Effects on pain of a stepwise multidisciplinary intervention (STA OP!) that targets pain and behaviour in advanced dementia: a cluster randomised controlled trial

Marjoleine JC Pieper, Jenny T van der Steen, Anneke L Francke, Erik JA Scherder, Jos WR Twisk, Wilco P Achterberg

KEY STATEMENTS

What is already known about the topic?
• Pain is highly prevalent in patients with dementia; studies suggest that over 50% of community-dwelling older persons and up to 80% of nursing home residents with dementia are in pain.
• Recognition of pain in dementia is challenging; it may be expressed as behaviour and due to severe cognitive and communication problems pain is commonly under detected and undertreated.
• Pain management in dementia requires an understanding of the neurobiology of both pain experience and the behavioural expression of pain, together with knowledge of the available range of clinical assessment instruments and a proper implementation in daily practice.
• STA OP!, a comprehensive approach based on a cyclical process of assessment, treatment and monitoring, has proven to be effective in improving behaviour in advanced dementia in the Netherlands and in the US.

What this paper adds?
• The STA OP!, stepwise, multidisciplinary and multicomponent approach improves the assessment and management of pain in addition to challenging behaviour.
• STA OP! is effective in reducing observed, but not estimated pain in patients with advanced dementia.
• Assessing behavioural cues for pain in dementia may be essential for better pain management because we found that a decrease in pain could be established through the observational instrument PACSLAC-D, but not with the MDS-RAI pain scale, which is considered an instrument for the ‘estimation’ of pain.

Implications for practice?
• This study indicates that STA OP! can help healthcare professionals to realize effective pain management in addition to effectively addressing behaviour in people with advanced dementia, both of which are crucial to establish an optimal quality of life.
• A systematic, stepwise approach is superior to knowledge, training or implementation without a systematic, stepwise approach.
ABSTRACT

Background  Pain in nursing home residents with advanced dementia remains a major challenge; it is difficult to detect and may be expressed as challenging behaviour. STA OP! aims to identify physical and other needs as causes of behavioural changes, and uses a stepwise approach for psychosocial and pharmacological management which was effective in improving challenging behaviour.

Aim  To assess whether implementation of the stepwise multidisciplinary intervention also reduces pain and improves pain management.

Design  In a cluster randomised controlled trial (Netherlands National Trial Register NTR1967), healthcare professionals of intervention units received the stepwise training, while training of the control group focused on knowledge and skills without the stepwise component. Observed and estimated pain was assessed at baseline, and at 3 and 6 months post-intervention. Logistic generalized estimating equations was used to test treatment and time effects.

Setting/participants  Twenty-one clusters (single nursing home units) in twelve Dutch nursing homes included 288 residents with advanced dementia (GDS-score 5, 6 or 7); 148 in the intervention and 140 in the control condition.

Results  The multilevel modelling showed an overall effect of the intervention on observed pain, but not on estimated pain; PACSLAC-D, mean difference -1.21 points (95% confidence interval [CI] -2.35, -0.06); MDS-RAI pain scale, mean difference -0.01 points (95% CI -0.36, 0.35). Opioid use increased (OR=3.08; 95% CI 1.08, 8.74); paracetamol use did not (OR=1.38; 95% CI 0.71, 2.68).

Conclusion  STA OP! was found to decrease ‘observed’ pain, but not estimated pain. Observing pain-related behaviour might help improve pain management in dementia.

Key words:  Pain, Pain management, Dementia, Nursing Homes, Randomised Controlled Trial.
INTRODUCTION

Pain is common amongst individuals with dementia. It is particularly difficult to detect in the more advanced stages due to severe cognitive and communication problems\(^1\), and this requires an understanding of the neurobiology of the pain experience and the behavioural expression of pain, together with knowledge of clinical assessment instruments.\(^2\)\(^-\)\(^4\) Therefore, it is recommended to combine different assessment techniques to detect pain\(^5\); this includes observation of verbal (e.g. calling out) and non-verbal (e.g. frowning, agitation) behaviour, with physical examination\(^6\) that may focus on musculoskeletal conditions, such as arthritis and osteoporosis, respiratory and urinary tract infection, injury from falls, orofacial pain, and pressure ulcers.\(^7\)

A similar complexity applies to the treatment of chronic pain in dementia, which justifies a combination of a non-pharmacological and a pharmacological approach.\(^8\)\(^,\)\(^9\) Especially in the advanced stages of dementia, with a high prevalence of multi-morbidity and polypharmacy, the safety of non-pharmacological interventions may have many benefits.\(^8\)

One of the few interventions that acknowledges the complexity of both assessment and treatment of pain in advanced stages of dementia, and combines non-pharmacological and pharmacological interventions for pain and challenging behaviour, is the Serial Trial Intervention (STI).\(^10\) This intervention (applying a stepwise protocol) was successful in decreasing discomfort and resulted in fewer expressions of challenging behaviour, in patients with dementia in nursing homes in the US, but effects on pain were not studied.\(^11\)

We translated (into Dutch) and adapted the STI and conducted a cluster randomised controlled trial (RCT) (STA OP!, STApsgewijs Onbegrepen gedrag en Pijn bij dementie de baas!)\(^12\); our trial has demonstrated positive effects on neuropsychiatric symptoms.\(^13\) The present study reports the effects of STA OP! on pain and pain management in Dutch nursing home patients with advanced dementia. The hypotheses were that residents receiving the STA OP! will, compared with residents receiving usual care without a stepwise component,

1. have significantly less pain and pain-related behaviours, and
2. use significantly more analgesics.
METHODS

Study design and participants
The STA OP! trial is a cluster RCT with primary outcomes pain and behaviour. The number of residents required for the trial was based on the CMAI, one of the primary outcomes of the RCT\textsuperscript{12}. To detect a 15% difference between the intervention and control condition with an $\alpha = .05$ and $\beta = .80$, and taken a design-effect of 1.5 and a lost to follow-up rate of 50% into account, it was estimated that a total of 168 residents was needed. The recruitment strategy, patient samples, study protocol\textsuperscript{12}, and outcomes on behaviour\textsuperscript{13} are described elsewhere. In brief\textsuperscript{12,13}, nursing homes with a psychogeriatric unit (mostly dementia) were recruited from the academic nursing home network of the VU University Medical Center (VUmc)\textsuperscript{14}. Eligible residents for the analyses had\textsuperscript{12} (A) Global Deterioration Scale (GDS) $\geq 5$\textsuperscript{15}, (B) no chronic psychiatric diagnosis other than dementia, and additionally to enrol in the study protocol (C) clinically significant symptoms of pain and/or challenging behaviour, defined as pain according to the Minimum Data Set of the Resident Assessment Instrument (MDS-RAI pain scale, intensity $\times$ frequency $\geq 2$, the cut off for pain)$\textsuperscript{16}$ at baseline and/or a Cohen-Mansfield Agitation Inventory (CMAI)$\textsuperscript{17,18}$ score $\geq 44$ or a score a Neuropsychiatric Inventory–Nursing Home version (NPI-NH, frequency x severity) score $\geq 4$).\textsuperscript{19} Proxy consent was solicited according to Dutch law with the legal representative of the resident, mostly a close family member.

Randomisation, masking and ethical approval
The trial was single blinded, with blinded outcome assessment by research assistants\textsuperscript{12} Residents were the targets of the intervention, but because the intervention was multidisciplinary, and training was given to staff, the nursing home unit was the unit of randomisation.\textsuperscript{12} An independent researcher unaware of the identity of the units allocated units using a computer-generated sequence program.\textsuperscript{20} Data were collected between January 2010 and June 2012. The study was approved by the Medical Ethics Review Committee of the VUmc (No. 2009/119). The trial is registered at the Netherlands National Trial Register (NTR1967).

Procedures
Trained research assistants (psychologists) assessed all outcome variables, including medication, demographics and control variables, in a face-to-face interview with the nursing staff member familiar with the resident, before implementation, at 3 months (end of the training period) and at 6 months post-intervention.
Chapter 6

Pain assessment: observation versus estimation

Symptoms of pain and/or pain-related behaviour were recorded using the Dutch version of the Pain Assessment Checklist for Seniors (PACSLAC-D)\textsuperscript{21} and the MDS-RAI pain scale\textsuperscript{16}, the primary outcomes for pain as per protocol.\textsuperscript{12}

Pain was assessed in a standardized manner by the nursing staff member who was familiar with the resident, and who was trained by an external certified trainer with a nursing background. The PACSLAC-D and the MDS-RAI pain scale were administered before, at 3 months, and at 6 months after the intervention started. The conditions of administration such as time of assessment were kept the same within each patient.

Observation of pain

The PACSLAC-D\textsuperscript{22} is a structured observational pain assessment instrument\textsuperscript{23,24} shortened to 24 items. High levels of internal consistency for the complete scale (Cronbach’s alpha range 0.82-0.86) have been established;\textsuperscript{25,26} a score of ≥ 4 is considered as indicative for pain\textsuperscript{22}. In a study in Dutch nursing homes, it was selected as one of the most feasible of the available valid pain observation scales.\textsuperscript{25}

Estimation of pain

The MDS-RAI pain scale reflects a caregiver’s estimate based on observations, patient files and experiences in patient contact, during the previous 7 days. Pain frequency is coded as no pain (0); less than daily pain (1); and daily pain (2), and pain intensity is categorized as no pain; mild pain (0); moderate pain (1); and severe pain (2; times when pain is horrible or excruciating). The validity and precision of pain assessment with these MDS-RAI items have been established against the Visual Analogue Scale\textsuperscript{16}, but not specifically for advanced dementia.

Pain medication

The use of pain medication was recorded and retrieved from medication lists and classified with the Anatomical Therapeutical Chemical classification (ATC).\textsuperscript{27} The drugs were categorized as ‘Opioids’ (ATC-code N02A), or ‘Paracetamol and other analgesics’ (ATC-code N02B).

Intervention, training and implementation

The intervention condition involved implementation of the STA OP! protocol. Herein, all healthcare professionals (i.e. nursing staff, physicians, psychologists, physiotherapists) received a comprehensive stepwise multidisciplinary training of 5 meetings lasting 3 hours each. The team members were trained in the stepwise working method of the protocol and also to improve physical and affective assessment
skills that target unmet needs. A summary of the steps described elsewhere is presented in Table 1.

To help implement the protocol in practice, it was linked to structured daily or weekly team meetings. Additionally, focus groups discussions held on the units facilitated implementation. Further, the project coordinator (MP) performed weekly site visits, conducted fidelity checks with nursing staff and elderly care physicians regarding their use of the STA OP! protocol, and answered any questions.

Healthcare professionals working on units in the control condition also received training. However, importantly, this training lacked the stepwise approach, while targeting general nursing skills, dementia management and knowledge about pain in dementia. The project coordinator (MP) also visited all the units in the control condition once a week and also answered questions, but in case of the control condition, provided general information on challenging behaviour, pain and dementia management.

A physician experienced in pain management in dementia (WA) trained all elderly care physicians responsible for the control and the intervention units, based on the guidelines for pain and behaviour of the Dutch Association of Elderly Care Physicians and Social Geriatricians.⁹
### Table 1. Description of the steps of STA OP!

<table>
<thead>
<tr>
<th>Steps</th>
<th>Description</th>
<th>Number of residents in which actions have been undertaken (n=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Perform a basic care needs assessment, and assess if basic care needs are fulfilled (e.g. hunger, thirst, eyeglasses, hearing aids or toileting). - If assessment is positive, a targeted intervention is implemented or the appropriate discipline is consulted to begin treatment. If the assessment is negative, or if treatment fails to decrease symptoms, the nurse moves to the next step (1).</td>
<td>58</td>
</tr>
<tr>
<td>1</td>
<td>Perform a pain and physical needs assessment. In addition to a brief physical nursing assessment (screening for pain) by the nurse (a), nurses fill out an observational pain instrument (PACSLAC-D) as well (b). This form is handed to the nursing home physician (or if available a nurse practitioner), who performs a more comprehensive physical assessment (c) in order to find other probable physical causes associated with discomfort. For those residents already using pain medication or psychotropic drugs, and still have behaviourally symptoms possibly related to pain or affective discomfort, the nursing home physician assesses whether the medication given is in accordance with the guidelines of the World Health Organization (WHO) and Verenso (the Dutch Association of Nursing Home Physicians) (also see steps 4 and 5). - If assessment is positive, a targeted intervention is implemented or the appropriate discipline is consulted to begin treatment. If the assessment is negative, or if treatment fails to decrease symptoms, the nurse moves to the next step (2).</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>Perform affective needs assessment that focuses on needs of people with dementia: (a) environmental stress threshold not exceeded, (b) balance between sensory-stimulating and sensory-calming activity throughout the day, and (c) receipt of meaningful human interaction each day. The psychologist (or social worker) working in the nursing home can be consulted at this step. - If assessment is positive, a targeted intervention is implemented or the appropriate discipline is consulted to begin treatment. If the assessment is negative, or if treatment fails to decrease symptoms, the nurse moves to the next step (3).</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>Administer a trial of non-pharmacological comfort treatment(s). Treatments used are customized to the person and the situation, and are based on a list of psychosocial and environmental treatments that have been associated with decreasing agitated behaviours. - If a one-time treatment is effective and continued use is desirable, take actions needed to ensure continued treatment (e.g. communicate new treatment to other staff and family, write it down in the patients care plan with prescribed times or administration). If a trial of non-pharmacological comfort treatment(s) does not ameliorate behaviours in a time frame likely to show outcomes, the nurse should move to the next step (4).</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>Administer a trial of analgesic agents by either administering the prescribed as-needed analgesic agent or obtaining orders to escalate a current analgesic medication. - If treatment is effective and continued use is desirable, take actions needed to ensure continued treatment (e.g. schedule dosing of effective treatments for continued use, write it down in the patients care plan with prescribed times or administration). If there is not a response to a trial course of analgesic medications, consider consultation regarding further escalation or proceed to the next step (5). Stop ineffective treatments.</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>Consult with other disciplines (e.g. psychiatrist) and/or administer a trial of a prescribed as-needed psychotropic drugs in this step if the behaviour continues and alternatives are carefully considered, and potential side effects are weighed against the comfort needs of the resident. - Monitor for recurrence and new problems. Conduct regular comprehensive assessments. Establish clear criteria for evaluation of problems and treatment effectiveness, need for treatments, and possible side effects. If treatment is negative, and/or behavioural symptoms continue, repeat consultation or the entire process at the initial ‘behavioural change identification’.</td>
<td>5</td>
</tr>
</tbody>
</table>

Start with a ‘Behavioural Change Identification’: define the target behaviour, its expression and when (in what situation) this behaviour is challenging. Check if the behaviour is new or recurrent. If the behaviour is recurrent, check what has been done in the past to treat it. Define for whom the behaviour is challenging: the patient, family, or caregivers? A psychologist can be consulted at this step. 

- If the nurses and the multidisciplinary team of healthcare professionals make a clear description of the targeted behaviour, the nurse moves to the next step (0).
Note: nurses, nursing home physicians and healthcare professionals (multidisciplinary team) should identify behavioural symptoms using an explicit schedule and procedures. When a resident exhibits changes in behaviour that are not effectively treated, and basic care provided is checked at step 0, the STA OP! is initiated by the nurse at step 1. The STA OP! process is stopped when behavioural symptoms decrease by 50% or more. Continued movement through the steps of the STA OP! is based on results of assessments and decreases in symptoms in time frames that have been established for specified treatments. If behavioural symptoms continue after completing these five steps, the process is repeated at the initial ‘behavioural change identification’. Copyright (2016) Wiley. Used with permission from (Marjoleine J.C. Pieper, Anneke L. Francke, Jenny T. van der Steen, Erik J.A. Scherder, Jos W.R. Twisk, Christine R. Kovach, and Wilco P. Achterberg. Effects of a Stepwise Multidisciplinary Intervention for Challenging Behaviour in Advanced Dementia: A Cluster Randomized Controlled Trial. J Am Geriatr Soc., John Wiley & Sons, Inc.)

Statistical analysis

Differences in residents’ baseline characteristics between the intervention and control group were tested with a χ² test for categorical variables, and for continuous variables, with the Mann-Whitney U-test in case of skewed distributions, and a one-way analysis of variance (ANOVA) for normally distributed continuous variables.

We used multilevel analyses with a five-level structure (Institute, nursing home, psychogeriatric unit, resident, and time) for continuous outcomes and logistic Generalized Estimating Equations (GEE) analysis for dichotomous outcomes. Logistic GEE is preferred over logistic multilevel analysis because of greater stability, and we expected only modest correlations in the higher levels of clustering. Although some outcome variables were skewed to the right, parametric analyses were allowed by normally distributed residuals in the analyses adjusted for baseline values. As planned, analyses were conducted on an intention-to-treat basis. Multilevel analyses were performed with MLwiN, version 2.26 (University of Bristol, Bristol, UK). We used IBM SPSS, version 21.0 (IBM Corp., Armonk, NY, USA) for all other analyses.

First, we investigated the overall treatment effect over time and, second, we evaluated the effect at the different time points. For this, we added time and the interaction between treatment and time to the model.

We performed unadjusted (crude) analyses including only a correction for the baseline value of the primary outcome, and adjusted analyses. We adjusted for dementia severity (GDS scores), age, gender, and pain medication use, comorbidity and functioning at baseline. We estimated main effects for treatment at different assessment points under these different models and we reported as differences, or odds ratios (OR).
RESULTS

Figure 1 shows the CONSORT flow chart of the STA OP! trial. Twelve nursing homes with 21 units participated and 363 residents of the 21 units were eligible for participation. For 56 residents (15.4%) the family did not provide consent to participate, 13 (3.6%) died, 3 (0.8%) did not meet the inclusion criteria, and 3 (0.8%) moved to another institution. Finally, 288 residents were included in the STA OP! trial; 148 in the intervention condition and 140 in the control condition.\textsuperscript{13}

Table 2 shows that the residents in the intervention condition were less severely impaired and used more pain medication (e.g. paracetamol) than residents in the control condition, but comorbidity (e.g. number of disorders) did not differ. During the 6-month study period, 59 residents (29 in the control group and 30 in the intervention group) were lost to follow-up (died or moved) (p=0.926).

Prevalence of pain
The prevalence rate of pain ranged from 30.7 to 54.1%. The prevalence of observed pain (PACSLAC-D, 49.7%) was higher than the prevalence of estimated pain (MDS-RAI pain scale, 33.3%). There were no significant differences between the intervention and control condition at baseline (PACSLAC-D, p=0.125 and MDS-RAI pain scale, p=0.360; Table 2).

Effect of the intervention
From the 148 residents, the nursing staff and physicians in the intervention condition selected 58 (39%) residents to receive the STA OP! protocol. This led to a total of 175 assessments (physical and psychosocial): 34 non-pharmacological interventions, 12 pharmacological pain trials and 5 external consultations (Table 1 shows the steps of STA OP!; the right column shows the number of times an action was undertaken). Of these 58 residents, in 10 (17.2%) individuals pain triggered the start of the protocol. However, 8 of these 10 residents had both pain and behavioural problems. Only 2 residents were analysed by the STA OP! protocol due to a suspicion of pain only, without any behavioural problems (Table 1).

Multilevel analyses on the PACSLAC-D and MDS-RAI pain scale according to the intention-to-treat principle indicated that correlations at the higher levels (institute and nursing home) were negligible and, therefore, we only considered clustering on the ‘unit’ (ICC=0.10) and ‘resident’ levels (ICC=0.70). Table 3 presents the results of the unadjusted and adjusted linear longitudinal multilevel regression analyses on the observed and estimated effect of pain.
Effects of STA OP! on pain: results cluster-RCT

Enrollment

Assessed for eligibility:
Nursing Home Units (n = 21)
Residents (n = 363)

No Nursing Homes Units were excluded from the study.
Excluded residents (n = 72)
• Declined to participate (n = 56)
• Died (n = 13)
• Transferred to another unit/facility (n = 3)

Randomised & screened for dementia (GDS > 5)
Nursing Home Units (n = 21)
Residents (n = 291)

Excluded residents (n = 3)
• Not meeting the inclusion criteria, GDS score 5, 6 or 7

Allocation (n = 288)

Allocated to receive STA OP! intervention
Nursing Home Units (n = 11)
Residents (n = 148)

Allocated to receive care as usual
Nursing Home Units (n = 10)
Residents (n = 140)

Follow-Up 1 (3 months)

Nursing Home Units (n = 11)
Residents (n = 131) with data after intervention
Lost to follow-up T1 (n = 17):
Died (n = 16), Transferred (n = 1)

Nursing Home Units (n = 10)
Residents (n = 126) with data after intervention
Lost to follow-up T1 (n = 14): all died

Follow-Up 2 (6 months)

Nursing Home Units (n = 11)
Residents (n = 118) with data at follow-up
Lost to follow-up T2 (n = 13): all died
Total: n = 30, Died (n = 29), Transferred (n = 1)

Nursing Home Units (n = 10)
Residents (n = 111) with data at follow-up
Lost to follow-up T2 (n = 15): all died
Total: n = 29, all died

Analysis

Analysed
Intention-to-treat (n = 148)

Analysed
Intention-to-treat (n = 140)

Figure 1. STA OP! flow chart

### Table 2. Baseline characteristics of the STA OP sample.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>Statistics (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years</strong></td>
<td>83.3 (6.9)</td>
<td>84.3 (7.4)</td>
<td>0.249</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Male</td>
<td>40 (28.6)</td>
<td>41 (27.7)</td>
<td>0.870</td>
</tr>
<tr>
<td>- Female</td>
<td>100 (71.4)</td>
<td>107 (72.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Dementia severity: Reisberg GDS</strong></td>
<td></td>
<td></td>
<td>0.041</td>
</tr>
<tr>
<td>- Moderately-Severe cognitive decline, stage 5</td>
<td>12 (8.6)</td>
<td>23 (15.5)</td>
<td></td>
</tr>
<tr>
<td>- Severe cognitive decline, stage 6</td>
<td>81 (57.9)</td>
<td>92 (62.2)</td>
<td></td>
</tr>
<tr>
<td>- Very Severe cognitive decline, stage 7</td>
<td>47 (33.6)</td>
<td>33 (22.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- PACSLAC-D</td>
<td>4.03 (3.79)</td>
<td>4.99 (4.77)</td>
<td>0.175</td>
</tr>
<tr>
<td>- PACSLAC-D &gt; 4 (cut-off point pain)</td>
<td>63 (45.0)</td>
<td>80 (54.1)</td>
<td>0.125</td>
</tr>
<tr>
<td>- MDS-RAI Pain scale</td>
<td>1.21 (1.84)</td>
<td>1.36 (1.84)</td>
<td>0.363</td>
</tr>
<tr>
<td>- MDS-RI &gt; 2 (clinically relevant pain cut-off)</td>
<td>43 (30.7)</td>
<td>53 (35.8)</td>
<td>0.360</td>
</tr>
<tr>
<td><strong>Functioning (ADL)</strong></td>
<td></td>
<td></td>
<td>0.010</td>
</tr>
<tr>
<td>- KATZ ADL scale</td>
<td>18.03 (5.19)</td>
<td>16.54 (5.18)</td>
<td></td>
</tr>
<tr>
<td><strong>Type of medication (ATC code)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group N02</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- No medication (N02)</td>
<td>90 (65.2)</td>
<td>66 (45.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Opioids (N02A)</td>
<td>12 (8.7)</td>
<td>11 (7.6)</td>
<td>0.746</td>
</tr>
<tr>
<td>- Paracetamol and other analgesics (N02B)</td>
<td>41 (29.7)</td>
<td>77 (53.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Comorbidity subgroups Minimum Dataset (MDS)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>Circulatory system:</strong></td>
<td>76 (54.3)</td>
<td>76 (51.4)</td>
<td>0.454</td>
</tr>
<tr>
<td>- e.g. ASHD, arteriosclerosis, thrombosis, high/low blood pressure</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- <strong>Respiratory system:</strong></td>
<td>12 (8.6)</td>
<td>18 (12.2)</td>
<td>0.319</td>
</tr>
<tr>
<td>- e.g. COPD/emphysema, asthma</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- <strong>Loco-motor system:</strong></td>
<td>41 (29.3)</td>
<td>34 (23.0)</td>
<td>0.446</td>
</tr>
<tr>
<td>- e.g. (rheumatoid)arthritis, osteoporosis, column or malign fractures, amputation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>Nervous system:</strong></td>
<td>39 (27.9)</td>
<td>32 (21.6)</td>
<td>0.388</td>
</tr>
<tr>
<td>- e.g. CVA/stroke, haemorrhages, aphasias, epilepsy, Parkinson's disease, hemiplegia, Cerebral Palsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>Endocrine/metabolic system:</strong></td>
<td>42 (30.0)</td>
<td>36 (24.2)</td>
<td>0.276</td>
</tr>
<tr>
<td>- e.g. diabetes mellitus, hyper-/hypothyroid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>Sensory system:</strong></td>
<td>31 (22.1)</td>
<td>21 (14.2)</td>
<td>0.255</td>
</tr>
<tr>
<td>- e.g. cataract, diabetes, retinopathy, glaucoma, macula degeneration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>Infections:</strong></td>
<td>9 (6.4)</td>
<td>9 (6.1)</td>
<td>0.903</td>
</tr>
<tr>
<td>- e.g. urinary tract &lt;30 days, pneumonia, airway infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>Other:</strong></td>
<td>20 (14.3)</td>
<td>22 (14.9)</td>
<td>0.988</td>
</tr>
<tr>
<td>- allergies, cancer, anaemia kidney insufficiency</td>
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</table>
**Effects on observation and estimation of pain**

The adjusted mean difference on the PACSLAC-D pain observations was -1.21 points (95% confidence interval [CI] -2.35 to -0.06; p=0.020) favouring the intervention condition. This was largely explained by the effect at 6 months post-intervention/implementation. The adjusted mean difference at 3 months was -0.91 points (95% CI -2.16 to -0.33; p=0.074), and the adjusted mean difference at 6 months was -1.54 (95% CI -2.82 to -0.27; p=0.009). On the MDS-RAI pain estimation scale, there was no difference between the intervention and the control condition; the overall adjusted mean difference was -0.01 points (95% CI -0.36 to 0.35; p=0.488) (Table 3).

**Effects on medication**

Table 4 shows the results of unadjusted and adjusted logistic GEE analyses on pain medication use. A significant higher odds was found for opioid use (OR=3.08; 95% CI 1.08 to 8.74), but not for paracetamol and other analgesics (OR=1.38; 95% CI 0.71 to 2.68). During the trial, residents in the intervention condition compared to the control condition were significantly more likely to receive opioids, but not paracetamol or other analgesics.
Table 3. Differences in symptoms of pain/pain-related behaviour, using the MDS-RAI pain scale and the PACSLAC-D, across follow-up measurements at 3 and 6 months post-intervention.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Unadjusted (crude) model</th>
<th>Adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>‘Observation’ of Pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACSLAC-D, overall</td>
<td>-0.89 (-2.09, 0.31)</td>
<td>0.074</td>
</tr>
<tr>
<td>PACSLAC-D, 3 months</td>
<td>-0.70 (-1.99, 0.60)</td>
<td>0.147</td>
</tr>
<tr>
<td>PACSLAC-D, 6 months</td>
<td>-1.11 (-2.44, 0.22)</td>
<td>0.051</td>
</tr>
<tr>
<td><strong>‘Estimation’ of Pain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS-RAI Pain scale, overall</td>
<td>0.01 (-0.36, 0.36)</td>
<td>0.508</td>
</tr>
<tr>
<td>MDS-RAI Pain scale, 3 months</td>
<td>0.07 (-0.38, 0.51)</td>
<td>0.618</td>
</tr>
<tr>
<td>MDS-RAI Pain scale, 6 months</td>
<td>-0.07 (-0.54, 0.40)</td>
<td>0.382</td>
</tr>
</tbody>
</table>

Note: CI = confidence intervals. PACSLAC-D = Pain Assessment Checklist for Seniors with Limited Ability to Communicate – Dutch version. MDS-Pain scale = Minimum Dataset Pain Scale. The intervention effect is in reference to the control condition. Regression coefficients (β) reflect the differences in pain during the study period regarding pain or pain-related symptoms (PACSLAC-D and MDS-RAI Pain scale) between baseline and the two follow-up measurements at 3 and 6 months post-intervention. A negative β value indicates a positive intervention effect of the STA OPI-protocol on pain or pain-related behaviour of residents (pain/pain-related behaviour in the intervention condition compared to the control condition over time, 3 and 6 months post-intervention). The β value reflects the decrease pain/pain-related symptoms during the 6-month study period of the intervention group compared to the control group. ^Crude model: adjusted for baseline value of pain/pain-related symptoms, and levels time, individual and nursing home unit. ^Adjusted model: further adjusted for gender, age, stage of the dementia, comorbidity, medication use (e.g. opioids and paracetamol), and functioning at baseline.
Table 4. Odd ratios (OR) of change in pain medication use, across follow-up measurements at 3 and 6 months post-intervention.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Unadjusted (crude) model</th>
<th>Adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Pain medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioids (N02A), overall</td>
<td>2.13 (0.66, 6.81)</td>
<td>0.205</td>
</tr>
<tr>
<td>Opioids (N02A), time 3 months</td>
<td>1.33 (0.33, 5.35)</td>
<td>0.685</td>
</tr>
<tr>
<td>Opioids (N02A), time 6 months</td>
<td>2.71 (0.69, 10.61)</td>
<td>0.153</td>
</tr>
<tr>
<td>Paracetamol and other analgesics (N02B), overall</td>
<td>1.40 (0.76, 2.60)</td>
<td>0.281</td>
</tr>
<tr>
<td>Paracetamol and other analgesics (N02B), time 3 months</td>
<td>1.68 (0.90, 3.17)</td>
<td>0.106</td>
</tr>
<tr>
<td>Paracetamol and other analgesics (N02B), time 6 months</td>
<td>1.03 (0.46, 2.32)</td>
<td>0.941</td>
</tr>
</tbody>
</table>

Note: CI = confidence intervals; OR= Odds Ratio. The intervention effect is in reference to the control condition. Odds ratios (OR) reflect pain medication use during the 6-month study period; opioids (N02A), and paracetamol & other analgesics (N02B) use over the two follow-up measurements (3 and 6 months post-intervention) from baseline. OR > 1.0 indicates an increase in pain medication use in the intervention condition (STA OPI program) compared to residents in the control condition over time (3 and 6 months post-intervention). 1Crude model: adjusted for baseline values of pain medication use, and levels time and individual. 2Adjusted model: further adjusted for gender, age, stage of the dementia, comorbidity, pain at baseline, and functioning at baseline.
DISCUSSION

Implementation of the stepwise Serial Trial Intervention (STA OP!) intervention was effective in decreasing pain in nursing home residents with advanced dementia, and while opioid use increased, paracetamol use did not. The tailored stepwise and multidisciplinary intervention focusing on physical and psychosocial unmet needs was more effective than a non-stepwise approach. Our findings are in line with effects on other outcomes in this study and in other studies that also showed positive effects of the stepwise approach on discomfort and behaviour, although a recent review did not evaluate the effectiveness of stepwise component. Our study is the first cluster randomised controlled study that examined and found effects on both pain and challenging behaviour.

A decrease in pain was reached through ‘observation’ of pain, as assessed with systematic objective observational scoring of a broad range of items with the PACSLAC-D, but not with the MDS-RAI pain scale, which is considered an instrument for the ‘estimation’ of pain. If we consider that in the present study the reduction of pain was established not by the ‘identification or awareness of pain’ by the staff, but mainly by the ‘identification of behavioural problems’ (Table 1), we can also conclude that the behavioural cues for pain in dementia are essential for better pain management. This is in line with other researchers who stressed the importance of behavioural identifiers for pain assessment in advanced dementia. We found that at baseline, nurses estimated a considerably lower prevalence of pain as assessed by the MDS-RAI pain scale (estimation of pain) compared to an observation of pain as assessed with the PACSLAC-D, but prevalence is related to cut-offs which can be more or less conservative. In people with advanced dementia, subtle changes of behaviour are best seen through observation and, as a result, observation of pain, or recollection of behaviour that may indicate pain, seems to be superior and more acceptable to nurses than estimation or ‘guessing’ of pain.

Further, pain assessment and management was being integrated in standardized daily (nursing) care, as a result of the intervention, health care professionals (especially nursing staff) may have become more aware of pain as a cause of challenging behaviour, and adopted the more systematic approach to needs assessment in daily practice; effects that may spill over to other residents.

Although the hypothesized increase of total pain medication use was confirmed, statistical significance was reached only for opioid use. In an advanced stage of dementia, agitation might be the reason for prescribing opioids and, considering
that residents were included in the STA OP! protocol mainly because of a change in
behaviour (e.g. agitation) it is encouraging that after training sessions the nursing staff
indeed indicated that they considered behavioural changes as a possible sign of pain.
Although many studies have suggested an association between pain and behaviour\textsuperscript{39,40},
such a relationship has not been unequivocally established\textsuperscript{37}.

In this trial, the treatments that were applied the most were non-pharmacological
comfort interventions (situated in the early steps of the STA OP! protocol) and these
probably account for a large part of the reduction in pain behaviour. Reduction of pain
behaviour in dementia through comfort interventions has also been documented by
others\textsuperscript{32,33}; therefore, pain management (and pain assessment in dementia) may require
a multidimensional approach.\textsuperscript{3,4} Approaches that use stepwise protocols, such as STA
OP!, therefore seem superior to and more effective than uni-dimensional programs.

This RCT has several limitations. The resident may have been unaware of being
included in the intervention or control condition, and the trained research assistants
who collected the outcome measurements were also blinded for the condition, but
the nurses on whose observations the outcome measurements were based, were not
blinded. Therefore, the possibility of bias, or Hawthorn effect, cannot be ruled out.
Residents in the intervention condition were less severely impaired and used more pain
medication than residents in the control condition at baseline. However, we adjusted for
differences in GDS scores 5 to 7 and medication use after baseline, and we therefore
feel that the results are not likely explained by greater capacity to ask for medication in
the intervention condition. The intervention was performed in only a small proportion
(39\%; 58/148) of the eligible residents. Nursing time was the main barrier to starting the
protocol on all the residents at the same time. For training and educational purposes,
the staff assembled a sample of residents to start the protocol, during the first meeting.
This raises questions about the fidelity of the implementation, and the knowledge, time
and resource requirements for implementing such a multi-component intervention in a
‘classic’ RCT. However, even though not all residents followed the stepwise protocol,
this approach showed clear benefits at the group level.

The relatively disappointing level of implementation suggests that future research should
examine more favourable implementation strategies in a long-term care setting. Also, the
specific challenges of implementation in long-term care should not be underestimated.\textsuperscript{41}
Nevertheless, this RCT shows that, although the setting differs between US and the
Netherlands, the STI could be used effectively with minor adaptions; i.e. the findings
may be generalizable to other settings.
The trial's strengths include that this is one of the few RCTs in advanced dementia on pain management, and one of the few to use reliable and valid observational instruments for the assessment of pain. Using two pain instruments allowed for identifying differences in pain prevalence and differential effects or sensitivity to change of observational (even though recall based) versus estimation approaches of pain assessment. The large differences found in earlier pain prevalence studies in nursing homes\(^{42}\) may be explained by the use of different assessment methods.

Despite the disappointing treatment fidelity and the fact that staff were expected to assess behaviour, pain, environmental stimuli, and the physical and psychosocial unmet needs of almost all residents on the unit in a relatively short period of time, it was possible to implement a tailored intervention trial within their daily routines and workload. In addition, we have shown the positive effects on pain assessment and management at the patient level, according to the intention-to-treat principle. Other strengths are the cluster randomised design and the sound methodological multilevel analytic approach, which accounts for clustering of the data.

Considerable growth in the number of people with dementia is expected\(^ {43}\) and, as a consequence, the burdens and challenges of caring for this group are formidable. This study indicates that STA OP! can help healthcare professionals to realize effective pain management in addition to effectively addressing behaviour\(^ {13}\) in people with advanced dementia, which is crucial to establish an optimal quality of life.

**Acknowledgments**

The authors thank all the healthcare professionals, and the management and staff of the participating nursing homes, for their collaboration.

**Conflict of Interest**

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/conflicts-of-interest/, and declare: no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Contributions of authors**

MP drafted the manuscript, coordinated the data collection and analysed the results. AF, WA, ES and JS designed the STA OP! trial and helped to draft the manuscript. JT advised on statistical analysis and results. All authors were involved in revising the manuscript. All authors read and approved the final version of the manuscript.
Role of the funding source
The funding source (Innovatiefonds Zorgverzekeraars) had no role in the study design, data collection, data analysis, or writing of the report. The corresponding author and all co-authors had full access to the study data and had final responsibility for the decision to submit for publication.
REFERENCES


