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Best Evidence Summaries of Topics in Mental Healthcare

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Question

In adults with progressed dementia, how effective is analgesia, compared with any other pharmacological intervention, in decreasing behavioural and psychological symptoms, specifically aggression and agitation?

Clarification of question using *PICO* structure

Patients:	Adults with progressed dementia
Intervention:	Analgesia
Comparator:	Any other pharmacological intervention
Outcome:	Behavioural and psychological symptoms, specifically aggression and agitation

Plain language summary

No studies could be identified that compared pain relief medication (Analgesia) to any other medication to measure how effective it was in reducing aggression/agitation in people with dementia. One study comparing pain relief to any other treatment provided limited evidence suggesting that pain relief may be linked to reduced agitation. Further research need to be conducted on this topic

Clinical and research implications

Limited evidence, from one randomised controlled trial, indicates that the use of a pain treatment protocol may be associated with reduced agitation (particularly verbal agitation behaviours) compared to treatment as usual, when used in very elderly patients with moderate to severe dementia. Two small crossover trials, included in two systematic reviews, did not provide significant additional evidence. No studies were identified which compared the effectiveness of analgesia to that of other active pharmacological interventions for behavioural disturbance.

Further studies are needed to fully evaluate the potential effects of pain management on behavioural disturbance in people with dementia.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified two systematic reviews[1,2] and one additional randomised controlled trial (RCT)[3] which were potentially relevant to this evidence summary. The two systematic reviews included a total of three trials which assessed the effects of analgesia on behavioural outcomes in people with dementia and which therefore had some relevance to this evidence summary; none of the trials compared analgesia with another active pharmacological intervention. The additional RCT publication[3] appeared to be reporting further analysis of a trial included in one of the systematic reviews.[2] All studies were conducted in very elderly (mean age >85 years) nursing home patients with moderate to severe, or severe dementia.

Main findings

Two small crossover trials, included in both systematic reviews,[1,2] reported, respectively, that treatment with acetaminophen (1000 mg, 3 to 7 times daily) was associated with improvements in engagement compared to placebo and that patients treated with a long acting opioid showed no difference in agitation on the Cohen-Mansfield Agitation Inventory (CMAI) compared to placebo; no numerical results were reported for either study, in either review. The remaining larger RCT was reported in two articles, one included in a systematic review, [2] and one identified as an additional RCT.[3] This study found that a stepwise pain protocol, involving acetaminophen oral (max. increase to 3 g/day), extended release morphine oral (max. 20 mg/day), pregabaline oral (max. 300 mg/day), buprenorphine transdermal plaster (max. 10 µg/hour/7 days) for patients with swallowing difficulties, was associated with reduced agitation (total CMAI score)[2] compared to treatment as usual. Analysis of the factor groups and individual items of the CMAI indicated that the pain treatment protocol was particularly associated with improvements in verbal agitation behaviours.[3]

Authors conclusions

Husebo 2011 – The authors concluded that the available studies do not support the hypothesis that pain management reduces agitation in nursing-home patients with dementia.

Pieper 2013 – The authors concluded that available evidence suggests that (pain) interventions targeting behaviour, and (behavioural) interventions targeting pain are effective in reducing pain and behavioural symptoms in dementia.

Husebo 2013 – The authors concluded that verbal agitation behaviours such as complaining, negativism, repetitious sentences and questions, constant request for attention, and cursing or verbal aggression responded to pain treatment.

Reliability of conclusions/Strength of evidence

This evidence summary includes one good quality[2] and one methodologically weak systematic[1] review. All studies included in the methodologically weak systematic review were also included in the good quality review. Primary studies included in the systematic reviews were generally small and of poor quality and the reviews reported only limited results. One larger RCT was reported in both the good quality systematic review,[2] and as a separate additional publication reporting further analyses.[3] The results of this trial form the main source of evidence for this summary. It should be noted that we did not identify any studies which compared analgesia to other active pharmacological interventions for the management of behavioural symptoms in people with dementia, therefore none of the included studies fully matched the specified PICO for the submitted question.

What do guidelines say?

NICE guidelines do not specifically discuss the use of analgesia for reducing the behavioural and psychological symptoms of dementia. NICE Guidelines for dementia (CG42 2006) makes the following recommendations for using pain relief;

"If a person with dementia has unexplained changes in behaviour and/or shows signs of distress, health and social care professionals should assess whether the person is in pain, using an observational pain assessment tool if helpful. However, the possibility of other causes should be considered.

The treatment of pain in people with severe dementia should involve both pharmacological and non-pharmacological measures. Non-pharmacological therapies should be used with the person's history and preferences in mind." (pg.37)

Date question received: 19/11/2015
Date searches conducted: 19/11/2015
Date answer completed: 07/12/2015

References

Systematic reviews

1. Husebo, B. S., Ballard, C., & Aarsland, D. (2011). Pain treatment of agitation in patients with dementia: a systematic review. *International journal of geriatric psychiatry*, *26*(10), 1012-1018.

2. Pieper, M. J., van Dalen-Kok, A. H., Francke, A. L., van der Steen, J. T., Scherder, E. J., Husebø, B. S., & Achterberg, W. P. (2013). Interventions targeting pain or behaviour in dementia: A systematic review. *Ageing research reviews*, *12*(4), 1042-1055.

Randomised controlled trials

3. Husebo, B. S., Ballard, C., Cohen-Mansfield, J., Seifert, R., & Aarsland, D. (2013). The response of agitated behavior to pain management in persons with dementia. *The American Journal of Geriatric Psychiatry*, *22*(7), 708-717.

Guidelines

National Institute for Clinical Excellence (2006) Dementia: Supporting people with dementia and their carers in health and social care. CG42 NICE.

Results

Systematic reviews

Author (year)	Search date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Husebo et al (2011)	May 2010	***Participants**:* Individuals with dementia ***Intervention**:* Pain medication ***Comparator**:* Any control condition ***Outcome**:* Agitation, or other related behavioural disturbances ***Study design**:* Prospective studies	3 studies (n=186 participants) were included in the review. 2 of the included studies (n=72) assessed the effects of analgesia on behavioural outcomes.	This systematic review aimed to assess whether pain medication can improve agitation in people with dementia. The two relevant studies included in this review were the two crossover trials included in Pieper 2013 (see below); no additional results were reported in this review.	The objective was clearly stated and appropriate inclusion criteria were defined. Medline and the Cochrane databases were searched and the reference lists of retrieved articles were screened for additional studies. Only English and German language articles were included. Two reviewers were involved in

					the data extraction process, but it was not clear how many reviewers were involved in study selection. No assessment of the methodological quality of included studies was reported. Results were summarised using a narrative synthesis and tables. This was appropriate given the differences in population, intervention, comparator and study design between the included studies.
Pieper et al (2013)		***Participants*:** Adults or elderly patients with a main diagnosis of dementia (e.g. Alzheimer's	16 studies (n=1003	This systematic review aimed to summarise the evidence on the effects of interventions	The objective was clearly stated and

		disease, Vascular dementia, Lewy body disease, Frontotemporal dementia). Studies involving participants with a diagnosis of dementia resulting from Parkinson's disease, Huntington's disease, AIDS dementia complex, Multiple Sclerosis or Creutzfeldt–Jakob disease were excluded. ***Intervention*****:** Any 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) ***Comparator*****:** Any ***Outcome*****:** Pain and/or behaviour ***Study design*****:** No inclusion criteria were specified for study design; all study designs appear to have been included. Studies published as abstracts only were excluded.	participants) were included in the review. 3 of the included studies (n=424) assessed the effects of analgesia on behavioural outcomes.	targeting pain, behaviour, or both, in people with dementia. Three of the 16 studies included in this review were of partial relevance to this evidence summary. These studies assessed the effects of analgesic interventions on behavioural outcomes in people with dementia. However, no study explicitly compared analgesia to another pharmacological intervention; two were placebo controlled trials and one used 'usual care and treatment' as the control condition. An eight week crossover trial (crossover after four weeks, with one week washout), with 25 participants, compared acetaminophen (1000 mg, 3 to 7 times daily) to placebo. Study participants were nursing home residents with a mean age of 85.9±7.4 years and moderate to severe dementia. "Participants spent more time in social interaction, engaged with media, talking to themselves, engaged in work-like activity, and experiencing unattended distress when they received acetaminophen than did they received placebo." No numerical results were reported.	appropriately broad inclusion criteria were defined. Six bibliographic databases were searched for relevant studies and additional publications were sought through screening the reference lists of included studies and contacting authors. No language restrictions were applied. Studies published as abstracts only were excluded. Two reviewers were involved in all stages of the review process,

				A second eight week crossover trial (four weeks treatment, washout period not reported), with 47 participants, compared long-acting opioid (20 mg oxycodone or 20 mg morphine) to placebo. Study participants were nursing home residents, with a mean age of 86.7±7.0 years and advanced stage dementia (MMSE score ≤21). There were no significant differences in agitation (CMAI) between opioid and placebo for the 25 patients who completed the study. However, the review reported that "low dose, long-acting opioids can lessen agitation that's difficult to control in very old patients (>85 years) with advanced dementia." No numerical results were reported. The third relevant study was an eight week RCT with 352 participants, which compared a stepwise pain treatment protocol (acetaminophen, morphine, buprenorphine transdermal patch, or pregabaline) to usual care and treatment. Study participants were nursing home residents with a mean age of 87 years (range 67 to 104) and moderate to severe dementia (DSM-IV). "A significant reduction of agitation (CMAI) and overall	reducing the potential for error and/or bias. The methodological quality of included studies was assessed using an appropriate instrument and results were reported in full. Results were summarised using a narrative synthesis and tables. This was appropriate given the differences in population, intervention, comparator and study design between the included studies.

				neuropsychiatric symptoms (NPI-NH) was observed in the intervention group after 8 weeks. The agitation in the intervention-group worsened after withdrawal of the pain treatment." No numerical results or between group comparisons were reported.	

Randomised controlled trials

Author (year)	**Inclusion criteria**	**Number of participants**	**Summary of results**	**Risk of bias**
Husebo et al (2013)	***Participants*:** adults 65 years and older, living in the nursing home for at least 4 weeks, with moderate or severe dementia and clinically relevant behavioural disturbances. Dementia severity was assessed according to DSM-IV, Functional Assessment Staging (FAST) score greater than 4 and Mini Mental State Examination (MMSE) score greater than 20. Behavioural disturbances were defined as CMAI score ≥39. People with advanced medical disease (expected survival ≤6 months), severe psychiatric or neurological disorders other than dementia, or allergy to study medications, were excluded. ***Intervention*:** Stepwise Protocol for the	n=352 (n=177 control condition, n=175 intervention condition)	This study aimed to determine which specific agitated behaviours respond to individualised pain treatment. This article appears to be a further publication relating to the third study included in Pieper 2013 (see above). The study was an eight week, cluster randomised controlled trial, with an additional four week post-treatment follow-up period. Age, gender and baseline measures of dementia severity, behavioural disturbance and pain were similar in the intervention and control groups. Depending on their ongoing medical treatment, participants in the pain intervention group received acetaminophen oral (max. increase to 3 g/day), extended release morphine oral (max. 20 mg/day), or pregabaline oral (max. 300 mg/day).	Cluster randomised trial, with nursing home units defined as a cluster. No information on allocation concealment was reported. Patients, research assistants

	Treatment of Pain (SPTP); all patients in the intervention group received individual daily pain treatment with acetaminophen, extended release morphine, buprenorphine transdermal patch, and/or pregabaline. 8 weeks (treatment period) with an additional follow-up 4 weeks after the end of treatment, at 12 weeks (wash-out period). ***Comparator*:** Treatment as usual ***Outcome*:** Pain and agitation according to Cohen-Mansfield Agitation Inventory subscales and items, pain diagnoses and ICD diagnoses.		Patients with swallowing difficulties were treated with buprenorphine transdermal plaster (max. 10 µg/hour/7 days). Participants in the pain treatment group showed greater improvements in three of the four factor groups of the CMAI, from baseline to eight weeks, than those in the treatment as usual group. For aggressive behaviour, the change from baseline was -2.2 (95% CI: -1.1 to -3.3) for the pain treatment group compared to -1.0 (95% CI: -0.1 to -2.0) for the treatment as usual group; p=0.037. For physically non-aggressive behaviour, the change from baseline was -2.9 (95% CI: -1.8 to -4.0) for the pain treatment group compared to -1.1 (95% CI: -0.1 to -2.2) for the treatment as usual group; p=0.008. For verbally agitated behaviour, the change from baseline was -2.9 (95% CI: -2.1 to -3.6) for the pain treatment group compared to -0.6 (95% CI: 0.2 to -1.5) for the treatment as usual group; p<0.001. There was no significant difference between the groups for the hiding and hording factor group. The background section notes that results published in an earlier article (included in the Pieper 2013 review, above) showed that the pain intervention was associated with a greater reduction in overall CMAI score compared to treatment as usual. Single CMAI items which showed a statistically significant benefit for pain treatment compared to treatment as usual were: pacing; cursing or verbal aggression; constant request	and care givers were blinded to group allocation. 20 Participants from the control group and 28 participants from the intervention group were excluded from the effectiveness analyses. Results were not reported for the overall CMAI score; the previous publication (included in

			for attention; repetitious sentences or questions; complaining; negativism; handling things inappropriately; general restlessness. Items which showed no difference between groups were: inappropriate robing or disrobing; spitting; hitting; kicking; grabbing; pushing; throwing things; biting; trying to get to a different place; intentional falling; eating inappropriate substances; hurting self or others; hiding; hoarding; tearing things; repetitious mannerisms; verbal sexual advances; physical sexual advances. CMAI items for which pain treatment was associated with greater improvement that treatment as usual, but where the difference did not reach statistical significance were: making strange noise; screaming; scratching.	Pieper 2010) is referred to for these results.

Risk of bias

Systematic reviews

Author (year)	RISK OF BIAS				
	Inclusion criteria	Searches	Review process	Quality assessment	Synthesis
Husebo et al (2011)	☺	☹	?	☹	☺
Pieper et al (2013)	☺	☺	☺	☺	☺

Randomised controlled trials

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Husebo et al (2012)	?	?	☺	☺	☹	☺

☺ Low risk ☹ High risk ? Unclear risk

Search details

Source	Search Strategy		Number of hits	Relevant evidence identified
Guidelines				
NICE	Dementia		47	1
Systematic Reviews & Primary Studies				
MEDLINE	1 exp Dementia/	132995	26	0
	2 "progress* dementia".ab,ti.	1351		
	3 exp "Anesthesia and Analgesia"/ or exp Analgesia/	205124		
	4 pain relief.ab,ti.	23927		
	5 "aggres*".ab,ti.	153296		
	6 agitation.ab,ti.	11719		
	7 exp Behavioral Symptoms/	282928		
	8 BPSD.ab,ti.	600		
	9 exp Aggression/	30720		
	10 1 or 2	133422		
	11 3 or 4	224039		
	12 4 or 5 or 6 or 7 or 8 or 9	450142		
	13 10 and 11 and 12	26		

EMBASE (SR)	1	exp Dementia/	258149	2
	2	"progress* dementia".ab,ti.	1876	
	3	exp "Anesthesia and Analgesia"/ or exp Analgesia/	603749	
	4	pain relief.ab,ti.	34446	
	5	"aggres*".ab,ti.	208796	
	6	agitation.ab,ti.	17586	
	7	exp Behavioral Symptoms/	3004552	
	8	BPSD.ab,ti.	913	
	9	exp Aggression/	78396	
	10	1 or 2	258371	
	11	3 or 4	616562	
	12	4 or 5 or 6 or 7 or 8 or 9	3200868	
	13	10 and 11 and 12	1183	
	14 - 43	***Systematic Review Filters applied***	508966	
	44	limit 43 to yr="2010 -Current"	234771	
	45	13 and 44	76	
EMBASE (RCT)	1	exp Dementia/	258149	1
	2	"progress* dementia".ab,ti.	1876	
	3	exp "Anesthesia and Analgesia"/ or exp Analgesia/	603749	
	4	pain relief.ab,ti.	34446	
	5	"aggres*".ab,ti.	208796	
	6	agitation.ab,ti.	17586	

	7 exp Behavioral Symptoms/ 3004552 8 BPSD.ab,ti. 913 9 exp Aggression/ 78396 10 1 or 2 258371 11 3 or 4 616562 12 4 or 5 or 6 or 7 or 8 or 9 3200868 13 10 and 11 and 12 1183 14 (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab. 1151514 15 RETRACTED ARTICLE/ 7871 16 14 or 15 1159198 17 (animal$ not human$).sh,hw. 3970902 18 (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/ 4293904 19 (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/ 68089 20 16 not (17 or 18 or 19) 891633 21 13 and 20 106		
PsycINFO/CINAHL	1 exp Dementia/ 56934 2 "progress* dementia".ab,ti. 468 3 exp "Anesthesia and Analgesia"/ or exp Analgesia/ 3245 4 pain relief.ab,ti. 2528		0

	5 "aggres*".ab,ti. 51496 6 agitation.ab,ti. 4358 7 BPSD.ab,ti. 533 8 exp Psychiatric Symptoms/ 12006 9 exp Behavior Problems/ 21408 10 exp Aggressive Behavior/ 110596 11 exp Agitation/ 1161 12 1 or 2 56999 13 "ANALGESI*".ab,ti. 10204 14 3 or 4 or 13 12457 15 5 or 6 or 7 or 8 or 9 or 10 or 11 169581 16 12 and 14 and 15 24		
CENTRAL	#1 MeSH descriptor: [Dementia] explode all trees 3993 #2 progress* dementia 1270 #3 MeSH descriptor: [Analgesia] explode all trees 6237 #4 MeSH descriptor: [Anesthesia and Analgesia] explode all trees 22206 #5 analgesi* 37714 #6 pain adj relief 452 #7 MeSH descriptor: [Behavioral Symptoms] explode all trees 11414 #8 MeSH descriptor: [Aggression] explode all trees 885 #9 BPSD 79 #10 aggress* 6637 #11 agitation 2389 #12 #1 or #2 4813		0

	#13	#3 or #4 or #5 or #6	49685		
	#14	#7 or #8 or #9 or #10 or #11	19020		
	#15	#12 and #13 and #14 in Trials	8		

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