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Driving, Opioid-maintenance, and Co-medications: A Comprehensive Assessment of 22 Cases

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Abstract

Introduction: Patients in stable Opioid Maintenance Treatment (OMT) for opioid-dependence are, as a rule, considered fit to drive a car. Polypharmacotherapy, however, is common in opioid-dependent patients, and its association with driving fitness is not well known. Therefore, we examined driving fitness of 22 OMT patients of whom the majority were multidrug-treated patients.

Material and methods: The assessment included a standard on-road driving test, clinical neurological examination, and cognitive driving-related tests. The OMT patients were grouped on the basis of their psychoactive medications into two groups. The first group was considered to have a low probability for drug-related driving impairment (n=10). This group included patients treated with opioid agonist alone or along with the second generation antidepressant or lithium. The second group included patients with probable drug-related driving impairment (n=12). All patients in this group were given at least one benzodiazepine (BZD) drug,

Results: In neurological evaluation all OMT patients met the basic requirements for driving. In the driving test, all patients in the group with 'improbable drug-related driving impairment' and all except one in the group with 'probable drug-related driving impairment' were found fit to drive. However, in the driving test total score and two driving-related cognitive tests, the group with 'probable drug-related driving impairment' scored significantly lower than the improbable group (p=0.021, 0.001, and 0.028, respectively). Two cases with 'probable drug-related driving impairment' are described in detail.

Conclusions: The results of this case series give support for the notion that OMT patients in stable treatment, in general, are fit to drive. When assessing the driving fitness of individual OMT patients with polypharmacy, combining pharmacological and non-pharmacological information is essential, as shown by two case descriptions.

Introduction

Opioid maintenance treatment, also known as opioid-substitution treatment, with long-acting opioid like oral methadone or sublingual buprenorphine is the standard treatment for opioid-dependence, if opioid withdrawal cannot be achieved [1]. While the OMT is effective in reducing use of illegal opioids, psychosocial and psychiatric condition of the patients is often complicated, and the duration of the treatment is usually several years, or even decades. On the basis of systematic review, it has been concluded that short-term treatment with an opioid drug is associated with cognitive deficits and reduces driving fitness [2]. Opioid-dependent patients, however, have high tolerance for opioid effects and many of them feel that they are competent to drive soon after a stable maintenance dose has been achieved. Yet, guidelines whether the patients are considered fit to drive vary a lot between countries, and research knowledge of this issue is still showing inconsistent findings between traffic crash data and experimental studies [3,4]. Statistics show that opioid users have elevated risk of traffic accidents, while experimental evidence on effects of long-term OMT on driving is limited [5].

Soon after initiation of OMT programs with methadone in 1965 the driving fitness of the patients became an issue of professional discussions and a research topic. Early studies concerning methadone treatment effects on driving ability were summarized by Vingilis in 2002 by noting that the results are mixed, and firm conclusions cannot be made [6]. One year later Fishbain reviewed the driving-related studies extensively and concluded that the majority of the studies indicate that either buprenorphine or methadone appears not to impair driving [7]. More recently some studies have shown that buprenorphine patients show slightly better performance than methadone patients in driving-related cognitive tests [8,9]. However, an advantage of buprenorphine over methadone has not been seen in all studies [10,11]. A recent

review concluded that there are still several shortcomings for making a general recommendation about driving fitness of OMT patients [4]. These include lack of actual driving performance tests, great variability in driving-related cognitive tests, and the lack of inclusion of other prescription drugs commonly used by the patients. Further study taking these problems into consideration was called for. In order to reduce the gaps in current knowledge we made a study in which driving ability of a natural sample of OMT patients was comprehensively assessed.

The present study had two major aims. First, driving fitness of opioid maintained patients was determined using comprehensive assessment methods including an on-road driving test. The result of the on-road driving test in a normal traffic was treated as the main variable of interest, because it is kept as the most valid assessment of the driving fitness [12,13]. Our second aim was to examine if co-medications given to OMT patients are associated with driving performance or driving-related cognitive test results.

Material and methods

The study participants were unpaid volunteer opioid-dependent patients admitted for OMT in the addiction clinics of Helsinki, Tampere, or Jyväskylä area. Inclusion criteria were the following: age 18–50 years, native Finnish speaker, opioid-dependence diagnosis, being at least of twelve months in OMT with buprenorphine, buprenorphine/naloxone, or methadone, and a valid driver's license. Exclusion criteria were the following: current polysubstance or alcohol abuse, acute axis I psychiatric morbidity other than substance abuse related, change in current drug doses or initiation of a new psychoactive drug within the past week, severe brain injury, chronic neurological disease, history of other than substance-induced psychoses, epileptic seizures, Human Immunodeficiency Virus (HIV) infection, pregnancy, or primary cognitive deficit. To ensure study eligibility, a clinical psychiatric interview was conducted for each participant using diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [14]. Each patient was screened by a urine sample for substance abuse on the day of testing and at least once in the preceding month. Participants showing signs of current intoxication or binge on any substance of abuse, and those with any non-prescribed psychoactive drug dose within 24 h, were all excluded.

Buprenorphine/naloxone was given to the majority (78%) of buprenorphine treated patients. Thus, they received a dose of naloxone in the ratio of 1:4 combined with their buprenorphine dose. When the tablet is given sublingually the absorption of naloxone is low and eliminates within the first hours [15]. It has been shown that naloxone has minimal, if any effect, on the bioavailability or pharmacokinetics of buprenorphine [16,17]. Therefore, patients using either one of the buprenorphine compounds were combined.

Research ethics

The study was approved by the independent Hospital District of Helsinki and Uusimaa Ethical Committee (permission 90/2001). The study was conducted in accordance with the 1964 Declaration of Helsinki. All study participants were able to read and understand the patient information sheet, and signed the informed consent form. The participants were free to discontinue their participation in the study whenever they wanted. No information about individual assessment results were passed to the authorities.

Procedure

The patients were tested with between 10 am and 2 pm, which means between two to seven hours after the administration of their opioid maintenance drug. They were divided into two groups (Table 1) based on their co-medication related risk of impairment on driving. This was based on the assumption that opioid agonist pharmacotherapy with buprenorphine or methadone, as a single drug, has only minor, if any, negative effect on driving performance [7,18]. The first group included all patients with no co-medication or with one additional drug with a low risk for driving impairment. Additional drugs classified as having a low risk for driving-impairment included new generation antidepressants and lithium [19,20]. The second group included patients using drugs for which there is relatively high risk for impairment on driving like benzodiazepines [21,22]. Possibilities for drug interactions were taken into account when classifying patients into these groups [23-26]. For the further analyses benzodiazepine doses of were converted to a diazepam equivalent using Bazire's equivalence table [27].

Driving experience information and the patient's own view about driving safety was asked by a questionnaire devised for the study.

Variable	Group		Statistical comparisons between groups[1]
	Patients with improbable drug-related driving impairment (n=10)	Patients with probable drug-related driving impairment (n=12)	
Age (years)	32 ± 8	38 ± 9	p=0.08
Sex			
Female (%)	40%	17%	p=0.35
Male (%)	60%	83%	
Opioid agonist drug			
Buprenorphine (%)/ Methadone (%)	80% / 20%	8% / 92%	p=0.002 **
Buprenorphine dose (M ± SD)	18 ± 7 mg	24 mg	-
Methadone dose (M ± SD)	115 ± 21 mg	133 ± 30 mg	-
Time in OMT (years)	3 ± 1	3 ± 2	p=0.75
Other drugs than opioid agonist			
Any drug (%)	40%	100%	p=0.09
Antihistamine (%)	0%	10%	p=1.00
BZD (%)	0%	100%	p=0.0001 ***
Dose (M ± SD)[2]	-	24 ± 22 mg	-
Mood stabilizer (%)[3]	10%	17%	p=1.00
Neuroleptic (%)	0%	25%	p=0.22
Non-BZD hypnotic (%)	0%	25%	p=0.22
Second generation antidepressant (%)	30%	8%	p=0.29
Tricyclic antidepressant (%)	0%	10%	p=1.00
Patients reporting opioid overdose (%)	10%	17%	p=1.00
Patients reporting minor head injury (%)	40%	42%	p=1.00

[1]Tested by Fisher's Exact Test
[2]BZD equivalent doses.
[3]These included anticonvulsants and lithium.

Table 1: Group comparisons on demographic and treatment variables.

In addition the patients evaluated distressing effects of 22 driving situations by choosing one out of four alternatives (not at all, somewhat, quite, or very distressing); and reported frequency of 22 driving errors by choosing one out of four alternatives (never, occasionally, quite often, almost every time while driving) [28]. More information about the topics covered by the questionnaires are presented in connection with case descriptions.

On-road driving assessment

On-road driving assessment was done by the same licensed driving instructor for each participant. The one-hour driving test using a car took place in city traffic during normal day- time instead of rush hours. The test included various car driving tasks typically done in driving evaluations devised for neurological patients [28]. This evaluation was meant for driving a car for non-professional purposes [29]. The driving instructor completed two formal evaluation sheets. Driving errors were classified as nonhazardous vs. hazardous errors. An error was classified as a hazardous one, if it exposed anyone on the road to a potential risk. The marking of the errors was done according to the manual developed by the Finnish Vehicle Administration [30]. In addition driving instructor gave a performance score for 11 driving domains. The scoring was done as follows: 5=definitely strong, 4=strong, 3=either strong or weak, 2=weak and 1=definitely weak [28]. Driving domains which were evaluated included the following: awareness of other vehicles and road users, appropriate adjustment of speed, signaling one's intentions, predictability, correctness of driving lines, understanding correct driving order, e.g., at intersections, junctions, roundabouts, ability to follow traffic lights and traffic signs, distance to other vehicles and obstacles , vehicle handling and vehicle control, independence and ability to map out one's driving, ability to anticipate events in traffic, and concentration on driving. Finally, an overall safety assessment was done using four levels [31]. The highest level of safety was 'safe driver in all conditions' meaning that she/he was considered as being a safe driver in all places and any road conditions. The next best level was 'safe driver in normal conditions' meaning that she/he was considered as a safe driver in all places but good road conditions were essential for safe driving. Third level was 'safe driver only in the best conditions' meaning that she/he was considered as a safe drive only in familiar places and in good road conditions. The last level was 'unsafe driver' meaning that driving was considered unsafe in all places and road conditions. According to the Finnish driving regulations drivers belonging to the classes 'safe drivers in all conditions' or 'in normal conditions' are considered fit to drive a car.

Medical examinations

Medical examinations included a clinical neurological status and a traffic vision evaluation done by a neurologist. In addition, a clinical psychiatric interview, based on DSM-IV axis 1 criteria, was done as described earlier. Psychiatric drug regimen of patients was not changed, and the severity of psychiatric disorder was used only as an exclusion criterion. Thus the groups were not compared in regards to psychiatric comorbidity.

Driving-related cognitive tests

Cognitive examinations done by a neuropsychologist included the Determination, Peripheral Perception, Signal Detection, Stroop Interference, and Tachistoscopic Traffic Perception tests from the computer-aided Vienna Test System [32-36]. The purpose of the Determination test is to measure 'Resilience of Attention and reaction speed under conditions of sensory stress'. The examinee is instructed to

identify color or sound stimuli and react to them pressing correspondent response button using a response panel. Adaptive version S1 was used. The number of correct reactions was chosen as the variable of interest as it has been shown to have specific predictive value for driving ability [37].

The purpose of the Peripheral Perception test is to assess the perception and processing of peripheral visual information. The examinee is instructed to focus on a simple visual tracking task presented on the computer screen. Simultaneously, she/he should react by pressing a pedal whenever they notice critical visual stimuli presented at their left or right periphery. 'Tracking deviation', a measure of divided attention, was used as a score [37].

The purpose of the Signal test is to test long-term selective attention, namely differentiation of relevant visual signals from the irrelevant ones. The score variables for the Signal test were median reaction time and the number of correct or delayed reactions. Test form S1 was used.

The purpose of the Stroop test is to evaluate inhibition of overlearned responses instead of consciously controlled ones. Poor performance in the Stroop interference condition has been shown to be associated with inappropriate reactions in critical traffic situations [38]. Therefore, variable 'median reaction time in interference condition' was used as a score. Version S4 (light pen) was used.

The purpose of the Traffic Perception Test is to evaluate visual observation ability and skill in obtaining an overview, and also of visual orientation ability and speed of perception. The examinee is shown 20 pictures of traffic scenes, for one second each. Then she/he has to select from a list that contains five different items those ones that she/he remembers to have seen in the picture. The number of correctly answered lists constitutes the main variable 'Overview'. This was chosen as a score of interest [37, 39]. Version S1 was used.

In evaluating the cognitive results age-independent norms were used, whenever possible, and scores that were not above the 16th percentile were considered to indicate problems in driving ability similarly to the 'passed test' methodology developed by Gaertner et al. [40]. Test norms from the norm sample were used except in the Peripheral Perception and Stroop tests where general adult norms were used for determining performance percentiles. Driving instructor was not informed about the results of the medical or cognitive examinations.

Statistical analyses

Group comparisons between patient groups were performed using the non-parametric Mann-Whitney U tests or Fisher's exact test. Correlations between driving test scores and drug doses were analyzed by the non-parametric Spearman's rho. In all analyses alpha-level was set to 0.05. Two-tailed tests from the Statistical Package for Social Sciences (SPSS) version 20.0 were used.

Results

Sample characteristics

Twenty –six volunteer patients met all the inclusion criteria. Four volunteer patients were excluded on the basis of a positive drug screen for illicit drug use. The mean age of included patients was 35 ± 9 years. Two thirds (68%) of them were male. The mean duration since obtaining a driver's license was 13 ± 9 years. One fifth of the patients (19 %) had professional car driving in their driving history. All patients had driven a car during the last year. Group-wise statistics of driving variables is shown in table 2. The mean time in OMT was 3 ± 2 years.

Test	Group		Statistical comparisons between groups[1]
	Patients with improbable drug-related driving impairment (n=10)	Patients with probable drug-related driving impairment (n=12)	
Years since obtaining a driver's license	10 ± 9	14 ± 10	p = .25
Driven kilometers within the last year, participants with more than 5000 km (%)	50%	25%	p=0.38
Patients with professional driving experience (%)	17%	20%	p=1.00
Driving test score (M ± SD, max = 55)	51 ± 3	46 ± 5	p=0.021 *
Safe drivers in all conditions according to driving instructor's assessment (%)	90%	83%	p=1.00
Participants driving the test route with no errors (%)	60%	55%	p=1.00
Participants showing no 'weak' or 'either weak or strong' driving domains (%)	0 %	58 %	p=0.005 **
Participants passing all driving-related cognitive tests above 'pass level' (%)	78%[2]	25%	p=0.024 *

[1]Tested by Fisher's Exact Test

[2]n=9

Table 2: Group comparisons on driving variables.

Forty-one percent of the patients were treated with buprenorphine and 59% with methadone. However, after the patients were divided into two groups on the basis of probability of drug-related driving impairment, nearly all buprenorphine patients were in the improbable group and nearly all methadone patients in the probable group. This difference was statistically significant (Table 1). Two thirds of the patients, as a whole, (67%) were treated with other psychoactive drug than opioid agonist drug. About half of them (55%) were given any BZD drug (including both anxiolytic and hypnotic prescriptions). In fact, having a BZD drug became the variable which showed precise 0/100% distribution between improbable vs. probable drug-related driving impairment (respectively). As shown in table 1 nearly all patients with 'improbable drug-related driving impairment' were treated with buprenorphine and had no BZD co- medication whereas the patients with 'probable drug-related driving impairment' were almost all treated with methadone along with a BZD drug. Case-wise listing of all drugs given to the two drug groups can be seen in tables 3 and 4. (Of note here, is the observation that all four patients with positive drug screen would have been in the group 'probable drug-related driving impairment' because of their BZD drug prescriptions). Patients with 'probable drug-related driving impairment' tended to be elder than the ones in the 'improbable' group, but this difference only approached significance.

On-road driving

In the on-road test the patients scored mean 49 ± 5 points out of 55 points. According to the driving instructor's overall safety assessment 83% of the patients belonged to highest safety class, 'safe drivers in all conditions' and 11% were 'safe drivers in normal conditions'. Thus, in total 94% of them were considered fit to drive a car for non-professional purposes (all except one patient). Forty-one percent of them drove the route without any driving error and 83% without any hazardous error. As shown in table 2 significant between groups differences favoring the 'improbable' group were seen in total score of the on-road driving test and domains evaluated as 'weak' or 'either weak or strong'. Also, it can be noted that 5 out of 6 patients treated with opioid agonist only drove the test route without committing any error in the route (cases 1-5 in table 3). On the contrary, all three patients that made any hazardous error in the driving test belonged to the group with 'probable drug-related driving impairment' (cases A, B and 21 in table 4).

Patients with 'probable drug-related driving impairment' scored statistically significantly lower in the on-road driving test (U=25.5, p=0.021). Figure 1 shows the group means and the individual data for scores for both groups in the on-road driving test. As can be seen in figure 1 there was much more variance in the driving test score among the patients with 'probable drug-related driving impairment'. Both buprenorphine and methadone dose negatively correlated with the driving test score (-.21, *ns* and -.68, *p* = .01, respectively). Figure 2 shows the correlation between methadone dose and driving test score. When the correlation between BZD equivalent dose and driving test was analyzed in the methadone patients, also that was negative (-0.40), but a non-significant one.

Medical examinations and cognitive-driving related tests

All patients (n=22) showed normal visual fields and were considered neurologically fit to drive. In driving-related cognitive tests, which are not mandatory in Finnish driving assessment about half of the patients (48%) passed every test above the 16th percentile criterion. As shown in table 2 the group with 'probable drug-related driving impairment' had more non-passed cognitive tests than the improbable group (78% *vs.* 25%). Figure 3 shows test-wise comparisons between the groups on cognitive tests. In group-wise raw score comparisons of cognitive driving-related tests two significant between groups differences were seen. Patients with 'probable drug-related driving impairment' scored significantly worse than the improbable group in the Determination
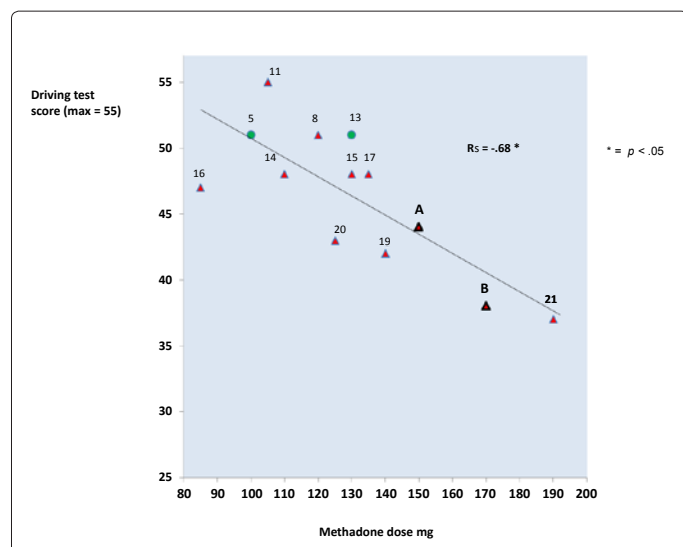

Figure 1: Relationship between medication groups and on-road driving test score.
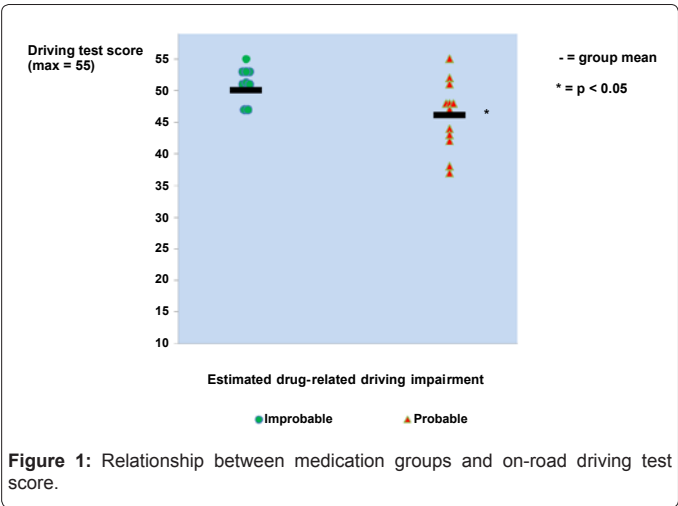
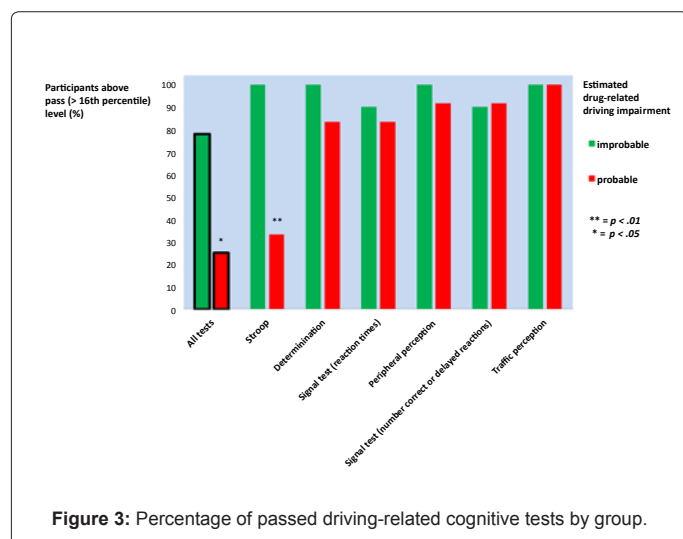**Figure 2:** Relationship between methadone dose and driving test score.

Figure 3: Percentage of passed driving-related cognitive tests by group.

test measuring 'resilience of attention under conditions of sensory stress' (number of correct reactions, respectively 429 ± 97 *vs.* 512 ± 56; $U=23.0$, $p=0.028$). In the Stroop interference test, the mean of median reaction time was significantly slower in patients with 'probable drug-related driving impairment' in relation to other patients (1.35 ± 0.55 sec *vs.* 0.88 ± 0.11 sec; $U=97.5$ $p=0.001$, respectively).

Finally, in order to elucidate the individual variance of driving fitness and potential factors affecting on it, two cases from the group 'probable drug-related driving impairment' are described.

Case A: When A came to driving test he was 47 years old. He had been in methadone maintenance treatment for 4 years, current dose 150 mg. In addition he was prescribed BZD oxazepam 90 mg a day (30 mg every 8 h) as an anxiolytic. In the evening he took a third prescribed medicine, tricyclic antidepressant doxepine 100 mg, as a somnolent and antidepressant. His depression, however, was considered as being in partial remission. A had obtained a driver's license 20 years ago, and he said that he had driven since then 'a huge amount of kilometers both

home and abroad', all non-professional driving. In a medical inspection he was considered fit to drive. During the four years in MMT, A had gained 35 kg weight. His BMI index was 36.2, which is considered as obese according to the World Health Organization classification, but this was not considered as a health problem affecting driving fitness.

Case A admitted that earlier his driver's license had been cancelled by the police for driving under influence of drugs. He got back his driver's license a year ago. He estimated that since then he has driven around 50000 km. He admitted that occasionally he is very tired when driving and that is very distressing for him. He reported that occasionally he finds himself making some driving errors like driving too fast or slow, or drives too close to the middle line. He considered that these never cause sudden danger on the road. Overall, A considered himself as a safe driver in all conditions.

In driving test A made two errors. He almost drove against red lights, and this was considered as a hazardous error. He made a second error in noticing a traffic sign telling to change a lane a little bit late, but he handled the situation very smoothly. In the driving test his total score was 44. This was below the mean of the all patients. Yet, driving instructor's overall assessment of driving safety was 'safe in all conditions'. This was motivated by his excellent vehicle handling and smooth and calm handling of problems encountered. Problems were found to be related to minor slowing of initial reactions. A's slowness was evident in cognitive tests as well. His performances were below critical values in the Determination and Stroop interference tests (Table 3).

Case B: When B came to driving test he was 26 years old. He had been in methadone maintenance treatment for 3 years, current dose 105 mg. In addition he was prescribed BZD clonazepam 6 mg as an anxiolytic, valproate 1000 mg for controlling borderline personality disorder related mood swings and neuroleptic levomepromazine 100 mg and zopiclone 7.5 mg for sleeping. B had suffered a minor head injury about 5 years ago when he had been intoxicated. He reported a black out and confusion period of few minutes. He was taken into hospital for a medical check-up and because he was orientated and in a good condition, he was soon released. B had obtained driver's license 9 years ago. He estimated that he had driven during the last year about 20000 kilometers. He felt none of the driving conditions given in the questionnaire would be quite or very distressing for him. He did report that he hardly ever notices vehicles that drive behind him, and occasionally makes some other driving errors. Yet, he considered that his driving errors never cause sudden danger on the road, and he is a safe driver in all conditions.

In driving test he made ten errors. Five of his driving errors were classified as hazardous ones (three in keeping safe distance to other road-users, one in perception, and one driving order). Another five were classified as non-hazardous. His overall score in the driving test (43 points) was below the mean of all patients, and his performance was evaluated as poor in two driving components, namely 'distance to other road users' and 'concentration on driving'. The driving instructor's overall assessment of driving safety was 'safe only in the best conditions'. This was motivated by his impulsive driving style and violations in keeping within speed limitations or safe distances to other road-users. His vehicle handling, however, was considered excellent. In cognitive testing B passed only three out of six tests above the critical value of 16th percentile. Non-passed tests included the Determination, Peripheral perception, and the Stroop tests (Table 3).

Case code Age / Sex Minor head injuries or opioid overdoses	Drugs: OMT drug BZD drugs Other drugs	Driving safety: Instructors overall assessment based on on-road driving test	On-road driving test score (max. = 55) Errors in on-road driving test (number and classification)	Domain-wise evaluation of driving performance (number of either strong or weak driving domains/ number of weak driving domains)	Driving-related cognitive tests (non-passed test; percentile)	Driving experience: Driver's license Professional driving experience The last year driving
Case 1 27 years / male Minor head injury +	Buprenorphine 24 mg - -	Safe driver in all conditions	55 points No errors in the on-road driving test	All driving domains evaluated as strong[2]	All cognitive tests above pass level [3]	Nine years since driver's license One year of professional driving 20000 km of driving during the last year
Case 2 28 years / male -	Buprenorphine 16 mg –	Safe driver in all conditions'	53 points No errors in the on-road driving test	All driving domains evaluated as strong	All cognitive tests above pass level	10 years since driver's license No professional driving 1000 km of driving during the last year
Case 3 32 years / male –	Buprenorphine 10 mg –	Safe driver in all conditions	53 points No errors in the on-road driving test	All driving domains evaluated as strong	All cognitive tests above pass level	Two years since driver's license No professional driving 15000 km of driving during the last year
Case 4 38 years /male Minor head injury +	Buprenorphine 24 mg –	Safe driver in all conditions	53 points No errors in the on-road driving test	All driving domains evaluated as strong	All cognitive tests above pass level	19 years since driver's license No professional driving 30000 km of driving during the last year
Case 5 33 years / female Opioid overdose +	Methadone 130 mg –	Safe driver in all conditions	51 points No errors in the on-road driving test	All driving domains evaluated as strong	All cognitive tests above pass level	One year since driver's license No professional driving 5000 km of driving during the last year
Case 6 28 years / female –	Buprenorphine 12 mg –	Safe driver in all conditions	53 points Three non-hazardous errors	All driving domains evaluated as strong	All cognitive tests above pass level	Two years since driver's license No professional driving 12000 km of driving during the last year
Case 7 28 years / male –	Buprenorphine 16 mg – Mirtatzapine 30 mg	Safe driver in all conditions	50 points No errors in the on-road driving test	All driving domains evaluated as strong	Signal test (number of correct or delayed reactions ; percentile 10)	Nine years since driver's license No of professional driving 3000 km of driving during the last year
Case 8 49 years / male Minor head injury +	Methadone 100 mg – Lithium 600 mg	Safe driver in all conditions	51 points One non-hazardous error	All driving domains evaluated as strong	Signal Test below pass level (reaction times; percentile 10)	32 years since driver's license 5 years of professional driving 5000 km of driving during the last year
Case 9 30 years / female –	Buprenorphine 28 mg – Venlafaxine 75 mg	Safe driver in all conditions	47 points Two non-hazardous errors	All driving domains evaluated as strong	All cognitive tests above pass level	10 years since driver's license No professional driving 5000 km of driving during the last year
Case 10 28 years / female Minor head injury +	Buprenorphine 12 mg – Essitalopram10 mg	Safe driver in normal conditions	47 points Three non-hazardous errors	All driving domains evaluated as strong	All cognitive tests above pass level	6 years since driver's license No professional driving 3000 km of driving during the last year

[1]Listed in the order driving safety, committed errors in the driving test, driving instructor's assessment of patients' performance in on-road driving test, age, sex, buprenorphine before methadone.
[2]This definition includes also 'definetely strong'
[3]Determination and Stroop tests are missing.

Table 3: Summary of cases with improbable drug-related driving impairment[1].

Discussion

This study was planned to examine driving fitness of stable OMT patients. All included patients had been at least one year in treatment and were tested negative in drug screens for substance abuse at least for one month. As expected more than half of the patients in the sample were currently using some other psychoactive prescription drug too. The main finding in our case-series of 22 OMT patients is that all expect one of the patients was found fit to drive according to an on-road driving test which followed official guidelines used for all drivers in Finland.

In order to assess the association between co-medications and driving fitness, the patients were divided into two groups according to their probability of drug-related driving impairment. The analyses showed that the patients with 'probable drug-related driving impairment' scored lower than other patients in the sum of on-road driving tests and in two out of six driving-related cognitive tests.

Patients with improbable drug-related driving impairment

The sample included five patients using only buprenorphine (cases 1-4 and 6) and one methadone (case 5). Five of them (except one

Case Age / Sex Minor head injuries opioid overdoses	Drugs: OMT drug BZD drugs Other drugs	Driving safety: Instructors overall assessment based on on-road driving test	On-road driving test score (max.=55) Errors in on-road driving test (number and classification)	Domain-wise evaluation of driving performance (number of either strong or weak driving domains/ number of weak driving domains)	Driving-related cognitive tests (non-passed test; percentile)	Driving experience: Driver's license Professional driving experience The last year driving
Case 11 32 years / male — —	Methadone 105 mg Oxazepam 40 mg Valproate 100 mg Zopiclone 7.5 mg d	Safe driver in all conditions	55 points No errors in the on-road driving test	All driving domains evaluated as strong[2]	Stroop test below pass level (percentile 12)	Nine years since driver's license Two years of professional driving 30000 km of driving during the last year
Case 12 50 years male Minor head injury + Opioid overdose +	Buprenorphine 24 mg Temazepam 20 mg as-needed taken in the night before the testing. Diazepam 10 mg as-needed. Reports no Diazepam use within the last 24 h –	Safe driver in all conditions	52 points No errors in the on-road driving test	All driving domains evaluated as strong no errors in the on-road driving test	Signal test (reaction time) and Stroop tests below pass level (percentiles 10 and 11, respectively)	29 years since driver's license No professional driving 40000 km of driving during the last year
Case 13 31 years / male –	Methadone 120 mg Clonazepam 5.5 mg Hydroxyzine 75 mg Quetiapine 25 mg	Safe driver in all conditions	51 points No errors in the on-road driving test	All driving domains evaluated as strong	Stroop test below pass level (reaction time; percentile 1)	Five years since driver's license No professional driving 20000 km of driving during the last year
Case 14 42 years / female –	Methadone 130 mg Diazepam 10 mg Zopiclone 7.5 mg	safe driver in all conditions	48 points No errors in the on-road driving test	One driving domain evaluated as either strong or weak	All cognitive tests above pass level	20 years since driver's license No professional driving 10000 km of driving during the last year
Case 15 37 years /& male –	Methadone 110 mg Temazepam 10 mg Risperidone 2 mg	safe driver in all conditions'	48 points No errors in the driving test	All driving domains evaluated as strong	Signal Test below pass level (number of correct or delayed reactions: percentile 1)	15 years since driver's license No professional driving 15000 km of driving during the last year
Case 16 24 years/ male –	Methadone 85 mg Oxazepam 90 mg	Safe driver in all conditions'	47 points No errors in the driving test	All driving domains evaluated as strong	All cognitive tests above pass level	6 years since driver's license No professional driving 20000 km of driving during the last year
Case 17 50 years / female –	Methadone 135 mg Oxazepam 45 mg Venlafaxine 150 mg	Safe driver in all conditions	48 points Two non-hazardous errors in the driving test	One driving domain evaluated as either strong or weak	Stroop test below pass level (percentile 5)	32 years since driver's license No professional driving 5000 km of driving during the last year
Case A[3] 47 years / male –	Methadone 150 mg Oxazepam 90 mg Doxepin 100 mg	Safe driver in all conditions	44 points in One non-hazardous error and One hazardous error in the driving test	Two driving domains evaluated as either strong or weak	Determination and Stroop tests below pass level (percentiles 4 and 1, respectively)	20 years since driver's license No professional driving 5000 km of driving during the last year
Case 19 female 39 years Minor head injury +	Methadone 140 mg Clonazepam 6 mg —	Safe driver in all conditions	42 points in Five non-hazardous errors in the driving test	Five driving domains evaluated as either strong or weak	Signal (reaction time) and Stroop tests below pass level (; percentiles 16 and 8, respectively)	17 years since driver's license No professional driving 2500 km of driving during the last year
Case 20 37 years / male Minor head injury + Opioid overdose +	Methadone 125 mg Oxazepam 15 mg –	Safe driver in all conditions	43 points Eight non-hazardous errors in the driving test	Three driving domains evaluated as either strong or weak	All cognitive tests above pass level	19 years since driver's license 10 years of professional driving 1000 km of driving during the last year
Case 21 50 years/ male Minor head injury +	Methadone 190 mg Oxazepam 30 mg Diazepam 20 mg as-needed (Reports no Diazepam use within the last 24 h)	Safe driver in normal conditions	37 points in the Five non-hazardous errors and one hazardous in the driving test	Seven driving domains evaluated as either strong or weak	Stroop test below pass level (percentile 6)	Two years since driver's license No professional driving 15000 km of driving during the last year
Case B 27 years /male Minor head injury +	Methadone 170 mg Clonazepam 6 mg Levomepromatzine 100 mg Valproate 1000 mg Zopiclone 7.5 mg	Safe driver only in best conditions	38 points Five non-hazardous errors and five hazardous errors	Three driving domains evaluated as either strong or weak and two as weak	Determination , Peripheral perception, and Stroop tests below pass level (percentiles 5, 13 and 1, respectively)	Nine years since driver's license No professional driving 20000 km of driving during the last year

[1] Listed in the order of driving safety, committed errors in the driving test, driving instructor's assessment of patients' performance in on-road driving test, age, sex, buprenorphine before methadone.
[2] Includes also 'definitely strong'.
[3] Bold indicates a case discussed in the text body.

Table 4: Summary of cases with probable drug-related impairment on driving[1].

buprenorphine-only patient) drove the test route without any error. Also, they performed every driving-related cognitive test above critical values (one buprenorphine patient missed data from two cognitive tests). The excellent driving-related performance of these patients is a one more piece of evidence for the notion that long-term treatment with long-acting opioid agonist drug, as a single drug, has only minor if any effect on driving fitness [7,41,42].

Four of the patients were considered to belong to the group with 'improbable drug-related driving impairment' although they had one additional psychoactive drug in their drug regimen. All of them were considered fit to drive, and none of them made any hazardous errors while driving, although one of them scored below the critical value in one driving-related cognitive test. Three of them used buprenorphine along with a second-generation antidepressant. According to the current knowledge second-generation antidepressant do not cause of driving impairment, or interact with buprenorphine [19,24]. One methadone-treated patient used lithium. Although the issue of driving-related cognitive effects of long-term lithium therapy is not fully resolved, controlled studies or traffic crash data do not show significant driving impairment among lithium users [21,43,44]. Pharmacokinetic interaction between methadone and lithium is unlikely [26]. Pharmocodynamic interaction is possible in some conditions like in pain behaviour [44,45]. Yet, there is no evidence that long-term treatment with methadone and lithium would show significant interaction in other areas of behaviour [24,26].

Patients with probable drug-related driving impairment

All patients in this group used a BZD drug along with methadone and in one case with buprenorphine. It is known that a BZD drug as such may affect negatively on driving fitness [46,47]. Moreover, the effects of opioid agonist drugs like methadone or buprenorphine are amplified by BZD co-drugs which promote GABA in the brain [48]. Thus, combined effects of these are possible, and this may show dose-effect as suggested by the figure 2. The association is, however, is not well evidenced by our data, because some patients in this group were also given a third or fourth drug with probable negative effect on driving. These included BZD-like hypnotic zopiclone, antihistamine hydroxyzine and first generation antidepressant doxepin [49,50]. Thus, it is not surprising that that patients with 'probable drug-related driving impairment', as a group, performed worse in driving test and in the Determination test and the Stroop test. There was, however, a large within-group variation in performance in these measures. This may indicate that some of the patients had developed full tolerance to the negative drug effects.

Individual assessment of driving fitness: Combining pharmacological and non-pharmacological information

The European research-based recommendation of driving assessment for patients treated with drugs states that each OMT patient's driving fitness should be individually evaluated, and in cases of other prescription drugs, tests of cognitive performance are recommended, especially for elder patients [51]. Although significant information about driving fitness of the patient can be inferred from her/his medication and cognitive performance, also other information needs to be taken into account. To illustrate this detailed information of two cases were reported in the results section. The first case (middle-aged patient A) has methadone 150 mg, oxazepam 90 mg, and doxepin 100 mg in his drug regimen. The driving impairing effect of each of these drugs is well-known for drug naïve individuals [52,53]. Yet, individual variation of drug effects is large and most of the patients using these drugs will eventually become tolerant for the negative effects on driving [54]. In

the case of A it can be noted that his doses for all drugs are relatively high, and it is possible that full tolerance for the day-time sedative effects of these may not have developed. In accordance with this idea two studies have reported that higher methadone dose is associated with longer reaction times in tasks measuring alertness or vigilance [55,56]. Furthermore, tricyclic antidepressant doxepin has potential for long-term negative effects on driving-related cognitive testing [50]. In medical examination of A nothing was found that would be make him unfit to drive. A, however, belongs to the minority of methadone-treated patients that had gained a lot of weight during the MMT. There is no consensus if this is a pharmacological side-effect of methadone or solely related to life-style changes among patients [57,58]. Case A complains daytime drowsiness as well, which is a common side effect of full opioid agonists [59]. It is known that methadone shows large interindividual variability both in pharmacokinetics and pharmacodynamics [60-62]. Thus, it is possible that A gets more side-effects from his drug regimen than OMT patients in general. In spite of this, A is considered fit to drive. It is likely that his long driving experience gave him some advantage in on-road assessment. Anyhow, his case illustrates that a methadone patient who is treated with three psychotropic medications can be considered fit to drive a car for non-professional purposes.

The second case description (young patient B) illustrates the common problem of weighing the effects of psychiatric comorbidity on driving. His drug regimen includes methadone 105 mg, BZD valproate 1000 mg, levomepromazine 100 mg, and non-benzodiazepine zopiclone 7.5 mg. Driving impairment caused by clonazepam and levomepromazine, or zopiclone are well-known when any of these are given to drug naïve individuals [63]. On the other hand, individual variation in drug effects on driving-related functioning is large, and impairment caused by the long-term use of drugs cannot be reliable determined in individual cases [64]. In regards to valproate, there is no firm evidence for driving impairment [20,42]. B has been diagnosed a borderline personality disorder, and has sustained a probable mild head injury, although the latter has not been formally diagnosed. Both of these conditions are known to be associated with impulsive driving behavior [65,66], which was the main problem in B's driving. Notably, in cognitive driving-related testing B passed only three out of six tests above the critical value of 16th percentile. In sum, a case like B shows that the current state of the patient's comorbidity may be more important for assessing her/his driving fitness than are drugs used to treat it.

Strengths and limitations of the current study

A case-series study, like the current study, is useful in situations in which randomization of variables is not possible for ethical reasons, such as giving a patient long-term drug treatment that is not necessary for her/him [67]. Another strength of case-series approach is the possibility of taken the extreme cases into consideration, whom are in randomized studies often treated as outliers [68]. However, a case-series is not useful in in discovering causal relationship between variables. For instance, our case-series is skewed in regards of distribution between buprenorphine, methadone, and co-medications. Although we found dose effect for methadone on driving (Figure 2), there also was a negative association between BZD equivalent dose and driving test score. Although these results fit well with the idea that methadone and BZDs have combined negative effects on driving, our case series should be seen as hypothesis generating, but not as hypothesis confirming. Controlled comparisons between buprenorphine- *vs.* methadone-treated patients need to follow our results. Further limitations include the following. Psychiatric comorbidity could not be taken into account

in our statistical analyses, and this should be taken into account when interpreting our results. Comorbid conditions, age and sex also are important factors for driving safety [69]. A case has been reported in which, a stabile long-term OMT patient apparently lost his tolerance for the sedative effects of methadone dose of 130 mg at the age of 66 without any concomitant health deterioration; and the patient returned to normal after reduction of the dose to 60 mg [70]. Keeping this in mind, our results may be best applicable to the OMT patients up to early middle-age. Finally, our study dealt with driving performance more than with driving behavior, and both should be taken into accounting in assessing driving safety [71]. However, on-road driving test gives some information about driving behavior as well; and cases like B show that it is often the driving behavior in real-life traffic which determines driving safety.

Conclusions

The results of this case series agree with earlier studies in showing that OMT patients in stable treatment, as group, can be considered fit to drive. On the other hand, for OMT patients with long-term psychiatric or neurological comorbidity, or probable problematic polypharmacy, individual assessment combing pharmacological and non-pharmacological factors is still essential. For this purpose multi-professional team-work like described in this study is an ideal solution.

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