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RESEARCH ARTICLE

Effects of methylphenidate on neuropsychiatric symptoms in Alzheimer's disease: Evidence from the ADMET 2 study

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Abstract

INTRODUCTION: Methylphenidate has been shown to improve apathy in patients with Alzheimer's disease (AD). The authors evaluated the impact of methylphenidate on neuropsychiatric symptoms (NPS) of AD, excluding apathy, using data from the Apathy in Dementia Methylphenidate Trial 2 (ADMET 2) study.

METHODS: A secondary analysis was conducted on data from the ADMET 2 study to determine the effect of methylphenidate on Neuropsychiatric Inventory (NPI) scores outside of apathy. Caregiver scores were compared from baseline to month 6 in 199 participants receiving methylphenidate (20 mg/day) or placebo regarding the presence or absence of individual neuropsychiatric symptoms, emergence of new symptoms, and individual domain scores.

RESULTS: No clinically meaningful improvement was observed in any NPI domain, excluding apathy, in participants treated with methylphenidate compared to placebo after 6 months. A statistical difference between groups was appreciated in the domains

of elation/euphoria ($P = 0.044$) and appetite/eating disorders ($P = 0.014$); however, these findings were not considered significant.

DISCUSSION: Methylphenidate is a selective agent for symptoms of apathy in patients with AD with no meaningful impact on other NPS. Findings from this secondary analysis are considered exploratory and multiple limitations should be considered when interpreting these results, including small sample size and use of a single questionnaire.

KEYWORDS

agitation, Alzheimer's disease, central nervous system stimulant, methylphenidate, Neuropsychiatric Inventory, neuropsychiatric symptoms, treatment

HIGHLIGHTS

- Methylphenidate was not associated with significant improvement on the Neuropsychiatric Inventory in domains outside of apathy.
- Methylphenidate did not show a statistically significant emergence of new neuropsychiatric symptoms (NPS) throughout the 6-month treatment period compared to placebo.
- Methylphenidate appears to be a highly selective agent for apathy in Alzheimer's disease, potentially supporting catecholaminergic dysfunction as the driving force behind this presentation of symptoms.

1 | INTRODUCTION

Alzheimer's disease (AD) currently impacts 6.5 million people in the United States, with an anticipated prevalence rate of 12.7 million by 2050.[1] Neuropsychiatric symptoms (NPS) are common in this population, spanning the AD spectrum with a prevalence as high as 81.2% in patients with mild cognitive impairment and 88.7% in patients with AD dementia.[2] Associations between NPS and worsening outcomes for patients with AD and their caregivers have been well established,[3] yet effective treatment options remain scarce.

This narrow treatment armamentarium is partially due to a limited understanding of the etiology behind NPS in AD. Disruptions in the frontal-subcortical circuits, cortico-cortical networks, and the ascending monoaminergic system are some of the major neurobiological models proposed in the pathophysiology of NPS.[4] Non-neurobiological factors have also been implicated in NPS, such as unmet personal needs, environmental triggers, pre-existing personality traits or disorders, and relationship dynamics between patients and caregivers.[5]

Non-pharmacologic treatment options remain the first-line approach to NPS in AD;[6] however, these have limitations in real-world practice.[5,7,8] Pharmacologic treatment options, such as antidepressants, atypical antipsychotics, and benzodiazepines are commonly prescribed in clinical practice to manage NPS in AD;[9] however, the efficacy of these agents vary between clinical trials[10] and they have been associated with serious safety concerns.[11] Furthermore, none of these mentioned agents are US Food and Drug Administration–approved for NPS of AD.

Apathy remains among the top treatment targets for NPS in AD, as it is among the most prevalent NPS[12] and is strongly associated with increased caregiver burn-out, higher service use, and increased mortality risk.[13–17] Methylphenidate has been proposed as an effective treatment option for apathy in AD and has shown a favorable safety profile.[18,19] The proposed mechanism of action against apathy in AD is in methylphenidate's catecholaminergic effect on cortical and subcortical structures, particularly within the anterior cingulate cortex (ACC), ventral striatum (VS), and prefrontal cortex (PCF).[20–23] Disruption in the normal activity of these same regions has also been established in individuals with attention deficit hyperactivity disorder (ADHD),[24,25] which could explain why methylphenidate has been found to be beneficial in both of these conditions.

The Apathy in Dementia Methylphenidate Trial 2 (ADMET 2) study set out to further investigate the safety and efficacy of methylphenidate in patients with AD and apathy.[26] Compared to placebo, treatment with methylphenidate at 6 months revealed a statistically significant decrease in apathy scores on the Neuropsychiatric Inventory (NPI)[27] with a mean difference of −1.25 points (95% confidence interval [CI]: 1.00–2.04, $P = 0.002$). Notably, the largest decrease in the NPI apathy score was seen within the first 100 days with a hazard ratio of 2.16 (95% CI: 1.19=-3.91, $P = 0.01$) for the proportion of participants with no apathy symptoms receiving methylphenidate compared to placebo. There was no statistically significant difference between groups on the Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCS-CGIC)[28] at 6 months. Methylphenidate treatment had no effect on cognition, daily functioning, or quality

of life. The safety profile of methylphenidate was favorable with no significant differences observed in adverse events between groups.

In this paper, we report the results of a prespecified secondary analysis examining the effect of methylphenidate on all individual NPS domains assessed by the NPI. As apathy has been proposed as a very distinct clinical syndrome in AD, we hypothesized that there would be no meaningful change in other NPS in individuals receiving methylphenidate compared to those receiving placebo. Furthermore, we hypothesized that the emergence of new NPS would not statistically differ between groups.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using traditional sources (e.g., PubMed). Methylphenidate's role in addressing apathy in Alzheimer's disease (AD) has been supported by data reported from the Apathy in Dementia Methylphenidate Trial 2. Its potential place in the management of other neuropsychiatric symptoms (NPS) has not been thoroughly explored despite there being a high demand for safe and efficacious treatment options for NPS in AD. The relevant publications are cited appropriately.
2. **Interpretation**: Our secondary analysis found methylphenidate to be a highly selective agent for symptoms of apathy in patients with AD without meaningful impact in other NPS domains compared to placebo. Treatment with methylphenidate was not associated with emergence of any new NPS as measured by the Neuropsychiatric Inventory compared to placebo. The specificity of methylphenidate's treatment effect on apathy in this analysis supports previous literature findings of apathy in AD as being a distinct NPS associated with specific pathology in the catecholaminergic system.
3. **Future Directions**: A future study assessing catecholaminergic biomarker profiles with the treatment effect of methylphenidate in AD apathy would be an important step forward in validating this as the proposed mechanism of action.

2 | METHODS

2.1 | Study population

The methods and primary results from ADMET 2 have been previously published and described in detail.[26,29] ADMET 2 was a 6-month, phase-III, placebo-controlled, double-blind, multicenter clinical trial with two treatment cohorts randomized and assigned in a 1:1 ratio.

A total of 200 participants with a diagnosis of possible or probable AD, as defined by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria,[30] were enrolled in this study. Participants had Mini-Mental State Examination (MMSE)[31] scores between 10 to 28 and were determined to have clinically significant apathy for at least 4 weeks for which a physician determined a medication was appropriate. The frequency in which apathy occurred was rated as "very frequently" or "frequently" with "moderate" or "marked" severity as assessed by the apathy item of the NPI. Study partners were required for participation and stable doses of AD medications, antidepressants, and benzodiazepines were permitted. Exclusion criteria included a current or previous diagnosis of a major depressive episode by the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM-IV-TR) criteria, and clinically significant agitation/aggression, delusions, or hallucinations as determined by frequency and severity scores on the NPI in each respective domain. Significant, unintentional weight loss within the previous 3 months excluded a participant from the study. A past failure of methylphenidate treatment, a medical condition for which methylphenidate was contraindicated, and the use of medications precluding the safe use of methylphenidate were also among the exclusionary factors.

Study conduct was overseen by a data and safety monitoring committee. The study adhered to the Declaration of Helsinki and was approved by the ethical review boards of each site.

2.2 | Intervention

Participants were randomized to receive methylphenidate (5 mg/capsule) or matching placebo on a twice daily dosing schedule with a target dose of 20 mg/day. Study clinicians could reduce the dose in response to an adverse event. In addition to pharmacotherapy, all participants and study partners received a standardized psychosocial intervention at each visit, which consisted of 20 to 30 minutes of counseling, supplemental educational materials, and 24-hour availability of study staff for crisis management. Patients and caregivers completed in-person visits monthly over the 6-month study period with telephone contacts at days 15, 45, and 75. Due to the COVID-19 pandemic, virtual or telephone visits were permitted in place of in-person visits when site staff or participants were unable to present to their site due to safety reasons.

2.3 | Outcomes

The ADMET 2 study had two coprimary efficacy outcome measures: the NPI apathy score[27] and the odds of improved rating on the ADCS-CGIC.[28] The secondary efficacy measure was the informant-based Dementia Apathy Interview and Rating.[32]

This analysis examines the effects of methylphenidate treatment on NPS beyond apathy, as assessed by the NPI. The NPI is a well-established clinical rating instrument developed to assess

psychopathology in patients with dementia.[27] Using an informant-based approach, the NPI assesses 12 domains of NPS, including agitation/aggression, depression/dysphoria, anxiety, delusions, hallucinations, elation/euphoria, apathy/indifference, irritability/lability, disinhibition, aberrant motor behavior, sleep/nighttime behavior, and appetite/eating disorders. The frequency of each symptom is rated on a 4-point scale with 1 indicating "rarely/less than once per week" and 4 indicating "very frequently/daily or continuously." Severity of symptoms is rated on a 3-point scale with 1 indicating "mild/not distressing" and 3 indicating "marked/very distressing and difficult to redirect." A composite score is calculated by multiplying the frequency and severity scores for each symptom, resulting in a score ranging from 0 to 12. A score of 0 indicated no presence of symptoms respective to that domain. In the ADMET 2 study, the 12-item NPI was administered to the caregiver at baseline and monthly for each of the site visits over 6 months.

2.4 | Statistical analyses

This secondary analysis examined the separate NPI domain scores at enrollment for all ADMET 2 study participants with descriptive statistics, using percent to describe how many participants experienced symptoms at any level, and using medians and interquartile ranges to examine the level among those with symptoms for each domain of the NPI among all patients and by treatment group. In addition to each separate NPI domain, the total NPI score was also examined as the sum of all NPI domains, excluding apathy. Individual NPI domains and total NPI scores were compared between the two arms of the ADMET 2 study at enrollment and again after 6 months of intervention. Logistic regression was used to estimate the relative likelihood of symptoms between arms over the follow-up period, when the difference was assessed with an odds ratio (OR). Repeated measures within participant were handled within this logistic regression using generalized estimating equations, assuming each patient was a longitudinal cluster of events with an exchangeable correlation structure. This logistic regression was adjusted for baseline MMSE score. The level of each NPS domain was assessed among those with symptoms present at 6-month follow-up, and the levels were compared by arm using the non-parametric Wilcoxon rank sum test.

In addition to the comparisons of symptom presence and symptom severity level for each NPI domain at 6-month follow-up, we examined whether participants experienced an emergence of new NPS during the study period. This was performed by excluding participants with symptoms in any NPI domain at baseline and running a time-to-event analysis on the remaining population, comparing the time until symptom emergence between arms, assuming that those without symptoms were censored when they were lost to the study or when the study was complete at 6 months after enrollment. Cox proportional hazards were used to compare the rate of symptom emergence between methylphenidate and placebo arms of the ADMET 2 study.

3 | RESULTS

The ADMET 2 study enrolled 200 participants; however, baseline data were only available for 199 participants due to 1 missing their baseline visit. Of these 199, 180 (90.5%) were retained during the study period, defined as the time from enrollment to the 6-month follow-up visit. An examination of NPI symptoms at enrollment among ADMET 2 participants is shown in Table 1. No significant differences were observed between groups at baseline. Apart from apathy/indifference, present in all individuals based on the inclusion criteria, depression was the most common NPI symptom at 37%. Agitation/aggression, anxiety, and irritability/lability were also fairly common at 32%, 30%, and 34%, respectively. Some NPI symptoms were uncommon, including hallucinations (4%) and elation/euphoria (4%). Among those with symptoms, the severity level tended to be in the low to moderate range, with elation, sleep behavior, appetite/eating disorders, and aberrant motor behavior among the highest, with medians of 5, 4, 4, and 4, respectively (out of the possible range of 0–12). Overall, 81% of ADMET 2 participants had at least one symptom other than apathy at baseline, based on the total NPI (excluding apathy), which was similar by arm at 77% in the methylphenidate group compared to 85% in the placebo group ($P = 0.153$).

The NPS in ADMET 2 participants at 6-month follow-up are described in Table 2 and Figure 1. In general, a decrease in NPI symptoms was seen in both arms at 6-month follow-up, with 58% of participants reporting at least one NPI symptom in the methylphenidate group, and 71% in the placebo group ($P = 0.086$, by Fisher's exact test), compared to 77% and 85% at baseline ($P = 0.153$, by Fisher's exact test), respectively. The most common non-apathy NPI symptom in both the methylphenidate and the placebo arms was agitation/aggression, at 28% and 35% ($P = 0.421$, by Fisher's exact test), respectively. Elation/euphoria, hallucinations, and disinhibition remained uncommon, especially in the methylphenidate group, in which they were all <5% at 6-month follow-up. Elation/euphoria was less likely in the methylphenidate group compared to placebo over the 6-month follow-up period, with an OR of 0.27 (95% CI: 0.08–0.97, $P = 0.044$), and similarly, appetite/eating disorders were less common in the methylphenidate group compared to placebo at 6 months, with an OR of 0.34 (95% CI: 0.14–0.80, $P = 0.014$). Among those with symptoms, the severity level of the NPI domain scores was similar between arms (Table 2).

In addition to these analyses, the team also examined the emergence of new symptoms among those not experiencing NPS at baseline, estimating a hazard ratio (HR) to compare the rate of symptom emergence between arms. Significant symptom emergence was observed among those without NPI symptoms at baseline, especially in the domains of agitation/aggression (38% in the participants receiving methylphenidate and 43% among those with placebo, $P = 0.651$), depression/dysphoria (29% and 41%, respectively, $P = 0.192$), anxiety (35% and 40%, respectively, $P = 0.648$), and irritability/lability (35% and 34%, respectively, $P = 0.852$). The estimated HRs for rate of new symptoms was often favoring the methylphenidate treatment (being

TABLE 1 Baseline NPI scores among 199 ADMET2 participants.

	Total sample (*N* = 199)				Methylphenidate (*N* = 99)				Placebo (*N* = 100)				
	All participants		Participants with symptoms		All participants		Participants with symptoms		All participants		Participants with symptoms		
NPI measure	N	%	Med	IQR	N	%	Med	IQR	N	%	Med	IQR	*P***
Delusions	11	6%	3	2, 3	4	4%	2.5	2, 3	7	7%	3	2, 3	0.537
Hallucinations	8	4%	2	1, 2	4	4%	1	1, 1	4	4%	2	2, 2	1.000
Agitation/aggression	63	32%	2	1, 3	34	34%	2	1, 3	29	29%	2	1, 3	0.449
Depression/dysphoria	73	37%	2	1, 3	37	37%	1	1, 3	36	36%	2	1, 3	0.884
Anxiety	59	30%	3	2, 5	26	26%	3	2, 4	33	33%	3	2, 6	0.352
Elation/euphoria	8	4%	5	1, 7	2	2%	1	1, 1	6	6%	5	5, 8	0.279
Apathy/indifference	199	100%	8	6, 8	99	100%	8	6, 9	100	100%	8	6, 8	0.445
Disinhibition	38	19%	2	1, 4	15	15%	2	2, 3	23	23%	2	1, 6	0.207
Irritability/lability	68	34%	3	2, 4	36	36%	3	2, 3	32	32%	3	2, 6	0.552
Aberrant motor behavior	50	25%	4	3, 6	24	24%	3	3, 4	26	26%	4	3, 8	0.870
Sleep/nighttime behavior	52	26%	4	2, 7	26	26%	4	2, 6	26	26%	4	3, 8	1.000
Appetite/eating disorders	48	24%	4	3, 6	20	20%	5	3, 7	28	28%	4	4, 6	0.246
Total NPI*	161	81%	7	4, 15	76	77%	8	4, 12	85	85%	7	4, 17	0.153

* Excluding NPI apathy.

** Difference between proportion with symptoms between arms.

Abbreviations: ADMET 2, Apathy in Dementia Methylphenidate Trial 2; IQR, interquartile range; NPI, Neuropsychiatric Inventory.

TABLE 2 Follow-up NPI scores among 180 ADMET 2 participants with NPI scores at 6-month follow-up.

	All participants with NPI at 6 months							Participants with symptoms at 6 months				
	Methylphenidate (*N* = 89)		Placebo (*N* = 91)					Methylphenidate		Placebo		
NPI measure	N	%	N	%	OR[a]	95% CI	*P*	Med	IQR	Med	IQR	*P*
Delusions	5	6%	13	14%	0.43	0.16, 1.18	0.103	3	2, 3	3	1, 4	0.919
Hallucinations	1	1%	4	4%	0.22	0.02, 2.14	0.191	3	3, 3	5	1, 10	1.000
Agitation/aggression	25	28%	32	35%	0.72	0.39, 1.35	0.308	3	2, 4	3	1, 6	0.935
Depression/dysphoria	17	19%	27	30%	0.59	0.31, 1.14	0.119	2	2, 4	2	1, 4	0.524
Anxiety	16	18%	24	26%	0.62	0.31, 1.22	0.167	3.5	3, 7	4	3, 6	0.978
Elation/euphoria	3	3%	10	11%	0.27	0.08, 0.97	0.044	1	1, 3	3	2, 5	0.342
Disinhibition	4	4%	10	11%	0.37	0.11, 1.26	0.113	4	3, 5	3	1, 6	1.000
Irritability/lability	20	22%	25	27%	0.83	0.43, 1.59	0.566	2.5	1, 4	3	2, 6	0.180
Aberrant motor behavior	18	20%	11	12%	2.08	0.93, 4.65	0.076	4	3, 6	6	4, 8	0.257
Sleep/nighttime behavior	16	18%	19	21%	0.80	0.38, 1.68	0.549	4	3, 7	6	3, 9	0.605
Appetite/eating disorders	8	9%	21	23%	0.34	0.14, 0.80	0.014	3	2, 4	4	3, 6	0.129
Total NPI[b]	52	58%	65	71%	0.59	0.32, 1.10	0.095	7	4, 12	9	4, 16	0.218

[a]Odds ratios are calculated with logistic regression including all follow-up visits using generalized estimating equations and exchangeable covariance structure. Odds are shown for reporting symptoms at month 6 for methylphenidate compared to placebo, adjusting for baseline Mini-Mental State Examination score.

[b]Excluding NPI Apathy.

Abbreviations: ADMET 2, Apathy in Dementia Methylphenidate Trial 2; CI, confidence interval; IQR, interquartile range; NPI, Neuropsychiatric Inventory; OR, odds ratio.

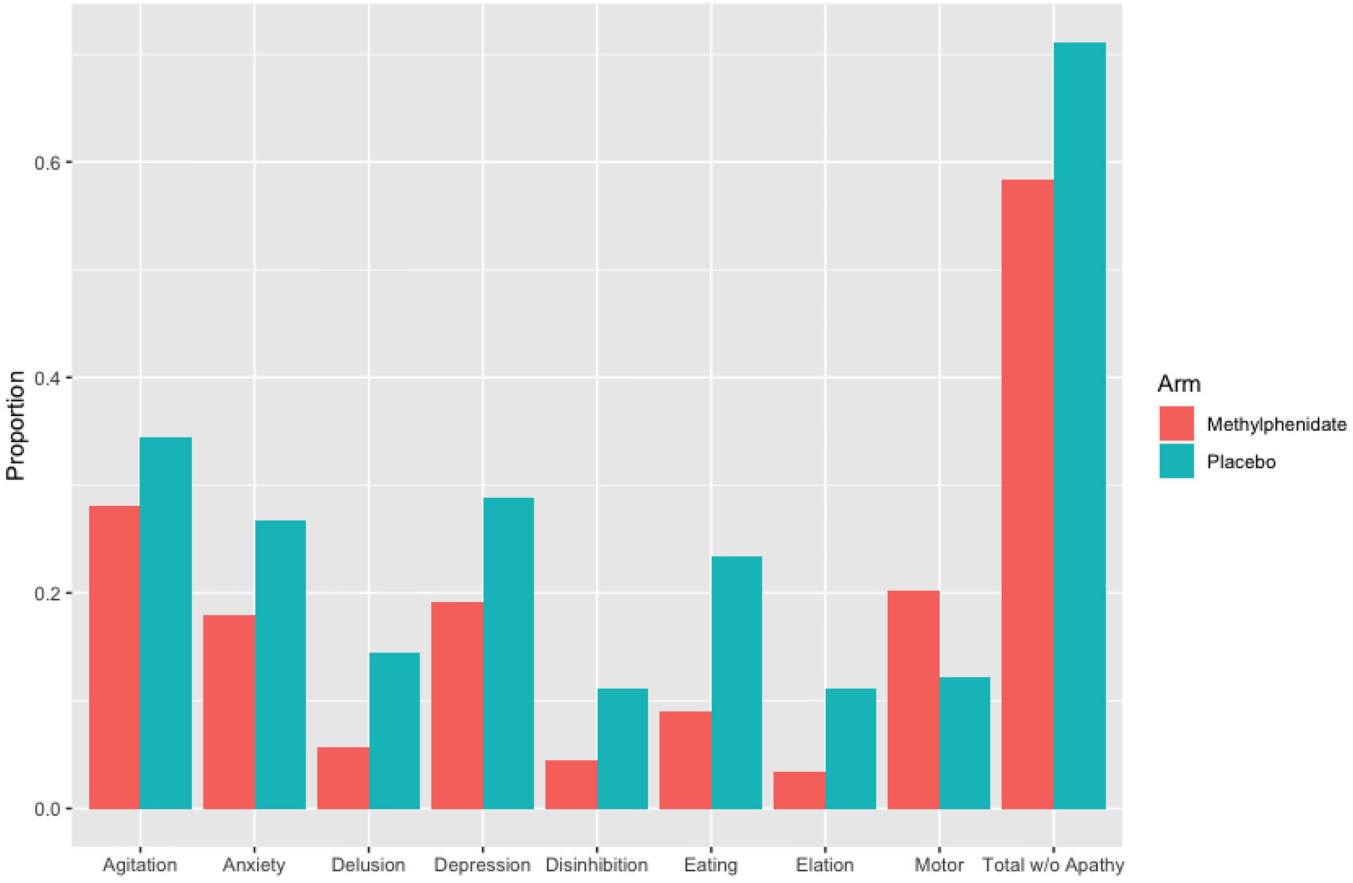

FIGURE 1 Proportion of participants at 6-month follow-up with symptoms by domain of the Neuropsychiatric Inventory among 180 Apathy in Dementia Methylphenidate Trial 2 participants.

less than 1), including for depression (HR 0.67, 95% CI: 0.37–1.22, $P = 0.192$); however, overall symptom emergence was statistically similar between treatment groups as shown in Table 3.

4 | DISCUSSION

In this secondary analysis, the effects of methylphenidate on NPS in individuals with AD and clinically significant apathy were examined, using data from the ADMET 2 study. We hypothesized there would be no meaningful difference between methylphenidate and placebo groups comparing the occurrence and severity of existing NPS (excluding apathy), and emergence of new NPS, over the 6-month study period. Our analyses found NPS outcomes in the methylphenidate group to be no worse than placebo, and somewhat in favor of methylphenidate when it came to a reduced risk of emerging symptoms in select domains. Examining individual NPI domain scores after 6 months, we observed no statistical difference between groups in symptoms of delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, disinhibition, irritability/lability, aberrant motor behavior, and sleep/nighttime behavior disorders. Symptoms of elation/euphoria were less likely in the methylphenidate group at month 6 with an OR of 0.27 (95% CI: 0.08–0.97, $P = 0.044$). The actual number of participants endorsing symptoms of elation/euphoria was low: 3 (3%) in the methylphenidate group and 10 (11%) in the placebo group. Similarly, individuals in the methylphenidate group were found less likely to report symptoms of appetite/eating disorders after 6 months with an OR of 0.34 (95% CI: 0.14–0.80, $P = 0.014$). The number of individuals reporting symptoms of appetite/eating disorders in the methylphenidate and placebo groups were 8 (9%) and 21 (23%), respectively. Information on the specific responses of these participants within the appetite/eating disorders domain on the NPI was not available due to the nature in which NPI domains were scored, so we were unable to extrapolate anything more meaningful than an observed change in symptom reporting. After adjusting for multiple comparisons and considering the small sample sizes, the results in the elation/euphoria and appetite/eating domains appeared to lack significance.

This paper further builds upon data presented in the online supplementary material section of the ADMET 2 primary publication (Supplement 2, eTable 4),[26] which presented an analysis of average change in NPI symptoms by domain from baseline to 6 months and revealed no statistically significant differences between groups in most domains, with the exception of apathy ($P = 0.002$) and motor symptoms ($P = 0.025$). Our approach differed in that we assessed the presence/absence of symptoms throughout the 6-month follow-up period

TABLE 3 Emergence of NPI symptoms among ADMET 2 participants over 6 months of follow-up among those without baseline symptoms.

	Methylphenidate			Placebo					
NPI measure	N without baseline symptom	N with follow-up symptom	%	N without baseline symptom	N with follow-up symptom	%	HR[a]	95% CI	*P*
Delusions	93	15	16%	92	21	23%	0.69	0.36, 1.34	0.277
Hallucinations	93	12	13%	95	15	16%	0.82	0.38, 1.75	0.609
Agitation/aggression	64	24	38%	70	30	43%	0.88	0.52, 1.51	0.651
Depression/dysphoria	62	18	29%	63	26	41%	0.67	0.37, 1.22	0.192
Anxiety	72	25	35%	67	27	40%	0.88	0.51, 1.52	0.648
Elation/euphoria	95	7	7%	93	8	9%	0.86	0.31, 2.37	0.767
Disinhibition	82	13	16%	76	10	13%	1.19	0.52, 2.71	0.683
Irritability/lability	62	22	35%	67	23	34%	1.06	0.59, 1.90	0.852
Aberrant motor behavior	73	20	27%	73	21	29%	0.94	0.51, 1.73	0.843
Sleep/nighttime behavior	71	16	23%	73	20	27%	0.82	0.43, 1.59	0.557
Appetite/eating disorders	77	24	31%	72	29	40%	0.77	0.45, 1.32	0.345
Total NPI[b]	23	16	70%	15	12	80%	0.89	0.42, 1.89	0.769

[a]Hazard ratios are estimated with cox proportional hazard regression for time until first follow-up within each separate NPI domain.
[b]Excluding NPI Apathy.
Abbreviations: ADMET 2, Apathy in Dementia Methylphenidate Trial 2; CI, confidence interval; HR, hazard ratio; NPI, Neuropsychiatric Inventory.

and additionally assessed the emergence of new symptoms during that time to see if a statistical difference could be appreciated between groups in NPI domains when analyzing the parent ADMET 2 data beyond averages. While our paper did not find a statistical significance between groups at month 6 in aberrant motor symptoms ($P = 0.07$), the OR was notable (OR = 2.08), and overall, our findings were consistent with the supplementary ADMET 2 data.

Our exploratory analysis assessed the emergence of new NPS per NPI domain among those without symptoms at baseline in the methylphenidate and placebo groups. Assessing new symptoms in the domains of delusions, hallucinations, and agitation/aggression was of particular interest as these symptoms have been reported adverse events with methylphenidate treatment in previous trials for apathy in dementia when administered at the same dose range as ADMET 2 (10 mg twice daily).[33–35] In our analysis, newly emergent symptoms of delusions, hallucinations, and agitation/aggression did not develop any more frequently with methylphenidate treatment than placebo, and in contrast, the emergence rates of these symptoms were numerically less frequent, though not statistically significantly different between groups.

The results of this paper are in line with the small amount of data that are available on methylphenidate's impact on NPS in dementia, outside of apathy. While methylphenidate has shown benefit as an adjunct in treating major depressive disorder in older adults,[36] we did not appreciate a statistically significant impact on symptoms of depression in those with co-occurring apathy receiving methylphenidate over 6 months. Other publications have found similar limitations in methylphenidate's treatment effect on depression in dementia;[33,34] however, this interpretation of findings should be viewed as exploratory considering the small sample sizes in our analysis.

Data on the safety and tolerability of methylphenidate in this study population were reported in the primary publication[26] finding no significant difference in the safety profile between groups. Of the 17 serious adverse events occurring in the methylphenidate group during the study, none were considered related to treatment. Our time-to-event analysis further supports the proposal of methylphenidate as a well-tolerated agent in dementia and apathy as it was not associated with the emergence of new NPS any more than placebo.

Limitations include the study population used in this analysis and sample size. By intentional design, the ADMET 2 study excluded participants with clinically significant NPS other than apathy, excluding those with a current or previous diagnosis of major depressive disorder (consistent with DSM-IV-TR criteria), or those with clinically significant symptoms of agitation/aggression, delusions, or hallucinations. The sample sizes available for our secondary analyses were, therefore, smaller and limited the power in some of our subanalyses. Our findings should be considered exploratory and reproducing these findings in a larger cohort will be an important step in further validating these data. Additionally, this secondary analysis focused on patient-centered NPS outcomes and did not include caregiver distress scores per NPI domain so this constitutes an additional limitation in our interpretation of clinically meaningful symptom responses. Other limitations that were cited in the primary analysis include: participants in ADMET 2 comprised a convenience sample of mainly White individuals in US and Canadian academic medical centers that may not generalize to other settings or non-AD forms of dementia; the diagnosis of AD was not confirmed by biomarkers; treatment duration was limited to 6 months; and data

were lacking on potential participants who declined to participate or failed screening.

5 | CONCLUSION

Methylphenidate appears to be a safe and well-tolerated agent when used in individuals with AD and apathy. The treatment effect of methylphenidate appears specific to apathy without significant changes, for better or worse, in other NPS domains when assessed by the NPI over a 6-month period, which is consistent with our hypothesis. The specificity of methylphenidate's treatment effect on apathy in this analysis supports previous literature findings of apathy in AD as being a distinct NPS associated with specific pathology in the catecholaminergic system.[20] A future study assessing catecholaminergic biomarker profiles with the treatment effect of methylphenidate in AD apathy would be an important step forward in validating this proposed mechanism of action.

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The authors have nothing to report.

CONFLICTS OF INTEREST STATEMENT

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He is a consultant for ACADIA, AiOmed, Corium, Exciva, Genentech (affiliate of F. Hoffmann-La Roche Ltd), Ironshore Pharmaceuticals, Lundbeck, Praxis Bioresearch, and Sygnature Discovery. Dr. Mintzer is a Steering Committee Member for the Alzheimer's Clinical Trials Consortium, Alzheimer's Disease Cooperative Study, and the Elder Court. He is a Board Member for the Alzheimer's Association, SC Chapter and the Technology Accelerator Company as well as an Association Member of the International Psychogeriatric Association. He is a Scientific Advisory Board Member for Exciva and Advisory Board Member for ACADIA. Dr. Mintzer is a stockholder and the VP for Clinical Affairs for NeuroQuest, a majority owner of Biopharma Connex, and a majority partner for Recruitment Partners. Dr. Mintzer has received payment or honoraria from ACADIA. 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Dr. van Dyck serves as a scientific advisor for Eisai, Roche, Ono, and Cerevel and reports grant support for clinical trials from Biogen, Biohaven, Cerevel, Eisai, Eli Lilly, Genentech, Janssen, Roche, and UCB. He also participates as a member of the Medical and Scientific Advisory Group for the Alzheimer's Association. Dr. Porsteinsson reports DSMB membership fees from Acadia, Cadent, Cognitive Research Corp, Functional Neuromodulation, Neurim, Novartis, and Tetra Discovery Partners; consulting fees from Athira, Avanir, Biogen, BioXcel, Eisai, Grifols, IQVIA, Lundbeck, Maplight Therapeutics, Merck, ONO Pharmaceuticals, Pfizer, and Toyama; grants for clinical trials from the National Institute on Aging, National Institute on Mental Health, the Department of Defense, Alector, AstraZeneca, Athira, Avanir, Biogen, Biohaven, Cassava, Eisai, Eli Lilly, Genentech/Roche, Janssen, Merck, Novartis, Toyama, and Vaccinex outside the submitted work. Dr. Herrmann declares no conflicts of interest. 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CONSENT STATEMENT

All human subjects provided consent for participation in the parent ADMET 2 study. Consent was not necessary for the conduct of this planned secondary analysis of data from the ADMET 2 study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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