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Abstract

The acute and subchronic effects of low doses nocturnally administered amitriptyline were compared to placebo in a double-blind crossover randomized study on driving ability and driving-related skills involving seven chronic neuropathic pain patients. Performance testing occurred at the first and last day of each 15-day drug administration period, which was preceded by a 6-day washout phase. A standardized method of measuring driving ability, the on-the-road driving test, was performed on all visits. Patients were instructed to drive with a steady lateral position while maintaining a constant speed of 95 km/h. The primary outcome of the driving test is the Standard Deviation of Lateral Position (SDLP, cm), which is an index of weaving of the car. At the first treatment day, driving performance was significantly impaired in patients after nocturnal administration of 25 mg amitriptyline compared to placebo. The increase

in SDLP of 3 cm was higher than the increment generally observed with a blood alcohol concentration of 0.5 mg/ml or higher, the legal limit for driving in many countries. Also, reaction times on a memory test were significantly increased, indicating worse performance after acute treatment of amitriptyline compared to placebo. In contrast, after 2 weeks of treatment, no significant differences were found between amitriptyline and placebo, suggesting that tolerance had developed to the impairing effects of amitriptyline.

Keywords

amitriptyline, driving, SDLP, neuropathic pain, psychomotor performance, cognition

Introduction

Amitriptyline, a tricyclic antidepressant (TCA), is routinely prescribed as a treatment for neuropathic pain. The efficacy of amitriptyline in this treatment has consistently been demonstrated in randomized controlled trials (e.g. Max, 1994; McQuay *et al.*, 1996; Kingerly, 1997; Dworkin *et al.*, 2003), although amitripty-

line is not FDA approved for the treatment of neuropathic pain. Amitriptyline is thought to exert its analgesic effects through inhibition of both norepinephrine and serotonin neurotransmitter reuptake (Atkinson *et al.*, 1999). The analgesic effect of amitriptyline appears to be independent of its antidepressant effect (McQuay *et al.*, 1996). That is, it has been reported that the onset of analgesic action of amitriptyline occurs earlier (3–5 days) than its antide-

pressant effect (up to 3 weeks) (Davis *et al.*, 1977). Further, the pain relieving effect occurs at lower doses, ranging between 10–75 mg daily, whereas for the antidepressant effect, doses normally range between 75–300 mg daily (Dworkin *et al.*, 2003). A major drawback of its use is that amitriptyline can produce side effects such as sedation (e.g. Stein and Strickland, 1998). The most prominent candidate mechanisms to account for these adverse events are anticholinergic and antihistaminergic actions and α_1 -adrenoceptor blocking (Hindmarch, 1997). The occurrence of side effects may result in performance deterioration, including the ability to drive a car.

Epidemiological data have indicated that the elderly using TCAs have an increased risk for traffic accident involvements and related injury. Moreover, the use of two or more TCAs simultaneously or higher dosages further increased risks in the elderly (Ray *et al.*, 1992; Leveille *et al.*, 1994). However, other epidemiological studies reported no association between the use of TCAs and road traffic accidents in the elderly (Barbone *et al.*, 1998; McGwin *et al.*, 2000).

Additionally, various laboratory studies have indicated that decrements in performance are most pronounced after acute dosages. Performance deficits after acute administration are quite consistently found in a variety of tasks, including measures of psychomotor performance, memory and attention, in both healthy volunteers and depressive patients (Thompson and Trimble, 1982; Deptula and Pomara, 1990; Thompson, 1991; Knegtering *et al.*, 1994; Amado-Boccaro *et al.*, 1995; Volz and Sturm, 1995). Most studies investigated dosages of 50 or 75 mg, however, even after low dosages of 10 to 25 mg of amitriptyline cognitive impairments were found (e.g. Seppälä *et al.*, 1984). It has been consistently demonstrated that tolerance to the adverse effects of amitriptyline on laboratory task performance develops within 1–2 weeks (e.g. Deptula and Pomara, 1990).

Two on-the-road driving studies examined the effects of amitriptyline on driving performance in healthy volunteers. These studies showed that acute administration of amitriptyline negatively affects driving performance. Louwerens *et al.* (1986) studied the acute effects of amitriptyline 75 mg (25 mg t.i.d. administered 10, 6 and 2 h before the driving test) compared to placebo, in 12 healthy volunteers. Driving performance was significantly impaired after amitriptyline compared to placebo, expressed as diminished control of the position of the car on the road. Moreover, for safety reasons, six subjects had to stop their driving test before completion in the amitriptyline condition. Robbe and O'Hanlon (1995) investigated acute and subchronic effects of amitriptyline 75 mg daily (divided into 50 mg at night and 25 mg in the morning) compared to placebo in 16 healthy controls. Seven driving tests were stopped prematurely after acute amitriptyline administration but none in the subchronic phase. The acute impairing effects of amitriptyline on road tracking ability were in line with the results of Louwerens *et al.* (1986). Consistently with the results of laboratory studies, impairing effects had practically vanished after 1 week of treatment.

Whether acute administration of amitriptyline will also affect driving performance negatively in pain patients is unknown. The results of previous studies may not necessarily apply to these

patients. Amitriptyline is administered nocturnally in low dosages in the treatment of neuropathic pain. Therefore, the occurrence of side effects may be less. Hence, it is important to investigate the effects of amitriptyline in the clinical pain population since performance changes reflect both occurrence of side effects and therapeutic responses. In contrast, performance changes in healthy volunteers solely reflect side effects.

The present study was designed to determine the effects of nocturnally administered 25 mg amitriptyline, compared to placebo, after single (Day 1, acute effects) and repeated (Day 15, subchronic effects) administration on driving performance in neuropathic pain patients. In addition to the on-the-road driving test, laboratory tests measuring driving-related skills were administered. It was hypothesized that nocturnally administered 25 mg amitriptyline might affect driving performance negatively after acute, but not after subchronic treatment.

Methods and materials

Participants

Patients were recruited by seven pain clinics in Utrecht and surroundings in the Netherlands during a 2-year period from October 2002 to December 2004. Patients were included if they had chronic benign neuropathic pain that was moderate to severe in intensity (at least 4 cm on a 10 cm Visual Analogue Scale (VAS) scale measured by the pain physician). Since the focus of the study was on studying amitriptyline as an effective analgesic therapy, we selected patients that were already effectively treated with 25 mg amitriptyline before the start of the study. Further, they were right-handed, had normal or corrected to normal vision, possessed a valid driver's licence and drove at least 5000 km per year for at least 3 years.

Patients were excluded from the study if they were not able to abstain from psychotropic medication, suffered from alcohol or drug dependence, psychological or psychiatric disorders or severe physical disorders, other than pain, as assessed by their physician and through a medical questionnaire by the investigators. The use of paracetamol and/or non-steroidal anti-inflammatory drugs (NSAIDs) was allowed, but patients were obliged to continue any additional concomitant analgesic medication at constant dose throughout the study. At all visits, patients were tested on the presence of drugs (amphetamines, barbiturates, benzodiazepines, cocaine, morphine and THC) using a urine drug detection device. The use of alcohol was tested with a breath alcohol analyser. The Medical Ethics Committee of the University Medical Centre Utrecht approved the study protocol and written informed consent was obtained from all patients. Procedures were in compliance with the Helsinki Declaration and its latest amendments.

Study design and treatments

The study was conducted according to a double-blind, placebo-controlled crossover randomized design. The within-subject crossover design involved two treatment conditions: placebo and

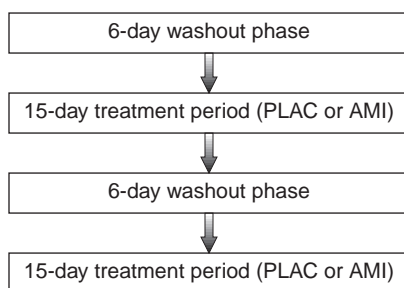


Figure 1 Design of the study. Abbreviations: PLAC, placebo; AMI, amitriptyline.

25 mg amitriptyline. After a training session, treatments were administered for 15 days, preceded by washout periods of 6 days (see Fig. 1). The treatments were identical in appearance. The first dose of the 25 mg amitriptyline study medication was administered nocturnally, i.e. before bedtime around 10.00 PM, before the first test day. Tests were performed after acute (Day 1) and sub-chronic administration (Day 15) in both treatment series. The driving test was performed the day following drug administration at 11.00 AM, approximately 13 h after drug intake, and the laboratory tests at 1.00 PM, approximately 15 h after drug intake.

Driving test

The standardized driving test (O'Hanlon *et al.*, 1982) was performed on a four-lane primary highway in real traffic on a 100-km track between the cities of Utrecht and Arnhem. Patients were instructed to drive with a steady lateral position within the right traffic lane while maintaining a constant speed of 95 km/h. Patients were allowed to overtake slower moving vehicles. A licensed driving instructor had access to dual controls and accompanied the patient, guarding the safety during the test. A camera mounted on the roof of the car continuously recorded the position of the car within the traffic lane, by tracking the relative distance of the car from the delineated stripe in the middle of the road. The vehicle's speed and lateral position were continuously recorded, digitally sampled at 2 Hz, and edited off-line to remove data that was disturbed by extraneous events (e.g. overtaking manoeuvres, traffic jam). The primary outcome parameter is the standard deviation of lateral position (SDLP, in cm), measuring the amount of weaving of the car. Further, the standard deviation of speed (SDS, km/h), mean speed (MS, km/h) and mean lateral position (MLP, cm) were recorded. An illustration of SDLP in relation to driving safety is given in Fig. 2.

Laboratory tests

Laboratory tests were performed in a dimly illuminated sound-proof test room.

The tracking test Patients were instructed to keep an unstable moving bar in the middle of a horizontal plane (Jex *et al.*, 1966).

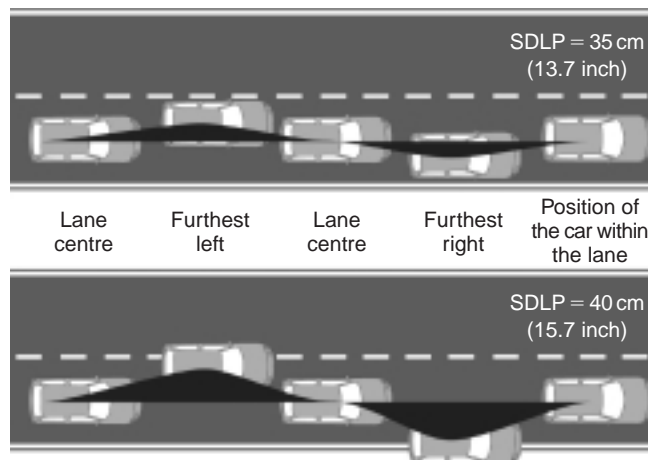


Figure 2 Meaning of the weaving index Standard Lateral Position of Lateral Position (SDLP).

They could counteract or reverse the movements of the unstable bar with the aid of a computer mouse. The root mean square of the tracking error (RMS) is the outcome of this test.

Sternberg memory scanning test (fixed version) After learning a fixed memory set of four digits, single digits were subsequently presented on the computer screen (Sternberg, 1966). By button-press, patients had to indicate whether a digit was part of the memory set or not. The mean reaction time (RT, ms) and percentage of errors are the parameters of interest.

Divided attention test In the divided attention test, the Sternberg memory scanning test and the tracking test were performed simultaneously. Parameters of the divided attention test are RMS, RT (ms) and percentage of errors.

Subjective assessments

All scales, except the driving-related scales, were administered before the driving test.

General functioning The following scales were administered to assess depression, anxiety and quality of life: Centre for Epidemiologic Studies Depression Scale (CES-D; Beekman *et al.*, 1997), Spielberger State-Trait Anxiety scales (STAI; Spielberger, 1983), five subscales (depression, anger, tension, vigour and fatigue) of the shortened version of the Profile of Mood State (POMS; McNair *et al.*, 1971) and the Short Form 36 Health Survey (SF-36; Ware *et al.*, 1993). A global measure of IQ was obtained with the Dutch reading test for adults (NLV; Schmand *et al.*, 1992), adapted from the National Adult Reading Test. Educational level was scored according to the five categories described in the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 2000). Each test day, a Sleep Quality Questionnaire was completed, consisting of 14 true-false statements assessing sleep over the previous night.

Pain Pain intensity was assessed using a Visual Analogue Scale (VAS) using the McGill Pain Questionnaire (MPQ; Melzack, 1975). Also, scores were calculated for quality of life and categorization of pain descriptors in three dimensions (sensory, affective and evaluative).

Driving Before and after the driving test patients indicated their alertness on a 21-point scale. After the driving test, patients indicated the perceived quality of their driving performance using a 20 cm scale that varied from 'I drove exceptionally poor' to 'I drove exceptionally well' around a midpoint of 'I drove normally'. Further, they indicated the level of effort they had to invest during driving on a 15 cm scale.

Adverse events Presence and intensity of side effects were reported on an adverse symptom checklist, including drowsiness, concentration problems, headache, dizziness, energetic feelings, drowsiness, feeling dazed, gastrointestinal disturbances and dry mouth.

Statistical analysis

Statistical analysis was performed by univariate analysis of variance (ANOVA) for repeated measures. Data of acute and subchronic effects were analysed separately. Within-subjects factor was treatment (two levels: placebo versus amitriptyline). Visual analogue scales assessing alertness also included the factor time (two levels: before versus after the driving test). When the criteria of normal distribution were not met, statistical analyses were performed using the Wilcoxon non-parametric test for two related samples. For all tests a critical α -level of 0.05 was used. Statistical analyses were performed with SPSS 11.0.1 for Windows.

Results

The 2-year inclusion period yielded seven eligible patients with chronic neuropathic pain who completed the study. The number of patients who took part in this study was low due to difficulties in

patient recruitment. Initially, 12 patients participated in the study. However, three patients withdrew after the training session; one because of pain complaints and two because of employment obligations that conflicted with study participation. Further, two patients used psychoactive medication during the study, therefore their data were excluded from analysis. Participants who completed the study were four men and three women, mean (\pm SD) age: 51 (\pm 5.9) years, age range: 42–58 years, mean weight: 83.9 (\pm 3.1) kg, mean duration of pain complaints: 57.4 (\pm 28.1) months (range: 24–96 months). Patients used amitriptyline prior to study participation for 11.6 (\pm 8.2) months (range: 5–27 months). Further, they drove 12 714 (\pm 9411) km per year (range: 5000–30 000 km). Demographic variables of patients are summarized in Table 1.

Driving test

Mean SDLP values for amitriptyline and placebo after acute and subchronic treatments are depicted in Fig. 3. Statistical analysis revealed a significant acute effect of treatment on SDLP scores ($F(1, 6) = 10.2, p < 0.019$). Mean SDLP was higher in the acute amitriptyline than in the placebo condition: 29.0 cm (SD = 8.1, range = 21.6–43.5) versus 26.0 cm (SD = 8.1, range = 17.0–37.1), respectively. Estimated observed power according to statistical analysis was 0.76 and estimated effect size was 0.63, indicating that sufficient power was obtained with seven patients. No significant differences were found between amitriptyline and placebo after subchronic treatment, indicating that amitriptyline did not impair driving ability after 2 weeks of treatment. Furthermore, no relevant significant differences between treatments, both after acute and subchronic administration, were found on mean speed, SD speed, mean lateral position or excursions out of lane (both left and right).

Subjective assessments

Overall, participants scored within the normal range on assessments of depression and anxiety (CES-D, STAI, POMS). No significant differences were found between treatments in the acute

Table 1 Pain-related demographic information displayed for each patient separately

Patient no./sex/age (years)	Diagnosis	Duration of pain complaints (months)	Duration of AMI use (months)	Concomitant analgesic medication
1/M/43	Lumbago	84	27	none
2/M/51	Lumbal radiculopathy	96	6	ibuprofen
3/F/54	Failed Back Surgery Syndrome (FBSS) with sacral radiculopathy	36	18	rofecoxib, paracetamol, naproxen
4/F/58	FBSS and spinal stenosis	60	12	rofecoxib, paracetamol
5/M/52	Mixed nociceptive and neuropathic local pain in arm	24	7	rofecoxib, lidocaine creme
6/F/54	FBSS	72	6	paracetamol, ibuprofen
7/M/42	Cervicobrachialgia	30	5	naproxen, acetylsalicylic acid, paracetamol

Abbreviations: F, female; M, male; SI, sacroiliac; AMI, amitriptyline.

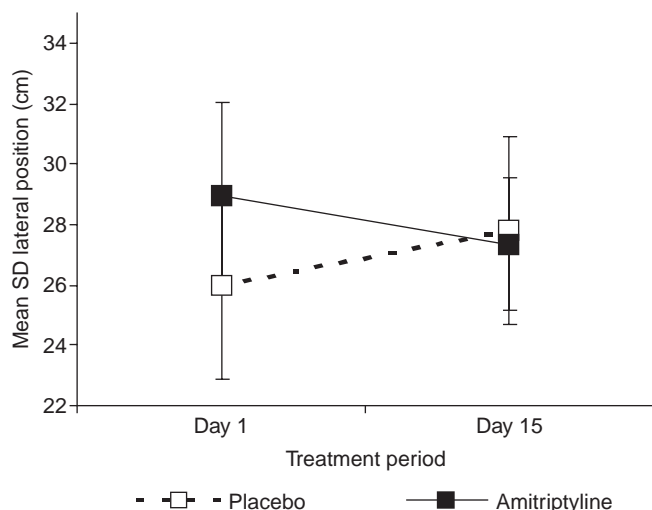


Figure 3 Mean (\pm SE) SDLP after acute (Day 1) and subchronic (Day 15) treatment in the amitriptyline and placebo condition.

or subchronic phase on these measures. Furthermore, no significant differences were found between treatments in both phases on sleeping quality, pain descriptors of the three dimensions of the MPQ, all subscales of the SF-36 or quality of life scores on the MPQ. Apparently, quality of life did not improve with treatment of amitriptyline. Moreover, pain intensity scores did not differ between treatment conditions, neither in the acute nor in the subchronic phase (Fig. 4).

Statistical analysis revealed no significant effect of acute or subchronic treatment for subjective driving quality, indicating that patients judged their driving quality the same in both phases of amitriptyline and placebo administration. Further, no statistically significant differences between treatments were found concerning mental effort during driving and alertness before or after driving.

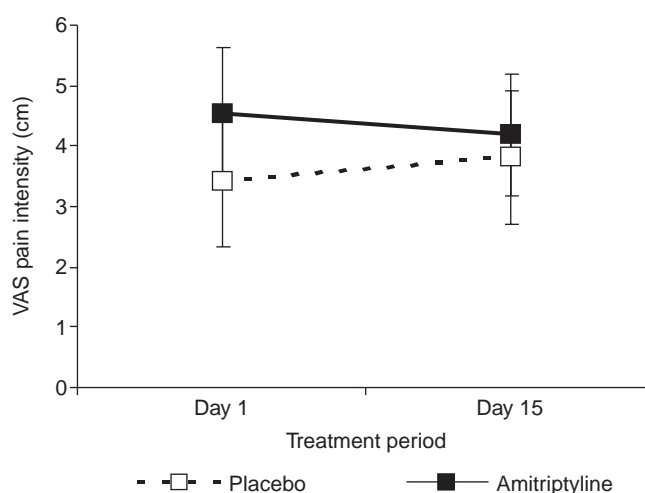


Figure 4 Mean (\pm SE) VAS pain intensity scores in cm after acute (Day 1) and subchronic (Day 15) treatment in the amitriptyline and placebo condition.

Laboratory test performance

Laboratory test results are summarized in Table 2. Statistical analysis revealed a significant difference between treatments in reaction times for the Sternberg Memory Scanning Test after acute treatment ($F(1, 6) = 6.1, p < 0.048$). Reaction times were longer after acute dosing of amitriptyline compared to placebo. Although inspection of the data presented in Table 2 seems to indicate that amitriptyline decreased performance compared to placebo on almost every parameter after acute dosing, no significant effects were found for any other variable. Estimated observed power according to statistical analysis was below 0.10 for all of these tests, indicating that power was not sufficient with seven patients to register any relevant change in performance.

Table 2 Means (\pm SE) are presented for the laboratory test results

	Amitriptyline		Placebo	
	Acute	Subchronic	Acute	Subchronic
Tracking test (RMS)	17.6 (2.8)	13.6 (1.7)	15.9 (2.7)	13.1 (2.0)
Sternberg Memory Scanning Test				
Reaction time (ms)	840.3* (49.0)	772.0 (63.0)	779.8 (43.2)	754.0 (188.4)
Errors (%)	1.2 (0.6)	2.8 (0.9)	0.7 (0.4)	1.5 (0.6)
Divided attention test				
Tracking (RMS)	23.3 (2.3)	22.6 (2.2)	21.6 (3.2)	20.8 (3.2)
Sternberg Memory Scanning				
Reaction time (ms)	933.3 (71.4)	809.5 (51.0)	909.9 (54.5)	832.8 (39.3)
Errors (%)	5.6 (1.5)	3.2 (1.4)	3.0 (1.3)	1.8 (0.3)

Abbreviations: SE, standard error; RMS, root mean square; ms, milliseconds. A significant difference is indicated by * ($p < 0.05$).

Adverse events

Reported adverse events were mild. In the acute phase of treatment with amitriptyline, patients felt more sedated ($Z = -2.0$, $p < 0.046$), and less energetic ($F(1, 6) = 6.8$, $p < 0.040$) when compared to placebo. In the subchronic phase of treatment with amitriptyline they were more confused compared to placebo ($Z = -2.1$, $p < 0.034$).

Discussion

The main finding of this study is that 25 mg amitriptyline significantly impairs driving performance after acute administration. Changes in mean SDLP scores after acute administration of amitriptyline were comparable to those generally observed with a blood alcohol concentration of 0.5 mg/ml or more (Louwerens *et al.*, 1987), the legal limit for driving in many countries. This result is in line with a huge amount of literature on the impairing acute effects of amitriptyline (e.g. Deptula and Pomara, 1990). Of concern, pain patients are not aware of their impaired driving ability after the acute dose of amitriptyline. Hence, it is important that physicians and pharmacists clearly advise patients about the start of their treatment with amitriptyline and possible effects on driving ability. Regarding laboratory test performance, reaction times on the Sternberg Memory Scanning Test were increased after the acute dose of amitriptyline compared to placebo, indicating worse performance. Although inspection of the data presented in Table 2 seems to indicate that after acute treatment of amitriptyline performance decreased on almost every parameter compared to placebo, no significant differences between amitriptyline and placebo were found on any other laboratory test measures. However, statistical power estimations indicated that power was not sufficient with seven patients to register any relevant change in performance. Therefore, this lack of result is most likely related to the low number of participating subjects. In contrast, no significant differences were found between amitriptyline and placebo after 2 weeks of treatment on driving performance and laboratory tests. As expected, tolerance developed rapidly to the sedative effects of amitriptyline treatment.

The results of this study are generalizable to patients with chronic neuropathic pain who are treated with nocturnally administered amitriptyline 25 mg and who do not use other concomitant psychoactive medication. One might argue that tolerance to the sedative side effects in the studied patient sample was due to the fact that they adapted more quickly because they were familiar with this drug. However, it is important to note that our results are in line with previous experimental data and data from driving studies in healthy volunteers and with higher dosages that found that impairment of performance due to amitriptyline administration usually lasts only the first few days of treatment (Ramaekers, 2003) and tolerance develops within a week or two. Therefore, it is likely that patients who are naive to amitriptyline treatment will also adapt to the side effects of amitriptyline in a week or two.

A limitation of our study is the small sample size. Although the observed power and effect size of the statistical analysis of the

driving data showed to be sufficient, larger studies are required to demonstrate these effects in a broader sample. It appeared very difficult to recruit patients using amitriptyline as psychoactive monotherapy. Most patients in clinical practice are treated with multiple psychoactive drugs simultaneously, e.g. tricyclic antidepressants, anticonvulsants and opioids. In this context, it is important to note that there may have been a selection bias with respect to participating patients. Patients who took part in the study may have had less severe pain than the majority of patients who use amitriptyline, since they were effectively treated with only one psychoactive drug. Indeed, pain intensity ratings were unexpectedly low and moreover, not reduced under amitriptyline treatment compared to placebo. This latter finding is even more remarkable since the participating patients were adequately treated with amitriptyline for 5 months or more prior to study participation. We do not have a clear explanation for this observation, but it cannot be ruled out that patients selectively participated to find out if they could do without their medication. Another, speculative, possibility is that no difference in pain relief was found due to carryover effects of amitriptyline that relieve pain for an extended period of time, at least beyond the 6-day washout phase. In this context, it is important to note that besides the occurrence of side effects, pain might have influenced performance negatively in the acute phase of treatment, which could have confounded results. Although no significant differences in pain intensity scores were found between all test days, this cannot be ruled out completely. Future studies should address the impact of pain on driving performance to enable disentangling of these effects.

The use of paracetamol and/or NSAIDs was not prohibited in this study to allow escape medication when needed, and to avoid drop outs because of severe pain. One could argue that the use of NSAIDs and/or paracetamol might have decreased pain intensity. During the study period, six out of seven patients used concomitant non-sedative analgesic medication. On the other hand, it is well known that NSAIDs and/or paracetamol have poor analgesic efficacy in the treatment of neuropathic pain (e.g. McClean, 2003). Furthermore, side effects of NSAIDs occur infrequently, are mild in intensity and are most often reported by the elderly (Wysenbeek *et al.*, 1988; Hanlon *et al.*, 1997).

In conclusion, this study showed that driving is impaired in pain patients who use low dosages of nocturnally administered amitriptyline as an analgesic drug. The results are consistent with previous findings, which showed that it is unsafe to drive a car after acute administration of amitriptyline. Additionally, this study demonstrated that this also applies to a low nocturnally administered dose of 25 mg amitriptyline. It was further demonstrated that tolerance to the sedative side effects developed after repeated dosing. Future studies should focus on replicating these findings in a larger sample and on higher dosages prescribed in the treatment of chronic neuropathic pain and its influence on driving safety. In addition, studies should concentrate on psychoactive polytherapy and driving ability, since this is common clinical practice.

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