A Comparison of Methylphenidate and Placebo Effects on Cardiac Function in the Elderly Population with Mild AD

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Background

Apathy in Alzheimer's disease (AD) is increasingly being recognized as a separate and distinct clinical syndrome from depression and has an out-sized effect on caregiver burden and quality of life. Evidence shows methylphenidate is an effective treatment for this condition, but fears regarding cardiovascular effects of methylphenidate (MPH) in the elderly have limited its widespread use.

Methods

We used a cohort of 59 community-dwelling veterans with mild AD (30 from MPH arm, 29 from placebo arm) obtained from a randomized controlled trial. All participants were started on 5 mg of methylphenidate or placebo twice daily and titrated to 10 mg twice daily at 2 weeks. EKG data collected at baseline, 4 weeks, and 12 weeks was analyzed for changes from baseline for PR interval, QRS interval, QT/QTc, and P/R/T axes via repeated measures mixed model analyses of covariance. We present vital sign data for comparison. Also, EKG interpretations were described and reported.

References

1. Padala PR, et al. Methylphenidate for apathy in community-dwelling older veterans. *Am Journal of Psychiatry.* 2017 PMID: 28945120
2. Herrmann N, et al. Methylphenidate for the treatment of apathy in Alzheimer disease. J of Clinical Psychopharmacology 2008;28(3):296-301. PMID: 18480686
3. Rosenberg PB, et al. Safety and efficacy of methylphenidate for apathy in Alzheimer's disease. *Journal of Clinical Psychiatry* 2013;74(8):810-6. PMID: 24021498
4. Schelleman H, et al. Methylphenidate and risk of serious cardiovascular events in adults. Am J Psychiatry. 2012 Feb;169(2):178-85. PMID: 22318795
5. Habel LA, et al. ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. JAMA. 2011 Dec 28;306(24):2673-83 PMID: 22161946
6. Wilkinson JD, et al. Long-term effects of methylphenidate on cardiovascular function and structure in rhesus monkeys. Pediatr Res. 2019 Feb;85(3):398-404. PMID: 30555154
7. Mosholder AD, et al. Heart Failure and Cardiomyopathy Following Initiation of Medications for Attention-Deficit/Hyperactivity Disorder. J Clin Psychopharmacol. 2018 Oct;38(5):505-508. PMID: 30102629

Results

Table 1: EKG Time Interval Changes from Baseline (at 4 and 12 Weeks) for Methylphenidate and Placebo Groups

	Change at 4 Weeks			Change at 12 Weeks		
	Mean	95% CI	p-value	Mean	95% CI	p-value
PR			0.8378			0.8007
Methylphenidate	1.2	(-4.5, 6.9)		-2.0	(-7.7, 3.7)	
Placebo	0.4	(-5.3, 6.0)		-3.1	(-9.4, 3.3)	
Difference	0.8	(-7.2, 8.8)		1.1	(-7.5, 9.7)	
QRS			0.6200			0.7142
Methylphenidate	-1.0	(-3.8, 1.9)		-1.8	(-4.7, 1.1)	
Placebo	-2.0	(-4.9, 1.0)		-2.6	(-5.8, 0.6)	
Difference	1.0	(-3.1, 5.1)		0.8	(-3.5, 5.1)	
QT			0.7886			0.2781
Methylphenidate	-5.7	(-14.5, 3.1)		-8.1	(-16.9, 0.6)	
Placebo	-4.0	(-12.9, 4.9)		-0.9	(-10.8, 9.1)	
Difference	-1.7	(-14.2, 10.8)		-7.3	(-20.5, 6.0)	
QT_c			0.8660			0.0743
Methylphenidate	-5.1	(-15.1, 4.9)		6.7	(-3.3, 16.7)	
Placebo	-6.3	(-16.5, 3.9)		-7.1	(-18.5, 4.3)	
Difference	1.2	(-13.1, 15.5)		13.8	(-1.4, 29.0)	

Table 1. EKG Time intervals were compared between the groups at both 4 and 12 weeks. No significant differences were found between MPH and placebo treatments.

Table 2: Changes from Baseline in Cardiac Vital Signs at 4 and 12 weeks

	Change at 4 Weeks			Change at 12 Weeks		
	Mean	95% CI	p-value	Mean	95% CI	p-value
Pulse			0.660			0.268
Methylphenidate	-1.9	(-4.9, 1.0)		-1.8	(-4.8, 1.3)	
Placebo	-2.9	(-5.9, 0.1)		-4.3	(-7.7, -1.0)	
Difference	0.9	(-3.3, 5.2)		2.6	(-2.0, 7.2)	
SBP			0.583			0.505
Methylphenidate	4.9	(-0.3, 10.1)		6.6	(1.3, 12.0)	
Placebo	2.9	(-2.4, 8.2)		9.3	(3.3, 15.3)	
Difference	2.1	(-5.4, 9.5)		-2.7	(-10.7, 5.3)	
DBP			0.626			0.825
Methylphenidate	0.4	(-3.4, 4.1)		2.7	(-1.2, 6.5)	
Placebo	-1.0	(-4.8, 2.9)		2.1	(-2.1, 6.4)	
Difference	1.3	(-4.0, 6.7)		0.7	(-5.1, 6.4)	

Table 2. Cardiac Vital Signs compared to baseline for the methylphenidate group vs. placebo at 4 and 12 weeks. No significant differences were found.

Table 3: Changes in EKG Interpretation Between Placebo and MPH Treatment from baseline to 12 weeks

Placebo	MPH
New RBBB	
QT Prolongation	QT Prolongation
Possible Anterior Infarct	New Septal Infarct
New Inferior Infarct	New Septal Infarct
Possible-> Septal Infarct	
New LBBB	
New LBBB	

Table 3. Of all the patients, 7 of the placebo group and 3 in the MPH demonstrated significant changes in EKG interpretation.

Evidence of Cardiac Safety in MPH Trials

- 3 RCTs tested methylphenidate for apathy in AD, with no adverse cardiac events reported.[1-3]
- Retrospective studies measured MI, Stroke, and sudden cardiac death had mixed results, with no dose-related increases in cardiac death, and one showed MPH was cardioprotective[4-5]
- Long-term MPH use in non-human primates showed no significant effects on echo- and electrocardiographic measures[6]
- One study measuring cardiomyopathy in new patients showed a trend of increased cardiomyopathic events in patients older than 65 (but no other age group), and only for the first 90 days.[7]

Conclusions

- In 59 community dwelling patients with mild AD, there were no significant changes in EKG time intervals, no serious adverse events were reported, and EKG interpretation results favored the MPH group.
- Appropriate risk-benefit decision-making should be discussed with patients prior to initiation of methylphenidate for apathy in AD, but RCTs have shown relative safety, and retrospective studies may show at most, modest risk, mainly in the first 90 days after initiation.