Medscape

Drug-Impaired Driving: Test Without Crashing

Carol Peckham, Gary G. Kay, PHD   June 21, 2013

Interview With Gary G. Kay, PhD, on Driving Simulation

The use of driving simulators in clinical trials is an interesting new development for testing the effects of drugs on impairment. Medscape interviewed Gary G. Kay, PhD, Associate Professor, Department of Neurology, Georgetown University School of Medicine and President, Cognitive Research Corporation, concerning his company's simulator -- the CRC MiniSim™ – and how it is being used in clinical research (Figure 1). Dr. Kay is the author of the CogScreen test battery and is also a senior neuropsychology consultant to the Federal Aviation Administration (FAA), evaluating pilots for certification who have medical conditions or who are taking medications that could impair flight performance.

Figure 1.

Driver's view of the simulator. Image courtesy of Cognitive Research Corporation.

Medscape: Let's start by asking how you became involved in driver impairment testing.

Dr. Kay: I was a Navy psychologist and worked on evaluating pilots to help determine when they could go back to flight status after they had been injured or when they were taking certain medications. After I left the Navy, I had the opportunity to work with the FAA, and I continue to be a consultant in helping them to evaluate pilots. I developed for them a computer-based cognitive test called CogScreen, which assesses the mental abilities that are involved in flying. The test is used in the United States and internationally by airlines and military organizations to evaluate pilots.

I began working with some very early primitive driving simulators around that time and became acquainted with James O'Hanlon, who was developing methods for conducting over-the-road driving tests, in which he would have somebody get into an instrumented vehicle on the highway in real traffic and drive. You could measure the effect of medications on their driving performance. He moved from California to The Netherlands, where he could perform over-the-road testing. I would say this dated back to the 1980s. One of the first vehicles was a Volvo with a camera mounted on it that could measure the position of the vehicle in the lane to assess weaving. O'Hanlon is probably the father of the term "standard deviation of lateral position (SDLP)," which basically is a measure of weaving and is the primary endpoint in much of driving research.

Meanwhile, advances in computer graphics and processing power led to higher-fidelity driving simulators that were more suitable for driving research.

Description of the Driving Simulator

Medscape: Can you describe how your driving simulator was developed?

Dr. Kay: Our driving simulator, the MiniSim, is basically a desktop computer version of the National Advanced Driving Simulator (NADS) at the University of Iowa. NADS is a full-motion driving simulator that was developed for the National Highway Traffic Safety Administration (NHTSA). It's a remarkable simulator. My company, Cognitive Research Corporation, is partnered with the University of Iowa and with NADS to provide the MiniSim for pharmaceutical research. The MiniSim makes full use of the scenarios and much of the advanced engineering that went into the development of the NADS.

Medscape: How is NADS, the full-motion driving simulator, used, and how is it related to the MiniSim?

Dr. Kay: The researchers involved with NADS are looking at areas that are of great interest to the Department of Transportation, such as distracted driving and alcohol effects. They do a lot of human-factors work. You can get an appreciation for the full NADS vehicle on their Website. It is probably the most advanced driving simulator available.

Regarding our simulator, the NADS staff were able to take the graphic environment and vehicle dynamics and incorporate them into the MiniSim, so that although we're not a motion-based simulator, we have superb graphics and can build environments that are appropriate for challenging the driver.

Our company has taken the MiniSim to the next step and made it ready for use in clinical trials research. That has meant undergoing extensive software and clinical trial validation, proving the sensitivity of the simulator to such things as low-dose alcohol and showing the reliability of the instrument.

Medscape: What is the current atmosphere on driver impairment data in the pharmaceutical industry?

Dr. Kay: There's been a lot of attention lately on the potentially impairing effects of medications on driving performance and the need to consider driving safety in assessing a drug. This past January, the US Food and Drug Administration (FDA) indicated the need to reduce the dose of the hypnotic zolpidem in women, owing to results from driving simulator research. In another example, a few weeks back, an FDA advisory committee issued a review of suvorexant, a new insomnia drug, which talked about its impairing effect on driving performance, particularly at higher doses. And last week, the FDA issued a press release reminding drivers that as we are now in the middle of allergy season, they should be aware of the potential risk of driving after taking sedating antihistamines, such as diphenhydramine. So there is a lot more attention to this issue now in the assessment of drugs.

I think there needs to be this attention, on the basis of what we are seeing from such reports as the 2007 National Roadside Survey of alcohol and drug use by drivers.[1] The NHTSA looked at 7719 weekend drivers who were randomly pulled over, to see what medications they were taking, including prescription drugs and illicit drugs.

Medscape: How does the simulator work when testing a drug's effect in a clinical trial?

Dr. Kay: People tend to drive more to the right or more to the left side of the lane. Our primary interest is not their lane position, but rather the consistency or variability in their lane position. Can they maintain their lane position over the course of the drive? (Figure 2). That is what SDLP is about; this measure of individual variability tends to be very sensitive to the effects of central nervous system depressant medications.
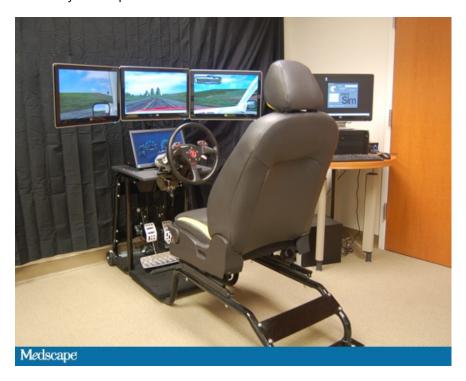

Figure 2.

The CRC MiniSim. Image courtesy of Cognitive Research Corporation.

A trial typically includes comparison with placebo and with an active control -- a drug likely to cause impairment -- and the target drug of interest. Naturally, the most studied drug known to be associated with impairment and crashes is alcohol. We have conducted trials to look at the effect of known doses of alcohol, as low as 0.05 blood alcohol content (BAC), and have been able to reliably demonstrate impairment using the simulator. Unlike the over-the-road testing, our findings at 0.05 BAC are obtained under the same driving conditions as we use with other drugs. When alcohol testing was conducted with over-the-road driving, they had to use a closed roadway, which obviously differs from the way in which they study other drugs.

Medscape: Do you have to worry about different skill levels of driving?

Dr. Kay: There certainly is a range of driving ability. It has been our experience that when you ask people to do self-rating, nearly everybody considers themselves to be a better-than-average driver. Before we begin a trial, we basically just require that the drivers have a valid license, be driving a certain number of miles per year, and be able operate and drive in a reasonable way relative to normative data.

It is also very important for these clinical trials to have standard training for the drivers and to familiarize them with the simulator so that their performance is stable. It's similar to renting a car; you are not in your own vehicle, and you need some time to become familiar with this vehicle. The simulator is a new vehicle, and the driver needs a standard method to become familiar with the controls, the environment, and the expectations.

Using the Driving Simulator in Clinical Trials

Medscape: Where does the driving simulator now fit in with clinical trials?

Dr. Kay: The most common studies are still over-the-road types, which use the 0.05 BAC as a benchmark. However, as I mentioned, the benchmark is not really based on the standard 100-km route that they use in drug studies. We now have very good empirical data where we looked at the same drug studied using over-the-road methods and in our driving simulator. The results from the 2 approaches were similar. You may get a different magnitude of differences in speed or different amounts of weaving, but the relative change in performance is similar.

We have standardized the driving simulator for use in pharmaceutical clinical trials. We have demonstrated sensitivity to an 0.05 BAC, daytime sleepiness, and the next-day residual effects of a nighttime dose of a medication; to the impairing effect of obstructive sleep apnea; and to an improvement in driving with treatment of sleep apnea.

Cognitive Research Corporation has a fleet of identical driving simulators and standardized training that allows for multicenter clinical trials. This gives our sponsors the opportunity to run trials at multiple centers. Staff at the sites are trained and certified as simulator operators for the trial. This is another advantage compared with over-the-road testing.

Although over-the-road testing has a lot of face validity, the driving simulator offers much greater standardization with respect to traffic and weather. You also don't have to worry about safety issues. Crashing a simulator, although rare in clinical trials, has far fewer consequences than crashing during an over-the-road test. One of our sponsors commented that the driving simulator generated comparable data in half the time at half the cost.

Medscape: What kind of clinical trials have been used for testing impairment with the simulator?

Dr. Kay: Most of the studies have been crossover studies where one driver is tested under several different conditions. We've also conducted studies where there have been parallel groups.

We just published a study looking at people with obstructive sleep apnea and daytime sleepiness. The participants were studied before starting continuous positive airway pressure (CPAP) treatment. We compared one group who received armodafinil with another group who received placebo. We measured their performance after 2 weeks of dosing. We showed improvement in simulated driving performance for participants who received armodafinil, and we later showed improvement for all participants after 6 weeks of CPAP treatment.[2]

Medscape: Where do the standards come from that you use for the simulations studies that you conduct?

Dr. Kay: Software validation standards come from the regulatory agency and are fairly generic in terms of how data are acquired, their integrity of data from the point of being acquired to the transfer of data across systems, and the validation of the algorithms used within the software. The whole process of software validation is fairly well defined.

In terms of demonstrating the clinical validity -- or what we call criterion validity -- regarding the ability of the simulator to detect impairing or enhancing drugs or situations, we have been able to show that the driving simulator is able to detect the impairment caused by such substances as alcohol, next-day residual effects of hypnotic drugs, and the effects of sleep apnea on driving. We are also able to demonstrate improvement in driving in young adults with attention-deficit/hyperactivity disorder (ADHD) when they are taking stimulant medication or in people with sleep apnea when they are given CPAP treatment.

Substances Used in Tests on Driving Impairment

Medscape: You mentioned ADHD stimulants and sleep apnea. Do you see the FDA expanding its requirements for driver impairment data beyond sleep medications or other drug categories that are known to cause sleepiness?

Dr. Kay: This is an interesting question. In 2000, the National Transportation Safety Board asked the Department of Transportation for a list of medications that would be safe for drivers -- primarily for commercial drivers. Although nobody is

willing to publish a list of "safe" drugs, you can identify drugs that impair driving. And the driving simulator is one of the methods for identifying drugs that are more likely to cause impairment. Driving simulators have been used to look at antihistamines, antidepressants, and anxiolytics.

The regulatory agency has requested driving data on certain classes of drugs. They initially focused on medications used for the treatment of insomnia, but there is certainly a reason to look at other classes of drugs that we know can potentially impair driving performance. In a good number of states, you can be arrested for driving under the influence of drugs, even prescription or over-the-counter medication, if your driving is found to be impaired.

Diphenhydramine is one of the drugs that particularly causes me concern. When driving, a 50-mg dose of this over-the-counter drug is similar to about a 0.07 BAC. In contrast, nonsedating antihistamines, such as loratadine and fexofenadine, don't cause impairment. When combined with alcohol, the effect is equal only to the effect of the alcohol. There's no synergy.

I conducted a study on loratadine with 100 participants.[3] One third received loratadine, one third diphenhydramine, and one third placebo. An hour and a half after they took these drugs, we asked them if they felt drowsy or tired. Those who took loratadine didn't report feeling any sleepier than those on placebo. Only one third of those taking diphenhydramine reported being sleepy or drowsy; the other two thirds said they felt fine, yet when we looked at their performance on cognitive testing, they were impaired. For many drugs, you can't rely on people's awareness of how impaired they are when they're take the medication. That is why we need to provide very good labeling, and very good instructions to people about how the drug affects driving.

Cetirizine is also a sedating drug. Studies were done years ago looking at cetirizine and driving that showed an effect on driving performance. For example, we don't allow pilots to take cetirizine or diphenhydramine.

Medscape: Are there protocols to help determine what kinds of drugs should be tested?

Dr. Kay: I happened to be the coauthor of a publication for the NHTSA that provided a standardized protocol for evaluating the potential for drugs to impair driving.[4] The protocoluses toxicology, epidemiology, pharmacology, and behavioral science for evaluating drug-impaired driving. This may become very helpful to the pharmaceutical industry in terms of providing a standardized approach to driving assessment. There's a lot of information that can help determine what drugs need to be studied. Then, the next logical phase is to determine the doses to be studied, over what period, and to determine when it is safe to drive after taking the medication. These are all questions that can be addressed using these methodologies.

Medscape: Wouldn't the government study impaired driving as well, particularly looking at substances that might not be tested by the pharmaceutical companies?

Dr. Kay: Yes; certainly, various government agencies would want to study such substances as cannabis. For example, NADS is currently being used in a federally funded study to look at cannabis and driving.

Medscape: Do you see your simulator being used by legal authorities, such as police, or are there other simulators that would be more appropriate?

Dr. Kay: They could certainly use our simulator for applications besides pharmaceutical ones -- everything from roadway design to reenactments of crash situations. It's a high-fidelity driving simulator, so it has many other capabilities.

When we have the opportunity to show our simulator to clinicians, they are very interested in clinical applications. They frequently say, "This would be a great way for me to show my patients how much better they are on treatment," We were at the SLEEP meeting recently, whose attendees treat patients with sleep apnea. They were saying how great it would be if they could have this clinically to demonstrate to their patients how much safer they are driving once their condition is treated. I have parents of driving-age children with ADHD who tell me that the simulator would be a great way to show how much safer their child's driving is when they take their medications.

So there are many potential clinical applications, and important applications in rehabilitation medicine, but our interest has focused on developing the simulator as a research tool.

Cost and Competition

Medscape: What does it cost?

Dr. Kay: There's a simple answer. You could probably put the hardware together for $15,000 to $20,000. So that costs about as much as a small car, but it won't take care of all of your needs. That will cover the cost of your car seat, chassis, computer, and monitors. However, the real cost is licensing and developing the software, and validating your system. This process takes a team of talented people.

Medscape: But you don't have the only driving simulator, right?

Dr. Kay: No, not at all. It is very important for your readers to appreciate that if they were to Google "driving simulator," they are going to see a wide range of different things -- from very simple video games to highly advanced research tools. Unfortunately, all of them are referred to as a driving simulator.

There have been driving simulator studies published in which the simulator basically consisted of a joystick and a video monitor, where the examinees' task was to keep a cursor between 2 weaving lines and avoiding objects. If you look at our video, we really try to create an immersive, high-fidelity situation, something that is very credible to the person. I think the key and the future in driving simulation is that this is one of the most common complex activities that we engage in, and it is very cognitively demanding. So our simulator is a very good test of functional ability.

Medscape: You mentioned that you do have competitors. Are they doing a similar work, and how would you differentiate yourself from them?

Dr. Kay: I have many colleagues who have simulators and who conduct driving research at universities, and they are doing fine work. However, these are single, one-of-a-kind simulators and are not standardized with respect to scenarios, driving controls, or participant training. The researchers also haven't done the kinds of software validation required for regulatory purposes. These simulators are certainly very important at an academic level for studying the effects of various drugs or various diseases on driving performance, but I don't really consider them to be competitors with respect to doing multicenter clinical trials. I think Cognitive Research Corporation may be the only research organization currently doing this kind of work.

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