

Mooney GF, Haas LJ. Effect of Methylphenidate on Brain Injury-Related Anger. Arch Phys Med Rehabil 1993;74:153-160.

Design: Randomized clinical trial

Population/sample size/setting:

- 38 adult men (mean age 29) with serious TBI treated at an outpatient rehabilitation center at the University of Utah
- Eligible for inclusion if they were at least six months out from date of injury, had been unconscious (GCS score less than 8) for at least 6 hours and had at least 24 hours of post-traumatic amnesia, and were classified on the Glasgow Outcome Scale in the Good Outcome category
 - o Mean time from injury was 27 months; mean length of unconsciousness was 16.7 days, mean duration of amnesia was 56.5 days; 92% were unable to work
 - o It was also required that they reside with another person who could function as an independent informant about study outcomes
- Exclusion criteria were major psychiatric diagnoses, serious dementia or mental retardation, substance abuse disorders, visual disturbances, vegetative state, seizure, communication disorders, or mobility impairments which would interfere with cooperation with the study

Main outcome measures:

- Anger, as measured on several questionnaire instruments, was the main outcome; some measured anger as perceived by the patient, and others measured anger as perceived by the informant
 - o State-Trait Anger Scale (STAS), Katz Adjustment Scale Belligerence score (KAS-Belligerence), and Profile of Mood States Anger-Hostility Score (POMS-Anger-Hostility) were the outcome measures
 - STAS-State measures transient states of anger or annoyance that change over time; STAS-Trait measures more consistent predisposition to respond with anger to a wide range of situations
 - KAS has 4 items on a 4-point rating scale of belligerent behaviors
 - POMS is a 65-item scale with 6 separate factors, of which Anger-Hostility was the one measured in this study
- Secondary outcomes included measures of memory and attention, general measures of social adjustment, organic signs and symptoms, and methylphenidate side effects
- Randomized to methylphenidate (n=19) or to placebo (n=19)
 - o Dose was titrated over the first 4 weeks to a final daily dose of 30 mg; the study outcomes were measured at baseline and again during the sixth week of the study
- Main analysis was done by MANOVA (multivariate analysis of variance) of all anger scores simultaneously; the effect of treatment was assessed by the

statistical significance of the treatment-by-time interaction term in the MANOVA output (i.e., the change in anger between baseline and six weeks depended on whether the patient was or was not taking methylphenidate)

- For STAS Trait Anger, the placebo group had a small increase (from 26.47 to 28.84), while the methylphenidate group had a decrease (from 33.58 to 24.11)
 - The methylphenidate group had a higher baseline score for STAS Trait Anger, but the authors did an analysis of covariance (ANCOVA) on the scores and found that the STAS Trait score change remained significant after the appropriate adjustment for baseline differences between groups
- Some secondary measures of outcome also showed changes in the methylphenidate group which, like the STAS Trait Anger, were greater in the methylphenidate group than in the placebo group after adjusting for the baseline differences in baseline scores between the groups
- No effect of methylphenidate was seen on the side effects checklist which was administered at baseline and at follow-up
- Attention and memory scores did not show an effect of methylphenidate
- A secondary post hoc exploration of the data showed that patients with higher pretreatment anger scores were more likely to respond to methylphenidate than patients with lower pretreatment scores

Authors' conclusions;

- Treatment with methylphenidate significantly reduced anger in men with TBI
- Although the methylphenidate group had higher baseline anger scores, raising the possibility that the treatment effect was due to regression to the mean, the further analyses make this an unlikely explanation of the measured drug effect
- The side effect profile of methylphenidate makes it likely that this drug will be acceptable to patients
- The study had only a short-term follow-up, and there can be no certainty that the results would apply to long-term use of methylphenidate

Comments:

- The analysis of the data by ANCOVA probably does support the authors' conclusion that regression to the mean does not explain away the measured changes in anger scores, even though the methylphenidate group did have higher baseline scores on the anger scales
- The method of randomization is not stated, and it is not clear whether concealment of allocation was attempted
 - In 1993, the importance of these features of a study were not as widely appreciated as they became in subsequent years
- The study is described as single-blind, with the patients not being told which treatment they were receiving; the family members and the rating clinicians may not have been blinded

- This is the main weakness of the study; some of the assessments of outcome could have been influenced by knowledge of the treatment group, which places the study at significant risk of bias
- Many of the post hoc analyses and analyses of secondary outcomes should be considered exploratory in nature
- Much attention is paid to statistical significance testing of standardized psychological questionnaires; the relevance of the changes to daily functioning in the real world are not explored

Assessment: Inadequate for evidence of the effect of methylphenidate on anger in TBI rehabilitation (incomplete blinding of assessment of outcome which depends on the observers' impressions of change leads to a risk of bias, compromising internal validity; the real-world functional meaning of the changes in anger scores are not apparent)