International Psychogeriatrics (2023), 35:11, 592–594 © International Psychogeriatric Association 2023
doi:10.1017/S1041610223000388

COMMENTARY

Magnets for motivation?

Commentary on "Treatment of Behavioral and Psychological Symptoms of Dementia Using Transcranial Magnetic Stimulation: A Systematic Review" by Murphy *et al.*

Kristina F. Zdanys

Department of Psychiatry, Division of Geriatric Psychiatry and Behavioral Health, University of Connecticut School of Medicine, Farmington, CT, USA
Email: zdanys@uchc.edu

Behavioral and psychological symptoms of dementia (BPSD) are neuropsychiatric symptoms that occur in the context of Alzheimer's disease and related dementias (ADRD). The range of symptoms may include anxiety, depression, irritability, sleep disturbance, agitation, aggression, psychosis, and apathy (Lyketsos *et al.*, 2002). BPSD are associated with poorer outcomes for patients with dementia, including mortality and earlier transition from living at home to higher levels of care. BPSD also have significant implications for caregivers, including increased anxiety, depression, sleep disturbance, and poor medical outcomes (Alzheimer's Association, 2023). In many ways, BPSD are more debilitating for patients and caregivers than the progressive memory decline that is the hallmark of ADRD.

Because of the burden of BPSD on our patients and their caregivers, effective treatment approaches are imperative. Nonpharmacological interventions are considered first line, and typically focus on addressing underlying medical, social, emotional, and environmental triggers leading to the development of symptoms (Kales *et al.*, 2014). BPSD are not "one size fits all" in either presentation or treatment, requiring close investigation of these and other triggers. Time and effort are required both by the treatment team and caregivers to develop individualized plans that are mindful of the specific variables involved in BPSD triggers and reactions.

When nonpharmacological approaches are either undereffective or ineffective, and also for situations in which there might be emergent safety concerns, pharmacological treatments of BPSD may be considered. There are no FDA-approved medications for the treatment of the neuropsychiatric symptoms of ADRD (Kales *et al.*, 2014). Choice of medications is made based on the patient's medical and psychiatric history, predominant symptom presentation, medication safety profile, and other individual factors. Among the most concerning safety issues is regarding the use of antipsychotics for patients with ADRD: in 2005, the FDA issued a black-box warning against the use of atypical antipsychotics in older adults with dementia due to increased risk of death. This warning was extended to all antipsychotics in 2008 (Rubino *et al.*, 2020). Due to safety concerns and a lack of convincing data for the use of medications in BPSD, alternative treatment approaches are needed.

In "Treatment of Behavioral and Psychological Symptoms of Dementia Using Transcranial Magnetic Stimulation: a Systematic Review," Murphy *et al.* present data from randomized controlled trials (RCTs) investigating the use of transcranial magnetic stimulation (TMS) for the treatment of BPSD. They identified 11 RCTs in which individuals with BSPD were treated with TMS and concluded based on the limited data that repetitive TMS may be beneficial for older adults with BPSD, although more data is needed. The best evidence for the use of TMS was for patients presenting with apathy (Murphy *et al.*, 2023).

In recent years, more attention has been given to apathy as a prominent symptom of BPSD, with efforts to better understand its underlying neural circuitry (Steffens *et al.*, 2022). While classically described as a loss of motivation and goal-directed activity, the diagnostic criteria for apathy are defined more specifically now. In 2021, a consensus panel published diagnostic criteria for apathy among people with neurocognitive disorders and described these patients as exhibiting diminished initiative, interest, and/or emotional expression (Miller *et al.*, 2021). These changes impair the individual's functioning and are not attributable to physical changes, psychiatric illness, or substance use (among other qualifiers).

With better definition of apathy, there has also been more scholarly exploration of apathy in the context of neurocognitive disorders. In *International Psychogeriatrics,* there have been several recent articles highlighting this topic beyond what is described in Murphy *et al.* Earlier this year, Connors *et al.* published their investigation of apathy, depression, and mild cognitive impairment (MCI). They found that apathy increases in MCI and is associated with worse clinical outcomes related to cognition, function, caregiver burden, and other neuropsychiatric symptoms (Connors *et al.*, 2023). An earlier systematic review in the journal examined the prevalence of depression, anxiety, and apathy across dementias less prevalent than Alzheimer's disease (AD) and found that these neuropsychiatric symptoms were inconsistently investigated with poor sample sizes, necessitating further research (Collins *et al.*, 2020).

Apathy is the most common behavioral symptom seen in AD with a prevalence estimated just below 50% (Zhao *et al.*, 2016). Rates vary across other etiologies of neurocognitive disorder, with apathy seen among 62 – 89% of patients with behavioral-variant frontotemporal dementia (FTD) (Mendez *et al.*, 2008) and 35 – 100% of patients with dementia with Lewy Bodies (DLB) (Liu *et al.*, 2019). Historically, apathy was likely under-recognized as a form of BPSD because patients with apathy may not have an identifiable symptom at first glance. This is especially true in higher levels of care such as the nursing home setting, in which patients who are more withdrawn are not considered "problematic" and caregivers may not be familiar with the individual's baseline level of activity and engagement. A psychiatric analogy might be that apathy is to negative symptoms of schizophrenia what agitation is to positive symptoms. The positive symptoms are often more apparent clinically.

Apathy is difficult to treat. Data to support non-pharmacological interventions are mixed with some evidence of benefit when tailored to the individual patient (Brodaty & Burns, 2012). There are no FDA-approved medications for the treatment of apathy in the context of BPSD (Steffens *et al.*, 2022). If medications are being prescribed, it is important to consider the etiology of the patient's dementia. Acetylcholinesterase inhibitors have demonstrated some benefits in DLB (Liu *et al.*, 2019). Selective serotonin reuptake inhibitors may be slightly beneficial for apathy in FTD (Young *et al.*, 2018). For the treatment of apathy in Alzheimer's disease, there is some evidence for the use of methylphenidate (Rosenberg *et al.*, 2013) with insufficient evidence to support the use of either acetylcholinesterase inhibitors or antidepressants (Ruthirakuhan *et al.*, 2008).

With this limited data as context, the systematic review of Murphy *et al.* addresses the need for alternative approaches to the treatment of apathy (and other symptoms of BPSD) by exploring the data to support TMS. TMS has been demonstrated to be a safe treatment for older adults with AD (Freitas *et al.*, 2011) and offers a safer alternative to electroconvulsive therapy, which has been shown to be somewhat effective for the management of agitation and aggression in dementia but has higher risk of delirium and potential cardiovascular complications (van den Berg *et al.*, 2018).

Although the results of Murphy *et al.*'s systematic review are encouraging, and the treatment appears safe for older adults with dementia, there are additional considerations that may impact the feasibility of using TMS in this population for the treatment of dementia-related apathy and other BPSD. As alluded to in their conclusion, TMS involves multiple sessions of treatment. This poses a logistical hurdle to patients with dementia who rely on caregivers for coordination of care and transportation support. Additionally, for patients with apathy who already are exhibiting diminished initiative, there may be difficulty engaging them to participate in treatments with that degree of frequency. Although there was some variability in duration across the trials cited by Murphy *et al.*, many required participation for as many as 5 days per week for 2 – 6 weeks. Even among studies that showed benefit for apathy, some did not demonstrate benefit for apathy until after 4 weeks of treatment (Zhang *et al.*, 2019) and another showed that benefit for apathy was not sustained 4 – 8 weeks after treatment (Padala *et al.*, 2020). Thus, TMS treatment for apathy may require intensive treatment for several weeks for a benefit that wanes quickly.

As an extension of the limitations of transportation, although TMS is increasingly available, it is not yet practiced in all areas and so it may not be available at a center (private or academic) close enough to the patients to participate. Another potential challenge is that Centers for Medicare and Medicaid Services (CMS) do not identify apathy or BPSD as a clinical indication for treatment with TMS, and a diagnosis of dementia is regarded as a relative contraindication for TMS treatment (cms.gov). More robust data will likely be needed for CMS to consider coverage for this indication.

It is interesting that among the available studies there did not appear to be a significant benefit of TMS for depressive symptoms. Part of the difficulty in evaluating the literature on TMS for BPSD is that BPSD are largely heterogeneous, so having enough subjects to participate in RCTs who have depression as a component of their BPSD presentation may be difficult. In a clinical setting, depression may be considered as a separate diagnosis rather than a neuropsychiatric symptom secondary to dementia. Some studies demonstrated global improvement for BPSD without reporting significant benefit for

https://doi.org/10.1017/S1041610223000388 Published online by Cambridge University Press

individual subscales (Murphy *et al.*, 2023), so it is possible that improvement for depressive symptoms contributed to the overall Neuropsychiatric Inventory (NPI) improvements.

In summary, effective nonpharmacological treatments for BPSD are needed. Among symptoms of BPSD, apathy is one of the most common and most difficult to treat. TMS shows some potential as an alternative and effective treatment for apathy in dementia, but logistical and financial challenges may make its implementation impractical. Despite these limitations, the research to date serves as a step in the right direction, especially for a neuropsychiatric symptom like apathy that often flies under the radar.

Conflicts of interest

None.

Acknowledgements

Thanks to Dr Neha Jain for assistance with the title of this paper.

References

Alzheimer's Association (2023). 2023 Alzheimer's disease facts and figures. *Alzheimer's & Dementia*, 19.

Brodaty, H. and Burns, K. (2012). Nonpharmacological management of apathy in dementia: a systematic review. *The American Journal of Geriatric Psychiatry*, 20, 549–564.

Centers for Medicare and Medicaid Services. (2022). LCD- Transcranial magnetic stimulation (TMS) in the treatment of adults with major depressive disorder (L34998). Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?LCDId=34998, Accessed 2 April 2023,

Collins, J. D., Henley, S. M. D. and Suarez-Gonzalez, A. (2020). A systematic review of the prevalence of depression, anxiety, and apathy in frontotemporal dementia, atypical and young-onset Alzheimer's disease, and inherited dementia. *International Psychogeriatrics*, 1–20.

Connors, M., Teixeira-Pinto, A., Ames, D., Woodward, M. and Brodaty, H. (2023). Apathy and depression in mild cognitive impairment: distinct longitudinal trajectories and clinical outcomes. *International Psychogeriatrics*, 30, 1–10.

Freitas, C., Mondragon-Llorca, H. and Pascual-Leone, A. (2011). Noninvasive brain stimulation in Alzheimer's disease: a systematic review and perspectives for the future. *Experimental Gerontology*, 46, 611–627.

Kales, H. C., Gitlin, L. N. and Lyketsos, C. G. (2014). Management of neuropsychiatric symptoms of dementia in clinical settings: recommendations from a multidisciplinary expert panel. *Journal of the American Geriatrics Society*, 62, 762–769.

Lyketsos, C. G., Lopez, O., Jones, B., Fitzpatrick, A. L., Breitner, J., DeKosky, S. (2002). Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the Cardiovascular Health Study. *JAMA.*, 288, 1475–1483.

Liu, J., Cooper, C. A., Weintraub, D. and Dahodwala, N. (2019). Pharmacological treatment of apathy in Lewy body disorders: a systematic review. *Parkinsonism & Related Disorders*, 60, 14–24.

Mendez, M. F., Lauterbach, E. C., Sampson, S. M. and ANPA Committee on Research (2008). An evidence-based review of the psychopathology of frontotemporal dementia: a report of the ANPA Committee on Research. *The Journal of Neuropsychiatry and Clinical Neurosciences.*, 20, 130–149.

Miller, D. S. *et al.* (2021). Diagnostic criteria for apathy in cognitive disorders. *Alzheimer's & Dementia*, 17, 1892–1904.

Murphy, K., Khan, A., Bachu, A. and Tampi, R. (2023). Treatment of behavioral and psychological symptoms of dementia using transcranial magnetic stimulation: a systematic review. *International Psychogeriatrics*, 1–12.

Padala, P. R. *et al.* (2020). Neuromodulation for apathy in Alzheimer's disease: a double-blind, randomized, sham-controlled pilot study. *Journal of Alzheimer's Disease*, 77, 1483–1493.

Rosenberg, P. B. *et al.* (2013). Safety and efficacy of methylphenidate for apathy in Alzheimer's disease: a randomized, placebo-controlled trial. *The Journal of Clinical Psychiatry.*, 74, 810–816.

Rubino, A. *et al.* (2020). Association of the US Food and Drug Administration antipsychotic drug boxed warning with medication use and health outcomes in elderly patients with dementia. *JAMA Network Open*, 3, e203630.

Ruthirakuhan, M. T., Herrmann, N., Abraham, E. H., Chan, S. and Lanctot, K. L. (2008). Pharmacological interventions for apathy in Alzheimer's disease. *The Cochrane Database of Systematic Reviews*, 5, CD012197.

Steffens, D., Fahed, M., Manning, K. and Wang, L. (2022). The neurobiology of apathy in depression and neurocognitive impairment in older adults: a review of epidemiological, clinical, neuropsychological and biological research. *Translational Psychiatry*, 12, 525.

Van den berg, J. F., Kruithof, H. C., Kok, R. M., Verwijk, E. and Spaans, H. P. (2018). Electroconvulsive therapy for agitation and aggression in dementia: a systematic review. *The American Journal of Geriatric Psychiatry*, 26, 419–434.

Young, J. J., Lavakumar, M., Tampi, D., Balachandran, S. and Tampi, R. R. (2018). Frontotemporal dementia: latest evidence and clinical implications. *Therapeutic Advances in Psychopharmacology*, 8, 33–48.

Zhang, F., Qin, Y., Xie, L., Zheng, C., Huang, X. and Zhang, M. (2019). High-frequency repetitive transcranial magnetic stimulation combined with cognitive training improves cognitive function and cortical metabolic ratios in Alzheimer's disease. *Journal of Neural Transmission (Vienna)*, 126, 1081–1094.

Zhao, Q. F. *et al.* (2016). The prevalence of neuropsychiatric symptoms in Alzheimer's disease: systematic review and metaanalysis. *Journal of Affective Disorders.*, 190, 264–271.

https://doi.org/10.1017/S1041610223000388 Published online by Cambridge University Press