CHAPTER 16

Effects of Psychotropics on Driving Performance

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Introduction

Driving a motorized vehicle is a complex task of information processing and motor skills, requiring a variety of cognitive and psychomotor performance abilities to be intact: alertness, attention, multitasking, memory, co-ordination and visuospatial perception, to name a few. Numerous prescription drugs acting within the central nervous system (CNS) have the potential to affect both sleep and daytime functioning.[1] While this phenomenon is well known to clinicians and researchers alike, it is sometimes discussed as if it was an abstract concept lacking any consequence to the functional abilities and consequences on the day-to-day lives of our patients. Furthermore, some performance situations, such as operation of a vehicle or other complex mechanical device represent real risks to both patients and the public, creating potential medicolegal liabilities for the prescribing physician.[2] As current medical research increasingly occupies itself with topics of ergonomics, human error and human-machine interface, effects of psychotropic medications on specific daytime performance tasks such as driving have become a more relevant topic.

Medical researchers, and specifically psychiatrists, have historically shown only passing interest in driving ability as an example of human interaction with machines. An article entitled 'The accident prone driver" (a term borrowed from the psychoanalytical literature's exploration of parapraxes in "the accident-prone individual") appeared in the American Journal of Psychiatry in 1949 which attempted to correlate individual psychopathology with poor driving records in two groups of taxi drivers.[3] Since then, the term 'accident' has long fallen out of favor in the medical and human factors literature, as this term would see a crash/error as a random/unpredictable event, as opposed to a possible predictable and/or preventable entity, based on particular risk factors.[4] These risk factors can be driver/operator-specific, machine/vehicle-specific, or relate to the human-machine interface.

While vehicle safety has increased dramatically since the introduction of the automobile, and psychopharmacological interventions have generally become more sophisticated in recent decades, current trends in telematic devices such as mobile phones and Global Positioning System (GPS) units have introduced an additional multi-tasking element to the driving task.[5] Thus an individual with reduced concentration due to mildly sedating effects of a medication may have had little trouble driving while attending exclusively to this task, but may struggle with competing attentional demands of conversing on a cellular telephone and navigating through urban rush-hour traffic.

Studies of drug consumption by patients involved in crashes in the United Kingdom have shown that between 11-20% are taking psychotropic drugs, however, as has been true of other epidemiological studies, the extent to which the drug(s) may have contributed remains difficult to ascertain.[6,7]

Perception, Cognition and Driving

This raises the issue of perceptual context in driving. The capacity for human attention and cognitive capacity in relation to bandwidth has been described as one of the most important economic commodities of the 21st century.[8] Research into the field of perceptual immersion or 'presence' has been progressing in parallel with research in the field of simulated environments.[9,10] Presence can be defined as the feeling a conscious organism experiences when immersed in a concrete external world, i.e., that one is "really there" in the environment. Converse to this exists a state of 'absence', in which an individual is preoccupied or engaged with an internally constructed world.[9] In fact, this spectrum coincides well with the neuroscience of sleep and wakefulness, which would attempt to correlate these fluctuations between 'absent' and 'present' states through electrophysiological patterns. When an individual is fully alert, i.e., 'on task' he would perceive a state of full presence/immersion, whereas increasing states of absence would likely be a precursor towards actual lapses into an unconscious state. Often this will involve a feedback loop between individual and environment. A lack of external stimulation, which is cognitively experienced as boredom, leads to metabolic lowering of brain activity. On the other end of the spectrum, neurocognitive overstimulation/overarousal results when mental tasks are excessively complex and sustained.[11]

Applying this to the study of automotive crashes, this can be exemplified by the contrasting (but both hazardous scenarios) of monotonous nighttime highway driving (Type 1) vs. rush hour "mid-town madness" (Type 2) (see Fig. 1). This implies that medications that impart a sedating effect on the patient's CNS may be hazardous in some driving environments requiring prolonged vigilance, while medicines with the potential to cause anxiety or agitation may be specifically dangerous in other situations. Returning to the previous topic of the 'distracting' effects of communication devices, long-haul truck drivers have long known that they can improve their wakefulness on long soporific drives through the use of CB radio, in an attempt to optimize their level of perceptual stimulation. While overall crash rates tend to be dependent on vehicle density and peak at rush hour, crashes where drowsiness due to medication or sleep disturbance plays a role have been shown to have a circadian variation correlating with

Sleep and Sleep Disorders: A Neuropsychopharmacological Approach, edited by Malcolm Lader, Daniel P. Cardinali and S.R. Pandi-Perumal.

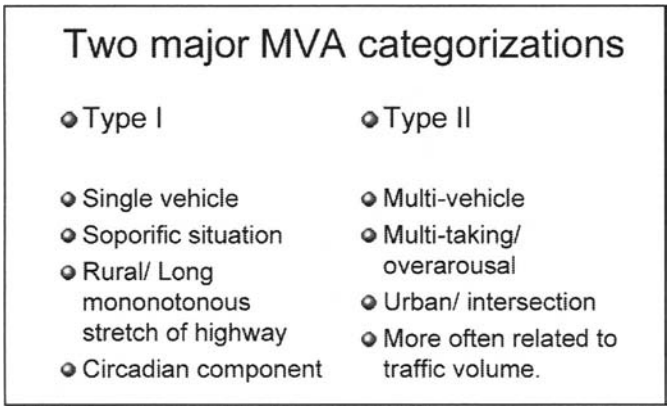

Figure 1. Stratification of motor vehicle "accidents" by interaction of environment and cognitive state.

periods of maximum sleepiness, between 2 and 4 a.m. and, to a lesser degree, the 'siesta period' during mid-afternoon.[12,13]

Classification and Measurement Issues in Quantifying Medication Effects

Classifying centrally acting medications is a complex endeavor. While some classifications use a system based on desired therapeutic action (e.g., sedative, antidepressant, anxiolytic, etc), others tend to base categorizations on pharmacodynamic properties (e.g., GABA- or serotonin- agonists, antihistamines, etc). In fact both classification systems are imperfect. Frequently, both therapeutic and neurochemical properties of CNS agents are mixed. As an example, the sedating antidepressant trazodone has both a serotonin 5HT-2 agonist as well as histamine antagonist properties. Furthermore, are the benzodiazepines best classified as anticonvulsants, hypnotics, sedatives or anxiolytics? Rather than adhering to simple-minded categorizations, it behooves the clinician to understand the unique biochemical and therapeutic properties of medications used to treat their patients.

Particularly with psychotropics, the prescribing physician needs to be aware of the drug's pharmacodynamic and pharmacokinetic characteristics. Factors such as hepatic interactions at the cytochrome p450 level and medication half-life must be monitored for; with respect to the latter, it is important to consider the individual neurochemical target receptor properties, as the wash-out period from the CNS is often significantly longer than from serum.

Another key clinical and research consideration relates to the terminology used to define phenomenology of these altered states of consciousness imparted upon the patient by psychotropics, and the methodology used to assess these. For example, drowsiness, lethargy, fatigue and somnolence are sometimes used interchangeably. While for one patient, these descriptors may seem interchangeable, others will be more specific in their descriptions of drug-related sedative effects. Researchers have used measurements of subjective states of consciousness, such as the Epworth Sleepiness Scale[14] (a more global subjective rating instrument) and the Stanford Sleepiness Scale (intended as a more instantaneous approximation of a subject's mental state. Alternately, physiological measures have been employed to study this problem, such as the Multiple Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT),[15] and more recently, pupillometrics.[16]

While such tests may accurately measure a subject's propensity to fall asleep or experience impaired alertness under controlled laboratory conditions, a difficulty remains regarding the ecological validity, i.e., relevance to 'real-world' situations. Alternately, in vivo testing centers exist that can perform on-road testing. This method, while more ecologically valid, is often more costly, and more difficult to standardize. Driving simulator studies have been used,[17,18] occasionally in conjunction with polygraphic monitoring[19,20] to approximate subject's driving impairment in a laboratory environment with increased ecological validity. The fact that such tests may yield discrepant results from traditional tests of daytime alertness[18] raises the question of which test is the most accurate approximation of an individual's mental state; ultimately, the medicated patient's behavior and subjective experience in their activities of daily living outside the hospital remains the gold standard, providing the clinician is able to obtain a reliable history. For this reason, the conservative clinician may need to gather collateral sources of information such as from the spouse or employer.

Alcohol and Illicit Substances

Alcohol and drugs of abuse have been studied in simulated driving environments. While the literature is near-unanimous on the impairing effects of alcohol in a dose-dependent fashion, legal standards in different countries vary in terms of acceptable breathalyzer sample readings, based on departure of test drivers' reaction times from a standardized normative reaction time and lane obedience in simulated driving tasks. The fact that states of sleepiness can result in severe driving impairment, analogous to states of intoxication with alcohol has been well described[21-23] However, it is also important to note that fatigue and sleepiness can exaggerate driving impairment exponentially, even in situations with conventionally acceptable blood alcohol concentrations. While studies comparing marijuana to alcohol have generally found both to impair driving abilities[24-26] patterns of driving behavior appear to differ for drivers intoxicated with the respective substance and the literature appears divided regarding the risk of driving while under the influence of cannabis. This may be due to the relative effect on insight into impairment that is generally lost with alcohol intoxication compared with cannabis intake. Combined intake of marijuana and alcohol has been shown to be more impairing than with either substance alone.[24,25] It has been reported that misuse of substances such as amphetamines, cocaine and other stimulants is a common coping strategy used by truck drivers to self-medicate their perceived risk of driving impairment due to sleep deprivation and periods of shift work.[27] Military pilots have also reportedly used medications such a methylphenidate or dextroamphetamine as provigilants.[28] While many of these stimulant substances do increase alertness in the short term, unsupervised and illicit use invariable increases crash risk. Firstly, there is a risk of rebound sleepiness during times of withdrawal; secondly, increased proneness to erratic and/or risk-taking behavior may accompany intake of excessively stimulating substances, especially if overtitrated. Thirdly, some studies have reported the induction of 'tunnel vision' with use of stimulant substances.[29] Use of stimulants is generally prohibited in commercial pilots. MDMA, a currently popular drug of abuse, has been shown to produce a disinhibited driving pattern elevating risks of errors of commission and crash risk.[30]

Therapeutic Medications

Not all centrally acting drugs are physician-prescribed. It is recognized even among the general public that commonly used over-the counter (OTC) drugs such as opiate-containing antitussives or anticholinergic antinauseants can impair alertness

relevant to driving.[1] Classic first-generation antihistamines, which far more readily enter the CNS than the liphophobic second-generation H1-receptor antagonists, are also well known to produce performance decrements and drowsiness.[1,31] Caffeine is the most commonly used centrally acting performance enhancing agent. A typical cup of American-style coffee has been estimated to contain about 100 mg of caffeine, and its provigilant effect has been estimated to last about 1 to 3 hours.[32] Tea and chocolate are among other caffeine-containing foodstuffs. However, if used as a countermeasure to physiologically occurring sleepiness, there appears to be a tendency towards diminishing alertness with repeated use. In fact, Rayner and Horne[33] demonstrated that a brief therapeutic 'powernap', followed by caffeine consumption, was far more effective than caffeine alone in improving driving performance.

A large literature already exists on the adverse effects of hypnotics and sedatives,[12] but there is also significant interest in the effects of widely prescribed psychotropic medications like anti-anxiety and antidepressant medications.[4,12,22] While it is known that conditions such as depression and anxiety disorders significantly affect cognitive functioning, the pharmacological mode of action of drugs used to combat these disorders may vary vastly in their therapeutic and adverse effects on the spectrum from highly sedating to activating, depending on the neurotransmitters affected by the medication in question.

The key issue with respect to sedatives and hypnotics regards medication half-life.[34,35] This issue is discussed more extensively elsewhere in this book. Virtually all benzodiazepine-like substances are known to cause drowsiness and decreased fine-motor coordination, and patients should generally expect impairments comparable to alcohol on driving ability. Less well known to the public is the danger of residual 'hang-over' sedation of medications of various classes taken during the night, or even at bed-time the night before a daytime driving task, a clinically common scenario in patients using CNS-active agents for sleep neuropsychiatric disturbance. In particular, the use of long-or medium-acting sedatives for middle insomnia can create significant driving impairment the morning following use, and for this reason, if patients need to use middle-of-the night hypnotics on an occasional p.r.n. basis, an ultra-short acting sedative such as zaleplon is recommended.[35]

Depressed patients show impaired information processing, learning, memory and tracking skills.[36-38] While all these are potential target symptoms of medication and psychological treatment, a judicious clinician should be aware of both risks and benefits of treatment options. The effects of antidepressants on driving ability have probably best been described by Hindmarch, using both 'in vivo' road tests and computer-based performance tests such as the critical flicker fusion frequency and choice reaction time tests.[39] A recent excellent review of antidepressant effects on driving ability by Ramaekers[37] has attempted to broadly divide antidepressant medicines into sedating and non-sedating groups, and found that on an actual road test using a car equipped with a telematic performance monitoring tracker, the measure standard deviation of lateral position (SDLP), an index of a driver's propensity to 'weave', was most sensitive in distinguishing differential performance due to various antidepressants. While an exhaustive discussion of specific drugs is beyond the scope of this article, tricyclic medications, and those novel antidepressants with antagonism of central histaminergic, muscarinic or adrenergic receptors do demonstrate a dose-dependent increase in a medicated test subject's SDLP. Furthermore, an important co-factor was the combined use of benzodiazepines (a clinically common scenario), particularly when there was a likely cytochrome p450 inhibitory interaction of the two drugs.

This is not to suggest that sedating antidepressants should be avoided in patients depending on their driving privileges. In fact, sleep disturbance is an extremely common clinical manifestation of depression, typically taking form in some combination of initial and middle ('early morning' insomnia) with anxious or depressive ruminations. Often, the sleeplessness associated with the psychiatric condition will pose more of a hazard than the possible residual effect of the antidepressant treatment. Sedating antidepressant agents such as mirtazapine or trazodone can be effective treatments for a combination of sleep and mood disturbance. Mirtazapine has been shown in at least one study of administration over a 5 day period to potentially impair driving performance at bed-time doses of 15 to 30 mg.[41] For more refractory mood and agitation states, it is reasonable to combine antidepressants with benzodiazepine-like sedatives; furthermore, sedating atypical antipsychotics such as olanzapine or quetiapine may be effective add-ons, and possibly less impairing than older neuroleptics.[42] What is important in the use of such medications is a clear discussion of risks and benefits with the patient. It is generally advised to avoid driving altogether within the initial titration period of treatment, as CNS-effects that impair co-ordination and mental alertness are usually most prominent then. Similarly, in the days following dosing adjustments, additional caution is warranted. For example, while Robbe and Ohanlon[43] found paroxetine showed no evidence of elevated psychomotor impairment on a divided attention task compared to placebo at 20mg, a mild increase in impairment began to appear at higher doses, although performance on a driving task remained preserved, illustrating the subtlety of performance testing. Similarly, acute administration of the now dicontinued antidepressive nefazodone showed impairment on lateral position control in an on-road driving test, at 200mg twice daily, but not 100 mg twice daily, in conjunction with dose-related mild cognitive and memory decrements.[44]

When used therapeutically, stimulant medicines have been shown to improve psychomotor performance on an acute basis in adolescent drivers with attention deficit disorder.[45] Alerting or provigilant medications may also come from the antidepressant class, where they activate combinations of serotonergic (e.g., fluoxetine), noradrenergic (venlafaxine) or dopaminergic (buproprion) most prominently.[1] As with stimulants, caution should be exercised to avoid inducing states of hypervigilance or agitation through overly aggressive dosing. Furthermore, it is not uncommon for individual psychomotor performance to vary significantly for different antidepressant agents.[37,39,40]

Not uncommonly, individuals with more serious mental disorders such as bipolar disorder or psychotic illnesses possess valid driver's licenses, and may even depend on driving as part of their activities of daily living. The effects of psychotropics used to treat these conditions is less well understood. There are reports of potentially impairing effects of lithium[46,47] as well anticonvulsants,[48] whether used as mood stabilizers or to control seizure disorders. The use of antipsychotics has been less extensively studied. Similarly to the treatment of depression, severe cognitive and psychomotor impairments are often a component of the illness state, and may improve with treatment. While acute administration of most antipsychotics in drug-naïve subjects results in psychomotor impairment, a review by Judd[49]

points out that generally, patients suffering from psychotic illness tend to demonstrate improved psychomotor performance during chronic treatment with these medications. Similarly to tricyclic antidepressant agents, sedating effects due to the anti-histaminergic, anti-α 1 adrenergic or anticholinergic systems, often quite prominent in acute antipsychotic administration, may abate with prolonged treatment.

Schweitzer's review of antihypertensives points out that beta-blockers, particularly those with α1-blocking activity have been associated with fatigue and somnolence.[1] However, there is a paucity of literature in the domain of alertness testing, and specifically, driving performance. In general, for cardiovascular medications, it is appropriate to be aware of potential idiosyncratic cognitive and/or performance decrements.

A recent controversy regarding psychotropic agents and driving has followed a report by Frucht,[50] alerting clinicians of the possibility of "sleep attacks" secondary to the novel anti-parkinsonian agents ropinirole and pramipexole. It has been pointed out that rather than dealing with an impairing risk relating to these specific drugs, a broader issue may reside in the frequently compromised driving ability of often elderly individuals with advanced Parkinson's disease. Furthermore, the potential class-effect of other dopaminergic agents including levo-dopa to at least have the potential to cause idiosyncratic and/or dose-related impairments of alertness has been noted.[51]

In general, elderly individuals are more likely to carry multiple medical diagnoses, to be treated with multiple medications, including psychotropics, and are more likely to have decrements in psychomotor skills. Clinicians must be cautious of the altered pharmacokinetics and pharmacodynamics of the elderly. While a recent large-scale study of nearly 1000 drivers revealed an increase in odds ratio for benzodiazepine use in at-fault crashes for seniors,[7] other medicines such as nonsteroidal anti-inflammatories, ACE inhibitors and anticoagulants also showed elevated odds ratios, possibly due to medical morbidity (muskuloskeltal and cardiovascular) associated with these drugs. This illustrates the challenge of examining causative drug effects on driving in epidemiological studies.

Conclusions

It is intuitive that CNS-active drugs have the potential to affect perceptual and psychomotor skills relevant to driving. Yet, variability in testing paradigms and difficulty in controlling performance-testing conditions continue to create challenges in achieving a more exact understanding of pharmacological influences on driving behavior. Advances in technology have created opportunities for better measurement, both in simulator and on-road testing. Controlled prospective, rather than retrospective epidemiological studies will be more likely to shed light on cause and effect of motor vehicle crashes in relation to drug use. Alternative comparison data for driving performance of healthy unmedicated individuals is urgently needed to further knowledge in this field.

Psychotropic medications have the potential to improve aspects of driving performance, however, this is dependent on factors such as perceptual driving context and trip duration. Cognitive and psychomotor aspects of psychiatric disorders often respond to pharmacological treatment, but care must be taken to avoid acute or persistent adverse effects such as sedation or agitation, which could equally elevate crash risk through separate mechanisms. The performance of driving will continue to evolve in coming years, along with sociological and technological developments, making this a topic of continued interest to researchers interested in psychopharmacology and human performance.

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