Methylphenidate, cognition, and epilepsy

A double-blind, placebo-controlled, single-dose study

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ABSTRACT

Objective: To evaluate the potential efficacy of immediate-release methylphenidate (MPH) for treating cognitive deficits in epilepsy.

Methods: This was a double-blind, randomized, single-dose, 3-period crossover study in patients with epilepsy and chronic cognitive complaints comparing the effects of placebo and MPH 10 and 20 mg given 1 week apart. Cognitive outcome was evaluated on the basis of an omnibus *z* score calculated from performance on the Conners Continuous Performance Test 3 (ability to discriminate between target and nontarget stimuli [d'] and hit reaction time standard deviation), Symbol-Digit Modalities Test, and Medical College of Georgia Paragraph Memory Test. Adverse events and seizure frequency were monitored. An open-label follow-up is reported elsewhere.

Results: Thirty-five adult patients with epilepsy participated, of whom 31 finished. Demographics included the following: mean age = 35.3 years (range 20–62 years), 13 men and 18 women, and baseline seizure frequency of 2.8 per month. Epilepsy types were focal (n = 24), generalized (n = 6), or unclassified (n = 1). Mean epilepsy duration was 12.5 years. A statistically significant performance benefit was present at both 10-mg ($p = 0.030$) and 20-mg ($p = 0.034$) MPH doses. No seizures were associated with either MPH dose. Adverse effects leading to withdrawal included cognitive "fogginess" (n = 1 on 20 mg), anxiety/agitation (n = 1 on 10 mg), and tachycardia (n = 1). One participant was lost to follow-up after one 20-mg dose without side effect.

Conclusions: This single-dose study suggests that MPH may be effective in ameliorating some cognitive deficits in patients with epilepsy. Additional studies are required.

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Classification of evidence: This study provides Class II evidence that single doses of MPH improve cognitive performance on some measures of attention and processing speed in patients with epilepsy and cognitive complaints. *Neurology*® 2017;88:470–476

GLOSSARY

ADHD = attention-deficit/hyperactivity disorder; **AED** = antiepileptic drug; **CPT 3** = Conners Continuous Performance Test Third Edition; **d'** = ability to discriminate between target and nontarget stimuli; **HRTSD** = hit reaction time standard deviation; **MCG** = Medical College of Georgia Paragraph Memory Test; **MPH** = methylphenidate; **SDMT** = Symbol Digit Modalities Test.

Patients with epilepsy often have deficits in attention, memory, and processing speed, resulting from seizures, interictal epileptiform discharges, underlying etiology, or antiepileptic drugs (AEDs).[1–5] Improving seizure control, decreasing AED polypharmacy, or switching AEDs may help but can be difficult and often does not resolve these deficits.[6]

Using psychostimulants to treat attention-deficit/hyperactivity disorder (ADHD) in this population has traditionally caused unease due to concerns of provoking seizures. The US Food and Drug Administration–approved insert for methylphenidate (MPH) warns as such.[7] Evidence supporting this is limited: a literature review yields an early study demonstrating prolonging of artificially induced seizures in a rat model,[8] 3 case reports,[9–11] and a study of seizures in MPH overdose.[12] One study of extended-release MPH observed a possible increase in seizures at high doses, but total seizures were "too few to confidently assess this risk."[13] Recent reviews of the child literature concluded that MPH

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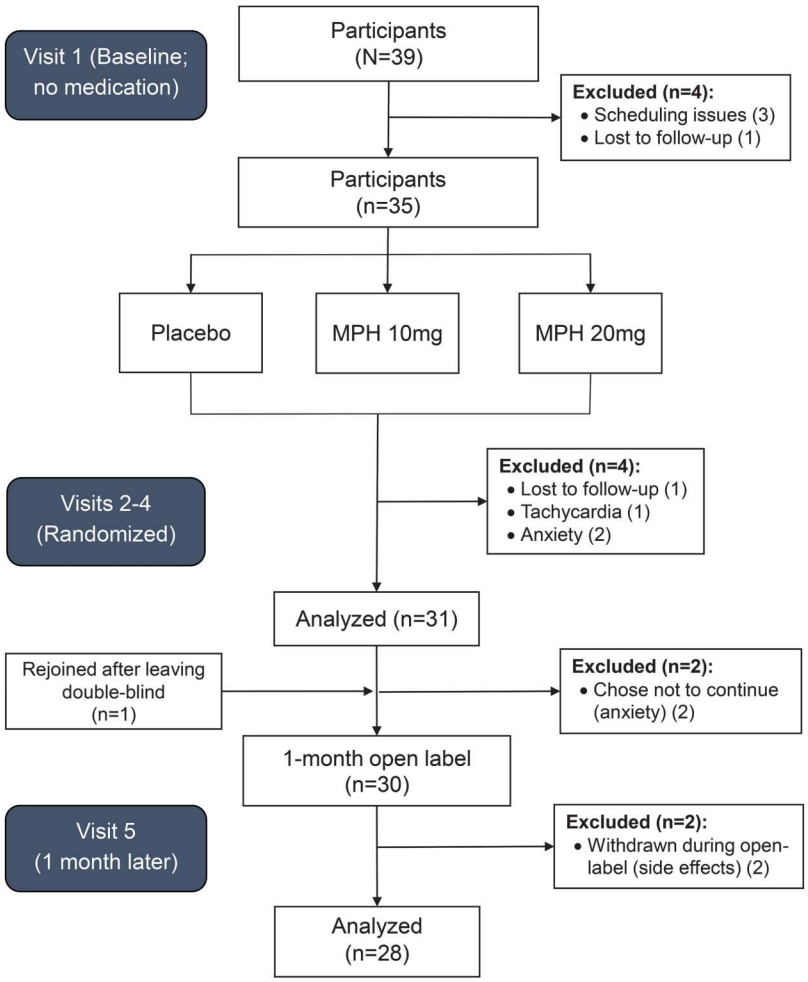
Figure Study flow diagram



A visual representation of participant flow through our trial. Participants received all 3 medication interventions, in randomized order, across visits 2, 3, and 4 before data were analyzed. Interested participants then continued into the 1-month open-label portion of our study. MPH = methylphenidate. *Tachycardia occurred on the higher 40-mg dose under original design. Patient rejoined the open-label phase.

has the most data to support its safety and efficacy for use in children with epilepsy and that MPH is not associated with a clinically significant increase in seizure risk.[3,5,6,14–19]

The few studies in adults with epilepsy corroborate the child data, demonstrating cognitive improvement without worsening seizures.[20,21] However, these studies suffer from small samples, the lack of objective measures, and a lack of blinding. There is a need for studies of MPH in adults with epilepsy using a well-controlled design with objective measures. We report a single-dose, randomized, double-blind, placebo-controlled trial investigating whether MPH improves performance on objective, standardized cognitive measures in adults with epilepsy.

METHODS

Design. This investigation was a single-dose, double-blind crossover study comparing MPH 10 mg, MPH 20 mg, and placebo. The primary research question for this study was as follows: does single-dose MPH improve performance on objective measures of cognition in adult patients with epilepsy and cognitive deficits? This study provides Class II evidence that single doses of MPH improve cognitive performance on some measures of attention and processing speed in patients with epilepsy and cognitive complaints.

Placebo and drug capsules were indistinguishable. The Stanford University investigational pharmacy maintained blinding and randomization. MPH has been shown to display wide individual variability in optimal dosage and peak plasma concentrations at a given dose, as well as a lack of correlation between plasma concentration and clinical efficacy. Reviews suggest that plasma levels are not helpful in determining an appropriate dose. Therefore, plasma levels were not drawn.[22]

All investigators involved in recruitment, testing, and data analysis were blinded until the completion of the analysis. One investigator (J.J.B.) was unblinded in the event of adverse effects to provide relevant information to the treating physicians but otherwise had no contact with the participants, investigators, or data during the trial. Participants completed a baseline visit, including informed consent, and then underwent physical examination and cognitive testing to introduce them to the test battery. No medication was given at this baseline visit. Subsequently, patients participated in 3 medication visits ≈1 week apart from each other, during which they were given one of the blinded preparations. All participants received each dose once by the end of visit 4, but the order in which they received the doses was randomized. A flow diagram of the study is presented in the figure. At the completion of the double-blind portion, participants were invited to participate in a 1-month open-label phase. Details and results of the open-label portion of the study will be reported elsewhere.

Participants. The participants were recruited primarily through the Stanford Neurology and Neuropsychiatry clinics at Stanford Medical Center between August 2014 and July 2015. Final study visits occurred in September 2015, with the completion of our final enrollee. A preliminary power analysis estimated that a sample size of 30 patients with a test-retest reliability of 0.92 yielded 85% power (one-tailed) to detect a 10% difference in our outcomes based on a 0.2 SD of the difference score. Inclusion criteria included epilepsy of any cause, cognitive complaints, stable AED doses that were not expected to change during the study, physical examination without concerning findings (e.g., cardiovascular), neurologist's judgment that the participant was clinically appropriate for this study, and capacity to consent. Exclusion criteria included age <18 or >65 years, other conditions that interfered with cognition, status epilepticus within the year before entry, neurosurgery in the 6 months before entry, the use of non-AED medications that may have interfered with cognition, any allergy or condition that was considered a contraindication to MPH, a substance use disorder within the last year, and pregnancy or breastfeeding.

Standard protocol approvals, registrations, and patient consents. This trial is registered on clinicaltrials.gov under the following listing: Methylphenidate Treatment of Attention Deficits in Epilepsy (NCT02178995). This study was approved by the Stanford University Institutional Review Board, and signed informed consent was obtained from all participants before participation.

Procedures. To avoid potential confounding side effects of medications, participants were asked to avoid taking any nonroutine

sedating medications 24 hours before their appointment time. Use of medications, including as-needed medications, was monitored. Participants were also asked to avoid caffeine or nicotine within 2 hours of their appointment. Administration with food may delay the absorption of MPH, but clinical data have not shown a significant effect on clinical efficacy to support requiring the medication to be taken in the fasting state.[22] Nevertheless, to reduce any potential differences in medication absorption based on food intake, all participants were asked not to eat within 2 hours of their appointment. On arrival, vital signs were obtained, and then participants were given a double-blinded capsule containing 1 of the 3 study doses. Participants waited 1 hour after dosing to allow medication absorption and peak effect, after which they completed a neurocognitive battery, described below. After the neurocognitive battery, participants were asked about any noticeable effects of the medication, and the visit concluded. Visits occurred ≈1 week apart, and the double-blind trial ended after the completion of the fourth visit.

Outcome measures. Participants were administered 3 neurocognitive tests in the following order: Symbol Digit Modalities Test (SDMT),[23] Medical College of Georgia Paragraph Memory Test (MCG),[24] and Conners Continuous Performance Test Third Edition (CPT 3).[25] These measures assess processing speed, immediate verbal recall, and attention-related issues, respectively. Five different versions of the SDMT and MCG were administered across visits, and the order in which these were administered was randomized to balance practice effects. The CPT 3 is a computerized go/no-go task that sequentially presents an examinee with both target and nontarget stimuli and requires the examinee to press the space bar for all stimuli except the target stimulus (the letter X). The resulting CPT 3 report provides data on the ability to discriminate between target and nontarget stimuli (d'), consistency in response speed (hit reaction time standard deviation [HRTSD]), number of omissions and commissions, and total hits.

Primary outcome variables of interest for our study were the following: SDMT total correct score, MCG total score, and the CPT variables d' and HRTSD. HRTSD and d' were chosen among the CPT variables available because reviews have suggested that they are sensitive to attentional issues in individuals with ADHD across all clinical symptom domains.[26,27] The other 2 primary outcome measures (SDMT total score and MCG total score) were chosen because of their demonstrated sensitivity to drug and disease effects.[24] The individual variable scores were converted to z scores based on performance during the placebo condition and then combined into a single dependent measure to avoid type I error concerns associated with multiple statistical tests. Independent, one-sample t tests were then performed for the 10- and 20-mg conditions against the expected null condition of 0 mg to evaluate for significant drug effects at each dose.

Secondary outcome variables included CPT variables omissions, commissions, and total hits, as well as seizure frequency. These were analyzed with a 3-level repeated-measures analysis of variance. Baseline seizure frequency was determined with a retrospective 28-day calendar filled out at the first visit from patient and family reports in conjunction with a review of medical records. A new weekly seizure calendar was filled out at each visit to monitor any events after enrollment. The raw number of seizures recorded was then converted to a rate of seizures per 28 patient-days. Particular attention was paid to any seizures near the time of MPH doses. Other adverse events were recorded. We hypothesized that MPH would improve cognitive performance on these measures of attention, memory, and processing speed, with no significant difference between the 2 doses and no increase in seizures.

RESULTS Thirty-nine participants signed consent forms, but 4 were unable to enter the double-blind portion of the trial because of scheduling constraints or being lost to follow-up. Thirty-five participants entered the full double-blind portion of the study, and 31 participants completed the study and were analyzed. Examination of all 6 treatment-order groups revealed that each group was of equal size insofar as sample size allowed (i.e., 5 or 6 per group), and there were no significant demographic differences between groups at baseline (data not shown). Demographic information for participants who completed the double-blind trial is reported in table 1.

Significant cognitive benefit was present for both the 10-mg ($p = 0.030$) and 20-mg ($p = 0.034$) conditions as measured by omnibus z score (table 2). The finding of comparable levels of benefit between the 2 active doses is consistent with reviews indicating that dose-specific responses for MPH are idiosyncratic in clinical ADHD.[28]

Secondary analyses of the nontransformed data for each of our primary variables (table 3) indicate significant improvement on both active doses for SDMT and HRTSD, with a trend toward improvement on d' and no significant difference in MCG scores. Note that higher scores on SDMT, MCG, and hits indicate better performance, while higher (or less negative) scores on all other variables indicate worse performance. Improvements were seen on secondary variables omissions and hits. No significant differences were found for commissions. Across all variables, placebo was worse than 10 and 20 mg MPH. The nontransformed data also indicate no difference between the 10- and 20-mg doses (table 4).

Adverse effects. MPH was generally well tolerated. No seizures were experienced by participants in association with receiving single doses of MPH, and seizure frequency did not change during this study (data not shown). Four participants withdrew during the

Table 1 Demographic information

Male/female	13/18
Mean age (range), y	35.3 (20–62)
Mean education (range), y	14.77 (12–20)
Mean duration of epilepsy (range), y	12.5 (1–41)
Seizure type, n	
Focal	24
Generalized	6
Unclassified (GTCS)	1

Abbreviation: GTCS = generalized tonic-clonic seizure.
Etiology: focal: 4 vascular (2 hemorrhagic stroke, 2 cavernous malformation), 4 traumatic brain injury, 3 brain tumor, 3 cortical dysplasia, 2 postinfection, 8 idiopathic; generalized: 3 juvenile myoclonic epilepsy, 3 idiopathic.

Table 2 Omnibus *z* score comparison, 10 and 20 mg vs placebo

MPH dose, mg	Mean (SD)	*t*	Significance (*p* value)	95% CI
10	0.25 (0.61)	2.3	0.030[a]	0.03–0.47
20	0.24 (0.61)	2.2	0.034[a]	0.02–0.47

Abbreviations: CI = confidence interval; MPH = methylphenidate.
Independent one-sample *t* test; n = 31, *df* = 30.
[a] Significant results ($p < 0.05$).

double-blind portion of this study: one was lost to follow-up without side effect, and 3 participants were withdrawn from the study following adverse events. These adverse events included anxiety and difficulty thinking (n = 1) on 20 mg, anxiety and agitation (n = 1) on 10 mg, and clinically significant but self-limited tachycardia (n = 1). In the initial design of this study, a 40 mg vs 20 mg vs placebo comparison was intended; however, this participant experienced tachycardia on the original 40-mg dose, so the doses were changed to the current design. This participant later entered and completed the open-label portion of the study after experiencing MPH as helpful for cognitive performance. Two additional participants experienced anxiety (20-mg dose) and agitation (placebo) without withdrawing. Other minor but infrequent side effects were reported, including headache and "feeling different."

DISCUSSION Our data demonstrate that patients with epilepsy and cognitive deficits perform better on MPH than placebo on a combined outcome score based on SDMT, MCG, and the CPT variables HRTSD and d'. When examined on the level of individual tests, our data indicate significant improvement on: SDMT; the CPT variables HRTSD, omissions, and hits; and a significant trend toward the same result on: d'. Other variables were not statistically significant but showed a similar pattern, with placebo performing worse than either active dose across variables. Cognitive deficits affect as many as 45% of patients with epilepsy,[29] and there are few proven treatment strategies. Thus, the availability of an adjunctive medication intervention to ameliorate these difficulties could provide significant clinical benefit. The results of this single-dose study support the idea that MPH may improve performance in adult patients with epilepsy and cognitive difficulties.

Although single-dose studies of MPH are few, the results obtained are similar to such studies in other clinical populations. Children with ADHD have been found to demonstrate improved performance on measures of attention after administration of immediate-release MPH.[30] Single 10-mg doses of MPH improved processing speed and attention compared to placebo in adult patients with multiple sclerosis.[31] Single 20-mg doses of MPH improved working memory and attention compared to placebo in adults with traumatic brain injury.[32] Interestingly, the review by Repantis et al.[33] of single-dose studies in healthy adults found beneficial effects primarily on memory rather than attention/executive function. It is unclear whether the slight differences in our findings are due to differences in chosen cognitive tasks or to differences in clinical populations compared to healthy individuals. Large-scale reviews of the ADHD literature suggest that stimulants demonstrate more prominent benefits on tasks without an executive function component such as reaction time, reaction time variability, and sustained attention than on those with an executive function component such as working memory, and this is consistent with our findings.[26]

Our results are also similar to previous studies in children indicating that MPH is an effective treatment for ADHD in patients with epilepsy and does not lead to a clinically significant increased risk in seizures,[3,5,6,14–19] as well as with the small-scale studies

Table 3 Placebo vs 10 vs 20 mg methylphenidate, individual measures

Measure	Placebo, mean (SD)	10 mg, mean (SD)	20 mg, mean (SD)	Significance (*p* value)	Effect size[a]
SDMT	49.8 (11.9)[b]	52.2 (11.6)[b]	50.6 (11.3)[b]	0.008[b]	0.215[b]
MCG	25.2 (14.8)	27.4 (15.4)	28 (15.3)	0.154	0.067
HRTSD	0.19 (0.048)[b]	0.17 (0.034)[b]	0.17 (0.036)[b]	0.037[b]	0.137[b]
d'	−3.3 (0.9)[c]	−3.58 (0.78)[c]	−3.66 (0.77)[c]	0.055[c]	0.118[c]
Hits	285.3 (4.5)[b]	286.9 (1.6)[b]	287 (2.7)[b]	0.04[b]	0.134[b]
Omissions	0.9 (1.5)[b]	0.3 (0.4)[b]	0.3 (0.8)[b]	0.038[b]	0.136[b]
Commissions	24 (19.9)	21.5 (18.2)	21.2 (15.1)	0.329	0.032

Abbreviations: d' = ability to discriminate between target and nontarget variables; HRTSD = hit reaction time standard deviation; MCG = Medical College of Georgia Paragraph Memory Test; SDMT = Symbol Digit Modalities Test.
Within-subjects contrasts, analysis of variance; n = 31, *df* = 1.
[a] Partial eta squared (η_p^2). Generally, 0.01 = small, 0.06 = medium, and 0.14 = large effect size.
[b] Significant results ($p < 0.05$).
[c] Statistical trend toward significance ($p < 0.10$).

Table 4 10 vs 20 mg methylphenidate, individual measures

Measure	MPH 10 mg, mean (SD)	MPH 20 mg, mean (SD)	Mean difference[a]	Significance (p value)
SDMT	52.2 (11.6)	50.6 (11.3)	−1.6	0.071[b,c]
MCG	27.4 (15.4)	28.0 (15.3)	0.6	0.779
HRTSD	0.17 (0.034)	0.17 (0.036)	0.00	0.758
d′	−3.58 (0.78)	−3.66 (0.77)	−0.08	0.499
Hits	286.9 (1.6)	287.0 (2.7)	0.1	0.876
Omissions	0.3 (0.4)	0.3 (0.8)	0.0	0.932
Commissions	21.5 (18.2)	21.2 (15.1)	−0.3	0.898

Abbreviations: d′ = ability to discriminate between target and nontarget variables; HRTSD = hit reaction time standard deviation; MCG = Medical College of Georgia Paragraph Memory Test; SDMT = Symbol Digit Modalities Test.
Paired differences, 2-tailed *t* test; n = 31, *df* = 30.
[a] Mean difference scores are expressed as mean (20 mg) − mean (10 mg). A negative value indicates that the raw score of the measure was lower on 20 than on 10 mg.
[b] Statistical trend toward significance ($p < 0.10$).
[c] Trend favors 10 mg.

available in the adult literature.[20,21] Furthermore, our data are similar to repeated-dose studies of MPH in other populations. Specifically, a meta-analysis found MPH to have positive effects compared to placebo on executive and nonexecutive memory, reaction time, reaction time variability, commission errors, and response inhibition in children and adolescents with ADHD.[34] Studies have also noted potential benefit for those with opiate-induced cognitive dysfunction,[35] brain tumors,[36] HIV,[37] Parkinson disease,[38] traumatic brain injury,[39] and the elderly.[40]

Important strengths of this study include the use of established, standardized, reproducible, objective cognitive measures across multiple cognitive domains and its randomized, double-blind, placebo-controlled, mixed-dose design. Other strengths include the use of a clinically diverse population and a relatively large sample size compared to prior studies, with equal baseline characteristics. The study design controlled for caffeine, nicotine, and medication effects on cognition, as well as any impact that food may have on the absorption of MPH. Multiple versions of each cognitive measure were used, in a randomized fashion, to control for practice and order effects. Procedures specifically precluded AED dose changes during the study to avoid confounding effects.

Our investigation also has several limitations to consider. A final sample size of 31, while larger than prior studies, is still relatively small, and larger studies with longer treatment duration are needed to corroborate the results. The mechanism of action by which MPH may benefit cognition in patients with epilepsy remains unclear. The results of our single-dose study may not be generalizable to long-term, clinical dosing schedules. Similarly, an improvement on cognitive tests does not necessarily indicate substantive clinical benefit. The inclusion of a matched, untreated control group of participants with epilepsy would help strengthen these results. The half-life of MPH is 2.6 to 3 hours, and the peak clinical effect is generally attained in 1 to 3 hours, with effects wearing off within ≈6 hours.[22] A 1-hour delay between ingestion and testing may therefore not be sufficient for MPH to take effect in some individuals, and this may lead to an underestimation of the effects of MPH. Single doses of MPH would not be expected to alter seizure control over multiple days. While no seizures were experienced with single doses and there was no observed worsening of seizure frequency, long-term clinical studies are needed to evaluate the impact of MPH on epilepsy. Finally, it is possible that specific subgroups of patients with epilepsy (for instance, those with traumatic brain injury or stroke) may respond differently from others, and the sample size in this study does not allow a thorough evaluation of this question. The open-label follow-up to this study will help to address some of these drawbacks, but blinded, long-term studies with a large cohort will ultimately be required.

In conclusion, MPH improved scores on objective cognitive measures in this single-dose study and may be a safe and effective treatment for cognitive difficulties experienced by adult patients with epilepsy. Additional double-blind, placebo-controlled, long-term trials using standard clinical dosing and standardized cognitive measures are needed.

AUTHOR CONTRIBUTIONS

Jesse Adams: study concept, design, supervision, literature review, acquisition and analysis of data, manuscript drafting and revision. Valerie Alipio-Jocson and Katherine Inoyama: study design, acquisition and analysis of data, manuscript drafting and revision. Victoria Bartlett: study coordination, acquisition and analysis of data, manuscript revision. Saira Sandhu and Jemima Oso: acquisition and analysis of data, manuscript revision. John Barry: study concept and design, manuscript revision. David W. Loring: statistical analysis, interpretation of data, manuscript

revision. Kimford Meador: study concept, design, funding, supervision, analysis of data, manuscript drafting and revision.

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DISCLOSURE

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