

Willmott C, Ponsford J. Efficacy of methylphenidate in the rehabilitation of attention following traumatic brain injury: a randomized, crossover, double blind, placebo controlled inpatient trial. J Neurol Neurosurg Psychiatry 2009;80:552-557.

Design: Randomized crossover trial

Population/sample size/setting:

- 40 patients (28 men, 12 women, mean age 26) with moderate or severe TBI admitted to an inpatient rehabilitation in Melbourne, Australia
- Eligibility criteria were age 16 to 60 with sufficient understanding of English, physical and cognitive abilities to undertake neuropsychological testing, and attentional impairment at a baseline assessment
- Exclusion criteria were any previous significant neurological diagnosis, treatment with methylphenidate for attentional disturbance, treatment for drug or alcohol problems, or current treatment with other psychoactive medication

Main outcome measures:

- All patients attended the clinic on six occasions for 2 weeks following entry into the trial
 - o On each clinic visit, the participants took standardized tests of attention and working memory, with reaction times and errors determining the scores on the tests
 - o The clinic visits and tests were scheduled in 3 blocks of 2 visits: the first block was on Monday and Wednesday of the first week; the second block on Friday of the first week and Monday of the second week; the third block on Wednesday and Friday of the second week
 - o On each clinic visit, each participant took an opaque capsule at 8 AM and at noon; the active capsules had methylphenidate at dose of 0.3 mg/kg, and the placebo capsules had lactose only
 - o For each block, one of the sessions was done after taking methylphenidate and one was done after taking placebo
- Tests were administered in the same order for each participant on each of the six visits, but the order of testing was randomized across patients
- The sequence of methylphenidate and placebo was determined by a random number table by independent pharmacists who dispensed the medication
- The test outcome for methylphenidate was determined by averaging the test scores for each of the three sessions taking methylphenidate; the same was done for the test outcome for placebo
- Some of the attentional tests were classified as “simple” and others as “complex,” depending on the test conditions and the task demands on working memory and attention
- In the “simple” test conditions, methylphenidate was significantly associated with shorter reaction times than was seen for placebo, without loss of accuracy or increase in error rate
- For the “complex” test conditions, the advantage of methylphenidate over placebo was not statistically significant

- Safety and adverse effects were reported in a separate article (**Willmott C, Ponsford J, et al. Safety of Methylphenidate Following Traumatic Brain Injury: Impact on Vital Signs and Side Effects During Inpatient Rehabilitation. J Rehabil Med 2009;41:585-587**)
 - o Compared to placebo, methylphenidate had an increase in heart rate of 12 beats per minute, an increase in diastolic blood pressure of 4.1 mmHg, and an increase in mean arterial pressure of 3.8 mmHg; systolic pressure was not increased
 - o The changes were not symptomatic, and blinding was not compromised
 - o No participant withdrew from the study because of adverse effects

Authors' conclusions:

- The use of methylphenidate increased speed of information processing without reducing accuracy of task performance for the simple tasks tested in the study
- More complex task conditions were not significantly improved by methylphenidate, perhaps due to differences in working memory demands with the more complex test conditions
- Methylphenidate resulted in a trend towards improved attentional behavior

Comments:

- The principal outcome is the score on a fairly specialized set of neuropsychological tests
- The crossover design is more statistically efficient than a parallel randomized trial design, but there are some problems with its use in this context
 - o A crossover study is best suited for measuring a variable which is likely to remain stable over a period of time and to return to a baseline value after the administration of a fairly short-acting intervention
 - o Methylphenidate is a fairly short-acting drug, which makes it suitable for a crossover trial
 - The interval between administration of the test capsules and the testing is not specified, but should have allowed time for drug absorption and brain uptake
 - o However, it is likely that repeated administration of a standardized test will improve over time, especially when the testing interval is short
 - o There is no discussion of this issue, nor is there any mention of the test-retest characteristics of the task performances in the clinic
 - o It is not clear whether a time trend in the test would inflate or diminish the measured effect of methylphenidate
 - In the patients who took placebo first, their second test score will show a mixed effect of retesting and methylphenidate; in this case, the second test could inflate the actual effect of methylphenidate on test performance
 - In the patients who took methylphenidate first, the second test score would mix the effects of retesting and placebo; in this

case, the second test would reduce the actual effect of methylphenidate on test performance

- The effect of the active drug and placebo were estimated by averaging three scores rather than a single score
- Overall, it appears unlikely that the comparison will significantly inflate the effect of methylphenidate
- The Bonferroni correction is appropriate for the multiple comparisons which were made
- One entry criterion was attentional impairment at baseline; it is not stated how this was determined (i.e. whether by one or more of the neuropsychological tests used as study outcomes)
- In spite of the gaps in reporting and discussion, the risk of a biased estimate inflating the effect of methylphenidate is probably not a large threat to the internal validity of the study

Assessment: Adequate for evidence that methylphenidate has a short-term effect on improving test performance on standardized measures of attention in patients with moderate to severe TBI