Chronic pain in people living with dementia: challenges to recognising and managing pain, and personalising intervention by phenotype.

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Abstract

Pain is common in people with dementia, and pain can exacerbate the behavioural and psychological symptoms of dementia. Effective pain management is challenging, not least in people with dementia. Impairments of cognition, communication and abstract thought can make communicating pain unreliable or impossible. It is unclear which biopsychosocial interventions for pain management are effective in people with dementia, and which interventions for behavioural and psychological symptoms of dementia are effective in people with pain. The result is that drugs, physical therapies and psychological therapies might be either under- or over-used. People with dementia and pain could be helped by assessment processes that characterise an individual's pain experience and dementia behaviours in a mechanistic manner; phenotyping. Chronic pain management has moved from a `one size fits all' approach, towards personalised medicine, where interventions recommended for an individual depend upon the key mechanisms underlying their pain, and the relative values they place on benefits and adverse effects. Mechanistic phenotyping through careful personalised evaluation would define the mechanisms driving pain and dementia behaviours in an individual, enabling the formulation of a personalised intervention strategy. Central pain processing mechanisms are particularly likely to be important in people with pain and dementia, and interventions to accommodate and address these may be particularly helpful, not only to relieve pain but also the symptoms of dementia.

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Dementia is a global health priority. It is a prevalent syndrome in older people, and is characterised by cognitive and functional decline and behavioural and psychological symptoms. Pain is an unpleasant sensory and emotional experience [1] and it is estimated that half of all people living with dementia have chronic pain [2]. Pain is associated with distress and behavioural symptoms of dementia [3], dementia makes the treatment of pain more difficult [4], and pain makes relieving the behavioural and psychological symptoms of dementia more challenging [5]. Pain and dementia interact, rather than simply co-occur.

Pain management is challenging in people living with dementia. Suboptimal pain management is largely attributed to difficulty in identifying pain in these individuals [6]. Self-report of pain is possible but potentially diminished in people with mild to moderate dementia. People with advanced dementia require observational methods of ascertaining pain, as the almost inevitable loss of communication and abstract thought renders self-report of pain (or its absence) unreliable or impossible. A variety of observational scales for pain in people with dementia assess body movements, behaviour or facial grimacing [7]. However, these scales are underutilised and under-implemented, attributed to a lack of training, education and time [8].

Difficulties in ascertaining pain contributes to suboptimal treatment of pain. There is a paradox in the way pain medications are prescribed for people with dementia. Certain schools of thought consider pain medications to be under-used, with potential loss of benefits for people living with dementia and pain [9]. On the other hand, there is a narrative that medications are over-used, only partly efficacious, prone to side-effects [10,11], and may distract from attempts to employ alternative strategies. A meta-analysis reported that people with dementia had a significantly lower prevalence of use of all analgesic medications, and of self-reported and observed pain, compared to people without dementia, despite similar prevalence of painful conditions [12]. However, randomised trials of regular paracetamol use in people with advanced dementia reported no significant impact on quality of life, depression, or pain, compared to placebo [13, 14]. These findings are tempered by the fact that individual cases did indeed derive benefit from paracetamol, both during and after the study [13], and that subgroup analyses revealed that paracetamol was effective in reducing pain in some people with advanced dementia [14]. This could have important implications for future prescriptions of pain medication in people with advanced dementia, and raises questions about statistical significance of studies, compared with the clinical relevance of results.

Behavioural and psychological symptoms of dementia pose additional barriers to effective pain management. Pain may exacerbate and even drive these symptoms [3]. These interactions are highlighted in that non-pharmacological interventions targeting behavioural and psychological

symptoms of dementia have an effect on pain, and vice versa [15]. Non-pharmacological interventions for pain are many and varied; amongst them are physical therapies, psychological therapies, and those that use sensory modalities such as massage and music. However, the evidence base is far from clear on which biopsychosocial interventions are effective to both manage pain and to relieve the symptoms of dementia, in whom, and in which combinations [16,17]. The result might be that non-pharmacological interventions as well as medicines are used suboptimally. A biopsychosocial approach to pain would consider both medicines and non-pharmacological interventions as components within a holistic, complex package of care. It is proposed that a sophisticated way forward for pain management will be to select personalised interventions which address potentially overlapping mechanisms underlying both pain and distress behaviours.

One way to achieve this personalised pain management is by describing pain and its observable characteristics – pain phenotyping. Pain phenotyping refers to a careful personalised evaluation of an individual's pain experience in order to characterise the mechanisms driving these symptoms, and subsequently design their care package to meet their particular needs. Low mood and anxiety enhance the responsiveness of the central nervous system to nociceptive signalling (also called central sensitisation) [18] in people without dementia. This might be even more important in people with dementia, in whom distress behaviours, anxiety and depression are extremely common [19]. While the reasons behind these symptoms may be complex, pain is one of the main reasons [3,5].

Clinical phenotyping of pain can describe how pain manifests in people with dementia, cognitive adaptations to pain, and associated low mood, anxiety and other psychological features and distress behaviours. Deep phenotyping of pain refers to observable pathophysiological measurements, which could include (but are not limited to) biomarkers in bodily fluid, imaging, and sensory thresholds such as are measured by quantitative sensory testing (QST). Deep phenotyping can complement clinical phenotyping, similar to the way in which certain cancers might appear clinically comparable but express different receptors, and are thus managed differently.

Evaluation tools developed with people without dementia might be adapted for those with dementia. Techniques of QST measure pain in response to a standardised stimulus, and have been adapted for use in people with early dementia [20]. In cognitively intact people with osteoarthritis pain, QST in combination with other phenotypic characteristics was able to predict the analgesic response to duloxetine [21]. Functional brain imaging using MRI has been used both for the assessment of central pain mechanisms as well as neurodegeneration mechanisms in people with dementia [22]. Further, tools for evaluating psychological symptoms, such as wearable sensors detecting signs of anxiety and stress, might also be investigated for evaluation of pain in people with dementia. All these tools might be used to explore potentially shared mechanisms between pain and dementia, enabling development of interventions which target pain and its associated symptoms.

Research questions should address these complex interactions. New research priorities should be developed in partnership between stakeholders including patients and their caregivers to answer important and tractable gaps in knowledge. A strong patient and public involvement and

engagement representation at every stage of research, from concept development to dissemination of results and implementation into clinical practice, is essential. Pain, especially when chronic and severe, interferes with an individual's ability to engage in activities and relationships that sustain their quality of life. The concept of "total pain" is used in terminal cancer [23] and places equal emphasis on physical, social, psychological and spiritual domains of pain and suffering. This approach may be usefully applied in people with advanced dementia who are frail and in their last years of life. Outcome measures for research should focus on not simply a cure for pain, but also the relative values that people with dementia place on benefits and adverse effects of any proposed intervention. This may include social participation, inclusion, occupation and comfort [24].

Although tools are available for pain recognition in people with dementia, their implementation in clinical practice has been limited [25]. Challenges exist at organisational, policy-making and funding levels and to address these would require engagement of stakeholders and an emphasis on education and training of staff. For example, barriers to implementation of pain recognition tools for people with advanced dementia include cost and training requirements, a lack of incentive and time by healthcare professionals, and difficulty in ascertaining pain while simultaneously providing care [8]. Similarly, effective pain management tools have had limited implementation. Pain medications have conflicting evidence for use in people living with dementia. Evidence based non-pharmacological interventions are not readily available and are likely to be resource-intensive. A robust evidence base of the efficacy and cost-effectiveness of both pharmacological and non-pharmacological treatments is required in order to use limited health and social resources to appropriately target those who will derive optimal benefit.

Despite considerable challenges for future research, the time is ripe to empower clinicians and patients to use what is already available in order to improve care for people living with dementia and pain. Using the comprehensive geriatric assessment approach to pain in dementia, in line with the total pain concept [23], would help to consider the impact of pain on functional, social and environmental limitations, and consider how existing interventions might improve these. Consciously applying, auditing and evaluating the use of available pain recognition tools in people with advanced dementia, will enable pain to be actively sought, recognised and treated. This may at the same time highlight other potentially unmet needs, such as companionship, stimulation, hydration, nutrition, and skin integrity. Education should be targeted to healthcare staff and community caregivers on how distress behaviours in people with dementia might reflect underlying pain, and is another way in which unmet needs essential to wellbeing may be recognised and treated.

Person-centred care principles of personalised care should be the encompassing approach, enabling people living with dementia to live as fulfilled a life as possible despite chronic pain [26]. Gaining an understanding of pain phenotypes in dementia should enable this personalisation of care, develop new treatments, and target existing interventions to those with the greatest potential to benefit. Future research should exploit the interactions between pain and behavioural and psychological symptoms of dementia, seeing both as dimensions of the same individual person.

References

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. PAIN. 2020;161(9):1976-82.

2. van Kooten J, Binnekade TT, van der Wouden JC, Stek ML, Scherder EJ, Husebø BS, Smalbrugge M, Hertogh CM. A Review of Pain Prevalence in Alzheimer's, Vascular, Frontotemporal and Lewy Body Dementias. Dement Geriatr Cogn Disord. 2016;41(3-4):220-32.

3. Sampson EL, White N, Lord K, et al. Pain, agitation, and behavioural problems in people with dementia admitted to general hospital wards: a longitudinal cohort study. *Pain*. 2015;156(4):675-683.

4. Lichtner, V., Dowding, D., Allcock, N. *et al.* The assessment and management of pain in patients with dementia in hospital settings: a multi-case exploratory study from a decision making perspective. *BMC Health Serv Res* **16,** 427 (2016).

5. Husebo BS, Ballard C, Fritze F, Sandvik RK, Aarsland D. Efficacy of pain treatment on mood syndrome in patients with dementia: a randomized clinical trial. Int J Geriatr Psychiatry. 2014 Aug;29(8):828-36.

6. Corbett A, Husebo BS, Achterberg WP et al. The importance of pain management in older people with dementia, *British Medical Bulletin* 2014; 111(1): 139–148.

7. Husebo BS, Ostelo R, Strand LI. The MOBID-2 pain scale: reliability and responsiveness to pain in patients with dementia. *Eur J Pain*. 2014;18(10):1419-1430. doi:10.1002/ejp.507

8. Pringle, J., Mellado, A.S.A.V., Haraldsdottir, E. *et al.* Pain assessment and management in care homes: understanding the context through a scoping review. *BMC Geriatr* **21,** 431 (2021).

9. Achterberg WP, Erdal A, Husebo BS, Kunz M, Lautenbacher S. Are Chronic Pain Patients with Dementia Being Undermedicated? J Pain Res. 2021 Feb 15;14:431-439.

10. Haasum Y, Fastbom J, Fratiglioni L, Kåreholt I, Johnell K. Pain treatment in elderly persons with and without dementia: a population-based study of institutionalized and home-dwelling elderly. Drugs Aging. 2011 Apr 1;28(4):283-93.

11. Rodger, KT, Greasley-Adams, C, Hodge, Z, Reynish E. Expert opinion on the management of pain in hospitalised older patients with cognitive impairment: a mixed methods analysis of a national survey. *BMC Geriatr*. 2015; 15:56.

12. Tan EC, Jokanovic N, Koponen MP, Thomas D, Hilmer SN, Bell JS. Prevalence of Analgesic Use and Pain in People with and without Dementia or Cognitive Impairment in Aged Care Facilities: A Systematic Review and Meta-Analysis. Curr Clin Pharmacol. 2015;10(3):194-203.

13. van Dam, P.H., Achterberg, W.P., Husebo, B.S. *et al.* Does paracetamol improve quality of life, discomfort, pain and neuropsychiatric symptoms in persons with advanced dementia living in long-term care facilities? A randomised double-blind placebo-controlled crossover (Q-PID) trial. *BMC Med* **18,** 407 (2020).

14. Erdal, A., Flo, E., Aarsland, D. *et al.* Efficacy and Safety of Analgesic Treatment for Depression in People with Advanced Dementia: Randomised, Multicentre, Double-Blind, Placebo-Controlled Trial (DEP.PAIN.DEM). *Drugs Aging* **35**, 545–558 (2018).

15. Pieper MJ, van Dalen-kok AH, Francke AL, et al. Interventions targeting pain or behaviour in dementia: a systematic review. *Ageing Res Rev*. 2013;12(4):1042–1055. doi:10.1016/j.arr.2013.05.002

16. Orgeta V, Leung P, del-Pino-Casado R, Qazi A, Orrell M, Spector AE, Methley AM. Psychological treatments for depression and anxiety in dementia and mild cognitive impairment. Cochrane Database of Systematic Reviews 2022, Issue 4. Art. No.: CD009125. DOI: 10.1002/14651858.CD009125.pub3.

17. Coronado RA, Albers HE, Allen JL, Clarke RG, Estrada VA, Simon CB, Galloway RV, Fisher SR. Pain-Reducing Effects of Physical Therapist-Delivered Interventions: A Systematic Review of Randomized Trials Among Older Adults With Dementia. J Geriatr Phys Ther. 2020 Jul/Sep;43(3):159-169.

18. Akin-Akinyosoye K, James RJE, McWilliams DF, Millar B, das Nair R, Ferguson E, Walsh DA. The Central Aspects of Pain in the Knee (CAP-Knee) questionnaire; a mixed-methods study of a self-report instrument for assessing central mechanisms in people with knee pain. Osteoarthritis Cartilage. 2021 Jun;29(6):802-814.

19. Steinberg M, Shao H, Zandi P, Lyketsos CG, Welsh-Bohmer KA, Norton MC, Breitner JC, Steffens DC, Tschanz JT. Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *Int J Geriatr Psychiatry* 2008;23:170–7.

20. Jensen-Dahm C, Werner MU, Dahl JB, Jensen TS, Ballegaard M, Hejl AM, Waldemar G. Quantitative sensory testing and pain tolerance in patients with mild to moderate Alzheimer disease compared to healthy control subjects. Pain. 2014 Aug;155(8):1439-1445.

21. Petersen KK, Drewes AM, Olesen AE, Ammitzbøll N, Bertoli D, Brock C, Arendt-Nielsen L. The effect of duloxetine on mechanistic pain profiles, cognitive factors and clinical pain in patients with painful knee osteoarthritis-A randomized, double-blind, placebo-controlled, crossover study. Eur J Pain. 2022 Sep;26(8):1650-1664.

22. Lawn T, Aman Y, Rukavina K, Sideris-Lampretsas G, Howard M, Ballard C, Ray Chaudhuri K, Malcangio M. Pain in the neurodegenerating brain: insights into pharmacotherapy for Alzheimer disease and Parkinson disease. Pain. 2021 Apr 1;162(4):999-1006.

23. Clark, D. 'Total pain', disciplinary power and the body in the work of Cicely Saunders, 1958-1967. *Social Science and Medicine* 1999; 49: 727-736.

24. Kitwood T: Dementia Reconsidered: The person comes first. Buckingham, UK: Open University Press,1997.

25. Achterberg WP, Pieper MJ, van Dalen-Kok AH, de Waal MW, Husebo BS, Lautenbacher S, Kunz M, Scherder EJ, Corbett A. Pain management in patients with dementia. Clin Interv Aging. 2013;8:1471-82.

26. Collins A. Measuring what really matters. Towards a coherent management system to support person-centred care. The Health Foundation Thought Paper 2014. Accessed at http://www.health.org.uk/sites/default/files/MeasuringWhatReallyMatters.pdf on 4/4/2022

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