

Whyte J, Hart T, et al. Effects of Methylphenidate on Attention Deficits After Traumatic Brain Injury. Am J Phys Med Rehabil 2004;83:401-420.

Design: Randomized crossover trial

Population/sample size/setting:

- 34 patients (29 men, 5 women, mean age 37) treated for the sequelae of moderate to severe closed head injury at a university rehabilitation clinic in Philadelphia
- Inclusion criteria were age 16 to 60 with nonpenetrating moderate or severe TBI at least 3 months prior to entry, with lowest GCS score <12 or documented posttraumatic amnesia > 1 hour or focal abnormality on a neuroimaging study which was attributable to the injury; a complaint of attentional difficulties by the patient, treating clinician, or caregiver was required, and patients needed to be able to perform tasks for 10-15 minutes semi-independently
- Exclusion criteria were pregnancy, premorbid neurologic/psychotic/major affective disorder, mental retardation, or ADHD; psychotropic medication other than anticonvulsant, current alcohol or drug abuse; impairments in hearing, vision, or motor function sufficient to preclude participation in research tasks

Main outcome measures:

- Each patient was involved in the study for 6 consecutive weeks, participating in a day activities program in a research classroom setting
 - o Classroom setting had 3 or 4 patients at a time, lasting from 9:30 AM to 3:30 PM Monday through Friday; there were 4 hours of classroom activity, 30 minutes of initial assessment, and 90 minutes for lunch
- All patients took both methylphenidate (MP) and placebo (P) alternating weekly, such that three weeks were on MP and three on P
- Order of treatment (whether they started on MP or P) was randomized
 - o MP was given at a dose of 0.3 mg/kg administered at 8:30 AM and at 12 noon; P was taken at the same time
 - o Study drugs were taken Monday through Saturday, with Sunday as a washout day on which no medication was taken
- Some of the study tasks were done with computers, some were done without a computer, and some tasks were scored by a trained observer unaware of which medication was being taken at the time
- The outcome was created as a composite score based on pilot data from the first 10 patients to have a full data set; this composite score was used as the measure of the treatment effect of MP in the remaining 24 patients
- From the extensive battery of classroom tasks, correlation analyses were done in order to identify factors which would allow a small number of variables making up the composite scores, and three were associated with a treatment effect for MP

- One composite score, taken from 8 different tasks, assessed speed of task performance, which was faster with MP than with P
- One score was based on home caregiver ratings of patient attention, cognition, and behavior (mostly based on weekend interactions in the patients' homes); it also was improved by MP compared with P
- The third score positively affected by MP was on-task behavior, composed of scores on attentive vs. inattentive behavior during task performances, some of which were done under conditions in which the investigators created distractions in order to test the capacity for sustained attention to the classroom tasks
 - This third score was more complex in its analysis, being a composite of frequency of inattentiveness and duration of individual off-task episodes recorded on videotape; the effect size was small to medium
 - Effects on sustained attention were not evident
- Although MP effect sizes were statistically significant, their magnitude was small to medium (absolute improvements ranging from 5% to 25%)
- Blinding of patients was judged to be generally successful; only one patient was consistently accurate in assessing which drug he was taking in each 1 week period

Author's conclusions:

- MP at a dose of 0.3 mg/kg twice daily seems to have positive effect on speed of cognitive processing and on caregiver ratings of attentiveness
- The study sample was derived from a very large number (n=1549) of patients who were assessed for eligibility; participants had to be willing to commit 6 weeks of their time 5 days per week, excluding potential participants who had returned to work or were too impaired to travel
- The complex statistical methods may have resulted in inferential errors which are difficult to quantify, but collapsing several scores into a single factor should improve the signal-to-noise ratio

Comments:

- The complex nature of the statistical construction and analysis of the outcome variable creates some problems with respect to the real-world clinical relevance of the outcome measures
- However, the treatment effect of MP does not appear to be likely to be at great risk of inflation through bias in treatment assignment or outcome assessment
- Table 1 reports the Disability Rating Scale for the participants with a mean score of 4 (moderate) and a range from 1 (mild) to 8 (moderate to severe); however, the standard Disability Rating Scale has a scoring range from 0 (no deficits) to 29 (maximal deficits), and the score of 8 is not in the moderate or severe range
- The reported effects of MP are consistent with its established pharmacodynamics and pharmacokinetics, which means that the study hypothesis has a reasonable prior probability of being correct

- The methods section states that the clinicians were trained not to intervene to increase attentiveness through cueing or reinforcement, but it is not clear how this was accomplished
- The study design called for daily reminders to take the medication on schedule, and if a participant missed a morning dose, the tasks for that morning were skipped and made up at another time under the correct medication condition; this may result in effect measures which are greater than those which are likely to occur in the real world when missed doses are a frequent occurrence
- The study is probably better characterized as a proof-of-principle experiment than as a guide to the overall therapeutic effect of MP

Assessment: Adequate for evidence that methylphenidate is able to increase the speed of cognitive processing in patients with moderate to severe TBI