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## DRUGS IMPAIRMENT ON DRIVING PERFORMANCE: AN OVERVIEW

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### ABSTRACT

*Background:* there are number of drugs in our community both as OTC as well as prescription which can influence the driving performance.

*Material and methods:* Relevant literature was identified through searches in Medline and Google scholar. The current stage of knowledge regarding effect of commonly used drugs on driving behavior is reviewed and discussed.

*Results:* there are large numbers of drugs which can influence driving performance, among them drug acting on CNS are more common. Elderly people are more susceptible for this effect. Theoretical consideration and empirical observation suggest that higher doses may impede performance.

*Interpretation:* There are conspicuous lacks of data on all the drugs and more studies are required to corroborate the influence of drugs on driving performance.

**Keywords:** Driving performance, Over the counter (OTC), International Council on Alcohol, Drugs and Traffic Safety.

### INTRODUCTION

Driving is a complex information processing task and is one of the most challenging activities people engage in on a daily basis. Driver health is an important consideration to prevent or decrease the risk of accidents. There are large numbers of drug and disease which can impair

driving skills nevertheless it also depends on some patient related factors. Drugs that affect mood cognition and psychomotor functioning can directly on indirectly impair driving ability. Many over the counter drug and prescription medication such as some cough and cold, flu

day and night formulas nonsteroidal anti-inflammatory, antihistamines, antibiotics, antidepressants, hypoglycemic drugs, a number of drugs for epilepsy and sleep medication such as benzodiazepine can potentially impair driving. Many of those who use psychoactive medication are outpatient and likely to drive a vehicle. Most common adverse effects that impair driving are dizziness, drowsiness, reduced alertness, affected psychomotor functioning; impair vision, sedation, and lethargy. Even though persons 65 years of age and older take these drugs and are more prone to these effects.<sup>[1]</sup> This review discusses the effects of commonly used OTC as well as prescribed drugs on driving.

Drug can be categorized on the basis of their effect on driving with the use of The International Council on Alcohol, Drugs and traffic safety (ICADTS) categorization. It can be helpful for physician also to make choice between treatments when patient want to drive a vehicle.<sup>[2]</sup> A survey of united state laboratories actively involved in providing analytical support to drug evaluation and classification program and identified marijuana, benzodiazepines, cocaine, prescription and elicit opiates, muscle relaxant, amphetamine, CNS depressant, and sleep aids used as hypnotics, as being the most frequently encountered drug in these cases.<sup>[3]</sup> Drugs such as sedative, antihistamines, benzodiazepine, some antidepressant, and antipsychotics are

estimated to have driving impairment equivalent to over 0.05% blood alcohol concentration.<sup>[4]</sup>

### ***OTC: are they safe for driving?***

Because of the widespread availability and perceived safety of OTC products, self medication with these drugs has become commonplace. Many patients are unaware of the potential for toxicity and adverse drug interactions associated with the long term and inappropriate use of OTC drugs.<sup>[5]</sup> A survey of medication use pattern in the united state found that more than 80% of American adults used at least once over the counter or prescription drug each week, and that 25% used at least 5.<sup>[6]</sup> While OTC packaging contains warning related to drowsiness and other side effects, they are often presented in very small print. If the message "To use caution when driving" appears at all, it is unlikely to influence individuals who may be unaware that their abilities are impaired.<sup>[7]</sup> The FDA does oversee the OTC drugs to ensure that they are properly labeled and that their benefits outweigh their risk; however products on the market today still be dangerous when performing certain task such as driving a motor vehicle, drowsiness is the most common potential driving impairing side effect of OTC.<sup>[8]</sup>

In 2004 the department for transport identified all the medicine available over the counter in the United Kingdom which has the potential to

cause drowsiness and therefore have the potential to be hazardous to driver and other users. They identified 102 medications for the treatment of cough and cold, allergies, pain, nausea and gastrointestinal upset, all with potential to cause sedation. The medication fell into three main groups: antihistaminics, opioids, muscarinic agents. The elderly taking the recommended dose of medication may be more likely to experience drowsiness and having driving performance affected. <sup>[9]</sup>

#### **ICADTS categorization:**

The categorization system of the International Council on Alcohol, Drugs and Traffic Safety (ICADTS) can be used to indicate whether or not it is safe to drive a car when using a specific psychoactive drug. <sup>[10]</sup>

Drugs are allocated to one of the following categories

1. presumed to be safe or unlikely to be produce any effect
2. likely to produce minor or moderate adverse effects
3. likely to produce severe effects or presumed to be potentially dangerous <sup>[2]</sup>

#### **Medical conditions:**

A number of medical conditions also affect the driving performance; differentiation should be made between temporary conditions affecting driving performance in the short term like

mydratics, general anesthetics fracture etc or serious conditions likely to affect driving in the medium to long term, like cardiac events, cerebrovascular accidents, neurological etc.

**Table 1: Some medical conditions and their impact on driving <sup>[11-16]</sup>**

<b>Medical condition</b>	<b>Impact on driving (factor that may increase risk of accidents)</b>
Epilepsy	Seizure risk
Cardiovascular disease	Increase diastolic blood pressure (>95 mm Hg), recurrent syncope, two or more transient ischemic attacks
Diabetes	Hypoglycemia symptoms
Psychiatric condition	Behavior disorder, alcohol and drug abuse, psychiatric condition and organic brain syndromes etc
Dementia	Refuse to give up driving and may continue to driving even when advised not to do
Sleep disorder	May lead to falling a sleep at the wheel
Visual function	Eye condition may affects driving performance

#### **Non steroidal anti-inflammatory drugs**

It has been suggested that driving is relatively safe when the driver is treated with non steroidal anti-inflammatory drugs as compared with opioid analgesics. However the evidence from this statement is scarce. <sup>[17]</sup> CNS side effects with NSAIDs were observed in about 1-10% of people. Side effects such as dizziness, headaches, drowsiness, mood alteration, confusion etc, seem to be more common during

treatment with indomethacin<sup>[18]</sup> and also other drugs like celecoxib, diclofenac, meloxicam, naproxen, phenylbutazone<sup>[19]</sup> Again these effects are more likely when higher than recommended doses are taken or when they are combined with other impairing medications. In a clinical study psychomotor effect of ketorolac and diclofenac was compared with buprenorphine and it was found that both drug has no clinical significant effects on psychomotor test and only minimal symptoms were reported.<sup>[20]</sup> A study was conducted to identify accidental risk in patient taking NSAIDs and it was found that there is 58% increase in crash risk for driver taking NSAIDs compared to driver not taking these medicines.<sup>[21]</sup>

**Antihistamines**

There are large numbers of antihistaminics available both as OTC as well as prescription drugs. These drugs are valuable for a wide variety of conditions but these drugs also associated with certain CNS side effects. Although the side effects associated with these drugs are very diverse and can be differentiated with their generation.

**Table 2: Antihistaminic drugs and their side effect on driving performance<sup>[22-29]</sup>**

Antihistamines	Example of some drugs	Side effects associated with driving impairment
First generation	Diphenhydramine, dimenhydrinate, chlorpheniramine,	Drowsiness, impaired thinking,

	clemastine, triprolidine, promethazine, hydroxyzine etc.	dizziness, daytime fatigue, sleepiness, nervousness, tremors and blurred vision
Second generation	Cetirizine, desloratadine, fexofenadine, laratadine	Driving should be avoided Sedation produce at higher dose Consult to your doctor if you are taking high doses
Third generation	Levocetirizine	Very few side effects Can be considered as safe in driving

First generation antihistamines, all of which have sedation, somnolence, impair learning and reduce work efficiency. These drugs have been repeatedly shown to diminish cognitive, psychomotor and driving performance in healthy volunteers.<sup>[22, 23]</sup> Sedation the most common adverse effect of these agents occurs in 10% to 25% of user.<sup>[24]</sup> A study was conducted to show the combined dextromethorphan and chlorpheniramine intoxication in drivers. They displayed symptoms of CNS depressant intoxication, and there was gross evidence of impairment in their driving, including weaving, leaving the lane of travel,

falling to obey traffic signals and involvement of collisions.<sup>[25]</sup>

Being relatively devoid of sedation and CNS impairment, second and third generation antihistamine are less likely to impair driving than first generation antihistamines. So it can be stated that new generation antihistamines are safe in driving. Although there are also differences within the antihistamines drug generations.<sup>[26]</sup>

Several agents (acrivastine, cetirizine and mizolastine) mildly affect driving performance when given at therapeutic doses. Other (ebastine, fexofenadine, loratadine and terfenadine) did not have significant effect after being taken in recommended doses, but had measurable effects at doses that were twice as high. Although mild impairment is sometime overcome by coadministering the sympathomimetic decongestant pseudoephedrine,<sup>[27-29]</sup> but the combination may also be associated with a higher frequency of subjective adverse effects such as insomnia and other symptom of CNS stimulation.<sup>[30]</sup> Impairment of actual, on road driving was found in 89% of the studies evaluating first generation antihistamines, and 10% of studies evaluating second generation antihistamines.<sup>[31]</sup>

### **Antidiabetic agents**

These drugs are used on a regular basis by the patient with diabetes. These drugs act through different mechanism and help in lowering blood

glucose level. Approx all the drugs of this class are responsible for producing hypoglycemia. Side effects associated with hypoglycemia such as shakiness, lightheadedness or dizziness, confusion, difficulty in concentrating, drowsiness, weakness, clumsy or jerky movement, seizure, shortness of breath and blurred vision may be responsible for driving impairment.<sup>[32]</sup> Insulin induced hypoglycemia and it's sequelae of cognitive impairment may place patient with type I diabetes at risk when driving and while making decisions about driving.<sup>[33]</sup> It is clear that progressive diabetic hypoglycemia leads to neuroglycopenia, which impair driving.<sup>[34]</sup> Other commonly used antidiabetic drug such as sulphonylureas, biguanides,  $\alpha$ -glucosidase inhibitors, meglitinides also have this potential but upto less extend. Among all OHA, sulphonylureas are the drug which have highest hypoglycemic potential.<sup>[35]</sup>

### **Anticholinergics**

These drugs are as well prone to have their CNS side effects which can impair driving performance includes confusion, blurred vision, dizziness and drossiness.<sup>[36]</sup> Pupil dilation due to anticholinergic drugs can impair selected aspects of driving and vision performance, patient should be caution about these side effects.<sup>[37]</sup> In a study it was found that driver taking anticholinergic/antispasmodic had a 20% increased like hood of crashing compared with driver not taking these medicines.<sup>[21]</sup>

**Antibiotics**

These drugs are less likely to affect driving but some of them can produce dizziness or other undesirable CNS effects. Fluroquinolones are associated with some CNS side effects like dizziness, convulsion, psychosis, and insomnia. Among the fluroquinolones currently available levofloxacin, ofloxacin and moxifloxacin reportedly have the lowest potential of inducing CNS side effects.<sup>[38]</sup> In some cases minocycline may cause severe dizziness.<sup>[39]</sup> Antimalarial drugs are also associated with some CNS side effects such as dizziness, drowsiness, muscle pain, decreased visual accommodation and visual field defects.<sup>[40]</sup> Some of the medications in this class contain a warning related to vision change, dizziness, drowsiness and ability to operate a motor vehicle safely. Griseofulvin and itraconazole are also having dizziness effect.<sup>[41]</sup> Other antifungal drugs also have potential to produce dizziness but with less or similar extend.

**Antiemetic/ Antivertigo agents**

Drugs such as prochlorperazine, ondansetron, meclizine, promethazine and scopolamine are used to prevent and treat nausea, vomiting and dizziness. These drugs have potential to cause driver impairing side effects, such as significant drowsiness, lowered alertness, blurred vision, disorientation, and muscle cramps.<sup>[42]</sup> A double blind prospective randomized crossover study was conducted to identify the effects of

betahistine and prochlorperazine on driving skills. The psychomotor effects of betahistine could not be distinguished from those of placebo but prochlorperazine can impair driving performance by increasing carelessness and slowing on the weaving test.<sup>[43]</sup>

**Adrenergic agents**

These drugs are less likely to have driver performance impairing side effects. Beta adrenergic selective agents (albuterol, pirbuterol, salmeterol, formoterol, levalbuterol etc) have been widely used in the treatment of asthma. This class of medicines is known to produce short term and long term side effects such as increase heart rate, lightheadedness anxiety, arrhythmia, nervousness, muscle cramps or pain, and extreme tiredness that are that are dose dependent.<sup>[44]</sup> In a study it was found that driver taking beta adrenergic drug had a 35% increased likelihood of accidental risk compared with driver not taking these medicines.<sup>[21]</sup>

**Beta blockers**

The efficacy of beta blocker has been proven predominantly for the treatment of cardiovascular disease. Beta blockers are also used for certain type of CNS disorders, such as anxiety disorder, essential tremor and migraine. These drugs have low toxicity profile which means that they have a favorable risk benefit ratio. Generally these drugs are given the high intensity of use, so it is essential to have a

comprehensive knowledge of all adverse events. Adverse events of beta blockers that can be related to CNS are quite often neglected, and thus often misdiagnosed. But beta blocker can affect driving performance because they have CNS side effect like depression, fatigue, somnolence and dizziness.<sup>[45, 46]</sup> The interclass deference of adverse events between these drugs depends upon selectivity of receptors.

### ***Gastrointestinal drugs***

Drugs such as esomeprazole, lansoprazole, pantoprazole and ranitidine block gastric acid secretion. These drugs are also having some CNS side effects because of their dopaminergic blocking action. The medications of this class vary in level of potency and carry the general caution label of “use caution when driving as this medication may cause some drowsiness or dizziness.”

### ***Skeletal Muscle Relaxants***

Medication that are used generally as a skeletal muscle relaxants include baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, methocarbamol, orphenadrine and tizanidine, patient taking these medicines should be warned that their mental and/or physical abilities required for driving may be impaired. As a class, skeletal muscle relaxants have CNS related side effects: drowsiness, dizziness, decrease alertness, blurred vision and clumsiness. Their uses have been associated with a 2 fold increase in the risk of motor

vehicle crashes.<sup>[21]</sup> They are poorly tolerated by elderly patients, because they cause anticholinergic side effects and also their effectiveness at doses tolerated by elderly patient is questionable. Centrally acting muscle relaxant carisoprodol and its metabolite meprobamate also have their undesirable effect on driving performance.

### ***Cardiovascular drugs***

A wide variety of drugs comes under this category. These drugs also have some CNS side effects but with a little extend and these effects also vary with class to class or drugs to drugs. The impact of these classes of drugs on driving is not studied well but consideration should be given specially in case of elderly people.

**Table 3: Cardiovascular drugs and their side effects on driving performance**

<b>Class</b>	<b>Example drugs</b>	<b>of Side effects (which have impact on driving)</b>
Sympatholytics	Clonidine, methyldopa, guanabenz	Insomnia, confusion, nervousness, drowsiness, muscle weakness, dizziness
Diuretics	Loop diuretics: furosamide, indepamide	Dizziness, weakness, drowsiness, fainting, blurred vision
	Potassium sparing diuretics: spironolactone	Dizziness, drowsiness and excessive tiredness

Angiotensine- converting enzyme inhibitors	Captopril, enalapril, lisinopril	Dizziness, drowsiness and excessive tiredness, weakness, lightheadedness
Calcium channel blockers	Amlodipine, nifedipine, varapamil	Dizziness, drowsiness and excessive tiredness, weakness
Vasodilators	Nitroglycerin	Dizziness, drowsiness, blurred vision
Antiarrhythmatics	Quinidine, mexiletine, procainamide, amiodarone, disopyramide	Dizziness, difficulty in sleeping, fatigue, weakness of arms or legs, blurred vision, decrease peripheral vision, blue green rings or helos around light, lowered alertness, trembling or shaking of the hands and numbness or tingling in the fingers or toes.
Digitalis glycosides	Digoxin	Dizziness, lightheadedness, drowsiness, blurred vision

deleterious effects of psychotropic medications such as benzodiazepines, typical antipsychotics and tricyclic antidepressants (TCAs) on human motor skills; in clinical studies it was found that BZDs and TCAs were most commonly associated with impairment, although the level of impairment was dependent on several other factors. <sup>[47]</sup>

**Barbiturates**

Barbiturates are categorized as ultrashort-, short-, intermediate-, and long acting, depending on how quickly they act and how long their effects last. Ultrashort barbiturates such as thiopental produce unconsciousness within about a minute of intravenous (IV) injection. These drugs are generally used in hospital setting, so less likely to produce drug abuse effects. Long acting barbiturates such as phenobarbital and mephobarbital is used as an anticonvulsant for people suffering from seizures. Barbiturates decrease anxiety and increase feeling of fatigue, dizziness, lightheadness and lethargy. Patient information cautions that even when taken at bedtime, barbiturates may cause some people to feel drowsy or less alert upon arising were associated with the highest risk of motor vehicle crashes among the 90 prescription drug classes studied. <sup>[21]</sup>

Moreover barbiturates are highly sedative. Patients reported that reduced alertness and sedation interfered with their daily functioning,

**Drug acting on CNS**

These drugs are most commonly associated with driving impairing side effects. Driving a motor vehicle is central to the functional anatomy of patients with psychiatric illness. There have been many studies of the

including driving a car. An on-the-road driving study showed that driving performance was significantly impaired up to 17 hours after bed time administration of secobarbital (200 mg).<sup>[27]</sup>

### ***Benzodiazepines***

Long acting BZD's are associated with greater effect on driving performance than short acting agents. BZD's significantly impaired driving performance after single dose administration. Impairment due to BZD's when used as anxiolytic is much more pronounced when compared to impairment when used as hypnotic drug. This difference is due to timing of drug administration, anxiolytics (during the day, i.e. after awaking) and hypnotics (at bed time).<sup>[2]</sup>

Studies indicates that greatest accident risk is associated with the use of long half life benzodiazepines, increasing dosage and the first few weeks use of BZD's. It has been showed that drivers using BZD's, anxiolytics (including alprazolam, chlordiazepoxide, clhorazepate, diazepam, lorazepam and oxazepam) had significantly increased numbers of accident related emergency outpatient visits.<sup>[48]</sup> Driving impairment was most pronounced in the morning. In the afternoon, driving impairment was less evident and absent for short acting BZD's. For long acting BZD's driving was also impaired in the afternoon; especially when using higher doses than recommended.

Most BZD's were categorized in ICADTS category 3. Among all BZD's zolpidem is the only drug present in category 2.<sup>[2, 17]</sup>

In a study the effect of zolpidem was identified for impaired driving. Subjects who received zolpidem with other drugs and/or alcohol; symptoms reported were generally those of CNS depression. Symptom slow movements and reactions slow and slurred speech, poor coordination, lack of balance, flaccid muscles tone, and horizontal and vertical gaze nystagmus. Subjects who received only zolpidem also showed signs of impairment which included slow and slurred speech, slow reflexes, and disorientation, lack of balance and coordination, and "blacking out". It is reasonable to conclude that because of its specific activity as sleep inducer, blood concentration consistent with therapeutic doses of zolpidem have the potential to affect driving in a negative way, and that concentration above the normal therapeutic range would further impair a person's level of consciousness and driving ability.<sup>[49]</sup>

### ***Antidepressant***

Antidepressant medication may cause impairment of psychomotor functioning relevant to psychosocial adaptation and fitness to drive. TCA's significantly impaired driving performance after single dose administration.<sup>[50]</sup> Driving after administration of TCA's (amitriptyline, doxepine and imipramine),

mianserin and mirtazepine was significantly impaired after treatment initiation. Although these side effect will be reduced due to development of tolerance. Nocturnal treatment with these antidepressants did not affect next day driving performance. <sup>[2]</sup>

These drugs also have antihistaminic activity, which may lead to reduced arousal and sleepiness. Their muscarinic activity may affect cognitive functioning. These activities of TCA's have synergistic effect on impairing driving performance. In contrast to the TCA's, SSRI's (including fluoxetine, paroxetine and escitalopram), related antidepressants (venlafaxin and nefazodone) and MAOI meclizemide showed no significant effect on driving performance. SSRI's and SNRI's are less likely to cause sedation or impair driving skills- may improve driving performance. Sertraline is chemically unrelated to other SSRI's, TCA's and other currently antidepressant medications. A case of motor vehicle accident was reported under the influence of sertraline. <sup>[17]</sup>

### ***Narcotic Analgesic***

These drugs are used to relieve pain especially chronic pain by acting on the CNS receptor. Drugs such as buprenorphine, codeine, dextropropoxyphen, fentanyl, hydromorphone, methadone, morphine, oxycodone, pethidine, tramadol may cause sedation and miosis effects. Doses more than 20 mg of codeine may impair driving performance.

### ***Anticonvulsants***

All commonly used antiepileptic drugs have some effects on cognitive function and the effect may be substantial when crucial functions like driving are involved. There are three factors which involve in declining of cognitive functions: the underlying etiology of epilepsy, the effects of seizures themselves, and the central nervous system of antiepileptic drugs (AED's). Already established evidence is available for conventional drugs such as lamotrigine, topiramate, and to a lesser extent oxcarbazepine. But the available evidence is insufficient to support definitive conclusion about the cognitive effects of three of the newer AED's, tigabine, gabapentin and levetiracetam. Although several cases of gabapentin associated driving accidents have been reported which might be due to the side effects of the drugs like somnolence, dizziness, ataxia, nystagmus and fatigue. <sup>[51]</sup>

### ***Antiparkinsonism drugs***

It is already well known that dopaminergic drugs are associated with potentially hazardous side effects (2-57%) and disabling parkinsonism non motor and motor disabilities (16-33%). Despite all these things the two existing studies on accident rates suggest that parkinsonism patients are not more prone to cause road accidents than the rate of population. Five further reports including 1346 patients and focusing on dopaminergically induced sleep

attacks provided comparably low accident figures (yearly incidence: 0-2%).<sup>[52]</sup>

### **CNS Stimulants**

Generally these drugs have their stimulant effect on driving performance but on chronic use the outcome may differ. The number of road fatalities related to the presence of amphetamines in drivers has been relatively constant over the past 10 years. However, low amphetamine doses have been associated with enhanced performance in studies of sleep deprived subjects. Theoretical considerations and empirical observations suggest that higher doses may impede performance, but not in accordance with usual concentration/effect relationship.<sup>[53]</sup>

In a study the acute effects of 0.42 mg/kg dexamphetamine on stimulated driving performance was investigated and it was found that driving ability was decreased following dexamphetamine administration during the day time but not the night time scenario task<sup>[54]</sup>. Methamphetamine incidence in driving under the influence cases is also significant and ongoing challenge. Cannabis contains a potent psychotropic substance delta (9)-tetrahydrocannabinol (THC) which is frequently detected in blood from apprehended drivers suspected for drugged driving. It has also been reported that there is a correlation between the degree of impairment, the drug dose and the THC blood concentration.<sup>[55]</sup> There is evidence

that caffeine increases alertness and reduce fatigue. This may be especially so in low arousal situation (i.e. working at night for prolonged hours). Caffeine has also been found to improve performance on vigilance task and simple task requiring sustained response.

Again these effects are often clearest when alertness is reduced, although there is evidence that benefits may still occur when the individual is unimpaired. Modafinil offers some benefits with respect to objective driving performance under conditions of sleep loss. However, it may induce over confidence, suggesting that its use as a cornerstone to drowsiness when driving requires further examination.<sup>[56]</sup>

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