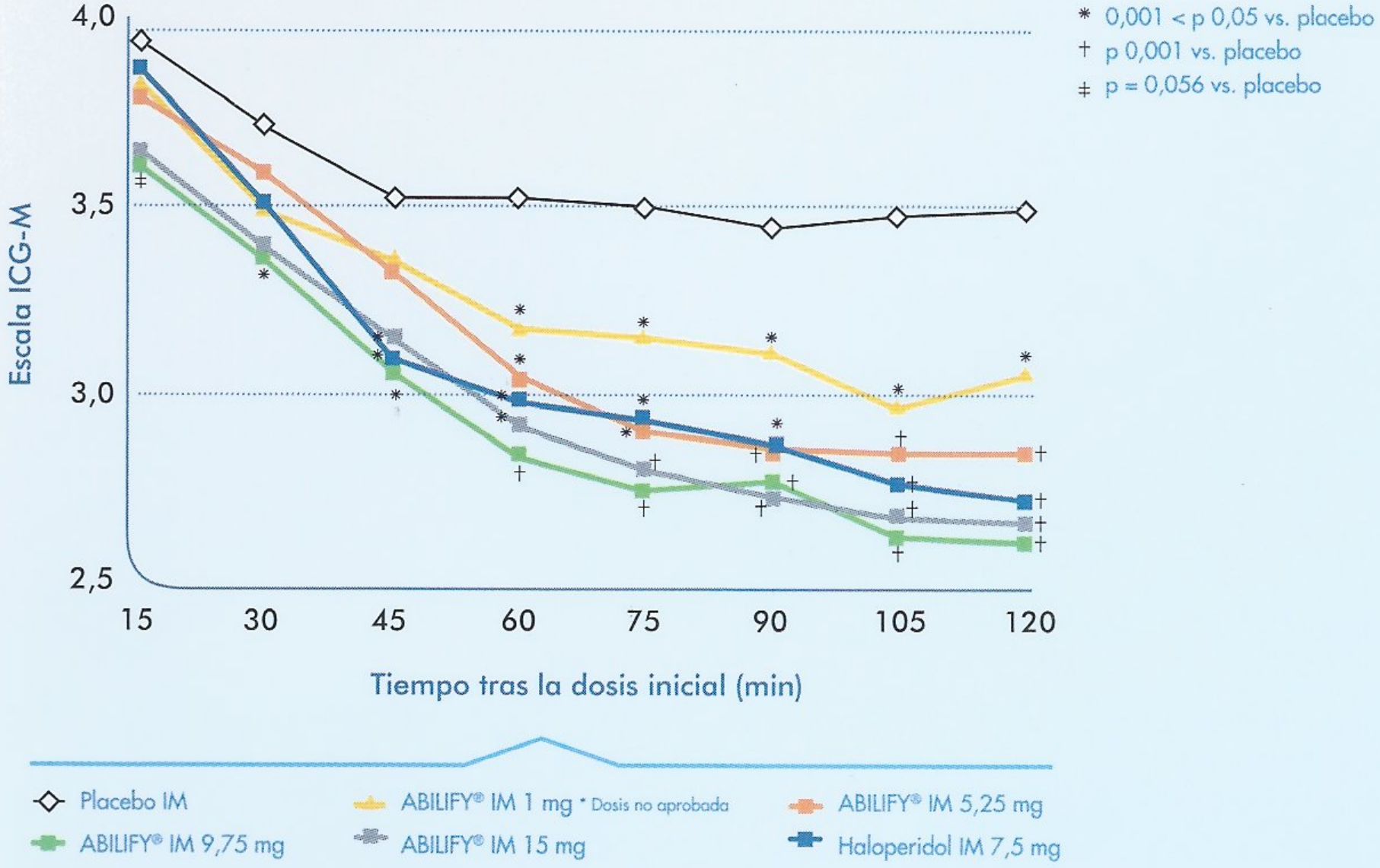
Table 3. *Incidence of Treatment-Emergent Adverse Events That Occurred in at Least 5% of Patients in any Treatment Group During the Study (Safety Sample)*

	IM Placebo (Total from 3 Cohorts)	IM Aripiprazole 5 mg (Cohort 1)	IM Aripiprazole 10 mg (Cohort 2)	IM Aripiprazole 15 mg (Cohort 3)	IM Aripiprazole (Total from 3 Cohorts)
N	25	12	76	15	103
During the whole study, n (%)					
Any adverse event	8 (32.0)	6 (50.0)	41 (54.0)	9 (60.0)	56 (54.4)
Somnolence	2 (8.0)	2 (16.7)	30 (39.5)	5 (33.3)	37 (35.9)
Dementia	0	3 (25.0)	0	0	3 (2.9)
Lethargy	0	0	0	1 (6.7)	1 (1.0)
Vomiting	0	1 (8.3)	3 (4.0)	0	4 (3.9)
Pyrexia	0	0	0	1 (6.7)	1 (1.0)
Skin laceration	2 (8.0)	0	1 (1.3)	1 (6.7)	2 (1.9)
Fall	1 (4.0)	0	0	1 (6.7)	1 (1.0)
Femoral neck fracture	0	0	0	1 (6.7)	1 (1.0)
Electrocardiogram change	0	0	0	1 (6.7)	1 (1.0)
Irregular heart rate	0	0	0	1 (6.7)	1 (1.0)
Insomnia	0	0	2 (2.6)	1 (6.7)	3 (2.9)
Agitation	2 (8.0)	0	1 (1.3)	0	1 (1.0)
First onset/increased severity after the second injection, n (%)					
Any adverse event	5 (21.7)	5 (45.5)	23 (31.1)	4 (30.8)	32 (32.7)
Somnolence	0	1 (9.1)	8 (10.81)	1 (7.7)	10 (10.2)
Dementia	0	3 (27.3)	0	0	3 (3.1)
Lethargy	0	0	0	1 (7.7)	1 (1.0)
Vomiting	0	1 (9.1)	3 (4.1)	0	4 (4.1)
Skin laceration	2 (8.7)	0	1 (1.4)	1 (7.7)	2 (2.0)
Fall	1 (4.4)	0	0	1 (7.7)	1 (1.0)
Femoral neck fracture	0	0	0	1 (7.7)	1 (1.0)
Insomnia	0	0	2 (2.7)	1 (7.7)	3 (3.1)
Agitation	2 (8.7)	0	1 (1.4)	0	1 (1.0)

ABILIFY® IM, eficaz en el control rápido de la agitación a los 15-30 min.[6]



Los ítems de PEC se puntúan entre 1 (sin agitación) y 7 (agitación extrema), oscilando las posibles puntuaciones totales entre 5 y 35.
Datos de última observación arrastrada (UOA).
PEC: Componente de excitación de la escala PANSS


* 0,001 < p 0,05 vs. placebo
† p 0,001 vs. placebo
‡ p = 0,056 vs. placebo
Escala ICG-M
4,0
3,5
3,0
2,5
15
30
45
60
75
90
105
120
Tiempo tras la dosis inicial (min)
Placebo IM
ABILIFY® IM 1 mg * Dosis no aprobada
ABILIFY® IM 5,25 mg
ABILIFY® IM 9,75 mg
ABILIFY® IM 15 mg
Haloperidol IM 7,5 mg

DISCUSSION

In elderly patients with agitation associated with Alzheimer's, vascular, or mixed dementia, IM aripiprazole in total daily doses of 5 to 15 mg was well tolerated and associated with improvements in efficacy measures when compared with IM placebo.

Since this study did not identify a maximum tolerated dose for this patient population, the 10-mg dose would be expected to be preferable to the 15-mg dose due to its similar safety and efficacy.

Somnolence was the only treatment-emergent AE reported at a higher incidence than IM placebo across all IM aripiprazole groups, but this was mild/moderate in severity, and no patient discontinued because of it. The ACES—a single-item scale designed to assess reduction in agitation—differentiates between the states of agitation, calmness, and sleep.[19,20] The incidence of ACES scores of 8 (deep sleep) or 9 (unarousable) was analyzed as a categorical measure of oversedation. That few IM aripiprazole-treated patients experienced ACES scores of 8 or 9 in the first 2 hours suggests this treatment resulted in a calming effect with a low risk for oversedation.

Movement Disorders
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Open-Label Flexible-Dose Pilot Study to Evaluate the Safety and Tolerability of Aripiprazole in Patients With Psychosis Associated With Parkinson's Disease

Joseph H. Friedman, MD,[1,2*] Robert M. Berman, MD,[3] Christopher G. Goetz, MD,[4] Stewart A. Factor, DO,[5] William G. Ondo, MD,[6] Joanne Wojcieszek, MD,[7] William H. Carson, MD,[8] and Ronald N. Marcus, MD[3]

[1]*Parkinson Disease and Movement Disorders Center, NeuroHealth, Warwick, Rhode Island, USA*
[2]*Department of Clinical Neurosciences, Brown University Medical School, Providence, Rhode Island, USA*
[3]*Bristol Myers Squibb, Wallingford, Connecticut, USA*
[4]*Department of Neurology, Rush University, Chicago, Illinois, USA*
[5]*Department of Neurology, Emory University, Atlanta, Georgia, USA*
[6]*Department of Neurology, Baylor College of Medicine, Houston, Texas, USA*
[7]*Department of Neurology, Indiana University, Indianapolis, Indiana, USA*
[8]*Otsuka America Pharmaceuticals, Inc., Princeton, New Jersey, USA*

TABLE 2. *Number of patients demonstrating changes in psychosis and Parkinson's symptoms during acute phase of study*

	Parkinson's symptoms		
Psychosis symptoms	Improvement	No change	Worsening
Improvement	1 (7%)	3 (21%)	2 (14%)
No change		3 (21%)	1 (7%)
Worsening		1 (7%)	3 (21%)

Clinically significant changes in symptoms were defined by changes on the outcomes scales (UPDRS and the BPRS core subscale) or by the presence of adverse effects attributed to a patient's discontinuation in the study. On the UPDRS scale, changes of 20% or greater were considered clinically meaningful (i.e., 20% increase corresponds to worsening; 20% decrease corresponds to improvement). On the core BPRS, changes of 25% or greater were considered clinically significant. Percentages do not add up to 100% due to rounding.

Risperidona (Risperdal®)

- Antisicótico del grupo benzisoxazole
  - Descubierto en 1988 y aprobado por la FDA en 1994
  - Alta afinidad de 5HT2A y moderada de D2
  - Bloqueo potente de 5HT2A y D2
  - No efecto colinérgico, poco H1, escasa alfa-adrenérgica
  - Más Efectos Extrap. que otros atipicos
- Buena absorción (1 h CPM y BD del 99 %). Unión 90 % PP
- Metabolismo hepático (metabolitos activos)
- Compr de 1,2,3,6 mgr y solución oral (1-3 al dia)
- Efectos secundarios:
  - Sedación, mareo, aumento de peso, aumento PRL, EPS…….
  - Incremento de AVCs, y de mortalidad
- Unico aprobado en España para ttº de SPCDs en demencia

A Randomized Placebo-Controlled Trial of Risperidone for the Treatment of Aggression, Agitation, and Psychosis of Dementia

Henry Brodaty, M.D.; David Ames, M.D.; John Snowdon, M.D.; Michael Woodward, M.B., B.S.; Jeff Kirwan, M.B., Ch.B.; Roger Clarnette, M.B., B.S.; Emma Lee, Ph.D.; Ben Lyons, Ph.D.; and Fred Grossman, D.O.

Background: This randomized, double-blind, placebo-controlled trial examined the efficacy and safety of risperidone in the treatment of aggression, agitation, and psychosis in elderly nursing-home patients with dementia.

Method: Elderly patients with a DSM-IV diagnosis of dementia of the Alzheimer's type, vascular dementia, or a combination of the 2 (i.e., mixed dementia) and significant aggressive behaviors were randomized to receive, for a period of 12 weeks, a flexible dose of either placebo or risperidone solution up to a maximum of 2 mg/day. Outcome measures were the Cohen-Mansfield Agitation Inventory (CMAI), the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) rating scale, and the Clinical Global Impression of Severity (CGI-S) and of Change (CGI-C) scales.

Results: A total of 345 patients were randomized to treatment with risperidone or placebo, and 337 patients received at least one dose of study drug. The trial was completed by 67% of patients in the placebo group and 73% of patients in the risperidone group. The mean ± SE dose of risperidone was 0.95 ± 0.03 mg/day. The primary endpoint of the study, the difference from baseline to endpoint in CMAI total aggres-

Received Feb. 15, 2002; accepted Nov. 21, 2002. *From the Academic Department for Old Age Psychiatry, School of Psychiatry, University of New South Wales, Sydney, Australia (Dr. Brodaty); the Department of Psychiatry, University of Melbourne, Melbourne, Australia (Dr. Ames); the Department of Psychological Medicine, University of Sydney, Sydney, Australia (Dr. Snowdon); the Austin and Repatriation Hospital, Victoria, Australia (Dr. Woodward); the Princess Margaret Hospital, Christchurch, New Zealand (Dr. Kirwan); Community and Geriatric Medicine, Fremantle Hospital, Fremantle, Australia (Dr. Clarnette); Janssen-Cilag Australia, North Ryde, New South Wales, Australia (Dr. Lee); and Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Titusville, New Jersey (Drs. Lyons and Grossman).*

This investigator-initiated study was supported by Janssen-Cilag Australia and Johnson & Johnson, L.L.C.

Individual financial disclosure and acknowledgments appear at the end of the article.

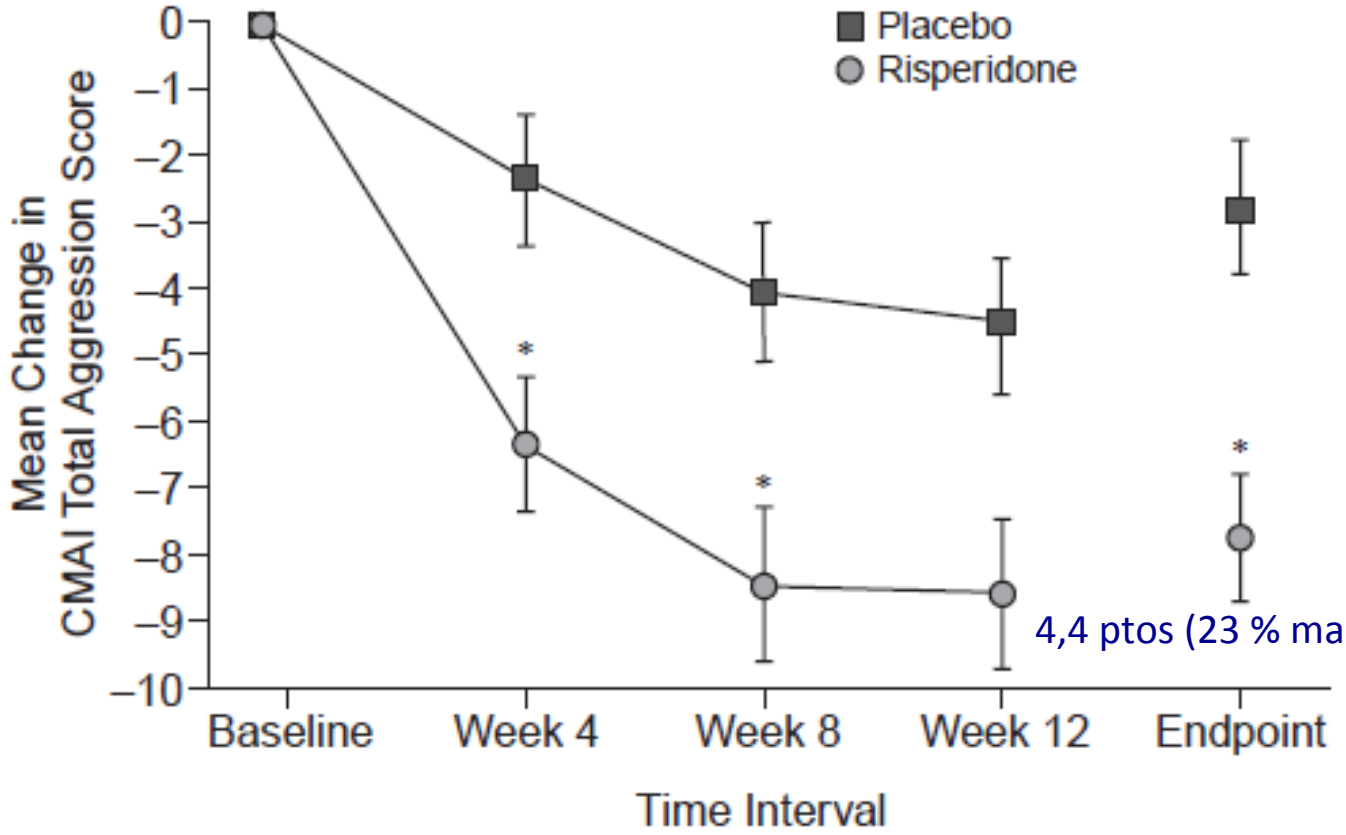
Corresponding author and reprints: H. Brodaty, M.D., Academic Department for Old Age Psychiatry, Euroa Centre, Prince of Wales Hospital, Randwick, Sydney, NSW, 2031, Australia (e-mail: h.brodaty@unsw.edu.au).

(J Clin Psychiatry 2003;64:134–143)

The number of people with dementia is expected to increase with the aging world population. It has been estimated that the prevalence of dementia doubles every 5 years after the age of 65 years,[1,2] with Alzheimer's

Figure 2. Change (mean and SE) in Total Aggression Subscale Score of the CMAI Over Time (intent-to-treat patients at included sites)

N = 337



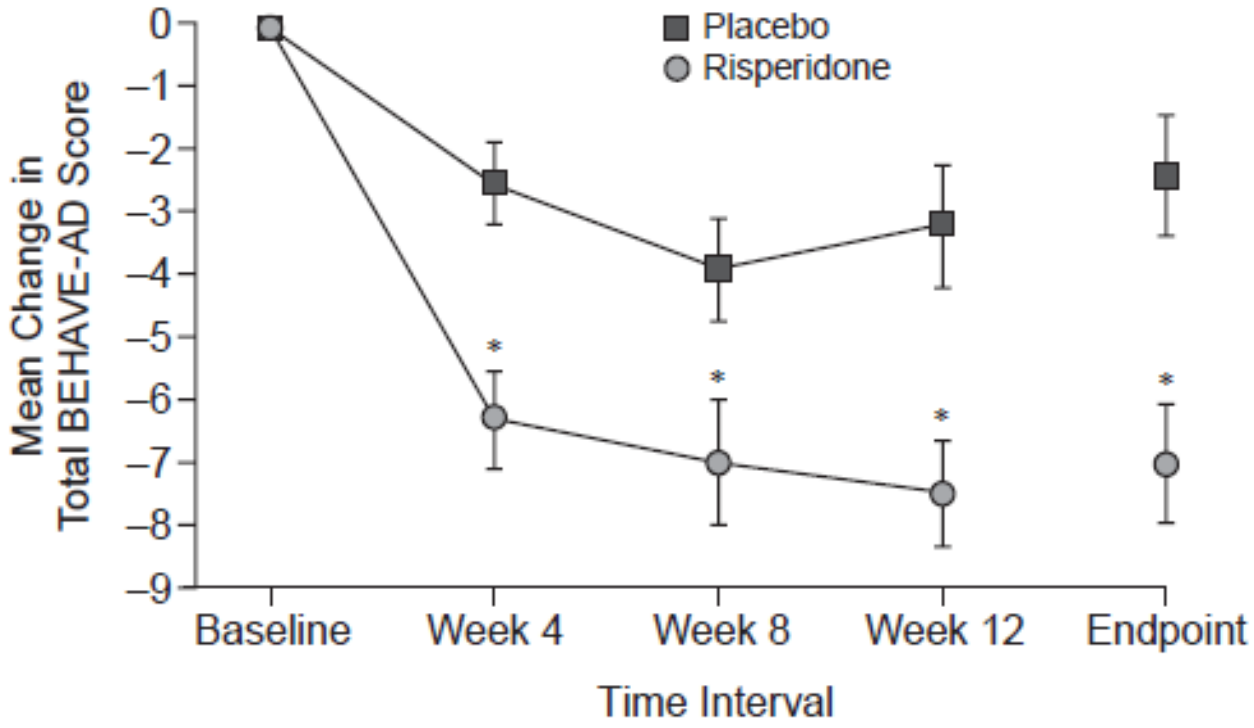
4,4 ptos (23 % mas respuesta)

Placebo:	N = 153	N = 138	N = 123	N = 112	N = 152
Risperidone:	N = 151	N = 141	N = 132	N = 119	N = 149

67 % Plc y 73 % activo acabaron el trial

*p < .01 vs. placebo.
Abbreviation: CMAI = Cohen-Mansfield Agitation Inventory.

Figure 3. Change (mean and SE) in BEHAVE-AD Total Score Over Time (intent-to-treat patients at included sites)



Placebo:	N = 153	N = 138	N = 123	N = 112	N = 152
Risperidone:	N = 151	N = 141	N = 132	N = 119	N = 149

*$p < .01$ vs. placebo.
Abbreviation: BEHAVE-AD = Behavioral Pathology of Alzheimer's Disease.

Fallecidos:
4 Plc
6 Ris

Ictus:
15 Ris
3 Plc

Extrap:
3 % Plac
6 % Ris

Table 4. Adverse Events Reported by at Least 5% of Patients in Either Group at All Sites

Adverse Event[a]	Placebo (N = 170) N (%)	Risperidone (N = 167) N (%)
Somnolence	43 (25.3)	61 (36.5)
Injury	63 (37.1)	60 (35.9)
Fall	46 (27.1)	42 (25.1)
Urinary tract infection	25 (14.7)	39 (23.4)
Agitation	42 (24.7)	33 (19.8)
Purpura	27 (15.9)	30 (18.0)
Conjunctivitis	18 (10.6)	20 (12.0)
Constipation	26 (15.3)	19 (11.4)
Skin disorder	16 (9.4)	18 (10.8)
Cerebrovascular adverse event	3 (1.8)	15 (9.0)
Vomiting	13 (7.6)	14 (8.4)
Edema peripheral	6 (3.5)	13 (7.8)
Rash	9 (5.3)	13 (7.8)
Upper respiratory tract infection	15 (8.8)	13 (7.8)
Skin ulceration	11 (6.5)	12 (7.2)
Extrapyramidal disorder	5 (2.9)	10 (6.0)
Tremor	3 (1.8)	10 (6.0)
Gait abnormal	2 (1.2)	10 (6.0)
Fever	4 (2.4)	9 (5.4)
Aggressive reaction	18 (10.6)	9 (5.4)
Coughing	5 (2.9)	9 (5.4)
Headache	11 (6.5)	8 (4.8)
Infection	12 (7.1)	6 (3.6)
Diarrhea	22 (12.9)	5 (3.0)
Dyskinesia	9 (5.3)	1 (0.6)
Total patients with adverse event	157 (92.4)	157 (94.0)

Table 5. Summary of ESRS Scores at Baseline and Changes From Baseline at Endpoint at All Sites

	Placebo		Risperidone		
ESRS	Baseline Mean (SE)[a]	Endpoint Mean Change (SE)[a]	Baseline Mean (SE)[a]	Endpoint Mean Change (SE)[a]	p Value[b]
Total ESRS questionnaire	4.9 (0.49)	0.5 (0.48)	4.5 (0.40)	0.7 (0.35)*	.407
Subscales					
Bucco-linguo-masticatory factor	0.9 (0.17)	–0.1 (0.17)	1.0 (0.18)	–0.0 (0.17)	.440
Parkinsonism/dystonia total	10.4 (0.54)	–0.7 (0.42)	11.0 (0.59)	1.6 (0.47)**	< .001
Parkinsonism total score	10.2 (0.52)	–0.6 (0.40)	10.7 (0.56)	1.5 (0.45)**	< .001

[a]Higher scores imply worsening condition.
[b]Test for no difference between treatments from ANCOVA model with factors for treatment, baseline score (as covariate), and investigator.
*$p < .050$ vs. baseline.
**$p < .001$ vs. baseline.
Abbreviation: ESRS = Extrapyramidal Symptom Rating Scale.

Quetiapina (Seroquel®)

- Antipsicótico del grupo dibenzothiazepina
  - Baja afinidad por D2 (30 %) y separación rápida del receptor
  - Moderada o intensa por 5HT2, menos de alfa-adrenergicos, histamina…
  - Descubierto en 1984 y aprobado pro la FDA en 1997
  - Perfil semejante a clozapina, pero más seguro
- Buena absorción (1-2 h CPM y BD del 99 %). Unión 83 % PP
  - Influida por alimentos
  - Se puede administrar 1-2 veces al dia
  - Metabolismo hepático (metabolitos activos), un 35 % menor en ancianos
- Compr de 25, 50, 100, 200 mgr (formas retard)
- Efectos secundarios:
  - Cefalea, somnolencia, mareo, discreta elevación de PRL, HipoTA, aumento de peso, endocrinológicos…
  - Menor efecto EPS de todos
  - El más seguro de los SAP en población anciana

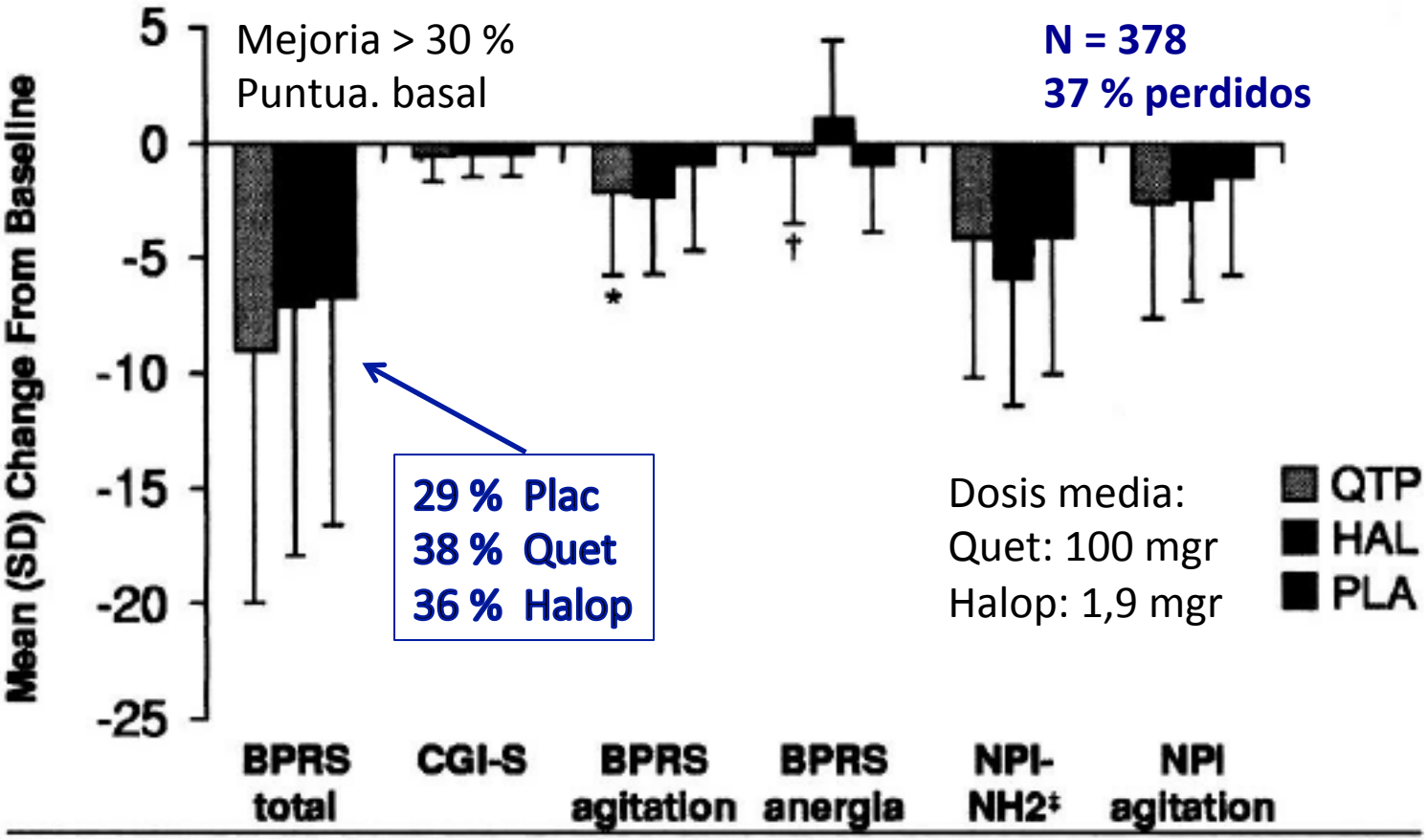
Quetiapine Treatment of Psychosis Associated With Dementia: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial

(Am J Geriatr Psychiatry 2006; 14:767–776)

Pierre N. Tariot, M.D., Lon Schneider, M.D.,
Ira R. Katz, M.D., Ph.D., Jacobo E. Mintzer, M.D.,
Jamie Street, M.D., Margaret Copenhaver, Ph.D.,
Celeste Williams-Hughes, B.A., E.L.S.

Objectives: *The objectives of this study were to evaluate the efficacy, safety, and tolerability of quetiapine for treating psychosis in patients with probable/possible Alzheimer disease and assess its impact on other psychopathology and social and daily functioning.* **Method:** *The authors conducted a multicenter, double-blind, placebo-controlled, randomized trial of flexibly dosed quetiapine and haloperidol. Primary outcomes were change in total Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions–Severity of Illness (CGI-S) scores at week 10. Secondary outcomes included BPRS factors, Neuropsychiatric Inventory (NPI), Multidimensional Observation Scale for Elderly Subjects (MOSES), and Physical Self-Maintenance Scale (PSMS).* **Results:** *Two hundred eighty-four participants (mean age: 83.2 years) were randomized; 63.4% completed; and mean Mini-Mental State Examination score was 12.8. Median of the mean daily dose was 96.9 mg for quetiapine and 1.9 mg for haloperidol. No differential benefit was seen on any psychosis measure. BPRS agitation factor scores improved with quetiapine versus placebo and not quetiapine versus haloperidol. BPRS anergia scores worsened with haloperidol versus quetiapine but not quetiapine versus placebo. No NPI factors showed change, including the agitation factor. MOSES Withdrawal Subscale and PSMS total scores worsened with haloperidol*

FIGURE 2. Mean (standard deviation) Changes From Baseline, Efficacy, Week 10 Last Observation Carried Forward



*p = 0.023 QTP vs PLA.
†p = 0.001 QTP vs HAL.
‡NPI-NH2: sum of hallucinations and delusions.
QTP: quetiapine; HAL: haloperidol; PLA: placebo.

284 EA
57 VD
28 Otras
11 Esq.

TABLE 3. Change From Baseline to Week 10 Last Observation Carried Forward, Various Outcomes

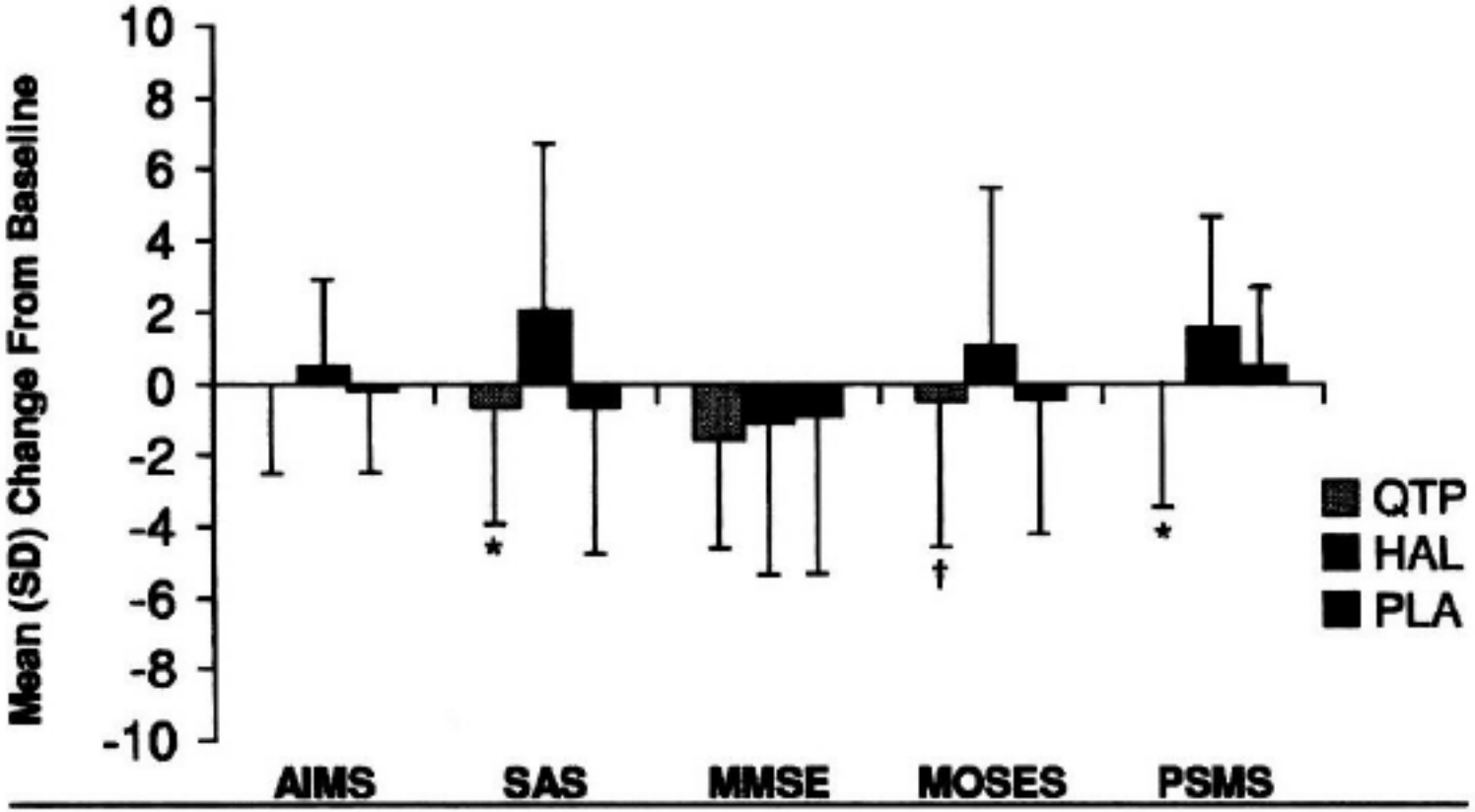
Assessment	Quetiapine	Haloperidol	Placebo
Change, mean (SD)	(N = 85)	(N = 86)	(N = 94)
BPRS total	−9.06 (11.07)	−7.13 (10.85)	−6.74 (9.88)
CGI-S	−0.60 (1.05)	−0.52 (1.00)	−0.47 (0.88)
BPRS agitation*	−2.14 (3.58)	−2.37 (3.43)	−0.96 (3.80)
BPRS anergia†	−0.53 (3.11)	1.01 (3.47)	−0.93 (2.95)
BPRS thought disturbance	−2.41 (3.14)	−2.29 (3.01)	−1.98 (3.19)
NPI-NH2	(N = 86)	(N = 86)	(N = 94)
	−4.14 (6.04)	−5.93 (5.58)	−4.11 (5.99)
NPI-NH agitation	(N = 86)	(N = 86)	(N = 93)
	−2.63 (4.99)	−2.43 (4.45)	−1.49 (4.33)
MMSE	(N = 69)	(N = 63)	(N = 72)
	−1.58 (2.98)	−1.06 (4.26)	−0.90 (4.42)
MOSES†	(N = 81)	(N = 78)	(N = 90)
	−0.44 (4.10)	1.06 (4.38)	−0.37 (3.78)
PSMS†	(N = 86)	(N = 85)	(N = 94)
	−0.01 (3.38)	1.59 (3.06)	0.47 (2.24)
AIMS	(N = 85)	(N = 86)	(N = 94)
	−0.02 (2.4)	0.44 (2.39)	−0.14 (2.25)
SAS†	(N = 73)	(N = 75)	(N = 83)
	−0.67 (3.21)	2.05 (4.61)	−0.67 (4.06)

TABLE 4. Change From Baseline in Brief Psychiatric Rating Scale Total Scores and CGI-S Scores (week 10 LOCF)

Population	Quetiapine	Haloperidol	Placebo
Mean Change (SD)			
Total (N = 354)	−8.94 (10.68)	−7.96 (11.73)	−7.04 (10.25)
AD (N = 265)	−9.06 (11.07)	−7.13 (10.85)	−6.74 (9.88)
Non-AD (N = 89)	−8.63 (9.74)	−10.19 (13.76)	−8.16 (11.70)
Mean Change (SD) CGI-S			
Total (N = 354)	−0.61 (1.02)	−0.59 (1.07)	−0.44 (0.84)
AD (N = 265)	−0.60 (1.05)	−0.52 (1.00)	−0.47 (0.88)
Non-AD (N = 89)	−0.63 (0.94)	−0.78 (1.24)	−0.32 (0.69)

SD: standard deviation; AD: Alzheimer disease; CGI-S: Clinical Global Impressions–Severity of Illness; LOCF: last observation carried forward.

FIGURE 3. Mean (standard deviation) Change From Baseline, Safety, and Tolerability, Week 10 Last Observation Carried Forward



*p <0.001 QTP vs HAL.
†p = 0.004 QTP vs HAL.
QTP: quetiapine; HAL: haloperidol; PLA: placebo.

TABLE 5. Treatment-Emergent Adverse Events Other Than Extrapyramidal Symptoms*

COSTART Designation	Quetiapine (N = 91)	Haloperidol (N = 94)	Placebo (N = 98)
Somnolence†	23 (25.3)	34 (36.2)	4 (4.1)
Infection†‡	13 (14.3)	5 (5.3)	5 (5.1)
Rash	12 (13.2)	12 (12.8)	13 (13.3)
Pain	12 (13.2)	9 (9.6)	11 (11.2)
Vomiting	11 (12.1)	6 (6.4)	5 (5.1)
Agitation†	7 (7.7)	13 (13.8)	21 (21.4)
Urinary tract infection	11 (12.1)	10 (10.6)	5 (5.1)
Fever‡	3 (3.3)	11 (11.7)	6 (6.1)
Pharyngitis	5 (5.5)	4 (4.3)	10 (10.2)
Abnormal gait	3 (3.3)	10 (10.6)	3 (3.1)
Urinary incontinence†	4 (4.4)	4 (4.3)	0
Dyspepsia‡	0	4 (4.3)	4 (4.1)
Insomnia‡	0	5 (5.3)	1 (1)
Pallor‡	0	4 (4.3)	0
Convulsion†‡	4 (4.4)	0	0
Fallecidos:	**3 %**	**7 %**	**3 %**
Ictus:	**2**	**1**	**3**
Extrap:	**9**	**32**	**12**

Quetiapine (BPSD), Meta-analysis

Cheung G, New Zealand Medical Journal 2011

- Incluyen 5 estudios
  - 1118 pacientes
  - 6-12 semanas, varios tipos de demencia, dosis desde 0-600 mgr
- - 3,05 (NPI) y - 0,31 (CGI-C) e.s.
- Resultados: Quetiapina es más eficaz que placebo en ttº de BPSD en ancianos con demencia
- Aunque los resultados son de escasa magnitud

Olanzapina (Zyprexa®)

- Antipsicótico del grupo de la thiobenzodazepina
  - Mayor 5HT2 que D2
  - Alta H1 y alfa-adrenergico
  - Descubierto en 1990 y aprobado pro la FDA en 1997
- Buena absorción (4-6 h CPM y BD del 99 %). Unión 83 % PP
  - Influida por alimentos
  - Se puede administrar 1-2 veces al dia
  - Metabolismo hepático primer paso (40 %), multiples metabolitos (interaccion CBZ, fluoxetina, imipramina, etc..)
  - Compr de 5, 10, 15, 20 mgr e injectable
- Efectos secundarios:
  - Somnolencia, elevación de PRL, aumento de peso, endocrinológico, efecto EPS (menos que risperidona)

Ziprasidona (Zeldox®)

- Antipsicótico del grupo benzisothiazolyl piperacina
  - Mayor 5HT2 que D2 (mas que clozapina y olanzapina)
  - Poco efecto adrenérgico e histamina
  - Descubierto en 1997 y aprobado pro la FDA en 2001
- Buena absorción (3 h CPM y BD del 60 %) Union a PP del 99 %
  - Metabolismo hepático completo (CBZ, ketoconazol)
  - Compr de 20, 40, 60, 80 mgr e injectable de 20 mgr
- Efectos secundarios:
  - Somnolencia, elevación de PRL, aumento de peso, endocrinológico, efecto EPS, incremento QT
- Menor experiencia en pacientes con demencia

Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE): Alzheimer's Disease Trial

*by Lon S. Schneider, M. Saleem Ismail, Karen Dagerman, Sonia Davis, Jason Olin, Dennis McManus, Eric Pfeiffer, J. Michael Ryan, David L. Sultzer, and Pierre N. Tariot**

Abstract

This article describes the development of the protocol for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Alzheimer's disease trial, which was developed in collaboration with the National Institute of Mental Health to assess the effectiveness of atypical antipsychotics for psychosis and/or agitation occurring in outpatients with Alzheimer's disease. The article provides a detailed description of the methodology used in the trial as well as the clinical outcomes and effectiveness measures incorporated into it, discussing the most salient issues encountered in developing the design of the trial, as well as the unique features of the trial.

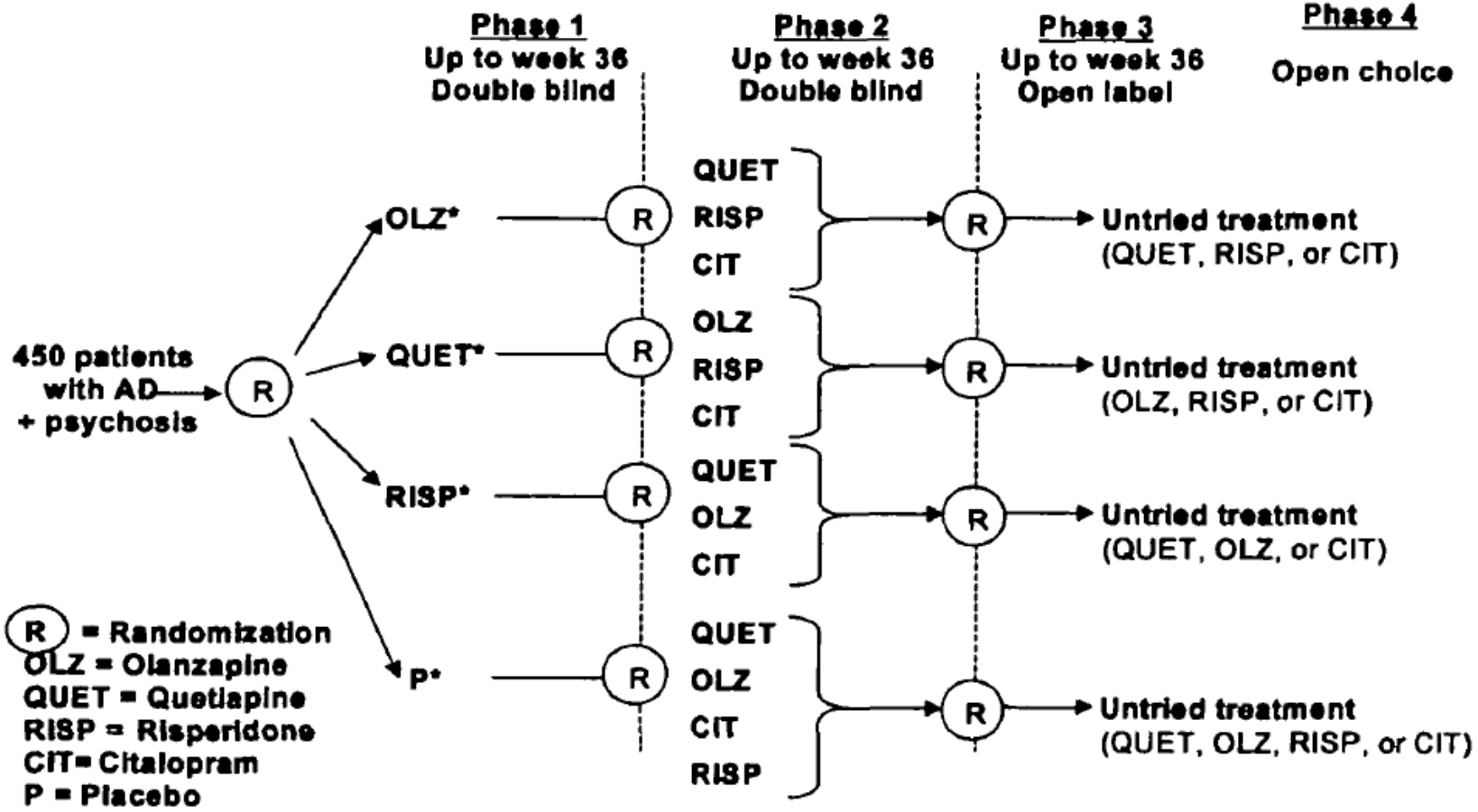
Keywords: Alzheimer's disease, atypical antipsychotic, psychosis, dementia, effectiveness.

***Schizophrenia Bulletin,* 29(1):57–72, 2003.**

in these patients, in part because cognitive impairment limits self-report of symptoms and hence the ability to identify typical features of psychosis. In many cases, the only manifestation of psychosis is a change in behavior, such as the common co-occurrence of agitation. There are also neurobiological correlates of delusions and hallucinations, suggesting that some of these phenomena are a direct result of the disease process (e.g., Zubenko et al. 1991; Lopez et al. 1996; Sweet et al. 1997). The available evidence indicates that up to one-half of patients with AD may develop psychosis and/or agitation at some point during their illness (Paulsen et al. 2000).

There are numerous significant and morbid consequences of psychosis in dementia. Hallucinations or delusions may cause subjective distress in patients and adverse effects on caregivers. Patients under the influence of delusions or hallucinations may be disruptive, troubled, or agitated, responding to internal stimuli rather than the environment. This may lead to unsafe and violent situations

Figure 1. AD trial design. Patients doing well on any assigned treatment continue on that treatment.



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

David L. Sultzer, M.D.

Sonia M. Davis, Dr.P.H.

Pierre N. Tariot, M.D.

Karen S. Dagerman, M.S.

Barry D. Lebowitz, Ph.D.

Constantine G. Lyketsos, M.D., M.H.S.

Robert A. Rosenheck, M.D.

John K. Hsiao, M.D.

Jeffrey A. Lieberman, M.D.

Lon S. Schneider, M.D.

CATIE-AD Study Group

Objective: The study measured the effects of atypical antipsychotics on psychiatric and behavioral symptoms in patients with Alzheimer's disease and psychosis or agitated behavior.

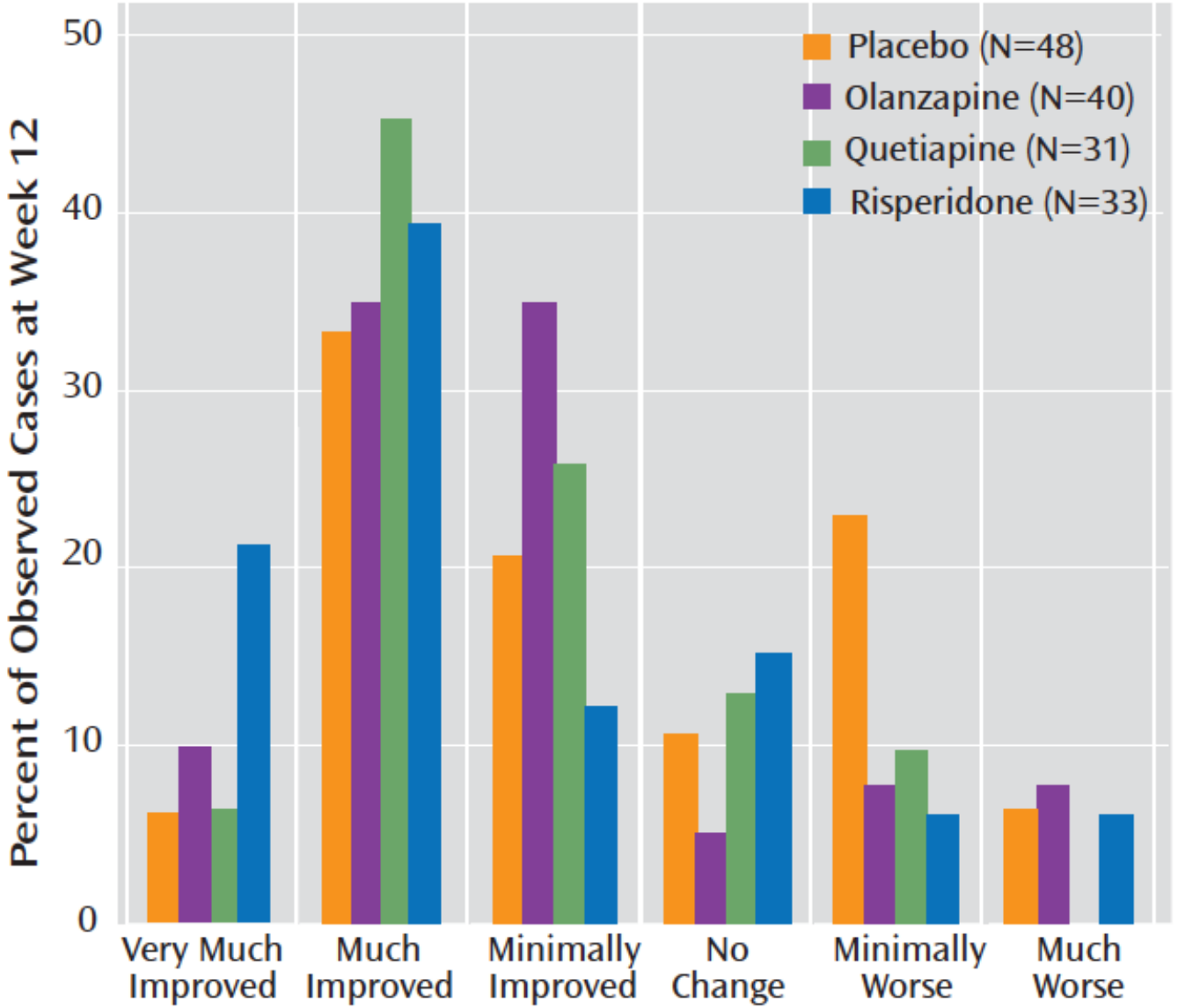
Method: The Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Disease (CATIE-AD) Alzheimer's disease effectiveness study included 421 outpatients with Alzheimer's disease and psychosis or agitated/aggressive behavior. Patients were assigned randomly to masked, flexible-dose treatment with olanzapine, quetiapine, risperidone, or placebo for up to 36 weeks. Patients could be randomly reassigned to a different medication at the clinician's discretion, which ended phase 1. Psychiatric and behavioral symptoms, functioning, cognition, care needs, and quality of life were measured at regular intervals.

Results: In relation to placebo, the last observation in phase 1 showed greater improvement with olanzapine or risperidone on the Neuropsychiatric Inventory total score, risperidone on the Clinical Global Impression of Changes, olanzapine and risperidone on the Brief Psychiatric Rating Scale (BPRS) hostile suspiciousness factor, and risperidone on the BPRS psychosis factor. There was worsening with olanzapine on the BPRS withdrawn depression factor. Among patients continuing phase 1 treatment at 12 weeks, there were no significant differences between antipsychotics and placebo on cognition, functioning, care needs, or quality of life, except for worsened functioning with olanzapine compared to placebo.

Conclusion: In this descriptive analysis of outpatients with Alzheimer's disease in usual care settings, some clinical symptoms improved with atypical antipsychotics. Antipsychotics may be more effective for particular symptoms, such as anger, aggression, and paranoid ideas. They do not appear to improve functioning, care needs, or quality of life.

(Am J Psychiatry 2008; 165:844–854)

FIGURE 2. Distribution of Improvement Ratings for Observed Cases[a] at 12 Weeks in Phase 1 of the CATIE Alzheimer's Disease Effectiveness Study



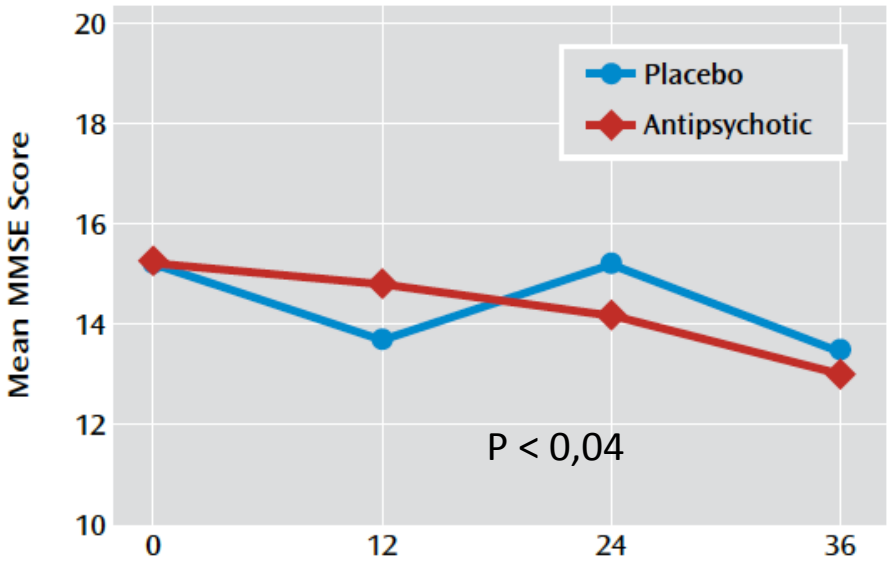
Some antipsychotic efficacy trials and the analyses reported here indicate that clinical symptoms may improve. However, the extent of mean improvement on rating scales is modest, it is not apparent for all symptoms or in all treatment studies, and beneficial effects on mean ratings of functional ability, quality of life, or cost-effectiveness (34) were not seen in CATIE-AD. Because of the unique design, the results of CATIE-AD are probably more generalizable to usual outpatient clinical settings than are results from efficacy trials. Whether the potentially beneficial effects of symptom reduction with antipsychotic treatment outweigh other undesirable clinical or adverse effects depends on an individual patient's circumstances, including severity of symptoms, vulnerability to adverse effects, and the effectiveness or opportunity for behavioral interventions. Additional studies to understand better the risk-benefit profile and effectiveness of specific treatments in individual patients will be valuable.

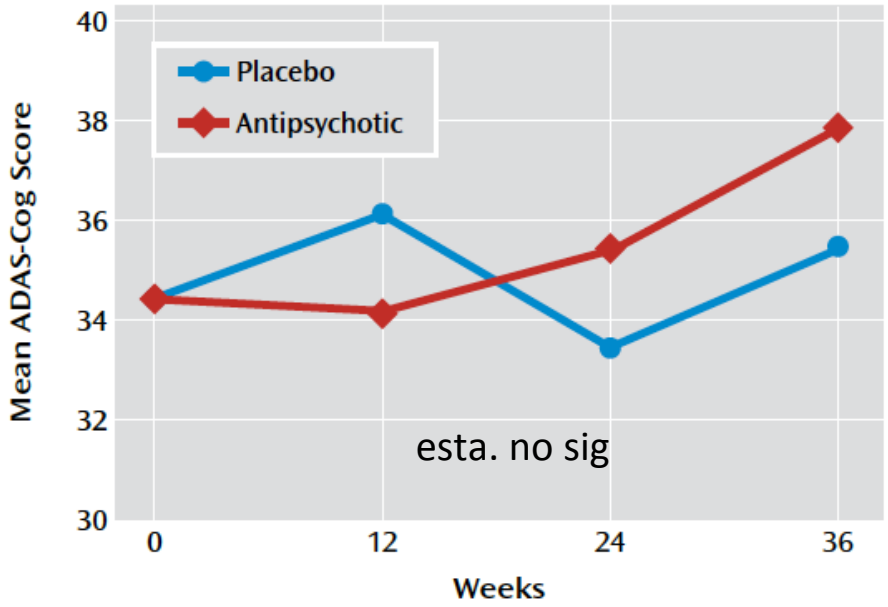
Cognitive Effects of Atypical Antipsychotic Medications in Patients With Alzheimer's Disease: Outcomes From CATIE-AD

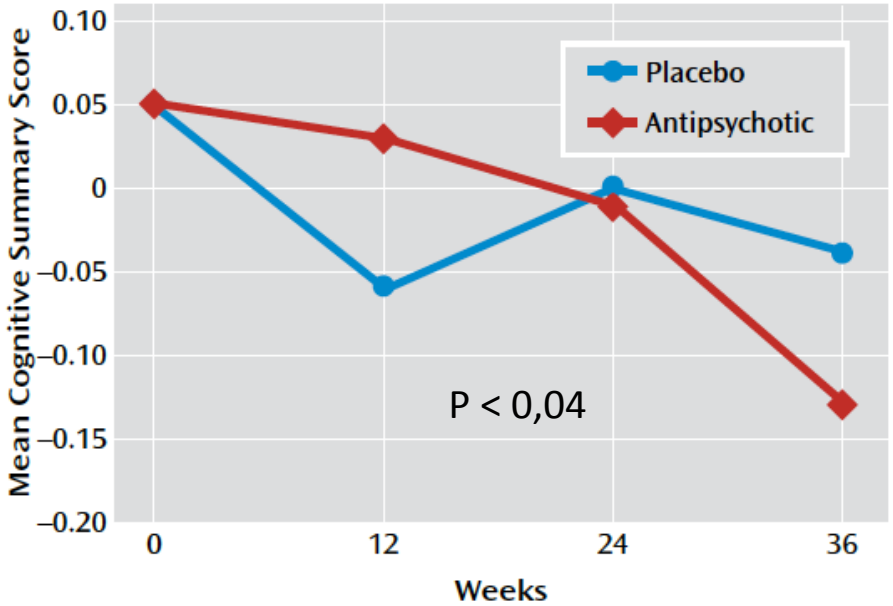
Cheryl L.P. Vigen, Ph.D.

(Am J Psychiatry 2011; 168:831–839)

36 semanas







Effect of Second Generation Antipsychotics on Caregiver Burden in Alzheimer Disease

Somaia Mohamed, M.D., Ph.D.[1,2], **Robert Rosenheck, M.D**[1,2], **Constantine G. Lyketsos, M.D., M.H.S.**[3], **Richard Kaczyinski, Ph.D.**[1], **David Sultzer, M.D.**[4], and **Lon S. Schneider, M.D.**

J Clin Psychiatry. 2012 January ; 73(1): 121–128.

Objective—In this study we use data from the CATIE-AD trial to evaluate the effect of atypical antipsychotics as compared to placebo on the experiences of caregivers of outpatients with Alzheimer disease.

Results—In both ITT and phase 1-only analyses, caregivers of patients treated with second generation antipsychotics (SGAs) scored significantly lower than those on placebo on both the Burden Interview ($p = 0.009$) and the NPI Caregiver Distress Scale's scores ($p = 0.0209$). These differences appeared to have been mediated by lower levels of agitation, hostility, and psychotic distortions.

Conclusion—In AD patients with symptoms of psychosis, agitation or aggressive behavior, medications can have a small but significant impact on caregiver burden.

Meta-análisis y Review Off-label, 2006

- Numerosos meta-análisis realizados (Cokraine, etc..)
- 15 ECR
  - **4 Risperidona**
  - **5 Olanzapina**
  - **3 Quetiapina**
  - **2 Aripiprazol**
- Falta de una evidencia de Alta calidad para alcanzar conclusiones definitivas
- Evidencias de efectos secundarios (peso, sedación, alt. gastro-intestinales
- Incremento de mortalidad en pacientes con demencia
  - 3,5 % SAP vs 2,3 % Plac OR: 1,54 (1,06-2,23) NNH: 100
- Eficacia e.s. de RIS y ARIP (aunque efecto pequeño) y tendencia positiva de OLA y QUET

Effective Health Care Program

Comparative Effectiveness Review
Number 43

Off-Label Use of Atypical Antipsychotics: An Update

AHRQ
Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

AHRQ Publication No. 11-EHC087-EF
September 2011

Review Off-label SAP 2011

- 37 ECR / Estudios cohortes:
  - **5 Risperidona, 10 Olanzapina, 6 Quetiapina, 8 Aripiprazol**
  - 5 ECR SAP vs Haloperidol
  - 3 ECR Head to Head SAP
- Evidencias + (e.s) de alta calidad para SPCD (agitación, agresividad y psicosis)
  - **Para Agresividad e Irritabilidad: RIS, OLA, ARIP > Placebo e.s**
  - **Para Psicosis: RIS > Plac (e.s.)**
  - **Para Agitación: RIS, OLA, ARIP > Plac (e.s.)**
  - Comparación head to head de SAP sin diferencias de eficacia
  - Comparación FAP con SAP no diferencias de eficacia
- Su significado clínico es incierto (¿efecto de pequeña magnitud?)
  - Mejoría de un 30 % de las escalas de SPCDs
  - Potenciales efectos secundarios
- Su uso ha aumentado mucho en residencias (25 % en el 2004), con ligera reducción (5 %) tras el black box del 2005

Table A. Summary of strength of evidence of efficacy, by drug and condition

	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
	O	-	++	-	-
	O	+	-	O	O
	O	O	O	+	O
	-	O	O	O	O
	O	O	O	+	O
Dementia overall	++	+	+	++	O
Dementia psychosis	+	+-	+-	++	O
Dementia agitation	+	++	+-	++	O
	++	+	++	++	+
	O	-	++	O	O
	O	--	-	O	O
Insomnia	O	O	-	O	O
	O	+	--	++	-
	O	O	+	+	O
	+	+-	+	O	-
	O	O	O	+-	O
	O	+-	+	++	O
	--	-	-	O	O
	O	-	O	-	O
	-	O	O	O	O
	O	O	O	-	O
	O	O	O	+	-

Table B. Summary update: efficacy of atypical antipsychotics for off-label use

Usage	Strength of Evidence	2006 Findings	2011 Findings
Dementia	High	A published meta-analysis of 15 placebo-controlled trials (PCTs) found small but statistically significant effects favoring treatment with risperidone and aripiprazole. There were effects that favored treatment with olanzapine for the BPRS and the NPI, but these differences were not statistically significant. Three studies of quetiapine were considered too clinically dissimilar to pool and results for the individual studies showed, with one exception, trends favoring treatment with quetiapine that did not reach conventional levels of statistical significance.	Overall – In our meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms as measured by total scores on BEHAVE-AD, BPRS, and NPI. Effect sizes were generally considered to be "small" in magnitude. Psychosis – In our meta-analysis risperidone was superior to placebo, as measured by the psychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance. Agitation – In our meta-analysis, aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI, and CMAI. Three head to head trials compared atypicals; none was found superior.

2006 Findings	2011 Findings
A published meta-analysis of 15 placebo-controlled trials (PCTs) found small but statistically significant effects favoring treatment with risperidone and aripiprazole. There were effects that favored treatment with olanzapine for the BPRS and the NPI, but these differences were not statistically significant. Three studies of quetiapine were considered too clinically dissimilar to pool and results for the individual studies showed, with one exception, trends favoring treatment with quetiapine that did not reach conventional levels of statistical significance.	Overall – In our meta-analysis of PCTs, aripiprazole, olanzapine, and risperidone were superior to placebo as treatment of behavioral symptoms as measured by total scores on BEHAVE-AD, BPRS, and NPI. Effect sizes were generally considered to be "small" in magnitude. Psychosis – In our meta-analysis risperidone was superior to placebo, as measured by the psychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for aripiprazole did not meet conventional levels of statistical significance. Agitation – In our meta-analysis, aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI, and CMAI. Three head to head trials compared atypicals; none was found superior.

Mortality Elderly Patients

Six large cohort studies compared mortality in elderly patients taking atypical and conventional antipsychotics. Four of these studies found a significantly higher rate of death with conventional antipsychotics, while two found no statistical difference in mortality between the drug classes.	The difference in risk for death was small but statistically significant for atypicals, according to a 2006 meta-analysis which remains the best available estimate. Sensitivity analyses found no difference between drugs in the class. Patients taking atypicals had higher odds of mortality than those taking no antipsychotics in the two cohort studies that made that comparison. There are no trials or large observational studies of ziprasidone in this population; therefore, we cannot make conclusions regarding safety here.

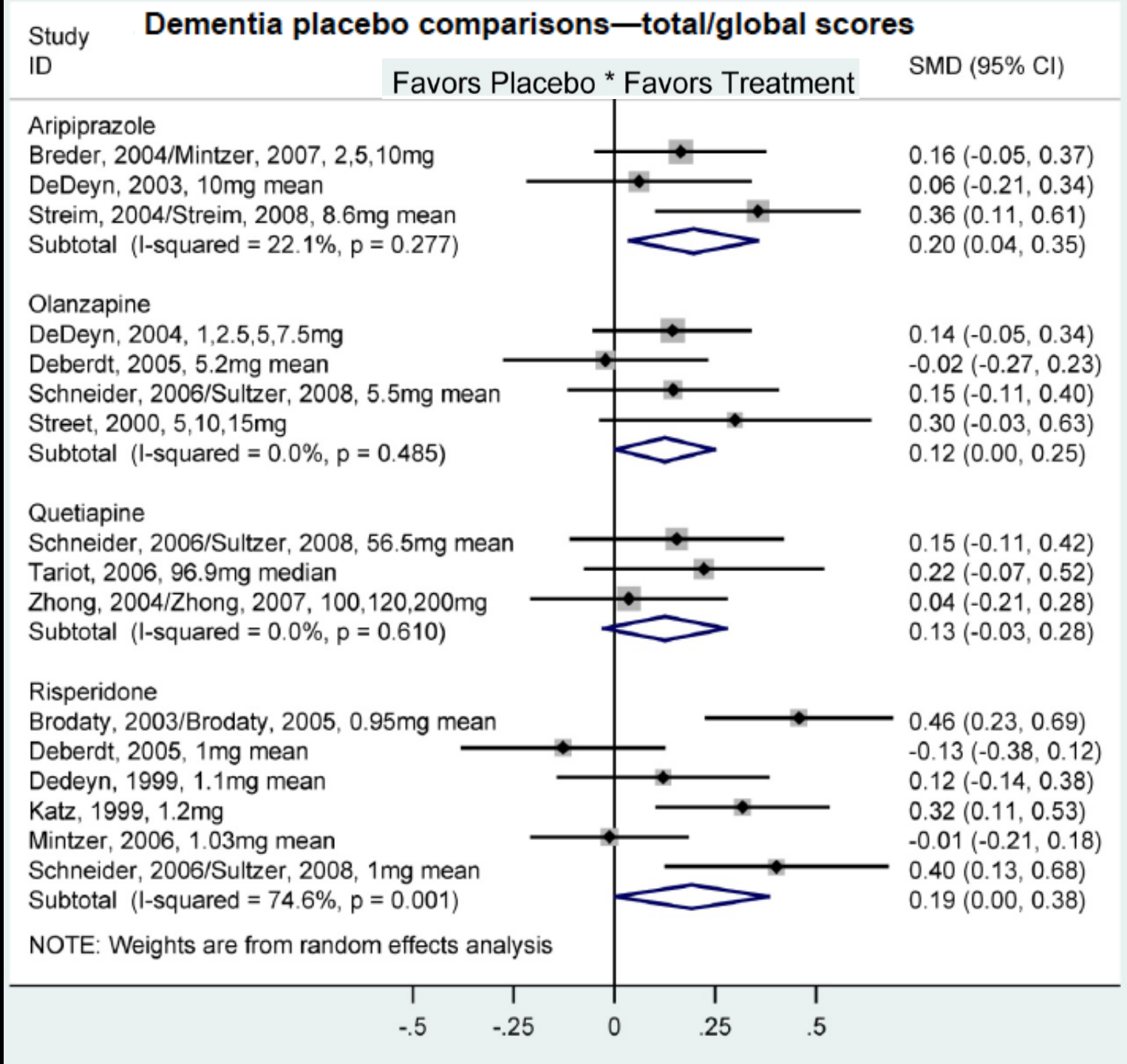
CVA	Elderly Patients
Hospitalization for CVA was increased in the first week after initiation of conventional antipsychotics, but not for initiation of atypicals in a large cohort study.	More common in risperidone patients than placebo according to four PCTs pooled by the manufacturer. In our new meta-analysis of PCTs, risperidone was the only drug associated with an increase. More common in olanzapine than placebo according to five PCTs pooled by the manufacturer.

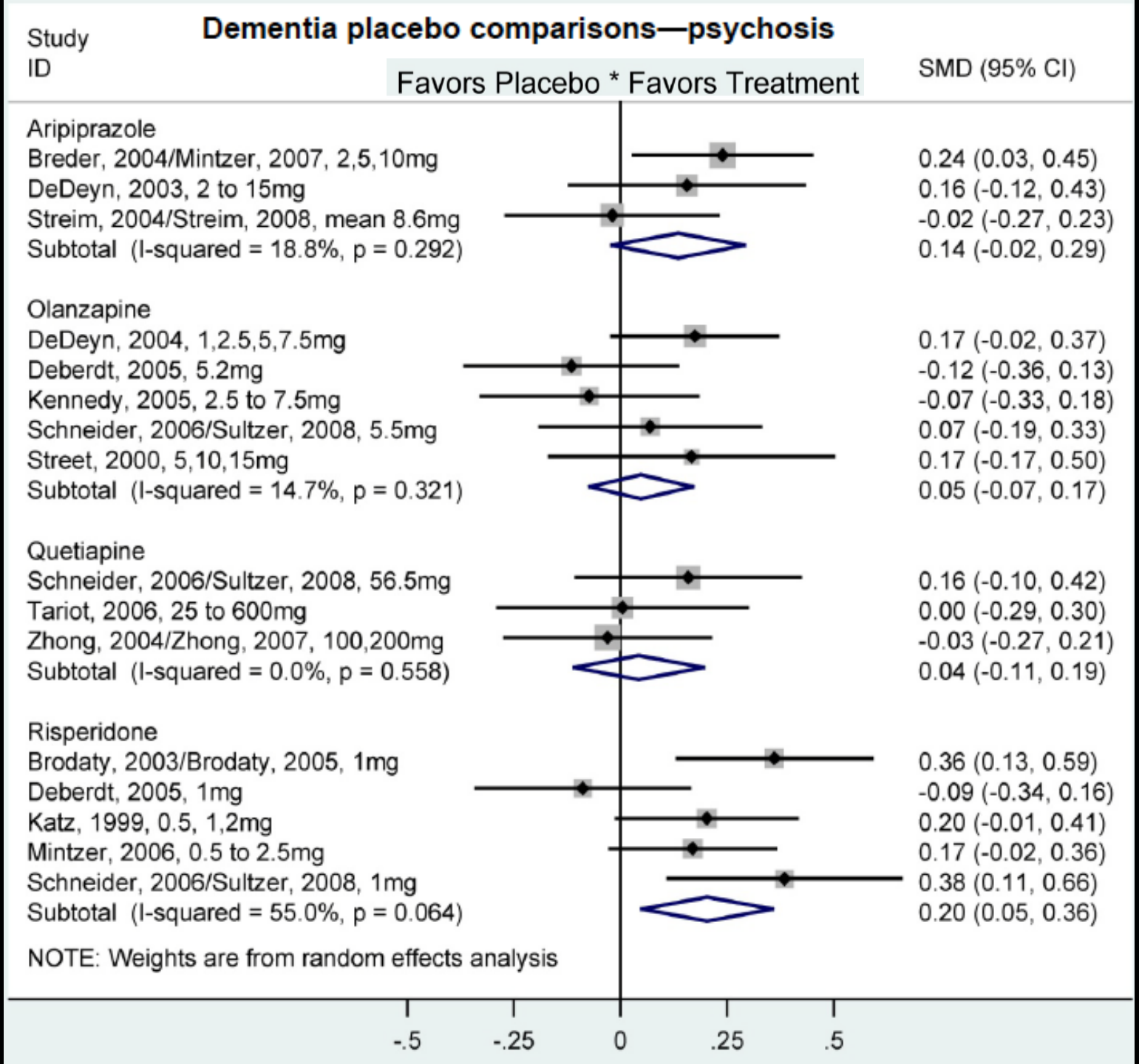
EPS Elderly Patients

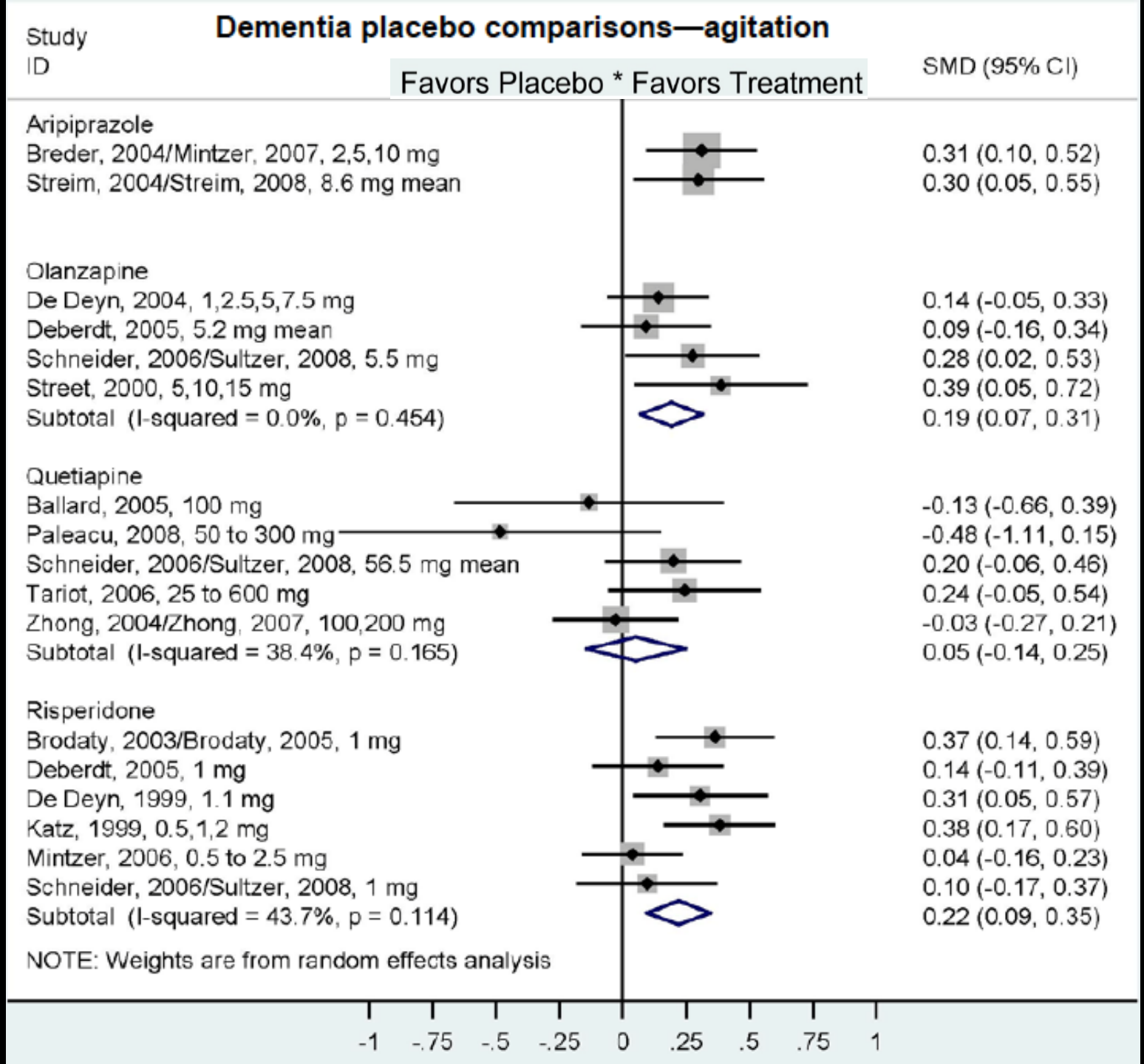
No evidence reported.	More common in patients taking risperidone, according to our meta-analysis. Quetiapine and aripiprazole were not associated with an increase. More common in olanzapine in one PCT.

Sedation Elderly Patients

No difference in one trial of olanzapine versus benzodiazepines. No difference in three trials of olanzapine and three of risperidone versus conventional antipsychotics.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone than placebo according to our meta-analysis.


Dementia placebo comparisons—total/global scores
Study ID
Favors Placebo * Favors Treatment
SMD (95% CI)
Aripiprazole
Breder, 2004/Mintzer, 2007, 2,5,10mg
0.16 (-0.05, 0.37)
DeDeyn, 2003, 10mg mean
0.06 (-0.21, 0.34)
Streim, 2004/Streim, 2008, 8.6mg mean
0.36 (0.11, 0.61)
Subtotal (I-squared = 22.1%, p = 0.277)
0.20 (0.04, 0.35)
Olanzapine
DeDeyn, 2004, 1,2.5,5,7.5mg
0.14 (-0.05, 0.34)
Deberdt, 2005, 5.2mg mean
-0.02 (-0.27, 0.23)
Schneider, 2006/Sultzer, 2008, 5.5mg mean
0.15 (-0.11, 0.40)
Street, 2000, 5,10,15mg
0.30 (-0.03, 0.63)
Subtotal (I-squared = 0.0%, p = 0.485)
0.12 (0.00, 0.25)
Quetiapine
Schneider, 2006/Sultzer, 2008, 56.5mg mean
0.15 (-0.11, 0.42)
Tariot, 2006, 96.9mg median
0.22 (-0.07, 0.52)
Zhong, 2004/Zhong, 2007, 100,120,200mg
0.04 (-0.21, 0.28)
Subtotal (I-squared = 0.0%, p = 0.610)
0.13 (-0.03, 0.28)
Risperidone
Brodaty, 2003/Brodaty, 2005, 0.95mg mean
0.46 (0.23, 0.69)
Deberdt, 2005, 1mg mean
-0.13 (-0.38, 0.12)
Dedeyn, 1999, 1.1mg mean
0.12 (-0.14, 0.38)
Katz, 1999, 1.2mg
0.32 (0.11, 0.53)
Mintzer, 2006, 1.03mg mean
-0.01 (-0.21, 0.18)
Schneider, 2006/Sultzer, 2008, 1mg mean
0.40 (0.13, 0.68)
Subtotal (I-squared = 74.6%, p = 0.001)
0.19 (0.00, 0.38)
NOTE: Weights are from random effects analysis
-.5
-.25
0
.25
.5


Dementia placebo comparisons—psychosis
Study ID
Favors Placebo * Favors Treatment
SMD (95% CI)
Aripiprazole
Breder, 2004/Mintzer, 2007, 2,5,10mg 0.24 (0.03, 0.45)
DeDeyn, 2003, 2 to 15mg 0.16 (-0.12, 0.43)
Streim, 2004/Streim, 2008, mean 8.6mg -0.02 (-0.27, 0.23)
Subtotal (I-squared = 18.8%, p = 0.292) 0.14 (-0.02, 0.29)
Olanzapine
DeDeyn, 2004, 1,2.5,5,7.5mg 0.17 (-0.02, 0.37)
Deberdt, 2005, 5.2mg -0.12 (-0.36, 0.13)
Kennedy, 2005, 2.5 to 7.5mg -0.07 (-0.33, 0.18)
Schneider, 2006/Sultzer, 2008, 5.5mg 0.07 (-0.19, 0.33)
Street, 2000, 5,10,15mg 0.17 (-0.17, 0.50)
Subtotal (I-squared = 14.7%, p = 0.321) 0.05 (-0.07, 0.17)
Quetiapine
Schneider, 2006/Sultzer, 2008, 56.5mg 0.16 (-0.10, 0.42)
Tariot, 2006, 25 to 600mg 0.00 (-0.29, 0.30)
Zhong, 2004/Zhong, 2007, 100,200mg -0.03 (-0.27, 0.21)
Subtotal (I-squared = 0.0%, p = 0.558) 0.04 (-0.11, 0.19)
Risperidone
Brodaty, 2003/Brodaty, 2005, 1mg 0.36 (0.13, 0.59)
Deberdt, 2005, 1mg -0.09 (-0.34, 0.16)
Katz, 1999, 0.5, 1,2mg 0.20 (-0.01, 0.41)
Mintzer, 2006, 0.5 to 2.5mg 0.17 (-0.02, 0.36)
Schneider, 2006/Sultzer, 2008, 1mg 0.38 (0.11, 0.66)
Subtotal (I-squared = 55.0%, p = 0.064) 0.20 (0.05, 0.36)
NOTE: Weights are from random effects analysis
-.5
-.25
0
.25
.5

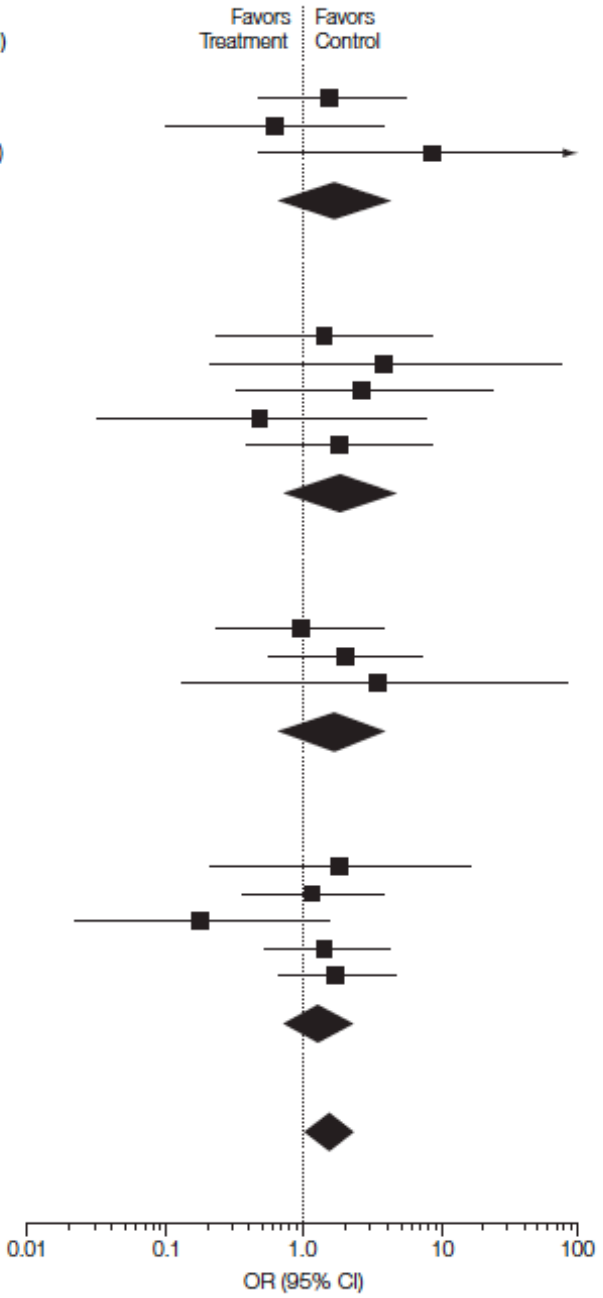

Dementia placebo comparisons—agitation
Study ID
Favors Placebo * Favors Treatment
SMD (95% CI)
Aripiprazole
Breder, 2004/Mintzer, 2007, 2,5,10 mg
0.31 (0.10, 0.52)
Streim, 2004/Streim, 2008, 8.6 mg mean
0.30 (0.05, 0.55)
Olanzapine
De Deyn, 2004, 1,2.5,5,7.5 mg
0.14 (-0.05, 0.33)
Deberdt, 2005, 5.2 mg mean
0.09 (-0.16, 0.34)
Schneider, 2006/Sultzer, 2008, 5.5 mg
0.28 (0.02, 0.53)
Street, 2000, 5,10,15 mg
0.39 (0.05, 0.72)
Subtotal (I-squared = 0.0%, p = 0.454)
0.19 (0.07, 0.31)
Quetiapine
Ballard, 2005, 100 mg
-0.13 (-0.66, 0.39)
Paleacu, 2008, 50 to 300 mg
-0.48 (-1.11, 0.15)
Schneider, 2006/Sultzer, 2008, 56.5 mg mean
0.20 (-0.06, 0.46)
Tariot, 2006, 25 to 600 mg
0.24 (-0.05, 0.54)
Zhong, 2004/Zhong, 2007, 100,200 mg
-0.03 (-0.27, 0.21)
Subtotal (I-squared = 38.4%, p = 0.165)
0.05 (-0.14, 0.25)
Risperidone
Brodaty, 2003/Brodaty, 2005, 1 mg
0.37 (0.14, 0.59)
Deberdt, 2005, 1 mg
0.14 (-0.11, 0.39)
De Deyn, 1999, 1.1 mg
0.31 (0.05, 0.57)
Katz, 1999, 0.5,1,2 mg
0.38 (0.17, 0.60)
Mintzer, 2006, 0.5 to 2.5 mg
0.04 (-0.16, 0.23)
Schneider, 2006/Sultzer, 2008, 1 mg
0.10 (-0.17, 0.37)
Subtotal (I-squared = 43.7%, p = 0.114)
0.22 (0.09, 0.35)
NOTE: Weights are from random effects analysis
-1
-.75
-.5
-.25
0
.25
.5
.75
1

Riesgos de SAP 2006-2011

- **2006:** Incremento de riesgo de muerte con SAP
  - En 2005 se publica el black box warning en USA por ↑ mortalidad
  - En 15 ECR riesgo de 3,5 % SAP vs 2,3 Plac (OR: 1,54) NNH: 100
- **2011:** Incremento de riesgo de muerte con SAP y con FAP y de ictus con RIS
  - En estudios de cohortes (6) se encuentra que hay un riesgo con FAP
  - Riesgo cerebro-vascular con RIS 3,13 y NNH: 53 (no con OLA, QUET, ARIP)
  - Riesgo cardio-vascular (RIS y OLA) (No con QUET o ARIP)
  - Sedación, aumento de peso (todos)
  - EPS con RIS
  - Evidencias de Aumento de Riesgo de Muerte con los SAP

Figure 2. Deaths by Individual Comparisons by Drugs and Overall Compared With Placebo

Source*	Deaths: Treatment, No. of Events/ Total No.	Deaths: Placebo, No. of Events/ Total No.	OR (95% CI) (Fixed-Effects Model)
Aripiprazole			
CN 138-004[38]	15/366	3/121	1.68 (0.48-5.91)
CN 138-005[39-41]	2/131	3/125	0.63 (0.10-3.84)
CN 138-006[40-42]	4/106	0/102	9.00 (0.48-169.32)
Subtotal	21/603	6/348	1.73 (0.70-4.30)
Test for Heterogeneity $\chi^2_2 = 2.42$, $I^2 = 17.2\%$ ($P = .30$)			
Test for Overall Effect $z = 1.18$ ($P = .24$)			
Olanzapine			
HGAO[37,43-45]	3/120	2/118	1.49 (0.24-9.06)
HGEU[6,45]	6/159	0/47	4.02 (0.22-72.73)
HGGU[45-47]	6/204	1/94	2.82 (0.33-23.75)
HGIC[45,48]	1/178	1/90	0.50 (0.03-8.13)
HGIM[8,45]	15/523	2/129	1.88 (0.42-8.30)
Subtotal	31/1184	6/478	1.91 (0.79-4.59)
Test for Heterogeneity $\chi^2_4 = 1.34$, $I^2 = 0\%$ ($P = .85$)			
Test for Overall Effect $z = 1.44$ ($P = .15$)			
Quetiapine			
5077 US-039[11,12]	4/124	4/125	1.01 (0.25-4.12)
5077 US-046[49]	16/241	3/92	2.11 (0.60-7.42)
Ballard[33]	1/26	0/29	3.47 (0.14-88.99)
Subtotal	21/391	7/246	1.67 (0.70-4.03)
Test for Heterogeneity $\chi^2_2 = 0.82$, $I^2 = 0\%$ ($P = .66$)			
Test for Overall Effect $z = 1.15$ ($P = .25$)			
Risperidone			
HGGU[45-47]	4/196	1/94	1.94 (0.21-17.58)
RIS-AUS-05[7]	6/167	5/170	1.23 (0.37-4.11)
RIS-INT-24[5,50]	1/115	5/114	0.19 (0.02-1.66)
RIS-USA-232[51]	9/235	6/238	1.54 (0.54-4.40)
RIS-USA-63[4]	25/462	5/163	1.81 (0.68-4.80)
Subtotal	45/1175	22/779	1.30 (0.76-2.23)
Test for Heterogeneity $\chi^2_4 = 3.69$, $I^2 = 0\%$ ($P = .45$)			
Test for Overall Effect $z = 0.94$ ($P = .35$)			
Overall	118/3353	41/1851	1.54 (1.06-2.23)
Test for Heterogeneity $\chi^2_{15} = 8.45$, $I^2 = 0\%$ ($P = .90$)			
Test for Overall Effect $z = 2.28$ ($P = .02$)			



Adverse Effects

Elderly Patients*

- Antipsychotics increase the risk of death in elderly patients with dementia.
  - Of every 100 patients treated with an atypical antipsychotic, 1 died due to treatment with the antipsychotic (NNH = 100) during the 10- to 12-week trials. ●●●
  - The mortality rate during treatment with typical antipsychotics was elevated, when compared with groups not receiving antipsychotics, but the data were not analyzed quantitatively (NNH not available). ●●○
- Risperidone is associated with an increased risk of cerebrovascular accidents (NNH = 34). Both risperidone (NNH = 53) and olanzapine (NNH = 48) are associated with an increased risk of cardiovascular events. ●●○
- In elderly adults, extrapyramidal symptoms (EPSs) are common with risperidone (NNH = 20) and olanzapine (NNH = 10). ●●○
- Atypical antipsychotics are associated with sedative effects (NNH = 8–16) and fatigue (NNH = 18–21). ●●○
- Atypical antipsychotics elevate the risk of urinary adverse effects (infections, incontinence) in elderly patients, but the evidence is too limited to permit conclusions about the degree of risk. ●○○

Riesgos de SAP 2013

- Sultana 2014, UK: 1531 pac. Demencia Vascular, no ↑ mortalidad
  - 31,8 % con SAP (2,6 % OLA, **22 % QUET**, 7,2 % RIS)
- Huybrechts 2013, USA
  - Ancianos en residencias en tt con SAP, N = 75445
  - El ttº con haloperidol duplica la mortalidad frente a RIS
  - Quetiapina tiene menor riesgo de mortalidad frente a RIS
- Melbye, 2013 Noruega: ↑mortalidad (x 2) a corto y largo plazo
  - Estudio poblacional (26940 pac no ingresados en residencias)
- Livingston 2007, UK: 224 pac. con EA, no ↑mortalidad
  - Laser Alzheimer longitudinal study (London) a 6 meses
  - La mortalidad se relaciona con edad mas avanzada y mayor afectación cognitiva (no con toma de SAP)
- López 2013, USA: no encuentra ↑ mortalidad
  - Estudio de cohorte (1886 pac con EA) 1983-2005

Article

The Long-Term Effects of Conventional and Atypical Antipsychotics in Patients With Probable Alzheimer's Disease

Oscar L. Lopez, M.D.

James T. Becker, Ph.D.

Yue-Fang Chang, Ph.D.

Robert A. Sweet, M.D.

Howard Aizenstein, M.D.

Beth Snitz, Ph.D.

Judith Saxton, Ph.D.

Eric McDade, D.O.

M. Ilyas Kamboh, Ph.D.

Steven T. DeKosky, M.D.

Charles F. Reynolds III, M.D.

William E. Klunk, M.D., Ph.D.

Objective: The authors sought to determine the effects of conventional and atypical antipsychotic use on time to nursing home admission and time to death in a group of outpatients with mild to moderate probable Alzheimer's disease.

Method: The authors examined time to nursing home admission and time to death in 957 patients with the diagnosis of probable Alzheimer's disease who had at least one follow-up evaluation (mean follow-up time, 4.3 years [SD=2.7]; range, 0.78–18.0 years) using Cox proportional hazard models adjusted for age, gender, education level, dementia severity, hypertension, diabetes mellitus, heart disease, extrapyramidal signs, depression, psychosis, aggression, agitation, and dementia medication use.

Results: A total of 241 patients (25%) were exposed to antipsychotics at some time during follow-up (conventional, N=138; atypical, N=95; both, N=8). Nursing home admission (63% compared with 23%) and death (69% compared with 34%) were more frequent in individuals taking conventional than atypical antipsychotics. In a model that included demographic and cognitive variables, hypertension, diabetes mellitus, heart disease, incident strokes, and extrapyramidal signs, only conventional antipsychotic use was associated with time to nursing home admission. However, the association was no longer significant after adjustment for psychiatric symptoms. Psychosis was strongly associated with nursing home admission and time to death, but neither conventional nor atypical antipsychotics were associated with time to death.

Conclusions: The use of antipsychotic medications, both conventional and atypical, was not associated with either time to nursing home admission or time to death after adjustment for relevant covariates. Rather, it was the presence of psychiatric symptoms, including psychosis and agitation, that was linked to increased risk of institutionalization and death after adjustment for exposure to antipsychotics.

(Am J Psychiatry 2013; 170:1051–1058)

Lopez O, 2013

- Los expuestos a AP eran más jovenes, menor nivel educativo y era mas probable que murieran o se institucionalizaran
  - La relación mayor con muerte era con AP clásicos y risperidona
- Tenían mayores grados de psicosis, agitación, agresión, uso de antidepresivos y menor uso de fármacos anti-demencia
- En los estudios estadísticos los AP no se relacionaron con mayor riesgo de muerte o institucionalización
  - cuando se ajustaba el modelo con la presencia de los síntomas que motivaron el inicio de ttº
  - Esto sugiere que la correlación primaria es con los síntomas psiquiátricos y no con los AP
- La psicosis es un predictor significativo de muerte en la EA, incluso tras el ajuste por el uso de AP

TABLE 1. Demographic and Clinical Characteristics of Patients With Probable Alzheimer's Disease Taking Conventional or Atypical Antipsychotics

Characteristic	Patient Sample						Patient Sample[a]					
	Unexposed to Antipsychotics (N=716)		Any Type of Antipsychotic (N=241)		Analysis		Conventional Antipsychotics (N=138)		Atypical Antipsychotics (N=95)		Analysis	
	Mean	SD	Mean	SD	t	p	Mean	SD	Mean	SD	t or F	p
Duration of the cognitive symptoms[b]	3.7	2.2	4.1	2.4	−1.94		4.0	2.6	4.3	2.1	2.61	
Age at study entry	73. 5	8.7	72.0	8.6	2.27	0.02	71.2	8.0	73. 1	9.5	3.78	0.02
Education level (years)	12.5	2.9	12.0	2.9	2.32	0.02	11.8	3.0	12.2	2.6	4.08	0.01
Baseline Mini-Mental State Examination (MMSE) score	18.9	5.2	16.1	5.2	7.12	<0.001	15.8	5.6	16.2	4.7	26.4	<0.0001
Clinical dementia rating	1.17	0.56	1.38	0.67	−4.64	<0.0001	1.37	0.66	1.42	0.71	11.5	<0.0001
Hamilton Depression Rating Scale score	5.9	4.4	7.0	4.5	−3.32	0.0001	7.1	4.1	6.9	5.7	5.61	0.004
Hachinski Ischemia Scale score	2.47	1.7	2.23	1.6	1.85		2.0	1.4	2.4	1.7	4.13	0.01
	N	%	N	%	t or χ^2	p	N	%	N	%	t or F	p
Female	482	67	163	68	0.008		91	66	65	68	0.15	
White	675	675	225	93	0.26		129	93.5	88	93	0.47	
Severity of dementia by MMSE scores												
Mild (≥20)	377	53	66	27.5			36	26	*25*	*26*		
Moderate (19–10)	297	41	146	61			83	60	60	63		
Severe (≤9)	42	6	29	12			19	14	10	10.5		
APOE-4 allele (N=734)	316	57	115	62	1.48		62	61	66	64.5	2.38	
Hypertension[c]	305	42.5	82	34	5.50	0.01	30	22	48	50.5	25.3	<0.0001
Diabetes mellitus[d]	48	7	15	6	0.070		7	5	8	8	1.03	
Heart disease[e]	108	15	25	10	3.36		14	10	11	12	2.88	
Deceased	267	37	137	57	28.6	<0.0001	97	70	36	38	52.7	<0.0001
Nursing home admission	198	28	110	46	26.7	<0.0001	83	60	24	25	58.1	<0.0001

TABLE 2. Clinical Characteristics of Patients With Probable Alzheimer's Disease Taking Conventional or Atypical Antipsychotics

	Patient Sample						Patient Sample[a]					
	Unexposed to Antipsychotics (N=716)		Any Type of Antipsychotic (N=241)		Analysis		Conventional Antipsychotics (N=138)		Atypical Antipsychotics (N=95)		Analysis	
Characteristic	N	%	N	%	t or χ^2	p	N	%	N	%	t or F	p
Psychiatric symptoms (baseline or incident)												
Major depression	152	21	60	25	1.40		20	14.5	24	25	5.10	
Psychosis	361	50	200	83	78.80	<0.0001	108	78.0	84	88	76.60	<0.0001
Aggression	141	20	111	46	64.20	<0.0001	53	38.0	54	57	72.10	<0.0001
Agitation	513	72	203	84	14.90	<0.001	105	76.0	90	95	23.60	<0.0001
Neurological syndromes												
Baseline extrapyramidal signs[b]	297	42	99	41	0.009		62	45.0	35	37	1.63	
Baseline or incident extrapyramidal signs[b]	457	64	170	71	3.71	0.05	113	82.5	52	55	23.10	<0.001
Incident stroke/transient ischemic attack	37	5	16	7	0.73		10	7.0	5	5	0.98	
Medications (baseline or incident)												
Antidepressants	257	36	116	48	11.30	0.001	49	35.5	61	64	29.20	<0.0001
Dementia medication	441	62	99	41	30.80	<0.0001	10	7.0	85	90	185.50	<0.0001

[a] Eight patients were taking conventional and atypical antipsychotics during follow-up and were excluded from the analysis.
[b] Presence of bradykinesia, tremors, increased motor tone, abnormal gait, or dyskinesias.

TABLE 3. Results of the Cox Regression Model Examining Risks Associated With Nursing Home Admission in Patients With Probable Alzheimer's Disease Taking Conventional or Atypical Antipsychotics[a]

	Model 1			Model 2			Model 3		
Variable	Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p
Conventional antipsychotics	2.21	1.68–2.90	<0.0001	2.27	1.71–3.01	<0.0001	1.30	0.95–1.79	0.10
Atypical antipsychotics	1.01	0.62–1.65	0.97	1.05	0.64–1.72	0.84	1.02	0.61–1.71	0.94
Age	1.00	0.99–1.01	0.93	0.99	0.98–1.01	0.30	1.00	0.98–1.01	0.59
Education	1.05	1.01–1.09	0.01	1.05	1.01–1.10	0.01	1.07	1.03–1.11	0.001
Gender	0.92	0.71–1.18	0.50	0.88	0.68–1.13	0.30	0.83	0.64–1.08	0.17
MMSE score	0.94	0.92–0.97	<0.0001	0.94	0.92–0.97	<0.0001	0.95	0.93–0.97	<0.0001
Extrapyramidal signs				1.28	1.00–1.64	0.05	1.29	1.00–1.65	0.04
Incident stroke				1.01	0.68–1.52	0.94	0.87	0.58–1.33	0.52
Hypertension				1.07	0.83–1.39	0.58	1.16	0.90–1.51	0.25
Diabetes mellitus				1.21	0.77–1.90	0.41	1.22	0.77–1.93	0.40
Heart disease				1.52	1.09–2.12	0.01	1.57	1.12–2.20	0.009
Aggression							1.26	0.95–1.69	0.11
Agitation							1.35	1.01–1.79	0.04
Depression							1.06	0.75–1.49	0.75
Psychosis							1.56	1.19–2.04	0.001
Dementia medication							0.38	0.28–0.52	<0.0001

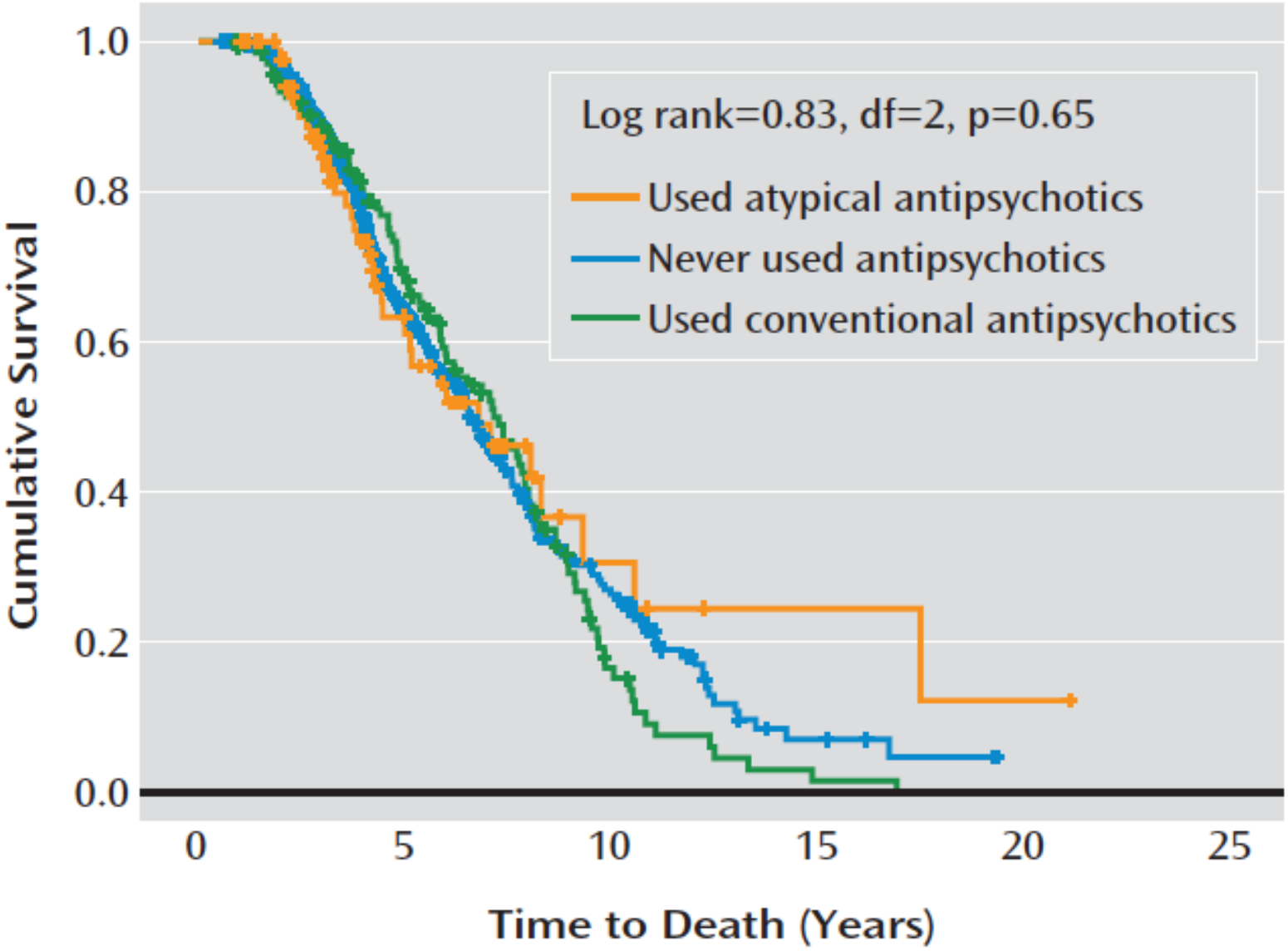
[a] Model 1 controlled for age, education level, gender, and baseline Mini-Mental State Examination (MMSE) score. Model 2 included items from model 1 plus extrapyramidal signs, incident stroke, heart disease, diabetes mellitus, and hypertension. Model 3 included items from models 1 and 2 plus psychosis, depression, aggression, agitation, and dementia medication.

TABLE 4. Results of the Cox Regression Model Examining Risks Associated With Death in Patients With Probable Alzheimer's Disease Taking Conventional or Atypical Antipsychotics[a]

	Model 1			Model 2			Model 3		
Variable	Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p	Hazard Ratio	95% CI	p
Conventional antipsychotics	0.94	0.73–1.20	0.60	0.92	0.71–1.19	0.52	0.83	0.63–1.09	0.17
Atypical antipsychotics	1.10	0.77–1.59	0.60	1.20	0.83–1.74	0.32	1.02	0.69–1.50	0.93
Age	1.03	1.02–1.05	<0.0001	1.03	1.02–1.04	<0.0001	1.03	1.01–1.04	<0.0001
Education	1.05	1.01–1.09	0.007	1.06	1.02–1.10	0.002	1.06	1.02–1.10	0.002
Gender	1.53	1.23–1.89	<0.0001	1.50	1.21–1.88	<0.0001	1.48	1.19–1.85	0.001
MMSE score	0.93	0.92–0.95	<0.0001	0.94	0.92–0.96	<0.0001	0.94	0.92–0.96	<0.0001
Extrapyramidal signs				1.55	1.26–1.92	<0.0001	1.61	1.30–2.00	<0.0001
Incident stroke				1.32	0.95–1.84	0.10	1.22	0.87–1.72	0.24
Hypertension				1.16	0.93–1.43	0.18	1.15	0.92–1.42	0.21
Diabetes mellitus				1.45	0.99–2.13	0.05	1.39	0.94–2.06	0.10
Heart disease				0.90	0.67–1.21	0.48	0.90	0.67–1.22	0.50
Aggression							1.25	0.97–1.61	0.08
Agitation							0.99	0.77–1.26	0.91
Depression							1.26	0.95–1.67	0.11
Psychosis							1.26	1.00–1.59	0.04
Dementia medication							1.00	0.77–1.29	0.97

[a] Model 1 controlled for age, education level, gender, and baseline Mini-Mental State Examination (MMSE) score. Model 2 included items from model 1 plus extrapyramidal signs, incident stroke, heart disease, diabetes mellitus, and hypertension. Model 3 included items from models 1 and 2 plus psychosis, depression, aggression, agitation, and dementia medication.

FIGURE 1. Kaplan-Meier Survival Analysis of Time to Death in Patients With Probable Alzheimer's Disease and Antipsychotic Use



The study of factors related to mortality in patients with Alzheimer's disease is complex, with multiple factors converging to increase the risks of nursing home admission and death. In this outpatient-based population with mild to moderate dementia, exposure to antipsychotics was not associated with an increased risk of nursing home admission after the presence of disruptive behaviors was taken into account. Rather, it was the psychotic/agitated phenotype that emerged as a critical factor influencing the natural and treated history of Alzheimer's disease.

ANTIPSYCHOTIC USE IN PATIENTS WITH PROBABLE ALZHEIMER'S DISEASE

LOPEZ, BECKER, CHANG, ET AL.

Am J Psychiatry 170:9, September 2013

Lopez O, 2013

- Sugiere que la EA + psicosis supone un fenotipo mas agresivo de la enfermedad, con una evolución más rápida
- No obstante el fenómeno de la mortalidad y los síntomas neuro-psiquiátricos en la EA es complejo
  - La psicosis suele acompañarse de otros SPCDs como agresividad, agitación, inquietud motora que puede condicionar también riesgo de mortalidad (caidas, etc..)
  - La presencia de Sintomas extrapiramidales son un predictor independiente de muerte e institucionalizacion
  - La mayoria de los estudios que relacionan la mortalidad con el uso de AP se han realizado en poblaciones en instituciones, en fases avanzadas de la demencia y en periodos cortos (12 semanas)

Uso de Antipsicóticos en Demencia
(Estudios de Bases de Datos)

- Myra 2011, USA VA **N = 19517**
  - Tt de SPCD (incluye AP y VPA)
  - 35,4 % (2004) al 43.4 % (2008)
  - ↑ Quetiapina, VPA y haloperidol y ↓ de Olanzapina
- Crugel 2012, UK **N = 946**
  - 20 % (186) en tt con AP
  - De ellos el 53 % en residencias
  - Quetiapina (50 %) (86 % dosis < 75 mgr)
- Schultze 2013, Alemania **N= 1846**
  - 25,4 % (demencia) AP frente al 4,3 % (población control)
  - F. Riesgo: edad, sexo femenino, residencia, cuidados

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013; **22**: 1308–1316
Published online 3 October 2013 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3527

ORIGINAL REPORT

Prescribing of antipsychotic drugs in patients with dementia: a comparison with age-matched and sex-matched non-demented controls

Jana Schulze[1]*, Gerd Glaeske[1], Hendrik van den Bussche[2], Hanna Kaduszkiewicz[2], Daniela Koller[1], Birgitt Wiese[3] and Falk Hoffmann[1]

[1] *Centre for Social Policy Research, Division Health Economics, Health Policy and Outcomes Research, University of Bremen, Bremen, Germany*
[2] *Institute of Primary Medical Care, University Medical Center Hamburg-Eppendorf, Hamburg, Germany*
[3] *Institute of Biometrics, Hannover Medical School, Hannover, Germany*

ABSTRACT

Purpose Since the beginning of the 21st century, serious adverse events and an increased risk of mortality have been documented in patients with dementia treated with antipsychotics. The aim of this study was to assess antipsychotic prescribing in patients with incident dementia compared with a non-demented control group.

Methods We analysed the claims data of a German health insurance company for incident dementia patients and age-matched and sex-matched non-demented controls aged 65 years and older in 2004 to 2006. The data were used to analyse the prescribing patterns of antipsychotics in the year of dementia incidence. We estimated odds ratios stratified by age, sex, care setting and care dependence and in a multivariate logistic regression.

Results The 1848 patients with and 7385 persons without dementia were on average 78.8 years old (standard deviation: 7.4), and 47.6% were women. A total of 25.4% of the dementia patients received antipsychotics compared with 4.3% of the controls (OR_{crude}: 7.61; 95%

Schultze, 2013 Alemania

- Estudio casos control de Demencia incipiente (2004-6) en una aseguradora (Alemania) que cubre 1,7 mill de hab
    - Prescripción de AP durante el año posterior al diagnostico
    - Uso de Base de Dtos
    - N= 1846
- 25,4 % (demencia) AP frente al 4,3 % (población control)
    - 56 % en residencias (frente al 26 % controles)
- F. Riesgo: edad, sexo femenino, residencia, cuidados
- AP tipicos (18,5 %) > atipicos (12 %)
    - Melperona (33 %), Risperidona (20 %), Pipamperona (8,6 %), Quetiapina (7,3 %), Haloperidol (6,3 %)

	Dementia cohort		
	ATC code	Agent	Frequency (%)
1.	N05AD03	Melperone	33.1
2.	N05AX08	Risperidone	20.3
3.	N05AD05	Pipamperone	8.6
4.	N05AH04	Quetiapine	7.3
5.	N05AD01	Haloperidol	6.3

ATC = Anatomical Therapeutic Chemical.

Prescribing of antipsychotic drugs in patients with dementia: a comparison with age-matched and sex-matched non-demented controls

Jana Schulze[1,] PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013; **22**: 1308–1316

Antipsychotics in people with dementia: frequency of use and rationale for prescribing in a UK mental health service

Monica Crugel,[1] Gilly Paton,[1] Pratima Singh,[1] Regina Jeboda,[1] Adrian Treloar[1,2]

The Psychiatrist (2012), **36**, 165–169, doi: 10.1192/pb.bp.111.034579

[1]Oxleas NHS Foundation Trust, London; [2]Institute of Psychiatry, King's College London

Correspondence to Monica Crugel (mcrugel@doctors.org.uk)

First received 13 Mar 2011, final revision 28 Sep 2011, accepted 4 Nov 2011

Aims and method To determine how often and why antipsychotic medicines are prescribed to people with dementia. A cross-sectional survey of all clinical records was conducted in one National Health Service mental health trust.

Results Of 946 people with dementia in the trust, 186 (20%) were prescribed an antipsychotic. Prevalence increased with the severity of dementia. The most common indication for initiating treatment was agitation/distress (70%), followed by verbal aggression (45%), psychotic symptoms (44%) and physical aggression (33%). The mean number of indications per patient was 2.6. In 58% of cases, the antipsychotic had been prescribed for more than a year, and a third of patients had not been reviewed in the past 6 months.

Clinical implications People with dementia who are prescribed antipsychotic drugs generally display a range of challenging behaviours, but most notably are distressed. Systems for ongoing clinical review need improvement.

Declaration of interest None.

Crugel, 2012 UK

- Estudio incluido en los audits de uso de AP en UK
- Estudio transversal (2010) de base de datos electrónica
- N = 946
  - 20 % (186) en tt con AP
  - Fase leve (4 %), moderada (17 %) y severa (42 %)
  - De ellos el 53 % en residencias
- Quetiapina (50 %) (86 % dosis < 75 mgr)
- Dosis media
  - Quetiapina (50 mgr)
  - Risperidona (1 mgr)
  - Olanzapina (5 mgr)

Table 1 Prevalence of antipsychotic use by severity of dementia

	Antipsychotic prescribed, *n* (%)		
Severity of dementia	No	Yes	Total, *n*
Mild	318 (96)	15 (4)	333
Moderate	292 (83)	61 (17)	353
Severe	149 (58)	110 (42)	259
Total	759 (80)	186 (20)	945

Table 2 Most commonly prescribed antipsychotics and doses

Antipsychotic	Cases, *n* (%)	Mean dose (s.d.), mg	Dosage range, mg
Quetiapine	92 (50)	49.8 (4.4)	12.5–200
Risperidone	64 (34)	0.95 (0.63)	0.25–4
Olanzapine	19 (10)	5 (4.1)	2.5–20
All other antipsychotics	11 (6)		

Table 3 Most common clinical reasons for initiating treatment with an antipsychotic drug in people with dementia

Clinical reason	Patients, *n* (%)
Agitation/distress	129 (70)
Verbal aggression	84 (45)
Psychotic symptoms	82 (44)
Physical aggression	62 (33)
Resisting help with personal care	53 (29)
Diagnosis of depression[a]	23 (12)

Sánchez, 2014

- Análisis transversal descriptivo (Enero-2014) mediante Abucasis II (GAIA)
  - de toda la población con E. Alzheimer del D^{pto} Valencia Hospital General, que presentaba prescripción farmaceútica
- La población obtenida fue de 1506 pacientes.
- Uso de Antipsicóticos en el 27,4 %
  - De ellos el 57 % quetiapina
- El 68,8 % tomaban IACHs y el 51,9 % Memantina.
- Encontramos una relación significativa inversa (χ^2 $p < 0.01$) entre el uso de APS y la toma de IACHs
  - Si toma IACHs: 24 % APS vs no: 34,9 %
  - No la encontramos con Memantina, ni con la combinación de ambas

Sánchez, 2014

- El uso de APS en la EA sigue siendo un tema controvertido por su seguridad y por la elevada frecuencia de prescripción
- Nuestro % de uso está dentro del rango de los países de nuestro entorno (20 - 40 %)
- Siendo igualmente la quetiapina el más usado
- Nuestros resultados apoyan la idea de que el uso de IACHs podría reducir la aparición de síntomas conductuales severos (que precisen APS), o bien podrían actuar específicamente como tratamiento de los mismos
- Aunque también podría explicarse porque los pacientes más evolucionados presentan mas SPCDs que precisen AP y en esa fase ya no llevan IACHs

Uso de AP Demencia (Bases de Datos)

- Canadá
  - El uso de AP en Residencias ha aumentado desde un 37 % (2001-2) a un 50,3 % (2010-2011)
  - Debido al ↑ pacientes con demencia en residencias
  - Sensación de que los SAP son mas seguros
- Kales 2011, USA
  - Trends in use of AP in dementia (1997-2007)
  - 17,7 % de pacientes en 1999 usaban AP
  - Tras el black box warning disminuyó su uso
  - Quetiapina ha ↑ su frecuencia
  - Olanzapina y Risperidona han ↓ su frecuencia

Uso de AP Demencia (Bases de Datos)

Autor	Nº Pacientes	% SAP	Frecuncia SAP
Myra 2011, USA VA	**19517**	35,4 % (2004) 43.4 % (2008)	↑ Quet, VPA, Halop ↓ de Olanz
Crugel 2012, UK	**946**	20 % 53 % (resi.)	Quet 50 % 86 % < 75 mgr
Schultze 2013, Alemania	**1846**	25,4 % demencia / 4,3 % control	edad, sexo femenino, residencia, cuidados
Sanchez, 2014 España	**1500**	29,7 %	50 % Queti
Kales 2011, USA	Trends in 1997-2007	17,7 % (1999)	↑ Queti ↓ Olanz y Rispe
Canadá		37 % (2001-2) 50,3 % (2010-1)	

Uso de Antipsicóticos en Demencia
(A través de Encuestas a Profesionales)

- Bishara 2009, UK
  - Psiquiatras en UK (N = 59)
  - El AP mas usado en demencia es la quetiapina
- Haw C, 2009 UK
  - Psiquiatras en UK (N = 202)
  - 66 % no están de acuerdo con la NICE, muy restrictiva
  - 78 % están de acuerdo con la asociacion de psiquiatras, ser mas realista
  - 95 % no están de acuerdo en que los AP nunca se puedan prescribir en la demencia
  - Indicaciones mas frecuentes de AP
    - Psicosis (93 %), Agresión (89 %), Agitación (79 %); A. Sexual (50 %)
  - El AP mas usado en demencia es la quetiapina
    - El segundo es el haloperidol

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Expert opinion on the management of behavioural and psychological symptoms of dementia (BPSD) and investigation into prescribing practices in the UK

Delia Bishara[1]*, David Taylor[1], Robert J. Howard[2] and Rauja Abdel-Tawab[3]

[1]*Pharmacy Department, Maudsley Hospital, London, UK*
[2]*Institute of Psychiatry, King's College, London, UK*
[3]*School of Pharmacy and Biomolecular Sciences, University of Brighton, UK*

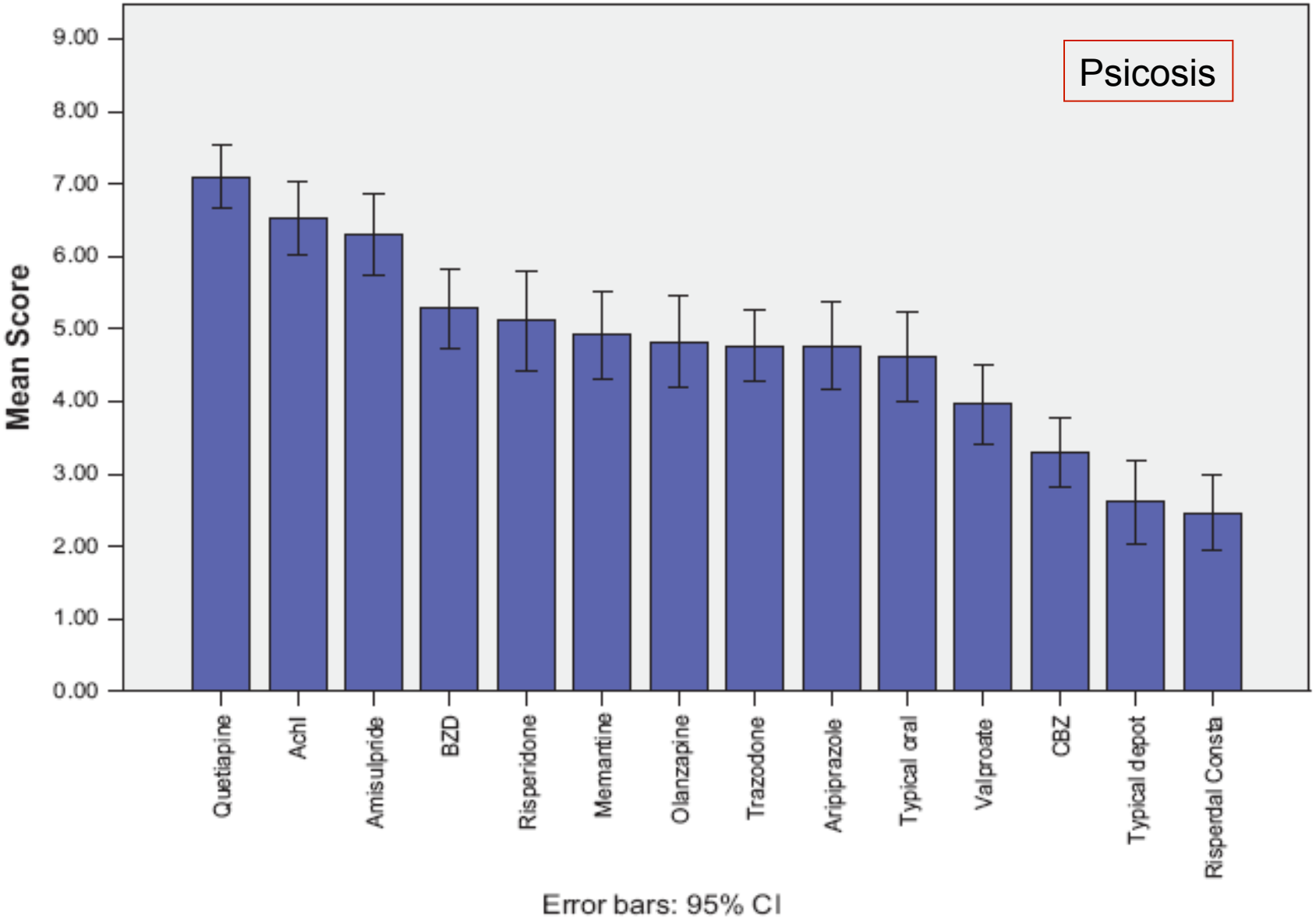
SUMMARY

Background The management of Behavioural and Psychological Symptoms of Dementia (BPSD) has been the subject of considerable debate over the last few years in view of the poor evidence base for pharmacological agents and concerns about their safety.

Objectives This study sought to obtain expert opinion on the management of BPSD and to investigate current prescribing practices in the UK.

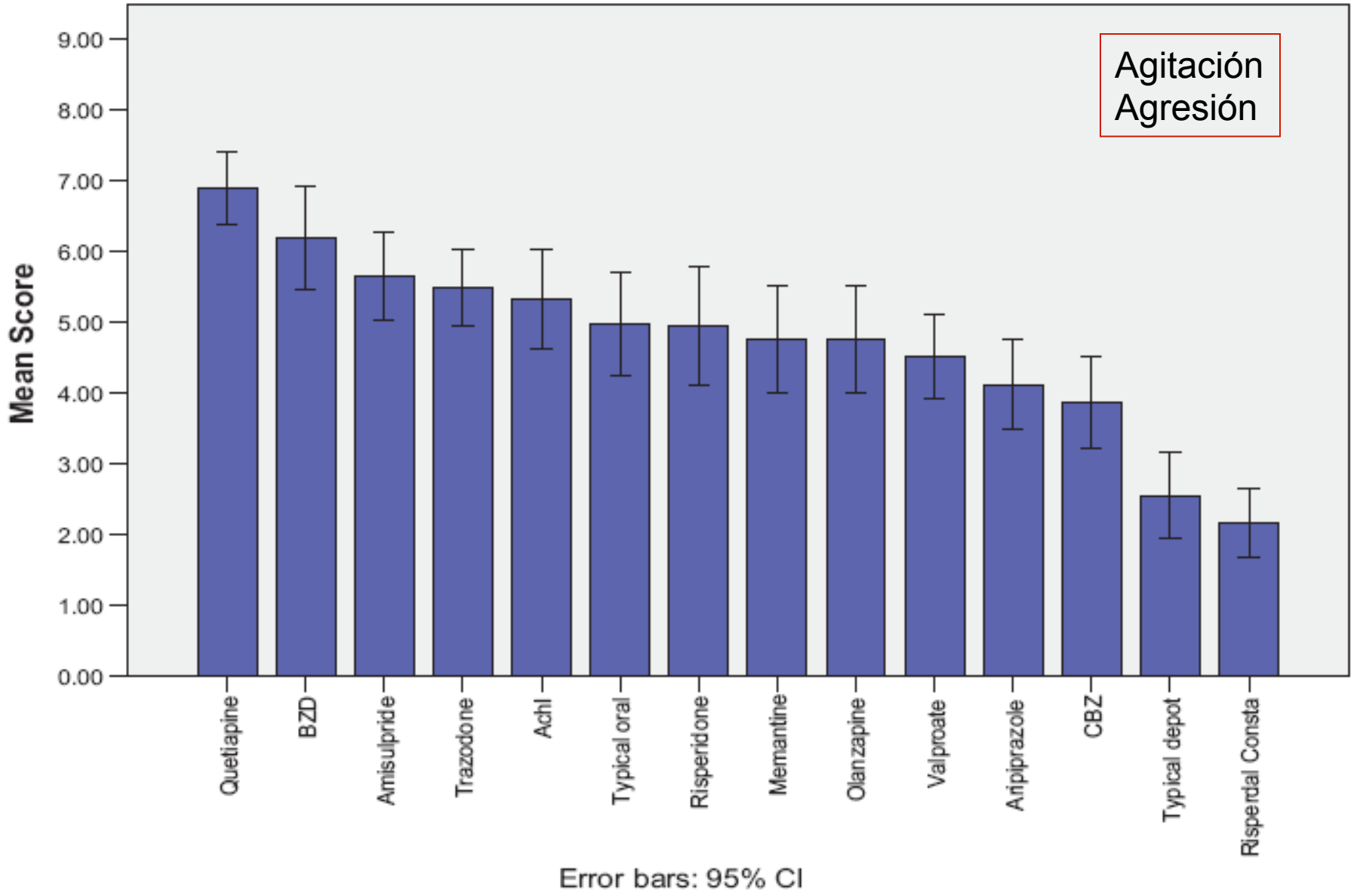
Method A total of 166 expert opinion surveys were emailed to UK consultants in Old Age Psychiatry asking them to rate the appropriateness of psychotropics in different aspects of BPSD. A service evaluation was also carried out in 8 UK centres to investigate prescribing patterns.

Results Overall, 59 consultants returned completed questionnaires, a response rate of 35%. Results revealed that experts rated quetiapine as the most appropriate agent for all BPSD followed by acetylcholinesterase inhibitors for psychotic symptoms, benzodiazepines for agitation or aggression and trazodone for behavioural symptoms such as disinhibition. The



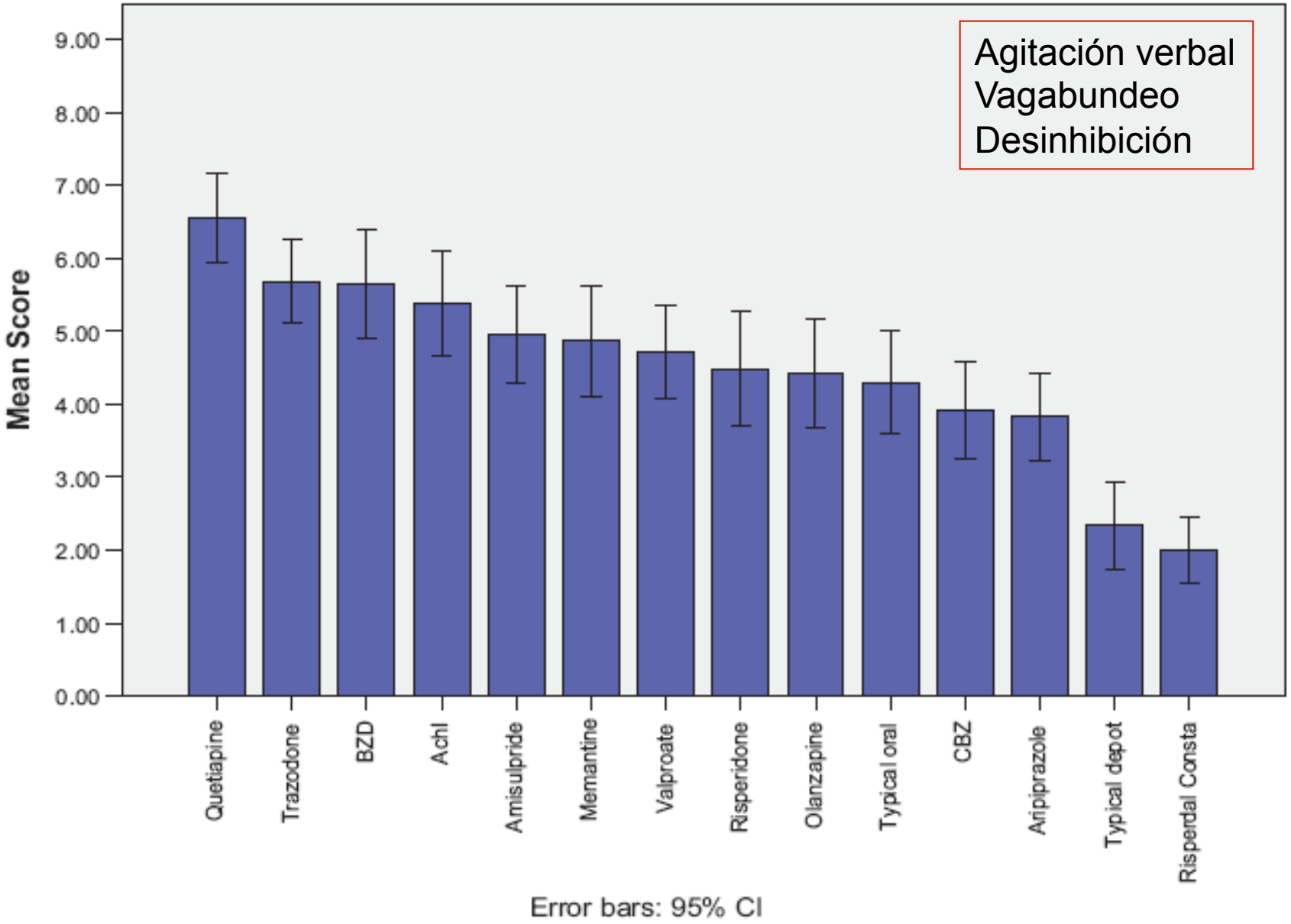
AchI = Acetylcholinesterase Inhibitor; BZD = Benzodiazepine; CBZ = Carbamazepine.

Figure 1. Mean rating scores of psychotropics for the management of psychotic features of dementia.



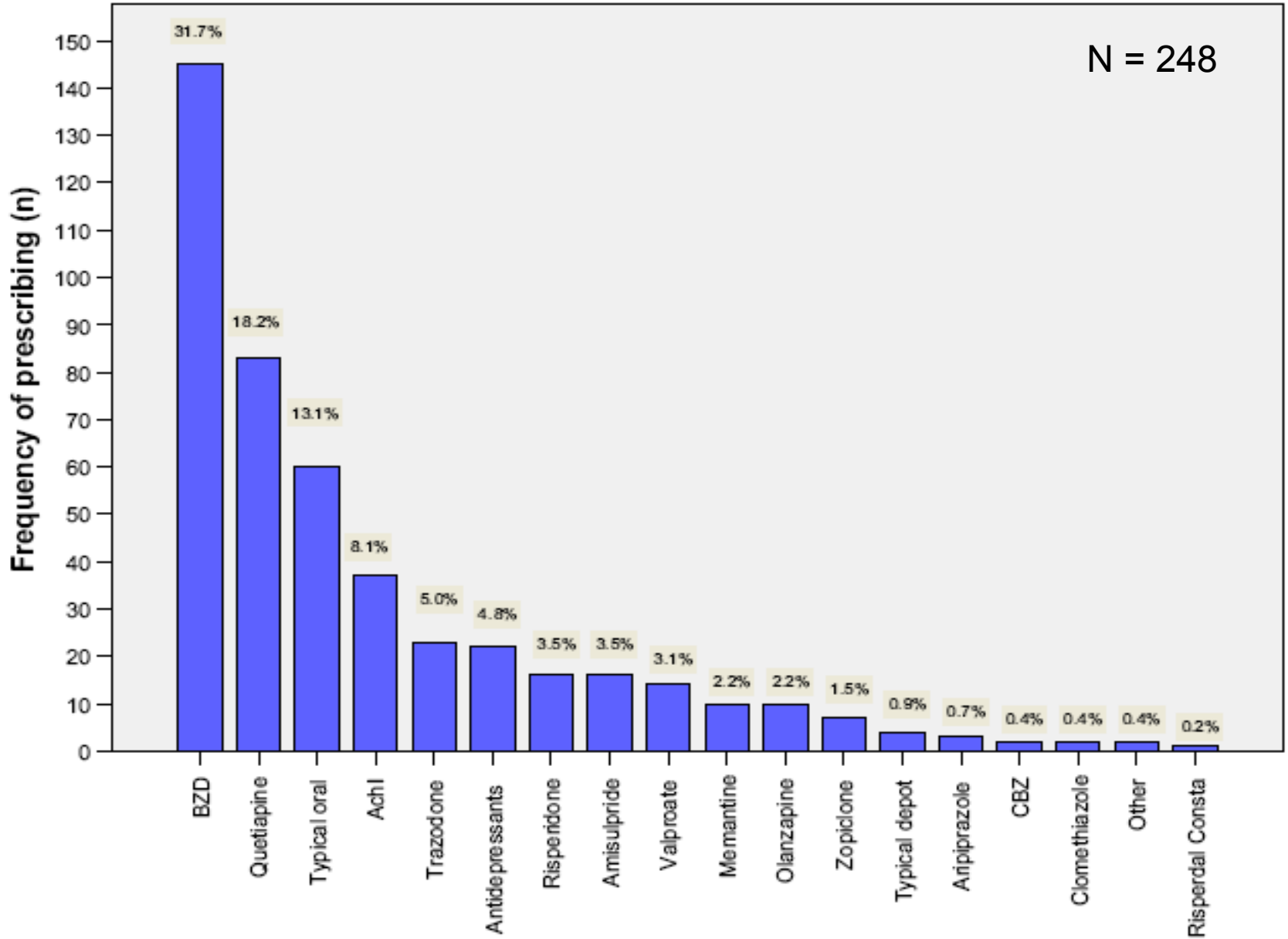
AchI = Acetylcholinesterase Inhibitor; BZD = Benzodiazepine; CBZ = Carbamazepine.

Figure 2. Mean rating scores of psychotropics for the management of agitation and aggression in dementia.



AchI = Acetylcholinesterase Inhibitor; BZD = Benzodiazepine; CBZ = Carbamazepine.

Figure 3. Mean rating of scores of psychotropics for behavioural features of dementia.



AchI = Acetylcholinesterase Inhibitor; BZD = Benzodiazepine; CBZ = Carbamazepine.

Figure 4. Prescribing pattern for psychotropics. Results of service evaluations in trusts.

Psychiatric Bulletin (2009), **33**, 57–60. doi: 10.1192/pb.bp.107.017947

CAMILLA HAW, GRAEME YORSTON AND JEAN STUBBS

Guidelines on antipsychotics for dementia: are we losing our minds?

AIMS AND METHOD
The National Institute for Health and Clinical Excellence (NICE) and the Royal College of Psychiatrists have each issued guidance on the use of antipsychotics for behavioural and psychiatric symptoms of dementia (BPSD). We sent all old age psychiatrists an anonymous questionnaire asking for their opinions on these documents and for details of their use of antipsychotics for BPSD.

RESULTS
The response rate was 202 out of 648 (31.2%). The two documents, though similar in content provoked very different responses, with the College guidance being much more favourably received. All respondents prescribed antipsychotics for BPSD, most commonly quetiapine.

CLINICAL IMPLICATIONS
When prescribing antipsychotics for behavioural and psychiatric symptoms of dementia, psychiatrists should take both NICE and College guidelines into account and use their clinical judgement.

Individuals with dementia commonly manifest behavioural and psychiatric symptoms of dementia (BPSD) such as aggression, agitation, psychotic symptoms, sleep disturbance and wandering. The off-label use of antipsychotic drugs to treat BPSD is widespread. Studies from around the world have reported that 25–40% of elderly residents in long-term institutional care receive antipsycho- dementia (Committee on Safety of Medicines, 2004). The Royal College of Psychiatrists' Faculty of the Psychiatry of Old Age and other stakeholders responded by issuing guidance laying down good practice guidelines for the use of antipsychotics in the treatment of BPSD (Working Group, 2004). Further guidance from the Royal College of Psychiatrists was later thought necessary due to reports

Table 2. Antipsychotics for BPSD: psychiatrists' reports of their three most commonly prescribed antipsychotics and usual dosage range

Antipsychotic	Psychiatrists prescribing the antipsychotic,[1] *n*	Usual daily dosage range (median values), mg
Quetiapine	165	25–150
Haloperidol	89	0.5–2
Risperidone	85	0.5–2
Amisulpride	85	50–150
Olanzapine	64	2.5–10
Sulpiride	23	100–200
Promazine	14	25–150
Trifluoperazine	13	1–4
Aripiprazole	9	5–17.5
Other typical antipsychotics	10	–

BPSD, behavioural and psychiatric symptoms of dementia.

1. Three most commonly prescribed drugs.

Uso de AP Demencia (Encuestas)

- Bishara 2009, UK
  - Psiquiatras en UK (N = 59)
  - El AP mas usado en demencia es la quetiapina
- Haw C, 2009 UK
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  - El AP mas usado en demencia es la quetiapina
    - El segundo es el haloperidol

Atypical antipsychotics for aggression and psychosis in Alzheimer's disease (Review)

Ballard CG, Waite J, Birks J

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2006, Issue 1

http://www.thecochranelibrary.com

Main results

Sixteen placebo controlled trials have been completed with atypical antipsychotics although only nine had sufficient data to contribute to a meta-analysis and only five have been published in full in peer reviewed journals. No trials of amisulpiride, sertindole or zotepine were identified which met the criteria for inclusion.

The included trials led to the following results:

1. There was a significant improvement in aggression with risperidone and olanzapine treatment compared to placebo.

2. There was a significant improvement in psychosis amongst risperidone treated patients.

3. Risperidone and olanzapine treated patients had a significantly higher incidence of serious adverse cerebrovascular events (including stroke), extrapyramidal side effects and other important adverse outcomes.

4. There was a significant increase in drop-outs in risperidone (2 mg) and olanzapine (5-10 mg) treated patients.

5. The data were insufficient to examine impact upon cognitive function.

Authors' conclusions

Evidence suggests that risperidone and olanzapine are useful in reducing aggression and risperidone reduces psychosis, but both are associated with serious adverse cerebrovascular events and extrapyramidal symptoms. Despite the modest efficacy, the significant increase in adverse events confirms that neither risperidone nor olanzapine should be used routinely to treat dementia patients with aggression or psychosis unless there is severe distress or risk of physical harm to those living and working with the patient. Although insufficient data were available from the considered trials, a meta-analysis of seventeen placebo controlled trials of atypical neuroleptics for the treatment of behavioural symptoms in people with dementia conducted by the Food and Drug Administration suggested a significant increase in mortality (OR 1.7). A peer-reviewed meta-analysis (Schneider 2005) of 15 placebo controlled studies (nine unpublished) found similarly increased risk in mortality (OR=1.54, 95% CI 0.004 to 0.02, p=0.01) for the atypical neuroleptics.

guías oficiales de la Sociedad Española de Neurología

Nº 8

Guía oficial para la práctica clínica en demencias: conceptos, criterios y recomendaciones 2009

Editores: José L. Molinuevo y Jordi Peña-Casanova

Grupo de Estudio de Neurología de la Conducta y Demencias

Sociedad Española de Neurología

THOMSON REUTERS

ENFERMEDAD DE ALZHEIMER

R. Alberca

Antipsicóticos

Se utilizan para tratar los síntomas psicóticos, la agitación y la agresividad. Con frecuencia resulta difícil deducir su eficacia y algunos de sus efectos adversos, porque los estudios clínicos incluyen pacientes con demencias de causa dispar, o en estadios diferentes o los seguimientos son cortos.

Los antipsicóticos típicos, como el haloperidol, son modestamente eficaces (nivel de evidencia I). Su uso prolongado causa abundantes efectos adversos, como hipotensión, sedación, somnolencia y signos extrapiramidales, incluso a dosis bajas (43) (nivel de evidencia I).

Los antipsicóticos atípicos risperidona y aripiprazol mejoran modestamente la agitación, la agresividad y la psicosis (nivel de evidencia I), mientras que los resultados con la olanzapina son discordantes (nivel de evidencia I). Estos medicamentos aumentan el riesgo de accidentes vasculares cerebrales en los ancianos con demencia (nivel de evidencia II). Sus efectos adversos, que consisten en trastornos extrapiramidales y cognitivos (nivel de evidencia I), provocan el abandono del tratamiento en un porcentaje alto de pacientes (44, 45).

Recomendaciones

Antes de comenzar el tratamiento de las alteraciones conductuales con otras actuaciones, es preciso evaluar el efecto de los inhibidores de la acetilcolinesterasa y la memantina sobre estos síntomas (recomendación de grado B). Si persisten y precisan tratamiento, se debe empezar por medidas no farmacológicas, y utilizar psicotrópicos si éstas fallan (buena práctica médica). Los antidepresivos más apropiados son los inhibidores de la recaptación de serotonina debido a su bajo perfil de efectos adversos (grado de recomendación B); la elección concreta del antidepresivo depende de numerosas variables, como la vía para su metabolización y el efecto que puede tener sobre otros medicamentos que tome el paciente, incluidos los inhibidores de la acetilcolinesterasa (buena práctica médica). Si uno no es eficaz, se debe sustituir por otro inhibidor de la recaptación de serotonina, por un antidepresivo tricíclico o por un antidepresivo de acción dual (grado de recomendación C). Los efectos adversos y la eficacia se evalúan en la cuarta semana, y la necesidad de mantener el tratamiento antidepresivo, después de 6 a 9 meses de haber remitido el cuadro. La retirada debe ser progresiva (buena práctica médica). Para la ansiedad se recomiendan las benzodiacepinas de vida media breve si el tratamiento es corto y antipsicóticos o antidepresivos del tipo inhibidores de la recaptación de serotonina si ha de ser prolongado (grado de recomendación C). Los síntomas psicóticos, la agitación y la agresividad se tratan con antipsicóticos, pero la elección de uno típico o atípico debe ser individualizada (buena práctica médica).

en los síntomas extrapiramidales no se ha analizado
hencia con cuerpos de Lewy, pero la impresión general es que es menos eficaz que en la enfermedad de Parkinson no complicada debido a la presencia de patología estriatal intrínseca y al predominio de los síntomas no dopaminérgicos. Sin embargo, la levodopa mejoró los síntomas parkinsonianos en un tercio de una serie corta de 14 pacientes (29) y no empeoró las manifestaciones neuropsiquiátricas en otra serie de 11 pacientes (30) (nivel de evidencia III). Se recomienda administrar la dosis más baja eficaz de levodopa en monoterapia y no emplear o retirar otros fármacos antiparkinsonianos como anticolinérgicos, amantadina, selegilina, inhibidores COMT y agonistas dopaminérgicos (1) (nivel de evidencia IV).

Algunos estudios abiertos han demostrado que los inhibidores de la acetilcolinesterasa son moderadamente eficaces en el control de las alucinaciones visuales, ideas delirantes, ansiedad, inatención y alteraciones del sueño, pero sólo disponemos de ensayos clínicos multicéntricos controlados con placebo en el caso de la rivastigmina (nivel de evidencia I). También son escasos los estudios sobre su eficacia a largo plazo (31, 32).

Si los síntomas neuropsiquiátricos son graves y no mejoran con inhibidores de la acetilcolinesterasa, puede intentarse un antipsicótico atípico de perfil favorable como la quetiapina (33), pero no hay datos procedentes de estudios sistemáticos que sustenten su uso (nivel de evidencia IV).

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REVIEW

Management of behavioral problems in Alzheimer's disease

Serge Gauthier,[1] Jeffrey Cummings,[2] Clive Ballard,[3] Henry Brodaty,[4] George Grossberg,[5] Philippe Robert[6] and Constantine Lyketsos[7]

[1]*Alzheimer's Disease and Related Disorders Unit at the McGill Center for Studies in Aging, Douglas Mental Health University Institute, Montreal, Canada*
[2]*Mary S. Easton Center for Alzheimer's Disease Research at UCLA, Los Angeles, California, U.S.A.*
[3]*Age Related Diseases, King's College London, London, U.K.*
[4]*Primary Dementia Collaborative Research Centre, School of Psychiatry, University of New South Wales, Sydney, Australia*
[5]*Department of Neurology and Psychiatry, St Louis University School of Medicine, St Louis, Missouri, U.S.A.*
[6]*Centre Mémoire de Ressources et de Recherche (Memory Centre for Care and Research), CHU de Nice, Hôpital Pasteur, Nice, France*
[7]*Department of Psychiatry, The Johns Hopkins Bayview Medical Center, Baltimore, Maryland, U.S.A.*

ABSTRACT

Alzheimer's disease (AD) is a complex progressive brain degenerative disorder that has effects on multiple cerebral systems. In addition to cognitive and functional decline, diverse behavioral changes manifest with increasing severity over time, presenting significant management challenges for caregivers and health care professionals. Almost all patients with AD are affected by neuropsychiatric symptoms at some point during their illness; in some cases, symptoms occur prior to diagnosis of the dementia syndrome. Further, behavioral factors have been identified, which may have their origins in particular neurobiological processes, and respond to particular management strategies. Improved clarification of causes, triggers, and presentation

Overall, antipsychotics clearly confer significant treatment benefit for the short-term (up to 12 weeks) treatment of aggression in people with AD, although the benefits must be weighed against the not insubstantial risk of serious adverse events. The evidence base is less robust for longer-term therapy, and for the treatment of psychosis, but the longer-term use of antipsychotics in people with AD is probably inadvisable, other than in exceptional clinical circumstances. Clinical trials to identify other safe and effective pharmacological and non-pharmacological treatments for neuropsychiatric symptoms in AD are an urgent clinical research priority.

European Journal of Neurology 2010, **17:** 1236–1248 doi:10.1111/j.1468-1331.2010.03040.x

EFNS GUIDELINES/CME ARTICLE

EFNS guidelines for the diagnosis and management of Alzheimer's disease

J. Hort[a], J. T. O'Brien[b], G. Gainotti[c], T. Pirttila[d,†], B. O. Popescu[e], I. Rektorova[f], S. Sorbi[g] and P. Scheltens[h] on behalf of the EFNS Scientist Panel on Dementia

[a]*Memory Disorders Clinic, Deartment of Neurology, Charles University in Prague, Second Faculty of Medicine and Motol Hospital, Prague, Czech Republic;* [b]*Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, UK;* [c]*Neuropsychology Service, Policlinico Gemelli/Catholic University, Rome, Italy;* [d]*Department of Neurology, Kuopio University Hospital, Kuopio, Finland;* [e]*Department of Neurology, University Hospital, 'Carol Davila' University of Medicine and Pharmacy, Bucharest, Romania;* [f]*First Department of Neurology, Masaryk University and St. Anne's Hospital, Brno, Czech Republic;* [g]*Department of Neurological and Psychiatric Sciences University of Florence, Italy; and* [h]*Department of Neurology and Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands*

Keywords:
Alzheimer's disease, dementia, diagnosis, guideline, management, review, treatment

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Background and objectives: In 2008 a task force was set up to develop a revision of the European Federation of the Neurological Societies (EFNS) guideline for the diagnosis and management of Alzheimer's disease (AD) and other disorders associated with dementia, published in early 2007. The aim of this revised international guideline was to present a peer-reviewed evidence-based statement for the guidance of practice for clinical neurologists, geriatricians, psychiatrists, and other specialist physicians responsible for the care of patients with AD. Mild cognitive impairment and non-Alzheimer dementias are not included in this guideline.

Methods: The task force working group reviewed evidence from original research articles, meta-analysis, and systematic reviews, published before May 2009. The evidence was classified and consensus recommendations graded (A, B, or C) according to the EFNS guidance. Where there was a lack of evidence, but clear consensus, good practice points were provided.

Antipsychotics should only be used for moderate or severe BPSD symptoms causing significant distress which have either not responded to other treatments (like non-pharmacological measures or ChEIs) or when other treatments are not appropriate (Level A). Low dose of atypical agents should be used only after assessment of risk benefit and full discussion with patient (when capacity allows) and caregiver (good practice point).

Atypical agents have fewer side effects and do not confer a greater risk of stroke or mortality than conventional drugs (Level B).

Selective serotonin reuptake inhibitors rather than tricyclic antidepressants should be used to treat depression in AD (Level B).

Guía de Práctica Clínica sobre la Atención Integral a las Personas con Enfermedad de Alzheimer y otras Demencias

GUÍAS DE PRÁCTICA CLÍNICA EN EL SNS

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Generalitat de Catalunya
Departament de Salut

Edita: Ministerio de Ciencia e Innovación
NIPO: en tramitación
Depósito Legal: B. 34.475-2011

Resumen de evidencia

4	Según las GPC y teniendo en cuenta los efectos adversos de los fármacos se considera razonable empezar por el manejo no farmacológico de los SCPD y emplear los fármacos en síntomas graves o rebeldes.[42,235]
1++	Los IACE han mostrado mayor eficacia que placebo sobre SCPD, evaluada generalmente mediante el cambio en la puntuación NPI.[239,240,253] Memantina ha mostrado una discreta eficacia sobre la agitación.[256,258]
1+	Rivastigmina ha mostrado una moderada mejoría sobre la puntuación NPI en pacientes con DLB y PDD.[272,277]
1–	Los estudios sobre tratamiento de los SCPD con psicofármacos específicos en pacientes con demencia son escasos y generalmente de baja calidad.

Recomendaciones

D	Se debe identificar el síntoma diana que hay que tratar y sus posibles causas o desencadenantes.
D	La recomendación general respecto al tratamiento farmacológico de los SCPD es comenzar con IACE y/o memantina y, si la respuesta no resulta suficiente, añadir un psicofármaco.
✓	Tener en cuenta la especial sensibilidad de estos pacientes a los efectos adversos, especialmente el riesgo de efectos anticolinérgicos, hipotensión ortostática, caídas, efectos extrapiramidales, empeoramiento de función cognitiva, confusión y delírium. Comenzar con dosis bajas y alcanzar las dosis mínimas eficaces de forma lenta. Utilización preferente de la vía oral.
✓	Revisar la dosis y la propia necesidad del tratamiento a intervalos regulares, generalmente cada 3 meses.
IACE y/o memantina	
B	Se recomienda el uso de los IACE y/o memantina como tratamiento de la demencia no sólo para los síntomas cognitivos sino también para los no cognitivos.
B	Se recomienda el uso de rivastigmina para el tratamiento de los SCPD en los pacientes con DLB o PDD.
Psicofármacos	
	Se recomienda el uso de psicofármacos para el tratamiento de los SCPD, aun-

Resumen de evidencia

IACE o memantina	
1++	El tratamiento específico con IACE o memantina puede mejorar de forma inespecífica algunos de los SCPD en pacientes con demencia en que esté indicado.[239,240,253,256,400]
Antipsicóticos	
1–	La eficacia de los antipsicóticos es similar entre ellos en estudios comparativos de baja potencia y corta duración.[42,399,400]
1+	Para el tratamiento del delirio en la EA, se ha observado mejoría con risperidona y donepezilo.[400,401,337]
1–	Rivastigmina ni galantamina mostraron mejoría del delirio en la EA.[400]
1+	Rivastigmina puede mejorar los síntomas psicóticos en la DLB.[277]
1+	Los antipsicóticos atípicos (aripiprazol, olanzapina, quetiapina y risperidona) han mostrado un pequeño beneficio respecto a placebo en el tratamiento de síntomas psicóticos en pacientes con EA y DV.[25,42]

Agitación y agresividad	
1++	Haloperidol 0,25-6 mg/día mejora la agresividad en pacientes con demencia pero no otros aspectos de la agitación, impresión clínica global de cambio, carga de los cuidadores y AVD.[402]
1++	Risperidona 1 mg/día y olanzapina 5-10 mg/día mejoran la agresividad en pacientes con EA.[401]
1+	Olanzapina y quetiapina no han mostrado beneficio en la agitación en pacientes con EA.[42]
1+	En pacientes ingresados con demencia y agitación, olanzapina y lorazepam intramuscular han mostrado una tasa de respuesta a las 2 horas doble al placebo.[42]
1+	Algunos ISRS, como citalopram o trazodona, han mostrado mejoría de la agitación en la DLFT. Paroxetina no mostró mejoría y empeoró la cognición.[42]
1–	Trazodona no mostró mejoría de la agitación en pacientes con EA sin depresión asociada.[42]
1+	Donepezilo 10 mg/día durante 12-52 semanas mostró beneficios sobre agitación y agresividad respecto a placebo en pacientes con EA.[25]
1+	Carbamazepina ha mostrado un beneficio modesto para la agitación en pacientes con demencia.[42]
1+	Valproato no ha mostrado eficacia para la agitación en pacientes con demencia.[42]
1++	No hay evidencia consistente de que los antipsicóticos mejoren conductas indeseadas que no sean la agresividad, y suele ser a expensas de sedación, aumento de peso, signos extrapiramidales y caídas.[5]

Antipsicóticos	
A	En pacientes con EA y síntomas psicóticos puede usarse risperidona.
B	En pacientes con EA y síntomas psicóticos puede usarse donepezilo. En el tratamiento de los síntomas psicóticos en la DLB puede usarse rivastigmina.
D	En pacientes con EA o DV y síntomas psicóticos pueden usarse antipsicóticos atípicos.

Antipsicóticos	
1+	Los antipsicóticos pueden producir aumento de mortalidad, ictus, sedación, confusión, somnolencia, parkinsonismo, distonía, discinesia tardía, acatisia, síndrome neuroléptico maligno, hiperlipidemia, hiperglucemia, aumento de peso, hipotensión postural, arritmias, alteraciones en el ECG, efectos anticolinérgicos y empeoramiento de la cognición.[5,42,404]
1++	Haloperidol produce síntomas extrapiramidales, somnolencia y fatiga con mayor frecuencia en pacientes con demencia que en controles.[402]
1++	Los antipsicóticos atípicos (aripiprazol, olanzapina, quetiapina o risperidona) producen mayor somnolencia (OR = 2,84) e infecciones urinarias (OR = 1,28) en pacientes con demencia que en controles.[405]
1++	Risperidona y olanzapina producen más síntomas extrapiramidales (OR = 1,51), trastornos del movimiento (OR = 3,42) y edema periférico (OR = 1,99) en pacientes con demencia que en controles, pero no más lesiones, caídas o síncope.[405]
1++	Los pacientes con demencia tratados con aripiprazol, olanzapina, quetiapina o risperidona empeoraron más en las puntuaciones cognitivas que los tratados con placebo en los ECA.[405]
1++	Risperidona duplica el riesgo de síntomas extrapiramidales frente a placebo en pacientes con demencia.[404,401,337]
1+	La somnolencia es más frecuente y los trastornos del movimiento son más frecuentes con risperidona u olanzapina que con placebo.[297,404,337]
1++	Las tasas de abandono entre los pacientes con demencia tratados con haloperidol o antipsicóticos atípicos fueron similares a los controles.[402,405]

1+	Clozapina se asocia con agranulocitosis que puede ser mortal.[42]
1++/ 2+	El uso de antipsicóticos atípicos (risperidona, olanzapina) se ha asociado con un ligero aumento de riesgo de ictus y de mortalidad en pacientes con demencia. En cambio, los estudios observacionales no apoyan que haya diferencias entre atípicos, típicos y placebo.[129,407,405,152,149,408,406]
2++	El 50% de los pacientes con DLB pueden tener marcada sensibilidad a antipsicóticos, con reacciones extrapiramidales, confusión, temblor, inestabilidad autonómica, caídas y aumento de la mortalidad.[25,5,129,404]

NHS
National Institute for Health and Clinical Excellence

social care institute for excellence

scie

Quick reference guide

Issue date: November 2006 (revised March 2011)

Dementia

Supporting people with dementia and their carers in health and social care

Antipsychotics

- Do not use antipsychotic drugs for mild-to-moderate non-cognitive symptoms in:
  - DLB, because of the risk of severe adverse reactions
  - Alzheimer's disease, vascular dementia or mixed dementias, because of the increased risk of cerebrovascular adverse events and death.
- Consider antipsychotics for severe non-cognitive symptoms (psychosis and/or agitated behaviour causing significant distress) only if:
  - risks and benefits have been fully discussed; assess cerebrovascular risk factors and discuss possible increased risk of stroke/transient ischaemic attack and possible adverse effects on cognition
  - changes in cognition are regularly assessed and recorded; consider alternative medication if necessary
  - target symptoms have been identified, quantified and documented, and changes are regularly assessed and recorded
  - comorbid conditions, such as depression, have been considered
  - the drug is chosen after an individual risk–benefit analysis
  - the dose is started low and titrated upwards
  - treatment is time limited and regularly reviewed (every 3 months or according to clinical need).

  In DLB, monitor for severe untoward reactions, particularly neuroleptic sensitivity reactions (development or worsening of extrapyramidal features or acute, severe physical deterioration).

Acetylcholinesterase inhibitors

- Consider an acetylcholinesterase inhibitor for:
  - people with DLB who have non-cognitive symptoms causing significant distress or leading to behaviour that challenges
  - people with mild, moderate or severe Alzheimer's disease who have non-cognitive symptoms and/or behaviour that challenges causing significant distress or potential harm to the individual if:
    - a non-pharmacological approach is inappropriate or has been ineffective, and
    - antipsychotic drugs are inappropriate or have been ineffective.
- Do not use acetylcholinesterase inhibitors for non-cognitive symptoms or behaviour that challenges in vascular dementia except as part of properly constructed clinical studies.

Behaviour that challenges requiring urgent treatment *continued*

Intramuscular agents for behavioural control

- Use lorazepam, haloperidol or olanzapine. If possible, use a single agent.
- For rapid tranquillisation, consider haloperidol and lorazepam in combination.
- Do not use diazepam or chlorpromazine.
- When using haloperidol (or any other conventional antipsychotic), monitor closely for dystonia and other extrapyramidal side effects.
- If side effects become distressing, consider an anticholinergic agent; monitor for deteriorating cognitive function if used.

AGÈNCIA VALENCIANA DE SALUT
GENERALITAT VALENCIANA
CONSELLERIA DE SANITAT

DEPARTAMENTO DE SALUD DE SAGUNTO

PROTOCOLO DE ACTUACIÓN EN SÍNTOMAS PSICOLÓGICOS Y CONDUCTUALES ASOCIADOS A LA DEMENCIA

DEPARTAMENTO DE SALUD DE SAGUNTO
2012

a. Síntomas psicóticos: DELIRIOS Y ALUCINACIONES

- En pacientes con EA y síntomas psicóticos puede usarse risperidona (Grado de recomendación A).
- En pacientes con EA o DV y síntomas psicóticos pueden usarse antipsicóticos atípicos (Grado de recomendación D)[1].
- La quetiapina es el antipsicótico de elección en pacientes con demencia asociada a enfermedad de parkinson o con DLB, si bien en estos pacientes deben evitarse por el riesgo de reacciones extrapiramidales (Grado de recomendación B)[1].

c. AGITACIÓN y AGRESIVIDAD

- Se recomienda el uso de neurolépticos para el tratamiento de la agitación y agresividad en presencia o ausencia de psicosis[3]. La evidencia es mayor para risperidona que para otros fármacos (Grado de recomendación B)[1], pero dada la modesta eficacia y el aumento significativo de acontecimientos adversos no se debe utilizar rutinariamente para tratar a pacientes con demencia y agresividad o psicosis a menos que haya afectación severa.

- En caso de intolerancia a antipsicóticos o como alternativa terapéutica se pueden usar los ISRS[1] o clometiazol para tratar la agitación y agresividad.

- No se recomienda el uso de otros anticomiciales, litio o beta-bloquenates para el tratamiento de la psicosis o agitación por la reducida evidencia en eficacia y elevados efectos adversos[3].

- El uso de benzodiacepinas es eficaz para el tratamiento de agitación con una importante componente ansiosa. Se debe evitar un uso prolongado, pero es recomendable una pauta a demanda para episodios raros de agitación[3].

Fármaco (dosis / día)	Precio € / mes
Haloperidol (5 - 10 mgr)	2,5 – 10
Risperidona (1-2 mgr)	8 – 30
Olanzapina (5-10 mgr)	30 - 55
Quetiapina (50 - 200 mgr)	8 - 30
Aripiprazol * (5 - 10 mgr)	100 – 200
Ziprasidona * (20 - 40 mgr)	50 - 140
Rivastigmina (9,5 mgr)	40 - 70
Memantina (20 mgr)	45

Psychosis, Agitation, and Antipsychotic Treatment in Dementia

D.P. DEVANAND, M.D.

So what should the psychiatrist do in clinical practice with these patients? The FDA has not approved the use of any antipsychotic to treat psychosis or agitation in patients with dementia, but off-label use is permitted, as occurs frequently in the treatment of many other disorders. Of note, risperidone is approved in Germany for the treatment of behavioral complications in dementia. Federal regulations in the United States require the discontinuation of antipsychotic medications in nursing homes every 3–6 months, and the Center for Medicare and Medicaid Services recently issued an additional regulation (12) requiring nursing homes to reduce antipsychotic usage by 15%, an arbitrary number. However, there is often a need to continue antipsychotics in many patients with dementia. The Antipsychotic Discontinuation in Alzheimer Disease trial reported that after treatment response to risperidone was maintained for 4 to 8 months, randomized double-blind discontinuation to placebo was associated with a markedly increased risk of relapse relative to continuation risperidone (13). Clearly, completely avoiding the use of antipsychotics is not feasible in many patients with dementia who develop symptoms of severe agitation and psychosis that require urgent treatment, particularly because no other class of medication has been shown to be consistently superior to placebo in controlled trials (14, 15). Behavioral strategies have

Conclusiones

- Los SAP son una alternativa terapeútica necesaria en el ttº de los SPCDs severos de los pacientes con demencia
- Existe evidencia de potenciales efectos secundarios graves
  - posible incremento de mortalidad con algunos (FAP, Risperidona, Olanzapina)
  - incremento de Enf. Cerebro-vascular con la Risperidona
- La Quetiapina es la más segura (menor mortalidad, EPS y AVCs), aunque también es la que tiene una menor evidencia de eficacia
- La Quetiapina es de elección en D. De Lewy y asociada a Parkinson (dado el riesgo de clozapina)
- Aripiprazol es una alternativa interesante (equilibrio seguridad / eficacia) con formulación oral e IM
- Disponemos de menos datos y experiencia con ziprasidona, y con los nuevos (paliperidona etc..)

Conclusiones

- Existe discordancia entre los datos de las evidencias (ECR, guías y meta-analisis) y la opinión y uso práctico diario de los profesionales
  - problemas metodológicos de los ensayos
  - elevado efecto placebo, duración corta, etc..
- Por tanto, que hacemos: ¿Primar seguridad o eficacia?
  - Tener en cuenta que los FGA tiene más riesgos que los SGA
- En otras demencias ¿Tener en cuenta la DV, Mixta y el Lewy?
  - Hay un número de demencias mixtas (vascular y EA, Lewy y EA)…..
- Tener siempre en cuenta: duración limitada del ttº (3-6 meses), revisión periódica, *"empezar despacio y subir despacio"…..*
  - Intento de tratamientos no farmacológicos
- Valorar el ttº con IACHs y/o Memantina