International Psychogeriatrics (2023), 35:11, 664–672
doi:10.1017/S1041610223000327

Cost consequence analysis of Apathy in Dementia Methylphenidate Trial 2 (ADMET 2)

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ABSTRACT

Background: This paper used data from the Apathy in Dementia Methylphenidate Trial 2 (NCT02346201) to conduct a planned cost consequence analysis to investigate whether treatment of apathy with methylphenidate is economically attractive.

Methods: A total of 167 patients with clinically significant apathy randomized to either methylphenidate or placebo were included. The Resource Utilization in Dementia Lite instrument assessed resource utilization for the past 30 days and the EuroQol five dimension five level questionnaire assessed health utility at baseline, 3 months, and 6 months. Resources were converted to costs using standard sources and reported in 2021 USD. A repeated measures analysis of variance compared change in costs and utility over time between the treatment and placebo groups. A binary logistic regression was used to assess cost predictors.

Results: Costs were not significantly different between groups whether the cost of methylphenidate was excluded ($F(2,330) = 0.626$, $\eta_p^2 = 0.004$, $p = 0.535$) or included ($F(2,330) = 0.629$, $\eta_p^2 = 0.004$, $p = 0.534$). Utility improved with methylphenidate treatment as there was a group by time interaction ($F(2,330) = 7.525$, $\eta_p^2 = 0.044$, $p < 0.001$).

Discussion: Results from this study indicated that there was no evidence for a difference in resource utilization costs between methylphenidate and placebo treatment. However, utility improved significantly over the 6-month follow-up period. These results can aid in decision-making to improve quality of life in patients with Alzheimer's disease while considering the burden on the healthcare system.

Key words: Alzheimer's disease (AD), apathy, dementia, health economics

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Received 21 Dec 2022; revised version received 20 Mar 2023; accepted 23 Mar 2023. First published online 17 April 2023.

Background

Dementia has an estimated prevalence of 50 million persons worldwide (Patterson, 2018) and an incidence of 10 million cases per year (Patterson, 2018; Qiu *et al.*, 2009; World Health Organization, 2019),

with about two-thirds of those cases attributed to Alzheimer's disease (AD), making AD the most common form of dementia (Patterson, 2018). It has been predicted that the number of Americans with AD will grow to 13.8 million by 2060 (2021). In the USA, total direct medical costs in 2019 for patients 65 years and older with AD have been estimated to be $25,213 per person, about 3 times higher than that in those without AD ($7750) (Wong, 2020). Indirect costs of patient care (e.g., costs for patient caregivers) for AD patients were estimated to be $20,590 in 1998, which doubled in 4 years (Wong, 2020).

While neuropsychiatric symptoms (NPS) are common in AD, apathy is particularly frequent, affecting up to 70% of patients (Mega *et al.*, 1996). Apathy in neurocognitive disorders is defined as a quantitative decline in goal-directed activity when compared to the patient's previous level of functioning, consistent with symptoms affecting two of the three apathy dimensions (diminished initiation, interest, and/or emotion) persistent for 4 weeks or more (Miller *et al.*, 2021). Apathy has been associated with faster progression from normal cognition to mild cognitive impairment and AD (Geda *et al.*, 2014; Richard *et al.*, 2012; Ruthirakuhan *et al.*, 2019). More specifically, the risk of progression to AD was almost seven-fold higher in those with apathy symptoms compared to those without in patients with amnestic mild cognitive impairment (Palmer *et al.*, 2010; Somme *et al.*, 2013). Additionally, apathy as a symptom in AD has been linked with more rapid cognitive decline (Starkstein *et al.*, 2006), more impaired basic and instrumental activities of daily living (Onyike *et al.*, 2007), as well as greater caregiver burden (Dauphinot *et al.*, 2015). Apathy symptoms have also been associated with increased mortality in nursing home (Nijsten *et al.*, 2017) and in community-dwelling patients with AD (Vilalta-Franch *et al.*, 2013).

NPS contribute to higher direct and indirect costs in patient care. Apathy in particular has been found to significantly increase total patient care costs (Herrmann *et al.*, 2006) with studies suggesting that a one-point worsening on the Neuropsychiatric Inventory (NPI) is associated with an incremental increase of USD$247 to USD$409 (Murman and Colenda, 2005). This suggests that targeting these symptoms may help reduce costs associated with dementia care.

Treating apathy has proven challenging and there are currently no approved treatments. However, a meta-analysis investigating pharmacological interventions for apathy in AD identified methylphenidate (MTP), a monoaminergic agent, as potentially useful for treating apathy in AD (Ruthirakuhan *et al.*, 2018). The Apathy in Dementia Methylphenidate Trial 2 (ADMET 2) study was a phase 3, placebo-controlled, masked, 6-month, multicenter randomized clinical trial that enrolled 200 participants with AD and apathy. ADMET 2 found that methylphenidate was safe and efficacious in apathy in AD, and that MTP had a small-to-medium effect on apathy symptoms, while cognitive measures and quality of life were not significantly different (Mintzer *et al.*, 2021).

This paper used data from ADMET 2 to conduct a cost consequence analysis to investigate whether apathy treatment with MTP is economically attractive.

Patients and methods

A cost consequence analysis was conducted to estimate the economic impact of using MTP as a treatment for apathy in dementia compared to placebo. Cost consequence analyses are a form of health economic evaluation in which all direct and indirect costs and different outcomes of alternatives are listed separately.

In ADMET 2, study participants were recruited from medical centers in Canada and the USA and randomized to MTP or placebo in a 1:1 ratio. Details of the study design were previously published (Scherer *et al.*, 2018). Briefly, participants were either outpatients recruited from clinical settings at the study centers or residents of nursing homes or assisted living facilities with a diagnosis of possible or probable AD, based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association criteria, with a Mini-Mental State Examination (MMSE) score of 10–28, clinically significant apathy (very frequently or frequently/often with a severity of moderate or marked for at least 4 weeks on the NPI apathy), and availability of a caregiver who spent more than 10 hours a week with the potential participant were included in the ADMET 2 study (Mintzer *et al.*, 2021). All participants received a psychosocial intervention. All participants with cost and utility data were used for this cost consequence analysis.

Assessments

The disease-specific Resource Utilization in Dementia – Lite Version (RUD-Lite) scale (Wimo *et al.*, 2013; Wimo, 2003) was used to quantify healthcare resource utilization over 30 days prior to each visit. Health-related quality of life was measured using the generic EuroQol five dimension five level (EQ-5D-5L) questionnaire (Herdman *et al.*, 2011; Johnson *et al.*, 1998), which considers five

https://doi.org/10.1017/S1041610223000327 Published online by Cambridge University Press

dimensions of health including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with five levels of severity at the time of each study visit. These levels are combined in a 5-digit code describing the patient's health state. For example, a state of 12,345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with performing usual activities, severe pain or discomfort, and extreme anxiety or depression. Health utility is the conversion and interpretation of this 5-digit health state into a country-specific utility index value, which reflects how good or bad a health state is according to the preferences of the general population of a country. Five-digit health states were converted into a country-specific single utility value using specific value sets, derived from large country-specific validation studies (Xie *et al.*, 2016). While Canada's single utility value has been directly validated from literature (Xie *et al.*, 2016), the utility index value for the USA was obtained via the EQ-5D-5L Crosswalk project. The Crosswalk project links the EQ-5D-5L and EQ-5D-3L descriptive systems to estimate a single utility index value for the EQ-5D-5L for other countries like the USA (Gerlinger *et al.*, 2019). A utility value of 1.0 represents full health and 0.0 represents a health state equal to death (Wolowacz *et al.*, 2016). The EQ-5D-5L is a general preference-based measure of health utility, rather than an AD-specific one, which allows patients to describe different aspects of their health and assigns a health utility score based on these descriptions (Wolowacz *et al.*, 2016). Both questionnaires were completed by the participant's caregiver and administered at 3 time points in ADMET 2 study: baseline (BL), 3 months (F3), and 6 months (F6).

Costs

The societal perspective was used. RUD-lite resources reported were costed in 2021 USD. The unit costs can be found in Table S1 published as supplementary material online attached to the electronic version of this paper.

Direct costs

Cost inputs were divided by country (Canada and the USA) and then further broken down into direct medical (hospitalization, healthcare resource utilization, outpatient) and other (day care, transportation, home care, meal delivery) costs. Healthcare-related costs were estimated based on provincial and government sources, while sources for patient incurred other costs were taken from public and private organizations providing services (Table S1 published as supplementary material online attached to the electronic version of this paper). The cost of 20 mg of MTP in Canada was taken from the Ontario Drug Formulary, and cost in the USA was obtained from the Central Arkansas Veterans Healthcare System.

Indirect costs

Informal care costs, including time spent providing care to the patient and supervision, were valued using 30% of the average wage in Canada and the USA, consistent with an analysis on informal care time by Lacey *et al.* (2017).

Statistical analyses

Baseline characteristics were summarized using descriptive statistics. An unpaired *t*-test was used to assess age, while chi-square or Fisher's exact tests were used to assess categorical demographic variables. Shapiro–Wilk test was used to assess normality of costs and utilities at all time points. Differences over time (BL, F3, F6) in total cost and utility were assessed using a repeated measures analysis of variance (ANOVA). This compared means of the total costs and utilities between the MTP and placebo group across the three time points. Separate models were run first excluding the cost of MTP, then including that cost. Individual categories of cost were analyzed using binary logistic regressions, comparing incurring a cost to not incurring a cost, as cost data were expected to be heavily skewed. Sensitivity analysis stratifying American and Canadian costs was conducted. IBM SPSS Statistics version 26 (IBM Corp, New York) was used for the analysis.

Results

A total of 167 patients in ADMET 2 had post-baseline RUD-lite and EQ-5D-5L data (86 received placebo and 81 were in the MTP group). Baseline demographics are included in Table 1.

Costs

Resource utilization during the study period by treatment group is found in Table 2. A summary of the repeated measures ANOVA results can be found in Table 3. Excluding the cost of MTP, there was no significant effect of time and treatment group on cost. There was also no significant interaction effect between time and treatment group (see Figure S1 published as supplementary material online attached to the electronic version of this paper). Including the cost of MTP, there was no significant effect of time and no significant effect of treatment group. There was no significant interaction effect between time and

https://doi.org/10.1017/S1041610223000327 Published online by Cambridge University Press

Table 1. Baseline demographic characteristics of study patients by treatment group

VARIABLE	TOTAL ($N = 167$)	PLACEBO ($N = 86$)	TREATMENT ($N = 81$)	TEST VALUE	P VALUE
Age, y [mean (SD)]	76.4 (7.6)	75.9 (7.4)	76.9 (7.7)	0.828	0.409
Sex, women [*n* (%)]	58 (34.7)	29 (33.7)	29 (35.8)	0.080	0.778
Married [*n* (%)]	142 (85.0)	76 (88.4)	66 (81.5)	1.556	0.212
Race [*n* (%)]					
White	154 (92.2)	79 (91.9)	75 (92.6)	0.031	0.860
Black	9 (5.4)	4 (4.7)	5 (6.2)	N/A	0.741
Other	4 (2.4)	3 (3.5)	1 (1.2)	N/A	0.621
Place of residence [*n* (%)]					
Own home	152 (91.0)	77 (89.5)	75 (92.6)	0.477	0.490
Caregiver's home	9 (5.4)	6 (7.0)	3 (3.7)	N/A	0.497
Assisted living	4 (2.4)	2 (2.3)	2 (2.5)	N/A	1.000
Other	2 (1.2)	1 (1.2)	1 (1.2)	N/A	1.000

Table 2. Resource utilization in USD during the study period by treatment group, mean (SD). Costs were quantified based on 30 days prior to study visit

	PLACEBO GROUP ($N = 86$)			TREATMENT GROUP($N = 81$)		
RESOURCE COSTS IN USD MEAN (SD)	BL	F3	F6	BL	F3	F6
Inpatient hospitalization	62 (574)	62 (574)	681 (5280)	0 (0)	854 (4796)	789 (6527)
Emergency room	4 (20)	1 (12)	31 (58)	3 (14)	7 (32)	56 (141)
Outpatient hospital	75 (89)	34 (58)	35 (69)	105 (270)	77 (179)	63 (192)
Additional resource utilization	140 (449)	112 (324)	211 (831)	26 (98)	92 (269)	112 (407)
Informal care	2086 (2048)	2095 (2006)	2271 (2410)	2207 (2326)	2403 (2260)	1918 (2119)
Total cost excluding MTP	2305 (2199)	2281 (2112)	3147 (5727)	2324 (2277)	3035 (5709)	2864 (7181)
Total cost including MTP	2305 (2199)	2281 (2112)	3147 (5727)	2324 (2277)	3042 (5709)	2871 (7181)
Sensitivity analysis						
USA total cost excluding MTP	2263 (2077)	2443 (2169)	3244 (5983)	2353 (2249)	3083 (5903)	2996 (7472)
USA total cost including MTP	2263 (2077)	2443 (2169)	3244 (5983)	2353 (2249)	3090 (5903)	3003 (7472)
Canadian total cost excluding MTP	2665 (3199)	896 (535)	2316 (2739)	2017 (2736)	2529 (3213)	1469 (2390)
Canadian total cost including MTP	2665 (3199)	896 (535)	2316 (2739)	2017 (2736)	2540 (3213)	1480 (2390)

treatment group (see Figure S2 published as supplementary material online attached to the electronic version of this paper).

Utility

Patient-reported utility outcomes during the study period by treatment group are included in Table 4. There was no significant effect of time or treatment group on utility (see Figure S3 published as supplementary material online attached to the electronic version of this paper). There was a significant interaction effect between time and treatment group ($F(2,330) = 7.525$, $p < 0.001$, $\eta_p^2 = 0.044$) and descriptive statistics showed that the placebo group had a higher mean utility at BL (0.788) compared to the treatment group (0.762). However, the treatment group had a higher mean utility at F3 (0.773 for placebo group, 0.790 for treatment group) and at F6 (0.762 for placebo group, 0.808 for treatment group) than the placebo group.

Associations between MTP treatment and resource utilization

Binary logistic regression results are summarized in Table 5. MTP treatment was not associated with incurring costs in inpatient hospitalization, emergency room use, or outpatient costs but was associated with increased likelihood of incurring costs for additional resource utilization (Exp(B) = 1.72, 95%CI 1.09–2.74, $p = 0.021$) and informal care (Exp(B) = 5.39, 95%CI 1.81–16.07, $p = 0.003$). Time was associated with an increased likelihood for incurring emergency room costs (Exp(B) = 7.43, 95% CI 4.36–12.67, $p < 0.0001$) and a decreased likelihood for incurring outpatient costs (Exp(B) = 0.605, 95% CI 0.49–0.76, $p < 0.0001$). Time was not associated

https://doi.org/10.1017/S1041610223000327 Published online by Cambridge University Press

Table 3. Results from repeated measures ANOVA

		DF	DF ERROR	*F* VALUE	*P* VALUE	η_p^2
Cost excluding MTP	Time	2	330	1.052	0.350	0.006
	Treatment	1	165	0.123	0.726	0.001
	Time * treatment	2	330	0.626	0.535	0.004
Cost including MTP	Time	2	330	1.063	0.346	0.006
	Treatment	1	165	0.131	0.718	0.001
	Time * treatment	2	330	0.629	0.534	0.004
Utility	Time	2	330	0.522	0.594	0.003
	Treatment	1	165	0.433	0.511	0.003
	Time * treatment	2	330	7.525	< 0.001	0.044
Sensitivity analysis						
USA, costs excluding MTP	Time	2	298	1.211	0.299	0.008
	Treatment	1	149	0.102	0.749	0.001
	Time * treatment	2	298	0.367	0.693	0.002
USA, costs including MTP	Time	2	298	1.222	0.296	0.008
	Treatment	1	149	0.109	0.742	0.001
	Time * treatment	2	298	0.368	0.692	0.002
USA, utility	Time	2	298	0.677	0.509	0.005
	Treatment	1	149	1.226	0.270	0.008
	Time * treatment	2	298	7.762	< 0.0001	0.050
Canada, costs excluding MTP	Time	2	28	0.620	0.545	0.042
	Treatment	1	14	0.002	0.968	0.000
	Time * treatment	2	28	2.813	0.077	0.167
Canada, costs including MTP	Time	2	28	0.609	0.551	0.042
	Treatment	1	14	0.002	0.963	0.000
	Time * treatment	2	28	2.825	0.076	0.168
Canada, utility	Time	2	28	0.313	0.734	0.022
	Treatment	1	14	0.763	0.397	0.052
	Time * treatment	2	28	0.807	0.456	0.055

* Computed using alpha = 0.05.

with incurring costs for inpatient hospital visits, additional resource utilization, or informal care.

Sensitivity analyses

A summary of the sensitivity analyses can be found in Table 3. For the USA, neither time, treatment, nor the interaction of the two affected total cost excluding or including MTP. Neither time nor treatment affected utility; however, there was a significant interaction effect ($F(2,298) = 7.762$, $p < 0.001$, $\eta_p^2 = 0.050$).

In Canada, neither time, treatment, nor the interaction of the two had significant effects on costs excluding MTP, cost including MTP, or utility.

Discussion

Overall, costs were not significantly different between the treatment and placebo groups, regardless of whether or not cost of MTP was included. Utility improved with MTP treatment as there was an interaction effect with treatment group and time. This complements results from the ADMET 2 study which suggested that MTP treatment modestly improved apathy symptoms (Mintzer *et al.*, 2021). This analysis extended that finding by further investigating economic outcomes relevant to using MTP to treat apathy in AD. It is also worth noting that while the ADMET 2 study found no significant differences in quality of life between the MTP and placebo group (Mintzer *et al.*, 2021), those results were taken from analyzing participants' scores on each individual domain of health on the EQ-5D-5L rather than the determined five number cumulative health state. An analysis on the EQ-5D-5L assigned health states was not planned in context of the main ADMET 2 study since there are 3125 possible health states as determined by the questionnaire. Utility, which is a continuous variable that reflects EQ-5D-5L assigned health states, may be a more robust and complete variable to assess quality of life, was calculated as part of this secondary analysis of the ADMET 2 study.

Excluding the cost of MTP, overall costs in the treatment and placebo groups were not significantly different over time. However, the cost breakdown analysis indicated that being in the treatment group meant patients were more likely to incur an additional cost, and from BL to F3 to F6 there was a significant increased likelihood of incurring an emergency room, or outpatient hospital cost, but

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Table 4. Patient-reported utility outcomes during the study period by treatment group, mean (SD)

	PLACEBO GROUP ($N = 86$)			TREATMENT GROUP ($N = 81$)		
OUTCOME MEAN (SD)	BL	F3	F6	BL	F3	F6
Utility	0.788 (0.121)	0.772 (0.155)	0.762 (0.171)	0.762 (0.117)	0.790 (0.123)	0.808 (0.146)
Sensitivity analysis						
USA, utility	0.782 (0.120)	0.772 (0.154)	0.754 (0.173)	0.765 (0.112)	0.793 (0.116)	0.813 (0.133)
Canada, utility	0.844 (0.123)	0.781 (0.173)	0.830 (0.138)	0.739 (0.175)	0.756 (0.189)	0.748 (0.257)

Table 5. Results from binary logistics regression for the cost breakdown analysis

RESOURCE	WALD	DF	*P* VALUE	EXP (B)	95% CL OF EXP (B)
Inpatient hospital					
Treatment	0.532	1	0.466	0.621	0.173–2.233
Time	1.331	1	0.249	1.610	0.717–3.615
Constant	20.707	1	<0.0005	0.009	
Emergency room					
Treatment	0.529	1	0.467	0.815	0.470–1.414
Time	54.309	1	<0.0005	7.430	4.359–12.667
Constant	72.575	1	<0.0005	0.002	
Outpatient					
Treatment	0.570	1	0.450	0.871	0.609–1.246
Time	19.752	1	<0.0005	0.605	0.485–0.755
Constant	15.026	1	<0.0005	2.754	
Additional resource utilization					
Treatment	5.332	1	0.021	1.724	1.086–2.738
Time	0.500	1	0.480	1.105	0.837–1.459
Constant	33.496	1	<0.0005	0.137	
Informal care					
Treatment	9.121	1	0.003	5.391	1.806–16.068
Time	0.279	1	0.597	0.869	0.516–1.463
Constant	20.946	1	<0.0005	15.693	

not an inpatient hospital cost. These results are difficult to interpret. Taken in the context of the efficacy and safety of MTP reported in the ADMET 2 MTP RCT (Mintzer *et al.*, 2021), where MTP treatment was relatively safe and efficacious, increased visits may reflect improved attention to health care or activities. The ADMET 2 trial found that while apathy and other NPS improved over time during the trial, changes in apathy and motor behavior were greater in the MTP compared to placebo group. As well, many of the participants in the trial had other comorbidities such as hypertension or diabetes, which could account for increased emergency room or outpatient hospital visits. The increased likelihood of incurring an additional resource utilization cost found in the treatment group might also be explained by adverse reactions to MTP treatment that may be inconvenient but not severe enough to require medical attention, such as weight loss, cough/bronchitis, falls, or confusion. In ADMET 2, 17% of patients in the treatment group and 12% in the placebo group sought hospitalization or emergency room visits for serious events during the study period, while the vast majority reported nonserious adverse events (Mintzer *et al.*, 2021). The serious adverse events were all deemed unrelated to the study drug by blinded investigators. Informal care costs took up the largest proportion of total costs, which is consistent with existing literature (Feldman *et al.*, 2004; McDaid, 2001; Moore *et al.*, 2001). The significantly increased likelihood of incurring an informal care cost in the MTP group could be due to adverse reactions to the drug, leading to caregivers dedicating more time, or the activating effects of MTP. While more active participants may have led to more caregiver time, this should be considered in the context of improved utilities. The low total cost for Canadian participants

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assigned to the placebo group at F3 may be explained by the low number of Canadian participants we had ($n = 16$). Most Canadian participants assigned to the placebo group at F3 did not incur a hospital or emergency room cost.

Importantly, this study found modestly improved health-related quality of life in the MTP group as measured by the EQ-5D-5L, but no group effect. While not AD specific, this scale measures aspects of quality of life including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, which are relevant in those with AD. It has previously been shown to be responsive to changes in NPS and function when measured by proxy (Martin *et al.*, 2019). As apathy has a demonstrated association with decreased quality of life (Hongisto *et al.*, 2018; Yeager and Hyer, 2008; Tierney *et al.*, 2018), and maintaining quality of life is an important goal for treatment (Mortby *et al.*, 2022), this secondary finding is an important addition to ADMET 2 apathy outcomes.

There is currently no literature that has looked at the minimal clinically important difference (MCID) in AD and utility in Canada or the USA. However, Coretti *et al.* (2014) investigated ranges of EQ-5D MCID and found overall ranges from 0.09 to 0.54 in disease areas such as musculoskeletal and psoriasis. A review conducted in 2020 (Mouelhi *et al.*, 2020) showed varied MCID values for the EQ-5D from 0.01 to 0.39 for patients with musculoskeletal disorders. McClure *et al.* (2018) reported that the MCID of the EQ-5D-5L index score in adults with type 2 diabetes is in the range of 0.03–0.05. In our analyses, we observed an effect size of 0.044, which is within the range with what the literature has reported in most disease areas.

Several design choices should be noted when interpreting the results of this study. First, quality of life was measured using a generic scale (the EQ-5D-5L). While this has the advantage of allowing calculation of utilities, a disease-specific scale may be more sensitive to change in AD patients. Second, the RUD-lite measures participants' use of resources over only 30 days prior to each study visit. According to Wimo and Nordberg (2007), interviews regarding resource utilization including the RUD-lite can be used as a valid and reliable alternative for observations, but 30 days is only a portion of the time between study visits and thus may limit generalizability of results. Moreover, resource utilization can fluctuate depending on factors including existing outpatient appointments, and the timing of other events prompting increased resource utilization (Wimo and Nordberg, 2007). Lastly, the RUD-lite and EQ-5D-5L were both completed by caregivers which may act as a limitation. While interviews can be used as a valid and reliable alternative to observations (Wimo and Nordberg, 2007), scores derived from caregiver interviews may be biased as they rely on caregivers' recall which could result in over or under estimations. Furthermore, as it heavily depends on self-reported values, the RUD-lite may be limited as a benchmark for measuring resource utilization of formal and informal care services (van Lier *et al.*, 2016). Finally, MTP administration would require a specialist consultation and follow-up in a practical scenario. While the RUD-lite asks caregivers about physician visits (general practitioner, geriatrician, neurologist, etc.) within the last 30 days prior to study visit, we did not specifically account for MTP-related physician visits in our cost data.

It should also be noted that cost and utility data in this analysis were not normally distributed. However, after ranking costs and utilities to fit the assumption of normality, repeated measures ANOVA analyses yielded the same results. A study by Doshi *et al.* (2006) reported that most other papers analyzed costs using parametric statistical tests, despite the highly skewed nature of cost data. Moreover, a publication exploring the analysis and interpretation of cost data in randomized trials found that all studies they included that gave a measure of precision for the estimated difference in costs used methods that assumed normality despite the fact that it might have been violated (Barber and Thompson, 1998). Finally, the sensitivity analysis in the Canadian population indicated that MTP had no significant effect on cost and utility but indicated that it could have improved utility in the USA population as an interaction effect exists. However, the Canadian data represented only 9.6% of the data. To get a more accurate representation of the true effect of MTP in Canada, specific data from a larger Canadian population would be necessary as the countries in this study have different healthcare provision policies that may affect cost. The USA typically has higher healthcare expenditure, while the Canadian system has lower costs, more services, and universal access to healthcare with smaller financial barriers (Ridic *et al.*, 2012).

Conclusion

Results from this study indicated that there was no evidence for a difference in resource utilization costs between MTP and placebo treatment. However, utility improved significantly over the 6-month follow-up period. The increase in outpatient and emergency room costs in those randomized to MTP as time progressed from BL may be explained by

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worsening AD symptoms excluding apathy, or other health issues unrelated to MTP treatment. These data are important to consider in healthcare decision making to determine treatments for apathy in AD that are economically attractive while improving quality of life for patients.

Conflicts of interest

KLL has received research grants from the National Institutes of Aging, Alzheimer's Drug Discovery Foundation, the Alzheimer Society of Canada, Alzheimer's Association, Canadian Institutes of Health Research, Weston Brain Institute; honoraria from BioXcel, Cerevel, Eisai, and Praxis.

NH has received peer-reviewed research grants from the Alzheimer Drug Discovery Foundation, the Alzheimer Society of Canada, the National Institute of Health, Canadian Institutes of Health Research.

PBR has received research grants from the National Institutes of Aging, Alzheimer's Clinical Trials Consortium, Richman Family Precision Medicine Center of Excellence on Alzheimer's Disease, Eisai, Functional Neuromodulation, and Lilly; honoraria from GLG, Leerink, Cerevel, Cerevance, Bioxcel, Sunovion, Acadia, Medalink, Novo Nordisk, Noble Insights, TwoLabs, Otsuka, Lundbeck, Acadia, MedaCorp, ExpertConnect, HMP Global, Synaptogenix, and Neurology Week.

The remaining authors have nothing to disclose.

Description of authors' roles

NH, JM, PBR, RWS, and KLL participated in the conception and design of the study. KLL, WB, AL, SC, AP, CHvD, OBM, PP, AL, NH, AL, and DV acquired data for the study. KLL, AL, DV, CC, EM, and NH drafted the manuscript; AL, CC, EM, HC, DS, and AK analyzed the study data. All authors critically reviewed and approved the manuscript.

Acknowledgments

ADMET 2 was funded by NIA, NIH, R01AG046543. The funders had no role in the design or conduct of the study, nor in the writing or approval for publication of the manuscript.

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1041610223000327

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https://doi.org/10.1017/S1041610223000327 Published online by Cambridge University Press