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DRUID
Driving under the Influence of Drugs, Alcohol and Medicines

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Psychomotor relevant performance:

1. After single dose administration of opioids, narcoanalgesics and hallucinogens to drug naïve subjects

2. In patients treated chronically with morphine or methadone / buprenorphine

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2. In patients treated chronically with morphine or methadone/buprenorphine

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1 ABBREVIATIONS

Abbreviation	TEST
APG	Aufmerksamkeitsprüfgerät
ART	Auditory Reaction Time
ART 2020	Act & React Test System
BAC	Blood Alcohol Concentration
BASt	Federal Highway Research Institute, Germany
CFF	Critical Flicker Fusion Frequency
CFF(T)	Critical Flicker Fusion (Test/Threshold)
COAT	Chronic Opioid Analgesic Treatment
CRT	Choice/Continuous/Complex Reaction Test
DAT	Divided attention task
DSST	Digit Symbol Substitution Test
DVA	Dynamic Visual Acuity
EHC	Eye-hand coordination
I.m.	Intramuscular
I.v.	Intravenous
LL5	Visual structuring ability (ART 2020)
M3G	Morphine-3-glucuronide
M6G	Morphine-6-glucuronide
MLP	Mean Lateral Position
MW	Maddox Wing Test
P.o.	Per oral
PSV	Peak Saccadic Velocity
RIT	Rapid information processing task
RT	Reaction Time
RTS3	Reactive Stress Tolerance (ART 2020)
S.c.	Subcutaneous
S.l.	Sublingual
SacEM	Saccadic Eye Movement
SD	Saccadic Duration
SDLP	Standard Deviation of Lateral Position
SRT	Simple Reaction Time
TAVT	Tachistoskopischer Auffassungsversuch
TT15	Traffic specific perception ability (ART 2020)
WCST	Wisconsin Card Sorting Test

2 INTRODUCTION

This review is performed as part of The Integrated Project DRUID (Driving under the Influence of Drugs, Alcohol and Medicines). The aim of DRUID is to gain new insights into the degree of impairment caused by psychoactive drugs and their actual impact on road safety. All in all this Integrated Project will try to fill the gaps of knowledge and provide a solid base to generate harmonized, EU-wide regulations for driving under the influence of alcohol, drugs and medicine (1).

Our task (Norwegian Institute of Public Health), as part of this project, was to perform a literature review on the results of experimental studies on drugs and driving or tasks related to driving for the following drugs: Opiates/opioids, narcoanalgesics/atypical opioids and hallucinogens. Initially we were asked to perform a literature review on the effects of single dose administration of these drugs on performance related to driving. In October 2008 we were also asked to broaden the review with data on maintenance use (i.e. methadone and buprenorphine). We also agreed to include chronic use of morphine as it is widely used and the most studied opioid. Studies on chronic use of opioids in general were, however, not meant to be a topic of this review. This review does therefore not include long term use of other drugs than morphine, methadone and buprenorphine.

The results for methadone and buprenorphine, and for morphine, will be presented separately in the present review, as these drugs are of particular interest in maintenance treatment of drug dependent subjects and pain treatment, respectively.

The literature on the effects of opioids on driving performance has previously been reviewed by a number of researchers. The most recent review, was by Fishbain et al. (2003) (2). He performed a structured evidence-based review of all available studies addressing the issue of whether opioid-dependent/tolerant patients are impaired in driving-related skills. He concluded that the majority of the reviewed studies indicated that opioids appear not to impair driving-related skills in patients on chronic opioid treatment. However, the references reviewed were not categorized according to type of opioid studied or the subjects experience with opioids. Hence, the review by Fishbain is not directly comparable to the present review.

The main purpose of the present review is to answer whether use of opiates/opioids, narcoanalgesics and hallucinogens cause impairment in performance tasks related to driving. This literature review will focus on the influence of single dose intake of opiates/opioids, narcoanalgesics and hallucinogens administered to healthy volunteers, and also include studies on administration to opioid maintenance patients, subjects with ongoing use of opioids and to previous opioid (ab)users, and use in patients treated chronically.

3 METHODS

In order to find relevant literature, searches were conducted in MEDLINE and EMBASE. Even though there is an overlap between these two major databases, it was essential to include EMBASE. EMBASE is known to have a better coverage regarding European journals, and is more comprehensive in the area of pharmacology. In addition, the database PSYCINFO was searched to include references from psychological journals. The searches were conducted in May/June 2007. An additional search was conducted for methadone and buprenorphine to supplement the studies on chronic treatment, and the search period for these studies was extended to March 2010. The reason for the extended search was to include the newest studies on methadone and buprenorphine as it was considered important to include the latest evidence on substitution treatment and driving since this topic has raised great public interest.

The search strategy consists of the following list of words searched separately, see appendix 1. The defined words were searched using two methods: 1. As controlled vocabulary (i.e. using own vocabulary/thesaurus of the databases). 2. As free text words (key words). The use of both these methods is necessary to ensure that the highest amount of relevant literature would be retrieved. Finally the relevant words were combined with the boolean operator 'OR' to broaden the search. The result was then limited to one of the following types of studies: Experimental, quasi-experimental and controlled. No limits were made as to publication year or publication language. The search strategy was combined with 38 different drugs from the following three groups of drugs: 1. Opiates/opioids 2. Narcoanalgesics 3. Hallucinogens. The individual drugs are listed in appendix 2.

The primary search isolated approximately 12.000 titles with abstracts. The available abstracts of these articles were then evaluated according to defined criteria by one expert, followed by collection of relevant full text articles. The full text articles were then evaluated according to the same criteria by two experts to be included in this review. Criteria for inclusion, acute and chronic use, are given in appendix 3. Concerning maintenance treatment with methadone, only studies published later than 2001 were systematically reviewed as one of the present authors earlier had summarized studies published to that point of time (3). A secondary manual search based on the primary references was also performed.

A total of 118 articles on effects of opioids (except buprenorphine, methadone and morphine), narcoanalgesics and hallucinogens were included. A total of 41 articles on effects of morphine were included, of which one was on chronic use in addition to the review by Fishbain et al. (2). 40 articles on the effects of methadone and/or buprenorphine, besides Mørland (3) and Fishbain et al. (2), were included. Figure 1 summarizes the search.

In those few cases where no test result was reported or the results were difficult to interpret, the result was registered as no impairment.

In appendix 4 are listed the tests that have been used to assess the effects of opioids/opiates, including morphine, narcoanalgesics/atypical opioids and hallucinogens on tasks of importance to driving; i.e. cognitive and psychomotor

performance. The tests are arranged into eight main groups based on a function-oriented classification system developed by Krüger et al. (4).

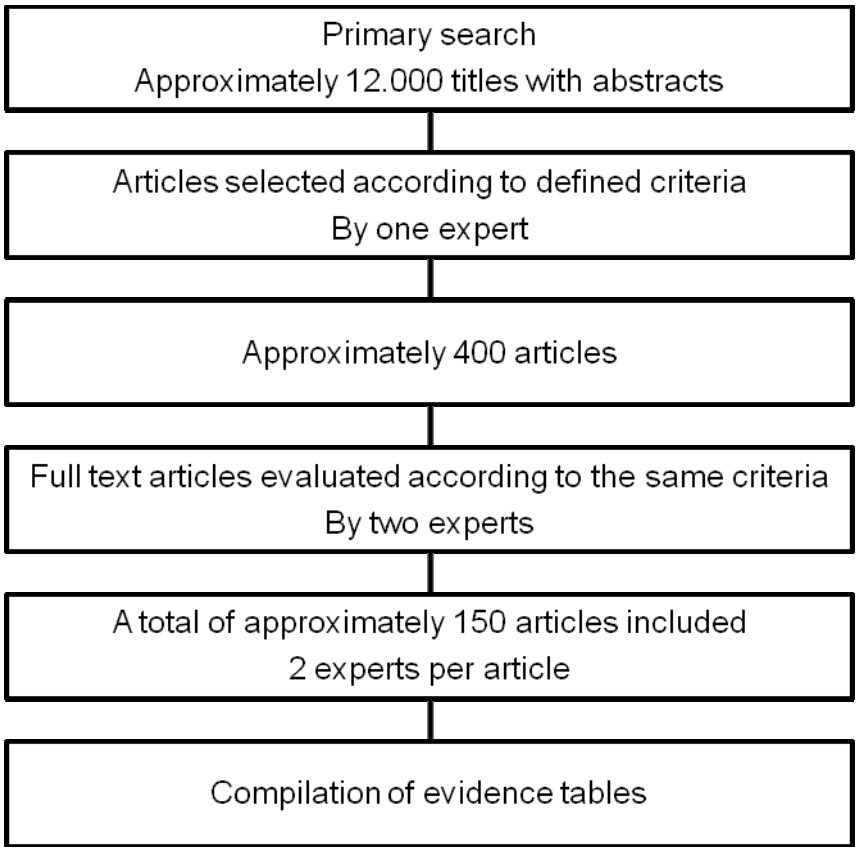

Figure 1: Summary of the search and the number of studies retrieved at the different levels

4 SUMMARY OPIOIDS, NARCOANALGESICS AND HALLUCINOGENS: SINGLE DOSE TO DRUG NAÏVE SUBJECTS

(except methadone, buprenorphine and morphine)

4.1 Limitations

Before trying to summarize and conclude from the results presented below, attention should be given to some limitations in the papers presented:

- The tests used in single dose experiments differed considerably between papers. There is no generally accepted list of tests which are particularly suited to test functions of critical importance to safe driving. It has been recommended that all studies include alcohol as a reference substance in all tests, since alcohol has a well-established concentration-effect relation in tests of relevance to traffic safety. In the studies included in this part of the report, a total of 12 out of 118 studies had included testing with alcohol. Some of the studies report that ethanol increased the drug effects when given in combination and/or that impairment was seen after intake of ethanol but not the drug primarily tested. But for all other studies reporting no impairment in a test, the lack of comparator drug is a considerable shortcoming.
- In 16 of the 118 studies included drug blood concentrations were measured. In all the other studies no blood samples for analysis were taken. It is well known that blood drug concentrations might show marked interindividual differences even if the same dose per kg is given to a group of subjects. To link individual effects to individual concentrations is therefore difficult. This is a major drawback in the papers reviewed when concentration-effect relationships are target issues. In addition the results are valid on group level and do therefore not directly apply to individual effects.
- In many of the studies the past and present drug use was unknown. As previous and present use of opioids might influence the effects of an acute dose of opioids (due to development of tolerance), this lack of knowledge is an important shortcoming. If associated drug use/dependence is not known we might have an unknown confounder of the results through e.g. drug-interactions or tolerance. Drug use might also lead to neuropsychological impairment secondary to brain injury.
- The present studies have not been evaluated for quality, except that all studies had n > 5, and most are randomized, controlled and double blind. Thus they represent studies of good quality in that sense.

4.2 Results

4.2.1 Opiates/opioids (except methadone, buprenorphine and morphine)

Alfentanil/ Fentanyl/ Remifentanil all caused impairment in three different main groups of tasks (Attention, En-/Decoding and Visual Functions). The two drugs that were studied with respect to Psychomotor Skills and Reaction Time, alfentanil and fentanyl, caused impairment in these tests. Dose and blood drug concentration related effects were found for all three drugs. The lowest impairing concentrations in blood were: Alfentanil 40 ng/ml, fentanyl 2.5 ng/ml and remifentanil target level of 1.5 ng/ml.

Butorphanol administration was followed by impairment in three main groups of tests; Attention, Psychomotor Skills and Visual Functions. The lowest impairing dose was 0.5 mg i.v., and some dose related effects were observed.

Codeine administration was followed by impairment in 7 of the 8 main test groups, including Simulated Driving. It was interesting to notice that Attention test and test of Visual Function appeared to be the least sensitive to codeine effects, while these tests were the most sensitive to the effects of morphine. No clear dose-effect relationship was found. The lowest impairing dose was 25 mg p.o.

Dextropropoxyphene/ Propoxyphene caused impairment in 5 test groups (Divided attention, En-/Decoding, Psychomotor Skills, Reaction Time and Visual Functions). No clear dose-effect relationship was observed. The lowest impairing dose was 65 mg p.o.

Hydrocodone/ Hydromorphone caused impairment in 4 of the main test groups (Attention, Psychomotor Skills, Reaction Time and Visual Functions). Some dose-effect relations were observed. The lowest impairing dose for hydrocodone was 7.5 mg i.v. or 20 mg p.o. and 1 mg i.v. hydromorphone.

Meperidine (Pethidine) caused impairment in 4 of the main test groups (Attention, Psychomotor Skills, Reaction Time and Visual Functions). Some dose-effect relation was observed. The lowest impairing dose was 70 mg i.v. or 75 mg i.m.

Meptizanol caused impairment in 2 test groups (Attention and Visual Functions). No dose-effect relations were observed. The lowest impairing dose was 50 mg i.v. or 100 mg i.m.

Nalbuphine caused impairment in 4 test groups (Attention, Psychomotor Skills, Reaction Time and Visual Functions). Dose-effect relationships were noted in several tests. The lowest impairing dose was 2.5 mg i.v. or 10.5 mg i.m.

Oxycodone administration was followed by impairment in 5 groups of tasks (Attention, Divided Attention, Psychomotor Skills, Reaction Time and Visual Functions). Some dose-effect relation was observed for Attention tasks. The lowest impairing dose was 9 mg i.v. or 20 mg p.o.

Pentazocine administration caused impairment in 5 groups (Attention, En-/Decoding, Reaction Time, Tracking and Visual Functions). Some dose related effects were observed. The lowest impairing dose was 7.5 mg i.v. and 30 mg p.o.

Dezocine, dipipanone, heroin and papaveretum were investigated in too few studies to draw conclusions.

Some publications have studied effects of some opioids in opioid maintained patients, subjects with ongoing use of opioids and previous opioid abusers, except for hydromorphone. The studies on hydromorphone indicated tolerance development in methadone and buprenorphine maintained patients, while results from studies on other drugs appeared more inconclusive.

4.2.2 Narcoanalgesics / atypical opioids

Impairment was observed after administration of 3 x 100 mg of flupirtine the day before testing and an additional 100 mg prior to testing, and after single dose of at least 600 mg.

When administered to healthy volunteers no impairment was observed after doses up to 100 mg p.o. tramadol. Administered to tolerant subjects no impairment was observed after doses up to 500 mg i.m.

4.2.3 Hallucinogens

Impairment was seen after doses from 0.1 mg/kg (7 mg) i.v. **ketamine**. Dose dependent impairment was seen from plasma concentration of 113 ng/ml.

After administration of **LSD** impairment was observed after doses from 50 µg.

Mescaline caused impairment after 0.5 g.

Subjective impairment was observed after a dose of 0.1 mg/kg (7 mg) phencyclidine (PCP).

Psilocybin caused impairment after doses from 115 µg/kg (8 mg) p.o.

4.3 Discussion

The literature on experimental tests of relevance to traffic safety is covering a large number of tests, but there is no agreed hierarchy with regard to relative test importance. An expert group has recently recommended that several tests, covering the fields of automotive behaviours, control behaviours and executive planning, together should constitute the best basis for evaluation on whether a certain drug (dose) contains a traffic risk. This approach appears to be lacking in the vast majority of the studies reviewed.

This leaves us with a series of difficulties when the results from the studies reviewed shall be evaluated:

- If a study has reported no significant differences between subjects given a certain drug and placebo, can that be taken as evidence for no important effect of that dose to the driving ability? Obviously not if the statistical power is low (low n), if the tests are insensitive, and if we only are looking at mean values and the interindividual range is large.
- If a study has reported a statistically significant impairment after one dose of a certain drug, is that to say that this dose can increase the risk of accidents in

real traffic? May be not, if the test is of little relevance to safe driving, and if e.g. a substantial fraction of the normal population would perform similarly in the same test without having taken any drug.

- For several of the drugs in this review only a low number of studies were included. This could bias the conclusions as the results could represent a high or low outcome.
- An important question is to what extent we can accept impairments and slight deviations from the norm in performance tasks. The studies reviewed have various results, but as impairment is found even at the lowest dosages administered to healthy subjects for most of the drugs investigated, it could indicate that caution with respect to driving could be needed for many of these drugs. On the other hand, some variation in performance is expected in a normal population.

4.4 Recommendations

Based on the findings for the different drugs included, the following section will focus on relating these findings to therapeutic doses and/or concentration levels and half-life of the drug (see table 1), and by combining these data attempt to make general recommendations for each drug. With respect to drugs that are often administered repeatedly (codeine, dextropropoxyphene, hydrocodone, hydromorphone and oxycodone) additional assessments are made.

4.4.1 Opiates/Opioids

(except methadone, buprenorphine and morphine)

Alfentanil usually produces pain relief at concentration around 40-90 ng/ml, but with large interpatient variability. This concentration range corresponds to the lowest causing impairment. Alfentanil has a half life of about 1.5 h. Thus patients receiving alfentanil in doses giving rise to concentrations within the range indicated above, might have impairing blood concentrations up to 3-4 hours after alfentanil administration.

Fentanyl can be used acutely in procedures requiring pain relief resulting in blood fentanyl concentrations up to 10 ng/ml before serious respiratory problems occur. Fentanyl has a half life of 1-6 h. This indicates that patients should refrain from driving for more than 12 h after such dosages.

Remifentanil has a therapeutic concentration range of 1-40 ng/ml. The half life is extremely short, 15 minutes or less. This means that concentrations lower than those shown to cause impairment might be reached within hours, even if the therapeutic concentration was high. Interindividual differences and redistribution phenomena, however, make such predictions uncertain.

Butorphanol can be used therapeutically in doses around 2 mg i.m. and the lowest impairing dose was 0.5 mg. The half life is usually 2-4 h. This means that 8 hours after administration impairing effects might still be present.

Table 1: The lowest impairing dose/concentration after single dose intake for different drugs in relation to dosages/concentrations related to treatment and drug half life

Drug	Lowest impairing dose	Regular dosages in treatment	Lowest impairing concentration	Regular concentrations in treatment	Half life
Group 1					
Alfentanil	0.5 mg	0.56 mg	40 ng/ml	40-90 ng/ml	1.5 h
Fentanyl	0.014 mg	3.5 mg	2.5 ng/ml	Up to 10 ng/ml	1-6 h
Remifentanil			1.5 ng/ml	1-40 ng/ml	Up to 15 min
Butorphanol	0.5 mg i.v.	1 mg i.v.			2-4 h
Codeine	25 mg p.o.	25-50 mg p.o.			2-4 h
Dextro-propoxyphene Propoxyphene	65 mg	65-130 mg			8-24 h
Hydrocodone (HC)	7.5 mg i.v. 20 mg p.o.	5-10 mg p.o. 3-6 times/day			3-4.5 h
Hydromorphone (HM)	1 mg i.v.	0.2-0.6 mg i.v. 6-8 times/day			1-3 h
Meperidine (Pethidine)	70 mg i.v. 75 mg i.m.	50-100 mg p.o.			
Meptazinol	50 mg i.v. 100 mg i.m.	50 mg i.m.			~ 2 h
Nalbuphine	2.5 mg i.v. ~ 10 mg i.m.	10-20 mg parenteral			2-4 h
Oxycodone	20 mg p.o.	2.25-20 mg p.o.			2-3 h
Pentazocine	7.5 mg i.v. 30 mg p.o.	20-60 mg parenteral 25-100 mg p.o.			~ 2 h
Group 2					
Tramadol	No impairment seen up to 100 mg p.o.	50-100 mg p.o.			~ 6-8 h
Group 3					
Ketamine	0.1 mg/kg i.v. (~ 7 mg)	0.5-4.5 mg/kg i.v. (~ 35-315 mg)	113 ng/ml		α-phase: 10-15 min β-phase: 2.5 h

Codeine is used therapeutically in single doses of 25-50 mg or more. The lowest impairing dose was 25 mg. The half life is 2-4 h. Thus 4 hours after intake of 50 mg there could still be impairing effects comparable to the acute effects after an intake of 25 mg codeine. A therapeutic schedule with dosing of 50 mg every 6 hours would probably be unsafe in the sense that it could cause impairment in some traffic relevant tasks.

Dextropropoxyphene / Propoxyphene is used therapeutically in single doses of 65 and 130 mg. The half life is in the range of 8-24 h. The lowest impairing dose was 65 mg. This indicates that functions of relevance to driving could be influenced 24 hours or more after single dose intake. Repeated therapeutic dosing three times daily, particularly with the highest dose, could be accompanied by some impairment during the whole day.

Hydrocodone (HC) / Hydromorphone (HM) is used therapeutically in doses of 5-10 mg p.o. 3-6 times/day (HC) and 0.2-0.6 mg i.v. 6-8 times/day (HM). The half life is

about 3-4.5 h (HC) and 1-3 h (HM). The lowest impairing dose for hydrocodone was 7.5 mg i.v. / 20 mg p.o. and 1 mg i.v. for hydromorphone. Regular doses are lower than doses shown to cause impairment, but after repeated intake impairing effects may be present even some hours after intake.

Meperidine / Pethidine is used therapeutically often in doses of 50-100 mg per orally. The lowest impairing doses are of the same magnitude. This indicates that during a period of about the half life impairing effects could be present.

Meptazinol can be used therapeutically in doses of 50 mg i.m. The half life is about 2 hours. The lowest impairing dose found was 50 mg i.v. or 100 mg i.m. This indicates that few impairing effects might be present a couple of hours after use of 50 mg i.m.

Nalbuphine is used parenterally in doses of 10-20 mg for therapeutic analgetic purposes. The half life is about 2-4 hours. The lowest impairing dose was 2.5 mg i.v. or about 10 mg i.m. Thus several hours should pass after therapeutic dosing before impairing effects will vanish.

Oxycodone is usually dosed per orally. Single doses can vary from 2.25 to 20 mg p.o. The half life is about 2-3 hours. The lowest impairing dose was 20 mg p.o. This indicates that therapeutic single dose use of 20 mg p.o. oxycodone should be followed by some hours with possible impairing effects.

Pentazocine is used therapeutically in doses 20-60 mg parenterally or 25-100 mg orally. The half life is about 2 hours. The lowest impairing dose given i.v. was 7.5 mg, and p.o. 30 mg. Two half lives (4 hours) after administration of respective highest therapeutic single doses impairing effects could still be expected.

4.4.2 Narcoanalgesics/Atypical opioids

The available data on flupirtin is scarce and includes multiple administrations from the day before testing up to the testing point, so estimating dose/concentration levels where caution is needed is problematic. Recommendations can not be given for this reason.

Few studies were included on tramadol, but from the scarce data available it seems that tramadol does not impair neither naïve nor tolerant subjects in therapeutic doses.

4.4.3 Hallucinogens

Ketamine is used therapeutically in doses from 0.5 mg/kg i.v. The half life of ketamine is 2.5 hours (β-phase). Impairment was observed after doses from 0.1 mg/kg i.v. (7 mg), and dose dependent impairment at plasma concentration level of 113 ng/ml. Two half lives (5 hours) after administration of the lowest therapeutic dose impairing effects might still be present.

For the remaining hallucinogens (LSD, mescaline, PCP and psilocybin) few available data makes it difficult to conclude.

5 SUMMARY MORPHINE: SINGLE DOSE AND CHRONIC TREATMENT RESULTS COMBINED

5.1 Limitations

Before trying to summarize and conclude from the results presented below, attention should be given to some limitations in the papers presented.

5.1.1 Single dose to drug naïve

In only 3 of the studies with single dose morphine administration (5-7), blood morphine concentrations were measured and mean concentrations presented. In all the other studies no blood samples for morphine analysis were taken. It is well known that blood drug concentrations might show marked interindividual differences even if the same dose per kg is given to a group of subjects. To link individual effects to individual concentrations is therefore not possible from the present studies. This is a major drawback in the papers reviewed when concentrations-effect relationships are target issues.

We included one study on chronic use of morphine and pain patients, and this study showed that pain deteriorates performance more than morphine treatment. One could argue that this also could be the case when administering single dose morphine to drug naïve pain patients. On the other hand, Conley et al. (8) showed that morphine reduced self-reported ratings of pain intensity when healthy volunteers immersed a forearm in respectively cold (2°C) and warm (37°C) water while DSST not was impaired.

5.1.2 Chronic use

In the patient studies the clinical situation did not allow randomization or cross-over design. The patients have been compared to healthy volunteers or patients not treated with opioids. Although some matching of groups was tried in some studies, this process was obviously not perfect.

Another problem related to this study design is that pain by itself can lead to reduced performance in psychomotor and cognitive tests. A study of SDLP (standard deviation of lateral position, i.e. the amount of weaving of the car in real driving) in pain patients showed that the patients performed significantly worse than controls (9). Reduction of pain might accordingly improve performance. The action of an opioid would represent an interaction between effects of pain (reduced by drug) and by drug on the test studied.

In the studies with patients on long-term opioid treatments the daily doses showed marked (more than 30 times) interindividual differences. Blood opioid concentrations were generally not measured, and when measured demonstrated interindividual differences by a factor higher than 10. The effects or lack of effects recorded were presented on group level with no possibility to link individual effects to neither dose nor blood drug concentration. Thus it is impossible from the studies performed to relate certain doses or concentrations to certain outcomes.

Few pain patients receive monotherapy with opioids. The studies do not reflect the multiple pharmacological treatments for chronic pain, and the results may therefore be less relevant for pain patients in long-term polydrug treatment.

5.2 Results

5.2.1 Single dose studies in volunteers

We were able to group the tests in 5 major groups: Reaction time, Attention, Psychomotor skills, Visual functions and En-/Decoding.

Impairment by morphine administration was found in some tests in all 5 groups.

Test of psychomotor skills appeared to be the test less sensitive to morphine administration, while tests of visual functions and attention appeared to be the most sensitive. Test of reaction time and En-/Decoding showed medium sensitivity.

Evidence for dose dependent impairment was found for some tests of reaction time and attention. The most obvious dose dependent impairment was found in the Digit Symbol Substitution Test (DSST) (attention) after morphine given i.v. A further analysis of these experiments by calculating blood morphine concentrations and linking these concentrations to effects, resulted in no clear concentration-effect relations. It was, however, found that calculated blood morphine concentrations lower that 50 nmol/L, were not accompanied by statistically significant impairment of DSST.

When a similar analysis was done for all studies with i.v. morphine administration, it appeared that the percentage of effects showing impairment started to become about 10 % or higher at plasma morphine concentrations above 50 nmol/L.

Two papers included pharmacokinetic data from experiments with healthy volunteers. In one (6) no impairment of auditory reaction time was found at blood morphine concentrations of 175 nmol/L. In the other (7) impairment of continuous reaction time was found at blood morphine concentrations probably as low as 15 nmol/L.

In two papers where morphine was infused i.v. to reach certain blood concentrations (10;11), levels up to 280 nmol/L were accompanied by impairment in several tests, 140 nmol/L caused impairment in one test, while no significant effects were found at concentrations around 70 nmol/L for these tests which appeared less sensitive than DSST.

Morphine was given by various routes of administration. When the same dose was given by different routes (i.v., p.o., i.m., s.c.) no clear differences were observed when comparing across different papers.

5.2.2 Chronic treatment with morphine (opioids)

Pain patients treated chronically with morphine showed some impairment in psychomotor abilities and probably in cognitive abilities when compared to healthy controls. When compared to patients with similar diseases (usually cancer) receiving non-opioids or no treatment for pain, no clear differences were observed for either psychomotor performance, cognitive abilities, or driving (simulator, road) performance. Pain by itself has been shown to reduce psychomotor functions (12).

Just a few studies investigated the effects of morphine given to subjects maintained on methadone, heroin users, and previous opioid users. These studies were too few and the results too varied to make any comparisons with the effects of morphine in healthy volunteers. This was also the case for the studies reviewed by Fishbain et al. (2) under the heading “Effects of new opioid dosing on psychomotor and cognitive abilities of opioid maintained patients” (see chapter 8.1.1.).

5.3 Discussion

The tests used in single dose experiments differed considerably between papers. There is no generally accepted list of tests which are particularly suited to test functions of critical importance to safe driving. It has been recommended that all studies should include alcohol as a reference substance in all tests, since alcohol has a well-established concentration-effect relation in tests of relevance to traffic safety. In the studies summarized for morphine, groups tested after alcohol intake were not included. This creates a problem with respect to how to consider a lack of effect of morphine in a certain test, as long as we do not know how alcohol intake would have affected the test result in the particular setting of the experiments performed. Thus in all studies reporting no impairment in a test, the lack of comparator drug is a considerable shortcoming. If a study has reported no significant differences between subjects given morphine and placebo, can that be taken as evidence for no important effect of that dose to the driving ability? Obviously not, if the statistical power is low (low n), if the tests are insensitive, and if we only are looking at mean values and the interindividual range is large.

In many of the studies the past and present drug use was unknown. As previous and present use of opioids might influence the effects of an acute dose of morphine, this lack of knowledge is an important shortcoming. If associated drug use/dependence is not known we might have an unknown confounder of the results through e.g. drug-interactions or tolerance. Drug use might also lead to neuropsychological impairment secondary to brain injury. One study (13) reported that all 9 subjects were occasional drug users but this was not further specified. Others reported current use of prescribed opioids (14) without mentioning the dosage. Some studies reported testing for drug use before and during the test period (14-18). Others did not report on (ab)use at all (5-7;10;19-28).

The present studies have not been evaluated for quality, except that all studies with single dose morphine administration had n > 5, and most are randomized, controlled and double blind. Thus they represent studies of good quality in that sense.

5.4 Recommendations

The literature on experimental tests of relevance to traffic safety test is covering a large number of tests, but there is no agreed hierarchy with regard to relative test importance. An expert group (29) has recently recommended that several tests, covering the fields of automative behaviours, control behaviours and executive planning, together should constitute the best basis for evaluation on whether a certain drug (dose) contains a traffic risk. This approach appears to be lacking in the

vast majority of the studies reviewed, and leaves us with a series of difficulties when the results from the studies reviewed shall be evaluated.

Morphine affects the brain differently from alcohol. It could affect the ability to drive safely, by mechanisms different from those involved in the actions of alcohol. Thus the test usually considered of importance to detect influence by alcohol, could be of less importance to detect influence of morphine, which e.g. on the other hand could influence test thought to be of less importance in alcohol studies. Thus any morphine effect in any psychomotor or cognitive test could have some importance to traffic safety. At the present stage, however, our knowledge related to this problem is limited, as is epidemiological data on morphine induced accident risks. Schnabel et al. (30) have used studies on alcohol to determine concentration related effects of alcohol on traffic related functions and the results will also be presented under the DRUID project as a meta-analysis. Data from this meta-analysis show that psychomotor skills are one of the most frequently impaired tests at 0.05-0.059 % BAC (Blood Alcohol Concentration), while tests of attention and en-/decoding are tests showing least impairment. The present review show that psychomotor skills is the test showing least impairment after morphine administration, while attention and en-/decoding are often impaired by morphine. These results suggest that alcohol has different effects from morphine, and that alcohol is therefore not always the right gold standard for morphine and similar drugs.

5.4.1 Single dose to drug naïve

If a study has reported a statistically significant impairment after one dose of morphine, is that to say that this dose can increase the risk of accidents in real traffic? May be not, if the test is of little relevance to safe driving, and if e.g. a substantial fraction of the normal population would perform similarly in the same test without having taken any drug.

However, when it comes to the possibility to extract information of the importance of blood morphine concentrations in relation to test impairment, there is almost a complete lack of data, i.e. measurements of blood/plasma/serum concentrations of morphine have only been performed in a few of single dose studies (and in addition in two infusion experiments). This leaves us with no real possibility of linking blood morphine concentrations to impairment data.

We tried also, as shown in chapter 7.1.4., to circumvent the lack of pharmacokinetic data by estimating blood morphine concentrations for the experiments reviewed, by stipulating morphine levels based on results from published pharmacokinetic experiments. This is a somewhat risky practice, which might idealize concentration-effect relationships, due to lack of individual data. It was interesting to notice that even by this procedure, no convincing concentration-effect relations were observed. The probable conclusion was that very few significant effects were observed at morphine concentrations lower than 50 nmol/L.

It was not advisable to perform similar calculations for studies in which morphine was taken p.o., due to the large and variable first pass effect (31).

Morphine metabolizes into two main metabolites, morphine-3-glucuronide (M3G, the major metabolite) and morphine-6-glucuronide (M6G) (32). The latter, M6G has effects similar to morphine (33). M3G has probably antagonistic effects (34). The

plasma concentrations of the glucuronides exceed the concentration of morphine by far, shortly after single dose administration (35). M3G/M6G ratios can differ markedly between individuals from > 10 to close to 1, depending on route of administration (35;36), environmental factors, previous drug use and use of interfering substances, in addition to constitutional individual differences. This tells us that any clear relationship between blood morphine concentrations on one hand and drug effect on the other is unlikely. A better relationship has recently been demonstrated (37) when the sum of morphine and M6G concentrations were related to effect. There appeared to be an intriguing contradiction when comparing the results from papers (6) and (7). In the former no effect was observed at morphine concentrations about 175 nmol/L (6), in the latter impairment was measured at 15 nmol/L morphine (7). Measurements of M6G was performed in (6) but not in (7). Peak impairment observed 2 h after i.v. injection of morphine e.g in (16) is also intriguing, as it would have been expected that the peak impairment would have occurred sooner than 2 hours after the injection. Again a role of M6G could be suspected as M6G would be expected to reach its highest concentrations 1-2 hours after an i.v. injection of morphine. Research remains, however, before the full pharmacodynamic-pharmacokinetic relations for morphine, M6G, and M3G are understood.

Single dose administration of morphine in doses up to 5 mg appears to cause very few effects in traffic relevant performance tasks. At higher doses impairment is found in various tasks, but with no clear dose-effect relationship except for DSST. Probably blood morphine concentrations < 50 nmol/L are accompanied by few effects in traffic relevant performance tasks. **Therefore this level, 50 nmol/L, could represent a level with little accompanying traffic risk.**

5.4.2 Chronic use

The question concerning effects of morphine together with its metabolites will also apply to studies on patients with chronic morphine treatment. In these studies patients with dosing that differed more than 10 times were grouped together as morphine treated, but usually without measurements of morphine or metabolites in blood samples. One study (38) reported no significant correlations between concentrations of morphine, M6G or M3G and effects. A second study (39) found no correlation between impairment of reaction time and plasma morphine concentration. A third study (40), however, found a correlation between plasma concentrations of morphine, morphine glucuronides and effects, but the concentrations differed about 100 times between the lowest and highest measured. Relating effects or lack of effects to blood drug concentrations based on these studies is, however, difficult.

The literature is too limited to draw clear conclusions regarding the effects of long-term medical use of morphine and driving. It is, however, possible that drug effects of relevance to driving are not marked in such patients. Therefore evaluation of individual performance of such patients seems with the present knowledge to be the only useful procedure to approach the question of fitness for driving.

5.5 Recommendations for future research

- Single dose experiments with morphine on effects in a **battery of tests** with concomitant measurement of **blood concentrations of morphine and metabolites** should be performed.
- Studies on patients **on defined morphine doses** in driving simulators or on the roads compared to different control groups should be performed. In such studies **blood morphine and metabolite concentrations should be measured.**
- **Some studies on additional opioid doses in maintenance treatment show improvement of performance. Multiple doses of opioids in treatment of chronic pain should be studied with respect to this effect.**
- **It seems that attention and en-/decoding are the most sensitive tests of the impairing effects of morphine, and therefore could probably be recommended in future studies of morphine and possible other opioids.**

6 SUMMARY METHADONE AND BUPRENORPHINE: SINGLE DOSE AND CHRONIC TREATMENT RESULTS COMBINED

6.1 Limitations

Before trying to summarize and conclude from the results presented below it is important to focus on some limitations which appear to be quite common for the papers included.

There could be marked differences between the subjects selected to methadone or buprenorphine treatment. It is important to realize that studies with methadone or buprenorphine treated subjects are not randomized, and that factors determining the selection to methadone or buprenorphine treatment groups could possibly be the explanation for all differences observed between the groups. The choice of drug depends on previous (drug) history and characteristics of the patient and these differences may be reflected in the various tests performed. Buprenorphine administered to pain patients is, however, an exception.

In many studies on methadone and buprenorphine maintained patients, the individual dosage reported for a group represents a wide range, the highest dose sometimes being close to 10 times higher than the lower. This fact would lead us to assume that drug blood concentrations in such a group of patients would represent an interindividual difference of the same order of magnitude, maybe even larger as there is a wide inter- and intra individual variation in drug blood concentrations for a given dosage of both methadone and buprenorphine (41;42). Furthermore none of the studies reviewed on maintenance patients measured blood drug concentration in a study with performance tasks.

Furthermore none of the studies on maintained patients reported results for subgroups or individuals on different dosage levels. Even if we could have made some theoretical calculation on blood drug concentrations in patients on steady state long-term dosing, we would not have had performance data corresponding to that concentration range. Such a concentration range would probably have had a span of 3 times (i.e. the highest concentration divided by the lowest) making its usefulness rather limited.

6.2 Results

In spite of the limitations prevailing for the studies reviewed some tentative conclusions can be made:

6.2.1 Single dose of methadone and buprenorphine to naïve subjects

Single doses of methadone and buprenorphine appears to be followed by impairment in drug naïve subjects, as 3 of 5 tests that examined the effects of single dose methadone to drug naive healthy volunteers found impairments of methadone doses

up to 10 mg, and 18 of 20 tests that examined the effects of single dose buprenorphine to drug naive healthy volunteers found impairments of buprenorphine (0.075-0.6 mg kg i.v., 0.4 mg p.o., 0.3 mg i.m.).

6.2.2 Single dose of methadone and buprenorphine to current users of opiates/opioids

When single doses were administered to opiate/opioid abusers these acute effects were less pronounced. Single dose methadone was given to current users of opiates/opioids in one test, and no impairment was found. When single dose buprenorphine was given to current users of opiates/opioids, only one out of 4 tests performed found impairment. The only study assessing the effect of daily buprenorphine dose in opioid dependents found no changes from predosing to postdosing on the test performed.

6.2.3 Single dose of methadone and buprenorphine to maintained patients

When single doses were administered to maintained patients the acute effects of methadone and buprenorphine also appeared to be less pronounced as 10 out of 50 tests found some dose-related effects for doses up to 120 mg methadone in methadone maintained patients. Only 2 out of 21 tests found impairment after doses up to 13.4 mg buprenorphine in patients maintained at methadone or buprenorphine. Furthermore, 3 out of 21 tests found improvement of performance after buprenorphine doses from 4 to 13.4 mg in buprenorphine maintained patients.

6.2.4 Methadone maintained patients compared to controls or pretreatment status

When it comes to performance of methadone maintenance patients compared to controls, 110 out of 236 tests showed impairments. 4 studies have compared the performance before and after long term methadone intake, one of the studies found impairment and one study found improvement from baseline measures.

6.2.5 Buprenorphine maintained patients compared to controls

When it comes to performance of buprenorphine maintained patients compared to controls, 14 out of 44 tests showed impairment.

6.2.6 Buprenorphine maintained patients compared to methadone maintained patient

8 studies have compared the performance of buprenorphine maintenance patients to methadone maintenance patients. 10 out of 59 tests found a better performance under buprenorphine treatment. The differences between buprenorphine maintained and matched controls seemed less evident than for methadone, and individuals under buprenorphine treatment performed somewhat better than individuals under methadone treatment.

6.3 Discussion

A major problem in assessing the true impact of drugs on driving and overall traffic safety is that the variables being measured across studies vary significantly. In research reported in a growing global literature, basic parameters assessed, analytical techniques and drugs tested are simply not comparable due to the lack of standardization in the field. An expert panel recently recommended that alcohol effects on performance could serve as a standard reference to quantify impairments for many other drugs. It is a general lack of comparator drug in the studies reviewed. Only one study (43) used alcohol as comparator drug. Especially for studies reporting no impairments, the lack of comparator drug is a considerable shortcoming.

The expert panel also recommended that researchers should use tests that have been validated to be sensitive to drug effects on driver performance, and to the extent possible, have demonstrated predictive validity of driving impairment (29). The problem is, however, how to do this for opioids. Another problem is to assess which type of tests that could be relevant for this patient group. Clearly real driving is the ultimate performance test, but is attention more important than visual functions in these subjects? Is motor performance less important than a psychological evaluation battery? One could argue that tests considered valuable in e.g. alcohol studies (the most studied drug in experimental and epidemiological traffic research) should be the tests most useful in studying relevant effects of opioids in relation to traffic safety. But we do not know whether opioids are potentially risky in traffic by the same (central nervous) effects as alcohol. Even if we postulate that the mechanisms are similar for alcohol and opiates (which from a pharmacological point of view is quite unlikely), we would have difficulties in applying this type of approach to the present material. We have only one study (43) where alcohol has been used as comparator drug. In all the other studies (n = 40, besides Mørland (3) and Fishbain et al. (2)) we have no data on how alcohol would have influenced the tests used in the particular setting of the experiments performed.

It is important to know the current and past drug-use history of all test subjects (29). Tolerance seems to be of great importance to draw into consideration for opioids like methadone and buprenorphine as there are not any clear dose response patterns like e.g. for alcohol. The majority of healthy volunteers included in the studies report some use of recreational drugs. In some of the studies the history of drug use is not well described. As such, the categorization of studies into groups based on the individual's opioid tolerance could be misleading. Also the use of drugs besides methadone and buprenorphine in maintenance patients is of importance, and such data were missing in many studies. Bernard et al. (44) investigated apprehended Norwegian drives that had methadone in their blood at the time of apprehension over the period 2001-2006 (n = 635). Methadone was the only psychoactive drug detected in blood in only 10 cases out of 635 drivers identified. The extensive use of other drugs among this group makes it more difficult to assess the effects of methadone and buprenorphine treatment alone. It is important to control for an associated drug abuse/dependence of other drugs in studies where opioid abuse/dependence subjects are utilized. If the associated drug abuse/dependence is not controlled for, it could confound the results. Hauri-Bionda et al. (45) found that the fraction of the methadone group screening positive for other psychoactive drugs in urine performed markedly worse than the remaining part of the group. The type of previous drug abuse/dependence is also potentially important to the neuropsychological impairment.

6.4 Recommendations

Recommendations regarding methadone and buprenorphine maintained patients will depend on the degree of impairment the society is willing to accept and at which point we would consider it to represent a major traffic risk. Almost all of the studies performed on patients in opioid maintenance treatment show some degree of impairment, but unfortunately none of the studies have tested real driving. Two studies used batteries of tests, and impairment was found in respectively 3 out of 13 and 1 out of 12 tests (46;47). This indicates one of the major problems with the maintenance patients and making recommendations; impairment is found in most of the studies but only in few of the tests. Due to the general lack of use of comparator drugs in these tests, we are not able to interpret the lack of influence by opioid treatment properly.

When we on the other hand observe an effect, is caution needed at any impairment, or where does one draw the line for an acceptable degree of impairment, like for other (legal) drugs or even normal variations in a normal population? In addition to this, most of the studies on maintenance patients do not give us the possibility to differentiate between effects of the drug used in maintenance treatment and individual effects due to the (previous) life as a drug abuser. The possibility also exist that methadone e.g. has been administered to people with more serious drug problems, than those being offered buprenorphine.

The question is to what extent we can accept impairments and slight deviations from the norm in performance tasks. If absolutely no malperformance can be accepted, the data demonstrate that no individuals treated with methadone or buprenorphine should be allowed to drive a car.

When evaluating if a subject is to be allowed a driving license it is strongly recommended to do screening for other psychoactive drugs, as data indicate that maintenance patients often use additional drugs during treatment (44).

Finally, the number of subjects needed to demonstrate an impairing effect of drugs will depend upon the design of the study and the measure to be studied. Many of the studies reviewed have small number of subjects included decreasing the power to identify differences between groups.

The literature in this field is too limited to draw clear conclusions regarding maintenance use of methadone/buprenorphine and driving. It seems, however, quite clear that low doses of both methadone and buprenorphine cause impairment in performance tasks related to driving in drug naïve as all of the studies in these groups show some level of impairment. It can thus be stated that both drugs have an impairing potential, but that the scientific literature so far does not allow us to draw any firm conclusions on whether this group or certain subgroups of maintenance patients should be allowed a driving license.

In some studies there are indications of large individual differences. Some authors imply that patients passing several tests without signs of impairment might be fit to drive. This might indicate that some patients could be allowed to drive, after some testing, but the scientific basis of doing so can still be debated.

6.5 Recommendations for further research

The complete lack of studies of methadone and buprenorphine (single dose or maintenance) on real driving is striking, and calls for such studies in the future.

This review has not included epidemiological studies on accident risks related to methadone and buprenorphine maintenance patients. It is possible that epidemiological accident analysis studies under the DRUID umbrella might be helpful in identifying the accident risk related to methadone and buprenorphine maintenance.

7 RESULTS SINGLE DOSE

The summary in italics reflects the data from the different studies. It reports the total number of studies/tests showing impairment and also the total number of studies/tests showing no impairment. Furthermore it summarizes the doses at which impairment is or is not observed. The n represents the range of number of subjects in the different studies.

In those few cases where no test result was reported or the results were difficult to interpret, the result was registered as no impairment.

Evidence tables of the included studies with references are given in the following:

Appendix 5 – Opioids/opiates, narcoanalgesics/atypical opioids and hallucinogens

Appendix 6 – Morphine

Appendix 7 – Methadone and buprenorphine

7.1 Single doses given to healthy volunteers

7.1.1 Effects of narcoanalgesics/atypical opioids in healthy volunteers

7.1.1.1 Flupirtine

Flupirtine is an analgesic administered in usual doses of 100 mg p.o. 3-4 times daily for relief of pain. It can also be administered as a rectal suppository or as intramuscular injection.

3 studies tested the effects of flupirtine on healthy volunteers (48-50). Impairment was observed after administration of 3 x 100 mg of flupirtine the day before testing and an additional 100 mg prior to testing, and after single dose of at least 600 mg. No impairment was seen after 100-200 mg.

Biehl (49) tested performance with a *battery of 5 tests*, and found no impairment in any of the tests. The subjects received 100 mg of flupirtine three times, administered with three hours between each dose, and the tests were performed between the 1st and 3rd dose. Muller-Limmroth (48) administered 3 x 100 mg of flupirtine on the day before testing, and an additional 100 mg prior to the testing, to 12 male patients. Impairment was seen in 3 out of 5 tasks tested; *reaction time*, *mental processing time* and *signals overlooked*. Preston et al. (50) studied volunteers with a history of sedative drug use. 3 out of 4 tests showed impairment (*tracking*, *DSST* and *enter and recall*), but it is not indicated at which dose the difference was significant (n = 12, 200-600 mg).

7.1.1.2 Tramadol

Tramadol is used to relief moderate to moderately-severe pain. It is administered per orally in doses of 50-100 mg every 4-6 hours as immediate release formulation.

3 studies dealt with the effects of tramadol (51-53). 7 tests were performed, and no impairment was seen after doses up to 100 mg p.o.

3 studies looked at the effects of single dose tramadol to healthy volunteers. Zacny (53) tested 5 different psychomotor tasks and found no impairment (n = 22, 50 and 100 mg p.o.). Pickering et al. (52) tested *CRT* and found no impairment (n = 24, 37.5 mg p.o.). Hummel et al. (51) found no impairment of tracking performance after administering 100 mg p.o. (n = 20).

7.1.2 Effects of single dose hallucinogens in healthy volunteers

7.1.2.1 Ketamine

Ketamine is used in induction and maintenance of general anaesthesia, as an analgesic and for sedation. For sedation and analgesia doses from 1 mg/kg/dose is administered i.v. Ketamine can also be administered i.m. and p.o.

7 studies were included that tested the effects of ketamine/ S-ketamine (54-60), in addition to 3 reviews (61-63). All of the 7 studies found impairment of one or more tests after doses from 0.1 mg/kg (7 mg) i.v., and some dose-response effects were observed. Dose dependent impairment was seen from plasma concentration of 113 ng/ml.

Morgan et al. (60) found dose dependent impairment of *SOA* (stimulus onset asynchrony) (mean plasma concentration 113 and 237 ng/ml 50 min. after administration, n = 48). Anand et al. (58) administered infusion of ketamine of 0.26 mg/kg and 0.65 mg/kg/h, resulting in plasma concentrations of 125-150 ng/ml after 30-60 min, and found that it caused impairment of *Hopkins verbal learning test* (n = 16). Krystal et al. (57) found impairment of *vigilance*, *verbal fluency* and *Wisconsin card sorting test (WCST)* for the high dose of ketamine (0.1 and 0.5 mg/kg ~ 7 and 35 mg, n = 19), and there was a dose-response effect for *verbal fluency* and *Wisconsin card sorting test*. Malhotra et al. (56) administered a bolus of 0.12 mg/kg i.v. followed by infusion of 0.65 mg/kg over 1 hour. Impairment was found in all tests performed: *Attention*, *recall* and *recognition* (n = 15). Krystal et al. (55) found impairment of *distractibility*, *verbal fluency*, *proverb interpretation*, *Wisconsin card sorting test* and *learning and memory*, but not of *vigilance* and *finger-tapping*, after a bolus of 0.12 mg/kg i.v. and 1 hour infusion of 0.65 mg/kg (n = 23). Ghoneim et al. (54) administered two doses of ketamine (0.25 and 0.5 mg/kg i.m.) and found impairment of *delayed free recall* for both doses, impairment of *immediate free recall* and *number learning* after the high dose, and no impairment of *delayed recognition*, *category generation*, *backward digit span* and *tapping* (n = 31). Gouzoulis-Mayfrank et al. (59) tested *reaction time in covert orienting of attention task* and found dose dependant impairment (0.1-0.15 mg/kg and 0.15-0.20 mg/kg, n = 15).

Other reviews ketamine: Wolff et al. (61) concluded that sub-anaesthetic doses cause impairment of attentional performance, including vigilance and memory. Mechri et al. (62) was used primarily as a source for references to primary research literature. Schmid et al. (63) found that doses up to 20 mg/kg/min (plasma concentration > 50 ng/ml) caused sedation and drowsiness but no impairment of

cognitive functioning. At higher doses (concentration > 200 ng/ml) the incidence of cognitive and memory impairment increased.

7.1.2.2 LSD

LSD, Lysergic Acid Diethylamide, has psychedelic effects and is used as a recreational drug. It has no medicinal use. A typical single dose is 50-100 µg of LSD, and it is usually taken p.o.

8 studies have tested the effects of LSD (28;64-70). 5 of 8 studies found impairment of one or more tasks tested after doses from 50 µg. No impairment was seen after doses up to 100 µg.

Kornetsky et al. (69) used a battery of 6 tests and found impairment in 4 of the tests: 100 µg impaired *speed of addition* (9 digits), *modified digit symbol test* and *tachistoscopic/visual discrimination*, while 50 and 100 µg impaired *speed of addition* (3 digits) (n = 10). Goldberger (65) studied the effects of 100 µg (p.o.) on 9 different tests, 8 of the tests showed impairment by LSD (n = 42). Wikler (28) found that 2-3 µg/kg (140-210 µg), but not 1 µg/kg (70 µg), administered orally to post addicts caused impairment of *auditory-manual reaction time* (n = 10). Holliday et al. (68) found impairment of *CFF (Critical Flicker Fusion)* after administering 1 µg/kg (70 µg) (n = 10). Silverstein et al. (66) found impairment of *digit span* after 100 µg (n = 24).

Primac et al. (70) found no impairment after administering 50 or 100 µg p.o. (*Wisconsin card sorting test* and *continuous performance test*) (n = 10). Mitrani et al. (67) administered 100 µg and found no impairment of *saccadic eye movements* (n = 5). Landis et al. (64) administered 0,1-0,12 mg (100-120 µg) p.o. to psychiatric patients and found no impairment of the tasks tested (n = 6).

7.1.2.3 Mescaline

Mescaline is an alkaloid obtained from the cactus *Lophophora williamsii.* Mescaline produces hallucinogenic and sympathomimetic effects. It has no therapeutic use.

Hermle et al. (71) administered 0.5 g to healthy subjects and found impairment on *BPRS* (Brief Psychiatric Rating Scale) compared to baseline (n = 12).

7.1.2.4 PCP (Phencyclidine)

PCP is a potent analgesic and anaesthetic. Due to severe adverse effects it is no longer used therapeutically, but is widely used for its hallucinogenic effects. It can be taken orally, sniffed, injected, or smoked.

2 reviews on the effects of PCP were included. Pradhan (72) concluded that 50 % of the subjects showed some kind of objective or subjective impairment (0.1-0.15 mg/kg, ~ 7-11 mg). Javitt et al. (73) reviewed 25 papers and concluded that PCP-induced psychotomimetic effects are associated with submicromolar serum concentrations of PCP in normal volunteers.

7.1.2.5 Psilocybin

Psilocybin is an indole alkaloid obtained from the sacred Mexican mushroom, *Psilocybe mexicana* (Agaricaceae). Psilocybine has hallucinogenic and sympathomimetic properties. It has no therapeutic use.

9 studies have tested the effects of psilocybin (74-82), and all found impairment of one or more tasks tested from doses of 115 µg/kg p.o. (~ 80 mg).

Carter et al. (77) studied visual tests, and found impairment of *coherence sensitivity* but no impairment of *contrast sensitivity*, after administering capsules of 215 µg/kg p.o. (n = 9). Hasler et al. (78) found that 215 and 315 µg/kg p.o. impaired *global score of altered state of consciousness* and *Frankfurt attention intervention*, while 115, 215 and 315 µg/kg impaired *vigilance* (n = 8). Umbricht et al. (79) found impairment of *AX-type continuous performed task*, but not of *mismatch negativity*, after 280 µg/kg p.o. (n = 18). Gouzoulis-Mayfrank et al. (80;81) administered 200 µg/kg p.o., and found impairment of *reaction time in covert orienting of attention task* and *association task,* but no impairment of *repetition task* (n = 32). Duke et al. (82) found impairment of *trail making test* (200 µg/kg p.o., n = 8). Wittmann et al. (74) found impairment of *temporal reproduction* and *sensorimotor synchronization* after 115 and 250 µg/kg p.o., and impairment of tapping speed after 250 µg/kg p.o. No impairment was found of spatial span task (n = 12). Carter et al. (76) found that 215 µg/kg p.o. gave impairment of *multiple-object tracking* and *spatial working memory* (n = 8). Carter et al. (75) found impairment of *binocular rivalry* after 115 and 250 µg/kg p.o. (n = 12).

7.1.3 Effects of single dose opiates/opioids in healthy volunteers

(except methadone, buprenorphine and morphine)

The opiates/opioids in this chapter are used in pain management and/or in relation to surgery. The results therefore reflect situations where a patient has received treatment for acute pain or after ambulatory surgery.

Evidence tables of the included studies with references are given in *appendix 5*.

The results for methadone, buprenorphine and morphine will be presented in own chapters in the present review.

Where doses are calculated a standard person of 70 kg is used. The test persons are healthy volunteers if not otherwise indicated.

7.1.3.1 Alfentanil/ fentanyl/ remifentanil

Alfentanil, fentanyl and remifentanil are all used as anaesthetics during surgery. Fentanyl is also frequently used for acute pain. A regular dose of alfentanil is from 8 µg/kg (0.56 mg), fentanyl from 50 µg/kg (3.5 mg) and remifentanil from 0.1 µg/kg/min (7 µg/min), depending on the duration of the procedure.

7.1.3.1.1 Attention

9 studies dealt with attention (83-90). 6 studies reported impairment (83-85;88;91;92).

*4 studies (n = 10-40) dealt with effects on attention after administering **alfentanil** (83-85;88;91;92). A total of 4 tests were performed, and impairment was found in 3 of the tests. A linear relationship between plasma concentration and effect measure was observed in a concentration range from 13.4-133.2 ng/ml, and impairment was seen from concentrations of 40 ng/ml. No impairment was seen after 0.5 and 1 mg i.v.*

*6 studies (n = 6-40) dealt with effects on attention after administration of **fentanyl** (86-88;90-92). 4 out of 7 tests showed impairment. Impairment was seen from 0.014 mg i.v., and concentration related impairment was observed from blood fentanyl concentrations of 2.5 ng/ml. No impairment was seen after doses up to 0.21 mg i.v.*

*One study dealt with the effects of **remifentanil** on attention (83). Concentration related impairment was observed in the test performed (1.5-3 ng/ml, n = 10).*

Angst et al. (85) found a linear relationship between plasma concentration and effect measure on the *trail-making test*, administering i.v. doses from 428 µg to 6341 µg alfentanil (step 1-4). However, it is not indicated at which dose step the difference was significant.

Schneider et al. (88) found impairment of *sustained attention* and *signal detection*. The subjects received 0.014 mg fentanyl (i.v.). Measured serum concentration of fentanyl after 15 minutes was 1.91 ng/ml and after 30 minutes 0.67 ng/ml. The test session started 15 minutes after fentanyl injection.

5 studies have tested *Digit Symbol Substitution Task (DSST)*, and 3 found impairment. Black et al. (83) found impairment at the highest target level of alfentanil blood concentration (64 ng/ml), and at the medium and highest target level of remifentanil blood concentration (1.5 and 3.0 ng/ml). Pavlin et al. (84) administered alfentanil to a steady state of 40 ng/ml and found impairment of DSST. Veselis et al. (91) studied fentanyl and found impairment of DSST at the highest target blood concentration (2.5-3.5 ng/ml). Thapar et al. (86) and Zacny et al. (93) found no impairment of DSST.

Sold et al. (92) tested *concentration* during infusion of fentanyl 0.15 mg and found impairment compared to baseline.

Scamman et al. (90) found no impairment of symbol cancellation for alfentanil (0.5-1 mg i.v.) or fentanyl (0.1-0.2 mg i.v.).

7.1.3.1.2 Divided attention

Schneider et al. (88) tested *divided attention* in subjects receiving 0.014 mg i.v. **fentanyl** and found no impairment (n = 12).

7.1.3.1.3 En-/Decoding

9 studies dealt with en-/decoding (10;83;88-92;94), 6 of the studies found impairment (10;83;88;91;92;94).

*3 studies (n = 15-40) dealt with the effect of **alfentanil** on en-/decoding (10;83;90), and one out of 5 tests showed impairment. Impairment was found at steady state concentration of 64 ng/ml (but not 16 and 32 ng/ml, n = 15). No impairment was seen after doses up to 1 mg i.v.*

*7 studies (n = 9-40) dealt with the effects of **fentanyl** on en-/decoding (86;88-92;94), and 6 out of 19 tests showed impairment. Some concentration related effects were observed (1.5-2.5 ng/ml), and impairment seen from 0.014 mg i.v. No impairment was seen after doses up 0.21 mg i.v.*

*One study dealt with the effects of **remifentanil** on en-/decoding (83), and impairment was found (concentration level of impairment was not indicated, target levels from 0.75 to 3 ng/m., n = 10).*

Coda et al. (10) tested *cognitive variable* and found that steady state concentration of 64 ng/ml alfentanil gave impairment. Veselis et al. (91) gave continuous infusion targeting three different plasma concentrations of fentanyl and tested *auditory-verbal recall task (AVLT)*, *picture recall* and *SN* (serial numbers), impairment was seen in *AVLT* and *SN* for the high concentration (2.5 ng/ml) and in *picture recall* for medium and high concentration (1.5 and 2.5 ng/ml) (n = 9). Sold et al. (92) administered 0.15 mg fentanyl i.v. and found impairment of *short term memory*, but no impairment of *word recognition task* (n = 28). Black et al. (83) found impairment of *backward digit span* when administering plasma target levels of 0.75 – 3 ng/ml remifentanil, but not for alfentanil (target level 16-64 ng/ml, n = 10). Ghoneim et al. (94) administered 0.1 and 0.2 mg fentanyl (i.v.) and found impairment of *backward digit span* at the highest dose, but no impairment of *serial learning, short term memory* or *delayed recall* (n = 10). Schneider et al. (88) administered 0.014 mg fentanyl i.v. and found impairment of *memory (distracting list)*, but no impairment of *memory (delayed free recall and words)* (n = 12).

Scamman et al. (90) tested alfentanil (0.5 and 1 mg i.v.) and fentanyl (0.1 and 0.2 mg i.v.) and found no impairment of *delayed free recall*, *immediate free recall* and *learning and recall* (n = 40). Veselis et al. (91) tested *picture recall*, *picture recognition* and *word recognition* at constant fentanyl serum concentration of 2.33 ng/ml and found no impairment. Thapar et al. (86) found no impairment of *short term memory* (0.05 mg i.v., n = 12).

7.1.3.1.4 Psychomotor Skills

*2 studies (n = 15-40) dealt with psychomotor skills after administration of **alfentanil** (10;90), concentration related effect and impairment was observed in one test (64 ng/ml). Both impairment and no impairment were observed after 0.5 and 1 mg i.v.*

*5 studies (n = 6-40) dealt with psychomotor skills after administration of **fentanyl** (86;87;90;93;94), dose related impairment was observed in 4 out of 6 tests performed after doses from 0.1 mg i.v. No impairment was seen after 3.5 mg.*

Coda et al. (10) administered 1 mg alfentanil i.v. and found impairment of *complex motor performance* at the highest steady state concentration (16, 32 and 64 ng/ml), but no impairment of *simple motor performance* (n = 15). Scamman et al. (90) gave 0.5-1 mg alfentanil i.v. and 0.1-0.2 mg fentanyl i.v. and tested *tapping* and *motor*. The high dose of fentanyl gave impairment of both tests. Zacny et al. (87) found that 0.05 and 0.1 mg fentanyl gave impairment of *eye-hand coordination* (n = 13). Ghoneim et al. (94) tested *tapping board* and found that 0.2 mg fentanyl i.v. caused impairment (n = 10).

Zacny et al. (93) tested *eye-hand coordination* after 0.05 mg fentanyl and found no impairment (n = 6). Thapar et al. (86) found that 0.05 mg fentanyl i.v. did not impair *eye-hand coordination* (n = 12).

7.1.3.1.5 Reaction time

7 studies dealt with reaction time (85-88;91;92;94), 4 studies found impairment (85;88;91;92).

*1 study dealt with reaction time after administration of **alfentanil** (85), and impairment was observed as well as a linear relationship between plasma concentration and effect measure (13.4-126.1 ng/ml (n = 12).*

*6 studies (n = 9-28) dealt with reaction time after administration of **fentanyl** (86-88;91;92;94) and 3 out of 8 tests found impairment, after doses from 0.014 mg and at target plasma concentration of 2.5 ng/ml (n = 9-28). No impairment was seen up to doses of 0.2 mg i.v.*

Veselis et al. (91) found impairment of *CRT* at the target level of infusion of 2.5 ng/ml fentanyl (n = 9). Angst et al. (85) found a linear relationship between plasma concentration and effect measure of *reaction time* (4 infusion steps with doses from 428 to 5346 µg alfentanil, n = 12). Sold et al. (92) found impairment of *reaction time* after 0.15 mg fentanyl i.v. (n = 28). Schneider et al. (88) tested *Vienna reaction time* and found impairment of the auditory part but not the visual (0.014 mg fentanyl i.v., n = 12).

Zacny et al. (87) administered 0.025-0.1 mg fentanyl i.v. and found no impairment of *ART* (auditory reaction time) (n = 13). Thapar et al. (86) found no impairment of *ART* after 0.05 mg fentanyl i.v. (n = 12). Ghoneim et al. (94) tested *CRT* and *SRT* and found no impairment (0.1 and 0.2 mg fentanyl i.v., n = 10).

7.1.3.1.6 Tracking

Stevenson et al. (95) tested *tracometer task* (with 6 dependent measures) and found impairment (0.1 mg fentanyl i.v., n = 9).

7.1.3.1.7 Visual Functions

7 studies dealt with visual functions (83;86;87;91;93;94;96), 4 found impairment (83;91;93;96).

*One study dealt with visual functions after administering **alfentanil** (83), and impairment was observed at the high target plasma level of 64 ng/ml (n = 10).*

*6 studies (n = 6-13) dealt with visual functions after administering **fentanyl** (86;87;91;93;94;96), and impairment was found in 4 out of 7 tests performed after doses from 0.05 mg and at plasma concentration target level of 2.5 ng/ml. No impairment was seen after doses up to 0.2 mg i.v.*

*One study dealt with visual functions after administration of **remifentanil** (83), and impairment was found at plasma target levels of 1.5 and 3 ng/ml (n = 10).*

Manner et al. (96) found impairment of *CFF* (critical flicker fusion test) and *Maddox Wing test* after 0.175 mg fentanyl i.v. (n = 7). Veselis et al. (91) found impairment of *CFFT* for the high plasma concentration (2.5 ng/ml) of fentanyl (n = 9). Black et al. (83) found impairment of *Maddox Wing* for the high plasma target concentration of alfentanil (64 ng/ml) and the medium and high plasma target concentration of remifentanil (1.5 and 3 ng/ml) (n = 10). Zacny et al. (93) administered 0.015 mg fentanyl i.v. and found impairment of *Maddox Wing* (n = 6).

Zacny et al. (87) found no impairment of *Maddox Wing* (0.025-0.1 mg i.v. fentanyl, n = 13). Thapar et al.(86) found that 0.05 mg i.v. fentanyl did not impair *Maddox Wing* (n = 12). Ghoneim et al. (94) found no impairment of *visual retention test* after 0.1-0.2 mg i.v. fentanyl (n = 10).

7.1.3.2 Butorphanol

Butorphanol is used in management of moderate-to-severe pain, as preoperative medication and as supplement to balanced anaesthesia. Doses from 1 mg i.v. are administered.

7.1.3.2.1 Attention

5 studies (n = 10-126) dealt with attention (8;15;97-99), and impairment was found in all of the studies (6 out of 8 tests showed impairment). Impairment was observed in a dose range from 1 mg to 71.4 µg/kg (~ 5 mg). No impairment was seen after doses up to 2 mg.

4 studies tested *DSST* and all found impairment (8;15;97;98). Walker et al. (98) found dose related impairment of *DSST* for the doses 1.5 mg and 3.5 mg (i.v.). Impairment was also found after administration of 2 mg, but not 1 mg, butorphanol transnasal, Zacny et al.(97) (n = 10). Conley et al. (8) found that 2 mg (i.v.) impaired *DSST*. Zacny et al. (15) found that *DSST* was impaired by 1.0 mg (i.v.) butorphanol, but not for 0.5 or 2.0 mg (n = 12).

Logical reasoning was tested in 3 studies. Walker et al. (98) found impairment, but did not indicate at which dose the difference was significant (doses from 0.5-3.5 mg i.v.). Zacny et al. (15;97) found no impairment after administering 0.5-2.0 mg (i.v.) and 1-2 mg intranasal (n = 10-12).

Dershwitz et al. (99) studied *trail-making test* and found dose related impairment after 22.5 µg/kg and 71.4 µg/kg (i.v.) (~ 1.5 and 5 mg) in patients scheduled for elective surgery.

7.1.3.2.2 En-/Decoding

Zacny et al. (97) found no impairment of *backward digit span* after administering 1 and 2 mg butorphanol intranasal (n = 10).

7.1.3.2.3 Psychomotor Skills

4 studies (n = 10-126) dealt with psychomotor skills after butorphanol (15;97-99), and 3 out of 4 tests showed impairment. Impairment was observed from 0.5 mg i.v., and some dose related effects were seen from 0.5 mg i.v. No impairment was seen after doses up to 2 mg.

Zacny et al. (15) found that 2.0 mg butorphanol i.v. impaired *eye-hand coordination* (dose-related impairment, 0.5-2 mg, n = 12). Walker et al. (98) administered 0.5-3.5 mg i.v. and found impairment of *eye-hand coordination* (n = 15). Dershwitz et al. (99) found impairment of *Trieger dot test* for the low and high dose (7.1, 22.5 and 71.4 µg/kg i.v. (~ 0.5, 1.6 and 5 mg), n = 126). Zacny et al. (97) found no impairment of *eye-hand coordination* after 1 and 2 mg transnasal (n = 10).

7.1.3.2.4 Reaction time

3 studies (n = 10-15) dealt with reaction time (15;97;98) and no impairment was observed after doses up to 2.0 mg i.v.

Zacny et al. (15) found no impairment of *ART* (auditory reaction time) after administering 0.5-2 mg butorphanol i.v. (n = 12). Walker et al. (98) tested *ART* and found no impairment (cumulative doses of 0.5, 1.5 and 3.5 mg i.v., n = 15). Zacny et al. (97) administered 1 and 2 mg transnasal and tested *ART* (n = 10), the results were unclear.

7.1.3.2.5 Visual Functions

3 studies (n = 10-15) dealt with visual functions (15;97;98), and impairment was found in all studies (2 mg transnasal, 1.0 mg i.v.).

Walker et al.(98) tested *Maddox Wing* and found impairment (0.5-3.5 mg i.v., n = 15). Zacny et al. (97) found impairment of *Maddox Wing* after 2 mg transnasal (n = 10). Zacny et al. (15) found that 1 mg i.v. impaired *Maddox Wing* (dose related impairment, n = 12).

7.1.3.3 Codeine / Dihydrocodeine

Codeine is used in treatment of mild-to-moderate pain and as antitussive in lower doses. In pain treatment regular dose is 30 mg every 4-6 hours.

Codeine metabolizes partly to morphine in the human body by hepatic CYP2D6, which is subject to genetic polymorphism. While some subjects can transform up to 15 % of a codeine dose to morphine (ultra extensive metabolizers), others (approximately 7% in western countries) produce only negligible amounts of morphine or are unable to produce any morphine at all (slow metabolizers). Most of the population will metabolize between 1 and 10 % of a codeine dose to morphine. It has been assumed that most codeine effects are due to the morphine metabolite. Bachs et al. (100) have, however, shown that clinical impairment was related to the concentration of codeine in blood, in subjects where no morphine could be detected.

The results of all tests performed after administration of codeine/dihydrocodeine is summarized in table 2.

7.1.3.3.1 Attention

7 studies (n = 6-16) dealt with attention (101-107), and 1 out of 9 tests found impairment (107) after 32 mg codeine. No impairment was seen up to doses of 120 mg p.o. Improvement was observed after 20 mg dihydrocodeine s.c.

Szekely et al. (102) found improvement of *symbol cancellation test* after administering 20 mg dihydrocodeine (s.c.).

Evans et al. (107) found impairment of *DSST* after administering 32 mg p.o. codeine at different altitudes (n = 16), table 2.

Walker et al. (103) tested *DSST* and *logical reasoning* and found no impairment (n = 12, 60 or 120 mg p.o. codeine). Bradley et al. (104) and Saarialho-Kere et al. (106) tested *DSST* and none showed impairment (n = 6-10, dose 30-100 mg p.o. codeine). Webb et al. (101) tested 90 mg dihydrocodeine (p.o.) and found no impairment of *DSST*. Redpath et al. (105) tested *DSST* and *zahlen-verbindung test* and found no impairment (30-60 mg p.o., n = 10).

7.1.3.3.2 Driving

2 studies tested simulated driving (108;109) and both found impairment (25-50 mg p.o., n = 70-90), table 2.

Linnoila et al. (108) used a driving simulator device (Sim-L-Car) and found that 25 mg of codeine p.o. potentiated the effects of alcohol on the collision frequency (alcohol alone increased the collision frequency), and found also that codeine alone affected the collision frequency (n = 90). Linnoila et al. (109) found impairment of simulated driving after administering 50 mg p.o. (n = 70).

7.1.3.3.3 En-/Decoding

4 studies (n = 12-33) dealt with the effects on en-/decoding (52;102;103;110), and none of the 20 tests performed showed impairment after doses up to 120 mg p.o. One study found improvement in 3 of 6 tasks after 25 and 100 mg codeine. Improvement was observed after 20 mg dihydrocodeine s.c.

Szekely et al. (102) administered 20 mg s.c. and found improvement of *digit forward/digit backward test* and no impairment of *word fluency test* (n = 8).

Liljequist (110) administered 25, 50 and 100 mg codeine p.o. and found improvement of memory tasks: *serial learning* and *recall serial learning* for high dose, and *recall concept learning* for low and possible high dose, but no impairment of *associative learning* or *recall associative* (n = 33).

Walker et al. (103) found no impairment of *memory test* (60 and 120 mg p.o., n = 12). Pickering et al. (52) found that *memory* was not impaired by 30 mg p.o. (n = 24).

7.1.3.3.4 Psychomotor Skills

3 studies (n = 6-12) dealt with psychomotor skills after administration of codeine (103;104;106), and in one of 3 tests performed impairment was dose related (60-90 mg p.o.), table 1. No impairment was seen after doses up to 120 mg p.o.

Bradley et al. (104) found no impairment of *VMC* (visuo-motor coordination) compared to placebo (30, 60 and 90 mg p.o., n = 6), but observed a significant difference between 60 and 90 mg.

Saarialho-Kere et al. (106) found that 100 mg p.o. did not impair *body sway* (n = 10). Walker et al. (103) found no impairment of *eye-hand coordination* (60 and 120 mg p.o., n = 12).

7.1.3.3.5 Reaction time

7 studies (n = 6-48) dealt with reaction time (52;101;103;104;111-113), 3 studies found impairment (52;111;112) in 3 out of 7 tests performed. Impairment was observed from 30 mg p.o., table 1. No impairment was seen after doses up to 120 mg p.o.

Stacher et al. (111;112) found impairment of *auditory reaction time* after administering 60 mg p.o. (n = 20-48).

Pickering et al. (52) tested *CRT* in subjects receiving 30 mg codeine and found impairment (n = 24).

Walker et al. (103) studied the effects of 60 and 120 mg p.o. on *auditory reaction time* and found no impairment (n = 12). Bradley et al. (104) found no impairment of *complex reaction time* at no dose level (30, 60, 90 mg p.o., n = 6). Stacher et al. (113) found that 60 mg p.o. gave no impairment on *reaction time to acoustic stimuli* (n = 32). Webb et al. (101) administered 90 mg dihydrocodeine p.o. and found no impairment of *CRT* (choice reaction time) (n = 12).

7.1.3.3.6 Tracking

2 studies dealt with tracking, Stacher et al. (111;112), but no impairment was observed (60 mg p.o., n = 20-48), table 2.

7.1.3.3.7 Visual Functions

5 studies (n = 6-33), and a total of 8 tests, dealt with visual functions (101;103;104;106;110), but no impairment was observed after doses up to 120 mg p.o., table 2.

Saarialho-Kere et al. (106) tested *CFF*, *Maddox Wing* and *nystagmus*, but did not find impairment (100 mg p.o., n = 10). Bradley et al. (104) found no impairment of *CFF* and *DVA* (dynamic visual acuity) after 30-90 mg p.o. (n = 6). Liljequist (110) found no impairment of *flicker fusion* (25-100 mg p.o., n = 33). Walker et al. (103) found that *Maddox Wing* was not impaired by 60 or 120 mg p.o. (n = 12). Webb et al. (101) administered 90 mg dihydrocodeine and found no impairment of *CFFT* (n = 12).

Table 2: Effects of codeine at different tests and dose levels (for each dose level is indicated number of tests where impairment is observed/total tests performed)

Dose	Atten-tion	Sim. driving	En-/de-coding	Psycho motor skills	Reac-tion time	Track-ing	Visual	Total
20 (s.c.)*	0/1		0/2					**0/3**
25 (p.o.)		1/1	0/5				0/1	**1/7**
30 (p.o.)	0/3		0/1	0/1	1/2		0/2	**1/9**
32 (p.o.)	1/1							**1/1**
50 (p.o.)		1/1	0/5				0/1	**1/7**
60 (p.o.)	0/5		0/1	0/2	2/5	0/2	0/3	**2/5**
90 (p.o.)	0/2			0/1	0/1		0/3	**0/7**
100 (p.o.)	0/1		0/5	0/1			0/4	**0/11**
120 (p.o.)	0/2		0/1	0/1	0/1		0/1	**0/6**
Total	**1/15**	**2/2**	**0/20**	**0/6**	**3/9**	**0/2**	**0/15**	**6/64**

* Dihydrocodeine

Based on data from different papers on codeine pharmacokinetics (114-123), Sticht calculated plasma concentration-time curves for codeine after p.o. administration (*appendix 9*). Based on these data we find that an oral intake of 50 mg of codeine phosphate results in a codeine plasma concentration > 200 nmol/L the first 4 hours after intake. The highest dose given in the included studies is 120 mg of codeine, and this would approximately result in a codeine plasma concentration level > 500 nmol/L the first 4 hours after intake. It is interesting, however, to observe that none of the 6 tests performed after an intake of 120 mg codeine caused impairment, see table 2. Further the table illustrates that there is no clear dose response pattern after intake of codeine.

7.1.3.4 Dextropropoxyphene / Propoxyphene

Dextropropoxyphene and propoxyphene is used in management of mild-to-moderate pain. Both drugs are administered in doses from 65 mg p.o. every 4 hours if needed.

7.1.3.4.1 Attention

5 studies (n = 10-18) dealt with attention (124-128), none of the studies found impairment at doses up to 400 mg (6 different tests).

Saarialho-Kere et al. (127) tested *DSST* and found no impairment after administering 130 mg p.o. dextropropoxyphene to patients with rheumatoid arthritis (n = 15). O'Neill et al. (125) administered 100 or 200 mg dextropropoxyphene p.o. and found no impairment of *digit vigilance*. O'Neill et al. (126) tested *number vigilance* after a

cumulative dose of 400 mg dextropropoxyphene p.o. and found no impairment. Zacny et al. (128) tested *DSST* and *logical reasoning* and found that doses from 50 to 200 mg propoxyphene p.o. gave no impairment (n = 18). Girre et al. (124) found no impairment of *DSST* or *two-symbol cancellation test* (130 mg p.o. propoxyphene, n = 12).

7.1.3.4.2 Divided attention

2 studies (n = 14-15) dealt with divided attention (127;129), and one study found impairment after 130 mg p.o. (127). No impairment was seen after 32.5 mg p.o.

Saarialho-Kere et al. (127) tested *divided attention* in patients with rheumatoid arthritis and found impairment after administering 130 mg dextropropoxyphene p.o. (n = 15).

Edwards et al. (129) tested *Peripheral vision light flash detection* (PDL) and found no impairment (n = 14, 32.5 mg dextropropoxyphene p.o. in combination with paracetamol).

7.1.3.4.3 En-/Decoding

3 studies (n = 10-18) dealt with en-/decoding (125;126;128), and 2 out of 9 tests showed impairment (dose 200-400 mg dextropropoxyphene). No impairment was seen after doses up to 400 mg p.o. dextropropoxyphene and 200 mg p.o. propoxyphene.

O'Neill et al. (125) tested *memory scanning*, *picture recognition*, *word recall* and *word recognition*, and found that 200 mg dextropropoxyphene p.o. impaired *word recognition* (100 and 200 mg p.o., n = 12). O'Neill et al. (126) administered a cumulative dose of 400 mg dextropropoxyphene and found impairment of *picture recognition*, but no impairment of *memory scanning*, *word recall* and *word recognition* (n = 10).

Zacny et al. (128) found no impairment of *recall memory test* (50-200 mg p.o. propoxyphene, n = 18).

7.1.3.4.4 Psychomotor Skills

4 studies (n = 8-18) dealt with psychomotor skills (124;127;128;130), and 2 out of 5 tests showed impairment (130 mg dextropropoxyphene). No impairment was seen after doses up to 200 mg p.o. (propoxyphene).

Saarialho-Kere et al. (127) found that 130 mg p.o. dextropropoxyphene impaired both *body balance* and *symbol copying* in patients with rheumatoid arthritis (n = 15).

Zacny et al. (128) tested *eye-hand coordination* and found no impairment (50-200 mg p.o. propoxyphene, n = 18). Girre et al. (124) found that 130 mg p.o. propoxyphene did not impair S*anta Ana dexterity test* (n = 12). Kiplinger et al. (130) administered 65 mg p.o. propoxyphene and found no impairment of *stability of stance* (n = 8).

7.1.3.4.5 Reaction time

6 studies (n = 8-15) dealt with reaction time (124-128;130), and 2 of 11 tests found impairment (130 mg p.o. propoxyphene and 400 mg p.o. dextropropoxyphene). No impairment was seen up to the same doses that caused impairment.

O'Neill et al. (125) administered a cumulative dose of 400 mg dextropropoxyphene p.o. and found impairment of *choice reaction time* but not of *simple reaction time* (n = 10). Girre et al. (124) administered 130 mg propoxyphene p.o. and found impairment of *visual reaction time*, but no impairment of *visual choice reaction time* or *simple visual reaction time* (n = 12).

O'Neill et al. (125) found no impairment of *choice reaction time* or *simple reaction time* (100 and 200 mg dextropropoxyphene p.o., n = 12). Saarialho-Kere et al. (127) administered 130 mg p.o. dextropropoxyphene to patients with rheumatoid arthritis and found no impairment of *CRT* (choice reaction time) (n = 15). Zacny et al. (128) found no impairment of *auditory reaction test* (50-200 mg p.o. propoxyphene, n = 18). Kiplinger et al. (130) tested *verbal tasks* and found no impairment after 65 mg p.o. propoxyphene (n = 8).

7.1.3.4.6 Tracking

2 studies (n = 8-15) dealt with tracking (127;130), and one of the studies found impairment after 65 mg propoxyphene (130).

Kiplinger et al. (130) administered 65 mg p.o. propoxyphene and found that *pursuit meter* was impaired (n = 8).

Saarialho-Kere et al. (127) tested *tracking* and found no impairment (130 mg p.o. dextropropoxyphene, patients with rheumatoid arthritis, n = 15).

7.1.3.4.7 Visual Functions

6 studies (n = 6-15) dealt with visual functions (124-127;129;131), and 2 of 8 tests showed impairment (130-200 mg, n = 12-15). No impairment was observed after doses up to 400 mg p.o.

Saarialho-Kere et al. (127) found impairment of *CFF*, *Maddox Wing* was also tested but no result was given (130 mg p.o. dextropropoxyphene, patients with rheumatoid arthritis, n = 15). O'Neill et al. (125) found impairment of *CFFT* after 200 mg p.o. dextropropoxyphene (n =12).

Edwards et al. (129) found that 32.5 mg dextropropoxyphene p.o. did not impair *CFF* (n = 14). O'Neill et al. (125) found no impairment of *CFFT* (cumulative dose 400 mg p.o. dextropropoxyphene, n = 10). Ali et al. (131) found no impairment of *saccadic eye movements* after 65 mg p.o. dextropropoxyphene (n = 6). Girre et al. (124) tested *critical flicker fusion threshold* and *visual half field test*, and found no impairment (130 mg p.o. propoxyphene, n = 12).

7.1.3.5 Dezocine

Dezocine is used for the relief of moderate to severe pain.

7.1.3.5.1 Attention

Zacny et al. (132) tested *DSST* and found impairment in the high dose (10 mg i.v.), but not for the low or medium dose (2.5 or 5.0 mg i.v.) (n = 10).

7.1.3.5.2 Psychomotor Skills

Zacny et al. (132) found that medium and high dose of dezocine impaired *eye-hand coordination* (2.5, 5.0 and 10 mg i.v., n = 10).

7.1.3.5.3 Visual Functions

Zacny et al. (132) found that low dose, but not medium or high dose, impaired *Maddox Wing* (2.5, 5 and 10 mg i.v., n = 10).

7.1.3.6 Dipipanone

Dipipanone is used in the treatment of moderate to severe pain. The usual dose of dipipanone is 10 mg p.o.

7.1.3.6.1 Reaction time

Telekes et al. (133) found impairment of *reaction time* after administering 8 mg dipipanone p.o. (n = 12). Posner et al. (134) tested *visual reaction time* and found no impairment (10 mg p.o., n = 12).

7.1.3.7 Heroin

Heroin is a drug of abuse. Heroin metabolizes to morphine during the first hours after intake.

7.1.3.7.1 Attention

Smith et al. (26) tested *distributed numbers* after administration of 4 mg (s.c.) heroin to non addict volunteers and found impairment (n = 24).

7.1.3.7.2 En-/Decoding

Smith et al. (26) studied the effects of 4 mg heroin s.c. and found impairment of *coding* and *written addition*, but no impairment of *verbal facility* or *color-shape* (n = 24).

7.1.3.8 Hydrocodone / Hydromorphone

Hydrocodone and hydromorphone are used in management of moderate-to-severe pain. Regular doses are 5-10 mg p.o. hydrocodone 3-6 times daily and 0.2-0.6 mg i.v. hydromorphone 6-8 times daily.

7.1.3.8.1 Attention

5 studies (n = 7-18) dealt with attention (14;135-138), 3 of the studies found impairment (14;135;137). 4 out of 8 tests performed showed impairment, and dose related effects were observed (20 mg p.o. hydrocodone and 1.3-2.28 mg i.v. hydromorphone. No impairment was seen after doses up to 6 mg p.o. hydromorphone.

One study dealt with attention in healthy volunteers receiving **hydrocodone**. Zacny et al. (137) studied *DSST* and *logical reasoning*, and found that both were impaired at the high dose (20 mg p.o., n = 18).

4 studies tested attention after administering **hydromorphone**, 2 of the studies found impairment. Walker et al. (14) tested *DSST* and *logical reasoning*. The highest dose gave impairment of *DSST* (cumulative dose of 2.28 mg). Hill et al. (135) also tested *DSST* and *logical reasoning*. Impairment of *DSST* was observed at the highest dose administered (1.3 mg). Rush (136) and Oliveto et al. (138) found no impairment of *DSST* (1-2 mg p.o. and 1-6 mg p.o., n = 7-9).

7.1.3.8.2 En-/Decoding

3 studies (n = 17-72) dealt with en-/decoding (135;137;139), and no impairment was observed after doses up to 20 mg.

Zacny et al. (137) found no impairment of *memory test* (5-20 mg hydrocodone p.o., n = 18). Allen et al. (139) tested *PASAT* (Paced Auditory Serial Addition Test) and found that 7.5 mg hydrocodone p.o. gave no impairment. Hill et al. (135) administered 0.33-1.3 mg hydromorphone i.v. and found no impairment of *immediate* and *delayed free recall* (n = 17).

7.1.3.8.3 Psychomotor Skills

4 studies (n = 9-18) dealt with psychomotor skills (14;135-137) and 2 of 4 tests found impairment (20 mg p.o. and 0.98 mg i.v.). No impairment was seen after doses up to 2 mg p.o. and 1.3 mg i.v.

Zacny et al. (137) found impairment of *eye-hand coordination* by 20 mg p.o. hydrocodone (n = 18). Walker et al. (14) administered three doses of hydromorphone by infusion, giving three cumulative doses (0.33, 0.98 and 2.28 mg), and found that the medium dose impaired *eye-hand coordination* (n = 16).

Hill et al. (135) found no impairment of *eye-hand coordination* (0.33-1.3 mg i.v., n = 17). Rush (136) found that 1 and 2 mg p.o. did not impair *circular lights* (n = 9).

7.1.3.8.4 Reaction time

4 studies (n = 16-72) dealt with reaction time (14;135;137;139), impairment was observed in one of 4 tests performed (7.5 mg hydrocodone i.v.). No impairment was found after doses up to 20 mg p.o. (hydrocodone) and 2.28 mg i.v. (hydromorphone).

Allen et al. (139) found impairment of *SRT,* but not *CRT,* after administering 7.5 mg hydrocodone i.v., n = 72).

Hill et al. (135) found no impairment of *auditory reaction test* after 0.33-1.3 mg hydromorphone i.v. (n = 17). Zacny et al. (137) tested *auditory reaction time test* and found no impairment (5-20 mg hydrocodone p.o., n = 18). Walker et al. (14) administered cumulative doses of hydromorphone 0.33-2.28 mg i.v. (n = 16) and found no impairment of *auditory reaction time*.

7.1.3.8.5 Tracking

Allen et al. (139) found that 7.5 mg p.o. did not impair *light-tracking test* (n = 72).

7.1.3.8.6 Visual Functions

2 studies (n = 16-17) dealt with visual functions (14;135), and both found impairment after doses of hydromorphone from 1.3 mg i.v. Some dose related effects was seen at the same dose level.

Walker et al. (14) found impairment of *Maddox Wing* after cumulative doses of 0.33-2.28 mg/70 kg hydromorphone (n = 16). Hill et al. (135) found that 1.3 mg/70 kg hydromorphone i.v. impaired *Maddox Wing* (n = 17).

7.1.3.9 Meperidine (Pethidine)

Meperidine (Pethidine) is used in treatment of moderate to severe pain and as an adjunct to anaesthesia and preoperative sedation. Doses from 50 mg p.o. are administered every 3-4 hours if needed.

7.1.3.9.1 Attention

4 studies (n = 10-16) dealt with attention (14;69;70;140), one out of 5 tests showed impairment and a dose related effect was observed (122.5 mg i.v.). No impairment was seen after doses up to 122.5 mg i.v.

Walker et al. (14) tested *DSST* and *logical-reasoning test*, and found impairment of *DSST* at the highest dose (cumulative dose of 122.5 mg i.v., n = 16).

Zacny et al. (140) found no impairment of *DSST* (0.25-1.0 mg/kg i.v., n = 10). Primac et al. (70) tested *continuous performance* and found no impairment (50-100 mg p.o., n = 10). Kornetsky et al. (69) found no impairment of *modified digit symbol test* (50-100 mg p.o., n = 10).

7.1.3.9.2 En-/Decoding

2 studies (n = 10) dealt with en-/decoding (69;70), no impairment was observed after doses up to 100 mg p.o.

Kornetsky et al. (69) administered 50 and 100 mg meperidine p.o. and found no impairment of *speed of addition* (3 or 9 digit) or *speed of copying numbers* (n = 10). Primac et al. (70) tested *Wisconsin card sorting test* and found no impairment (50 and 100 mg p.o., n = 10).

7.1.3.9.3 Psychomotor Skills

3 studies (n = 10-16) tested eye-hand coordination (14;140;141), all found impairment (dose level where impairment was observed is not indicated in all studies, but impairment was at least seen after doses of 70-122.5 mg i.v.).

Walker et al. (14) administered cumulative injections of 17.5, 52.5 and 122.5 mg (n = 16), Zacny et al. (140) gave injections of 0.25, 0.5 and 1 mg/kg (n = 10), and Korttila et al. (141) gave 75 mg i.m. (n = 11).

7.1.3.9.4 Reaction time

3 studies (n = 10-16) dealt with reaction time (14;140;141), impairment was found in one of 3 tests (75 mg i.m.), no impairment was found after doses up to 122.5 mg i.v.

Korttila et al. (141) found that 75 mg i.m. impaired *CRT* (choice reaction time) (n = 11).

Zacny et al. (140) administered 0.25-1mg/kg meperidine i.v. and found no impairment of *auditory reaction time* (n = 10). Walker et al. (14) found no impairment of *auditory-reaction test* (cumulative doses 17.5-122.5mg, n = 16).

7.1.3.9.5 Tracking

Kornetsky et al. (69) found no impairment of *pursuit rotor* (50 and 100 mg p.o., n = 10).

7.1.3.9.6 Visual Functions

4 studies (n = 10-16) dealt with visual functions (14;69;140;141) and one out of 4 tests showed impairment (75 mg i.m.). No impairment was seen up to doses of 100 mg p.o. and 122.5 mg i.v.

Korttila et al. (141) found impairment of *CFF* after 75 mg i.m. (n = 11).

Walker et al. (14) found no impairment of *Maddox Wing* (17.5-122.5 mg i.v., n = 16). Zacny et al. (140) administered 0.25-1 mg/kg meperidine i.v. and found no impairment of *Maddox Wing* (n = 10). Kornetsky et al. (69) tested *tachistoscopic discrimination* and found no impairment (50 and 100 mg p.o., n = 10).

7.1.3.10 Meptazinol

Meptazinol is used in the treatment of moderate to severe pain in doses from 50 mg i.m.

7.1.3.10.1 Attention

2 studies (n = 6-7) dealt with attention (142;143), one study found impairment after administering 100 mg i.m. No impairment was seen after doses up to 400 mg p.o.

Richens et al. (143) tested *stroop colour word test* and found impairment (100 mg i.m., n = 6). Bradley et al. (142) found no impairment of *DSST* (100-400 mg p.o., n = 7).

7.1.3.10.2 En-/Decoding

Richens et al. (143) tested *running memory* and *syntactic reasoning test* and found no impairment (100 mg i.m., n = 6).

7.1.3.10.3 Psychomotor Skills

Bradley et al. (142) tested *VMC* (visuo-motor coordination) and found no impairment (100-400 mg p.o., n = 7).

7.1.3.10.4 Reaction time

3 studies (n = 6-8) tested CRT (choice reaction time) (142-144) and none found impairment after doses up to 200 mg x 4 p.o.

Tedeschi et al. (144) tested *CRT* after 4 doses of 200 mg and found no impairment (n = 8). Bradley et al. (142) found no impairment of *CRT* after 100-400 mg p.o., n = 7. Richens et al. (143) administered 100 mg i.m. and found no impairment of *CRT* (n = 6).

7.1.3.10.5 Tracking

Richens et al. (143) found that 100 mg p.o. did not impair *tracking* (n = 6).

7.1.3.10.6 Visual Functions

6 studies (n = 6-12) dealt with visual functions (131;142-146), and 2 of the studies found impairment (143;146). 3 out of 15 tests performed showed impairment, after 100 mg i.m. and 0.7-1.4 mg/kg i.v. (49-98 mg) (dose dependant effect). No impairment was seen after doses up to 200 mg x 4 p.o.

Manner et al. (146) found that 0.7 and 1.4 mg/kg i.v. (49-98 mg) impaired both *CFF* and *Maddox Wing* (dose dependant effect of *CFF*, n = 6). Richens et al. (143) found that 100 mg i.m. impaired *saccadic eye movement* but not *CFF* (n = 6).

Bradley et al.(142) found no impairment of *CFF* or *DVA* (Dynamic Visual Acuity) (100-400 mg p.o., n = 7). Tedeschi et al. (144) tested *CFF*, *eye movements*, *peak saccadic velocity (PSV)*, *saccadic duration (SD)* and *smooth pursuit velocity* and found no impairment (200 mg p.o. x 4, n = 8). Tedeschi et al. (145) found no impairment of *PSV* or *SD* after 200 mg p.o. x 4 (n = 12). Ali et al. (131) found that 200 mg p.o. did not impair *saccadic eye movement* (n = 6).

7.1.3.11 Nalbuphine

Nalbuphine is used to relief moderate to severe pain and before, during and after surgery as anaesthetic. Doses from 10-20 mg p.o. and 20 mg i.v. are administered.

7.1.3.11.1 Attention

3 studies (n = 12-16) dealt with attention (17;98;147), and all found impairment (3 out of 5 tests showed impairment). Impairment was seen after 0.15 mg/kg i.m. (~ 10.5 mg), and a dose related effect was observed (2.5-17.5 mg i.v.). No impairment was seen after doses up to 17.5 mg i.v.

Saarialho-Kere (147) tested *DSST* and found impairment (0.15 mg/kg ~ 10.5 mg, n = 12). Walker et al. (98) tested *DSST* and *logical reasoning* and found impairment of *DSST* at the highest dose (cumulative dose 2.5, 7.5, 17.5 mg i.v., n = 15). Zacny et al. (17) found no impairment of *logical reasoning*, but impairment of *DSST* at the high dose (10 mg i.v., n = 16).

7.1.3.11.2 Divided attention

Saarialho-Kere (147) tested *divided attention test*, but the results were inconclusive (0.15 mg/kg ~ 10.5 mg, n = 12).

7.1.3.11.3 En-/Decoding

Zacny et al. (17) tested 2.5-10 mg nalbuphine i.v. and found no impairment of *memory test* (n = 16).

7.1.3.11.4 Psychomotor Skills

2 studies (n = 15-16) dealt with psychomotor skills (17;98), and both found impairment, but it is not indicated at which dose the tests showed impairment (2.5-17.5 mg). Dose related effect was also observed (2.5-10 mg).

Zacny et al. (17) found dose related impairment of *eye-hand coordination* (2.5-10 mg i.v., n = 16). Walker et al. (98) administered cumulative doses of 2.5, 7.5 and 17.5 mg i.v. and found impairment of *eye-hand coordination* (n = 15).

7.1.3.11.5 Reaction time

3 studies (n = 12-16) dealt with reaction time (17;98;147) and one of 3 tests found impairment (0.15 mg/kg i.m.). No impairment was seen after doses up to 17.5 mg i.v.

Saarialho-Kere (147) found impairment of *combined tracking and choice reaction test* (0.15mg/kg i.m., n = 12).

Zacny et al. (17) administered 2.5-10 mg i.v. and found no impairment of *auditory reaction test* (n = 16). Walker et al. (98) tested *auditory reaction time* and found that cumulative doses of 2.5-17.5 mg i.v. gave no impairment (n = 15).

7.1.3.11.6 Visual Functions

3 studies (n = 12-16) dealt with visual functions (17;98;147), and all found impairment (4 out of 4 tests performed) after doses from 2.5-17.5 mg i.v. Some dose related effects were observed.

Saarialho-Kere (147) found impairment of *critical flicker fusion* and *Maddox Wing* after 0.15 mg/kg i.m. (n = 12). Walker et al. (98) found impairment of *Maddox Wing* after cumulative doses of 2.5-17.5 mg i.v. (n = 15). Zacny et al. (17) found dose related impairment of *Maddox Wing* (2.5-10 mg i.v., n = 16).

7.1.3.12 Oxycodone

Oxycodone is used in management of moderate to severe pain, often in combination with non-opioid analgesics. Doses from 2.25 mg p.o. is administered.

7.1.3.12.1 Attention

3 studies (n = 9-18) dealt with attention (148-150), 2 studies found impairment. 3 of 4 tests showed impairment. Impairment was observed after 0.28 mg/kg (~ 20 mg) i.v., and dose related impairment was found after 20-30 mg p.o.

Zacny et al. (148) tested *DSST* and *logical reasoning test* and found impairment of both for the medium and high dose (20 and 30 mg p.o., n = 18). Pöyhiä et al. (150) found impairment of *DSST* after administering 0.28 mg/kg i.v. (n = 9). Saarialho-Kere et al. (149) tested *DSST* but the results were excluded.

7.1.3.12.2 Divided attention

Saarialho-Kere et al. (149) tested *divided attentio*n and found impairment (0.13 mg/kg i.v., n = 9). Verster et al. (151) found no impairment of *divided attention* test (5 and 10 mg p.o., n = 18).

7.1.3.12.3 Driving

Verster et al. (151) found no impairment of *driving test* (SDLP, MLP, speed) of 5 or 10 mg oxycodone p.o. (n = 18).

7.1.3.12.4 En-/Decoding

2 studies (n = 18) dealt with en-/decoding (148;151), and no impairment was observed after doses up to 30 mg p.o.

Zacny et al. (148) administered 10-30 mg oxycodone p.o. and found no impairment of *memory test* (n = 18). Verster et al. (151) tested *Sternberg memory scanning test* and found no impairment (5 or 10 mg p.o., n = 18).

7.1.3.12.5 Psychomotor Skills

2 studies (n = 9-18) dealt with psychomotor skills (148;149), and impairment was found in 2 of 3 tests performed (0.13 mg/kg i.v., ~ 9 mg) and dose related effect was observed (30 mg p.o.). No impairment was seen after 0.13 mg/kg i.v.

Saarialho-Kere et al. (149) found impairment of *body balance*, but not *tapping task*, after administering 0.13 mg/kg i.v. (~ 9 mg*)* (n = 9). Zacny et al. (148) found dose related impairment of *eye-hand coordination* for the highest dose (10, 20 and 30 mg p.o., n = 18).

7.1.3.12.6 Reaction time

2 studies (n = 9-18) dealt with reaction time (148;149), and impairment was found in one of 2 tests after 0.13 mg/kg i.v. No impairment was seen after 10-30 mg p.o.

Saarialho-Kere et al. (149) found impairment of *CRT* after 0.13 mg/kg i.v. (n = 9). Zacny et al. (148) tested *auditory reaction test* after 10-30 mg p.o. and found no impairment (n = 18).

7.1.3.12.7 Tracking

2 studies (n = 9-18) dealt with tracking (149;151), and none found impairment after doses up to 10 mg.

Verster et al. (151) found no impairment of *tracking test* after 5 or 10 mg p.o. (n = 18). Saarialho-Kere et al. (149) administered infusion of 0.13 mg/kg and found no impairment of *tracking* (n = 9).

7.1.3.12.8 Visual Functions

2 studies (n = 9) dealt with visual functions (149;150), and 3 out of 4 tests showed impairment from 0.13 mg/kg i.v. No impairment was seen after 0.13 mg/kg i.v.

Pöyhiä et al. (150) found impairment of *CFF* and *Maddox Wing* after 0.28 mg/kg i.v. (n = 9). Saarialho-Kere et al. (149) administered 0.13 mg/kg i.v. and found that it impaired *CFF* but not *Maddox Wing* (n = 9).

7.1.3.13 Papaveretum

Papaveretum is used to relief moderate to severe pain. Regular dose is 1 suppository 1-2 daily.

7.1.3.13.1 Attention

Richens et al. (143) tested *stroop colour word test* and found no impairment of 20 mg i.m. (n = 6).

7.1.3.13.2 En-/Decoding

Richens et al. (143) administered 20 mg i.m. and found impairment of *syntactic reasoning test*, but no impairment of *running memory* (n = 6).

7.1.3.13.3 Reaction time

Richens et al. (143) found that 20 mg i.m. did not impair *CRT* (n = 6).

7.1.3.13.4 Tracking

Richens et al. (143) found no impairment of *tracking* after 20 mg p.o. papaveretum (n = 6).

7.1.3.13.5 Visual Functions

Richens et al. (143) found impairment of *saccadic eye movement*, but no impairment of *CFF*, after 20 mg i.m. (n = 6).

7.1.3.14 Pentazocine

Pentazocine is used to relief moderate to severe pain and can also be used as a sedative in relation to surgery. Regular doses are 20-60 mg parenteral and 25-100 mg p.o.

7.1.3.14.1 Attention

6 studies (n = 7-15) dealt with attention (18;49;98;106;142;152), 3 studies found impairment. 4 out of 10 tests showed impairment, and some dose related effects were observed (impairment from 25 mg p.o. and 30 mg i.v.). Impairment was observed at concentrations of 59 and 86 ng/ml. No impairment was seen after doses up to 22.5 mg i.v. and 75 mg p.o.

Saarialho-Kere et al. (152) found impairment of *DSST* for both low and high concentration (59 ng/ml and 86 ng/ml, n = 11). Bradley et al. (142) found that 25 mg (p.o.), but not 50 mg, impaired *DSST* (n = 7). Zacny et al. (18) tested *DSST* and

logical reasoning and found impairment of both at the highest dose (30 mg i.v., n = 16).

Biehl (49) tested *APG* (aufmerksamkeitsprueferaet), *vigilance* and *konzentrationstest* after administering 50 mg p.o. pentazocine, and found no impairment of the tests. Walker et al. (98) tested *DSST* and *logical reasoning* and found no impairment (cumulative dose 7.5-22.5 mg i.v., n = 15). Saarialho-Kere et al. (106) found that 75 mg p.o. gave no impairment of DSST (n = 10).

7.1.3.14.2 En-/Decoding

2 studies (n = 11-16) dealt with en-/decoding (18;152), and one study found impairment after 30 mg i.v. No impairment was seen after 30 mg p.o.

Zacny et al. (18) found that 30 mg pentazocine i.v. impaired *memory test* (n = 16). Saarialho-Kere et al. (152) tested *short memory* and found no impairment (30 mg p.o., n = 11).

7.1.3.14.3 Psychomotor Skills

6 studies (n = 7-24) dealt with psychomotor skills (18;98;106;142;152;153), one study found impairment (18). Zacny et al. (18) found impairment of eye-hand coordination in females after administering 30 mg i.v.

Saarialho-Kere et al. (106) found no impairment of *body sway* after 75 mg p.o. (n = 10). Walker et al. (98) gave cumulative doses of 7.5 and 22.5 mg i.v. and found no impairment of *eye-hand coordination* (n = 15). Stacher et al. (153) tested *psychomotor performance* and found no impairment (0.4 mg/kg/h, n = 24). Saarialho-Kere et al. (152) found no impairment of *tapping task* from 30 mg p.o. (n = 11). Bradley et al. (142) administered 25 and 50 mg p.o. and found no impairment of *VMC* (visuo-motor coordination) (n = 7).

7.1.3.14.4 Reaction time

5 studies (n = 7-24) dealt with reaction time (18;98;142;152;153). Impairment was observed in 2 of 5 tests performed after dose of 0.4 mg/kg/h and at plasma concentration of 86 ng/ml. No impairment was seen up to doses of 50 mg p.o. and 30 mg i.v.

Saarialho-Kere et al. (152) found that 30 mg p.o. impaired *reaction time* at high concentration (86 ng/ml, measured after 1.5 h, n = 11). Stacher et al. (153) tested *reaction time* after 0.4 mg/kg/h pentazocine and found impairment (n = 24).

Walker et al. (98) tested *auditory reaction time* after cumulative doses of 7.5 and 22.5 mg i.v. and found no impairment (n = 15). Bradley et al. (142) found no impairment of *CRT* (complex reaction time) after 25 and 50 mg p.o. (n = 7). Zacny et al. (18) administered 7.5-30 mg i.v. and found no clear results of *auditory reaction test* (n = 16).

7.1.3.14.5 Tracking

2 studies (n = 7-14) dealt with tracking (154;155), and impairment was found in both studies after doses from 22.5 mg i.m. up to 45 mg i.v. and 50 mg p.o.

Belleville et al. (154) found impairment of *critical tracking test* after high dose (45 mg i.m.) and after low dose 0.5 h after administration (22.5 mg i.m.) (n = 7). Kobal et al. (155) tested *tracking performance* and found that 50 mg i.v. gave impairment (n = 14).

7.1.3.14.6 Visual Functions

9 studies (n = 6-24) dealt with visual functions (18;49;98;106;142;146;152;153;156), 4 studies found impairment (18;49;146;152). 5 out of 16 tests performed showed impairment from 7.5 mg i.v. and 30 mg p.o. Some dose related effects were observed. No impairment was observed after doses up to 22.5 mg i.v. and 75 mg p.o.

Manner et al. (146) found impairment of *CFF* and *Maddox Wing* (0.3 and 0.6 mg/kg i.v., n = 6). Zacny et al. (18) found dose related impairment of *Maddox Wing* (7.5-30 mg i.v., n = 16). Biehl (49) found impairment of *FVF* (Flimmer-verschmelzungs-frequenz=CFF Critical Fusion Frequency), but not for *TAVT* (Tachistoskopischer auffassungsversuch), after 50 mg p.o., n = 12). Saarialho-Kere et al. (152) found impairment of *Maddox Wing* for both measured concentrations (59 and 86 ng/ml, n = 11), but no impairment of *CFFT* and *gaze nystagmus*.

Bradley et al. (142) found no impairment of *CFF* or *DVA* (25 and 50 mg p.o., n = 7). Saarialho-Kere et al. (106) tested *CFF*, *Maddox Wing* and *nystagmus* after 75 mg p.o. and found no impairment (n =10). Stacher et al. (153) administered 0.4 mg/kg/h and found no impairment of *CFF* (n =24). Walker et al. (98) found no impairment of *Maddox Wing* (7.5 and 22.5 mg i.v., n = 15). Stacher et al. (156) tested *optical reaction time* after 50 mg p.o. and found no impairment (n = 10).

7.1.4 Effects of single dose morphine on healthy volunteers

Evidence tables of the included studies with references are given in *appendix 6*.

Morphine is a potent opiate extracted from opium, and is one of the most widely used analgesics. It is used in the treatment of moderate to severe pain and has found broad clinical application despite the development of tolerance to the desired effects and the occurrence of possible serious side effects. Besides the most predominant acute effects of analgesia and sedation, morphine causes changes in mood including euphoria. The mood elevating effects are closely linked to morphine's abuse potential, and repeated use may result in development of addiction (34). Numerous studies on pain relief use morphine as reference drug.

The most common routes of administration of morphine are intravenously or per orally. The concentration level after these two different routes of administration will vary greatly because of the first pass effects after oral intake. In studies where blood morphine concentrations not have been measured it is difficult to interpret the results after per oral administration in relation to estimated blood morphine concentrations because of the large and variable first-pass effect (31). Doses and dosage intervals are titrated to pain relief, but guidelines to opioid naïve patients are from 10 mg every

4 hours per orally, from 5-10 mg every 4 hours intramuscularly or subcutaneously, or 2.5-5 mg every 3-4 hours intravenously (157).

Most studies reviewed do not report blood morphine concentration, only the dose given. Since the individual variation after i.v. administration is much less than after administration by other routes; we calculated the plasma morphine concentration of various points of testing, based on pharmacokinetic data (*Appendix 8*). Based on data from different papers on morphine pharmacokinetics (7;35;36;158-165), Sticht calculated plasma concentration-time curves for morphine after i.v. administration (*appendix 8*). Figure 2 summarizes the results of the effects of single dose of intravenous morphine as reported for all the tests reported below, as well as from studies with plasma morphine concentration measurements and studies where morphine was given by other routes of administration, taken together from all the studies in relation to estimated blood morphine concentration (5-8;10;11;14-19;21;98;135;166;167). The columns represent the number of findings showing impairment in relation to findings showing no impairment. Table 3 summarizes the percentage of impaired test in different morphine plasma concentration levels.

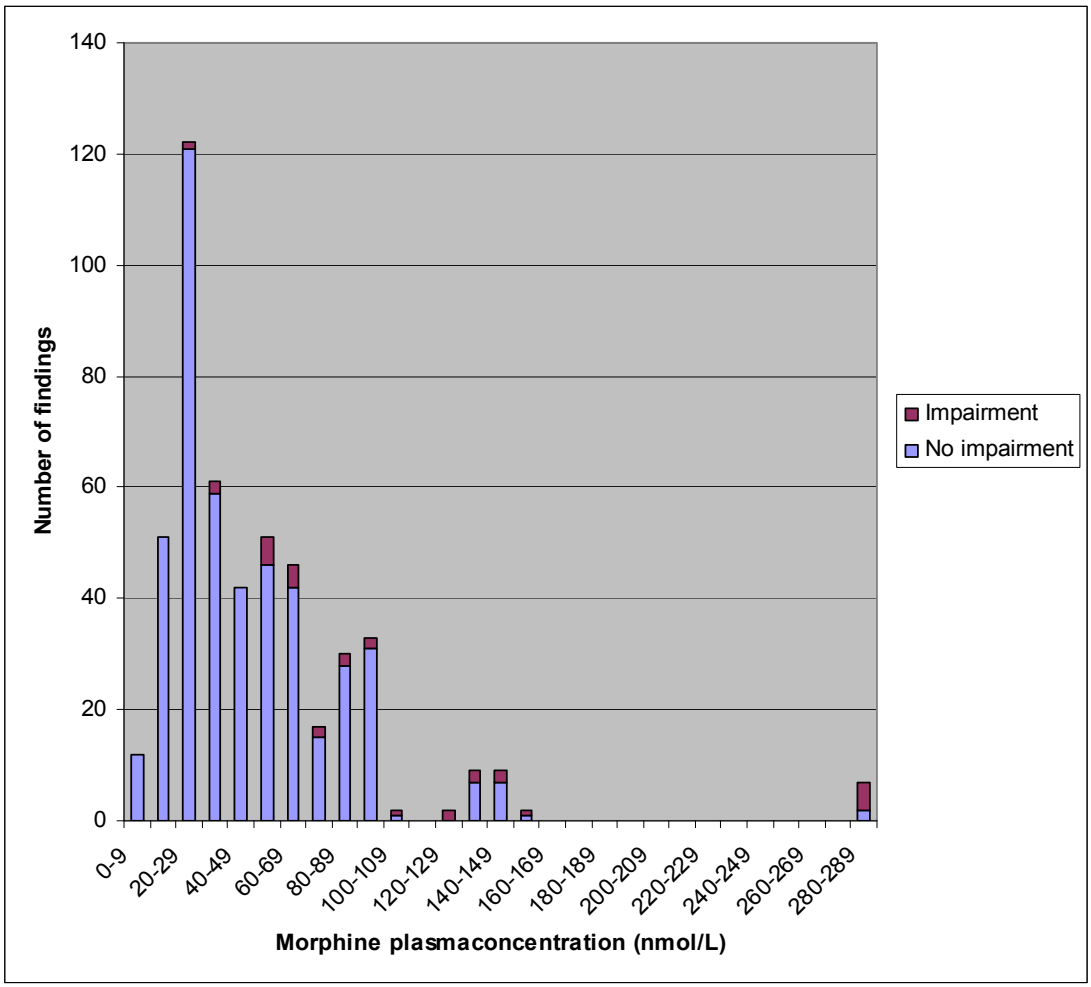

Figure 2: Effects of single dose of intravenous morphine summarized for all tests

Table 3: Percentage of impaired tests at different plasma morphine concentration levels

Concentration level (nmol/L)	**0-49**	**50-99**	**100-149**	**150 →**
% impairment	1	8	32	67

In the following a presentation is given of the results obtained in various task groups after administration of morphine intravenously and by other routes.

7.1.4.1 Reaction time

20 studies dealt with reaction time (7;14-18;23-25;53;98;103;111;126;128;135;137; 148;167;168) (n=7-22); in 11 of the studies morphine was administered intravenously (i.v.), in 9 studies orally (p.o.), and 1 study administered intramuscularly (i.m.) and subcutaneously (s.c.). In some studies several tests were performed, giving a total of

36 tests performed in the 20 studies. An overview of the outcome of the studies after intravenous and per oral administration is presented in Table 4.

Table 4: Results of single dose morphine on reaction time

Reaction time	**Number Tests impaired / total number**	
Dose (mg) per 70 kg or per subject	Administration i.v.	Administration p.o.
2.5-5	0 / 5	
> 5 – 10	2 / 10	1 / 4
> 10 – 20	0 / 2	2 / 4
> 20 – 30		1 / 3
> 30 – 40		1 / 5
Total	**2 / 17**	**5 / 16**

Several studies have been done on reaction time, mainly *Auditory Reaction Time (ART)*. Doses from 2.5 mg (i.v.) up to 40 mg (p.o.) were given (n = 7-24). Dose-dependant impairment was found within some studies in which more than one dose were tested (16;24), but most of the studies on ART did not find impairment, even at the highest dosages (no impairment in 11 of 15 studies).

5 of 6 *Choice / Continuous Reaction time (CRT)* tests with different dosage showed impairment, from 10 mg (i.v. or p.o.) up to 40 mg (p.o.) (n = 8-12). O'Neill et al. (126) found that 10 mg (p.o.) (n = 10) improved the performance in CRT, but gave impairment on *simple reaction time*.

In total 8 of 36 tests showed impairment of reaction time. No clear dose response patterns were observed. Impairment was found in a dose range from 10 to 40 mg p.o., after 8-15 mg i.m./ s.c. and 10 mg i.v.

7.1.4.2 Attention

24 studies dealt with attention (8;13-18;22-24;26;53;98;103;111;126;128;135;137; 148;166-169) (n = 7-60); in 11 of the studies morphine was administered intravenously (i.v.), in 10 studies orally (p.o.), and 2 studies intramuscularly (i.m.) and subcutaneously (s.c.). In some studies several tests were performed, giving a total of 66 tests performed in the 24 studies. An overview of the outcome of the studies after intravenous and per oral administration is presented in Table 5.

Table 5: Results of single dose morphine on attention.

Attention	**Number Tests [DSST] impaired / total number**	
Dose (mg) per 70 kg or per subject	Administration i.v.	Administration i.v.
2.5 - 5	0 / 9 [0 / 6]	
> 5 - 10	4 / 18 [4 / 10]	
> 10 - 20	2 / 4 [2 / 2]	3 / 7
> 20 - 30		1 / 3
> 30 - 40		3 / 12
> 40		2 / 2
Total	**6 / 31**	**9 / 24**

18 studies tested *Digit Symbol Substitution Task (DSST)* (8;13-18;53;98;103;128;135;137;148;166-169), and 8 found impairment (13;14;16-18;98;128;166). In 10 studies DSST was performed after i.v. administration and the results are presented in brackets in the first column of table 5 (8;14-18;98;135;166;167). These results indicated a possible dose dependent impairment of DSST, and accordingly a possibility of a blood morphine concentration-effect relation. Blood morphine concentrations were, however, not measured in any of these experiments. Based on the data from Sticht (*appendix 8*) we could calculate the theoretical mean blood morphine concentrations over time in the 8 studies that included DSST at various time points after 10 mg i.v. morphine administration (8;15-18;135;166;167). This is shown in figure 2. Table 6 shows the highest concentration not accompanied with impairment, and the lowest concentration accompanied with impairment in each of the 10 DSST studies. In 4 out of 6 studies with impairment there was considerable overlap between impairing and not impairing blood morphine concentrations. This is also illustrated in figure 2. Taken together figure 2 and table 6 showed no clear relation between estimated plasma morphine concentration and impairment.

Dosage of 40 mg (p.o.) gave impairment in 1 of 6 different studies of DSST (n = 12-22) (53;103;128;137;148;168). On the other hand, Jarvik et al. (169) found that 10 mg (i.m.) improved DSST as it was performed significantly faster than placebo (n = 20).

Figure 3: Impairment of DSST in relation to time and estimated concentration after 10 mg intravenous morphine. Figure 3 shows a plasma concentration-time curve for 10 mg i.v. morphine, based on the pharmacokinetic data from Sticht (appendix 5). Number of studies with impairment of DSST in relation to total studies testing DSST is indicated for different time points, e.g. 15 minutes after administering 10 mg morphine 1 out of 6 studies found impairment of DSST.

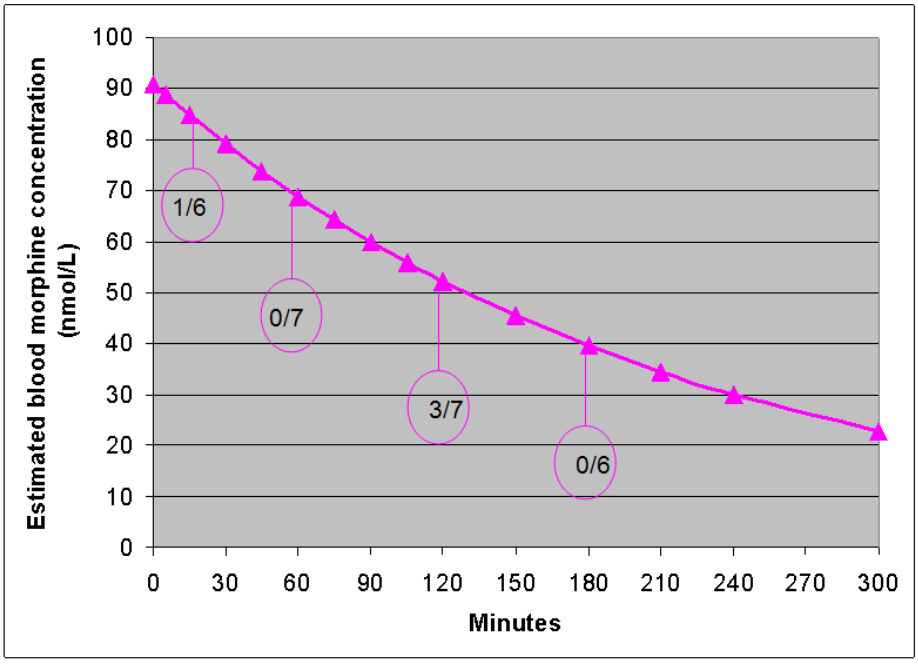

Table 6: Concentration level related to impairment or no impairment. The highest concentration (nmol/L) not accompanied by impairment (NI) and the lowest concentration accompanied by impairment (I) for the different DSST studies after 10 mg of morphine i.v.

Ref.	**NI** (ax conc., nmol/L)	**I** (min conc., nmol/l)
(167)	85	No impairment observed
(166)	43	85?
(14)	59	53
(17)	85	52
(18)	85	52
(135)	85	No impairment observed
(8)	79	No impairment observed
(15)	85	No impairment observed
(98)	130	53
(16)	43	52
(167)	85	No impairment observed

3 of 14 studies showed impairment of *logical reasoning*. Evans et al. (22), Zacny (168) and Zacny et al. (137) found impairment at doses of 16 and 40 mg (p.o.) (n = 18-60).

Smith et al. (26) tested *attention* (concentration) on subjects given 10 mg (s.c.) and found impairment (n = 24).

In total 18 of 66 tests showed impairment of attention. Impairment was found in a dose range from 10 mg (i.v./ p.o./ s.c.) to 100 mg (p.o.).

7.1.4.3 Psychomotor Skills

20 studies dealt with psychomotor skills (10;11;14-19;21;27;53;98;103;128;135;137; 148;167-169) (n = 5-96); in 12 of the studies morphine was administered intravenously (i.v.), in 6 studies orally (p.o.), in 2 studies intramuscularly (i.m.) and 1 study extradurally. In some studies several tests were performed, giving a total of 35 tests performed in the 20 studies. An overview of the outcome of the studies after intravenous and per oral administration is presented in Table 7.

Table 7: Results of single dose morphine on psychomotor skills.

Psychomotor skills	**Number Tests impaired / total number**	
Dose (mg) per 70 kg or per subject	Administration i.v.	Administration i.v.
2.5 - 5	0 / 5	
> 5 - 10	0 / 9	
> 10 - 20	0 / 4	0 / 1
> 20 - 30		0 / 1
> 30		0 / 6
Total	**0 / 18**	**0 / 8**

Jarvik et al. (169) tested *tapping* and found impairment (10 mg i.m., n = 20).

15 studies tested *eye-hand coordination*, none showed impairment (dosage from 2.5 mg i.v. to 40 mg p.o., n = 5-22) (14-18;27;53;98;103;128;135;137;148;167;168).

In total 1 of 35 tests showed impairment on psychomotor skills. Impairment was found after administering 10 mg (i.m.).

7.1.4.4 Visual Functions

14 studies dealt with visual functions (11;14-18;22;23;26;98;103;126;135;167) (n = 10-60); in 8 of the studies morphine was administered intravenously (i.v.), in 4 studies orally (p.o.), and 1 study subcutaneously (s.c.). In some studies several tests were performed, giving a total of 22 tests performed in the 10 studies. An overview of the

outcome of the studies after intravenous and per oral administration is presented in Table 8.

Table 8: Results of single dose morphine on visual functions.

Visual functions	**Number Tests impaired / total number**	
Dose (mg) per 70 kg or per subject	Administration i.v.	Administration i.v.
2.5 - 5	1/5	
> 5 - 10	5/8	1/2
> 10 - 20	1/2	2/3
> 20 - 30		0/1
> 30		0 / 6
Total	**7/15**	**3/6**

The Maddox Wing test has been performed in 9 of the included studies (14-18;98;103;135;167) (n = 12-17). Dose dependant / dose related impairment was found in 2 of the studies (14;16).

Hanks et al. (23) found impairment of *Critical Flicker Fusion Test (CFFT)* giving 10 and 15 mg (p.o.), while O'Neill et al. (126) found no impairment after a dose of 10 mg (n = 10-12).

Evans et al. (22) found impairment of *perceptual speed* (16 mg p.o., n = 60). Smith et al. (26) tested *copying* and found no impairment (10 mg s.c., n = 24).

In total 9 of 22 tests showed impairment of visual functions. Impairment was found in a dose range from 2.5 mg to 17.5 mg i.v. and from 10 to 16 mg p.o. No clear dose response patterns were observed.

7.1.4.5 En-/Decoding

15 studies dealt with en-/decoding (10;17;18;23;25-27;53;103;126;128;135; 137;148;168) (n = 5-48); in 4 of the studies morphine was administered intravenously (i.v.), in 8 studies orally (p.o.), and in 1 study intramuscularly (i.m.), extradurally and/or subcutaneously (s.c.). In some studies several tests were performed, giving a total of 37 tests performed in the 15 studies. An overview of the outcome of the studies after intravenous and per oral administration is presented in Table 9.

Table 9: Results of single dose morphine on en-/decoding.

En/Decoding	Number Tests impaired / total number	
Dose (mg) per 70 kg or per subject	Administration i.v.	Administration i.v.
2.5 - 5	0/2	
> 5 - 10	0/2	4/9
> 10 - 20		2/6
> 20 - 30		0/1
> 30		0/6
Total	**0/4**	**6/22**

O'Neill et al. (126) tested *memory* after administering 10 mg (p.o.) and found impairment (n = 10). Torda et al. (27) also found impairment on testing of memory (10 and 15 mg i.m., n = 5). The remaining 7 studies which tested memory found no impairment (17;18;23;103;137;148;168) (n = 12-18), 4 of these studies administering doses of 40 mg p.o. (103;137;148;168) (n = 12-18).

5 studies looked at different *recall* tests (23;53;126;128;135). Hanks et al. (23) found impairment on *immediate word recall* for 10 mg, but not 15 mg (p.o.), and impairment for both doses on *delayed word recall* (n = 12). 4 of 5 studies found no impairment, 2 of these studies administered up to 40 mg (p.o.) (n = 10-22).

Smith et al. (26) used a battery of 11 mental tests, of which 5 tests of en-/decoding, administered 10 mg subcutaneous and found impairment on *coding* but none of the other tests (see evidence table for further details) (n = 24).

2 studies looked at *picture recognition*. Hanks et al. (23) found impairment at doses of 10 and 15 mg p.o. (n =12), while O'Neill et al. (126) found no impairment with 10 mg p.o. (n = 10).

O'Neill et al. (126) also tested *word recognition* and found no impairment (10 mg p.o., n = 10).

In total 8 of 37 tests showed impairment on en-/decoding. Impairment was found in a dose range from 10 to 15 mg (p.o./i.m./s.c.), no impairment was seen up to 40 mg p.o. No clear dose response patterns were observed.

7.1.5 Effects of morphine infusions in studies with different defined concentration levels in healthy volunteers

In two studies morphine was administered somewhat different from all the other papers presented above. Morphine was given by intravenous infusion to reach certain plasma concentration levels. Subjects were then tested at the time of steady state concentration of morphine in plasma. Coda et al. (10) tested *reading speed*, *force* and *tapping* at steady state morphine concentrations of 20, 40 and 80 ng/ml (70, 140 and 280 nmol/l) (n = 15), see evidence table for further details. The study

showed that the highest plasma concentration impaired *reading speed* and *force*, while the other concentration levels were not related to any significant effects.

Kerr et al. (11) tested *isometric force*, *tapping*, *visual perception* and *rapid single visual presentation (RSVP)* at steady state concentrations of 20, 40 and 80 ng/ml morphine (70, 140 and 280 nmol/l) (n = 15). Impairment was observed at the high concentration for isometric force, tapping and RSVP, for the medium concentration impairment was found for RSVP.

There seemed to be concentration dependent impairment for most of the tests performed (5 of 7 tests).

7.1.6 Effects of single dose methadone/buprenorphine on healthy volunteers

7.1.6.1 Methadone

Methadone is a synthetic, long-acting opioid receptor agonist that acts primarily on the μ-opioid receptor. It was first synthesized as an analgesic, although it is now used primarily in the treatment of heroin addiction as maintenance therapy and is, world-wide, the most frequently prescribed medication for this aim (44;170).

Methadone is rarely given to naïve subjects except in experimental studies, and must not be confused with patients at the beginning of maintenance treatment. Those patients have a history of opioid dependency and are therefore tolerant to opioid effects, and are also affected by the effects of long term drug abuse.

3 studies dealt with single dose of methadone to drug naïve subjects, and all 3 studies found impairment (171-173). A total of 5 tests were performed, and impairment was found in 3 of the tests. Impairment was found in a dose range from 5 to 10 mg methadone p.o. (n = 7-12). Dose related impairment was observed for one of the tests (171).

Rothenberg et al. (171) found dose-related increases of *reaction time* and decrements of *vigilance* for methadone doses up to 10 mg. Later studies by the same group (Rothenberg et al.) (172;173) showed that similar doses of methadone decreases *pursuit performance* and depressed the gain of *horizontal tracking movements*.

7.1.6.2 Buprenorphine

Buprenorphine is a semi-synthetic opioid that binds with high affinity to both the μ-opioid receptor (as a partial agonist) and the kappa receptor (as an antagonist). It was originally marketed for parenteral treatment of acute pain, but has now been introduced into clinical practice as an alternative to methadone for maintenance treatment of drug dependence (174). Buprenorphine given to naïve subjects usually reflects patients who are treated a few days with buprenorphine for pain. Regular doses in pain treatment are 0.2-0.6 mg administered 3-4 times/day as tablets, injections or patches. In addition buprenorphine has been given in experimental studies.

5 studies (n = 7-16) dealt with single dose of buprenorphine to drug naïve subjects, and all studies found impairment (96;167;175-177). A total of 20 tests were

performed, and impairment was found in 18 of the tests. Impairment was found in a dose range from 0.075 mg to 0.6 mg i.v. Some dose related impairment was observed.

Several researchers have studied the effects of single doses buprenorphine to drug naïve healthy volunteers. Manner et al. (96) found extraocular imbalance of buprenorphine (0.5 mg i.v.) on the *Maddox wing test*. Saarialho-Kere et al. (177) found that buprenorphine (0.4 mg s.l.) impaired *DSST* and caused *exophoria*, but it did not have significant effects on *tracking*. Mac Donald et al. (176) found significant impairments of buprenorphine (0.3 mg i.m.) on 6 out of 7 tasks tested. The test of *digit span* was the only test without significant changes after administration of buprenorphine. Zacny et al. (167) found impaired performance of buprenorphine (0.075-0.3 mg i.v.) in a dose related fashion on all 5 psychomotor tasks tested in his study. Jensen et al. (175) administered an infusion of 0.6 mg buprenorphine over 150 minutes to healthy volunteers. *Trail-making test*, *finger-tapping test* and *CRT* (Continuous Reaction Time) were tested, and all three tests deteriorated relative to baseline following administration of buprenorphine. Maximum effect was observed at the time of drug infusion completion (n = 23).

8 USE IN PATIENTS TREATED CHRONICALLY

We have only included data on chronic use of morphine, methadone and buprenorphine. This is due to the task as defined by DRUID, see also introduction.

8.1 Morphine

Chronic treatment with morphine and other opioids in pain patients might constitute a particular problem. The literature on the effects of opioids on driving performance has recently been reviewed by Fishbain et al. (2). They performed a structured evidence-based review of all available studies addressing mainly the issue of whether acute and chronic opioid use in opioid-dependent/tolerant patients impaired driving-related skills. All searches were conducted through 2001 if possible. Fishbain et al. (2) evaluated the strength of that evidence through an evidence-based structured review process utilizing the Agency for Health Care Policy and Research (AHCPR) categories for review of research evidence. After the meeting at BASt in September 2008 our group was recommended to complete the report by also including chronic opioid treatment. We decided to review the full text articles selected on basis of the criteria for acute use in addition to the available abstracts on morphine from 2002 using new inclusion criteria made for chronic use, see *appendix 2*. This search resulted in one article on chronic use. The results from this article, in addition to the findings from the review by Fishbain et al.(2), are summarized and discussed in the present report.

8.1.1 Chronic use of morphine/opioids in pain treatment

Only one article on chronic use of morphine was included from our search, see methods. Lorenz et al. (178) tested *Auditory Oddball Task* on pain patients stabilized on sustained-release morphine for at least 3 days, and found no impairment (dose 30-150 mg/day, n = 6).

Fishbain et al. (2) published a structured evidence-based review on opioid dependent/ tolerant patients and impairment of driving-related skills in 2003. The included studies were classified into five topic areas, where four of the areas were of interest to this report: (A) psychomotor abilities in opioid maintained patients, (B) cognitive function studies on opioid maintained patients, (C) studies of effects of new opioid dosing on psychomotor abilities of opioid maintained patients and (D) to answer the question “Do patients on stable opioid doses demonstrate driving impairments, as measured in a driving simulator, once off/on road driving?”.

A: Psychomotor abilities in opioid maintained patients

7 studies on opioid stabilized cancer/pain patients have been summarized (12;39;40;179-182). 3 studies (12;39;179) tested CRT (Continuous Reaction Time) and 2 of the studies (12;179) found that cancer patients on opioid treatment had impaired CRT compared to controls or cancer patients without opioid treatment. 2 studies (181;182) found that pain patients and chronic non-malignant pain patients had impaired RT compared to healthy volunteers.

Banning et al. (179) studied continuous reaction time (CRT) in 34 cancer patients treated with stable doses of 30 to 920 mg/ 24 h morphine. A significant prolonged CRT was observed for the patients compared to healthy volunteers with no use of opioids. Sjøgren et al. (12) tested cancer patients with pain/no pain on stable and regular doses of morphine, and found that the use of long-term oral opioid treatment did not affect the neuropsychological tests. The no pain patients performed better than the pain patients, and the paper concluded that pain itself deteriorates the performance of the neuropsychological test (attention test) more than opioid treatment. Sjøgren et al. (39) tested CRT on 14 cancer patients on chronic morphine therapy (oral and epidural). Patients on oral treatment performed worse than controls. Sjøgren et al. (181) also tested reaction time in cancer patients receiving oral or epidural morphine. Compared to controls the opioid naïve showed the greatest difference in the shortest RT while chronic opioid users showed the greatest difference for the longest RT. Sjøgren et al. (182) tested vigilance/attention, psychomotor speed and working memory in chronic pain patients. 23 of 40 patients received sustained-release morphine (15-300 mg oral morphine). The study showed impairment of the tests in pain patients, but could not determine which factors influenced the results. Haythornthwaite et al. (180) found that psychomotor speed was improved in chronic pain patients compared to non-treated chronic pain patients. All patients received non-morphine opioids. Vainio et al. (40) compared cancer patients on stable doses of opioids (morphine, mean daily dose 209 mg) and no opioid treatment and found no impairment on psychomotor abilities (n = 24).

B: Cognitive function studies on opioid maintained patients

In this group 6 studies on opioid maintained patients were reviewed, and only one study found that opioid treatment affected cognitive functions (38;40;180;182-184). Sjøgren et al. (182) observed that chronic pain patients on long-term opioid treatment were impaired when testing Paced Auditory Addition Tasks.

Haythonthwaite et al. (180) reported that in chronic pain patients non-morphine opioid treatment did not appear to negatively affect measured cognitive function. Clemons et al. (183) tested alertness in cancer patients and found that they were more affected by the disease itself than the opioids. Patients with advanced cancer participated, and the patients received either morphine or controlled-release morphine (n = 7). Wood et al. (38) found a subtle effect on cognitive functions in patients with cancer pain dosed with 10-600 mg morphine per day (n = 18). Vianio et al. (40) and Moulin et al. (184) both reported that no difference in cognitive function was observed between morphine treated patients and controls receiving non-opioid pain treatment.

C: Effects of new opioid dosing on psychomotor and cognitive abilities of opioid maintained patients

4 of 5 studies in this group did not find significant impairment on psychomotor performance (185-189). Comer et al. (185) showed impairment in 2 of 4 psychomotor tests in heroin-addicts maintained on morphine when exposed to an additional opioid (100 mg heroin intranasal).

Bruera et al. (187) tested cognitive and psychomotor performance on 40 pain patients receiving opioids, 16 of them treated with morphine, and found no effect except drowsiness. Preston et al. (186) tested psychomotor performance on 6 postaddicts treated with non-morphine opioids and found no impairment. Pickworth et al. (188) studied the effects of buprenorphine in non-dependent previous opioid abusers and found no significant effects. Preston et al. (189) administered non-morphine opioids to nonaddicts and found no impairment on the psychomotor test.

D: Do patients on stable opioid doses demonstrate driving impairments, as measured in a driving simulator, once off/on road driving?

2 studies tested driving performance. Galski et al. (190) tested performance in a driving simulator and found that patients on chronic opioid analgesic treatment (COAT) performed better than controls (cerebrally compromised patients). Some of the COAT patients used morphine, but there were no details on how many used which opioid. Chapman (191) performed testing in a driving simulator and actual road driving with COAT patients and observed that the patients performed similar to controls (pain patients not on opioids and patients without pain). The COAT patients were stabilized on a mean daily dose equivalent to 90 mg morphine.

Fishbain (2) concluded that the majority of the reviewed studies indicated that opioids appeared not to impair driving-related skills in opioid-dependent patients. However, some of the evidence was inconsistent, and additional well-controlled studies were considered to be required to definitely answer the question of whether patients treated chronically with opioids are impaired in their driving skills.

Of the 17 studies described above, 8 performed testing on patients maintained on morphine, 4 on patients on morphine or other opioids and 5 on non-morphine opioids or unspecified.

8.1.2 Single dose morphine to opioid maintenance patients

Lamas et al. (192) found no impairment of *Maddox Wing* in patients maintained on methadone (30 mg/24 h) who were given 20, 40 or 60 mg morphine (i.m.). Morphine was administered 20 h after the last dose of methadone. Naloxone and pentazocine was also tested and showed no impairment as well (n = 6).

8.1.3 Single dose morphine to non-dependent heroin abusers

Only one study has tested the effects of single doses of morphine (15 or 30 mg) on current non-dependent users of heroin. Greenwald et al. (193) found that neither of the doses showed impairment on *psychomotor balance* (n = 6).

8.1.4 Single dose morphine to previous opioid (ab)users

This group consists of subjects with previous dependency, abuse or addiction to opioids, and 6 studies tested performance in this group (5;20;28;194-196).

3 of 4 studies on *Reaction Time (RT)* showed impairment. Wikler et al. (28) tested *auditory manual RT* and both 15 and 30 mg (i.m.) showed impairment (n = 10). Hill et al. (196) gave 15 mg (i.m.) or placebo, and found impairment (significant?) on *RT* (n = 72). 15 mg (i.m.) was administered to former morphine addicts, and compared to controls, who received no drug, and showed impairment on *Simple Reaction Time (SRT*), Belleville/Hill et al. (20) (n = 182). Preston et al. (194) found that doses up to 30 mg morphine (i.m.) had no effect on *Choice Reaction Time (CRT)* compared to placebo (n = 15).

Preston et al. (194) and Higgins et al. (195) both tested *DSST* in their studies, and found no impairment (doses from 4 mg to 30 mg i.m., n = 5-15).

Preston et al. (194) tested *memory task* and found dose related impairment, while *hand-eye coordination* showed no impairment (doses on 7.5, 15 and 30 mg i.m., n = 15). Foltin et al. (5) tested *serial acquisition task* and found no impairment (5 and 10 mg i.v., n = 9).

8.2 Methadone

Mørland (2003) (3) performed a review that dealt with the question of to what extent methadone maintenance treatment programs represent a potential risk to traffic safety. His literature search was conducted through 2001 and contained all the papers reviewed by Fishbain et al. (2) plus some additional papers. He concluded that there is substantial evidence that methadone intake might impair functions that are of importance to safe driving. This also appears to be the case in patients dosed with methadone over long periods of time. He also concluded that the scientific literature did not constitute a platform for clear conclusions with respect to guidelines concerning methadone and driving. Mintzer (197) reviewed the literature on human laboratory studies of methadone and buprenorphine maintenance and single dose in 2007 and proposed recommendations for further studies in this area. Group comparison studies and drug administration studies on the effects of opioid pharmacotherapy on performance were reported, and most of these studies are also included in the present review.

In the present review the acute effects of both single doses of buprenorphine and methadone as well as buprenorphine maintenance treatment will be discussed for studies published since 1977. When it comes to effects of methadone maintenance treatment, this review will complement the review made by Mørland (3), and as a consequence only include studies published later than 2001. The main objective was to summarize the effects of these drugs on traffic relevant psychomotor, cognitive

and other tests thought to be of importance to safe driving. Tests concerning subjective observations of mood, mental state and behavior are not included. The papers reviewed by Mørland (3) and the recent literature will be summarized in the discussion.

A regular dose of methadone used in maintenance treatment is 60-130 mg/day usually administered as a mixture.

8.2.1 Methadone maintenance patients compared to control groups

28 studies dealing with performance of methadone maintenance patients compared to various control groups were included (43;45-47;198-221) . Sizes of the groups were from 9 – 54 subjects (dose range 2-150 mg). In 27 studies some significant impairment was found, in some studies in all tests performed. A total of 220 tests were performed, and impairment was observed in 104 of the tests. The percent of impaired tests was calculated for each of the 28 studies, ranging from 0 to 100 percent. The mean percentage of significantly impaired tests was 44 %. 2 studies also observed some improvement in performance (200;218).

When the studies clearly indicating the duration of treatment were divided into those with patients treated for more than 1 year and those with shorter treatment , the percentage of findings of impairment were 63 % (n = 9) and 56 % (n = 4) respectively, not significantly different.

When the studies were divided in those where the mean daily methadone dose was above 70 mg and those with lower daily dosage, the percentage of findings of impairment were 40 % (n =12) and 52 % (n = 14) respectively, not differing significantly.

In some of the studies methadone patients were compared to ex-heroin users only or to a control group of matched non-users as well. Methadone maintained patients always performed worse than controls, and similar or worse than ex-users in the 7 studies that allowed such comparisons.

Use of other drugs that could be impairing at the time of testing was another important point which was looked for in 20 studies, and the drug positives (urine analysis) were excluded from the study. The percentage of findings of impairment in these 20 studies were 55 %, in the other studies where side use was not corrected for, not measured or not further specified, the percentage of findings of impairment was 32 %. In one study, however, where a methadone group without use of other drugs, was compared with the whole group of methadone users with 2/3 using other drugs, the performance in those using methadone was markedly better (45).

Mørland (3), reviewing 14 papers (45;198;199;201;202;204-208;210;215;219;220) stated that few differences were found between the performance by maintenance patients and different control groups in earlier studies. In more recent studies including somewhat larger groups of patients and a wider variety of tests, he found that more negative observations in methadone patients had been made, although several types of performance appeared to be unaffected.

Some studies have been published after Mørlands review. Hornung et al. (47) tested whether patients undergoing levomethadone substitution (10-60 mg) were fit to drive.

He found that the levomethadone patients achieved statistically significantly poorer results than did the control group in 3 out of 13 performance-related areas. Davis et al. (46) examined cognitive functioning in opiate dependent patients receiving stable and long term methadone treatment (15-60 mg), currently drug free ex-opiate users and a control group of pain patients. The 3 groups differed significantly in only one out of 12 neuropsychological measures. Mintzer et al. (208) (also reported by Mørland (3)) found significantly impaired performance of methadone maintenance patients (mean dose 67.2 mg) relative to matched controls on the DSST, trail-making tasks, two-back task and decision making. In another study Minzer et al. (209) found that performance of abstinent opioid abusers fell between that of methadone maintenance patients and controls in many measures. Schindler et al. (217) assessed the influence of methadone maintenance treatment on driving aptitude using ART 2020 (the Act & React Test system, a set of 7 traffic relevant psychological tests). When the performance by methadone maintained patients (45.7 ± 21.4 mg) were compared with data obtained from control subjects, significant differences were apparent for 2 out of 7 tests. Rotheram-Fuller (216) found that methadone-maintained smokers (mean dose 68.0 mg), but not non-smokers (mean dose 55.3 mg) performed more poorly than smoker and non-smoker control groups on decision-making task. There were no significant group differences on the WCST. Verdejo et al. (221) compared the neuropsychological performance of methadone maintenance patients stabilized in their current methadone dose (83.8 ± 29.6 mg) for at least 15 days with that of abstinent heroin abusers. He found that methadone maintenance patients showed slower performance on tests of processing speed, visuo-spatial attention and cognitive flexibility, and impaired performance on tests of working memory and analogical reasoning. Prosser et al. (212) administered a series of neuropsychological tests to former heroin addicts receiving methadone maintenance treatment with a stabile methadone dose for the previous 6 month, former heroin addicts withdrawn from all opiates and healthy controls without history of drug dependence. Both methadone-maintained (highest methadone dose 73.8 ± 23.1 mg) and opiate free abstinent subject groups performed worse than controls on tasks that measured verbal function, visuospatial analysis and memory, and resistance to distractibility. Abstinent subjects performed worse than their methadone counterparts on tests measuring visual memory and construct formation. Pirastu et al (211) compared the decision-making ability of methadone maintained (2-150 mg) individuals to non opiate dependent drug-free controls. Methadone maintained individuals had more perseverative errors on the WCST as compared with non opiate-dependent drug free controls. Rapeli et al. (214) found that controls performed better than morphine maintained patients in 6 out of 11 tests measuring attention, working memory and memory (mean dose 53.4 mg, n = 16). Prosser et al. (213) compared methadone maintained patients (n = 10) to healthy controls and former opiate-dependent subjects. Healthy controls performed better than the two other groups on the different measures of the Continuous Performance Task (measures of sustained attention), while former opiate-dependent subjects scored better than the methadone patients.

Baewert et al. (200) found that methadone-maintained patients and buprenorphine maintained patients (all included in one group) performed worse than the normal controls on 3 out of 7 tests performed (ART 2020). It was, however, also observed that patients within maintenance treatment had a significantly lower percentage of incorrect reactions and fewer simple errors in RST3 (Reactive Stress Tolerance) compared with control subjects. When comparing the two substitute groups

methadone patients performed worse than buprenorphine patients in 4 out of 7 tests (mean dose methadone 52.7 ± 21.6 mg, mean dose buprenorphine 13.4 ± 4.3 mg, n = 40). Soyka et al. (218) tested the effects of methadone after ≥ 14 days (t1) and 8-10 weeks (t2) of stable treatment, and in addition compared the results with controls. No significant differences were seen between the groups at t1. Methadone patients showed significantly improved concentration and executive functions at t2. On the other hand, at t2 the control group achieved better results in most cognitive domains, indicating cognitive impairment in the patients (n = 24).

Lenné at al. (43) found no differences in driving skills in simulated driving between patients stabilized on methadone (48.1 ± 2.8 mg) treatment program for 3 months and a control group of non-drug-using participants. Ersche et al. (203) found that decision-making performance was not measurably impaired in methadone (20-80 mg) users compared to matched controls and opioid-dependent individuals using only street heroin.

8.2.2 Performance before and after long-term methadone intake

4 studies dealt with performance before and after long-term methadone intake (205;222-224), and 2 studies found impairment. A total of 16 tests were performed, and possible impairment was found in 6 of the tests (n = 7-30, dose range 10-400 mg). One study found improvement of several tasks after daily dose of methadone.

Mørland (3) concluded, based on 2 papers (205;224), that for subjects acting as their own controls low to medium daily doses of long-term methadone intake will not necessarily reduce memory, but that other aspects of psychological functioning might be inhibited by long-term high dose methadone intake.

In later studies Gruber et al. (223) examined cognitive function in opiate-dependent subjects at baseline and after 2 months of methadone (68 ± 21.7 mg) treatment. Subjects demonstrated significant improvement from baseline on measures of verbal learning and memory, visuospatial memory, and psychomotor speed. No impairments were observed on any of the tests. Fredheim et al. (222) performed 3 neuropsychological tests in non-malignant pain patients after switching from morphine to methadone. No consistent improvement was detected, neither immediately after the switch to methadone nor at the three-month follow-up evaluation.

8.2.3 Single dose methadone to methadone maintenance patients

10 studies dealt with single dose of methadone administered to methadone maintenance patients (171;200;210;215;225-230), and 7 studies found impairment. A total of 50 tests were performed, and impairment was found in 10 of the tests. Impairment was found after a dose ranging from 10 to 120 mg methadone p.o., and after an addition of 50 or 100 % of daily dose (n = 10-39). Some dose related impairment was observed.

Mørland (3) have summarized 4 relevant studies (210;215;226;227). In one out of the 4 studies small, but statistically significant differences were found with respect to distance perception only. The other studies testing tracking performance, information

processing, visual functioning and driving performance in a simulator found no significant effects of the daily maintenance dose.

Rothenberg et al. (171) tested methadone maintenance patients and non addict controls before and after receiving methadone on simple visual reaction time tests and a vigilance type visual attention test. The patient group was maintained at 20-70 mg constant dose for at least one month prior to the start of testing. Additional methadone up to 10 mg did not affect patient performance in any of the tasks. Walsh et al. (230) studied the effects of 15-60 mg methadone given to patients stabilized on either 30 or 60 mg/day oral methadone for 2 weeks prior to the first test session. There were some dose related negative effects on a digit recall task, but no significant effects observed on the DSST. Curran et al. (225) studied opiate addicts who were stabilized on 10-50 mg methadone daily for 5 days. He found memory impairment after the intake of methadone if the daily dose was given as a single dose, but not if the dose was divided and given twice daily. In a later study Lyvers et al. (229) assessed the performance on WCST in methadone maintained patients (mean dose 66.9 mg) 24 h after the last dose and 90 min after receiving methadone. He found that patients in early methadone withdrawal made selectively more stabilized responses and errors than did recently dosed patients. Baewert et al. (200) compared methadone maintained patients 1.5 hours (peak) and 20 hours (trough) after intake of methadone. 2 of 7 tests showed significant differences between the groups. Patients at trough level performed worse in the RTS3 tests, having more incorrect reactions, but performed better than patients at peak level in the traffic-specific perception ability (TT15) (mean dose 52.7 mg, n = 20). Loeber et al. (228) found a significant negative correlation between methadone dose and number of correct answers and mean reaction time for correct responses in the vigilance task, indicating that cognitive impairment increases with the increase of the administered methadone dose (mean dose 74.3 mg/day ± 30.9, n = 30).

8.2.4 Single dose methadone to current users of opiates/opioids

One study dealt with single dose of methadone (dose range 15-60 mg) to current users of intravenous heroin, and one test was performed. No impairment was found (n = 5).

Walsh et al. (231) studied the effect of 15-60 mg methadone given to healthy adult volunteers who were current intravenous users of heroin. He found that methadone produced no significant dose effects on DSST performance.

8.3 Buprenorphine

A regular dose of buprenorphine in maintenance treatment is 8-16 mg/day administered sublingual. Buprenorphine can be administered in combination with naloxone. Naloxone is an opioid-receptor antagonist that after intravenous administration blocks the effects of opioids, and this combination is used to avoid abuse of substitution drug intravenously during treatment. When administered per orally this effect does not occur due to poor absorption, and the combination used sublingually has practically equal pharmacokinetic properties as buprenorphine alone.

8.3.1 Buprenorphine maintenance patients compared to control groups

7 studies dealt with performance of buprenorphine maintenance patients compared to control groups (43;200;211;214;217;218;232) , and 5 studies found impairment. A total of 44 tests were performed, and impairment was found in 14 of the tests (32%). Impairment was found at a maintenance dose range of 6.78-15.8 mg buprenorphine/day (n = 15-40). No clear dose response patterns were observed.

Schindler et al. (217) assessed the influence of buprenorphine maintenance treatment on driving aptitude using ART 2020 (a set of seven traffic relevant psychology tests). When buprenorphine maintained patients (10.0 ± 3.9 mg) were compared with data obtained from control subjects, significant difference was only noted for one out of the 7 tests. Baewert et al. (200) found that methadone-maintained patients and buprenorphine maintained patients (all included in one group) performed worse than the normal controls on 3 out of 7 tests performed (ART 2020). It was, however, also observed that patients within maintenance treatment had a significantly lower percentage of incorrect reactions and fewer simple errors in RST3 compared with control subjects. When comparing the two substitute groups methadone patients performed worse than buprenorphine patients in 4 out of 7 tests (mean dose methadone 52.7 ± 21.6 mg, mean dose buprenorphine 13.4 ± 4.3 mg, n = 40). Rapeli et al. (214) found that buprenorphine/naloxone-treated patients performed worse than controls in 4 out of 11 tests measuring attention, working memory and memory (mean dose 15.8 mg buprenorphine and 3.9 mg naloxone, n = 17). Soyka et al. (218) tested the effects of buprenorphine after ≥ 14 days (t1) and 8-10 weeks (t2) of stable treatment, and in addition compared the results with controls. No significant differences were seen between the groups at t1. Buprenorphine patients showed significantly improved concentration and executive functions at t2. On the other hand, at t2 the control group achieved better results in most cognitive domains, indicating cognitive impairment in the patients. Messinis et al. (232) performed a neuropsychological test battery and compared buprenorphine maintained patients (mean dose 6.78 mg/day, n = 18) to non-drug dependent controls and abstinent heroin abusers on naltrexone therapy. The buprenorphine patients performed poorer than controls on verbal learning/memory, psychomotor speed, executive functions and visual learning/memory. No significant differences in performance were seen between controls and abstinent heroin abusers.

Lenné at al. (43) found no differences in driving skills in simulated driving between patients stabilized on buprenorphine treatment (14.4 ± 1.8 mg) program for 3 months and a control group of non-drug-using participants. Pirastu et al. (211) compared the decision-making ability of buprenorphine maintained (2-20 mg) individuals to non opiate-dependent drug free controls, and found that buprenorphine maintained individuals performed not differently from the controls.

8.3.2 Buprenorphine maintenance patients compared to methadone maintenance patients

8 studies dealt with performance of buprenorphine maintenance patients compared to methadone maintenance patients (43;200;211;214;218;228;233;234). Two studies showed that buprenorphine and methadone patients performed equally (buprenorphine 9.4-14.4 mg, methadone 48.1-74.3 mg) (43;228). 6 studies showed that buprenorphine patients performed better than the methadone patients

(buprenorphine dose range 0.2-20 mg, methadone dose range 2-150 mg). A total of 59 tests were performed, and 10 of the tests showed that buprenorphine patients performed better than methadone patients.

Lenné at al. (43) found no differences in driving skills in simulated driving between patients stabilized on methadone (48.1 ± 2.8 mg) or buprenorphine (14.4 ± 1.8 mg) treatment programs for 3 months. Loeber et al. (228) found that methadone maintained patients and buprenorphine maintained patients performed equally on all measures of neuropsychological functioning, no significant group differences were found for any of the measures (15 tests totally) (mean dose methadone 74.3 mg/day, mean dose buprenorphine 9.4 mg/day, n = 56).

Kagerer et al. (233) examined driving performance in opioid-dependent patients under buprenorphine (0.2-16 mg) treatment. Data of these subjects were compared with a similar study of methadone patients by Dittert et al. (202) (dose given as ml). In 3 of 5 psychomotor tests subjects under buprenorphine treatment achieved significant better scores than subjects under methadone treatment. Soyka et al. (234) performed a clinical trial in drug-dependent patients under either buprenorphine (2-18 mg) or methadone (18-120 mg) treatment in 8-10 weeks of steady state conditions. Several subtests of the Act & React Test System test battery were used measuring visual perception, selective attention, vigilance, reactivity and stress tolerance. The patients under buprenorphine treatment showed a better performance in 2 out of 6 tests. Pirastu et al. (211) compared the decision-making ability of methadone maintained (2-150 mg) individuals to buprenorphine (2-20 mg) maintained individuals, and found that buprenorphine maintained individuals performed better than methadone maintained individuals. Baewert et al. (200) used the ART 2020 (a set of 7 traffic psychology tests) to compare methadone maintained and buprenorphine maintained patients. The tests showed that methadone patients had a significant longer mean and maximum decision time and longer reaction time than the buprenorphine patients. There were no significant differences between these groups in the other performance tests. When methadone patients were compared to buprenorphine patients at peak medication (i.e. 1.5 h after intake of medication) the methadone group had longer mean and maximum reaction time as well as longer reaction decision time. They also had a higher percentage of incorrect answers in RTS3 and fewer correct answers in the TT15 than buprenorphine-maintained patients. At trough level (i.e. 20 h after medication intake) the methadone-maintained patients had a lower number of total and correct answers in the LL5 and a higher number of delayed reactions in RST3 compared with the buprenorphine group. In total methadone patients performed worse than buprenorphine patients in 4 out of 7 tests (mean dose methadone 52.7 ± 21.6 mg, mean dose buprenorphine 13.4 ± 4.3 mg, n = 40). Rapeli et al. (214) tested cognitive performance with 11 different tests. One test, simple reaction time, showed that buprenorphine/naloxone-treated patients performed better than methadone patients, in the remaining tests no significant differences were found (mean dose methadone 53.4 mg, buprenorphine/naloxone 15.8/3.9 mg, n = 16 and 17). Soyka et al. (218) tested the effects of methadone and buprenorphine after ≥ 14 days (t1) and 8-10 weeks (t2) of stable treatment. No significant differences were seen between the groups at t1. At t2 the buprenorphine group performed better in 2 out of 11 tests. However, improvement of concentration and executive functions were seen for both groups after 8-10 weeks.

8.3.3 Single dose buprenorphine to methadone or buprenorphine maintenance patients

7 studies dealt with single dose of buprenorphine to methadone or buprenorphine maintenance patients (200;230;235-239). 2 studies found impairment (200;230) and 2 studies observed improvement of performance (200;236). A total of 21 tests were performed, and impairment was found in 2 of the tests. Impairment was found in a dose range from 2 to 13.4 mg (n = 13-20). No clear dose response patterns were observed. Improvement was observed in 3 out of 21 tests, in a dose range from 4 to 13.4 mg (n = 19-20).

Walsh et al. (230) studied the effects of buprenorphine (2-8 mg s.l.) in subjects maintained on either 30 or 60 mg/day oral methadone. Buprenorphine reduced recall performance slightly with no dose related effects.

Baewert et al. (200) compared the effect of buprenorphine 1.5 h after intake (peak level) and 20 h after intake (trough level). Patients at trough level had more incorrect reactions and multiple errors in the RST3 test of the ART 2020, but fewer delayed reactions, when compared to patients at peak level. Also the patients at trough level had a higher number of correct answers and answered more questions than those at peak level in the LL5 test (mean dose: 13.4 mg, n = 20). Singhal et al. (236) found that performance of DSST and Trail Making Test improved significantly after administration of additional buprenorphine to buprenorphine maintenance patients. Maintenance dose of 4 mg/day was followed by three administrations of 2 mg buprenorphine with two hours intervals, and after each administration the subjects were assessed on DSST, Trail Making Test, digit span and delayed recall. Digit span and delayed recall were unaffected (n = 19).

Preston et al. (235) studied the effects of buprenorphine (0.2-0.3 mg s.c.) in subjects stabilized on methadone 30 mg at least 7 days prior to the experimental session. Buprenorphine had no significant effects on any variable measured (recall task and DSST). Strain et al. (237) studied the effects of buprenorphine (0.5-8 mg i.m) in opioid-dependent volunteers stabilized on 30 mg methadone daily for a minimum of 2 weeks before admission. Buprenorphine produced no significant effects on DSST and a recall task. A later study by the same group (238) with similar doses of buprenorphine did neither show any effects on the same tasks. Strain et al. (239) studied the effects of buprenorphine (4-16 mg i.m) given to opioid-dependent volunteers stabilized on buprenorphine 8 mg sublingual daily for a minimum of 2 weeks. None of the buprenorphine doses produced significant effects on a recall (memory) task and the DSST.

8.3.4 Single dose buprenorphine to current users of opiates/opioids

3 studies dealt with single dose of buprenorphine to non-physically-dependent opioid abusers (188;240;241), and one study found impairment. A total of 4 tests were performed, and impairment was found in one of the tests. Dose related impairment was observed after 0.4-0.8 mg i.m. (n = 7).

Weinhold et al. (241) found that buprenorphine (0.4-0.8 mg i.m) produced a significant small dose-related performance decrement in the number of correct responses on the DSST task. No significant effects were observed on the digit recall task.

Pickworth et al. (188) found a slight but sustained decrease in response rate of buprenorphine (0.3-1.2 mg i.v, n = 6) on the circular lights task, but the significance of this effect was not stated. Marsch et al. (240) studied the effects of daily buprenorphine doses (6-8 mg) in opioid dependent adolescents. He found no changes from predosing to postdosing during the first week on the DSST.

8.4 Single dose opioids/opiates to opioid maintenance patients

(except methadone, buprenorphine and morphine)

8.4.1 Butorphanol

2 studies dealt with the effects of butorphanol (235;242), and no impairment was seen in the 3 tests performed after doses up to 6 mg i.m.

Preston et al. (242) tested *DSST* in methadone maintained subjects and found no impairment after 0-1.5 mg/70 kg i.m. (n = 5). Preston et al. (235) administered 0.375-6 mg i.m. to methadone maintained subjects and found no impairment of *recall (memory) test* or *DSST* (n = 5).

8.4.2 Hydromorphone

10 studies dealt with different tests after administration of hydromorphone to maintenance patients (235;237-239;242-247), none found impairment after doses up to 18 mg i.m. or after 6 mg s.c. (n = 5-8)

Preston et al. (242) found no impairment of *DSST* after doses of hydromorphone up to 10 mg i.m. in methadone maintained patients (n = 5). Preston et al. (235) tested *recall (memory) test* and *DSST* in methadone maintained subjects after 6 mg s.c. and found no impairment (n = 6). Carroll et al. (243) found no impairment of *DSST* (5 and 10 mg i.m. to methadone patients, n = 8). Strain et al. (239) found no impairment of *recall test* and *DSST* in opioid dependent subjects maintained on buprenorphine after 9 and 18 mg hydromorphone i.m. (n = 8). Strain et al. (247) found no impairment of *DSST*, *circular lights task* and *trail-making b test* in volunteers maintained on buprenorphine/naloxone or buprenorphine (12 mg i.m., n = 6). Strain et al. (237;238;246) tested *recall (memory) test* and *DSST* in methadone maintained subjects after administration of 5 and 10 mg hydromorphone i.m., and found no impairment (n = 5-7). Preston et al. (235;245) found no impairment of *DSST* and *recall (memory) test* in methadone patients after 4 and 8 mg i.m. (n = 5).

8.4.3 Nalbuphine

2 studies dealt with nalbuphine (242;245), none of the 3 tests performed showed impairment after doses up to 6 mg i.m.

Preston et al. (245) found no impairment of *DSST* or *recall (memory) test* in methadone maintained subjects who received 0.375-6 mg nalbuphine i.m. (n = 5). Preston et al. (242) tested *DSST* in methadone substituted patients, and found no impairment (0-3 mg i.m., n = 5).

8.4.4 Naloxone

2 studies dealt with naloxone (192;235), none of the 3 tests performed showed impairment after doses up to 0.2 mg i.m./s.c. (n = 6).

Preston et al. (235) found no impairment of *DSST* or *recall (memory) test* after 0.2 mg naloxone or combination of buprenorphine/naloxone 0.2-0.3/0.2 mg s.c. in methadone patients (n = 6). Lamas et al. (192) tested *Maddox Wing* and found no impairment (0.1-0.2 mg naloxone i.m. to methadone maintained subjects, n = 6).

8.4.5 Pentazocine

2 studies dealt with pentazocine (192;246), none of the 3 tests performed showed impairment after doses up to 120 mg i.m.

Lamas et al. (192) tested *Maddox wing* in methadone maintained patients (30 mg/ 24 h) who received 45 or 60 mg pentazocine i.m., and found no impairment of the test (n = 6). Strain et al. (246) found no impairment of *recall test* or *DSST* in methadone maintained patients (30 mg/ 24 h) at any dose level of pentazocine (7,5-120 mg i.m., n = 5).

8.5 Single dose opioids/opiates to subjects with ongoing use of opioids

(except methadone, buprenorphine and morphine)

Greenwald et al. (193) tested *psychomotor balance* in non-dependent heroin-users after administering 3 and 6 mg/70 kg i.m. **butorphanol**, and found no impairment (n = 6).

Comer et al. (185) gave 12.5-100 mg **heroin** intranasal to heroin/polydrug users maintained on morphine (n = 5). Impairment was found for *DSST* and *divided attention task* for the highest dose compared to placebo, but no impairment of *rapid information processing task* or *response sequence task* was found. Fraser et al. (248) found no impairment of *pursuit rotor test* in prisoner addicts who injected up to 95 mg of heroin. The testing was performed 1 hour after administration (n = 5).

Carrroll et al. (243) found no impairment of *DSST* in volunteers with active opioid dependence who received 5 or 10 mg **hydromorphone** i.m. (subjects stabilized on 10 mg x 4 hydromorphone, n = 6). Pickworth et al. (249) found impairment of *six letter search task*, but no impairment of *circular lights task*, *DSST*, *serial-addition subtraction task* or *card sorting*, in drug users who received capsules of 1 and 3 mg hydromorphone. Preston et al. (250) administered 1 mg hydromorphone to opioid dependent volunteers (tested during methadone detoxification) and found no impairment of *DSST* and improvement of *circular lights* (hand-eye coordination) (n = 18).

8.6 Single dose opioids/opiates to previous opioid (ab)users

(except methadone, buprenorphine and morphine)

This group consists of subjects with previous dependency, abuse or addiction to opioids.

Preston et al. (251) found that **butorphanol** (6 mg i.m.), but not **hydromorphone** (3 mg i.m.), impaired *DSST* in post addict volunteers (n = 6).

Preston et al. (194) administered 22.5-90 mg **pentazocine** i.m. to post addict volunteers and found dose related impairment of *DSST*, but no impairment of *CRT*, *hand-eye coordination* or *memory task* (n = 15).

8.7 Single dose tramadol to hydromorphone stabilized patients

Carroll et al. (243) studied the effect of different doses of tramadol in patients stabilized on hydromorphone, and found no effect on *DSST* (n = 6, 50-500 mg i.m.).

8.8 Single dose tramadol to methadone maintenance patients

Carroll et al. (243) administered tramadol to patients maintained on methadone (60 mg/day). None of the doses (74-300 mg) affected the performance of *DSST* (n = 8).

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10 APPENDIX

10.1 Appendix 1: Search strategy

The search strategy consists of the following list of words searched separately:

Automobile driving	Psychomotor performance	Aggression
Driving ability	Visual perception	Aggressive behaviour
Motor skills	Attention	Impulsive behaviour
Cognition	Tracking	Impulsivity
Cognitive processes	Steering	Judgment
Cognitive function	Vigilance	Hypnotics and sedatives
Psychomotor effect	Memory	Sedatives
Psychomotor impairment	Error detection	Sedation

10.2 Appendix 2: Drugs for inclusion

Group 1: Opiates/ Opioids	
Acetylmethadol	Levomethadone
Alfentanil	Levorphanol
Buprenorphine	Meperidine
Butorphanol	Meptazinol
Codeine	Methadone
Dextromoramide	Morphine
Dextropropoxyphene	Nalbuphine
Dezocine	Oxycodone
Dihydrocodeine	Oxymorphone
Dipipanone	Papaveretum/opium
Etorphine	Pentazocine
Fentanyl	Pethidine
Heroin (Diamorphine)	Propoxyphene
Hydrocodone	Sufentanil
Hydromorphone	Tilidine
Ketobemidon	

Group 2: Narcoanalgesics/ atypical opioids
Flupertin
Tramadol

Group 2: Hallucinogenes
Dextromethorphan
Ketamine
LSD
Mescaline
Phencyclidine (PCP)
Psilocybin

10.3 Appendix 3: Criteria for inclusion

Criteria for inclusion – Acute use

1. Drugs to be included: see appendix 2
2. In humans
3. Drug
   - Given acute (single dose)
   - Only experimental studies
4. Known concentration and/or dose
5. Patients
   - Healthy volunteers (no known history of drug abuse)
   - Nondependent opioid abusers (history of drug abuse)
   - Opioid-dependent abusers (current drug abuse)
6. Control group
   - Placebo
   - No drug/ baseline
7. Effects
   - Objective
     - Drugs and driving
     - Tasks related to driving
8. Minimal 5 participants
9. Reviews
10. Published in journals
11. Significance $p \leq 0,05$
12. Result must be significant

Criteria for inclusion – Chronic use

1. Drugs to be included: methadone, levomethadone, buprenorphine and morphine
2. Only experimental studies
3. In humans
4. Patients
   - Pain patients treated with drugs included
   - Abusers in substitution treatment with drugs included
   - Nondependent opioid abusers (previous history of drug abuse)
   - Opioid-dependent abusers (current drug abuse)
5. Control group and/or baseline
6. Effects
   - Objective
     - Drugs and driving
     - Tasks related to driving
7. Minimal 5 participants
8. Reviews
9. Published in journals

10.4 Appendix 4: Task Classification

	Main Group	Sub Group	Examples for Tasks
PERFORMANCE TASKS	**Reaction Time**	Simple reaction time	Visual or auditory stimuli: press a button (or a switch or a foot pedal…) as quickly as possible
		Choice reaction time	Diverse visual or auditory stimuli: respond only to the target stimulus or with different keys to correspondent stimuli
	Attention	Categorization tasks	Card sorting tasks; Digit symbol substitution task; Trail making test
		Vigilance	Respond to rare target stimuli (Mackworth Clock Test)
		Cancellation tests	Cross out target letters among distractors (D2-Test)
		Mental arithmetics	Pauli test (addition); Serial seven (subtraction)
		Other attention tests	Go/no go tasks; Stroop test; logical reasoning
	Divided Attention	Reactions to 2 stimuli	Reaction to central & peripheral stimuli; auditory 2-channel signal detection task
		Reaction to 2 tasks	Tracking or cancellation test & visual/auditory stimuli; many tasks simultaneously
	Psychomotor Skills	Hand/eye coordination	Circular lights; hand steadiness; pin test
		Posture	Standing steadiness (Romberg or balance test)
		Other motor functions	Tapping test; tremor; proprioceptive coordination
	Visual Functions	Physiology of the eye	Visual acuity; critical flicker fusion frequency
		Eye movements	Visual tracking; nystagmus
		Binocular vision	Heterophoria; stereopsis; exophoria
		Complex perceptual functions	Spatial orientation; time or length estimation
	Tracking	Easy compensatory tracking	Possible horizontal deviations have to be regulated with a steering wheel
		Difficult compensatory tracking	Critical tracking: automatic deviations have to be compensated
		Easy pursuit tracking	Pursuit rotor: pursuit of a moving light (time on target); spiral maze
		Difficult pursuit tracking	Stressalyzer (Tracometer): catch a target with a steering wheel
	En-/Decoding	Information processing	Cognitive speed: recognition of a tachistoscopically presented stimulus
		Memory	Free recall, cued recall or recognition tasks
	Driving	Driving simulator	Road tracking, car follow, braking task
		Closed course	Road tracking, car follow, braking task
		Flight simulator	Routine scenarios, communication, approaches

10.5 Appendix 5: Evidence table for opioids/opiates (except methadone, buprenorphine and morphine), narcoanalgesics/atypical opioids and hallucinogens

Abbreviation	TEST
ART 2020	Act & React Test System
ART	Auditory Reaction Time
APG	Aufmerksamkeitsprüfgerät
BAC	Blood Alcohol Concentration
CRT	Choice/Continuous/Complex Reaction Test
CFF(T)	Critical Flicker Fusion (Test/Threshold)
CFF	Critical Flicker Fusion Frequency
DSST	Digit Symbol Substitution Test
DAT	Divided attention task
DVA	Dynamic Visual Acuity
EHC	Eye-hand coordination
MW	Maddox Wing Test
MLP	Mean Lateral Position
PSV	Peak Saccadic Velocity
RIT	Rapid information processing task
RT	Reaction Time
RTS3	Reactive Stress Tolerance (ART 2020)
SacEM	Saccadic Eye Movement
SD	Saccadic Duration
SDLP	Standard Deviation of Lane Position
SRT	Simple Reaction Time
TAVT	Tachistoskopischer Auffassungsversuch
TT15	Traffic specific perception ability (ART 2020)
LL5	Visual structuring ability (ART 2020)
WCST	Wisconsin Card Sorting Test

* Study Type: Db=Double blind; Co=Crossover; Rd=Randomized, Pc=Placebo controlled

Ref.	Drug Dose (adminis-tration)	Measured Cmax/ Tmax	Persons -Number (n) -Sex (m/f)	Type study * Db / Rd Co / Pc	Control Placebo Baseline	Time of testing (after given drug)	Tests (effect) Impaired I/ Not Impaired NI Placebo (p) / Baseline (b) Low/medium/high dose (LD/MD/HD)	Comments Other drugs Improved performance
Ali 1985 (131)	Dextro-propoxyphene 65 mg (po)	Cmax: 96,3 +/-66,6 µg/l Tmax: 2,4 +/-0,6 h	Healthy volunteers n = 6	Db Rd Co	Placebo Baseline	0.5-4 h	**SacEM:** NI (p)	Mixture with paracetamol (650 mg). Ethanol (0,8 g/kg) and Meptazinol also tested Impairment seen in combination with ethanol Impairment seen with ethanol alone
Ali 1985 (131)	Meptazinol 200 mg (po)	Cmax: 38.4 +/-8.0 µg/l Tmax: 1.6 +/-0.42 h	Healthy volunteers N = 6	Db Rd Co	Placebo Baseline	0.5-4 h	**SacEM:** NI (p)	Ethanol (0,8 g/kg)and Dextropropoxyphene also tested Impairment seen in combination with ethanol Impairment seen with ethanol alone
Allen 2003 (139)	Hydrocodone bitartrate 7,5 mg plus ibuprofen 200 mg (po)	Not measured	Healthy men n = 72	Db Rd Pc Repeated-dose clinical trial	Placebo	40 min	**Paced auditory serial addition test** (PASAT): NI (p) **Light-tracking test**: NI (p) **CRT:** NI (p) **SRT**: I (p)	Also tested: ibuprofen ? mg
Anand 2000 (58)	Ketamine 0,26 mg/kg (iv)+ 0,65 mg/kg/h (iv) Infusion	$C_{30\text{-}60}$: 125-150 ng/ml	Volunteers n = 16	Db Rd Co	Placebo Baseline	30-90 min	**Hopkins verbal learning test**: I (p)	Lamotrigin was also tested as attenuator of ketamine effects K gave rise to several psychiatric symptoms
Angst 2004 (85)	Alfentanil <u>Cumulative Dose Step 1-4</u> 428 µg (iv) 1130 µg (iv) 2532 µg (iv) 5346 µg (iv) (mean) **Max cumulative dose: 6341 µg**	<u>Infusion Step 1-4</u> 13.4 ng/ml 33.8 ng/ml 67.8 ng/ml 126.1 ng/ml (median) **Cmax: 133.2 ng/ml** <u>Post infusion</u> 84.6 ng/ml 52.2 ng/ml (mean)	Healthy Volunteers n = 12 8 (m) / 4 (f)	Db Rd Co	Placebo Baseline	15 min into each infusion step and 15-30 min after termination of infusion.	**Trail-making test**: I (p) linear relationship between plasma concentration and effect measure **RT**: I (p) linear relationship between plasma concentration and effect measure	4 infusion steps with increasing plasma-concentrations. 2 post infusion steps. Dexmedetomide was also studied. Not indicated at which dose step the difference was significant
Belleville 1979 (154)	Pentazocine 22,5 mg (im) (LD) 45 mg (im) (HD)	Not measured	Healthy n = 7 (m)	Db	Placebo Baseline	0,5-4 h	**Critical tracking test**: I (p) (HD) (I LD 0,5 h)	Nefopam also tested

Biehl 1985 (49)	Pentazocine 50 mg (po)	Not measured	Healthy volunteers n = 12 6 (m) / 6 (f)	Db Co	Placebo	After 1st and 3rd administration	**Vigilance**: NI (p) **APG**: NI (p) **CFF:**I (p) **Konzentrationstest**: NI (p) **TAVT**: NI (p)	Flupirtin main drug Article in German
Biehl 1985 (49)	Flupirtine 100 mg (po) x 3 with 3 h between doses?	Not measured	Healthy volunteers n = 12 6 (m) / 6 (f)	Db Co	Placebo	After 1st and 3rd administration	**Vigilance**: NI (p) **APG**: NI (p) **CFF:** NI (p) **Konzentrationstest**: NI (p) **TAVT**: NI (p)	Pentazocine used as comparative drug Article in German
Black 1999 (83)	Alfentanil (iv)	Target level 16 ng/ml (LC) 32 ng/ml (MC) 64 ng/ml (HC)	Healthy Volunteers n = 10 8 (m) / 2 (f)	Db Rd Co	Placebo	20 min into each infusion period and 15-180 min after the infusion was discont.	**MW:** I (p) (HC) **DSST**: I (p) (HC) **Backward digit span**: NI (p)	3 infusion periods with increasing dose. C max levels are target plasma levels. Plasma drug concentrations were not verified. Remifentanil also tested: I (p) all tests
Black 1999 (83)	Remifentanil (iv)	Target level: 0.75 ng/ml (LC) 1.5 ng/ml (MC) 3 ng/ml (HC)	Healthy Volunteers n = 10 8 (m) / 2 (f)	Db Rd Co	Placebo	20 min into each infusion period and 15-180 min after the infusion was discont.	**MW**: I (p) MC/HC **DSST**: I (p) MC/HC **Backward digit span**: I (p)	3 infusion periods with increasing dose. C max levels are target plasma levels. Plasma drug concentrations were not verified. Alfentanil also tested: MW, DSST: I (p)
Bradley 1986 (104)	Codeine 30 mg (po) (LD) 60 mg (po) (MD) 90 mg (po) (HD)	Not measured	Healthy volunteers n = 6 (f)	Db Co	Placebo	0,75-2 h	**VMC** (visuo-motor coordination): I (p) dose related effect (MD/HD) **DVA** (dynamic visual acuity): NI (p) **CFF**: NI (p) **DSST**: NI (p) **CRT**: NI (p)	Triprolidine (antihistamine) used as positive control
Bradley 1987 (142)	Meptazinol 100 mg (po) 200 mg (po) 400 mg (po)	Not measured	Healthy Volunteers n = 7 (f)	Db Rd? Co (5)	Placebo	0.74-2.0 h	**VMC** (Visuo-Motor coordinat.): NI(p) **DVA** (Dynamic Visual Acuity): NI (p) **CRT**: NI (p) **DSST**: NI (p) **CFF:** NI (p)	Aspirin, pentazocine paracetamol and tripolidine were also studied. Pentazocine (25,50 mg): DSST: I (p) 25 mg
Bradley 1987 (142)	Pentazocine 25 mg (po) 50 mg (po)	Not measured	Healthy Volunteers n = 7 (f)	Db Rd? Co (5)	Placebo	0.74-2.0 h	**VMC** (Visuo-Motor coordinat.): NI (p) **DVA** (Dynamic Visual Acuity): NI (p) **CRT:** NI (p) **DSST:** I (p) 25 mg **CFF:** NI (p)	Aspirin, meptazinol, paracetamol and tripolidine were also studied. Meptazinol (100,200,400 mg): NI (p) all tests
Carroll 2006 (243)	Hydromorphone 5 mg (im) 10 mg (im)	Not measured	Volunteers with active opioid dependence. n = 8 5 (m) / 3 (f) Stabilized on methadone (60 mg/day)	Db Rd Co	Placebo Baseline	Every 15 min	**DSST**: NI (p)	Naloxone was also studied. Tramadol also tested: NI (p)

Carroll 2006 (243)	Hydromorphone 5 mg (im) 10 mg (im)	Not measured	Volunteers with active opioid dependence. n = 6 2 (m) / 4 (f) Stabilized on hydromorphone (10 mg x 4)	Db Rd Co	Placebo Baseline	Every 15 min	**DSST**: NI (p)	Naloxone was also studied. Tramadol also tested: NI (p)
Carroll 2006 (243)	Tramadol 50 mg (im) 100 mg (im) 200 mg (im) 400 mg (im)	Not measured	Volunteers with active opioid dependence. n = 6 2 (m) / 4 (f) Stabilized on hydromorphone (10 mg x 4)	Db Rd Co	Placebo Baseline	Every 15 min	**DSST**: NI (p)	Naloxone was also studied. Hydromorphone also tested: NI (p)
Carroll 2006 (243)	Tramadol 74 mg (im) 150 mg (im) 300 mg (im)	Not measured	Volunteers with active opioid dependence. n = 8 5 (m) / 3 (f) Stabilized on methadone (60 mg/day)	Db Rd Co	Placebo Baseline	Every 15 min	**DSST:** NI (p)	Naloxone was also studied. Hydromorphone also tested: NI (p)
Carter 2004 (77)	Psilocybin 215 μg/kg (po) (capsules)	Not measured	Volunteers n = 9 5 (m) / 4 (f)	Db Co	Placebo Baseline	120 min	Vision tests: **Contrast sensitivity**: NI (p,b) **Coherence sensitivity**: I (p,b)	120 min: assumed Tmax
Carter 2005 (75)	Psilocybin 215 μg/kg (po)	Not measured	Healthy Volunteers n = 8 5 (m) / 3 (f) (5 with previous exp. with psilocybin	Db Co	Placebo Baseline	120 min	**Multiple-object tracking**: I (p) **Spatial Working memory**: I (p)	Ketanserin was also studied.
Carter 2005 (76)	Psilocybin 115 μg/kg (po) (8.2 mg) (MD) 250 μg/kg (po) (17.6 mg) (HD)	Not measured	Healthy Volunteers n = 12 6 (m) / 6 (f) 6 with previous exp. with psilocybin		Placebo Baseline	90-360 min	**Binocular rivalry**: I (p) (MD/HD)	
Coda 1993 (10)	Alfentanil 15 mcg/kg (iv)	Steady state concentrations of 16 ng/ml (LC) 32 ng/ml (MC) 64 ng/ml (HC)	Healthy volunteers n = 15 (m)	Db Co	Placebo Baseline	At steady state	**Simple motor performance** (tapping): NI (b) **Complex motor performance** (force): I (b) (HC) **Cognitive variable** (reading speed): I (b) (HC)	Morphine also tested: Complex motor performance, cognitive variable: I (b)

Comer 1997 (8)	Heroin 12,5 mg (VLD) 25 mg (LD) 50 mg (MD) 100 mg (HD) intranasal	H and 6MAM were measured! Cmax H: 4min Cmax 6MAM: 10 min Cmax morph: 20 min	Heroin/polydrug users, maintained on morphine before the study n = 5 (m)	Db Co Single blind?	Placebo	10-60min	**DAT:** I (p) (HD) **DSST**: I (p) (HD) **RIT:** NI (p) **Response sequence task** (RA): NI (p)	The primary goal of the study was to compare the choice between money and intranasal heroin
Conley 1997 (8)	Butorphanol 2 mg/ 70 kg (iv)	Not measured	Healthy volunteers n = 13 12 (m) / 1 (f) Some prior use recreational drugs No past history indicative of dependency	Rd Pc Db Co trial	Placebo Baseline	15-300 min	**DSST**: I (p)	Periodic forearm immersions into ice-cold water (2°C) or into warm water (37°C), while receiving saline, butorphanol or morphine Morphine: NI (p)
Dershwitz 1991 (99)	Butorphanol 7.1 µg/kg (iv) LD 22.5 µg/kg (iv) MD 71.4 µg/kg (iv) HD	Not measured	Patients scheduled for elective surgery N=126	Rd 9 treatment groups	Baseline	?	Trieger dot test: I (LD + HD) Trail-making test: I (MD + HD)	Midazolam and combination midazolam/butorphanolalso tested
Duke 1968 (82)	Psilocybin 200 µg/kg (po) (capsules)	Not measured	Volunteers n = 8 (m)	Db Co	Placebo	"Sufficient time"	**Trail making test**: I (p)	d-Met-amphetamine also tested I: P > dM d-Metamphet: 30 mg: I (p)
Edwards 1982 (129)	Dextro-propoxyphene 32,5 mg (po) In combination with 325 mg paracetamol	Not measured	Healthy? volunteers <u>Placebo</u> n = 14 <u>Dextroprop.</u> n= 16 m (?) f (?)	Db	Placebo Baseline	30-90 min	**CFF:** NI (b?) **PDL** (Periph. vision light flash det.): NI (b?)	Dextropropoxyphene was not given alone, but in combination with paracetamol 325 mg. Ethanol was also tested.
Evans 1966 (107)	Codeine 32 mg (po)	Not measured	Healthy volunteers n = 16 Tested at different altitudes 2000 feet 11000 " 15000 "	Db Co Rd	Placebo	?	**DSST**: I (p)	Desoxyephedrine was also studied
Fraser 1963 (248)	Heroin Chronically i.v.	Not measured	Prisoner addicts n = 5	30 days placebo followed by 60 d of i.v. heroin Db	Placebo	1 hour after admin.	**Pursuit rotor test**: Acute H:NI (?)	4 injections/day First 10 mg, increase to 95 in 18 days, then 95 mg next 42 days (Training)

Ghoneim 1975 (94)	Fentanyl 0.1 mg (iv) LD 0.2 mg (iv) HD	Not measured	Healthy volunteers n = 10 (m)	Db Rd Co?	Placebo	0.5-8 h	**Backward digit span**: I (p) (HD) **Tapping board**: I (p) (HD) **Serial learning**: NI (p) **Short term memory**: NI (p) **Delayed recall**: NI (p) **SRT**: NI (p) **CRT**: NI (p) **Visual retention test**: NI (p)	Diazepam also tested
Ghoneim 1985 (54)	Ketamine 0,25mg/kg (im) LD 0,5 mg/kg (im) HD	Not measured	Healthy volunteers n = 31 m (16) f (15) **not cross-over** → K 0,25 (12) K 0,5 (9) P (10)	Db Rd	Placebo Baseline	18-85 min → 15-120 min → 50-120 min → 35-100 min → 60-115 min → 45-110 min → 60-115 min →	**Immediate free recall**: I (p) HD **Delayed free recall**: I (p) LD/HD **Delayed recognition**: NI (p) **Number learning**: I (p) HD **Category generation**: NI (p) **Backward digit span**: NI (p) **Tapping**: NI (p)	
Girre 1991 (124)	Propoxyphene 130 mg (po) propoxyphene + ethanol, placebo + ethanol, propoxyphene	Cmax: 135 ng/ml Tmax: 1,33 h	Healthy volunteers n = 12 (m)	Db Three ways Co	Ethanol Baseline	0,25-31 h	**Visual reaction time**: I (b) **Simple visual reaction time**: NI (b) **Visual choice reaction time**: NI (b) **Visual half field test**: NI (b) **DSST**: NI (b) **Two-symbol cancellation test**: NI (b) **Santa ana dexterity test**: NI (b) **Critical flicker fusion threshold**: NI (b)	Ethanol (0,5g/kg bodyweight) also tested: Visual reaction time: I (b) Propoxyphene + ethanol Placebo + ethanol Propoxyphene
Goldberger 1966 (65)	LSD 100 γ (p.o.)	Not measured	Healthy volunteers n = 42 (m)	Db	Placebo	At peak effect	Digit span: NI (p) Short Passage Comprehension: I (p) Serial seven (error): I (p) Serial seven (time): I (p) Rhyming: I (p) Robinson's Rhymes (error): I (p) Robinson's Numbers (error). I (p) Robinson's Numbers (no. request for repetition): I (p) Long passage comprehension: I (p)	Effect also compared to isolation
Gouzoulis-Mayfrank 1999 (81)	Psilocybin 200 μg/kg (po) (capsules)	Not measured	Volunteers n = 32 21 (m) / 11 (f) 8 in each Treatment group	Db Co (max 2 gr)	Placebo	1-2 h (?)	<u>Cognitive test</u>: **Repetition task**: NI (p) **Association task**: I (p)	Looked at MRI and PET MDE and d-Met-amphetamine also tested MDE 2mg/kg: NI(p)/NI (p) d-Metamphet 0,2/0,4 mg/kg: NI(p)/NI (p)
Gouzoulis-Mayfrank 2002 (80)	Psilocybin 200 μg/kg (po) (capsules)	Not measured	Volunteers 32 21 (m) / 11 (f)	Double bind 8 subjects in each treatment group	Placebo Baseline	75-95 min	**Reaction time in covert orienting of attention task**: I (p,b)	MDE and d-Met-amphetamine also tested MDE: 2mg/kg: I (p,b) d-Methamphetamine 0,2/0,4 mg/kg: NI I: P > M

Gouzoulis-Mayfrank 2006 (59)	S-ketamine 0,1-0,15 mg/kg + infusion (LD) 0,15-0,20 mg/kg + infusion (HD)	Not measured	Volunteers n = 15 9 (m) / 6 (f) 9 completed both exp. with both doses	Db Rd	Baseline	15-90 min	**Reaction time in covert orienting of attention task**: I (b) (dose dep) (LD/HD)	Plasma levels of drugs presented, in another paper I: D > S-k Also tested Dimetyl-tryptamine (5-HT_{2A}-agonist): 0,15-0,2 mg/kg + infusion(LD) 0,2-0,3 mg/kg + infusion (HD) Reaction time: I (b) (dose dep)
Greenwald 1998 (193)	Butorphanol 3 mg/ 70 kg (im) (LD) 6 mg/ 70 kg (im) (HD)	Not measured	Volunteers n = 6 (m) Non-dependent heroin-users	Db Placebo Cross-over	Placebo Baseline	0,5-5 h	**Psychomotor balance**: NI (p)	Morphine also tested. NI (p)
Hasler 2004 (78)	Psilocybin 45 μg/kg (po) (VLD) 115 μg/kg (po) (LD) 215 μg/kg (po) (MD) 315 μg/kg (po) (HD) (capsules)	Not measured	Volunteers n = 8 4 (m) / 4 (f)	Db Co	Placebo	95 min (Assumed peak effect)	**Altered state of consciousness**: - Vigilance: I (p) LD/MD/HD) - Global score : I (p) (dose dep) (MD/HD) **Frankfurt Attention Invention**: I (p) (MD, HD)	
Hermle 1992 (71)	Mescaline 0,5 g m-sulphate (po) (powder with some liquid)	Not measured	Volunteers n = 12 (m)	Open	Baseline	0,5-7 h	**BPRS** (brief psychiatric rating scale): I (b)	
Hill 2000 (135)	Hydromorphone 0,33 mg/ 70 kg (iv) (LD) 0,65 mg/ 70 kg (iv) (MD) 1,3 mg/ 70 kg (iv) (HD)	Not measured	Healthy volunteers n = 17 12 (m) / 5 (f) Some prior use recreational drugs No histories indicative of dependence	Rd Db Incomplete Latin square Co design	Placebo Baseline	15-300 min	**DSST**: I (p) (HD) **MW:** I (p) (HD) **ART:** NI (p) **EHC:**: NI (p) **Logical reasoning ability**: NI (p) **Immediate + delayed free recall**: NI (p)	**DSST**: (number completed/time, number correct/time
Holliday 1965 (68)	LSD 1 μg/kg	Not measured	Healthy volunteers n = 10 (m)	Co Rd Blinded	Placebo Baseline	120 min	**CFF**: I (b)	
Hummel 1996 (51)	Tramadol 100 mg po	Not measured	Healthy volunteers n = 20 13 (m) 7 (f)	Db Rd Controlled Three-ways-cross-over	Baseline	2,4, 6 and 12 h after administration	**Tracking performance:** NI (b)	Tramadol controlled release (100 and 150 mg) also tested.
Javitt 1991 (73)	PCP	Not measured					PCP-induced psychotomimetic effects are associated with submicromolar serum concentrations of PCP in normal volunteers	**Review** paper, 25 different articles (1991)
Kiplinger 1974 (130)	Propoxyphene 65 mg (po)	Not measured	Healthy volunteers n = 8 m (?) / f (?)	Db Rd Co	Placebo Baseline		**Pursuit meter**: I (p/b) **Verbal tasks**: NI (p/b) **Stability of stance**: NI (p/b)	Ethanol was also tested

Kobal 1990 (155)	Pentazocine 50 mg (iv)	1000 ng/ml	Volunteers n = 14 7 (m) / 7 (f) 9 fulfilled	Single blind	Placebo	0-64 min	**Tracking performance**: I (b,p)	Complicated design, pain induced Acetyl-salicylic acid 1000 mg iv (conc 100 ng/ml for most of the period)
Kornetsky 1957 (69)	Mepheridine 50 mg (po) (LD) 100 mg (po) (HD)	Not measured	Healthy volunteers n = 10 6 (m) / 4 (f)	Rd Co Db	Placebo	75 min	**Modified digit symbol test**: NI **Pursuit rotor**: NI **Speed of addition** (3 digit): NI **Speed of addition** (9 digit): NI **Speed of copying numbers**: NI **Tachistoscopic discrimination**: NI	LSD, chlorpromazine and secobarbital also tested
Kornetsky 1957 (69)	LSD 50 γ (po) LD 100 γ (po) HD	Not measured	Healthy volunteers n = 10 6 (m) / 4 (f)	Rd Co Db	Placebo	75 min	**Speed of addition** (3 digit): I (p) (LD + HD) **Speed of addition** (9 digit): I (p) (HD) **Modified digit symbol test**: I (p) (HD) **Speed of copying numbers**: NI **Pursuit rotor**: NI **Tachistoscopic/visual discrimination**: I (p) (HD)	Meperidine, chlorpromazine and secobarbital also tested
Korttila 1975 (141)	Meperidine 75 mg (im)	Not measured	Healthy volunteers n = 11 m (8) / f (3)	Db Rd Co	Placebo Baseline	1-7 h	**CRT**: I (p) **EHC:** I (p) **CFF:** I (p)	Diazepam was also tested
Krystal 1994 (57)	Ketamine 0.1 mg/kg (LD) 0.5 mg/kg (HD)	Not measured	Healthy volunteers n = 19 12 (m) / 7 (f)	Db Rd Co	Placebo Baseline	10 - 30 min	**Vigilance**: I (HD vs p) **Verbal fluency**: I dose-response effect (p) (HD) **Wisconsin card sorting test**: I dose-response effect (p) (HD)	Ketamine produced behaviours similar to positive and negative effects of schizophrenia
Krystal 1998 (55)	Ketamine Bolus of 0,26 mg/kg (iv) foll. by infusion of 0,65 mg/kg over 1h	Not measured	Healthy volunteers n = 23 m (?) / f (?)	Db Rd Co	Placebo Baseline	10 min 10 min 10 min 10 min 40 min 5-180min ???	**Vigilance**: NI (p) **Distractibility**: I (p) **Verbal fluency**: I (p) **Proverb interpretation**: I (p) **Wisconsin Card sorting test**: I (p) **Learning and memory**: I (b) **Finger-tapping**: NI (p)	Lorazepam was also tested
Lamas 1994 (192)	Naloxone 0.1 mg (im) (LD) 0.2 mg (im) (HD)	Not measured	Opioid dependent volunteers n = 6 (m)	Db Rd	Placebo Baseline	20-240 min	**MW:** NI (p)	Methadone maintained (30 mg/24 h). Drugs administered 20 h after last dose of methadone. Pentazocine and morphine also tested: NI (p)
Lamas 1994 (192)	Pentazocine 45 mg (im) (LD) 60 mg (im) (HD)	Not measured	Opioid dependent volunteers n = 6 (m)	Db Rd	Placebo Baseline	20-240 min	**MW**: NI (p)	Methadone maintained (30 mg/24 h). Drugs administered 20 h after last doe of methadone. Naloxone and morphine also tested: NI (p)
Landis 1954 (64)	LSD 0,1-0,12 mg (p.o.)	Not measured	Psychiatric patients n = 6		Controls	1,5-6 hours	**Purdue Assembly**: NI **Tapping speed**: NI **Tapping Endurance**: NI **CFF**: NI	Mescaline also tested

Liljequist 1981 (110)	Codeine 25 mg (LD) 50 mg (MD) 100 mg (HD) (some given naloxone in addition) p.o.	Not measured	Healthy Volunteers n = 33 27 (m) / 6 (f) 1) n = 12 2) n = 12 3) n = 9	Rd Co for subgroup 3.	Placebo	Special time scheme. 1-3.45 h Next day also for memory tests.	**Memory tasks**: -Associative learning: NI (p) -Serial learning: Improvement (p) (HD) -Recall associative: NI -Recall serial learning: Improvement (p) (HD) -Recall Concept learning: Improvement (p) (LD/HD) **Flicker fusion**: NI	<u>3 subgroups:</u> 1) 25 mg Codeine PPCP-PCCP (4 consecutive days, 3 day wash-out, 4 consecutive days) 2) 100 mg Codeine PPCP- PCCP (same treatment scheme as 1) 3) 50 mg Codeine +/- naloxone (0,4 mg im) C = codeine P = placebo
Linnoila 1973 (108)	Codeine 25 mg (po) (C-Ph)	Not measured	Volunteers 10 per group (Total n = 90)	Db Rd	Placebo	30-70 min	Sim-L-Car (driving simulator device): **Collision frequency**: codeine alone not reported, but codeine potentiated the effects of alcohol	Alcohol alone increased collision frequency. Ethanol increased drug effects Diazepam as reference
Linnoila 1974 (109)	Codeine 50 mg (po)	Not measured	Healthy volunteers n = 70 ? (m) / ? (f)	Db 7 groups (n=10)	Placebo Zero (z) group	30 - 70 min	**Simulated driving**: I (z)	Alcohol 0.5 gm/kg and diazepam 10 mg also tested
Malhotra 1996 (56)	Ketamine Bolus of 0,12 mg/kg (iv) foll.by infusion of 0,65 mg/kg over 1h	Not measured	Healthy volunteers n = 15 m (12) / f (3)	Db Rd Co	Placebo Baseline	10-120 min	**Attention**: I (p) **Recall**: I (p) **Recognition**: I (p)	
Manner 1987 (96)	Fentanyl 2.5 µg/kg (iv)	Not measured	Healthy Volunteers n = 7 3 (m) 4 (f)	Db Rd Co	Placebo Baseline	5-180 min	**MW**: I (p) ? **CFF:** I (p) ?	Buprenorfin also tested: I (p) (?) all tests When the data were evaluated statistically by analysis of variance for repeated measurements, a marked interaction in most variables became evident, thus preventing conclusions about the magnitude of the drug effects.
Manner 1987 (146)	Meptazinol 0.7 mg/kg (iv) (LD) 1.4 mg/kg (iv) (HD)	Not measured	Healthy volunteers n = 6 3 (m) / 3 (f)	Db Rd Co	Placebo Baseline	5-180 min	**CFF:** I (b) dose dependant effect (LD/HD) **MW**: I (b) (LD+HD)	Pentazocine also tested: CFF, MW: I (b)
Manner 1987 (146)	Pentazocine 0.3 mg/kg (iv) (LD) 0.6 mg/kg (iv) (HD)	Not measured	Healthy volunteers n = 6 3 (m) / 3 (f)	Db Rd Co	Placebo Baseline	5-180 min	**CFF**: I (b) (LD+HD) **MW:** I (b) (LD+HD)	Meptazinol also tested: CFF I (b) (dose dep) MW: I (b)
Mechri 2001 (62)	Ketamine						(Used as source for references to primary research literature)	**Review** paper (2001)
Mitrani 1972 (67)	LSD 100 µg (p.o.)	Not measured	Volunteers n = 5 (m = 4 / f = 1)		Baseline	90-120 min	**SacEM:** NI (b)	
Morgan 2006 (60)	Ketamine Low dose i.v. infusion High dose i.v. infusion	 Conc. after 50 min: 113 ng/ml Conc. after 50min: 237 ng/ml	Volunteers n = 48 24 (m) / 24 (f) n = 16 8 (m) / 8 (f) In each treatment group	Db Rd	Placebo And Baseline	15-180 min	Semantic priming task: Stimulus onset asynchrony (SOA) I (p) (dose dep) (LD/HD)	Results indicate controlled processing impairment (Authors also studied similar effects in chronic users, with no acute adm of ketamine)

Muller-Limmoth 1985 (48)	Flupirtine 3 x 100 mg one day prior to testing 100 mg (po) prior to test	Not measured	Patients n = 12 12 (m)	?	Placebo	1 h	Combined multiple problems/vigilance testing - **RT**: I (p) **Mental processing time**: I (p) **Standard errors**: NI (p) **Uniformity of performance**: NI (p) **Signals overlooked**: I (p)	Diazepam 5/10 mg and chlorphenoxamine 20/40 mg used as comparative drugs
O'Neill 1994 (252)	Opioid drugs						(Used as source for references to primary research literature)	**Review** paper (1994)
O'Neill 1995 (125)	Dextro-propoxyphene 100 mg (po) (LD) 200 mg (po) (HD)	Not measured	Healthy subjects n = 12 3 (m) / 9 (f) No history of drug or alcohol abuse	Rd / Db Four way Co	Placebo Baseline	1-6 h	**CFFT**: I (p) (HD) **Word recognition**: I (p) (HD) **CRT**: NI (p) **Digit vigilance**: NI (p) **Memory scanning** : NI (p) **Picture recognition**: NI (p) **SRT:** NI (p) **Word recall** : NI (p)	Lorazepam also tested
O'Neill 2000 (126)	Dextro-propoxyphene 100 mg (po) 4 doses given with 4-h interval (cum. dose 400 mg)	Not measured	Healthy n = 10 4 (m) / 6 (f)	Rd Db Four-way Co	Placebo Baseline	4-36 h	**CRT:** I **Picture recognition**: I **CFFT:** NI **Memory scanning:** NI **Number vigilance**: NI **SRT:** NI **Word recall** (immediate/ delayed): NI **Word recognition**: NI	Morphine also tested: SRT, memory scanning: I CRT: improved performance Lorazapam also tested
Oliveto 1994 (138)	Hydromorphone 1-6 mg /70 kg (po)	Not measured	Healthy volunteers n = 7 5 (m) / 2 (f)			120-150 min	**DSST**: NI	Subjects were trained on discrimination between triazolam and placebo
Pavlin 1996 (84)	Alfentanil 40 ng/ml (iv) – steady state for 3h	Steady plasma concentrat. of 40 ng/ml	Healthy volunteers n =10 (m)	Co Blind	Baseline	25-300 min	**DSST**: I (b)	Propofol infusion and combination propofol/alfentanil also tested
Pickering 2005 (52)	Codeine 30 mg (po) + 500 mg paracetamol	Not measured	Healthy volunteers n =24 (m)	Rd Db Co	Baseline	60-240 min	**CRT**: I (b) **Memory**: NI (b)	Combination codeine/paracetamol. Tramadol/paracetamol also tested
Pickering 2005 (52)	Tramadol 37.5 mg (po) + 325 mg paracetamol	Not measured	Healthy volunteers n =24 (m)	Rd Db Co	Baseline	60-240 min	**CRT**: NI	Combination tramadol/paracetamol. Codeine/paracetamol also tested

Pickworth 1997 (249)	Hydromorphone 1 mg (po) 3 mg (po) (capsules)	Not measured	Volunteers Drug users Paid USD 1000	Db Co Rd	Placebo (twice)	30-300 min	**Card sorting**: NI (b) **Circular light task**: NI (b) **DSST**: NI (b) **Serial-addition subtraction task**: NI (b) **Six letter search task**: I (b) (1,3)	Few effects for the drug looked for, i.e. hydromorphone **Ethanol**: po 0,3/1 g/kg Circ. Light: I (0,3/1) (b) DSST: I (1) (b) Serial-addition subtraction task: I (1)(b) Card sorting: I (1)(b) Six letter: NI (b) **Marihuana**: inh. 1,3/3,9% THC Card, six, DSST: NI (b) **Pento-barbital**: po (capsules) 150/450 mg Circular light: I (150/450) (b) DSST: : I (450) (b) Serial-addition subtraction task: I (450) (b) Card sorting: I (450) (b) Six letter: NI (b) **Amphetamine**: po (capsules) 10/30 mg Circular lights I (b) (10) DSST, six, card: NI (b)
Posner 1990 (134)	Dipipanone 10 mg (po)	Not measured	Healthy volunteers n = 12 (m)	Db / Rd Balanced Co	Placebo	120-180 min ?	**Visual reaction time**: NI	
Pöyhiä 1992 (150)	Oxycodone 0.28 mg/kg (iv)	Not measured	Healthy volunteers n = 9 4 (m) / 5 (f)	Db Rd Co	Baseline	1-8 h	**CFF** I (b) **DSST**: (digit symbol subst.test) I (b) **MW**: I (b)	
Pradhan 1984 (72)	PCP 0,1-0,15 mg/kg						50 per cent responding with feeling of unreality, affective changes, spatial misconception, nystagmus, ataxia, intellectual and markmanship impairments.	**Review** paper (1984)
Preston 1985 (250)	Hydromorphone 1 mg (po)	Not measured	Opioid dependant volunteers n = 18 (m) 3 groups, n = 6 (m) for each drug	Rd Db	Placebo	1.5-7 h	**DSST**: NI **Circular lights** (hand-eye coordination): NI	Drugs tested during methadone detoxification. Hydromorphone IMPROVED hand-eye coordination at two testing times
Preston 1987 (194)	Pentazocine 22.5 mg (im) (LD) 45 mg (im) (MD) 90 mg (im) (HD)	Not measured	Post addict volunteers n = 15 (m)	Db Rd	Placebo Baseline	60-240 min	**EHC:** (saccadic): NI (p) **Memory task**: NI (p) **CRT**: NI (p) **DSST**: I (p) (dose related)	Significance for doses not given Morphine and ciramadol (?) also tested Morphine: Memory task: I (p) (dose rel)
Preston 1988 (244)	Butorphanol 0.375 mg (im) 0.75 mg (im) 4.5 mg (im) 3 mg (im) 6 mg (im)	Not measured	Opioid-dependant volunteers n = 5 (m)	Rd Db Co	Placebo Baseline	60-120 min	**DSST**: NI **Recall (memory) test**: NI	Methadone maintained on 30 mg daily. Injections given 20 h after last dose of methadone. Hydromorphone and naloxone also tested

Preston 1988 (235)	Hydromorphone 6 mg (sc)	Not measured	Volunteers adult n = 6 (m)	Rd Placebo -contr. Db	Placebo Baseline	60-120 min	**DSST**: NI (p) **Recall (memory) test**: NI (p)	Opioid-dependent Maintained on methadone Buprenorphine and naloxone also tested: NI (p) all tests
Preston 1988 (244)	Hydromorphone 4 mg (im) LD 8 mg (im) HD	Not measured	Opioid-dependant volunteers n = 5 (m).	Rd Db Co	Placebo Baseline	60-120 min	**DSST**: NI **Recall (memory) test**: NI	Methadone maintained on 30 mg daily. Injections given 20 h after last dose of methadone Butorphanol and naloxone also tested
Preston 1988 (235)	Naloxone 0,2 mg (sc) Combination bup + naloxon: 0,2/0,2 mg (sc) 0,3/0,2 mg (sc)	Not measured	Volunteers adult n = 6 (m)	Rd Placebo -controlled Db	Placebo Baseline	60-120 min	**DSST**: NI (p) **Recall (memory) test**: NI (p)	Opioid-dependent Maintained on methadone Buprenorphine and hydromorphone also tested: NI (p) all tests
Preston 1989 (245)	Hydromorphone 4 mg (im) LD 8 mg (im) HD	Not measured	Opioid-dependant volunteers n = 5 (m)	Rd Db Co	Placebo Baseline	60-120 min	**DSST**: NI **Recall (memory) test**: NI	Methadone maintained on 30 mg daily. Injections given 20 h after last dose of methadone. Nalbuphine and naloxone also tested
Preston 1989 (245)	Nalbuphine 0.375 mg (im) 0.75 mg (im) 4.5 mg (im) 3 mg (im) 6 mg (im)	Not measured	Opioid-dependant volunteers n = 5 (m)	Rd Db Co	Placebo Baseline	60-120 min	**Recall (memory) test**: NI **DSST**: NI	Methadone maintained on 30 mg daily. Injections given 20 h after last dose of methadone. Hydromorphone and naloxone also tested
Preston 1990 (242)	Butorphanol 0-1,5 mg / 70 kg (im)	Not measured	n = 5 (m)	Co	Baseline	60 min	**DSST**: NI (b)	Methadone maintenance patients on 30 mg per day, last dose 22 h before exp session Drug discrimination tests were also performed Nalbuphine and hydromorphone also tested
Preston 1990 (242)	Hydromorphone 10mg/70 kg (im)	Not measured	n = 5 (m) Physically dependent methadone maintenance patients, 30 mg/day, last dose 22 h before testing	Db Co	Placebo Baseline	60 min	**DSST**: NI (p)	Drug discrimination tests were also performed Butorphanol and nalbuphine also tested
Preston 1990 (242)	Nalbuphine 0-3 mg / 70 kg (im)	Not measured	Methadone maintenance patients on 30 mg per day, last dose 22 h before exp session n = 5 (m)	Co	Baseline	60 min	**DSST**: NI (b)	Drug discrimination tests were also performed Butorphanol and hydromorphone also tested
Preston 1991 (50)	Flupirtine 200 mg (po) 400 mg (po) 600 mg (po)	Not measured	Volunteers with history of sedative drug use n = 12 (m)	Db Rd Co	Placebo Baseline	0.5-1 h	**Circular Lights**: NI (p) **Tracking**: I (p) **DSST**: I (p) **Enter and Recall**: I (p)	Lorazepam was also studied. Not indicated at which dose the difference was significant

Preston 1994 (251)	Butorphanol 4 mg (im) (LD) 6 mg (im) (HD)	Not measured	Post addict volunteers n = 6 (m)	Db Rd	Placebo Baseline	20-100 min	**DSST**: I (p) HD	Drug discrimination test including hydromorphone, butorphanol, pentazocine, nalbuphine and buprenorphine Hydromorphone: NI (p)
Preston 1994 (251)	Hydromorphone 3 mg (im)	Not measured	Post addict volunteers n = 6 (m)	Db Rd	Placebo Baseline	20-100 min	**DSST**: NI (p)	Drug discrimination test including hydromorphone, butorphanol, pentazocine, nalbuphine and buprenorphine Butorphanol: I (p) (HD)
Primac 1957 (70)	Mepheridine 50 mg (po) (LD) 100 mg (po) (HD)	Not measured	Healthy volunteers n = 10 6 (m) / 4 (f)	Rd Co	Placebo	3.5 h	**Continuous performance test** (visual discrimination/sustained attention): NI **WCST**: NI	LSD, chlorpromazine and secobarbital also tested
Primac 1957 (70)	LSD 50 γ (po) (LD) 100 γ (po) (HD)	Not measured	Healthy volunteers n = 10 6 (m) / 4 (f)	Rd Co	Placebo	3.5 h	**WCST**: NI **Continuous performance test** (visual discrimination/sustained attention): NI	Meperidine, chlorpromazine and secobarbital also tested
Ray 1993 (253)	Opioid analgesics						(Used as source for references to primary research literature)	**Review** paper (1993)
Redpath 1982 (105)	Codeine 30 mg (po) (LD) 60 mg (po) (HD)	Not measured	Healthy volunteers n = 10 6 (m) / 4 (f)	Db Co	Placebo Baseline	0-6 h	**DSST**: no result given **Zahlen-verbindung test** (reaction time?): NI	Gluacine (opioid?) also tested Given as syrup
Richens 1983 (143)	Meptazinol 100 mg (im)	Not measured	Healthy volunteers n = 6 (m)	Rd Co	Placebo	1-3 h	**CFF**: NI (p) **CRT**: NI (p) **Running memory**: NI (p) **SacEM:** I (p) **Stroop colour word test**: I (p) **Syntactic reasoning test**: NI (p) **Tracking**: NI (p)	Papaveretum also tested: Saccadic eye movement, syntactic reasoning: I (p)
Richens 1983 (143)	Papaveretum 20 mg (im)	Not measured	Healthy volunteers n = 6 (m)	Rd Co	Placebo	1-3 h	**CFF**: NI (p) **CRT**: NI (p) **Running memory**: NI (p) **SacEM:** I (p) **Stroop colour word test**: NI (p) **Syntactic reasoning test**: I (p) **Tracking**: NI (p)	Meptazinol also tested: Saccadic eye movement, syntactic reasoning, stroop colour word test: I (p)
Rush 2001 (136)	Hydromorphone 1 mg (po) (LD) 2 mg (po) (HD)	Not measured	Healthy volunteers n = 9 6 (m) / 3 (f)	Placebo Db	Placebo Baseline	0,5-5 h	**Circular lights**: NI **DSST**: NI	Ethanol also tested: 0,5 and 1,0 g/ kg ethanol DSST, Circular lights: I Pre-treatment with hydromorphone before ethanol intake, no effect on psychomotor tests
Saarialho -Kere 1986 (106)	Codeine 100 mg (po)	C: 105 +/- 2 ng/ml T: 1.5 h	Healthy volunteers N=10 5 (m) / 5 (f)	Db Co	Placebo Baseline	1.5 h	**Body sway**: NI **CFF**: NI **DSST**: NI **MW**: NI **Nystagmus**: NI	Pentazocine also tested: NI all tests Interaction with diazepam tested after 1,5 h, impairment seen
Saarialho -Kere 1986 (106)	Pentazocine 75 mg (po)	C: 12 +/- 4 ng/ml T: 1.5 h	Healthy volunteers n = 10 5 (m) / 5 (f)	Db Co	Placebo Baseline	1.5 h	**Body sway**: NI **CFF**: NI **DSST**: NI **MW**: NI **Nystagmus**: NI	Codeine also tested: NI all tests Interaction with diazepam tested after 1.5 h, impairment seen

Saarialho-Kere 1988 (127)	Dextro-propoxyphene 130 mg (po)	Drug levels measured at baseline, 2 h and 4 h; no values reported	Patients (rheumatoid arthritis) n = 15 2 (m) / 14 (f)	Db Rd Co	Placebo Baseline	2-4 h	**Body balance**: I **CFF**: I **Divided attention**: I (p) **MW**: no result given **Symbol copying**: I **CRT:** NI **DSST**: NI **Tracking**: NI	DXP alone or in combination with amitriptylin or indomethacin tested All patients treated with paracetamol 3 days prior to testing DXT 65 mg given 1-2 days prior to testing with 130 mg. Drug level at baseline not zero
Saarialho-Kere 1988 (147)	Nalbuphine 0,5 mg haloperidol or placebo (po) 1 hour later: 0,15 mg kg^{-1} NLB or placebo (im)	1 hour: 35 ±2 ng/ml 2,5 h: 21±2 ng/ml 4 h: 14±2 ng/ml	Healthy volunteers n = 12 7 (m) / 5 (f)	Cross-over Db	Placebo Baseline	1-4 h	**Combined tracking and choice reaction test**: I (b) **CFF:** I (p) **DAT**: ? **DSST**: I (p+b) **MW**: I (p+b)	**Combined tracking and choice reaction test**: tracking error and tracking severity
Saarialho-Kere 1988 (152)	Pentazocine 30 mg (po) (40mg, >70kg po)	1.5 h: 86 ng/ml (HC) 3.5 h: 59 ng/ml (LC)	Healthy Volunteers n = 11 ? (m) / ? (f)	Db Rd Co	Placebo Baseline	1.5-3.5 h	**CFF:** NI (p) **DSST**: I (p) (HC:p/b) (LC:p) **Gaze nystagmus**: NI (p) **MW**: I (HC:p/b) (LC:b) **RT:** I (b) (HC) **Short memory**: NI (p) **Tapping task**: NI (p)	Amitriptyline was also studied.
Saarialho-Kere 1989 (149)	Oxycodone 0.13 mg/kg (iv)	Cmax: 22.0 +/- 105 ng/ml Tmax: 1.5 t	Healthy volunteers n = 9 6 (m) / 3 (f)	Db Co	Placebo Baseline	1.5-4.5 h	**Body balance**: I (p,b) **CFF**: I (p,b) **CRT**: I (p) **DAT**: I (p) **DSST**: results excluded **MW**: NI (p,b) **Tapping task**: NI (p) **Tracking**: NI (p)	Diphenhydramine (antihistamine) also tested
Scamman 1984 (90)	Alfentanil 7,5 μg/kg (iv) 15 μg/kg (iv)	Not measured	Volunteers n = 40 20 (m) / 20 (f) 8 per treatment group (4 m, 4 f)	Db Rd	Placebo Baseline	10-180 min	**Immediate free recall**: NI **Delayed free recall**: NI **Symbol cancellation**: NI **Tapping**: NI	Fentanyl also tested: 1,5 and 3 μg/kg Motor: I (p) (3)
Scamman 1984 (90)	Fentanyl 1,5 μg/kg (iv) (LD) 3 μg/kg (iv) (HD)	1.5 → 0,3 ng/ml	Volunteers n = 40 20 (m) / 20 (f) 8 per treatment group (4 m, 4 f)	Db Rd	Placebo Baseline	10-180 min	**Immediate and free recall**: NI **Tapping**: I (p) (HD) **Symbol cancellation**: NI **Delayed free recall**: NI	Alfentanil also tested: 7,5 and 15 μg/kg NI all tests Figure showing the plasma concentration-time for fentanyl 3 μg/l given; no Cmax/Tmax??
Schmid 1999 (63)	Ketamine LD: defined as: < 1 mg/kg (iv) <2 mg/kg (im) <20 mg/kg/min infused HD:	< 50 ng/ml ~ 200 ng/ml					LD: Several adverse effects reported as: Sedation, dizziness, drowsiness, but no impairment of cognitive functioning HD: Incidence of cognitive and memory impairment increases	**Review** paper (1966-1998)

Schneider 1999 (88)	Fentanyl 0.2 µg/kg (iv)	<u>15 min:</u> 1.91 ng/ml <u>30 min:</u> 0.67 ng/ml	Healthy Volunteers n = 12 (m)	Rd Co (No information about blinding)	Placebo	15 min	**DAT:** (binary-choice reaction) -time : NI (p) -hits : NI (p) **Vienna Reaction time** -visual: NI (p) -auditory: I (p) **Signal detection**: I (p) **Sustained attention**: I (p) **Memory** -delayed free recall: NI (p) -distracting list: I (p) -words: NI (p)	Alcohol was also tested The test sessions started 15 min after fentanyl injection
Silverstein 1960 (66)	LSD 2 µg/kg (p.o.)	Not measured	Volunteers n = 24 (m)	Co	Controls	90 min	Digit span: I (c)	
Smith 1962 (26)	Heroin 4 mg/70kg (sc)	Not measured	Nonaddict volunteers n = 24 (m)	Rd Co Db	Placebo	II: 75-240 min	<u>Study II –</u> **Coding**: I (p) **Colour-shape**: NI **Distributed numbers**: I (p) **Verbal facility**: NI **Written addition**: I (p)	Morphine also studied (study II)
Sold 1983 (92)	Fentanyl 0.15 mg/70 kg (iv)	Not measured	Volunteers n = 28 4 groups (n=7)	Db Rd	Placebo	Drug given during testing. Testing lasted 3 h	**Concentration**: I (b) **RT:** I (b) **Short term memory**: I (b) **Word recognition task**: NI (b)	Diazepam 10 mg/70 kg and flunitrazepam 1 mg/70 kg also tested Article in German
Stacher 1976 (156)	Pentazocine 50 mg (po) + 500 mg acetylsalicylic acid	Not measured	Healthy volunteers n = 10 5 (m) / 5 (f)	Db Co	Placebo Baseline	60-90 min	**Optical reaction time**: NI (p)	Pentazocine was not given alone, but in combination with acetylsalicylic acid.
Stacher 1982 (113)	Codeine 60 mg (po)	Not measured	n = 32 16 (m) / 16 (f)	Db Co	Placebo Baseline	30- 120 min	**Reaction time to acoustic stimuli**: NI	
Stacher 1982 (153)	Pentazocine 0,4 mg/kg/h	Not measured	Healthy volunteers n = 24 12 (m) / 12 (f)	Rd Db	Placebo Baseline	15-90 min	**CFF:** NI (p) **Psychomotor performance**: NI (p) **RT:** I (p)	?
Stacher 1986 (112)	Codeine 60 mg (po)	Not measured	Healthy volunteers n = 48 24 (m) / 24 (f)	Db Rd Co	Placebo Baseline	30-180 min	**ART:** I (p) **Tracking**: NI (p)	Diclofenac main drug. Codeine comparative drug.
Stacher 1987 (111)	Codeine 60 mg (po)	Not measured	Healthy volunteers n = 20 (m)	Db Rd Co	Placebo Baseline	30-360 min	**ART:** I (p) **Tracking** (fine motor control): NI (p)	5-hydroxytryptamine /noradrenaline uptake inhibitor Ro 15-8081 (antidepressant) main drug. Codeine comparative drug.
Stevenson 1986 (95)	Fentanyl 100 µg (iv)	Not measured	Volunteers n = 9 5 (m) / 4 (f)	Db Rd Co	Placebo Baseline	30-120 min	**Tracometer task** with 6 dependent measures (testing cognitive decisions): I (b,p)	Effects of fentanyl compared to diazepam (7,5 mg iv, tracometer → I (b,p)) I : F > D
Strain 1992 (237)	Hydromorphone 5 mg (im) LD 10 mg (im) HD	Not measured	Opioid-dependant volunteers n = 6 (m)	Rd Db Co	Placebo Baseline	60-120 min	**DSST**: NI **Recall (memory) test**: NI	Methadone maintained on 30 mg daily. Injections given 20 h after last dose of methadone. Buprenorphine and naloxone also tested

Strain 1993 (246)	Hydromorphone 5 mg (im) LD 10 mg (im) HD	Not measured	Opioid-dependant volunteers n = 5 (m)	Rd Db Co	Placebo Baseline	60-120 min	**DSST**: NI **Recall (memory) test**: NI	Methadone maintained on 30 mg daily. Injections given 20 h after last dose of methadone. Pentazocine and naloxone also tested
Strain 1993 (246)	Pentazocine 7.5 mg (im) 14 mg (im) 30 mg (im) 60 mg (im) 120 mg (im)	Not measured	Opioid-dependant volunteers n = 5 (m)	Rd Db Co	Placebo Baseline	60-120 min	**DSST**: NI **Recall (memory) test**: NI	Methadone maintained on 30 mg daily. Injections given 20 h after last dose of methadone. Hydromorphone and naloxone also tested
Strain 1995 (238)	Hydromorphone 5 mg (im) 10 mg (im)	Not measured	Opioid-dependent n = 7 (m)	Db Cross-over?	Placebo Baseline	60-120 min	**DSST**: NI **Recall (memory) task**: NI	Maintained on 30 mg methadone daily
Strain 1997 (239)	Hydromorphone 9 mg (im) (LD) 18 mg (im) (HD)	Not measured	Volunteers n = 8 5 (m) / 3 (f)	Db	Placebo Baseline	15-120 min	**DSST**: NI (p) **Recall (memory) task**: NI (p)	Opioid-dependent, maintained on buprenorphine 8 mg sl daily Buprenorphine also tested
Strain 2002 (247)	Hydromorphone 12 mg (im)	Not measured	Volunteers n = 6 5 (m) / 1 (f) Active opioid dependence Maintained on buprenorphine/naloxone or buprenorphine	Db	Placebo Baseline	15-180 min	**Circular lights task**: ? **DSST**: ? **Trail-making b test**: ?	Subjects maintained on different double-blind dose levels of buprenorphine/ naloxone (4/1,8/2,16/4,32/8 mg) and buprenorphine (32 mg) for 6 days periods and challenged with hydromorphone Time of testing till 25 hours?
Szekely 1986 (102)	Dihydrocodeine 20 mg (iv)	Not measured	Healthy Volunteers n = 8 8 (m)	Db Rd? Co	Placebo Baseline	30-180 min	**Digit forward/digit backward test**: Improvement (p) **Symbol cancellation test**: Improvement (p) **Word fluency test**: NI (p)	An overall improvement of performance was detected for symbol cancellation test and digit forward/digit backward test. Enkephalin analogues were also studied.
Tedeschi 1984 (144)	Meptazinol 200 mg x 4 (po) (3 h between doses)	Not measured	Healthy volunteers n = 8 (m)	Db Rd Co	Placebo	30 min – 45 min	**Peak saccadic velocity (PSV)**: NI (p) **Saccadic duration (SD)**: NI (p) **Smooth pursuit velocity (PSV)**: NI (p) **CFF**: NI (p) **CRT**: NI (p)	Ethanol as verum 0,8 g/kg affected PSV, SD, SPV Meptazinol: opiate antagonist?
Tedeschi 1986 (145)	Meptazinol 200 mg x 4 (po)	Not measured	Healthy Volunteers n = 12 ? (m) / ? (f)	Db Rd Co?	Placebo	1 h after the last dose	**PSV** (peak saccadic velocity): NI (p) **SD**: NI (p)	200 mg meptazinol were given at 08, 11, 14 and 17, making a total meptazinol dose of 800 mg. Amylobarbitone, diazepam, lorazepam, temazepam, nitrazepam, ethanol, and chlordiazepoxide were also studied.
Telekes 1987 (133)	Dipipanone 8 mg (po)	Not measured	Healthy volunteers n = 12 7 (m) / 5 (f)	Db Rd Balanced Co	Placebo Baseline	45-165 min	**RT:** I (p)	Subjects no history of drug abuse

Thapar 1995 (86)	Fentanyl 50µg/70 kg (iv)	Not measured	Healthy Volunteers n = 12 10 (m) / 1 (f)	Db Rd Co	Placebo Baseline	15-240 min DSST 5-240 min	**ART**: NI (p) **DSST**: NI (p) **EHC:** NI (p) **MW** (Maddox Wing test): NI (p) **Short term memory**: NI (p)	3 Subjects had a history of smoking marijuana Propofol, midazolam and alcohol were also studied.
Umbricht 2003 (79)	Psilocybin 280 µg/kg (po) (capsules)	Not measured	Volunteers n = 18 10 (m) / 8 (f)	Db Co	Placebo Baseline	60-90 min	**AX-type continuous performed task**: I (p) **Mismatch negativity**: NI (p)	ERP and EEG-recordings
Verster 2006 (151)	Oxycodone 5 mg (po) (LD) + 325 mg paracetamol 10 mg (po) (HD) + 650 mg paracetamol	Not measured	Healthy Volunteers n = 18 6 (m) / 12 (f)	Db Rd Co	Placebo	Driving test: 1 h Other tests: 2.5 h	**DAT:** NI (p) **Driving test** (SDLP,MLP,speed): NI (p) **Sternberg Memory Scan. test**: NI (p) **Tracking test**: NI (p)	Oxycodone given in combination with paracetamol
Veselis 1994 (91)	Fentanyl Continuous infusion targeting three different plasma conc. in succession	1 ng/ml (LC) (0,5-1.3) 1,5 ng/ml (MC) (1,5-2,3) 2,5 ng/ml (HC) (2,5-3,5)	Volunteers n = 9 5 (m) / 4 (f) 6 given fentanyl 3 given placebo	Rd	Placebo Baseline	0-6 h	**Auditory-Verbal Recall task** (AVLT): I (b) (HC) **Picture recall**: I (p) (MC/HC) Psychomotor performance: **CFFT**: I (b) (HC) **CRT**: I (b) (HC) **DSST**: I (b) (HC) **SN**: I (b) (HC)	Concluded that low plasma concentrations of fentanyl can be found in awake patients who have significantly impaired memory
Veselis 1997 (89)	Fentanyl ? (iv)	2.33 ng/ml	Healthy Volunteers F+O = 10 O = 8 P =15 ? (m) / ? (f)	Db Rd	Placebo Baseline Ondansetron (O)	End of study day	**Memory tests** -word recognition: NI (p) -picture recall: NI (p) -picture recognition: NI (p)	Participants receiving fentanyl also received ondansetron (O) (4 mg iv). Ondansetron is also given alone. 3 increasing concentrations followed by 2 decreasing concentrations were used. Words and pictures were presented at each target concentrations. Midazolam, propofol and thiopental were also studied.
Walker 1998 (103)	Codeine 60 mg (po) 120 mg (po)	Not measured	Healthy Volunteers n = 12 9 (m) / 3 (f)	Db Rd Co	Placebo Baseline	40-310 min Memory 100, 300 min	**ART:** NI (p) **DSST** (Digit symbol subst.tes) : NI (p) **EHC:** NI (p) **Logical reasoning test**: NI (p) **MW**: NI (p) **Memory test**: NI (p)	Subjects had some prior use of recreational drugs Morphine also tested: NI (p) all tests
Walker 1999 (14)	Hydromorphone 0,33 mg/ 70 kg (iv) (LD) 0,65 mg/ 70 kg (iv) (MD) 1,3 mg/ 70 kg (iv) (HD) per injection Cumulative doses: 0,33, 0,98, 2,28 mg/70 kg	Not measured	Volunteers n = 16 6 (f) 10 (m) No history of drug abuse	Rd Pc Db Co	Placebo Baseline	30-210 min	**ART:** NI (p) **DSST**: I (p) (after 3rd injection) **EHC**: I (p) (MD) **Logical-reasoning test**: NI (p) **MW**: I (p)	Morphine (M) and meperidine (MEP) also tested: M: MW, DSST: I (p) MEP: eye-hand, DSST: I (p)

Walker 1999 (14)	Meperidine 17,5 mg/ 70 kg (iv) 35 mg/ 70 kg (iv) 70 mg/ 70 kg (iv) Cumulative dose: 17,5, 52,5, 122,5 mg/70 kg	Not measured	Volunteers n = 16 6 (f) / 10 (m) No history of drug abuse	Rd Pc Db Co	Placebo Baseline	30-210 min	**ART:** NI (p) **DSST**: I (p) (after 3rd injection) **EHC**: I (p) **Logical-reasoning test**: NI (p) **Maddox wing**: NI (p)	Hydromorphone (HM) and morphine(M) also tested: HM: MW, eye-hand, DSST: I (p) M: MW, DSST: I (p)
Walker 2001 (98)	Butorphanol **Cumulative:** 0.5 mg/70 kg (iv) (LD) 1.5 mg/70 kg (iv) (MD) 3.5 mg /70 kg (iv) (HD)	Not measured	Healthy Volunteers 3 currently smoked marijuana. N = 15 10 (m) / 5 (f) Some prior use of recreational drugs	Db Rd Co	Placebo Baseline	30 min after each injection	**ART:** NI **DSST**: I (p) (dose rel) (MD/HD) **EHC**: I (p) **Logical reasoning**: I (p) **MW**: I (p)	Increasing doses of each drug were administered every hour. Nalbuphine, morphine and pentazocine also tested DSST: I (p) N+M (dose rel) MW: I (p) N Eye-hand: I (p) N Not indicated (except DSST) at which dose the difference was significant
Walker 2001 (98)	Nalbuphine **Cumulative:** 2.5 mg/70 kg (iv) (LD) 7.5 mg /70 kg (iv) (MD) 17.5 mg/70 kg (iv) (HD)	Not measured	cp. Ref. (98) above	Db Rd Co	Placebo Baseline	30 min after each injection	**ART:** NI **DSST**: I (p) (dose rel) (HD) **EHC**: I (p) **Logical reasoning**: NI (p) **MW**: I (p)	Increasing doses of each drug were administered every hour. Not indicated at which dose MW+eye-hand is significant. Morphine, butorphanol and pentazocine also tested DSST: I (p) B+M (dose rel) MW: I (p) B Eye-hand: I (p) B Logical reasoning: I (p) B
Walker 2001 (98)	Pentazocine **Cumulative:** 7.5 mg/70 kg (iv) 22.5 mg/70 kg (iv)	Not measured	cp. Ref. (98) above	Db Rd Co	Placebo Baseline	30 min after each injection	**ART:** NI **DSST**: NI (p) **EHC:** NI (p) **Logical reasoning**: NI (p) **MW**: NI (p)	Increasing doses of each drug were administered every hour. Pentazozine appeared to impair performance slightly on the DSST and Maddox Wing test. The last dose of pentazocine was omitted because of the risk of dysphoria and psychotomimesis. Nalbuphine, morphine and butorphanol also tested: DSST: I (p) N+B+M (dose rel) MW: I (p) N+B Eye-hand: I (p) N+B Logical reasoning: I (p) B
Webb 1998 (101)	Dihydrocodeine 90 mg (po)	Not measured	Healthy Volunteers n =12 10 (m) / 5 (f)	Db Rd Co	Placebo Baseline	1.25-5.75 h	**CFF:** NI (p) **CRT** (Choice reaction time): NI (p) **DSST** (Digit symbol subst. test): NI (p)	Lamotrigine and phenytoin were also studied.
Wikler 1965 (28)	LSD-25 1 µg/kg (p.o.) (LD) 2-3 µg/kg (p.o.) (HD)	Not measured	"Post addicts" n = 10	Co	Controls (healthy) Placebo	90 min	Auditory-manual reaction time: I (p) (LD/HD)	Morphine also tested: effects of 15 and 30 mg morphine similar effects on RT as 2-3 µg/kg LSD
Wittmann 2007 (74)	Psilocybin 115 µg/kg (po) (8.2 mg) (MD) 250 µg/kg (po) (17.6 mg) (HD)	Not measured	Healthy Volunteers n = 12 6 (m) / 6 (f)	Db Within-subject	Placebo Baseline	90-240 min	**Temporal reproduction**: (b) (P/MD/HD) **Sensorimotor synchronization**: I (b) (MD/HD) **Tapping Speed**: I (b) (HD) **Spatial span task**: ?	6 Subjects reported previous experience with psilocybin, 7 had used cannabis sporadically Also significant difference in the placebo condition for temporal reproduction.

Wolff 2006 (61)	Ketamine Sub-anaesthihetic doses						One-off use has lead to disrupted attentional performance on test of vigilance, recognition memory, verbal fluency, working memory and episodic memory, i.e. Concl: I	**Review** paper 2006
Zacny 1992 (87)	Fentanyl 0 µg /70 kg (iv) 25 µg /70 kg (iv) 50 µg /70 kg (iv) 100µg /70 kg (iv)	Not measured	Healthy Volunteers n = 13 10 (m) / 3 (f)	Db Rd Co	Placebo Baseline	15-180 min	**ART**: NI **EHC:** I (p) (50/100 µg) **MW** (Maddox wing test): NI	
Zacny 1992 (93)	Fentanyl 50 µ/ 70 kg (iv)	Not measured	Healthy volunteers n = 6 (m)	Db Rd Co	Placebo	15-180 min	**DSST**: NI (p) **EHC**: NI (p) **MW**: I (p)	Tested effect of fasting up to 24 h on responses to fentanyl (no effect)
Zacny 1992 (132)	Dezocine 2,5 mg/ 70 kg (iv) (LD) 5,0 mg/ 70 kg (iv) (MD) 10 mg/ 70 kg (iv) (HD)	Not measured	Healthy volunteers n = 10 6 (m) / 4 (f)	Placebo Db Rd Cross-over	Placebo Baseline	15-300 min	**DSST**: I (p) (HD) **EHC:** I (p) (MD/HD) **MW**: I (p) (LD)	
Zacny 1993 (140)	Meperidine 0.25 mg/kg (iv) 0.5 mg/kg (iv) 1.0 mg/kg (iv)	Not measured	Healthy Volunteers n = 10 9 (m) / 1 (f)	Db Rd Co	Placebo Baseline	15-300 min	**ART**: NI (p) **DSST** (Digit symbol subst. test): NI (p) **EHC:** I (p) not dose-related **MW**: NI (p)	Not indicated at which dose eye-hand coordination was significant
Zacn 1994 (15)	Butorphanol 0.5 mg/70kg (iv) (LD) 1.0 mg/70kg (iv) (MD) 2.0 mg/70kg (iv) (HD)	Not measured	Healthy volunteers n = 12 7 (m) / 5 (f)	Db Rd Co	Placebo Baseline	15-300 min	**ART**: NI (p) **DSST**: I (p) (dose rel) (MD) **EHC:** I (p) (dose rel) (HD) **Logical reasoning test**: NI (p) **MW**: I (p) (dose rel) (MD)	Morphine also tested: NI all tests Significance for individual LD/MD/HD not given
Zacny 1996 (97)	Butorphanol 1 mg (transnasal) 2 mg (transnasal)	Not measured	Healthy volunteers n = 10 7 (m) / 3 (f)	Prospective Latin-square Co / Db Triple-dummy design	Placebo Baseline	15-300 min	<u>Two cognitive tests</u>: **Backward digit span**: NI **Logical reasoning test**: NI <u>Psychomotor tests</u>: **MW**: I (b) (HD) **ART**: ? **EHC**: NI **DSST**: I (b) (HD)	Acetaminophen/codeine 600/60 mg also tested
Zacny 1997 (17)	Nalbuphine 2,5 mg/ 70kg (iv) (LD) 5 mg/ 70kg (iv) (MD) 10 mg/ 70kg (iv) (HD)	Not measured	Volunteers n = 16 12 (m) / 4 (f)	Rd Db Co Placebo	Placebo Baseline	15-300 min	**ART**: NI (p) **DSST**: I (p) (dose rel) (HD) **EHC:** I (p) (dose rel) **Logical reasoning test**: NI (p) **MW**: I (p) (dose rel) **Memory test**: NI (p)	Subjects no history of opiate dependency Morphine also tested: MW, DSST: I (p)
Zacny 1998 (18)	Pentazocine 7,5 mg/70 kg (iv) 15 mg/70 kg (iv) 30 mg/ 70 kg (iv)	Not measured	Healthy volunteers n = 16 8 (m) / 8 (f)	Rd Db Co Placebo	Placebo Baseline	15-300 min	**ART** ? **DSST**: I (p) (HD) **EHC:** I (females) (p) (HD) **Logical reasoning test**: I (p) (HD) **MW**: I (p) (dose rel) **Memory test**: I (p) (HD)	Subjects no history of opiate dependence DSST and logical reasoning test: Females performed better than men Morphine also tested MW, DSST: I (p)

Zacny 2003 (148)	Oxycodone 10 mg (po) 20 mg (po) 30 mg (po)	Not measured	Healthy Volunteers n = 18 9 (m) / 9 (f)	Db Rd Co	Placebo Baseline	60-300 min DSST 15-300 min Memory 90, 210 min	**ART**: NI (p) **DSST**: I (p) (20/30mg) (dose rel) **EHC**: I (p) (30mg) (dose rel) **Logical reasoning test**: I (p) (20/30mg) (dose rel) **Memory test**: NI (p)	Subjects had some prior use of recreational drugs Lorazepam was also studied.
Zacny 2004 (128)	Propoxyphene 50 mg (po) (LD) 100 mg (po) (MD) 200 mg (po) (HD)	Not measured	Volunteers n = 18	Co Rd Db	Placebo Baseline	30-300 min	**ART**: NI (p) **DSST**: NI (p) **EHC**: NI (p) **Logical reasoning test**: NI (p) **Recall memory test**: NI (p)	Morphine also tested DSST: I (p)
Zacny 2005 (137)	Hydrocodone 5 mg (po) (LD) + 500 mg acetaminophen 10 mg (po) (MD) + 500 mg acetaminophen 20 mg (po) (HD) + 1000 mg acetaminophen	Not measured	Healthy Volunteers Some prior use of recreational drug. n = 18 9 (m) / 9 (f)	Db Rd Co	Placebo Baseline Acetamino fen	60-300 min 15-300 min 90, 210 min	**ART**: NI (p) **DSST**: I (p) (HD) **EHC**: I (p) (HD) **Logical reasoning test**: I (p) (HD) **Memory test**: NI (p)	Participants receiving hydrocodone also received acetaminophen. Acetaminophen is also given alone (1000 mg). Morphine also tested: Logical reasoning test, auditory reaction time test: I (p)
Zacny 2005 (53)	Tramadol 50 mg (po) 100 mg (po)	Not measured	Healthy volunteers n = 22 13 (m) / 9 (f)	Db Rd Co	Placebo Baseline	Periodic intervals	**EHC**: NI (p) **DSST**: NI (p) **ART**: NI (p) **Logical reasoning test**: NI (p) **Recall memory test**: NI (p)	Subjects had recreational drug use. Lorazepam was also studied.

10.6 Appendix 6: Evidence table for morphine

Ref.	Drug Dose (adminis-tration)	Measured Cmax/ Tmax	Persons -Number (n) -Sex (m/f)	Type study Db / Rd Co / Pc	Control Placebo Baseline	Time of testing (after given drug)	Tests (effect) Impaired I/ Not Impaired NI Placebo (p) / Baseline (b) Low/medium/high dose (LD/MD/HD)	Comments Other drugs Improved performance
Bauer 1956 (19)	8 mg Injection	Not measured	Volunteers n = 96 (m)	Rd	Placebo Baseline (learning)	15-240 min	**Perceptual-motor task**: NI (p)	Also: 8 mg in combination with Nalorphine: 1/2/4 mg I (p)
Belleville 1957 (20)	15 mg (im)	Not measured	Volunteers n = 182 Former morphine addicts	Blinded	Control – No drug	50- min	**SRT**: I (control)	Incentive ?
Bourke 1984 (21)	0,21 mg/kg (iv)	Not measured	Healthy volunteers n = 6	Db Rd Co	Placebo	2-4 h	**Continuous performance test**: NI (p) **Trieger-Dot Test** (TDT): NI (p)	Diazepam was also tested CPT I (p), TDT NI (p)
Coda 1993 (10)	142 mcg/kg (iv)	Steady state concentrations of 20, 40 and 80 ng/ml	Healthy volunteers n = 15 (m)	Db Co	Placebo Baseline	At steady state	**Cognitive variable** (reading speed): I (b) (HC) **Complex motor performance** (force): I (b) (HC) **Simple motor performance** (tapping): NI (b)	Alfentanil also tested: Complex motor performance, cognitive variable: I (b)
Conley 1997 (8)	10 mg/ 70 kg (iv)	Not measured	Healthy volunteers n = 13 12 (m) / 1 (f)	Rd Pc Db Co	Placebo Baseline	15-300 min	**DSST**: NI (p)	Subjects: Some prior use recreational drugs No past history indicative of dependency Periodic forearm immersions into ice-cold water (2°C) or into warm water (37°C), while receiving saline, butorphanol or morphine Butorphanol: NI (p)
Evans 1964 (22)	16 mg (po)	Not measured	Healthy fasting volunteers n = 60 (m, f) 15 per group	-	Placebo		**Logical reasoning**: I (p) **Perceptual speed**: I (p)	Amphetamine used as comparator Improvement by morphine in tests based upon logical reasoning
Foltin 1992 (5)	5 mg/70 kg (iv) 10 mg/70 kg (iv)	Cmax: ? ng/ml (only figure) Tmax: 30 min	Opioid and cocaine dependant volunteers n = 9 9 (m)	Co	Placebo Baseline	34-70 min	**Serial acquisition task**: NI (p)	Tested alone and in combinations with cocaine ("speedballs")
Greenwald 1998 (193)	15 mg/ 70 kg (im) 30 mg/ 70 kg (im)	Not measured	Volunteers n = 6 (m) Non-dependent heroin-users	Db Placebo Co	Placebo Baseline	0,5-5 h	**Psychomotor balance**: NI (p)	Subjects: Current sporadic use of drugs Butorphanol also tested: NI (p)

Hanks 1995 (23)	10 mg (po) LD 15 mg (po) HD	Not measured	Healthy volunteers n = 12 m (8) / f (4)	Db Rd Co	Placebo Baseline	1-6 h	**CFF:** I (p) LD/HD **CRT** (Choice reaction test): I (p) HD **Delayed word recall**: I (p) LD/HD **Delayed word recognition**: NI (p) **Digit vigilance task**: I (p) HD **Memory scanning task**: NI (p) **Immediate word recall**: I (p) LD **Picture recognition task**: I (p) LD/HD **SRT**: NI (p)	Lorazepam was also tested
Higgins 1992 (195)	4 mg/ 70kg (im) (LD) 8 mg/ 70 kg (im) (MD) 16 mg / 70 kg (im) (HD)	Not measured	Post addict, current sporadic users n = 5 (m)	Db Rd Co	Placebo	45-90 min	**DSST**: NI (p)	Naloxone given after morphine resulted in withdrawal reactions
Hill 1955 (196)	15 mg (im)	Not measured	Prisoner patients?? Former addicts n = 72 (m) 6 groups, n = 12	?	Placebo Baseline (reward)	50 min	**RT**: I (p) – significant?	Pentobarbital also tested. For 3 groups drug/placebo + shock was given
Hill 2000 (135)	5 mg / 70 kg (iv) 10 mg / 70 kg (iv)	Not measured	Healthy volunteers n = 17 12 (m) / 5 (f)	Rd Db Incomplete Latin square Co design	Placebo Baseline	15-300 min	**ART**: NI (p) **DSST**: NI (p) **EHC:** NI (p) **Immediate + delayed free recall**: NI (p) **Logical reasoning ability**: NI (p) **MW**: NI (p)	Subjects: Some prior use recreational drugs; no histories indicative of dependence
Jarvik 1981 (169)	10 mg/ 70 kg (im)	Not measured	Healthy men n = 20 (10 monozygotic twins) No chronic drug abuse	Pc	Placebo Baseline	150-325 min	**DSS**: NI (p) **Tapping speed**: I (p)	DSS: faster (significant)
Kerr 1991 (11)	142 mcg/kg (iv)	Steady state concentrations of 20, 40 and 80 ng/ml	Healthy volunteers n = 15 (m)	Rd Co	Placebo	0-1 h	**Isometric force**: I (p) (HC) **Tapping**: I (p) (HC) **Visual perception**: NI (p) **RSVP** (rapid single visual presentation): I (p) (MC + HC)	Subjects: No history of drug use No current medication
Lamas 1994 (192)	20 mg (im) 40 mg (im) 60 mg (im)	Not measured	Opioid dependent volunteers n = 6 (m)	Db Rd	Placebo Baseline	20-240 min	**MW**: NI (p)	All Subjects had previous experience with drugs. Methadone maintained (30 mg/24 h). Drugs administered 20 h after last doe of methadone. Naloxone and pentazocine also tested: NI (p)
Lorenz 1997 (178)	30 mg-150 mg (po)	Not measured	Non-malignant pain patients stabilized on sustained-release morphine for at least 3 days n = 6		Baseline		**Auditory oddball task**: -Reaction time NI (b) -Errors ?	Some occasional administration of tramadol or tilidin, but no history of regular use of opioids) **Chronic use**
Macht 1917 (24)	4-6 mg (LD) 8-15 mg (HD) (sc/ im)	Not measured	Volunteers n = 12			2-4 h	**Multiplication and addition**: NI (LD/HD) **RT**: LD : NI (→ I) / HD : I (b)	Some improvement of reaction times initially at low doses Some improvement in mathematical tests

Marsch 2001 (166)	5 mg/70 kg (iv) (LD) 10 mg/70 kg (iv) (HD) 2 min bolus (iv) 15 min (iv) 60 min (iv)	Cmax (5 mg): ~ 45 nmol/L Cmax (10 mg): ~ 90 nmol/L	Healthy subjects n = 18 (m) Opioid naïve or some experience No drug history past or current	Pc Rd Db (triple)	Placebo Baseline	15-60 min: During drug infusion 15-120 min: After drug infusion	**DSST**: I (p) (HD)	Infusion rate: no effect Measured M6G and M3G
Naef 2003 (254)	30 mg (po)	Time (hours) after adm: plasma conc (ng/ml) 0,5: 4,5 1: 10 2: 6 4: 1,5 8: 0	Healthy volunteers n = 12 6 (m) / 6 (f) No drug abuse past or present	Rd Pc Db Co	Placebo Baseline	30 min-8 hours	**RT:** NI (b)	THC also tested: NI
O'Neill 2000 (126)	10 mg (po)	Not measured	Healthy n = 10 4 (m) / 6 (f) No history of drug abuse	Rd Db 4-way Co	Placebo Baseline	4-36 h	**CRT**: NI **CFFT**: NI **Memory scanning:** I **Number vigilance**: NI **Picture recognition**: NI **SRT:** I **Word recall** (immediate/ delayed): NI **Word recognition:**	CRT: Improved performance (significant) Dextropropoxyphene also tested: picture recognition: I
Petry 1998 (13)	10 mg (po) 30 mg (po) 56 mg (po) 100 mg (po)	Not measured	Healthy volunteers n = 9 (m)	Pc Db	Placebo Baseline	30-240 min	**DSST**: I (p) (dose effect)	Subjects= Occasional drug users; no history of drug dependence
Preston 1987 (194)	7.5 mg (im) 15 mg (im) 30 mg (im)	Not measured	Post addict volunteers n = 15 (m)	Db Rd	Placebo Baseline	60-240 min	**CRT**: NI (p) **DSST**: NI (p) **EHC** (saccadic): NI (p) **Memory task**: I (p) (dose related)	Pentazocine and ciramadol (?) also tested Pentazocine: DSST: I (p) (dose rel)
Quante 2004 (6)	10 mg (iv)	C max: 50 +/- 3.7 ng/ml T max: 15 min	Healthy volunteers n = 7 (7)	Blinded	Placebo Baseline	40 min – 3 h	Vigilance/sedation – **ART**: NI (p) **Mood scale**: NI (p)	Pain induced during experiment in blocks between vigilance testing M6G and M3G measured
Saddler 1985 (25)	Bolus of 0,2 mg/kg (iv) over 20 min followed by infusion of 0,004 mg/kg per min.	Not measured	Healthy volunteers n = 8 (m)	Db Rd Co	Baseline	15 min after start of steady state infusion	**Motor skills** (tracking): NI (b) **RT**: NI (b) **Short-term memory**: NI (b)	Ethanol was also tested: I (p) Dose ethanol: loading dose 0,75 ml/kg with infusion of 0,0025 ml/kg per min
Smith 1962 (26)	10 mg/70kg (sc)	Not measured	Non addict volunteers n = 24+24 (I+II) 48 (m)	Rd Co Db	Placebo	I: 40-440 min II: 75-240 min	<u>Study I -</u> **Analogies**: NI / **Attention**: I (p) **Coding**: I (p) / **Color-shape**: NI **Copying**: NI / **Distributed numbers**: NI **Hidden figures**: NI / **Name-face**: NI **Oral addition**: I (p) <u>Study II –</u> **Coding**: I (p) / **Color-shape**: NI **Distributed numbers**: NI **Verbal facility**: NI **/ Written addition**: I (p)	Morphine alone (study I) or morphine and heroin (study II) tested

Torda 1980 (27)	3 mg (extradural) (LD) 4 mg (extradural) (HD) 10 mg (im) (LD) 15 mg (im) (HD)	Not measured	Healthy volunteers n = 5 4 (m) / 1 (f)	Co	Baseline Morphine i.m.	60 min	**Memory**: I (im, LD/HD) (b) **EHC**: NI (b) **Walking**: NI (b)	Number of errors in the memory task was increased significantly by i.m. morphine
Walker 1998 (103)	20 mg (po) 40 mg (po)	Not measured	Healthy Volunteers n = 12 9 (m) 3 (f) Some prior use of recreational drugs	Db Rd Co	Placebo Baseline	40-310 min Memory 100, 300 min	**ART**: NI (p) **DSST** (Digit symbol subst.tes) : NI (p) **EHC:** NI (p) **Logical reasoning test**: NI (p) **MW**: NI (p) **Memory test**: NI (p)	Codeine also tested: NI (p) all tests
Walker 1999 (14)	2,5 mg/70 kg (iv) 5 mg/70 kg (iv) 10 mg/ 70 kg (iv) (results in cumulative doses 2,5 (LD), 7,5 (MD) and 17,5 (HD) mg/70 kg)	Not measured	Volunteers n = 16 6 (f) 10 (m) Current prescribed opioids (n=6) Some prior use of drugs	Rd Pc Db Co	Placebo Baseline	30-210 min	**ART**: NI (p) **DSST**: I (p) (HD) **EHC**: NI (p) **Logical-reasoning test**: NI (p) **MW**: I (p) (dose rel)	Hydromorphone (HM) and meperidine MEP) also tested: HM: MW, eye-hand, DSST: I (p) MEP: eye-hand, DSST: I (p)
Walker 2001 (98)	Cumulative: 2.5 mg/70 kg (iv) (LD) 7.5 mg /70 kg (iv) (MD) 17.5mg/70 kg (iv) (HD)	Not measured	Healthy Volunteers 3 currently smoked marijuana. N = 15 10 (m) / 5 (f)	Db Rd Co	Placebo Baseline	30 min after each injection	**ART**: NI **DSST:** I (p) (dose rel/HD) **EHC**: NI (p) **Logical reasoning**: NI (p) **MW**: NI (p)	Subjects: Some prior use of recreational drugs Increasing doses of each drug were administered every hour. Nalbuphine, butorphanol and pentazocine also tested DSST: I (p) N+B(dose rel) MW: I (p) N+B Eye-hand: I (p) N+B Logical reasoning: I (p) B
Westerling 1993 (7)	10 mg (iv) 20 mg (po) 30 mg (po) (controlled release)	Ca. 400-500 nmol/L 54,7 nmol/L 15.6 nmol/L	Healthy volunteers n = 10 6 (m) / 4 (f)	Open labeled Rd Co	Baseline	10 min -6 h 20 min-6 h 30 min-12 h	**CRT (Continuous reaction time)**: I (b) **CRT**: I (b) **CRT**: I (b)	
Wikler 1965 (28)	15 mg (im) 30 mg (im)	Not measured	"Post addicts" n = 10	Pc	Placebo	60 min	**Auditory manual RT**: I (?)	? Chronic schizophrenic n = 13 Control group n = 10
Zacny 1994 (15)	10 mg/70kg (iv)	Not measured	Healthy volunteers n = 12 7 (m) / 5 (f)	Db Rd Co	Placebo Baseline	15-300 min	**ART** (auditory reaction time): NI (p) **DSST**: NI (p) **EHC:** NI (p) **Logical reasoning test**: NI (p) **MW**: NI (p)	Subjects: Opioids as pain relief in past (n=8); No history of drug dependency Butorphanol also tested: MW, DSST, eye-hand: I (p)
Zacny 1994 (16)	2.5 mg/70 kg (iv) (LD) 5.0 mg/70 kg (iv) (MD) 10 mg/70kg (iv) (HD)	Not measured	Healthy volunteers n = 12 10 (m) / 2 (f)	Db Rd Co	Placebo Baseline	15-300 min	**ART**: I (dose dependant/HD) **DSST**: I (dose dependant/HD) **EHC**: NI **MW**: I (dose-dependant/MD+HD)	Subjects: Opioids as pain relief in past (n=2); No history of drug dependency Peak impairment 2 h after injection.

Zacny 1997 (167)	10 mg/70 kg (iv)	Not measured	n = 16 No history of opiate dependence	Rd Pc Db Co	Placebo Baseline	15-300 min	**ART** (s): NI (p) **DSST** (n completed + n correct): NI (p) **EHC**: NI (p) **Logical reasoning** (n correct): NI (p) **MW**: I (p)	Subjects: Some prior use of recreational drugs Buprenorphine also tested: MW, eye-hand coordination, DSST, auditory reaction time, logical reasoning: I (p)
Zacny 1997 (17)	10 mg/ 70 kg (iv)	Not measured	Volunteers n = 16 12 (m) 4 (f) No history of opiate dependency Some current and prior use of drugs	Rd Db Co Placebo	Placebo Baseline	15-300 min	**ART**: ? **DSST**: I (p) **EHC**: NI (p) **Logical reasoning test**: ? **MW**: I (p) **Memory test**: ?	Nalbuphine also tested: MW, eye-hand, DSST: I (p)
Zacny 1998 (18)	10 mg/ 70 kg (iv)	Not measured	Healthy volunteers n = 16 8 (m) / 8 (f)	Rd Db Co Placebo	Placebo Baseline	15-300 min	**ART: ?** **DSST**: I (p) **EHC**: NI (p) **Logical reasoning test**: NI (p) **MW**: I (p) **Memory test**: NI (p)	Subjects: No history of opiate dependence DSST and logical reasoning test: Females performed better than men Pentazocine also tested MW, eye-hand coordination, DSST, logical reasoning test: I (p)
Zacny 2003 (168)	40 mg (po)	Not measured	Healthy Volunteers n = 18 9 (m) / 9 (f)	Db Rd Co	Placebo Baseline	60-300 min DSST 15-300 min Memory 90, 210 min	**ART**: NI (p) **DSST** (Digit symbol subst.test): NI (p) **EHC**: NI (p) **Logical reasoning test**: I (p) **Memory test**: NI (p)	Subjects: Some prior use of recreational drugs Hydrocodone/homatropine (combination product) and lorazepam were also studied.
Zacny 2003 (148)	40 mg (po)	Not measured	Healthy Volunteers n = 18 9 (m) / 9 (f)	Db Rd Co	Placebo Baseline	60-300 min DSST 15-300 min Memory 90, 210 min	**ART:** NI (p) **DSST:** NI (p) **EHC**: NI (p) **Logical reasoning test**: NI (p) **Memory test**: NI (p)	Subjects: Some prior use of drugs Lorazepam was also studied.
Zacny 2004 (128)	40 mg (po)	Not measured	Volunteers n = 18	Co Rd Db	Placebo Baseline	30-300 min	**ART**: NI (p) **DSST**: I (p) **EHC**: NI (p) **Logical reasoning test**: NI (p) **Recall memory test**: NI (p)	Subjcets: Recreational use of drugs, inclusive opioids Propoxyphene also tested NI all tests
Zacny 2005 (53)	25 mg (po) 40 mg (po)	Not measured	Healthy volunteers n = 22 13 (m) / 9 (f)	Db Rd Co	Placebo Baseline	Periodic intervals	**ART**: NI (p) **DSST**: NI (p) **EHC**: NI (p) **Logical reasoning test**: NI (p) **Recall memory test**: NI (p)	Subjects: Recreational drug use Lorazepam was also studied.
Zacny 2005 (137)	40 mg (po)	Not measured	Healthy Volunteers n = 18 9 (m) / 9 (f)	Db Rd Co	Placebo Baseline Acetaminofen	60-300 min 15-300 min 90, 210 min	**ART**: I (p) **DSST**: NI (p) **EHC**: NI (p) **Logical reasoning test**: I (p) **Memory test**: NI (p)	Subjects: Recreational drug use Participants receiving hydrocodone also received acetaminophen. Acetaminophen is also given alone (1000 mg). Hydrocodone also tested: DSST, logical reasoning, eye-hand: I (p)

10.7 Appendix 7: Evidence table for methadone and buprenorphine

Besides Walsh 1994 (Ref: 231) in no publication the Concentration was measured, therefore this column was skipped.

Concentration Methadone in Walsh:

Dose:	Tmax 90-120 min Cmax plasma
15 mg (po)	100 ng/ml
30 mg (po)	225 ng/ml
45 mg (po)	325 ng/ml
60 mg (po)	475 ng/ml
(Increasing dose?)	

Autor **Year** **(Ref.)**	**Dose** Range Administration Duration of treatment	Persons - Number (n) - Sex (m/f) - Pain patients - Maintenance	**Type study** **Db / Rd** **Co / Pc**	**Control** **Baseline,** **control healthy volunteers,** **control others,** **control current drug abuse**	**Time of testing** **(related to daily dose)**	**Tests (effect)** Impaired I/ Not Impaired **NI** Placebo **(p)** Baseline **(b)** Control **(c)** impaired effects/total effects **(Σ)**	**Control for other drugs Y/N**	**Comments** **Other drugs** **Improved performance**
Appel 1976 (198)	Methadone 80-120 mg > 11 months (11 months-8 years, mean 2.55 years)	Methadone patients - working (MW) - non-working (MNW) Former heroin addicts (DF) Working, non dependent (ND) n = 24 in all groups		No history of dependence		**DSST** x 2 MNW < ND MW = ND Σ: 1/2 (0,5)	Y (drug positives excluded)	No detoriation of with increasing duration of methadone treatment
Appel 1982 (199)	Methadone 70-120 mg	Methadone patients - working (MW) - non-working (MNW) Former heroin addicts (DF) Working, non dependent (ND) n = 24 in all groups		No history of dependence		**Continuous performance tests:** MNW: I Σ: 1/4 (0,25)	Y (excluded drug users)	
Baewert 2007 (200)	Methadone Mean 52.7 mg (21-80 mg) Buprenorphine Mean: 13.4 ± 4.3 mg	n = 40 (20 methadone, 20 buprenorphine)		Matched controls	1.5 (peak) and 20 h (trough)	**ART 2020 (7 traffic psychology tests)** Σ (methadone + buprenorphine vs controls: 3/7 (0.43)	Y	Methadone patients performed worse than buprenorphine patients in 4 of 7 tests

Curran 2001 (225)	Randomly allocated to one of two groups who received either 100% or 0% of their daily dose in the morning, or 50% or 0% of their daily dose in the morning. (po)	Opiate-dependent patients stabilized on methadone n = 20 m = 16 f = 4 40% had psychiatric history and 2 used antidepressant, 9 were co-dependent on benzodiazepines, also additional self-reported drug-use.	Db Co Rd	The other groups (see dose)	Testing before and after morning dose.	**Immediate recall**: **Delayed recall**: **Digit cancellation test**: **DSST**: **Finger tapping speed**: **SRT**: See comments		Scores were significantly better when participants received placebo first than when they received a dose of methadone first on immediate recall. Delayed recall was significantly impaired by 100% methadone. No significant treatment effects on DSST. Reaction times were slightly faster after both the 50% and 100% methadone. No significant effect on digit cancellation tests or finger tapping speed.
Darke 2000 (201)	Methadone Mean dose: 78.6 mg (15-200 mg) Mean duration of treatment: 60 months (5-192 months)	Methadone maintained patients n = 30 Matched controls n = 30		30 controls matched for age, gender and education		**Info processing, attention, short-term visual and verbal memory, long-term visual and verbal memory, problem solving** Σ: 7/7 (1.0)	Y Excluded intoxicated subjects (clinical examination)	
Davis 2002 (46)	Methadone Mean 32.5 mg (15 – 60 mg) 30 weeks	n = 15 from meth program n = 16 ex-opiate users, drug free 1.5-12 months n = 14 Pain patients		Methadone pat compared to ex-users and controls(pain pat)		**Battery of 12 measures of cognitive function:** **Most tests:** NI **Word fluency:** I (vs both other groups) Σ: 1/12 (0.08)		Analysis of impaired numbers per group: Meth: 9/15; I Ex.op: 5/16 : I Pain : 1/14
Dittert 1999 (202)	Methadone 7 ml (~70 mg?)	Methadone maintained patients n = 28 (5 HIV positive)		Non users		**ART-90** Σ: 6/7 (0.86)		- No correlation between test results and patients age or dose - Large inter-individual differences - HIV± no difference
Ershe 2006 (203)	Methadone Mean dose: 39.4 mg (20-80 mg)	Methadone n = 9 Heroin n = 6 Control n = 15	3 parallel groups	Control group of healthy volunteers	?	**Cambridge risk task**: NI (c) Σ: 0/1 (0)	Y Side abuse reported (cannabis, amf, cocaine, benzos)	Heroin users also tested.
Fredheim 2006 (222)	Methadone 10 – 100 mg - > 9 months	n = 7 (5m,2f) switched from slow-release morphine, mean dose 202mg(50-800mg)>1 year to Methadone		Baseline , immediately after the switch, and after 3 months on Methadone		**Selective attention (Stroop**): no improvement = I (?) **Working memory (PASAT, Number – Letter span**: no improvement=I(?)		
Gordon 1970 (204)	Methadone 100 mg	n = 27		Non drug users and users recently withdrawn from narcotic drugs		**SRT, MSMRT, MSSRT** Σ: 0/3 (0.0)		Methadone maintained patients performed <u>better</u> in the SRT

Grevert 1977 (205)	Methadone 52 mg (20-80 mg) LAAM: 54 mg (3 x week)	n = 30 (methadone) n = 31 (LAAM)		Matched non-opiate users	Tested after 1 and 3 months	**Memory/learning** n ~ 4 Σ: 1/4 (0.25) (at three months)		LAAM: levo-alpha-acetylmethadol
Gritz 1975 (206)	Methadone 65 mg/day (35-85 mg) ~ 5 months	n = 10		- Abstinent ex addicts n = 10 (- Normal subjects)		**Hidden word, story recall, total learning, Wechsler pair total, Wechsler pair average hard** Σ: 5/5 (1.0)	Y (one urine positive in the control group)	
Gruber 2006 (223)	Methadone Mean dose met: 68 mg/kg	n = 17	-	Baseline (opioid dependant)	After 2 mo of MM treatment	**Verbal learning test (RAVLT):** NI **Complex figure test (Rey-O):** NI **DSST:** NI **Oral word association test (FAS):** NI **Trail-making tests A+B:** NI **Stroop color-.word test:** NI		Improvement from baseline seen for RAVLT, Rey-O, DSST,
Hauri-Bionda 1998 (45)	Methadone Up to 60 mg/day	n = 34		Matched normal population n = 34		**10 different psychomotor/cognitive tests, 17 tests** Σ: 16/17 (0.94) (methadone vs control) Σ: 16/17 (0.94) (for n = 12, drug free subjects)	Y Positive findings in approx. 2/3 Totally drug free 1/3, n = 12	
Hornung 1995 (47)	Levomethadone Median 45 mg (10-60 mg) 19 months	n = 20 (11m,9f) from meth program n = 20 matched controls		Methadone pat compared to controls	2-4 h after last meth dose	**Battery of 13 performance areas: 10 tests:** NI **3 tests including reaction time:** I Σ: 3/10 (0.3)	Y	18 of 20 meth pat used other psychotropic substances
Jensen 2008 (175)	Buprenorphine 0.16 mg	n = 23		Drug naïve controls	0, 20, 60, 105, 150, 210 and 480 min after infusion	**Trail-making test:** I (c) **Finger-tapping test:** I (c) **Continuous reaction time:** I (c) Σ: 3/3 (1)	N	
Kagerer 2002 (233)	Buprenorphine 5.8mg (0.2-16 mg) 3 months	n = 27 (17m,10f) form bup program n = 28 (17m,11f) from Meth program(=ref 360)		Bup group compared to meth group		Battery of several psychomotor tests: In 3 of 5 tests Bup scored better than Meth, Other tests: Bup=Meth		Data suggest better psychomotor functioning after B than M Bup maintenance does not seem to impair driving fitness in general Methadone also tested
Kubitzki 1997 (207)	Methadone Mean: 77 mg (14-120 mg) 1-5 years	n = 22 (16m/ 6f)		22 matched non addicts		**Driving in closed area:** similar performance in both groups except parking Σ: 1/10 (0.1)	Y Drug screening, users excluded	
Lenné 2003 (43)	Methadone Mean dose: 48.1 mg After stabilized on maintenance treatment 3 months	Met n = 10 (67% m) LAAM n = 13 (48% m) Bup n = 11 (73% m) Control n = 21 (41% m)	4 parallel groups	Control group of healthy volunteers	4 hours after last dose	**Driving simulator**: NI I Σ: 0/4 (0)	N	Bup and LAAM also tested. Met alone or in combination with alcohol Alcohol impaired driving performance in all combinations

Lenné 2003 (43)	Buprenorphine Mean dose: 14.4 mg After stabilized on maintenance treatment 3 months	Met n = 10 (67% m) LAAM n = 13 (48% m) Bup n = 11 (73% m) Control n = 21 (41% m)	4 parallel groups	Control group of healthy volunteers		**Driving simulator**: NI I		Methadone and LAAM also tested. Bup alone or in combination with alcohol Alcohol impaired driving performance in all combinations
Loeber 2008 (228)	Methadone Mean 74.3 mg/day Buprenorphine Mean 9.4 mg/day ≥ 14 days of treatment	n = 56 methadone n = 30 buprenorphine n = 26		Methadone vs buprenorphine	After daily dose	**Vigilance and sustained attention, selecting and focusing on sensory stimuli, response selection and control, memory (totally 15 tests):** No difference between methadone and buprenorphine patients in all measures	Y Substance consumption controlled by urine tests and breathe analysis	
Lyvers 2003 (229)	Methadone 66.9 mg (mean) (po)	Patients stabilized on a daily dose of 25 mg or more of methadone. n = 39 m =18 f = 21 Asked to refrain from alcohol and any other psychoactive drugs for 24 h prior to the experimental session.	Rd to group 1 or 2	Comparison to the other group	Group 1: (n =21) tested 90 min after the last methadone dose. Group 2: (n=18) tested 24 h after the last methadone dose.	**WCST:** see comments		Subjects: Screened by interview and excluded if average alcohol consumption exceeding 14 drinks per week, recent or continuing administration of any neurologically active drugs other than methadone, prior history of treatment/arrest for alcohol or nonopioid illicit drug-related problems. Methadone patients in group 2 scored significantly higher on perseverative responses and errors than did group 1.
MacDonald 1989 (176)	Buprenorphine 0,3 mg (im)	Healthy volunteers n = 12 (m)	Db Rd Co	Placebo Baseline	1,5-8 h	**CRT** (choice reaction time): I (p) **Driving skills**: I (p) **CFF:** I (p) **DS** (digit span): NI (p) **CTA** (computer. Test of attention): I (p) **WDSS** (Wesch. Dig. Symb. Sub.): I (p) **Ataxia**: I (p)		Ketorolac and diclofenac were also tested.
Manner 1987 (96)	Buprenorphine 7.5 µg/kg (iv) (~ 5 mg)	Healthy Volunteers n = 7 3 (m) / 4 (f)	Db Rd Co	Placebo Baseline	5-180 min	**Maddox wing**: I (p) **CFF:** I (p) ?		Fentanyl also tested: I (p) (?) all tests When the data were evaluated statistically by analysis of variance for repeated measurements, a marked interaction in most variables became evident, thus preventing conclusions about the magnitude of the drug effects.
Marsch 2005 (240)	Buprenorphine Daily adm. 6-8 mg Sublingual	n = 36 (some dropout) 18 (m) / 18 (f) Adolescents (13-18 y) Maintenance	Parallel groups Db	Placebo (+clonidine) Baseline	1 hour post dose	**DSST**: NI (b + clonidine)		Clonodine also tested. Some side abuse, only opioids reported (36%)

Messinis 2009 (232)	Buprenorphine 6.78 mg/day	n = 18 (83.3 % male)		- Controls (c) (n = 34) - Abstinent heroin abusers (HA) (n = 32)		**Verbal fluency:** NI (c) **Verbal learning:** I (c) **Visual learning:** I (c) **Psychomotor speed:** I (c) **Executive functioning:** I (c) **Selective-sustained attention:** NI (c) Σ: 4/6 (0.67)	Y Urine screening as part of program requirements, no illicit substances used	No sign. difference between buprenorphine patients and abstinent heroin abusers in any cognitive measure, no significant difference HA/c
Mintzer 2002 (208)	Methadone Mean 67.2 mg (po)	Methadone maintenance patients n =18 7 (m) / 11 (f)		Control group n = 21 10 (m) / 11 (f)		**DSST:** I (c) **Trail making:** I (c) **Time estimation:** NI (c) **Two-back task:** I (c) **Word recog. memory/free recall:** NI (c) **Gambling task (decision- making:** I (c) **Stroop color-word paradigm (selective attention):** NI Σ: 10/21 (0.48)	Y - Methadone patients: Excluded if positive urine test for benzodiazepines or breathanalyzer positive for alcohol, abstain from heroin or cocaine for 24 hour prior to the testing. - Control group: Excluded if urine test positive for benzo, opiates, methadone, cocaine or breathanalyzer test positive for alcohol.	
Mintzer 2005 (209)	Methadone	Methadone n = 18 Former opioid n = 20 Controls n = 21	3 parallel groups	Non-drug abusing controls + Abstinent former opioid abusers		**DSST:** I (c) **Trail-making A+B:** I (c) **Two-back task:** I (c) **Recognition memory:** NI **Free recall:** I (c) **Gambling task:** I (c) Σ: 8/21 (0.38)	Y Users were excluded from experiment	Abstinent former opioid abuser primary study group.
Mintzer 2007 (197)								Review
Moskowitz 1985 (210)	Methadone 60-100 mg/day > 6 months	n = 12 n = 15		n = 12 drug free ex heroin addicts n = 15 drug free ex heroin addicts	2 hours post methadone dose	Σ: 0/2 (0.0) Σ: 0/2 (0.0)		
Pickworth 1993 (188)	Buprenorphine 0,3 mg (iv) LD 0,6 mg (iv) MD 1,2 mg (iv) HD	Healthy volunteers n = 6 Nondependent History of opioid use	Pc	Placebo	1-24 h	**Circular lights task:** NI		Impairment significant? “Slight but sustained decrease in response rate”
Pirastu 2006 (211)	Methadone Mean 66 mg (2-150 mg) 8.3 years	n = 30 (29m,1f) from met program n =n18 (17m,1f) from bup program n = 21 matched controls		Group comparisons		**Iowa gambling task:** I **Wisconsin card sorting:** M<B<C **WAIS-R: M=B<C** **Benton visual retention test:** M=B<C Σ: 3/3 (1)	Y Similar side abuse in methadone and buprenorphine patients, not tested in relation to experiment?	Number of pat performing in the negative range: M: ca 50 % B: ca 18 % C: ca 25 % Buprenorphine also tested
Pirastu 2006 (211)	Buprenorphine Mean 9 mg (2-20 mg) 5.4 years	n = 30 (29m,1f) from meth program n = 18 (17m,1f) from bup program n = 21 matched controls		Group comparisons		**Iowa gambling task**: NI **Wisconsin card sorting:** M<B<C **WAIS-R:** M=B<C **Benton visual retention test:** M=B<C		Number of pat performing in the negative range: M: ca 50 % B: ca 18 % C: ca 25 % Methadone also tested

Preston 1988 (235)	Buprenorphine 0,2 mg (sc) (LD) 0,3 mg (sc) (HD) Combination bup + stabiliz: 0,2/0,2 mg (sc) 0,3/0,2 mg (sc)	Volunteers adult n = 6 (m) Opioid-dependent Maintained on methadone	Rd Pc Db	Placebo Baseline	60-120 min	**Recall (memory) test**: NI (p) **DSST**: NI (p)		Maintained on methadone Naloxone and hydromorphone also tested: NI (p) all tests
Prosser 2006 (212)	Methadone < 73.8 mg	Met n = 29 (23 m) Former met n = 27 (20 m) Controls n = 29 (21 m)	3 parallel groups	Control group of healthy volunteers	?	**WAIS vocabulary test**: I (c) **Stroop color-word test**: NI **Oral word association test** (COWA): NI **Visual retention test** (BVRT) : I (c) Σ: 2/8 (0.25)	Y Patients with positive urine screening were not tested	Former heroin abusers/methadone patients, now drug free, also tested
Prosser 2009 (213)	Methadone Mean: 76 mg (±20.1) Treatment > 1 year	n = 10		- Former opiate-dependent subjects, abstinent (n = 13) - Healthy controls (n = 14)		**CPT** performance measures (sustained attention) Σ: 4/9 (0.44)	Y Urine toxicity test to ensure absence of illicit drugs	
Rapeli 2007 (214)	Methadone 40 mg (LD) 67 mg (HD) Treatment < 6 weeks (14.3 days) Buprenorphine/ naloxone 15.8/ 3.9 mg	n = 16 n = 8 (LD) n = 8 (HD) n = 17		Healthy controls n = 17		Attention, working memory, memory Σ methadone: 6/11 (0.55)	Y 81% use benzodiazepines	Slight differences between low and high dose
Robinson 1985 (215)	Methadone 60-80 mg/day > 6 months	n = 15 n = 12		n = 16 former heroin addicts n = 12 former heroin addicts		**5 tests of visual functions** Σ: 0/5 (0.0) **Visual search rate, rate of info processing, divided attention** Σ: 1/3 (0.33)	Y Drug screening, users excluded	
Rothenberg 1977 (171)	Methadone 5 mg (po) (LD) 10 mg (po) (HD)	Non-addict controls (no habitual drug use in history) n = 12 5 (m) / 7 (f)	Db	Placebo Baseline	2 h 15 min	**Letter recognition test**: ? **Continuous performance test**: NI (b) **RT**: I (b) (dose rel.)		Addicts vs. non-addicts Control group Methadone group also tested: NI (b) all tests Addicts faster than non-addicts in pre-drug session
Rothenberg 1977 (171)	Methadone 5 mg (po) (LD) 10 mg (po) (HD)	Maintained on methadone 20-70 mg n = 12 7 (m) / 5 (f)	Db	Placebo Baseline	1,5-2,5 h	**Letter recognition test:** NI (b) **Continuous performance test:** NI (b) **RT:** NI (b)		Addicts vs. non-addicts Methadone group Control group also tested: Reaction time test I (b) (dose rel) Addicts faster than non-addicts in pre-drug session

Rothenberg 1980 (172)	Methadone 5 mg (po) LD 10 mg (po) HD	Healthy volunteers (low-drug-using) n = 7 m (?) / f (?)	Db Rd Co	Placebo Baseline	2,25 h	**Smooth pursuit eye tracking**: I (p) HD		Low-drug using: Little or no prior experience with opiates (less than 2 days continuous opiate use). Use of recreational drugs (alcohol, marijuana etc) less than 3 times/week and not at all for 36 h preceding testing.
Rothenberg 1980 (173)	Methadone 5 mg (po) LD 10 mg (po) HD	Healthy volunteers (low-drug-using) n = 7 m (?) / f (?)	Db Rd Co	Placebo Baseline	2,25 h	**SacEM:** I (p) LD/HD		Low-drug using: Little or no prior experience with opiates (less than 2 days continuous opiate use). Use of recreational drugs (alcohol, marijuana etc) less than 3 times/week and not at all for 36 h preceding testing.
Rotheram-Fuller 2004 (216)	Methadone Smokers mean dose 68 mg Non-smokers mean dose 55.3 mg	Met + smoke n = 9 Met – smoke n = 9 Control + smoke n = 9 Control – smoke n = 10	4 parallel groups	Control group of healthy volunteers	-	**Gambling task:** I (met smokers vs controls) **WCST:** NI Σ: ½ (0.5)	N	Smokers vs non-smokers in both groups
Saarialho-Kere 1987 (177)	Buprenorphine 0,4 (s.l)	Volunteers n = 12	Db Rd Co	Placebo Baseline	2-4 h	**DSST**: I b,p) **MW**: I (b,p) **Tracking**: NI (b,p)		Interaction between B and AMI was mild Pre-treatment amitriptylin
Schindler 2004 (217)	Methadone 45,7 ± 21,4 mg Duration opioid dependence 51,3 ± 33,9 months Duration maintenance therapy 18,6 ± 24,6 months	Methadone patients n = 15 9 (m) 6 (f)		Each patient was matched with a group of control subjects, n = 3-56	21,3 ± 3,0 h	**Matrices test:** NI (c) **Attention Test under Monotonous Circumstanc.:** I (c) **Test for attention flexib.:** NI (c) **Test for vis. structuring ability:** NI (c) **Traffic-specific perc. ability:** NI (c) **Decision and reaction behavior in a dynamic driving environment:** I (c) **Reactive stress tolerance:** NI (c) Σ: 2/7 (0.29)	Y Subjects were more impaired if side abuse	Buprenorphine also tested
Schindler 2004 (217)	Buprenorphine 10,0 ± 3,9 mg Duration opioid dependence 43,6 ± 21,8 months Duration maintenance therapy 11,2 ± 7,7 months	Buprenorphine patients n = 15 5 (m) 10 (f)		Each patient was matched with a group of control subjects, n = 3-56	22,6 ± 7,2 h	**Matrices test:** NI (c) **Attention Test under Monotonous Circumstances:** I (c) **Test for attention flexibility:** NI (c) **Test for visual structuring ability:** NI (c) **Traffic-specific perception ability:** NI (c) **Decision and reaction behavior in a dynamic driving environment**: NI (c) **Reactive stress tolerance:** NI (c)		Methadone also tested

Singhal 2008 (236)	Buprenorphine Daily dose 4 mg/day Additional 2 mg/2 h (x3) Mean duration treatment 14.37 years (5-22 years)	n = 19 (m)		Baseline	0, 2, 4, 6 and 8 hours after treatment administration, in combination with additional 2 mg buprenorphine	**Digit span:** NI (b) **DSST:** improvement, increasing per assessment **Trail making test:** improvement, increasing per assessment **Delayed recall:** NI (b) Σ: 2/4 (0.5)	Y Most of the subjects were using additional substances at inclusion	
Soyka 2005 (234)	Methadone Buprenorphine	n = 46 (completed) Sex: m 26, f 19 Maintenance	Parallel groups	Baseline Methadone	Under steady-state after 8-10 weeks	<u>Baseline:</u> **D2**: NI (met) **Digit span**: NI (met) **RWT**: NI (met) <u>8-10 weeks:</u> **PVT**: NI (met) **TT15**: NI (met) **Q1**: NI (met) **RST3**: NI (met) **DR2**: NI (met) – better performance than met patients		Methadone also tested. Extensive side abuse (85%) of opioids, cannabis and benzos. Not same tests at baseline and at 8-10 weeks
Soyka 2008 (218)	Methadone Buprenorphine ≥ 14 days = t_1 8-10 weeks = t_2	n = 46 (methadone n = 24) (buprenorphine n = 22)		Healthy controls n = 24		Attention, RWT, stress, VLMT, TMT Methadone: Σ: t_1: 0/9; t_2: 3/11 (0.28) Buprenorphine: Σ: t_1: 0/9; t_2: 2/11 (0.18)	Y More than 50% tested positive for cannabis, benzodiazepines or opioids at t2	Buprenorphine performed better than methadone in 2 out of 11 tests
Specka 2000 (219)	Methadone 93 mg (10-240 mg)	n = 54		54 healthy controls		**LL5, DR2, Q11, CORT, TT15** Σ: 7/11 (0.64)	Y Users excluded	
Staak 1993 (220)	Methadone ~ 50 mg Mean 2 years (1-6 years)	34 → n =13		Controls n = 13		Σ: 10/10 (1.0)	Y Users excluded	A subgroup of 6 methadone maintained patients with the least psycho-pathology performed more like controls
Strain 1992 (237)	Buprenorphine 0.5 mg (im) 1.0 mg (im) 2.0 mg (im) 4.0 mg (im) 8.0 mg (im)	Opioid-dependant volunteers n = 6 (m)	Rd Db Co	Placebo Baseline	60-120 min	**Recall (memory) test**: NI **DSST**: NI		Methadone maintained on 30 mg daily. Injections given 20 h after last dose of methadone. Hydromorphone and naloxone also tested.
Strain 1995 (238)	Buprenorphine 0,5 mg (im) 1 mg (im) 2 mg (im) 4 mg (im) 8 mg (im)	Opioid-dependent n = 7 (m) Maintained on 30 mg methadone daily	Db Co?	Placebo Baseline	60-120 min	**Recall (memory) task**: NI **DSST**: NI		
Strain 1997 (239)	Buprenorphine 4 mg (im) (LD) 8 mg (im) (MD) 16 mg (im) (HD)	Volunteers n = 8 5 (m) / 3 (f)	Db	Placebo Baseline	15-120 min	**Recall (memory) task**: NI (p) **DSST**: NI (p)		Subjects: Opioid-dependent, maintained on buprenorphine 8 mg sl daily Hydromorphone also tested

Verdejo 2005 (221)	Methadone Mean dose: 83.82 mg	Met n = 18 (m) Heroin n = 23 (m)	2 parallel groups	Abstinent heroin abusers (no control group of healthy volunteers)	Tested 2.44 h (mean) after dd	**FAS:** NI **Letter number sequencing test:** NI **Oral trails:** I (h) **Stroop colour-word test:** NI **Similarities subtest:** I (h) **Five digit test:** I (h) **WCST:** NI Σ: 3/7 (0.43)	Y Side abuse seen (cannabis, cocaine, heroin, alcohol, benzo's)	Abstinent heroin abusers also tested (min 15 days abstinent).
Walsh 1994 (231)	Methadone 15 mg (po) 30 mg (po) 45 mg (po) 60 mg (po) (Increasing dose?)	Healthy volunteers n = 5 (m) Current users of intravenous heroin	Db Rd	Placebo Baseline ?	15-180 min	**DSST**: NI		5 of 9 received methadone in increasing dose p/b ?
Walsh 1995 (230)	Methadone 15 mg (po) (LD) 30 mg (po) (MD) 60 mg (po) (HD)	Volunteers, maintained on methadone 30 or 60 mg/day n = 13 (m)	Db Double-dummy	Placebo Baseline	30-390 min	**Memory task (recall):** I **DSST:** NI		Digit recall: I , some dose related effects. p/b?
Walsh 1995 (230)	Buprenorphine 2 mg (sl) (LD) 4 mg (sl) (MD) 8 mg (sl) (HD)	Volunteers, maintained on methadone 30 or 60 mg/day n = 13 (m)	Db Double-dummy	Placebo Baseline	30-390 min	**Memory task (recall)**: I **DSST**: NI		p/b??
Weinhold 1992 (241)	Buprenorphine 0.4 mg LD 0.8 mg HD pr. 70 kg (im)	Nonphysically-dependent opioid abuser volunteers n = 7	Db Rd Co	Placebo Baseline	60-120 min	**DSST**: I(p) HD **Digit recall task**: NI		Naloxone was also tested
Zacny 1997 (167)	Buprenorphine 0,075 mg/70 kg (iv) (LD) 0,15 mg/70 kg (iv) (MD) 0,3 mg/70 kg (iv) (HD)	n = 16 No history of opiate dependence	Rd Pc Db Co trial	Placebo Baseline	15-300 min	**MW**: I (p) (HD) **EHC**: I (p) (HD) **DSST** (n compl. + n corr.): I (p) (LD) **ART** (s): I (p) (HD) **Logical reasoning** (number correct+completed): I (p) (HD)		Morphine also tested: MW: I (p)

10.8 Appendix 8: Metaanalysis of morphine and its 3- and 6-glucuronidate pharmacokinetics after intravenous administration to young and elderly volunteers (Guido Sticht, Köln)

Table 10: 5 mg Morphine hydrochloride (sulphate) intravenous (absorption. distribution and elimination)

Evaluated studies	**Data from single dose studies**	**Age (years)**	**Dose (µmol)**	**Cp0 (nmol/L)**	**$t_{½}K_1$ (h)**	**$t_{½}K_2$ (h)**	**$t_{½}\beta$ (h)**	**V_1 (%)**	**V_2 (%)**
Skarke et al., 2003	Gilbert`syndrome (7M/4F)	26-30	19.8	42.1(2!)	0.0306(2!)	0.0951(2!)	2.15(2!)	1.03(2!)	87.5(2!)
Osborne et al., 1990	different routes of administration (7M/3F)	25-44	13.2	50.7(2!)	0.043(2!)	0.66(2!)	2.31(2!)	6.25(2!)	49.9(2!)
Baillie et al., 1989	young + (elderly)(5M/3F)	26-30	26.4	23.4(2!)	0.0201(2!)	0.32(2!)	4.07(2!)	75(2!)	12.5(2!)
Dershwitz et al., 2000	+ (inhaled morphine) (10M/3F)	22-45	23.2	25.4(2!)	0.0116(2!)	0.156(2!)	1.81(2!)	3.13(2!)	21.1(2!)
Hoskin et al., 1989	+ (oral & buccal) (2M/4F)	26-40	26.4	-	-	-	1.90(2)	-	-
Hasselström et al., 1989	metabolism (3M/4F)	27-55	13.3	30.7(2!)	0.0632(2!)	0.126(2!)	2.21(2!)	49.8(2!)	98.4(2!)
Westerling et al., 2007	effects on salivation (6M/4F)	25-56	26.6	31.9(2!)	0.0120(2!)	0.284(2!)	2.49(2!)	50.0(2!)	12.1(2!)
	Mean ± SD			**34.3 ±9.7**	**0.0278 ±0.0173**	**0.270 ±0.194**	**2.38 ±0.68**	**26.5 ±28.2**	**44.8 ±33.8**

Data from comparative single dose studies	Evaluated studies	AUC_{o-oo} (nmol·h/mL)	G (kg)	V_β (L/kg)			
Skarke et al., 2003	Gilbert`syndrome (7M/4F)	355.2(2!)	71.0	4.51(2!)			
Osborne et al., 1990	different routes of administration (7M/3F)	279,4(2!)	72.0	3.75(2!)			
Baillie et al., 1989	young + (elderly)(5M/3F)	216.0(2!)	67.6±4.5	8.12(2!)			
Dershwitz et al., 2000	+ (inhaled morphine) (10M/3F)	106.4(2!)	74.0	7.48(2!)			
Hoskin et al., 1989	+ (oral & buccal) (2M/4F)	322.1(1)	-	-			
Hasselström et al., 1989	metabolism (3M/4F)	101.8(2!)	65.0	6.19(2!)			
Westerling et al., 2007	effects on salivation (6M/4F)	214.3(2!)	73.1±12.6	5.96(2!)	Number of trials	7	6
	Mean ± SD	**219.9 ±93.2**		**5.97 ±1.55**	Number of observations	65	59

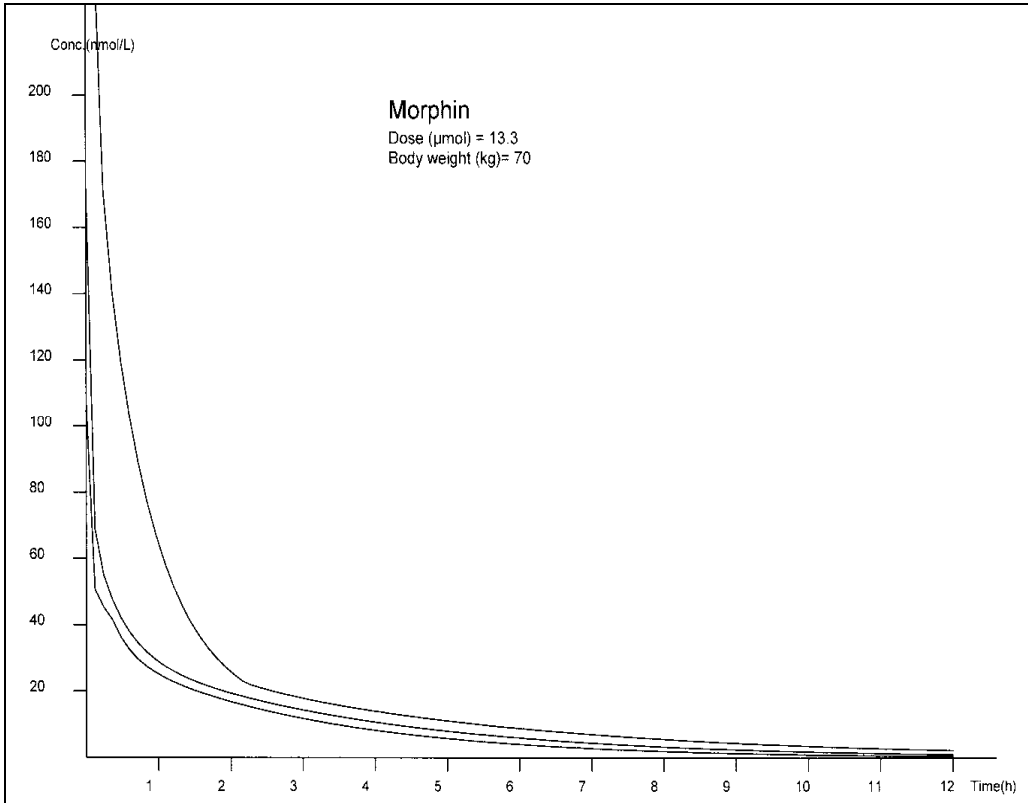


Figure 4: Plasma concentration-time curve of morphine after intravenous administration of morphine

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	34.3	±	9.7	nmol/L
K_1 (rapid):	24.9	±	9.5	h^{-1}
V_1 (rapid):	26.5	±	20	%
K_2 (slow):	2.57	±	1.08	h^{-1}
V_2 (slow):	44.8	±	33.8	%
β:	0.291	±	0.065	h^{-1}

			derived from time course of plasma concentrations	
$V_β$:	5.97 ± 0.065		5.54 ± 2.18	L/kg
C_{max}:			174.6 (106.6-577.4)	nmol/L
t_{max}:			0 (0-0)	h
AUC_{o-oo}:	219.9 ± 93.2	ng*h/mL	153.6 (114.7-328.7)	nmol*h/L

Morphin

Time (h)	Concentration (nmol/L)	Time (h)	Concentration (nmol/L)	Time (h)	Concentration (nmol/L)	Time (h)	Concentration (nmol/L)
.25	54.31 (45.07- 167.9)	6.25	5.564 (3.706- 8.357)	12.25	.9708 (.4378- 2.152)	18.25	.1693 (.0517- .5546)
.5	41.34 (35.52- 116.6)	6.5	5.173 (3.391- 7.896)	12.5	.9027 (.4005- 2.034)	18.5	.1574 (4.731- .5242)
.75	33.72 (28.99- 85.87)	6.75	4.810 (3.102- 7.462)	12.75	.8393 (.3664- 1.922)	18.75	.1464 (4.328- .4954)
1	28.87 (25.12- 64.48)	7	4.473 (2.838- 7.052)	13	.7804 (.3352- 1.816)	19	.1361 (3.960- .4682)
1.25	25.54 (22.42- 49.45)	7.25	4.159 (2.596- 6.664)	13.25	.7257 (.3067- 1.717)	19.25	.1266 (3.623- .4424)
1.5	23.06 (20.28- 38.82)	7.5	3.867 (2.375- 6.298)	13.5	.6747 (.2805- 1.622)	19.5	.1177 (3.314- .4181)
1.75	21.08 (18.46- 31.23)	7.75	3.596 (2.173- 5.951)	13.75	.6274 (.2566- 1.533)	19.75	.1094 (3.032- .3952)
2	19.41 (16.85- 25.76)	8	3.343 (1.988- 5.624)	14	.5834 (.2348- 1.449)	20	.1017 (2.774- .3734)
2.25	17.95 (15.40- 22.10)	8.25	3.109 (1.818- 5.315)	14.25	.5424 (.2148- 1.369)	20.25	9.464 (2.537- .3529)
2.5	16.63 (14.09- 20.51)	8.5	2.891 (1.663- 5.023)	14.5	.5044 (.1965- 1.294)	20.5	.0880 (2.321- .3335)
2.75	15.44 (12.88- 19.12)	8.75	2.688 (1.522- 4.747)	14.75	.4690 (.1798- 1.223)	20.75	8.183 (.0212- .3152)
3	14.34 (11.78- 17.89)	9	2.499 (1.392- 4.486)	15	.4361 (.1644- 1.156)	21	7.608 (.0194- .2979)
3.25	13.33 (10.78- 16.78)	9.25	2.324 (1.273- 4.240)	15.25	.4055 (.1504- 1.092)	21.25	7.074 (1.777- .2815)
3.5	12.39 (9.866- 15.78)	9.5	2.161 (1.165- 4.007)	15.5	.3770 (.1376- 1.032)	21.5	6.578 (1.626- .2661)
3.75	11.52 (9.026- 14.85)	9.75	2.009 (1.066- 3.787)	15.75	.3506 (.1259- .9759)	21.75	6.116 (1.487- .2514)
4	10.71 (8.257- 13.99)	10	1.868 (.9754- 3.579)	16	.3260 (.1152- .9223)	22	5.687 (.0136- .2376)
4.25	9.958 (7.554- 13.20)	10.25	1.737 (.8923- 3.382)	16.25	.3031 (.1054- .8716)	22.25	5.288 (1.245- .2246)
4.5	9.259 (6.911- 12.45)	10.5	1.615 (.8163- 3.196)	16.5	.2818 (9.643- .8237)	22.5	4.917 (1.139- .2122)
4.75	8.609 (6.322- 11.75)	10.75	1.502 (.7468- 3.021)	16.75	.2620 (8.822- .7785)	22.75	4.572 (1.042- .2006)
5	8.005 (5.784- 11.10)	11	1.396 (.6832- 2.855)	17	.2436 (8.071- .7357)	23	4.251 (9.534- .1895)
5.25	7.443 (5.291- 10.48)	11.25	1.298 (.6250- 2.698)	17.25	.2265 (7.383- .6953)	23.25	3.953 (8.722- .1791)
5.5	6.921 (4.841- 9.907)	11.5	1.207 (.5718- 2.550)	17.5	.2106 (6.755- .6571)	23.5	3.675 (7.979- .1693)
5.75	6.435 (4.428- 9.360)	11.75	1.122 (.5231- 2.410)	17.75	.1959 (6.179- .6210)	23.75	3.418 (7.300- .1600)
6	5.984 (4.051- 8.844)	12	1.044 (.4786- 2.277)	18	.1821 (5.653- .5869)	24	3.178 (6.678- .1512)

Table 11: 5 mg Morphine hydrochloride (sulphate) intravenous in elderly (absorption. distribution and elimination)

Evaluated studies	**Data from single dose studies**	**Age (years)**	**Dose (µmol)**	**Cp0 (nmol/L)**	**$t_{½}K_1$ (h)**	**$t_{½}K_2$ (h)**	**$t_{½}\beta$ (h)**	**V_1 (%)**	**V_2 (%)**
Hand et al., 1987	radioimmunoassay (7M/6F)	69.2±3.4	26.4	79.7(2!)	0.0217(2!)	0.1086(2!)	3.28(2!)	4.40(2!)	75.0(2!)
Säwe et al., 1985	cancer patients (1M)	70	10.6	33.9(2!)	0.0200(2!)	0.136(2!)	2.10(2!)	1.17(2!)	66.6(2!)
Baillie et al., 1989	elderly + (young)(5M/4F)	66.4±4.5	26.4	32.2(2!)	0.0201(2!)	0.255(2!)	4.49(2!)	2.72(2!)	12.5(2!)
	Mean ± SD			**59.1 ±23.7**	**0.0210 ±0.008**	**0.167 ±0.071**	**3.70 ±0.68**	**3.60 ±0.97**	**50.2 ±30.6**
	Number of trials			3	3	3	3	3	3
	Number of observations			23	23	23	23	23	23

Data from comparative single dose studies	**Evaluated studies**	**AUC_{o-oo} (nmol*h/L)**	**G (kg)**	**V_β**
Hand et al., 1987	radioimmunoassay (7M/6F)	433.3(2!)	63.4±2.8	2.38
Säwe et al., 1985	cancer patients (1)	221,4(2!)	54.0	5.60
Baillie et al., 1989	elderly + (young)(5M/4F)	297.2(2!)	66.4±3.2	5.90
	Mean ± SD	**370.8 ±73.6**		**3.90 ±1.75**
	Number of trials	3		3
	Number of observations	21		23

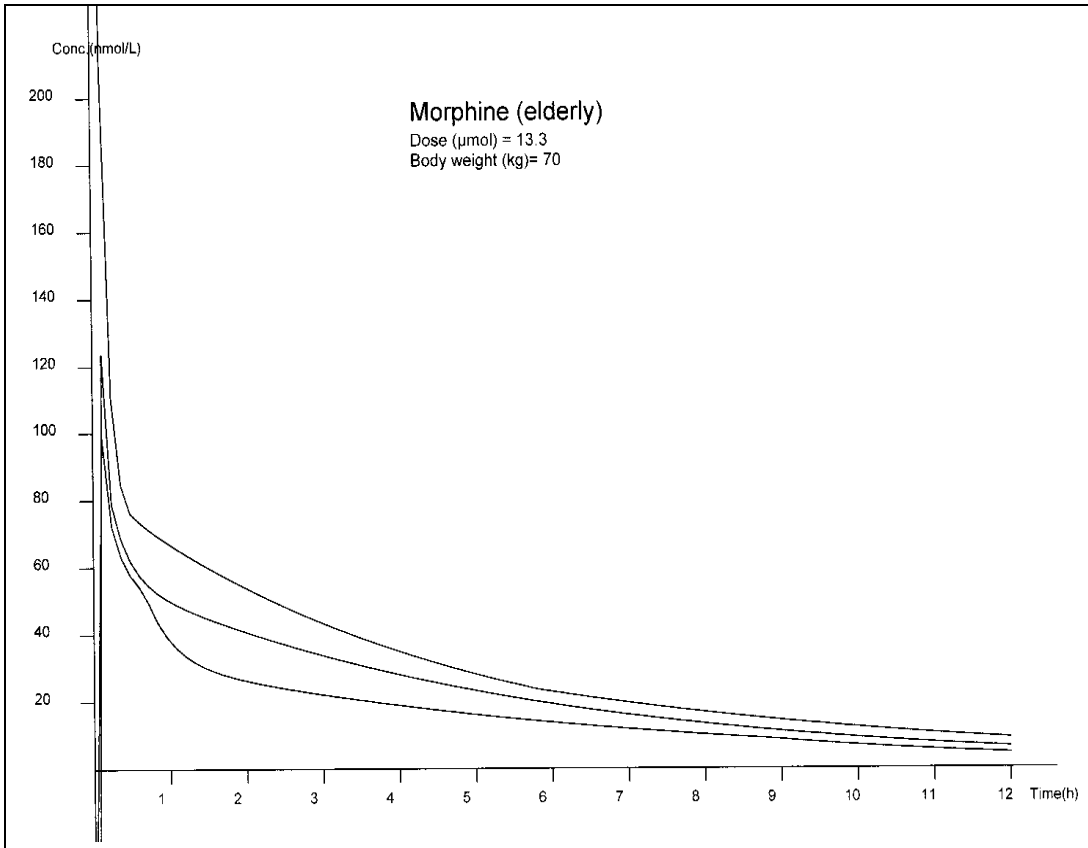


Figure 5: Plasma concentration-time curve of morphine after intravenous administration of morphine in elderly subjects

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	59.1	±	23.7	nmol/L
K_1 (rapid):	33.0	±	9.1	h^{-1}
V_1 (rapid):	3.6	±	0.97	%
K_2 (slow):	4.15	±	1.24	h^{-1}
V_2 (slow):	50.2	±	30.6	%
β:	0.187	±	0.029	h^{-1}

		derived from time-course of plasma concentrations	
$V_β$:	3.90 ± 1.75	3.21 ± 2.15	L/kg
C_{max}:		1700 (1490-1831)	nmol/L
t_{max}:		0 (0-0)	h
AUC_{o-oo}:	370.8 ± 73.6ng*h/mL	562.5 (414.6-659.1)	nmol*h/L

Morphine (elderly)

Time (h)	Concentration (nmol/L)	Time (h)	Concentration (nmol/L)	Time (h)	Concentration (nmol/L)	Time (h)	Concentration (nmol/L)
.25	77.58 (71.27- 107.5)	6.25	18.36 (13.18- 22.01)	12.25	5.980 (4.192- 8.531)	18.25	1.947 (1.147- 3.305)
.5	61.18 (57.00- 75.65)	6.5	17.52 (12.67- 21.16)	12.5	5.707 (3.971- 8.200)	18.5	1.858 (1.086- 3.177)
.75	53.97 (47.81- 70.76)	6.75	16.72 (12.18- 20.34)	12.75	5.446 (3.763- 7.883)	18.75	1.773 (1.029- 3.054)
1	49.94 (38.13- 66.80)	7	15.96 (11.71- 19.55)	13	5.197 (3.565- 7.577)	19	1.692 (.9755- 2.936)
1.25	47.10 (32.87- 63.23)	7.25	15.23 (11.25- 18.79)	13.25	4.960 (3.377- 7.284)	19.25	1.615 (.9242- 2.822)
1.5	44.76 (29.77- 59.89)	7.5	14.53 (10.82- 18.06)	13.5	4.733 (3.200- 7.002)	19.5	1.541 (.8756- 2.713)
1.75	42.64 (27.74- 56.73)	7.75	13.87 (10.40- 17.36)	13.75	4.517 (3.032- 6.731)	19.75	1.471 (.8296- 2.608)
2	40.67 (26.23- 53.75)	8	13.23 (10.00- 16.69)	14	4.311 (2.872- 6.470)	20	1.403 (.7860- 2.507)
2.25	38.80 (25.01- 50.92)	8.25	12.63 (9.613- 16.05)	14.25	4.114 (2.721- 6.219)	20.25	1.339 (.7447- 2.410)
2.5	37.03 (23.94- 48.25)	8.5	12.05 (9.241- 15.42)	14.5	3.926 (2.578- 5.978)	20.5	1.278 (.7055- 2.316)
2.75	35.33 (22.97- 45.71)	8.75	11.50 (8.883- 14.83)	14.75	3.747 (2.443- 5.747)	20.75	1.220 (.6684- 2.227)
3	33.72 (22.06- 43.31)	9	10.98 (8.459- 14.25)	15	3.575 (2.314- 5.524)	21	1.164 (.6333- 2.140)
3.25	32.18 (21.19- 41.03)	9.25	10.48 (8.014- 13.70)	15.25	3.412 (2.192- 5.310)	21.25	1.111 (.6000- 2.057)
3.5	30.71 (20.36- 38.87)	9.5	10.00 (7.593- 13.17)	15.5	3.256 (2.077- 5.105)	21.5	1.060 (.5684- 1.978)
3.75	29.31 (19.57- 36.83)	9.75	9.544 (7.193- 12.66)	15.75	3.108 (1.968- 4.907)	21.75	1.012 (.5386- 1.901)
4	27.97 (18.81- 34.89)	10	9.108 (6.815- 12.17)	16	2.966 (1.864- 4.717)	22	.9658 (.5102- 1.828)
4.25	26.69 (18.08- 33.06)	10.25	8.692 (6.457- 11.70)	16.25	2.830 (1.766- 4.534)	22.25	.9217 (.4834- 1.757)
4.5	25.47 (17.38- 31.32)	10.5	8.295 (6.117- 11.24)	16.5	2.701 (1.674- 4.358)	22.5	.8796 (.4580- 1.689)
4.75	24.31 (16.71- 29.67)	10.75	7.916 (5.796- 10.81)	16.75	2.577 (1.586- 4.190)	22.75	.8394 (.4339- 1.623)
5	23.20 (16.06- 28.11)	11	7.555 (5.491- 10.39)	17	2.460 (1.502- 4.027)	23	.8011 (.4111- 1.560)
5.25	22.14 (15.44- 26.64)	11.25	7.210 (5.202- 9.991)	17.25	2.347 (1.423- 3.871)	23.25	.7645 (.3895- 1.500)
5.5	21.13 (14.84- 25.23)	11.5	6.880 (4.929- 9.604)	17.5	2.240 (1.348- 3.721)	23.5	.7295 (.3690- 1.442)
5.75	20.16 (14.27- 23.91)	11.75	6.566 (4.670- 9.232)	17.75	2.138 (1.277- 3.577)	23.75	.6962 (.3496- 1.386)
6	19.24 (13.71- 22.90)	12	6.266 (4.424- 8.874)	18	2.040 (1.210- 3.439)	24	.6644 (.3312- 1.332)

Table 12: Morphine-3-glucuronide from 5 mg Morphine hydrochloride (sulphate) intravenous (absorption. distribution and elimination)

Evaluated studies	**Data from comparative single dose studies**	**Age (years)**	**Dose (µmol)**	**Cp0 (nmol/L)**	**$t_{½}$Ka (h)**	**$t_{½}$α (h)**	**$t_{½}$β (h)**	**t_0 (h)**	**V% (%)**
Skarke et al., 2003	Gilbert`syndrome (7M/4F)	23-30	19.8	235.3(2!)	0.076(2!)	0.663(2!)	3.27 (2!)	0.039(2!)	65.1(2!)
Osborne et al., 1990	different routes of administration (7M/3F)	25-44	13.2	390.2(2!)	0.038(2!)	1.37(2!)	2.31(2!)	0.032(2!)	93.0(2!)
Hasselström et al., 1989	metabolism (3M/4F)	27-55	13.3	148.8(2!)	0.045(2!)	3.01(2!)	3.14(2!)	0.001(2!)	96.5(2!)
Säwe et al., 1985	cancer patients (1)	19-41	50	212.2(2!)	0.121(2!)	3.05(2!)	3.25(2!)	0.004(2!)	99.9(2!)
Hand et al., 1987	radioimmunoassay (7M/6F)	69.2±3.4	26.4	235.3(2!)	0.076(2!)	0.66(2!)	3.27 (2!)	0.039(2!)	65.1(2!)
	Mean ± SD			**257.2 ±81.1**	**0.0629 ±0.0196**	**1.28 ±0.90**	**3.02 ±0.40**	**0.030 ±0.014**	**77.8 ±14.8**
	Number of trials			5	5	5	5	5	5
	Number of observations			42	42	42	42	42	42

Data from comparative single dose studies	**Evaluated studies**	**C_{max} (nmol/L)**	**t_{max} (h)**	**AUC_{o-oo} (nmol*h/L)**	**G (kg)**	**B (%)**	**$V_β$/B (L)**	**$V_β$/G (L/kg)**
Skarke et al., 2003	Gilbert`syndrome (7M/4F)	295.2(2)	0.25(2)	1189(2!)	71.0			
Osborne et al., 1990	different routes of administration (7M/3F)	395.1(2)	0.25(2)	1709(2!)	72.0			
Hasselström et al., 1989	metabolism (3M/4F)	138.9(2)	0.33(2)	786(2!)	65.0			
Säwe et al., 1985	cancer patients (1)	171.2(2)	0.33(2!)	966(2!)	54.0			
Hand et al., 1987	radioimmunoassay (7M/6F)	295.2(2)	0.25(2)	1189(2!)	63.4±2.8			
	Mean ± SD	**290.0 ±82.9**	**0.27 ±0.03**	**1240 ±302**				
	Number of trials	5	5	5				
	Number of observations	42	42	42				

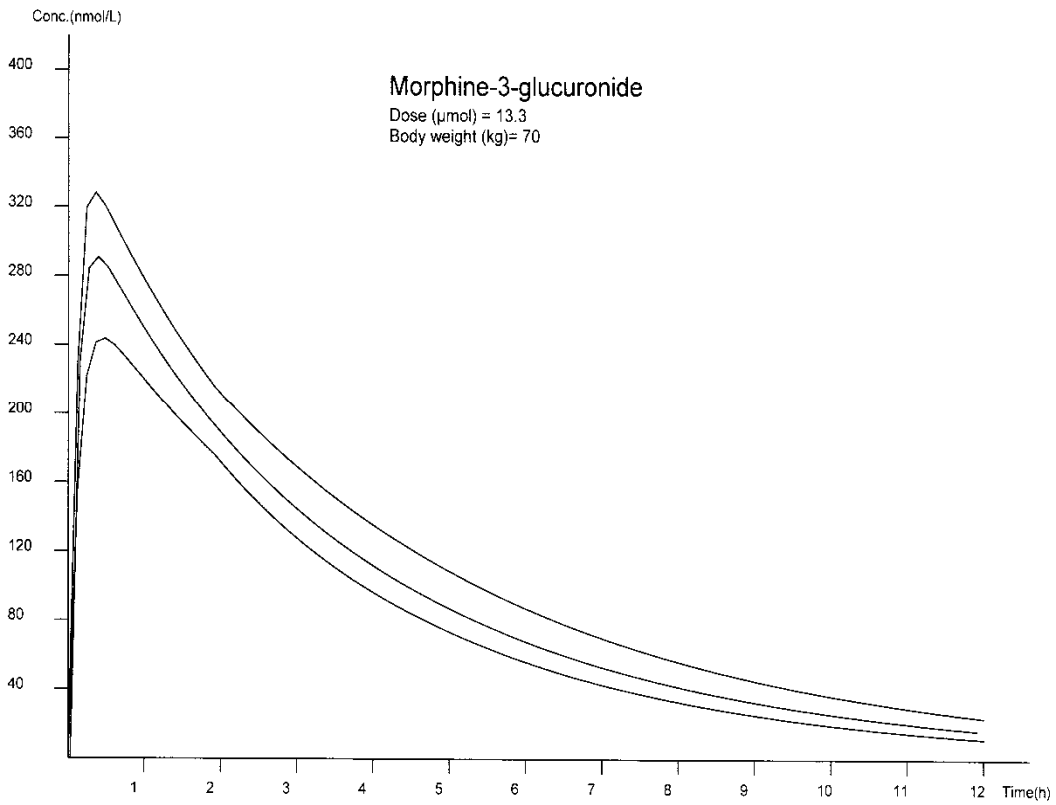


Figure 6: Plasma concentration-time curve of morphine-3-glucuronide after intravenous administration of morphine

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	257.2	±	81.1	nmol/L
Ka:	11.0	±	2.6	h^{-1}
α:	0.54	±	0.22	h^{-1}
β:	0. 230	±	0.027	h^{-1}
t_0:	0.030	±	0.014	h
V%:	77.8	±	14.8	%

				derived from time-course of plasma concentrations	
C_{max}:	290.0	±	82.9	289.0 (243.7-328.2)	nmol/L
$t_{max:}$	0.27	±	0.03	0.31 (0.31-0.48)	h
AUC_{o-oo}:	1240	±	302	1220 (1032-1495)	nmol*h/L

Morphine-3-glucuronide

Time (h)	Concentration (nmol/L)	Time (h)	Concentration (nmol/L)	Time (h)	Concentration (nmol/L)	Time (h)	Concentration (nmol/L)
.25	280.3 (224.7- 321.8)	6.25	64.25 (52.88- 82.92)	12.25	15.67 (11.22- 23.07)	18.25	3.932 (2.411- 6.617)
.5	285.9 (243.4- 319.3)	6.5	60.49 (49.52- 78.55)	12.5	14.78 (10.53- 21.89)	18.5	3.713 (2.261- 6.284)
.75	267.6 (232.9- 298.0)	6.75	56.96 (46.39- 74.41)	12.75	13.95 (9.876- 20.77)	18.75	3.505 (2.121- 5.968)
1	249.3 (219.6- 277.8)	7	53.65 (43.46- 70.50)	13	13.17 (9.263- 19.71)	19	3.310 (1.989- 5.668)
1.25	232.3 (206.8- 259.1)	7.25	50.53 (40.72- 66.80)	13.25	12.43 (8.687- 18.70)	19.25	3.125 (1.865- 5.384)
1.5	216.7 (194.6- 241.8)	7.5	47.61 (38.16- 63.30)	13.5	11.73 (8.148- 17.75)	19.5	2.951 (1.750- 5.113)
1.75	202.3 (183.2- 225.8)	7.75	44.86 (35.76- 59.99)	13.75	11.07 (7.642- 16.84)	19.75	2.786 (1.641- 4.857)
2	188.9 (171.6- 211.5)	8	42.28 (33.52- 56.85)	14	10.45 (7.167- 15.99)	20	2.630 (1.539- 4.613)
2.25	176.6 (159.1- 200.0)	8.25	39.85 (31.42- 53.88)	14.25	9.873 (6.722- 15.17)	20.25	2.484 (1.444- 4.382)
2.5	165.2 (147.7- 189.1)	8.5	37.57 (29.45- 51.08)	14.5	9.320 (6.305- 14.40)	20.5	2.345 (1.354- 4.162)
2.75	154.6 (137.3- 178.9)	8.75	35.42 (27.61- 48.42)	14.75	8.798 (5.913- 13.67)	20.75	2.214 (1.270- 3.953)
3	144.8 (127.8- 169.2)	9	33.40 (25.89- 45.90)	15	8.305 (5.546- 12.98)	21	2.091 (1.191- 3.755)
3.25	135.7 (119.0- 160.0)	9.25	31.50 (24.27- 43.52)	15.25	7.841 (5.202- 12.32)	21.25	1.974 (1.117- 3.567)
3.5	127.2 (110.9- 151.4)	9.5	29.70 (22.76- 41.26)	15.5	7.402 (4.879- 11.69)	21.5	1.864 (1.048- 3.389)
3.75	119.3 (103.4- 143.3)	9.75	28.02 (21.34- 39.13)	15.75	6.988 (4.576- 11.10)	21.75	1.760 (.9831- 3.219)
4	112.0 (96.56- 135.6)	10	26.43 (20.01- 37.10)	16	6.597 (4.292- 10.54)	22	1.662 (.9221- 3.058)
4.25	105.1 (90.17- 128.3)	10.25	24.93 (18.76- 35.19)	16.25	6.229 (4.025- 10.01)	22.25	1.569 (.8649- 2.905)
4.5	98.76 (84.24- 121.4)	10.5	23.52 (17.59- 33.37)	16.5	5.880 (3.775- 9.505)	22.5	1.481 (.8112- 2.760)
4.75	92.79 (78.74- 115.0)	10.75	22.19 (16.50- 31.65)	16.75	5.552 (3.541- 9.025)	22.75	1.399 (.7608- 2.622)
5	87.21 (73.63- 108.8)	11	20.93 (15.47- 30.02)	17	5.242 (3.321- 8.570)	23	1.321 (.7136- 2.491)
5.25	82.00 (68.87- 103.0)	11.25	19.75 (14.51- 28.48)	17.25	4.949 (3.115- 8.137)	23.25	1.247 (.6693- 2.367)
5.5	77.12 (64.44- 97.61)	11.5	18.64 (13.61- 27.01)	17.5	4.672 (2.922- 7.727)	23.5	1.177 (.6278- 2.249)
5.75	72.55 (60.32- 92.44)	11.75	17.59 (12.76- 25.63)	17.75	4.411 (2.740- 7.338)	23.75	1.112 (.5888- 2.136)
6	68.27 (56.47- 87.55)	12	16.60 (11.97- 24.31)	18	4.165 (2.570- 6.968)	24	1.050 (.5523- 2.030)

Table 13: Morphine-6-glucuronide from 5 mg Morphine hydrochloride (sulphate) intravenous (absorption. distribution and elimination)

Evaluated studies	**Data from single dose studies**	**Age (years)**	**Dose (µmol**	**Cp0 (nmol/L)**	**$t_{½}$Ka (h)**	**$t_{½}$α (h)**	**$t_{½}$β (h)**	**t_0 (h)**	**V% (%)**
Skarke et al., 2003	Gilbert`syndrome (7M/4F)	23-30	19.8	54.9(2!)	0.183(2!)	4.42(2!)	2.66(2!)	0.050(2!)	96.1(2!)
Osborne et al., 1985	different routes of administration (7M/3F)	25-44	13.2	67.3(2!)	0.143(2!)	1.27(2!)	3.04(2!)	0.043(2!)	65.6(2!)
Hasselström et al., 1989	metabolism (3M/4F)	27-55	13.3	19.9(2!)	0.147(2!)	2.03(2!)	3.25(2!)	0.033(2!)	84.8(2!)
Hand et al., 1987	radioimmunoassay (7M/6F)	69.2±3.4	26.4	32.2(2!)	0.226(2!)	3.21(2!)	3.10(2!)	0.004(2!)	93.0(2!)
	Mean ± SD			**44.8 ±17.6**	**0.181 ±0.035**	**2.86 ±1.20**	**2.99 ±0.21**	**0.031 ±0.019**	**85.7 ±12.1**
	Number of trials			4	4	4	4	4	4
	Number of observations			41	41	41	41	41	41

Data from comparative single dose studies	**Evaluated studies**	**C_{max} (nmol/L)**	**t_{max} (h)**	**AUC_{o-oo} (nmol*h/L)**	**G (kg)**	**B (%)**	**$V_β$/B (L)**	**$V_β$/G (L/kg)**
Skarke et al., 2003	Gilbert`syndrome (7M/4F)	48.1(2!)	0.50	210.0	71.0			
Osborne et al., 1985	different routes of administration (7M/3F)	83,3(2!)	0.75	337.4	72.0			
Hasselström et al., 1989	metabolism (3M/4F)	18.9(2!)	1.0	98.3	65.0			
Hand et al., 1987	radioimmunoassay (7M/6F)	26.6(1)	1.0	144.2	63.4±2.8			
	Mean ± SD	**44.9 ±24.3**	**0.80 ±0.21**	**201.1 ±86.5**				
	Number of trials	4	4	4				
	Number of observations	41	41	41				

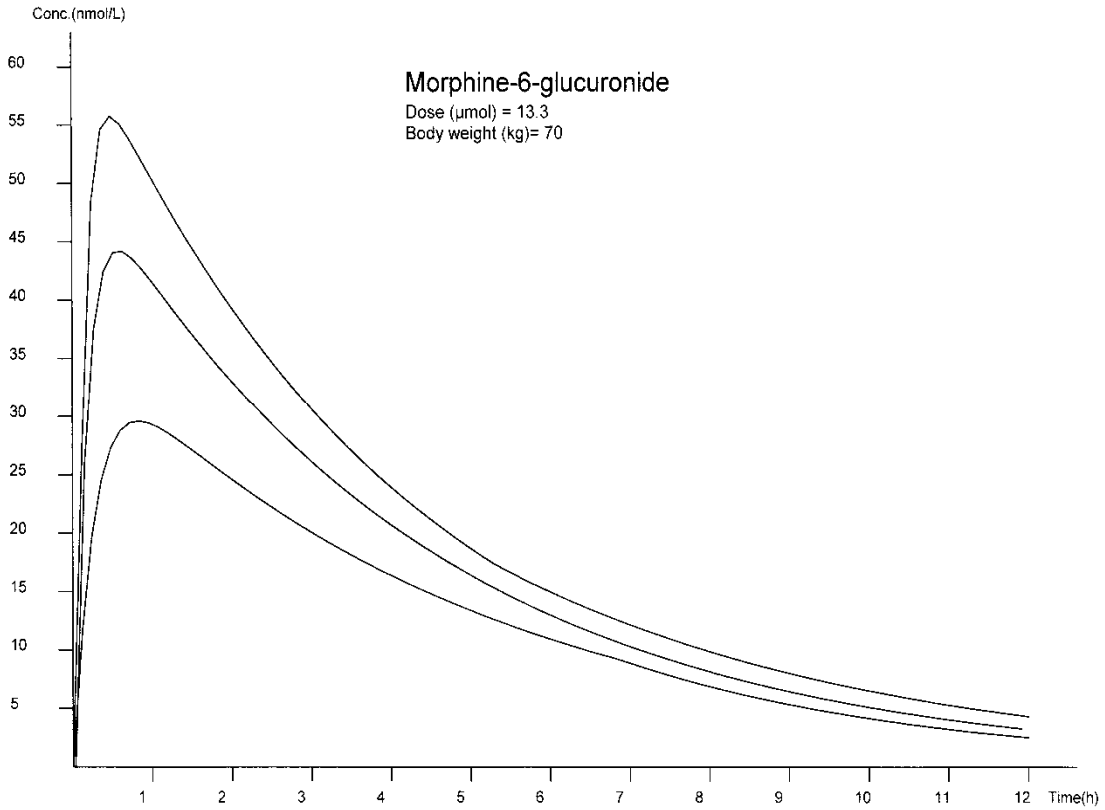


Figure 7: Plasma concentration-time curve of morphine-6-glucuronide after intravenous administration of morphine

Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	44.8	±	17.6	nmol/L
Ka:	6.19	±	2.40	h^{-1}
α:	0.242	±	0.071	h^{-1}
β:	0.232	±	0.015	h^{-1}
t_0:	0.031	±	0.019	h
V%:	85.7	±	12.1	%

				derived from time-course of plasma concentrations	
C_{max}:	44.9	±	24.3	44.2 (29.6-55.8)	nmol/L
t_{max}:	0.80	±	0.21	0.59 (0.48-0.84)	h
AUC_{o-oo}:	201.1	±	86.5	215.0 (162.9-263.5)	nmol*h/L

Morphine-6-glucuronide

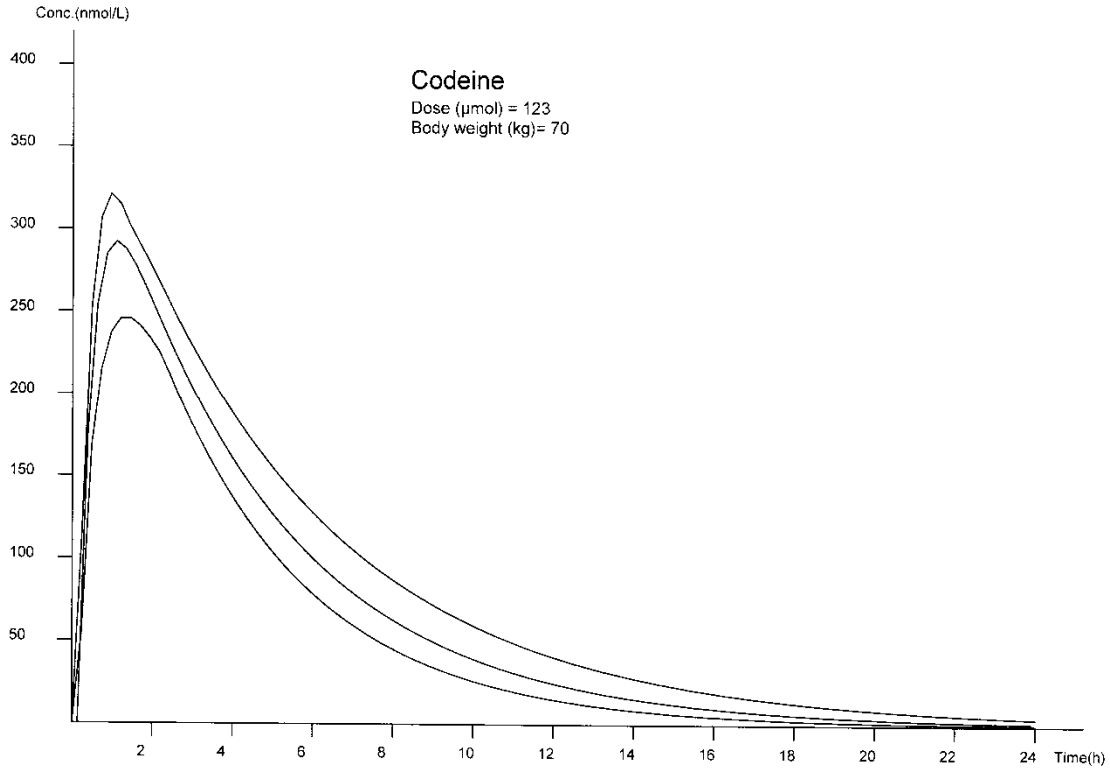
Time (h)	Concentration (nmol/L)	Time (h)	Concentration (nmol/L)	Time (h)	Concentration (nmol/L)	Time (h)	Concentration (nmol/L)
.25	36.19 (20.20- 49.26)	6.25	12.24 (10.38- 14.20)	12.25	3.019 (2.353- 4.085)	18.25	.7449 (.5225- 1.191)
.5	43.98 (27.62- 55.71)	6.5	11.55 (9.871- 13.47)	12.5	2.848 (2.210- 3.879)	18.5	.7027 (.4909- 1.131)
.75	43.58 (29.52- 53.46)	6.75	10.89 (9.385- 12.79)	12.75	2.687 (2.075- 3.684)	18.75	.6629 (.4611- 1.075)
1	41.56 (29.31- 50.37)	7	10.27 (8.855- 12.14)	13	2.534 (1.949- 3.499)	19	.6254 (.4332- 1.022)
1.25	39.30 (28.34- 47.35)	7.25	9.695 (8.312- 11.52)	13.25	2.391 (1.830- 3.323)	19.25	.5900 (.4069- .9713)
1.5	37.09 (27.12- 44.50)	7.5	9.146 (7.802- 10.94)	13.5	2.255 (1.718- 3.156)	19.5	.5566 (.3823- .9231)
1.75	34.99 (25.85- 41.82)	7.75	8.628 (7.323- 10.38)	13.75	2.128 (1.614- 2.998)	19.75	.5250 (.3591- .8773)
2	33.01 (24.59- 39.31)	8	8.139 (6.875- 9.861)	14	2.007 (1.516- 2.847)	20	.4953 (.3374- .8338)
2.25	31.14 (23.38- 36.94)	8.25	7.678 (6.453- 9.361)	14.25	1.893 (1.423- 2.704)	20.25	.4672 (.3169- .7924)
2.5	29.37 (22.22- 34.72)	8.5	7.243 (6.058- 8.887)	14.5	1.786 (1.337- 2.569)	20.5	.4408 (.2978- .7532)
2.75	27.71 (21.12- 32.63)	8.75	6.832 (5.687- 8.437)	14.75	1.685 (1.255- 2.440)	20.75	.4158 (.2797- .7159)
3	26.14 (20.07- 30.66)	9	6.445 (5.339- 8.010)	15	1.589 (1.179- 2.318)	21	.3923 (.2628- .6804)
3.25	24.65 (19.07- 28.82)	9.25	6.080 (5.012- 7.605)	15.25	1.499 (1.107- 2.202)	21.25	.3700 (.2469- .6468)
3.5	23.26 (18.13- 27.09)	9.5	5.735 (4.706- 7.220)	15.5	1.414 (1.040- 2.091)	21.5	.3491 (.2320- .6148)
3.75	21.94 (17.23- 25.46)	9.75	5.410 (4.418- 6.855)	15.75	1.334 (.9773- 1.987)	21.75	.3293 (.2179- .5844)
4	20.70 (16.38- 23.92)	10	5.104 (4.148- 6.508)	16	1.259 (.9179- 1.887)	22	.3107 (.2047- .5555)
4.25	19.52 (15.57- 22.49)	10.25	4.814 (3.895- 6.180)	16.25	1.187 (.8622- 1.793)	22.25	.2931 (.1924- .5281)
4.5	18.42 (14.79- 21.13)	10.5	4.542 (3.657- 5.868)	16.5	1.120 (.8098- 1.703)	22.5	.2765 (.1807- .5021)
4.75	17.37 (14.06- 19.86)	10.75	4.284 (3.433- 5.571)	16.75	1.057 (.7607- 1.618)	22.75	.2608 (.1698- .4773)
5	16.39 (13.37- 18.67)	11	4.042 (3.224- 5.290)	17	.9971 (.7145- 1.538)	23	.2460 (.1595- .4538)
5.25	15.46 (12.71- 17.54)	11.25	3.813 (3.027- 5.023)	17.25	.9406 (.6711- 1.461)	23.25	.2321 (.1499- .4314)
5.5	14.58 (12.08- 16.60)	11.5	3.597 (2.842- 4.770)	17.5	.8873 (.6304- 1.388)	23.5	.2190 (.1408- .4102)
5.75	13.75 (11.48- 15.76)	11.75	3.393 (2.669- 4.530)	17.75	.8371 (.5922- 1.319)	23.75	.2066 (.1323- .3900)
6	12.97 (10.92- 14.96)	12	3.200 (2.506- 4.302)	18	.7897 (.5563- 1.253)	24	.1949 (.1243- .3708)

10.9 Appendix 9: Metaanalysis of codeine pharmacokinetics after oral administration (Guido Sticht ,Köln)

Table 14: 123 µmole Codeine (50 mg phosphate or 43 mg sulphate) (absorption, distribution and elimination)

Evaluated studies	**Data from comparative single dose studies**	**Age (years)**	**Dose (µmol)**	**Cp0 (nmol/L)**	**$t_{½}$Ka (h)**	**$t_{½}$α (h)**	**$t_{½}$β (h)**	**t_0 (h)**	**V% (%)**
Eckhardt et al., 1998	extensive metabolizers (5M/4F)	29.7±3.2	418.4	-	-	-	3.9(2)	-	-
«	poor metabolizers (5M/4F)	34.6±4.6	418.4	-	-	-	3.8(2)	-	-
Caraco et al., 1996	extensive metabolizers (10M)	32.1±1.1	295.4	439(2!)	0.149(2!)	2.84(2!)	2.76(2!)	0.141(2!)	98.4(2!)
«	poor metabolizers (6M)	34.2±1.3	295.4	391(2!)	0.085(2!)	0.72(2!)	2.96(2!)	0.158(2!)	98.4(2!)
Guay et al., 1987	single + (multiple) dose (6M/4F)	27.8±3.7	172.2	187(2!)	0.137(2!)	1.14(2!)	4.38(2!)	0.142(2!)	32.8(2!)
Lafolie et al., 1996	plasma + (urine) pharmacokin. (6)	22-61	123	222(2!)	0.188(2!)	2.44(2!)	3.32(2!)	0.102(2!)	65.1(2!)
Yue et al., 1991a	extensive metabolizers (3M/5F)	33±3.9	123	275(2!)	0.270(2!)	1.22(2!)	3.61(2!)	0.093(2!)	65.1(2!)
«	poor metabolizers (2M/4F)	30±6	123	196(2!)	0.271(2!)	1.91(2!)	3.04(2!)	0.219(2!)	98.4(2!)
Yue et al., 1991b	Caucasian + (Chinese) (3M/5F)	33.4±3.9	123	172(2!)	0.128(2!)	0.89(2!)	3.33(2!)	0.237(2!)	99.2(2!)
Chen et al., 1991	extensive metabolizers (7M/1F)	25-37	73.8	299(2!)	0.185(2!)	2.02(2!)	3.32(2!)	0.096(2!)	96.5(2!)
Findlay et al., 1978	+ (aspirin) (12M)	-	147	384(1!)	0.301(2!)	3.32(2!)	3.47(2!)	0.166(2!)	86.1(2!)
«	+ (acetaminophen) (20M)	-	147	315(1!)	0.268(2!)	2.37(2!)	3.75(2!)	0.163(2!)	65.1(2!)
Mikus et al., 1997	extensive metabolizers (5)	21-26	147	429(2!)	0.106(2!)	0.68(2!)	1.96(2!)	0.003(2!)	65.1(2!)
«	poor metabolizers (5)	24-29	147	332(2!)	0.223(2!)	1.53(2!)	2.33(2!)	0.004(2!)	63.6(2!)
Quiding et al., 1993	analgesic effect (25M)	20-39	111	486(1!)	0.420(2!)	2.79(2!)	1.99(2!)	(0.001)	93.8(2!)
«	after oral surgery (25M)	20-35	222	378(1!)	0.242(2!)	3.15(2!)	2.54(2!)	(0.001)	93.4(2!)
	Mean ± SD			**329 ± 101**	**0.246 ± 0.097**	**2.27 ± 0.85**	**3.08 ± 0.72**	**0.138 ± 0.059**	**82.0 ± 18.7**
	Number of trials			14	14	14	16	12	14
	Number of observations			154	154	154	172	104	154

Data from comparative single dose studies	**Evaluated studies**	**C_{max} (nmol/L)**	**t_{max} (h)**	**AUC_{o-oo} (nmol*h/L)**	**G (kg)**
Eckhardt et al., 1998	extensive metabolizers (5M/4F)	288(1)	-	1181(1)	-
«	poor metabolizers (5M/4F)	362(1)	-	1623(1)	-
Caraco et al., 1996	extensive metabolizers (10M)	339(2)	0.83(2)	1678(2!)	78.7±2.1
«	poor metabolizers (6M)	356(2)	0.58(2)	1623(2!)	87.3±2.1
Guay et al., 1987	single + (multiple) dose (6M/4F)	447(2)	0.60(2)	1669(2!)	73.1±11.6
Lafolie et al., 1996	plasma + (urine) pharmacokin. (6)	341(2)	1.10(2)	1377(2!)	76.9±10.8
Yue et al., 1991a	extensive metabolizers (3M/5F)	275(2)	1.0(2)	828(2!)	66±10
«	poor metabolizers (2M/4F)	266(2)	0.86(2)	788(2!)	69±11
Yue et al., 1991b	Caucasian + (Chinese) (3M/5F)	146(2)	0.88(2)	792(2!)	66±10
Chen et al., 1991	extensive metabolizers (7M/1F)	294(2)	0.97(2)	1381(2!)	67.9±11.9
Findlay et al., 1978	+ (aspirin) (12M)	442(1)	1.0(2)	2015(1!)	-
«	+ (acetaminophen) (20M)	381(1)	1.1(2)	2083(1!)	-
Mikus et al., 1997	extensive metabolizers (5)	601(2)	0.54(2)	1325	76±9
«	poor metabolizers (5)	505(2)	0.62(2)	1365	80.4±7
Quiding et al., 1993	analgesic effect (25M)	266(1)	1.0(2)	1167	-
«	after oral surgery (25M)	268(1)	1.0(2)	1362	-
	Mean ± SD	**336 ± 99**	**0.92 ± 0.17**	**1400 ± 382**	
	Number of trials	16	14	16	



Pharmacokinetic parameters derived from evaluation of pharmacokinetic studies

Cp0:	329	±	101	nmol/L
Ka:	2.82	±	0.80	h^{-1}
α:	0.305	±	0.030	h^{-1}
β:	0. 225	±	0.043	h^{-1}
t_0:	0.138	±	0.059	h
%:	82.0	±	18.7	%
B:	90			%

				derived from time-course of plasma concentrations		
C_{max}:	336	±	99	292	(246-321)	nmol/L
t_{max}:	00.92	±	0.17	1.12	(0.96-1.44)	h
AUC_{o-oo}:	1400	±	382	1555	(1244-1957)	nmol*h/L

Figure 8: Plasma concentration-time curve of morphine-6-glucuronide after intravenous administration of morphine

Codeine

Time (h)	Concentration (nmol/L)	Time (h)	Concentration (nmol/L)	Time (h)	Concentration (nmol/L)	Time (h)	Concentration (nmol/L)
.25	98.04 (68.53- 123.1)	6.25	94.36 (73.26- 121.6)	12.25	23.35 (14.05- 38.87)	18.25	5.877 (2.732- 12.67)
.5	223.3 (174.8- 259.7)	6.5	88.99 (68.37- 115.9)	12.5	22.04 (13.12- 37.09)	18.5	5.550 (2.552- 12.09)
.75	275.1 (218.8- 310.6)	6.75	83.93 (63.80- 110.4)	12.75	20.80 (12.25- 35.38)	18.75	5.241 (2.385- 11.55)
1	291.2 (239.3- 321.1)	7	79.16 (59.55- 105.3)	13	19.64 (11.44- 33.76)	19	4.950 (2.228- 11.02)
1.25	290.1 (246.2- 312.7)	7.25	74.66 (55.58- 100.3)	13.25	18.54 (10.68- 32.21)	19.25	4.675 (2.081- 10.52)
1.5	281.2 (245.0- 297.8)	7.5	70.42 (51.87- 95.69)	13.5	17.50 (9.983- 30.74)	19.5	4.415 (1.945- 10.05)
1.75	268.8 (239.3- 287.4)	7.75	66.42 (48.41- 91.22)	13.75	16.52 (9.323- 29.33)	19.75	4.170 (1.817- 9.597)
2	255.2 (231.2- 275.6)	8	62.66 (45.19- 86.97)	14	15.59 (8.707- 27.99)	20	3.939 (1.697- 9.163)
2.25	241.4 (221.3- 263.3)	8.25	59.11 (42.18- 82.92)	14.25	14.72 (8.132- 26.71)	20.25	3.720 (1.586- 8.748)
2.5	227.9 (206.9- 251.2)	8.5	55.76 (39.37- 79.06)	14.5	13.89 (7.595- 25.49)	20.5	3.514 (1.482- 8.353)
2.75	215.0 (193.2- 239.4)	8.75	52.61 (36.75- 75.38)	14.75	13.12 (7.094- 24.32)	20.75	3.319 (1.385- 7.976)
3	202.8 (180.3- 228.1)	9	49.63 (34.31- 71.88)	15	12.38 (6.626- 23.21)	21	3.135 (1.294- 7.615)
3.25	191.2 (168.2- 217.3)	9.25	46.82 (32.02- 68.55)	15.25	11.69 (6.188- 22.15)	21.25	2.961 (1.209- 7.271)
3.5	180.2 (157.0- 207.0)	9.5	44.18 (29.90- 65.37)	15.5	11.04 (5.780- 21.14)	21.5	2.797 (1.129- 6.943)
3.75	169.9 (146.4- 197.2)	9.75	41.68 (27.91- 62.34)	15.75	10.42 (5.399- 20.18)	21.75	2.642 (1.055- 6.630)
4	160.2 (136.6- 187.8)	10	39.33 (26.06- 59.45)	16	9.845 (5.043- 19.26)	22	2.495 (.9866- 6.331)
4.25	151.0 (127.5- 178.9)	10.25	37.11 (24.33- 56.70)	16.25	9.296 (4.711- 18.38)	22.25	2.357 (.9219- 6.045)
4.5	142.3 (118.9- 170.4)	10.5	35.02 (22.71- 54.08)	16.5	8.777 (4.400- 17.54)	22.5	2.226 (.8615- 5.773)
4.75	134.2 (110.9- 162.4)	10.75	33.05 (21.20- 51.58)	16.75	8.288 (4.111- 16.75)	22.75	2.103 (.8050- 5.513)
5	126.5 (103.5- 154.7)	11	31.19 (19.80- 49.20)	17	7.826 (3.840- 15.98)	23	1.987 (.7523- 5.264)
5.25	119.3 (96.62- 147.4)	11.25	29.43 (18.48- 46.94)	17.25	7.390 (3.587- 15.26)	23.25	1.877 (.7030- 5.027)
5.5	112.5 (90.16- 140.5)	11.5	27.78 (17.26- 44.77)	17.5	6.978 (3.351- 14.56)	23.5	1.773 (.6569- 4.801)
5.75	106.1 (84.13- 133.9)	11.75	26.21 (16.12- 42.71)	17.75	6.590 (3.130- 13.90)	23.75	1.675 (.6139- 4.585)
6	100.0 (78.51- 127.6)	12	24.74 (15.05- 40.75)	18	6.223 (2.924- 13.27)	24	1.582 (.5737- 4.378)

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