International Psychogeriatrics (2023), 35:11, 608–610 © International Psychogeriatric Association 2023
doi:10.1017/S1041610223000418

COMMENTARY

Alleviating the social, health, and economic costs of apathy in dementia

Commentary on "Cost Consequence Analysis of Apathy in Dementia Methylphenidate Trial 2 (ADMET 2)" by Lanctôt *et al.*

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Apathy is characterized by diminished motivation that is associated with reduced goal-directed activity, goal-directed cognitive activity, and emotion (Robert *et al.*, 2006). It is the most common neuropsychiatric symptom in dementia and manifests in the pre-dementia stage of mild cognitive impairment (MCI) (Brodaty *et al.*, 2010; Sherman *et al.*, 2018). Several adverse consequences of apathy have been noted. Not only does it lead to poorer quality of life and reduced life satisfaction, it also causes greater functional impairment and thereby increases caregiver burden (Feast *et al.*, 2016). It has been associated with a greater risk of progression to dementia in MCI and poorer outcomes across a range of neurocognitive disorders (Connors *et al.*, 2023), including increased mortality (Lansdall *et al.*, 2019). Not surprisingly, apathy is associated with increased total patient care costs (Herrmann *et al.*, 2006), with a recent German study estimating that one point increase in the Apathy Evaluation Scale resulted in a 4.1% increase in total care costs, primarily due to increased caregiver burden (Kruse *et al.*, 2023).

Apathy has therefore been a treatment target in many trials. Of the pharmacological strategies, psychostimulants, and in particular methylphenidate, have been used most often. A meta-analysis (Kishi *et al.*, 2020) examined three double-blind placebo-controlled studies of methylphenidate for the treatment of apathy in Alzheimer's disease (AD). The drug resulted in an improvement in apathy scores [standardized mean difference SMD = −0.82 (−1.43 to −0.20) as well as cognition [SMD = −0.58 (−1.14 to −0.02). However, the duration of the trials was short, the sample sizes were small, and there was considerable heterogeneity. In this context, the trial by Mintzer *et al.* (2021) is noteworthy. This randomized control trial of methylphenidate included 200 patients (mean age 76 years) with clinically significant apathy of moderate to marked severity in patients with AD who were concurrently on cholinesterase inhibitors. The treatment group had a greater reduction in apathy at 6 months on the Neuropsychiatric Inventory [mean difference = −1.25 (−2.03 to −0.47), equivalent to Cohen d of 0.364], with the largest change occurring in the first 2 months. There were however no significant group differences in measures of cognition, activities of daily living, and quality of life. Other drugs that have been studied for the treatment of apathy include modafinil, Gingko biloba, cholinesterase inhibitors, memantine, antidepressants, review and discontinuation of atypical antipsychotics, caffeine, agomelatine, analgesics, oxytocin, tetrahydrocannabinol, mibampator (an AMPA receptor modulator), lavender, valproate, and semagacestat (a γ-secretase inhibitor), but with limited or no success (Harrison *et al.*, 2016; Mortby *et al.*, 2022). There is consequently no approved pharmacological treatment for apathy in dementia.

Considering that methylphenidate led to significant improvement in apathy, which persisted for 6 months in the Mintzer *et al.* (2021) trial, these authors have gone on to perform a cost consequence analysis of apathy treatment in this issue of the Journal (Lanctôt *et al.*, 2023). They examined resource utilization and quality of life at baseline, 3 months, and 6 months. They found that the costs were no different in the two groups, whether the cost of the medication was included or not. This is not surprising, given that the methylphenidate was not observed to improve function or cognition. Furthermore, the authors note that patients in the treatment group had a significantly increased likelihood of incurring an emergency room or outpatient, but not in-patient, hospital cost. This finding was

difficult to interpret as the drug group had not shown greater adverse effects, and the authors speculated that this was possibly due to greater attention to health care or activities in this group. However, the likelihood of incurring an additional healthcare cost when on methylphenidate cannot be discounted as the drug has been associated with adverse effects (Herrmann and Lanctôt, 2007).

Lanctôt *et al.* (2023) also examined the change in health-related quality of life using the EuroQol-five dimension-five level (EQ-5D-5L) questionnaire and converting this into a single country-specific utility value which reflects good or poor health state, with a value of 1.0 reflecting full health and 0.0 equal to being dead. This was a different analysis from what had been reported in the original report by Mintzer *et al.* (2021). The treatment group had higher utility values than the placebo group at 3 and 6 months, with a significant group-by-time interaction. However, this was a modest effect, and its clinical and economic value is difficult to judge.

It is reasonable to conclude that while treatment with methylphenidate does appear to reduce apathy, it does not lead to reduced cost or care, and the improvement in quality of life, if any, is modest. Similar cost–benefit analyses have not been performed with the other drugs listed above, ostensibly because the clinical benefits were not convincingly demonstrated.

Several nonpharmacological treatments for methylphenidate have been examined and these have previously been reviewed (Dykstra Goris *et al.*, 2016; Harrison *et al.*, 2016; Mortby *et al.*, 2022). The modalities of interventions have included social interaction, multi-sensory stimulation, engagement in creative activities, pet therapy, music therapy, art therapy, recreational activities, exercise, brief emotional shaping intervention, progressive muscle relaxation, and individualized cognitive behavior therapy. Recent work has included the application of brain stimulation techniques such as transcranial direct current stimulation (tDCS) (Nguyen *et al.*, 2018) and repetitive transcranial magnetic stimulation (rTMS) (Padala *et al.*, 2018; 2020). Most of these studies have been limited by small sample sizes, limited duration of follow-up, inadequate tools for the assessment of apathy, and the study of apathy often as a secondary outcome variable.

We therefore are still at an unsatisfactory stage of treatment development for apathy in dementia patients. Pharmacological strategies will benefit from a better understanding of the biological underpinnings of apathy and the examination of the subdomains of apathy. Nonpharmacological strategies, which are often the first-line treatments in clinical settings, need larger and longer studies in well-characterized patients, paying attention to the heterogeneity of the settings in which these interventions occur, and the therapists involved in the delivery of these treatments. Recommendations on the design of clinical trials for apathy in neurodegenerative diseases should be followed (Cummings *et al.*, 2015) to advance this field and reduce the considerable social, health, and economic burden imposed by apathy.

Conflicts of interest

The author participated in expert panels for Biogen Australia and Roche Australia in 2020 and 2021. No other conflicts of interest are reported.

Acknowledgements

PSS is supported by an Investigator grant from the National Health and Medical Research Council of Australia.

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https://doi.org/10.1017/S1041610223000418 Published online by Cambridge University Press

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