RESEARCH ARTICLE

Comparison of cognitive functioning in abstinent opiate-dependent individuals, methadone-maintenance patients and healthy controls: study protocol and update of the existing literature

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Practice points

- Neurotoxic effects in opioid dependence are controversial.
- Cognitive dysfunction has been described in long-term opioid users.
- Frontal lobe dysfunction and impairment of executive functions may be of special relevance for opioid dependence.
- Driving ability is affected by opioid use but many patients under opioid maintenance therapy may be fit to drive.
- Effects of opioid maintenance therapy on cognitive function will be studied.
- Length of treatment and dosage may not be predictors of cognitive function.
- Abstinent opioid users may have little or no cognitive dysfunction.

SUMMARY  Aims: Cognitive dysfunction plays an important role in the treatment of opioid dependence but the extent of this role and the question of whether the cognitive dysfunction is primary or secondary are matters of controversy. Few studies have been conducted in this area, particularly in abstinent opioid users. This article will give a comprehensive update of the existing literature on this issue and will also describe the protocol of a study on cognitive function in opioid dependence. Methods: The study will compare abstinent opiate-dependent patients, opiate-dependent individuals on stable maintenance treatment with no substance use and matched healthy controls. Results: We are expecting the study to provide information about the severity or possible reversal of cognitive impairment in formerly opiate-dependent patients and opiate-dependent patients on stable maintenance treatment. Conclusion: The study will answer the question of whether opioid dependence can cause impairment in cognitive and executive functions.
Background

- Prevalence & treatment of opioid dependence

The prevalence of opiate dependence in the adult population of western countries is estimated to be approximately 0.4–1% [1,2]. Long-term studies show that opiate abuse and dependence have significant health-related, mental and social sequelae, and are associated with high mortality and morbidity [3,4]. Maintenance treatment with methadone-type opioid antagonists is one of the most efficient and commonly practiced treatments for opiate-dependent patients [5–8]. Studies have proven that a reduction in the consumption of opioids is accompanied by an improvement in psychosocial reintegration, a reduction in criminal behavior, and also a lower rate of HIV and hepatitis infections [9,10].

- Cognitive functions in opioid dependence

Cognitive functions play an important role in the treatment and rehabilitation of drug-dependent patients because they are of prime importance for the ability to work and for mental performance in general. Of the various cognitive functions, the executive functions are particularly important for controlling behavior. Deficits in executive function and decision-making are of great relevance in impulse control and the ability to resist drugs [11]. However, this issue has not been studied in much detail.

Changes in cortical reward pathways and also dysfunctions in the prefrontal cortex [12], which are probably relevant for executive functions (e.g., self-control), have been found in opioid dependence. In their review of neuropsychological hypotheses for the development of dependence, George and Koob proposed that disturbances of self-regulation and cognitive dysfunctions are the neuronal basis for vulnerability to drug consumption and development of dependence [13]. In particular, dysfunctions in executive systems are involved, including the lack of so-called ‘decision-making skills’.

Neurotoxic effects of opioids and consecutive brain dysfunction have been postulated, mostly in the context of oxidative stress, mitochondrial dysfunction, apoptosis and inhibition of neurogenesis [14], but not many studies have evaluated such effects in clinical samples. Clearly, cognitive deficits in otherwise healthy opiate-dependent patients are not as severe as in other psychiatric disorders, for example, dementias or schizophrenia [15,16]; however, they seem to be a risk factor for the development of substance use disorders [17]. The role of frontal lobe dysfunction, including decision-making impairments, has been stressed in this respect [18,19]. Currently, only limited data are available for opioid dependence [20,21]. Some studies have found deficits in the areas of attention, concentration, memory, psychomotor speed and performance, and also in the processing of emotional stimuli and decision-making processes [22]. These processes can be seen as belonging to the executive functions; functions in which drug-dependent patients have repeatedly shown cognitive deficits compared with healthy controls. Thus, in a recent review van Holst and Schilt described deficits in executive functions in opiate-dependent patients, among others, in the area of inhibition [21]. Ersche et al. showed moderate differences between the sexes: compared with female drug consumers, male drug consumers had significant impairments in executive and memory tasks [23]. Some findings indicate deficits in the area of verbal fluency in opiate dependence in particular [21]. Among the numerous concomitant diseases in opiate dependence, cognitive deficits were found primarily in patients infected with HIV [24].

Neuropsychological deficits can also have predictive relevance for treatment outcomes [25] and allocation to different treatments [21]. Performance in decision-making tasks predicted future abstinence from illegal drugs for 3 months after completion of treatment. Furthermore, opiate-dependent patients demonstrated changes in emotion-processing mechanisms [26], reward processes [27] and the interaction of these systems with cognitive processes [28].

Only a few studies have dealt with cognitive deficits in previously opiate (heroin)-dependent, long-term abstinent individuals [15,29–34]; some data are available on patients with polydrug dependence [35]. Only a few studies have compared maintenance patients with abstinent opiate-dependent individuals [15,32,33,36]. Most studies described some deficits [15,16,29,33], but not, for example, Prosser et al. [32]. Cognitive deficits, mostly of a milder form, were also reported in studies with opiate-dependent patients receiving methadone-maintenance treatment [16,29,32,37–39].

- Effects of opioid maintenance therapy

Few studies have investigated the cognitive effects of former consumers and the long-term effects of opioid maintenance treatment
(methadone and buprenorphine) on cognition; however, both issues are relevant for safety and other aspects of treatment [40–43]. Negative effects of long-term administration of metha-
done on cognitive functions have been shown in animal models [44]. In an experimental setting, acute administration of morphine to opio-
ate-dependent patients did not result in deficits in psychomotor or cognitive performance [45]. While marked effects of opioids in drug-naïve patients have been clearly demonstrated [43], long-term effects are less clear. Specka et al. described deficits in cognitive performance in 54 methadone-maintenance patients compared with healthy controls [46]. Mintzer and Stitzer compared 18 opiate-dependent patients on stable methadone maintenance with 21 healthy controls and showed, in particular, decreased responsiveness and impairments in working memory [16]. Darke et al. compared 30 metha-
done-maintenance patients with 30 healthy controls and found deficits in areas such as verbal long-term memory, visual memory and the use of problem-solving strategies, among others [38]. There is a complete lack of studies in main-
tenance patients showing a connection, under structured conditions, between cognition and treatment outcome. The duration of maintenance treatment and the prescribed dose may also be relevant [8]. Bracken et al. found better cognitive perfor-
ance in patients after long-term maintenance treatment (at least 12 months) than in those who had received it for less than 1 year [47]. Patients with higher methadone doses of at least 80 mg showed better selective attention than those who had been maintained with less than 80 mg. Previous studies showed that long-term methadone-maintenance patients perform considerably better in some cognitive domains than short-term methadone-maintenance patients; a somewhat better performance in the long-term group was found in one executive function (category word fluency) and with respect to visual construction (Rey complex figure test) [48]. No differences were found in attention functions or in the areas of learning and memory. Messinis et al. found deficits in the processing of verbal informa-
tion, visual perception and executive functions, among others, in patients on buprenorphine-
maintenance treatment compared with healthy controls, and no impairment in cognitive func-
tions in abstinent opiate-dependent individu-
als under treatment with the opiate antagonist naltrexone compared with healthy controls [49]. However, this study had a very small sample size (n = 18 in the buprenorphine group).

It is questionable whether cognitive perfor-
mance differs between stable methadone-
maintenance patients and abstinent opiate-
dependent patients. Only a handful of studies have been performed, most of which were pilot studies. Verdejo et al. studied neuropsychological functions in methadone-maintenance patients compared with abstinent heroin-dependent indi-
viduals [33]. From a critical standpoint, it should be noted that only 15 days of abstinence from the drug was required. Methadone-maintenance opiate-dependent patients performed worse in some domains than abstinent opiate-dependent individuals, from which Verdejo et al. concluded that methadone itself cannot cause significant cognitive impairments, a conclusion that is not otherwise sufficiently proven in the literature [33]. Conversely, Gruber et al., for example, described improvements in cognitive perfor-
mance over the course of methadone mainte-
nance [50], and Ersche et al. found no differ-
eence between the performance of patients with earlier opiate consumption and those with cur-
rent consumption [23]. Messinis et al. found less impairment in former heroin users treated with naltrexone (32 patients) than in buprenorphine-
maintained patients (18 patients); the former group did not show significant differences when compared with a control group [49].

**Limitations of studies to date**
The published literature on cognitive deficits, including the relevance of executive functions in acute and chronic opiate consumption, is very limited and controversial [9,15,23,30–58]. Studies on abstinent opiate-dependent individu-
als are particularly rare [21]. In addition, the methodology, particularly in earlier studies, was frequently considered to have problems [15]. Only a few controlled studies are available [19]. Adequate inclusion and exclusion criteria are often missing. Furthermore, the studies do not consider the confounding of cognitive perfor-
ance areas. Impaired attention or a reduced capacity to deal with new or abstract tasks have to be evaluated with suitable methods to be able to control for factors that may be influencing memory performance.

Previous criticisms of methodology and current research were considered in the plan-
ing of the present study [21,22,34]. The study’s
methodology is clearly structured, inclusion and exclusion criteria are described, and the working hypothesis has been formulated. To our knowledge, this is the first direct comparison of these three groups (abstinent opiate-dependent individuals, stable methadone-maintenance patients and healthy controls). Knowledge about the extent to which methadone maintenance results in cognitive impairment, and opiate abstinence in an improvement of cognitive functioning, is important to allow reliable statements to be made on clinically relevant follow-up questions, such as coping with everyday life, ability to work and rehabilitation in opiate-dependent patients.

**Key questions of the planned study**
To what extent do the following groups differ with respect to cognitive functioning:
- Formerly opiate-dependent, long-term abstinent patients;
- Stable methadone-maintenance patients with no substance use (matched with formerly opiate-dependent, long-term abstinent patients);
- Healthy individuals as a control group (matched with formerly opiate-dependent, long-term abstinent patients, and thus also with stable methadone-maintenance patients with no substance use).

**Hypotheses**
We expect to find significant differences in the cognitive performance of the groups. Consideration of the above mentioned critical methodological points is a prerequisite for obtaining clear results.

**Hypothesis one**
The cognitive performance of abstinent opiate-dependent individuals does not differ in all areas from that of healthy controls. Impairments in abstinent opiate-dependent individuals are expected mainly in attention/concentration, memory, information processing speed and executive functions.

The rationale behind this is that previous studies have shown deficits in drug-dependent individuals compared with healthy controls in the areas of attention/concentration, memory, and psychomotor speed and performance, and also in the processing of emotional stimuli and in executive functions [33,43,46].

**Hypothesis two**
Compared with healthy controls, methadone-dependent patients on maintenance treatment show deficits in the areas of attention, learning, memory performance and executive functions.

The rationale behind this is that negative effects of long-term administration of methadone on cognitive functions were seen in the animal model [9,21]. Deficits in cognitive performance in methadone-maintenance patients compared with healthy controls were described in previous studies, primarily in the areas of responsiveness, processing of verbal information, visual perception, working memory, visual memory, verbal long-term memory and executive functions [33].

**Secondary hypotheses**
We also hypothesise that long-term methadone-maintenance patients (≥12 months of treatment) have better cognitive functions than short-term maintenance patients (<12 months of treatment).

In addition, we expect cognitive performance to be better at higher doses (≥80 mg methadone) than at lower doses. These hypotheses are based on the findings of Bracken et al., who found better cognitive performance in patients who had received maintenance treatment for ≥12 months than in those who had received treatment for <12 months [47]. Patients with higher methadone doses (≥80 mg) showed better selective attention than patients with lower doses (<80 mg).

A further secondary hypothesis is that cognitive deficits and disorders of executive functions in decision-making behavior correlate with the severity of addictive disorders or the individual disorder profile in different areas, measured with the European Addiction Severity Index.

**Additional questions**
An additional query is to what extent does decision-making behavior differ between abstinent opiate-dependent patients and stable methadone-maintenance patients, and between each of these groups and healthy controls?

According to George and Koob, impairment of decision-making is a key feature of dependence disorders and could persist in abstinence [13]. Study results differ greatly; in some studies, methadone-maintenance opiate-dependent patients performed worse in some domains than abstinent opiate-dependent individuals [16,38,46], and in others they showed improvements in cognitive performance over the course of methadone
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**Methods**

The subtests were selected because they were mainly used in most of the earlier studies on this topic and represent the established standard repertoire in this area [36,59,60]. This will ensure the comparability of the results.

- **Sample size estimation**
  
  In a study by Kagerer et al., a group of opiate-dependent patients receiving buprenorphine-maintenance treatment performed better in diverse driving ability tests than another group receiving methadone-maintenance treatment [59]. In those subtests that measured mainly quick and correct actions, the mean effect strength was approximately \( d = 0.6 \) in favor of the buprenorphine maintenance group. If one assumes similar effect sizes for the planned study, differences of this size will be statistically valid with sample sizes of 50 per group, at a significance level of \( \alpha = 0.05 \) and a test power \( (1 - \beta) \) of 0.90 (\( f = 0.29 \) corresponds to mean effects).

  In addition, the optimal sample size was calculated *a priori* with the program Gpower [101]. A significance level of \( \alpha = 0.05 \) and a mean effect were also chosen for this calculation. In consideration of the variance in analytical differentiation between the groups, this corresponds to an effect size value \( (f) \) of 0.25 (mean effect; small effect: \( f = 0.10 \); larger effect: \( f = 0.40 \)). A total sample size of 155 was calculated, which corresponds to 52 participants per group when distributed over the three predefined groups (power = 0.8002; \( F^{\text{crit}} \) [degrees of freedom: 2 and 152, respectively] = 3.0556). The sample size estimation for the Iowa Gambling Task was based on the preparatory work of a masters thesis [61]. On the basis of the sample size estimations, we decided to include 52 patients in each of the three groups.

- **Inclusion & exclusion criteria**

  **Inclusion criteria**

  The inclusion criteria for the clinical group A (abstinent opiate-dependent patients) included the following:
  
  - Main diagnosis of opiate dependence according to the International Classification of Mental Disorders 10th edition criteria [62];
  - Minimum age of 18 years;
  - Adequate German language skills;
  - Abstinent from opiates for at least 12 months.

  The inclusion criteria for the clinical group B (stable methadone-maintenance patients with no substance use) were as follows:
  
  - Main diagnosis of opiate dependence according to International Classification of Mental Disorders 10th edition criteria;
  - On methadone maintenance; dose stable for at least 4 weeks;
  - Matched with group A with respect to age, sex, education, and lifestyle and dietary habits.

  **Exclusion criteria**

  The exclusion criteria for the control group C were as follows:
  
  - A total of 52 healthy individuals, matched with respect to age, sex, education, and lifestyle and dietary habits;
  - No psychiatric, neurological or dependence disorder.

  The exclusion criteria for all study participants were as follows:
  
  - Mental disorders that may impair the ability to be tested (e.g., psychoses, including disorders from the spectrum of schizophreniform disorders and depression);
  - Current drug consumption (urine test; clinical groups A and B);
  - Neurological abnormalities (i.e., current withdrawal symptoms and tremor);
  - Previous craniocerebral trauma or epilepsy;
  - Intelligence quotient <85 (indicates inability to give informed consent);
  - Severe somatic and neurological diseases (e.g., HIV infection, epilepsy, head trauma, brain tumor and other CNS disorders).

  Opiate-dependent patients on stable maintenance treatment and with no concomitant opioid use are to be evaluated and recruited in either the comprehensive drug outpatient clinic of the Department of Psychiatry and Psychotherapy of the Ludwig Maximilian University (LMU; Munich, Germany), or other (inpatient) treatment facilities. Abstinence will be verified by urine drug analysis.
Abstinent opiate-dependent patients also are to be recruited at these facilities, as well as at numerous long-term treatment facilities and specialized outpatient clinics that have agreed to cooperate in the study.

Since the study is to be performed at and coordinated by the LMU, approval was obtained from the LMU ethics committee.

- **Screening/baseline interview**
  The somatic, psychiatric and specific substance use-related history will be recorded for all study participants upon recruitment into the study. In detail, a medical and neurological–psychiatric structured interview will be performed to collect information on the following: duration, length and amount of opiate consumption; possible overdoses, emergency treatments, reanimations or suicide attempts; relevant injuries, including craniocerebral trauma, HIV and hepatitis infections; and relevant social parameters, such as school education, occupational education, and lifestyle and dietary habits. The interview will allow relevant cerebro-organic disorders and previous conditions to be excluded and patients to be matched according to social parameters.

  The cognitive test battery will be performed after completion of the screening. The tests cover reaction speed, premorbid and current intelligence, learning and memory, attention, and executive functions. Patients will take approximately 2 h to complete the test battery.

- **Measurement procedures**
  Symptom severity and psychopathology will be assessed with the Beck Depression Inventory and Brief Symptom Inventory. The cognitive test battery is described in detail below.

**Premorbid & current intelligence**

*Multiple choice vocabulary test (‘Mehrfachwahl Wortschatz test’)*

The Mehrfachwahl Wortschatz test assesses verbal, premorbid intelligence and is approximately 5 min long. It consists of 37 lines with five words each. In each line, a word that exists in German has to be identified and discriminated from made-up words. The task increases in difficulty. The raw score on the test is converted to an intelligence quotient value [63].

*Mosaic test*

The mosaic test is a subtest of the revised Hamburg-Wechsler Intelligence Test for Adults that assesses spatial and visual construction abilities, and is approximately 10 min long. Patterns of cubes shown on cards have to be copied with four and then nine multi-colored cubes, whereby the tasks increase in difficulty [64].

**Vocabulary test**

This subtest of the revised Hamburg-Wechsler Intelligence Test for Adults is approximately 5 min in length and is used as a measure of verbal intelligence. The meaning of 32 words of increasing difficulty is to be explained sequentially [64].

**Attention/concentration/information processing speed**

*Trail-making test part A*

This test is used to measure cognitive and perceptual speed and takes 1 min to complete. The test requires immediate recognition of the symbolic importance of numbers and letters and the flexibility to put them into a sequence under time pressure. Part A measures information processing and psychomotor speed. The participant has to connect the numbers 1–25, which are randomly distributed over a page [65].

*Test battery for attentional performance (‘Testbatterie zur Aufmerksamkeitsprüfung’)*

The computerized test battery evaluates attention to measure reaction time, standard deviation and errors as independent variables [66].

The subtest ‘alertness’ (8 min) measures basal responsiveness (tonic alertness) and the ability to increase alertness in expectation of a stimulus (phasic alertness). A button has to be pressed as quickly as possible when a cross appears on the screen. In a further round, an acoustic alert signals the appearance of the cross.

The subtest ‘divided attention’ (8 min) measures the ability to divide attention. Attention has to be divided simultaneously between two tasks: an acoustic task (sequence of sounds) and a visual task (crosses arranged in the shape of a square). Again, participants have to react to both target stimuli as quickly as possible by pressing a button.

The subtest ‘go/no go’ (5 min) records the participant’s ability to focus attention on certain stimuli and suppress responses to irrelevant stimuli. A button has to be pressed in response to certain patterns but not to others.
Learning & memory
Rey complex figure task
The Rey complex figure task is a test of visual construction and implicit visual memory, and takes 15 min to complete. The test consists of three tasks. First, the individual’s ability to analyze a complex drawing and copy it by hand is tested. Immediate (after 3 min) and delayed (after 30 min) recall, but not preannounced recall, are subsequently tested. Both the correctly remembered elements of the drawing and the wrongly positively remembered elements are evaluated [67].

Verbal learning & memory test (‘Verbaler Lern & Merkfähigkeits test’)
The German version of the ‘Rey Auditory Verbal Learning Test’ includes serial learning of lists (15 semantically independent words) with subsequent interference, recall after interference and temporal delay, and a recognition test. This takes 15 min to complete. The recognition list contains 30 words from the two word lists and 20 additional, semantically or phonetically similar distraction words. The Verbaler Lern und Merkfähigkeits test assesses different parameters of verbal declarative memory such as learning performance, long-term-encoding and recall performance, and recognition performance [68].

Executive functions
Trail-Making Test Part B
Part B of this test evaluates cognitive flexibility and the ability to switch between amounts, and is 2 min long. The patient has to alternately connect numbers and letters in sequential order (e.g., A-1-B-2-C-3) [64].

Planning test
This test evaluates the ability to plan and execute directed planning behavior (executive function), and is 8 min long [69]. The planning test corresponds with the Tower of London task [70] and is performed on a computer. The screen shows three rods of different sizes with three balls of different colors distributed across them. The task consists of using as few moves as possible to bring the balls from a given starting arrangement into a target arrangement. The increasing degree of difficulty of the tasks varies from three to eight moves. The time, required number of moves and number of errors are recorded.

Regensburg word fluency test (Regensburger Wortflüssigkeits test)
In this test as many words as possible have to be generated over periods of 2 min each. The test is 10 min long. The Regensburger Wortflüssigkeits test consists of subtests of formal and semantic word fluency and subtests to evaluate word production in changing categories [71]. In every subtest, the number of correct answers is recorded as a measure of word fluency (executive function). Formal word fluency is the production of words that start with a certain letter (e.g., ‘P’) and with alternating letters (e.g., ‘G’ and ‘R’). Category word fluency is the production of words in a category (e.g., ‘first names’) and alternating between categories (e.g., ‘type of sport’ and ‘fruit’).

Statistical analysis
The data will be analyzed with the statistics program PASW® Statistics 18 (formerly ‘SPSS’; SPSS Inc., IL, USA). The descriptive part of the data analysis will include the calculation of means and standard deviations to summarize the individual patient raw data in group statistical form.

The analytical evaluation will take place in several steps. Hypothesis-oriented calculations will precede analyses to reveal potential systematic distortions between the two clinical samples (methadone maintenance vs abstinent opiate-dependent patients) with respect to sex-specific differences in performance and effects of age. The analyses of categorical data will be performed with the χ² test for ordinal data using the Mann–Whitney U test and for metric data using the Kolmogorov–Smirnov Z test. A general comparison of baseline data will be performed for alternative and categorical data with the χ² test, and using the Kruskal–Wallis H test for ordinal and metric data.

To test the different hypotheses, the test performance of the three groups (maintenance vs
abstinent vs healthy controls) will be compared, depending on the result of the preceding analyses and controlling for additional variables. The model will be formed according to the general linear model. This model formation will include multiple comparisons between the three study groups. If no variance homogeneity is found, the Games and Howell procedure will be used during post hoc testing.

Ethics approval & informed consent
As mentioned above, the study has been considered and approved by the ethics committee of the LMU. Study participants will be informed about the study by the respective partner institutions and asked if they want to participate. If they agree, the principal investigator or member of staff responsible for recruitment will contact the potential study participant and inform them by telephone about the study objectives, inclusion and exclusion criteria, planned test duration, urine tests to be performed and compensation. At the interview appointment, open questions will be answered and the participant will complete the informed consent form.

Discussion
We expect this study to provide some clinically relevant data on cognitive function in abstinent and methadone-maintained opioid-dependent patients. Abstinent opioid users in particular have hardly been studied, probably owing to the problems in identifying previous users. This comprehensive study may contribute to a better understanding of the effects of opioid intake on brain function. In particular, data on cognitive function in stable opioid maintained patients or abstinent opioid users will be helpful in the assessment of driving ability [48] or related areas.

Conclusion & future perspective
Opioids may have fewer neurotoxic effects than other drugs of abuse (alcohol, psychostimulants and cocaine) but such effects cannot be ruled out in chronic users. The study will evaluate whether otherwise nonimpaired former opioid users demonstrate cognitive dysfunction, as has been shown for chronic users, because this question has not been addressed in depth. We hope that our study will find subtle or no abnormalities in this area and, therefore, may encourage abstinence-oriented treatment approaches. Furthermore, additional data on cognitive function in opioid maintenance therapy programs are necessary for safety reasons, including working and driving ability.

Financial & competing interests disclosure
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Writing assistance was utilized in the production of this manuscript. The authors thank J Kleising, board-certified Editor in the Life Sciences, for editing assistance with the manuscript. Writing assistance was funded by Privatklinik Meiringen.

Ethical conduct of research
The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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**RESEARCH ARTICLE**


- Relevant overview on this issue.


- Updated review on neurotoxic effects of opioids.


- Excellent, comprehensive and clinically relevant update.


- Excellent neuropsychological study.


- Excellent review on this issue.


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- Recent, updated, comprehensive review on cognitive function and driving ability in opioid maintenance therapy.


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