

# Nonpharmacological Therapies in Alzheimer's Disease: A Systematic Review of Efficacy

Javier Olazarán<sup>a</sup> Barry Reisberg<sup>i</sup> Linda Clare<sup>e</sup> Isabel Cruz<sup>a</sup> Jordi Peña-Casanova<sup>a,d</sup>  
Teodoro del Ser<sup>a,b</sup> Bob Woods<sup>e</sup> Cornelia Beck<sup>j</sup> Stefanie Auer<sup>m</sup> Claudia Lai<sup>n</sup> Aimee Spector<sup>f</sup>  
Sam Fazio<sup>k</sup> John Bond<sup>g</sup> Miia Kivipelto<sup>o</sup> Henry Brodaty<sup>p</sup> José Manuel Rojo<sup>c</sup> Helen Collins<sup>h</sup>  
Linda Teri<sup>l</sup> Mary Mittelman<sup>i</sup> Martin Orrell<sup>f</sup> Howard H. Feldman<sup>q,r</sup> Ruben Muñoz<sup>a</sup>

<sup>a</sup>Maria Wolff Foundation, <sup>b</sup>Noscira and <sup>c</sup>Superior Council of Scientific Research, Madrid, and <sup>d</sup>Hospital del Mar and Municipal Institute of Medical Research, Barcelona, Spain; <sup>e</sup>Bangor University, Bangor, <sup>f</sup>University College London, London, <sup>g</sup>Newcastle University, Newcastle, and <sup>h</sup>Cochrane Dementia and Cognitive Improvement Group, Oxford, UK; <sup>i</sup>New York University Medical Center, New York, N.Y., <sup>j</sup>University of Arkansas for Medical Sciences, Little Rock, Ark., <sup>k</sup>Alzheimer's Association, Chicago, Ill., and <sup>l</sup>University of Washington School of Nursing, Seattle, Wash., USA; <sup>m</sup>MAS Alzheimerhelp, Bad Ischl, Austria; <sup>n</sup>Hong Kong Polytechnic University, Hong Kong, SAR, China; <sup>o</sup>Karolinska Institutet, Stockholm, Sweden; <sup>p</sup>University of New South Wales, Sydney, N.S.W., Australia; <sup>q</sup>Division of Neurology, University of British Columbia, Vancouver, B.C., Canada, and <sup>r</sup>Neuroscience, Bristol Myers Squibb, Wallingford, Conn., USA

## Key Words

Alzheimer's disease, nonpharmacological therapy · Efficacy evaluation

## Abstract

**Introduction:** Nonpharmacological therapies (NPTs) can improve the quality of life (QoL) of people with Alzheimer's disease (AD) and their carers. The objective of this study was to evaluate the best evidence on the effects of NPTs in AD and related disorders (ADRD) by performing a systematic review and meta-analysis of the entire field. **Methods:** Existing reviews and major electronic databases were searched for randomized controlled trials (RCTs). The deadline for study inclusion was September 15, 2008. Intervention categories and outcome domains were predefined by consensus. Two researchers working together detected 1,313 candidate studies of which 179 RCTs belonging to 26 intervention categories were selected. Cognitive deterioration had to be documented in all participants, and degenerative etiology

(indicating dementia) had to be present or presumed in at least 80% of the subjects. Evidence tables, meta-analysis and summaries of results were elaborated by the first author and reviewed by author subgroups. Methods for rating level of evidence and grading practice recommendations were adapted from the Oxford Center for Evidence-Based Medicine. **Results:** Grade A treatment recommendation was achieved for institutionalization delay (multicomponent interventions for the caregiver, CG). Grade B recommendation was reached for the person with dementia (PWD) for: improvement in cognition (cognitive training, cognitive stimulation, multicomponent interventions for the PWD); activities of daily living (ADL) (ADL training, multicomponent interventions for the PWD); behavior (cognitive stimulation,

Steering Committee: J.O., B.R., L.C. and R.M.; Project Workgroup: J.O., B.R., L.C., I.C., J.P.-C., T. del S., B.W., C.B., S.A., C.L., A.S., S.F., J.B., M.K., H.B., J.M.R., H.C., L.T., M.M., M.O., H.H.F. and R.M.; principal author: J.O.

multicomponent interventions for the PWD, behavioral interventions, professional CG training); mood (multicomponent interventions for the PWD); QoL (multicomponent interventions for PWD and CG) and restraint prevention (professional CG training); for the CG, grade B was also reached for: CG mood (CG education, CG support, multicomponent interventions for the CG); CG psychological well-being (cognitive stimulation, multicomponent interventions for the CG); CG QoL (multicomponent interventions for PWD and CG). **Conclusion:** NPTs emerge as a useful, versatile and potentially cost-effective approach to improve outcomes and QoL in ADRD for both the PWD and CG.

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## Introduction

Alzheimer's disease (AD), which is frequently preceded by a prodromal mild cognitive impairment (MCI) stage, is a long process with a potential duration of 20 years or even longer, for people who survive into the final substages of the disease process [1]. For all stages of dementia, particularly for the most severely impaired individuals with immobility, inability to speak and other disabilities, it is vital that the basic human needs for well-being, movement, dignity, social interaction and fundamental human rights are protected [2]. It is important to ensure that basic and higher human needs are met and to be aware of the continued capacity to learn, to think, to feel, to seek to influence their environment, experience the sense of being loved and cared for, and the potential for happiness and equanimity of the person with dementia (PWD) [3].

The pathological process in AD, affecting cognition, functioning and behavior, and the continuing human needs accompanying the evolution of AD provide a wealth of opportunities for environmental, social and therapeutic intervention. Although pharmacotherapies appear to slow aspects of AD symptom progression, the current limits on the effectiveness of drugs and the requirement for a range of options highlight the need for robust evaluations of nonpharmacological therapeutic intervention in AD. Considering the millions of people worldwide with AD [4] and corresponding societal costs in terms of management and care [5], there is a significant lack of funding for the systematic research of nonpharmacological therapy (NPT). Moreover, the need for NPT research in AD is made more acute because of the suffering that results from the widespread suboptimal care due to the absence of the essential evidence required to show

what is useful and cost-effective. Despite this there has been an exponential increase in the research literature on NPTs in AD. This paper presents the results of a worldwide research collaboration to review the evidence for the effectiveness of NPTs in AD and related disorders (ADRD). We hope that this review will provide a platform for continuing advances as well as a rationale for immediate improvements in therapeutic interventions, to improve services and care for persons with ADRD.

## Methods

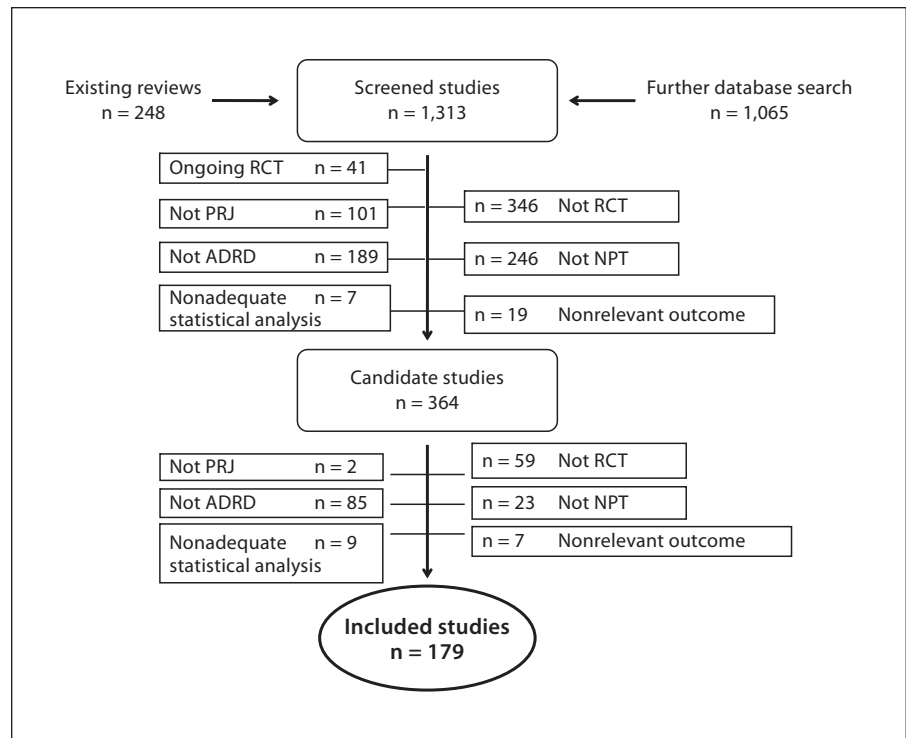
A core Steering Committee subgroup of 4 NPT Project Workgroup members formulated the methodology of the review, coordinated the efforts of other involved investigators and wrote the manuscript. A nonpharmacological intervention was defined as 'any theoretically based, nonchemical, focused and replicable intervention, conducted with the patient or the caregiver (CG), which potentially provided some relevant benefit'.

Candidate studies were first identified by existing reviews, which were obtained from electronic databases and via the input of NPT Project members (online supplementary material, [www.karger.com/doi/10.1159/000316119](http://www.karger.com/doi/10.1159/000316119)). In a second step, additional candidate studies were identified by searches of the following electronic databases: Medline, PsycINFO, CINAHL, Embase, Lillacs and the Cochrane Dementia and Cognitive Improvement Group Specialized Register. The deadline for study inclusion was a publication date of September 15, 2008.

For a candidate study to be selected, 5 inclusion criteria had to be fulfilled:

- (1) parallel-group randomized controlled trial (RCT);
- (2) publication in a peer-reviewed journal;
- (3) all participants had cognitive impairment or dementia, at least 80% due to ADRD; degenerative and mixed dementias were included under the ADRD rubric, but pure vascular dementia and other dementias secondary to non-degenerative, identified conditions, were not included. For MCI and other descriptions of cognitive impairment, an underlying ADRD etiology was assumed unless otherwise specified;
- (4) the efficacy of a nonpharmacological intervention was tested in at least 1 of the following domains: (a) *for the patient* – cognition, activities of daily living (ADLs), behavior, mood, combined scales, physical domain, quality of life (QoL), institutionalization, restraint usage (either physical or chemical restraint) or mortality; (b) *for the CG* (professional or non-professional) – mood, psychological well-being (PWB), objective burden or QoL; (c) *cost-effectiveness*;
- (5) appropriate statistical analyses were required; both within- and between-group comparisons were acceptable; an RCT was classified as 'positive' if statistically significant differences between experimental and control groups were reported ( $p < 0.05$ ); post-hoc within-group comparisons were accepted without adjustments for multiple comparisons.

All assessments were considered valid for interpretation of results, including follow-up assessments once the intervention program had ended. Usual care was accepted as an adequate control condition.



**Fig. 1.** Literature search and study selection process. PRJ = Peer-reviewed journal; RCT = randomized controlled trial.

Before initiating the search, the Project Workgroup delineated a set of intervention categories (e.g. cognitive stimulation, music therapy etc.) and key words (fig. 1). Categories and key words were modified and combined when these procedures were considered useful in the search process. In a first step, reviews and paper abstracts were used to discard studies that clearly did not fulfill at least 1 of the 5 inclusion criteria. In all other cases, the complete paper was consulted for decisions regarding inclusion (online supplementary material, [www.karger.com/doi/10.1159/000316119](http://www.karger.com/doi/10.1159/000316119)). The process of collecting information with respect to study inclusion in this analysis was performed collectively by 2 Workgroup members (J.O. and I.C.). Doubts and discrepancies were resolved by discussion.

An evidence table was developed for each intervention category by the principal author (J.O.). These tables contained sample characteristics, descriptions of interventions, outcomes in the different domains and time periods, data quality descriptors and reference citations of all the included RCTs which fulfilled the study criteria. Where adequate data were available, meta-analysis was performed. When several measures belonging to a single domain were utilized in the same RCT, the measure that was mentioned first in the study method section was selected for the meta-analysis. If necessary data from an included study were not available from the published papers, the study authors were contacted in an effort to include applicable information. Overall effect sizes and odds ratios were calculated using a fixed-effects model. For continuous variables, effect sizes were defined as posttreatment change in the experimental condition minus post-treatment change in the control condition, divided by the pooled standard deviation [6]. For the analysis of institutionalization

and death, odds ratios were calculated using Peto's log rank test [7]. Software Stata V10, SSC METAN (Bradburn M.J., Deeks J.J., Altman D.G., University of Bristol, UK) was used for analyses ([www.stata.com](http://www.stata.com)).

An evidence table and corresponding materials for each intervention category were sent to 2 NPT Project Workgroup members for review. Workgroup members were not permitted to review their own studies or any studies within the same intervention category as their published work. Recommendations for practice were established by consensus between the principal author (J.O.) and the 2 Workgroup members reviewing the intervention category after appraising both individual studies within the category and meta-analysis results. Oxford Center of Evidence-Based Medicine guidelines were followed ([www.cebm.net](http://www.cebm.net)). The Oxford guideline grading of practice recommendations scores a grade A recommendation for consistent high-quality RCTs and a grade B recommendation for consistent low-quality RCTs. A high-quality RCT was defined for this systematic review if it fulfilled all of the following criteria:

- (1) cognitive impairment of degenerative or mixed (i.e. degenerative + secondary) etiology was documented in all participant subjects;
- (2) study groups had comparable (or statistically controlled) characteristics at baseline;
- (3) a detailed description of intervention was given;
- (4) effects were measured by independent and blind evaluators (nonblind assessments were accepted for institutionalization and death);
- (5) validated outcome measures were used;

**Table 1.** Results in the intervention categories by outcome domains

	RCTs		Outcome domains <sup>1</sup>							
	n	control conditions	PWD							
			cog.	ADLs	behavior	mood	comb.	phys.	QoL	
<b>Interventions for PWDs</b>										
Cognitive training	14	6/7; 0/1; 3/6	9/14	2/8	2/5	1/4	0/4	1/1	0/1	
Behavioral interventions	11	2/4; 0/2; 3/5	1/3	1/4	2/5	1/2	0/4	–	1/1	
Cognitive stimulation	10	6/7; 1/1; 1/2	6/8	0/3	0/5	2/6	2/6	–	1/2	
Transcutaneous electrical stimulation	10	0/0; 0/0; 5/10	2/7	1/6	3/8	1/5	–	–	–	
Physical exercise	9	1/1; 2/2; 3/6	3/5	0/2	–	1/1	0/1	3/5	0/1	
Use of music	7	3/4; 0/1; 1/2	3/5	0/1	3/4	1/2	0/1	–	–	
Reminiscence	6	4/5; 0/0; 1/1	2/5	2/5	2/3	2/4	1/4	–	0/1	
ADL training	4	4/4; 0/0; 0/0	0/1	4/4	0/1	–	–	–	–	
Massage and touch	4	3/3; 1/1; 0/0	–	–	4/4	–	–	–	–	
Recreation therapy	4	3/4; 0/0; 0/0	1/1	–	1/3	0/1	1/2	–	1/1	
Use of light	4	0/1; 0/0; 1/3	0/1	–	1/4	0/1	–	–	–	
Multisensory stimulation	3	1/1; 0/0; 1/2	0/2	1/2	2/3	0/1	1/2	–	–	
Support and psychotherapy	3	1/3; 0/0; 0/0	0/2	0/1	0/1	1/2	0/2	–	–	
Validation	2	1/2; 0/0; 0/0	0/1	0/1	1/2	1/2	–	–	–	
Acupuncture	1	0/0; 0/0; 1/1	0/1	–	–	–	–	–	–	
Transcranial magnetic stimulation	1	0/0; 0/0; 1/1	1/1	–	–	–	–	–	–	
Muscle relaxation	1	0/0; 0/0; 1/1	1/1	–	1/1	0/1	1/1	–	–	
Multicomponent	19	9/13; 3/3; 1/3	5/11	3/11	4/9	5/9	2/4	1/5	2/3	
<b>Interventions for CGs</b>										
CG education	33	13/16; 5/9; 7/8	0/6	1/5	2/6	0/2	2/11	0/1	1/1	
CG support	8	0/4; 2/3; 0/1	–	0/1	0/1	–	0/3	–	–	
Case management	4	3/3; 0/1; 0/0	–	–	–	0/1	–	–	1/1	
Respite care	2	1/2; 0/0; 0/0	–	–	–	–	–	–	–	
Multicomponent	6	1/1; 5/5; 0/0	–	–	–	–	0/3	–	1/1	
<b>Other interventions</b>										
Multicomponent for PWD and CG	18	6/10; 5/6; 1/2	1/8	2/11	4/8	2/5	1/7	0/1	3/4	
Professional CG training	10	7/8; 1/2; 0/0	0/1	0/4	4/9	4/5	0/1	–	–	
Special units	1	0/0; 1/1; 0/0	0/1	0/1	0/1	–	–	–	–	

n = Number of RCTs for each intervention category (some RCTs tested interventions from more than one category); control conditions: first ratio = number of positive RCTs among those including a usual-care control group; second ratio = number of positive RCTs among those including some (usually minimal) social attention control group but not a usual-care control group;

third ratio = number of positive RCTs among those that only included a control group offering a similar level of social attention compared to the experimental group. Cog. = Cognition; comb. = scales combining cognition, ADLs, behavior and mood; phys. = physical domain; PWB = psychological well-being; obj. = objective; inst. = institutionalization.

(6) intention-to-treat principles were applied; observed cases, last-observation-carried-forward- and regression-based analyses were accepted); exclusions from analyses on the basis of intervention compliance were not permitted;

(7) effect was assessed in at least 30 patients and 80% of randomized patients per study group, and all losses were explained.

Interventions were considered for recommendation when data from at least 2 studies that tested the effect of a set of similar interventions, in the same outcome domain, were available. To establish practice recommendation, positive results (i.e. 95% confidence interval of global effect size not including zero), homogeneous results (p for Cochran Q < 0.05) and clinical relevance had to be present.

In the textual descriptions, the following definitions were used: MCI, mild dementia, moderate dementia, moderately severe dementia and severe dementia, which were equivalent to Global Deterioration Scale [8] stages 3, 4, 5, 6 and 7, respectively. When the Global Deterioration Scale severity was not specified in the publication, it was estimated in accordance with collateral clinical data. In the assessment of potential recommendations, RCTs conducted exclusively on MCI were analyzed separately. Once the results and discussion sections had been compiled, a complete draft of the manuscript was sent to all NPT Project Workgroup members for final comments and approval.

							References <sup>2</sup>
CG				other			
mood	PWB	QoL	obj. burden	inst.	re-straints	cost	
1/2	0/2	0/1	-	-	-	-	9-[15, 16]-23
3/6	3/9	1/1	0/2	0/2	0/1	-	24-29, 30*, 31, 32*-34
0/1	1/3	0/1	-	-	-	1/1	35-[42, 43]-45*
-	-	-	-	-	-	-	46-[48, 49]-[54, 55]*, [56, 57], 58
-	-	-	-	-	-	-	[15, 16], 59-[65, 66]*, 67
-	-	-	-	-	-	-	68-74
-	0/1	0/1	-	-	-	-	36, 75-79
-	-	-	-	-	-	-	80-83
-	-	-	-	-	-	-	72, 84-86
-	-	-	-	-	-	-	37, 87-89
-	-	-	-	-	-	-	[90, 91]-94
-	-	-	-	-	-	-	95-97
0/2	0/2	0/1	-	-	-	-	14, 98, 99
-	-	-	-	-	0/1	0/1	100, 101
-	-	-	-	-	-	-	102
-	-	-	-	-	-	-	103
-	-	-	-	-	0/1	-	104
0/1	1/5	-	-	0/1	-	0/1	27, 75, 105-107*-118*-121
9/22	21/31	3/5	1/3	0/3	-	0/5	24, 29, 31, [122, 123]-[127, 128]-[131, 132]-[136, 137]-[148, 149]-156
1/6	1/5	0/2	-	0/1	-	0/2	26, 141, 157, [158, 159]-161*-163
2/2	1/3	0/1	1/2	0/1	-	0/3	164-[166-169], [170, 171]
0/1	1/2	-	-	-	-	0/1	172, 173
4/6	4/5	1/3	1/1	1/5	-	1/2	141, 174*, [175, 176], [177-185]*, [186, 187]*, 188
4/11	7/16	3/4	1/3	0/3	0/3	2/4	9, 14, 26, [189-191]-194*-[197-199]-[203-205]-208*, 209
0/1	4/7	-	-	0/1	2/3	-	210, [211, 212]-[214, 215]-221
1/1	1/1	1/1	-	-	-	-	222

<sup>1</sup> Figures represent number of positive RCTs per total number of RCTs that tested the corresponding outcome domain; mood items were sometimes included in behavior (PWD) or PWB (CG) scales; - = no RCTs were identified.

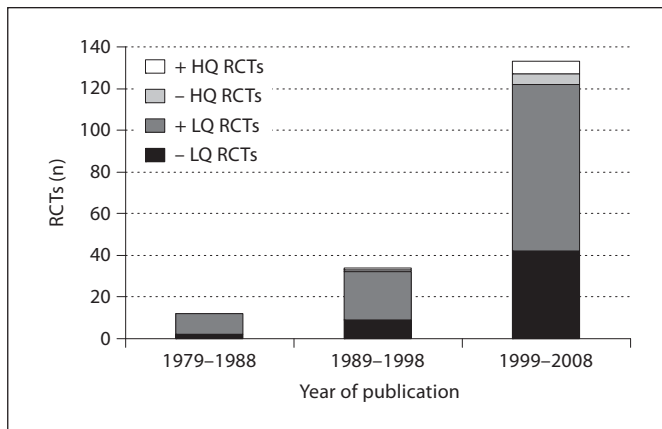
<sup>2</sup> References from the same RCT are in square brackets; high-quality RCTs are marked with an asterisk.

## Results

A comprehensive summary of intervention categories, results and the included publications [9-222] is shown in table 1. Most publications (97%) were in English. The number of randomized participants ranged from 8 [68] to 7,949 [166], and intervention duration varied from a few minutes (i.e. short single sessions) [51, 52, 152] to 11 years [184]. A chronological perspective shows an exponential increase in the number of RCTs (fig. 2). The pro-

portion of positive RCTs among all RCTs conducted remained stable over time. Only 13 high-quality trials were found [30, 32, 45, 54, 65, 107, 118, 161, 174, 177, 186, 194, 208] of which 7 (54%) were positive; 113 of 166 (68%) low-quality trials were positive ( $p = 0.360$ , Fisher's exact test).

Many categories had only 1 RCT (e.g. acupuncture), and these are shown in table 1, but are no longer mentioned in this paper. Due to intervention heterogeneity, some categories were segmented or narrowed for analysis of results. The resulting subcategories were as fol-



**Fig. 2.** RCTs included in this review by quality and results. LQ = Low quality; HQ = high quality; + = RCT showing a positive result ( $p < 0.05$ ) in at least 1 domain; - = RCT showing neutral results.

lows: cognitive training (individual, group or computer-based sessions); cognitive stimulation (group or individual sessions); reminiscence (group or individual sessions); use of music (recorded music); transcutaneous electrical stimulation (cranial or dorsal stimulation); use of light (morning bright light); massage and touch (therapeutic touch); physical exercise (walking or comprehensive exercise); multicomponent interventions for the PWD (enriched group cognitive stimulation, enriched group cognitive training or physical exercise and music); CG support (electronic devices); CG education (coping skills individual sessions, coping skills group sessions for community-dwelling PWD or coping skills group sessions for institutionalized PWD); multicomponent interventions for PWD and CG (in-home counseling or support groups); professional CG interventions (education on dementia management or alternatives to restraint).

Given the paucity of high-quality data, potential grade A recommendations could only be addressed for the effect of multicomponent interventions for the CG on institutionalization and death. Considering high- and low-quality evidence together, limited or inconclusive results were found in the following domains: combined domain, physical domain, objective burden, cost and death. For the remaining domains, recommendations could be established at grade B level.

#### *NPTs to Delay Institutionalization*

The pooling of 3 high-quality RCTs testing multicomponent interventions for the CG demonstrated a delay in

the institutionalization of mild to moderately severe AD persons when compared to usual care [174, 177, 186]. The essential components of these interventions were individual assessment, information, counseling and support. Sessions lasted from 30 to 90 min and were conducted with a frequency of every 2 months to twice monthly by social workers [174], nurses [177] or trained personnel [186]. Skill training [177, 186], respite services [174], support groups [177, 186] and continuous availability of a therapist [174, 177] were particularly stressed. After 6 or 12 months of intervention, the overall institutionalization rate was 10.6% in the intervention groups versus 14.9% in the control groups (risk reduction 0.67, 95% confidence interval 0.49–0.92; fig. 3). In one of these RCTs, after more than 11 years of intervention, the delay in nursing home placement reached 557 days [183] (grade A recommendation).

#### *NPTs to Improve Cognition*

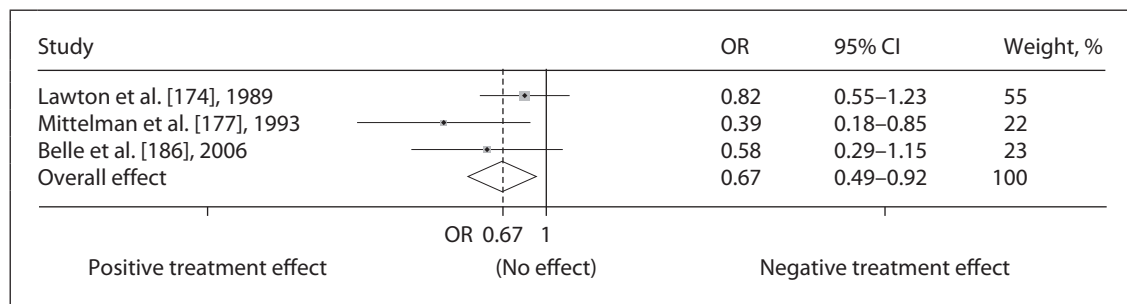
The training of specific cognitive abilities in small groups (cognitive training, group sessions) produced an improvement specific to those cognitive skills. Two small RCTs demonstrated improvement of verbal and visual learning after teaching of memory strategies had been conducted daily [11] or twice weekly [9]. Another small RCT, conducting weekly sessions, was neutral [18] but meta-analysis yielded homogenous and positive results (table 2). Positive effects on cognition were also demonstrated when cognitive training in individual sessions was conducted. In 2 RCTs, this intervention was administered by the family CG [13, 14].

For cognitive stimulation group sessions, there were trials indicating significant improvements in measures of attention, memory [35, 40], orientation, language [37] and general cognition [38, 42]. The augmentation of cognitive stimulation with other components (e.g. relaxation) produced benefits in general cognition (multicomponent interventions for the PWD, enriched group cognitive stimulation; table 2).

In a high-quality RCT, cognitive stimulation was delivered by CGs in patients' homes as an adjunct to donepezil. A benefit of 2.9 points over medication alone was shown on the cognitive subscale of the Alzheimer's Disease Assessment Scale [223] for those receiving the combined treatments ( $p = 0.01$ ) [45].

#### *NPTs to Improve ADLs*

ADL training was used to ameliorate the performance of ADL decrements in cognitively impaired nursing home residents. Positive results compared to a usual-care



**Fig. 3.** Multicomponent interventions for the CG and institutionalization delay: meta-analysis of high-quality RCTs. The odds ratio (OR) of 0.67 indicates 33% less institutionalization after 6–12 months of multicomponent intervention compared to the minimal support or usual-care control group ( $Q = 2.95$ ,  $p = 0.228$ ). CI = Confidence interval;  $Q$  = test for heterogeneity of effects ( $p > 0.05$  indicates homogeneity).

control group were reported in all the identified studies. The interventions included: scheduling and prompting used to reduce urinary incontinence [80]; graded assistance to improve individual autonomy [81]; prompting and reinforcement during meals to improve eating independence [82], and a specific way-finding intervention to assist residents in locating a dining room [83].

Group sessions of cognitive stimulation, reminiscence and relaxation (multicomponent interventions for PWD, enriched group cognitive stimulation) improved orientation after 3 months whereas persons receiving usual care deteriorated [110]. Within this subcategory, a trend of less deterioration in instrumental ADLs was observed after 1 year of cognitive stimulation plus psychomotor exercises, using minimal support as a control group [109]. Another RCT conducting less frequent sessions was neutral [108]; however, meta-analysis of the subcategory indicated positive results (table 2).

#### *NPTs to Improve Behavior*

The highest effect on behavior was attained by pooling 3 individually neutral small RCTs of cognitive stimulation group sessions that were performed in behaviorally disturbed PWDs who lived in institutions. The measures utilized included problem behavior [36], control of emotions [37] and disruptive behavior [39]. A moderate improvement in general behavior [108] and withdrawal [110] was also attained in less behaviorally disturbed community-dwelling PWDs after conducting multicomponent interventions in the PWD (enriched group cognitive stimulation).

Interventions specifically targeted at behavior (i.e. behavioral interventions) performed by individual work with the family CG reduced behavior disturbance in

PWDs displaying agitation [27, 32], aggressive behavior [28], depression [32] or problem behaviors [29]. One of these RCTs compared behavioral management, haloperidol, trazodone and placebo pills. A similar improvement was observed in the 4 groups, but behavioral management produced fewer adverse events than the 2 medications [27]. In a high-quality RCT, behavior management was not superior to usual care in 2 traditional measures of behavior disturbance; however, a reduction in the frequency and severity of problematic behaviors identified at baseline by CGs of the experimental group was reported by 57 and 52% of CGs, respectively [32].

Four RCTs tested the effect of professional CG training as dementia management on the behavior of institutionalized PWDs. Agitation was reduced after treatment in 2 individual RCTs [210, 217] and meta-analysis yielded a mild positive effect.

#### *NPTs to Improve Mood*

Multicomponent interventions for PWD (enriched group cognitive stimulation) produced a progressive improvement of affective symptoms that reached statistical significance after 1 year of treatment. Although not reported, baseline prevalence of clinical depression in these RCTs seemed to be low [108, 109]. Another RCT conducting a 10-week intervention produced a neutral result [110]. The pooled results of the 3 RCTs were positive (table 2).

In a high-quality trial, a 6-month individualized program of physical exercise plus behavioral management was implemented. CGs (80% spouses) were encouraged to identify pleasant activities and to promote positive interactions. Benefits in mood were observed that reached statistical significance after the 3-month period of inten-

**Table 2.** NPTs recommended in ADRD on the basis of homogeneous evidence from low-quality RCTs (grade B recommendations)

Outcome	NPT essential characteristics	Session format and intervention duration	PWD characteristics and setting	Effect size and homogeneity <sup>1</sup>	Ref. <sup>2</sup>
Cognition	<i>Cognitive training, group sessions:</i> the teaching of strategies (e.g. mental imagery) to improve verbal learning and other cognitive functions	45–90 min, 2–7/week, 11–25 days	GDS 3–4, community	0.594 (0.052–1.137), k = 3, n = 67, Q = 2.34, p = 0.310	9, 11, 18
	<i>Cognitive stimulation, group sessions:</i> themed activities to orientate and actively stimulate cognition through, e.g., association and categorization	30–60 min, 2–5/week, 4–24 weeks	GDS 4–6, community (day center), nursing home, residential home, long-term care hospital	0.442 (0.197–0.688), k = 6, n = 270, Q = 4.09, p = 0.537	35–37, 38 <sup>3</sup> , 40–42
	<i>Cognitive training, individual sessions:</i> the teaching of strategies (e.g. spaced retrieval, dual cognitive support) to improve verbal learning and other cognitive functions	20–60 min, 2–6/week, 6–26 weeks	GDS 3–5, community, nursing home	0.403 (0.085–0.721), k = 7, n = 255, Q = 9.45, p = 0.150	10, 13, 14, 16, 17, 19, 20
	<i>Multicomponent interventions for PWD, enriched group cognitive stimulation:</i> cognitive stimulation and some of the following: reminiscence, physical exercise, ADL training, support	90–210 min, 1–2/week, 6–52 weeks	GDS 3–5, community, nursing home	0.307 (0.036–0.578), k = 5, n = 213, Q = 1.60, p = 0.808	108–110, 114, 120
ADLs	<i>ADL training:</i> guided performance providing the minimal required assistance to complete target ADLs, e.g. verbal prompting and reinforcement to avoid incontinence	Intervention integrated in usual care, or individual (30 min, 3/week) or group (2.5 h, 5/week) sessions, 3 days to 20 weeks	GDS 3–6, nursing home	0.412 (0.003–0.821), k = 3, n = 95, Q = 1.33, p = 0.514	80 <sup>3</sup> , 81–83
	<i>Multicomponent interventions for the PWD, enriched group cognitive stimulation:</i> cognitive stimulation and some of the following: reminiscence, physical exercise, ADL training, support	90–210 min, 1–2/week, 10–52 weeks	GDS 3–5, community	0.369 (0.062–0.676), k = 3, n = 167, Q = 1.25, p = 0.535	108–110
Behavior	<i>Cognitive stimulation, group sessions:</i> themed activities to orientate and actively stimulate cognition through, e.g. association and categorization	30–60 min, 3–5/week, 4–11 weeks	GDS 5–6, behavior disturbance, nursing home, long-term care hospital	0.608 (0.092–1.124), k = 3, n = 62, Q = 1.03, p = 0.598	36, 37, 39
	<i>Multicomponent interventions for the PWD, enriched group cognitive stimulation:</i> cognitive stimulation, reminiscence and some of the following: relaxation, support	90 min, 1–2/week, 10–52 weeks	GDS 3–5, community	0.604 (0.181–1.027), k = 2, n = 90, Q = 0.00, p = 0.952	108, 110
	<i>Behavioral interventions:</i> analysis and modification of antecedents and consequences of behavior, e.g. use of distraction techniques to mitigate aggressive episodes	Individual or group sessions with family CG, 60–90 min, 1/week to 1/month, 1–26 weeks	GDS 4–6, behavior disturbance, community	0.565 (0.209–0.921), k = 3, n = 167, Q = 2.48, p = 0.290	27 <sup>3</sup> –29, 32 <sup>*3</sup> , 33
	<i>Professional CG training, dementia management:</i> education and training of nursing assistants and other direct care staff in knowledge of dementia, acknowledgement of resident's experiences, communication techniques and behavior management	Group workshops followed by individual sessions, 30 min to half day, 3/month, 8 weeks to 3 months	GDS 4–7, mood or behavior disturbance, nursing home, assisted living residence	0.223 (0.017–0.428), k = 4, n = 370, Q = 2.08, p = 0.557	210, 212, 214, 217
Mood	<i>Multicomponent interventions for the PWD, enriched group cognitive stimulation:</i> cognitive stimulation and some of the following: reminiscence, physical exercise, ADL training, support	90–210 min, 1–2/week, 10–52 weeks	GDS 3–5, community	0.376 (0.066–0.686), k = 3, n = 164, Q = 1.75, p = 0.417	108–110



**Table 2** (continued)

Outcome	NPT essential characteristics	Session format and intervention duration	PWD characteristics and setting	Effect size and homogeneity <sup>1</sup>	Ref. <sup>2</sup>
QoL	<i>Multicomponent interventions for PWD and CG, in-home counseling:</i> individualized programs for effective dementia care based on comprehensive assessment, environment modifications and continuous counseling and support	Individual sessions with family CG, 60–90 min, 1–2/week, 6 weeks to 4 months	GDS 4–5, community	0.561 (0.087–1.035), k = 2, n = 170, Q = 2.17, p = 0.141	204, 209
CG mood	<i>CG education, coping skills, individual sessions:</i> intervention based on individual assessment, information, problem solving, cognitive restructuring and emotional support to mitigate stress derived from caregiving	Sessions usually at home, 45–90 min, sometimes additional phone calls, 1/week to 1/3 months, 6 weeks to 24 months	GDS 4–6, community	0.269 (0.027–0.511), k = 9 <sup>4</sup> , n = 431, Q = 12.34, p = 0.137	29, 125 <sup>3</sup> , 134, 139–141, 146 <sup>3</sup> , 152, 156
	<i>CG support, electronic devices:</i> computer or telephone systems providing information and support	Home installation of electronic device for use as needed or regular support groups, 6–12 months	GDS 4–6, community	0.196 (–0.004 to 0.395), k = 5 <sup>5</sup> , n = 390, Q = 0.64, p = 0.959	141, 158, 161*, 162
	<i>CG education, coping skills, group sessions, community-dwelling PWD:</i> interventions based on information, problem solving and cognitive restructuring to mitigate stress derived from caregiving	90–180 min, 1/week, 4–16 weeks	GDS 4–6, community	0.179 (0.018–0.340), k = 11 <sup>6</sup> , n = 636, Q = 10.27, p = 0.417	31, 127, 129, 131, 135, 142–145, 154
	<i>Multicomponent interventions for the CG:</i> long-term programs based on CG education and support; other components (e.g. respite care, support groups) are utilized according to individual needs and possibilities	Individual sessions with family CG and (option) other family members, 60–90 min, 1/1–3 weeks (sessions may become less frequent or substituted by contacts as needed), 6–12 months	GDS 4–6, community	0.166 (0.039–0.293), k = 8 <sup>7</sup> , n = 1,102, Q = 7.54, p = 0.375	141, 174 <sup>3</sup> , 175, 181, 186, 188
CG PWB	<i>Cognitive stimulation, group sessions:</i> themed activities to orientate and actively stimulate cognition through, e.g. association and categorization	30–45 min, 2–3/week, 8–10 weeks	GDS 4–6, nursing home, residential home, day center	0.898 (0.005–1.791), k = 2, n = 67, Q = 2.78, p = 0.095	39, 41
	<i>Multicomponent interventions for the CG:</i> Long-term programs based on CG education and support; other components (e.g. respite care, support groups) are utilized according to individual needs and possibilities	Individual sessions with family CG and (option) other family members, 90 min, 1/1–3 weeks (sessions may be substituted by contacts as needed), 6–8 months	GDS 4–6, community	0.139 (0.015–0.264), k = 6 <sup>8</sup> , n = 991, Q = 4.25, p = 0.514	174 <sup>3</sup> , 175, 178, 186, 188
CG QoL	<i>Multicomponent interventions for PWD and CG, in-home counseling:</i> individualized programs for effective dementia care based on comprehensive assessment, environment modifications and continuous CG counseling and support	Home visits with family CG, 60 min, 2/week to 1/2 weeks, 5 weeks to 6 months	GDS 4–6, community	0.678 (0.357–0.998), k = 2, n = 220, Q = 1.36, p = 0.243	204, 208*
Restraints	<i>Professional CG training, alternatives to restraint:</i> education of nursing staff on individualized care to avoid physical restraint	Group sessions, 1–6 h, 1/week to 1/month, 7 months	GDS 4–7, nursing and residential homes	–0.284 (–0.529 to –0.039), k = 2, n = 268, Q = 0.28, p = 0.596	218, 220

GDS = Global Deterioration Scale [8]; PWB = psychological well-being.  
<sup>1</sup> Overall effect size (95% confidence intervals in parentheses) was calculated, representing the difference between experimental and control groups at the end of intervention divided by the pooled standard deviation at baseline (<0.2 = no relevant effect, 0.2–0.5 = mild effect, 0.5–0.8 = moderate effect, >0.8 = intense effect); a fixed-effect model was applied; k = number of pooled RCTs; n = total number of analyzed individuals; homogeneity of effects among the individual studies was evaluated using the Cochran Q test (p < 0.05 indicates heterogeneity of effects).<sup>2</sup> High-quality RCTs are marked with an asterisk.<sup>3</sup> Data from these RCTs were not available or could not be pooled

for meta-analysis.<sup>4</sup> Data of White and African American participants [139] and of White non-Hispanic and Cuban American participants [141] were considered individual studies.<sup>5</sup> Data of White non-Hispanic and Cuban American participants [141] were considered individual studies.<sup>6</sup> Data of Latino and Anglo participants [142] were considered individual studies.<sup>7</sup> Data of White non-Hispanic and Cuban American participants [141] and of Hispanic, White and Black participants [186] were considered individual studies.<sup>8</sup> Data of Hispanic, White and Black participants [186] were considered individual studies.

sive treatment, but not after 3 months of additional maintenance treatment or up to 2-year follow-up assessments [107].

#### *NPTs to Improve QoL*

One intervention aimed at adapting home environment to PWD capacities and providing continuous counseling and support to the CG (multicomponent interventions for PWD and CG, in-home counseling) improved QoL as rated by the PWD [204]. Another intervention conducting less frequent sessions and measuring QoL as rated by the CG was neutral [209].

#### *NPTs to Improve CG Mood*

Four NPT categories demonstrated mild mood benefits in family CGs of community-dwelling PWDs. To deal with the stress derived from caregiving, CG education programs added problem-solving and cognitive restructuring techniques to the traditional information and support components of support groups. Particularly high responses were described in those CGs displaying high levels of depression [131] or anxiety [145] at baseline, and an association was described between the decrease in emotional involvement and improvement in mood after treatment [132]. Cognitive-behavioral therapy was superior to an information- and emotion-oriented approach in 1 study [142], but 2 other studies were neutral [129, 143].

CG education for coping skills in individual sessions was of particular success when conducted on CGs displaying psychological morbidity [134] or when an emotion-oriented approach was used [125]. A program focusing on family interactions [141] and an information-oriented program [125] failed to improve CG mood. The enrichment of CG education with other components (multicomponent intervention in the CG) also improved CG mood. For instance, after 6 months of intervention, the prevalence of clinical depression in CGs who received in-home education sessions and participated in a telephone support group was lower than that of CGs who only received minimal support (12.6 vs. 22.7%,  $p = 0.001$ ) [186].

In-home implementation of computer or telephone systems providing information and facilitating communication among family CGs (CG support, electronic devices) improved CG mood after 6–12 months of use. In a high-quality trial, a reduction in depressive symptoms and anxious complaints was demonstrated, but only in those CGs who reported low-mid level of life own control at baseline [161]. Age [162], relationship and ethnic characteristics [141] predicted response in other RCTs.

#### *NPTs to Improve CG PWB*

The PWB of the CG (either family or professional CG) was substantially improved after 8 or 10 weeks of cognitive stimulation in group sessions that were conducted on PWDs attending day centers or living in institutions. As for interventions more specifically targeted at CG PWB, only multicomponent interventions for the CG demonstrated benefits. For instance, a long-term program of counseling and continuous support improved the CG reaction to memory and behavior problems, satisfaction with social support and subjective burden, and these benefits mediated institutionalization delay [183].

#### *NPTs to Improve CG QoL*

Two highly individualized interventions built on comprehensive assessment of PWD and CG characteristics and needs (multicomponent interventions for PWD and CG, in-home counseling) improved CG QoL. One of these interventions, tested in a high-quality RCT, consisted of home visits by a case manager nurse and education and support groups for family CGs. After 6 months of intervention, an improvement in CG QoL was attained that persisted at the 12-month follow-up [208].

#### *NPTs to Avoid Restraints*

Professional CG training for alternatives to restraint avoided mechanical restraint, compared to usual care, in institutionalized PWDs. At the end of treatment, no differences were found in falls, mobility [220] and use of psychotropic drugs [218, 220] between experimental and control groups, although an increase in agitation was reported in the experimental group in one of the RCTs [218].

## **Discussion**

This review provides a comprehensive assessment of nonpharmacological interventions in dementia building on previous reviews, but also extending the scope to all documented NPTs [224–227]. Most RCTs showed positive results, and solid (i.e. grade A or B) recommendations could be established for most domains (fig. 3, table 2). Absence of a clear association between RCT quality and positive results suggests that publication bias would not on its own be an adequate explanation for the rates of intervention success (fig. 2). In order to obtain high-quality evidence, we used clearly specified and rigorous inclusion criteria, such as narrowing candidate studies to only

RCTs documenting cognitive deterioration of degenerative etiology in all participants.

#### *Methodological Problems*

Despite the high number of RCTs included, the proportion of high-quality studies was low (fig. 2). Limitations such as often small and poorly defined samples may in part reflect the restricted financial support available for research of this kind. Other problems such as poorly specified interventions, absence of a theoretical model and lack of blind outcome measurements illustrate methodological difficulties commonly encountered in this research field. Our hope is that the growing number of low-quality RCTs lays the groundwork for and precedes a large cohort of high-quality RCTs in future years. Sometimes numerous outcome measures were used, and adjustments for multiple comparisons were lacking. In addition, most RCTs utilized usual care or minimal attention conditions as the control group. When experimental and control groups were exposed to similar social attention, positive results were less frequent, and intervention specificity became blurred (table 1). In addition, many studies did not have a clear theoretical model with a defined active agent intended to lead to a specific outcome. Instead, research has often been oriented towards the development and evaluation of multicomponent interventions for the PWD, CG or both and almost half of the findings and recommendations came from multicomponent categories, each category improving several domains. This means it is hard to know what element worked, how it worked and for whom.

#### *Key Findings*

Multicomponent interventions based on CG education and support delayed the institutionalization of AD/DR persons (fig. 3) with only modest amounts of resources used. This important outcome in relation to both QoL and cost was not found with any other treatment approach on the basis of high-quality evidence. For other outcomes (cognition, ADLs, behavior, mood), the magnitude of the effect seemed to be similar to the effect obtained by drugs (table 2) [228]. Due to the general absence of side effects and since they can be more readily individualized, NPTs are preferable when particular ADLs or behaviors are targeted [229, 230]. Moreover, higher responsiveness to NPTs than to drugs should be expected for some other outcomes (QoL, CG psychological well-being, CG QoL). However, rather than being viewed as an alternative to medications, NPTs and drugs should be understood as complementary approaches [18, 19, 21, 45, 108, 109].

Some intervention categories (e.g. cognitive training, ADL training) related to specific benefits in the targeted domains whereas others (e.g. reminiscence, recreation therapy) may have more diffuse effects. NPTs lacking any recommendation were: transcutaneous electrical stimulation, physical exercise, use of music, reminiscence, massage and touch, recreation therapy, use of light, multisensory stimulation, support and psychotherapy, validation, case management and respite care. Problems included lack of studies, lack of adequate measures, poor design and insufficient duration of intervention.

Response predictors were extensively investigated in CG interventions [133, 134, 159, 161, 183, 227] but that was not the case for the studies of PWDs. Samples were frequently selected according to intervention aims (e.g. behaviorally disturbed persons for behavioral interventions), and response scales were similarly targeted. A large majority of participants in NPT studies were female, yet only 2 RCTs reported analyses according to the gender of the care receiver [42, 109]. Some studies suggest that greater cognitive, functional and behavioral responses might be observed in less advanced dementia [231, 232], but these hypotheses were barely explored [212].

#### *Limitations*

The map and definitions of intervention categories and subcategories are open to future modifications, although they were developed and agreed upon by the expert consensus group, because of the complex and inconsistent nature of the interventions (particularly multicomponent). Although our methodology was rigorous, the need to achieve a comprehensive coverage meant that many low-quality RCTs were included with the inherent problem of bias in a number of areas. Hence, many of the RCTs included may not have met the methodological criteria for inclusion in Cochrane reviews. Cochrane reviews on cognitive stimulation and case management for dementia are currently in preparation, and we await these results with interest.

#### *Future Research*

Persons who were medically ill, sensorily impaired or nonnative language speakers, were usually excluded from studies, and interventions aimed at the even larger group of people with severe dementia were scarce. Specific programs should be carried out for these neglected groups. An emerging area of interest is the study of variables that may act as response mediators (i.e. variables that are amenable to modification as a result of the intervention and predict response). Some of these potential mediators (e.g.

CG distress) were included in the PWB domain; others (e.g. CG knowledge, attitudes and beliefs towards dementia) were outside the focus of the present review. Better understanding of response predictors and mediators will help in selecting and optimizing interventions according to individual settings, circumstances and needs [154, 183, 199, 233]. Important challenges ahead concern research methodology: (a) interventions should be better described to facilitate replicability; (b) the lack of placebo (intervention and control conditions cannot be hidden) highlights the need for more elaborated blind assessment procedures; (c) the measurement of each component's dose and differential effects will gain importance due to their impact on the cost/benefit ratio; (d) contamination between study groups should be carefully addressed, and (e) motivation of the therapists could have an effect on results and should be accounted for. There is a clear need for further RCTs particularly in areas which are widely used, have a theoretical framework and can be clearly defined and provided at relatively low cost. In particular, high-quality large-scale RCTs are required in the areas of reminiscence, use of music and physical exercise.

Future studies could profitably compare different forms of intervention to elicit differential effects but, until the effects of interventions are better established, a usual-care comparison group is necessary. In addition, as illustrated in many head-to-head drug studies, comparing two active interventions is likely to reduce effect size leading to the need for much inflated sample sizes. In the early stages of an intervention, evaluation and development will be more modest, and less expensive designs (e.g.  $n = 1$  trials, quasi-experimental trials) could precede RCTs or may need to be accepted as the only possible evidence to guide treatment of rare but very disruptive behavioral symptoms where RCTs cannot be performed due to sample size requirements. QoL and cost-related measures should be systematically added to the trials.

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## Conclusion

The results of this review indicate that NPTs can make both a realistic and affordable contribution to the improvement and provision of care for people with ADRD and their CGs. In contrast to drugs, nonpharmacological interventions are often of low cost, and the cost relates to human endeavor rather than expensive technology or medication. This means that NPTs of demonstrated effectiveness might be made available cheaply in developing countries. However, it also means that for business interests there is likely to be a relative lack of return on research investment in comparison with, say, a newly licensed medication. Governments, research charities and financially strong philanthropic organizations should make significant investments in the development and dissemination of NPTs to support research to improve the evidence for their effectiveness. The benefits to PWDs, their carers and society may be great, the investments comparatively modest and potential savings for the economy may be substantial.

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