

QUANTIFYING THE BENEFITS OF ENHANCING MEDICATIONS ON DRIVING PERFORMANCE: COMPARING OROS[®] MPH VS. se-AMPH ER[®] IN DRIVING SAFETY OF ADHD TEENAGERS AS CASE EXAMPLE

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Summary: Driving simulation is the best way to safely and reliably assess the impact of medical parameters on driving in a controlled, replicable environment. Driving performance should be evaluated using a composite driving score, since the pathway to impaired driving is highly idiosyncratic and could involve any number of individual driving parameters. Although simulators still do not have accepted standards for hardware, driving scenarios, or performance variables, we propose a partial solution to permit comparisons of composite scores across simulators. We recommend presenting simulator data via a standardized average effect size, which we call the Impaired Driving Score (IDS). We describe how the IDS is calculated, and present data comparing 16 male and 15 female teenage drivers with ADHD who participated in a double-blind, placebo-controlled, cross-over study. Using an equivalent-dose regimen, we compared the effects of 72 mg of OROS[®] MPH (Concerta[®]), 30mg of se-AMPH XR[®] (Adderall XR[®]) and placebo on driving performance. Participants drove our Atari Research Driving Simulator at 5, 8, and 11 pm under all three medication conditions with at least a week between conditions/drives. The primary outcome measure was participants' IDS. Across all three times, performance on Concerta[®] was superior to placebo ($p=.005$), while Adderall XR[®] was not ($p=.14$). When analyzed separately, however, only one variable was statistically significant (seconds spent speeding, $p<.01$). Composite driving scores permit the comparison of driving performance across various experimental conditions and with a normative database. Furthermore, since the IDS is based on a multi-faceted assessment of driving performance, it is less vulnerable to random effects and offers a more robust indicator of driving performance.

INTRODUCTION

According to estimates by the World Health Organization (WHO), road traffic crashes kill 1.2 million people annually, making them the world's 11th leading cause of death (Peden et al., 2004). Unfortunately, this number is on the rise. By 2020, traffic accidents are expected to be the third most common cause of death (Peden et al., 2004). The public health costs of these accidents are staggering (\$518 billion annually), placing enormous strain on nations and individuals. Although teenage drivers represent a major hazard across the world, the problem is worse in the United States, where teenagers have the highest crash risk of any age group (Insurance Institute for Highway Safety, 2000). Fortunately, motor vehicle accidents can often be prevented. The

WHO has charged the health sector with collecting data, researching the causes of motor vehicle accidents, and implementing road safety interventions (Peden et al., 2004).

Safe driving is a complex task that requires a dynamic coordination between reaction skills and attentional, cognitive, and mental processes. An interruption in any of these interconnected processes is first reflected by aberrations in single aspects of driving performance (e.g., maintaining lane position, speeding, braking). If these aberrations progress, they may result in an accident. Researchers have begun examining the role of medical disease and interventions in motor vehicle accidents. Diseases, and the interventions used to treat them, can impact cognitive and motor functioning, potentially affecting driving performance. Traumatic brain injuries, alcohol intoxication, cerebrovascular accidents, and other central nervous system disease are among the most common problems known to disrupt various parameters of driving. For example, patients with Huntington's Disease performed significantly worse than those without the disease on driving-simulator tasks and were more likely to have been involved in a collision in the preceding 2 years (Rebok, Bylsma, Keyl, Brandt, & Folstein, 1995). Rizzo and colleagues found that 33% of drivers with Alzheimer's Disease (AD) experienced crashes on a driving simulator intersection task, whereas none of the nondemented drivers of similar age crashed (Rizzo, McGehee, Dawson, & Anderson, 2001). Other researchers, however, found no differences in the frequency of driving mishaps between healthy elderly drivers and those with mild chronic medical conditions and impairments, except those with arrhythmias (Gresset & Meyer, 1994).

Medical Interventions and Driving

Driving abilities can be compromised by underlying disease, medications used to treat the disease, or the combination of both (Pullen, 1999). As with alcohol, numerous medications have been found to interfere with driving performance, and several classes of legal drugs have been targeted as areas of concern: the benzodiazepines, other psychoactive medications, and narcotics. Hypnotics (Vermeeren, 2004) and antidepressants (Hu, Trumble, Foley, Eberhard, & Wallace, 1998) have both been shown to increase a patient's risk for traffic accidents. Teasing apart the effect of medication on driving, however, is complicated due to the complexity of evaluating the impact of drugs on driving performance. Estimating drug levels and assessing drug/patient interactions is particularly difficult (Ogden & Moskowitz, 2004).

While some medical treatments may interfere with driving, others may help. Five controlled studies have found that active treatment of ADHD with stimulant medications significantly improved on-road and simulator driving performance (Barkley, Murphy, O'Connell, & Connor, submitted; Cox, Merkel, Kovatchev, & Seward, 2000; Cox et al., 2004; Cox, Humphrey, Merkel, Penberthy, & Kovatchev, 2004; Cox, Merkel, Penberthy, Kovatchev, & Hankin, 2004). Ganz and colleagues found that driving reaction time on a driving simulator worsened 1 week after total hip arthroplasty but then subsequently improved, leading them to recommend patients wait 4 to 6 weeks after surgery before resuming driving (Ganz, Levin, Peterson, & Ranawat, 2003).

Further complicating matters, treatments that help one driver may impair another. For example, Cox and colleagues found that stimulant medications reduced inattentive driving errors and improved overall driving performance among teenagers with ADHD (Cox et al., 2000; Cox et al., 2004; Cox, Merkel, Penberthy, et al., 2004), whereas Mills et al. (2001) found that amphetamines caused deficits in certain driving skills among healthy adults (e.g., increased

tunnel vision). Pullen also warned that medications used to treat the same disease may hinder driving performance in some patients but improve driving in others (Pullen, 1999).

Different medications used to treat the same disorder may differentially affect driving. Tricyclic antidepressants impaired driving performance to a higher degree than selective serotonin reuptake inhibitors (SSRI) or MAO inhibitors (Pullen, 1999). Among those taking traditional antipsychotic medications for schizophrenia, only 32.5% passed the psychomotor assessment targeting driving skills, whereas those treated with the newer, atypical antipsychotic medications or clozapine performed significantly better (Brunnauer, Laux, Geiger, & Möller, 2004). Although it is unclear whether the cognitive impairments are drug side effects or syndrome-related, it is clear that schizophrenics taking atypical medications have better neuropsychological profiles.

Many progressive disorders reach a critical threshold, after which they impair driving. Within three years of diagnosis, patients with AD are only at slightly higher risk for driving accidents than that for drivers of all ages in the United States (Staplin, Lococo, McKnight, McKnight, & Odenheimer, 1998). But the crash risk increases toward the end of the third year and more than doubles in the fourth year (Staplin et al., 2004). Visuospatial impairments, disordered attention, reduced processing of visual motion cues, and overall cognitive decline contribute to an increased crash risk in those with AD (Rizzo et al., 2001).

In order to engage in safe medical practices and make appropriate treatment recommendations, health care providers and pharmaceutical companies must know which interventions improve and impair driving, as well as the timeline of these effects. In many cases, the deleterious effects of an intervention may be time-limited (e.g., analgesics, electroconvulsive therapy), but providers need data to inform patients about when it is safe to return to driving. This information would not only protect patients, but it would also shield providers from lawsuits. Providers should encourage patients to adhere to medications that enhance driving performance. Teens with ADHD and their parents, for instance, should be told that the single best hope for reducing driving risks is medication compliance. Pharmaceutical companies must determine the degree and duration of the impact of their drugs on driving in order to create warnings on labels.

Driving Simulation

Physicians, patients, and pharmaceutical companies need safe, reliable means of measuring driving competence. Although on-road evaluations have historically been considered the “gold-standard” in driving assessments, such evaluations are notoriously subjective and unreliable. On-road exams are fraught with shifting driving demands due to inconsistencies in evaluator, weather, road, and traffic. Also, evaluators cannot place drivers under high-demand situations for a more thorough evaluation due to safety concerns and liability. On-road evaluations are also potentially dangerous when assessing high-risk drivers, placing the driver, evaluator, and other drivers and pedestrians at risk.

Driving simulation is the best way to safely and reliably assess the impact of medical parameters on driving in a controlled, replicable environment. Through simulation, researchers and clinicians can manipulate driving demands (e.g., introduce unusual events [sudden stopping of lead car]) and quantify numerous driving skills. Simulation can also assess multiple driving

performance parameters that are related to specific on-road demands for safe driving (attention, information processing, reaction), such as driving over speed limit, inappropriate braking, and lane position. Since the pathway to accidents is also highly idiosyncratic, both in terms of between-driver and between-accident differences, the simultaneous evaluation of multiple parameters would result in a more comprehensive assessment of general driving safety. That is, some drivers are unsafe due to speeding, whereas others are unsafe because of inattention to peripheral objects or their inability to maintain a steady lane position. Consequently, to assess general driving safety, it is essential to develop a composite driving score, much like Departments of Motor Vehicles rely on a composite knowledge test derived from a series of driving knowledge questions.

Unfortunately, simulators still do not have accepted standards for hardware, driving scenarios, or performance variables, making it difficult to develop a standard composite driving score used across simulators. To address this limitation, we propose a partial solution to permit comparisons across simulators/laboratories. We recommend presenting simulator data via a *standardized average effect size*, which we refer to as the Impaired Driving Score (*IDS*). The IDS can be used in two ways: (1) comparing an individual to a large representative normative data set, or (2) comparing an individual to a smaller “normative” data set determined by the experimental design. For example, in the Virginia Driving Safety Laboratory, we generate and then compare each potentially impaired driver’s IDS to a large normative data set previously collected in our lab (D. J. Cox et al., 2002). When our experimental conditions are so different that they are no longer comparable to the conditions under which normative data was collected, we suggest defining the IDS as a deviation score from the average performance of everyone who participated in that unique experimental condition. For example, in a study evaluating the impact of hypoglycemia on driving performance of drivers with Type 1 diabetes, participants were tested with three IV’s in their arms, EEG electrodes attached to their heads, and EKG electrodes attached to their chest (Cox, Kovatchev, Gonder-Frederick, & Clarke, 2003). We determined that these participants should not be compared to our normative database because the study requirements (e.g., EEG, IVs) put drivers under a significant stress and likely altered the definition of normative driving (Cox et al., 2003). Instead, we only compared these participants to drivers who had experienced similar conditions.

Impaired Driving Score

To generate the IDS, we use appropriate normative data (general or study-specific) to calculate means and standard deviations for a set of specific driving parameters (e.g., time spent driving >5% over the speed limit). Then each parameter of each individual’s driving performance is converted into a z-score (number of standard deviations from the normative mean). Z-scores for the different performance variables are then summed for that subject’s IDS and divided by the number of parameters included in the IDS. In this way, an IDS of 0 reflects average driving performance, whereas an IDS of +1 reflects driving one standard deviation worse than the mean. That is, positive scores reflect poorer driving performance. Composite driving scores allows us to compare the effect size (drivers’ standardized and averaged z-scores) for various experimental conditions (e.g., on and off medication, ADHD to controls).

METHOD

Illustrative Example

We are conducting a series of studies investigating the benefits of various stimulant medications on the driving performance of teenagers with ADHD at different times throughout the day. This is important because the core symptoms of ADHD (inattention, impulsivity and hyperactivity) may be responsible for ADHD drivers' increased risk of driving accidents (Barkley, Guevremont, Anastopoulos, DuPaul, & Shelton, 1993) and associated injuries (Barkley, Murphy, & Kwasnik, 1996).

Sixteen male and fifteen female teenage drivers with ADHD, between the ages of 16-19, participated in a double-blind, placebo-controlled, cross-over study. Using an equivalent dose regimen (Biederman, 2002), we compared the effects of 72 mg of OROS[®] MPH (Concerta[®]), 30mg of se-AMPH XR[®] (Adderall XR[®]) and placebo on driving performance. Under all three medication conditions, separated by approximately seven days, participants drove our Atari Research Driving Simulator at 5, 8, and 11 pm. The primary outcome measure was each participant's computer-quantified IDS. Secondarily, individual driving parameters were investigated.

Our Driving Simulator. To objectively quantify driving performance in a safe, controlled environment, we use the Atari Research Driving Simulator. It is an interactive, fixed-platform simulator that generates reliable, accurate, sensitive, and valid driving performance data (Cox & Cox, 1998; Cox, Taylor, & Kovatchev, 1999). The simulator has three 25-inch computer screens that "wrap around" the driver, providing a 155-degree visual field, along with a programmed rear-view mirror depicting rear traffic. The driving environment is realistic, incorporating a standard-sized steering wheel, gas pedal, brake pedal, seat, and seat belt. Driving performance feedback is provided to the driver *visually* through the three screens updated at a rate of 60 times per second, *auditorially* through quadraphonic speakers delivering engine, tire, and road noises, and *kinesthetically* through forced feedback from the steering wheel and pedal pressure, which gives an authentic feeling of road grip. There are two equivalent driving courses, with similar driving demands, designed to simulate the driving burdens of a typical grade-2 U.S. highway.

The simulator records data four times per second, generating ten driving performance variables. Three of these variables reflect *steering control* (standard deviation of steering, driving off the road, and veering across the midline), four reflect *braking* (inappropriate braking while on the open road, missed stop signals, bumps with impact ≤ 5 mph, and collisions with impact > 5 mph), and three reflect *speed control* (exceeding speed limit, standard deviation of speed, time to execute left turns).

Measures. As explained above, the overall mean and standard deviation were first computed for the most discriminating variables: seconds off road, deviations across the midline, seconds spent driving $>5\%$ over the speed limit, seconds spent executing left turns, SD of speed, and percentages of crashes and bumps per potentially risky zone in the road. Z-scores were then generated for each of these variables. Based on this, a subject's IDS for each medication condition was computed as the average per variable number of standard deviations from the grand mean. These IDS were then analyzed with an ANOVA.

RESULTS

The IDS were compared using three (medication: placebo, Adderall XR[®], Concerta[®]) X three (time: 5pm, 8pm, 11pm) analyses of variance. Across all three times, performance on Concerta[®] was superior to placebo ($p=.005$), while Adderall XR[®] was not ($p=.14$). Table 1 below depicts the IDS for each group at each time of day. When evaluating only the evening hours of 8pm and 11pm, performance on Concerta[®] was significantly better than Adderall XR[®] ($p=.007$) and placebo ($p=.001$), whereas performance on Adderall XR was no better than placebo ($p=.44$). In contrast, when we analyzed the different driving variables separately, only one was statistically significant (seconds spent speeding, $p<.01$).

Table 1. Impaired Driving Score on Placebo, Adderall XR[®], and Concerta[®]

	5 pm	8 pm	11 pm
Placebo	+0.08	+0.16	+0.14
Adderall XR [®]	-0.10	+0.12	-0.07
Concerta [®]	-0.02	-0.14	-0.18

DISCUSSION

As noted above, motor vehicle accidents are a leading cause of death throughout the world. Driving involves a complex set of external and internal conditions, and driving safety depends on a number of interconnected skills and behaviors. To address the global concern with driving safety, we must better evaluate the complexity of safe driving and develop feasible interventions. Toward this aim, we propose using driving simulation to assess the impact of medical disease and medical interventions on driving. We have found driving simulation to be a reliable, objective, sensitive indicator of driving performance, informing us about the nature of driving impairments and the benefit of treatments. More specifically, we propose using a composite index of driving (the Impaired Driving Score) rather than individually evaluating separate driving parameters (e.g., speed, inappropriate braking), which are more vulnerable to chance and can lead to ambiguous results. Drivers can be unsafe by different mechanisms (speed, failure to maintain lane position), and evaluation at the level of the individual driving parameter might fail to detect risky drivers. In contrast, composite driving scores permit the comparison of driving performance across various experimental conditions (e.g., on and off medication), as well as comparison of various conditions to a normative database. In addition, since the IDS is based on a multi-faceted assessment of driving performance, it is less vulnerable to random effects potentially influencing each of its particular components. We urge others to follow suit in an effort to expand our knowledge about driving impairments and interventions.

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