



A Systematic Review of Nonpharmacological Interventions for Moderate to Severe Dementia: A Study Protocol for a Systematic Review and Meta-Analysis

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The study is designed as a systematic review on nonpharmacological interventions for patients with moderate to severe dementia. This review will be conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions. The following databases will be searched: Cochrane CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO, KoreaMED, KMBase, and KISS. The primary outcome will include the effect of the interventions on activities of daily living and behavioral and psychological symptoms of dementia. The literature search will be conducted based on search strategies designed for each database. The reviewers will independently assess the identified studies and extract the data. The risk of bias will be assessed and a meta-analysis will be conducted in accordance with the methodology for meta-analysis described in the Cochrane handbook. This systematic review will provide clinicians and policy makers with reliable evidence for developing and implementing nonpharmacological interventions for moderate to severe patients with dementia.

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Key Words Dementia, Activities of daily living, Behavioral and psychological symptoms of dementia.

INTRODUCTION

Dementia is a common neuropsychiatric syndrome that is usually chronic or progressive and causes deterioration of various mental functions, including cognitive, emotional, and mental.¹ Dementia results in deterioration of the quality of life (QoL) of people with dementia (PWD) and their caregivers² and the imposition of an enormous economic burden on the families of PWD and the public healthcare system.^{2,3} The global epidemic of dementia has caused pertinent global costs to rapidly increase. In 2010, the cost was 604 billion USD, and it is expected to reach 1 trillion USD by 2018.⁴

Unfortunately, a cure for dementia has not been found. Although pharmacological agents, such as acetylcholinesterase

inhibitors and N-methyl-D-aspartate receptor antagonists, are effective for temporary control of the symptoms of cognitive decline and improvement of the activities of daily living (ADL) of patients with Alzheimer's disease (AD), they cannot restore premorbid levels of function or maintain adequate levels of function in patients in later stages of dementia.^{5,6} Furthermore, medications, such as antipsychotics, should be sparingly used to manage the behavioral and psychological symptoms of dementia (BPSD) due to the risk of adverse events, including cerebrovascular events, tardive dyskinesia, neuroleptic malignant syndrome, agranulocytosis, and mortality.^{7,8} Therefore, multifactorial therapeutic approaches that include pharmacological and nonpharmacological interventions (NPIVs) are increasingly advocated to improve the cognitive, affective, and global functioning of PWD, particularly for those in the later stages of dementia.^{7,9-11}

Recent systematic reviews have shown that several NPIVs may improve the cognition, communication, interactions, BPSD, ADL, and/or QoL of PWD.¹²⁻¹⁵ However, many of these reviews did not conduct meta-analyses due to lack of qualified studies and/or excessive study heterogeneity.¹⁶⁻²³ Furthermore, most studies on NPIVs did not consider the severity of de-

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mentia or included PWD in the later stages,^{16-18,24-30} and the efficacy and/or mechanisms of NPIVs may differ in later stages of dementia compared to those in the earlier stages.^{7,8} Although three systematic reviews on the efficacy of NPIVs in people with moderate to severe dementia (PWMSD) have been conducted, the effect sizes of the NPIVs were not reported because the reviews were not meta-analyses. Furthermore, the times of publication or intervention settings of the studies included in the meta-analyses were limited.^{16,17,23,31,32}

The principal strength of a systematic review is the capacity to identify salient and critical studies through the unmanageable numbers of existing medical literature using critical exploration, valuation, and synthesis.³³ Second, the results of a systematic review could satisfy the need of decision makers for evidence-based integrated results.³³ Conducting a systematic review, it is possible to refine the literature on the efficacy of NPIV in PWMSD by conducting qualitative synthesis and quantitative analysis, and also provide decision makers with reliable and pertinent evidence.

METHODS

Purpose

This systematic review, which will include a meta-analysis, aims to identify and evaluate the efficacy of NPIVs on the ADL and BPSD of PWMSD. Thus, the proposed systematic review will attempt to answer the following research questions:

- 1) Which NPIVs improve the ADL and BPSD of PWMSD?
- 2) What are the effects of NPIVs on the ADL and BPSD of PWMSD?

Methodology

This systematic review will be conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement³⁴ and Cochrane Handbook for Systematic Reviews of Interventions.³⁵ This systematic review protocol is registered with the PROSPERO (CRD42017058020).³⁶

Eligibility criteria

Populations

The systematic review will include studies involving people diagnosed with any type of dementia according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III); Fourth Edition, Text Revision (DSM-IV-TR); or Fifth Edition (DSM-5); International Classification of Diseases, Tenth Revision (ICD-10); or other accepted diagnostic criteria.

This systematic review will include PWD in the moderate

to severe stages who met one of the following criteria: Clinical Dementia Rating score of 2 or more, Global Deterioration Scale score of 5 or more, Functional Assessment Staging score of 5 or more, Mini-Mental State Examination (MMSE) score of 20 or less, or Revised Hasegawa's Dementia Scale score of 20 or less.

Interventions

This systematic review will include studies involving any type of NPIV that were conducted in community settings or institutional settings. NPIVs can be categorized in four broad groups following the practice guideline,⁸ and we will include several treatments such as cognitive therapy, art therapy, aromatherapy, massage, animal assisted therapy, exercise, or horticultural therapy.

Outcomes

This systematic review will employ ADL and BPSD as the primary outcomes and cognitive function and QoL as the secondary outcomes.

Study design

This systematic review will include randomized control trials (RCTs), quasi RCTs, non RCTs, cross-sectional studies, interrupted time series, and before-after studies that used the Study Design Algorithm for Medical Literature on Intervention.³⁷

Information sources

This systematic review will search the following databases and reference lists of the included studies: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE®, EMBASE®, CINAHL, PsycINFO, KoreaMED, KMBASE, and KISS. This systematic review will not limit the geography or time of the study, but only publications written in English or Korean will be included.

Search strategy

One reviewer (R Na) will search the information sources. The search strategy will include the study population and intervention terms suggested by Medical Subject Headings (MeSH®) and Emtree®. The search terms will be adapted for use in other bibliographic databases with database-specific filters when available. Some syntax, including truncation, or Boolean operators, will be amended to the specific databases. A draft EMBASE search strategy is shown in Table 1. This EMBASE search strategy will be adapted to the syntax and subject headings of the other databases.

Table 1. Example of an advanced search strategy-EMBASE

1	'dementia'/exp
2	'alzheimer disease'/exp
3	'frontotemporal dementia'/exp
4	'lewy body'/exp
5	'multiinfarct dementia'/exp
6	'normotensive hydrocephalus'/exp
7	'huntington chorea'/exp
8	parkinson AND disease AND dementia
9	vascular AND dementia
10	alcohol AND related AND dementia
11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12	moderate:ab,ti
13	severe:ab,ti
14	moderate AND to AND severe:ab,ti
15	advanced:ab,ti
16	profound:ab,ti
17	#12 OR #13 OR #14 OR #15 OR #16
18	#11 AND #17
19	'therapy'/exp
20	'cognitive therapy'/exp
21	'art therapy'/exp
22	'aromatherapy'/exp
23	'massage'/exp
24	'touch'/exp
25	'animal assisted therapy'/exp
26	'exercise'/exp
27	'horticultural therapy'/exp
28	'virtual reality'/exp
29	'telerehabilitation'/exp
30	(nonpharmacological AND treatment\$) OR (nonpharmacological AND therap\$) OR (nonpharmacological AND intervention\$)
31	(nondrug AND treatment\$) OR (nondrug AND therap\$) OR (nondrug AND intervention\$)
32	emotion AND oriented AND intervention\$:ab,ti
33	cognitive AND oriented AND intervention\$:ab,ti
34	psychotherapy\$:ab,ti
35	recreation AND therapy\$:ab,ti
36	validation AND therapy\$:ab,ti
37	reminiscence AND therapy\$:ab,ti
38	sensory AND stimulation AND intervention\$:ab,ti
39	light AND therapy\$:ab,ti
40	music AND therapy\$:ab,ti
41	(snoezelen:ab,ti) OR (snoezelen AND multisensory AND stimulation:ab,ti)
42	doll AND therapy\$:ab,ti

Table 1. Continued

43	robot AND therapy\$:ab,ti
44	multimodal AND therapy\$:ab,ti
45	occupational AND therapy\$:ab,ti
46	behavior AND therapy\$:ab,ti
47	computer AND assisted AND therapy\$:ab,ti
48	reality AND orientation\$:ab,ti
49	cognitive AND training\$:ab,ti
50	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49
51	#18 AND #50
52	'randomized controlled trial'/exp
53	'multicenter study'/exp
54	'clinical trial'/exp
55	'randomization'/exp
56	'single blind procedure'/exp
57	'crossover procedure'/exp
58	'placebo'/exp
59	'prospective study'/exp
60	double AND blind AND procedure
61	randomized AND controlled AND trial\$
62	rct:ab,ti
63	random AND allocation
64	randomly AND allocated
65	allocated AND randomly
66	single AND blind\$:ab,ti
67	double AND blind\$:ab,ti
68	cross AND sectional AND study
69	before AND after AND study
70	#52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69
71	'retrospective study'/exp
72	'cohort'/exp
73	'letter'/exp
74	case AND report
75	case AND study
76	abstract AND report
77	#71 OR #72 OR #73 OR #74 OR #75 OR #76
78	#70 NOT #77
79	#51 AND #78
80	animal
81	human
82	#80 NOT (#80 AND #81)
83	#79 NOT #82

Study records

Data management

This systematic review will export the search results to End-Note™ X8.0.1 [Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA] in which all reference records will be managed.

Selection process

Two reviewers (R Na and YJ Kim) will independently select studies in the three phases listed below. If any discrepancies occur between the two reviewers, two additional reviewers (KW Kim and K Kim) will amend the decision. This systematic review will create a PRISMA flow diagram of the included and excluded studies.

1) Initial screening: potential papers will be identified for abstract retrieval, and any obviously irrelevant studies will be eliminated by screening their titles.

2) Secondary screening: potential papers will be identified for full text retrieval by screening their abstracts.

3) Tertiary screening: papers that should be included in the current systematic review will be identified by reading the full text, and the reasons for exclusion will be documented.

Data collection process

Two reviewers (R Na and YJ Kim) will collect the data. Eli-

gible data will be independently extracted with a standardized form. Any discrepancies will be resolved by deliberation between R Na and YJ Kim or, if needed, with two other reviewers (KW Kim and K Kim).

Data items

Two reviewers (R Na and YJ Kim) will extract the data from the publications with a standardized data extraction form. The extracted data will be summarized as shown in Table 2.

Outcomes and prioritization

Primary outcomes

The primary outcomes of this systematic review will be ADL and BPSD of PWMSD. ADL, which will include Basic and Instrumental ADL,³⁸ will be measured with standardized assessment scales, including the AD Cooperative Study's ADL scale, Barthel Index, Disability Assessment for Dementia, D-Scale of Change, Katz Index, modified instrumental ADL scale, modified Physical Self-Maintenance Scale, Functional Independence Measure, and Nurse Informant Index of Activities of Daily Living.^{12,38-43}

The other primary outcome, BPSD, represents a heterogeneous group of noncognitive symptoms and behaviors.⁴⁴ BPSD includes agitation, aggression, aberrant motor behavior, anxiety, elation, irritability, depression, dysphoria, apathy, dis-

Table 2. Data extraction variables

Content	Data items
Prospective study information	Author(s), Year of publication, Country
Study design	Trial design
Number of participants	Number of participants invited, number of participants screened, number of participants eligible, number of participants randomized, reasons for non-eligibility, reasons for drop-out
Population	Severity of dementia, Type of dementia (e.g. Alzheimer's disease, vascular dementia, dementia with Lewy bodies, frontotemporal dementia, etc.) Average age, Gender, ethnicity, Diagnostic criteria for dementia (e.g. DSM-III, DSM-IV, DSM-5, ICD-10, etc.), Diagnostic tool for severity of dementia (e.g. CDR, GDS, FAST, MMSE, etc.), Physical health comorbidity, Usage of antedementia drug
Intervention	Name of treatment group, Type of non-pharmacological intervention, Frequency and duration of intervention, Intervention provider, length of intervention session, Mode of delivery (e.g. individual, group, combination)
Comparison	Name and type of control group, Frequency and duration of intervention, Intervention provider, length of intervention session, Mode of delivery (e.g. individual, group, combination)
Outcome	Detail of outcome measure
Outcome measure	Baseline, Follow-up assessment, Losses to follow-up, Result
Follow-up	Duration of follow-up, Drop-out rate
Setting	Community, Institution

DSM-III: Diagnostic and Statistical Manual of Mental Disorders, Third Edition, DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, ICD-10: International Classification of Diseases, Tenth Revision, CDR: Clinical Dementia Rating, GDS: Global Deterioration Scale, FAST: Functional Assessment Staging, MMSE: Mini-Mental State Examination

inhibition, delusions, hallucinations, appetite or eating changes, euphoria, sleep and night-time behavior changes, vegetative features, fear, phobia, wandering, threat, violence, fearfulness, diurnal rhythm disturbances, psychosis, and mood changes.⁴⁴⁻⁴⁷ BPSD assessments require standardized clinical assessments, such as the Behavioral Pathology in AD Scale, Neuropsychiatric Inventory, Behavior Rating Scale for Dementia, Cornell Scale for Depression in Dementia, Geriatric Depression Scale, Behavior and Mood Disturbance Scale, Rehabilitation Evaluation of Hall and Baker, Clifton Assessment Procedures for the Elderly, Cohen-Mansfield Agitation Inventory, and Actigraphy.^{31,44,48-51}

Secondary outcomes

The secondary outcomes will include the cognitive function and QoL of PWD. Cognitive function will be measured with standardized assessment tools, such as the Mini-Mental State Examination (MMSE), Severe Impairment Battery, Kingston Dementia Rating Scale, AD Assessment Scale-Cognitive Subscale, Brief Cognitive Screening Battery, Consortium to Establish a Registry for AD Assessment Tool (Korean version), Modified MMSE, and Montreal Cognitive Assessment.^{12,32,52-54} The evaluations of the QoL variables in PWD will require standardized and validated QoL scales, such as the Quality of Life scale in AD, AD Related Quality of Life, Dementia-Quality of Life, EuroQoL-Five Dimensions Questionnaire, and Blau's QoL Scale.^{14,55-59}

Risk of bias in individual studies

Two reviewers (R Na and YJ Kim) will independently assess the risk of bias (RoB) in each study. All reviewers will discuss the quality of a study if the two reviewers disagree. The RoB of RCTs will be assessed with the RoB scale,⁶⁰ while the RoB of nonRCTs will be assessed with the RoB Assessment Tool for Nonrandomized Studies (RoBANS).⁶¹ Each included study will be classified as low risk, high risk, or unclear according to the RoB and/or RoBANS.

Data synthesis

Two reviewers (YJ Kim and R Na) will conduct a meta-analysis of the outcomes with Review Manager if a sufficient number of studies are included. They will employ risk and odds ratios with 95% confidence intervals (CIs) for dichotomous outcomes and weighted mean differences (with 95% CIs) or standardized mean differences (with 95% CIs) for continuous outcomes. For missing data, we will attempt to contact the authors of the study to obtain the relevant information. Intention-to-treat data, if available, will be preferred.

This systematic review will consider the various characteristics of the participants and the study designs when evaluat-

ing the heterogeneity of the studies. Heterogeneity will be statistically tested with the chi-squared and I-squared tests.³⁵ To address heterogeneity, a meta-analysis will be conducted by considering the following: re-examining the data for accuracy, canceling the meta-analysis, exploring the heterogeneity, ignoring the heterogeneity, performing a random-effects meta-analysis, changing the effect measure, and/or excluding studies.³⁵

This systematic review will conduct subgroup analyses of the participants (e.g., dementia subtype, dementia severity, or participant characteristics), interventions (types, providers, or settings), study designs, and follow-up periods if sufficient data are available.

Meta-biases

This systematic review will assess publication bias with funnel plots of potential reporting bias if the number of studies in the meta-analysis is over 10.

Confidence in the cumulative estimates

This systematic review will assess the quality of the evidence for all outcomes with the Grading of Recommendations Assessment, Development and Evaluation (GRADE).⁶² All reviewers will determine the quality of the evidence according to the GRADE guidelines.⁶²⁻⁷⁰

CONCLUSION

This systematic review will examine the clinical efficacy of NPIVs on the ADL, BPSD, cognitive function, and QoL of PWMSD. Although the efficacy of NPIVs on PWD may differ according to the severity of dementia, recent reviews on NPIVs for PWD have not separately evaluated NPIVs efficacy on PWMSD or conducted relevant meta-analyses. To maximize the power of systematic reviews, restriction of publication language is not recommended. However, this systematic review will include studies written in English or Korean only for practical reasons, which will be a limitation of this study.

Nonetheless, this systematic review will provide clinicians and policy makers with reliable evidence for developing and implementing NPIVs for PWMSD.

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