Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial

Bettina S Husebo postdoctoral fellow1, Clive Ballard professor2, Reidun Sandvik registered nurse1, Odd Bjarte Nilsen statistician3, Dag Aarsland professor4

1Department of Public Health and Primary Health Care, University of Bergen, 5020 Bergen, Norway; 2Wolfson Centre for Age-Related Diseases, Wolfson Wing and Hodgkin Building, Guy’s Campus, Kings College, London SE1 1UL, UK; 3Department of Psychiatry, Stavanger University Hospital, 4011 Stavanger, Norway; 4Karolinska Institute, Department of Neurobiology, Care Sciences and Society, Karolinska Institute-Alzheimer Disease Research Center, Novum, Stockholm, Stavanger University Hospital, Department of Psychiatry, Stavanger, Norway, and University of Oslo, Oslo, Norway

Abstract

Objective To determine whether a systematic approach to the treatment of pain can reduce agitation in people with moderate to severe dementia living in nursing homes.

Design Cluster randomised controlled trial.

Setting 60 clusters (single independent nursing home units) in 18 nursing homes within five municipalities of western Norway.

Participants 352 residents with moderate to severe dementia and clinically significant behavioural disturbances randomised to a stepwise protocol for the treatment of pain for eight weeks with additional follow-up four weeks after the end of treatment (33 clusters; n=175) or to usual treatment (control, 27 clusters; n=177).

Intervention Participants in the intervention group received individual daily treatment of pain for eight weeks according to the stepwise protocol, with paracetamol (acetaminophen), morphine, buprenorphine transdermal patch, or pregabalin. The control group received usual treatment and care.

Main outcome measures Primary outcome measure was agitation (scores on Cohen-Mansfield agitation inventory). Secondary outcome measures were aggression (scores on neuropsychiatric inventory—nursing home version), pain (scores on mobilisation-observation-behaviour-intensity-dementia-2), activities of daily living, and cognition (mini-mental state examination).

Results Agitation was significantly reduced in the intervention group compared with control group after eight weeks (repeated measures analysis of covariance adjusting for baseline score, P<0.001): the average reduction in scores for agitation was 17% (treatment effect estimate −7.0, 95% confidence interval −3.7 to −10.3). Treatment of pain was also significantly beneficial for the overall severity of neuropsychiatric symptoms (−9.0, −5.5 to −12.6) and pain (−1.3, −0.8 to −1.7), but the groups did not differ significantly for activities of daily living or cognition.

Conclusion A systematic approach to the management of pain significantly reduced agitation in residents of nursing homes with moderate to severe dementia. Effective management of pain can play an important part in the treatment of agitation and could reduce the number of unnecessary prescriptions for psychotropic drugs in this population.

Trial registration ClinicalTrials.gov NCT01021696 and Norwegian Medicines Agency EudraCT nr 2008-007490-20.

Introduction

Thirty five million people worldwide have dementia, and this number is expected to increase to 115 million by 2050.1 Agitation and aggression are common in people with dementia, in particular those with moderate to severe dementia living in nursing homes, where the cross sectional prevalence of these symptoms exceeds 50%.2,3 Agitation is associated with increased distress to residents and a burden to family and professional caregivers4 and is one of the most challenging symptoms for clinical management.

Antipsychotics are often used as first line drug treatment for agitation and aggression, with 40-60% of residents with dementia in nursing homes prescribed such treatment.5 In the United Kingdom alone, a report for the Department of Health estimated that 180 000 people with dementia were being prescribed antipsychotics, causing 1620 excess strokes and 1800 deaths a year.6 These figures emphasise the importance of finding safe and effective ways to reduce agitation and aggression in people with dementia.

Many people with dementia have painful conditions,7 and it has been proposed that pain in patients with impaired language and abstract thinking may manifest as agitation.8 Thus more effective treatment of undiagnosed pain may contribute to the overall prevention and management of agitation. Overall, 50-80% of
Residents in nursing homes are affected by pain and most good practice guidelines emphasise the importance of pain management in the treatment of neuropsychiatric symptoms in people with dementia. Few studies have, however, explored the potential utility of treating pain as a way of improving agitation. We evaluated whether systemic use of analgesics can reduce agitation in residents of nursing homes with moderate to severe dementia.

Methods
During October 2009 to June 2010 we carried out a multicentre, cluster randomised controlled trial for eight weeks, with an additional follow-up at 12 weeks (four weeks after the end of treatment) in 60 nursing home units within five municipalities of western Norway. A cluster was defined as a single independent nursing home unit (with no crossover of staff). We chose this design primarily to avoid contamination, because care staff receiving training in the assessment and treatment of pain cannot be expected to treat individual residents differently. The study statistician (OBN) used Stata version 8 to generate a list of random numbers for allocation of clusters to one of the two groups.

Eligible participants were adults aged 65 or more, living in one of the nursing homes for at least four weeks, with dementia according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition, functional assessment staging score of more than 4, and clinically relevant behavioural disturbances, defined as a score of 39 or more on the Cohen-Mansfield Agitation Inventory—that is, clinically significant agitation for at least one week. Exclusion criteria were advanced severe medical disease with expected survival of less than six months, severe psychiatric or neurological disorder, severe aggression (agitation score ≥8 on the neuropsychiatric inventory-nursing home version), severe liver or renal failure, severe injury or anaemia (haemoglobin concentration <8.5 mmol/L), and known allergy to paracetamol (acetaminophen), morphine, buprenorphine, or pregabalin.

Intervention
We randomly assigned patients to receive either treatment for pain according to a stepwise protocol for eight weeks or their usual management (the control group). The stepwise protocol followed the recommendations of the American Geriatrics Society. Participants in the intervention group received analgesics according to the standardised protocol. Depending on the ongoing medical treatment, participants allocated to the treatment protocol started at step 1 (oral paracetamol, maximum increase to 3 g/day) or, if they were already receiving treatment were adjusted to either step 2 (oral morphine, maximum 20 mg/day), step 3 (buprenorphine transdermal patch, maximum 10 µg/h), or step 4 (oral pregabalin, maximum 300 mg/day), using a fixed dose regimen throughout the eight week treatment period. Residents with swallowing difficulties were started at step 3. Drugs were offered at breakfast, lunch, and dinner (about 08:00, noon, 18:00), respectively. If needed, combination therapy was allowed. In those who were not able to tolerate this treatment, the dosage was either reduced or the participant was withdrawn from the study and treated as clinically appropriate.

Concomitant drugs
Anti-dementia drugs, psychotropics, aspirin (one dose daily), or anti-inflammatory drugs (for example, ibuprofen) were allowed if participants had remained stable on these for four weeks before study inclusion. We allowed the use of analgesics as needed (other than paracetamol) and monitored this during the study. Clinicians were advised to keep prescriptions and doses of psychotropics unchanged when possible.

Primary and secondary outcome measures
The primary outcome was agitation, as measured on the Cohen-Mansfield agitation inventory, a nurses’ rating questionnaire consisting of 29 agitated behaviours, each rated on a 7 point scale of frequency (1=not present, 7=several times an hour; range 29-203). Secondary outcome measures were aggression (neuropsychiatric inventory-nursing home version), pain (mobilisation-observation-behaviour-intensity-dementia-2), cognition (mini-mental state examination), activities of daily living, and functional assessment staging. The Cohen-Mansfield agitation inventory, neuropsychiatric inventory-nursing home version, and mobilisation-observation-behaviour-intensity-dementia-2 pain scale were completed at baseline, at two, four, and eight weeks after baseline, and at four weeks after the conclusion of treatment. We evaluated cognition (mini-mental state examination), activities of daily living, functional assessment staging, and drugs at baseline and after eight weeks of treatment.

Procedures
After receiving specific training in use of the instruments two research assistants carried out assessments by interviewing the primary caregiver during enrolment. A consultant for old age psychiatry (DA), an anaesthetist and pain therapist (BSH), one of the research assistants (RS), and a senior member of staff from each nursing home reviewed the outcomes of assessment and drug prescriptions for each patient after completion of baseline assessment but before randomisation.

Research assistants and caregivers were blinded to group allocation during assessments of the primary and secondary outcomes. Staff members in direct care contact with participants were unaware of the type of intervention. To ensure blindness, researchers and nurses with responsibility for carrying out the intervention did not participate in data collection. Nursing home staff were instructed not to discuss management procedures. Safety and tolerability were monitored at each assessment and all adverse events and vital signs recorded.

Sample size
Based on the magnitude of improvement in randomised controlled trials of non-drug interventions for agitation in residents of nursing homes, we estimated that a 25% greater reduction of Cohen-Mansfield agitation inventory score in the intervention group compared with control group would indicate equivalence to the best currently available approaches. For example, in a recent study we found that the largest improvement for a psychosocial intervention was 7.1 points, and thus a 25% difference would be about a 5 versus 7 point improvement in the two groups. To measure a difference of this magnitude would require a minimum of 81 patients allocated to each arm of the trial, for a significance level of 5% (two sided), a power of 95%, and equal allocation. Cluster randomisation leads to loss of power. To retain power, the sample size should be multiplied by 1+(m−1)p, called the design effect, where m is the average cluster size and \(\varphi\) is the intracluster correlation coefficient, where \(s^2_i\) is the variance between clusters and \(s^2_c\) is the variance within clusters. Based on additional assumption of an estimated
intraclustercorrelationcoefficientof0.13,anaverageofseven
eligibleandconsentingparticipantsineachcluster,theformulagives
adesigneffectof1.78(1+(7−1)×0.13).Thuswewhiddeterminedthatweneededaminimumof169.1
eligiblereceivingsanarypercluster,whichisinorderto26clusters
perarm,or52clusterswith338participantsinta. Toallow
fordropoutofindividualparticipantsandlossofclusters,wewantedai
cluding60clusters.

Statisticalanalysis

WeusedχandMann-Whitneyteststoproperlycomparepersonalandclinicalcharacteristicsbetweenthetwogroups.
Theanalysisofcovariancewasusedtoestimatethemeaneffectineachtreatmentarm,weightedacrossclustersaccording
tothenumberofparticipantswithineachcluster,andonthisweobtainedthemeaneffectestimate(difference
betweenclusters)ateachtimepoint.14Theintraclustercorrelation
coefficientexpressedtheproportionofthetotalvarianceinthe
dataduetothebetweenclustervariability.Theprimaryefficacy
populationincludedallresidentswithatleastonepost-baseline
assessment,usalstheobservationcarriedforwardprocedure
toaccountformissingvalues.Treatmenteffectwassexpressed
asestimatedeffectofintervention,alongwitha95%confidence
intervalandthePvaluesforeachtimepoint.Additionalanalyses
includedrepeatedmeasurementanalysisofcovariationwithout
thelastobservationcarriedforwardandcomparisonofchange
atweeks2,4,8usingStudent’sttest.Wesetthesame
proceduresotypicalanalysistothedeterminateoutcomeofpains
andaggression,whereasanalysisoftheeffectonthesecondaryoutcome
measuresofcognitionandoactivitiesofdailylivingw
usedStudent’syttotestthecomparisonbetweenbaseline
andweek8betweenthetwogroups.Analyseswere
carriedoutusingpredictiveanalyticsoftwarestatistics17
(SPSS;Chicago,IL).

Results

Intotal,920nursinghomeresidentswerescreened;420hade
hibitedtoseveredementiasmenduralbehaviouraldisturbancesand
wereassessedforeligibility.Sixtyeightwereexcludedfrom
randomisationbecausetheydidnotmeettheinclusioncriteria,
theydeclinedtoparticipate,ortherewereotherreasons(fig1).
Overall,352residentsin60clustersunderwentrandomisation
(27controlclusters(n=177),33interventionclusters(n=175),
fig1).Themediannumberofparticipantsineachclusterw
5.5(range2-11).Thegroupswh.hadsimilarpersonalandclinical
characteristicsandoutcomeevaluationatbaseline(table1).
Inall,59%(n=103)oftheinterventiongroupand55%(n=98)
ofthecontrolgrouphadclinicallyrelevantpainscoresof3ormore
on themobilisation-observation-behaviour-intensity-dementia-2
painscaleatbaseline.

Duringtheeightweek20participantswereinthecontrol
groupand28intheinterventiongroup(P=0.298).Fourteen
participantsdiedduringthestudyperiod,eightinthecontrol
and6intheinterventiongroup(fig1).

Analgesicsduringintervention

Table2showsthestrengtheoftreatmentsforpain.Inthe
interventiongroup,111(63%)participantsreachedstep1
(paracetamol3g/day)ofthetreatmentprotocol,andinaddition
nineparticipants(5%)anexistinglowdosagewasincreased.
sFourparticipants(2%)receivedstep2(threestartedwithmorphine;
inonepatienttheprescriptionwasadjusted).Thirty
oneparticipants(18%)receivedstep3(buprenorphine
transdermalpatch),andindeightparticipants(5%)the
dosagewasincreased.Twelveparticipants(7%)receivedstep
4(pregabaline).

Outcome

Table3andfigure2showthechangeinscoresonthe
Cohen-Mansfieldagitationinventoryinthe2groups.Ther
epeteadmeasurementanalysisofcovariance,usingthepopulationwithlastobservationcarriedforward,was
significantlydifferentbetweentheinterventionandcontrol
groupsaftereighth weeks,infavourofpaintreatment(P<0.001);
theaveragereductioninagitationwas17%(treatmenteffect
estimate−7.0,95%confidenceinterval−3.7to−10.3).The
findingsweresimilarwhentanalysedbasedonlyoncompleters
(P<0.001),andthechangefrombaseline differedbetween
thegroupsatweeks2,4,8.Intheinterventiongroupthere
wasaworseningofscoresontheCohen-Mansfieldagitation
inventorybetweenweek8andweek12,afterwithdrawal
ofpaintedreatment.

Betweengroupdifferencesinfavortofaintreatmentwere
alsosignificantforaggression(−9.0,−5.5to−12.6)andpain
(−1.3,−0.8tovo)atweeks2,4,8(table4and5).Thecorrelationbetween
painandaggressionwassignificantatweek8(P=0.01).Atweek
8theinterventionandcontrolgroupsdidnotdiffersignificantly
forcognition(mini-mentalstateexamination)(P=0.127;mean
7.4and8.6,respectively)oractivitiesofdailyliving(P=0.443;
mean7.9and8.4,respectively).

Discussion

Astandardisedstepwiseprotocoloftreatmentwithanalgesics
inresidentsofnursinghomestrawitodeserivedementiaand
agitationsignificantlyimprovedagitation,overall
neuropsychiatricssymptoms,andpain.Thesefindingsemphasise
theimportanceofassessingandtreatingpaineffectivelyaspart
oftheoveralltreatmentandpreventionofagitationand
aggressioninpatientswithdementia.Theseresultalsohighlight
theimportanceofeffectivevantreatmentofpainasakeypart
ofreducingtheuseofantipsychoticsandotherpsychotropic
medicinesinresidentsofnursinghomes.

Thecurrentstudyisthefirstadequatelypoweredparallel
grouprandomisedcontrolledtrialoffaintmanagementfortreatment
ofagitationinpatientswithmoderate
to severe dementiaincluding167patientsin
nursinghomes,providing
further supportfortheclinical
effectivenessoffndagitationand
aggressioninpatientswithdementia.
Theresultalsohighlight
theimportanceoffinef
treatmentofpainasakeypart
ofreducingtheuseofantipsychoticsandotherpsychotropic
medicinesinresidentsofnursinghomes.

Thecurrentstudyistheirstudythatadequatepower
parallel
group
randomisedcontrolledtrialofpainmanagementfortreatment
ofagitationinpatientswithmoderate
to severe dementiaилась
theinterventionandcontrolgroupsatweeks2,4,8.
Theinterventiongrouphadtaworseningofagitation
overthefourweeksfollow-upaftertheinterventionhad
stopped.Attheendoftheinterventionthegroupsdiffere
by7.0points,witha17%advantageovercontrolintheproportion
changeinscoreontheCohen-Mansfieldagitation
inventoryoverthedurationofthetrial.Toputthisintocontext,
thethree
usedtheCohen-Mansfieldagitationinventoryasan
outcomeinrandomisedcontrolledtrials_of
risperidone(thelicensed
ateddrugtreatmentforagitationandaggressioninpeople
withdementia)reported3%,13%,and18%advantages
comparedwithplacebo,respectively.25-27Theclinical
significancethatbenefitthereforecompareswelltothe
currentlybestavailabledrugtherapy.
Theclinicalrelevanceis
further supportedbythefromificantcorrelationobservedbetween
changeinagitationandchangeinpain.
Thefindingsfrom
withpreviousopenstudiescasevariable.A placebo
controlledstudyof167patientsinnursinghomes,providing
implementationofpersonalised,non-drugintervention,
resultedd
agitationintheinterventiongroup,21but
the
didnotreplicateinanopenstudyof114residents
in
nursinghomes,whichincludedpainmanagementaspartof
protocoltodealunmetneeds.13A subsequent trial of
pain treatmentwithparacetamol(acetaminophen)in25residentsin
nursing homes reported an increase in general activities and social interaction but no direct improvement in agitation.\textsuperscript{11} Finally, a double blind crossover trial of pain treatment with oxycodone and morphine in 47 residents in nursing homes, improved agitation in older but not in younger patients and showed a high frequency of dropouts.\textsuperscript{12} These studies show some support for the potential benefit of managing agitation by treating unmet needs such as pain, but with considerable differences in the type and magnitude of benefit, emphasising the need for a robust randomised controlled trial.\textsuperscript{13} The current, adequately powered parallel group randomised controlled trial shows more clear benefits. In clinical practice, by providing an effective treatment approach for people with dementia and agitation, improved management of pain should also help to reduce the number of prescriptions for antipsychotics in this population.

It is possible that agitation declined as a result of residents receiving sedation with opioid analgesics. However, only a few (25.6\%) were treated with sedative agents (table 2), and few residents (n=3) were excluded because of drowsiness and nausea. Neither activities of daily living nor cognition worsened in the treatment group compared with control group, suggesting that sedation could not explain the reduction of agitation in the active group.

In this study, some behavioural symptoms improved in both intervention and control clusters. That may indicate a Hawthorne effect,\textsuperscript{20} perhaps related to factors such as increased staff training and support. Improvements in control groups is similar to other studies investigating drug and non-drug treatments for neuropsychiatric symptoms in people with dementia and is consistent with the potential benefits of interventions such as social interaction and reminiscence.\textsuperscript{21} Precautions were taken to blind research assistants and caregivers to group allocation, but despite these efforts these studies will always be difficult to fully blind because of the requirements in a nursing home setting.

Importantly, in the current study, active intervention conferred significantly greater benefits over and above non-specific effects. The results highlight that a standardised approach to improved pain management is a practical intervention that would be straightforward to implement widely for the benefit of agitation in residents of nursing homes with dementia.

We thank the residents, their relatives, and nursing home staff for their willingness and motivation that made this study possible.

Contributors: BSH, CB, and DA conceived the study and obtained funding. All authors contributed to the study design, carrying out the study, and the writing of the manuscript. BSH and RS collected data. OBN and BSH contributed to the statistical analysis. BSH and DA are guarantors for the study.

Funding: This study was funded by the Norwegian Research Council (protocol code 189439), the University of Bergen (09/1568), and Kavli's Research Centre for Ageing and Dementia, Haraldsplass Diakonast Hospital, Bergen, Norway.

Competing interests: All authors have completed the ICJME uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations 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.

Ethical approval: This study was approved by the regional committee for medical ethics, western Norway (REK-Vest 248.08).

---

was given by all participants who had sufficient capacity. If participants did not have the capacity to give consent, written assent was provided by the next of kin in accordance with the requirements of the research ethics committee and Norwegian law at the time of the study.

Data sharing: No additional data available.

---

1. Dartigues JF. Alzheimer’s disease: a global challenge for the 21st century. Lancet Neurol 2009;8:1082-3.
2. Cohen-Mansfield J, Libin A. Verbal and physical non-aggressive agitated behaviors in elderly persons with dementia: robustness of syndromes. J Psychiatr Res 2005;39:325-32.
3. Testa I, Aasland AM, Aarland D. Prevalence and correlates of disruptive behavior in patients in Norwegian nursing homes. Int J Geriatr Psychiatry 2007;22:916-21.
4. Risvik P, Spazuzumo L, Mastrorilli R, Mattfeldt P, Manverd M, Polikorpi MC, et al. Predictors of high level of burden and distress in caregivers of demented patients: results of an Italian multicenter study. Int J Geriatr Psychiatry 2005;20:168-74.
5. Selbaek G, Kvisvik D, Engedal K. Prevalence of psychiatric symptoms and behavioural disturbances and the use of psychotropic drugs in Norwegian nursing homes. Int J Geriatr Psychiatry 2007;22:843-9.
6. Bannejee S. The use of antipsychotic medication for people with dementia. Time for action. A report for the Minister of State for Care Services. 2009. www.dh.gov.uk.
7. Husebo BS, Strand LI, Mo-Nilssen R, Husebo SB, Aarland D, Lyngjegren AE. Who suffers most? Dementia and pain in nursing home patients: a cross-sectional study. J Am Med Dir Assoc 2008;9:427-33.
8. Cohen-Mansfield J, Lipson S. The utility of pain assessment for analgesic use in persons with dementia. Pain 2008;134:16-23.
9. Mahoney AE, Peters L. The Mahoney pain scale: examining pain and agitation in advanced dementia. Am J Alzheimer Dis Other Demen 2008;23:250-61.
10. Lyketsos CG, Colenda CC, Beck C, Brock K, Drazinewycz MP, Kulurian DA, et al. Position statement of the American Association for Geriatric Psychiatry regarding principles of care for patients with dementia resulting from Alzheimer disease. Am J Geriatr Psychiatry 2008;16:561-73.
11. Husebo BS, Ballard C, Aarland D. Pain treatment of agitation in patients with dementia: a systematic review. Int J Geriatr Psychiatry 2011; published online 9 February.
12. Chinball JT, Tark RC, Harman B, Luddtba RA. Effect of acetycholinesterase on behavior, well-being, and psychotropic medication use in nursing home residents with moderate-severe dementia. J Am Geriatr Soc 2005;53:1921-9.
13. Kovach CR, Logan BR, Noonan PE, Schild AM, Sinar J, Simpson M, et al. Effects of the Serial Trial Intervention on discomfort and behavior of nursing home residents with dementia. Am J Alzheimer Dis Other Demen 2006;21:147-55.
14. Marhedi PL, Breuer B, Wallenstein S, Stegmann M, Bottomly G, Libow L. Opioid treatment for agitation in patients with advanced dementia. Int J Geriatr Psychiatry 2003;18:700-5.
15. Cohen-Mansfield J, Libin A. Assessment of agitation in elderly patients with dementia: correlations between informant rating and direct observation. Int J Geriatr Psychiatry 2004;19:881-91.
16. Cummings JL, Aarland D. Neuropsychiatric Inventory. NPI. Neurology 1994;44:2308-14.
17. American Geriatric Society Panel. The management of chronic pain in older persons. J Am Geriatr Soc 1998;46:635-51.
18. Husebo BS, Strand LI, Mo-Nilssen R, Husebo SB, Lyngjegren AE. Pain in older persons with severe dementia. Psychometric properties of the Mobilization Observation-Behaviour Intensity Dementia (MOBID-2) Pain Scale in a clinical setting. Scand J Caring Sci 2010;24:385-91.
19. Foslin MF, Foslin SE, McHugh PR. Mini mental-state—practical method for grading cognitive state of patients for clinicians. J Psychiatr Res 1975;1:57-63.
20. Sheikh K, Smith DS, Meade TW, Goldberg E, Brennan PJ, Kinsella G. Repeatability and validity of a modified activities of daily living (ADL) index in studies of chronic disability. Int Rehab Med 1979;1:51-8.
21. Cohen-Mansfield J, Libin A, Mark MS. Nonpharmacological treatment of agitation: a controlled trial of systematic individualized intervention. J Gerontol A Biol Sci Med Sci 2007;62:908-16.
22. Ballard C, Brown R, Fossey J, Douglas S, Bradley R, Hancock J, et al. Brief psychosocial therapy for the treatment of agitation in Alzheimer’s disease (the CALM-AD trial). Am J Geriatr Psychiatry 2009;17:726-33.
23. Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster randomised trials. BMJ 2004;328:702-8.
24. Vickers AJ, Altman DG. Analysing controlled trials with baseline and follow up measurements. BMJ 2001;323:1123-4.
25. Debertin WG, Duyken MW, Rampens SA, Feldman PD, Young CA, Hey DP, et al. Comparison of olanzapine and risperidone in the treatment of psychosis and associated behavioral disturbances in patients with dementia. Am J Geriatr Psychiatry 2005;13:722-30.
26. Brotad H, Arnes D, Snowdon J, Woodward M, Kwan J, Clarrette R, et al. A randomized placebo-controlled trial of risperidone for the treatment of agitation, aggression, and psychosis of dementia. J Clin Psychopharmacol 2003;23:143-4.
27. De Deyn PP, Ranthu R, Rasmussen A, Bocksberger JP, Dautzenberg PL, Eriksson S, et al. A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology 1995;53:899-901.
28. McCannery R, Warner J, Ilfts S, van Haselen R, Griffin M, Fisher P. The Hawthorne Effect: A randomized, controlled trial. BMC Med Res Methods 2007;7:30.
29. Livingston G, Johnston K, Katona C, Paton J, Lykecte GC. Systematic review of psychological approaches to the management of neuropsychiatric symptoms of dementia. Am J Psychiatr 2005;162:1996-2021.

Accepted: 14 May 2011
What is already known on this topic

Many people with dementia have painful conditions, which in people with impaired language and abstract thinking may manifest as agitation.

An estimated 180 000 people with dementia in the United Kingdom are prescribed antipsychotics for agitation.

What this study adds

A standardised protocol to treat pain in residents of nursing homes with moderate to severe dementia significantly improved agitation, aggression, and pain. Improved treatment of pain could help to reduce the unnecessary use of antipsychotics in people with dementia in nursing homes. Standardised assessment and treatment of pain should be an integral part of the clinical management pathway for people with dementia in nursing homes.

Tables

| Characteristics                                                                 | Control group (n=177 residents) | Intervention group (n=175 residents) |
|---------------------------------------------------------------------------------|---------------------------------|-------------------------------------|
| No of clusters*                                                                 | 27                              | 33                                  |
| Median (range) of patients per cluster                                          | 7 (3-10)                        | 6 (2-10)                           |
| Mean (range) age (years)                                                        | 87 (67-104)                     | 85 (65-101)                        |
| Women                                                                           | 131 (74)                        | 132 (75)                           |
| Prescribed drugs:                                                              |                                 |                                     |
| Antipsychotics                                                                  | 47 (27)                         | 43 (25)                            |
| Anxiolytics or hypnotics                                                        | 88 (50)                         | 80 (46)                            |
| Anti-dementia                                                                   | 44 (25)                         | 53 (30)                            |
| Opioid analgesics                                                               | 32 (18)                         | 35 (20)                            |
| Peripheral analgesics                                                           | 71 (40)                         | 75 (43)                            |
| Median (range) Cohen-Mansfield agitation inventory (scores 29-203)†             | 51 (39-114)                     | 53 (39-126)                        |
| Median (range) mini-mental state examination (scores 0-30)‡                     | 8 (0-20)                        | 7 (0-20)                           |
| Median (range) functional assessment staging (scores 1-7)§                      | 6 (4-7)                         | 6 (4-7)                            |
| Median (range) neuropsychiatric inventory—nursing home version (scores 1-144)¶  | 29 (0-97)                       | 32 (1-101)                         |
| Median (range) MOBID-2 pain scale (scores 0-10)**; pain ≥3                     | 3.0 (0-10); 98 (55)             | 4.0 (0-10); 103 (59)               |
| Median (range) activities of daily living (scores 0-20)††                      | 8.0 (0-20)                      | 7.00 (0-19)                        |

MOBID-2=mobilisation-observation-behaviour-intensity-dementia-2.

*Cluster defined as a single independent nursing home unit.
†Higher scores indicate more agitation (scores ≥39 usually accepted as clinically significant).
‡Higher scores indicate more cognitive impairment.
§Higher scores indicate more cognitive impairment.
¶Higher scores indicate more agitation.
**Higher scores indicate more pain (scores ≥3 accepted as clinically relevant).
††Higher scores indicate more activities of daily living.
### Table 2: Stepwise protocol for treatment of pain

| Step | Pain treatment at baseline | Study treatment | Dosage | No (%) of residents (n=175) |
|------|----------------------------|----------------|--------|-----------------------------|
| 1    | No analgesics, or low dose of paracetamol | Paracetamol (acetaminophen) | Maximum dose 3 g/day | 120 (69)* |
| 2    | Full dose of paracetamol or low dose morphine | Morphine | 5 mg twice daily; maximum dose 10 mg twice daily | 4 (2) |
| 3    | Low dose buprenorphine or inability to swallow | Buprenorphine transdermal patch | 5 µg/h, maximum dose 10 µg/h | 39 (22)† |
| 4    | Neuropathic pain | Pregabalin | 25 mg once daily; maximum dose 300 mg/day | 12 (7) |

*In nine participants an existing low dosage was increased.
†Dosage was increased in eight participants.
| Week | Control group Mean (SD) CMAI total score | Intervention group Mean (SD) CMAI total score | Effect of intervention on CMAI total† Estimate (95% CI) P value | Intracluster correlation coefficient‡ |
|------|-----------------------------------------|---------------------------------------------|-------------------------------------------------------------|-----------------------------------|
| 0    | 56.2 (16.1), n=177                      | 56.5 (15.2), n=175                         | ---                                                         | 0.162                             |
| 2    | 53.9 (17.0), n=161                      | 52.0 (19.5), n=158                         | −3.6 (−0.5 to −6.7)                                        | 0.022                             |
| 4    | 52.5 (16.3), n=160                      | 49.4 (19.0), n=148                         | −4.1 (−0.9 to −7.4)                                        | 0.012                             |
| 8    | 52.8 (16.8), n=157                      | 46.9 (18.7), n=147                         | −7.0 (−3.7 to −10.3)                                       | <0.001                            |
| 12   | 52.5 (16.0), n=152                      | 50.3 (20.3), n=142                         | −2.2 (0.1 to −6.4)                                         | 0.058                             |

*Baseline score as covariate and least squares weighted by number of patients within cluster; P value from multivariate test of intervention was 0.002, and cross effect between week and intervention was <0.001.
†Variable estimate by week of effect of intervention on CMAI score from estimated model.
‡Proportion of total variance between clusters, and measured within framework of ANCOVA.
Table 4 | Comparison of neuropsychiatric inventory-nursing home version (NPI-NH) total score between control and intervention (stepwise protocol for treatment of pain) groups using repeated measures analysis of covariance (ANCOVA)*

| Week | Intracluster correlation coefficient‡ | Mean (SD) NPI-NH total | Effect of intervention on NPI-NH total† | P value | Intracluster correlation coefficient‡ |
|------|--------------------------------------|------------------------|----------------------------------------|---------|--------------------------------------|
| 0    | 0.106                                | 31.4 (21.4), n=177     | 34.8 (21.9), n=175                     | —       | 0.106                                |
| 2    | 0.129                                | 26.1 (19.2), n=161     | 26.5 (20.3), n=158                     | -2.9 (0.03 to -5.9) | 0.052 | 0.129                                |
| 4    | 0.116                                | 26.0 (20.1), n=160     | 23.4 (20.0), n=148                     | -5.7 (-2.3 to -9.1) | 0.001 | 0.116                                |
| 8    | 0.157                                | 26.9 (20.7), n=157     | 21.0 (19.3), n=147                     | -9.0 (-5.5 to -12.6) | <0.001 | 0.157                                |
| 12   | 0.210                                | 28.0 (21.1), n=152     | 23.0 (20.0), n=142                     | -8.4 (-4.7 to -12.2) | <0.001 | 0.210                                |

*Baseline score as covariate and least squares weighted by number of patients within cluster; P values from multivariate test of intervention and cross effect between week and intervention were both <0.001.
†Variable estimate by week of effect of intervention on NPI-NH from estimated model.
‡Proportion of total variance between clusters, and measured within framework of ANCOVA.
Table 5 | Comparison of mobilisation-observation-behaviour-intensity-dementia-2 (MOBID-2) pain scale total score between control and intervention (stepwise protocol for treatment of pain) groups using repeated measures analysis of covariance (ANCOVA)*

| Week | Control group Mean (SD) | Intervention group Mean (SD) | Effect of intervention on MOBID-2 total† | P value | Intracluster correlation coefficient‡ |
|------|-------------------------|-------------------------------|-----------------------------------------|---------|--------------------------------------|
| 0    | 3.7 (2.5), n=163        | 3.8 (2.7), n=164              |                                          | 0.094   |                                      |
| 2    | 3.5 (2.4), n=159        | 2.9 (2.5), n=152              | −0.7 (−0.4 to −1.1)                     | <0.001  | 0.070                                |
| 4    | 3.3 (2.4), n=155        | 2.7 (2.2), n=146              | −0.8 (−0.4 to −1.2)                     | <0.001  | 0.059                                |
| 8    | 3.5 (2.6), n=154        | 2.3 (2.1), n=145              | −1.3 (−0.8 to −1.7)                     | <0.001  | 0.082                                |
| 12   | 3.5 (2.5), n=151        | 2.9 (2.6), n=140              | −0.8 (−0.3 to −1.2)                     | 0.001   | 0.139                                |

*Baseline score as covariate and least squares weighted by number of patients within cluster; P value from multivariate test of intervention was <0.001, and cross effect between week and intervention was 0.009.
†Variable estimate by week of effect of intervention on MOBID-2 from estimated model.
‡Proportion of total variance between clusters, and measured within framework of ANCOVA.
Figures

Fig 1 Flow of participants through trial

Fig 2 Cohen-Mansfield agitation inventory scores, with 95% confidence intervals, over study period