Interventions targeting pain or behaviour in dementia: a systematic review

Marjoleine JC Pieper, Annelore H van Dalen-Kok, Anneke L Francke, Jenny T van der Steen, Erik JA Scherder, Bettina S Husebø, Wilco P Achterberg

ABSTRACT

Background Both pain and challenging behaviour are highly prevalent in dementia, and multiple studies show that some of these behaviours may be correlated. Pain, especially in non-communicative patients, can cause challenging behaviour, and treatment of pain therefore may have an effect on behaviour. This review aims to provide a comprehensive overview of the current state of evidence regarding the effectiveness of interventions targeting pain on the outcome behaviour, and interventions targeting behaviour on pain, in dementia.

Method PubMed (MEDLINE), EMBASE, COCHRANE, CINAHL, PsychINFO and Web of Science were searched systematically. Studies were included if they focused on an intervention targeting a reduction in the person’s distress, pain, and/or behaviour, and included adults with a main diagnosis of dementia.

Results Of a total of 893 potentially relevant publications that were identified, 16 publications met the inclusion criteria and were eligible for further analysis; 6 studies focused on a pain intervention targeting behaviour, 1 study focused on a behavioural intervention targeting pain, and 9 studies focused on an intervention targeting both pain and behaviour.

Conclusion Available evidence suggests that (pain) interventions targeting behaviour, and (behavioural) interventions targeting pain are effective in reducing pain and behavioural symptoms in dementia.

Highlights

- Pain interventions targeting behaviour and behavioural interventions targeting pain are effective in reducing pain/discomfort, and behavioural symptoms, such as depression, agitation/aggression and anxiety, in dementia.
- Evidence is limited and interventions and outcomes are heterogeneous. Replication of the results is warranted and more large-scaled research into these complex interventions is desperately needed.
- This is the first systematic review that has combined the effectiveness of interventions targeting both pain and behaviour in dementia.

Keywords: Dementia, pain, behaviour, neuropsychiatric symptoms, non-pharmacological and pharmacological interventions.
BACKGROUND

Dementia is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical and neuropsychological functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement.\(^1\)

Next to cognitive dysfunction, neuropsychiatric symptoms are prominent in most patients during the disease. These symptoms include delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, night-time disturbances and appetite/eating disturbances. In patients with dementia up to 80-85% have one or more of these (clinically relevant) neuropsychiatric symptoms.\(^2-4\) Often, these symptoms are also referred to as challenging behaviour.\(^2-4\)

Pain is also highly prevalent in patients suffering from dementia. Epidemiologic studies have shown a very high prevalence of persistent pain, often exceeding 50% of community-dwelling older persons and up to 80% of nursing home residents.\(^5-10\) Behaviours, such as verbalizations/vocalizations (e.g. sighing, moaning, calling out, verbal abuse), noisy breathing, facial expressions (e.g. grimacing, frowning), restless or strained body expressions (e.g. rigid, tense, guarding, fidgeting, increased pacing/rocking), agitation/aggressiveness and resistance to care, are frequently the most prominent, or even the only feature of pain.\(^11-15\) These behaviours are, however, often not recognized as a symptom of pain, but frequently interpreted as a symptom of the dementia. As the prevalence of dementia will rise exponentially within the next few years, behaviours like pain and neuropsychiatric symptoms, will consequently rise exponentially as well. To date, these behaviours already have a tremendous impact on the quality of life in patients with dementia, on caregiver-burden and earlier institutionalizations, and are furthermore associated with a rapid progression of cognitive & functional decline.\(^16,17\) So, this impact will only increase, and will affect patients, caregivers and society.

In literature, it has been shown consistently that patients with dementia are undertreated for pain.\(^18-22\) In addition, research also indicates that pharmacological interventions (analgesic medication), as well as non-pharmacological comfort measures for pain and behavioural disturbances are underutilized.\(^23-25\) The main explanation for this under-detection and under-treatment of pain is, that people with dementia report pain less often, less spontaneously, and at a lower intensity than those without a cognitive impairment do.\(^26\) Generally, the more severe the dementia, the less capable patients become of being able to verbally express their pain or discomfort.\(^27\) Because they become less capable of verbally expressing their pain or discomfort, important information
becomes inaccessible for caregivers. Before specific therapies can be considered, a comprehensive assessment is therefore essential. A thorough clinical evaluation is likely to highlight pharmacological and non-pharmacological opportunities for treatment of both the behavioural symptoms and pain. A recent study of Cohen-Mansfield showed that this ‘recognition of pain’ is one of the barriers for caregivers. And because of this barrier, people with dementia are more likely to receive psychotropic medications rather than adequate pain treatment, despite all the adverse effects of these psychotropic drugs (e.g. drowsiness, depressed mood and falls).

Pharmacological interventions traditionally have had an important role in influencing challenging behaviour, but as mentioned above they have serious side effects and a potential harmful impact on the quality of life. Relatively recent research demonstrated the efficacy of pain treatment, in order to reduce behavioural symptoms in dementia. An increasing amount of evidence has shown that psychosocial- and behavioural interventions are effective in reducing challenging behaviours, but the connection with pain - as a cause of underlying pain or distress - has been made by only a few studies, and very little is known about the influence of these behavioural interventions on pain. How pain and challenging behaviour co-occur is still unclear, but multiple studies have shown they are strongly correlated. Although research on the ‘recognition of pain in dementia’ is receiving more attention, it is still unclear which interventions are effective in reducing pain and behavioural symptoms in dementia at the same time.

Therefore, this review aims to provide a comprehensive overview of the current state of evidence regarding the effectiveness of interventions targeting pain on the outcome behaviour, and interventions targeting behaviour on pain in dementia.
METHODS

Search
A systematic search of the literature was conducted in March 2012. Databases searched included PubMed (MEDLINE), EMBASE, COCHRANE, CINAHL, PsychINFO and Web of Science. Text words and MESH terms for dementia, intervention(s), pain/discomfort and challenging or disruptive behaviour were combined to identify relevant studies (see Appendix A). Additional studies were identified by hand searching of reference lists, by contacting authors of included studies and experts. Duplicates were removed and subsequently, a two-step inclusion process was conducted; (1) screening on the basis of title, references and abstracts, and (2) screening based on full-text papers. Two reviewers (AvD/MP) independently conducted the searches as detailed above and identified all relevant published studies. The date and time of each search were documented, together with the details of the version of the database used. The reviewers’ selections of studies were compared and consensus between the two reviewers was achieved for the list of ‘included studies’ (see Tables 2-4). In case of disagreement, a third reviewer (WA/AF/JS) was asked for advice to reach consensus.

Inclusion- and exclusion criteria
Studies were included if they met the following criteria:
1) the study included adults or elderly patients with a main diagnosis of dementia (e.g. Alzheimer’s disease, Vascular dementia, Lewy body disease, Frontotemporal dementia);
2) focused on an intervention (e.g. (pain) medication, analgesics, drug therapy, movement, snoezelen, aromatherapy, music therapy, reminiscence, complementary therapies) targeting a reduction in the person’s pain or distress (chronic or acute), and/or behaviour (Behavioural and Psychological Symptoms of Dementia (BPSD), wandering, neuropsychiatric symptoms; e.g. aggression, apathy, depression, agitation), and
3) included outcome measurements on pain and/or behaviour in dementia. Specific and existing (observation or self-rating) scales, questionnaires, or items that were part of an existing instrument measuring pain, discomfort, and/or behaviour were eligible for inclusion.

Studies were excluded if the study:
1) involved participants with a diagnosis of dementia resulting from Parkinson’s disease, Huntington’s disease, AIDS dementia complex, Multiple Sclerosis and Creutzfeldt-Jakob disease;
2) focused on an intervention targeting behaviour but did not measure pain or distress, either focused on an intervention targeting pain or distress but did not measure behaviour;
3) focused on infants or children, and
4) was not based on primary empirical data, or was published as an abstract, editorial, commentary, letter or a study protocol (although these publications were screened for possible relevant references that were missed during the initial search).

No language restrictions were used.

**Quality assessment**

The final list of studies was ranked for quality according to the Mixed Methods Appraisal Tool (MMAT-version 2011). The MMAT is a recently developed tool that has demonstrated an intra-class correlation of 0.8 based on a pilot testing in 2009 and has proven to be effective and practical for the quality assessment of a mixed methods review. Four criteria for appraising quantitative and qualitative studies are included in the MMAT (see Table 1). Each study type is judged within its methodological domain. For example, appraising the quality of a cohort study involves the ‘non-randomised’ set. For qualitative and quantitative studies, the score is the number of criteria met, divided by four. For mixed methods studies, both the appropriate section for the quantitative component and the qualitative component are used, and the overall score is the lowest score of the quantitative and qualitative study components. Scores of the MMAT vary from 25% (one criteria met) to 100% (all criteria met). Disagreements in MMAT-scores between the two reviewers (MP/AvD) were resolved by discussion.

**Data extraction**

A data extraction form was designed and tested before the two reviewers (MP/AvD) independently extracted data on the: (1) characteristics of the study samples (e.g. sample size, age, dementia stage); (2) characteristics of the pain- or behavioural-interventions (e.g. duration, length, dosages used); (3) outcome measures of interest (on pain and behaviour), and (4) findings of the included studies.
Interventions targeting pain or behaviour in dementia: systematic review
**Table 1. Criteria Mixed Methods Appraisal Tool (MMAT), by Pluye et al. (2011)**

<table>
<thead>
<tr>
<th>Types of mixed methods study components or primary studies</th>
<th>Methodological quality criteria (see tutorial for definitions and examples)</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening questions (for all types)</td>
<td>Are there clear qualitative and quantitative research questions (or objectives*), or a clear mixed methods question (or objective*)?</td>
<td></td>
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<tr>
<td></td>
<td>Do the collected data allow address the research (objective)? E.g., consider whether the follow-up period is long enough for the outcome to occur (for longitudinal studies or study components).</td>
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</tr>
<tr>
<td></td>
<td><strong>Further appraisal may be not feasible or appropriate when the answer is ‘No’ or ‘Can’t tell’ to one or both screening questions.</strong></td>
<td></td>
</tr>
<tr>
<td>1. Qualitative</td>
<td>1.1 Are the sources of qualitative data (archives, documents, informants, observations) relevant to address the research question (objective)?</td>
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</tr>
<tr>
<td></td>
<td>1.2 Is the process for analyzing qualitative data relevant to address the research question (objective)?</td>
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<td></td>
<td>1.3 Is appropriate consideration given to how finding relate to the context, e.g. the setting, in which the data were collected?</td>
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<tr>
<td></td>
<td>1.4 Is appropriate consideration given to how findings relate to researchers’ influence, e.g., through their interactions with participants?</td>
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<tr>
<td>2. Quantitative randomised controlled (trials)</td>
<td>2.1 Is there a clear description of the randomisation (or an appropriate sequence generation)?</td>
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<td></td>
<td>2.2 Is there a clear description of the allocation concealment (or blinding when applicable)?</td>
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<tr>
<td></td>
<td>2.3 Are there complete outcome data (80% or above)?</td>
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<tr>
<td></td>
<td>2.4 Is there low withdrawal/drop-out (below 20%)</td>
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<tr>
<td>3. Quantitative non-randomised</td>
<td>3.1 Are participants (organizations) recruited in a way that minimizes selection bias?</td>
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<tr>
<td>3.2 Are instruments appropriate (clear origin, or validity known, or standard instrument; and absence of contamination between groups when appropriate) regarding the exposure/intervention and outcomes?</td>
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<tr>
<td>3.3 In the groups being compared (exposed vs. non-exposed; with intervention vs. without; cases vs. controls), are the participants comparable, or do researchers take into account (control for) the difference between these groups?</td>
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</tr>
<tr>
<td>3.4 Are there complete outcome data (80% or above), and, when applicable, an acceptable response rate (60% or above), or an acceptable follow-up rate for cohort studies (depending on the duration of follow-up)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Quantitative descriptive</th>
<th>4.1 Is the sampling strategy relevant to address the quantitative research question (quantitative aspect of the mixed methods question)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2 Is the sample representative of the population understudy?</td>
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<tr>
<td>4.3 Are measurements appropriate (clear origin, or validity known, or standard instrument)?</td>
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<tr>
<td>4.4 Is there an acceptable response rate (60% or above)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Mixed methods</th>
<th>5.1 Is the mixed methods research design relevant to address the qualitative and quantitative research questions (or objectives), or the qualitative and quantitative aspects of the mixed methods question (or objective)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.2 Is the integration of qualitative and quantitative data (or results*) relevant to address the research question (objective)?</td>
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</tr>
<tr>
<td>5.3 Is appropriate consideration given to the limitations associated with this integration, e.g., the divergence of qualitative and quantitative data (or results*) in a triangulation design?</td>
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</table>

Criteria for the qualitative component (1.1. to 1.4) and appropriate criteria for the quantitative component (2.1 to 2.4, or 3.1 to 3.4, or 4.1 to 4.4), must be also applied.

* These two items are not considered as double-barreled items since in mixed methods research, (1) there may be research questions (quantitative research) or research objectives (qualitative research), and (2) data may be integrated, and/or qualitative findings and quantitative results can be integrated.
Chapter 3

RESULTS

The initial literature search yielded 893 hits: 570 from PubMed (MEDLINE), 139 EMBASE, 52 from CINAHL, 37 from PsycINFO, 67 from COCHRANE, and 28 from Web of Science. After checking for duplicates, there were 743 unique hits. An additional 35 publications were identified during the course of the search through others sources, mainly by reference checking. Careful analysis of the titles abstracts and references resulted in 167 full-text papers that were screened for inclusion. Sixteen studies met the inclusion criteria, and were included in the review (see Figure 1 and Tables 2-4); six studies focused on a pain intervention targeting behaviour, one study focused on a behavioural intervention targeting pain and nine studies focused on an intervention targeting both pain and behaviour. The majority of studies took place in the USA (twelve out of sixteen studies) and were conducted in nursing homes or in long-term care facilities (thirteen out of sixteen studies). Although the search was conducted from the inception of the databases until March 2012, the included studies were published within the limited range of 1998-2011. Characteristics of the included studies are presented in Tables 2-4.

Quality assessment

Quality assessment scores using the MMAT were calculated for the sixteen included studies in this review. An overview is shown in Tables 2-4. There was great variety in research designs and in MMAT-scores; scores ranged from 25% (one criteria met) – 100% (all criteria met).

The quality, as reported within the MMAT section ‘quantitative randomised controlled trials’, ranged from 50-100%. Only the RCT performed by Kovach et al. (2006) obtained a score of 100%. The other RCTs scored 75% or lower, due to limitations in terms of an incomplete or lacking description of the randomisation, allocation concealment, and/or dropout rate. Within the MMAT section ‘quantitative non-randomised’, the quality as reported ranged from 50-100%. A cohort study performed by Dunn et al. (2002) obtained a score of 100%. The quality of the remaining studies was limited in terms of the recruitment of participants, comparable groups, and complete outcome data. The studies performed by Meland (2009) and Passmore (2011) were each assigned a score of 25% within the MMAT section ‘quantitative descriptive’. The quality of both studies was limited in terms of the sampling strategy, representativeness of the study population, and appropriateness of the measurements used.

No relevant mixed-methods or qualitative studies were identified.
Records identified through database searching (n = 893)

Additional records identified through other sources (n = 35)

Records after duplicates removed (n = 778)

Records screened on Title (n = 778)

Records excluded (n = 450)

Reasons for exclusion:
- No intervention targeting pain and/or behaviour (114)
- No outcome measurements on pain and/or behaviour (30)
- No main diagnosis of dementia (29)
- Not published as primary empirical data (4)
- Duplicates (2)

Records screened on Abstract (n = 328)

Records excluded (n = 179)

Reasons for exclusion:
- No intervention targeting pain and/or behaviour (115)
- Not published as primary empirical data (17)
- No outcome measurements on pain and/or behaviour (12)
- No main diagnosis of dementia (5)
- No adults/elderly population (2)

Full-text articles assessed for eligibility (n = 167)

Full-text articles excluded (n = 151)

Reasons for exclusion:
- No intervention targeting pain and/or behaviour (115)
- Not published as primary empirical data (17)
- No outcome measurements on pain and/or behaviour (12)
- No main diagnosis of dementia (5)
- No adults/elderly population (2)

Studies included in qualitative synthesis (n = 16)

Figure 1. Flow diagram of the inclusion of studies.
<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Design &amp; methodological-score (MMAT)</th>
<th>Sample</th>
<th>Intervention</th>
<th>Outcome measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buffum et al., 2004, USA</td>
<td>RCT</td>
<td>MMAT-score: 75%</td>
<td>N=39, Age: mean 85.7 years (range 67-101), Nursing home residents.</td>
<td>Period: 4 weeks, crossover after 2 weeks without a washout period.</td>
<td>Primary: DS-DAT Secondary: -</td>
</tr>
<tr>
<td>Chibnall et al., 2005, USA</td>
<td>RCT</td>
<td>MMAT-score: 75%</td>
<td>N=25, Age: mean 85.9 (SD=7.4), Nursing home residents.</td>
<td>Period: 8-weeks, crossover after 4 weeks with 1 week washout period.</td>
<td>Primary: Dementia Care Mapping (DCM) Secondary: CMAI, use of psychotropic medications.</td>
</tr>
<tr>
<td>Elliott and Horgas, 2009, USA</td>
<td>ABAB-single case-design</td>
<td>MMAT-score: 75%</td>
<td>N=3, Age: mean 85 (SD=unknown), Participants at home.</td>
<td>Period: daily for 24 days.</td>
<td>&quot;Pain behaviours&quot;: guarding, bracing, stopping, rigidity, rubbing, grimacing, sighing/nonsensical, shifting and vocalizations: score with Noldes the Observer behaviour analysis software.</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>MMAT-score</td>
<td>N/Age</td>
<td>Type/Cause of Pain</td>
<td>Intervention</td>
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<tr>
<td>Husebo et al., 2011b, Norway</td>
<td>RCT</td>
<td>MMAT-score: 75%</td>
<td>N=352, Age: I: mean 85 years (range65-101), C: 87 years (range 67-104), Nursing home residents.</td>
<td>Dementia: Moderate-severe dementia according to the DSM-IV criteria. Type/Cause of Pain: not specified, excluded severe injury</td>
<td>Intervention: participants received individual daily treatment of pain, according to the stepwise protocol, with paracetamol (acetaminophen), morphine, buprenorphine transdermal patch, or pregabalin. Control: usual care and treatment</td>
</tr>
<tr>
<td>Manfredi et al., 2003, USA</td>
<td>Placebo-contr. cross-over trial</td>
<td>MMAT-score: 50%</td>
<td>N=47, Age: mean 86.7 years (SD=7.0), Nursing home residents.</td>
<td>Dementia: Advanced stage, MMSE &lt; 21. Type/Cause of Pain: not specified, excluded obviously painful conditions.</td>
<td>Intervention: opioid treatment for agitation: 4 weeks long-acting opioid (20 mg oxycodone, or 20 mg morphine). Control: 4 weeks placebo</td>
</tr>
<tr>
<td>Passmore, 2011, Canada</td>
<td>Case-report</td>
<td>MMAT-score: 25%</td>
<td>N=1, Age: 104, Nursing home resident.</td>
<td>Dementia: Alzheimer’s disease, severe stage. Type/Cause of Pain: hip replacement hardware and degenerative joint changes to osteoarthritis. No acute pain.</td>
<td>Intervention: extended care needs after fall, resulting in hip # + surgery. Sublingual sufentanil for incident pain and dementia related agitation: 50mg/ml, start at 5 mg/0.1ml. Management of pain, incl. regular dosing of acetaminophen was ineffective in reducing agitation during care, and a disappointing response to pharmaco-therapy.</td>
</tr>
<tr>
<td>Author, year, country</td>
<td>Design &amp; methodological score (MMAT)</td>
<td>Sample</td>
<td>Group</td>
<td>Outcome measures</td>
<td>Findings</td>
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<tr>
<td>Park, 2010, South Korea</td>
<td>Quasi-experimental MMAT-score: 75%</td>
<td>N=15, Age: &gt; 60 years, Participants living at home.</td>
<td><strong>Period:</strong> 4-week cycle. <strong>Intervention:</strong> effect of music on pain: preferred music, 30 min., 2 days a week for 2 weeks, followed by no music 2 weeks (repeated once).</td>
<td>Primary: M-PADE Secondary: APMP; music preference at baseline, M-CMAI (modified CMAI used to measure the peak agitation, no severity) Control: -</td>
<td>Mean pain levels after listening to music were significantly lower than before listening to music. However, no significant effects were found for mean pain levels 'while listening and during listening' to music.</td>
</tr>
</tbody>
</table>
Table 4. Interventions targeting both PAIN and BEHAVIOUR (part I)

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Design &amp; methodological-score (MMAT)</th>
<th>Sample</th>
<th>Group</th>
<th>Outcome measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapman and Toseland, 2007, USA</td>
<td>RCT, 2x2 partial cross-over</td>
<td>N=118, Age: AICTs: mean 84.82 years (SD=6.804) and usual care: mean 88.00 years (SD=6.661), Nursing home residents.</td>
<td>Period: 8-weeks, 5 times a meeting during period.</td>
<td>CMAI, Cornell Depression-scale, FLACC (behavioural pain scale), PAINNAD</td>
<td>Effective in reducing pain. The AICTs compared to usual care, were effective in reducing agitated behaviour, but not depression.</td>
</tr>
<tr>
<td></td>
<td>MMAT-score: 50%</td>
<td></td>
<td>Intervention: Effectiveness of Advanced Illness care teams (AICTs) on 4 domains: medical, meaningful activities, psychological, and behavioural.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Control: Usual care, after 8-weeks they crossed-over to the treatment condition.</td>
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<td></td>
</tr>
<tr>
<td>Cipher et al., 2007, USA</td>
<td>Cohort</td>
<td>N=44, Age: mean 82 years (SD=9.3), Long-term care residents.</td>
<td>Period: 5-weeks</td>
<td>Geriatric Multidimensional Pain and Illness Inventory (GMPI), GDS-depression scale, PRADLI (ADL), NCSE, GLDS</td>
<td>Study 1: significant reduction in depression, and significant increase in most activities of daily living, significant reductions in intensity, frequency and duration of their behavioural disturbances.</td>
</tr>
<tr>
<td></td>
<td>MMAT-score: 50%</td>
<td></td>
<td>Intervention: Impact of Multimodal Cognitive- Behavioural Therapy (MCBT) for the treatment of pain, depression, behavioural dysfunction, functional disability and health care utilization: 8 sessions over 5 week period in residents living in LTC, chronic/daily pain, mild-moderate dementia diagnosis, at least 1 psychiatric disorder that involved depression, anxiety, and/or behavioural disturbances.</td>
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<td></td>
<td>Control: -</td>
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</tbody>
</table>

Type/Cause of Pain: not specified, excluded serious emergent medical conditions (e.g. decubitis ulcers)
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>MMAT-score</th>
<th>Sample Size</th>
<th>Age</th>
<th>Dementia</th>
<th>Type/Cause of Pain</th>
<th>Period</th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunn et al., 2002, Canada</td>
<td>Exp. design</td>
<td>100%</td>
<td>N=16, Age: 81 years (SD=7), (range 67-93), Residents of an urban care facility.</td>
<td></td>
<td>Dementia: Advanced stage, not further specified.</td>
<td>Type/Cause of Pain: not specified.</td>
<td>Period: observation of 4 sessions of 2 different methods.</td>
<td>Intervention: Bathing methods; conventional tub bath and a modification of the bed bath, Thermal Bath.</td>
<td>Control: -</td>
</tr>
<tr>
<td>Hodgson and Andersen, 2008, USA</td>
<td>RCT, cross-over trial</td>
<td>75%</td>
<td>N=21, Age: Group 1: mean 87.2 years (SD=7.8), Group 2: mean 88.6 years (SD=8.6), Nursing home residents.</td>
<td></td>
<td>Dementia: Mild-moderate stage, according to the FAST criteria.</td>
<td>Type/Cause of Pain: not specified, excluded history of deep vein thrombosis, open foot wounds, bile or kidney stones, fever or foot fractures.</td>
<td>Period: 8-weeks</td>
<td>Intervention: The first group received 4 weeks of weekly reflexology treatments (30 min.) followed by 4 weeks of a control condition of friendly visits (30 min.).</td>
<td>Control: The second group received 4 weeks of friendly visits followed by 4 weeks of reflexology.</td>
</tr>
<tr>
<td>Kovach et al., 1999, USA</td>
<td>Cohort</td>
<td>50%</td>
<td>N=104, Age: mean 85 years (range 46-100), Nursing home residents.</td>
<td></td>
<td>Dementia: Probable Alzheimer's disease, multi-infarct dementia or unknown aetiology. Dementia severity not specified.</td>
<td>Type/Cause of Pain: physical causes for discomfort; infections, acute illness, chronic conditions</td>
<td>Period: 1-year.</td>
<td>Intervention: dementia patients unable to communicate unmet needs, and exhibited sign or symptoms that commonly indicate the presence of physical pain or affective discomfort were treated with the ADD-protocol. The contained pain assessment, drug behavioural treatments, policy development, staff competencies, education programming, and quality improvement.</td>
<td>Control -</td>
</tr>
</tbody>
</table>

The summed frequencies of all agitated behaviours was significantly less for the Thermal Bath, than the tub bath. This overall effect was greater in men than women, and in one particular behaviour: shivering. All participants, except one, showed fewer total agitated behaviours in the Thermal Bath, than the Tub bath condition.
<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>Design &amp; methodological-score (MMAT)</th>
<th>Sample</th>
<th>Group</th>
<th>Outcome measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kovach et al., 2006, USA</td>
<td>RCT</td>
<td>MMAT-score: 100%</td>
<td>N=114, Age: mean 86.6 years (SD=6.91), Residents of long-term care facilities. Dementia: Moderate-severe stage, according to the FAST stage 6 or 7 and the MMSE: mean 7.81 (SD=6.20). Type/Cause of Pain: not specified, overall discomfort.</td>
<td>Period: 4-weeks Intervention: treatment according to the Serial Trial Intervention for unmet needs in people with late-stage dementia. Control care as usual</td>
<td>DS-DAT, BEHAVE-AD</td>
</tr>
<tr>
<td>Meland, 2009, USA</td>
<td>Case series</td>
<td>MMAT-score: 25%</td>
<td>N=6, Age: 68-74-79-82-86-91 years, Nursing home residents. Dementia: Diagnosis of dementia, moderate-severe stage according to the MMSE &lt;20. Type/Cause of Pain: stomach discomfort, leg/shoulder pain, arthritis.</td>
<td>Period: 4-weeks Intervention: effect of 20 min. Reiki sessions, (2x week) on pain and anxiety. Control -</td>
<td>Behavioural changes documented with observational surveys used by an activities therapist &amp; recreational therapist, as well as family members. Blood pressure/heart rate before &amp; after session. Wong-Baker Smiley Face Scale; general well-being &amp; pain</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>MMAT-score</td>
<td>Sample Size</td>
<td>Age</td>
<td>Type/Cause of Pain</td>
</tr>
<tr>
<td>--------------------------------</td>
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<tr>
<td>Sloane et al., 2004, USA</td>
<td>RCT</td>
<td>75%</td>
<td>N=73</td>
<td>I: 86.0 (SD=8.6), C: 86.9 (SD=6.1), Nursing home residents.</td>
<td>Period: 12-weeks, crossover between PC and TB method after 6 weeks.</td>
</tr>
<tr>
<td>Watson et al., 1998, USA</td>
<td>RCT Cross-over design</td>
<td>50%</td>
<td>N=25</td>
<td>Age: 83.2 (range 72-95), Nursing home residents.</td>
<td>Period: 6-week program A, 2 weeks washout, 2 weeks program B</td>
</tr>
</tbody>
</table>
**(Pain) Interventions targeting behaviour**

Six studies were identified as a pain intervention targeting behaviour in dementia (Table 2); three RCTs, one ABAB single-case design, one pseudo-RCT; placebo-controlled, double-blinded crossover trial and one case-report. All studies focused on pharmacological treatment (use of pain medication) and its effect on behaviour. Five out of six studies showed a positive effect of pain medication on reducing challenging or disruptive behaviour in dementia. Of the six studies identified, one study used an individually tailored and stepwise protocol for the treatment of pain and behaviour. The other five studies examined the effects of fixed dosages of pain medication on behaviour.

Manfredi et al. (2003) performed a placebo-controlled, double-blinded crossover trial to evaluate if fixed dosages of opioids (oxycodone or morphine) could reduce agitation in patients with advanced dementia. The participants had all previously received antipsychotic medications with unsatisfactory outcomes with regard to agitation. Each patient entered a 4-week placebo phase, followed by a 4-week treatment phase to avoid confounding effects from opioid withdrawal. Because of this design, randomisation of the treatment order was not possible. Only 25 out of the 47 included patients completed the trial. Medication was administered as 10 mg oral oxycodone twice a day, or as 20 mg morphine once a day for participants who were unable to swallow. The (per protocol) analysis of agitation, using the Cohen-Mansfield Agitation Inventory (CMAI), showed no significant difference between the placebo and treatment phases. However, subgroup analysis of 13 patients over the age of 85 years revealed a statistically significant reduction in agitation at the end of the opioid treatment phase. There was no difference in sedation or use of as-required antipsychotic medication between the two phases of the study. A case-report conducted by Passmore (2011) also showed similar positive findings of low dose opioid use (sublingual sufentanil) on agitation in a 104-year old patient with dementia.

Buffum et al. (2004) evaluated the efficacy of regularly scheduled analgesic treatment for discomfort in 39 people with moderate to severe dementia in a 4-week placebo-controlled crossover study. Participants with a diagnosis associated with pain (e.g. degenerative joint disease, osteoporosis, fractures, back pain, skin ulcer), as assessed by chart documents, and unable to request pain medication, were randomly assigned to receive either 650 mg/day acetaminophen (paracetamol) as needed and a placebo administered four times per day, or placebo as needed and 650 mg acetaminophen (paracetamol) four times per day, for a period of 2 weeks; after 2 weeks participants switched to the other treatment arm. Regularly scheduled, fixed dosages of acetaminophen did not decrease discomfort, as measured with the Discomfort Scale - Dementia of the Alzheimer Type (DS-DAT).
Treatment with acetaminophen (paracetamol) was also tested in a RCT by Chibnall et al. (2005)\textsuperscript{33}, which included 25 people with moderate to severe dementia from two nursing homes. Patients were randomly assigned to a control group, or to an intervention consisting of acetaminophen (3000 mg/day) for 4 weeks, and a 4-week placebo phase. Between the two phases there was a 1-week washout period. Significant improvement in activities, as measured with the Dementia Care Mapping (DCM), was reported in patients who received acetaminophen compared to those in the placebo group. More patients participated in media-engagement, work-like activities and social interaction, and in addition they experienced less unattended distress when they received acetaminophen, than when they received placebo. No reduction was identified in agitation, as measured with the Cohen-Mansfield Agitation Inventory (CMAI). The findings in a pilot study, involving three patients, performed by Elliott and Horgas (2009)\textsuperscript{53}, indicate also a positive effect of regular scheduled acetaminophen (1300 mg every 8 hours) on reducing pain behaviours (e.g. guarding, bracing, grimacing, vocalizations) in older adults with dementia. In a within-subject ABAB withdrawal design over a period of 24 days, acetaminophen use reduced pain behaviours associated with musculoskeletal pain. During the treatment phase, they decreased in duration and frequency relative to control and baseline, and increased again when the treatment was withdrawn.

The largest and most comprehensive study is performed by Husebo et al. (2011).\textsuperscript{34} They conducted a cluster RCT to evaluate a stepwise pain treatment protocol in 352 people with moderate to severe dementia and significant behavioural symptoms. Patients from 18 Norwegian nursing homes were cluster-randomised to receive either usual treatment (control group) or an 8-week stepwise protocol of analgesic administration, with medication choice depending on prior treatment and assessment of pain. This systematic approach to the management of pain significantly reduced agitation in residents of nursing homes with moderate-severe dementia. An overall statistically significant improvement in agitation (as measured with the CMAI), neuropsychiatric symptoms (measured with the Neuropsychiatric Inventory-Nursing Home version (NPI-NH)), and pain (measured with the Mobilization-Observation-Behaviour-Intensity-Dementia (MOBID-2) Pain Scale) was revealed for the intervention group compared to control group (usual care). Furthermore, patients in the intervention group showed worsening of symptoms during the 4-week withdrawal phase compared with those who received usual care.\textsuperscript{34}

**(Behavioural) Interventions targeting pain**

We considered studies as being a ‘behavioural’ intervention if they focused on pharmacological or non-pharmacological interventions, and had a pain outcome measurement (e.g. self-reports on pain or observation-scales like the PACSLAC, PADE,
PAINAD, CNPI, MOBID-2). We found one behavioural (non-pharmacological) intervention study targeting pain in dementia (Table 3): a small quasi-experimental study investigating the effect of music on pain, in home-dwelling patients with dementia.55 A modification of the original Pain Assessment for the dementing elderly (PADE), the M-PADE, was used to measure pain, and included only the first part of the original PADE, ‘the physical signs’. Furthermore, the 1-4 scale was collapsed into ‘pain presence’ or ‘no pain’. Fifteen patients listened to their preferred music for 30 minutes before peak agitation time (measured with a modification of the CMAI at baseline, the M-CMAI), for 2 days a week in a period of 2 weeks, followed by no music for 2 weeks. This process was repeated once. No significant reduction in pain was found while listening to the music, but pain levels were reduced after listening to the music compared to baseline. No studies on pharmacological interventions targeting behaviour (e.g. treatments with antipsychotics or anti-depressants) that also measured pain were identified.

**Interventions targeting both pain and behaviour**

A total of nine studies were identified as interventions targeting both pain and behaviour in dementia (Table 4, part I and II): five RCTs, two cohorts, one experimental design and one case-report. The interventions described in the literature may target the patient (e.g. reflexology, Reiki, rocking chair therapy, cognitive behavioural therapy, physical care)\(^{47,49-52,56}\), the caregiver/caregivers (e.g. multidisciplinary AiCT’s, ADD-protocol)\(^{44,46,54}\), and/or the environment (education and stepwise approach of challenging behaviour; STI-protocol).\(^{44}\)

An intervention targeting the patient was performed by Hodgson and Andersen (2008).\(^{47}\) They conducted a randomised crossover trial, involving 21 patients, to evaluate the efficacy of reflexology in patients with mild to moderate dementia. Participants received a 30-minute reflexology session weekly for 4 weeks at the same time, or weekly a friendly visit by a certified reflexologist. The study tested whether a weekly reflexology intervention contributed to the patient’s outcomes of reduced physiologic distress, reduced pain, and improved affect. Comparison of the outcome measures between the two conditions demonstrated a significant decline in pain (as measured with the Checklist of Nonverbal Pain Indicators; CNPI), and physiological distress (as measured with salivary Alfa-Amylase; sAA). No significant improvements in observed affect were demonstrated, only a modest improvement in sadness (measured with the Apparent Affect Rating Scale; AARS).

Non-pharmacological interventions for pain management overlap somewhat with interventions for psychological and behavioural symptoms.\(^{62}\) Pain is associated with mood disturbance and often co-occurs with depression and/or anxiety.\(^{42,63}\) A study
performed by Cipher et al. (2007)\textsuperscript{52} suggests that a Multimodal Cognitive-Behavioural Therapy (MCBT) tailored for long-term care residents with pain and dementia, reduces pain, depression, and behavioural disturbance. Similar findings are reported in a study conducted by Watson et al. (1998).\textsuperscript{50} They performed a crossover trial in 25 nursing home residents with dementia and behaviour problems, to evaluate rocking chair therapy and its effect on psychosocial well being (e.g. depression/anxiety, use of pain medication). Significant, but small reductions were found on depression/anxiety, irritability, withdrawal, and disorientation (as measured with the Multidimensional Observation Scale for Elderly Subjects (MOSES)), and in PRN pain medication use in response to rocking. No significant reduction was found on agitation (as measured with the CMAI) in response to rocking. A series of case-reports showed some limited benefits of 20 minutes Reiki-sessons for 2 weeks, on pain and anxiety in patients with moderate to severe dementia.\textsuperscript{55}

Two studies focused on behavioural interventions targeting the physical care of a patient. They evaluated its effect on pain, discomfort, agitation, and aggression. Sloane et al. (2004)\textsuperscript{49} showed in a randomised controlled trial of 73 patients with dementia and agitation during bathing, that person-centred showering and the towel bath method are effective methods in reducing agitation, aggression, and discomfort. Dunn et al. (2002)\textsuperscript{51} reported similar findings in their trial.

Several studies reported findings of interventions that target the patient, the caregiver(s) and/or the environment, and utilized a combination of non-pharmacological treatments along with pharmacological treatments, as well as multidisciplinary approaches.\textsuperscript{44,46,54} Kovach et al. (1999)\textsuperscript{54} developed the Assessment and Treatment of Discomfort (ADD)-protocol for people with late-stage dementia, and tested this protocol in a cohort of 104 nursing home residents. A significant decrease in discomfort (measured with the DS-DAT) was found, and an increase of non-pharmacological ‘comfort’ interventions as well as an increase in scheduled analgesics. The ADD-protocol was further developed into the Serial Trial Intervention (STI)\textsuperscript{44}, and was then tested in a 4-week double-blind RCT involving 114 nursing home residents with moderate to severe dementia and behavioural symptoms. Patients were randomly assigned to either a stepped-care treatment programme - the ‘Serial Trial Intervention’ (STI), or a control programme of usual care. Following assessment of physical and affective factors, patients in the STI group initially received non-pharmacological ‘comfort’ treatments based on principles of person-centred care. If symptoms did not improve by at least 50%, the patient received as-required prescription of an analgesic. The intervention group had significantly reduced levels of discomfort (measured with the DS-DAT) compared to patients in the control group, as well as improved behavioural symptoms on the
nurse-administered Visual Analogue Scale (VAS), and pharmacological treatments: 46% of the patients in the intervention group received pharmacological pain treatment, compared to only 3% of the patients in the control group. No significant improvements were found on the Behavioural Pathology in Alzheimer’s Disease Scale (BEHAVE-AD). Another study, performed by Chapman and Toseland (2007)\textsuperscript{46}, showed similar results; advanced illness care teams (AiCTs) were effective in reducing pain (measured with the Pain Assessment IN Advanced Dementia (PAINAD) scale) and agitated behaviour (measured with the CMAI), but were not effective in reducing depression (measured with the Cornell Depression-scale).
DISCUSSION

This review provides a comprehensive overview of current evidence regarding effectiveness of interventions targeting pain, behaviour or both in dementia. To achieve this goal, we systematically searched the literature for existing scientific evidence, using a broad search strategy. Analysis of 893 hits resulted in sixteen publications that actually described the effects of interventions targeting pain or behaviour in people with dementia. Overall, our results indicate that pain interventions targeting behaviour and behavioural interventions targeting pain are effective in reducing pain or discomfort and behavioural symptoms such as depression, agitation/aggression and anxiety in dementia.

(Pain) Interventions targeting behaviour

Both fixed and individual dosages of pain medications were effective in reducing challenging or disruptive behaviour in dementia. However, a fixed dosage of analgesics may be less effective, compared to an individually tailored and stepwise approach. As the dosages of acetaminophen and opioids were low in some of the reviewed studies, the medication might have been insufficient to address pain or behaviour disturbances in older adults with dementia, but not in the very old (> 85 years), since they experience a larger therapeutic effect from small dosages compared to younger adults. In agreement with guidelines from the American Geriatrics Society (AGS) panel on pharmacological treatments, the evidence supports the use of acetaminophen as a first-line treatment approach to pain in dementia, but it should be noted that this evidence regarding pain treatment in individuals with dementia is restricted to findings from studies that focused only on the use of acetaminophen or opioids. Research to investigate the benefits of other analgesics (e.g. non-opioids, NSAIDs, COX-2 inhibitors) targeting challenging or disruptive behaviour, in patients with dementia is lacking and needed.

Interventions targeting both pain and behaviour

The interventions targeting both pain and behaviour disturbances were heterogeneous and may target the patient, the caregiver/caregivers and/or the environment. Non-pharmacological interventions for pain management overlap somewhat with interventions for psychological and behavioural symptoms. Furthermore, pain has been associated with mood disturbance and often co-occurs with depression and/or anxiety. We found that interventions, such as rocking chair therapy, music therapy, Reiki, reflexology, person-centred showering or bathing and multimodal cognitive-behavioural therapies can be effective in reducing pain, discomfort and behavioural disturbances, such as agitation, depression and anxiety, in persons with dementia. Additionally, untreated pain also inhibits activity in nursing home patients with moderate to severe dementia.
Before considering an intervention, one must recognize the underlying cause of the problem. In case of behavioural disturbances in dementia, a central issue is the recognition of pain. Cohen-Mansfield and colleagues recently conducted a study investigating the barriers of performing non-pharmacological interventions for behavioural symptoms in the nursing home residents. One of the barriers described in the study was the recognition of pain: in 24% of the cases the physician concluded that the resident had no pain, despite detection of pain through formal assessment or observation. Additionally, they concluded that participants for whom staff barriers were noted had more pain, than those without staff barriers. Thus, interventions with caregivers should focus first on appropriate recognition of pain. A study conducted by Fuchs-Lacelle et al. (2008) reported similar findings: improved pain assessment alone improved management of pain in people with dementia. Our findings are in line with this hypothesis: promising findings were reported in studies that focused on interventions that targeted the patient, the caregiver(s) and/or the environment, and utilized a combination of non-pharmacological treatments along with pharmacological treatments, as well as a tailored approach (effect sizes: 0.25-0.89).

Strengths and limitations
One of the strengths of this study is that we searched for publications that are often not used in systematic reviews, because of the entanglement of interventions and outcomes. The approach of only looking at pain interventions on pain, and behavioural interventions on behaviour, does not appreciate the complex relation between pain and behaviour in dementia. Several authors have published results of pain interventions on pain outcomes in dementia, and this holds also for results of behavioural interventions on behavioural outcomes in dementia, but we would like to emphasize the importance of using validated instruments for both outcomes when studying the effectiveness of interventions targeting pain or behaviour. Only then the complex relationship between pain and behaviour in dementia could be entangled.

This study is the first to systematically approach and acknowledge this complex relation. We included studies on pain, and in a broad range of behavioural variety; not only studies that focused on agitation in dementia, but also on depression, anxiety, apathy or other behaviour that can be characterized as ‘challenging’ behaviour and neuropsychiatric symptoms were included. It should be noted, however, that this broad approach has one difficulty; what to do with studies that only use the Discomfort Scale-Dementia of Alzheimer Type (DS-DAT) as an outcome measures? The DS-DAT is originally a behavioural scale that can be used to assess discomfort in patients who cannot reliably self-report pain, and has also a high correlation with the PAINAD (Cronbach’s alfa = 0.76); a scale that is specifically developed to measure pain. Therefore, the DS-DAT
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is being used as either an interpretation of pain, or as a behavioural component in this review, depending on the author’s interpretation of the DS-DAT in the research-article.

Because of the limited number of studies, the often, small sample sizes, and the moderate methodological quality; a limitation of this study is the modest strength of the encountered evidence. Research to assess efficacy of interventions becomes even more challenging, when patients start at a low frequency of behavioural symptoms at baseline, for example seen in the study performed by Chibnall et al. (2005).\(^{33}\) Therefore, the results have to be interpreted with caution, even though all of the findings are pointing in the same direction. Due to methodological heterogeneity and differences in interventions and outcomes, statistical pooling of the results was not possible.

Another strength of this study is the used quality assessment. The research question and aims resulted in the inclusion of studies that comprised different interventions, designs and outcome measures. Therefore, we used a comprehensive quality-assessment appraisal tool specifically designed for systematic reviews that include qualitative, quantitative and mixed-methods studies. A recent study by Pace and colleagues showed also that this tool is very promising, reliable and efficient.\(^{68}\)

Overall, we conclude that more large-scaled research into these complex interventions is desperately needed, to give more insight into which interventions are most effective, and in which clinical situations. The majority of the included interventions were only studied once, and replication of these results is warranted. Because of the complex entanglement of the concepts pain and behaviour, they challenge the quality of life of dementia patients to a great extent, as well as the assessment and management skills of caregivers.

To our knowledge, this systematic review is the first that has combined interventions targeting both pain and behaviour. This approach may contribute to a better clinical management of challenging behaviour and pain in people with dementia. The literature suggests an association between pain and (specific forms of) challenging behaviour (e.g. agitation, depression), but a common causal pathway has yet to be determined. Understanding the complex relationship between pain and behaviour in dementia may help create a more comprehensive assessment of challenging behaviour in daily practice, and might also add to effective treatments that can help both patients and caregivers.

The evidence in the current review supports the idea that better pain assessment and management, preferably individually tailored, may also be an effective strategy in managing challenging behaviour. And because behavioural symptoms may arise from a variety of physical or psychological needs, an approach targeting both pain
and behaviour is recommended. Notably, most studies that have met our inclusion criteria did not specify pain in terms of chronic or acute pain. Therefore, further research into this area is needed in order to assess whether the effectiveness of such targeted interventions is dependent on specific types and causes of pain.

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Contributions of authors
MP conducted the literature searches and wrote the manuscript. MP and AvD screened all references on title, abstract and full-text for relevant studies, conducted a quality assessment and a data-extraction of the included studies. MP, AF, JS, ES, WA, and BH contributed to the overall manuscript and the final draft. AF, JS, ES, WA and BH were consulted if no consensus between the two reviewers (MP/AvD) could be obtained.

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External sources
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Chapter 3


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APPENDIX A.

Search terms used in electronic databases

The following search terms were used in the different electronic databases:

**Dementia:**


**Pain:**

(pain OR pain* OR “Analgesics”[mesh] OR Analgesic[tw] OR Analgesics[tw] OR discomfort[tw] OR discomfort*)

**Behaviour:**


**Interventions:**

(therapy OR therapeutic OR therapeutics OR management OR treatment OR treatments OR intervention OR interventions OR medication OR medications OR medicated OR medicines OR drug OR drugs OR pharmacological OR nonpharmacological OR non-pharmacological OR physiotherapy OR rehabilitation OR aromatherapy OR snoezelen OR “Sensory Art Therapies” OR “Sensory Art Therapy” OR “Acoustic Stimulation” OR “Art Therapy” OR “Color Therapy” OR “Dance Therapy” OR “Music Therapy” OR “Play Therapy” OR movement OR reminiscence OR reminiscences OR reminisc* OR “occupational therapy” OR ergotherapy).