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Review Article

Psychopathology and Road Traffic Accidents

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Summary

Road traffic accidents are a major cause of morbidity and mortality in developed and developing countries, and while human error is a rather unavoidable cause, driving under the influence of drugs or while suffering from medical conditions of physical and mental pathology can potentially be avoided. Driving is a complex psychomotor activity and deficiency at any functional level brings about adverse effects on driving behaviour. Numerous causes have been identified that make driving unsafe, including alcohol, illicit drugs, legal medications, fatigue, distraction, and various medical conditions. There is considerable controversy regarding the driving ability of patients with mental disorders, which may vary between patients, both because of the type of disorder and because of the effects of psychiatric medication on driving. This review article seeks answers in the literature to key questions such as whether individuals with a psychiatric disorder are at increased risk of a road traffic accident and whether there are specific psychiatric disorders that present a particularly high risk, whether individuals taking psychiatric medications are at increased risk of a road traffic accident compared to individuals not taking similar medications, and which personality disorders' characteristics are associated with risky driving behavior.

Keywords: traffic accidents, psychopathology

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Introduction

According to the World Health Organization, 1.25 million people worldwide lose their life every year as a result of road traffic accidents. Many factors appear to contribute to their cause, but it is very difficult to determine the extent to which medical conditions of physical and mental pathology are involved.

A 2003 meta-analysis (1), with data from 19 countries, investigating the contribution of drivers' medical conditions to causing road traffic accidents reported that psychiatric disorders increase the likelihood of causing road accidents with a relative risk 1.72, major mental disorders with a relative risk 2.01, depression or the presence of depressive symptoms with a relative risk of 1.67, alcohol use disorders with a relative risk of 2.00 and substance and drug use disorders with a relative risk of 1.58 (cannabis 1.79, opioids 1.83, benzodiazepines 1.54), compared with drivers without a disease.

A percentage of 90% of road traffic accidents are attributed to human error. Although speed is a contributing factor in around 15% of all road accidents and 30% of all road fatalities (2), road accidents can also occur at low speeds.

There is considerable controversy regarding the driving ability of patients with mental disorders, which may vary between patients, both because of the type of the disorder and because of the effects of psychiatric medication on driving. Patients with mental disorders may have deficits in attention, impulse control, visuospatial and neurocognitive abilities as well as in information processing and psychomotor skills (3-6). These difficulties may impair driving capacity and may necessitate recommendations for restriction, suspension or even prohibition of driving. It is important that these restrictions are, as far as possible, evidence-based and reflect a balance between road mobility and safety (7).

The United Nations International Convention on the Rights of People with Disabilities, and in particular Article 20 on individual mobility, states that States Parties shall take effective measures to ensure that people with disabilities assure the greatest possible degree of individual mobility with the greatest possible degree of autonomy. In developed societies, the most important and widespread means of personal mobility is driving a motor vehicle. On the other hand, the cognitive, emotional and behavioural disorders experienced by patients with mental disorders can be a risk factor during driving.

A multicentre study in Germany (8) with data from 1546 hospitalized psychiatric patients reported that 67% of them had a valid driving license and 77 % of them admitted to driving frequently. Among those with a driving license, patients with organic mental disorders (32%), addictions (37%) and psychotic disorders (40%) drove less frequently com-

pared with patients with other diagnoses.

Driving is a complex psychomotor function involving 3 hierarchically organized levels of competence: functional competence, tactical competence, and strategic competence (9). The first level includes basic neurocognitive abilities necessary for driving; the second level includes behaviours, skills, and decisions necessary for driving in traffic, such as speed adjustment, overtaking, etc. The third level involves decisions and planning related to the reasons for which the vehicle is being used at a given moment (choice of direction, risk assessment, etc.). A disturbance at any level has a secondary impact on various areas of functioning that support driving behaviour and make driving unsafe for the driver and others.

LITERATURE REVIEW

A 2008 review article (10) reported on the scientific evidence on the driving abilities of patients with psychiatric disorders and those receiving psychiatric medication. Of the 14 studies reviewed, 8 studies claimed that mental disorders were associated with increased rates of road traffic accidents. Also some psychiatric drugs, such as benzodiazepines and tricyclic antidepressants, had a negative effect on driving ability, particularly in the initiation phase of treatment, or during changes in treatment. They concluded that although there are few relevant studies, the scientific evidence suggests that mental illness potentially has different effects on driving depending on the type and severity of the disorder, and the same is true for specific types of psychotropic medications.

A 2011 review article (11), which investigated the associations between 4 groups of psychiatric disorders and safe driving, and the relationship between the likelihood of causing road accidents in drivers with specific personality disorder characteristics, reported that evidence regarding the increased likelihood of causing road accidents in drivers with psychotic, emotional, anxiety disorder or personality disorder were currently inconclusive although some evidence suggested that patients with emotional disorders (3 studies) had an increased likelihood of causing road accidents (of the 8 studies included, 6 supported an increased likelihood of causing road accidents among drivers with psychiatric disorders, but only 2 reported results with statistical significance). There was also evidence that certain characteristics of patients with personality disorders (aggression, hostility, impulsivity, contempt for the law and various psychological symptoms) were associated with dangerous driving behaviours and increased the likelihood of causing road accidents (21 studies). Traffic code violations were associated with dangerous driving behaviours and aggression.

In a more recent review article (12) on the assessment of driving competence in patients with mental disorders, among only 58 articles that have dealt with driving and mental disorders in general, 16 studies were selected that focused on the assessment of driving competence in patients with mental disorders (7 studies on the factors affecting the ability to drive safely in patients with mental disorders, 5 studies on the perceptions and abilities of healthcare professionals to assess driving competence in patients with mental disorders, and 4 studies on the rates of road traffic accidents in patients with mental disorders). They concluded that behavioural, cognitive and psychomotor deficits that reduce driving ability differ between different diagnostic categories. Patients with major depression, who were not on medication, showed increased drowsiness while driving and significantly delayed reaction time and increased rates of traffic accidents compared to controls. Patients with bipolar disorder who had committed traffic violations had cognitive deficits (executive functions, alertness, etc.) that were attributed to the psychiatric disorder and/or pharmacotherapy. First-episode psychotic and schizophrenic patients who did not follow pharmacotherapy showed severe deficits in psychomotor skills. Patients in mania and hypomania reported driving at increased speed, loss of control, impulsive behavior, decreased concentration and judgment, and making wrong decisions. One group of patients overrepresented in road accidents, even after treatment, was personality disorder patients. Similarly, patients with Attention Deficit Hyperactivity Disorder (ADHD) were overrepresented in traffic violations. Regarding the perceptions and abilities of healthcare professionals to assess driving ability in patients with mental disorders, only ¼ of psychiatrists believed they could make decisions about driving ability in patients with mental disorders and half of them believed that patients with mental disorders were more likely to be involved in road traffic accidents. There were minimal references about driving ability in patients' medical records, the emphasis was on the effects of medication on driving ability rather than on the psychiatric disorder itself and its effects, and only for ¼ of patients their medical records included information about the status of driving.

In a 2007 review article (13) investigating the effects of psychotropic drugs on simulated driving, 25 out of the 44 studies investigated exclusively the effects of benzodiazepines, 10 investigated the effects of benzodiazepines in comparison with other drugs (hypnotics, antidepressants, anxiolytics, antipsychotics, lithium) and the other 8 investigated the effects of antidepressants, anxiolytics, antipsychotics and lithium only. The type, dosage of the drugs and the time interval between administration and driving the simulator shaped the results of the studies. Benzodiazepines acutely increased reaction time and vehicle lateral position deviation, lane drifting and affected braking accuracy, driving errors and coordination, but after 1 week of repeated administration these effects did not persist. Of the antidepressants, amitriptyline and trazodone increased reaction time which was not the case with the newer antidepressants. Lithium in healthy and bipolar patients increased reaction time and coordination mistakes.

Another 2014 review article (14) investigating the harmful effects of drugs on driving reported that benzodiazepines with a half-life >24 hours increased the odds of driving accidents by 1.45 times, over a week in people older than 65 years, while in another study the increase was 1.88 times and in anxiolytic benzodiazepines 2.39 times, for patients on diazepam 20 mg/day the increase was 2.4 times and for patients on tricyclics 2.2 times (for amitriptyline >125 mg/day 5.5 times). For zolpidem the increase was 1.29-fold and for

patients receiving >10mg/day the increase was 2.46-fold. Another study claimed that traffic accident rates increased 1.4 times in patients on tricyclics or mirtazapine and 1.6 times in patients taking selective serotonin reuptake inhibitors (SSRI's) or venlafaxine. In a study of hospitalized patients with a major depressive episode, only 10% of those taking tricyclics successfully passed a driving performance test compared to 20-50% of patients taking newer antidepressants.

An extensive 2008 study (15) by the National Highway Traffic Safety Administration (NHTSA) in America examining factors associated with traffic accidents in people over 50 years of age, reported that barbiturates increased the odds of traffic accidents by 7.5 times, benzodiazepines increasing the odds of traffic accidents by 2 times, non-benzodiazepine hypnotics which increased the odds of road accidents by 48%, tricyclics by 41%, SSRIs by 59%, selective serotonin and noradrenaline reuptake inhibitors (SNRIs) by 78%, trazodone by 90%, while mirtazapine and bupropion were negligible, antiepileptics by 97% and antipsychotics by 120%.

A study (16) examined the effects of psychiatric medications on driving behaviour in 77 patients who relapsed, restarted medication and were followed up in the outpatient department for 6 weeks. A proportion of 83% evidenced improvement and 17% either remained stagnant or worsened. Of those who showed improvement 25% were able to drive legally, and the rest of them improved their driving skills compared to the baseline where only 10% had satisfactory scores. Therefore, the medication had a favorable effect on driving skills.

SCHIZOPHRENIA & DRIVING

In America 43% of middle-aged and elderly outpatients with schizophrenia were currently drivers (17) and in Germany 40% of middle-aged hospitalised schizophrenia patients also drove on a regular basis (18). Epidemiological studies suggest that patients with schizophrenia are more likely to be involved in road traffic accidents compared to age-matched controls (19,20). Even if mileage was taken into account, several studies have reported a 2-fold higher risk of traffic accidents per kilometer in patients with schizophrenia compared to age-matched controls (21,22).

Neurocognitive and psychomotor deficits in patients with schizophrenia result in impaired functioning in all domains and impair driving ability. A study (23) of younger hospitalized schizophrenic patients (1st psychotic episode and relapsing) who were not receiving treatment reported deficits in psychomotor functioning related to driving ability. 38% of 1st psychotic episode patients and 25% of relapsed patients had severe deficits.

Other studies (24-29) regarding driving ability in patients with schizophrenia suggest that rates of 10-40% of those discharged and on stable medication show severe problems in driving ability (failure in more than 40% of driving tests). According to a study (25) 25% of 80 hospitalised schizophrenics, before discharge, had severe deficits in simulated driving. Also, in another simulator study (30), patients with schizophrenia were more likely than controls to deviate from lateral position, to be involved in a traffic collision 2.5 times more often and to drive at a significantly slower median speed than controls.

Positive symptoms, negative symptoms (psychomotor retardation), cognitive deficits (attention and concentration deficits), antipsychotic drugs, which of course improve psychotic symptoms but have side effects such as drowsiness (24), and an approximately 4-fold higher co-morbidity with substance abuse compared to the general population (31), cause significant compromise in driving ability. On the other hand, schizophrenics represent a group of patients with severe early deficits needing support to participate in activities and integrate into society (32).

Retrospectively, the first study in America compared 103 outpatients with schizophrenia with 123 matched controls. 68% of patients with schizophrenia and almost all controls drove; patients drove less and caused more accidents (33). Another study in California compared 83 outpatients with schizophrenia with a mean age of 59 years with 46 matched controls. 52% of the participants had a driver's license and 43% of patients and almost all of controls were driving at the time of the study (17). In a recent study in Mexico in a sample of 28 patients with schizophrenia, only 3.6% were driving (34). Another study in Germany (35) in a sample of 150 patients with schizophrenia, or schizoaffective disorder, 66 inpatients and 84 outpatients, reported that 64% had a driver's license, 32% had driven in the previous year, 31% owned a car and 2% a motorcycle. Driving license had been revoked in 24.7% of patients and 32.7% reported involvement in a traffic accident. Patients drove less hours and shorter distances compared to the general population. The study also reported that a history of driving under the influence of alcohol or drugs was the most important factor in driving license revocation in patients with psychotic disorders as in the general population.

Patients with schizophrenia do not seem to be responsible for significant rates of road accidents (36), which may be explained by the fact that they drive less frequently and the actual incidents are more likely to be caused secondarily by alcohol and substance abuse than by the psychotic disorder. With regard to antipsychotic medication, it is known from simulator driving studies that it can have negative effects on psychomotor function, such as slower cognitive processing and slowed reflexes, but less so than benzodiazepines and tricyclic antidepressants (37). On the other hand, patients benefit from treatment that improves their positive symptoms and thus their cognitive functions, so compliance with pharmacotherapy is a prerequisite for the ability to drive (38). Also research studies suggest superiority of atypical antipsychotics compared to neuroleptics on skills related to driving ability. However, in everyday life a significant proportion of patients with schizophrenia have significant dysfunction and deficits in their ability to drive due to their disorder itself (25).

BIPOLAR DISORDER & DRIVING

A percentage of 30% of Canadian psychiatrists agree that bipolar disorder is the mental disorder that most often affects safe driving (10). Levine et al. (2001) reported that 55% of 170 patients with bipolar disorder admitted past or present inability to drive (39).

An increased rate of traffic accidents has been associated with lithium treatment among elderly patients (40). However, it has also been suggested that treatment with similar medication may have positive effects on driving ability (16).

In a clinical comparative study of 24 (12 men, 12 women) outpatients with bipolar disorder, only 45% of euthymic bipolar patients had scores sufficiently high to drive safely according to the German guidelines, and 17% of patients were found to have severe impairment in driving ability.

Recent studies report high rates of bipolar patients among offenders who were driving under the influence. A lifetime prevalence rate for bipolar disorder of 7.3% was reported among repeated drunk-driving offenders (41), 1.7 times higher than the general population (42,43), taking into account the sex ratio.

DEPRESSION & DRIVING

It has been reported that depression can affect driving ability, but the literature examining these effects is limited and inconclusive. Since depression is one of the most common mental disorders with an increased prevalence in the general population, the effects on driving behaviour and the increased likelihood of causing road accidents may result in substantial impairments in many areas of driving safety and quality of life for these patients.

Patients with mental disorders, particularly in the acute phase, have obviously impaired cognitive functions, inability to concentrate and psychomotor retardation, functions that are considered essential for safe driving. Approximately 80% of inpatients with depression have a driving license and 70% of them drive regularly (44). Medical guidelines urge caution against driving in patients with psychiatric disorder in the acute phase (45-47).

Research studies suggest that patients with depression are at increased risk of premature mortality (48,49). Contrary to expectations, this increased risk associated with depression is not explained by suicide (49,50). Suicides in traffic accidents are estimated at only 2% of all suicides (51), but at higher rates in all fatal traffic accidents with estimates of up to 15%, averaging 8 to 9% (52, 54).

I. EPIDEMIOLOGICAL STUDIES IN PATIENTS WITH DEPRESSION

Studies focusing on depressed patients have been case-control or prospective. They examined the impact of depression on (1) the risk of causing traffic accidents and the likelihood of culpability and (2) aggressive or dangerous driving.

Several case-control studies investigated the impact of depression on the risk of causing traffic accidents. The results of the studies were mixed, with the majority of studies suggesting depression as a contributing factor for increased traffic accidents (55-58). A case-control study (59) of drivers aged over 65 years old reported that drivers who were injured were more likely (OR = 1.7) to have been diagnosed with depression during the 3 years prior to the accident compared with non-injured drivers with similar demographic characteristics. Sims et al. (2000) followed a cohort of 174 elders from 1991 to 1996 (60). Drivers who reported symptoms of geriatric depression in 1991 were 2.5 times more likely to have been involved in a car crash in the following 5 years. Similarly Cross et al. (2009) with data from 4 prospective studies of elderly drivers reported that depression was associated with an increased risk of being involved in a traffic accident (61).

A study (62) examined reports of 542 fatal road accidents in Finland. The results showed that psychiatric disorders, including depression, were diagnosed more frequently among dead drivers who were considered to be the main culprits in road accidents compared with all other driver groups, which included drivers who survived and were considered to be the main culprits in road accidents and for the loss of life of the passengers.

A study (63) of heavy goods vehicle drivers in Australia reported an association between depressive symptoms and driving ability. Severe and extreme depressive symptoms were associated with more than a fourfold increase in the risk of being involved in a road traffic accident (OR = 4.4) and a fivefold increase in the risk of being almost involved in a road traffic accident (OR = 5.0).

II. EPIDEMIOLOGICAL STUDIES IN PATIENTS WITH DEPRESSION - AGGRESSIVE AND DANGEROUS DRIVING

Aggressive and dangerous driving behaviour contributes to the increased number of traffic accidents with injuries, as well as fatalities (64,65). Studies examining the association between depression and aggressive and dangerous driving behaviour have evidenced explicit results, predominantly supporting a positive association.

A study in the general population in Ontario (66) attempted to predict involvement in serious episodes of aggressive driving behaviour, perpetrator behaviour as well as victim behaviour. The results indicated that the presence of psychological distress significantly increased the odds of experiencing victim behaviour as well as involvement in serious episodes of aggressive driving behaviour.

In another study (67) by Yu et al. (2004) in a sample of 431 participants attending alcohol and drug rehabilitation programs, following a conviction for driving under the influence, depression predicted dangerous driving behavior (increased speed, traffic light and other traffic signal violations), as well as aggressive behavior (failure to maintain a safe distance, and other broad spectrum aggressive driving behaviors).

Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), following struc-

tured psychiatric interviews reported that a diagnosis of major depression was associated with an increased risk of reckless driving behaviour (adjusted OR=1.16), (68).

In summary, the majority of epidemiological studies provide evidence suggesting that depression contributes to aggressive driving behavior. Neurobiological findings suggest that depression and aggression share a common etiological mechanism, namely the serotonergic system's dysregulation. Furthermore, epidemiological evidence suggests that depression can have detrimental effects by increasing the risk of being involved in a road traffic accident. Additional research is needed to identify the factors that mediate or mitigate these effects to explain the conflicting findings.

III. EXPERIMENTAL STUDIES ON DRIVERS WITH DEPRESSION

Several experimental studies have examined the effects of depression on cognitive and psychomotor function related to driving ability (69, 70).

A semi-experimental study was conducted by Bulmash et al. (2006) that compared driving abilities in a simulator in 18 outpatients with a diagnosis of major depression compared with 29 controls. The sample of depressed patients not receiving medication had a slowed reaction time and increased number of collisions compared to controls (71).

Brunnauer et al. (2008) studied 40 inpatients with depression, administered either mirtazapine or reboxetine (random assignment) and assessed driving ability in a simulator before and after medication initiation. Compared with a sample of 10 controls, depressed patients before treatment had significantly more crashes in the simulator. After 14 days of treatment there was significant improvement in the patients' driving ability (72).

Wingen et al. (2006) assessed driving ability in 24 depressed patients who were treated with SSRI's or SNRI's for 6-52 weeks, compared to controls. The results showed that depressed patients had greater lateral deviation as well as difficulty adjusting to speed changes of the vehicle ahead. The authors concluded that impairment in driving ability in depressed patients was more likely due to residual symptoms of depression rather than the side effects of the medications (73).

Results from experimental studies in depressed patients demonstrate deficits in driving ability (slower reaction time, attention deficits, difficulty following the vehicle ahead, stopping distance and greater lateral deviation, and thus increased likelihood of collision probability).

ADHD & DRIVING

ADHD includes symptoms such as difficulty maintaining attention and easy distraction, deficits in impulse control and hyperactivity. Inattention and difficulty maintaining attention were found to account for ¼ of road traffic collisions (74).

In a review article on cognitive deficits, inattention and impulsivity were associated with problems in driving behaviour. Slower cognitive processing and easy distraction also resulted in impaired driving. In theory, impulsivity predisposes to driving over the speed limit and dangerous manoeuvres which, combined with problems in attention, increase risk (75).

Driving involves complex cognitive functions such as perception, motor coordination, and executive functions that are commonly compromised in ADHD patients (76,77), resulting in impaired driving ability and dangerous driving (78). Studies report that adults with ADHD are more likely to be involved in a driving accident, injuries, fines, and driver's license revocation (79-82). One study reported twice the likelihood of involvement in traffic accidents among drivers with ADHD compared with drivers without ADHD (83).

In a recent meta-analysis (1) the relative risk for ADHD patients in terms of involvement in traffic accidents was 1.54 (1.12- 2.13) (in the IMMORTAL study, T. Vaa, 2003). This association is most evident for traffic violations and fines, rather than for motor vehicle collisions (84).

A review article (2006) with results from prospective and retrospective studies reported a relative risk of 1.88 (1.42, 2.50) for patients with ADHD and traffic collisions (85).

People with ADHD are more likely to exhibit characteristics of antisocial behaviour and alcohol abuse (86,87) and other studies have suggested that difficulties in anger control are common in adults and adolescents with ADHD (88), so there is an increased predisposition to aggressive driving behaviour.

In a more recent meta-analysis, Vaa (2014) reported that the relative risk for traffic accidents in drivers with ADHD was 1.36 but decreased to 1.23 when mileage was taken into account since people with ADHD drive long distances compared to drivers without ADHD (89). The main factor contributing to the increased relative risk was speed limit violations. The relative risk was not significant when property damage was taken into account (RR=1.07) but was significant 1.80 ($p<0.05$) for human injuries. In drivers with ADHD and comorbidities the relative risk was 1.86 ($p<0.05$) and 1.31 (non-significant) in drivers with ADHD without comorbidities.

Comorbidity with oppositional- defiant disorder and conduct disorders often complicate the relationship between ADHD and driving behaviour. Males with conduct disorder and antisocial characteristics are known to have difficulties in driving (90-93), and this may in part modulate the relationship between ADHD and driving behavior.

Barkley et al. (1996, 2002) in studies (80,92) reported an increased incidence of dependence and alcohol abuse in patients with ADHD. Several observational studies reported an increased frequency of driving under the influence in people with ADHD. The effects of alcohol use on executive functions are similar to the effects of ADHD, i.e., disinhibition and increased impulsivity (94). Alcohol use appears to impair mainly attention in patients with ADHD.

Weiss et al. (1979), who followed the course in individuals with ADHD from childhood to adulthood, found that both adolescents and adults with ADHD were more likely to be involved in traffic accidents compared to individuals with-

out ADHD (95). In addition, Fischer et al. (2007) reported that young adults with ADHD had more fines for careless driving and driving without a license, were involved in a greater number of minor accidents, had more license revocations, more impulsive errors, and less safe driving behaviours compared to the general population (82).

Studies of adults with ADHD have reported an increased likelihood of traffic violations, crashes, and even increased severity of crashes and driver's license revocation compared to patients with other mental disorders (93,96) or controls (80,92,96,97).

Experimental studies and a review article (2013) suggested that psychostimulants and other medications prescribed for the treatment of ADHD improved driving ability (98). Extended-release medications are more effective compared to immediate-release medications since they achieve therapeutic levels during nighttime driving as well, improving attention and reducing impulsivity (99). Previous reviews (81,85) based on only 7 randomized trials concluded that treatments in ADHD patients improve driving behaviour. Subsequently, Cox et al. (2011) validated the findings (78).

A research study (2017) of 2 319 450 ADHD patients showed that traffic accident rates were lower when patients received their treatment and suggested that rates of up to 22.1% of traffic accidents could have been avoided if patients had received their treatment during follow-up (January 2005-December 2014) (100). Considering the high prevalence of ADHD (5.3% in children and 4.4% in adults worldwide) and its association with traffic accidents, these findings are important for prevention purposes in order to reduce morbidity and mortality (101,102).

Experimental simulator studies report that individuals with ADHD are more likely to be involved in a road traffic collision during monotonous driving conditions compared to controls (103), often associated with fatigue and more likely occurred in the early morning or late afternoon (104). Two recent studies, one with a simulator (105), and the other in a car equipped with a camera recording driving faults (106), showed that untreated ADHD patients had more line crossing errors, more frequent driving speed changes, more crashes and sudden braking compared to controls. Distractions such as texting on a mobile phone while driving additionally impaired driving ability in ADHD patients (105).

Driving in a simulator for people with ADHD suggested an increased frequency of impulsive behaviors, inattention, and reduced ability to adjust to changes in driving conditions. Fried et al. (2006) reported decreased neurocognitive processing speed in individuals with ADHD who exhibited risky driving behavior (107).

Nuclear deficits related to response inhibition, working memory, and flexible response and decision-making strategies appear to be involved. Immature or poorly developed executive functions possibly explain risky behavior and impaired ability in risk assessment.

A study (2008) compared adults with ADHD to adults under the influence of alcohol in a driving simulator and demonstrated that the cognitive and behavioural deficits associated with ADHD may impair driving ability in a manner similar to that which impairs the ability to drive under the influence of alcohol. Furthermore, alcohol in drivers with ADHD causes additional impairments that make driving unacceptable even at concentrations below the legal limit (108).

Studies rarely include people with hyperactive type ADHD, so the effects of pharmacotherapy cannot be evaluated in these patients, who are at least theoretically more prone to impulsive driving offences than to inattentive errors with more serious consequences (89). The most recent longitudinal study in subjects with hyperactive type ADHD (82), reported slowing and variation in reaction times, impulsive errors, course deviations, and crashes during driving in a simulator compared with a control group.

Young drivers with ADHD were 2 to 4 times more likely to be involved in traffic accidents (79,109,110), 3 times more likely to be injured (79), 4 times more likely to make a driving error (109), and 6 to 8 times more likely to have their driver's license revoked (93,109). Other co-occurring conditions that increase risk are uncontrolled anger, aggressive and dangerous driving (111-115), not wearing a seat belt, using alcohol and drugs, and having friends who endorse such behaviours, lack of parental care, and the presence of persistent behavioural and emotional difficulties (116-119).

The results suggest that ADHD has a negative impact on driving ability, and attention deficits, noncompliance with regulations, reduced inhibition, and easy distractibility are mechanisms likely to be involved in conjunction with an increased likelihood of comorbid conditions.

ALCOHOL AND DRIVING

The Centers for Disease Control and Prevention (CDC) and the National Highway Traffic Safety Administration (NHTSA) have issued a report on the effects of drinking alcohol and driving, effects that are preventable based on Blood Alcohol Concentration (BAC) measurements. In addition to the reduction in driving ability, the American Medical Association's Council for Scientific Affairs concluded that there is a direct correlation between serum alcohol levels in drivers and their likelihood of being involved in a traffic accident. With a BAC of 0.080-0.089, there was almost twice the risk of traffic accidents (120) compared with drivers with zero BAC (RR 1.88, 95% CI: 1.16-3.05).

Both young age and male sex increased the relative risk (121). Age and sex modified the relationship between BAC and culpability in traffic accidents. Female drivers were more likely to be at fault for any given BAC, and both young (under 21 years) and older drivers (over 60 years) were more likely to be at fault compared with drivers between 21 and 60 years old (122).

In America, driving under the influence of alcohol is responsible for 13,000-18,000 deaths per year, accounting for 40% of all traffic fatalities (123). The rate equates to 3 deaths every 2 hours in alcohol-related traffic accidents and one death every 51 minutes. The majority involves drivers and passengers, but alcohol-related road accidents are more likely than non-alcohol-related accidents to involve pedestrian fatalities. In 2010, driving under the influence of alcohol caused 40.6% of all deaths but 47.2% of pedestrian-related deaths.

The 'gold standard' for other potential risk factors in driving is drunk driving with a BAC of 80 mg/100 ml (0.08%). In America, the law prohibits driving with a BAC greater than or equal to this BAC (124). This limit was set because of results from simulator driving studies that reported serious deficits at a value greater than or equal to this value (125, 126) and from epidemiological studies of traffic accidents that indicated a significantly increased risk at a value greater than or equal to this value (126,127; NIAAA, 1996). This limit has been established and is directly related to road safety.

The impairment of driving ability caused by alcohol is considered the most important factor in causing road accidents, particularly fatal ones (127). Blomberg et al, in a case-control study, found that overall crash risk increases significantly at BACs .04-.05 and this increase rises dramatically at BACs above .15. At BAC values above .195, the same investigators reported a 120-fold increase in traffic accident risk compared with a zero BAC (128).

Accident reports indicate that up to 40% of fatal traffic crashes in the US involve alcohol (127). Information from the Fatality Analysis Reporting System in 2002 showed that the average BAC in drivers in fatal crashes was 173 mg/dl, more than twice the legal limit (127). Laboratory studies confirm that average doses of alcohol impair a wide range of functions related to driving ability (125, 129-131). Alcohol slows reaction time, (125), decreases upper limb stability (132), reduces inhibitory control (133), and reduces the driver's tracking ability during tests (134). Deficient functionality occurs at BAC values of 50 mg/100 ml, with higher BAC resulting in greater functional impairment (124). Individual differences in the effect of alcohol have been identified in experimental studies (135, 136). A study (134) found that individuals with impaired driving abilities before alcohol consumption had the greatest effects after consumption.

According to a study (2008) positive BAC in drivers under 21 was associated with a higher, than would be predicted from the additive effect of BAC and age, risk of car crashes (137). It appears that the two mechanisms act synergistically, possibly because of the inexperience of young drivers in driving and alcohol use, and because young people in this age group who choose to drive under the influence are likely to have personality traits that predispose them to dangerous driving and involvement in traffic accidents.

From previous studies, the direct effects of alcohol consumption on driving ability were known (138,139), and the likelihood of traffic collisions increased exponentially with increasing serum alcohol levels (140-142).

Patients with chronic alcohol use disorder are almost twice as likely to have a road traffic collision (143-147) and the risk of fatality as a consequence of a road traffic accident is also increased (148). Smart (1969) noted that in patients with severe and problematic alcohol use, the likelihood of being involved in a traffic accident is increased primarily or exclusively because of the harmful effects of acute alcohol consumption, while less is known about other factors that may increase the risk (146).

Haberman (1987b) reported that while about 10% of the population in America is considered to have a chronic alcohol use disorder, among drivers involved in fatal traffic accidents the figure is 17% (149).

Severe alcohol use and abuse can lead to mental disorders - depression (150-153) which also has an impact by increasing the likelihood of road accidents (154,155).

Vingilis and Wilk (2008), based on a longitudinal population study in Canada, reported that alcohol abuse, not total consumption, was associated with injuries in traffic crashes (156). Evidence suggests that alcohol abuse or dependence also predicts impaired driving, including road traffic collisions. Fear et al. (2008) in armed forces personnel in England noted high Alcohol Use Disorders Identification Test (AUDIT) scores (157, 158) associated with dangerous driving by means of exceeding the speed limit and not wearing a seat belt (159).

A study (154) of a representative sample (n = 4935) of adults 18 and older examined the effects of alcohol on self-reported traffic crashes in the past 12 months considering demographic and other driving related factors. In addition to the direct effects of alcohol consumption on driving ability, it has been suggested that alcohol consumption may increase the likelihood of traffic crashes in other ways (146,155). Self-reported driving immediately after alcohol consumption reflected specific driving behaviors which significantly predicted the likelihood of reporting involvement in a traffic collision (OR = 1.51). The effect of this variable remained significant after the addition of other variables, suggesting that driving immediately after drinking alcohol was the most significant predictor of traffic crashes.

The AUDIT alcohol consumption subscale, which included (frequency, number of drinks, frequency of drinking 5+ drinks on one occasion), was not found to be a significant predictor of road accidents when the factor of driving immediately after drinking alcohol was taken into account, and this observation leads to the conclusion that any effect of drinking alcohol alone on road accidents was determined by whether the driver consumed alcohol and then immediately drove. Also, as the symptoms of alcohol dependence increased, so did the reports of traffic accidents (for every one point increase in AUDIT dependence scores, the probability of reporting a traffic accident increased by 13%).

Alcohol dependence brings about many physical and psychological changes that can have an independent effect by increasing the likelihood of road accidents (changes in CNS function as well as emotional changes, etc.) (154,160,161). Among those convicted of driving under the influence, high rates of traffic crashes were consistent with elevated rates of problematic alcohol use, even though alcohol dependence scores were relatively low (162,163). Although individuals with problem alcohol use generally exceeded habits of social drinkers, they did not display physical changes resulting from alcohol dependence (160).

Individuals who exhibited problematic alcohol use or abuse but not dependence may have personality traits that differentiate them from social drinkers, such as displaying risky behaviours or seeking new experiences (164,165). These individuals may also show physical and psychological changes that can have an independent effect by increasing the likelihood of road accidents (166).

A study (n=11,017, 1999) on the association between the age of onset of driving immediately after drinking alcohol, psychiatric morbidity and/or criminality, reported that almost half of violent offenders with psychiatric morbidity had

an experience of driving immediately after drinking alcohol before the age of 18. The younger the age of this experience, the greater the likelihood of violent behavior and mental illness (167).

A study (2007) on the associations between crime and mental disorders among male adolescents in a representative sample of 2,712 Finnish boys born in 1981, indicated that any psychiatric disorder was associated with driving immediately after drinking alcohol (168).

In another study (2001) of the prevalence of mental disorders among 612 women and 493 men who were examined 5 years after a driving under the influence conviction, 85% of women and 91% of men reported an alcohol use disorder, compared with 22% and 44%, respectively, in a National Comorbidity Survey sample. 32% of female and 38% of male offenders had a substance use disorder, compared to 16% and 21%, respectively, in a National Comorbidity Survey sample. For offenders with an alcohol use disorder, 50% of women and 33% of men had at least one additional psychiatric disorder other than a substance use disorder, primarily posttraumatic stress disorder or depression (169).

MENTAL DISORDERS RELATED TO DRIVING UNDER THE INFLUENCE OF ALCOHOL AND/OR DRUGS

A case-control study (170) of 44,188 individuals found to have driven under the influence in 1997-2007 and 45,148 controls from the general population in Finland reported that psychoactive substance use disorder increased the risk of driving under the influence. Psychiatric disorders with onset in childhood and adolescence were strong predictors of drunk-driving and bipolar disorder and depression predicted driving under the influence of alcohol and prescribed psychoactive substances. The risk was highest immediately after admission to hospital with a psychiatric diagnosis and decreased over time. Women with mental disorders had a higher risk of driving under the influence compared to men.

A study (2012) among 1,134 drivers (171) evidenced the presence of any psychiatric disorder in 40.5% of drivers with recent alcohol or drug use compared to 12.9% among other drivers. Drivers with recent alcohol or drug use were 2.5 times more likely to have a psychiatric diagnosis (CI: 1.8-3.6, $p < 0.001$).

In a long-term follow-up study retrospectively (over 16 years) of California inpatients from 1990 to 2005 with diagnoses of substance use disorders: methamphetamine (n = 74,170), alcohol (n = 592,406), opioids (n = 68,066), cannabis (n = 47,048), cocaine (n = 48,949), or multiple psychoactive substances (n = 411,175), the sex-, age-, and race-specific standardized mortality ratios (SMRs) for traffic fatalities were higher for all substance use disorders: alcohol (4.5, 95% CI, 4.1-4.9), cocaine (3.8, 95% CI, 2.3-5.3), opioids (2.8, 95% CI, 2.1-3.5), methamphetamine (2.6, 95% CI, 2-3.1), cannabis (2.3, 95% CI, 1.5-3.2), and multiple psychoactive substances (2.6, 95% CI, 2.4-2.9). Men and women had similar SMRs for traffic fatalities, possibly due to lower numbers of traffic fatalities in the female general population, with the exception of the cannabis group where men had more than double the SMR compared with women (172). Approximately 40-60% of fatal crashes involved drivers, but previous research has reported that drug users are often passengers in cars where the driver is under the influence of alcohol or drugs (173).

Approximately 4.2% of the US population (10.6 million) reported driving after using drugs in the past 12 months (174), but this profile of driving under the influence increases dramatically in special populations, such as young drivers (175-177), intravenous drug users, and drug users seeking treatment in the community (144,178,179).

Toxic drug screen of people injured in road traffic accidents and fatalities often detect the use of illicit drugs, or prescription drugs, with cannabis being detected most frequently (2-32%), followed by benzodiazepines (2-15%), cocaine (0.4-11%), amphetamines (0.8-6%) and opioids (0.5-11.5%), (180-190).

A recent meta-analysis investigating the risk of crashes associated with driving under the influence showed an increased risk of fatal crashes associated with prescription of psychoactive drugs with depressant properties [benzodiazepines, tricyclic antidepressants and opioids (191,192)], amphetamines and cocaine (193).

Statistical studies in the general population report that the majority of road fatalities involve males (194,195). Males are more likely than females to exhibit risky driving behaviour (195), and male drug users are more likely than females to report injury in road traffic accidents while driving under the influence of drugs (179).

The high rate of fatal road accidents due to alcohol or drug use is a major concern for road safety, public health and health care providers. Drug users report driving immediately after using drugs at rates as high as 70% during the previous week (196), and at rates ranging from 82%-88% during the previous year (179,197). Rates of 20-30% of substance abusers report involvement in a traffic accident while driving under the influence (179,196,197). Furthermore, drug and alcohol users not only underestimate the effects of drugs on driving, but also believe that drug use improves their driving skills (173), which could be a target for treatment interventions.

A recent case-control study reported that individuals with toxicology tests positive only for amphetamines/methamphetamine had a relative risk of 20.9 (95% CI 7.3-60.0) for fatal traffic crashes (184).

A study from Canada reported that 18.9% of people who had used cocaine in the past year had been involved in a traffic accident and that cocaine users had more than twice the frequency of traffic accidents compared with non-users (198).

The use of multiple psychoactive substances is often detected in both traffic injuries and fatalities. It is estimated that up to 20% of people who are injured or die in traffic crashes were under the influence at the time of the incident (185,188) and that multiple psychoactive substance use increases the risk of serious or fatal traffic crashes in proportion to the use of other toxic substances alone, with the exception of heavy alcohol use (184,188,199).

In a Los Angeles study of drivers in fatal traffic accidents conducted in 1987-1988, alcohol was detected in 41%,

barbiturates in 2%, cocaine in 8%, PCP in 0.5%, and cannabinoids in 18.5% of drivers. Approximately 25% of drivers with positive alcohol levels also had one or more toxic substances detected, with cocaine and cannabis as more frequent combinations (200).

In Spain, in a study of fatal road accidents in 1991-2000, one or more psychoactive substances were detected in 50.1% of drivers. Alcohol was most frequently detected (43.8%) then illegal toxic drugs (8.8%) and prescription drugs (4.7%). Cocaine metabolites were the most commonly detected illicit substances (5.2%), while benzodiazepines were the most commonly detected prescription drugs (3.4%). Combinations of illicit and legal substances were frequently detected (201).

In Great Britain, 4.7% of 386 randomly selected drivers tested positive for substances of abuse compared with 22.9 % of 411 drivers who were involved in fatal road accidents (202,203).

In a study in Victoria, Australia in 2009 (204) of injured drivers attending a hospital, 12.5% of them were found to have used illicit substances, with cannabis being the most common (9.8%), methamphetamine (3.1%) and MDMA (0.8%). In another extensive study (205) of a random sample of drivers in Victoria in 2004-2005, 2.4% tested positive for use, 2.1% for methamphetamine, 1.3% for MDMA, 0.7% for THC, and 0.6% for THC and amphetamines. Overall, 80% of the positive toxicology referred to males.

Importantly, driving under the influence of illicit drugs appears to have a rising trend. The aetiology is multifactorial and appears to involve mechanisms of compulsive, regular use and the illusion that driving under the influence is safe. Recent research demonstrates the ways in which driving under the influence of psychoactive substances is responsible for deaths and serious injuries in road accidents in Europe.

Driving under the influence of toxic substances is not as well studied as driving under the influence of alcohol, both because of the variety of toxic substances and the effects they cause. Some substances are depressants and may cause drowsiness and attention deficits, while others may have stimulant effects, increasing confidence and impulsivity (speeding, reckless driving, lane drifting, traffic light violations).

The international study (2012) Driving Under the Influence of Drugs (2006-2011 DRUID project -DRUID) collected data on driving under the influence of drugs in Europe, reported on how toxic substances influence road accident rates and the prevalence of use of different toxic substances, in different individuals, in different regions. Some substances that influence driving are legal, available as prescription drugs, taken to treat various diseases. But some people may be taking these substances incorrectly, in dosages and combinations. Driving under the influence of drugs is of less interest compared to driving under the influence of alcohol, which is more common as a cause of fatalities and injuries in road accidents than driving under the influence of psychoactive substances. The DRUID study reported that alcohol was detected in 24.4% of drivers who suffered serious injury and 32.8% of drivers who died, while the use of illegal and legal psychoactive substances was detected in 15.2% and 15.6% respectively (206).

PREVALENCE OF USE OF PSYCHOACTIVE SUBSTANCES IN DRIVERS

According to the DRUID international study in 2012, the estimated average prevalence among drivers in the general population in Europe of the use of all illicit toxic substances was 1.9% (amphetamines, cocaine, cannabis and illicit opioids), and for prescription drugs 1.36%. In contrast, the prevalence of alcohol use was 3.5% at levels > 0.1 g/L and 1.5% at levels > 0.5 g/L. Combinations of toxic substances or prescription drugs were at 0.39% and combinations of alcohol with toxic substances or prescription drugs were at 0.37% (207). Of course, this study investigated a limited number of prescription drugs.

Approximately 4% of drivers in Europe drive after taking psychoactive substances and/or prescription drugs, with the exception of GHB and antidepressants (208). Self-report rates for driving under the influence are higher, ranging from 3% in Finland to 16% in France, with an average for Europe of 11% (209,210).

Psychoactive substances predominate in the 15-34 age group and males tend to use psychoactive substances more frequently than females (211). Despite an upward trend in substance use among young people around 1990, it has remained largely unchanged since 2003 (212). Prescription psychoactive drugs are used primarily among middle-aged men and older women and are found during morning driving (213).

Psychoactive drugs increase traffic crash and fatalities rates and serious injuries as a consequence of traffic crashes -KSI (killed and seriously injured) as follows: amphetamines (alone) 5-30 times higher, cocaine 2-10 times higher, cannabis and illicit opiates 1-3 times higher (208). Despite the increased prevalence in cannabis use in drivers, it is estimated that amphetamines are responsible for about half of fatal traffic crashes related to illicit drug use, with cannabis considered responsible for 1/5 of fatal traffic crashes (214). The use of multiple psychoactive substances in combination and simultaneously significantly increases risk and is often found among seriously injured or killed drivers (215).

EFFECTS OF NEUROLEPTICS ON DRIVING ABILITY IN PATIENTS WITH SCHIZOPHRENIA

The effects of psychotropic drugs in causing road accidents are difficult to be precisely determined. Studies in many countries report rates of 8% to 10% of drivers injured or involved in road accidents whose tests revealed the use of psychotropic drugs (216).

On the other hand, it is practically impossible to say with certainty whether or not these substances were the cause of the accidents, since the underlying pathology can create problems such as inattention and reduced alertness. There is also the possibility of aggressive tendencies or sui-

cidal behaviour (217).

There is difficulty in separating the disability caused by the psychiatric disorder from the side effects caused by antipsychotic medication. Evidence suggests that atypical antipsychotics improve cognitive functions and psychomotor performance, and a recent meta-analysis has shown that some atypical antipsychotics are superior to classical antipsychotics (218). Approximately 30-40% of patients treated with haloperidol or flupenthixol had severe deficits regarding driving ability, compared with 15-30% when treated with atypical antipsychotics (24).

A review article (2005) of 11 studies (219) reported that schizophrenia patients treated with various neuroleptics had impaired performance compared to healthy controls in several domains related to driving ability. In a simulator study (30) they drove at significantly lower speeds compared to healthy controls, deviated more frequently from the median line and were 2.5 times more likely to be involved in a traffic accident (42 vs. 16%). Only 10% of patients treated with neuroleptics had no deficits in driving ability during their last 2 weeks of hospitalization (220). Grabe et al. noted that patients on clozapine compared with patients on neuroleptics had better performance (221). Also in patients treated with haloperidol and risperidone, treatment with an atypical antipsychotic showed a benefit in psychomotor and driving ability (222).

Brunnauer et al. (24) studied 120 schizophrenic patients before discharge and patients treated with classic antipsychotics performed worse compared to patients treated with atypical antipsychotics in terms of reflexes, orientation, attention and monitoring. One third of the sample had no severe deficits.

According to a simulator study (2009) of 80 schizophrenic patients, pre-discharge, on antipsychotic medication, 25% were found to have severe deficits in driving ability. There were differences between groups according to the medication followed, with superior efficacy of atypical antipsychotics. After adjusting for age, psychopathological symptoms and extrapyramidal side effects, differences in psychomotor performance were mainly due to concentration and alertness. Patients under amisulpride or quetiapine seemed to have an advantage in driving compared to patients under haloperidol and flupenthixol (25).

Many studies reporting on the effects of drugs on driving involve normal controls taking the drugs under study usually once before driving. It is clear that acute administration of antipsychotics to healthy volunteers induces sedation and impairs visuomotor coordination as well as attention function and apparently results in adverse effects on driving ability.

In a non-randomized clinical study of 30 hospitalized schizophrenic patients (26) receiving sertindole (n = 10), risperidone (n = 10) or quetiapine (n = 10) before discharge, 26% had very severe deficits in driving ability and 64% had performance that did not allow them to drive safely according to road safety regulations in Germany. As to driving ability, no differences were found between patients treated with either one of the 3 antipsychotics. A large proportion of patients in remission were deemed to be unable to drive despite stabilization with atypical antipsychotics.

EFFECTS OF ANTIDEPRESSANTS

Up to 80% of hospitalized depressed patients have a valid driver's license and 70% of these patients drive regularly (18).

Tricyclic antidepressants (TCAs) with their sedative properties impair driving ability when administered once in healthy volunteers.

A case-control study in France demonstrated that the prevalence of antidepressant use in drivers involved in road traffic accidents was 1.8%, compared with 1.1% in the control sample (223).

In another study in Norway (224) investigating whether antidepressants increased the risk of being involved in a road traffic accident, it was reported that from April 2004 to September 2006, 20,494 road traffic accidents with injuries occurred, including 204 and 884 incidents where the driver was taking sedative antidepressants or newer non-sedatives, respectively. The risk of a road traffic accident increased for drivers taking sedative antidepressants (SIR = 1.4, 95% CI = 1.2-1.6) or non- sedative (SIR = 1.6, 95% CI = 1.5-1.7). Older adults taking sedative antidepressants had more than twice the risk of being involved in a motor vehicle crash (225,226). Tricyclics in particular at the onset of treatment significantly affect driving ability (227).

In a study assessing the risk of traffic accidents associated with antidepressant prescription (228) in 72,685 drivers involved in a serious traffic accident in France, from July 2005 to May 2008, 4% of drivers were taking at least one antidepressant on the day of the accident. The results showed that there was a significant association between the risk of being at fault for the accident and the prescription of antidepressants (OR=1.34 (1.22-1.47)). The risk of car accident increased after starting antidepressant treatment (OR=1.49 (1.24-1.79)) and after changing it (OR=1.32 (1.09-1.60)).

A review article (2012) of 21 published studies (1980-2011) regarding commonly prescribed antidepressants and driving ability concluded that there is evidence that SSRIs (citalopram, esitalopram, fluoxetine, fluvoxamine, sertraline, paroxetine) and the SNRI venlafaxine do not cause adverse effects on driving ability. Acute administration of mirtazapine induces deficits that are reduced to some extent when given at night and subside after repeated administration in healthy volunteers. Patients apparently benefit from treatment with newer antidepressants, yet some of them do not match the driving performance of healthy volunteers (229).

EFFECTS OF SECOND GENERATION ANTIDEPRESSANTS

Of the 21 studies in the 2012 review article (229), 14 were double-blind controlled trials in healthy volunteers and 7 in samples of depressed patients. A total of 341 healthy volunteers, 33% female, with a mean age of 31 years (range 21-67), and 305 depressed patients, 54% female, with a mean age of 46 years (range 20-78), were included. 2 patient studies examined the long-term effects of treatment with tri-

cyclics, SSRIs, venlafaxine, and mirtazapine on psychomotor functions related to driving ability 230) or actual driving behavior on road tests (231).

Most studies demonstrated that the majority of depressed patients under stable psychopharmacological conditions performed worse compared to healthy volunteers. Approximately 16% of patients in the study by Brunnauer et al. were severely impaired, failing more than 40% of tests, and were considered unfit to drive (230). There appears to be an advantage for patients receiving SSRIs or mirtazapine compared with patients receiving tricyclics. It was suggested that deficits in driving ability after long-term antidepressant treatment could be attributed to residual depressive symptoms rather than to side effects from antidepressants (231).

All studies with SSRIs included in the review article (229) involved healthy volunteers. Acute or short-term administration of citalopram (232), esitalopram (233), fluoxetine (234-236), fluvoxamine (237), paroxetine (238-241) had no adverse effects on psychomotor activity, simulator driving, or road driving tests in healthy volunteers. In one study, long-term effects, over 5 weeks with fluoxetine administration, (242) showed no adverse effects on simulator driving in healthy volunteers. A randomized controlled crossover study with placebo and venlafaxine in healthy volunteers did not demonstrate acute or short-term adverse effects on road driving (243). However, 19% discontinued treatment due to side effects.

Three healthy control studies and 2 patient studies investigated the effects of mirtazapine. Acute administration at daily dosage impaired psychomotor and driving ability on the road (233) and simulator tests (244). When administered at night, side effects were absent or mild. Short-term administration had no effect on driving ability apparently due to tolerance (244,245). Mirtazapine-treated patients showed significant short-term improvement in psychomotor and simulator driving, suggesting that patients in partial remission on treatment perform better than patients remaining untreated. Of course, the performance of patients in incomplete remission was worse than that of healthy volunteers (72, 246).

SSRIs, and of the SNRIs, venlafaxine in acute or short-term administration, do not appear to produce adverse effects on psychomotor performance related to driving ability (247), on simulated driving (234,237,238,240,241,242,248), or on road driving tests (234,237,238,240,241,242,248).

There is probably an advantage of treatment with SSRIs, compared with tricyclics, but antidepressant treatments do not achieve retrieval of driving ability, at least for the majority of depressed patients (72,230,231). Under stabilization doses, pre-discharge, there were no significant differences in the percentages of patients able to drive according to road safety criteria (72,230,249,250). However, patients who also received benzodiazepines had long-term deterioration in driving ability (251).

In a clinical study of 100 hospitalized patients with major depression (230), in trials under stabilization doses, before discharge, 24% did not show significant deficits in psychomotor activity. 60% were found to have mild to moderate deficits and 16% were found to have severe deficits in driving ability. Patients treated with SSRIs or mirtazapine performed better overall compared to patients receiving tricyclics. Differences mainly existed in terms of reflexes, stress tolerance and selective attention. No significant differences were found between patients treated with venlafaxine compared to patients receiving tricyclics. A superiority of mirtazapine with improved performance was found.

In a randomized case-control study of pre-discharge depressed inpatients (252) for effects on psychomotor activity related to driving ability from agomelatine and venlafaxine treatment (day 28), 72.5% were deemed fit to drive in road tests (day 28). No significant drug differences were found and patients' performance was worse than that of healthy volunteers.

A patient-control study in the Netherlands, with 3,963 patients and 18,828 controls (253), reported a significant association in the likelihood of a road accident and exposure to anxiolytics (OR=1.54, 95% CI 1.11, 2.15), and SSRIs (OR=2.03, 95% CI 1.31, 3.14). A statistically significant increased risk was also seen in chronic anxiolytic users, females and young users (18 to 29 years old), chronic SSRI users, females and middle-aged users (30 to 59 years old), and intermediate half-life hypnotic users (OR=6.44, 95% CI 1.44, 28.78). Contrary to predictions, a significant association was found between the risk of being involved in a car crash as a driver and receiving SSRIs (OR=2.03, 95% CI=1.31, 3.14).

A review article (2003) includes results from published studies from 1983 to 2000 (9 double-blind, crossover, placebo-controlled studies in healthy volunteers and 1 double-blind controlled study in patients) investigating the effects of antidepressants in real-world driving conditions with roadside testing (227). Changes in vehicle lateral positional deviation after administration of sedative antidepressants (amitriptyline, imipramine, doxepin, and mianserin) were reported compared with those experienced by drivers under the influence of alcohol at levels of 0.8 mg/mL or above. Driving performance returned to normal after one week of treatment, except for the treatment with mianserin. Taking sedative medication at night did not produce residual symptoms the following morning to affect driving. Non-sadative antidepressants (moclobemide, fluoxetine, paroxetine, venlafaxine) generally did not affect vehicle lateral position deviation, but when pharmacokinetically incompatible benzodiazepines were combined with non-sedative antidepressants, there were significant changes in vehicle lateral position deviation.

From experimental and epidemiological studies, in a review article, 15 of them reported on the association between SSRIs' intake and driving ability or accident risk. It is concluded that the role of SSRIs in relation to driving safety is presented as vague with contradictory findings. Inconsistency is also observed in classification systems regarding the ability to drive safely in patients receiving these drugs (254).

Prescribing second-generation antidepressants to elderly patients is associated with a modest increase in the risk of traffic accidents, particularly when combined with other drugs that impair cognitive functions. In a study in Canada of older people over 65 years old, from 2000 to 2007, a total of 159,678 were involved in a road traffic accident and 7,393 (5%) were treated with an antidepressant in the month prior to the accident (255). The relative accident risk associated

with second-generation antidepressants was 1.10 p < 0.0001, adjusted for age and other medications, and was limited to those simultaneously receiving benzodiazepines (standardized HR: 1.23, 95% CI: 1.17-1.28, $\chi 2 = 85.28$, df = 1, p < 0. 0001) or anticholinergics (standardized HR: 1.63, 95% CI: 1.57-1.69, $\chi 2 = 627.31$, df = 1, p < 0.0001), and to those who were culpable for the accident. The increased risk persisted for the first 3-4 months after the initiation of treatment and gradually declined thereafter.

Literature regarding antidepressants and safe driving ability gives conflicting results, and in conclusion the potential risk depends on factors such as, prescription of sedative antidepressants, patient's age, type of antidepressant medication and phase of treatment, dosing regimen, severity of depressive symptoms as well as co-administered medications (256).

A higher risk of hospitalization after a motor vehicle accident was for older patients receiving benzodiazepines (OR 5.3), antidepressants (OR 1.8), and opioid analgesics (OR 1.5), (257).

LITHIUM

Sixteen psychiatric outpatients in remission, receiving lithium monotherapy for at least 3 months, were compared with 22 healthy volunteers in a driving simulator, and patients presented with significant slower steering reaction times (258).

Between April 2004 and September 2006, in Norway, from data on traffic accidents and prescriptions, the overall risk of traffic accidents was not increased following prescription of lithium or valproic acid, with the exception of a 3-fold increase in risk for young female drivers treated with lithium (259).

In a comparative clinical study of 24 (12 men, 12 women) with bipolar disorder in euthymic state, 45% of patients treated with mood stabilizers could drive according to road safety criteria in Germany. 17% of patients displayed significant impairment in psychomotor performance and they were considered unfit to drive. Lithium-treated patients had significant differences in psychomotor activity related to driving ability compared with lamotrigine-treated patients (260).

BENZODIAZEPINES AND ROAD ACCIDENTS

In 1960, Murray first reported a 10-fold increase in the probability of road accidents in 68 drivers taking benzodiazepines (261).

A review article (2010) of epidemiological studies published between 1960 and 2009 investigating the association between traffic accidents and benzodiazepine exposure identified a significantly increased risk associated with long half-life benzodiazepines, increased dosage, especially during the first few weeks of treatment with these drugs (262).

Movig et al. reported (188) that among 110 injured drivers and 816 randomly selected drivers, benzodiazepines were detected in 10% of injured drivers and 1.5% of controls, and thus the risk of injury in benzodiazepine-induced traffic accidents was 5.1.

Neutel studied the relationship between first benzodiazepine prescription and hospitalization after a traffic accident in injured drivers and passengers. As reported the highest risk for car crashes was within the first few weeks after prescription (263).

Barbone et al. suggested (264) that the risk from benzodiazepines was higher for anxiolytics compared to hypnotics and long half-life (OR 2.03) compared to intermediate half-life (OR 1.19).

There was also evidence of increased risk depending on the benzodiazepine dosage. Longo et al. demonstrated a linear relationship between serum concentrations of benzodiazepines and driver culpability for traffic accidents (265).

In a review article on the effects of psychotropic drugs on driving in a simulator (13), of 44 studies, 25 investigated the effects of benzodiazepines, mainly diazepam and lorazepam, within the first 2 hours after administration. Many studies reporting on the effects of drugs on driving involve normal volunteers who are usually exposed to the effects of drugs under study once, before participating. Lorazepam produced effects objectively and subjectively between 3 and 4.5 hours. Diazepam comparatively produced fewer effects objectively, with a peak at 1.5 hours after ingestion. Subjectively it effectuated drowsiness, clumsiness, slowing of cognitive functions, as much or more than lorazepam. Harmful effects of psychotropic drugs such as benzodiazepines, classic antipsychotics and tricyclic antidepressants on psychomotor functions have been evidenced. The literature suggests a slowing of reflexes and higher levels of sleepiness, and consequently impaired driving ability.

A 1998 study examined the relationship between psychoactive drug use and road accidents (266) in 19,386 drivers involved in the first road accident between 1992 and 1995. 1731 of them were receiving psychoactive drugs. On the day of the accident, 189 were receiving tricyclic antidepressants, 84 SSRIs, 235 benzodiazepines (OR 1.62) and 47 other psychoactive drugs. The risk associated with benzodiazepines was greater when alcohol was also detected; there was a dose-dependent increase in risk and a significantly greater risk for long half-life benzodiazepines given as anxiolytics and for short half-life hypnotics (zopiclone).

A study of 1,200 drivers in Spain, aged 18-64 years (267), reported that 15% of them were under treatment with psychotropic drugs for depression, anxiety disorders and insomnia. 13.5% were taking the drugs to treat one mental disorder, while 1.5% to treat more than one disorder. 2.5% of drivers were receiving medication for depression, 2.6% for anxiety, and 3.7% for insomnia. A proportion of 8.3% of these drivers were occasionally receiving sedatives. Benzodiazepines and SSRIs were the most commonly taken medications among drivers. According to epidemiology, benzodiazepines and Z-hypnotics have a lower risk of injury (1.5-3) and a higher risk of death (5-7). Inversely, the risk for prescription opioids is higher for injury (5-8) and lowers for death (5), (268,269).

CONCLUSION

It is difficult to determine the proportion of traffic accidents involving drivers with a known psychiatric medical record or receiving psychiatric medication.

The variation in the course of psychiatric disorders and their symptoms, the level of driver‘s insight and overall behaviour, cognitive and psychomotor deficits, independently or in conjunction with medication use, and the absence of sufficient scientific evidence to provide appropriate recommendations from health professionals, are the main issues that arise during the assessment of driving ability in patients with psychiatric disorders.

The question is to determine whether the driver with a mental disorder is more dangerous than other drivers and there is currently insufficient evidence to guide this decision (270). The ability to understand and predict the factors that contribute to risky driving behaviour is prerequisite in order to improve driving safety conditions.

Road accidents are mostly predictable, potentially avoidable and the relevant authorities need to speed up efforts to increase public awareness of the value of safe driving behaviour.

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