Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms: A Cluster Randomized Controlled Trial

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Objective: *To determine the effectiveness of the Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms (TIME) for treatment of moderate to severe agitation in people with dementia.* **Methods:** *In a single-blinded, cluster randomized controlled trial in 33 nursing homes (clusters) from 20 municipalities in Norway, 229 patients (104 patients in 17 nursing homes and 125 patients in 16 nursing homes) were randomized to an intervention or control group, respectively. The intervention group received TIME, and the control group received a brief education-only intervention. TIME is an interdisciplinary multicomponent intervention and consists of a comprehensive assessment of the patient with the goal to create and put into action a tailored treatment plan. The primary outcome was the between-group difference in change at the agitation/aggression item of the Neuropsychiatric Inventory Nursing Home version between baseline and 8 weeks. Secondary outcomes were the between-group difference in change at the agitation/aggression between baseline and 12 weeks in other neuropsychiatric symptoms, quality of life, and use of psychotropic and analgesic medications between baseline and 8 and 12 weeks.* **Results:** *A significant between-group difference in reduction of agitation at both 8 weeks (1.1; 95% confidence interval: 0.1–2.1; p = 0.03) and 12 weeks (1.6; 95% confidence interval: 0.6–2.7; p = 0.002) in favor of the TIME intervention was found.* **Conclusion:** *The implementation of TIME resulted in a significant reduction of agitation among nursing homes patients with dementia. These results should inform training programs for care staff in Norway and internationally.* (Am J Geriatr Psychiatry 2018; 26:25–38)

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Highlights

- Agitation in dementia is common, and causes profound suffering for patients and caregivers. Because psychotropic drugs are associated with serious side-effects, non-pharmacological interventions are recommended as a first-line approach.
- There is conflicting evidence about the effectiveness of non-pharmacological interventions for agitation in patients with dementia. Trials of multicomponent interventions are requested.
- A multicomponent biopsychosocial approach (TIME) significantly reduced agitation in patients with dementia living in nursing homes.
- Since agitation in dementia often represent complex problems with multifactorial causes, multicomponent interventions with a comprehensive biopsychosocial approach should be applied.

INTRODUCTION

Neuropsychiatric symptoms (NPS) are very common in patients with dementia.[1] Approximately 70% of patients with dementia in nursing homes exhibit clinically significant NPS, and nearly all of them will experience NPS during the course of the disease.[2–4] Agitation, defined as a group of symptoms including verbal and physical aggression and excessive motor activity, is frequent and is among the most persistent symptoms.[2,4] Agitation is associated with increased patient suffering, reduced quality of life, and a more rapid progression toward severe dementia and death and is a predictor of referral to specialist healthcare and hospitalization.[5,6] These symptoms also create a great burden and distress for caregivers.[7]

Although there is conflicting evidence about their effectiveness, nonpharmacologic interventions are recommended as a first-line approach for agitation.[8] Psychotropic drugs are associated with serious side effects and safety concerns, and their effects are, at best, modest.[9] A literature review by Livingston et al.[10] concluded that behavioral therapeutic techniques and psychoeducation aimed at altering caregiver behavior seemed to reduce NPS. However, findings regarding other types of treatment were inconclusive and inadequately documented. A systematic review of nonpharmacologic interventions for agitation and aggression in dementia, published by the Agency for Healthcare Research and Quality in 2016,[11] concluded that the evidence is weak because of methodologic limitations. When evidence was sufficient to draw conclusions, the outcomes at the patient level showed no difference between intervention and control groups.[11] Safe and effective approaches targeting agitation in dementia are needed. Multicomponent models that enable simple implementation of evidence-informed recommendations are requested but have not yet been tested in controlled trials.[8]

The Targeted Interdisciplinary Model for Evaluation and Treatment of Neuropsychiatric Symptoms (TIME) represents a biopsychosocial approach and is a multicomponent intervention for nursing home staff and physicians. It is based on the theoretical framework of cognitive behavioral therapy and person-centered care.[12] To our knowledge, no trials have used the principles of cognitive behavioral therapy to structure care-delivery interventions to manage NPS in nursing homes. The primary purpose of this trial was to test whether TIME can reduce agitation in nursing homes patients with dementia. Herein we report from the part of the TIME trial dealing with outcomes at the patient level.[13]

METHODS

Trial Design and Oversight

We conducted a single-blinded, cluster randomized trial in 33 nursing homes in Norway using two parallel groups: patients of Intervention Nursing Homes (INHs) who received TIME and patients of Control Nursing Homes (CNHs), referred to as the control group, who received a brief education-only intervention. The protocol for the trial is published and available

at biomedcentral.com.[13] Our report follows CONSORT (Consolidated Standards of Reporting Trials) guidelines and the CONSORT extension to cluster randomised trials.[14] The trial was funded in total by a grant from the Innlandet Hospital Trust. Patients with the capacity to provide consent were asked to give written consent. For those who lacked the capacity to provide consent, next of kin was informed of the study and asked to give consent on behalf of the patients. The Regional Committee for Medical and Health Research Ethics in eastern Norway (REC South East) approved the trial on October 19, 2015 (Project No. 2015/1549). The trial was registered January 6, 2016 with clinicaltrials.gov (NCT02655003).

Sites and Participants

Across 63 municipalities, 130 nursing homes located in the north, middle, and southeastern parts of Norway were invited to participate in the trial. Nursing homes already using TIME as part of their clinical routines and those engaged in other research projects or that primarily offered short-term care were not invited. The project management team arranged information meetings for managers and physicians from nursing homes in 32 municipalities that included 63 nursing homes. Finally, 33 nursing homes in 20 municipalities agreed to take part in the trial (Figure 1).

All patients in wards in participating nursing homes were considered eligible for inclusion in the trial and were assessed against our inclusion criteria. Inclusion criteria were probable dementia, defined as a Clinical Dementia Rating (CDR)[15] score of 1 or higher; a moderate to high degree of agitation, defined as a score of at least 6 on the single agitation/aggression item of the Neuropsychiatric Inventory Nursing Home version (NPI-NH);[16] and being a long-term patient, residing in the nursing home for at least 2 weeks before inclusion. The exclusion criterion was a life expectancy of less than 6 weeks.

We performed cluster randomization, using the nursing home as the cluster, because of the risk of transmitting all or parts of the intervention model to the control units or individual control patients at the same nursing home.[17] Thus, nursing homes were first stratified by size into three blocks to ensure approximately equal numbers of patients in the two trial arms. Block size was fixed, depending on the number of patients fulfilling the inclusion criteria in each cluster: Block 1 was 1–5 patients, Block 2 was 6–9 patients, and Block 3 had 10 or more patients.

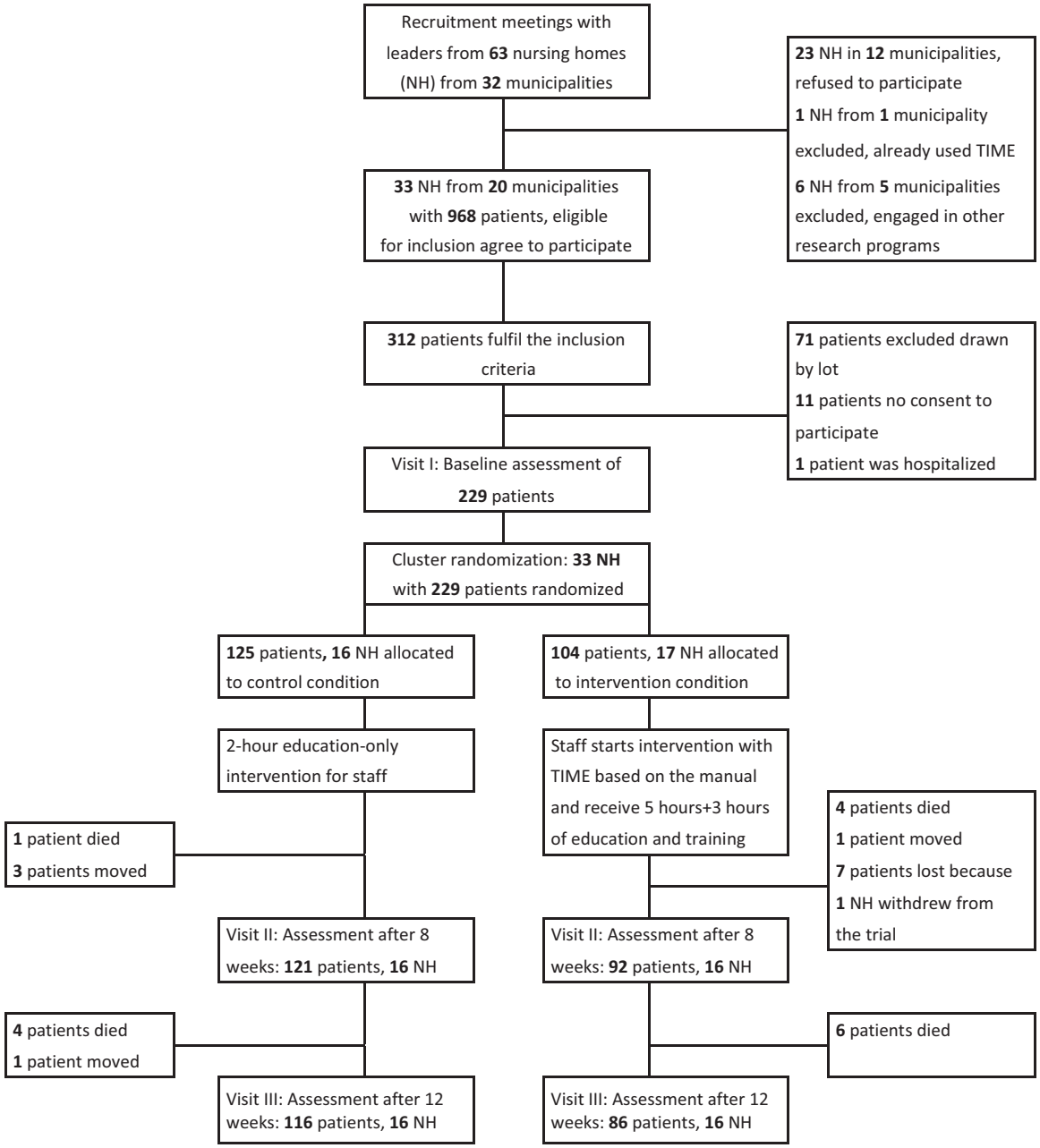
Within each block, nursing homes were randomly assigned 1:1 to either the intervention group or the control group. A researcher performed the randomization procedure independently of the project management team and the nursing homes. The project management team then provided the nursing homes with the randomization and allocation results immediately after this procedure. Elapsed time between baseline assessment and intervention initiation varied from 1 to 6 days. Specially trained project nurses not affiliated with the nursing homes assessed patients' baseline characteristics before randomization. The same assessors also assessed the effects of interventions 8 and 12 weeks later via telephone by interviewing staff members who best knew the patients. The assessors were blinded to the randomization.

Control and Intervention Phases of the Study

A detailed description of the control and intervention phases in the trial is available in the study protocol.[13] The staff in both the INH and the CNH were offered a 2-hour lecture covering dementia and NPS. This lecture represented the education-only intervention administered to the staffs of the CNH. In addition, three nurses in each ward in both the CNH and INH completed a 3-hour lecture (before randomization) about the trial and the clinical instruments used to assess patients during the trial. The staff of the CNH then continued practice as usual for the patients throughout the remainder of the trial. The staff in the INH were offered an additional training program that included a 3-hour lecture and role play following the steps in the TIME manual. In each ward of each INH, three nurses who had the responsibility for implementing TIME were given 3 additional hours of lecture. One specialist registered nurse from the education and training team attended and supervised the TIME administrators' first case conference on their first patient in their nursing home.

Intervention with TIME consists of three overlapping phases: a registration and assessment phase; a guided reflection phase, including one or more case conferences; and an action and evaluation phase. These phases were adapted from and based on problem-solving methods used in CBT[18] and coincide with reviews describing the "state of the art" for

FIGURE 1. The TIME trial: flowchart of the clusters and individuals throughout the phases of the trial.



management of NPS.[8,19] In the registration and assessment phase, the nursing home physician performs an examination of the patient and the patient's previous medical records and medications are critically reviewed. The staff gather personal background information, pain is assessed, behavior and symptoms are registered in detailed 24-hour daily records, and behavior and symptoms are monitored with established clinical instruments. In the case conferences the staff, the leading registered nurse, and the physician carry out a systematic reflection based on cognitive therapeutic principles. The goal is to create a mutual understanding of the actual NPS and to tailor a detailed treatment plan. In the action and evaluation phase

each treatment measure in the plan is put into action and systematically evaluated. The time spend over usual care in the registration and assessment phase varies depending on the already established clinical routines for assessing patients with agitation in the wards before the intervention. Based on our clinical experience in using the model, we estimated that this will normally vary between 1 and 2 hours per patient, including the examination done by the physician. A case conferences is assumed to last between 60 and 90 minutes for each patient. Because the actions and treatment measures are supposed to be tailored to each patient, they will display great variations between patients. In summary, TIME serves as a guide for the staff to create treatment measures that are tailored to the patient. The TIME manual is available in Norwegian and English versions at www.tidmodell.no.[12]

Outcome Measures

The primary outcome was the difference in the change between the intervention and control groups in agitation/aggression at 8 weeks from baseline, as measured by the single item agitation/aggression of the NPI-NH. The secondary outcomes were the difference in change between the two groups in agitation/aggression from baseline to 12 weeks as well as the changes from baseline to 8 and to 12 weeks in all other single NPI-NH items, NPI-10 sum, NPI-subsyndromal agitation score, NPI-subsyndromal psychosis score, NPI-subsyndromal affective symptoms, and NPI-Sum of caregiver disruptiveness. Similarly, the Cohen-Mansfield Agitation Inventory (CMAI),[20] the Cornell Scale for Depression in Dementia,[21,22] the Quality of Life in Late-stage Dementia Scale,[23,24] and use of psychotropic and analgesic medications given regularly, coded and grouped according to the Anatomical Therapeutic Chemical index,[25] were also measured at similar time frames.

The Norwegian version of the NPI-NH has shown high inter-rater reliability and validity.[24] The NPI-NH assesses the frequency (range: 0–4) and the severity (range: 0–3) of 12 psychiatric and behavioral symptoms. An item score is generated by multiplying frequency by severity, giving a range of 0–12 where higher scores indicate more frequent and severe NPS. The NPI-NH 10 sum score (range: 0–120) represents the sum of all NPI-NH items except the last two, nighttime behavior and appetite disturbance/eating change, which primarily capture vegetative symptoms. The NPI-subsyndromal agitation score is the sum of the aggression/agitation, disinhibition, and irritability items and ranges from 0 to 36. The NPI-subsyndromal psychosis score (range: 0–24) is the sum of the delusions and hallucinations items, and the NPI-subsyndromal affective score (range: 0–24) is the sum of the depression and anxiety items. These subsyndromes are based on data from a previous principal component analysis among nursing home patients with dementia.[26] In the NPI-Sum of occupational disruptiveness, the caregiver rates the disruptiveness of each behavior or symptom on a five-point scale, resulting in a range of 0–60, where higher scores indicate more disruptive behavior. The CMAI measures 29 types of agitation symptoms and the frequency at which they occur. Each item is scored between 1 and 7, where higher scores indicate more frequent agitation. The range for the total score is 29–203. The Cornell Scale for Depression in Dementia assesses symptoms of depression, and higher scores indicate greater severity (range: 0–38). The Quality of Life in Late-stage Dementia assesses quality of life by rating 11 behaviors on a five-point Likert scale, where lower scores indicate higher quality of life (range: 11–55).

Measured covariates were level of dementia, as assessed by the CDR; level of functioning in daily activities, as measured by the Physical Self-Maintenance Scale;[27] and physical health, as measured by the General Medical Health Rating Scale.[28] The CDR is a six-item instrument where the total score is produced using an algorithm giving precedence to memory. Scores of 0, 0.5, 1, 2, and 3 indicate no dementia, questionable dementia, mild dementia, moderate dementia, and severe dementia, respectively. The Physical Self-Maintenance Scale is a six-item scale that produces a sum score ranging from 6 to 30, where higher scores denote more severe functional impairment. The General Medical Health Rating Scale is a one-item global rating scale with categories of good, fairly good, poor, and very poor. Compliance with the intervention protocol was assessed by interviewing the TIME administrators by telephone during the trial using a brief checklist based on the main components in the TIME model.

Statistical Analysis

A power calculation was performed based on the following assumptions. A previous noncontrolled pilot study of TIME showed that the intervention reduced the NPI-NH agitation item score by an average of 2.8

(standard deviation [SD]: 3.1).[29] We assumed that the education-only intervention would have some effect on the control group but less than that in the intervention group. We then assumed a mean difference between the groups would be 1.5, as measured by the NPI-NH agitation item. We assumed the SD would be 3.1. Based on this, we estimated that 65 participants were needed in each group to observe a statistically significant difference with a power of 80% and a significance level of 5%. Because of the possible cluster effect within nursing homes, we assumed an intraclass correlation coefficient of 0.05. Adjusted power calculations suggested that at least 78 participants were needed in each of the intervention and control groups, totaling 156. According to the pilot study, approximately 12% of patients in nursing homes had dementia and the necessary NPI-NH agitation item score, our main criterion for inclusion. Previous studies have shown that we can anticipate a 30% loss to follow-up per year (resulting from, e.g., mortality, relocation, or withdrawal from the study) or 7.5% in 3 months. With these two assumptions, we aimed to include a total of at least 168 patients, implying that approximately 1,400 nursing home patients would be needed for screening against our inclusion criteria.

All primary analyses were performed by a statistician who was not affiliated with the research center and who was blinded to the randomization. Analyses were performed as intention-to-treat analyses. Differences in the outcomes between the intervention group and the control group were assessed by a linear mixed model with fixed effects for the time and group components and the interaction between the two. A significant interaction implies differences between the groups. Random effects for patients nested within nursing homes were included in the model. Differences between groups in change in medication were assessed by a generalized linear model with the same fixed effects but random effects for patients only, because nursing home effect was negligible. Individual time point contrasts were derived within each group at each time point with the corresponding 95% confidence interval (CI). Such models correctly adjust estimates for intracluster correlations as well as for intraindividual correlations due to repeated measurements in time. The model also addressed unbalanced data by allowing inclusion of all available information, including that from dropouts. Standardized mean differences (SMDs) were calculated by rerunning the mixed models with the outcome variables divided by the SD. The intraclass correlation coefficient assessing the level of clustering within nursing homes was calculated from a random effects model. Statistical analyses were performed using R version 3.2.0, lme4 version 1.1–12 (R Foundation for Statistical Computing, Vienna, Austria), and SAS version 9.4 (SAS Institute, Cary, NC). All tests were two-sided, and results with $p < 0.05$ were considered statistically significant.

RESULTS

Patients

Two hundred twenty-nine patients were recruited between January 7, 2016 and April 6, 2016. The last patient was assessed for outcomes on July 1, 2016. In total, 968 eligible patients were screened, of which 312 fulfilled the inclusion criteria. Eleven patients did not consent to participate, and 1 was hospitalized before randomization. Seventy-one patients were excluded from participation by lot before randomization because of lack of resources in the nursing homes. Finally, 17 nursing homes with 104 patients were randomly assigned to the intervention group and 16 nursing homes with 125 patients to the control group. One INH with 7 patients withdrew from the trial approximately 2 weeks after the start of the intervention. Because of extremely high level of sick leave in the staff, it was not possible for the leading ward registered nurse to release someone from the staff to be interviewed for the assessments at 8 and 12 weeks. Two hundred two patients (88.2%) and 32 nursing homes (97%) completed the study and the final analysis (Figure 1).

No between-group differences were found in baseline demographics, ward, or clinical characteristics (Table 1). A diagnosis of dementia was confirmed from patient medical records in approximately 90% of the participants. Regarding compliance with the intervention protocol, the INHs performed a case conference in 91% of the included patients. No nursing home performed more than one case conference for each included patient during the trial. The staff performed 80% or more of the components in the model for approximately 89% of the included patients.

Primary Outcome

The intervention with TIME improved agitation as measured by the NPI-NH single agitation/aggression

TABLE 1. Baseline Demographic and Clinical Characteristics

Characteristics	Intervention Group (N = 104)	Control Group (N = 125)
Age, yr	82.2 (9.8)	84.1 (9.0)
Female sex, N (%)	64 (61.5)	74 (59.2)
Ward type		
Regular, N (%)	8 (7.7)	33 (26.4)
Special care unit, N (%)	96 (92.3)	92 (73.6)
Residents per ward	24.7 (8.3)	24.2 (7.8)
Staff per ward on day shift	8.6 (3.3)	8.1 (2.8)
Staff per ward on evening shift	7.2 (2.9)	7.1 (2.6)
Hours per resident per week for nursing home physician	0.3 (0.1)	0.3 (0.2)
Diagnosis of dementia, N (%)	92 (88.5)	112 (89.6)
CDR scale		
Mild dementia, N (%)	4 (3.9)	6 (4.8)
Moderate dementia, N (%)	28 (27.2)	31 (24.8)
Severe dementia, N (%)	71 (68.9)	88 (70.4)
General Medical Health Rating		
Very poor, N (%)	7 (6.7)	10 (8.0)
Poor, N (%)	46 (44.2)	62 (49.6)
Fairly good, N (%)	32 (30.8)	45 (36.0)
Good, N (%)	19 (18.3)	8 (6.4)
Physical Self-Maintenance Scale	20.4 (5.5)	20.1 (5.0)
CMAI	68.5 (17.5)	70.7 (18.5)
Cornell Scale for Depression in Dementia	12.6 (6.3)	13.0 (5.7)
Quality of Life in Late-stage Dementia Scale	28.6 (7.7)	29.7 (7.9)
Neuropsychiatric Inventory		
Nursing Home version		
NPI-10 Sum	44.1 (18.7)	49.4 (20.9)
Subsyndromal agitation score	21.7 (7.1)	22.5 (7.5)
Subsyndromal affective score	7.3 (6.4)	8.6 (7.4)
Subsyndromal psychosis score	6.0 (6.0)	7.8 (6.6)
Sum of occupational disruptiveness	20.1 (9.2)	23.7 (10.4)
Delusions	4.1 (4.1)	4.8 (4.4)
Hallucinations	1.9 (3.2)	3.0 (3.8)
Agitation/aggression	8.7 (2.5)	8.5 (2.6)
Depression	3.6 (3.8)	4.1 (4.3)
Anxiety	3.8 (4.0)	4.5 (4.5)
Euphoria	1.2 (2.5)	1.9 (2.9)
Apathy	3.4 (3.8)	4.1 (4.2)
Disinhibition	5.7 (4.4)	6.3 (4.1)
Irritability	7.3 (3.6)	7.8 (3.3)
Aberrant motor behavior	4.6 (4.4)	4.6 (4.6)
Sleep and night-time behavior	3.1 (3.9)	4.2 (4.6)
Appetite and eating disorders	1.9 (3.7)	2.4 (4.0)

Notes: Values are means with SD in parentheses, unless otherwise specified. NPI-10 Sum: sum of all NPI-NH single items except the last two items, night-time behavior and appetite disturbance/eating change (range: 0–120); subsyndromal agitation score: sum of the NPI-NH items aggression/agitation, disinhibition, and irritability (range: 0–36); subsyndromal affective score: sum of the NPI-NH items depression + anxiety (range: 0–24). subsyndromal psychosis score: sum of the NPI-NH items delusions and hallucinations (range: 0–24); sum of occupational disruptiveness: in NPI-NH, the caregiver rates how disruptive they consider each behavior or symptom on a five-point scale. Higher score indicates a more disruptive behavior (range: 0–60).

item compared with the brief education-only intervention. The between-group difference in change at 8 weeks was 1.1 in favor of the intervention with TIME (95% CI: 0.1–2.1; p = 0.031). The SMD between groups for this change was 0.32 (Table 2). Both groups showed significant reductions in this measure from baseline to 8 weeks. With TIME, it was reduced from 8.7 (95% CI: 8.1–9.4) at baseline to 6.1 (95% CI: 5.4–6.8) at 8 weeks, whereas in the control group it was reduced from 8.4 (95% CI: 7.8–9.0) to 6.8 (95% CI: 6.2–7.5; Table 2 and Figure 2A).

Secondary Outcomes

Both groups also showed significant reductions in the NPI agitation/aggression item from baseline to 12 weeks (Table 2 and Figure 2A). The between-group difference was 1.6 (95% CI: 0.6–2.7; p = 0.002) in favor of the intervention with TIME. The between-group SMD was 0.47 (Table 2). With TIME, the score was reduced from 8.7 (95% CI: 8.1–9.4) at baseline to 5.7 (95% CI: 4.9–6.4) at 12 weeks, and with the education-only intervention it was reduced from 8.4 (95% CI: 7.8–9.0) to 7.0 (95% CI: 6.3–7.6).

Intervention with TIME improved agitation as measured by the CMAI at 8 and 12 weeks compared with the control group. The between-group differences at 8 weeks and 12 weeks were 4.7 (95% CI: 0.6–8.8; p = 0.02) and 5.9 (95% CI: 1.7–10.1; p = 0.006), respectively. The between-group SMD were 0.23 and 0.29, respectively (Table 2 and Figure 2B).

Similarly, significant improvements were seen in the NPI-subsyndromal agitation score at 12 weeks and the NPI single items delusions and disinhibition at 8 weeks and 12 weeks, favoring the TIME intervention (Table 2). Symptoms of depression were reduced at 12 weeks in favor of the TIME intervention (Table 2 and Figure 2C). The between-group differences in change at 12 weeks for symptoms of depression as measured by the Cornell Scale for Depression in Dementia was 2.0 (95% CI: 0.5–3.5; p = 0.01). Quality of life was ameliorated at 12 weeks in favor of the TIME intervention (Table 2 and Figure 2D). The between-group differences in change at 12 weeks for quality of life measured by Quality of Life in Late-stage Dementia was 1.6 (95% CI: 0.04–3.5; p = 0.01).

Changes in the other single NPI-NH items, NPI-subsyndromal psychosis score, and affective symptoms did not differ significantly between the two groups.

TABLE 2. Efficacy Outcome Measures: Results of Linear Mixed Model, Mean Scores at Baseline (Week 0) and at 8 and 12 Weeks

	Within-Group Values								Difference in Change Between Groups			
	Week 0		Week 8		Week 12		p for Change		Week 0 vs. week 8		Week 0 vs. week 12	
Group	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	Week 0–8	Week 0–12	SMD	p	SMD	p
NPI-NH agitation/aggression (ICC = 5.3%)												
Intervention	104	8.7 (8.1–9.4)	92	6.1 (5.4–6.8)	86	5.7 (4.9–6.4)	<0.001	<0.001	0.32	0.031	0.47	0.002
Control	125	8.4 (7.8–9.0)	121	6.8 (6.2–7.5)	116	7.0 (6.3–7.6)	<0.001	<0.001				
NPI-NH anxiety (ICC = 8.6%)												
Intervention	104	3.7 (2.9–4.6)	92	2.9 (2.0–3.8)	86	2.3 (1.4–3.2)	0.031	<0.001	−0.02	0.878	0.14	0.241
Control	125	4.5 (3.7–5.2)	121	3.5 (2.8–4.3)	116	3.6 (2.8–4.4)	0.007	0.018				
NPI-NH apathy (ICC = 13.0%)												
Intervention	104	3.4 (2.5–4.3)	92	3.3 (2.3–4.2)	86	2.7 (1.8–3.7)	0.822	0.104	−0.03	0.743	0.11	0.308
Control	125	4.0 (3.1–4.8)	121	3.7 (2.9–4.6)	116	3.9 (3.0–4.8)	0.451	0.754				
NPI-NH appetite (ICC = 5.0%)												
Intervention	104	1.9 (1.2–2.7)	92	2.2 (1.4–2.9)	86	1.6 (0.9–2.4)	0.556	0.432	−0.11	0.421	−0.02	0.886
Control	125	2.4 (1.7–3.0)	121	2.2 (1.6–2.9)	116	2.0 (1.4–2.7)	0.584	0.264				
NPI-NH depression (ICC = 4.1%)												
Intervention	104	3.6 (2.9–4.3)	91	2.6 (1.9–3.4)	85	2.7 (1.9–3.4)	0.007	0.010	0.06	0.656	0.02	0.885
Control	125	4.1 (3.4–4.7)	121	3.4 (2.7–4.0)	116	3.2 (2.6–3.9)	0.016	0.006				
NPI-NH hallucinations (ICC = 14.3%)												
Intervention	104	1.9 (1.1–2.7)	92	1.2 (0.4–2.0)	86	1.3 (0.5–2.1)	0.023	0.079	0.09	0.403	0.02	0.839
Control	124	2.8 (1.7–3.2)	120	2.4 (1.7–3.2)	116	2.3 (1.5–3.1)	0.193	0.088				
NPI-NH irritability (ICC = 8.1%)												
Intervention	104	7.3 (6.5–8.0)	92	6.0 (5.3–6.8)	85	5.5 (4.7–6.3)	0.001	<0.001	−0.05	0.726	0.19	0.162
Control	125	7.7 (7.1–8.4)	121	6.3 (5.6–7.0)	116	6.7 (6.0–7.4)	<0.001	0.003				
NPI-NH disinhibition (ICC = 6.8%)												
Intervention	104	5.7 (4.9–6.6)	92	4.3 (3.4–5.2)	86	3.9 (3.0–4.7)	0.001	<0.001	0.15	0.241	0.29	0.032
Control	125	6.3 (5.5–7.0)	121	5.5 (4.7–6.2)	116	5.6 (4.8–6.4)	0.032	0.072				
NPI-NH aberrant motor behavior (ICC = 6.6%)												
Intervention	104	4.5 (3.6–5.4)	92	3.8 (2.8–4.7)	86	3.3 (2.3–4.2)	0.095	0.006	−0.10	0.452	−0.06	0.659
Control	125	4.7 (3.8–5.5)	121	3.5 (2.6–4.3)	116	3.1 (2.3–4.0)	0.002	<0.001				
NPI-NH sleep/night-time behavior (ICC = 5.5%)												
Intervention	104	3.1 (2.4–3.8)	92	2.2 (1.4–3.0)	86	1.8 (1.0–2.5)	0.008	<0.001	−0.01	0.927	0.05	0.691
Control	125	4.2 (3.5–4.9)	121	3.3 (2.6–3.9)	116	3.1 (2.4–3.7)	0.002	<0.001				
NPI-NH euphoria (ICC = 19.2%)												
Intervention	104	1.3 (0.6–2.0)	92	1.2 (0.5–1.9)	86	1.3 (0.6–2.0)	0.642	0.825	−0.01	0.956	−0.08	0.429
Control	125	1.8 (1.1–2.5)	121	1.6 (1.0–2.3)	116	1.4 (0.8–2.1)	0.540	0.144				
NPI-NH delusions (ICC = 10.7%)												
Intervention	104	4.1 (3.3–5.0)	91	2.5 (1.6–3.4)	86	2.7 (1.8–3.6)	<0.001	0.001	0.28	0.028	0.24	0.066
Control	123	4.7 (3.9–5.6)	121	4.4 (3.6–5.2)	116	4.4 (3.5–5.2)	0.410	0.352				

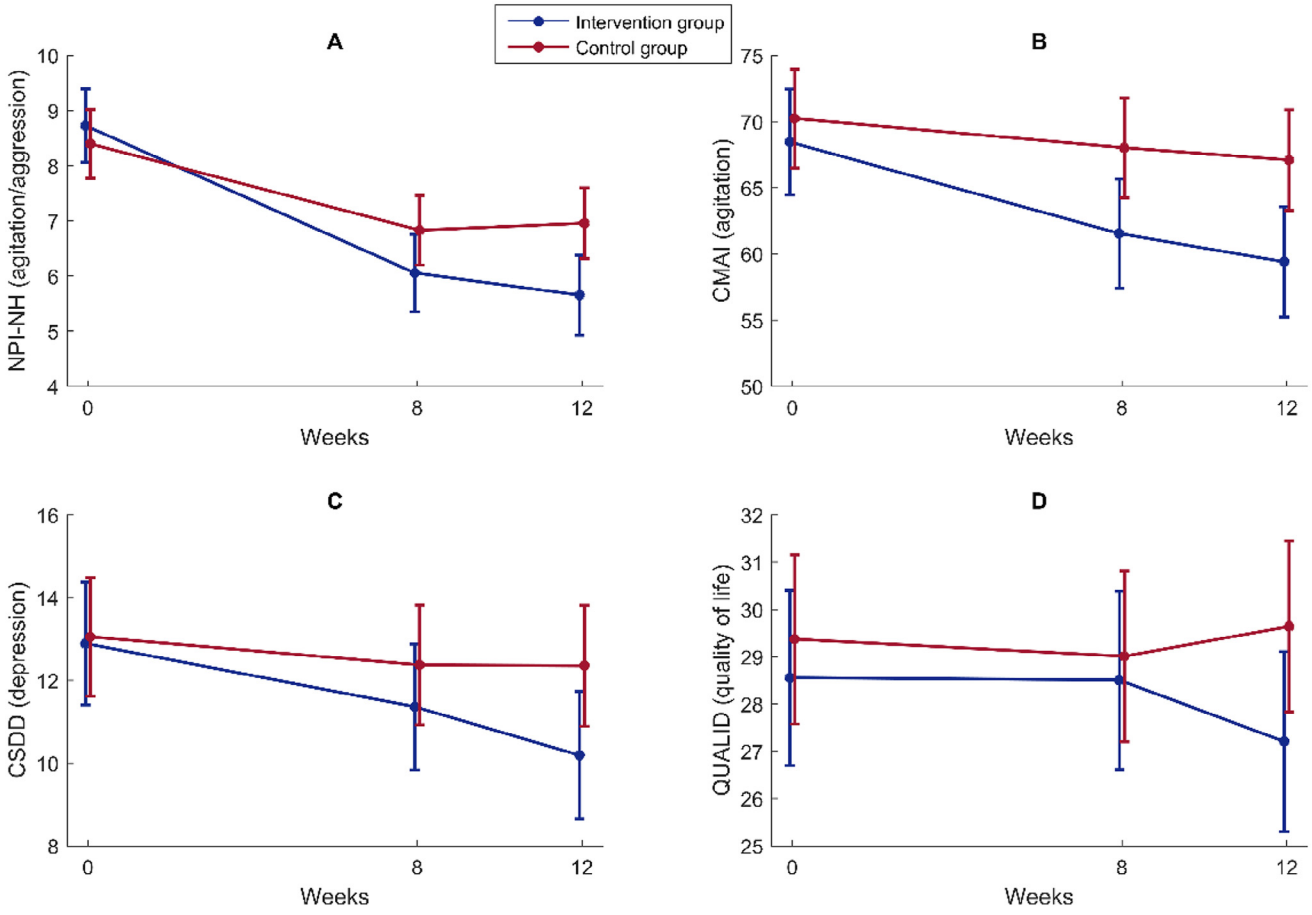
(*continued on next page*)

TABLE 2. (*continued*)

	Within-Group Values							Difference in Change Between Groups			
	Week 0		Week 8		Week 12		p for Change	Week 0 vs. week 8		Week 0 vs. week 12	
Group	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	Week 0–8	Week 0–12	SMD	p	SMD	p
NPI-NH subsyndromal affective (ICC = 7.1%)												
Intervention	104	7.3 (6.0–8.6)	91	5.6 (4.2–6.9)	85	5.0 (3.6–6.4)	0.005	<0.001	0.01	0.913	0.09	0.454
Control	125	8.5 (7.3–9.7)	121	6.9 (5.7–8.1)	116	6.9 (5.6–8.1)	0.002	0.002				
NPI-NH subsyndromal agitation (ICC = 7.8%)												
Intervention	104	21.7 (20.0–23.5)	92	16.4 (14.6–18.2)	86	15.0 (13.1–16.9)	<0.001	<0.001	0.17	0.180	0.39	0.002
Control	125	22.4 (20.8–24.1)	121	18.6 (17.0–20.3)	116	19.3 (17.6–21.0)	<0.001	<0.001				
NPI-NH subsyndromal psychosis (ICC = 12.9%)												
Intervention	104	6.0 (4.7–7.4)	91	3.7 (2.3–5.1)	86	4.0 (2.5–5.5)	<0.001	0.002	0.23	0.053	0.16	0.178
Control	123	7.5 (6.2–8.9)	120	6.9 (5.5–8.2)	116	6.7 (5.3–8.0)	0.230	0.126				
NPI-NH-10 Sum (ICC = 10.7%)												
Intervention	104	44.2 (39.9–48.5)	92	33.7 (29.3–38.2)	86	31.1 (26.7–35.6)	<0.001	<0.001	0.12	0.317	0.25	0.053
Control	125	49.0 (45.0–53.0)	121	41.3 (37.3–45.4)	116	41.4 (37.3–45.5)	<0.001	<0.001				
NPI-NH sum of occupational disruptiveness (ICC = 12.4%)												
Intervention	104	20.2 (17.9–22.4)	92	16.6 (14.4–18.9)	86	15.0 (12.7–17.4)	<0.001	<0.001	−0.02	0.879	0.13	0.244
Control	125	23.3 (21.1–25.4)	121	19.5 (17.4–21.7)	116	19.7 (17.5–21.8)	<0.001	<0.001				
CMAI (ICC = 10.3%)												
Intervention	104	68.5 (64.5–72.5)	92	61.5 (57.4–65.7)	86	59.4 (55.2–63.6)	<0.001	<0.001	0.23	0.026	0.29	0.006
Control	125	70.2 (66.5–74.0)	121	68.0 (64.3–71.8)	116	67.1 (63.3–70.9)	0.112	0.026				
CSDD (ICC = 14.6%)												
Intervention	101	12.9 (11.4–14.4)	87	11.4 (9.8–12.9)	80	10.2 (8.7–11.7)	0.007	<0.001	0.11	0.261	0.26	0.010
Control	121	13.1 (11.6–14.5)	115	12.4 (10.9–13.8)	113	12.4 (10.9–13.8)	0.174	0.169				
QUALID (ICC = 14.6%)												
Intervention	104	28.6 (26.7–30.4)	92	28.5 (26.6–30.4)	86	27.2 (25.3–29.1)	0.935	0.027	−0.03	0.691	0.17	0.044
Control	125	29.4 (27.6–31.2)	121	29.0 (27.2–30.8)	116	29.6 (27.8–31.5)	0.486	0.607				

Notes: All numbers were derived from linear mixed models with random effects for patients nested within nursing homes. ICC: intraclass correlation coefficient; NPI-NH subsyndromal affective score: Sum of the NPI-NH items depression + anxiety (range: 0–24); NPI-NH subsyndromal agitation score: sum of the NPI-NH items aggression/agitation, disinhibition, and irritability (range: 0–36); NPI-NH subsyndromal psychosis score, sum of the NPI-NH items delusions and hallucinations (range: 0–24); NPI–10 Sum: sum of all NPI-NH single items except the last two items, night-time behavior and appetite disturbance/eating change (range: 0–120); NPI-NH sum of occupational disruptiveness: the caregiver rates how disruptive they consider each behavior or symptom on a five-point scale (range: 0–60); CMAI: range: 29–203; CSDD: Cornell Scale of Depression in Dementia (range: 0–38); QUALID: Quality of Life in Late-stage Dementia (range: 11–55). For QUALID a higher score indicates lesser quality of life. For all other scales a higher score means more frequent and/or more intense symptoms. The primary outcome was the difference in the change between the intervention and control groups in NPI-NH agitation/aggression at 8 weeks from baseline, as measured by the single item agitation/aggression of the NPI-NH. The secondary outcomes included the difference in change between the two groups in NPI-NH agitation/aggression from baseline to 12 weeks, and the difference in change from baseline to 8 and 12 weeks on the following scales: all other NPI-NH items, CMAI, CSDD, and QUALID.

FIGURE 2. **Mean scores and 95% CI for efficacy outcomes from baseline (0) to 8 and 12 weeks. [A] The Neuropsychiatric Inventory Nursing Home version single item agitation/aggression (NPI-NH; range: 0–12), [B] the Cohen Mansfield Agitation Inventory (CMAI; range: 29–203), [C] the Cornell Scale for Depression in Dementia (CSDD; range: 0–38), and [D] the Quality of Life in Late-stage Dementia Scale (QUALID; range: 0–55). For QUALID a higher score indicates lesser quality of life. For the other scales a higher score means more frequent and/or more intense symptoms.**



The use of psychotropic and analgesic medications did not change significantly within groups or between groups (Table 3).

DISCUSSION

This single-blinded, cluster randomized controlled trial showed that TIME, a nonpharmacologic intervention, compared with a brief education-only intervention, reduced agitation after 8 and 12 weeks in nursing homes patients with dementia and moderate to high levels of agitation. These findings were strengthened by significant results in the secondary outcomes both at 8 and 12 weeks using another validated instrument that measures agitation (i.e., CMAI). Definitions of agitation usually include verbal and physical aggression and excessive motor activity consistent with emotional distress for the patient.[30] The definition of agitation used to enroll patients in this trial was pragmatic, using the NPI-NH description of the single item agitation/aggression.

To compare the effect size in randomized trials, the SMD between treatment groups is commonly used.[31] The SMD for our primary outcome was estimated at 0.32 and 0.47 at 8 weeks and 12 weeks, respectively. This implies a small to moderate effect size, but it is equal to or even higher than what has been reported in most trials for the treatment of NPS.[9,11]

TABLE 3. Changes in Medication: Secondary Outcomes Analyses, Dichotomous Outcomes

	Within-Group Values							Difference in Change Between Groups			
	Week 0	Week 8	Week 12	Week 0 (ref) vs. Week 8		Week 0 (ref) vs. Week 12		Week 0 (ref) vs. Week 8		Week 0 (ref) vs. Week 12	
Group	N (%)	N (%)	N (%)	OR[a] (95% CI)	p	OR[a] (95% CI)	p	OR[b] (95% CI)	p	OR[b] (95% CI)	p
Analgesics											
Intervention	80 (76.9)	73 (79.3)	69 (80.2)	2.40 (0.59–9.73)	0.220	2.52 (0.60–10.57)	0.206	1.62 (0.26–10.06)	0.604	1.17 (0.18–7.58)	0.868
Control	84 (67.2)	84 (69.4)	82 (70.7)	1.48 (0.45–4.83)	0.516	2.15 (0.64–7.29)	0.218	1		1	
Antidepressants											
Intervention	34 (32.7)	37 (40.2)	38 (44.2)	1.78 (0.65–4.84)	0.259	2.44 (0.88–6.78)	0.087	1.64 (0.42–6.37)	0.475	0.98 (0.25–3.93)	0.983
Control	39 (31.2)	38 (31.4)	43 (37.1)	1.08 (0.43–2.72)	0.863	2.48 (0.96–6.40)	0.061	1		1	
Antidementia drugs[c]											
Intervention	20 (19.2)	16 (17.4)	14 (16.3)	0.49 (0.09–2.58)	0.396	0.25 (0.04–1.58)	0.141	0.50 (0.05–5.50)	0.573	0.60 (0.05–8.02)	0.702
Control	17 (13.6)	16 (13.2)	14 (12.1)	0.97 (0.17–5.35)	0.968	0.41 (0.06–2.67)	0.354	1		1	
Antipsychotics											
Intervention	30 (28.8)	25 (27.2)	26 (30.2)	0.56 (0.17–1.81)	0.331	0.82 (0.25–2.66)	0.745	0.25 (0.05–1.23)	0.088	0.30 (0.06–1.50)	0.141
Control	32 (25.6)	36 (29.8)	35 (30.2)	2.25 (0.77–6.51)	0.136	2.76 (0.93–8.22)	0.068	1		1	
Anxiolytics											
Intervention	36 (34.6)	28 (30.4)	25 (29.1)	0.50 (0.18–1.39)	0.184	0.40 (0.14–1.15)	0.088	0.70 (0.18–2.78)	0.614	0.63 (0.15–2.63)	0.529
Control	32 (25.6)	28 (23.1)	26 (22.4)	0.71 (0.28–1.81)	0.478	0.63 (0.24–1.63)	0.338	1		1	
Sedatives											
Intervention	26 (25.0)	22 (23.9)	20 (23.3)	0.78 (0.27–2.28)	0.655	0.77 (0.26–2.28)	0.632	0.95 (0.20–4.48)	0.948	1.28 (0.26–6.39)	0.761
Control	20 (16.0)	18 (14.9)	15 (12.9)	0.83 (0.27–2.55)	0.740	0.60 (0.18–1.95)	0.393	1		1	
Any psychotropic drug											
Intervention	73 (70.2)	71 (77.2)	67 (77.9)	2.26 (0.64–7.96)	0.206	2.16 (0.59–7.91)	0.245	2.36 (0.47–11.90)	0.299	1.62 (0.31–8.52)	0.572
Control	90 (72.0)	86 (71.1)	84 (72.4)	0.96 (0.35–2.64)	0.932	1.34 (0.47–3.80)	0.586	1		1	

Notes: All numbers were derived from generalized liner models with random effects for patients. OR: odds ratio.

[a]OR describing odds for use of at least one drug at week 8 (12) with respect to baseline in the group.

[b]OR describing odds for change from baseline to week 8 (12) in use of a drug in the intervention group compared with the control group.

[c]Antidementia drugs include donepezil, rivastigmine, galantamine, and/or memantine.

Both the intervention group and the control group showed significant reductions in agitation from baseline to 8 weeks and from baseline to 12 weeks. The range of the single NPI-NH item is 0–12, and reductions of 2.6 and 3.0 points, respectively, in the TIME intervention group is most likely clinically significant. These reductions in the agitation item in the intervention group mean that there was either a decrease in the frequency of agitation from daily to a few times a week or a decrease in the degree of the intensity of the behavior from severe moderate. However, reductions of 1.6 and 1.4, respectively, in the control group are more difficult to interpret. No general definition of a minimal clinically important difference has been identified for trials measuring agitation/aggression in dementia,[32] but a common threshold used to determine minimal clinically important difference is 0.4 times the SD of the change in score from baseline.[33] The minimal clinically important difference in our trial for the changes in both groups from baseline to 8 and 12 weeks was 1.4. Thus, the changes observed within the control group just reached this threshold, whereas the changes observed in the TIME intervention group were far above it.

There are several possible explanations for the reduction in agitation observed in the control group. The phenomena regression to the mean could have an effect, but because the baseline values did not differ between the groups, this effect should have had an equal impact on both groups.[34] The nursing home staff in the control group did receive a 2-hour lecture about dementia and NPS. In addition, three nurses in each ward also completed a 3-hour lecture about the trial and the clinical instruments to assess patients during the trial. Another is the assessment of patients three times during a 12-week period, which could have had a positive impact on the treatment of these patients.

The use of psychotropic drugs did not change despite the reduction in NPS. This might be explained by the short duration of the trial. The most prominent reductions in the NPS were seen after 12 weeks from baseline, consistent with the fact that the intervention starts with a comprehensive assessment of patients. Most treatment measures were therefore first put into action after 6–7 weeks from baseline. We believe that reductions in psychotropic drugs only will take place when symptoms are perceived as stable by the staff and the physician.

Our study has several strengths. The inclusion criteria were wide, adding to its generalizability. Baseline demographic, ward, and clinical characteristics did not differ between groups, ensuring a low risk of bias. We used well-validated instruments for both the primary and secondary outcomes. The retention rate was high (88.2% during 12 weeks), and all losses to follow-up were accounted for. After a short education and training program, the staffs in the nursing homes carried out the intervention independent of the research team. This increases the possibility for maintenance of the intervention, reduces the cost for implementation, and eases the proliferation of the model. We also followed the Medical Resource Council framework for evaluating complex interventions.[35] This systematic process evaluation will be reported in a future study as outlined in the trial protocol.[13]

One important limitation is the limited duration of the trial, which makes drawing conclusions about long-term effectiveness difficult. The implementation process at the staff and organization level will nevertheless continue for 1 year to measure the sustainability of the intervention. We did not require a precise diagnosis of dementia but included patients with probable dementia, defined as a CDR of 1 or higher. Nevertheless, we confirmed dementia diagnoses from patient medical records in approximately 90% of participants. We did not gather data describing the characteristics of the nursing homes who refused to participate in the trial. This limits our possibilities to compare these nursing homes with those that agreed to participate. Norwegian nursing homes generally have fairly the same organizational structure and the same groups of patients. To test the representativeness of the material we compared our data with two large cross-sectional samples of Norwegian nursing homes (N = 3,021).[36] Among those with a CDR score of 1 or higher and a, NPI-NH item-score agitation/aggression of 6 or higher, the mean age was 82.5 (SD: 7.4), proportion of women was 68%, and the Physical Self-Maintenance Scale score was 20.12 (SD: 5.4). Apart from the proportion of women, the figures are similar with the sample in our present study. We therefore have reasons to assume that the 33 nursing homes in the study are representative of Norwegian nursing homes.

Finally, one limitation is that outcome measures relied on interviews of staff members who best knew a given patient. Although the assessors of the outcomes were blinded to the randomization, the staff was not. It is

possible that this could have created a bias in favor of the TIME intervention group. The education-only intervention in the CNHs was an effort to minimize the risk of this possible bias.

In conclusion, this 3-month cluster randomized trial showed that TIME, a nonpharmacologic intervention, reduced agitation for patients with dementia living in nursing homes. The effect was clinically significant. Although these results need to be replicated, they are unique and convincing and should inform national training programs for care staff both in Norway and internationally.

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