DEMENTIA

Pain relief—a first-line response to agitation in dementia?

Bob Woods and Esme Moniz–Cook

Now that antipsychotic medication is all but proscribed for the treatment of distress and disturbed behavior in people with dementia in care homes, the drive to identify effective alternative approaches is pressing. A study from Norway suggests that paracetamol may be effective in many cases, but some caution is required.

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The use of antipsychotic medication to treat people with dementia has become something of a cause celebre in recent years after an authoritative report highlighted the excess mortality associated with the use of these medications.[1] Following this report, the UK government set ambitious targets for a two-thirds reduction in the use of antipsychotic drugs for the treatment of individuals with dementia.[2] Particular concern has been raised over the use of antipsychotic medication in care homes to assist in the management of people with dementia-related disturbed behavior; thus, alternative approaches are urgently required. In this context, much encouragement should be taken from a report from Norway of a cluster randomized controlled trial in residents of nursing homes, which showed the positive effect of a step-wise protocol for the treatment of pain on reducing behavioral disturbance in people with dementia.[3]

The rationale for treating pain in people with dementia is clear: people with severe dementia could have difficulty in communicating pain, so behavioral disturbance might be viewed as a means of communicating an unmet need,[4] which could plausibly be a need for pain relief. Providing pain relief could, therefore, assist in reducing behavioral disturbance in individuals with dementia. Indeed, Husebo *et al.*[3] showed that treatment of people with dementia by use of analgesic medication over an 8-week period reduced agitation by an average of 17% compared with residents who received standard care (control group).

Most of the 352 participants in the Norwegian study were managed at the first stage of the step-wise protocol: 63% of the residents were prescribed 3 g of paracetamol (acetaminophen) per day, and around 5% who were already receiving low-dose paracetamol had their dosage increased.[3] Nearly one-quarter of the residents who were already receiving analgesic treatment were prescribed morphine or opioid patches, or had their dosage of opioid treatment increased. Treatment with opioid medications could have caused adverse effects, such as constipation, nausea and/or sedation.[5] Husebo *et al.*[3] argue that reduced agitation in the treated individuals could not simply be attributed to sedation, as no decline in either activities of daily living or cognition was observed in the intervention group compared with the control group. However, the authors acknowledge that a small number of participants were withdrawn from the study due to drowsiness, with more withdrawals overall in the intervention group than in the control group (5.1% versus 1.7%).

> “Assessment of pain in people with severe dementia is difficult...”

This study has its limitations. The primary outcome measure—the Cohen–Mansfield Agitation Inventory[6]—was completed on the basis of staff observations of resident agitation over a 2-week period. These observations may have been influenced by various factors, including the amount of contact between the staff member and the resident, as well as negative bias introduced by staff distress and burnout. To retain the blind nature of the study must have been challenging, as no placebo medication or patches were offered to residents in the control units, so the researchers and staff could have been aware of which residents were receiving medication. The agitation measure included a diverse range of behavior, ranging from screaming or spitting to hoarding or hitting,[6] and future studies should address which specific aspects of behavior are affected by each type of intervention.

Clinicians were encouraged to maintain the administration of stable doses of psychotropic drugs to the residents throughout the study, so we can only speculate as to whether a reduction in agitation would ultimately lead to a reduction in the use of antipsychotic medication.[3] At baseline, one-quarter of the participants were already being prescribed antipsychotic drugs, half were receiving anxiolytic or hypnotic medication, and a further quarter were receiving drugs to treat dementia. Two-fifths of the participants were also receiving peripheral analgesics, and one-fifth were already receiving opioid analgesics, so the study cohort seems to have been a heavily medicated sample of nursing home residents with dementia, which included residents who were receiving multiple medications. An investigation into the effects of the pain-relief protocol in patients who are not receiving such high levels of psychotropic medication would be of interest.

In the National Institute for Health and Clinical Excellence–Social Care Institute for Excellence (NICE–SCIE) guidelines,[7] the preferred term to describe agitation and behavioral disturbance is ‘behavior that challenges’. This wording implies that the distress or the behavior not only affects the person with dementia, but also affects other individuals, such as their relatives and other residents and staff members of the care homes. Doctors are, therefore, placed in a position of needing to respond to care-home staff who feel powerless to respond to the distress and/or disturbance of the people with dementia in their care. The doctor may be well-aware that guidelines on managing patients with challenging behavior stipulate that non-pharmacological approaches should be tried first,[7] that as many as 14% of behavioral problems will remit within 4 weeks in the absence of pharmacological intervention,[8] and that physical factors and the patient’s social environment have roles in the development and maintenance of behavioral disturbance. However, an intervention is needed to manage the behavioral disturbance, so we run the risk that one pharmacological response (with well-documented adverse effects) may be replaced by another (with as yet unknown adverse effects).

The NICE–SCIE guidelines[7] recommend that the comprehensive assessment of a

person with dementia should specifically include an investigation into 'undetected pain or discomfort'. Assessment of pain in people with severe dementia is difficult, but by using observational measures (rather than relying on self-reporting) we may be able to make a reasonable assessment of pain in many individuals.[9,10] An alternative approach to the current study would have been to assess all residents on the pain scale and then perform a thorough review of the potential causes of the pain in those found to be above a defined threshold score. An intervention plan—possibly including non-pharmacological approaches, such as improving the person's comfort or using massage—could then be developed for those individuals.

In our ongoing NIHR-funded work on challenging behavior in care homes (Challenge ResCare), we routinely use the Abbey Pain Scale. In our last 50 residents for whom a care plan was developed, 40% scored above the accepted threshold score for mild pain on this observational scale. Multiple physical factors were identified that could have contributed to the pain, including osteoarthritis (50%), back pain (35%) and recent fractures (20%). However, the most frequent physical health problem associated with pain was constipation (present in 55% of cases)—a common side effect of treatment with opioid analgesics. This factor, and other physical health factors, must be assessed carefully when the need for pain relief medication is being reviewed.

Interestingly, Husebo *et al.*[3] reported a statistically significant reduction in scores on the pain scale in the residents who were treated with analgesics, and the treatment effect (reduced agitation) was associated with a reduction in pain. A more rational approach might have begun by examining the effects of pain relief on pain, with the effects of the intervention on disturbed behavior as a secondary outcome. This study could have led on to a trial of reducing antipsychotic medication in individuals with dementia and treating pain to reduce behavioral disturbances.

What is the take-home message from the current study? Should analgesics replace antipsychotics as the first line of medical response in people with behavioral disturbances? A switch to analgesics might reduce some adverse events associated with the use of antipsychotics, but this approach would move us little further forward in addressing the complexities of challenging behavior in patients with dementia. Furthermore, we need to understand why the inappropriate use of antipsychotic medication has arisen. Husebo *et al.*'s study validates the importance of including pain in the multidimensional assessment of 'behavior that challenges' in people with dementia (as recommended by NICE–SCIE[7]), and suggests that an adequate dose of paracetamol should be considered for pain relief in these individuals. However, the results should not be taken as a blanket invitation for doctors to substitute antipsychotic medication with pain-relieving medication for the treatment of challenging behavior in people with dementia.

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Competing interests
The authors declare no competing interests.

1. Banerjee, S. The use of anti-psychotic medication for people with dementia: time for action. A report for the Minister of State for Care Services. *Department of Health* [online], http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_108303 (2009).
2. Quality outcomes for people with dementia: building on the work of the National Dementia Strategy. *Department of Health* [online] http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_119827 (2010).
3. Husebo, B. S., Ballard, C., Sandvik, R., Nilsen, O. B. & Aarsland, D. Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial. *BMJ* **343**, d4065 (2011).
4. Cohen-Mansfield, J. Nonpharmacologic interventions for inappropriate behaviors in dementia: a review, summary, and critique. *Am. J. Geriatr. Psychiatr.* **9**, 361–381 (2001).
5. Regnard, C. Pain is not the only cause of distress in dementia. *BMJ* **343**, d5355 (2011).
6. Rabinowitz, J. *et al.* Factor analysis of the Cohen-Mansfield Agitation Inventory in three large samples of nursing home patients with dementia and behavioral disturbance. *Am. J. Geriatr. Psychiatr.* **13**, 991–998 (2005).
7. Dementia: supporting people with dementia and their carers in health and social care. Clinical Guideline 42. *National Institute for Health and Clinical Excellence* [online], http://guidance.nice.org.uk/CG42 (2006).
8. Howard, R. *et al.* Donepezil for treatment of agitation in Alzheimer's disease. *N. Engl. J. Med.* **357**, 1382–1392 (2007).
9. Horgas, A. L., Elliott, A. F. & Marsiske, M. Pain assessment in persons with dementia: relationship between self-report and behavioral observation. *J. Am. Geriatr. Soc.* **57**, 126–132 (2009).
10. Zwakhalen, S. M., Hamers, J. P. H., Abu-Saad, H. H. & Berger, M. P. Pain in elderly people with severe dementia: a systematic review of behavioural pain assessment tools. *BMC Geriatr.* **6**, 3 (2006).

PARKINSON DISEASE

The controversy of levodopa toxicity in Parkinson disease

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In the past two decades, there has been concern that levodopa—the gold-standard therapy for Parkinson disease (PD)—may be toxic to dopaminergic neurons. However, findings from a recent study suggest that chronic use of levodopa does not enhance progression of PD pathology. Can we make sense of this controversy?

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Parkinson disease (PD) is a prevalent neurodegenerative disease that causes both motor and nonmotor symptoms. Over the past two decades, concern has been raised that levodopa—the gold-standard therapy for patients with PD—could have toxic effects on dopaminergic neurons. Although several *in vitro* studies found high doses of levodopa to be toxic to cultured dopaminergic neurons,[1] little evidence has been found to suggest that this drug causes harm to the neurons in either *in vivo* animal models of disease or patients with PD.[2,3] The toxicity of levodopa has, therefore, become a controversial issue. In a recent study published in *Neurology*, Parkkinen *et al.*[4] evaluated the relationship between cumulative lifetime dose of levodopa and nigral neuronal count and Lewy body pathology in patients with PD. The authors concluded that chronic levodopa use in patients with PD did not enhance progression of PD pathology.