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Exploring Factors Associated With Successful Nonpharmacological Interventions for People With Dementia

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ABSTRACT

Background and purpose: We investigated existing nonpharmacological programs for people with dementia (PWD) to explore critical factors related to the effectiveness of these types of programs.
Methods: We conducted a qualitative systematic literature review to identify nonpharmacological intervention programs developed for PWD and reviewed 36 randomized controlled trials. Among several outcomes reported in each study, we focused on the most common outcomes including quality of life (QoL), neuropsychiatric symptoms, depression, agitation, and cognition for further review.
Results: Several factors were identified that might affect the outcomes of nonpharmacological interventions for PWD including study design, characteristics of the intervention, maintaining research participants, heterogeneity issues, and implementation fidelity. About half of studies in this review reported positive program effects on their targeted outcomes such as Well-being and Health for PWD on improving quality of life, neuropsychiatric symptoms and agitation; cognitive stimulation therapy on QoL, neuropsychiatric symptoms and cognition; and a stepwise multicomponent intervention on neuropsychiatric symptoms, depression and agitation.
Conclusions: We found some programs even with a rigorous study design did not produce expected outcomes while other programs with poor designs reported positive outcomes, which necessitates further investigation on the validity of the assessments. Factors such as individual tailored and customized interventions, promoting social interactions, ease of administration and compatibility of interventions, and developing program theory need to be considered when developing nonpharmacological intervention programs.

Keywords: Dementia; Alzheimer Disease; Nonpharmacological Intervention; Program Theory

INTRODUCTION

Dementia is a medical condition characterized by a decline in memory, language, problem-solving and other thinking skills that affect a person's ability to perform everyday activities.[1]

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World Health Organization (WHO, 2019) reported that around 50 million people have dementia worldwide, and there are nearly 10 million new cases every year.[2] The most common type of dementia is Alzheimer's dementia (AD) accounting for 60%–80% of all cases, an estimated 5.8 million people within the United States (US). The number of people with AD continues to increase rapidly due to the rise in the aging population age 65 and older.[1] AD is the 6th leading cause of death in the US and the 5th leading cause of death among adults aged 65 years or older.[3]

As a neurodegenerative disease, AD causes progressive cognitive and functional decline,[4,5] destroying memory and thinking skills and, eventually, the ability to carry out the simplest tasks.[6] There are no pharmacological treatments available today for AD to slow or stop the damage and destruction of neurons that cause Alzheimer's symptoms, but AD medications—acetylcholinesterase inhibitors(AChEIs) —remain the mainstay of AD treatment to manage behavioral and psychological symptoms of dementia.[1,7,8] However, AChEIs' effect is not curative but rather temporarily mitigates some symptoms up to 2 years and only apparently after several weeks of treatment—a finding with inconsistent evidence.[8-10]

Considering that the neuropsychiatric and behavior symptoms of AD patients cause substantial distress for both AD patients and their caregivers, it is important to develop practical, evidence-based nonpharmacological interventions that not only decrease dementia-related behavioral symptoms and improve the ability to function in everyday life, but also support the caregivers, enabling effective care at home.[11-15]

Various nonpharmacological programs from different disciplines have been developed and evaluated for their impact on the cognitive, behavioral and psychological symptoms, along with the quality of life (QoL) and activities of daily living (ADL) for either or both the people with dementia (PWD) and their caregivers. However, there has been no consensus reached on a classification system for the types of interventions due to the complexity and multifacetedness of the interventions addressing care for PWD.[16]

Many of nonpharmacological intervention trials are small-scale with poor methodologies and inconsistent outcome measures, which makes it difficult to compare the results and effects across programs; yet some of these interventions' effects are still touted as effective on certain individuals or groups.[17-19] For example, cognitive training (CT)/cognitive stimulation therapy (CST) is a common intervention designed to address difficulties with different aspects of cognition[12] and has been reported to improve cognition function and QoL of PWD.[20] However, the quality of evidence for CT's effectiveness was low and not consistent.[21-23]

Therefore, it is critical to investigate how nonpharmacological interventions were planned, implemented and evaluated. Based on this information, we might identify what factors may impact the effectiveness of nonpharmacological interventions so that these factors can be considered in developing and/or implementing programs in different settings, such as, individual homes, community settings, nursing homes, and long-term care facilities. The review of existing nonpharmacological interventions to understand what was working and why would maximize the effects of those programs in treating and caring for PWD. The purpose of this study is to summarize and investigate existing nonpharmacological programs for PWD to explore critical factors related to the effectiveness of these care programs for PWD.

METHODS

To identify the nonpharmacological programs that were developed for PWD, we conducted an extensive literature review by searching PubMed & MEDLINE using the following keywords: Dementia or Alzheimer Disease and nonpharmacological interventions or treatment AND Health Outcomes. These 2 databases were selected as they would contain the majority of published nonpharmacological interventions for PWD. The date limits ranged from January 2015 to December 2019, and relevant articles were also reviewed to identify any studies that were not included in primary search but listed as additional references in the PubMed & MEDLINE sites. For additional data, authors were contacted.

To be included in the literature review, articles needed to be primary research in PWD in which nonpharmacological programs were evaluated by randomized controlled trials (RCTs) with health-related outcomes (e.g., cognitive function, neuropsychiatric symptoms, depression, QoL, and ADL). Additionally, the search was restricted to studies published in English that targeted PWD whose ages were 45 years and older, and conducted clinical study. We did not review studies that targeted mainly caregivers. A total of 3,742 articles were identified from the original search "Dementia or Alzheimer Disease and nonpharmacological interventions or treatment AND Health Outcomes." After restricting them by ages, clinical study and English, 262 articles were extracted. Among these articles, 32 abstracts met our final restrictions and were selected. Additionally, 4 articles were identified from the relevant references and were added to the 32 studies for a total number of 36 studies.

RESULTS

Overview of nonpharmacological interventions

Table 1 summarized all 36 programs for a comprehensive overview. Thirty-six articles can be classified into approximately 6 categories, such as, psychosocial practices, training program for staff or caregiver, cognitive therapy, exercise program, occupational therapy, and sensory practices. However, this classification is not exclusive as some programs contained more than one type of classifications within the program or it is indistinct to classify the program into a certain category.

Among the 36 articles, 14 studies used less than 100 people in their trials (47.4%) ranging from 20 to 99, and 16 studies targeted both PWD and caregivers (44.4%). Nine studies were implemented in the United Kingdom (UK), followed by Australia, Finland and the US (4); Germany and the Netherlands (3); China (2); and Denmark, Belgium, Italia, New Zealand, Norway, Spain and Tanzania (1).

The duration for the intervention varied, ranging from 2 sessions to 1 year, with follow-up periods ranging from 0 to 3 years. Some studies did not clarify the duration of the intervention. Study settings were participant's home, nursing homes, hospitals/clinics, adult day care center, community settings, and long-term care facilities.

Factors to be considered for developing effective nonpharmacological interventions

To evaluate nonpharmacological programs for PWD, it is critical to consider their complicated and complex aspects, in addition to the contexts in which they would operate.

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Table 1. Summary of nonpharmacological intervention studies

Authors/Year (Category)*	Program type/ Level of severity	Sample size/ Country	Setting	Duration	Measures	Results
1. Ballard et al., 2018 (T)[43]	WHELD-PCC; mild to severe	I=404→257, C=443→296; UK	69 UK NH	9 mon	QoL, agitation, NPI, antipsychotic use, global deterioration, mood, unmet needs, mortality, quality of interaction, pain, cost	Significant improvement in QoL, benefits in agitation & overall NPI in people with moderately severe dementia, benefit in positive care interactions
2. Charlesworth et al., 2016 (P, T)[24]	CSP, RYCT	CSP=48, RYCT=97, CSP-RYCT=97, TAU=47; UK	The client's home	12 mon	QoL, quality of relationship for PWD and carers	No significant effect for family carers & PWD; verified no difference between completers and those who withdrew
3. Clare et al., 2019 (C)[15]	CR; mild to moderate	CR=239, TAU=236; UK	8 centers	9 mon	Self-reported goal attainment, self-efficacy, mood, QOL, a brief cognitive test battery	Only effective in improving functioning in targeted areas at 3 mon by both participants and study partners, maintained at 9 mon; no improvement in DEMQOL, HADS depression and HADS anxiety
4. Churcher Clarke et al., 2017 (C, S)[30]	MBIs; mild to moderate	I=20 (5 per site), C=11→8; UK	4 sites care homes	5 wk	Depression, anxiety, QoL, cognitive function, stress, mindfulness, adherence to the intervention, acceptability	No significant differences in depression, anxiety, cognitive functioning, stress or mindfulness; a significant & positive difference between groups over time in QoL
5. Döpp et al., 2015 (O)[44]	COTiD program; mild to moderate	I=44 (17 unit), C=27 (28 unit); The Netherlands	The client's home	12 mon	The daily functioning of clients, performance-deterioration, QoL	No significant differences between groups for adherence & low adherence, in client and caregiver outcomes
6. Galik et al., 2015 (T)[25]	FFC; moderate to severe	I=48→44→40, C=48→43→41; US	4 dementia specific AL	6 mon	Physical function, anxiety/ agitation, depression, apathy	No significant difference in the outcomes of agitation, depression and apathy
7. Gitlin et al., 2018 (O)[40]	TAP; dementia	I=76→51→50, C=84→60→53; US	Veteran's homes	8 mon	NPI-C, CAFU, total functional dependence score, ADLs, veterans' pain	Greater improvement in behavioral symptoms, functional dependence & pain; non completers-more distressed & financially strained, behavioral symptoms & functional dependencies
8. Hoffmann et al., 2016 (E)[28]	Aerobic exercise; mild AD	I=107→102, C=93→88; Denmark	Community-dwelling patients	16 wk	Cognitive performance, QoL, ability to perform ADL, depressive & neuropsychiatric symptoms	Significantly reduced NPI in the treatment group; no significant differences in SDMT, other cognitive tests, QoL, or ADL
9. Jones et al., 2018 (P)[58]	PARO; diagnosis of dementia	I=138, 9 facilities; Australia	Long term care facilities	10 wk	Participants' levels of engagement, mood states, agitation after 10 wk	Low levels of agitation at baseline→greater positive behavioral engagement with PARO
10. Kallio et al., 2018 (C)[12]	FINCOG; mild to moderate	I=76→68, C=71→49; Finland	Adult day care centers	9 mon	Cognition, HRQoL, dementia severity	No effect on global cognition and HRQoL
11. Koivisto et al., 2016 (P)[51]	Psychosocial intervention; very mild–mild AD	I=84→81→69→54, C=152→117→ 100→76; Finland	Home-dwelling persons	3 yr	Delay the institutionalization, AD progression, behavioral symptoms, HRQoL	No significant differences in NH placement & NPI, QoL
12. Laakkonen et al., 2016 (P)[20]	Self-management rehab	I=67→67, C=69→67; Finland	Primary care & memory clinics	8 wk	HRQoL, cognition	No change in HRQoL, significant improvement in the cognition in intervention group
13. Lamb et al., 2018 (E)[39]	Aerobic & strength exercise; mild to moderate	I=329→300→281, C=165→145→137; UK	Community gym facilities, NHS premises	4 mon	Cognitive subscale, ADL, health related quality of life, neuropsychiatric symptoms	Greater cognitive impairment in the exercise group
14. Lemke et al., 2019 (C)[56]	Specific DT training; mild to moderate	I=56→40, C=49→37; Germany	Geriatric hospital & associated NH	3 mon	Psychological status, fear of falling, functional status, cognitive status	Effective in improving trained DT performances in PWD; demonstrated sustainability of training
15. Liang et al., 2017 (P)[34]	PARO	I=15 dyads→13, C=15 dyads→11; New Zealand	2 dementia day care centers & patients' home	6 wk	Cognition, agitation, neuropsychiatric, depressive symptoms, medication usage; behavioral, affective & social responses	No significant differences in agitation, NPI & medication usage; significant improvement in facial expressions, communication with staff at the centers
16. Liu et al., 2018 (E)[31]	Passive finger movement exercise	I=18, C=18; China	Hangzhou Older's home	12 wk	Grip strength, ADL	No obvious influences on the grip strength; improved overall ability of ADL
17. Livingston et al., 2019 (T)[41]	DREAMS-START: cognitive-behavioral components	I=42, C=20; UK	The client's home	3 mon	Feasibility of recruitment & treatment adherence; sleep measures, sleep disturbance, daytime sleepiness, QoL	88% adhered to the intervention, achieved high fidelity/completion rates of questionnaire measures; did not affect sleep time; significant improvements in ESS, DEMQOL-Proxy, and ZBI among the intervention

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Table 1. (Continued) Summary of nonpharmacological intervention studies

Authors/Year (Category)*	Program type/ Level of severity	Sample size/ Country	Setting	Duration	Measures	Results
18. Lyu et al., 2018 (P)[13]	Music therapy, lyric reading group; mild to severe	M=100, L=99, C=99; China	Geriatric hospital	3 mon	Cognitive functions, short/long-term memory, neuropsychological symptoms, verbal fluency and activities of daily living	Music therapy: more effective for improving verbal fluency & alleviating psychiatric symptoms than lyrics reading, effective for enhancing memory & language ability in patients with mild AD & reducing the psychiatric symptoms in patients with moderate or severe AD; no significant effect for ADL
19. MacNeil et al., 2015 (T)[45]	Case management; dementia	ICMM=234, LM=214, Control=73; The Netherlands	The client's home	2 yr	Neuropsychiatric problems, care and support needs, QoL & institutionalization	No differences in NPI scores & GHQ-12 scores between the 2 case management groups and the control group
20. Mansbach et al., 2017 (P)[48]	MemPics™: meaningful activity; mild to moderate	I=48, C=46; US	LTC facility residents	2 sessions†	Affective and experiential qualities that underlie meaningful activity; cognitive functioning	Both residents & staff valued MemPics™ as a meaningful activity
21. Moyle et al., 2017 (P)[35]	PARO	PARO (9: n=138), Plush toy (10: n=140), Control (9: n=137)	28 LTC facilities	10 wk	Engagement, mood states, & agitation	PARO group: more verbally & visually engaged than plush toy group; more effective than usual care in improving pleasure & agitation; both PARO & plush toy-significantly greater reduce in neutral affect
22. O'Connor et al., 2019 (O)[14]	TAP; frontotemporal dementia	I=9 dyads, C=11 dyads; Australia	The client's home	4 mon	Dementia stage, cognition; TAP intervention acceptability, response to intervention, NPI, Disability Assessment for Dementia, HRQoL	Significant decline in NPI-C for the TAP group; maintained instrumental ADL function over the same time frame; more engaged in activities less functionally impaired & had better QoL
23. Olsen et al., 2016 (P)[37]	AAA (AAI)	I=28 (5 NH), C=30 (5 NH); Norway	10 nursing homes	12 wk	Depression, agitation and QoL, cognitive and functional performance	Significant decline in CSDD & increase in QoL among severe dementia, no effects on agitation; more severe dementia, more significant effects on depression & QoL
24. Orrell et al., 2019 (T, C)[22]	iCST; mild/ moderate	I=180→134, C=176→139; UK	The client's home	25 wk	Cognition, self-reported QoL, depressive symptoms	No significant in cognition and QOL (ADAS-Cog, QoL-AD); significant improvement in QCPR in iCST group
25. Paddick et al., 2017 (C)[32]	CST; mild to moderate	4 groups: A=8, B=8, C=8, D=10; Tanzania	A meeting hall or health facility	7 wk	QoL, Impairment and disability, BPS of dementia-NPI, cognition	A significant improvement in physical QoL, cognition & NPI-reduced in both number and severity of BPS; use control as delayed start groups
26. Pieper et al., 2016 (T)[26]	STA OP!; advanced dementia	I=148 (NH=11), C=140 (NH=10); The Netherlands	12 nursing homes	6 mon	Agitation, psychotropic medication use, neuropsychiatric symptoms, symptoms of depression	CMAI, NPI-NH, CSDD and MDS-DRS-significantly lower in the intervention condition; a significant reduction of antidepressants; improved overall agitation, depression, & other neuropsychiatric symptoms
27. Prick et al., 2016 (E)[27]	Exercise: multicomponent dyadic intervention; dementia dx by Dr.	I=57 dyads, C=54 dyads; The Netherlands	Community settings	6 mon	Physical functioning & physical role functioning, depression, behavioral disturbance	No benefits on mood, behavior, and physical health
28. Raglio et al., 2015 (P)[38]	Music therapy	MT=40, LtM=40, C=40; Italian	9 nursing homes	10 wk	Functional, cognitive, behavioral evaluations, musical, nonverbal/verbal behavior	No significant differences between groups after the intervention; all groups showed a significant reduction in NPI, CSDD & CBS-QoL score
29. Rajkumar et al., 2016 (T)[36]	WHELD: antipsychotic review/social interaction/ exercise	N=273; I=8 NH, C=8 NH; UK	16 nursing homes	9 mon	Apathy; depression, anxiety, and agitation, needs and QoL	Antipsychotic review: reduced antipsychotic use, but significantly increased apathy; antipsychotic review + social interaction or exercise significantly reduced apathy
30. Regan et al., 2017 (C)[49]	MAXCOG cognitive rehabilitation; MCI/early dementia	I=37, C=18; Australia	The client's home	4 wk	Personally relevant goals→ selfcare, leisure, productivity, depression, cognition, QoL, memory & behavior problem	Significant higher performance & satisfaction with primary goals in the intervention group; worse memory abilities, significantly greater number of problem behaviors both pre and post assessment in the intervention group

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Table 1. (Continued) Summary of nonpharmacological intervention studies

Authors/Year (Category)*	Program type/ Level of severity	Sample size/ Country	Setting	Duration	Measures	Results
31. Sánchez et al., 2016 (S)[33]	Multisensory stimulation environment; severe/very severe	I=11, C=11; Spain	Institutionalized elderly individuals	16 wk	Agitation, emotional & cognitive status, and dementia severity	Improvement in both groups, and no significant differences between groups in agitation, mood, anxiety, cognitive status
32. Suominen et al., 2015 (T)[53]	Tailored nutritional guidance; AD	I=50, C=49; Finland	The client's home	12 mon	Weight, BMI, protein micronutrient intakes, clinical dementia rating scale, nutritional assessment, QoL, rate of falls	No difference in weight change; improved HRQoL in the intervention group; significant decrease in the rate of falls compared to the controls
33. Thyrian et al., 2017 (T)[29]	DCM	I=337 (GP=56), C=164 (GP=35); Germany	The client's home	6 mon	QOL, behavioral & psychological symptoms, pharmacotherapy with antidementia drugs, inappropriate medication use	Significant decrease in behavioral, psychological symptoms of dementia; significant increase in chance of receiving antidementia drug treatment; no effect on QOL, cognition, ADL, institutionalization
34. Van Bogaert et al., 2016 (P)[50]	Individual reminiscence; mild to moderate	I=36, C=36; Belgium	2 nursing homes	8 wk	Depressive symptoms, cognition and behavior; residents' attention and participation survey	Significantly lower CSDD scores in post session & lower group delta score in the intervention group, no impact on cognition and behavior
35. Voigt-Radloff et al., 2017 (P)[54]	Errorless learning; mild to moderate AD or mixed-type dementia	I=81, C=80; Germany	The client's home	20 wk	Task performance, daily functioning, cognitive status, dementia stage, challenging behavior, treatment costs, intervention adherence	An improved post-treatment performance of daily living tasks in both arms, but no difference between EL and TEL; no improvement on secondary outcomes
36. Woods et al., 2016 (P)[52]	Joint reminiscence groups (RYCT); mild to moderate	I=268, C=219; UK	8 mental health services/clinics	12 wk	Self-reported QoL, autobiographical memory & ADL, mood, relationship quality and service use and costs	No differences in outcome between groups on primary outcomes and secondary outcome measures

WHELD: Well-being and Health for People with Dementia, PCC: person-centred care, UK: United Kingdom, QoL: quality of life, NPI: Neuropsychiatric Inventory, CSP: Carer Supporter Programme, RYCT: Remembering Yesterday Caring Today, TAU: treatment as usual, PWD: people with dementia, CR: cognitive rehabilitation, DEMQOL: Dementia Quality of Life Instrument, HADS: Hospital Anxiety and Depression Scale, MBI: mindfulness-based intervention, COTiD: Community Occupational Therapy in Dementia, FFC: function focused care, AL: assistant livings, TAP: Tailored Activity Program, NPI-C: Neuropsychiatric Inventory-Clinician rating scale, CAFU: Caregiver Assessment of Function and Upset Scale, ADL: activities of daily living, AD: Alzheimer's dementia, US: United States, SDMT: Symbol Digit Modalities Test, PARO: therapeutic pet-type robot as an alternative to animal-assisted therapy, FINCOG: Cognitive Treatment: Finnish Cognitive Training, HRQoL: health related quality of life, NH: nursing home, DT: dual-task, ESS: Epworth Sleepiness Scale, ZBI: Zarit Burden Interview, ICMM: International Council on Mining and Metals, LM: Linkage Models, GHQ: General Health Questionnaire, LTC: long term care, AAA: animal-assisted activities, AAI: animal assisted intervention, CSDD: Cornell Scale for Depression in Dementia, ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale test, iCST: individual cognitive stimulation therapy, CST: Cognitive stimulation therapy, BPS: Behavioral or Psychological Symptoms, STA OP!: stepwise multicomponent intervention, CMAI: Cohen-Mansfield Agitation Inventory, MDS-DRS: minimum data set depression rating scale, CBS: Cornell-Brown Scale, DREAMS-START: Dementia RElAted Manual for Sleep/STrAtegies for RelaTives, MAXCOG: Maximizing Cognition, MCI: mild cognitive impairment, DCM: dementia care management, EL: Errorless learning, TEL: Trial and Error Learning.
*Program category: P: psychosocial practices, T: training program for staff or caregiver, C: cognitive therapy, E: exercise program, O: occupational therapy, S: sensory practices.
†The author was contacted but did not provide the information on the duration of their program.

Based on the results of each study, several factors were elicited that need to be considered in developing nonpharmacological interventions for PWD.

Study design

Randomization

To design the study to be able to elicit discriminative power from the program, applying proper randomization is crucial. The benefit of using a RCT is to make one program comparable to another by minimizing bias and confounding factors, so the results would be statistically reliable. All studies in this review applied RCT, but the successfulness of the randomization is questionable as some RCTs showed differences at baseline between the intervention and control group in age, gender, level of depression or impairment, readiness (e.g., physical activity levels), motivation to participate in the program, or the number of participants and staff.[20,24-29] In one study,[24] regardless of randomization, less impaired PWD were allocated in the control group, which led to no difference in study outcomes between the intervention and control groups. The level of randomization also needs to be carefully considered in interpreting and generalizing program outcomes (e.g., individual, gender, age, settings or region).

Sample size

Many studies conducted small-scale clinical trials or used one site or region for study setting, which limits the power and addresses the issue of reliability of their results.[14,30-34] For example, the report on the effects of using the therapeutic pet-type robot as an alternative to animal-assisted therapy (PARO) was inconsistent across studies, and the results are limited as most of the studies used small sample size and restricted settings. Also, it was questionable if its unique benefits would be significant enough to offset the cost and management of PARO.[35] In another approach, some studies conducted multimodal interventions by dividing their samples into several groups, which makes the sample sizes too small to assess their effectiveness.[24,36]

History

When evaluating the program, the effect of history should be also carefully investigated, such as, other programs or activities that long-term care facilities and nursing homes developed have been implemented along with the original program. In this case the program's effect cannot be isolated and attributed solely to the program under assessment. For instance, study participants who continue to receive routine health care for dementia during the study period may produce floor or ceiling effects,[12,27,37] possibly causing interactive effects.

Study participants

To assess the specific aspects of the program, it is critical to choose proper study participants, especially to identify the distinguishing effects between the program of interest and the control group. For example, setting the inclusion threshold too low, such as including people with mild dementia, may produce study results that are vague or marginal.[26] Instead, it may be useful to consider choosing clients with more severe neuropsychiatric symptoms, so that the effects of the nonpharmacological interventions may be more evident.[38]

Study measurements and data collection methods

We found various assessment tools were used to evaluate the outcomes with a wide range of measurements (**Table 2**). These outcomes were measured by research or program staff, self-report of participants, proxy respondents (e.g., caregivers), neuropsychologists, nurses,

Table 2. Tools frequently used to assess study measurements

Measurement	Instruments
Cognitive function	Mini-Mental State Examination (MMSE)
	Clinical Dementia Rating (CDR)
	Alzheimer's Disease Assessment Scale-Cognitive Subscale test (ADAS-Cog)
Neuropsychiatric symptoms	Neuropsychiatric Inventory-Nursing Home (NPI-NH)
	Cornell Scale for Depression in Dementia (CSDD)
	Cohen-Mansfield Agitation Inventory (CMAI)
	Hospital Anxiety and Depression Scale (HADS)
QoL	QoL in Alzheimer's Disease (QoL-AD)
	QoL-AD proxy
	QoL in Late-stage Dementia (QUALID)
	Health-Related QoL (HRQoL)
	Dementia QoL Instrument (DEMQOL)
	DEMQOL-Proxy
	EuroQol-5D (EQ-5D) (patients' EQ-5D profile data)
	Self-reported EQ-VAS
ADL	Alzheimer's Disease Cooperative Study ADL Scale (ADCS-ADL)
	KATZ-6
	Instrumental ADL (IADL)
	Bristol ADL Scale (B-ADL)
	Barthel Scale/Index (BI)

QoL: quality of life, ADL: activities of daily living.

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and physiotherapists. When using self-report by either the participant and/or the caregiver to assess outcomes, several issues such as recall bias, social desirability, and discrepancies between the participants' and caregivers' reporting may be problematic. With respect to caregiver reporting, for example, caregivers reported the number of falls based on their memory, which may lead to recall bias.[39] As caregivers are given more attention during the intervention, this additional attention may contribute to positive outcomes and might cause other social desirability effects.[40,41] Relying on a caregiver-rated measure of QoL for the PWD possibly could lead to over/under-estimated ratings,[14] so the influence of raters should be carefully considered when selecting QoL outcome measures.[42] Also, the Hawthorn effect was reported when observations by nurses were used to assess the outcome while the intervention was not blinded to them.[26] While valid outcome measures need to be clarified, reliable data collection methods should be also established and ensured.[35]

Characteristics of the intervention

To make a program successful and sustainable, it is critical that the program itself needs to be simple and easily integrated into routine clinical practice so that the program can be implemented by care staff with minimal adjustment.[43] For example, by involving too many healthcare staff, the intervention becomes more complex, leading to higher attrition of staff in the treatment group.[44] As recipients of the intervention, PWD and their caregiver also need a program that is not a burden, which may lead to high drop-out rates and less compliance.[25,27,33,44,45] Thus, the program should be carefully designed to minimize patient, caregiver, and interventionist burden and to maximize the effectiveness of the program.[26,30,45] Here we cannot emphasize enough the importance of the collaborative aspect among PWD, their caregiver, and care staff to implement the intervention as planned.

Second, it is critical to identify factors that encourage the PWD to engage positively with their care. Familiarity with the present situation along with a familiarity of the social and physical environment promotes involvement in activities.[46,47] By promoting active participation, a sense of connection and belonging, a sense of autonomy and personal identity, and activity content related to the interests and past roles of the participants, program activities can lead to more meaningful engagement.[48] Supporting active participation and focusing on the needs of PWD and their caregivers are also critical to make psychosocial interventions successful.[20] Readiness to make changes was found to predict outcome, so it may be useful to assess it before implementing the program. This will help make the program flexible to be adapted to different contexts to satisfy diverse needs.[15]

Third, the optimal dose and duration of the intervention should be considered to effectively mitigate behavioral and psychological symptoms of dementia.[48] For example, short time of the intervention may not have been sufficient to produce substantially cognitive, behavioral, or other positive outcomes and benefits.[12,24,39,49] The frequency of the intervention is also important. A study using group music interventions twice daily for 3 months reported that music therapy was effective in controlling psychiatric and behavioral symptoms and that their effects lasted for 3 months after the intervention completed.[13] In another study investigating the effect of an occupational therapy program, the investigators reported more coaching sessions positively affected adherence scores.[44] These examples address the necessity to consider the intervention time or period and its feasibility, including frequency, intensity and duration, in order to produce expected outcomes and have lasting effects.[27] Considering the symptoms of dementia, such as difficulty to sustain long term effect, continuous program implementation or repeated exposure to the treatment would be beneficial to PWD.[40] It was reported that least 6

months of exercise is necessary to induce cognitive changes.[28] The dose of intervention has also been associated with developing a relationship with PWD, so further investigation and research to identify proper dose and duration are crucial to develop nonpharmacological programs.[38]

Fourth, nonpharmacological programs need to be carefully designed to be distinctive and evaluable. Several studies reported improvement from both the intervention and control groups,[33,38] which may be due to the study's lack of the power. When using different approaches in the program and implementing the program across intervention sites, the effect of each approach on participants needs to be carefully observed and assessed for its balance and frequency.[50]

Maintaining research participation

It is challenging to recruit participants and maintain their participation during the study period considering target population's characteristics such as old age and severity of the disease. Many studies reported high drop-out rates up to more than 50% and uneven dropouts between the intervention and control groups, which is challenging to validly assess the effectiveness and outcomes of the program.[29,44,50-52] Reasons for drop-out were health problems such as disruptive or aggressive behavior, sudden illness or death, change of circumstances that limited attendance, and overburden due to the program. Also, caregivers were influential in the withdrawal of the participants from the study. If the caregiver felt uncomfortable with the activities or doubted the potential benefits from the program, the caregiver would withdraw the participant even though the PWD enjoyed the program activities.[25,44,49,52] Good adherence and reducing dropouts are key factors that lead to program success.[20]

Heterogeneity issues

Many studies reported the issue of heterogeneity in gender, severity of disease, type of dementia, nutrition status, readiness, willingness to attend the intervention, tasks assigned to participants, and facilitators who were trained for the program.[12,14,27,30,36,49,50,53,54] Allowing various dementia diagnoses, mild to severe stages of dementia, and very old persons with comorbid conditions and multiple concurrent medications when recruiting participants may make it difficult to investigate the true intervention effect and to compare the outcomes between the intervention and control groups. When physically active patients with mild stages of dementia are recruited, those results may not apply to the general AD population due to the difference in the severity of disease and the type of dementia.[28] When designing the intervention, it may be challenging to plan the long-term intervention as AD participants have a complex condition and their severity of the disease changes over time, creating another heterogeneity issue.

Implementation fidelity

No matter how good programs are developed, if they are not implemented as planned, program success cannot be expected. When using the existing staff to implement the intervention, the level of implementation may not reach expected levels due to intervention burdens, creating a feasibility issue in care facilities including nursing homes.[26,49]

Relying on caregivers to do exercise homework also resulted in implementation failure.[27] Orgeta and associates[55] reported that they used 8 study sites across the UK and trained caregivers to deliver the intervention and report outcomes in the absence of a researcher's monitor on exactly what was delivered. This method of self-report and self-monitoring leads to a question of program fidelity and whether the intervention was delivered as intended and assessed reliably. Considering the results of a positive association between study outcomes

and, high attendance and intensity,[28] it is critical to communicate clear expectations on participating in the program with participants and program staff and to monitor program implementation including training and confidence of the caregiver to adjust a program accordingly through the process and outcome evaluation.[55]

Study outcomes

About half of studies in this review reported positive effects of their programs on their targeted outcome(s). These programs took place in either care facilities or homes targeting patients as an individual or a group, their caregivers, and/or program staff. The interventions for PWD living in care facilities consisted of Well-being and Health for People with Dementia (WHELD), music therapy, animal-assisted activities (AAA), and a stepwise multicomponent intervention (STA OP!). The interventions for PWD living at home consisted of Tailored Activity Program (TAP), aerobic exercise, CST, tailored nutritional guidance and dementia care management (DCM). As major outcomes, we reviewed the effects of the program on QoL, neuropsychiatric symptoms, depression, agitation and cognition.

QoL

WHELD,[43] AAA,[37] CST,[32] and tailored nutritional guidance[53] reported their effect on improving QoL. WHELD[43] focused on training staff for person-centered care and promoting tailored person-centered activities and social interactions. With a robust and well-powered RCT design and a larger sample size in nursing homes, the study retained surviving participants, and the intervention was easily incorporated into the routine clinical practice. On the other hand, AAA,[37] CST[32] (both were group interventions), and the tailored nutritional guidance (individual intervention)[53] used a small sample size with several design issues such as unblinded raters, possible confounding factors (e.g., whether the decisive factor in animal assisted interventions is the dog handler, not the dog, which presents the necessity of clarifying its program theory) and a large number of dropouts; thus, the replication of these studies with larger sample sizes and the correction of design issues are necessary to confirm the effects reported.

Neuropsychiatric symptoms

WHELD,[43] TAP,[14,40] aerobic exercise,[28] music therapy,[13] CST,[32] STA OP!,[26] and DCM[29] reported the reduction of neuropsychiatric symptoms. These programs addressed the importance of adherence to the intervention and individual tailored/customized intervention.[26,28,40] When developing intervention programs for PWD, the severity of disease needs to be considered to produce expected outcomes[13] along with the implementation fidelity,[26] duration of intervention, social interaction[28] and dropout.[29]

Depression

AAA,[37] STA OP!,[26] and individual reminiscence program[50] reported the reduction of depression. Van Bogaert et al.[50] used a convenience sample and reported potential bias due to varied performed sessions by each facilitator. Thus, the individual reminiscence program should be re-examined to verify its outcomes.

Agitation

WHELD[43] and STA OP![26] reported the reduction of agitation. Both programs were implemented in nursing home settings. Again, with a robust and well-powered RCT design, and a larger sample size in nursing homes, their study methods and results can be generalized to implement similar programs in similar settings.

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Cognition

In this review, there were 7 programs targeting people with mild to moderate dementia and using cognitive rehabilitation.[12,15,22,30,32,49,56] Among them, 3 programs, such as, specific dual-task training,[56] CST[32] and Maximizing Cognition cognitive rehabilitation,[49] reported the improvement of cognition but used a small sample size; thus, to improve external validity, these studies should be examined further using different subject and setting characteristics.

DISCUSSION

We identified and reviewed several RCTs evaluating the effect of nonpharmacological intervention programs to decrease dementia-related behavioral and psychological symptoms, hoping to find critical factors to develop effective nonpharmacological interventions. Many studies in this review failed to find significant effects on their targeted outcomes, which addresses deep challenges in developing nonpharmacological interventions for dementia aimed at slowing down the progression of cognitive symptoms, improving the participant's QoL, and postponing institutional care.[12] Regardless of adopting a rigorous study design and diverse approaches in many studies, we still found methodological flaws and challenges in program implementation. Therefore, it is possible that weak evidence of study results could be attributed to poor quality of research, such as limitations in study design or implementation, imprecision of estimates, inconsistency in results, or vagueness of evidence rather than actual lack of efficacy of these interventions.[36,57] From the review of programs that reported the improvement of targeted outcomes, we suggest several key factors that need to be considered in developing nonpharmacological interventions for PWD.

Interventions need to be person-centered, individual tailored and customized, and consider different individual and contextual factors. As each individual has different health conditions, preferences and backgrounds in addition to different readiness levels to participate in the program, no program can be suitable or effective for all.[22,39,52,58] Therefore, patients with dementia should be assessed for the type, frequency, severity, pattern, and timing of symptoms to identify the specific needs of each PWD.[59] Based on thorough evaluation of the individual's behavioral and psychological symptoms, key areas of needs and interest of each person need to be determined and customized, so PWD can engage in the intervention meaningfully and benefit from it.[40] Care management programs or group interventions in care facilities also need to consider the individuality of the patient not only to understand and provide support for his/her unmet needs but also to identify why certain symptoms appear in different individuals.

The QoL of PWD is significantly determined by social interactions with others, not by cognitive capabilities.[60] The absence of interaction with others is associated with the increased prevalence of neurological diseases.[61] Therefore, targeting social interactions would be an important strategy to improve the QoL. Several programs, including music therapy, AAA, aerobic exercise and CST, were implemented as a group promoting social interactions and reported their positive effects. Interestingly, using animals and PARO presented the possibility of promoting social interactions and engagement of PWD.[34,37,62] The friendships between the group members were also considered as a possible factor contributing to self-management skills.[20]

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To make nonpharmacological interventions for PWD successful, they need to be easy to implement and incorporated into the routine clinical practice without challenging existing tasks or roles. Staff in care facilities who experience heavy workload would not be able to implement program contents as planned.[22,26] When a program is poorly operated and/or managed,[44] quality of care is negatively affected and costs for providers and patients may increase unnecessarily. This factor is also closely associated with participant compliance and dropout rates.[27] Many nonpharmacological programs rely on caregivers not only in implementing the program but also in assessing the effect of the program so their role and influence on program outcomes should be carefully considered when developing intervention components.[14,15,40]

Nonpharmacological interventions have many components with complicated (multi-level and multi-site) and complex (emergent outcomes) aspects, which is challenging for evaluation as the number of variables that can be identified and investigated is limited while the path to success is variable and cannot be formulated in advance.[63] Whether the program targets care in the home or long-term care facilities, and care provided by a caregiver or the healthcare staff, developing program theory can be helpful not only in developing evidence-based intervention programs but also in evaluating the effects of the program by defining appropriate outcomes to measure. To evaluate whether a program was successful or not, an evaluation is needed to assess the ability of the program to influence the causal process—the why and how the program worked or did not work.[64] Several studies in this review, for example, reported both the intervention and control groups showed a significant reduction in the outcomes; yet there was no significant difference between groups in Neuropsychiatric Inventory, Cornell Scale for Depression in Dementia, QoL, agitation, mood, anxiety, and cognitive status.[33,38] One possible reason for this result, besides the factors discussed previously, is program failure in which the program was not fully implemented and managed as planned. This addresses the importance of ensuring that participants needing service receive it. No studies in this review developed its own program theory to explain how the expected or desired outcomes of the program would be produced. It is invaluable to identify a program theory so that future program development and implementation activities can be directed.[65]

These key factors need to be considered in developing nonpharmacological intervention programs so more effective nonpharmacological intervention programs can be available as first-option interventions to care for PWD.

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