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HOW MISSING A TREATMENT OF MIXED AMPHETAMINE SALTS EXTENDED RELEASE AFFECTS PERFORMANCE IN TEEN DRIVERS WITH ADHD

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Summary: Mixed Amphetamine Salts Extended Release (MAS-XR or *Adderall XR®*) is a stimulant medication used to control symptoms of ADHD. People occasionally fail to take their medications. The goal of this pilot study was to assess the impact of a single missed medication on driving performance in 14 teen drivers with ADHD mixed type as a function of driving skill. A double-blind placebo control crossover design was used and participants were tested in a driving simulator. On the evening of the first day, baseline measures of driving performance were taken to assess driving skills (on medication). Then on two consecutive days drivers were tested three times a day, one day on medication and the other day off. Results indicated increased collisions and hazard response time off medication, with performance worst on 36 hours post-medication. Participants with the least developed driving skills benefited most from medication. This highlights the importance of consistent medication use in inexperienced teen drivers with ADHD.

OBJECTIVES

Drivers with Attention-Deficit-Hyperactivity-Disorder (ADHD) are at higher risk for adverse driving outcomes (e.g., Barkley 2007). These dangers are especially notable for teens with ADHD given teens are generally at higher risk (e.g. Transport Canada, 2011). Studies suggest some ADHD medications may improve driving performance (e.g. Barkley & Cox, 2007; Biederman et al. 2012; Cox et al. 2012) but it is not at all uncommon for teens with ADHD to skip medications. One goal of this pilot study is to investigate how driving performance changes over the course of a day as a function of a single missed dose of Mixed Amphetamine Salts Extended Release capsules (MAS-XR known as *Adderall XR®*: a 3:1 mixture of d- to l-amphetamine salts with respective peak plasma concentration times of 7 and 8 hours; post-administration elimination half lives of 9 and 11 hours in adults and 11 and 13 hours for adolescents $\leq$ 75 kg, Shire 2012). There is less research on the effect of MAS-XR on driving than there is on the other stimulant medications and results are mixed (e.g. Cox et al. 2008; Kay, Michaels, & Pakull, 2009; Thorndike et al. 2005). Nonetheless, it is important to note that at this point, there has never been a study focusing on individuals for whom MAS-XR is the treatment of choice. A double blind placebo control crossover design was used in driving simulator testing.

As driving skills develop certain aspects of driving performance become automatic, which is to say that they do not require as much attention. The second goal of the study was to determine whether the effects of withdrawing medication vary depending on the level of driving skill in teen drivers with ADHD. There are a number of different driving skills and in particular, it is possible that braking and steering performance may be governed by different attentional

mechanisms (Wickens, 2002). Thus, as an initial strategy, three different aspects of poor driving skill were assessed in the baseline drive (on medication), to be later used as covariates in analysis of covariance. Two indices of braking skill were derived. One was designed to measure inattention and delayed response (the *delayed hazard response index*). The other was designed to measure variability in braking, which includes unnecessary braking, hitting the gas too quickly before coming to a full stop at stop signs (rolling stops), and SD of hazard RT, all of which may reflect problems in impulse control (the *erratic braking index*). The *delayed hazard response* index was created by calculating each driver's z score for collisions and median hazard RT in the baseline drive. These z scores were averaged to create the delayed hazard response composite, with low scores indicating rapid hazard response compared to the other drivers in the sample. The *erratic braking* index was created by taking z scores for the SD of hazard RT, the number of rolling stops, and the number of unnecessary braking events in the baseline drive, and then averaging the z scores to obtain an index of erratic braking, with high scores indicating erratic response compared to the other drivers in the sample. A third measure, the *erratic steering* index, was calculated based on averaged z scores for the SD of lane position in different speed zones and in straight and winding areas. The three indices seem to represent different aspects of driving skill, insofar as correlations between indices were weak and non-significant: r (12) = -0.15, +0.06, and +0.27, $p > .2$ for delayed hazard response and erratic braking, delayed hazard response and steering, and erratic braking and steering respectively.

There were two predictions. The first was that driving performance would be worse on the no medication day, and in particular, at the final test on that day. The second was that the difference between medicated an un-medicated driving performance would be largest for those with the least developed driving skills as measured in the baseline drive (on medication).

METHODS

Participants

Participants were 14 healthy drivers with ADHD combined type (*M* age = 17 years: 2 months; 2 females). They were selected because MAS-XR was treatment of choice (other medications were less effective). All had used MAS-XR for 2 or more years: Males *M* weight = 73 kg; *M* dosage = 55 grams (*SD* = 8.2); Females *M* weight = 63 kg; *M* dosage = 45 grams (*SD* = 7.1). Participants with social anxiety were excluded because procedure required driving with a research assistant. Other diagnosed co-morbidities were allowed: 6 had co-morbid Anxiety, 8 had Learning Disabilities, and all 14 had Oppositional Behaviour. MAS-XR dosage was manipulated but other medications were maintained: 1 used Respiridol, 1 used Wellbutrin, 2 used Atomoxetine. (When the study began there was no research on these drugs and driving. The inclusion of participants using this Atomoxetine means the study may underestimate the influence of MAS-XR.) All drivers had been licensed less than 3 years but none had a full Ontario (G) license. Eleven had a G1, which requires driving under supervision and can be obtained at the age of 16 with a written test. The remaining 3 had a G2, which can be obtained 1 year after the G1 with a road test.

Design

This study used a double-blind placebo control design, where individuals experienced both medication and placebo conditions but on different days. There were two within-subjects

independent variables: Condition (Medication, No medication), and time of test (1, 8, and 12 hours post-administration). Three indices of driving skill were measured on the evening of the first day, before the manipulation began: delayed hazard response, erratic braking, and erratic steering. These baseline measures were used as covariates in later analyses. Then on the second and third days participants were tested three times a day, one day on medication and one day off medication. Seven participants were randomly assigned to do the medication day first and the no medication day second. The remaining seven did the conditions in the opposite order. (For each order of presentation there were six males and one female.)

Apparatus and Stimuli

Testing was performed in a *DriveSafety DS-600c* high fidelity fixed base driving simulator. This simulator includes a full car body surrounded by viewing screens that afford a 300° wrap around virtual field of view (five-50° screens in front, and one behind). Seven unique 25-minute drives through the country and small towns were created: a baseline drive and six experimental drives. All involved straight and winding sections and oncoming and trailing traffic. Speed limit postings ranging between 50-80 kph appeared on the side of the road every 200 meters. Hazards emerged periodically from the periphery (cyclists, pedestrians, vehicles, and animals) and drivers had to brake to avoid them (hazards appeared 3.5 seconds before collision point on the road).

Procedure

Simulator testing occurred on three consecutive days. In each case a research assistant was present in the vehicle with the driver to administer instructions and ensure they were followed. This control was necessary given that it is important to distinguish deficits in driving *per se* from deficits in the comprehension and adherence to instructions for the experimental protocol. On the evening of the first day, participants were given a 10-minute training drive to familiarize themselves with the simulator and then they did their first 25-minute drive (8-10 hours post-medication), the baseline drive, that was used to create indices of driving skill. The second day of testing began with administration of the treatments at 7:30 – 8 a.m. At that time participants ate breakfast. They were also required to consume 2 tbsp of raspberry jam that had been prepared by the study coordinator. The jam was either pure raspberry jam or jam with the participant's normal dosage of MAS-XR sprinkled in so that it was undetectable. Mixing MAS-XR with food in this way does not compromise bioavailability or the drug's effect (Shire, 2012). Participants were tested in the simulator 1, 8, and 12 hours after administration of the jam (with a different 25-minute drive for each test). The third day was similar to the second, but the participants that received medication on the first day received no medication on the second, and vice versa. Personnel involved in testing the drivers were kept blind to the manipulation.

RESULTS

No data were lost due to simulator sickness. Three indices of driving skill were derived from the baseline drive to include as co-variates: delayed hazard response, erratic braking, and erratic steering. Factorial analyses of covariance were then performed, using these covariates and partial $\eta2$ was used as an index of effect size. There were two within subjects factors: Condition (Medication, No medication) and Test (1, 8, and 12 hours post-administration of the jam). The

Geisser-Greenhouse correction was applied to modify the degrees of freedom as needed in the event of violation of the sphericity assumption. Tukey's HSD was used for post-hoc tests of means. The following strategy was used in data analysis. Because of the limited sample size, care was taken to minimize the number of factors/covariates and thus maximize degrees of freedom. In each analysis, only one index of driving skill was entered at a time as a covariate, beginning with the covariate most closely related to the dependent measure in question. If the covariate interacted with condition, and moreover, the effects remained significant when order of presentation (medication day first, no medication day first) was also entered in as a covariate, groups were created based on the index, comparing the best and worst seven drivers to clarify the nature of the interaction. (In each case, approximately half of each group of seven drivers experienced the medication condition first.)

Although many measures of driving performance were collected, the focus will be on collisions and median hazard RT in this paper. There will be no further discussion of the erratic steering index, as it did not enter into any effects ($F < 1$ for all). There will also be no further discussion of driving speed because it was unrelated to medication condition ($p > .1$) and drivers generally adhered to posted limits (e.g. M speeds = 52.7 and 82.8 kph in the 50 and 80 kph zones).

The medication condition had an effect on the number of collisions, but the effect was most pronounced at the end of the day (Figure 1). Analyses of covariance were performed with baseline delayed hazard response index as a covariate. This analysis revealed a significant Condition X Test interaction ($F(1.94,23.32) = 3.60$, $p = .045$, partial $\eta2 = .23$). Tests of means revealed that on the Medication day there was a significant drop in the number of collisions over successive tests (M reduction = 0.5 collisions per drive from the first to the third drive, $p = .03$) whereas on the No medication day the number of collisions increased over the course of the day (M increase = 0.14 collisions per drive, $p > .1$). Overall, the difference between the medication and no medication condition only approached significance on the third and last testing of the day (M difference = 0.5 collisions/drive, $p = .054$).
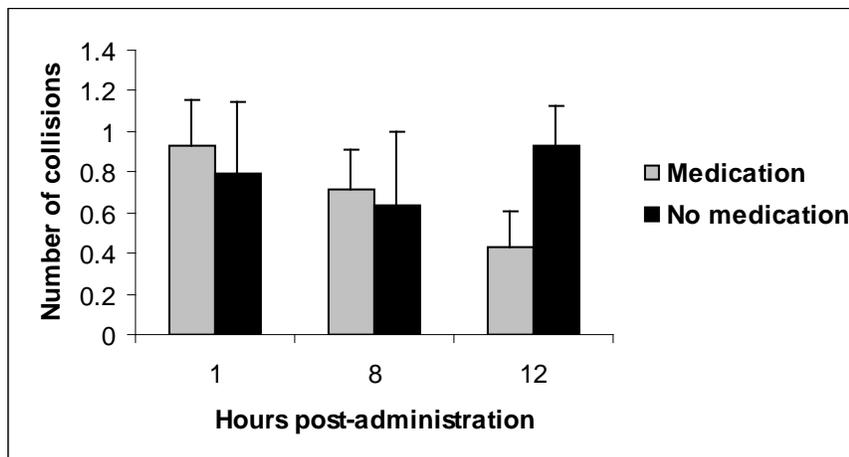

Figure 1. Adjusted mean number of collisions per drive co-varying out the effects of the delayed braking index. SE bars included

There were individual differences in the response to medication. Surprisingly, it was erratic braking index that proved to be the more interesting covariate insofar as it interacted with the manipulations. There was a significant Erratic braking X Condition interaction ($F(1,12) = 9.41$, $p = .01$, partial $\eta2 = .44$), and an Erratic braking X Test interaction ($F(1.29,15.5) = 9.58$, $p = .005$, partial $\eta2 = .44$). These effects remained significant when order of presentation was included as a covariate ($p < .005$ for all after order was included as a covariate; order did not enter into any effects or interactions so it will not be included in the following analyses). To clarify the nature of these interactions, the participants were divided into two groups in terms of their erratic braking scores (less erratic, more erratic). A Braking group X Condition interaction emerged ($F(1,12) = 5.15$, $p = .042$, partial $\eta2 = .30$). The group that had the most erratic braking in the baseline drive benefited most from the treatment. For the seven drivers who were most erratic in their braking, medication reduced the number of collisions per drive by $M = 0.48$ ($p = .12$) whereas for the ones who were least erratic in their braking, the medication produced a slight increase in the collisions per drive (with 0.29 more collisions per drive with medication, $p > .2$).

Medication condition had an effect on hazard RT, but once again, effects were strongest at the end of the day (see Figure 2). Analyses of covariance revealed that the delayed hazard response index was a significant covariate in analyses of median hazard RT ($F(1,12) = 6.08$, $p = .03$, partial $\eta2 = .34$). Test had a significant effect ($F(1.88, 22.58) = 3.93$, $p = .037$) and there was also a marginal Condition X Test interaction ($F(1.89, 22.74) = 3.16$, $p = .064$, partial $\eta2 = .21$). Tests of means revealed a significant reduction in median hazard RT over the course of the day in the medication condition (M reduction from time 1 to time 2 = 66 ms, $p = .051$; M reduction from Time 1 to time 3 = 92 ms, $p = .004$) whereas there was only a 13 ms reduction in hazard response time over the course of the day in the no medication condition ($p > .2$). The difference between the medication and no medication conditions only became significant on the final testing of the day (reduction in median RT = 54 ms, $p = .029$).
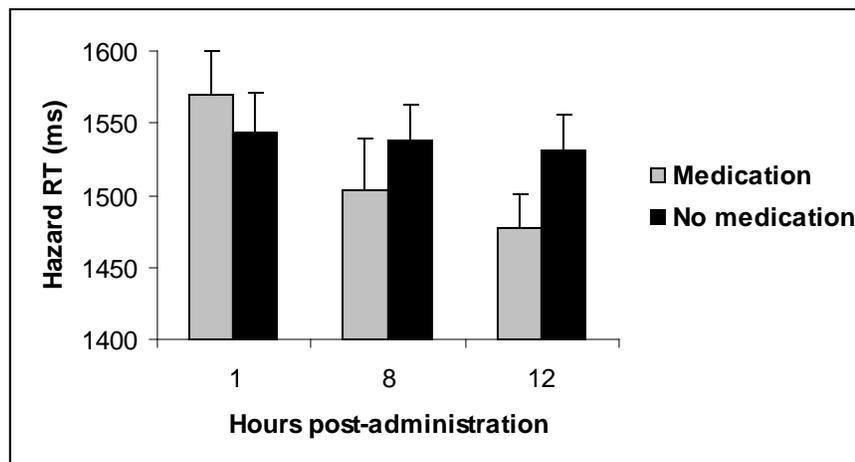

Figure 2. Adjusted median hazard RT co-varying out the effects of the delayed braking index. SE bars included

These effects of the delayed hazard response index remained significant when order of presentation was included as a covariate ($p < .05$). Order did not enter into any effects or interactions so it was not included in the following covariate analysis (approximately half of each

group experienced the Medication condition first). To clarify the nature of the effect, participants were divided into two groups based on their delayed hazard response index, and there was an effect of Test ($F(1.93, 23.12) = 4.19$, $p = .029$, partial $\eta 2 = .26$), a Condition X Test interaction ($F(1.87, 22.45) = 3.86$, $p = .039$, partial $\eta 2 = .24$) and Condition X Test X Hazard skill group interaction ($F(1.87, 22.45) = 3.58$, $p = .047$, partial $\eta 2 = .23$). Overall this analysis revealed that the medication produced the largest reduction in hazard RT in the group that had the most delayed hazard response on the baseline drive. For the drivers with the most delayed hazard response, medication produced a 137 ms reduction in median hazard RT from the first to the third testing ($p = .025$ for time 1 and time 2, and $p = .007$ for Time 1 and Time 3) whereas on the No Medication day, there was only a 17 ms reduction in median hazard RT from the first to third testing ($p > .1$) for the drivers with delayed hazard response. Hazard RTs in for drivers with the group with the least delayed hazard response were marginally lower on the Medication than No Medication day at the second testing (M difference $= 97$ ms, $p = .059$, and at the third testing M difference $= 76$ ms, $p = .089$). For the more skilled drivers, medication produced a 48 ms reduction in median hazard RT ($p = .16$ though) whereas the improvement from test 1 to test 3 was only 8 ms in the No Medication condition, and the differences between the Medication and No Medication hazard RT never approached statistical significance ($p > .2$). Scores on the erratic braking index were not significant predictors of median hazard RT ($p > .1$).

CONCLUSIONS

When teen drivers missed a single treatment of MAS-XR their driving performance deteriorated on the following day. Effects were strongest 36 after their last treatment of MAS-XR (the last testing of the day). Median hazard RT was slightly higher off medication (M difference = 54 ms at the last test of the day) but more important, when drivers were off medication there were more collisions: M difference = 0.5 collision at the final test of the day. This finding that is especially alarming given that each test drive was only 25 minutes long. The amount of deterioration off-medication varied as a function of driver skill as measured on the baseline drive. Drivers with an erratic braking style (unnecessary stops, high SD of hazard RT, rolling stops at stop signs, etc.) displayed a bigger increase in the number of collisions off medication. Similarly, drivers with delayed hazard response in the baseline drive displayed a significantly larger increase in median RT on days where they were off medication. Thus, it appears that there is deterioration in performance given the time off medication, but the amount of deterioration varied based on the skills of the driver. This finding highlights the importance of consistent medication use when teen drivers with ADHD are first learning to drive.

This study is limited by small sample size and the heterogeneity of the participants, who were chosen based on their age and response to MAS-XR. Some had co-morbid disorders and were using other medications (maintained throughout the study), complicating interpretation of results. Most important, it seems probable that that the participants were not driving the way that they might normally choose. The need to control the conditions during the drive also forced drivers to be on their best behaviour. For example, a number of the participants complained that they wanted to have music on in the car. As well, the research assistant in the vehicle had to resist many conversational gambits (she was directed to avoid entering into conversation during the drive and participants knew this). The presence of the research assistant, the frequent reminders of the speed limit (every 200 m), the absence of in-vehicle distractions (conversation, the radio,

cellular phones and portable computing devices), and the relatively novelty of the situation may have served to make the teen drivers drive more conservatively.

ACKNOWLEDGEMENTS

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