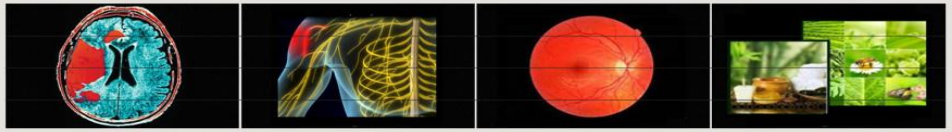
UNIVERSITA' DELLA CALABRIA

DIPARTIMENTO DI FARMACIA E SCIENZE DELLA SALUTE E DELLA NUTRIZIONE

SEZIONE DI FARMACOLOGIA PRECLINICA E TRASLAZIONALE

In search of new therapeutics...



Indagine farmacoepidemiologica sul trattamento antidolorifico dei pazienti affetti da demenza in Calabria

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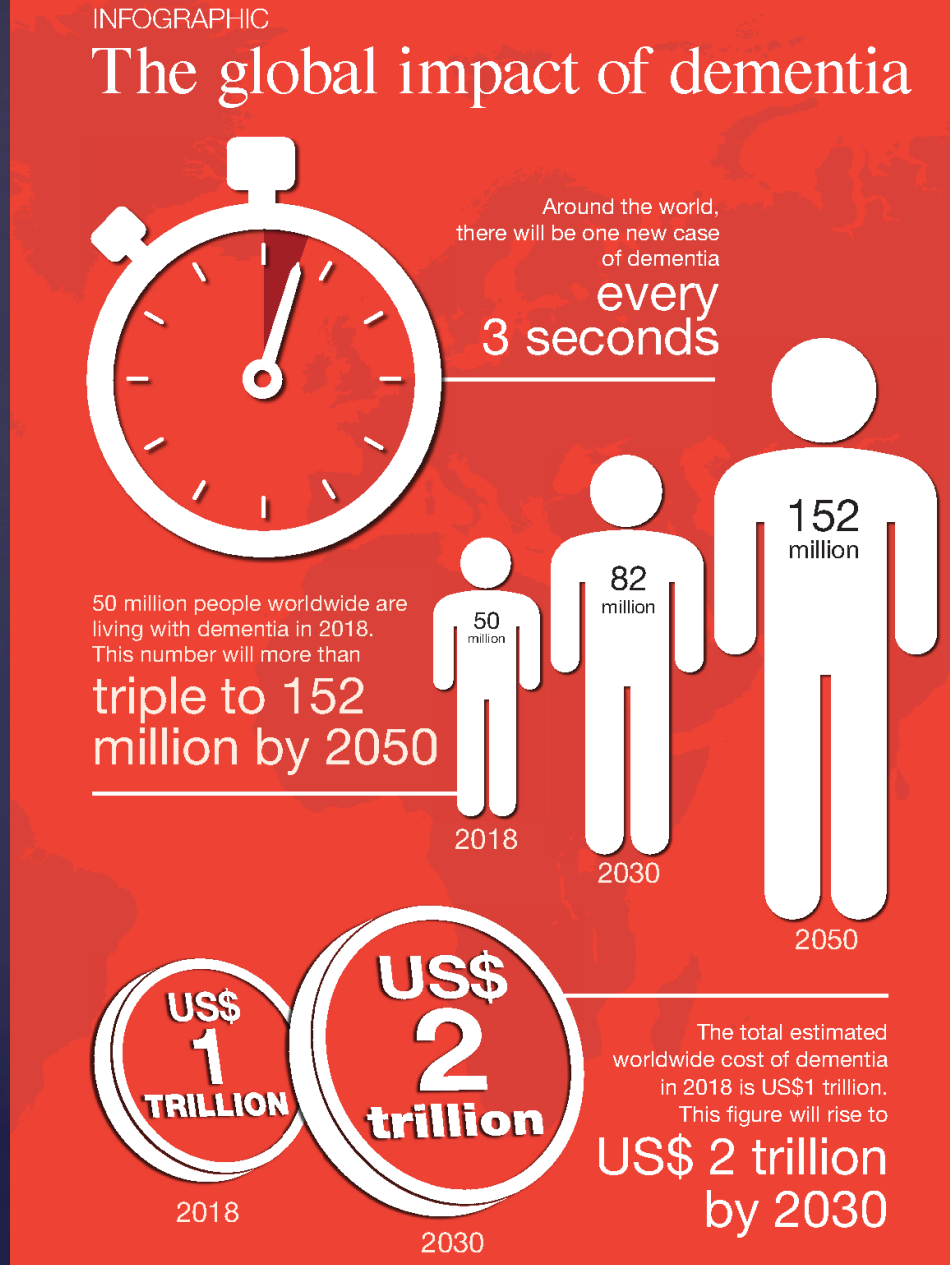
ISTITUTO SUPERIORE DI SANITÀ

XII Convegno - Il contributo dei centri per i disturbi cognitivi e le demenze nella gestione integrata dei pazienti

15 – 16 Novembre 2018
Istituto Superiore di Sanità

Epidemiology of dementia



World Alzheimer Report 2018

Table 1. Current licensed therapies for Alzheimer's disease.

Drug name	Donepezil	Rivagistimine	Galantamine	Memantine
Drug class	Cholinesterase inhibitor	Cholinesterase inhibitor	Cholinesterase inhibitor	NMDA receptor antagonist
Mechanism	Prevents ACh break down	Prevents ACh and butyl chloride break down	Prevents ACh break down and stimulates nicotinic receptors	Regulates glutamate activity by non-competitive antagonism
Indication	Mild-moderate Moderate-severe	Mild-moderate Severe	Mild-moderate	Moderate-severe
Dose forms	Oral tablet	IR tablet or oral solution or ER capsule	Capsule or oral solution or transdermal patch	Oral solution tablet or ER capsule
Side effects	Nausea Vomiting Lowered appetite Diarrhea	Nausea Vomiting Lowered appetite Diarrhea	Nausea Vomiting Lowered appetite Diarrhea	Headache Constipation Confusion Dizziness

NMDA: n-methyl-D – aspartate; IR: immediate release; ER: extended release

Khan et al., Expert Rev Neurother. 2017

Lack of disease-modifying drugs and neuropsychiatric symptoms of dementia (NPS)

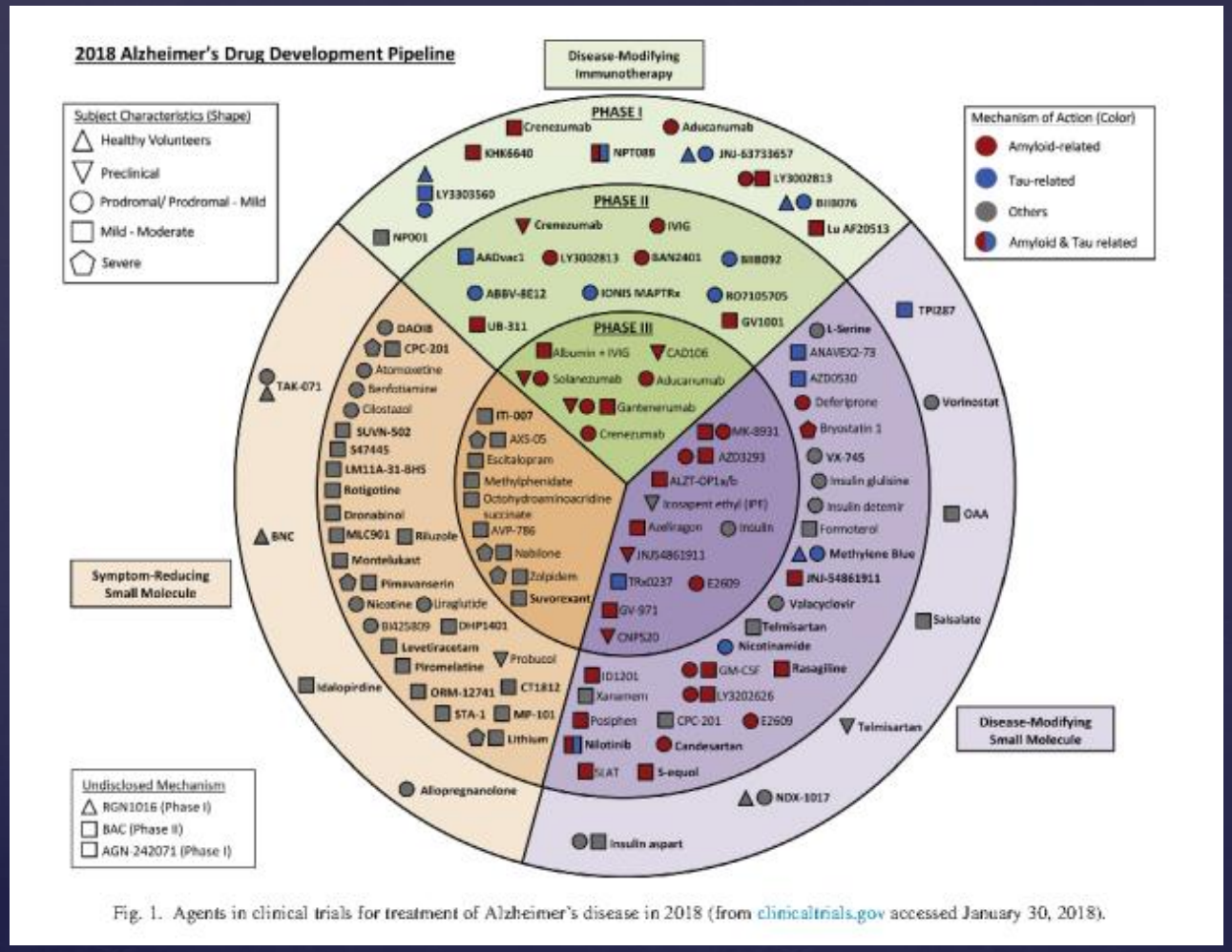


Fig. 1. Agents in clinical trials for treatment of Alzheimer's disease in 2018 (from clinicaltrials.gov accessed January 30, 2018).

Cummings et al., Alzheimers Dement (N Y). 2018

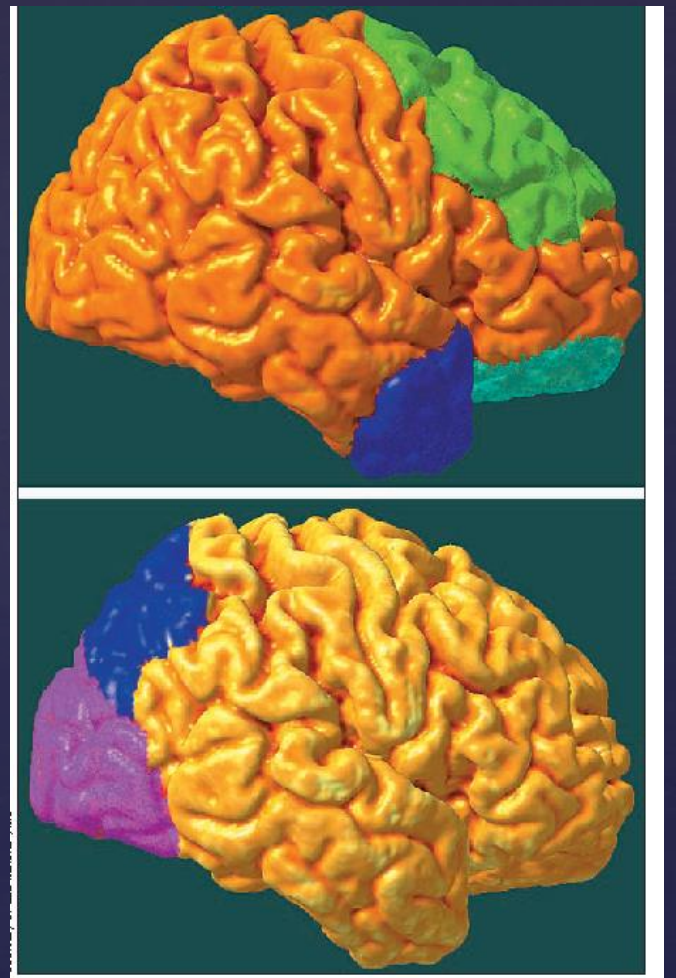


Figure: **The influence of regional pathologies on neuropsychiatric symptom formation**
Top: apathy and behavioural disinhibition in Alzheimer's disease are associated with reduced frontal lobe activity. Bottom: visual hallucinations and misidentification syndromes in DLB are by contrast, probably generated by reductions in posterior visual cortical activity.

McKeith et al., Lancet Neurol 2005

Symptoms attributed to dementia may be an indication of pain

Table 2. Consensus on current treatments for overall BPSD and agitation

TREATMENT OF OVERALL BSPD WITHIN AND AGITATION*	% AGREEMENT ACROSS PANEL +/−1 RANK SCORE	RANK
Thorough assessment and management of underlying causes	100%	1
Caregiver problem –solving/information/education	91%	2
Environmental adaptation/approaches	70%	3
Person-centered care	70%	4
Tailored activity program	70%	5
Citalopram	81%	6
Treat pain – Paracetamol/Analgesia	81%	7
Risperidone	64%	8

*Rank order identical for BPSD overall and for agitation.

BPSD=Behavioural and Psychological Symptoms of Dementia
Kales et al., Int Psychogeriatr. 2018

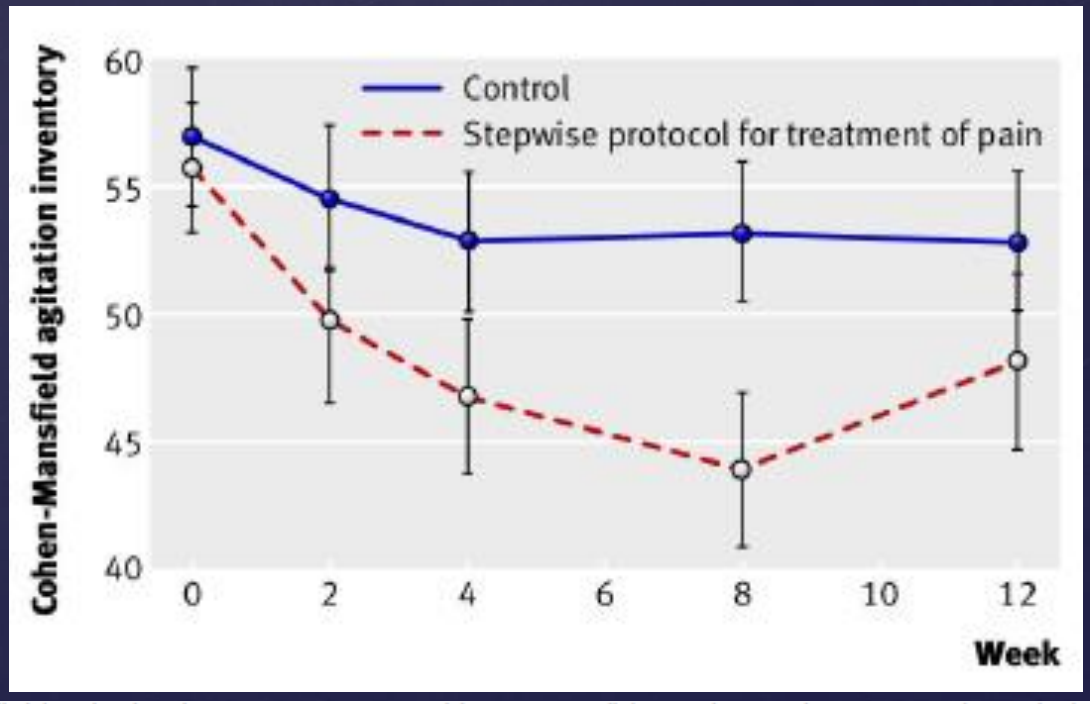


Fig 2 Cohen-Mansfield agitation inventory scores, with 95% confidence intervals, over study period

Husebo et al., BMJ. 2011

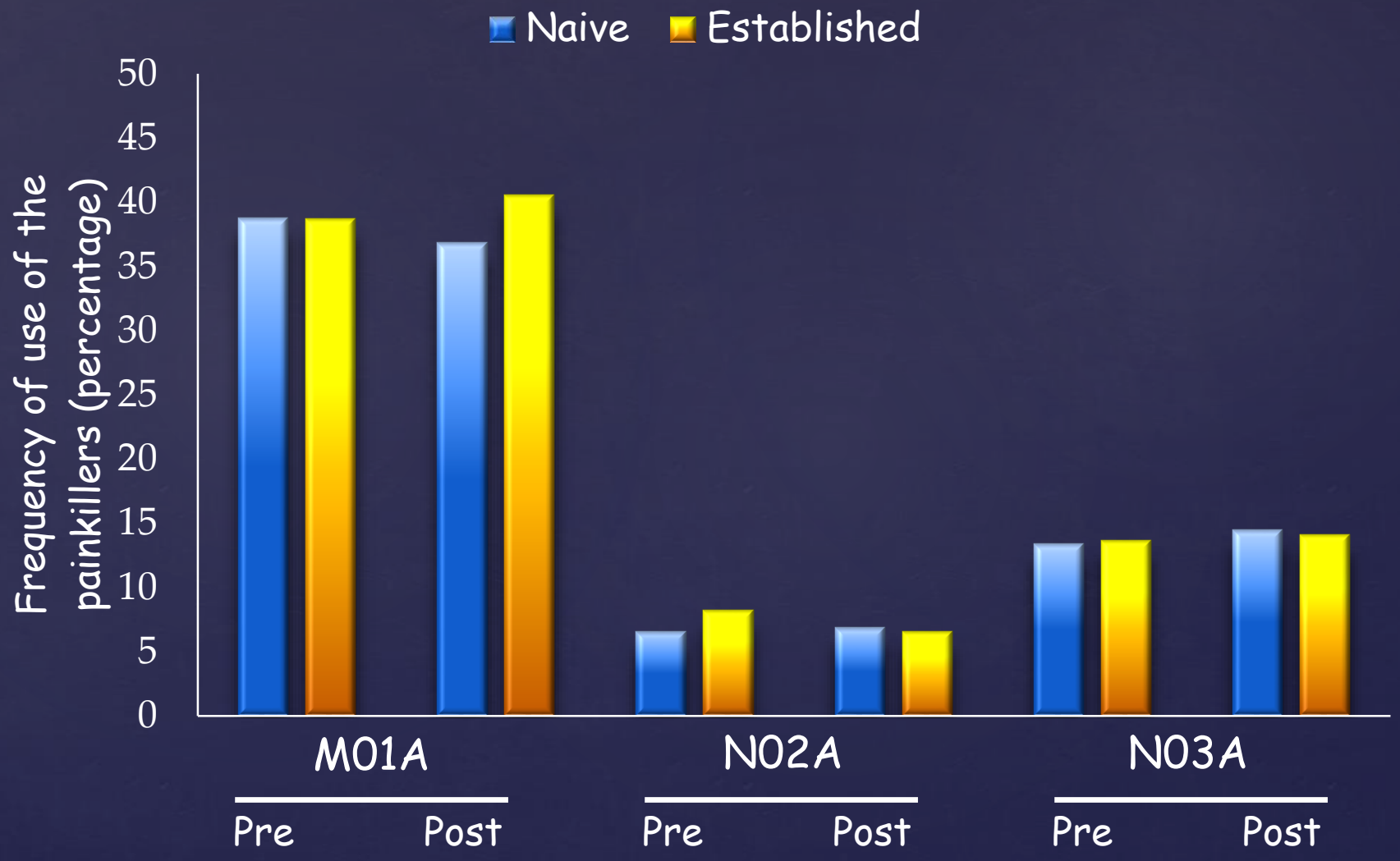
Scope

Because of the tight link between **underestimated pain** and **NPS**, the aim of this retrospective pharmacoepidemiologic survey was to assess accuracy in painkillers utilization in patients suffering from dementia in Calabria.

Experimental procedures

- ✓ Evaluation of prescriptions of acetylcholinesterase inhibitors (AChEI) and memantine (N06D WHO ATC classification) from July 2015 to June 2016;
- ✓ Monitoring of the percentage of demented patients treated against pain with non steroidal antinflammatory drugs (FANS; M01A), opioids (N02A) and antiepileptics (N03A);
- ✓ Statistical analyisis for difference (Chi-Square test) between the frequency of treatment before (pre) and after (post) the settlement of dementia therapy.

Percentage of demented patients treated with FANS (M01A), opioids (N02A) and antiepileptics (N03A) against pain



Scuteri et al., Neural Regen Res 2018

Dementia as a barrier to pain assessment

TABLE 2. Efficacy of Pain Treatment for the Factor Groups (1–4)

	Control (N = 157)			Intervention (N = 147)					
Factor group 1–4	Baseline Mean (SD)[a]	Week 8	Difference (95% CI)	Baseline Mean (SD)[a]	Week 8	Difference (95% CI)	DF[a]	t[a]	p[a]
1 Aggressive behavior	18.8 (7.1)	17.6 (6.6)	1.0 (0.1, 2.0)	18.9 (6.6)	16.7 (6.5)	2.2 (1.1, 3.3)	1196.0	−2.093	0.037
2 Physically nonaggressive behavior	15.0 (7.8)	13.9 (7.4)	1.1 (0.1, 2.2)	15.0 (7.0)	12.1 (6.8)	2.9 (1.8, 4.0)	1198.0	−2.672	0.008
3 Verbally agitated behavior	11.7 (5.7)	11.3 (5.9)	0.6 (0.2, 1.5)	11.3 (5.0)	8.4 (4.9)	2.9 (2.1, 3.6)	1204.0	−4.308	<0.001
4 Hiding and hoarding	3.8 (2.9)	3.5 (2.9)	0.5 (0.1, 0.9)	3.6 (2.4)	3.0 (2.2)	0.6 (0.2, 1.0)	1203.0	−0.655	0.513

Notes: Mean (SD) at week 8 and difference from baseline for the control and intervention groups.
[a]Analyzing the Factor group scores for the control versus the intervention group from baseline to week 8 using random-intercept model in a two-way repeated-measure configuration.

Husebo et al., Am J Geriatr Psychiatry. 2014

Table 5
Associations Between the Changes in Pain Severity* and the Changes in Each of These NPI-NH Domains† of Participants Who Completed Follow-Up

Dependent Variables†	B§	95% CI of β‖	z	*P*
A. Delusions	0.03	−0.03 to 0.08	1.04	.30
B. Hallucinations	0.01	−0.02 to 0.05	0.71	.48
C. Agitation/aggression	0.12	0.06–0.17	3.99	<.001
D. Depression/dysphoria	0.06	−0.01 to −0.13	1.80	.07
E. Anxiety	−0.01	−0.05 to 0.04	−0.27	.79
F. Elation/euphoria	0.02	−0.01 to 0.05	1.18	.24
G. Apathy/indifference	0.05	−0.10 to 0.19	0.66	.51
H. Disinhibition	0.00	−0.04 to 0.04	0.13	.90
I. Irritability/lability	0.03	−0.09 to 0.16	0.52	.60
J. Aberrant motor behavior	0.01	−0.09 to 0.12	0.28	.78

Rajkumar et al., J Am Med Dir Assoc. 2017

Need for pain diagnosis and assessment → caregivers'training

Aromatherapy to treat agitation and aggression in people affected with dementia

Trials conducted	Evidence	Major adverse effects	Interpretation
Psychological therapies[31–33,36,37]			
Two RCTs examined whether staff training can reduce antipsychotic use Two RCTs of individualized psychological intervention, one RCT and one open trial of 'tool box' psychological intervention Three RCTs of validation therapy, several trials of other specific therapies such as reminiscence	Robust evidence from two large RCTs indicates that staff training in nursing homes can reduce use of atypical antipsychotics without worsening patients' behavior The RCTs of individualized psychological intervention and 'tool box' intervention suggest significant benefit In small preliminary RCTs, validation therapy seems to be better than treatment as usual but comparable to social interaction	None—well tolerated and popular therapeutic approaches	Emerging evidence indicates that several methods of training and psychological interventions work well, but these approaches are only effective if implemented systematically by appropriately trained staff—which could limit potential availability Probably the preferred first-line treatment option when no high level of risk or extreme distress is present
Aromatherapy or herbal remedies[38,40,43,85]			
Three short (all ≤4 weeks) placebo-controlled RCTs, two with lavender oil, one with melissa oil	All three trials demonstrated significant benefits, but only the trial with melissa oil was included in the Cochrane meta-analysis because of methodological issues One additional trial that used oral melissa also indicated benefit	None—extremely well tolerated	Safe and popular treatment approach with encouraging emerging evidence

Abbreviation: RCT, randomized controlled trial.

Ballard et al.,, Nat Rev Neurol 2009

Contributors

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THANK YOU FOR YOUR ATTENTION

Senato della Repubblica

XVII LEGISLATURA

N. 2840

DISEGNO DI LEGGE

d'iniziativa dei senatori AIELLO, MANDELLI, RIZZOTTI, FLORIS, ZIZZA, LIUZZI, PAGANO, BILARDI, GUALDANI e SPILABOTTE

COMUNICATO ALLA PRESIDENZA IL 24 MAGGIO 2017

Disposizioni per garantire l'accesso alle cure dei pazienti con disturbo comportamentale e psicologico associato a demenza