Is it Safe to Drive a Car when Treated with Anxiolytics? Evidence from on-the-Road Driving Studies During Normal Traffic

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Abstract: *Background*. The majority of those suffering from anxiety or related disorders are outpatients, and presumably involved in daily activities such as driving a car. However, anxiolytic drugs may possess sedative properties that reduce alertness and produce sleepiness. Therefore, it must be questioned whether it is safe to drive a car when treated with these drugs.

Methods. A MEDLINE literature search (keywords *driving* and *anxiety*) and cross-references identified 14 placebo-controlled, double-blind studies that examined the effects of anxiolytic drugs on driving ability by conducting the on-the-road driving test during normal traffic. Primary parameter of the driving test is the Standard Deviation of Lateral Position (SDLP), the weaving of the car. Data from epidemiological studies was summarized as supportive evidence.

Results. After single dose administration of benzodiazepines and related GABA*ergic* compounds (*diazepam, lorazepam, alprazolam, oxazepam, alpidem, suriclone, zolpidem*) driving performance was significantly impaired. Further, although tolerance develops, driving studies show that the impairing effects of benzodiazepines and related GABA*ergic* compounds may still be present after on week of daily treatment (demonstrated for *diazepam, lorazepam, alpidem, suriclone*). Driving performance was also significantly impaired after single dose administration of TCAs (*imipramine, amitriptyline*), but after repeated use of TCAs tolerance developed to the impairing effects on driving ability. In contrast, SSRIs (*paroxetine, fluoxetine), venlafaxine*, 5HT-antagonists (*ritanserin, ondansetron*) and *buspirone* produced no significant impairment on the driving test after both acute and repeated administration. These findings were in line with epidemiological evidence.

Conclusions. Patients treated with benzodiazepines, GABA*ergic* compounds, or TCAs should be cautioned when driving a car. Driving a car when treated with buspirone, venlafaxine, 5HT-antagonists, and SSRIs seems relatively safe.

Keywords: Driving, anxiolytic, benzodiazepine, TCA, SSRI, buspirone.

INTRODUCTION

Up to 50% of the patients visiting their physician suffer from anxiety disorders, including generalized anxiety disorder (GAD), panic disorder (PD), post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), social anxiety disorder, or phobias. A substantial number of those patients use prescription drugs with anxiolitic properties such as benzodiazepines, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), or buspirone. Other patients self-medicate, find relief in alcohol consumption, or receive psychological or relaxation therapy.

Most people suffering from anxiety disorders are outpatients. Hence, it is reasonable to assume that they are involved in daily activities such as driving a car. Since driving a car is a potentially dangerous activity with the risk of becoming involved in traffic accidents it is important to examine whether treatment with anxiolytics affect skills and abilities needed during driving. This review will summarize and discuss results from on-the-road studies that examined the effects of anxiolytic drugs on driving ability, complemented with epidemiological evidence.

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METHODS

The on-the-Road Driving Test

The on-the-road driving test during normal traffic was developed in the 1980s and has been applied in over 50 studies to determine the effects of psychoactive drugs on driving ability. The test has been highly standardized and has shown to be sensitive to dose-dependent impairment after administration a variety of psychoactive drugs including hypnotics [1], antidepressants [2], and antihistamines [3]. In the standardized driving test, subjects are instructed to drive a car over a 100-km (61 miles) highway while maintaining a constant speed (58 miles/h) and a steady lateral position within the right (slower) traffic lane. The primary parameter of the test is the Standard Deviation of Lateral Position (SDLP, cm): the weaving of the car. This is shown in (Fig. **1**).

It is evident from (Fig. **1**) that SDLP represents the amount of vehicle control. That is, higher SDLP values represent increased weaving of the car. A camera, mounted

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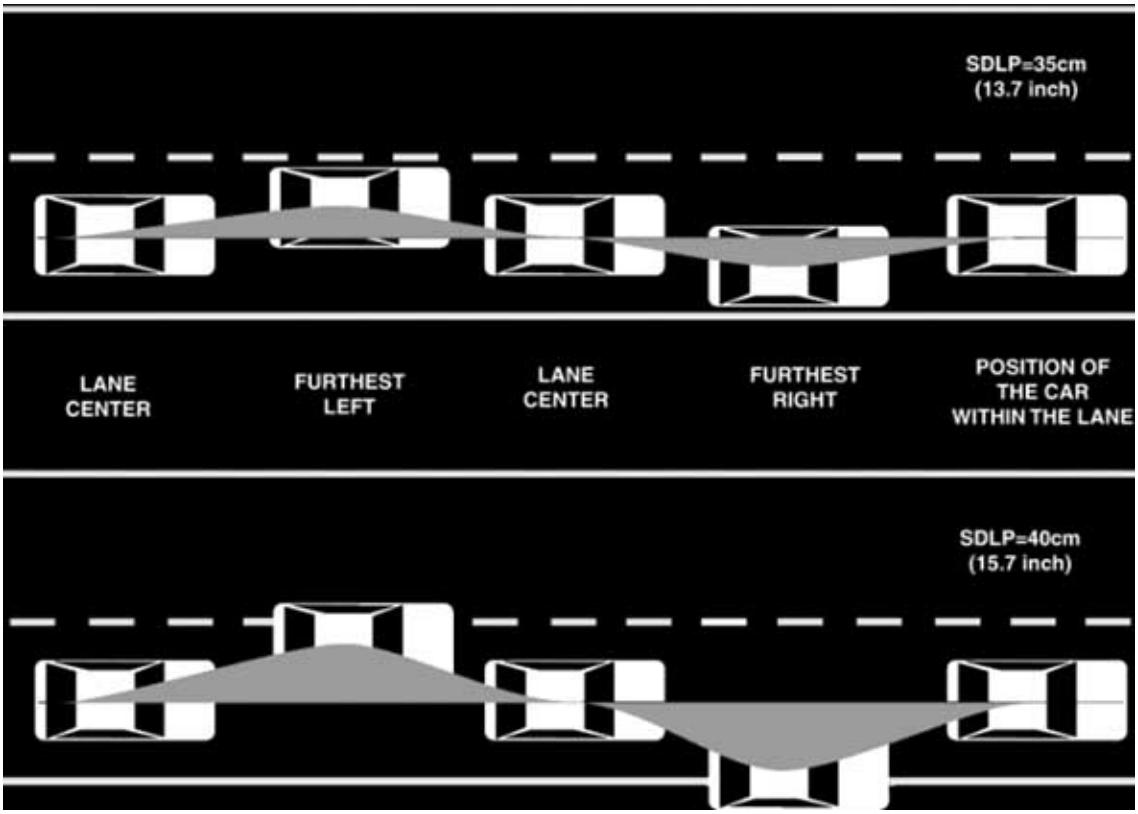

Fig. (1). Meaning and calculation of the Standard Deviation of Lateral Position (SDLP).

on the roof of the car, continuously records the position of the car within the right traffic lane, by tracking the relative distance of the car from delineated stripe in the middle of the road. This is illustrated in (Fig. **2**).

In the right front seat, a licensed driving instructor accompanies the subject. His main responsibility is to guard safety during the driving test, and he is equipped with a brake and clutch system. If the subject or the driving instructor judges that it is unsafe to continue driving, the

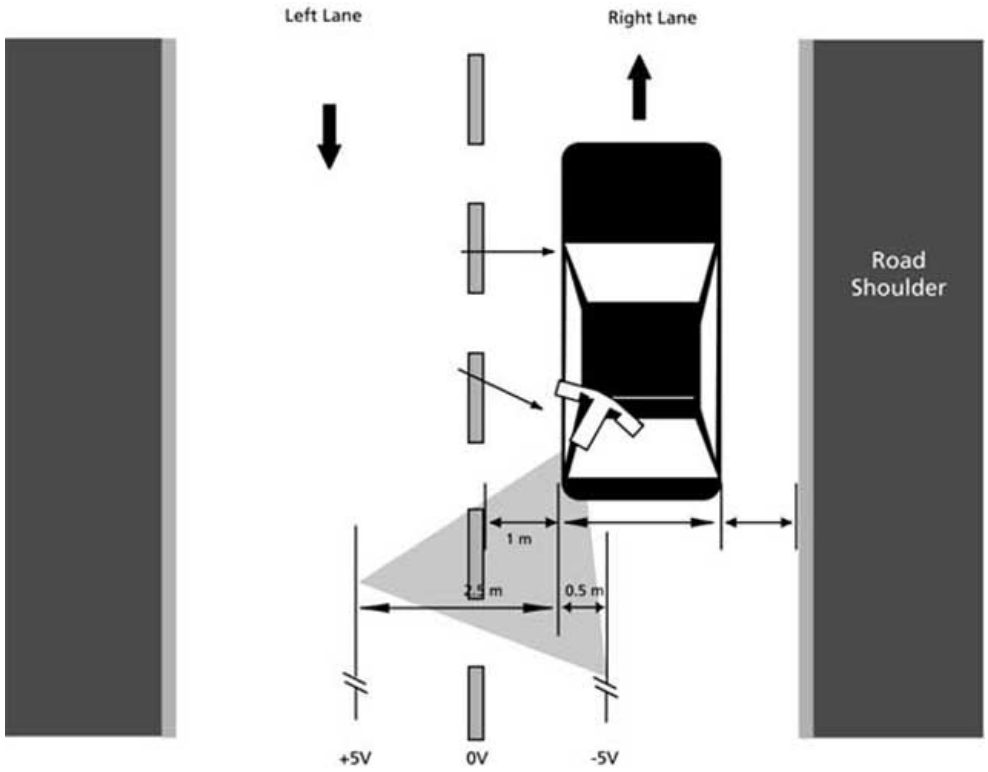

Fig. (2). Schematic representation of the on-the-road driving test.

test is terminated before completion and the driving instructor transports the subject back to the Institute.

Data Collection and Study Selection

A literature search using Medline (keywords *driving* and *anxiety*) and cross-references was performed to identify all studies examining drugs with anxiolytic properties that used the on-the-road driving test during normal traffic. Studies were included if subjects were either healthy volunteers or anxious outpatients. In addition, studies had to be placebo-controlled and double blind. Studies were excluded if driving tests were performed in other patient populations (e.g. depressed outpatients). Design and results from 14 eligible studies included in this review are summarized in Table **1**. Treatments used for their anxiolytic properties that have been studied by using the on-the-road driving test include benzodiazepines (diazepam, lorazepam, alprazolam, and oxazepam), other GABAergic compounds (alpidem, suriclone, and zolpidem), tricyclic antidepressants (imipramine and amitriptyline), selective serotonin reuptake inhibitors (paroxetine, fluoxetine), venlafaxine, 5HT-antagonists (ritanserin and ondansetron), and buspirone. Not included in Table **1** (but discussed in the result section) are studies that examined the effects on driving ability of alcohol (not a prescription drug) or barbiturates (no longer prescribed).

RESULTS

Alcohol

Many patients use alcohol to find anxiety relief. Performance impairing effects of alcohol are well known, and are observed both during acute intoxication [4] and during alcohol hangover [5].

In the 1960s, Borkenstein and colleagues [6] performed a study that turned out to be a major breakthrough in

Table 1. Summary of Design and Outcome of Included Driving Studies

Ref	Year	Subjects	Design	Time[1]	Treatment	Day 1	Day 8
[21]	1982	9 HV,m	C, Pc	1h, e	diazepam 5 mg	NS	------
					diazepam 10 mg	*	------
[22_I]	1995	16 HV,b	C, Pc	1-2h,e	diazepam 5 mg tid	*	*
					ondansetron 1 mg bid	NS	NS
					ondansetron 4 mg bid	NS	NS
[22II]	1995	18 HV,b	C, Pc	2-3h,a	suriclone 0.2 mg tid	*	*
					lorazepam 0.5 mg tid	*	*
[22_III]	1995	19 AO,b	B, Pg	3-4h,m	alpidem 50 mg bid	*	*
		18 AO,b	B, Pg	3-4h,m	lorazepam 2 mg bid	*	*
[23]	1992	12 AO,b	B, Pb	1-2h,e	diazepam 5 mg tid	*	*
					buspirone 5 mg tid	NS	NS
[24]	2001	18 HV,m	C, Pc	3h,a	lorazepam 1.5 mg bid	-----	*
					ritanserin 5 mg bid	-----	NS
[25]	2002	20 HV,b	C, Pc	1h	alprazolam 1 mg	*	-----
[27]	1992	18 HV,m	C, Pc	10h[2]	oxazepam 50 mg	*	-----
[28]	1995	17 HV,w	C, Pc	10h[2]	zolpidem 10 mg	NS	-----
[7]	2002	30 HV,b	C, Pc	4h[6]	zolpidem 10 mg	*	-----
					zolpidem 20 mg	*	-----
[30]	1995	24 HV,b[3]	C, Pc	2.5h	impiramine 50 mg bid	*	*
[31]	1995	16 HV,b	C, Pc	1.5/5h,m	amitriptyline 75 mg bid[4]	*	NS
					paroxetine 10 mg bid	NS	NS
[32]	1995	18 HV,b	C, Pc	14.5h[2]	fluoxetine 20 mg	NS	NS
[33]	1998	22 HV,b	C, Pc	2h,m	venlafaxine 37.5 mg bid	NS	NS
					venlafaxine 75 mg bid[5]	NS	NS

(1) Time of testing after administration, (2) administered at bedtime, tested the following morning, (3) subjects were 12 healthy adults and 12 elderly, (4) 50 mg was administered at night and 25 mg in the morning, (5) starting dose of 37.5 mg bid on Day 1 increased to 75 mg bid on Day 8, (6) administrated during the night, tested the following morning.

* = significantly different from placebo, NS = not significantly different from placebo, ----- = not tested.

Ref. = Reference number. Note that Reference [22] reports the results from 3 independent studies, labeled I, II, and III.

C = cross-over, B = between groups, Pb = Placebo Baseline, Pc = Placebo Condition, Pg = Placebo Group, HV = Healthy Volunteers, AO = Anxious Outpatients, M = men, w = women, b = both sexes, e= tested after the third or evening dose, a= tested after the second (afternoon) dose, m = tested after the first (morning) dose. bid = two times a day, tid = three times a day.

epidemiological research on ethanol effects on driving performance, because they clearly showed a correlation between BAC and the probability of becoming involved in a traffic accident. From several thousand drivers involved in car accidents breath samples were obtained to determine BAC and compared to those of a control group consisting of drivers passing at the same road, at the same time of the day who were not involved in any accident. From these data, a relationship between BAC and accident risk was calculated. The investigators concluded that with rising BAC, the risk of becoming involved in a traffic accident increased exponentially.

Several on-the-road driving studies examined the effects of low dosages of alcohol (0.03% < BAC < 0.05%) on driving ability [7,8]. SDLP increments relative to placebo ranged between 1 and 2 centimeters. From laboratory tests, it is evident that performance impairment after alcohol consumption is dose-dependent. Since the Dutch law prohibits driving with BAC at or above 0.05%, higher dosages have not been tested during normal traffic. Therefore, the on-the-road driving test methodology was calibrated on a closed road [9]. The effects of different blood alcohol concentrations (BAC) on driving ability were determined in 24 social drinkers. SDLP increments corresponding to the most common legal limits for driving were +2.4 cm (0.05%), +4.1 cm (0.08%), and +5.3 cm (0.10%). The study revealed a steady correlation between BAC and SDLP (r=0.98). This is illustrated in (Fig. **3**).

Barbiturates

Around 1900, barbiturates were introduced as pharmacological treatment of anxiety disorders. For a long time, barbiturates such as barbital, pentobarbital and secobarbital were the most important clinically effective treatments. Unfortunately, barbiturates proved to be addictive and fatal in overdose. Further, tolerance to their clinical effects develops rapidly, requiring subsequent dose increments over time. Moreover, barbiturates are highly sedative. Patients reported that reduced alertness and sedation interfered with their daily functioning, including driving a car. An on-the-road driving study [10] showed that driving performance was significantly impaired up to 17 hours after bedtime administration of secobarbital (200 mg).

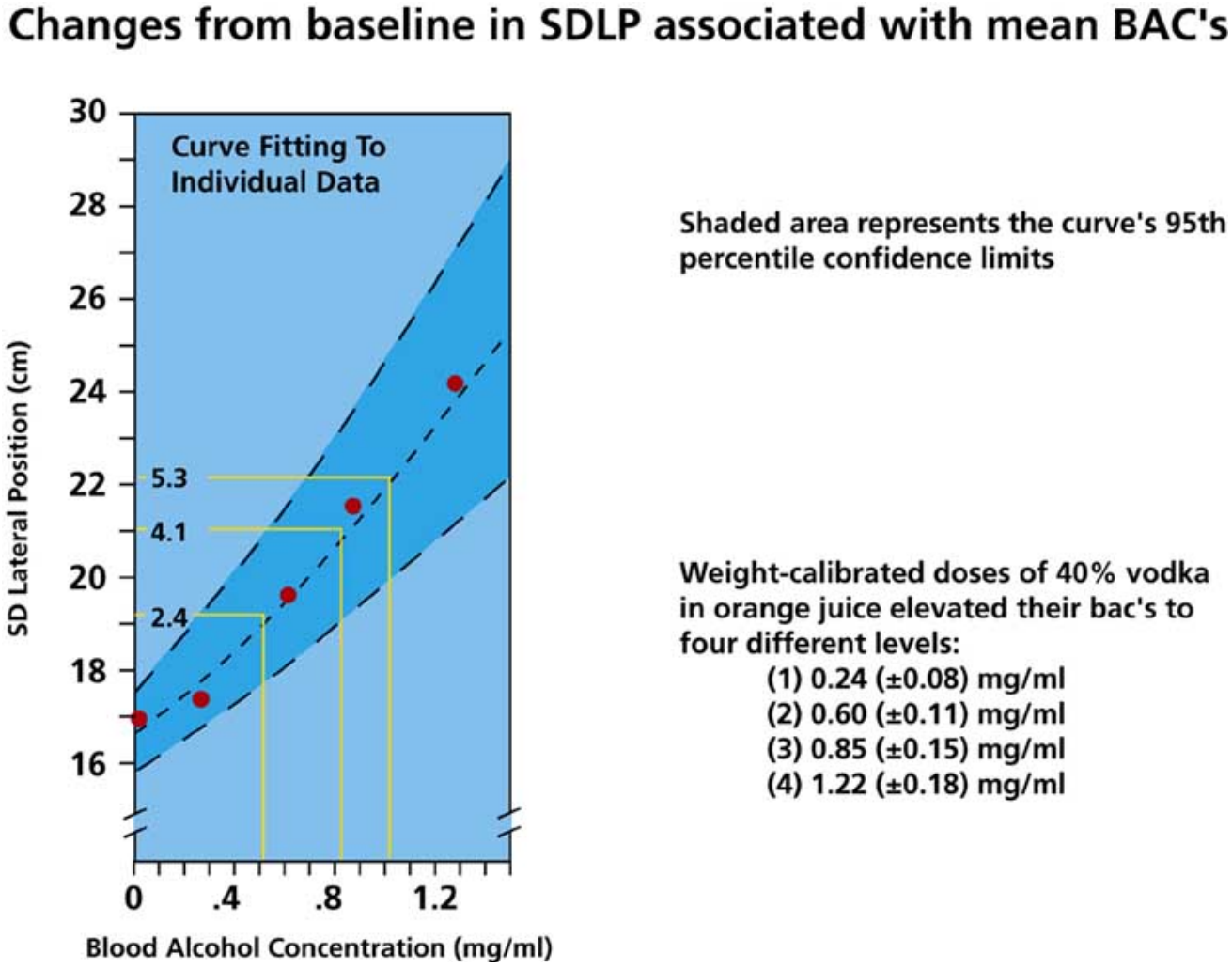

Fig. (3). The relationship between blood alcohol concentration and driving performance (SDLP).

(Data from reference [9]).

Subjects drove repeatedly out of lane, into both the adjacent traffic lane and the road shoulder. Moreover, some of the tests had to be terminated before completion. Overall, SDLP increments were comparable with those observed with blood alcohol concentration higher than 0.10%. Hence, driving while treated with barbiturates showed to be very unsafe. Currently, barbiturates are no longer used as anxiolytics.

Benzodiazepines

Benzodiazepine anxiolytics were introduced in the 1960s. They easily cross the blood brain barrier into the CNS (Central Nervous System) and bind nonselective to the $GABA_A$ benzodiazepine receptor complex. The latter is a pentameric structure, composed of protein units surrounding a chloride channel. Different protein units have been identified, labeled as α, β or γ, which can be further differentiated in several subunits (distinguished by numbering). It appeared that benzodiazepine receptors can be differentiated upon their subunit structure: type 1 receptors are composed of $\alpha_1\beta_{1\text{-}3}\gamma_2$ subunits whereas type 2 receptors are $\alpha_{2,3,5}\beta_{1\text{-}3}\gamma_2$ subunits. Sedation and anterograde amnesia are mediated by α_1 receptors, whereas α_2 receptors mediate anxiolytic effects [11,12].

The presence of benzodiazepines facilitates the binding of GABA to the receptor complex. GABA-interactions with the serotonergic and noradrenergic pathways connecting to the limbic system and brain stem structures contribute to the clinical effectiveness of benzodiazepines in the treatment of anxiety. Unfortunately, benzodiazepine anxiolytics bind nonselective to both α_1 and α_2 receptors. Hence, binding of GABA, which is facilitated by the presence of benzodiazepines, may also result in unwanted sedation and reduced alertness. The latter may affect skilled performance, including driving a car.

The effects of benzodiazepine anxiolytics on driving safety have been reported by various epidemiological studies. For example, significantly increased traffic accident risks in diazepam users [13] and significantly higher percentages of patients requiring medical attention due to traffic accidents or injury have been reported for users of benzodiazepine anxiolytics when compared to healthy controls [14].

Oster and colleagues [15] showed that drivers using benzodiazepine anxiolytics (including alprazolam, chlordiazepoxide, chlorazepate, diazepam, lorazepam, and oxazepam) had significantly increased numbers of accident-related emergency outpatient visits (OR=2.09; 95%CI=1.27-3.42). The effect was more pronounced in case of multiple benzodiazepine use (OR=3.7; 95%CI=2.05-6.68). Interestingly, the authors also examined this risk at baseline, i.e. before the start of benzodiazepine therapy. The analysis revealed that untreated anxiety symptoms itself also increased the numbers of accident-related emergency outpatient visits (OR=2.0; 95%CI=0.96-4.44).

Ray and colleagues [16] reported significantly increased traffic accident risks (OR=1.5; 95%CI=1.2-1.9) in elderly patients treated with diazepam (38%), lorazepam (29%), chlordiazepoxide (16%), clorazepate (9%), or other anxiolytics (8%). These risks were significantly more pronounced when the administered dosages were equivalent to 20 mg diazepam or higher (OR=2.4; 95%CI=1.3-4.4), or in case of multiple drugs use (OR=4.8; 95%CI=1.6-14.5).

On the other hand, Leveille and colleagues [17] did not report significantly increased traffic accident risk (OR=0.9; 95%CI=0.4-2.0) in elderly. However, the majority of these patients used triazolam (50%) and flurazepam (27%), and to a lesser extent diazepam (9%), chlordiazepoxide (5%), and alprazolam (5%).

Neutel [18] examined the risk of traffic accident injury in 147.726 patients starting treatment with a benzodiazepine anxiolytic (oxazepam, lorazepam, or diazepam). Odds ratios were compared with those from 97.862 healthy control subjects. Analyses revealed that over an 8 week period, patients receiving a benzodiazepine anxiolytic had a 2.5 times increased risk of becoming hospitalized due to traffic accident injury. As is evident from (Fig. **4**), odds ratios were highest in the first week after treatment administration. Thereafter, odds ratios gradually decrease, but were still significant in week 8.

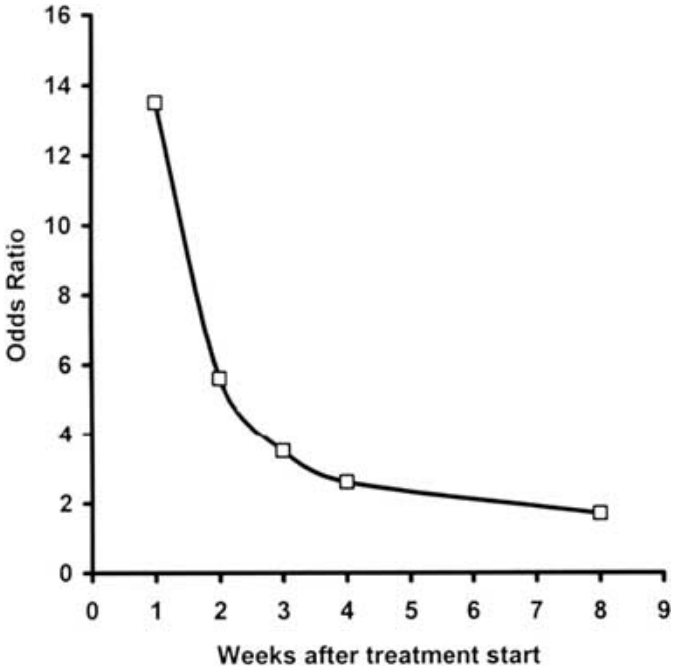

Fig. (4). Risk of hospitalization for traffic accident injury when treated with benzodiazepine anxiolytics. Traffic accident risk is expressed in terms of an odds ratio (OR) with an accompanying 95% confidence interval (CI). The odds ratio expresses the relative risk compared to normal (OR=1), which is significant when the confidence interval is greater than 1. (Data from reference [18]).

Hemmelgarn and colleagues [19] examined the risk of traffic accident involvement in elderly subjects. Those using benzodiazepines with a long half-life (clonazepam, diazepam, clorazepate, chlordiazepoxide, flurazepam, and nitrazepam) showed significant increased accident risks within the first week after treatment initiation (OR=1.45; 95%CI=1.04-2.03), which was also significantly increased after 1 year of treatment (OR=1.26; 95%CI=1.09-1.45). On the other hand, for benzodiazepines with a shorter half-life (alprazolam, bromazepam, lorazepam, oxazepam, temazepam, and triazolam), risks were not significant within 1 week

(OR=1.04; 95%CI=0.80-1.34) and after 1 year (OR=0.91; 95%CI=0.82-1.01).

In line, Barbone and colleagues [20] reported a significantly increased traffic accident risk for users of benzodiazepine anxiolytics (OR=2.18; 95%CI=1.52-3.13). Further examination showed that benzodiazepines with intermediate (6-24 h) half-life (OR=1.59; 95%CI=0.71-3.57) and those with a long (> 24h) half-life (OR=2.22; 95%CI=1.47-3.37) are responsible for this effect.

From these epidemiological studies it is evident that traffic accident risks are significantly increased in both elderly and adult users of benzodiazepine anxiolytics. These effects are most profound after treatment initiation, especially when treated with benzodiazepines with a long half-life, at higher dosages, and in case of multiple drug use. Although substantial tolerance develops to the impairing effects of benzodiazepine anxiolytics, in elderly significantly increased traffic accident risks have been reported after prolonged use [19].

The results from several on-the-road driving studies are summarized in (Fig. **5**). It shows the differences in SDLP relative to those obtained in the placebo conditions in the same subjects. SDLP increments obtained after administration of different dosages of alcohol (0.05%, 0.08%, and 0.10%), corresponding to the most common legal limits for driving, are depicted in (Fig. **5**) as well.

Diazepam

O'Hanlon and colleagues [21] examined driving performance of 9 professional drivers (healthy volunteers) one hour after acute administration of diazepam (5 mg or 10 mg). The 10 mg dose produced severe driving impairment, whereas the 5 mg dose did not.

Driving performance was also significantly impaired after both acute (Day 1) and sub-chronic (Day 8) administration of diazepam (5 mg t.i.d.) in 16 healthy volunteers [22]. Compared to Day 1, driving performance was worse after 7 days of administration, probably due to the accumulation of active metabolites. As evident from (Fig. **5**), the amount of vehicle control (i.e. SDLP increment relative to placebo) was much more pronounced than that observed with a BAC of 0.10%.

Tolerance to the impairing effects of diazepam develops slowly. This was shown in a driving study with anxious outpatients treated during 4 weeks with diazepam, 5 mg tid [23]. As evident from (Fig. **6**), driving performance during diazepam treatment was significantly worse when compared to placebo-baseline measurements. Although some tolerance developed during treatment, driving impairment was

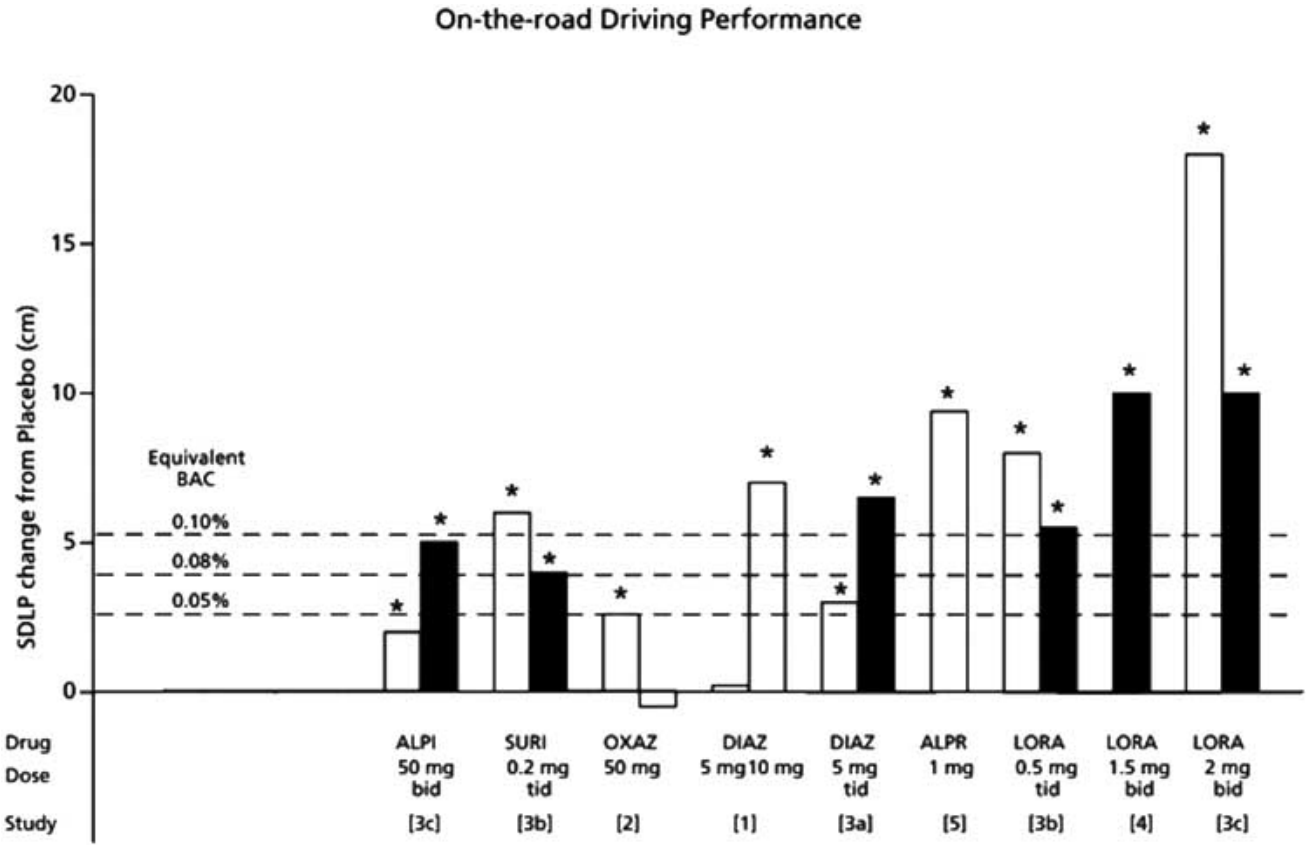

Fig. (5). Effects on driving ability of benzodiazepines and other GABAergic compounds.

SDLP changes from placebo are shown. Note that the impairment found with benzodiazepine anxiolytics is higher than the most commonly used legal limit for driving a car (0.05%). Black bars = repeated administration, white bars = acute administration. Abbreviations: ALPI = alpidem, SURI = suriclone, OXAZ = oxazepam, DIAZ = diazepam, ALPR = alprazolam, LORA = lorazepam, BAC = blood alcohol concentration, bid = 2 times daily, tid = three times daily. Significant ($p<0.05$) differences from placebo are indicated by asterisks (*). Study 1 = [21], study 2 = [27], study 3 = [22], study 4 = [24], study 5 = [25].

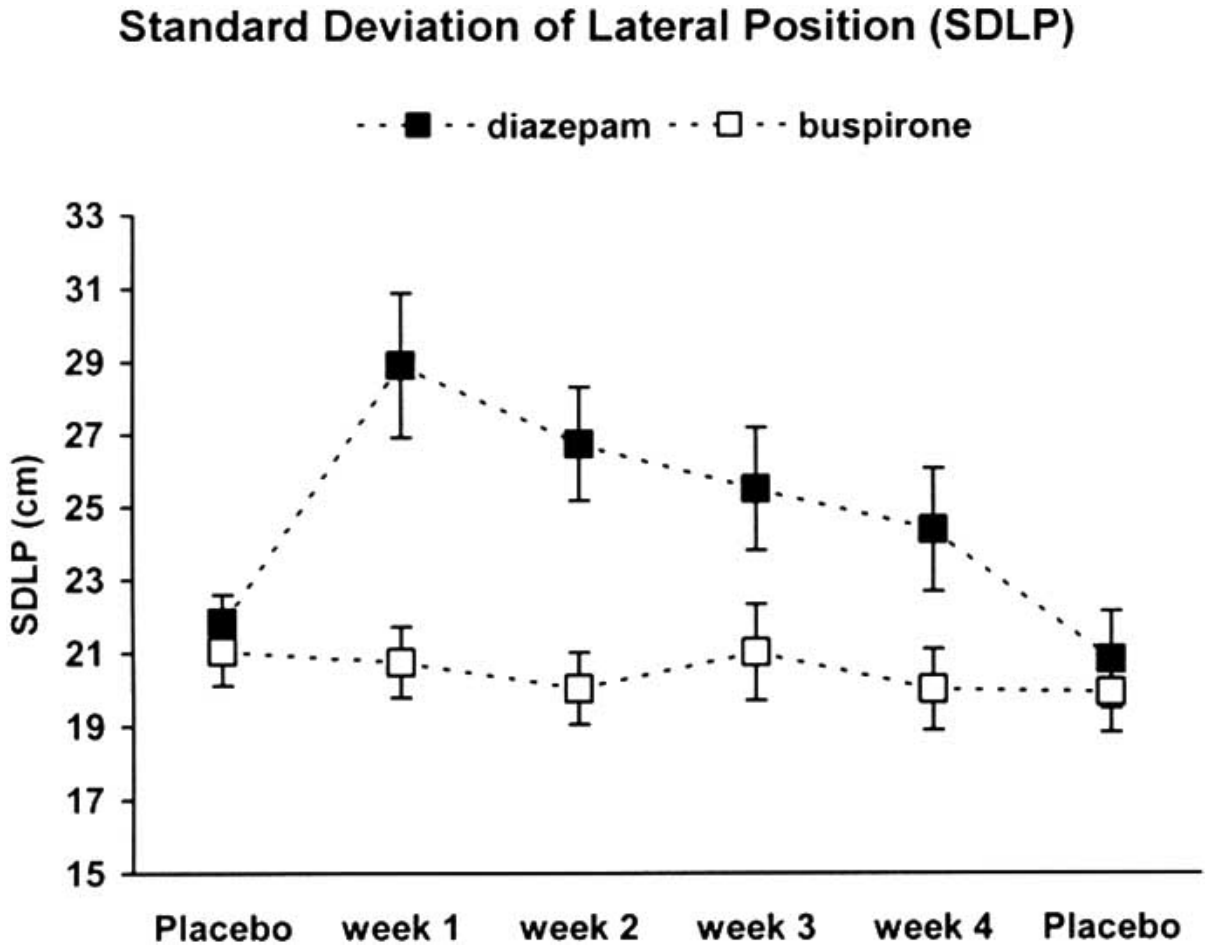

Fig. (6). Driving performance of anxious outpatients during 4 weeks of treatment with diazepam or buspirone. During week 0 (wash-in placebo) and week 5 (wash-out placebo) driving performance did not differ significantly between patients. During active treatment, driving performance was significantly worse in the diazepam group. (Data from reference [23]).

significant during the first three weeks of diazepam treatment.

Lorazepam

Anxious outpatients treated for 8 days with lorazepam (2 mg bid) showed significant driving impairment. Patients with generalized anxiety disorder or adjustment disorder with anxious mood (DSM III-R criteria) were included if Hamilton Rating Scales for anxiety (HAM-A) scores were ≥ 18 and scores on the Montgomery Asberg Depression Rating Scale (MADRS) were ≤ 19. Patients ceased their regular medication, followed by subsequent periods of placebo wash-in (7 days), active treatment (8 days), and placebo wash-out (7 days). On day 1, relative to placebo, SDLP increment was 18 cm and after 8 days of treatment SDLP increment was 10 cm [22]. These highly significant SDLP increments are much more pronounced than those observed with a blood alcohol concentration of 0.10%. Of major concern was the fact that subjects did not recognize their individual driving impairment on day 8 (they reported that they drove as safe as without any medication). In 18 healthy volunteers treated with lorazepam (0.5 mg t.i.d.), significant impairment was observed on Day 1 and Day 8 [22]. Van Laar and colleagues [24] reported that in 18 healthy male volunteers, driving performance was significantly impaired after 7 days of treatment with lorazepam (1.5 mg bid).

Alprazolam

Verster and colleagues [25] examined the acute effects of alprazolam (1 mg) in 20 healthy volunteers. Driving performance was seriously impaired after alprazolam administration. Impaired vehicle control was expressed in both significantly increased weaving of the car (SDLP increment of 9.4 cm) and increased speed variability. Moreover, 6 out of 20 subjects were unable to complete their driving test. These subjects drove repeatedly out-of-lane and finally fell asleep during the test.

A recent review on the behavioral effects of alprazolam [26] revealed that psychomotor performance is also significantly impaired at lower dosages of alprazolam. Thirty-nine double blind, placebo-controlled studies (a total of 130 tests) were identified that examined psychomotor performance after acute administration of alprazolam. Percentages of tests showing significant impairment increased with higher dosages: 0.25 mg (13.0% of 23 tests), 0.50 mg (28.6% of 28 tests), 0.75 mg (66.7% of 15 tests), 1.0 mg (84.2% of 38 tests), 1.5 mg (92.9% of 14 tests), and 2.0 mg (75.0% of 12 tests).

Oxazepam

Volkerts and colleagues [27] investigated the residual effects of oxazepam (50 mg) in healthy male volunteers.

Oxazepam was administered at bedtime (as a hypnotic) and driving tests were performed the following morning and afternoon. Oxazepam significantly impaired on-the-road driving performance in the morning (10-11 hours after administration). SDLP increment after oxazepam was significant and comparable to that observed after a BAC of 0.05%. In the afternoon driving test, 16-17 hours after bedtime administration, driving was not significantly affected.

Other GABAergic Compounds

Other drugs that also act at the $GABA_A$ receptor complex have been developed for anxiolytic purposes. Among those are the imidazopyrimidine alpidem and the cyclopyrrolones suriclone and zolpidem. Since these drugs act at more specifically and at different $GABA_A$ receptor subtypes when compared to the benzodiazepines, it was assumed that their adverse effect profile would be favorable.

Alpidem

A study in anxious outpatients showed that alpidem (50 mg bid), an imidazopyridine, significantly impaired driving performance after both acute (Day 1) and sub-chronic (Day 8) administration [22]. Patients with generalized anxiety disorder or adjustment disorder with anxious mood (DSM III-R criteria) were included if Hamilton Rating Scales for anxiety (HAM-A) scores were ≥ 18 and scores on the Montgomery Asberg Depression Rating Scale (MADRS) were ≤ 19. Impairment was most pronounced after 1 week of treatment, and comparable to driving impairment observed with blood alcohol concentrations between 0.05% and 0.08%. Alpidem has been withdrawn.

Suriclone

Suriclone (0.2 mg tid), a cyclopyrrolone, produced serious driving impairment after both acute (Day 1) and sub-chronic (Day 8) administration in 18 healthy volunteers [22]. On both test days, subjects drove significantly worse than observed with blood alcohol concentrations higher than 0.08%.

Zolpidem

Zolpidem is a cyclopyrrolone marketed as a sleep medicine. Hence, its effects on driving ability have only been investigated in this context. Results from this study show that when administered at bedtime zolpidem 10 mg does not affect driving ability the following morning [28]. However 4 hours after middle-of-the-night administration, zolpidem (10 mg and 20 mg) produced significant driving impairment, in a dose-dependent manner [7].

Tricyclic Antidepressants (TCAs)

TCAs such as imipramine and amitriptyline have antihistaminergic activity, which may lead to reduced arousal and sleepiness. Their muscarinergic activity may affect cognitive functioning. Hence, it can be expected that they also will impair driving performance. The latter has also been suggested by epidemiological studies.

For example, Ray and colleagues [16] revealed that traffic accident risk was significantly increased for elderly users of TCAs (OR=2.2; 95%CI=1.3-3.5). Treatments included amitriptyline (50%), doxepin (24%), trazodone (9%), imipramine (6%) or other TCAs (11%). When dosages equivalent to 125 mg amitriptyline or higher were administered the risk was more profound (OR=5.5; 95%CI=2.6-11.6). Also, they found that the use of 2 or more TCAs significantly increases traffic accident risks (OR=9.8; 95%CI=2.4-39.5), as did combined administration of a benzodiazepine and a TCA (OR=2.1; 95%CI=1.1-4.2). In line with these results, Leveille *et al*. [17] reported a significantly increased traffic accident risk (OR=2.3; 95%CI=1.1-4.8) for elderly patients using imipramine (35%), doxepin (26%), amitriptyline (26%) or other TCAs (13%).

However, more recent studies did not report significantly increased traffic accident risks for patients treated with TCAs. For example, Neutel [18] did not find significantly increased traffic accident risks after two weeks (OR=1.0; 95%CI=0.4-2.6) or 4 weeks (OR=1.0; 95%CI=0.5-2.1) of treatment with TCAs. Also, Barbone *et al*. [20] reported no significantly increased traffic accident risk in patients treated with TCAs (OR=0.93, 95%CI=0.72-1.21), as did McGwin *et al*. [29] in elderly using TCAs (OR=0.8; 95%CI=0.2-3.0).

Imipramine

Imipramine has been approved for the treatment of panic disorder. In 12 young and 12 elderly healthy volunteers (mean age 28 and 65 years, respectively), impiramine (50 mg bid) was administered over a 7-day period [30]. On-the-road driving tests were performed after acute (Day 1) and sub-chronic administration (Day 7), 2.5-3.5 hours after treatment administration. On day 1, imipramine significantly impaired driving performance. Surprisingly, further analyses showed that impairment was significant in young drivers, but not reached significance in elderly healthy volunteers. On Day 7, driving performance was also significantly impaired, but much less pronounced (SDLP increment of 1.35 cm) when compared to acute administration. No significant age differences were found on Day 7. Relative to placebo, no significant differences on a sleep latency test were found than can explain the effects of imipramine on driving ability in terms of sleepiness.

Amitriptyline

Amitriptyline was administered for 8 days in healthy volunteers; 50 mg at bedtime and 25 mg in the morning [31]. After the first treatment night (1.5 hours after the morning dose) driving performance was significantly impaired. After 8 days, driving performance was not significantly different from placebo.

Selective serotonin reuptake inhibitors (SSRIs)

SSRIs are the first-choice antidepressant treatment, because their safety profile is favorable above that of the TCAs. Their serotonergic activity may also facilitate anxiety relief. Epidemiological evidence on the effects of SSRIs on traffic accidents is limited, but Barbone and colleagues [20] have shown that SSRIs caused no significantly increased traffic accident risk (OR=0.85; 95%CI=0.55-1.33). Various SSRIs have been tested on the road.

Paroxetine

Paroxetine is a selective serotonin reuptake inhibitor, approved for PTSD, GAD, panic disorder, OCD, and social anxiety disorder. An on-the-road driving study in 16 healthy volunteers examined the effects of paroxetine (10 mg or 20 mg bid) on actual driving after acute (Day 1) and subchronic administration (Day 8), 1.5 and 5 hours after the morning dose [31]. Both dosages of paroxetine did not significantly impair driving performance on Day 1 and Day 8 at any time of testing.

Fluoxetine

Fluoxetine, a selective serotonin reuptake inhibitor, is approved only as antidepressant, but is sometimes prescribed also for its anxiolytic purposes. The acute and subchronic effects of fluoxetine (20 mg, administered for 22 days) on driving ability have been studied in 18 healthy volunteers [32]. On Day 1, day 8, and day 22, driving tests were performed, 14.5 hours after bedtime administration. Driving performance was not significantly impaired at any test day. However, it must be taken into account that fluoxetine was administered at night, whereas normally anxiolytic treatment is taken during daytime. Then, the time between treatment administration and driving is much shorter than in this study, making it more likely that commonly reported adverse effects of fluoxetine such as dizziness and concentration problems may compromise driving performance.

Sertraline and Fluvoxamine

The selective serotonin reuptake inhibitors sertraline (approved for the treatment of PTSD, panic disorder, and OCD) and fluvoxamine (approved for the treatment of OCD) have not been examined in on-the-road driving studies. It can be assumed that, like other SSRIs that have been investigated, at clinically relevant dosages these drugs will not significantly affect driving performance. This has to be demonstrated, however, in future on-the-road studies.

Venlafaxine

Venlafaxine, a serotonin-norepinephrine reuptake inhibitor, has been approved for the treatment of GAD.

An on-the-road driving study examined the effects of venlafaxine in 22 healthy volunteers [33]. Two dose regimens were administrated over a 14-day period: a fixed dose of 37.5 mg b.i.d., or a starting dose of 37.5 mg b.i.d. that was increased to 75 mg b.i.d on Day 8. Driving tests were performed on day 1, 7, 8 and 15, 2-3 hours after administration of the morning dose. On all test days, driving performance was not significantly impaired. In addition, no significant effect was found on driving performance after dose increment on Day 8.

5HT-Antagonists

Ritanserin

Ritanserin (5 mg bid), a $5HT_{2A/2C}$ receptor antagonist, produced no significant driving impairment in 18 healthy young male volunteers after 7 days of administration [24].

Ondansetron

In 16 healthy volunteers, driving ability after acute (Day 1) and sub-chronic (Day 8) administration of ondansetron (1 or 4 mg bid), a $5HT_3$ receptor antagonist, was not significantly impaired [22].

Buspirone

Buspirone, a $5HT_{1A}$ receptor partial agonist, exerts its activity primarily through the serotonergic system and is used in the treatment of generalized anxiety disorder. An on-the-road driving study in 12 anxious outpatients examined the effects of buspirone on driving ability during a 4-week treatment period [23]. Two groups of twelve outpatients with mild to moderate generalized anxiety disorder (DSM III-R criteria) were included, with Hamilton Rating Scales for anxiety (HAM-A) scores were ≥ 14 and Hamilton Rating Scale for Depression (HAM-D) scores were ≤ 15. In the first treatment week, patients received 5 mg buspirone three times a day; thereafter the morning dose was doubled to 10 mg (total daily dose of 20 mg). Driving test results were compared with another patient group receiving diazepam (5 mg t.i.d.). The 4-week treatment period was proceeded and followed by a placebo week in which no active treatment was administered. Both diazepam and buspirone treatment significantly reduced overall anxiety symptoms. In contrast to diazepam, buspirone also produced significant improvement in depressive symptoms. Abrupt discontinuation of diazepam treatment after 4 weeks resulted in a relapse of anxiety symptoms, whereas discontinuation of buspirone treatment did not. As depicted in (Fig. **6**), when treated with buspirone weekly driving tests showed no significant performance differences relative to baseline placebo. In contrast, diazepam significantly impaired driving ability. Since both buspirone and diazepam were equally effective in reducing overall anxiety symptoms, the advantage on buspirone with respect to driving safety should be taken into account when prescribing an anxiolytic drug to outpatients.

DISCUSSION

Benzodiazepines are the most frequently prescribed pharmacological treatment of anxiety disorders. In addition to their clinical efficacy, the main advantage of benzodiazepine anxiolytics is their fast onset (within days after treatment initiation). In contrast, TCAs, SSRIs, venlafaxine, and buspirone have a much slower on set of action (several weeks).

Although benzodiazepines have an improved safety profile relative to the barbiturates, common adverse effects are sedation and reduced alertness. These are predominantly caused by their activity at the GABA system. Results from on-the-road driving tests show that driving performance is seriously impaired after acute administration of benzodiazepines and other GABAergic anxiolytics. The magnitude of impairment depends on various factors including the administered dose, time after administration, half-life, and the presence of active metabolites. Nevertheless, as summarized in (Fig. **5**), benzodiazepines

and other GABAergic anxiolytics produce significant performance impairment on the driving tests.

After several days or weeks of administration, benzodiazepine anxiolytics show gradual development of tolerance to the impairing effects on driving performance. For example, (Fig. **6**) shows that diazepam produced impairment up to 3 weeks after treatment initiation. However, (Fig. **6**) also shows that although significant impairment persists, over the weeks it becomes less pronounced when compared with impairment observed after a single dose administration. The observations of impaired driving after repeated administration are in line with the epidemiological evidence presented in (Fig. **4**): The risk of becoming injured in a traffic accident is high after treatment initiation, and less pronounced after several weeks of treatment. Nevertheless, (Fig. **4**) further shows that the risk is still significantly higher 8 weeks after treatment initiation.

In this context, a recent meta-analysis examined the cognitive effects of long-term benzodiazepine use as determined in laboratory studies [34]. Data from 13 studies examining the effects of long-term benzodiazepine use (mean duration of treatment was 9.9 years) were included. Results from the analysis showed that compared to healthy controls performance was significantly impaired in 12 cognitive domains, including attention, memory functioning, psychomotor speed, motor control, and problem-solving. These results suggest generalized performance impairment in long-term benzodiazepine users, which makes it likely that complex behavior such as driving will also be impaired during chronic treatment. However, the number of studies is low, as are the number of participants in these studies. As the authors state, more powerful large-scale studies are needed to draw firm conclusions whether performance impairment persists after months or years of daily benzodiazepine use. It will be necessary to examine driving ability in long-term benzodiazepine users as well, because data from present on-the-road studies is generally limited to a couple of weeks of treatment.

Over the years, several alternative treatments have been developed including TCAs, SSRIs and buspirone. Single dose administration of TCAs such as amitriptyline and imipramine produces similar driving impairment as the benzodiazepines. However, after one week of administration, impairment was limited (imipramine) or absent (amitriptyline) on driving tests examining TCAs. Although significantly increased traffic accident risks have been reported within the first weeks after treatment initiation, epidemiological data are limited and conflicting. The more rapid development of tolerance relative to the benzodiazepines may explain why in some epidemiological studies effects were found and in others not. However, there is no epidemiological evidence showing significantly increased traffic accident risks after long-term use (a year or longer). In contrast, the SSRIs, venlafaxine, and buspirone did not impair driving ability after both single dose and repeated daily administration.

As is evident from this review, the majority of on-the-road driving studies have been performed in healthy volunteers. However, it can be argued that anxiety itself may impair driving ability. In that case, successful treatment may improve driving performance in patients, while healthy volunteers only experience possible adverse treatment effects. In other words, if anxiety itself affects driving ability the relevance of results obtained in healthy volunteers for the patient population can be questioned. In this context, a recent driving study in depressed patients [35] showed that driving performance was significantly impaired in untreated patients when compared to healthy controls. Up to now, no direct matched comparisons on driving ability have been made between anxious patients and healthy controls. Future studies should investigate to what extent anxiety itself also affects driving ability.

In conclusion, research and development should aim at finding non-sedative anxiolytics that show immediate therapeutic activity. Until then, patients have to be cautioned when driving during treatment with benzodiazepines and TCAs.

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