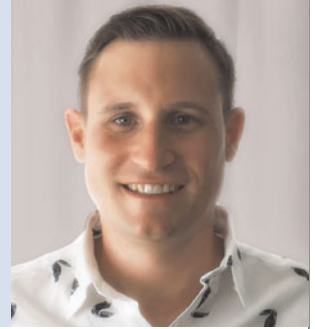


## Editorial

# Are neuropsychiatric symptoms modifiable risk factors for cognitive decline in Alzheimer's disease and vascular dementia?<sup>†</sup>

George Savulich, John T. O'Brien and Barbara J. Sahakian



## Summary

Alzheimer's disease and vascular dementia are associated with overlapping symptoms of anxiety and depression. More accurate discrimination between emerging neuropsychiatric and cognitive symptoms would better assist illness detection. The potential for protection against cognitive decline and dementia following early identification and intervention of neuropsychiatric symptoms warrants investigation.

## Declaration of interest

B.J.S. consults for Peak, Mundipharma and Cambridge Cognition. J.T.O. has acted as a consultant for TauRx, Axon, GE Healthcare and Lilly.

## Keywords

Dementia; anxiety; depression; neuropsychiatric symptoms.

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**George Savulich** (pictured) is Research Associate at the Department of Psychiatry, University of Cambridge, UK. **John T. O'Brien** is Foundation Professor of Old Age Psychiatry at the Department of Psychiatry, University of Cambridge, UK. **Barbara J. Sahakian** is Professor of Clinical Neuropsychiatry at the Department of Psychiatry, University of Cambridge, UK.

Innovations in the field of public health have lengthened the average human lifespan considerably. Nonetheless, in the UK there are currently over 800 000 people living with dementia, including Alzheimer's disease and vascular dementia, with cases expected to double every 20 years. Both of these conditions are characterised by highly comorbid symptoms of anxiety and depression. However, poor discrimination between the primary affective pathology and the pathology inherent to the onset of dementia complicates early detection. For example, apathy can occur in depression but is also a core feature of Alzheimer's disease and related dementias that has shown to manifest early in prodromal phases of the disease.<sup>1</sup> Whereas the onset of cognitive symptoms is likely to precipitate anxiety before receiving a diagnosis, other neuropsychiatric symptoms may become exacerbated at later stages of disease progression (e.g. aggression, psychosis). However, growing interest in the association between premorbid neuropsychiatric symptoms and early cognitive decline now highlights their prognostic impact on a future diagnosis of dementia. Better discrimination between the neuropsychiatric and cognitive symptoms would not only help ensure accurate diagnosis but also facilitate more targeted interventions earlier in the course of the neurodegenerative process.

## Anxiety and depression in dementia

Neuropsychiatric symptoms are associated with poor outcome, limitations in activities of daily living and reduced quality of life in people with dementia<sup>11</sup>. Anxiety and behavioural disturbances are also prominent in vascular dementia, although very few studies have investigated their association with cognitive impairment. A recent

systematic review and meta-analysis reported that the presence of anxiety predicts both Alzheimer's disease and vascular dementia.<sup>2</sup> These authors recommend that the potential mitigating effects of early anxiety treatment on subsequent cognitive decline should be explored further, thus raising the possibility that neuropsychiatric symptoms may be modifiable risk factors for dementia. However, it is important to remember that reverse causality is also possible, such that anxiety and depressive symptoms may be early manifestations of Alzheimer and vascular pathology, which subsequently causes the dementia. Others have supported a positive association between anxiety and an increased risk of cognitive impairment and dementia in community samples. A significant proportion of older adults with mild cognitive impairment (MCI), often the prodromal stage of Alzheimer's disease, will also experience comorbid depression. People with MCI and depression are at more than twice the risk of converting to Alzheimer's disease, with evidence showing increased rates of brain atrophy. Whether such evidence indicates that depression confers additional risk, or represents a marker of a 'more severe' form of MCI that is more likely to progress rapidly, remains to be clarified. For example, depression occurring more than ten years before dementia may be a clearer risk factor through long-term effects on neurotransmitter systems and possible structural changes in the brain including the hippocampal formation. In contrast, depression first occurring at the MCI stage may not be a 'true' risk factor for Alzheimer's disease and could plausibly reflect early degenerative changes in brain areas that regulate mood. Such comorbidities pose a significant challenge to clinical management and outcome. Differentiating neuropsychiatric symptoms from dementia is made even more difficult due to the lack of valid instruments, potential discrepancies between patient and caregiver reports and the lack of consensus around how to best define them.

## Early identification and classification

Undiagnosed depression in older adults often produces cognitive impairments that are mistaken for the first symptoms of dementia or MCI. If depressive symptoms are confused with early cognitive decline, then a potentially treatable problem may go undetected. However, objective and reliable tests of cognition can be used to

<sup>†</sup> See Becker *et al.*<sup>2</sup>

identify episodic memory impairment that is characteristic of the first symptoms of MCI-related Alzheimer's disease. The Cambridge Neuropsychological Test Automated Battery (CANTAB) Paired Associates Learning (PAL) task, for example, is a non-verbal measure of hippocampal-dependent learning and memory that is known to be sensitive to preclinical Alzheimer's disease. Errors at the six-pattern stage have shown to classify patients with Alzheimer's disease with 98% accuracy.<sup>3</sup> Performance on this task has also shown to distinguish questionable dementia from major depression not related to Alzheimer's disease. Furthermore, impaired memory processes such as recognition, recall, naming and fluency tasks were more specific to people with questionable dementia, whereas impairments in tests of attentional and executive function were more specific to people with depression. The CANTAB PAL task can therefore be used as an appropriate screening tool for selecting patients who meet criteria for preclinical Alzheimer's disease for inclusion in clinical trials of new antidementia therapies. In MCI, poor performance on this task has shown to be associated with reduced hippocampal volume, increased cerebrospinal fluid markers of amyloid- $\beta$  and tau and reduced activities of daily living. Using CANTAB PAL as a neuropsychological marker of cognitive decline ensures that memory deficits can be accurately attributed to the cognitive symptoms of dementia, thereby increasing the likelihood of selecting the best treatment option. Unlike Alzheimer's disease, cognitive decline in vascular dementia is more variable and represents a range of pathology, with no clear diagnostic criteria for vascular cognitive impairment. Subcortical vascular pathology typically involves disrupted frontostriatal circuits. As memory is relatively preserved in vascular dementia compared with Alzheimer's disease, tests of attention and executive function such as the Montreal Cognitive Assessment Scale and the cognitive subscale of the Vascular Dementia Assessment Scale (VADAS-cog) are more likely to be sensitive.<sup>4</sup>

A number of approaches useful for identifying and classifying neuropsychiatric symptoms require more detailed investigation. These include cluster and confirmatory factor analyses of neuropsychiatric symptoms for establishing shared or unique aetiologies, positron emission tomography (PET) ligand imaging of neurotransmitter systems implicated in the pathophysiology of neurodegeneration (e.g. increased striatal dopamine D2/D3 receptor availability in Alzheimer's disease with delusions; an association between reduced 5-HTC receptor expression and symptoms of major depression in Alzheimer's disease) and predictive genotyping.<sup>1</sup> The extent to which neural networks underlying neuropsychiatric symptoms overlap with neural networks underlying cognitive impairments in people with Alzheimer's disease and vascular dementia pose additional avenues of research (e.g. apathy and executive dysfunction). Investigating the associations between neuropsychiatric symptoms, cognitive performance and biomarkers of tau and amyloid- $\beta$  burden would also help better understand key predictors.

### Effective intervention

No new drugs have been approved for Alzheimer's disease since 2003, and there are currently no licenced drug treatments for vascular dementia. As the cholinergic system is involved in the control of attentional processes, anticholinesterase drugs are more likely to be effective for the treatment of attentional rather than memory dysfunction in Alzheimer's disease. Very little research has examined treatment effects in vascular cognitive impairment.<sup>4</sup> However, non-pharmacological interventions for neuropsychiatric symptoms in dementia have shown considerable promise. A meta-analysis has shown that non-pharmacological interventions delivered by caregivers significantly reduce the frequency and severity of neuropsychiatric and

behavioural symptoms in people with dementia.<sup>5</sup> Caregiver's negative reactions toward these symptoms were also significantly reduced. It was further identified that the most successful non-pharmacological interventions were multicomponent, tailored to the needs of the patient and their caregiver and delivered at home. We propose that novel non-pharmacological interventions that target both neuropsychiatric and cognitive symptoms are needed, such as cognitively stimulating games and activities that use exciting new devices or rewarding technology-based interventions. Targeting symptoms, rather than diagnostic category, may be particularly useful for promoting goal-directed behaviour in those with psychiatric comorbidities. Increasing engagement with non-pharmacological interventions could also reduce apathetic or depressive symptoms that most frequently occur in MCI/early Alzheimer's disease and also persist in vascular dementia. Importantly, use of technology allows for the optimal titration of task-related difficulty for the individual participant in real time, thus ensuring high levels of confidence, motivation and a personalised approach. Gaming technology also helps reduce some of the stigma associated with mental health treatments. Simultaneously remediating cognitive and motivational deficits may further yield direct benefits on mood or self-esteem, as achieving better cognitive performance can be attributed to the self as opposed to a drug. We further recommend delivering such interventions as early as possible in the course of the illness, before damage to the brain is usually too severe for improvements in functional outcome measures.

### Comment

Dementia continues to be a growing problem, with total costs surpassing £20 billion per year. However, as yet no drug therapies have shown to be effective for the prevention of cognitive decline and dementia. Longitudinal studies with large sample sizes and in pre-symptomatic populations are needed to better address the role of neuropsychiatric symptoms in the development and disease progression of Alzheimer's disease, vascular dementia and other dementias. Standardised cognitive testing should be routinely used to enable early illness detection and facilitate appropriate trial selection among subgroups of patients. This would also help in choosing the best strategy for treatment. Increasing evidence indicates the prediction of neuropsychiatric symptoms on a future diagnosis of dementia. Although causality cannot be definitely assumed, randomised controlled trials using novel pharmacological and non-pharmacological interventions to investigate the effects of early anxiety and depression treatment on subsequent cognitive outcome in dementia are needed. Effective non-pharmacological interventions that target both cognitive and neuropsychiatric symptoms may synergise to alter the course of dementia-related cognitive decline and achieve the best possible outcome.

**George Savulich** , PhD, Research Associate, Department of Psychiatry, University of Cambridge, UK; **John T. O'Brien**, DM, FMedSci, Foundation Professor of Old Age Psychiatry, Department of Psychiatry, University of Cambridge, UK; **Barbara J. Sahakian**, DSc, FMedSci, Professor of Clinical Neuropsychiatry, Department of Psychiatry, University of Cambridge, UK

**Correspondence:** Dr George Savulich, Department of Psychiatry, University of Cambridge, Forvie Site, Robinson Way, Cambridge CB2 0SZ, UK.  
Email: [gjs46@medschl.cam.ac.uk](mailto:gjs46@medschl.cam.ac.uk)

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