



Medicines evidence commentary

commentary on important new evidence from medicines awareness weekly

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Pharmacological and non-pharmacological interventions for treating aggression and agitation in people living with dementia

A systematic review and network meta-analysis found that some non-pharmacological interventions were clinically more effective than usual care or pharmacological interventions for treating aggression and agitation in people living with dementia. Despite some limitations, the findings of this review support NICE recommendations that people living with dementia who experience agitation or aggression should be offered personalised activities to promote engagement, pleasure and interest.

Overview and current advice

The NICE guideline on [dementia](#) covers diagnosing and managing dementia and makes recommendations on training staff and helping carers to support people living with dementia. This includes managing non-cognitive symptoms of dementia such as agitation, aggression, distress and psychosis. NICE recommends that before starting non-pharmacological or pharmacological treatment for distress in people living with dementia, a structured assessment should be conducted to explore possible reasons for the distress and to check for and address clinical or environmental causes (for example pain, delirium or inappropriate care). People living with dementia should be offered psychosocial and environmental interventions to reduce distress as initial and ongoing management, and they should also be offered personalised activities to promote engagement, pleasure and interest if they become agitated or aggressive.

NICE recommends that antipsychotics should only be offered to people living with dementia who are either at risk of harming themselves or others, or who are experiencing agitation, hallucinations or delusions that are causing them severe distress. Before starting antipsychotics, the benefits and harms should be discussed with the person and their family members or carers (as appropriate). NICE has produced a patient decision aid on [antipsychotic medicines for treating agitation, aggression and distress in people living with dementia](#) to support this discussion.

Valproate should not be offered to manage agitation or aggression in people living with dementia, unless it is indicated for another condition.

New evidence

A systematic review and network meta-analysis ([Watt et al. 2019](#)) compared pharmacological and non-pharmacological interventions for treating aggression and agitation in people living with dementia.

A total of 163 [randomised controlled trials](#) (23,143 people) were included in the [network meta-analysis](#). Nearly all studies included people with a mean age of 70 years or older, and in most studies at least 50% of participants were women. The review included studies reporting on people diagnosed with Alzheimer's disease (27.5%) and with different dementia types such as vascular or mixed dementia (32.8%). Many studies did not report participant diagnosis (37%) or specify the severity of dementia. Most studies were completed in a nursing home or assisted living facility setting (65.1%) and were less than 11 weeks duration (54.5%). Interventions included pharmacological treatments such as antidepressants, anticonvulsants, antipsychotics, cannabinoids, cholinesterase inhibitors and memantine, and non-pharmacological interventions such as modification of activities of daily living, outdoor activities, exercise, music, massage, reminiscence and touch therapies. Eligible comparators were usual care or another pharmacological or non-pharmacological intervention. The primary outcome was change in aggression with change in agitation as a secondary outcome. The authors also reported on the combined outcome of agitation and aggression.

The network meta-analysis attempted to rank all of the interventions included in the systematic review. Non-pharmacological interventions were the most highly ranked interventions in nearly all subgroups. The analysis comparing interventions for physical aggression (22 studies; 2,780 people) found that outdoor activities were more effective than antipsychotics (standardised mean difference [SMD]: -1.68, 95% [confidence interval](#) [CI] -3.35 to -0.09), and that modification of activities of daily living, massage and touch therapy, and outdoor activities were all more effective than caregiver education. For verbal aggression, the analysis (15 studies; 1,736 people) found that modification of activities of daily living (SMD:-0.97, 95% CI: -1.76 to -0.97) and massage and touch therapy (SMD:-1.21, 95% CI: -2.1 to -0.25) were more effective than caregiver education and support, and that massage and touch therapy (SMD:-0.53, 95% CI: -0.95 to -0.1) was more effective than usual care. All these differences were clinically important based on the Cohen-Mansfield Agitation Inventory. Additionally, people treated with certain non-pharmacological interventions such as massage and touch therapy showed a clinically important improvement compared with usual care or caregiver education for physical agitation. Similar

results were achieved for the combined outcome of agitation and aggression. No intervention was shown to be effective for treating verbal agitation. Limitations of this systematic review and network meta-analysis included missing outcome data and inclusion of studies at high or unclear risk of bias. The authors were unable to describe the effectiveness of interventions for different types of dementia or for people with more severe violent and aggressive behaviour. Additionally, the review did not assess adherence, costs or harms associated with the different interventions.

Commentary

**Commentary provided by Professor Robert Howard, Professor of Old Age Psychiatry,
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Good practice in the management of behavioural symptoms that arise in people with dementia should always involve an initial consideration of environmental and psychosocial interventions. However, there will be situations where such strategies have been tried and have failed or when the behaviour results in such distress or risk that a pharmacological intervention will be needed. The medicines with the best evidence, particularly for the treatment of aggression in people with dementia, are atypical antipsychotics but with associated adverse effects.

This comprehensive systematic literature review and network meta-analysis found that a number of psychosocial interventions were effective against aggressive and agitated behaviours in dementia when they were compared with usual treatment. The authors of the review compared pharmacological and non-pharmacological intervention studies and concluded, based on effect sizes that emerged from a network meta-analysis of both direct and indirect evidence, that non-pharmacological interventions appeared to be more effective in reducing agitation and aggression.

This would be a remarkable conclusion with profound consequences for clinical practice. But, there's an important question as to just how directly we should compare treatment effect sizes from pharmacological trials, that are generally placebo-controlled and blinded, with those from non-pharmacological (psychosocial intervention) studies, which have used usual care or an educational intervention as a control and where blinding of participants and outcomes assessors is likely to be less complete. These factors would tend to favour the apparent effectiveness of the psychosocial interventions, and consequently we should consider the results of any comparisons between the pharmacological and non-pharmacological approaches to agitation and aggression cautiously. Head-to-head comparisons of these approaches in clinical trials, or more rigorous use of active control conditions and participant and outcomes assessor blinding in non-pharmacological trials would be needed before we could draw useful conclusions.

The value in this review is that it supports the recommendations in the NICE guideline on [dementia](#), that a wide range of environmental and psychosocial interventions can make a positive difference to agitation and aggression in people with dementia. In practice, such interventions may not always be considered before pharmacological interventions are used. Dementia and other care facilities should have sufficient numbers of trained staff to be able to deliver such evidenced interventions and equivalent community-based services should be available to people with dementia living in their own homes.

Declaration of interests:

Professor Robert Howard, Trustee of Alzheimer's Research UK

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References

Watt JA, Goodarzi Z, Veroniki AA et al. (2019). [Comparative efficacy of interventions for aggressive and agitated behaviors in dementia: a systematic review and meta-analysis](#). *Annals of Internal Medicine* 171: 633–42

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