Daytime Sleepiness and Traffic-Relevant Psychophysical Capability of Patients with Chronic Pain Under Long-Term Therapy with Opioids

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Keywords
Sleepiness, psychophysical tests, driver fitness, patients with chronic pains, opioid therapy.

Abstract
It is questionable whether patients under a long-term therapy with oral opioids suffer from impairments of their driver fitness. In the present study, 20 ambulant patients with malignant and mainly non-malignant pains, 12 males and 8 females, with an average age of 50.6 ± 10.4 years were included on a voluntary basis. They were treated with opioids of the WHO-stages II (n = 9) and III (n = 11). The test persons had to pass a computer-assisted test battery examining psychophysical parameters such as capacity, reaction time and alertness. Pupillographic sleepiness testing (PST) for the objective evaluation of daytime sleepiness was performed twice, before and after the test battery. There was a considerable interindividual variability concerning the measurable traffic-relevant capability. The total test group of opioid patients showed significant results below average of normal persons in the following parameters (p < 0.05): correct and omitted reactions in the determination test, reaction time and motor time in complex reaction tests. The PST parameters, pupillary unrest index (PUI) and amplitude spectrum, exceeded normal values significantly already in the first test and developed even worse in the second test after psychomotor evaluation. Patients under opioids WHO III revealed poor test results being significantly below the average in a greater number of testing methods than persons with opioids WHO II. The results point to the fact that patients under long-term opioid therapy show a significantly elevated daytime sleepiness that even increases after permanent performance. Psychophysical tests exhibited considerable prolongation especially in complex reaction tests with particularly marked deficits in patients under opioids of WHO-stage III. Some of the patients tested may therefore tend to fail in critical traffic situations or will not be able to meet all driving requirements. The driver fitness of opioid patients should be finally judged only after careful additional examinations in each single case.

Introduction
Chronic pains can be treated according to the WHO protocol (1) with non-opioid analgetics (WHO-stage I), weak opioids (WHO-stage II, e.g. tramadol, tilidine) and strong opioids (WHO-stage III, e.g. morphine, fentanyl). There is little doubt that patients are not fit to drive in the first phase of an opioid therapy before stabilization or when the medication is changed (2). However, it is questionable whether patients under a long-term therapy with oral opioids
suffer from impairments of their driver fitness (3-5). We used a new approach in the evaluation of the psychophysical capability of opioid patients by means of a computer-assisted version of the so called Wiener (Vienna) test system. Moreover, the degree of the daytime sleepiness was measured by the objective pupillographic sleepiness test (PST). This test is based on recording of the spontaneous and involuntary pupil movement in the dark; an increased sleepiness - here due to the sedating effect of opioids - leads to typical pupil diameter changes (slow oscillations, fatigue waves) (6-10).

**Material and methods**

In the present study, 20 ambulant patients with malignant (n = 5) and mainly non-malignant (n = 15) pains, 12 males and 8 females, with an average age of 50.6 ± 10.4 years were included on a voluntary basis. They have been treated with opioids of the WHO-stages II (n = 9) and III (n = 11) for at least 2 weeks. The following opioids were administered in therapeutic dosages and in a stable long-term way: tramadol and tilidine/naloxone (WHO II), morphine, fentanyl (adhesive plaster) and oxycodone (WHO III). In 75 % of cases an additional therapy with antidepressants (mainly amitriptyline) was conducted. The intake of the prescribed drugs could be confirmed by toxicological analyses in urine and/or serum.

The test persons had to pass a computer-assisted traffic psychology test battery according to the Wiener (Vienna) test system (11) comprising the following 7 test groups and 9 single tests (German abbreviations and tested parameters in parenthesis):

1. Determination test (DT; complex multiple-stimulus multiple-choice reaction experiment, reactive capacity under conditions of stress).
2. Corsi-Block-Tapping-Test (CORSI; registration of the capacities of visual-spatial short-term memory and implicit-spatial learning potential, memorization ability).
3. Visual pursuit test (LVT; orientation, visual structuring ability).
4. Tachistoscopic traffic perception test (TAVT; procedure for the checking of optical perception performance and attention).
5. Cognitrone (COG; general performance test for the registration of attention and concentration).
6. Two-hand coordination (2-HAND; checking of visual-motor coordination, sensory-motor ability and concentration).
7. Reaction tests (RT) in 3 variants (measurement of total reaction time for optic and acoustic stimuli consisting of reaction time and motor time): RT1 (simple reaction yellow), RT5 (choice reaction yellow/tone, yellow/red), RT6 (simple reaction white under monotony).

For each single test several parameters were automatically registered by the software. They were compared with internal norm values resulting in percent ranges.

Pupillographic sleepiness testing (PST, AMTech, Weinheim/Germany) for the objective evaluation of daytime sleepiness was performed twice, before and after the Vienna test battery (= permanent performance of the test person). In the dark the subject had to wear black goggles (transparent for infrared light) and had to fixate a dimly visible infrared illumination over a period of 11 minutes. The spontaneous and involuntary pupillary oscillations were recorded by computer aid. Main parameters were the pupillary unrest index (PUI, normal values: 5.1 ± 2.8 mm/min) and the power spectrum up to 0.8 Hz (Power, normal values: 1194 ± 766 mm) (normal values according to Wilhelm et al, Tübingen/Germany).
The total test procedure including PST and Vienna test battery took between 1.5 and 2 hours and was carried out in the morning. The statistical evaluation was done by Wilcoxon test and t-test.

**Results**

**Daytime sleepiness**

The PST parameters, pupillary unrest index (PUI 1) and amplitude spectrum (Power 1), exceeded normal values significantly already in the first test and corresponded to each other (Fig. 1, Table 1). They developed even worse in the second test after psychomotor evaluation in the Vienna test battery (PUI 2 and Power 2). 4 out of 20 patients were not able to perform the second PST, several individuals had to be woken up.

![Total test group](image)

**Fig. 1:** Pupillary unrest index before (PUI 1) and after (PUI 2) permanent performance.

There were no essential differences between patients under weak (stage II) or very strong (stage III) opioids. Both the PUI and the power were significantly increased in the first and second PST giving evidence of an elevated sleepiness. In patients with opioids WHO III an additional significant increase between the first and the second PST could be observed.

**Table 1:** Summary of PST results. PUI = pupillary unrest index in mm/min (normal: 5.1 ± 2.8). Power = spectrum up to 0.8 Hz in mm (normal: 1194 ± 766). Mean ± SD.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total test group</th>
<th>Opioids stage II</th>
<th>Opioids stage III</th>
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<tbody>
<tr>
<td>PUI 1</td>
<td>8,5 ± 3,1</td>
<td>8,6 ± 3,0</td>
<td>8,3 ± 3,4</td>
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<td>PUI 2</td>
<td>10,6 ± 3,4</td>
<td>10,4 ± 3,3</td>
<td>10,8 ± 3,7</td>
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<td>Power 1</td>
<td>2081 ± 935</td>
<td>1969 ± 843</td>
<td>2172 ± 1035</td>
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<tr>
<td>Power 2</td>
<td>2821 ± 1182</td>
<td>2527 ± 964</td>
<td>3051 ± 1337</td>
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Concomitant medication with antidepressants was given in 15 of 20 patients. Both groups of patients with and without this potentially sedating medication revealed a significantly increased daytime sleepiness.

**Psychophysical capability in the Vienna test battery**

There was a considerable interindividual variability concerning the measurable traffic-relevant capability. The main results for the total test group of chronic pain patients are shown in Figs. 2 and 3. Various parameters for each single test are depicted with means and standard deviations. The comparison was drawn with age-correlated norm values, the p-values are given for parameters being significantly above or below the average (percentile 50). The Corsi-Block-Tapping-Test is missing, because there are no percentiles. On an average the opioid patients achieved an immediate block span of 6 what was above the median level of 5.
Fig. 2: Total test group: determination test (DT), visual pursuit test (LVT), tachistoscopic traffic perception test (TAVT), Cognitrone (COG).

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<thead>
<tr>
<th>Percentile (mean ± SD)</th>
<th>100</th>
<th>90</th>
<th>80</th>
<th>70</th>
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<td>2-HAND-duration p &lt; 0.001</td>
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<td>2-HAND-error-dur. p = 0.025</td>
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<td>RT1-reaction time p &lt; 0.001</td>
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<td>RT1-motor time p &lt; 0.001</td>
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<td>RT1-react.time-distrib.</td>
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<td>RT5-reaction time p = 0.045</td>
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<td>RT5-react.time-distrib. p = 0.045</td>
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<td>RT5-mot. time-distrib.</td>
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<td>RT6-reaction time p &lt; 0.001</td>
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<td>RT6-react.time-distrib.</td>
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Fig. 3: Total test group: two-hand coordination (2-HAND), reaction tests (RT) in 3 variants. The total test group showed significant results below the average of normal persons in the following parameters (p < 0.05): correct and omitted reactions in the determination test, reaction time and motor time in complex reaction tests (RT5, RT6). Conversely, the reaction time in the simple reaction test (RT1) was above the average. The partly very good results in the two-hand coordination are due to the fact that only 60% of patients were able to finish the test successfully.

Patients with opioids WHO II showed significant results below the average (p < 0.05) in only two parameters, the correct reactions in the determination test and the motor time in the complex reaction test RT5. Conversely, patients with strong opioids WHO III revealed poorer test results being significantly below the average in a greater number of testing methods. This was appropriate for the same parameters as in the total test group and in addition for variables of the visual pursuit test (LVT).

It must be considered that on the one hand some patients proved to have nearly normal results or showed impairments only in some sectors. On the other hand there were numerous subjects with poor results below the lower standard deviation also in test parameters with normal average values.

**Discussion**

Against the background of a great interindividual variability, the psychophysical tests exhibited considerable deficits in a number of traffic-relevant parameters. Whereas patients with opioids of WHO-stage II failed in few tests, subjects taking opioids of the stronger WHO-stage III showed numerous impairments concerning reaction, permanent performance under stress and orientation. In both groups prolonged reaction and motor times were especially striking in complex reaction tests. We could not confirm the results of Kolibay et al. (4) who did not find significant differences between patients with opioids of stage II and
III. Our data are also not in concordance with Vainio et al. (3) and Strumpf et al. (5) who negated essential psychophysical deficits in morphine and opioid patients. But we could affirm the well-known reduction of the reaction time in opioid treatment (12-15).

In addition, our results point to the fact that patients under long-term opioid therapy show a significantly elevated daytime sleepiness that partially even increases after permanent performance. Essential differences between weak and strong opioids or individuals with and without a sedating antidepressant medication could not be observed. To our knowledge comparable studies with opioid patients do not exist as the PST has been developed only several years ago.

Summarizing both the results of the psychophysical investigations and the sleepiness testing, it is not possible to draw simple conclusions. Despite increased daytime fatigue some patients proved to have good results in the traffic psychology test battery. They obviously were able to compensate their objective tiredness. Individual motivation plays an important part. On the other hand the alert persons owed their vigilance to the poor relief of pains and were not very efficient in the tests. In this sense the medical intention of a sufficient therapy was partly realized with an improvement of the health state and positive consequences on the driver fitness.

However, our collective was positively selected as less motivated patients did not take part in the voluntary study. Against this background the considerable deficits in many cases both in the Vienna test system and the sleepiness test must be seen very critical. Some of the patients may be able to cope with simple and average demands in traffic, in particular when they have great routine in driving. But they may tend to fail in difficult traffic situations or will not be able to meet all driving requirements. The driver fitness of opioid patients should be finally judged only after careful additional examinations in each single case. More complex tests should not be absent in this evaluation process.

References