Pain treatment of agitation in patients with dementia: a systematic review

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Background: Advancing age is associated with high prevalence of both dementia and pain. Dementia is frequently accompanied by distressing behavioral and psychological symptoms, including agitation and aggression, particularly in nursing home patients. The etiology of agitation is multifactorial. It has been suggested that un-diagnosed and untreated pain may contribute to agitation in people with dementia. If this is correct, individual pain treatment could be of benefit in ameliorating agitation and other behavioral changes in people with dementia.

Objective: The objective of this paper is to conduct a systematic review of studies of whether pain medication can improve agitation in people with dementia.

Methods: A systematic search of the PubMed and Cochrane databases for the period 1992–2010 was performed, using dementia, agitation, aggression, depression, behavioral disturbances, behavioral and psychological symptoms (BPSD), pain, pain assessment, pain treatment, pain management, and analgesics as search terms. Inclusion criteria were: prospective studies including patients with dementia, interventions focusing on pain reduction, inclusion of a control condition, and outcome measures including agitation or other related behavioral disturbances.

Results: Only three controlled trials were identified; all were cross-over trials, and two included small sample sizes (<50). Findings were inconsistent, and although some correlations were reported, these did not support the hypothesis that pain management reduced agitation.

Conclusion: There is a profound dearth of rigorous studies of the effect of pain treatment in patients with dementia and agitation. The available studies do not support the hypothesis that pain management reduces agitation in nursing-home patients with dementia. Randomized, controlled parallel-group studies are needed. Copyright © 2011 John Wiley & Sons, Ltd.

Key words: dementia; agitation; aggression; behavioral disturbances; pain; pain treatment

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Introduction

Behavioral and psychological symptoms (BPSD) are common in Alzheimer’s disease (AD) and related dementias, particularly in nursing homes (NH) (Lyketsos, 2007; Selbaek et al., 2007; Steinberg et al., 2008). Agitation, psychosis, and mood disorders are the three main syndromes of BPSD (Cohen-Mansfield and Libin, 2004; Testad et al., 2007; Petrovic et al., 2007; Selbaek et al., 2007) causing tremendous distress for the patient (Chung and Cummings, 2000; Ballard et al., 2008), and caregivers (Rabins, 1998; Sourial et al., 2001; Rymer et al., 2002; Rinaldi et al., 2005 1222/id; De Vugt et al., 2006).

The aetiology of agitation is poorly understood, but it is generally considered to be multifactorial, including
suggest that psychosocial strategies may decrease distressing symptoms. Although some recent studies have been developed and tested to manage agitation and other behavioral disturbances (Chenoweth et al., 2005; Testad et al., 2005; Cohen-Mansfield et al., 2007; Ballard et al., 2009b) have been developed and tested to manage agitation and other distressing symptoms. Although some recent studies suggest that psychosocial strategies may decrease agitation (Chenoweth et al., 2009), few adequately studies exist (Ballard et al., 2009b). Neuroleptics are commonly used (De Deyn et al., 1999; Gobert and D’hoore, 2005; Lovheim et al., 2006), but have shown modest or no improvement (Ballard and Howard, 2006). Neuroleptics have a poor tolerability with frequent and troublesome side-effects, increased risk for cerebrovascular incidents (Wooltorton, 2002; Wooltorton, 2004; Schneider et al., 2006a) and increased mortality (Ballard et al., 2009a). Identifying alternative treatments is therefore a priority.

Advancing age is also associated with high prevalence of pain based on complex medical conditions like muscle skeletal diseases, neuropathics, cancer, vascular diseases, and wounds, often with pain duration of 3 months or more (Pickering et al., 2006). Acute and chronically pain combined with BPSD is common in NH patients, but diagnostic and treatment is challenging (Cohen-Mansfield et al., 1990; Cohen-Mansfield and Werner, 1997; Geda and Rummans, 1999; Cipher and Clifford, 2004; Cipher et al., 2006). Pain may remain unrecognized and untreated by the patients’ limited language, memory, and reflection (Herr et al., 2006a, b). Pain can be idiosyncratic and present as agitation and other BPSD in people with dementia (Morrison and Siu, 2000; Herr, 2004; Mahoney and Peters, 2008). For example a person with arthritic pain might resist movement into the bathtub and reacts with aggression (Mahoney and Peters, 2008). Further expressions of pain could be apathy and depression which have different biological and psychological triggers than aggression and agitation (Moretti et al., 2006; Steinberg et al., 2008). However, there is no standard method for differentiating typical behavior caused by pain from other behavior in dementia (Husebo et al., 2009). Consequently, patients with pain may receive treatment with psychotropic drugs and restraint instead of thorough pain assessment and pain management (Herr et al., 2006a). Since older persons with dementia have fewer skills to communicate, pain may contribute to BPSD. These symptoms become increasingly evident in patients with mixed AD and vascular dementia with high level of psychiatric disturbances, high prevalence of ICC diagnoses and untreated pain (Scherder et al., 2003; Shelley and Al Khabouri, 2007; Husebo et al., 2008). However, studies failed to find an association between agitation and pain, but some evidence was found suggesting that depression and pain were associated (Bartels et al., 2003; Snow et al., 2009).

The objective of this paper is to systematically review the evidence that analgesics can improve agitation in patients with dementia. Only studies reporting the effect of pain management on agitation or other related behavioral changes in people with dementia were included.

Methods

A systematic search of the PubMed and Cochrane databases for the period 1992–2010 was performed by BH (on May 2010). The following search terms were employed: dementia, agitation, aggression, depression, behavioral disturbances, BPSD, pain, pain assessment, pain treatment, pain management, and analgesics. In addition, the reference lists of retrieved articles were used to generate more papers and search terms. Only papers in English or German were included. Two of the authors (BH, DA) extracted data from included trials. Inclusion criteria were: prospective studies, including patients with dementia, interventions focusing on pain reduction, inclusion of a control condition, and outcome measures including agitation or other related behavioral disturbances.

Results

One thousand, one hundred and ninety one publications addressed the primary selection criterion for dementia and pain, 380 focused on different aspects of behavioral changes, 37 studies and literature reviews were identified, and seven studies investigated the impact of pain treatment on aspects of BPSD. Only three studies matched the inclusion criteria (Figure 1).

Studies fulfilling inclusion criteria

Key features of the three included studies are shown in Table 1. Manfredi et al. (2003) studied the effect of
 opioids on agitation in patients with severe dementia. Forty-seven NH patients received placebo for 4 weeks and a long-acting opioid for another 4 weeks period in a double-blind cross-over study with fixed treatment order. Twenty-five patients completed the two phases. No significant differences of agitation were found between the placebo and opioid phase. However, the subgroup older ≥85 years old (N = 13), demonstrated significantly lower agitation level at the end of the opioid phase without sedation.

In a randomized, double-blind, placebo-controlled cross-over trial Chibnall et al. (2005) evaluated the effect of acetaminophen on behavior, emotional well-being, and use of as-needed psychotropic medications in 25 NH patients with moderate-to-severe dementia. Twenty-five patients received 4 weeks acetaminophen 1 g × 3/day and 4 weeks placebo in random order with a 1-week wash-out period; 23 patients completed both study phases. There was no effect on agitation, emotional well-being, or as-needed psychotropic medication.
during treatment with acetaminophen. However, during treatment with acetaminophen, patients exhibit higher levels of general activity, work-like activity, and they spent more time in social interaction and less time performing personal care activities.

The effect of a stepwise, clinical protocol for assessment and management of unmet needs (Serial Trial Intervention—STI) in people with moderate-to-severe dementia was assessed in a double-blind cluster-randomized study including 14 NHs with 114 patients, 57 in each group (Kovach et al., 2006). The STI included administration of analgesics at Step 4, including ‘as-needed’ or escalation of a current analgesic, and 26 of the patients in the STI group received analgesics, compared to only two in the control group. The active treatment group had significantly less discomfort than the control group at post-testing and more frequently had behavioral symptoms return to baseline. However, no significant difference in behavioral problems was found between the groups.

### Other studies related to the research question

Four other studies explored whether analgesics would influence agitation using a retrospective or observational design without a comparison group (Table 2). Douzjian et al. (1998) included 10 NH patients with dementia related ‘difficult’ behavior and standard treatment of psychotropic drugs. Eight patients started with written orders for acetaminophen 650 mg x 3/day. It was concluded that behavioral symptoms decreased for five patients during pain treatment. Four orders for antipsychotics and two for antidepressant drugs were discontinued. A psychotropic sheet collected behavioral data and pain assessment tool identified inadequate pain control.

Kovach et al. (2001) demonstrated reduction of behavioral changes in patients with dementia following the Assessment of Discomfort in Dementia (ADD), an assessment and treatment plan for discomfort. The ADD was used for 2 month when basic care interventions did not ameliorate agitation. Ninety-one patients with severe dementia were included, of whom 86% had a painful condition and 70% received analgesics. No significant associations were found between conversational ability and analgesic prescription and dosage, but patients who were prescribed opioids spent more time being active than those not prescribed analgesics.

### Discussion

Only three randomized controlled trials (RCT) of the effect of analgesics on agitation and related behavioral changes in people with dementia were identified. Two studies were cross-over trials (Manfredi et al., 2003; Chibnall et al., 2005), including only 25 and 47 patients, and only one study recruited subjects with agitation at baseline (Manfredi et al., 2003). The third study was larger, but only a small proportion received analgesics. The findings were inconsistent, and none of the studies reported unequivocal reduction of agitation after pain management. In one study, patients aged 85 or older showed reduced agitation (Manfredi et al., 2003), suggesting the possibility that in very old patients opioids may be a useful management of agitation.

The studies have several methodological limitations which make the interpretation of the findings difficult and preclude the conclusion that pain management does not reduce agitation. Although using cross-over design provides a larger statistical power than a parallel-group design, limitations with this design include the risk of carry-over effects. In addition, the placebo-active order was fixed in one study, suggesting that confounding factors might influence the results, including regression to the mean and spontaneous fluctuations. The small sample sizes severely reduce the statistical power to detect smaller differences, leading to an increased risk for false-negative findings, and thus the lack of difference between the groups might not be valid.
<table>
<thead>
<tr>
<th>Study</th>
<th>N*</th>
<th>MMSE, mean ± SD</th>
<th>Design</th>
<th>Inclusion criteria</th>
<th>Outcome measures</th>
<th>Treatment</th>
<th>Result</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doujian et al., 1998</td>
<td>8</td>
<td>NA</td>
<td>6 months, observational study</td>
<td>Dementia, Use of psychotropic medication due to ‘difficult’ behavior’ Dementia</td>
<td>Psychotropic sheet and pain assessment tool, once a month</td>
<td>Acetaminophen 650mg × 3/day</td>
<td>Behavioral symptoms decreased during pain treatment</td>
<td>Small sample size, no control, outcome measures not validated</td>
</tr>
<tr>
<td>Kovach et al., 2001</td>
<td>91</td>
<td>5.45 (range 0–20) ± 6.16</td>
<td>2 months, multi-centre observational study</td>
<td>Dementia Assessment of discomfort in dementia (ADD)</td>
<td>Acetaminophen, propoxyphene, darvocet, dosage unknown</td>
<td>Analgesics reduce comfort; use of analgesics not correlated to severity of dementia and functional behavior</td>
<td>No control, no randomization, no defined primary outcome measures for agitation and aggression</td>
<td></td>
</tr>
<tr>
<td>Brummel-Smith et al., 2002</td>
<td>51</td>
<td>15.6 (range 0–26) ± 5.9</td>
<td>12 months retrospective review of an observational cohort control group</td>
<td>Dementia and performed self-report of pain</td>
<td>Program of All-inclusive care, ADL, IADLs, BPSD, face pain scale, VAS</td>
<td>No active intervention</td>
<td>MMSE is associated with BPSD, but level of pain is independent from level of dementia and BPSD</td>
<td>Subjects unable for self-report of their pain-level are excluded, Retrospective, Single point measure</td>
</tr>
<tr>
<td>Allen et al., 2003</td>
<td>64</td>
<td>13.81 (range 0–29) ± 6.34</td>
<td>1 month multi-centre (5 NHs) cross-sectional</td>
<td>Patients completed a 5-min semi-structured conversation to express multiword phrases</td>
<td>Chart review, computer-assisted behavioral observation of conversational abilities</td>
<td>No active intervention</td>
<td>Use of analgesics is related to self-report capacity, levels of dementia and time to being active</td>
<td>No intervention, no control, no randomization, no assessment of pain or BPSD</td>
</tr>
</tbody>
</table>

NA: No analyzes.
*Patients who received some kind of pain treatment.
The study by Chibnall et al. (2005) indicated some positive behavioral changes associated with pain management. The fact that agitation did not decrease may be explained by low prevalence of agitation in the sample with an average frequency of agitation of less than one incident per week. The intervention therefore had little room to effect improvement in outcome measures. The choice of analgesics also must be taken into account and individual pain treatment should be recommended. The finding that the oldest patients demonstrated reduced agitation during treatment with analgesics (Manfredi et al., 2003) is interesting. However, two different types of opioids were used, (oxycodone hydrochloride 10 mg × 2/day (equivalent morphine 40 mg) and long acting morphine 20 mg × 1/day). The oxycodonhydrochloride is a relative high dosage for starting pain treatment in older patients, who are not used to morphine, and is twice as high as the morphine dose. This may, additionally, explain the high drop-out rate of the participants.

Finally, in one of the studies (Kovach et al., 2006), the intervention, STI, included a range of different strategies, analgesic being only one of several strategies used. This makes it impossible to distinctly interpret the effect of analgesics distributed to a small sample size (N = 26). Type, dosage, and duration of analgesic treatment are not mentioned, as well as drop-out rates. Further, the possible treatment effect of analgesics on behavioral disturbances is not discussed. To gain additional information, we studied four observational, uncontrolled studies which also did not suggest a clear-cut association between pain and use of analgesics.

To conclude, only three small cross-over RCT studies exploring the effect of pain management on agitation in patients with dementia were identified. The results did not support the hypothesis that pain management improves agitation. However, there is a need for adequately designed studies, using parallel-group design, adequate sample sizes and individual pain treatment.

Conflict of interest

None declared.

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References


