FONDAZIONE
CASSA DI RISPARMIO
DI PISTOIA E PESCIA

Centro Monteoliveto

"Casa dell'Anziano"

6° CONVEGNO NAZIONALE SUI CENTRI DIURNI ALZHEIMER

15-16 Maggio 2015

Auditorium
Via Panconi, 14 - Pistoia

Pistoia, 15-16 maggio 2015

6° CONVEGNO NAZIONALE SUI CENTRI DIURNI ALZHEIMER

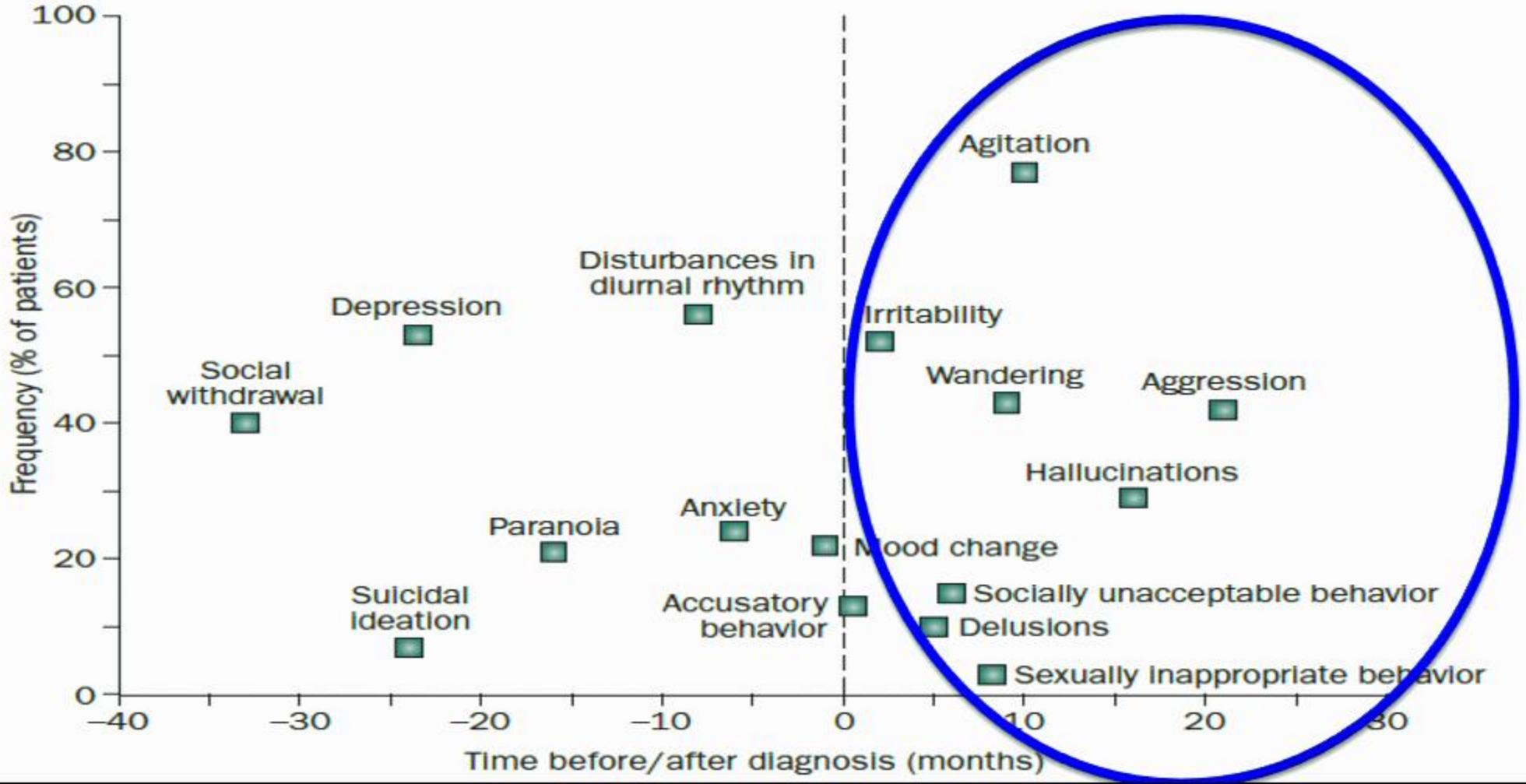
Antipsicotici nella demenza: sempre e solo brutti e cattivi?

Francesco Nifosì, Claudio Vampini – DSM Verona

Management of agitation and aggression associated with Alzheimer disease

Clive G. Ballard, Serge Gauthier, Jeffrey L. Cummings, Henry Brodaty, George T. Grossberg, Philippe Robert and Constantine G. Lyketsos

Ballard, C. G. *et al. Nat. Rev. Neurol.* **5**, 245–255 (2009); doi:10.1038/nrneurol.2009.39



REVIEW

Psychosis in Alzheimer's Disease

Patrick S. Murray, Sanjeev Kumar, Mary Ann A. DeMichele-Sweet, and Robert A. Sweet

Psychotic symptoms, delusions and hallucinations, occur in approximately 50% of individuals with Alzheimer's disease (AD) (AD with psychosis [AD + P]). Pharmacotherapies for AD + P have limited efficacy and can increase short-term mortality. These observations have motivated efforts to identify the underlying biology of AD + P. Psychosis in AD indicates a more severe phenotype, with more rapid cognitive decline beginning even before psychosis onset. Neuroimaging studies suggest that AD + P subjects demonstrate greater cortical synaptic impairments than AD subjects without psychosis, reflected in reduced gray matter volume, reduced regional blood flow, and reduced regional glucose metabolism. Neuroimaging and available postmortem evidence further indicate that the impairments in AD + P, relative to AD subjects without psychosis, are localized to neocortex rather than medial temporal lobe. Neuropathologic studies provide consistent evidence of accelerated accumulation of hyperphosphorylated microtubule associated protein tau in AD + P. Finally, studies of familial aggregation of AD + P have established that the risk for psychosis in AD is, in part, genetically mediated. Although no genes are established as associated with AD + P, the first genome-wide association study of AD + P has generated some promising leads. The study of the neurobiology of AD + P is rapidly accelerating and may be poised for translational discovery. This process can be enhanced by identifying points of convergence and divergence with the neurobiology of AD proper and of schizophrenia, by innovative extension of current approaches, and by development of relevant animal models.

BIOL PSYCHIATRY 2014;75:542–552

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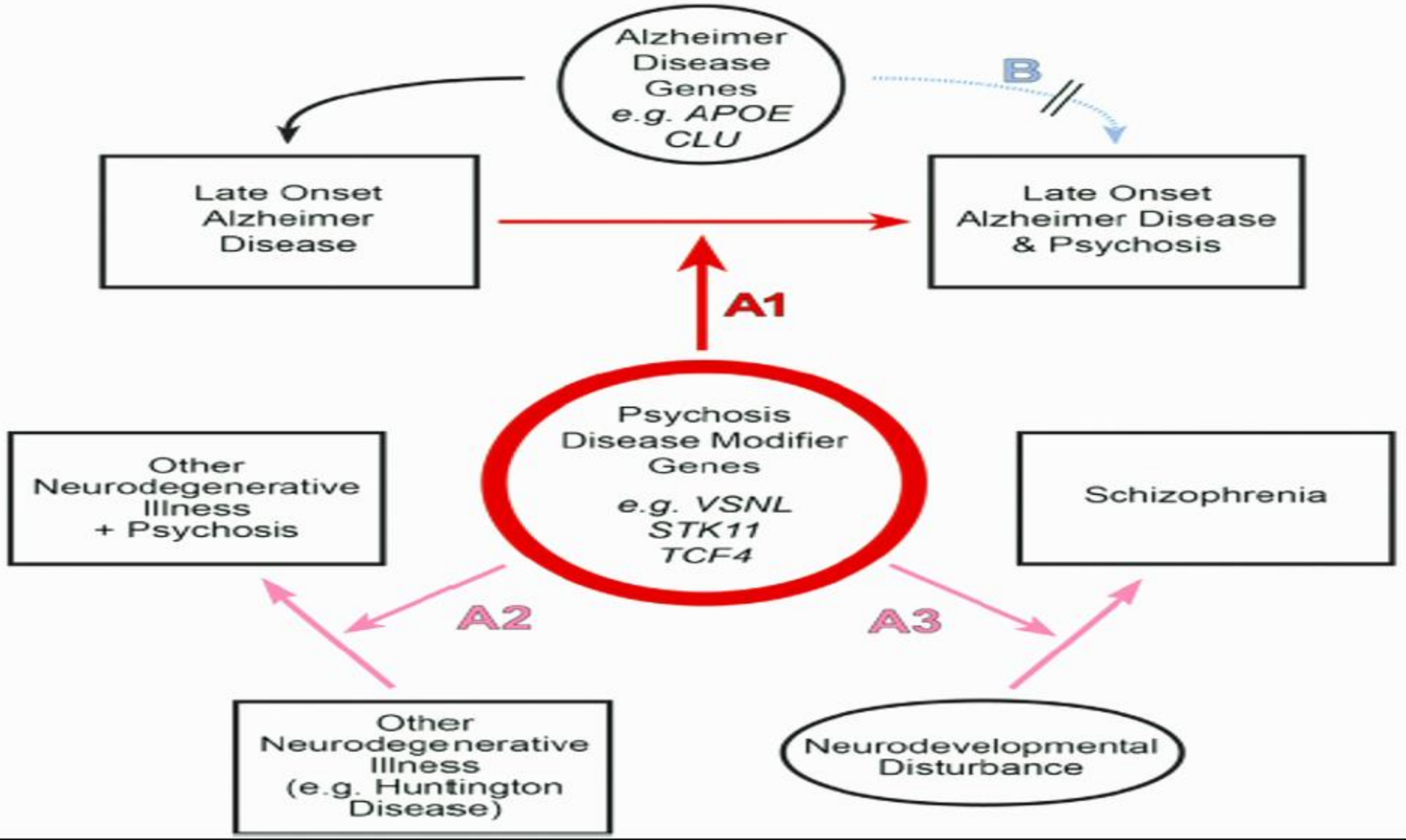

BPSD:
Trattamento Farmacologico Sintomatico

- Nuovi antipsicotici
- Anticonvulsivanti
- Antidepressivi 5-HTergici

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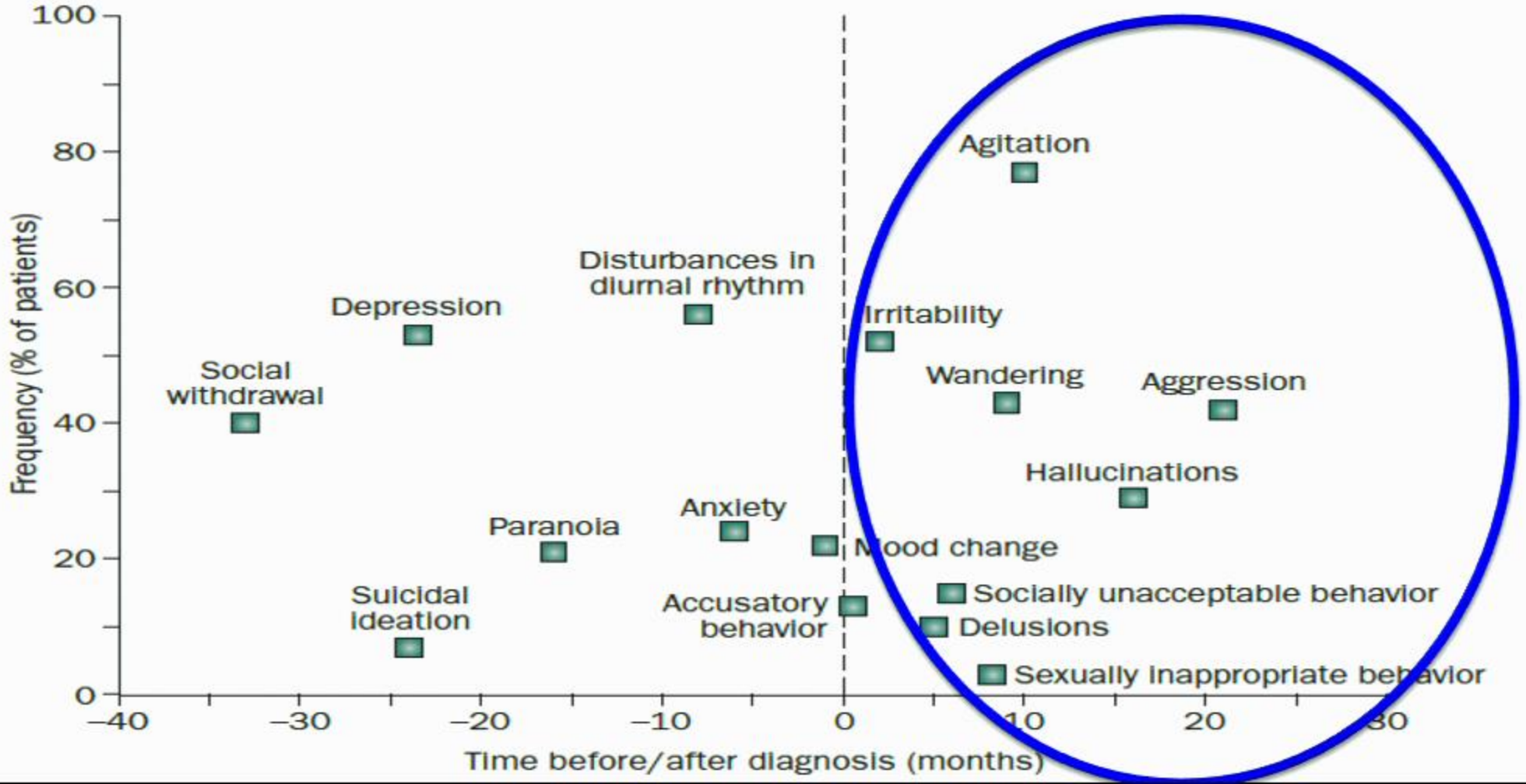

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BIOL PSYCHIATRY 2014;75:542–552

Meta-Analysis of Nonpharmacological Interventions for Neuropsychiatric Symptoms of Dementia

Henry Brodaty, D.Sc.

Caroline Arasaratnam, B.Psych. (Hons)

Objective: Behavioral and psychological symptoms are common in dementia, and they are especially stressful for family caregivers. Nonpharmacological (or psychosocial) interventions have been shown to be effective in managing behavioral and psychological symptoms, but mainly in institutional settings. The authors reviewed the effectiveness of community-based nonpharmacological interventions delivered through family caregivers.

Method: Of 1,665 articles identified in a literature search, 23 included unique randomized or pseudorandomized nonpharmacological interventions with family caregivers and outcomes related to the frequency or severity of behavioral and psychological symptoms of dementia, caregiver reactions to these symptoms, or caregiver distress attributed to these symptoms. Studies were rated according to an evidence hierarchy for intervention research.

Results: Nonpharmacological interventions were effective in reducing behavioral and psychological symptoms, with an overall effect size of 0.34 (95% CI= 0.20–0.48; $z=4.87$; $p<0.01$), as well as in ameliorating caregiver reactions to these behaviors, with an overall effect size of 0.15 (95% CI=0.04–0.26; $z=2.76$; $p=0.006$).

Conclusions: Nonpharmacological interventions delivered by family caregivers have the potential to reduce the frequency and severity of behavioral and psychological symptoms of dementia, with effect sizes at least equaling those of pharmacotherapy, as well as to reduce caregivers' adverse reactions. The successful interventions identified included approximately nine to 12 sessions tailored to the needs of the person with dementia and the caregiver and were delivered individually in the home using multiple components over 3–6 months with periodic follow-up.

(Am J Psychiatry 2012; 169:946–953)

Article

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Table 1 | Pharmacological treatment of agitation and aggression in people with dementia

Trials conducted	Evidence	Major adverse effects	Interpretation
Typical antipsychotics[9,10,12,13,15,16,18]			
11 randomized, placebo-controlled trials, mostly small sample sizes and of 4–12 weeks' duration one up to 16 weeks' duration	Significant but modest advantage over placebo for behavioral symptoms in early meta-analysis Thioridazine: only one placebo-controlled trial showed significant benefit in recent meta-analysis Thiothixine: a small study suggested efficacy at low doses but that symptoms return after discontinuation Haloperidol: meta-analysis indicated improvement in aggression but not in other symptoms of agitation	Parkinsonism, dystonia, tardive dyskinesias; QTc-interval prolongation; significant increase in mortality compared with atypical antipsychotics (administered for ≤180 days, relative risk 1.37)	Adverse events associated with typical antipsychotics make their use inadvisable in people with Alzheimer disease
Atypical antipsychotics[18,19,22,25]			
18 placebo-controlled trials over 6–12 weeks; only three trials of 6–12 months	Significant benefit in the treatment of aggression over 12 weeks Limited benefit for other symptoms and lack of benefit over treatment periods longer than 12 weeks	Parkinsonism; sedation; increased mortality (1.5–1.7-fold); increased cerebrovascular adverse events (threefold)	Probably still the best option for short-term (6–12 weeks) treatment of aggression that is severe, persistent, and treatment resistant, but serious adverse events are a major contraindication to long-term therapy

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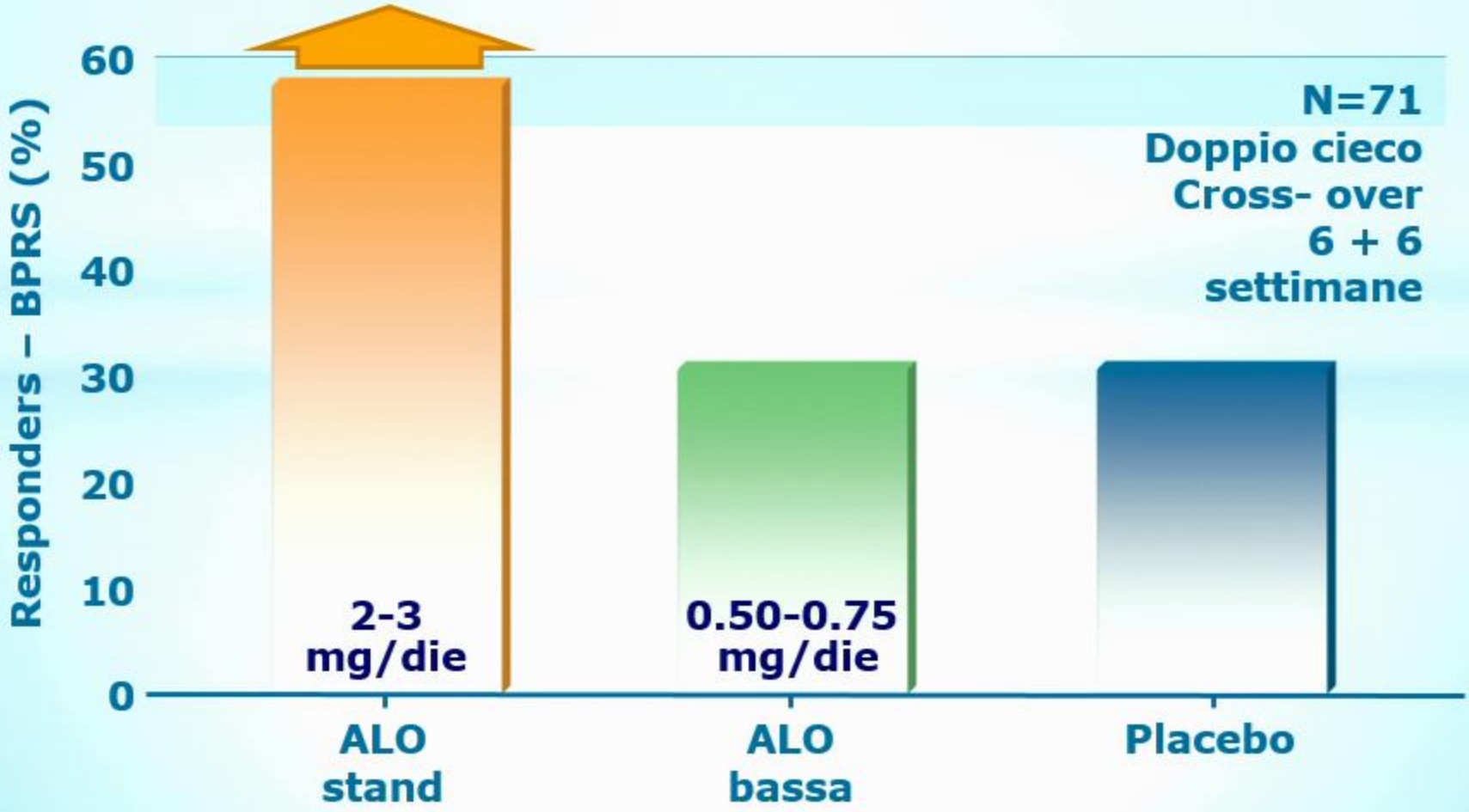
Ballard, C. G. *et al. Nat. Rev. Neurol.* **5**, 245–255 (2009); doi:10.1038/nrneurol.2009.39

Aloperidolo vs placebo nei BPSD in corso di Malattia di Alzheimer

20% EPS moderati o gravi



Devanand et al, Am J Psychiatry, 1998, 155, 1512-1520

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SCIENCE AND SOCIETY

Neuroleptic drugs in dementia: benefits and harm

Clive Ballard and Robert Howard

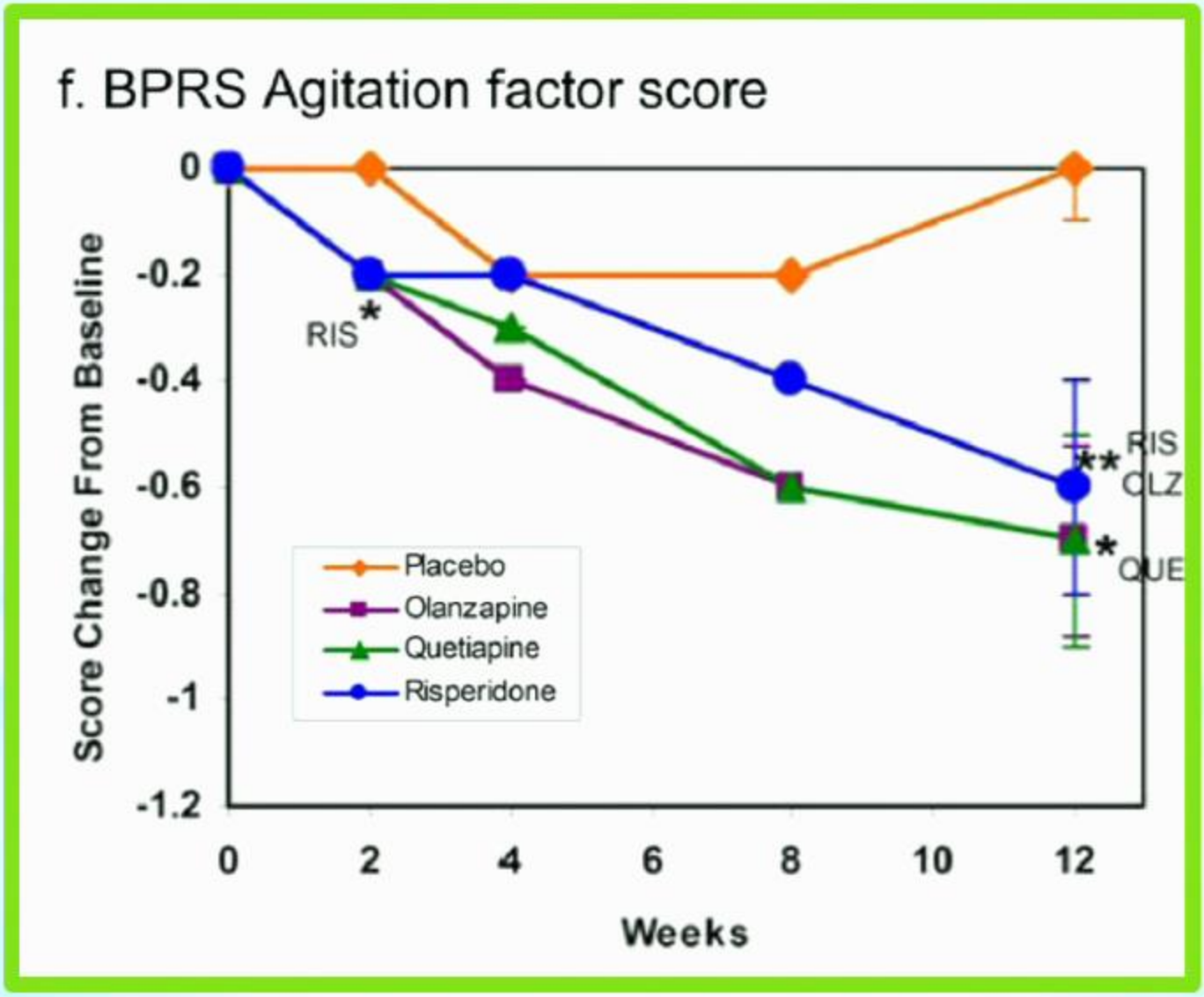
> "... atypical neuroleptics should only be used... when severe and distressing symptoms are occurring...and when the affected individual or others are at risk."

Table 1 | **Efficacy of neuroleptics for the treatment of Alzheimer's disease**

Drug	Symptoms	Scale	Number of people in meta-analysis	Weighted mean difference*	Included studies‡
Haloperidol					
1–2 mg	Aggression	BEHAV-AD aggression subscale	489	–0.31 [–0.49, –0.13] p=0.0006§	36
Risperidone					
0.5 mg	Aggression	BEHAV-AD aggression subscale	307	–0.40 [–1.10, 0.30] NS	39
1 mg	Aggression	CMAI verbal and physical aggression scales	809	–1.17 [–2.02, –0.32] p=0.0002§	33,37,38
1 mg	Aggression	BEHAV-AD aggression subscale	538	–0.84 [–1.28, –0.40] p=0.007§	33,39
2 mg	Aggression	BEHAV-AD aggression subscale	323	–1.50 [–2.05, –0.95] p<0.0001§	39

Risperidone					
0.5 mg	Psychosis	BEHAV-AD psychosis subscale	307	–0.03 [–0.25, 0.20] NS	39
1 mg	Psychosis	BEHAV-AD psychosis subscale	1,304	–0.14 [–0.25, –0.03] p=0.01§	37–40
2 mg	Psychosis	BEHAV-AD psychosis subscale	323	–0.18 [–0.40, 0.03] NS	39
Olanzapine					
<5 mg	Aggression/ agitation	NPI subscale	391	–0.40 [–1.14, 0.34] NS	43
5–10 mg	Aggression/ agitation	NPI subscale	529	–0.77 [–1.44, –0.10] p=0.03§	42,43
>10 mg	Aggression/ agitation	NPI subscale	96	–1.00 [–2.75, 0.75] NS	42
<5 mg	Psychosis	NPI subscale	391	–0.9 [–2.11, 0.31] NS	43
5–10 mg	Psychosis	NPI subscale	813	–0.36 [–1.22, 0.50] NS	37,42,43
>10 mg	Psychosis	NPI subscale	96	–0.30 [–2.88, 2.28] NS	42

Clinical Symptom Responses to Atypical Antipsychotic Medications in Alzheimer's Disease: Phase 1 Outcomes from the CATIE-AD Effectiveness Trial *Am J Psychiatry*. Author manuscript; available in PMC 2009 July 22.



Risperidone and Falls in Ambulatory Nursing Home Residents With Dementia and Psychosis or Agitation

Secondary Analysis of Double Blind, Placebo-Controlled Trial

	Placebo (N=139)	RSP 0.5 mg (N=133)	RSP 1 mg (N=126)	RSP 2 mg (N=139)
Pazienti che cadono, N (%)	**31 (22.3%)**	**24 (18.0%)**	**16 (12.7%)***	**38 (27.3%)**

- **RSP 1 mg:**
  - ✓ **Prevenzione cadute in caso di "wandering"**
  - ✓ **Efficacia terapeutica senza indurre EPS**

* P= 0.041 vs. Placebo

(Am J Geriatr Psychiatry 2004; 12:499–508)

The NEW ENGLAND JOURNAL of MEDICINE

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

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

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

CONCLUSIONS

Adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease. (ClinicalTrials.gov number, NCT00015548.)

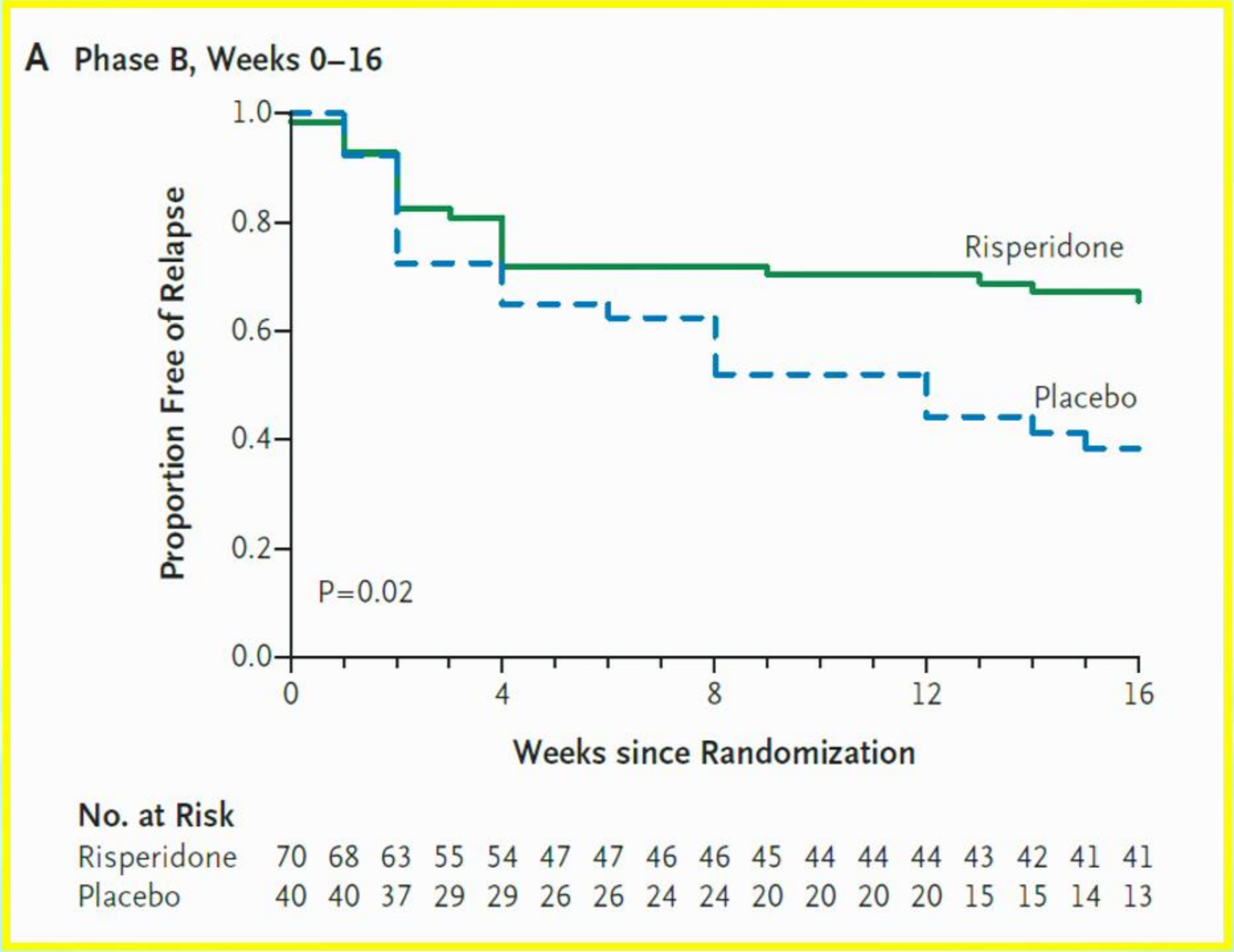
The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 367;16 NEJM.ORG OCTOBER 18, 2012

ORIGINAL ARTICLE

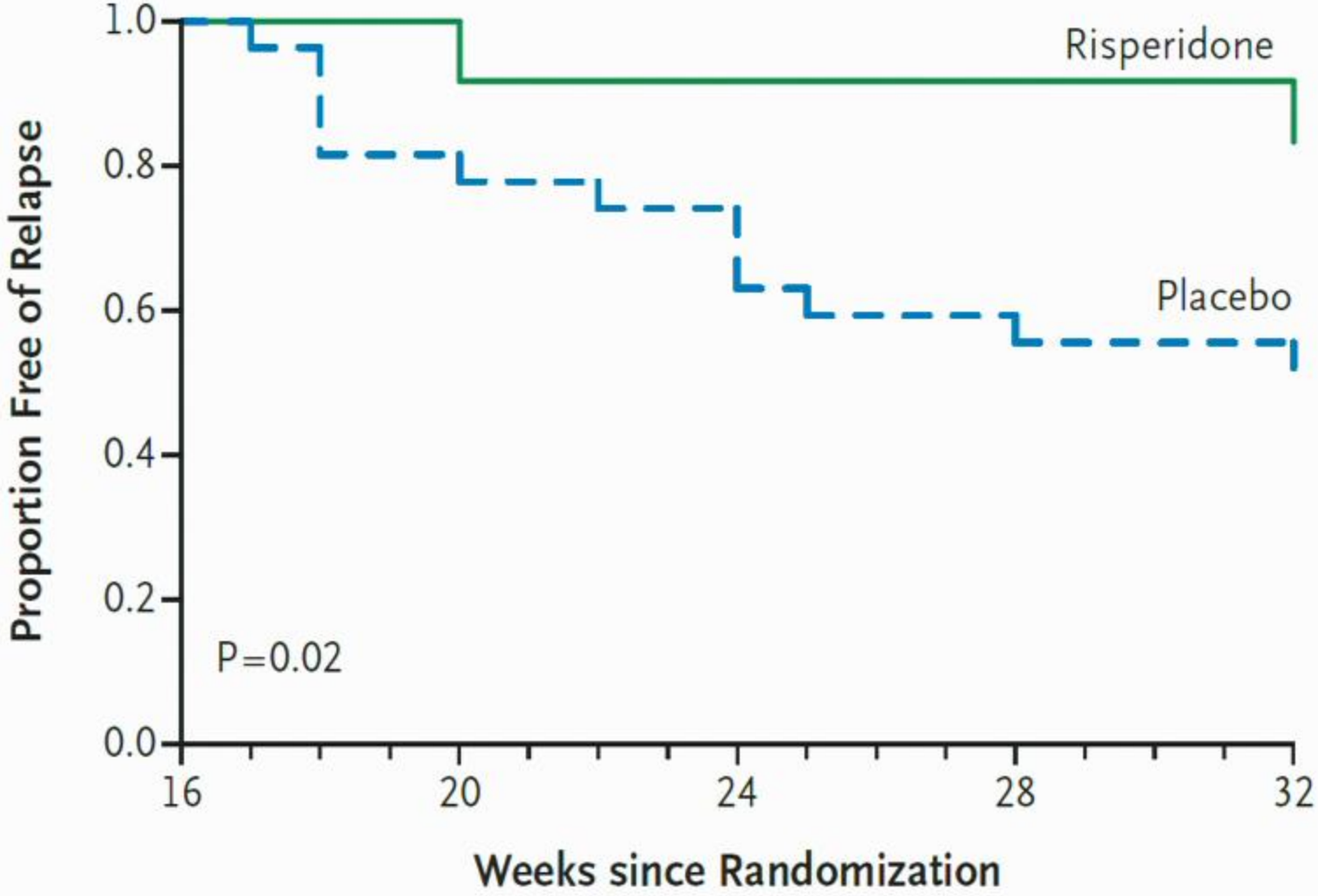
Relapse Risk after Discontinuation of Risperidone in Alzheimer's Disease

D.P. Devanand, M.D., Jacobo Mintzer, M.D., M.B.A., Susan K. Schultz, M.D., Howard F. Andrews, Ph.D., David L. Sultzer, M.D., Danilo de la Pena, M.D., Sanjay Gupta, M.D., Sylvia Colon, M.D., Corbett Schimming, M.D., Gregory H. Pelton, M.D., and Bruce Levin, Ph.D.

- Open-label treatment with RSP for 16 weeks (n 180)
- Responders (n 110) (DB fashion):
  - G1: RSP for 32 weeks
  - G2: RSP for 16 weeks followed by PBO for 16 weeks
  - G3: PBO for 32 weeks


A Phase B, Weeks 0–16
Proportion Free of Relapse
1.0
0.8
0.6
0.4
0.2
0.0
Risperidone
Placebo
P=0.02
0
4
8
12
16
Weeks since Randomization
No. at Risk
Risperidone 70 68 63 55 54 47 47 46 46 45 44 44 44 43 42 41 41
Placebo 40 40 37 29 29 26 26 24 24 20 20 20 20 15 15 14 13

B Phase B, Weeks 17–32



No. at Risk

Risperidone	13	13	13	13	12	11	11	11	11	11	11	11	11	11	11	11	11
Placebo	27	27	26	22	22	21	21	20	20	17	16	16	16	15	15	15	15

The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial

Clive Ballard, Maria Luisa Hanney, Megan Theodoulou, Simon Douglas, Rupert McShane, Katja Kossakowski, Randeep Gill, Edmund Juszczak, Ly-Mee Yu, Robin Jacoby, for the DART-AD investigators

Interpretation There is an increased long-term risk of mortality in patients with AD who are prescribed antipsychotic medication; these results further highlight the need to seek less harmful alternatives for the long-term treatment of neuropsychiatric symptoms in these patients.

Lancet Neurol 2009; 8: 151–57

The association of psychotropic medication use with the cognitive, functional, and neuropsychiatric trajectory of Alzheimer's disease

P. B. Rosenberg[1,2], M. M. Mielke[1,2,3], D. Han[1,2], J. S. Leoutsakos[1,2,4], C. G. Lyketsos[1,2,4], P. V. Rabins[1,2], P. P. Zandi[4], J. C. S. Breitner[5,6], M. C. Norton[7,13], K. A. Welsh-Bohmer[8,9], I. H. Zuckerman[10], G. B. Rattinger[10], R. C. Green[11,12], C. Corcoran[7], and J. T. Tschanz[7]

Results—At baseline, psychotropic medication use was associated with greater severity of dementia and poorer medical status. Higher PI for all medication classes was associated with a more rapid decline in MMSE. For antidepressant, SSRI, benzodiazepine, and typical antipsychotic use, a higher PI was associated with a more rapid increase in CDR-Sum. For SSRIs, antipsychotics, and typical antipsychotics, a higher PI was associated with more rapid increase in NPI-Total.

Conclusions—Psychotropic medication use was associated with more rapid cognitive and functional decline in AD, and not with improved NPS. Clinicians may tend to prescribe psychotropic medications to AD patients at risk of poorer outcomes, but one cannot rule out the possibility of poorer outcomes being caused by psychotropic medications.

Int J Geriatr Psychiatry. 2012 December ; 27(12): 1248–1257.

Risks associated with the use of APs in elderly dementia patients with BPSD

- **Increased mortality**
- **Cerebrovascular events**
- **Cardiac arrhythmias**
- **Extrapyramidal effects**
- **Venous thromboembolism**
- **Pneumonia**
- **Falls and fractures**

Trifirò GL, Spina E, Gambassi G, Pharmacological Research 59 (2009) 1–12

Raccomandazioni sul trattamento dei BPSD nei CDA

- ✓ L'utilizzo dei trattamenti farmacologici dei BPSD deve essere messo in atto quando gli interventi psicosociali e comportamentali non sono sufficienti

- ✓ Un trattamento farmacologico efficace nel trattamento dei BPSD, quando questi si manifestino nella loro maggiore pervasività e gravità, rappresenta spesso la base preliminare per poter effettuare un intervento psicosociale.

- ✓ Il trattamento con farmaci antipsicotici può essere indicato in presenza di aggressività, psicosi e gravi disturbi del sonno con agitazione notturna. Per altri disturbi del comportamento, quali l'attività motoria aberrante diurna, non esistono evidenze di efficacia e il trattamento deve essere di tipo psicosociale e comportamentale.

Raccomandazioni sul trattamento dei BPSD nei CDA

- ✓ All'ingresso in CDA è necessario effettuare un'approfondita anamnesi psicofarmacologica per quanto concerne efficacia e tollerabilità delle terapie precedentemente prescritte.

- ✓ Durante i primi giorni di accesso un'attenta osservazione e valutazione clinica del paziente e delle manifestazioni del BPSD, sarà utile nella valutazione di eventuali tempi e modalità di una possibile diminuzione dei dosaggi dei trattamenti e una successiva graduale sospensione.

- ✓ La scelta di un'eventuale terapia psicofarmacologica deve tener conto della tollerabilità, valutando in particolare la presenza di parkinsonismo ed il rischio di immobilizzazione e cadute prima e dopo l'inizio (o la sospensione) delle terapie.

Raccomandazioni sul trattamento dei BPSD nei CDA

- ✓ E' necessario valutare con attenzione la presenza di disturbi cardiovascolari, l'intervallo QTc all'ECG, l'equilibrio elettrolitico, in particolare la potassiemia, la presenza di trattamenti concomitanti, anche transitori (in particolare antidepressivi e antibiotici) potenzialmente in grado di aumentare l'intervallo QT

- ✓ Qualora non sussistano le condizioni cliniche per permettere una sospensione del farmaco AP, individuare la dose minima efficace del trattamento.

- ✓ Privilegiare quanto possibile la monoterapia.

Raccomandazioni sul trattamento dei BPSD nei CDA

- ✓ In generale l'utilizzo di farmaci AP nel trattamento dei BPSD necessita di un attento e stretto "case-by-case assessment", e il setting dei CDA può rappresentare una condizione favorevole ad un utilizzo che integri al meglio efficacia e sicurezza dei trattamenti.

- ✓ La presenza della figura di un medico consulente con specifiche competenze psicogeriatriche rappresenta un decisivo fattore facilitante per una efficace sinergia con la Medicina Generale e i Centri UVA, allo scopo di individuare la terapia farmacologica meglio efficace e tollerata.

Vedi, io vivo. Di cosa? Né infanzia né futuro

vanno calando… Esistenza in eccesso

mi sgorga dal cuore.

Rainer Maria Rilke, Elegie Duinesi, dalla nona elegia