ORIGINAL ARTICLE

Non-Pharmacological Treatment in People With Cognitive Impairment

Results From the Randomized Controlled German Day Care Study

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SUMMARY

Background: A number of non-pharmacological methods are available to help elderly people with cognitive impairment. Unstructured and non-evidence-based interventions are commonly used. The multicomponent therapy MAKs (a German acronym for Motor, Activities of daily living, Cognitive, Social) has already been evaluated in nursing homes; in this study, we investigated its use in day care centers (DCCs).

Methods: A cluster-randomized, controlled, single-blinded trial involving a 6-month intervention phase was performed. 362 cognitively impaired persons in 32 DCCs took part in the trial. Multiple regression analyses were used to determine whether MAKs therapy led to any statistically significant and clinically relevant improvement over time (compared to membership in the control group) in these persons' cognitive abilities and activities of daily living (ADL) abilities, as assessed, respectively, with the Mini-Mental State Examination (MMSE) and the Erlangen Test of Activities of Daily Living in Persons with Mild Dementia or Mild Cognitive Impairment (ETAM). A primary per-protocol analysis was supplemented by an intention-to-treat analysis. Two secondary outcomes (social behavior and neuropsychiatric symptoms) were analyzed exploratively as well. Study registration: ISRCTN16412551.

Results: In the primary per-protocol analysis at 6 months, the intervention group had significantly better MMSE and ETAM scores than the control group (Cohen's d , 0.26 and 0.21, respectively; $p = 0.012$ for both). The same was found in the ITT analysis at 6 months (Cohen's $d = 0.21$, $p = 0.033$; and Cohen's $d = 0.20$, $p = 0.019$, respectively). Neuropsychiatric symptoms, one of the secondary outcomes, also evolved more favorably in the intervention group (Cohen's $d = 0.23$, $p = 0.055$).

Conclusion: MAKs therapy is effective for persons with cognitive impairment ranging from mild cognitive impairment (MCI) to moderate dementia who live at home and regularly visit a day care center. The fact that 32 day care facilities from all over Germany participated in this study gives its findings high external validity.

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In Germany, day care centers are currently used by only a small proportion (approximately 4%) of people who require care and are cared for at home (1). The largest subgroup of day care center users are older individuals with more or less severe cognitive impairment (2). This includes dementia syndrome and mild cognitive impairment (MCI); the latter is the beginning of cognitive impairment that can be measured psychometrically but is not yet included in ICD diagnoses. There is evidence that attending day care centers has a positive effect on the wellbeing of those who require care (3, 4). The findings of 2 recent reviews, however, show that there is currently no scientifically tested care plan for day care centers (3, 5) with specific aims and a structured instruction manual.

A randomized, controlled intervention study has already investigated the multicomponent therapy MAKs (a German acronym for Motor, Activities of daily living, Cognitive, Social) (6) in an institutional setting in individuals with degenerative dementia (7, 8).

The present study, DeTaMAKS (dementia day care MAKs), aims to test the following research hypothesis: MAKs therapy in day care leads to significantly better progression of activities of daily living (ADL) abilities and cognitive abilities of individuals with mild cognitive impairment (MCI) or dementia than treatment as usual in the control group.

Methods

Study design

A cluster-randomized, controlled, multicenter, prospective study with a waitlist control group design was conducted between April 1, 2015 and March 31, 2017 to test the research hypothesis. The primary outcomes were the cognitive and ADL abilities of individuals with mild cognitive impairment or dementia. Neuropsychiatric symptoms and social behavior were recorded as secondary outcomes. All aspects of the research were approved by the Ethics Committee of the Faculty of Medicine of Friedrich Alexander University Erlangen–Nuremberg. The study protocol was published in advance (9). Study conduct did not deviate from study design. See *eBox 1* for the responsibilities of the authors for individual elements of the study.

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FIGURE 1

Flow diagram according to CONSORT statement: cluster-randomization, baseline, dropouts, follow-up.

CONSORT, Consolidated Standards of Reporting Trials; MAKS, Motor, Activities of daily living, Cognitive, Social (German acronym)

All participating day care centers (clusters) were assigned at random to the intervention group or the control group. During the 6-month intervention phase, the day care centers in the intervention group administered MAKS therapy following suitable training of their employees. The day care centers in the control group administered treatment as usual.

Study participants, sample size

Four hundred fifty-three day care center users were enrolled at the beginning of the study (9). Cognitive impairment was assessed using the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) (10). The study participants were recruited in line with the inclusion criteria published in the study protocol. One day care center in the intervention group had to be excluded because it had not administered the intervention according to the instruction manual, and one day care center in the control group terminated its collaboration agreement. The evaluated sample therefore included participants from 32 centers. At the end of the 6-month intervention phase the

sample consisted of 362 individuals, excluding the 91 dropouts. These 362 individuals were all included in primary, per-protocol analysis, regardless of the number of days on which they had attended day care centers (frequency of attendance) during the 6-month intervention phase. Sixty-one percent of the day care center users in the sample were women, and users' mean age was 81.3 years (standard deviation [SD] = 7.5) (eTable). There were no significant differences between the baseline values in the intervention and control groups (eTable).

The reasons for dropping out—death, transfer to a nursing home, termination of day care—are shown in detail in Figure 1. There were no statistically significant differences between the day care center users who dropped out and the evaluated sample, particularly in terms of the primary and secondary outcomes. Dropouts were approximately equal in frequency in the 2 study groups (intervention group: 20.9%; control group: 18.9%). There were no statistically significant differences between study participants who died during the study period and those who did not except for their age (died: mean [M] = 86.4 years, SD = 6.0; survived: M = 81.5 years, SD = 7.0; $p = 0.005$). Study participants who died participated in the study for a mean of 3 months. The death rates in the 2 groups were also similar (intervention group: 4.6%; control group: 3.7%).

The intervention and its implementation

MAKS therapy (6, 7) consists of 4 components that are always implemented in the same order and form an intervention unit lasting approximately 2 hours per day. There is an instruction manual for this group therapy: The daily unit begins with a social warm-up session (e.g. a greetings round) that lasts approximately 10 minutes. This is followed by sensorimotor activation lasting around 30 minutes in which general mobility, gross and fine motor skills, balance, and sensory perception are practiced using warm-up exercises, mobility games, and various games and sports. After a break comes cognitive activation, in which memorizing, recognizing, forming associations, and special cognitive abilities such as language comprehension and logical thinking are developed using projector or pen-and-paper exercises for around 30 minutes. The final part, activation of activities of daily living, lasts approximately 40 minutes. This develops gross and fine motor skills, mobility, and in particular procedural memory; it also includes housework or craftwork (6). In the intervention group, MAKS therapy was administered from Mondays to Fridays for 6 months. On every treatment day, all study participants who attended the day care centers on that day took part in MAKS therapy. This resulted in mean "treatment doses" of between 1 and 5 treatment days per week. Other provisions of the day care centers, participants' medication, and their frequency of attendance were not determined by the study. Any changes in frequency of attendance were documented for all study participants.

TABLE 1

Multiple regression with MMSE and ETAM at 6 months (t_1) as dependent variable (per-protocol analysis, $n = 362$)

Independent variable	MMSE (6-month follow-up)			ETAM (6-month follow-up)		
	Estimate	95% CI	p-value	Estimate	95% CI	p-value
Baseline score* ¹	0.945	[0.857; 1.033]	<0.001	0.838	[0.771; 0.905]	<0.001
Intervention group (comparator = control group)	1.079	[0.234; 1.924]	0.012	1.247	[0.276; 2.218]	0.012
Age	-0.035	[-0.093; 0.022]	0.229	-0.037	[-0.104; 0.029]	0.267
Male sex (comparator = female)	-0.717	[-1.597; 0.164]	0.110	-0.559	[-1.571; 0.453]	0.278
Frequency of attendance* ²	-0.137	[-0.511; 0.237]	0.470	-0.199	[-0.628; 0.230]	0.362
Dementia specific medication taken (comparator = no)* ³	-0.333	[-1.265; 0.599]	0.483	-0.844	[-1.910; 0.222]	0.120
Depression improved (comparator = no)* ⁴	0.799	[-0.404; 2.001]	0.193	-0.590	[-1.972; 0.793]	0.402

Statistically significant p -values ($p < 0.05$) are shown in bold.

Overall model for MMSE: coefficient of determination $R^2 = 0.575$; $p < 0.001$; Cohen's $d = 0.26$

Overall model for ETAM: $R^2 = 0.646$; $p < 0.001$; Cohen's $d = 0.21$

*¹MMSE score at baseline with MMSE score at 6-month follow-up as dependent variable; ETAM score at baseline with ETAM score at 6-month follow-up as dependent variable

*²Mean frequency of attendance in sixth month

*³Dementia specific medication is a dichotomous variable with the answer "yes" if memantine or acetylcholinesterase inhibitors prescribed.

*⁴Depression was assessed as a dichotomous variable in NPI (yes or no): "improved," i.e. depression at t_1 "no", at t_0 "yes", versus "not improved", i.e. no change between t_0 and t_1 or depression at t_1 "yes", at t_0 "no".

95% CI, 95% confidence interval; ETAM, Erlangen Test of Activities of Daily Living in Persons with Mild Dementia or Mild Cognitive Impairment; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory

Outcomes: data collection and tools

eBox 2 describes in detail the performance tests (cognition and ADL abilities) and external assessment procedures (neuropsychiatric symptoms and social behavior) used. It also contains detailed information on randomization and blinding.

Statistical analysis

There were no deviations from the planned inclusion and exclusion criteria or the planned 6-month duration of the intervention. Because the primary outcomes could no longer be recorded for the remainder of the study period for participants who dropped out (due to death, transfer to a nursing home, or termination of day care), primary analysis was per-protocol. To perform additional evaluation based on all patients enrolled in the study (intention-to-treat [ITT] analysis), we replaced the missing data at 6 months using a statistical model (imputation using the expectation–maximization algorithm). For this we used values of the variables that showed the greatest correlation with the variables to be replaced. This secondary analysis was performed in order to examine and reinforce our main finding. It was performed for all study participants who were not deceased at the 6-month point of the study.

The research hypothesis was tested using multiple linear regression analyses. The variables used were the baseline values of the dependent variables (MMSE score and ETAM [Erlangen Test of Activities of Daily Living in Persons with Mild Dementia or Mild Cogni-

tive Impairment] score at the beginning of the study), the group individuals belonged to (intervention or control), and 2 adjustment variables (age and sex). Analysis also included predictors with a potential effect on the outcomes that could not be affected by the study design. Theoretically, there are 3 significant variables here: pharmacological treatment for dementia syndrome (dementia medication taken: yes/no), dose of non-pharmacological treatment (frequency of attendance at day care center), and changes in depression symptoms (depression improved: yes/no). There were no variables that had to be excluded because they were so closely associated with another variable as to be superfluous (multicollinearity).

For the secondary outcomes social behavior and neuropsychiatric symptoms, an exploratory comparison of mean differences between baseline and postintervention values was calculated (t -test for independent samples). Differences between the groups were analyzed using the t -test for independent samples, the Mann–Whitney U -test, or the chi-square test, depending on the data level. Cohen's d was used as a measure of effect size.

Subgroup analysis investigated whether the effects of the intervention were dependent on severity of cognitive impairment (MCI, mild dementia, or moderate dementia) or on frequency of attendance at the day care center and thus "treatment dose."

$p = 0.05$ was used as the statistical significance level for both primary outcomes. Data was evaluated using the statistics program IBM SPSS Statistics 21.

FIGURE 2

Changes in cognitive abilities over time in DeTaMAKS intervention and control groups versus untreated progression (based on the literature)

*Decrease in cognitive abilities (MMSE) during untreated progression before beginning of dementia medication with an assumed baseline score of 19.6; in this sample, this score corresponds to the mean in the control group at time t_0 . The decrease in MMSE score of 3 points per year shown here is taken from the study that shows progression without intervention, which uses MMSE as a measure of cognition and best matches our research in terms of target group and setting (day care centers) (18). Other publications describe comparable cognitive decreases (19).

DeTaMAKS, Dementia day care MAKS; MAKS, Motor, Activities of daily living, Cognitive, Social (German acronym); MMSE, Mini-Mental State Examination

Results

Findings on primary outcomes (research hypothesis)

After 6 months, there were better results for cognitive and ADL abilities in the intervention group than in the control group. In both regression equations (Table 1) the variable “group membership” (membership in intervention or control group) was found to be a significant predictor of the outcome after 6 months (MMSE: $p = 0.012$; ETAM: $p = 0.012$). Cohen’s d was 0.26 for MMSE and 0.21 for ETAM. Pharmacological treatment for dementia syndrome (dementia specific medication taken: yes/no), dose of non-pharmacological treatment (frequency of attendance at day care center), and changes in depression symptoms (depression improved: yes/no) had no statistically significant effect on either outcome.

Analyses of means show that cognitive and ADL abilities remained constant in the intervention group (mean MMSE [SD] = 19.8 [4.8] at t_0 and 19.9 [6.0] at t_1 ; mean ETAM [SD] = 17.9 [6.9] at t_0 and 18.2 [7.0] at t_1), whereas the means in the control group deteriorated (MMSE [SD] = 19.3 [4.8] at t_0 and 18.3 [6.2] at t_1 ; ETAM [SD] = 17.1 [7.5] at t_0 and 16.4 [8.4] at t_1). Comparison of MMSE score with the untreated course

before introduction of dementia specific treatment shows that this decrease is plausible (Figure 2).

ITT analysis ($n = 433$) also found statistically significant values for the variable “group membership” in terms of both outcomes ($p = 0.033$ for MMSE; $p = 0.019$ for ETAM). Cohen’s d was 0.21 and 0.20 respectively.

No harm or unwanted effects on the participants occurred in terms of either of the investigated outcomes.

Findings concerning secondary outcomes

Descriptively, the course of non-cognitive symptoms of dementia was more favorable in the intervention group than in the control group (Table 2). For social behavior, which was recorded on a scale, $p = 0.148$; for presence/absence of neuropsychiatric symptoms $p = 0.055$ (effect size $d = 0.23$).

Subgroup analyses

Subgroup analyses were performed on an exploratory basis to investigate whether the effects of the intervention were dependent on the severity of cognitive impairment or frequency of attendance at day care center and thus “treatment dose” (Table 3). For MCI and moderate dementia the effect sizes were somewhat higher for both outcomes (MMSE: 0.29 and 0.34 respectively; ETAM: 0.37 and 0.27 respectively) than for mild dementia (MMSE: 0.19; ETAM: 0.10).

No systematic benefit can be identified for either low (1 to 2 days per week) or high (3 to 5 days per week) frequency of attendance (Table 3). For low frequency of attendance, the effect sizes were 0.31 (MMSE) and 0.19 (ETAM); for high frequency of attendance 0.11 (MMSE) and 0.27 (ETAM). There was no evidence of a correlation between frequency of attendance and care level, respectively the benefits to which individuals are entitled according to Germany’s long-term care funds ($p = 0.619$). Frequency of attendance was also independent of severity of cognitive impairment (correlation between frequency of attendance and MMSE score: $p = 0.581$).

Discussion

Our findings show that cognitive and ADL abilities stabilized in the study group that underwent a 6-month MAKS intervention according to an instruction manual. In the comparison group, there was a decrease of one MMSE point within 6 months. These findings are in line with both theory and empirical findings. Like all non-pharmacological treatments, MAKS therapy is symptom-based. No average improvement in cognitive performance can be expected with this type of noncausal therapy for a neurodegenerative process; instead, a realistic optimum aim of treatment is for performance to stabilize on average for a particular period of time. In this context, MAKS therapy is effective with regard to the outcome “cognition”. Its effects can be seen even in the subgroup of day care users with only MCI.

Comparison with 3 randomized controlled trials in which a comparable target group—individuals living at

TABLE 2

Exploratory findings on secondary outcomes

Scale	Intervention (n = 208)	Control (n = 154)	t-test for independent samples		Cohen's d
	ΔM (SD)	ΔM (SD)	t	p	d
Social behavior (NOSGER)	-0.21 (3.2)	-0.73 (3.6)	-1.45	0.148	0.16
Neuropsychiatric symptoms (NPI-Q)	0.16 (1.8)	-0.27 (1.9)	-1.92	0.055	0.23

Comparison of differences between t_0 and t_1 ($t_0 - t_1$). Negative values of $t_0 - t_1$ for NOSGER and NPI-Q indicate that symptoms deteriorated.
M, mean; NOSGER, Nurses' Observation Scale for Geriatric Patients, social behavior subscale; NPI-Q, Neuropsychiatric Inventory Questionnaire; SD, standard deviation

TABLE 3

Exploratory subgroup analysis on cognitive (MMSE) and activities of daily living (ETAM) abilities by severity of cognitive impairment and weekly frequency of attendance at day care center (n = 362)

	Severity of cognitive impairment			Frequency of attendance at day care center	
	MCI	Mild dementia	Moderate dementia	1 to 2 days	3 to 5 days
MMSE					
Intervention: ΔM (SD)* ¹	0.36 (3.12)	0.16 (3.48)	-0.75 (4.56)	-0.05 (3.75)	-0.22 (4.01)
Control: ΔM (SD)* ¹	1.45 (4.38)	0.90 (4.39)	0.73 (4.11)	1.18 (4.24)	0.25 (4.28)
T^2	1.308	1.144	1.944	2.480	0.567
p^3	0.195	0.255	0.054	0.014	0.572
Cohen's d	0.29	0.19	0.34	0.31	0.11
ETAM					
Intervention: ΔM (SD)* ¹	-0.62 (3.46)	-0.21 (4.45)	-0.11 (3.73)	-0.26 (3.75)	-0.30 (4.49)
Control: ΔM (SD)* ¹	0.71 (3.78)	0.34 (6.50)	1.13 (5.44)	0.64 (5.68)	1.00 (5.39)
T^2	1.622	0.613	1.514	1.464	1.330
p^3	0.109	0.541	0.133	0.145	0.188
Cohen's d	0.37	0.10	0.27	0.19	0.27

*¹ $\Delta M = M(t_0) - M(t_1)$. Positive values indicate a decline in abilities during the intervention period.

*²t-test for independent samples

*³Statistically significant p-values ($p < 0.05$) are shown in bold.

ETAM, Erlangen Test of Activities of Daily Living in Persons with Mild Dementia or Mild Cognitive Impairment; M, mean; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SD, standard deviation

home with MCI or dementia—were treated (20–22) can aid in understanding our findings. Interventions consisted of at least 3 components and always included cognitive and sensorimotor training. The significant effects on cognition were similar to those in our study: it stabilized in the intervention group and deteriorated in the control group. Olazarán et al. (20) found this, according to MMSE and Alzheimer's Disease Assessment Scale—cognitive subscale (ADAS-cog) scores, after 6 months in both MCI and dementia patients who were treated at a day care center twice per week. According to Buschert et al. (21), 6-month results in MMSE and ADAS-cog are dependent on the severity of cognitive impairment. With a “treatment dose” of one unit per week, there were no effects in dementia patients but statistically significant differences in MCI patients. In shorter (10-week) but more intensive

(3 times per week) therapy, Baglio et al. (22) found no significant differences in ADAS-cog score between intervention and control group in dementia patients. These comparable studies thus showed that treatment effects on cognition were more likely to be found in individuals with MCI than in those with dementia. In contrast, MAKs therapy was equally effective in both MCI and moderate dementia.

Activities of daily living abilities were measured only in the study by Baglio et al. (22). No statistically significant effects were found. This may be because changes were observed only for a short, 10-week period. In contrast, both Baglio et al. (22) and Olazarán et al. (20) found significantly less severe neuropsychiatric symptoms (recorded using the Neuropsychiatric Inventory [NPI]) in their intervention groups. This is in line with our findings, if the fact is taken into account that

we chose a less change-sensitive procedure: to ask only whether or not neuropsychiatric symptoms according to the NPI were present, not how severe they were.

The mean decrease in the control group, one point in 6 months, was slightly better than untreated progression according to the literature, which states a mean decrease in MMSE score of 1.5 points in 6 months (*Figure 2*). This is plausible if one considers that the day care centers of the control group were free to choose the treatment they offered (23).

Interestingly, our study found no significant positive effect for frequency of attendance at day care centers on either primary outcome; in other words, MAKS therapy was effective even with a frequency of attendance of only 1 to 2 days per week. In addition, frequency of attendance was independent of severity of cognitive impairment. However, this lack of dose-dependency of the effects of treatment was found only in interindividual comparison. Intraindividually, effects may well be stronger when the “dose” is increased. This should be investigated in future studies.

Recording of cognition and ADL abilities covers the two cardinal symptoms of dementia syndrome. The ETAM test to measure ADL abilities is based on the International Classification of Functioning (ICF) (11) and thus reflects the fundamental areas of independence in everyday living and social participation.

Existing diagnoses of dementia were recorded. However, for study-related reasons it was not possible to determine whether participants not medically diagnosed with dementia in fact suffered from it, other than psychometric recording of cognitive impairment. However, psychometric examination offered the benefit of also including individuals with MCI and making it possible to investigate the efficacy of MAKS therapy for this particular group.

In parallel to MAKS therapy at the day care centers, patients’ relatives were counseled up to 3 times on their care situation. Both a meta-analysis (23) and the review by Germany’s Institute for Quality and Efficiency in Health Care (IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) (24) have found that relative-based procedures, particularly psychosocial measures, have no effect on ADL abilities or cognition in dementia patients. It can therefore be assumed that our “low-dose” relative-based intervention had no confounding effect on the results in terms of the patient-related outcomes.

It would be very interesting to determine for how long it is possible for cognitive and ADL abilities to remain stable; in nursing homes this positive effect has been identified over a 12-month period (7); a longer intervention period would also be helpful in an outpatient setting. One limitation of our work in this respect is that because of the waitlist control group design an interval of more than 6 months of differentiating between intervention and control group would not have been accepted by the day care centers. For similar reasons of practicability, we preferred the MMSE over other, more differentiated cognitive tests. Firstly, because the day

care centers were located all over Germany external testers in all study regions were trained, and the easy-to-perform MMSE is particularly suited to this. Secondly, the fact that there are so many studies using the MMSE makes it easy to compare our own results with the literature.

The external validity of this research is high, as 32 day care centers all over Germany participated in it. This means that MAKS therapy can easily be implemented. Only training for employees is needed, as the curriculum and treatment materials have already been developed and are in the process of being published.

KEY MESSAGES

- MAKS is a multicomponent, non-pharmacological, group therapy administered according to an instruction manual for individuals with cognitive impairment in old age. It consists of specific exercises to activate motor skills, activities of daily living (ADL) abilities, and cognition, together with a social warm-up session.
- On average, MAKS therapy stabilized the outcomes “cognitive abilities” and “ADL abilities”, which are relevant to everyday life. These abilities deteriorated significantly in the control group.
- The controlled intervention phase was limited to 6 months. Future studies should use a substantially longer intervention period to determine the total duration of MAKS’ stabilizing effect on patient’s abilities.
- MAKS therapy was investigated in existing care facilities. This increases the external validity of the results and highlights the chances of implementing MAKS.
- Given the existing evidence for its efficacy, the next step for MAKS therapy is its broader implementation. This can be achieved by training staff.

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Declarations

Ethics committee and informed consent:

All aspects of the study were examined and approved by the Ethics Committee of the Faculty of Medicine of Friedrich Alexander University Erlangen–Nuremberg (ref. no.: 170_14 B). Study participation was voluntary, and all participants were free to end their study participation at any time. All participants received information, after which a declaration of consent to participate was obtained (informed consent).

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Conflict of interest statement

Prof. Dr. Elmar Graessel is a co-editor and co-author of the book on MAKs therapy listed in the bibliography under (6).

The other authors declare that no conflict of interest exists.

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Supplementary material

For eReferences please refer to:
www.aerzteblatt-international.de/de/ref4817

eTable, eBoxes:

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Supplementary material to:

Non-pharmacological Treatment in People With Cognitive Impairment

Results From the Randomized Controlled German Day Care Study

by Melanie Straubmeier, Elisa-Marie Behrndt, Hildegard Seidl, Dominik Özbe, Katharina Luttenberger, and Elmar Graessel

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eTABLE

Description of sample (randomized at beginning of study, n = 362)

	Intervention group (n = 208)	Control group (n = 154)	Total (n = 362)	Tests for differences between groups		
				Chi-square	T/U	p
Dementia patients						
Age, M (SD)	81.5 (7.5)	81.1 (7.5)	81.3 (7.5)		−0.544	0.587
Women, n (%)	127 (61.1)	94 (61.0)	221 (61.0)	0.000		0.997
Education completed (years), M (SD)* ¹	9.8 (2.5)	9.6 (2.1)	9.7 (2.3)		−0.610	0.542
Marital status, n (%)				0.063		0.996
Married/long-term partnership	85 (40.9)	64 (41.6)	149 (41.2)			
Widowed	111 (53.4)	82 (53.2)	193 (53.3)			
Divorced	6 (2.9)	4 (2.6)	10 (2.8)			
Single	6 (2.9)	4 (2.6)	10 (2.8)			
Cognitive impairment (MMSE), M (SD)* ²	19.8 (4.8)	19.3 (4.8)	19.6 (4.8)		−0.973	0.331
Mild cognitive impairment	25.8 (1.5)	26.3 (1.4)	26.0 (1.5)		1.295	0.200
Mild dementia	20.6 (1.7)	20.5 (1.6)	20.6 (1.7)		−0.406	0.686
Moderate dementia	14.4 (2.4)	14.6 (2.2)	14.5 (2.3)		0.284	0.777
Activities of daily living (ETAM), M (SD)	17.9 (6.9)	17.1 (7.5)	17.6 (7.2)		−1.000	0.318
Care level* ³ , n (%)					15 875.0* ⁴	0.875
None	8 (3.8)	12 (7.8)	20 (5.5)			
Limited abilities in activities of daily living	25 (12.0)	15 (9.7)	40 (11.0)			
1	111 (53.4)	75 (48.7)	186 (51.4)			
2	62 (29.8)	50 (32.5)	112 (30.9)			
3	2 (1.0)	2 (1.3)	4 (1.1)			
Dementia specific medication taken* ⁵ , n (%)	62 (29.8)	40 (26.0)	102 (28.2)	0.643		0.423
Memantine taken, n (%)	27 (13.0)	19 (12.3)	46 (12.7)	0.033		0.856
Cholinesterase inhibitor taken, n (%)	41 (19.7)	21 (13.6)	62 (17.1)	2.301		0.129
Social behavior (NOSGER), M (SD)	15.5 (4.2)	15.6 (4.6)	15.5 (4.3)		0.053	0.958
Neuropsychiatric symptoms (NPI-Q), M (SD)	5.2 (2.7)	5.3 (2.7)	5.3 (2.7)		0.597	0.551
Depression “yes” * ⁶ , n (%)	119 (57.2)	91 (59.1)	210 (58.0)	0.128		0.720
Relatives						
Age, M (SD)	59.6 (11.6)	59.3 (11.2)	59.5 (11.4)		−0.231	0.818
Women, n (%)	152 (73.1)	118 (76.6)	270 (74.6)	0.587		0.444
Education (years), M (SD)* ¹	10.9 (2.9)	10.8 (2.8)	10.8 (2.9)		−0.370	0.712
Employment: employed, n (%)	112 (53.8)	83 (53.9)	195 (53.9)	0.000		0.992
Marital status, n (%)				9.550		0.023
Married/long-term partnership	160 (76.9)	125 (81.2)	285 (78.7)			
Widowed	12 (5.8)	2 (1.3)	14 (3.9)			

	Intervention group (n = 208)	Control group (n = 154)	Total (n = 362)	Tests for differences between groups		
				Chi-square	T/U	p
Divorced	14 (6.7)	18 (11.7)	32 (8.8)			
Single	22 (10.6)	9 (5.8)	31 (8.6)			
Relationship to person cared for, n (%)				0.856		0.652
Wife/husband	54 (26.0)	43 (27.9)	97 (26.8)			
Son/daughter (-in-law)	140 (67.3)	104 (67.5)	244 (67.4)			
Other	14 (6.7)	7 (4.5)	21 (5.8)			
Caregiver burden (BSFC-s), M (SD)	12.0 (8.2)	13.2 (7.6)	12.5 (8.0)		1.479	0.140
Relatives' well-being (depressiveness) (WHO-5), M (SD)	11.9 (6.2)	12.0 (5.6)	11.9 (6.0)		0.084	0.933
Care status						
Main caregiver, n (%)	180 (86.5)	139 (90.3)	319 (88.1)	1.171		0.279
Main caregiver is the only informal caregiver, n (%)	111 (53.4)	83 (53.9)	194 (53.6)	0.010		0.920
Sharing home, n (%)	88 (42.3)	68 (44.2)	156 (43.1)	0.123		0.726
Duration of informal care (months), M (SD)	59.9 (48.9)	59.0 (52.2)	59.5 (50.2)		-0.168	0.867
No. of weekly visits to day care center (first month), M (SD) ^{*7}	1.9 (1.2)	1.9 (1.1)	1.9 (1.2)		-0.066	0.948
Informal care time (hours per day), M (SD) ^{*8}	3.0 (2.2)	3.3 (2.0)	3.1 (2.1)		1.130	0.259

^{*1}Min. 7 years (school not completed) to max. 18 years (university graduation)

^{*2}Mild cognitive impairment, MMSE 30 to 24 and Montreal Cognitive Assessment <23; mild dementia: MMSE 23 to 18; moderate dementia: MMSE 17 to 10

^{*3}Care level describes the extent to which care is required: none (not needed), LDL (limited abilities in activities of daily living, often described as "care level 0"), 1 (moderate need), 2 (great need), or 3 (very great need). This scale is used in Germany to classify entitlement to care (German system of statutory long-term care funds).

^{*4}U-test

^{*5}"Yes" recorded if either memantine or a cholinesterase inhibitor prescribed according to day care center records.

^{*6}NPI item depression (yes/no); known pre-existing severe depression was one of the study's exclusion criteria.

^{*7}Mean weekly frequency of attendance at day care center during first month

^{*8}Mean number of hours of informal care per day, taking into account the differing amount of care time on days day care centers were or were not attended.

BSFC-s, Burden Scale for Family Caregivers, short version; ETAM, Erlangen Test of Activities of Daily Living in Persons with Mild Dementia or Mild Cognitive Impairment; M, mean; MMSE, Mini-Mental State Examination Score; NOSGER, Nurses' Observation Scale for Geriatric Patients, social behavior subscale; NPI-Q, Neuropsychiatric Inventory Questionnaire; SD, standard deviation; WHO-5, WHO-5 Well-Being Index (measures depressiveness)

eBOX 1

Contributions of the authors

MS was responsible for the study arm investigating the effects of the intervention on individuals with cognitive impairment. She further developed MAKs therapy, analyzed the corresponding data, and drafted this manuscript. EMB was responsible for data monitoring and made a substantial contribution to data analysis. HS was responsible for health economics-related evaluation and aided in the drafting of the manuscript. DÖ performed the search of the literature and contributed to the manuscript. EG and KL designed the study, oversaw study conduct, and contributed to the manuscript. All the authors read and approved the final version of this manuscript.

eBOX 2

Outcomes: data collection and tools

The primary outcomes required to test the hypothesis (MMSE and ETAM; see following paragraph) were measured using psychometric tests before and after the intervention phase at the day care centers by trained staff who were not involved in treatment (9).

The Erlangen Test of Activities of Daily Living in Persons with Mild Dementia or Mild Cognitive Impairment (ETAM) (11) is a performance test designed to measure abilities in activities of daily living (ADL). Scores range from 0 to 30. It is based on the E-ADL (Erlangen Test of Activities of Daily Living) test and is particularly suitable for use in cases of mild cognitive impairment and mild to moderate dementia. The Mini-Mental State Examination (MMSE) (12) is the most commonly used dementia screening test (13). A score of 18 to 23 indicates "mild" dementia, 10 to 17 "moderate," and 0 to 9 "severe" (14). The MMSE also measures changes in cognition over time (14). The Montreal Cognitive Assessment (MoCA) was used in the recruitment process for this study, to detect mild cognitive impairment (MCI). The cut-off score was 22 (15). The psychometric definition of MCI was thus MMSE score above 23 and MoCA score below 23.

The secondary outcomes were measured at the same point in time, via external assessment in computer-aided interviews with family caregivers. The Neuropsychiatric Inventory Questionnaire (NPI-Q) recorded neuropsychiatric symptoms in the form of screening questions (yes or no) concerning 12 symptom domains (16). The "social behavior" subscale of the Nurses' Observation Scale for Geriatric Patients (NOSGER) was used to determine social behavior (17).

MAKS is a German acronym for Motor, Activities of daily living, Cognitive, Social. MAKs therapists at the day care centers where the intervention was performed also recorded, on a daily basis, study participants' attendance and any deviations from the procedure stated in the MAKs instruction manual.

Randomization and blinding

To prevent diffusion of treatment within an individual center, the clusters, i.e. the participating day care centers, were randomized to the study groups. A lottery procedure employing paper lottery tickets was used for this, as was stratification by region (north-east, south-east, and west). It was not possible to blind therapists or participants to study groups (control versus intervention), as the non-pharmacological intervention (MAKS or treatment as usual) was "visible." The outcome testers, who had received training, were not involved in the care of the day care center users (quasiblinding).