NATIONAL INSTITUTE FOR HEALTH AND WELFARE

Pekka Rapeli

Cognitive function in opioid substitution treated patients

Associations with drug treatment variables

RESEARCH

Research 130

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Associations with drug treatment variables

ACADEMIC DISSERTAITON

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Addiction is a brain disease, and it matters

Alan Leshner 1997

Dedicated to my family

Abstract

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Opioid-substitution treatment (OST) with the long-acting opioid agonist buprenorphine or methadone has proven to be the most effective treatment for opioid-dependence. The duration of treatment is typically years or even decades. Thus, the psychosocial rehabilitation of patients needs to be initiated simultaneously with drug treatment. Rehabilitation may include education, participation in employment programs, or getting a driver's license. Patients, their significant others, or the treatment team are often perplexed by the goal-setting of rehabilitation. It is not uncommon for them to think that an opioid-substitution drug as such would negatively affect mental capacities and therefore the rehabilitation goals need to be set low. On the basis of findings made in this thesis, a more optimistic view about the cognitive competence of OST patients is better founded.

In this thesis, cognitive performance of OST patients was examined by attention, working memory, and episodic memory tests. The participants also completed a memory complaint questionnaire. Patients who had recently entered OST were examined three times within the first year in the OST. Normal control participants did the tests at similar intervals. Fourteen buprenorphine and 12 methadone patients and 14 normal controls were examined at each time points (T1, T2, and T3). The largest study examined drug treatment variables as predictors of cognitive performance by using data from 104 patients. The final study was a case series examining driving fitness using data from 22 patients.

Methadone patients performed worse in many attention-related reaction time tasks in relation to normal controls or buprenorphine patients. In each OST drug group, approximately 10% of the attention performance could be predicted by drug treatment variables. In working memory both drug groups were impaired relative to controls in most tests. Improvement of working memory function in one test among buprenorphine patients between T2 and T3 was an exception. In the regression analysis, use of benzodiazepine (BZD) medication predicted impaired working memory performance. In episodic memory tests both drug groups lagged behind controls, although not all differences were statistically significant. Treatment with more than one other psychoactive drug (than opioid or BZD) and frequent substance abuse during the past month predicted about 20% of verbal episodic memory performance. Subjective memory problems were common in OST patients. In an on-road driving test all except one of 22 OST patients were found to be fit to drive a car.

The close to normal cognitive performance in stable OST patients supports the idea of efficient compensation of the neural burden that is related to their previous opioid abuse history. This compensation may not be as efficient among those with recent frequent substance use or with concurrent psychoactive polypharmacy. The results of these studies bring relevant new information for patients and prescribers when choosing between different pharmacological and non-pharmacological treatment options. Also, the results may encourage OST patients for setting education and employment goals with normal cognitive demands.

Keywords: opioid use disorder, neurocognition, opioid agonist therapy

Tiivistelmä

Pekka Rapeli, Cognitive function in opioid substitution treated patients. Associations with drug treatment variables [Kognitiiviset toiminnot opioidiriippuvuuden korvaushoitopotilailla: Yhteydet lääkemuuttujiin]. Terveyden ja hyvinvoinnin laitos. Tutkimus 130. 174 sivua. Helsinki, Finland 2014.
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Opioidiriippuvuuden korvaushoidossa on tällä hetkellä n. 2400 suomalaista henkilöä. Aivojen opioidireseptoreita pitkäaikaisesti aktivoiva korvaushoitolääkitys buprenorfiinilla tai metadonilla ei aiheuta päihtymystä, mutta vähentää merkittävästi opioidien väärinkäyttöä. Korvaushoito onkin todettu tehokkaimmaksi tavaksi hoitaa opioidiriippuvuutta. Tyypillisesti hoito kestää vuosia tai vuosikymmeniä ja potilaiden psykososiaalinen kuntoutus on syytä aloittaa samanaikaisesti lääkehoidon kanssa. Kuntoutukseen voi kuulua koulutuksen täydentäminen, työllistyminen ja ajokortin hankkiminen. Potilailla ja heidän asioitaan hoitavilla tahoilla on usein epätietoisuutta kuntoutuksen mahdollisuuksista. Ajatellaan esimerkiksi, että korvaushoitolääkitys heikentää tiedonkäsittelyn suoriutumisedellytyksiä ja tavoitetasoa on siksi laskettava. Tämän väitöskirjan tulosten perusteella melko optimistinen arvio korvaushoitopotilaiden tiedonkäsittelystä on paremmin perusteltavissa.

Tässä väitöskirjassa tutkittiin korvaushoitopotilaiden kognitiivista suoriutumista eli tiedonkäsittelyä tarkkaavuutta, työmuistia ja tapahtumamuistia arvioivilla testitehtävillä. Lisäksi osallistujat arvioivat omaa kokemustaan muististaan eli subjektiivista muistia. Hoidon äskettäin aloittaneiden potilaiden suoriutumista arvioitiin kolme kertaa ensimmäisen hoitovuoden aikana. Verrokkiryhmänä käytettiin normaaliväestöä edustavia verrokkeja. Kaikkiin seurantapisteisiin osallistui 14 buprenorfiinilla ja 12 metadonilla hoidettua potilasta ja 14 verrokkia. Laajimmassa tutkimuksessa selvitettiin, kuinka hyvin lääkemuuttujat ennustavat vähintään puoli vuotta hoidossa olleiden potilaiden kognitiivista suoriutumista (n=104). Viimeisimmässä tutkimuksessa arvioitiin 22:n korvaushoidossa olevan potilaan ajokykyä.

Metadonipotilaat suoriutuvat verrokkeja ja buprenorfiinipotilaita heikommin useissa tarkkaavuuttaa arvioivissa reaktioaikatehtävissä. Regressionanalyysissa, joka tehtiin erikseen molemmille potilasryhmille, lääkemuuttujat ennustivat kummassakin ryhmässä n. 10 % vireystilaa arvioivien reaktioaikojen vaihtelusta. Työmuistitehtävissä molemmat potilasryhmät suoriutuivat verrokkeja heikommin useimmissa testipisteissä. Buprenorfiinipotilailla havaittiin seurannan aikana toisessa työmuistitehtävässä tilastollisesti merkitsevää suoriutumisen kohentumista. Bentsodiatsepiinilääkityksen käyttö ennusti heikkoa työmuistisuoriutumista. Muistitehtävissä havaittiin molempien potilasryhmien suoriutuvan verrokkeja

heikommin, mutta suoriutumisen erot eivät aina yltäneet tilastollisesti merkitseviksi. Viimeisen kuukauden aikainen keskimäärin vähintään kolmena päivänä viikoittain tapahtuva päihteidenkäyttö sekä runsas muu psyykenlääkitys kuin opioidi- tai bentsodiatsepiinilääkitys ennustivat n. 20 % kielellisen muistin vaihtelusta. Potilaat kokivat subjektiivisen muistinsa selvästi verrokkeja heikommaksi. Ajokokeessa kaikki paitsi yksi potilas 22:sta todettiin kykeneväksi ajamaan henkilöautoa.

Potilailla havaittu lähelle normaalia yltävä suoriutuminen tukee käsitystä, jonka mukaan ihmisen keskushermostolla on hyvä kyky korvata opioidien väärinkäyttöhistoriaan liittyviä tiedonkäsittelytoimintojen haittavaikutuksia. Niillä potilailla, joilla viimeaikainen päihteidenkäyttö tai samanaikainen muu ajankohtainen keskushermostolääkitys on runsasta, tiedonkäsittelypuutosten korvaaminen ei näyttäisi onnistuvan yhtä hyvin. Tuloksilla arvioidaan olevan merkitystä, kun potilaat ja hoitotahot pohtivat lääkkeellisiä ja ei-lääkkeellisiä hoitovaihtoehtoja. Tulokset voivat myös kannustaa potilaita pyrkimään tiedonkäsittelyvaatimuksiltaan normaaleihin koulutuksiin ja työpaikkoihin.

Avainsanat: opioidiriippuvuus, korvaushoito, kognitiivinen suoriutuminen

Contents

List of original papers

This thesis is based on the following original articles referred to in the text by their Roman numerals I–V.

I Rapeli P. Fabritius C, Alho H, Salaspuro M, Wahlbeck K, Kalska H. Methadone vs. buprenorphine/naloxone during early opioid substitution treatment: a naturalistic comparison of cognitive performance relative to healthy controls. BMC Clinical Pharmacology 2007; 7: 5. doi: 10.1186/1472-6904-7-5

II Rapeli P, Fabritius C, Kalska H, Alho H. Memory function in opioid-dependent patients treated with methadone or buprenorphine along with benzodiazepine: longitudinal change in comparison to healthy individuals. Substance Abuse Treatment, Prevention, and Policy 2009, 4:6. doi:10.1186/1747-597X-4-6

III Rapeli P, Fabritius C, Kalska H, Alho H. Cognitive functioning in opioid-dependent patients treated with buprenorphine, methadone, and other psychoactive medications: stability and correlates. BMC Clinical Pharmacology 2011, 11:13. doi:10.1186/1472-6904-11-13

IV Rapeli P, Fabritius C, Kalska, Alho H. Do drug treatment variables predict cognitive performance in multidrug-treated opioid-dependent patients? A regression analysis study. Substance Abuse Treatment, Prevention, and Policy 2012, 7:45. doi:10.1186/1747-597X-7-45

V Rapeli P, Kuikka P, Sillanpää H, Simojoki K, Kalska H, Lillsunde P., Alho H. Driving, opioid maintenance and co-medications: A comprehensive assessment of 22 cases. Journal of Alcoholism and Drug Dependence 2013, 1:113. doi: 10.4172/jaldd.1000113

Abbreviations

5-HT	Serotonin
ACh	Acetylcholine
AMG	Amygdala
BA	Brodmann area
BZD	Benzodiazepine
CNS	Central nervous system
DA	Dopamine
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
GABA	Gamma aspartic butyric acid
HPC	Hippocampus
HPA	Hypothalamus-pituitary adrenal axis
M	Mean
MMT	Methadone maintenance treatment
n	Number of participants
NA	Noradrenaline
ns	Not statistically significant
OST	Opioid-substitution treatment
p	Probability
PASAT	Paced Auditory Serial Addition Task
PFC	Prefrontal cortex
RT	Reaction time
SD	Standard deviation
SUD	Substance use disorder
VIQ	Verbal Intelligence Quotient
WAIS-R	Wechsler Adult Intelligence Scale – Revised
WMS-R	Wechsler Memory Scale – third edition

1 Introduction

Opioid dependence means, in general, uncontrolled use of opioids despite negative consequences. Opioid abuse is a worldwide problem affecting 0.4% of the population over 15 years ("UNODC, World Drug Report ", 2013). Globally, heroin is still largely the most abused opioid. However, prevalence of abuse of prescription drugs such as buprenorphine, methadone, or oxycodone has surpassed heroin abuse in many countries. For instance, according to the latest Finnish statistics, about two thirds of those patients seeking treatment for opioid abuse are using mainly pharmaceutical opioids, with about half using buprenorphine (Subutex) intravenously (Varjonen, Tanhua, Forsell, & Perälä, 2012). Typically individuals who seek treatment for opioid dependence have a long history of substance abuse that started with other substances of abuse (Ross et al., 2005). Prescription opioids are often used along with other drugs or alcohol (Fischer et al., 2005). Thus, these individuals are in fact polysubstance abusers. In some rare cases, abuse of opioid drugs started as normal medical use of opioid drugs for pain relief, which then turned into abuse. Surveys have shown that among those who are given prescription opioids for chronic pain the prevalence of opioid abuse is between 2–6 % (Fields, 2011).

Opioid abuse is notorious for its high mortality rate, which is at least three times, and in some cases up to 50 times higher, than in the general population (Bargagli et al., 2006). Eventually most opioid abusers want a safer life without uncontrolled use of opioids. However, long-term abstinence from opioid-dependence is not easily achieved. Patients entering non-opioid treatment for opioid-dependence usually resume their opioid abuse (Kakko, Svanborg, Kreek, & Heilig, 2003). Instead, when opioid-dependent patients are admitted for opioid-substitution treatment (OST), also known as opioid maintenance treatment, in which they are given a slow-releasing opioid agonist orally, such as buprenorphine or methadone, treatment retention is high; many users stop illicit opioid use (Kakko et al., 2007). During OST, mortality of opioid-dependent individuals reduces steeply, but it rises again steeply if treatment is stopped (Cornish, Macleod, Strang, Vickerman, & Hickman, 2010; Degenhardt et al., 2009). It has been shown that OST is many times more cost-effective than no treatment (Connock et al., 2007). Consequently, most countries around the world have adopted OST as a treatment for opioid-dependence.

Some opioid-dependent patients, however, experience cognitive function problems during OST. In one survey half of OST patients complained about recent attention and memory problems while in another survey a third complaint about "troubles thinking clearly" or "confusion"(Dursteler-MacFarland et al., 2010; Dyer & White, 1997). This should be taken seriously as drug-dependent patients experiencing difficulties with concentrating and remembering have a poor treatment

prognosis (Fiorentine, Nakashima, & Anglin, 1999; Gossop, Stewart, & Marsden, 2003). Thus, it is important to objectively study cognitive function of OST patients and its correlates.

In addiction studies, cognitive functioning is often conceptualized as control of behavior or simply as cognitive control (Cheetham, Allen, Yuecel, & Lubman, 2010; Garavan & Weierstall, 2012). In this thesis cognitive function refers to cognitive functioning in real-life and cognitive performance refers to the performance in standardized neuropsychological tests. Cognitive function (for example memory functioning) correlates well with cognitive performance (memory test score), but these are not equivalent.

1.1 Substance use disorders

1.1.1 Addiction defined: diminshed control and behavioral changes

In order to define addiction it is relevant to first consult with the addicted individuals themselves. One of the few studies adopting this approach achieved the following written definitions from a highly experienced sample of abstinent male inmates (Walters & Gilbert, 2000). The most cited definition was "diminished control over substance use", followed by "need for survival", "urge or craving", "dependence, psychological", and "immediate gratification". In sum, an individual with a serious substance use problem commonly experiences diminished control over needs and urges.

In the field of medicine, addiction is considered a psychiatric diagnosis and referred to as dependence. Current definitions for dependence are given in the International Classification of Diseases, 10th version (ICD-10) or in the Diagnostic and Statistical Manual of the American Psychiatric Association, 4th version (DSM-IV) (Saunders, 2006). The common element in both classifications includes meeting three or more dependence sub-criteria that occur within a specified time frame: These include: (1) tolerance to the effects of substance abuse for achieving intoxication, or markedly diminished effects with continued use; (2) withdrawal symptoms that are specific to the substance being used; (3) impaired control over substance abuse; (4) neglect of important activities; (5) time spent in substance-related activity; (6) continued use despite adverse physical or psychological consequences; and (7) compulsive use or strong desire to use the substance. The last criterion is not included in the DSM-IV, and there are also other small differences between these definitions. However, both diagnostic definitions are highly reliable (Hasin, Hatzenbuehler, Keyes, & Ogburn, 2006). The recently launched DSM-V psychiatric diagnostics uses the term "substance use disorder" rather than "dependence" and 'abuse' (Regier, Kuhl, & Kupfer, 2013). In this thesis 'drug addiction' and 'substance

use disorder' (abbreviated as SUD) are used synonymously and 'dependence' refers to addiction as a psychiatric diagnosis according to the DSM-IV.

While medical definition of addiction is very important for scientific studies some of the abnormalities which are commonly related to addiction may exist before any development of addictive behavior, although these tend to become worse when addiction develops. These include individual 'motivational system' abnormalities like propensity to anxiety, depression, or impulsivity (West, 2006). Also, there are social conditions in which addiction is seen as normal behavior. These include conditions that lack of other sources of contentment than easily available substances of abuse or reduce individual sense of self-worth, and thus reduce desire for self-protection or reflection (Davies, 1992; West, 2006).

Although scientific definitions of addiction are likely to remain somewhat fuzzy due to ongoing evolution of human social life, the idea that prolonged drug use brings about major changes in the brain is now well evidenced. Brain changes can be molecular, cellular, structural, or functional, and they may be manifested by brain metabolism, receptor function, gene experession or behavioral responses to various cues (Leshner, 1997). Therefore, the rest of the introduction section will deal with neurobehavioral changes in addiction.

1.1.2 Addiction neurocircuitry is a cascade of neurobehavioral changes

It has been postulated that vulnerability towards development of a SUD among many individuals stems from an initially abnormal processing of reward in the brain (Blum, Liu, Shriner, & Gold, 2011). In concert with this idea a well-known neurobiological model of addiction describes it as a spiraling *addiction cycle* in which binge-like substance use dominates first and the *brain reward system* is over activated (Koob & Le Moal, 2008b). The repeated higher-than-normal reward, however, does not come without a cost. In order to reach a homeostatic balance, the *brains stress systems* (HPA axis and extrahypotothalamic stress system) are also activated (Koob & Le Moal, 2001). Initially HPA axis activity paradoxically intensifies reward, and increases impulsive substance use, but then more widespread activation of brain stress systems starts to decrease reward (Koob & Le Moal, 2008a). This second phase of addiction cycle is dominated by withdrawal symptoms and negative affect such as anhedonia or dysphoria. These are only temporarily relieved by substance use periods (Koob & Volkow, 2010) In the third phase of addiction cycle compulsive preoccupation with drug use and craving for drug reward (or anticipation of drug relief) dominate (Koob Le Moal 2008a). Although hard to measure precisely, it is widely asserted that while the initiation of drug use can be related to unfavorable social and cultural factors the later phases of addiction cycle are more related to neurobiological vulnerabilities (Koob & Le Moal, 2006).

Many findings support the conclusion that frequent use of addictive drugs produces profound changes in brain pathways, and these persist long after the dependent person stops abusing drugs. The brain changes are thought to be common for all the major drugs of abuse, and they have been summarized as a cascade of discrete but linked neuro-adaptions called *addiction neurocircuitry.* Five neural circuits are shown to be engaged sequentially, starting from reward processing in the mesolimbic dopamine system, extending finally to brain stress systems in the extended AMG (Koob & Volkow, 2010). The experimentally supported neuro-computational model of addiction circuitry currently lists 19 distinct neural locations and includes the major excitatory and inhibitory neurotransmitters (glutamate and GABA), monoamines (DA, NA, and 5-HT), ACh, and the corticotropin-releasing factor system (Noori, Spanagel, & Hansson, 2012). In more behavioral terms, cumulative evidence has linked the transition to drug addiction with the "reprogramming" of neuronal circuits that process important behavioral functions:

1. *Reward and motivation* engaging first the mesolimbic DA system originating in the ventral tegmental area and then neurotransmitters DA and opioid peptides in nucleus accumbens (shell and core) and dorsal striatum (Koob & Volkow, 2010; Luescher & Malenka, 2011);
2. *Conditioning and habit-formation* that has been linked to the activity in the ventral striatum, and thalamus circuits with output to the PFC (Depoy et al., 2013; Koob & Volkow, 2010; Le Moal & Koob, 2007);
3. *Cognitive control* (working memory, episodic memory, inhibitory control, and executive function) linked to dorsolateral, anterior, and inferior PFC, parietal cortex, and the hippocampal circuits (Koob & Volkow, 2010; Krmpotich et al., 2013);
4. *Interoception and self-awareness* associated with a proposed salience network which activates when the individual is integrating highly processed sensory data with visceral, autonomic, and hedonic "markers," (Seeley et al., 2007). The salience network gives the individual intuitive knowledge so that she/he can decide what to do (or not to do). The brain networks for interoception and salience processing include widely distributed midbrain areas such as insula, ventromedial and orbitofrontal cortex, anterior cingulate cortex, parts of the extended AMG and periaqueductal gray. At rest, there is overlapping activity between the salience network and the well-known 'resting state' or default mode networks (Cauda et al., 2013);
5. *Stress reactivity, emotional pain, and arousal* linked to the extended AMG and brain stress systems. Extended AMG represents a macrostructure composed of several basal forebrain structures: the bed nucleus of the stria terminalis, central medial AMG, and a transition zone in the posterior part of the medial nucleus accumbens.

As shown in Figure 1, it can by hypothesized that the cognitive control system loses its relative strength over other regulatory neural circuits. Instead, recip-

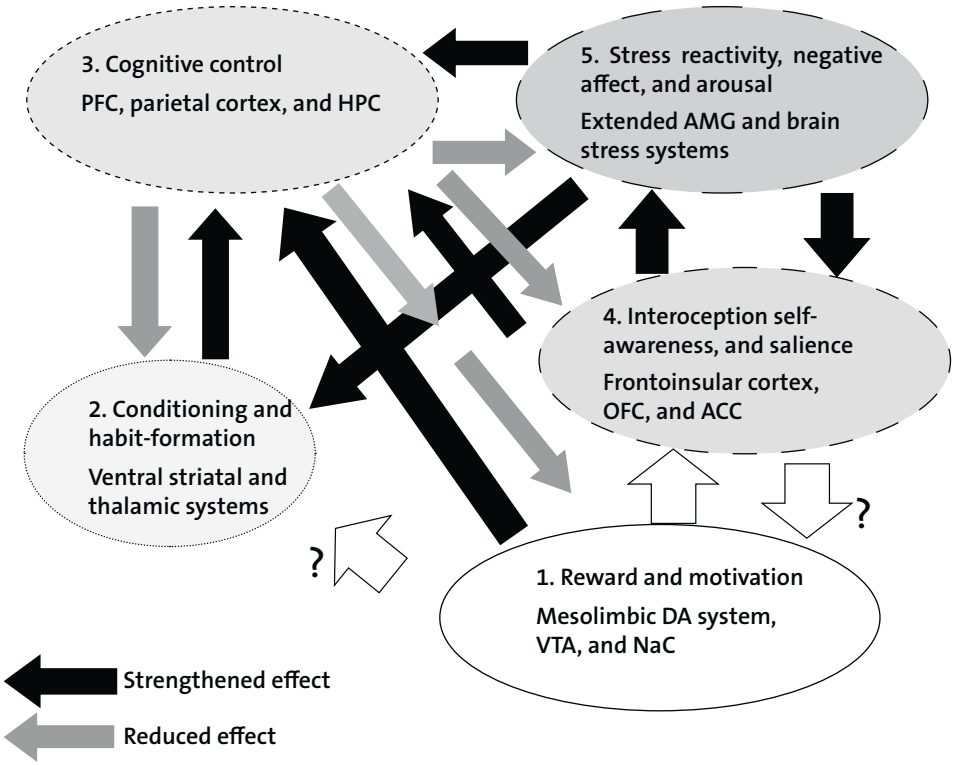


FIGURE 1. Neural cascade of behavioral dysfunction in addiction.

ACC = anterior congulate cortex; AMG = amygdala; DA = dopamine; HPC = hippocampus; NAc = nucleus accumbens; OFC = orbitofrontal cortex; PFC = prefrontal cortex; VTA = ventral tegmental area.

rocal connections between many other neural systems are hypothesized to become stronger.

1.1.3 Opioid abuse induces widespread neurotoxicity in the brain

A substance is considered neurotoxic if it causes any adverse effect on the structure or function of the central and/or peripheral nervous system (Erinoff, 1995). Neurotoxicity may be reversible or permanent; masked by temporary compensatory mechanisms; or show lifetime temporal and within-species variability (Wallace, 2005). Opioid dependence has been associated with increased cell death through activating mitochondrial and death-receptor apoptotic pathways, causing alteration in the dendrites, abnormal neurogenesis, neuro-degeneration, and dysfunctional connectivity (J. X. Liu et al., 2009; Shen, Wang, Wang, & Lou, 2012; Upadhyay et al., 2010).

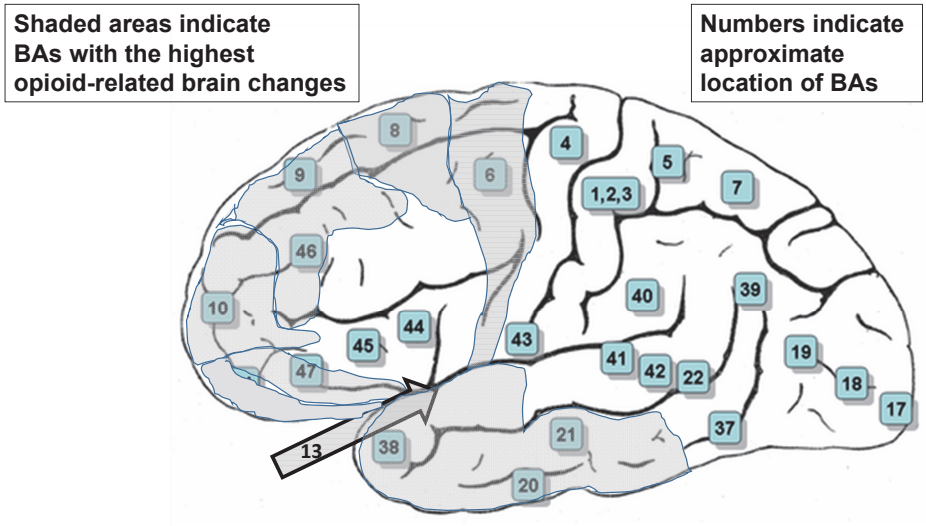


FIGURE 2A. Schematic presentation of lateral cortical areas linked to opioid-dependence.

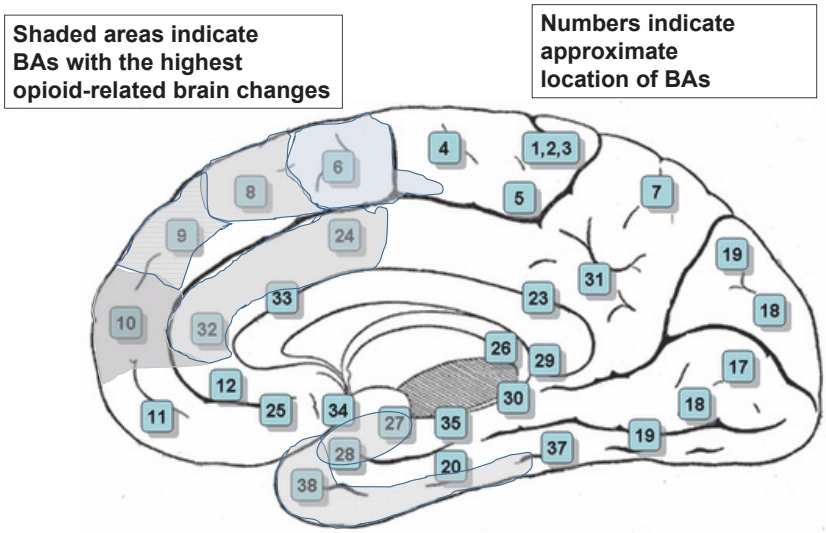


FIGURE 2B. Schematic presentation of medial cortical areas linked to opioid-dependence.

(Modified from Wikipedia: http://en.wikipedia.org/wiki/Brodmann_area (Access date 15.11.2013)

Brain structure comparisons between opioid-dependent patients and normal controls typically show signs of cerebral atrophy with increased size of the lateral ventricles and increased width of the sylvian fissures (Borne, Riascos, Cuellar, Vargas, & Rojas, 2005; Kivisaari et al., 2004; Pezawas et al., 1998). Some atrophy findings like those in the cerebellum or thalamus have been associated with concomitant polysubstance and alcohol use (Aasly, Storsaeter, Nilsen, Smevik, & Rinck, 1993; Anderson, Rabi, Lukas, & Teicher, 2010). More specifically 'pure' opioid-dependent patients have shown decreased gray matter density in the bilateral PFC cortex (BA 6, 8, 9, 10, 11, 46, and 47), the bilateral insular cortex (BA 13), the bilateral anterior cingulate (BA 24, 32), the bilateral temporal cortex (BA 20, 21 and 38), the left fusiform cortex (BA 37), and the right uncus (BA 28) (H. H. Liu et al., 2009; Lyoo et al., 2006; X. Wang et al., 2012; Yuan et al., 2009). Figures 2a and 2b show the cortical Brodman areas with the highest opioid-related neuropathology.

In subcortical areas, decreased AMG volumes have been reported in one study (Upadhyay et al., 2010). White matter integrity deficits have been found predominantly in the right PFC, right temporal cortex, and right parietal, cingulate, corpus callosum, and thalamic radiation; and some of these deficits correlate with the duration of opioid abuse, indicating probable neurotoxicity (Li et al., 2013; Liu et al., 2008; Qiu et al., 2013). There is evidence that among those with a ten-year or so history of opioid dependence, the white matter deficit is even more diffuse, extending from myelin damage to axon damage (Bora et al., 2012; Qiu et al., 2013). In fact, it is not clear if any brain area is fully protected against widespread cellular or microvascular damage found in polysubstance using opioid-dependent patients (Buttner, Rohrmoser, Mall, Penning, & Weis, 2006; Ferrer-Alcon, La Harpe, & Garcia-Sevilla, 2004; Ferrer-Alcon, La Harpe, Guimon, & Garcia-Sevilla, 2003) .

The cellular route to neuropathology includes mitochondrial dysfunction, oxidative stress, damage to the neurofilaments of the cytoskeleton, and dendritic spines (Cunha-Oliveira, Rego, & Oliueira, 2008; Ferrer-Alcon et al., 2004; Ferrer-Alcon et al., 2003; T. E. Robinson & Kolb, 2004). Animal studies have shown that chronic opioid use increases the expression of apoptosis-related proteins and impairs memory performance (Tramullas, Martinez-Cue, & Hurle, 2007, 2008). Neuron loss is increased by a concomitant decrease of hippocampal neurogenesis (Cunha-Oliveira et al., 2008). Chronic opioid use as such creates immunosuppression (Roy et al., 2011). As opioids are often used intravenously with dirty needles, hepatitis C or human immunodeficiency virus (HIV) infections are not uncommon among opioid abusers. Also, bacterial infections in skin or soft-tissues, endocarditis, pulmonary, or sexually transmitted infections are common. For instance, chronic hepatitis C has been associated with cognitive impairment (Hilsabeck et al., 2010). Endocrine changes of opioid abusing patients include both hypothalamic-pituitary-gonadal and hypothalamic-pituitary-adrenal system (Brennan, 2013). Lower than normal sex hormone level can be seen in both sexes, and this may affect up to 90% of chronic opioid users (Katz & Mazer, 2009). Also, lower than normal

cortisol levels are found in opioid abusers (Abs et al., 2000). Optimal cortisol level is important for several cognitive functions (Kukolja, Thiel, Wolf, & Fink, 2008; Van Houdenhove, Van den Eede, & Luyten, 2009). Activation of mu opioid receptor increase sweet preference and this may lead to high sugar intake, and eventually to reduced glycemic control. In fact, delayed and increased insulin response to glucose loads and increased fasting insulin levels have been found in both heroin addicts and methadone patients (Mysels & Sullivan, 2010). Transient brain dysfunction and cognitive impairment is common in hypo- or hyperglycemic conditions (Weston, 2012), while long-term brain dysfunction is possible (Mattson, 2012; Suh, Hamby, & Swanson, 2007). Some of the cellular and synaptic adaptations leading to the development of opioid tolerance and dependence may then lead to further adaptations "downstream" from the actual opioid synapses. This could regulate two or more synapses in series through a domino effect involving at least glutamate, GABA, and NA synapses (Williams, Christie, & Manzoni, 2001).

1.1.4 The human brain may counterbalance opioid-abuse related neurotoxicity by neuroprotective adaptations

The neurotoxic changes decribed in the previous chapter indicate that cognitive performance deficits could be seen in opioid-dependent patients. For instance, working memory impairment in methadone-treated opioid dependent patients has been associated with altered white matter integrity in the left superior fasciculus that connects the superior temporal gyrus (BA 41) with the dorsolater PFC, and memory impairment with white matter deficits in the left para-hippocampal area of the cingulum (BA 30) (W.-C. Lin et al., 2012). However, with neuropathology, cognitive deficits are not always found. Thus, it is likely that some of the neural adaptations in chronic opioid users could be compensatory and neuroprotective rather than neurotoxic (Weber et al., 2006). The hypothesized interplay between neuropathology and compensatory mechanisms related to opioid abuse is described in Figure 3. Notably, there is evidence that the adenosine A1 receptor and glial activity could prevent glutamate-induced excitotoxicity in the CNS (Castillo, Leon, Ballesteros-Yanez, Albasanz, & Martin, 2010; Lauro et al., 2010; Lauro et al., 2008). The role of these changes in cognitive functioning among opioid abusers is, however, not well-known although there is preliminary evidence supporting compensatory mechanisms for preserving working memory function (Marvel, Faulkner, Strain, Mintzer, & Desmond, 2012). Also, there is some evidence that opioid agonism in delta receptors can be neuroprotective against hypoxia (Benarroch, 2012). It is not known if buprenorphine or methadone use would have this effect, although mild delta agonist action is possible.

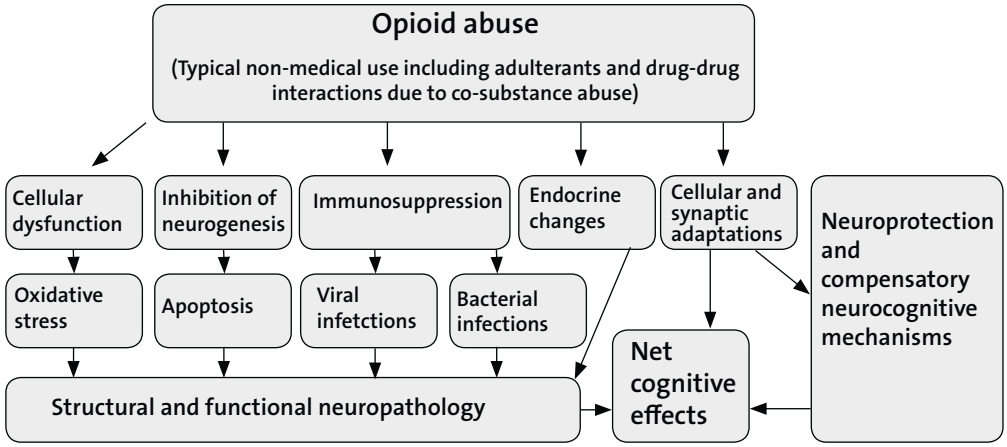


FIGURE 3. Opioid abuse related neural changes and cognitive function.

11.5 Neurotoxicity of a substance does not equal a neuropsychological deficit related to its use

As outlined in the previous chapter, the neurotoxic potential of substance abuse may be high, but may be functionally well compensated for and not observed in neuropsychological testing. Furthermore, when neuropsychological deficits are found in SUD patients some of these may be premorbid. For instance, a longitudinal study including alcohol dependent patients instead of opioid-dependent patients showed that premorbid general cognitive performance deficit predicted failure to recover from dependence by the age of 40 years (Penick et al., 2010). Table 1 shows an overview of findings of premorbid cognitive deficits among individuals who develop SUD and are likely to seek help for it. In this table and the following tables, domains of cognitive performance are classified according to factor analysis studies and theoretical accounts based on them (Ardila & Bernal, 2007; Fals-Stewart & Bates, 2003; Friedman et al., 2006; Jurado & Rosselli, 2007; Tulsky & Price, 2003). In the tables of the Introduction section, attention and working memory are grouped together even though they are later dealt with separately. This is based on the fact that some cognitive tests, such as the Digit Span, seem to tap both constructs equally, indicating an overlap of the constructs (Postle, 2006).

As shown in the Table 1, so far, there is no evidence for a higher than normal prevalence of premorbid learning and memory or motor performance deficit among those seeking treatment for SUD. Notably, among non-treatment seeking individuals with SUD, cognitive performance deficits are likely to be minor if any. For instance, a recent large (n=8992) prospective cohort study found that in the

TABLE 1. Premorbid cognitive deficits among individuals with SUD

attention or working memory	Attention score obtained from five attention tests (Tapert, Baratta, Abrantes, & Brown, 2002)
Motor performance	?
Processing speed	?
Executive function	Response inhibition measure from the Stop task (Nigg et al., 2006; Wong, Brower, Nigg, & Zucker, 2010)
Verbal	?
Visuoperceptual	Mazes subtests from the Wechsler Preschool and Primary Scale of Intelligence. (Pechtel, Woodman, & Lyons-Ruth, 2012)
Verbal learning and memory	?
Visual learning and memory	?
Overall cognitive performance	Standardized sum measure of four reasoning test including verbal, logical, spatial, and technical knowledge subtests (Gale, Batty, Tynelius, Deary, & Rasmussen, 2010) Combination of premorbid cognitive and neurological measures (Penick et al., 2010)

middle-aged general population, illicit lifetime drug use shows actually positive association with general cognitive functioning (Dregan & Gulliford, 2012). However, this association was not seen for current use and there was a tendency for more serious drug use disorder (lifetime drug dependence) to be associated slightly negatively with general cognitive performance.

1.2 Opioids and cognitive function disorders

1.2.1 The opioid receptor family includes four known members

Opiates that can be derived from the poppy plant include opium, morphine, and codeine, to name the most well-known. The term "opiate" is also used for the semisynthetic drug heroin that is produced from poppy compounds. The term "opioids" has broader meaning, referring to endogenous opioids, opiates, and other semisynthetic and synthetic compounds with similar (morphine-like) properties (Trescot, Datta, Lee, & Hansen, 2008).

The scientific basis for the effects of opioids was established in the 1970s, when opioid receptors were found in the human CNS and in peripheral tissues. On the basis of their pharmacological profiles, opioid receptors are classified as mu, delta, kappa or nociceptin (also known as the orphanin-FQ) receptors (Corbett, Henderson, McKnight, & Paterson, 2006). Opioid receptors belong to the G protein-coupled group of receptors like the majority of known neurotransmitters and hormones. Opioid receptors in the brain are activated both by endogenously produced

opioid peptides and by exogenously administered opioid compounds (Waldhoer, Bartlett, & Whistler, 2004)

Opioids are not considered neurotransmitters because their activity cycle is different to that of a neurotransmitter. For instance, opioids lack a re-uptake mechanism and their release requires greater stimulation than that of neurotransmitters (Kandel, Schwartz, & Jessell, 2000). However, in some cases, opioids are co-released with a neurotransmitter and act like a neurotransmitter. Furthermore, opioid receptor activity is able to modify the function of a neurotransmitter and neurohormone systems (Fichna, Janecka, Costentin, & Do Rego, 2007). Opioid *agonists* are able to *inhibit* the main CNS neurotransmitter systems (ACh, glutamate, GABA, DA, 5-HT, and NA) (Corbett et al., 2006). However, opioids may also *excite* neurotransmitter release via disinhibition (Benarroch, 2012).

1.2.2 Endogenous opioids modulate cognitive function

Endogenous opioids are supposed to have only minor effects on cognitive function under normal conditions (Carlsson & Carlsson, 2002). However, when an individual is exposed to situations with high relevance for survival or reproduction, or to serious stress, opioids play an important role by eliciting pleasure or pain and modulating cognitive function (Guarna, Ghelardini, Galeotti, Stefano, & Bianchi, 2005). For instance, endogenous opioids may promote forgetting pain producing experiences, and thus help survival under threat (Guarna et al., 2005). In support of this, one study found that when drug-naïve individuals were exposed to verbal and visual material causing high negative emotional arousal, those receiving a dose of non-specific opioid antagonist naltrexone before the exposure performed better than those receiving a placebo on a memory test related to the emotional material (Katzen-Perez, Jacobs, Lincoln, & Ellis, 2001). In contrast, when the same individuals were exposed to emotionally neutral stimuli, those receiving naltrexone performed worse than those receiving placebo. In another study, the mu opioid receptor agonist naloxone was given as pretreatment before (stressful) electroconvulsive therapy and resulted in better attention task performance and verbal memory in comparison to placebo (Prudic, Fitzsimons, Nobler, & Sackeim, 1999).

1.2.3 Cognitive deficits are pronounced in opioid-dependent patients seeking treatment

Neuropsychological studies reveal quite general cognitive deficits during opioid abuse. Table 2 shows cognitive performance findings from four selected well-controlled studies of opioid abusing individuals. As shown by the table, cognitive deficits have been found in verbal performance, visuoperceptual performance, attention/working memory, verbal learning and memory, executive function, and overall executive function. Other domains have not shown deficits or not been explored. Of note here is the fact that the Stevens et al. study is one of the few studies

that included a non-treatment seeking sample. Also, many of the well-known earlier studies have pooled methadone-treated and active opioid-abusers into the same group, and therefore the results of these studies are not reviewed here.

TABLE 2. Cognitive performance of among individuals with active opioid abuse in relation to normal controls

	Study			
	(Guerra, Sole, Cami, & Tobena, 1987)	**(Montoya, Hess, Covi, Fudala, & Johnson, 1994)**	**(Soyka et al., 2011)**	**(Stevens, Peschk, & Schwarz, 2007)**
Study characteristics	Heroin users tested before entering treatment (n = 93). Compared against normal controls (n = 30).	Heroin using opioid-dependent patients tested when entering treatment, most of them using recently cocaine or alcohol (n =162). Compared against norms from the general populations.	Opioid-dependent patients allowed to self-administer heroin maximum three times a day in a outpatient clinic (n = 20). Compared against normal controls (n = 25).	Community sample of polydrug abusing males with opiate dependence tested when positive for opioid and almost all to some other illicit drug too (n = 25). Compared against normal non-drug using controls (n = 26).
Tests and findings				
Attention or working memory	↓ Digit Span; ↓Toulouse-Pieron cancellation test		↓ 4/5 attention tests from the ART-90	↔ Delayed matching to sample RT ↓ Implicit sequence learning
Motor performance				
Processing speed				
Verbal		↓ WAIS-R Vocabulary score		↔ Multiple choice Word Comprehension Test
Visuoperceptual	↔ Raven matrices			↓ Figural reasoning
Visual learning and memory				
Executive function	↓ Verbal fluency test			↓ Trail Making Test B
Overall cognitive performance		↓ Shipley Institute of Living Scale, total score.		

ART-90 = Act and React Test System 90; ↔ = no significant difference between patients and normal controls: ↓ = patients impaired in relation to normal controls.

1.3 Opioid substitution treatment drugs

1.3.1 The scientific basis of opioid substitution treatment: long action of methadone and buprenorphine

In the latter part of the 1940s, some good experiences of using long-acting methadone as a morphine or heroin withdrawal drug were documented (Harris Isbell & Vogel, 1949). With the idea of "metabolic disease" and "neurologic susceptibility" in mind, the Rockefeller Institute team in New York started trials in 1964 with methadone to produce a "narcotic blockade". Results of the initial success of these trials were published the following year (Dole & Nyswander, 1965). Since then the development of Methadone Maintenance Treatment programs has led to well-established knowledge on the dosing procedures needed for successful treatment (Green, Kellogg, & Kreek, 2004). In most cases, an oral methadone dose from 80–120 mg is sufficient to reach the desired effects of the drug, that is, to relieve opioid craving, suppress opioid withdrawal effects for 24–36 hours, block the effects of administered heroin, and develop tolerance to the narcotic or analgesic effects of methadone (Joseph, Stancliff, & Langrod, 2000).

Methadone is a full mu opioid receptor agonist and may cause a fatal respiratory depression if a significantly higher than usual dose is administered or the dose is injected. Therefore, *buprenorphine*, which is safer because of its partial mu agonist effect, has been increasingly used in OST programs (Vadivelu & Hines, 2004). Buprenorphine, which absorbs well if given sublingually, has an even longer effect than methadone (M. Greenwald et al., 2007). Unfortunately, if buprenorphine is abused intravenously in combination with other psychoactive substances, it may be hazardous. Therefore, a combined *buprenorphine/naloxone* preparation with a reduced intravenous abuse potential has been developed to replace buprenorphine in OST programs (Stoller, Bigelow, Walsh, & Strain, 2001). This compound contains the mu agonist buprenorphine and the antagonist naloxone in a 4:1 ratio. When the compound is used sublingually, the naloxone is not absorbed. Thus, it has similar pharmacokinetic properties as buprenorphine used alone (Comer, Walker, & Collins, 2005; Harris, Mendelson, Lin, Upton, & Jones, 2004). However, when the compound is used intravenously, the naloxone is activated and this reduces the abuse potential (Alho, Sinclair, Vuori, & Holopainen, 2007).

1.3.2 Milestones of opioid-substitution treatment in Finland

After the Second World War methadone had become available in Finland as a prescription medicine for severe pain with special permission from the prescription regulators. In 1973 few physicians were given permission to use methadone for individual opioid-dependent patients (Fabritius & Granström, 1999). In the early 1990s two physicians had started to prescribe buprenorphine for opioid-dependent patients, which led to restrictions being imposed on their prescription rights

(Selin, Hakkarainen, Partanen, Tammi, & Tigerstedt, 2013). However, these first treatments led to pressure for broader treatment availability. The first official regulations of OST with methadone or buprenorphine (Subutex) for a restricted period for each patient were given in 1997 (Simojoki, 2013). This initiated the slow spread of the treatment. However, as the advantages of OST programs become better known, restrictions on the treatment length were soon abolished. At the beginning of the 2000s, the Ministry of Social and Welfare wanted to speed up the spread of OST and criteria for OST were lowered. The current legislation issued by means of a decree in 2008 implied a significant change in the policy. OST is now the first choice treatment for opioid-dependence (Selin et al., 2013). Currently the buprenorphine/naloxone compound (Suboxone) is the most used drug therapy for opioid-dependence in Finland, with methadone used slightly less (Simojoki, 2013). Buprenorphine as a monotherapy is rarely used due its high demand in the illicit drug market.

1.4 Opioid substitution treatment drugs and cognitive function

1.4.1 Opioid-naive individuals show cognitive deficits when given buprenorphine or methadone

In order to have functional relevance to cognitive function, a drug needs to reach a threshold for clinical effects. In the case of G protein coupled receptor *antagonists*, such as opioid antagonists, at least 60% of receptor occupancy seems to be a threshold for noticeable cognitive effects (Grimwood & Hartig, 2009; Hirst et al., 2008). Opioid antagonist naloxone is able to occupy at least 80% of mu opioid receptors, and to a lesser degree, also kappa, delta, and nociceptin/orphanin receptors (Kim et al., 1997; Melichar, Nutt, & Malizia, 2003; Nicholson, Paterson, Menzies, Corbett, & McKnight, 1998; D. X. Wang, Sun, & Sadee, 2007). As basal opioid receptor tone is likely to have only a small, if any, effect on cognitive function in normal conditions, mixed results have been obtained after non-selective opioid antagonist naloxone administration: improvement, impairment, or no effect (Arnsten et al., 1983; Martin del Campo, McMurray, Besser, & Grossman, 1992; Prudic et al., 1999; Volavka, Dornbush, Mallya, & Cho, 1979; Wolkowitz & Tinklenberg, 1985).

The effects of opioid *agonist* administration on cognitive function are likely to be dependent on other receptor-binding parameters than the magnitude of receptor occupancy. High efficacy mu opioid receptor drugs like methadone show behavioral effects associated with the mu receptor in spite of very low receptor occupancy. In contrast to this, a low-efficacy mu agonist drug like buprenorphine needs high mu receptor occupancy to achieve the same behavioral effects (Grimwood &

Hartig, 2009). In addition, cognitive effects of the drugs are highly dependent on receptor location and density in the CNS.

When given intravenously to healthy opioid-naïve individuals, the prototypical mu opioid agonist drug morphine produces motor, attention/working memory, or visuospatial impairments in a dose-dependent manner. However, oral administration produces less cognitive effects (Stout & Farrell, 2003; Zacny & Gutierrez, 2003). For instance, one study found that an orally administered standard pain treatment dose of morphine (10 mg) produced a small negative effect on working memory but had no effect on episodic memory (Friswell et al., 2008).

Other opioid receptor agonist drugs are known to affect cognitive function, although the issue has not been studied well. In one study, the highly selective kappa agonist Salvinorin A produced dose-dependent verbal memory deficits, while in another study it failed to affect working memory (MacLean, Johnson, Reissig, Prisinzano, & Griffiths, 2013; Ranganathan et al., 2012). In both of these studies the participants had prior recreational experience with psychoactive Salvinorin A, but were without psychiatric diagnoses. Delta opioid agonists have been attributed with the enhancement of inhibitory control, while nociceptin/orphanin-FQ agonists have been attributed with a negative effect on long-term memory (Befort et al., 2011; Reiss, Prinssen, Wichmann, Kieffer, & Ouagazzal, 2012). However, only animal studies have so far been reported.

Table 3 shows the main pharmacological properties of buprenorphine and methadone and the related cognitive findings for both compounds on drug-naïve individuals. As can be noted from the Table, the cognitive effects of buprenorphine or methadone are not easily predicted from the findings for the single opioid receptor function of these drugs. This is because both compounds affect several opioid receptor types, and these may produce opposite cognitive effects. Of note here are the differences between buprenorphine and methadone on the mu and kappa receptor functions. Buprenorphine is a partial agonist for the mu receptor and an antagonist for the kappa receptor, while methadone is a full agonist for both receptors. The negative effect of methadone on memory function may reportedly be based on mu-receptor agonism-induced inhibition of ACh release in the NAc, HPC, and PFC (Hepner, Homewood, & Taylor, 2002). Thus, buprenorphine may not have as strong a negative effect on memory as methadone. In addition, it has been suggested that kappa antagonism of buprenorphine has a positive effect on cognitive functioning via restoration of optimal dopaminergic tone, while methadone as a dopaminergic inhibitor may not have a similar property (Spiga, Lintas, & Diana, 2008). However, if an individual uses opioids chronically, the pharmacology of buprenorphine and methadone becomes more complex than in short-term administration (Trescot et al., 2008).

TABLE 3. Pharmacology of buprenorphine and methadone in relation to cognitive performance in normal conditions

	Cognitive effects of the drug when given to healthy individuals	Opioid receptor activity	Opioid receptor activity
Buprenorphine	Intravenous administration produces dose dependent negative effect on attention/working memory, motor function, processing speed, and general cognitive function.	**Mu**: partial agonist with partial efficacy, which is compensated by high receptor affinity and occupancy. **Delta**: mixed agonist antagonist action possible. Efficacy is not well known. **Kappa**: antagonist activity. Efficacy in drug-naïve humans is not well known. **Nociceptin/Orphanin-FQ:** agonist activity. Efficacy not well-known. Interaction with mu activity likely.	Three active metabolites which may have contradictory activity on the opioid receptors. However, metabolites show low concentration in the brain. No significant effects on other neurotransmitter systems if not abused.
Methadone	Negative effect on attention. Other cognitive functions not studied in healthy individuals.	**Mu**: agonist with high efficacy despite low receptor occupancy **Delta**: agonist which may result in reduction of opioid tolerance **Kappa**: agonist with low efficacy **Nociceptin/Orphanin-FQ:** no known activity	Major metabolites inactive Weak glutamate NMDA receptor antagonist and monoamine reuptake inhibitor

Buprenorphine: (Brown, Holtzman, Kim, & Kharasch, 2011; Davids & Gastpar, 2004; Englberger, Kogel, Friderichs, Strassburger, & Germann, 2006; Jensen et al., 2008; Negus et al., 2002; S. E. Robinson, 2002; Smith, 2011; Walsh & Eissenberg, 2003; Zacny, Conley, & Galinkin, 1997; Zacny, Conley, Young, et al., 1997) Methadone: (M. P. Davis & Walsh, 2001; Kapur, Hutson, Chibber, Luk, & Selby, 2011; Neil, 1984; Raynor et al., 1994; Zacny, 1995) Cognitive effects of opioid receptors activity: (Friswell et al., 2008; Kuzmin, Madjid, Johansson, Terenius, & Ogren, 2009; MacLean et al., 2013; Pradhan, Befort, Nozaki, Gaveriaux-Ruff, & Kieffer, 2011; Stout & Farrell, 2003; Zacny, 1995).

1.4.2 No studies have compared short-term cognitive effects of buprenorphine vs. methadone in opioid-dependent patients

In their seminal study examining methadone as a withdrawal drug, Isbell and his collaborators had examined already in the 1940s the short-term cognitive effects of methadone in opioid-dependent patients. A deterioration of performance was seen in the Otis test, a timed multiple-choice intelligence test with both verbal and non-verbal items. The methadone dose varied in these experiments, ranging from a high 180 mg to an ultrahigh 800 mg (H. Isbell, Wikler, Eisenman, Daingerfield, & Frank, 1948). Surprisingly, later studies have not compared the short-term cognitive effects of buprenorphine and methadone. Instead, to my knowledge there are only a few separate studies examining one drug. The results of two well-controlled studies are summarized in Table 4. As shown by the Table a dose-effect after short-term buprenorphine treatment was seen in the recognition memory of a word list. No dose-effect was seen in attention/working memory or processing speed measures. Moreover, in the methadone study of Curran et al. (2001) verbal memory was the only impaired cognitive domain. A 100% daily stabilization dose of methadone was associated with impaired delayed story recall performance as compared to a placebo or a 50% methadone dose. Attention performance as measured by a RT task improved after 100% or 50% of daily methadone dose in comparison to a placebo. In motor performance or processing speed, no methadone effects were found.

1.4.3 Studies of cognitive performance in stable OST patients have shown mixed results

Dole and other pioneers of OST were aware of the studies of Isbell et al., reviewed in the previous section, which indicated an overall cognitive deficit due to methadone. Therefore, several neuropsychological studies were conducted using early patient samples. The results of these studies showed no overall cognitive deficits or slowing of RT that could be attributed to methadone (N.B. Gordon & Appel, 1995). Methadone doses in these studies were in the middle ranges, with a mean of 100 mg. Unfortunately, timing of the testing that followed the administration of the dose was not clearly specified.

Although early studies did not yield evidence of cognitive deficits among stable MMT patients, later studies have shown substantial cognitive impairment among them. The often-cited study by Darke et al (Darke, Sims, McDonald, & Wickes, 2000) showed that stabilized patients who were given a mean 79 mg of methadone showed substantial cognitive deficits in all major domains: attention, processing speed, verbal and visuoperceptal performance, memory, and executive function (Darke et al., 2000).

Table 5 summarizes the findings of three selected well-controlled studies, including for both buprenorphine and methadone patients in stable OST and com-

TABLE 4. Cognitive performance of opioid-dependent patients after short-term administration of buprenorphine or methadone in relation to dose

	BUPRENORPHINE		METHADONE	
	Study			
	(Mintzer, Correia, & Strain, 2004)		(Curran, Kleckham, Bearn, Strang, & Wanigaratne, 2001)	
	Study design	Participants	Study design	Participants
Study characteristics	Experimental double-blind cross-over study in inpatient settings No other medications were given (M.Z. Mintzer, personal communication, March 2, 2007)	Opioid-dependent patients (n = 8) with unknown opioid use history were given buprenorphine/naloxone 8/2 mg – 32/8 mg for 7–10 days before tests. Time of the test (1, 6 or 12 h after the dose) had no effect on the results and therefore test points were collapsed (except memory).	Experimental double-blind study in inpatient settings Non-specified number of the participants were given BZD doses. No other medications were given.	Opioid-dependent outpatients (n =20) were given a daily dose of methadone for relieving withdrawal symptoms (M = 33 ± 11 mg) for 3 or 5 days period. Then there were given normal dose, 50 %, or placebo. Tested 3 h after the dose.
Tests and findings				
Attention or working memory	↔ Trail Making A ↔ n – back ↔ Digit recall		↑ Faster simpe RTs after 50 % or 100 % of daily methadone dose ↔ Digit cancellation test	
Motor performance			↔ Finger tapping speed.	
Processing speed	↔ Digit Symbol		↔ Digit-Symbol	
Verbal				
Visuoperceptual				
Verbal or visual learning and memory	↓ Verbal recognition memory for the 32 mg condition. Test done 1 h from the dose		↓ Delayed story recall after full withdrawal methadone dose in relation to placebo or 50 % methadone dose	
Executive function	↔ Trail Making B			
Overall cognitive performance				

↔ = no dose effect; ↑ = Improved performance after a higher dose. ↓ = Impaired performance after a higher dose.

paring them separately against normal controls. As seen in the table, methadone patients seem to show slightly more deficits and executive function than buprenorphine patients. Meta-analyses, however, are lacking.

TABLE 5. Results from the selected studies comparing cognitive performance in buprenorphine- or methadone-treated opioid-dependent patients in stable treatment against normal controls

	Study					
	(Soyka et al., 2008)		(Baewert et al., 2007)		(Pirastu et al., 2006)	
	Study design	Participants	Study design	Participants	Study design	Participants
Study characteristisc	Randomized sample of OST outpatients tested at baseline and then after two weeks and eigth weeks. Controls tested once. No differences between patient groups on non-specified additional medications. Test time after dose n/a	BN = 29(T1) or 22(T2), dose n/a. METH = 30(T1) or 24 (T2), dose n/a NC = 24	Non-randomized sample of OST outpatients with no other medications or illicit use on any substance Tested 1.5 and 20 h after dose[a]	BN = 20 patients, mean dose 13 ±4 mg METH = 20 patients mean dose 53 ±22 mg NC = 20	Non-randomized sample of OST outpatients. with no other medications known to affect cognition Test time after dose n/a	BN = 18 patients, mean dose 9 ±1 mg METH = 30 patients mean dose 66 ±7 mg NC = 21
Duration of OST at test	**Minimum 2 weeks (T1)**	**Minimum 8 weeks (T2)**	**Minimum 2 months**		**Minimum of 12 months**	
Tests and findings						
Attention or working memory	↔ d2 test Digit Span	BN < NC d2 test (accuracy)	BN/METH (combined) < NC in two; and NC < BN/METH(combined) < in one subtest of the Act and React Test System –ART-2020			
Processing speed		BN < NC METH < NC Trail Making Test A				
Verbal						
Visuoperceptual			Patients and controls matched on visual matrices test of the ART-2020			
Verbal learning and memory	↔ Auditory Verbal Learning Test	BN < NC METH < NC Auditory Verbal Learning Test (sum of learning trials)				
Visual learning and memory					BN < NC METH < NC Benton Visual Retention Test	
Executive function	↔ verbal fluency	BN < NC METH < NC Trail Making Test B verbal fluency			METH < NC Wisconsin Card Sorting Test (persevative errors) METH < NC Iowa Gambling Task (net score)	
Overall cognitive performance					BN < NC METH < NC WAIS-R total score	

Note. BN = buprenorphine; METH = methadone; NC = normal control. ↔ = no significant difference between patients and normal controls; < = inferior than or less than; n/a = not available.

[a]Results in the Table show performance that combines both test times.

1.4.4 Studies examining drug treatment variables as correlates of cognitive performance in OST have yielded few consistent findings

1.4.4.1 Opioid drug treatment variables as correlates of cognitive performance

Opioid drug dose is often the only drug treatment variable that is included in the analyses of correlates of cognitive performance. In specific cognitive tests, mild to moderate dose correlations have been reported in several studies. For instance, one study reported a statistically significant correlation (.37) between methadone dose and trials needed for correct visual recognition (Grevert, Masover, & Goldstein, 1977). Another study found slightly higher correlations between methadone dose and slow performance in two attention measures (.48 and .43) (Loeber, Kniest, Diehl, Mann, & Croissant, 2008). However, when more rigorous statistical methods have been used, such as covariance or regression analyses, the relationship between methadone dose and cognitive performance has turned out to be very low and statistically non-significant (Prosser et al., 2008; Soyka et al., 2008; Specka et al., 2000). Low correlations in the expected direction may be related to the fact that methadone's effects on behavior are highly variable and non-linearly affected by the dose and receptor occupancy (Grimwood & Hartig, 2009; Hume et al., 2007; Leimanis, Best, Atayee, & Pesce, 2012). Buprenorphine, however, occupies mu opioid receptors in a linear fashion in up to at least 16 mg doses in opioid-dependent patients (Becerra et al., 2013; M. K. Greenwald et al., 2003). Studies that examined this issue, however, have reported no correlation between buprenorphine dose and cognitive performance in opioid-dependent patients in spite of the dose-dependent cognitive effect on drug-naïve individuals (Table 3) (Lintzeris, Mitchell, Bond, Nestor, & Strang, 2007; Loeber et al., 2008; Shmygalev et al., 2011). The study of Mintzer et al. reviewed in Table 4 is an exception. The highest clinical dose of 32 mg buprenorphine was shown to be negatively associated with one memory measure (Mintzer et al., 2004).

Other opioid drug treatment variables that could have an effect on cognitive performance are time from the administration of the dose and drug treatment duration. The most comprehensive study examining peak dose vs. trough dose effects on OST patients is that of Baewert et al., which was reviewed in Table 5. Although some findings were found the authors concluded that OST patients do not differ significantly at peak vs. trough level in the majority of the attention tests (Baewert et al., 2007). The findings of a regression analysis study by Loeber et al. are harder to interpret. They found that the duration of OST predicted poor scores in the attention test (Loeber et al., 2012), with the authors suggesting that this may relate to the neurotoxicity of long-term opioid-dependence.

1.4.4.2 Other drug treatment variables as correlates of cognitive performance

Psychiatric comorbidity is high among OST patients. The most common non-substance-use psychiatric disorders are depressive, anxiety, and personality disorders; while psychotic disorders more common than in general population; and neuropsychiatric disorders are too often overlooked (Carpentier, Knapen, van Gogh, Buitelaar, & De Jong, 2012; Lieb et al., 2010; Strain, 2002). Thus treatment with other psychoactive drugs is common in OST programs, although there are major differences between treatment providers in their drug policy. In one of the few studies taking several clinically relevant variables into account, drug treatment, substance abuse, and personality pathology variables were entered into regression analysis predicting composite cognitive performance (Prosser et al., 2008). Sum of personality pathology was the only significant predictor of overall cognitive performance. In another study (Henry et al., 2012) concerning methadone-treated patients self-rated anxiety or depression measures did not correlate with memory measures although results indicated clinically significant level of current anxiety and depression symptom. In a more recent study comorbid depressive symptoms, however, predicted worse performance in one attention test (Loeber et al., 2012). Regarding neuropsychiatric variables Brooks et al. have reported that OST patients with ADHD or conduct disorder perform worse in tests measuring attention and psychomotor function than patients without these conditions (Brooks, Vosburg, Evans, & Levin, 2006).

Drug interactions are likely between OST drugs and many commonly used psychiatric drugs (McCance-Katz, Sullivan, & Nallani, 2010), yet these are seldom taken into account in the analyses of cognitive performance. The studies of Lintzeris et al are an exception in this respect. In the first study patients treated with buprenorphine or methadone, with a history of BZD use but who had been not used BZDs with the last two weeks, were given 10 mg or 20 mg of diazepam, which had a negative effect on many attention tests done at peak dose approximately one hour after the dose (Lintzeris, Mitchell, Bond, Nestor, & Strang, 2006). Thus, having a BZD drug seems to increase the peak effects of opioid drugs. In the second study higher than clinically normal diazepam dose of 40 mg was associated with decreased performance in attention and processing speed tests (simple RT and Digit Symbol, respecitively) for both methadone and buprenorphine patients (Lintzeris et al., 2007). These effects were independent of the opioid dose administered.

1.4.4.3 Other variables as correlates of cognitive performance

Other possible correlates of cognitive performance include demographic variables such as age, sex, or education as well as substance abuse variables. Some of aging-related neurodegenerative processs are accelerated in opioid-dependent patients (Nandhu, Naijil, Smijin, Jayanarayanan, & Paulose, 2010; Reece, 2012a, 2012b), which can make negative age-associated correlations with cognition steep-

er among OST patients. Sex of the opioid-dependent patients may correlate with cognitive performance because human endogenous opioid system and opioid responses show slight differences between sexes (Dahan, Kest, Waxman, & Sarton, 2008; Mogil, 2012). Correlations between cognitive performance and demographic factors are usually low and abolish when several variables are controlled. However, a recent study found that female sex predicted better in one test of attention and one test of memory (Loeber et al., 2012); but the authors consider this finding being related to sample bias.

A surprising finding is the fact the current or lifetime illicit drug use data, like drug screen results typically shows no effect or only small effect on cognitive functioning in OST patients (Prosser et al., 2008; Rounsaville, Novelly, Kleber, & Jones, 1981; Shmygalev et al., 2011; Specka et al., 2000). However, a recent study which analysed specific cognitive domains, found several substance use history variables as predictors for attention, memory and executive function (Loeber et al., 2012).

1.4.5 Few studies have examined the longitudinal changes of cognitive performance during OST

In the study by Grevert et al. (1977), memory performance was tested before methadone treatment and then one and three months after treatment initiation. No differences between patients and matched controls at baseline or later were found. Gordon et al. (1995) reported re-testing of overall cognitive performance of methadone-treated patients using the WAIS intelligence test after a mean interval of 9 years and 10 months. The majority of patients studied (25/30) showed improved performance. With this re-testing interval, a practice effect is not likely. The study of Gruber et al. (2006) found a statistically significant improvement in the processing speed, verbal list learning, and delayed visual memory in methadone patients between measurements at baseline and after two months of treatment (Gruber et al., 2006). However, the study lacked a control group, and a practice effect due to repeated testing within a short test interval cannot be ruled out. The need for more longitudinal studies is obvious. For instance, there are no longitudinal studies concerning buprenorphine-treated patients.

1.4.6 There is no consensus about driving fitness in OST patients

Safe driving depends on a driver's abilities and the way those abilities are used, that is, on performance and behavior (Lee, 2008). However, when the driving fitness of an individual is assessed, the main focus is on driving performance. When an individual has a valid driver's license, can handle a vehicle, and has no known major sensory or cognitive deficits affecting driving, then by definition she/he is considered fit to drive. Yet, in the case of OST patients the issue of driving fitness seems to be hard to decide.

The first studies dealing with driving fitness in OST patients were based on the driving records of MMT patients, which already gave inconsistent findings. While one study concluded that methadone treatment is not a risk for driving (N.B. Gordon, 1976), another study published alarming figures about the driving safety of OST patient (Edwards & Quartaro, 1978). In a sample of 100 patients from a single clinic in the United States, 87% of the patients drove a car. Most of them (82%) admitted driving while under the influence of the drug. Road traffic accidents were common among them. A third of accidents occurred when the patients felt that they were under the influence of the drug. While the findings of Edwards and Quartaro, for example, have raised concerns among clinicians, it has taken many years for a series of well-controlled experimental studies focusing on the driving fitness of OST patients to be reported (Chesher, Lemon, Gomel, & Murphy, 1995). In these studies Australian patients who had been on the same dose of methadone (mean 85 mg) for at least six months were tested with driving-related cognitive tests before and 1 h after the dose. A second group of patients, who were not in a stabile phase yet, were tested when they were receiving an increase in their dose of methadone of 10 mg per day. A third patient group was tested while they were starting OST. Also, normal controls and abstinent ex-opioid users did the same tests. In order to ascertain that the test battery would be sensitive to the negative effects of the psychoactive substance, each group was also tested after doses of alcohol (mean blood alcohol concentration 0.064g %) or diazepam (15 mg). The test battery proved to be sensitive to the effects of alcohol and diazepam. Instead, there was no evidence for an effect of the acute dose of methadone on any of the patient groups. The authors concluded that patients in the methadone treatment program should be considered as non-impaired in their ability to drive a motor vehicle.

In the same year that the Australian studies were reported, a series of German studies were also reported (Friedel & Berghaus, 1995). Surprisingly, the conclusion of the German studies was very different: "Heroin addicts treated with methadone are generally not fit to drive. A positive evaluation might be possible in exceptional cases when there are special circumstances justifying it". This conclusion was based mainly on the level of psychiatric comorbidity and especially personality disorders and lack of self-control in the traffic. Also, some problems in cognitive driving-related tasks were noticed in the experiments made in the German patient samples.

During the first decade of the current millenium, many well-controlled studies concerning driving performance in OST patients have been published. However, a recent review dismissed the idea that a recommendation of driving fitness of OST patients could be determined on the basis of research findings (Strand, Fjeld, Arnestad, & Mørland, 2010). Several shortcomings in the studies so far were noted. These include a lack of actual driving performance tests, great variability in the driving-related cognitive tests employed, and not analyzing the effects of other prescription drugs commonly used by the patients.

2 Aims of the study

The major aim of this series of studies was to compare cognitive performance between OST patients and normal controls and to analyze drug treatment variables as correlates of performance. More specifically the aims of the studies were as follows:

1. Compare cognitive performance in OST patients in early treatment (study I);
2. Analyze cognitive performance in OST patients over time. This was done in two parts: 2.
   a) Longitudinal change of memory performance during the half year of OST (study II); and
   b) Longitudinal change of cognitive performance during the first year of OST (study III);
3. Analyze drug treatment variables as correlates of cognitive performance of OST patients. This was done in two parts:
   a) Drug treatment variables as predictors of cognitive performance in OST patients (study IV)
   b) Comparison of patients treated with opioid drug only (Additional analyses, unpublished); and
4. Examine driving fitness of OST patients (study V).

The main hypotheses concerning drug treatment were as follows: First, we hypothesized that because buprenorphine is a partial mu opioid receptor agonist and kappa antagonist, and may have less interaction effects with BZDs than methadone patients, patients treated with buprenorphine would show less cognitive deficits than those with methadone. Second, we hypothesized that memory consolidation would be impaired in OST patients treated along with a BZD drug. This hypotheses was based on experimental findings showing that mu opioid receptor agonists and BZDs both negatively affect memory consolidation (Curran, 1999; Guarna et al., 2004; Izquierdo & Medina, 1991). Third, we hypothesized that patients treated with buprenorphine would show greater cognitive improvement in long-term treatment in comparison to methadone-treated ones. This, hypothesis was based on the findings that buprenorphine may have cognition restoring effects that methadone is lacking (Spiga et al., 2008). Fourth, we hypothesized that there would be negative associations between opioid agonist dose and cognitive performance, BZD dose and cognitive performance, and the number of psychoactive drugs (other than opioid or BZD) and cognitive performance in opioid-dependent patients treated either with buprenorphine or methadone. Patients treated with several psychoactive drugs typically perform worse in cognitive tests than patients treated with a single drug (Meador, 1998; Starr et al., 2004).

3 Methods

3.1 Study participants

The inclusion criteria for all participants were age between 18–50 years. We excluded participants with current uncontrolled polysubstance abuse, acute alcohol abuse, or acute axis I psychiatric morbidity according to DSM-IV, other than substance abuse disorders. We also excluded participants with severe brain injury, chronic neurological disease, and history of other than substance-induced psychoses, epileptic seizures, human immunodeficiency virus (HIV) infection, pregnancy, or primary cognitive deficit. All included OST patients were voluntarily admitted for first-time OST. All samples were natural and non-randomized.

In study I, the additional inclusion criteria for OST patients were starting of OST during the last six weeks and treatment with either buprenorphine/naloxone or methadone. Seventeen buprenorphine/naloxone-treated patients, 16 methadone-treated ones, and 17 normal controls were tested. *In study II*, additional inclusion criteria for OST patients were BZD dependence or abuse diagnosis, start of OST with methadone, buprenorphine, or buprenorphine/naloxone during the last two months, and attendance at retesting between 6 and 9 months (T2) after OST admission. Normal controls were tested according to similar time intervals. Based on these criteria, 15 buprenorphine/naloxone- or buprenorphine-treated patients, 13 methadone-treated patients and 15 normal control participants were tested twice. *In study III*, fourteen buprenorphine- or buprenorphine/naloxone-treated and 12 methadone-treated patients were three times tested with cognitive tests: within two months (T1), 6–9 months (T2), and 12–17 months (T3) from the start of OST. Fourteen normal controls were examined at similar intervals. In part II of the study the patient sample was extended to include 36 patients at T2 and T3 (18 patients in both drug groups). *In study IV* the sample included 104 OST patients who had been in treatment for a minimum of six months and who were treated either with buprenorphine or methadone (n=52 in both drug groups). Thirty of them came from the longitudinal sample used in the previous studies. *In study V* the sample included 22 OST patients who had been in treatment for a minimum for one year and had a valid driver's license.

3.2 Study ethics and funding

The studies were approved by the independent Hospital District of Helsinki and Uusimaa Ethical Committee (permission 90/2001), the A-Clinic Foundation, and the Helsinki City Bureau of Social and Welfare, all studies were conducted in accordance with the 1964 Declaration of Helsinki.

3.3 Study designs and measures

Studies I to IV used a non-randomized, quasi-experimental study design. This was because randomization of the participants into different opioid drug treatment groups was not possible as drug choices were done in the clinics according to clinical guidelines. Study V describes a case series although a post-hoc group comparison between drug treatment groups is included. Cognitive measures and driving performance were considered as outcome variables and other measures as background variables. Although verbal intelligence is a cognitive measure, it was however treated as a proxy for cognitive baseline, and thus used as a background variable.

3.3.1 Cognitive and other outcome measures: rationale and descriptions

Attention, working memory, and episodic memory were chosen as the cognitive variables of interest. All of these have practical relevance and tests for them are suitable for longitudinal testing. *Attention* is the spotlighting system of the human mind that is governed by external cues as well as internal states. The attention system of the brain is anatomically separate, though not fully independent, from the data processing systems that perform operations on specific inputs even when attention is oriented elsewhere (Posner & Petersen, 1990). *Working memory* is a system that stores and manipulates 'spotted' or otherwise selected items. Thus, working memory refers to the limited capacity short-term store that temporarily maintains information, which is lost without rehearsal (Baddeley, 2003). Working memory function is considered a gateway for problem-solving in new situations that partly overlaps with fluid intelligence and executive function. *Episodic memory*, often called simply memory, is central to human life since almost everything in mental life is based on memory, except for the thin slice of the present time in which attention and working memory operate; but seldom without interaction with long-term memory stores. Episodic memory of events is the central form of long-term memory together with semantic and procedural long-term memory. In psychology, memory of events, however, is split into sensory-specific forms like verbal, visual, and tactual memory. This is based on the findings of brain lesion

studies showing that the size of the lesion and its location brings about memory disorders in one sensory modality with intact performance in another. It is still vividly discussed what kind of memory functions should be called working memory, short-term memory, episodic, or long-term memory (Cowan, 2008; Henke, 2010; Squire, 2004). Yet, in various patient groups it is possible to find cases with preserved working memory and impaired episodic memory functions as well as the opposite (Frisk & Milner, 1990). Driving fitness of OST patients was assessed because there is no consensus about this issue and it is associated with cognitive performance and drug treatment variables.

Attention tests included the Alertness and Go/NoGo- tasks from the Test for Attentional Performance (TAP) using computer software and an RT key-pad. (Zimmermann & Fimm, 1995). In the Alertness task, visual RT was assessed with and without preceding auditory warning signal. The 'without signal' condition of the Alertness test is a simple RT task, and is thought to reflect tonic alertness (Sturm et al., 1999). The 'with signal' condition is thought to reflect both tonic and phasic alertness. The Go/NoGo condition assessed the integrity of response-selection and executive control of attention (Posner, Sheese, Odludas, & Tang, 2006; Rubia et al., 2001). Visual stimuli were presented one by one. For two out of five stimuli an instant reaction is required, and for the others a reaction needs to be inhibited. Reaction times and correctness of responses were recorded. Reaction times, like those examined in our studies are thought to reflect alerting and orienting functions of the brain's attentional networks. Executive control of action is involved to a lesser degree, although at least slightly, in the Go/NoGo task.

Working memory tests included the Letter-Number-Sequencing task from the WMS-III and a computerized version of the Paced Auditory Serial Addition Task (PASAT) from the FORAMENRehab software package (Gronwall, 1977; Koskinen & Sarajuuri, 2002; Wecshler, 1996). The Letter Number Sequencing task assesses verbal working memory storage with added processing demands. In the PASAT, the complex working memory functions that are required are continuous storage of previous number, rapid arithmetical processing, and executive control of interference from previous items or from ongoing adding process. In our study, the presentation rate of a new number to be added to the previous one was set as one every 1.6 second. The Letter Number Sequencing and the PASAT both draw on the resources of the verbal/auditory component of working memory and also to some degree on other components like the central executive. The PASAT, however, is not considered a pure cognitive test since emotional reactivity to stress may also modulate performance in the PASAT (Mathias, Stanford, & Houston, 2004).

Episodic memory tests included two verbally presented list-learning and story recall tasks: the Memory for Persons Data and the Logical Memory (Kaitaro, Koskinen, & Kaipio, 1995; Lezak, 1995; Wecshler, 1996). Both tests were presented in modified versions. In the Logical Memory, which is a subtest of WMS-III, only one story was presented and recalled immediately and again after 30 minutes.

For those participants tested repeatedly a different story was given than previously (Studies II – IV). In the Memory for Persons Data only three persons, each with 5 items, were presented. First there were two learning trials with immediate recall. If the participant could recall all 15 items correctly in both trials, no more learning trials were administered. If this condition was not met, there were additional trials until the participant was able to recall all the items correctly in two consecutive trials. A maximum of four trials were administered. After five minutes, recall of the items was requested and possible errors were corrected for. Finally, after 30 minutes, delayed recall of all the items was requested. This measure was used in Study I as described here, with long-term delayed recall of the items (4–8 months after learning) tested in Study II. Study IV included also a visual memory measure, the Benton Visual Retention Test. It measures immediate visual memory by asking the examinee to draw a copy of a design that is first shown for a study period of 10 seconds (Benton, 1963). The number of correctly drawn designs was used as a score. In Study II subjective memory functioning was assessed by the Finnish version of the Memory Complaint Questionnaire (Antikainen et al., 2001; Crook, Feher, & Larrabee, 1992).

Verbal intelligence estimation was based on WAIS-R Vocabulary score (Wechsler, 1993).

On-road driving test was done by the same licensed driving instructor for each participant. The test included various car driving tasks done in driving evaluations devised for neurological patients (Peräaho & Keskinen, 2005). This evaluation was meant for driving a car for non-professional purposes (Kuikka & Mäkinen, 2004). The driving instructor completed two formal evaluation sheets. Driving errors were classified as nonhazardous vs. hazardous errors. An error was classified as hazardous if it exposed anyone on the road to a potential risk. The marking of the errors was done according to the manual developed by the Finnish Vehicle Administration (Keskinen, Hatakka, & Laapotti, 1998). In addition, the driving instructor gave a performance score for each of 11 driving domains. Scoring for performance was as follows: 5=clearly strong, 4=strong, 3=neither strong nor weak, 2=weak and 1=clearly weak (Peräaho & Keskinen, 2005). Finally, an overall driving safety assessment was done using four levels (Ramet & Summala, 2004). The highest level of driving safety was 'safe driver in all conditions', meaning that she/he was considered to be a safe driver in all places and in any road conditions. The next best level was 'safe driver in normal conditions', meaning that she/he was considered as a safe driver in all places, though good road conditions were necessary for safe driving. According to Finnish driving regulations, drivers belonging to the classes 'safe driver in all conditions' or 'in normal conditions' are considered fit to drive a car. The last two classifications 'safe driver only in the best conditions' and 'unsafe driver' are not considered fit to drive.

Driving-related cognitive tests included the Determination, Peripheral Perception, Signal Detection, Stroop Interference, and Tachistoscopic Traffic Perception tests from the computer-aided Vienna Test System (Biehl, 1996; Neuwirth & Benesch, 2003; Puhr & Wagner, 2004; Schuhfried, 2004; Schuhfried, Prieler, & Bauer, 2004). The determination test measures 'resilience of attention and reaction speed under conditions of sensory stress'. The examinee is instructed to identify color or sound stimuli and react to them by pressing a correspondent response button using a response panel. The number of correct reactions was used as a score. The Peripheral Perception test measures visual perception and processing of peripheral information. The examinee is instructed to focus on a simple visual tracking task presented on the computer screen. Simultaneously, she/he should react by pressing a pedal whenever a critical visual stimuli is presented at their left or right periphery. Tracking deviation, a measure of divided attention, was used as a score. The Signal test measures long-term selective attention by demanding differentiation of relevant visual signals from irrelevant ones. Median RT and the number of correct or delayed reactions were used as score variables. The purpose of the Stroop test is to evaluate inhibition of overlearned responses as opposed to consciously controlled ones. Median RT in the interference condition was used as a score. Version S4 (light pen) was used. The purpose of the Traffic Perception Test is to evaluate visual observation ability and skill in obtaining an overview, and also of visual orientation ability and speed of perception. The examinee is shown 20 pictures of traffic scenes for one second each. Then she/he has to select from a list that contains five different items those that she/he remembers having seen in the picture. The number of correctly answered lists for the 'Overview' was used a score. In evaluating cognitive results age-independent norms were used, whenever possible. Scores that were not above the 16th percentile were considered to indicate problems in driving ability according to the 'passed/non-passed test method' (Gaertner et al., 2006).

3.3.2 Other measures

In each study the eligibility of all participants was checked by *a clinical psychiatric interview* SCID I and diagnostic criteria from DSM-IV were applied (First, Gibbon, Spitzer, Williams, & Benjamin, 1997). Study V included also a *clinical neurological status and a traffic vision evaluation* done by a neurologist. All studies included urine *drug screening*, which was carried out in the clinics. For normal controls, drug screening was done on a random basis (one third were screened at each test point). Screening was done by using the Nano5 test (from Ferle Produkter AB; Helsingborg, Sweden). Also, the participants were interviewed about their recent and lifetime substance abuse history and medication use. Whenever possible, the data were checked against medical reports. In Study III, data about *childhood mental health or behavioral problems* were gathered using the Childhood Behavioral Checklist (Tarter, McBride, Buonpane, & Schneider, 1977) as a basis for interview, with medical reports used whenever possible. *Driving experience information* and the patient's

own view about driving safety in Study V was asked by a questionnaire devised for the study. In addition the patients evaluated the distressing effects of 22 driving situations by choosing one of four alternatives (not at all distressing, somewhat distressing, quite distressing, or very distressing); they also reported the frequency of 22 driving errors by choosing one of four alternatives (never, occasionally, quite often, almost every time I drive) (Peräaho & Keskinen, 2005). Table 6 presents the variables used in each study.

3.3.3 Procedures

Since the timing of the test after administration of a psychoactive drug is an important variable when cognitive performance is examined, cognitive testing was done to all participants according to the same time frame: three to six hours (Studies I – IV) or two to seven hours after the administration of opioid substitution drug (Study V). In order to estimate the current benzodiazepine doses of the groups, all benzodiazepines were converted to diazepam equivalent doses. There was, however, slight variation on the conversion tables used in the studies. In Studies I and II the Ashton table was used (Ashton, 2005). In Studies III and IV the Nelson's and Chouinard's table was used (Nelson & Chouinard, 1999). In Study V Bazire's psychotropic drug directory was used (Bazire, 2003). The changes in the conversion tables were motivated by the search for the clinically most relevant table. For the drugs used only as hypnotics, the dose was halved before conversion.

3.4 Statistical analyses

In all analyses, statistical significance was set at $p < 0.05$ (two-tailed).

3.4.1 Comparison of cognitive performance in OST patients in early treatment against normal controls (Study I)

Analysis of variance (ANOVA) was used to study the overall group effect in each cognitive measure of the study. This was followed, when appropriate, by pairwise group comparisons (patient groups against normal controls). We used multiple planned ANOVAs because comparisons were aimed at each variable separately. The Holm's sequential Bonferroni procedure was used to control for Type I error across the pairwise comparisons (Holm, 1979). We examined the homogeneity of variances in each measure by means of Levene's test. Whenever necessary, the data were first transformed by reciprocal or logarithmic transformation to normalize the distributions. For both of the Go/NoGo conditions, the last two learning trials of the Memory for Persons Data, and in the delayed recall of the Memory for Persons Data, the distributions could not be normalized. We analyzed these results by non-parametric Kruskal-Wallis ANOVA, which were then followed, when appro-

TABLE 6. Measures and background variables used in the studies

Time	Outcomes				
	Attention	**Working memory**	**Memory**	**Driving-related cognitive tests**	**Other variables of interest**
T1	Alertness and Go/NoGo tests from the TAP (I and III)	The Letter Number Sequencing from the WMS-III (I, II and III) The PASAT (I, II and III)	The Logical Memory from the WMS-III (I, II and III) The Memory for Persons Data (I and II)		
T2	Alertness and Go/NoGo tests from the TAP (III)	The Letter Number Sequencing (II and III) The PASAT (III and III)	The Logical Memory (II and III) The Memory for Persons Data (II)		Subjective memory complaints (II)
T3	Alertness (III and IV)) and Go/No-Go (III) tests from the TAP	The Letter Number Sequencing (III and IV) The PASAT (III)	The Benton Visual Retention Test (IV) The Logical Memory (III and IV)	Five subtests from the Vienna Test System (V)	Driving safety assessment (V) Driving performance assessment (V)

Time	Background variables and other measures		
	Demographic and comorbidity variables	**SUD variables**	**Drug treatment variables**
T1	Age, education, sex, and VIQ (I, II, III) DSM-IV diagnostic (prevalence of axis I and II diagnoses; II)	Drug screen (I–III), Current SUD (dependencies; I and II), The past month substance use (substances abused I and II), Frequency of substance abuse in the past month (IIII and IV), Duration of any substance abuse (I and II), Onset age of any substance abuse (II–III), Onset age of opioid abuse (II – III)	OST drug (type, duration I–V), BZD (type; I (prevalence, diazepam equivalent dose), Other psychoactive drugs (type; I and II), Other psychoactive drugs (number: III and VI)
T2	Age, education, sex, and VIQ (I, II, III), Early neurobehavioral problems (III)	Drug screen (II–III), Duration of substance any abuse history (II), Duration of opioid abuse (II) Frequency of substance abuse in the past month (III and IV), Years of heavy alcohol abuse (III)	OST drug (type, duration I–V), BZD drugs (prevalence, diazepam equivalent dose) Other psychoactive drugs by type (type I and II; number III and IV)
T3	Age, education, and sex (V), Age, driving information, mild head injurius, and sex (V)	Drug screen (III and IV), Onset age of any substance abuse (IV, and Opioid overdoses (V)	OST drug (type, duration I–V), BZD drugs (prevalence, type, diazepam equivalent dose), and Other psychoactive drugs by type (type I and II; number III and IV)

priate, by a pair-wise Mann-Whitney U test. We did not covary for the group difference in education, which favored the control group over the methadone group. This was based on the contention that the assumption of a similar linear relation between education and cognitive performance in both groups needed for an analysis of covariance (ANCOVA) was not met. All participants with opioid dependence had started substance abuse in their early teen years. Once the substance abuse history begins it soon affects educational achievement through class non-attendance etc. So, years of education does not reflect cognitive ability in this population similarly to the general population (Lynskey & Hall, 2000). However, in the second phase of the analysis, in order to evaluate the role of premorbid intellectual factors, we set verbal IQ as a covariate for other measures than RT measures. The association between simple RT measures and intelligence is weak and may not be linear (Der & Deary, 2003). Demographic data was studied as pairwise group comparisons without first requiring a significant overall group effect.

3.4.2 Longitudinal change of memory performance during the first half year of OST in patients treated with benzodiazepines (Study II)

Overall group differences in memory performance at T1 and T2 were tested for statistical significance using multiple planned analyses of covariance (ANCOVA) with years of education and verbal IQ estimate as covariates. Although there were no statistically significant differences between the groups in the verbal IQ, it was used as a covariate since it is known to affect memory performance in tasks with verbal content (Alexander & Smales, 1997). ANCOVA was followed, when appropriate, by pairwise group comparisons using the normal comparison group as a reference group. Similarly to Study I the Holm's sequential Bonferroni procedure was used to control for Type I error. In the Memory for Persons Data, the data were highly skewed at T1 and T2. Therefore, we analyzed these conditions by means of Kruskal-Wallis ANOVAs, which were followed, when appropriate, by pairwise Mann-Whitney U tests. In order to confirm the validity of combining buprenorphine/naloxone and buprenorphine-only patients, the ANCOVAs and ANOVAs were also performed with buprenorphine/naloxone patients (n=12). The cross-sectional Memory Complaint Questionnaire scores and the Memory Complaint Questionnaire differences between high vs. low score groups at T2 were analyzed by t-tests or Mann-Whitney U tests. Correlations between the Memory Complaint Questionnaire values and cognitive variables were analyzed by Pearson's product moment correlation or Spearman's rho correlations, depending on the normality of the variables. The statistical significance of correlations was determined by using the Holm-Bonferroni procedure. Longitudinal changes were analyzed by repeated measures ANCOVA, using education and VIQ as covariates and normal controls as a reference group.

3.4.3 Longitudinal change of cognitive performance during the first year of OST and its correlates (Study III)

Longitudinal changes in cognitive performance were examined by repeated-measures analysis of variance (ANOVA) using a general linear model approach. Group was used as a between-subjects factor and time as a within-subjects factor. Before the analyses, the normality assumptions of cognitive variables were examined by Shapiro-Wilk's test and homogeneity of variance by Levene's test. The data were also screened for outlying values. On the basis of these procedures, RT and the PASAT scores were subjected to log transformations before further analyses, and the Go/NoGo errors were examined by non-parametric Kruskal-Wallis ANOVA. Sphericity assumption was tested by Mauchly's test, and when appropriate, analyses of effects were interpreted using the Huynh-Feldt correction. The effects of demographic variables on cognitive performance were tested as covariates. Only significant covariates were retained in the model. Statistically significant between-groups effects were followed by planned contrast using normal controls as a reference group. Significant time-effects were examined using repeated contrast (T2 vs. T1 and T3 vs. T2). When a significant group-by-time interaction effect was noted, it was examined further by combining previous contrasts (normal control vs. buprenorphine group * T2 vs. T1, normal control vs. buprenorphine group * T3 vs. T2; and normal control vs. methadone group, respectively).

Cognitive tests selected for the *analyses of correlations* were the same as used when analyzing longitudinal changes, except that the PASAT was excluded from the analyses because of the practice effect on this measure. In order to reduce the number of cognitive variables, correlations between the variables analyzed—and whenever justified, domain-wise cognitive sum scores for T2 and T3 performances—were formed. T2 performance was used as a reference point in T3 summed scores. A mean composite score called attention performance was calculated after converting the test scores into z-scores. The working memory measure, the Letter-Number Sequencing task, showed only low to moderate correlations with other measures and therefore it was not combined with other measures. The verbal memory measures used in the study, that is immediate and delayed recall of the Logical Memory, correlated strongly at both test points (.80 at T2 and .91 at T3). Therefore, a mean sum score called verbal memory was formed after z-score conversion. Then group differences in cognitive function were examined by a repeated-measures analysis of variance (ANOVA) using a general linear model approach. After this all significant or the three highest correlates of each cognitive variable were further examined by checking for any intercorrelations between these variables and other variables of interest. Also, medication variables were checked for significant intercorrelations. Then the three highest correlations for each cognitive domain were investigated by an analyses of semipartial correlations.

3.4.4 Drug treatment variables as predictors of cognitive performance in OST patients (Study IV)

Group-wise comparisons of cognitive performance between buprenorphine and methadone patients were done by an analysis of variance (ANOVA). As our verbal and visual memory tests lacked age-corrected norm values and there was a significant difference between the patient groups on age, an analysis of covariance (ANCOVA) using age as a covariate was done when testing these parameters. In all group-wise comparisons, the normality assumptions of the cognitive variables were first examined by Shapiro-Wilk's test and the homogeneity of variance by the Levene's test. When appropriate, analyses of the main effects were interpreted using the Welch correction for heterogeneous variances. The data were also screened for outlying values. There was a strong positive correlation (.78) between the alertness task conditions, and therefore these measures were combined by standardizing the values and pooling them. The assumption of a linear relationship between the dependent variable and predictors was checked by plotting the data (LOWESS curves) and by a lack-of-fit test. In order to ascertain the linearity between the dependent variable and predictors, many of the predictors were transformed into dichotomous ordinal variables. Buprenorphine doses up to 16 mg were considered as low dose and higher values as high. BZD doses were considered as low if lower than 20 mg and higher if 20 mg or above. The number of prescribed psychoactive drugs, other than OST or BZD drug, was considered as low if up to one drug, and high if two or more other drugs. Duration of OST was considered as short if between six and twelve months, and long if above this. Substance abuse in the previous month was dichotomized as high vs. low frequency of abuse. Abstinence or substance abuse up to two days a week was considered low-frequency substance abuse, and values above this as high-frequency substance abuse. Age of onset for substance abuse was considered as early onset up to 14 years of age, and as late onset if aged 15 years or older. Education was considered as low if no higher education than primary education had been completed, and as high if any secondary education had been completed. Homogeneity of error variance (homoscedasticity) was confirmed graphically by plotting the standardized residual against the predicted values. Independence of errors was checked using the Durbin-Watson test. Normality of residuals was checked by normality plots and using the Shapiro-Wilk's test. Because our main interest was to examine drug treatment variables as predictors of cognitive performance, we employed multiple sequential/hierarchical linear regression analysis. First, the full model was examined as follows. Demographic variables, substance abuse variables, and the number of tests (one vs. more than one), were first entered into the model as control variables. Demographic variables included sex, level of education, and age if the test values were not age-corrected initially. Substance abuse variables included age of onset of substance abuse and frequency of substance abuse in the past month. Control variables were re-

tained in the subsequent reduced model only if they gave a statistically significant contribution to the full model as a block or individually. The number of tests was also checked for the direction of association, with a positive association indicating a practice effect of repeated testing. Drug treatment variables included opioid drug type (buprenorphine vs. methadone), BZD treatment (yes vs. no), the number of psychoactive drugs (other than opioid or BZD drugs), and duration of OST (long vs. short). All drug treatment variables were entered sequentially into the reduced model. Unless otherwise stated, explained variance (R^2) is reported as an adjusted value, and the regression coefficient as a standardized value (beta).

3.4.5 Driving fitness of OST patients (study V)

Group comparisons between patients with probable vs. improbable drug-related driving impairment were performed using the non-parametric Mann-Whitney U tests or Fisher's exact test. Correlations between driving test scores and drug doses were analyzed by the non-parametric Spearman's rho.

In all studies statistical analyses were done by IBM SPSS statistical software ("IBM SPSS Statistics for Windows," 2011). Versions 13.0 (Study I), 15.0 (Studies II and III), and 20.0 (Studies IV, V, and additional analyses) were used. Effect sizes, however, were calculated by an effect-size calculator provided by Durham University, UK ("Effect size calculator," 2006). In the effect-size analyses we used pooled samples and corrected the values by means of Hedge's correction for small sample bias.

4 Results

4.1 Cognitive performance of OST patients in early treatment (Studies I and II)

The main demographic characteristics of the samples in Studies I and II are shown in Table 7. As presented in the table the patient groups had attained less education than the controls.

TABLE 7. Group demographics in studies I and II

Study I	**Buprenorphine/ Naloxone (n = 17)** M ± SD	**Methadone (n =16)** M ± SD	**Normal Control (n = 17)** M ± SD	**Group comparison p-values**
Age (years)	28.1 ± 6.3	30.8 ± 8.8	31.1 ± 11.2	ns
Sex (female/ male)	7/10	9/7	9/8	ns
Verbal intelligence [a]	102.4 ± 8.4	98.4 ± 8.7	105.4 ± 9.8	METH < NC*
Education, (years)	11.1 ± 2.2	10.4 ± 2.0	13.0 ± 1.7	BN < NC** METH < NC**
Days in OST	11.0 ± 8.1	14.3 ± 7.4	–	ns

Study II	**Buprenorphine and BZD (n = 15)[b]** M ± SD	**Methadone and BZD (n =13)** M ± SD	**Normal Control (n = 15)** M ± SD	
Age (years)	27.7 ± 6.8	29.2 ± 6.8	28.7 ± 9.6	ns
Sex (female/ male)	4/11	7/6	8/7	ns
Verbal intelligence [a]	99.4 ± 9.3	100.6 ± 11.4	104.1 ± 9.6	ns
Education (years)	10.5 ± 2.0	10.1 ± 1.2	12.6 ± 1.3	METH < NC*** BN < NC**
Days in OST at T1	19 ± 12	21 ± 14	–	ns
Days in OST at T2	224 ± 17	213 ± 25	–	ns

Note. Modifed from publications I and II. BN = buprenorphine/naloxone; METH = methadone, NC = Normal control.
[a]Estimation based on WAIS-R Vocabulary score.
[b]Includes buprenorphine and buprenorphine/naloxone treated patients.

TABLE 8. Statistically significant differences in cognitive measures and subjective memory complaints between patient groups and normal controls during early treatment

	Buprenorphine patients in comparison to normal controls	Methadone patients in comparison to normal controls
Attention		METH < NC* Go/NoGo RT d = 0.88 (I)
Working memory	BN < NC** Letter Number Sequencing d = 1.21 (I) BN + BZD < NC** Letter Number Sequencing d = 1.01 (II)	METH < NC** Letter Number Sequencing d = 1.02 (I)
	BN < NC*** PASAT d = 1.60 (I)	METH < NC** PASAT d = 1.27 (I)
	BN + BZD < NC*** PASAT d = 1.54 (II)	METH + BZD < NC*** PASAT d = 1.43 (II)
Episodic memory	BN < NC* Memory for Persons Data, first trial d = 1.19 (I)	METH < NC * Memory for Persons Data, first trial d = 1.22 (I)
	BN + BZD < NC* Memory for Persons Data, first trial (II)	METH + BZD < NC * Memory for Persons Data, first trial (II)
		METH < NC ** Logical Memory d = 1.17(I)
	BN < NC* Memory for Persons Data, delayed (I)	METH < NC* Memory for Persons Data, delayed (I)
Subjective memory complaints[a]	NC < BN + BZD** Memory Complaint Questionnaire (II)	NC < METH + BZD ** Memory Complaint Questionnaire (II)

Note. Modifed from publications I and II. BN = buprenorphine/naloxone; METH = methadone; NC = Normal control.
[a]Smaller indicates less complaints.
< = inferior than or less than; ***= statistically significant at level p < .0.001; **= statistically significant at level p < .0.01; *= statistically significant at level p < .0.05; d = effect size.

Tables 8 and 9 summarize the statistically significant group differences found in early treatment studies in each cognitive domain examined. As presented in Table 8, methadone patients showed inferior performance in relation to normal controls in the Go/NoGo RT. In working memory, episodic memory, and subjective memory complaints patients showed deficits in nearly every measure.

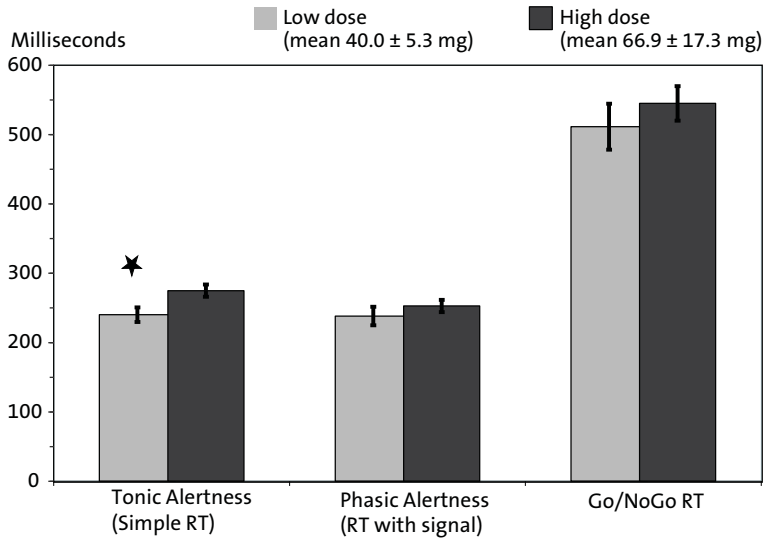
As presented in Table 9, methadone-treated patients were inferior in comparison to buprenorphine/naloxone ones in tonic alertness (simple RT). This difference remained significant when the comparison was done in the subsample of patients having an opioid drug along with a BZD drug (n=13 in both opioid drug groups). In addition, patients treated with methadone (mean dose 54.2 mg ± *SD*=18.7) along with a BZD drug (mean diazepam equivalent dose 28.3 mg ± 18.6) were inferior to the respective buprenorphine/naloxone ones (mean dose 16.3 mg ± 2.9 for buprenorphine and 25.6 mg ± 10.1 for BZD) in the delayed story recall (the Logical Memory). All participants in both groups were dependent on BZDs and had used them in the month before OST. In the demographic variables, there were no significant differences between these subgroups.

TABLE 9. Statistically significant comparisons between opioid drug groups during early treatment

	Group comparison significance level Measure, Effect size, if possible (Study number)
Attention	METH < BN **
	TAP, tonic alertness
	d = 1.11 (I)
	METH + BZD < BN + BZD*[a]
	TAP, tonic alertness (I)
Working memory	All comparisons ns
Memory	METH + BZD < BN + BZD*[a]
	Logical Memory
	d = 0.94 (I)

Note. Modifed from publications I and II. BN = buprenorphine/naloxone; METH = methadone; NC = Normal control.
[a]Subsample of patients in study I.
< = inferior than or less than; ***= statistically significant at level p < .0.001; **= statistically significant at level p < .0.01; *= statistically significant at level p < .0.05; d = effect size.

Further post hoc analyses were done to study the role of OST doses on cognitive performance in Study I. For these analyses, we split the patient groups into low vs. high dose groups, depending on their median OST drug dosage. After this division the mean doses of methadone in the low dose (n=8) and high dose group (n=8) were 40.0 ± 5.3 mg and 66.9 ± 17.3 mg, respectively. Patients with a low methadone dose had faster RTs in all conditions than patients with high dose. Figure 4 depicts these differences. In the tonic alertness (simple RT) the difference reached statistical significance (p=0.025, d=1.19). The mean simple RT time in the low methadone dose group was 240 ± 30 ms which practically equals the performance of the normal control group (244 ± 30 ms). The low dose group had been fewer days on OST medication than the high dose group (9 ± 2 vs. 20 ± 6, respectively, $p < 0.001$). No other significant differences between the groups emerged in the demographic or medication variables. Among buprenorphine/naloxone patients, nine patients received the same dose of 16 mg, and very few cases fell in the tails of the dose distribution. As a result, dose analyses were not carried out.



Note. Modified from publication I.

FIGURE 4. Comparison of high vs. low methadone dose groups in reaction times in early treatment (Study I).

4.2 Longitudinal change (Studies II and III)

4.2.1 Longitudinal change of memory performance during the first half year of OST in patients treated with benzodiazepines (II)

The main demographic characteristics of the sample in Study II are presented in the lower part of the Table 7. Results concerning T1 (within two months from OST initiation) are presented in Table 8 (marked with II). Analyses of T2 results (after 6–9 months from OST initiation) are presented in Table 10. As shown by Tables 8 and 10, both patient groups were inferior in comparison to normal controls in both working memory tests and memory complaints. As the overall group effect was non-significant in all episodic memory tests, pairwise comparisons were not performed in these measures. All time or group-by-time effects were non-significant.

After correction for multiple comparisons, the only significant correlation between objective and subjective memory performance was the one between the Memory Complaint Questionnaire score at T1 and the long delay free recall of the Memory for Persons Data items at T2; that is, at least four months after initial learning, (-.58 , p =0.028). This relationship is depicted in Figure 5.

TABLE 10. Group comparisons of memory functions at T2

	BN along with BZD (n = 15) **M ± SD**	**METH along with BZD** (n = 13) **M ± SD**	**Normal** Control n = 15) **M ± SD**	**Statistical comparisons between normal control and patient groups[a,b]**	**Effect sizes as Cohen's d whenever possible**
Working memory					
Letter Number Sequencing (raw score)	9.2 ± 2.3	8.6 ± 2.1	11.6 ± 2.9	BN + BDZ < NC* M+ BZD < NC*	0.83 1.05
PASAT (raw score)	34.1 ± 8.4[a]	31.6 ± 8.6	46.0 ± 8. 7[c]	BN + BZD < NC** M + BZD < NC**	1.24 1.42
Immediate episodic memory					
Logical Memory immediate recall (raw score)	14.1 ± 3.3	14.2 ± 3.1	16.3 ± 3.1	-	-
Episodic memory consolidation					
Logical Memory (free recall retention % after short-term delay of 30 min)	93.8 ± 17.1	87.1 ±14.4	98.3 ± 14.1		-
Memory for Persons Data (free recall retention % after long delay of 4–8 mo)	29.8 ± 23.2	22.1 ± 18.1	32.4 ± 22.1	-	-
Memory for Persons Data (recognition % after long delay of 4–8 mo)	82.1 ± 12.9	79.6 ± 10.6	81.3 ± 10.7	-	-
Memory complaints					
Memory Complaint Questionnaire (raw score[d])	24.5 ± 6.7	25.6 ± 3.2	20.4 ± 1.5	NC < BN + BZD* NC < M + BZD***	n/a n/a

Note. Modified from study publication II. BN = buprenorphine or buprenorphine/naloxone; METH or METH or M = methadone.NC = Normal control; n/a = not available

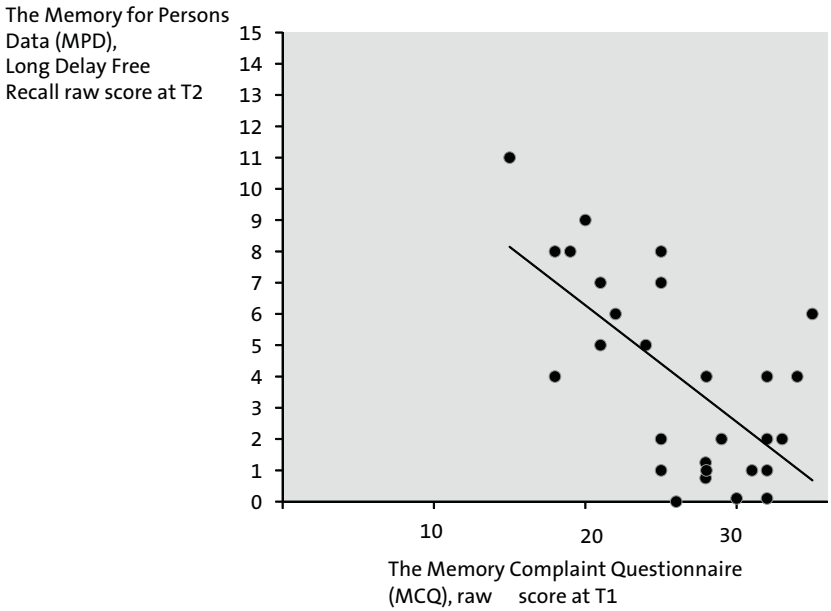
[a] = using years of education and VIQ adjusted scores, whenever possible;

[b] = done only if overall ANOVA is significant and the corrected for multiple comparisons by Bonferroni-Holm method.

[c] = Missing value of one participant was substituted by carry-over value from the first test;

[d] = smaller indicates less complaints.

< = inferior than or less than; *** = statistically significant at level $p < 0.001$, ** = statistically significant at level $p < 0.01$, * = statistically significant at level $p < 0.05$.



Note. Modified from publication II.

FIGURE 5. Correlation between memory complaints (T1) and the Memory for Persons Data, delayed recall (T2).

4.2.2 Longitudinal change of cognitive performance during the first year of OST and its correlates (III)

There were two parts in Study III. Part I presents the results of the follow-up study of fourteen buprenorphine-treated and 12 methadone-treated patients in comparison to 14 normal controls. Tests were done within two months (T1), 6–9 months (T2) and 12–17 months (T3) from the beginning of OST. The controls were tested at similar intervals. Part II analyzed the correlates for cognitive performance at T2 and T3 using a sample of 36 patients. Table 11 shows the main demographic characteristics of the samples.

The pattern of means in Table 12 identifies change over time in cognitive performance in each group. There were statistically significant overall group differences in all attention and memory measures. As is apparent from the Table, the methadone-treated patient group constantly lagged behind the normal control group in the TAP RT tests that measured attention. Planned contrasts confirmed that the normal controls outperformed the methadone group in these measures (p=0.002 for the TAP tonic alertness/simple RT; p=0.002 for the TAP phasic alertness/RT with-auditory-warning-signal; and p=0.001 for the TAP Go/NoGo RT). There

TABLE 11. Group demographics in Study III

	Group			Group comparison p-values	Group		Group or time point comparison p-values
	BN part I (n = 14)[a]	METH part I (n = 12)	NC (n = 14)		BN part II (n = 18)[a]	METH part II (n =18)	
	M ± SD	M ± SD	M ± SD		M ± SD	M ± SD	
Age (years)	30 ± 7	31 ± 8	29 ± 10	ns	30 ± 8	32 ± 8	ns
Sex (female /male)	36 / 64%	50 / 50%	50 / 50 %	ns	28 / 72%	33 / 67%	ns
Intelligence[b]	101 ± 11	98 ± 9	105 ± 8	ns	101 ± 8	100 ± 11	ns
Education (years)	10 ± 2	10 ± 1	13 ± 1	BN < NC *** METH < NC***	10 ± 2	11 ± 1	ns
Days in OST at test[c]							
T1	21 ± 15	20 ± 14	–	ns			
T2	210 ± 20	200 ± 28	–	ns	211 ±19	196 ± 27	ns
T3	414 ± 46	405 ± 31	–	ns	411 ± 43	405 ± 29	ns

Note. Modified from study publication III. BN = buprenorphine patients, METH = methadone patients, and NC = normal controls.
[a] Includes buprenorphine/naloxone-treated patients.
[b] Estimation based on the vocabulary and picture completion subtests of the Wechsler Adult Intelligence Scale – Revised (WAIS-R) (Wechsler, 1993).
[c] Tested only between patient groups.
< = inferior than, *** = statistically significant at level p < 0.001, ** = statistically significant at level p < 0.01, * = statistically significant at level p < 0.05.

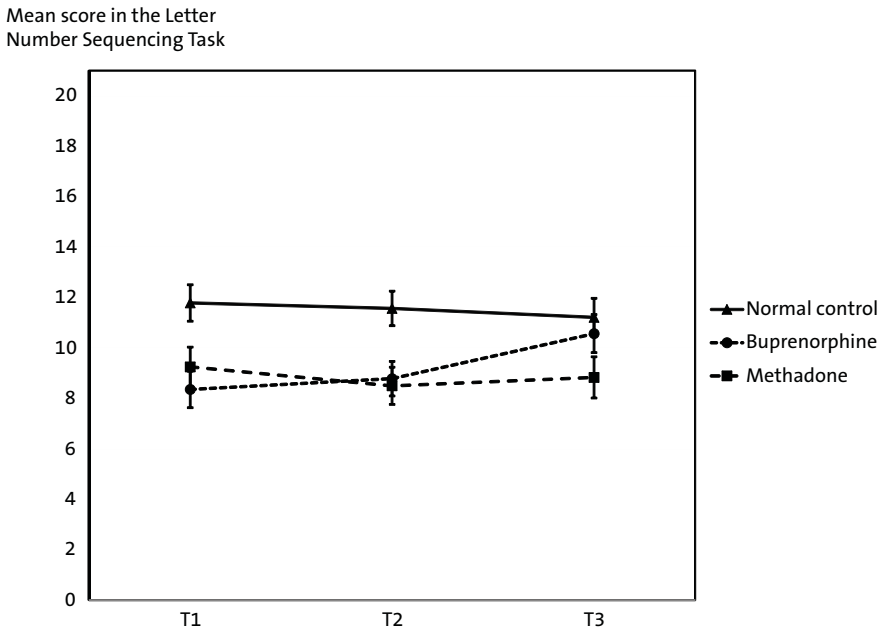
were no significant time or group-by-time interaction effects in these measures. Errors in the Go/NoGo task were rare in all groups, and no significant between-group differences were observed. In both working memory measures there was an overall group effect. In the PASAT the planned contrast revealed that both patient groups performed *overall* worse than the normal controls at the level of p=0.001. In the Letter-Number Sequencing the values were p=0.016, for normal controls vs. buprenorphine patients and p=0.008 for normal controls vs. methadone patients. However, since there was also a time effect (the PASAT), or a group-by-time interaction effect (the Letter-Number Sequencing) in these measures, further analyses are needed before making a final interpretation. In the PASAT the improvement in overall performance between T1 and T2 turned out to be non-significant, but the overall improvement betweenT2t and T3 was significant (p=0.01). As apparent from Figure 6, the source of the group-by-time interaction in the Letter-Number Sequencing was due to differences between the groups between T2 and T3. This was confirmed by a planned contrast that showed improved performance in the buprenorphine patients between T2 and T3 relative to the normal control group, p=0.017. Effect size of the T2–T3 improvement in the buprenorphine group, as measured by Cohen's **d,** was 0.77.

TABLE 12. Group comparisons of cognitive performances using repeated measures ANOVA in the part I sample

	Buprenorphine (n = 14) M ± SD	Methadone (n = 12) M ± SD	Normal control (n = 14) M ± SD	Statistical comparison p-values
TAP Tonic Alertness/ simple RT (ms)				
T1	232 ± 25	261 ± 21	238 ± 22	**Group, p = 0.002**
T2	236 ± 18	263.± 21	233 ± 21[a]	Time, ns
T3	242 ± 25	267 ± 36	241 ± 25	Group x Time, ns
TAP Phasic Alertness/ RT with warning signal (ms)				
T1	227 ± 24	244 ± 20	226 ±21	**Group, p = 0.005**
T2	229 ± 21	255 ±28	224 ± 21 [a]	Time, ns
T3	229 ± 19	254 ±45	225 ± 22	Group x Time, ns
TAP Go-NoGo RT (ms)				
T1	490 ± 50	548 ± 74	460 ± 41	**Group, p = 0.001**
T2	480 ± 42	548 ± 104	443 ± 72 [a]	Time, ns
T3	493 ± 43	529 ± 63	462 ± 47	Group x Time, ns
TAP Go-NoGo errors				
T1	1.1 ± 1.3	0.7 ± 0.6	0.5 ± 0.5	ns
T2	0.5 ± 0.7	1.0 ± 0.9	0.5 ± 0.8 [a]	ns
T3	0.6 ± 0.8	0.5 ± 1.0	0.2 ± 0.4	ns
The Letter-Number Sequencing (raw score)				
T1	8.4 ± 2.2	9.3 ± 2.4	11.8 ± 3.4	**Group, p = 0.009**
T2	8.8 ± 2.2	8.5 ± 2.3	11.6 ± 3.0	Time, ns
T3	10.6 ± 2.2	8.8 ± 2.4	11.2 ± 3.2	**Group x Time, p = 0.007**
The PASAT (raw score)				
T1	32.4 ± 10.5	31.0 ± 8.5	46.3 ± 9.7	**Group, p = 0.001**
T2	35.0 ± 6.8	33.4 ± 10.1	45.8 ± 9.0 [a]	Time, p = 0.013
T3	35.8 ± 10.0	34.9 ± 11.0	49.8 ± 8.4	Group x Time, ns
Logical memory, immediate(raw score)				
T1	12.8 ± 2.6	14.9 ± 4.5	15.9 ± 3.3	**Group, p = 0.016**
T2	13.8 ± 3.1	14.8 ± 3.7	16.3 ± 3.2	Time, ns
T3	15.5 ± 4.1	14.3 ± 4.3	17.9 ± 2.9	Group x Time, ns
Logical memory, delayed (raw score)				
T1	11.8 ± 3.0	13.1 ± 4.0	13.9 ± 4.0	**Group, p = 0.013**
T2	12.0 ± 4.0	13.7 ± 4.0	15.6 ± 3.1	Time, ns
T3	12.4 ± 4.1	11.8 ± 4.7	15.9 ± 3.6	Group x Time, ns

Note. Modified from study publication III. Bold indicates a statistically significant effect.
[a] One missing value was replaced by the carry-over value from the preceding testing point.

In verbal memory, there was a significant overall group effect both in immediate and delayed condition of the Logical Memory. Both patient groups performed worse than the normal controls in the immediate Logical Memory, p=0.029 for the buprenorphine group; and p=0.007 for the methadone group. In the delayed Logical Memory the values were p=0.005, and p=0.028, respectively.



Note. Modified from publication III.

FIGURE 6. Longitudinal change of group performances in the Letter Number Sequencing Task in the sample I of study III.

4.3 Drug treatment variables as predictors of cognitive performance in OST patients (study IV)

There were equal number of buprenorphine- and methadone treated patients in the sample (n=52 in both groups). Methadone patients were four years older on average than the buprenorphine ones (35 ± 8 and 31 ±7 years, respectively), and this difference was statistically significant (p=0.007). Buprenorphine patients had been in treatment for a slightly, non-significantly, shorter time than methadone patients (14 ± 7 vs. 17 ± 10 months, respectively; p=0.08). Otherwise the groups were very close to each other in terms of demographic variables. The mean dose of buprenorphine was 20 ± 6 mg and 113 ± 49 mg of methadone in the respective patient groups. Other prescribed co-mediations and especially BZD prescriptions were common in both opioid drug groups (81 and 71% in buprenorphine patients vs. 83 and 73% in methadone patients, respectively). Sixty-five percent in the buprenorphine group and 63% in the methadone group were prescribed some other psychoactive drug than opioid or BZD drugs. These could include anticonvulsants (used as mood stabilizers), antidepressants, neuroleptics (used with anxiolytic indications), non-benzodiazepine hypnotics, and non-opioid pain killers. Thirty-five percent of patients in the buprenorphine group and 42% in the methadone groups had high-frequency substance abuse in the past month. In group comparisons of cognitive performance buprenorphine-treated patients showed statistically significantly faster simple RTs than methadone-treated ones (the 'without warning signal' condition of the alertness test, 247 ± 21 and 260 ± 30, respectively; $F(1,100)=5.00$, p=0.028). No other significant differences emerged.

4.3.1 Predictors of attention performance

When control variables were first entered into the full model they could predict only 1.3% of the performance variance (2.8% in the sample) of the combined alertness measure. In contrast, drug treatment variables as a block could predict an additional 6.3% (9.7% in the sample). The increment of drug treatment variables as a block significantly improved the model ($F(4, 93)=2.59$, p=0.041), but the full model remained statistically non-significant (p=0.12). None of the individual predictors turned out to be significant in the full model. When the reduced model including only the drug treatment variables was tested, the OST drug group turned out to be the only significant predictor in the model (beta=.20, $t(97)=2.09$, p=0.040). The reduced model was significant (R^2, adjusted)=.056, $F(4, 97)=2.51$, p=0.047). In order to examine the role of the opioid drug further, we then separately analyzed models for buprenorphine- and methadone-treated patients. As shown in Table 13, in the buprenorphine group, being on BZD drug treatment was the only significant predictor in the model. In the methadone group, the high number of other psychoactive drugs was the best predictor in the model. Adding methadone dose to the model made it significant. However, the negative association of methadone dose only approached significance.

TABLE 13. Hierarchical regression results for combined RTs in the Alertness test by opioid drug group

Buprenorphine (n = 51)				
Predictors in the reduced model	**Step1 Beta [a]**	**Step 2 Beta**	**Step 3 Beta**	**Step 4 Beta**
Drug treatment variables				
BZD treatment (yes vs. no)	**.34***	**.36***	**.37***	**.38***
Buprenorphine dose (high vs. low)[b]		-.16	-.17	-.19
The number of psychoactive drugs, other than opioid or BZD (high vs. low)[c]			.05	.05
Duration of OST (long vs. short)[d]				-.05
R^2 (adjusted) and significance of the model (ANOVA)	**.096***	**.103***	**.084#**	**.069**
Change (ANOVA)[a]		ns	ns	ns
Methadone- (n = 51)				
Predictors in the reduced model	**Step1 Beta**	**Step2 Beta**	**Step3[f] Beta**	
Drug treatment variables				
The number of psychoactive drugs, other than opioid or BZD (high vs. low)	.27#	**.30***	**.31***	
Methadone dose		.26 #	.26 #	
BZD treatment (yes vs. no)			-.02	
R^2 (adjusted) and model (ANOVA)	**.051#**	**.098***	**.073 #**	
Change (ANOVA)		**0.066 #**	ns	

Note. Modified from publication IV. P-value shown when p ≥ 0.10. Bold indicates a statistically significant effect.
[a] Signs of beta values are reversed so that positive values refer to slower RTs.
[b] Considered as low up to 16 mg.
[c] Considered as low up to one drug.
[d] Considered as short when between six and twelve months.
*p < 0.05. #p < 0.10.

4.3.2 Predictors of working memory performance

The full model including control variables predicted 8.2% of the variance (16.4% in the sample). The model as a whole was significant ($F(8, 93)=2.28$, $p=0.028$). None of the control variables as a block or individually gave a significant contribution to the model. Consequently the control variables predicted a very low proportion of the variance (−2.5%). In contrast, the drug treatment variables as a block significantly improved the full model ($F(4, 93)=4.13$, $p=0.004$), predicting 11.7% of the variance above the control variables. Therefore, the control variables were removed from the model. As shown in Table 14, treatment with a BZD drug was

TABLE 14. Hierarchical regression results for working memory (n=102)

Predictors in the reduced model	Step 1 Beta	Step 2 Beta	Step 3 Beta	Step 4 Beta
Drug treatment variables				
BZD treatment (yes vs. no)	**-.34 *** **	**-.30 ** **	**-.28 * **	**-.28***
Duration of OST (long vs. short)[a]		.17 #	.17 #	.16 #
The number of psychoactive drugs, other than opioid or BZD (high vs. low)[b]			-.06	.07
OST drug type (buprenorphine vs. methadone)				-.03
R^2 (adjusted) and model (ANOVA)	**.104 *** **	**.124*** **	**.119** **	**.100** **
Change (ANOVA)		**0.074#**	**ns**	**ns**

Note. Modified from from publication IV. P-value shown when p ≥ 0.10. Bold indicates a statistically significant effect.
[a]Considered as short when between six and twelve months.
[b]Considered as low up to one drug.
***p < 0.00. **p < 0.01. *p < 0.05. #p < 0.10.

negatively associated with working memory performance while being in OST for more than one year was positively associated with working memory performance. The BZD drug treatment effect was significant but the duration of the treatment effect only approached significance. Finally, the predictive power of the drug treatment variables, including the BZD variables (type or dose), on working memory performance was tested using the group that included only patients with BZD in their drug regimen (n=75). However, this model had very low predictive power on working memory (– 0.6%) and was statistically non-significant (p=0.48).

4.3.3 Predictors of episodic memory performance

When repeated testing was entered as the first variable of the full model, it was significantly associated with verbal memory performance (beta=.36, t (93)=3.49, p=0.0007). Therefore, in order to eliminate the significant effect of repeated testing from the model, a model including only patients tested once was formed (n=74). Because demographic variables had a minimal effect in the initial full model, this block was dropped from the next model. Thus, the model included substance abuse variables and drug treatment variables. Because age of onset of substance abuse (early vs. late) showed a non-significant effect in the model, it was dropped from the final model. As shown in Table 15, high-frequency substance abuse and a high number of other psychoactive drugs (other than opioid or BZD drug) were the only individual significant predictors of verbal memory performance, both of which were associated negatively with verbal memory performance.

TABLE 15. Hierarchical regression results for verbal memory (n=74)

Predictors in the reduced model	Step 1 Beta	Step 2 Beta	Step 3 Beta	Step 4 Beta	Step 5 Beta
Substance abuse variable					
Frequency of the past month substance abuse (high vs. low)[a]	**.35****	**-.34 ****	**-.36 ****	**-.35 ****	**-.36 ****
Drug treatment variables					
The number of psychoactive drugs, other than opioid or BZD (high vs. low)[b]		**-.32 ****	**-.35****	**-.35****	**-.35****
BZD treatment (yes vs. no)			.10	.10	.10
OST drug type (buprenorphine vs. methadone)				-.03	-.03
Duration of OST (long vs. short)[c]					.01
R2 (adjusted) and model (ANOVA)	**.110****	**.203*****	**.199*****	**.189*****	**.177***
Change (ANOVA)		**0.003****	ns	ns	ns

Note. Modified from from publication IV. P-value shown when p ≥ 0.10. Bold indicates a statistically significant effect.
[a]Considered as high when three or more days a week. Alcohol use was taken into account if it was at least mean weekly 16 portions (12 g) for females and 24 portions for males or binge drinking occurred on any day.
[b]Considered as low up to one drug.
[c]Considered as short when between six and twelve months.
***p <0.001. **p < 0. 01. *p < 0.05. #p < 0.10.

4.4 Additional analyses: opioid drug only patients in comparison to normal controls (combination of Study I and IV data)

In our samples patients with opioid drug only and without co-substance were rare. This made the analysis of pure opioid-drug associated cognitive performance very challenging. Comparing a subsample of OST patients from Study IV against normal controls from Study I, however, gave us an opportunity for examining this issue. When we excluded all other patients than those treated with opioid drug-only, with low or no past-month substance abuse, and who had been in treatment for a minimum of one year, this left us with 14 OST patients (7 buprenorphine and 7 methadone). Between-drug group (buprenorphine vs. methadone) analyses on demographic and cognitive variables showed no significant differences between them. In these analyses, age-corrected values of cognitive scores were used whenever possible. On the basis of this observation, which is in line with our previous observations and those of other research groups (Darke, McDonald, Kaye, & Torok, 2012; Soyka et al., 2008) we combined the patient groups. Table 16 shows the demographic characteristics of the new patient sample in comparison to our previ-

TABLE 16. Group demographics in the additional analyses

	OST patients with opioid drug-only (n = 14)	Normal controls (n = 17)	Group comparisons[a]
Age (years; M ± SD)	37 ± 8	31 ± 11	ns
Sex (female/male)	50 / 50%	53 / 47%	ns
Verbal intelligence	102 ± 10	105 ± 10	ns
(M ± SD)[b]			
Education (patients with primary education only)	79%	24%	OST < NC p = .004
Opioid drug treatment characteristics	50% with buprenorphine, mean dose 19 ± 6 mg 50% with methadone, mean dose 140 ± 37 mg		
Duration of OST (months; M ± SD)	23 ± 5		
Number of cognitive testing (patients with two or three testing)	14%	0%	ns
Patients with high-frequency substance abuse in the past month[c]	0%	6%	ns

Note. Unpublished data. OST = Opioid-substitution treated patients; NC = Normal control.
[a] Tested with t-test or Fisher's Exact Test.
[b] Estimation based on the vocabulary subtest of the WAIS-R.
[c] Considered as high when three or more days a week. Alcohol use was taken into account if it was at least mean weekly 16 portions (12 g) for females and 24 portions for males or binge drinking occurred on any day.

ous control sample from Study I. As presented in the table the combined patients had a lower level of education than the normal controls. Also, the patient group tended to be elder, although the between-group difference was non-significant.

As shown in Table 17 the normal control group outperformed opioid-drug-only patients in one test in each of the cognitive domains. However, in all measures with Finnish general population norms available (the Letter Number Sequencing task, Logical Memory, and the Benton Visual Retention Test), the performances in the opioid drug-only group were also very close to the 50th percentile. For the TAP tests the norms are available only for the German population, and the mean GoNo-Go RT time of OST patients remained between the 31st and 34th percentiles, giving a preliminary indication of deviation from the normality. Also notable here is the finding that subjective memory complaints showed a higher effect size than any of the objective cognitive tests.

TABLE 17. Comparison of opioid-drug-only patients with minimum of one year in OST and normal controls on cognitive performance and subjective memory complaints title

	OST patients with opioid drug only (n = 14)	Normal controls (n = 17)	Statistical comparisons between groups	Effect size (Cohen's d)	Power of the analysis
Attention	**M ± SD**	**M ± SD**			
TAP Tonic Alertness/ simple RT (age corrected ms)	248 ± 32	257 ± 31	ns	–	0.13
TAP Phasic Alertness/ RT with warning signal (age corrected ms)	243 ± 28	244 ± 31	ns	–	0.52
TAP Go/NoGo RT (age corrected ms)	558 ± 95	487 ± 42	OST > NC **p = 0.01**	0.98	0.76
TAP Go/NoG errors	0.2 ±0.4	0.5 ± 0.6	ns	–	
Working memory					
Letter Number Sequencing (standard score)	9.9 ± 2.5	11.3 ± 2.9	ns	–	0.28
PASAT (raw score)	36 ± 13	48 ± 9	OST < NC **p = 0.007**	1.02	0.80
Memory					
Logical memory, immediate recall (raw score)	14.3 ± 3.3	16.3 ± 3.3	ns	–	0.33
Logical memory, delayed recall (raw score)	13.1 ± 3.2	14.5 ± 4.1	ns	–	0.17
Benton Visual Retention Test (correct figures)	7.9 ± 1.4	8.9 ± 1.1	OST > NC **p = 0.024**	0.83	0.63
Subjective memory complaints / The Memory Complaint Questionnaire (raw score)	26 ± 3	21 ± 2[a]	OST < NC **p = 0.0006**	1.70	0.996

Note. Unpublished data. OST = Opioid-substitution treated patients; NC = Normal control.
All other cognitive performance test values are age-corrected except the PASAT and Logical memory.
[a] Tested by analysis of variance (ANOVA).
[a]n = 13.

4.5 Driving fitness of OST patients (Study V)

Study V was a case series including both buprenorphine- and methadone-treated patients. However, the sample was not analyzed on the basis of opioid drug. Instead, two groups were formed on the basis of probability of *total* drug-related driving impairment. Notably, as shown in Table 18, all patients considered to have a probable drug-related driving impairment had at least one BZD drug on their drug regimen while in the 'improbable' group none had a BZD drug.

TABLE 18. Demographic and other background variables in two groups of Study V

	Patients with improbable drug-related driving impairment (n =10)	**Patients with probable drug-related driving impairment (n =12)**	**Statistical comparisons between groups[a]**
Age (years; M ± SD)	32 ± 8	38 ± 9	p = .08
Sex (Female/Male)	40 / 60%	17 / 83%	p = .35
Opioid agonist drug			
Buprenorphine /Methadone	80 / 20 %	8 / 92 %	**p = .002**
Buprenorphine dose, if any (M ± SD)	18 ± 7 mg	24 mg	–
Methadone dose, if any (M ± SD)	115 ± 21 mg	133 ± 30 mg	–
Time in OMT (years; M ± SD)	3 ± 1	3 ± 2	p = .75
Other drugs than opioid agonist			
Any drug	40%	100%	p = .09
Antihistamine	0%	8%	p = 1.00
BZD drug	0%	100%	**p = .0001**
BZD dose, if any (M ± SD)[b]	–	24 ± 22 mg	–
Mood stabilizer[c]	10%	17%	p = 1.00
Neuroleptic	0%	25%	p = .22
Non-BZD hypnotic	0%	25%	p = .22
Second generation antidepressant	30%	8%	p = .29
Tricyclic antidepressant	0%	8%	p = 1.00
Years since obtaining a driver's license	10 ± 9	14 ± 10	p = .25
Driven kilometers within the last year (participants with more than 5000 km)	50%	25%	p = .38
Patients with professional driving experience	17%	20%	p = 1.00
Minor head injury	40%	42%	p = 1.00

Note. Modified from publication V. Bold indicates a statistically significant effect.
[a]Tested by Fisher's Exact Test.
[b]BZD equivalent doses (Bazire, 2003).
[c]These included anticonvulsants and lithium.

4.5.1 On-road driving

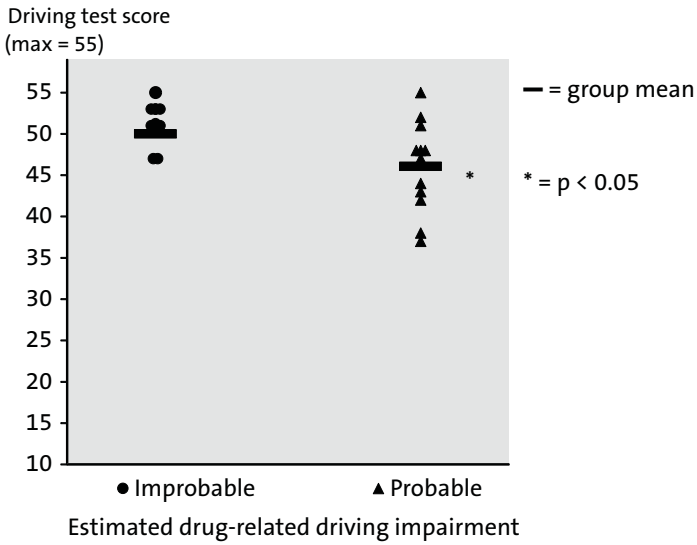
All patients (n=22) showed normal visual fields and were considered neurologically fit to drive. According to the driving instructor's overall safety assessment 94% of the patients were 'safe drivers in all conditions' or 'safe drivers in normal conditions' and thus considered fit to drive a car for non-professional purposes (all except one patient). Fifty-five percent of them drove the route without any driving errors and 83% without any hazardous error. As shown in Table 19, significant between-group differences favoring the 'improbable' group were seen in the total score for the on-road driving test and domains evaluated as 'weak' or 'either weak or strong'. Also, it can be noted that 5 out of 6 patients treated with an opioid drug only drove the test route without committing any error in the route. On the contrary, all three patients that made any hazardous errors in the driving test belonged to the group with 'probable drug-related driving impairment.

Patients with 'probable drug-related driving impairment' scored statistically significantly lower in the on-road driving test (Table 19). As can be seen in Figure 7 there was much more variance in the driving test score among the patients with 'probable drug-related driving impairment'. In order to explore the possible association of drug doses with driving performance we analyzed the correlations between these variables. Both buprenorphine and methadone dose negatively correlated with the driving test score (-.21, *ns* and -.68, p=.01, respectively). Figure 8 depicts the relationship between methadone dose and driving test score, and the number of driving errors. The correlation between BZD equivalent dose and driving test score could be analyzed in the methadone patients. It was negative (-.40), but non-significant.

TABLE 19. Results from the driving-related tests by group

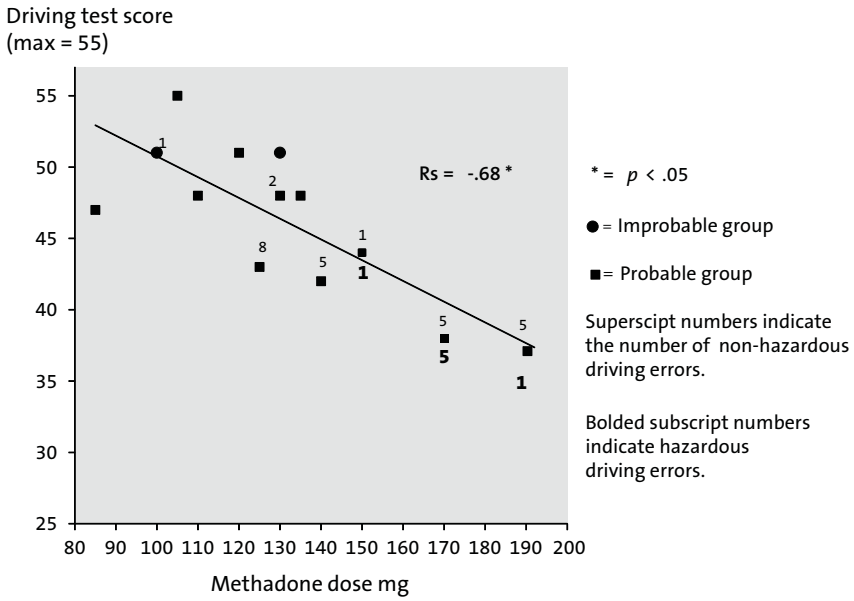
	Patients with improbable drug-related driving impairment (n =10)	Patients with probable drug-related driving impairment (n = 12)	Statistical comparisons between drug groups[a]
Driving test score (M ± SD, max = 55)	51 ± 3	46 ± 5	p = .021
Safe drivers in all conditions according to driving instructor's assessment	90%	83%	p = 1.00
Participants driving the test route with no errors	60%	55%	p = 1.00
Participants showing no 'weak' or 'either weak or strong' driving domains	100%	42%	p = .005
Participants passing all driving-related cognitive tests above 'passed' level[b]	80%	25%	p = .030

Note. Modified from publication V.
[a]Tested by Fisher's Exact Test .
[b]n = 9.



Note. Modified from publication V.

FIGURE 7. On-road driving test scores by group.



Note. Modified from publication V.

FIGURE 8. The relationship between methadone dose and driving test performance.

4.5.2 Performance in cognitive driving related tests

In driving-related cognitive tests, which are not mandatory in the Finnish driving assessment, half of the patients passed every test above the 16th percentile, a recommended 'passed test', criterion. As shown by Table 19 performing in all cognitive tests above the pass level was more common in the 'improbable drug-related driving impairment' group. Of note here is the observation of high variance of cognitive performance in the group with 'probable drug-related driving group'. For instance in the median RT in the Stroop interference condition the values were 1.35 ± 0.55 s in the 'probable' group and 0.88 ± 0.11 s in the 'improbable' group.

5 Discussion

The studies in this thesis were designed to examine cognitive performance in OST patients treated with buprenorphine or methadone and to analyze the role of drug treatment variables as correlates of cognitive performance.

5.1 Main findings in relation to the hypotheses

Attention was the only cognitive domain that was consistent with our first hypotheses of buprenorphine advantage over methadone. Methadone-treated patients' RTs in the attention tests were slower than RTs of normal controls in most of our studies while buprenorphine patients showed no deficits in the attention measures. As an exception, when we compared the pooled opioid drug-only patients (n=14 in the unpublished analyses) against normal controls, a significant difference between the pooled opioid drug-only patients and normal controls emerged in the Go/NoGo RT. In this test there were no significant differences between opioid drugs groups. However, due to small sample size, the comparison between buprenorphine and methadone-only patients (n=7 in both group) remain underpowered, and needs to be repeated with more a powerful sample before a conclusion can be reached. In working memory both buprenorphine- and methadone-treated patients lagged behind normal controls fairly consistently, which does not support the advantage of buprenorphine over methadone in working memory. As an exception, however, the results of the longitudinal study (Study III) showed working memory improvement in the Letter Number Sequencing task between 6–9 and 12–17 months into treatment, while no such improvement was seen in methadone patients. In episodic memory, both opioid drug groups showed impaired performance in most of the studies. In the early-treatment comparison (Study I) an exception was seen, since methadone patients treated also with a BZD drug showed impaired delayed verbal memory performance in relation to buprenorphine/naloxone patients treated also with a BZD drug.

Contrary to our hypothesis we could did not find evidence of a memory consolidation impairment in OST patients treated also with a BZD drug (Study II). The only finding concerning memory consolidation was the substantial negative correlation between memory complaints at early treatment (T1) and free recall after a minimum of four months (T2). Thus, memory complaints in OST patients may indicate a memory problem that is not easily captured by objective tests.

Our third hypothesis predicted greater cognitive improvement in buprenorphine-treated patients. In Study III there was a group-by-time interaction in the Letter-Number Sequencing task, revealing a greater cognitive improvement for bu-

prenorphine patients in long-term treatment relative to methadone-treated patients. However, in our largest sample of long-term treated patients (Study IV) no difference in this measure was seen in buprenorphine- vs. methadone-treated patients. Thus, the evidence supporting the potential for greater cognitive improvement with buprenorphine remains preliminary.

We hypothesized that there would be negative associations between various drug treatment variables and cognitive performance in OST patients. In the regression analysis study, about 10% of the variance in methadone-treated patients' RT performance was related to the number of other psychoactive drugs (other than opioid or BZD) and the methadone dose. Thus, our result supports the idea that drug-treatment variables have a negative effect on attention performance in methadone patients. A further indication of a negative association between methadone treatment and attention-related behavior appeared in our driving fitness study, in which a significant negative correlation was seen between methadone dose and driving test score.

In the regression analysis study (IV), about 10% of the attention performance variance in buprenorphine-treated patients was associated with having BZD drug-treatment along with buprenorphine. This supports our hypotheses that among buprenorphine patients, co-treatment with a BZD drug is negatively associated with attention performance. Since BZD dose had no effect on this relationship, the nature of this relationship (pharmacological or non-pharmacological) remains to be determined. In the same study, about 10% of working memory impairment in the combined opioid drug groups was associated with having a BZD drug and about 10% of episodic memory impairment with the number of psychoactive drugs (other than opioid or BZD). In sum, there are several indications showing negative drug associations with cognitive performance in multidrug treated OST patients, but the drug specificity of the associations remains to be determined.

5.2 Attention findings in relation to other studies

In methadone patients there were two indications of dose-related negative association with attention performance. In early treatment, patients with higher methadone dose (mean 67 mg) showed slower RTs than those with lower doses of 40 mg (Figure 5). In the regression analysis study higher methadone dose predicted, as a statistical trend, longer RT in the combined alertness measure (Table 13). The findings of other research groups, however, do not indicate a negative methadone effect on RT measures. For instance, in the Curran et al. study, short-term treated (five days) methadone patients actually had faster RTs 3 h after the dose (mean 33 mg) than before the dose (Curran et al., 2001). In Baewert et al., opioid-dependent patients treated for a mean two years did driving-related RT tests 1.5 or 20 h after the methadone dose (mean 53 mg) (Baewert et al., 2007). No differences in RTs were

observed. Thus, there is no consistent evidence that methadone dose alone would be associated with RTs among OST patients. However, on the basis of our results a negative association between methadone and RTs in OST patients may be seen when methadone is used along with other psychoactive drugs. Notably, most patients in our methadone-patient samples were given a BZD drug and there is evidence for pharmacodynamic interactions between these drugs (Lintzeris & Nielsen, 2010).

5.3 Working memory findings in relation to other studies

Our second working memory measure, the Letter Number Sequencing task, resembles the better known Digit Span because the storage demands are nearly similar in both tasks. Several studies have examined the Digit Span performance of methadone or buprenorphine patients. The results of these studies show almost consistently no difference between OST patients and normal controls (Darke et al., 2012; Gritz et al., 1975; Lombardo, Lombardo, & Goldstein, 1976; Mintzer & Stitzer, 2002; Soyka et al., 2008; Z. X. Wang, Xiao, Zhang, Liang, & Zhang, 2008). Two studies showing impaired performance in the Digit Span both compared methadone patients against normal controls (Darke et al., 2000; W.-C. Lin et al., 2012). The Letter Number Sequencing task and the PASAT, however, are considered more sensitive tasks than the Digit Span for discovering a working memory deficit in various populations. Both include the processing demand of the presented items, which is not included in the Digit Span task. This idea is supported by our results and by at least two other opioid-related studies. In the first of these latter studies, short-term abstinent opioid-dependent patients showed intact Digit Span performance, although the PASAT performance was impaired (Rapeli et al., 2006). In another study, short-term abstinent opioid-dependent patients were administered the Digit Span and the Letter Number Sequencing tasks (Verdejo-Garcia & Perez-Garcia, 2007). Although the patients were impaired in both of the working memory measures, the Letter Number Sequencing task performance was more impaired than the Digit Span performance (Cohen's d-values, 1.83 and 0.80 respectively). In addition, our results support the idea that the PASAT as a multimodal test would be more sensitive for showing cognitive deficits in OST patients than the relatively pure working memory measure, the Letter Number sequencing task (Study III and additional analyses for opioid drug-only patients).

5.4 Episodic memory findings in relation to other studies

In our studies the only episodic memory performance difference between opioid drug groups was the better performance seen in buprenorphine patients treated along with BZDs in comparison to methadone patients treated along with BZDs in early treatment (Study I). However, in later studies, no differences between the opioids drug groups were seen. The other studies with relatively large samples have likewise not found differences between opioid drug groups in episodic memory, namely the Darke et al. study (2012) with 125 OST patients (buprenorphine; n=31 and methadone, n=94) and the Loeber et al. study (2012) with 54 patients (n=24 and 30, respectively). A study with a smaller sample size of 37 patients (n=24 and 13, respectively) is an exception, showing a buprenorphine advantage in verbal memory (Giacomuzzi, Thill, Riemer, Garber, & Ertl, 2008). However, as the evidence for very small, if any, differences between opioid drug groups in episodic memory is stronger than the opposite, the findings of both drugs groups are discussed together.

Many studies have shown memory deficits in OST patients when compared against normal controls (Darke et al., 2012; Darke et al., 2000; Messinis et al., 2009; Soyka et al., 2008). For, instance in the Darke et al. study (2000) a verbal list-learning test administered to methadone patients showed the most pronounced cognitive deficits out of a great number of cognitive tests. However, there are also many studies which have found no significant memory performance differences between OST patients and controls (P. E. Davis, Liddiard, & McMillan, 2002; Grevert et al., 1977; W.-C. Lin et al., 2012; W. C. Lin et al., 2012; Mintzer & Stitzer, 2002). An important study was performed already in 1977 in which memory performance of methadone patients was longitudinally tested using a word-list learning task and a visual matrix memory task (Grevert et al., 1977). The patients were first tested before the treatment and then twice within the first three months of treatment. No baseline or subsequent differences between the methadone patients and a comparison group were seen in objective or subjective memory function. Thus the results of Grevert et al. provide evidence for normal memory performance in OST patients. However, it can be noted that the patients performed the tests immediately before or after the administration of the methadone dose, that is, when their plasma concentration is known to be at the lowest level. Therefore short-term negative effects of high methadone concentrations may have been missed. More recently, this issue has been controlled in two studies. In Curran et al., opioid-dependent patients treated with methadone for a minimum of 6 months were randomly allocated to either normal dose, 33% increased dose, or placebo linctus; they were tested both pre-drug and again 3 hours after the dose (Curran, Bolton, Wanigaratne, & Smyth, 1999). No significant treatment effect was seen, and the authors concluded that single doses of higher methadone are devoid of verbal memory effects among

long-term methadone users. The issue, however, may not be fully resolved, because in a later study the same study group got a different result (Curran et al., 2001). After five days in methadone treatment, opioid-dependent patients who were given a withdrawal stabilization dose of the drug showed significantly worse performance in comparison to the placebo condition in a story recall test repeated 3 h after the dose. Furthermore, a recent study using a long-term treated sample of OST patients (minimum three months in treatment) found that after controlling for several demographic variables and recent polydrug use, OST patients still showed verbal memory deficit in the Logical Memory test (Darke et al., 2012). The magnitude of deficit was substantial for immediate memory (d=0.72) and strong for delayed memory (d=0.93). Nevertheless, no opioid dose effect on verbal memory was observed.

In visual memory, buprenorphine and methadone patients showed similar performance (Study IV); and in the comparison against normal controls, opioid-drug-only patients showed impaired performance in the Benton Visual Retention Test (unpublished additional analysis). The only other study that has used this test for both main OST drugs also found a visual memory deficit when buprenorphine or methadone patients treated for a minimum of 12 months were compared separately against normal controls (Pirastu et al., 2006). As reviewed by Gruber et al. a visual memory deficit using this test has been reported in early studies focusing on methadone patients only (Gruber, Silveri, & Yurgelun-Todd, 2007). Thus, our result adds to the evidence for visual memory deficit among buprenorphine- or methadone-treated opioid-dependent patients.

Our studies are one the first studies to examine simultaneously several correlates of episodic memory performance among OST patients. Whereas our study found a negative association between the past month substance abuse and verbal memory, the only other study dealing with the same issue (Loeber et al. 2012) found an association between impaired verbal memory performance and male sex and duration of cocaine use. Thus, both studies just mentioned found an association between memory deficit and drug use, though rather different assocations. Interestingly a recent study of a different population, but with high frequency of drug use, namely HIV positive women, also found a significant negative association with recent substance use and memory performance in a multivariate regression analysis (Meyer et al., 2013). In sum, the evidence that buprenorphine or methadone as such would affect negatively on memory functioning is not convincing, since there are many confounding variables that need to be controlled for before strong conclusions can be made.

5.5 Driving fitness findings in relation other studies

Our study of driving fitness in OST patients fits to the case series approach rather than the experimental control approach. Thus, our study had no control group as a reference for normality. Instead, a driving safety assessment carried out by a licensed driving instructor was used as a reference for normality. The major outcome was that 21 out of 22 participants were considered as safe drivers. Thus, our finding is in agreement with earlier studies using an on-road driving test (Fishbain, Cutler, Rosomoff, & Rosomoff, 2003; Strand, Fjeld, Arnestad, & Morland, 2013). In spite of this general finding of driving fitness, important points of caution need to be mentioned. First, when we divide our case-series of patients into those with improbable vs. probable drug-related driving impairment, significant differences emerged. Patients with 'probable drug-related driving impairment' scored statistically significantly lower in the on-road driving test total score and in the number of 'passed' cognitive tests. Second, further analyses showed that higher methadone dose was significantly associated with lower driving test scores as well as more errors while driving. Notably, four out of 26 voluntary patients with a valid driving license coming into the driving test were found to be positive in the preceding drug screen. This raises concerns about the proportion of OST patients driving under the influence of drugs.

5.6 Implications of the findings on the neuropsychology of opioid-dependence

Our results give preliminary support to the idea of the compensatory plasticity of the human brain, with a high tendency for preserving cognitive functioning (Figure 3 and related review in the Introduction section). For instance, we could not evidence any negative correlations with lifetime substance abuse measures and cognitive performance (Study III). Instead, there was a negative association between the past month substance abuse and verbal memory in the largest sample (Study IV) and working memory at T2 and T3 in the longitudinal study (III). Thus, these findings are in line with the hypothesis of short-term neurotoxic effects of substance use but do not support the hypothesis of negative long-term effects. Yet, there is a lot of evidence indicating long-term negative brain changes in opioid-dependent patients (section 1.1.3 in the Introduction). Furthermore, a study concerning chronic pain patients without opioid-dependence (n=10) indicated that after one month of mu agonist morphine use with adequate pain relieving doses (maximum of 120 mg/day), 13 brain regions showed significant volumetric changes, and many of these correlated significantly with morphine dosage (Younger et al., 2011).

There are many routes to compensatory neural activity in continuous working memory tasks like the PASAT, but the most consistent brain areas linked to it are

the middle and medial frontal gyrus (BA 6,8, 9, and 10), the bilateral insular cortex (BA 13), and parts of the parietal cortex (BA 7 and 40) (Bryer, Medaglia, Rostami, & Hillary, 2013; Caseras et al., 2006; Fassbender et al., 2011a; Paskavitz et al., 2010; Squeglia et al., 2012). Medial frontal gyrus hyperactivity (BA 10) is supposed to be only relatively due to the lack of deactivation of the default-mode network in this area (Fassbender et al., 2011a). The need for the insular cortex activation in working memory may be especially pertinent to our findings. The insula is an area with very high mu opioid receptor density; and it plays a major role as a switch between task-irrelevant and task-relevant mental states (Baumgartner et al., 2006; Naqvi & Bechara, 2010; Tang, Rothbart, & Posner, 2012). Although OST has been shown to restore cortical activity in many brain areas, the insula is one of the areas in which activity remains abnormally low in relation to normal controls (Galynker et al., 2007). This hypoactivation could be related to working memory performance in OST patients. Also, our results may indicate that working memory deficits in opioid-dependent patients are related to incomplete switching from task-irrelevant neural networks to task-relevant/specific brain networks while on task. Of relevance in this matter is the observation that several brain areas with probable compensatory activity are the same areas that show cortical atrophy among opioid-dependent patients (section 1.1.3 in the introduction). Simultaneous cortical thinning and hyperactivation, however, are a possible combination in cognitive deficits (Reuter-Lorenz & Cappell, 2008; Schneider-Garces et al., 2010).

5.7 Implications of the findings on the opioid-substitution treatment

As reviewed in the previous section the human brain may have a high capacity to compensate for neurotoxic costs from substance abuse or side-effects of polypharmacy. Thus, OST patients, in general, have better cognitive functioning than commonly believed. Therefore, psychoeducation about the positive side of our findings is needed. In fact, positivity in itself may improve cognitive function, create curiosity, and foster creative problem solving (Ashby, Isen, & Turken, 1999; Johnson, Waugh, & Fredrickson, 2010). On the other hand, cognitive deficits among OST patients should not be underestimated.

Our results indicate that episodic memory deficits persist among multidrug-treated patients (Study III), and working memory deficits may be partly persistent among all OST patients (Study III and the additional analyses of opioid-drug only patients). These findings are of practical relevance, since the episodic memory test used, The Logical memory, correlates well with everyday memory functioning (Sunderland, Harris, & Baddeley, 1983), while optimal working memory function is vital for reading comprehension, learning, and reasoning (Baddeley, 2003). Furthermore, if working memory is compromised, drug cues are harder to resist

(Goldstein & Volkow, 2011). There are some preliminary findings that working memory training may improve cognitive control in drug addiction patients (Bickel 2011) but transfer from laboratory to real-life remains to be shown.

Our case-series findings of well-preserved driving fitness in 21 out of 22 examined patients is in line with the idea that OST patients in stable treatment without co-substance abuse are fit to drive. One may ask if the driving fitness of OST patients could be approached using the same guidelines as exist for long-term pain patients with opioid agonist medications. The relevant European guidelines are as follows: "If a patient on long-term, stable opioid therapy is considering driving a car, the health care provider should make sure that the patient: should do this only if the opioid dose has been stable at least for 14 days; should never drive if he/she feels tired, sedated, fatigued, dizzy, sleepy; should always report to the physician when feeling tired, sedated, or fatigued and discuss with the doctor the possibility of reducing the opioid dose; must never combine opioid medication with alcohol, sedatives, anxiolytics, or any other psychoactive medications (or illegal drugs of any kind). The physician, at all times, should inform the patient about the effects of opioids on driving ability and the regulations made by the authorities of their country"(Monteiro & De Gier, 2011). However, another expert opinion from the same project recommends that if a patient is given methadone or buprenorphine for addictive disorders then driving during the treatment should require an approval from a driving license administration (Gómez-Talegón, Fierro, Del Río, & Alvarez, F.J., 2011). On the basis of our case-series with OST patients, this requirement seems valid.

5.8 Strengths, limitations, and other methodological considerations

A notable strength in our studies was the use of relatively liberal inclusion criteria for patients. Thus our study samples represent typical opioid-dependent patients in OST in Finland. In terms of the clinical relevance of a study, having a representative sample is often more important than having full control of all known confounding factors. Also, ethical and practical concerns limit the possibilities for fully controlled trials (= inpatient settings) in longitudinal studies.

The strength of Study I was the inclusion of both buprenorphine and methadone patients in the same study during early treatment. The strength in our longitudinal studies (II–III) was the use of a control group, because otherwise the practice effects that were seen in some measures would not have been reliably controlled for. Study II was the first outpatient study with a representative sample of OST patients treated along with benzodiazepines, which is a common combination in real-life patients. Study III was among the most comprehensive longitudinal studies carried out to date, and it included analyses of correlates of performance, which served as a preparation for the more detailed analyses of Study IV.

Moreover, Study IV was one of the most comprehensive studies examining drug treatment variables as predictors of cognitive performance in OST patients. Study V was one of the few studies with an actual driving test in normal traffic carried out by OST patients.

Some of the characteristics of our study can be considered both a strength and a limitation. In our studies, the substance abuse history of the patients is reported in more detail than in many previous studies. The sample descriptions show that our results do not concern "pure" opioid-dependence. In fact, pure opioid-dependence with heroin, which used to be quite common some decades ago, has become much rarer in Finland as well as in many other countries. However, having a representative sample limits a comparison of our results with many of the earlier studies that used "pure" opioid-dependent patients.

In most of our group comparisons the sample sizes are lower than initially planned (the aim was for 25 participants/group). For this reason some of our analyses are statistically underpowered and strong conclusions about group differences need to be avoided. Non-randomized sampling and small sample size may produce false positive findings (Ioannidis, 2005). Some important information about participants' lifetime and current characteristics, such as learning disability histories, are missing from our analyses, and this may affect our results. Premorbid cognitive functioning was estimated only on the basis of a vocabulary test. However, to my knowledge, in the only addiction study with the available data of comprehensive childhood cognitive testing, the analyses showed premorbid vocabulary deficits in mixed-type drug-dependent patients (Block, Erwin, & Ghoneim, 2002). On the other hand, in the most comprehensive study of methadone patients' cognitive performance, the same premorbid verbal IQ estimate that was used in our study, the WAIS-R vocabulary test, was the only test not showing a difference between patients and age-, gender-, and education-matched controls (Darke et al., 2000). In our study, matching for education was not done, since it is not a valid method for matching in our country, in which continuous vocational education after primary school is very common, and patients with opioid-dependence typically drop-out from vocational education. Lifetime or current psychiatric and neuropsychiatric morbidity was screened for acute DSM-IV axis I. Thus, axis II morbidity with a potential to affect the results was not taken into account in the analyses. Nicotine dependence or hepatitis C status, both with a probable role in cognitive functioning in substance dependence, was not controlled for in the analyses, which limits the specificity of our findings. Time of the tests after administration of the dose may have been too late to capture the cognitive effects of peak drug-concentrations (Lintzeris et al., 2006).

Our analyses were focused on attention, working memory, and episodic memory. However, even within these cognitive domains we could cover only some of the essential components. Furthermore, only some of the cognitive control functions related to addictive behaviors can be revealed by "cold" cognitive tests. Thus, tests with affective neutral material may not reveal cognitive control deficits which be-

come evident only after a shift from "cold" memory systems to "hot" memory systems (Schwabe, Dickinson, & Wolf, 2011). "Hot" memory systems are found to be active for instance during withdrawal augmented antirewad/anhedonia or stress-precipated discomfort (Bonson et al., 2002; Schwabe et al., 2011). Hot mental states are thought to able to activate rigid conditioned motivational memory circuits and thus act like a bottleneck for "cold" and flexible higher order cognitive control circuits (Volkow et al., 2010)

Our study design was quasi-experimental, without randomization of the samples, and this needs be taken into account in comparisons between buprenorphine- vs. methadone-treated patients. In order to corroborate our findings these studies should be complemented with longitudinal studies that include cognitive pretreatment assessment and, if possible, more accurate information about premorbid functioning (school records or similar).

5.9 Conclusions

OST patients treated with buprenorphine or methadone tend to show cognitive deficits in working memory and episodic memory. Methadone patients tend to show also attention deficits. Buprenorphine patients tend to show less attention deficits than methadone patients or possibly none of them. Although the magnitude of cognitive performance deficits in stable OST patients cannot be fully determined in our study, the results give a preliminary indication that the deficits are of smaller magnitude than often believed. Also, the results give preliminary support to the idea of improvement cognitive function during OST. The close to normal cognitive function in stable OST patients may indicate an efficient compensation of neural burden related to opioid abuse history. On the other hand, the findings indicate negative associations between recent frequent substance use and poor episodic memory as well as between polypharmacy and poor working and episodic memory. OST patients in stable treatment are, in general, fit to drive a car. Patients with high methadone dose treated along with a BZD drug may be more prone to driving errors than patients with buprenorphine medication only.

The findings may be relevant for patients and prescribers when discussing the choice of OST or co-medication drugs. Also, our results may be informative when the patient and her/his treatment team discuss the time and intensity of psychosocial rehabilitation, such as participation in employment programs, psychotherapy or education.

Finally, opioid substitution is in many cases a lifelong treatment, and this should be taken into account in future research. Does the hypothesized neural compensation taking place in OST patients, which counterbalances their previous and current neural burden on cognition, break down earlier among them than in normal aging?

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Original publications

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Research article

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Methadone vs. buprenorphine/naloxone during early opioid substitution treatment: a naturalistic comparison of cognitive performance relative to healthy controls

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Abstract

Background: Both methadone- and buprenorphine-treated opioid-dependent patients frequently show cognitive deficits in attention, working memory, and verbal memory. However, no study has compared these patient groups with each other during early opioid substitution treatment (OST). Therefore, we investigated attention, working memory, and verbal memory of opioid-dependent patients within six weeks after the introduction of OST in a naturalistic setting and compared to those of healthy controls.

Methods: The sample included 16 methadone-, 17 buprenorphine/naloxone-treated patients, and 17 healthy controls matched for sex and age. In both groups buprenorphine was the main opioid of abuse during the recent month. Benzodiazepine codependence, recent use, and comedication were also common in both patient groups. Analysis of variance was used to study the overall group effect in each cognitive test. Pair-wise group comparisons were made, when appropriate

Results: Methadone-treated patients, as a group, had significantly slower simple reaction time (RT) compared to buprenorphine/naloxone-treated patients. In Go/NoGo RT methadone patients were significantly slower than controls. Both patient groups were significantly debilitated compared to controls in working memory and verbal list learning. Only methadone patients were inferior to controls in story recall. In simple RT and delayed story recall buprenorphine/naloxone patients with current benzodiazepine medication (n = 13) were superior to methadone patients with current benzodiazepine medication (n = 13). When methadone patients were divided into two groups according to their mean dose, the patient group with a low dose (mean 40 mg, n = 8) showed significantly faster simple RT than the high dose group (mean 67 mg, n = 8).

Conclusion: Deficits in attention may only be present in methadone-treated early phase OST patients and may be dose-dependent. Working memory deficit is common in both patient groups. Verbal memory deficit may be more pronounced in methadone-treated patients than in

buprenorphine/naloxone-treated patients. In sum, to preserve cognitive function in early OST, the use of buprenorphine/naloxone may be more preferable to methadone use of, at least if buprenorphine has been recently abused and when benzodiazepine comedication is used. Longitudinal studies are needed to investigate if the better performance of buprenorphine/naloxone-treated patients is a relatively permanent effect or reflects "only" transient opioid switching effect.

Background

In opioid substitution treatment, the opioid-dependent patient receives long-acting mu opioid receptor agonists in order to prevent withdrawal symptoms and to reduce craving for street opioids. The full mu opioid agonist methadone is the most commonly used drug in OST programs. If overdosed, which may happen in cases of abuse, methadone may cause fatal respiratory depression. Therefore, partial mu opioid receptor agonist and kappa receptor antagonist buprenorphine, with a ceiling effect on respiratory depression, has been increasingly used in OST programs. Buprenorphine, however, is commonly abused in several countries; and in combination with other psychoactive substances it may also be hazardous [1,2]. Therefore, a safer drug combining buprenorphine and naloxone has been developed. The compound contains buprenorphine and naloxone in 4:1 ratio, and if used sublingually, it has practically equal pharmacokinetic properties as buprenorphine alone [3,4].

Already during the first few weeks of their OST patients often show reduction of use of illegal opioids and related problem behaviors [5,6]. Some patients, however, experience negative treatment effects including cognitive disturbances and relate them to their OST drug. This needs to taken seriously as drug-dependent patients experiencing troubles in concentrating and remembering have poor treatment engagement and treatment prognosis [7,8]. Thus, it is relevant to study objective cognitive function of early OST patients.

When given to healthy volunteers, both methadone and buprenorphine have shown adverse effects on attention and memory [9,10]. When these drugs are given to opioid-dependent patients, their cognitive effects may be different because these patients have tolerance for opioids. As an example of this, a single dose of methadone (5 or 10 mg) slowed down simple RT of healthy volunteers but had no such an effect on methadone-treated opioid-dependent patients in stabilized treatment (a stable methadone dose regimen from 20 mg to 70 mg for at least one month) [11]. In the same vein, a one third increase in methadone did not affect memory or RT performance of opioid-dependent patients who had been in treatment at least for 6 months [12]. However, switching from opioid of abuse to different opioid for OST purposes may cause transient cognitive side-effects. In accordance with this idea heroin abusing opioid-dependent patients studied during the first week of methadone-aided withdrawal treatment showed verbal memory deterioration after the full methadone dose of 35 mg on average compared to placebo or to halved dose [13].

Cognitive effects of buprenorphine in OST patients are not well known. Some evidence exists for buprenorphine having less adverse effect on driving-related attention than methadone [3,4,14,15]. However, in a recent comparison, made after 12 months of OST, both buprenorphine and methadone-treated patients were inferior to controls in visual memory [16].

In clinical settings, OST patients typically have used, and may still use, other substances of abuse. Benzodiazepine abuse is particularly common among individuals starting OST [17]. At the same time other psychoactive drugs are often prescribed to them. Yet, few studies have dealt with this issue. For instance, the studies of Soyka et al., which showed better performance among buprenorphine-than among methadone-treated OST patients, mainly describe patients with current polysubstance abuse and psychoactive polytherapy [14,15].

In sum, both methadone and buprenorphine/naloxone as such or in combination with other psychoactive medications may have negative effect on cognition in OST patients. To our knowledge, no study has addressed this issue in a naturalistic clinical sample of patients who are starting their OST – a period when cognitive deficits might be pronounced. Therefore, we evaluated attention, working memory, and verbal memory of methadone- or buprenorphine/naloxone-treated patients starting OST and compared these to those of controls.

Methods

Participants

The study participants with opioid dependence were volunteers from a consecutive series of patients accepted for standard OST in the addiction clinics of Helsinki area. The introduction of combined buprenorphine/naloxone OST in Helsinki in 2004 enabled a comparison of cognitive abilities between the methadone-treated and the buprenorphine/naloxone-treated patients. Healthy con-

trol participants were recruited from adult education centers and by word of mouth.

The inclusion criteria for all participants were age between 18 – 50 years. The additional inclusion criteria for OST patients were opioid dependence according to DSM-IV, and the start of OST during the last six weeks. We excluded participants with current uncontrolled polysubstance abuse, acute alcohol abuse, or acute axis I psychiatric morbidity according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) other than substance abuse disorders. Also we excluded participants with severe brain injury, chronic neurological disease, history of other than substance-induced psychoses, epileptic seizures, human immunodeficiency virus (HIV) infection, pregnancy, or primary cognitive deficit. Each opioid-dependent participant eligible for our study was screened by urine sample for substance abuse on the day of testing and at least once in the preceding week. Healthy controls were selected for substance abuse screening at random and we screened one third of them. After excluding participants showing positive drug screen on the day of testing we included 16 methadone-, 17 buprenorphine/naloxone-treated patients, and 17 healthy controls.

The study protocol was accepted by the Ethics Committee of Helsinki University Central Hospital. We obtained a written informed consent according to the Declaration of Helsinki from all participants, and paid them € 60 if they attended all the necessary visits.

Table 1 shows major demographic variables of each group. When appropriate, we performed pair-wise group comparisons with analysis of variance (ANOVA) or with chi-square-test. The groups did not differ in age or sex distribution. The OST groups did not differ in history of substance abuse or duration of OST. As shown in Table 1 the control group had more education than the patient groups. The control group had superior verbal intelligence (Verbal IQ) relative to the methadone patients but not to the buprenorphine/naloxone patients. The main opioid of abuse within the last month was buprenorphine among all participants of the buprenorphine/naloxone group and among most participants (75%) in the metha-

Table 1: Group demographics

	Methadone (*n* = 16)	Buprenorphine/Naloxone (*n* = 17)	Control (*n* = 17)	Group comparison *p*-values
Age, years (*M, SD*)	30.8 (8.8)	28.1 (6.3)	31.1 (11.2)	*ns*
Sex: females/males	9/7	7/10	9/8	*ns*
Verbal intelligence [a] (*M, SD*)	98.4 (8.7)	102.4 (8.4)	105.4 (9.8)	C > M*
Education, years (M, SD)	10.4 (2.0)	11.1 (2.2)	13,0 (1.7)	C > M** C > BN**
Dependencies				
Opioid	100%	100%	-	*ns*[b]
Alcohol	0%	6%		*ns*[b]
Amphetamine	0%	11%		*ns*[b]
Benzodiazepines	100%	89%		*ns*[b]
Cannabis	6%	11%		*ns*[b]
Main opioid of abuse used within last month (%)				
Buprenorphine	75%	100%	-	*ns*[b]
Heroin	13%	0%		*ns*[b]
Methadone	13%	0%		*ns*[b]
Other substances of abuse used within last month (%)				
Alcohol (heavy use)[c]	6%	17%	6%	*ns*
Amphetamine	19%	29%	0%	*ns*
Benzodiazepine[d]	94%	94%	0%	M & BN > C**
Cannabis	38%	24%	0%	M > C*
Nicotine (daily use)	100%	100%	35%	M & BN > C**
Duration of opioid substitution treatment in the day of testing, days (M, SD)	14.3 (7.4)	11.0 (8.1)	-	*ns*[b]
Duration of opioid abuse, years (M, SD)	12.1 (7.7)	10.0 (3.5)	-	*ns*[b]
Duration of any substance abuse, years (M, SD)	16.9 (8.7)	15.7 (5.0)	-	*ns*[b]

[a]Estimation based on WAIS-R Vocabulary score.
[b]Tested only between methadone- and buprenorphine/naloxone-treated patients.
[c]Alcohol use was considered heavy if it was at least mean weekly 16 portions (12 g) for females and 24 weekly portions for males.
[d]Includes benzodiazepines used on prescription.
M = methadone, BN = buprenorphine/naloxone
> = superior than, *** = statistically significant at level $p < 0.001$. ** = statistically significant at level $p < 0.01$. * = statistically significant at level $p < 0.05$.

done group. There were four cases (25%) of recent month abuse of heroin or methadone in the methadone-treated group. Also participants in the buprenorphine/naloxone group reported, however, earlier periods of heroin or methadone abuse. As expected, nearly all opioid-dependent participants had used also other substances of abuse within the last month. In general, these non-selected opioid-dependent participants represent reasonably well current opioid abusing populations in Finland where buprenorphine has become the main street opioid [18]. There has been a similar trend for increase of buprenorphine abuse world-wide [2].

Procedure

Cognitive testing was done three to six hours after the administration of opioid substitution drug, i.e. when drug plasma concentration is known to be highest [19]. Under supervision, the methadone patients were given a mean dose of 53.4 mg (*SD* = 18.6) of methadone, range 30 – 105 mg, in liquid form on the test day morning. The buprenorphine/naloxone patients, also under supervision, received a mean dose of 15.8 mg (SD = 3.2) of buprenorphine and 3.9 mg (SD = 0.8) of naloxone (range 8 – 24 mg of buprenorphine and 2 – 6 mg of naloxone) as a sublingual tablet. In this naturalistic study, all participants received their prescribed psychoactive medications on the test morning according to their clinical dose regimen. After that, however, opioid withdrawal syndrome relievers were given according to individual needs of the patients. Medications taken by the patients in the 24 hour period before the test are described in Table 2. Notably, all participants in both groups were either dependent on benzodiazepines, had abused them during last month, or were given them as a part of their early OST medications.

Table 2: Comedications among OST patients within the last 24 h before testing

Medications used within 24 hours of test	Methadone-treated patients (*n* = 16)		Buprenorphine/Naloxone-treated patients (*n* = 17)	
	Proportion of patients	Dose, range	Proportion of patients	Dose, range
Antidepressives (any)	44 %		35'%	
Essitalopram	6%	5 mg		
Citalopram	6 %	20 mg		
Doxepine			12%	75 – 100 mg
Fluoxetine	13%	20 – 30 mg		
Mirtazapine	13%	15 mg		
Paroxetine			6%	50 mg
Sertraline	6%	50 mg	12%	50 mg
Venlaflaxine			12%	75 mg
Anxiolytics, sedatives and hypnotics:				
Benzodiazepines (any)	81 %		76%	
Diazepam	38%	5–20 mg	29%	15 -40 mg
Oxazepam	44%	45 – 120 mg	47%	30 – 90 mg
Nitratzepam*	6%	20 mg		
Tematzepam *	19%	20 mg	12%	20 mg
Non-benzodiazepine hypnotics (any)	25%		35%	
Zolpidem *	6%	10 mg	6%	15 mg
Zopiclone *	19%	7.5 – 15 mg	24%	7.5 – 15 mg
Neuroleptics † (any)	25%		18%	
Chlorpromazine			6%	50 mg
Flupenthixole	6%	0.5 mg		
Levomepromazine	6%	150 mg	6%	100 mg
Quetiapine	13%	50–100 mg	6%	300 mg
Opioid withdrawal symptom or pain relievers (any)	69 %		53%	
Hydroxyzine	38%	25–200 mg	24%	75 – 300 mg
Ibuprofeine	13%	600– 2400 mg	6%	400 mg
Lofexidine	6%	0.2mg	18%	0.2 – 0.6 mg
Metoclopramide	6%	10 mg		
Naproxen	6%	500 mg	6%	500 mg
Propranol	6%	20 mg		
Valproate	13%	500 – 1000 mg	24%	500 – 1000 mg
None medication	13%		12%	

* Used as a hypnotic the night before testing.
† Used with anxiolytic indications

In order to estimate the current benzodiazepine doses of the groups, all benzodiazepines were converted to diazepam equivalent doses according to the Ashton table [20]. In the cases of nitrazepam and temazepam the diazepam equivalent doses were halved in order to account for their use as hypnotics prior the night before testing. After this conversion no statistically significant difference existed between the patient groups in their mean estimated diazepam equivalent dose, 23.0 mg (SD = 20.2) in the methadone group and 19.6 mg (SD = 14.2) in the buprenorphine/naloxone group.

Cognitive tests

A battery of cognitive tests included tests of attention, working memory, and verbal memory.

Attention was assessed by the Alertness and Go/NoGo-tasks from the Test for Attentional Performance (TAP) which include computer software and RT key-pad. [21]. In the Alertness task, visual RT was assessed with and without preceding auditory warning signal. The without signal condition of the Alertness test is a simple RT task, and is thought to reflect tonic or intrinsic alertness [22]. The with signal condition is thought to reflect both tonic and phasic alertness. The conditions were presented in the A-B-B-A – order. The Go/NoGo condition assessed integrity of response-selection and executive control of attention [23,24]. Visual stimuli were presented one by one. For two stimuli out of five an instant reaction is required, and for the others a reaction needs to be inhibited. Reaction times and correctness of responses were recorded. In all the TAP tests median of RTs was used as a RT parameter.

Working memory was assessed by the Letter-Number-Sequencing task (LNS) from the Wechsler Memory Scale-third version (WMS-III) and by the computerized version of the Paced Auditory Serial Addition Task (PASAT) from the FORAMENRehab software package [25-27]. The LNS assesses verbal working memory storage added with processing demand. In the PASAT complex working memory functions required are continuous storage of previous number, rapid arithmetical processing, and executive control of interference from previous items or from ongoing adding process. In our study presentation rate of a new number to be added to the previous one was set as one in every 1.6 second.

Verbal memory was assessed by a list learning task and by a story recall task: the Memory for Persons Data (MPD) and The Logical Memory (LM), respectively [25,28,29]. Both tests were presented in modified versions. In the LM, which is a subtest of the WMS-III, only one story was presented and recalled immediately and again after 30 minutes. In the MPD only three persons, each with 5 items, were presented. First there were two learning trials with immediate recall. If the participant could recall all 15 items correctly in both trials no more learning trials were administered. If this condition was not met, there were additional trials until the participant was able to recall all the items correctly in two consecutive trials. A maximum of four trials were administered. After five minutes recall of the items was asked for and possible errors were corrected for. Finally, after 30 minutes delayed recall of all the items was asked for.

Statistical analysis

Analysis of variance (ANOVA) was used to study the overall group effect in each cognitive test. This was followed, when appropriate, by pair-wise group comparisons. We used multiple planned ANOVAs because comparisons were aimed at each variable separately. In all analyses, statistical significance was set at 0.05 (two-tailed). For each variable we corrected multiple pair-wise comparisons by Holm's procedure. We examined homogeneity of variances in each measure by Levene's test. In the simple RT and the MPD first trial performance, the data was first transformed by reciprocal or logarithmic transformation to normalize the distributions. For the both of the Go/NoGo conditions, the MPD last two last learning trials, and in the MPD delayed recall the distributions could not be normalized. First, we analyzed these results by non-parametric Kruskal-Wallis ANOVA, which then were followed, when appropriate, by pair-wise Mann-Whitney U test. We did not covary for the group difference in education favoring the control group over methadone group. This was based on the contention that the assumption of similar linear relation between education and cognitive performance in both groups needed for analysis of covariance (ANCOVA) was not met. All participants with opioid dependence had started substance abuse in their early teen years. Once the substance abuse history begins it soon affects educational achievement by class non-attendance etc. So, years of education does not reflect cognitive ability in this populations similarly to the general population [30]. However, in the second phase of the analysis, in order to evaluate the role of premorbid intellectual factors, we set verbal IQ as a covariate for other measures than RT measures. The association between simple RT measures and intelligence is weak and may not be linear [31]. Demographic data was studied as pair-wise group comparisons without first requiring significant overall group effect. Statistical analyses were done by SPSS statistical software, version 13.0, with an exception of the effect size calculations. For this purpose an effect size calculator provided by Durham University, UK was employed [32]. In these analyses we used pooled samples and corrected the values by Hedge's correction for small sample bias.

Results

In the attention domain there were significant overall group effects in two tasks: in the simple and Go/NoGo RTs ($F_{2,47} = 4.77$, $p = 0.013$; $\chi^2_2 = 6.39$, $p = 0.041$, respectively). In working memory, significant group effects were found in both tasks employed; the LNS and the PASAT ($F_{2,46} = 11.99$, $p = 0.0001$, $F_{2,46} = 7.81$, $p = 0.001$). In verbal memory the group effect was significant in the verbal list learning as measured by the MPD first trial and the MPD delayed recall, and also in the immediate story recall as measured by the LM ($F_{2,47} = 7.29$, $p = 0.002$, $\chi^2_2 = 9.24$, $p = 0.01$, $F_{2,47} = 5.49$, $p = 0.007$). Table 3 shows group performances in each cognitive test, along with statistical analyses of pair-wise ANOVAs or Mann-Whitney U tests. As seen in Table 3 buprenorphine/naloxone patients were superior to methadone patients in the simple RT. The buprenorphine/naloxone patients showed no difference in attention tests compared to the control group. Rather surprisingly, buprenorphine/naloxone patients were slightly, but not statistically significantly, faster than controls in simple RT. In this task their performance variance was also reduced compared to other groups, which was confirmed by Levene's test of equality of variances ($F_{2,47} = 4.13$, $p = 0.022$). Both methadone patients and controls showed improvement of performance when RT was performed after warning signal whereas buprenorphine/naloxone patients showed no such improvement. In the Go/NoGo RT, controls were superior to methadone patients. In working memory tests controls were superior to both groups of OST patients. In verbal memory controls were superior to both patient groups in the MPD first learning trial. In the immediate LM controls were superior to methadone patients.

In order to investigate if group differences were due to differences in premorbid intelligence between the groups, the Verbal IQ estimate was set as a covariate for all tasks with verbal stimuli. All statistically significant group differences remained significant after adjusting for the covariate. Statistically significant group by Verbal IQ interactions were not found.

Post hoc analyses were done in order to investigate the role of benzodiazepine comedication on cognitive performance between the OST drug groups. In these analyses patients without current benzodiazepine medication were

Table 3: Groups comparisons of cognitive measures using ANOVA

Domain Test	Methadone (*n* = 16)	Buprenorphine/ Naloxone (*n* = 17)	Control (*n* = 17)	Statistical comparisons between groups showing better performance first	Effect size (Cohen's d)
	Mean ± SD	**Mean ± SD**	**Mean ± SD**		
Attention					
TAP Tonic Alertness, simple reaction time	257.6 ± 32.1	228.0 ± 13.0	244.4 ± 30.0	BN < M **	1.11
TAP Phasic Alertness, reaction time after warning signal	245.6 ± 30.4	227.4 ± 17.0	230.3 ± 31.7		
TAP Go/NoGo, reaction time	528.3 ± 82.0	496.9 ± 65.3[a]	465.5 ± 39.5	C < M*	0.88
TAP Go/NoGo, errors	0.6 ± 0.7	1.2 ± 1.4[a]	0.5 ± 0.6		
Working memory					
WMS-III LNS	8.8 ± 2.6[b]	8.7 ± 1.7	11.8 ± 3.1	C > M**	1.02
				C > BN**	1.21
PASAT	34.9 ± 10.6[b]	31.3 ± 10.8	47.8 ± 9.3	C > M**	1.27
				C > BN***	1.60
Memory					
MPD, first trial	10.1 ± 3.0	10.6 ± 2.4	13.0 ± 1.4	C > M**	1.22
				C > BN*	1.19
MPD, sum of two last trials	14.6 ± 1.0	14.8 ± 0.4	14.9 ± 0.2		
MPD, delayed recall	13.9 ± 1.0	14.2 ± 1.0	14.8 ± 0.4	C > M**	
				C > BN*	
WMS-III logical memory, immediate recall	12.5 ± 2.9	14.3 ± 3.6	16.3 ± 3.4	C > M**	1.17
WMS-III logical memory, delayed recall	11.1 ± 4.3	13.4 ± 3.3	14.5 ± 4.1		

TAP = Test for Attentional Performance;
PASAT = Paced Auditory Serial Addition Task;
WMS-III = Wechsler Memory Scale-third version;
MPD = Memory for Persons Data.
C = control, M = methadone, BN = buprenorphine/naloxone
*** = statistically significant at level $p < 0.001$.
** = statistically significant at level $p < 0.01$. * = statistically significant at level $p < 0.05$.
[a] $n = 16$.
[b] $n = 15$.

excluded leaving 13 patients in both groups. After exclusion all participants in both groups were dependent on benzodiazepines and had used them within the last month before the OST. The mean dose in the methadone group was 54.2 mg (*SD* = 18.7) of methadone and 28.3 mg (*SD* = 18.6) of diazepam equivalent. The mean dose in the buprenorphine/naloxone group was group was 16.3 mg (*SD* = 2.9) of buprenorphine and 25.6 mg (*SD* = 10.1) of diazepam equivalent. For demographic variables there no significant differences emerged between groups. The group with buprenorphine/naloxone and benzodiazepine medication was superior to the methadone group with benzodiazepine medication in simple RT ($U = 38.00$, $p = 0.017$) and in delayed recall of the LM ($F_{1,24} = 6.15$, $p = 0.021$, d = 0.94)). Figure 1 depicts group performances in both conditions of the LM.

Finally, post hoc analyses were made to study the role of OST doses on cognitive performance. For these analyses we split the patients groups into low and high dose groups depending on their median OST drug dosage. After this division the mean doses of methadone in the low dose ($n = 8$) and high dose group ($n = 8$) were 40.0 mg (*SD* = 5.3) and 66.9 mg (*SD* = 17.3). Among buprenorphine/naloxone patients nine patients received the same dose of 16 mg, and very few cases fell in the tails of the dose distribution. Therefore, dose analyses were restricted to methadone patients. Patients with low a methadone dose had faster RTs in all conditions than patients with high dose. Figure 2 depicts these differences. In the simple RT the difference reached statistical significance ($p = 0.025$, d = 1.19). The mean simple RT time in the low methadone dose group was 240.3 ms (SD = 29.9), which was very close to the performance of the control group. No significant differences between the groups were found in demographic variables except in days in the OST. The low dose group had been fewer days on OST medication, mean 8.6 days, and high dose group, mean 20.0 days (*SD* = 1.9 vs. 6.3 respectively, $p < 0.001$). No significant differences between the groups emerged in other psychoactive medications. In the low dose group 75% of the participants had benzodiazepine and 25% had neuroleptic medication, the corresponding figures being 88% and 25% in the high dose group. In the low dose group 38% received hydroxyzine vs. 25% in the high dose group. Conversion of long or intermediate acting benzodiazepines to a diazepam equivalent dose neither showed significant difference between the groups, mean dose for the low dose group being 29.6 mg (*SD* = 28.7) and 18.1 in the high group (*SD* = 10.9).

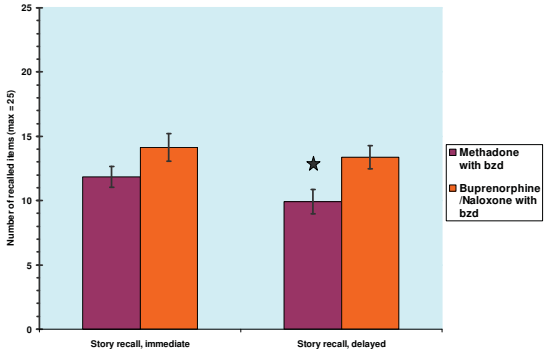

Figure 1
Story recall performance of methadone- vs. buprenorphine/naloxone-treated patients with benzodiazepine (bzd) comedication. * = $p < 0.05$

Discussion

In this first study comparing cognitive function of methadone- and buprenorphine/naloxone-treated patients during early OST both patient groups were inferior to controls in working memory and verbal memory. Methadone-treated patients showed inferior performance also in attention and more deficits in verbal memory. In the attention task measuring alertness methadone-treated patient were inferior to buprenorphine/naloxone-treated patients. The effect sizes of group differences in comparison to controls in working memory and verbal memory were close to the ones obtained in other studies of opioid-dependent populations [33-35]. In attention tasks studies with stabile OST patients the effect sizes have been variable depending on specific tasks used [36].

Working memory performance, which was inferior in both patient groups, was measured by the PASAT and the LNS tasks combining maintenance with organization of material or with interference. Efficient performance of these tasks depends on activation of widespread neural networks including bilateral frontal and parietal cortices. Especially pronounced activity is seen in right hemisphere

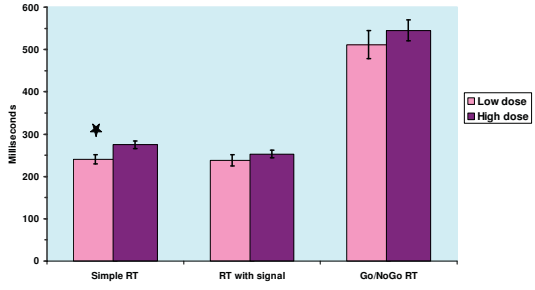

Figure 2
Comparison of high vs. low methadone dose groups in reaction times (RT). * = $p < 0.05$

[37,38]. Methadone-treatment of opioid-dependence reduces cerebral blood flow (CBF) particularly in frontal cortices and the patients often have left-greater-than-right CBF asymmetry [39]. There are no similar studies concerning buprenorphine treatment though buprenorphine administration has been shown to reduce brain CBF in substance abusing population [40]. In general, the CBF reductions associated with opioid-dependence are probably linked to inadequate energy supply to the brain and changes in releases of several neurotransmitters such as catecholamines and acetylcholine [41,42]. Catecholamines are important for integrity of working memory, while acetylcholine is important also for learning and memory consolidation. [43,44]. Thus, it does not astonish that both OST groups showed inferior verbal list learning performance relative to controls. Methadone patients' performance was reduced also in immediate story recall.

After excluding patients without benzodiazepine medication the difference between the methadone and buprenorphine group in delayed story recall appeared statistically significant and showed a large effect size. Thus, it is possible that full mu opioid agonist methadone disrupts more acetylcholine release and consequently impairs more verbal memory than partial mu opioid agonist buprenorphine. Other factors that may be involved in memory deficits of the OST patients are alterations of glutamatergic synapses after chronic opioid administration or inhibition of new cell formation in the hippocampus after chronic mu opioid receptor activation [45,46].

Methadone patients were slower than buprenorphine/naloxone patients in simple RT reflecting alertness and slower than controls in the Go/NoGo RT task reflecting response selection and executive control of attention. On test day methadone patients received a mean dose of 23 mg diazepam equivalent medication and buprenorphine/naloxone patients had been given 20 mg. It is known that benzodiazepines such as diazepam or oxazepam, which were commonly administered to the patients in this study may have a slight negative effect on simple RT even among long-term benzodiazepine users [47,48]. Thus, benzodiazepine comedication may have affected the results in RT tasks. It also possible that benzodiazepine comedication would interact differently with methadone than with buprenorphine/naloxone. This possibility is supported by the results of a recent study by Lintzeris et al. showing that mixing 10 or 20 mg of diazepam with a mean 55 mg of methadone had significant detrimental effect on simple RT and focused attention in methadone patients [49]. Mixing the same amounts of diazepam with mean 11 mg of buprenorphine had, however, minimal effect on buprenorphine patients. In sum, we suggest that methadone-treated patients with current benzodiazepine medication tend to show inferior performance in attention tests relative to buprenorphine/naloxone-treated patients with the same characteristics during early OST. Consequently, it cannot be concluded that methadone, as an OST *monotherapy*, would have different effect on attention performance than buprenorphine/naloxone monotherapy.

The good performance of buprenorphine/naloxone patients in simple RT without warning signal along with their reduced performance variance in this measure is a surprising finding because buprenorphine has adverse effect on RTs in healthy controls [9]. In some earlier studies methadone patients with stable doses also have outperformed healthy controls in simple RT [11,50]. In one study, a relatively low dose of methadone of, 33 mg or 16 mg, given during early inpatient opioid withdrawal treatment actually *speeded* RTs of opioid-dependent patients in comparison to placebo condition [12]. In our study methadone patients on 40 mg outperformed methadone patients on 67 mg dose. Together these observations raise the possibility that a low dose of full mu opioid agonist methadone or normal dose of partial mu opioid agonist buprenorphine may have a minimal effect on simple RTs of opioid-dependent patients in OST with high tolerance for these opioids – and also for benzodiazepine comedication.

Limitations

Cognitive differences between the patient groups may partly relate to differences in their OST drug-tolerance. The majority of the patients in both groups had abused buprenorphine during the recent month. In spite of cross-tolerance to opioids, it is possible that switching from buprenorphine to methadone results in transient cognitive deficits in methadone patients. Thus, the possibility of opioid switching effect in methadone-treated patients during early OST cannot be ruled out. In order to investigate this issue we are currently working on a follow-up study with same patients.

Several psychoactive medications were used nearly similarly in both groups to treat psychiatric comorbidity during the OST initiation. These drugs, such as short acting non-benzodiazepine zopiclone, neuroleptics, anticonvulsant valproate, or antihistamine hydroxyzine may have slight adverse cognitive effects [51-54]. The interactions of OST medications and all these medications warrant for further studies.

All our participants were free from current substance abuse as confirmed by drug screens. Instead, during the recent month preceding the OST patients had used several psychoactive substances. There were no major differences between the uses of these substances within the patient groups. Thus, these substances such as cannabis may

explain the differences between the studied OST patient groups only if they have long-term effects and they interact differently with the OST drugs. Therefore, long-term benzodiazepine use may explain part of the *similarities* between the OST patient groups. Long-term benzodiazepine monotherapy has adverse affect on several cognitive functions, which may last at least for six months [55].

Opioid-dependent patients may already differ from the general population in premorbid cognitive functions. Yet, when we controlled for premorbid verbal intelligence by using Verbal IQ estimate as a covariate in ANCOVA procedure, this did not affect the results. Actually, this procedure may be too conservative. A recent study has shown that current smoking (if more than 8 cigarettes per day) affects Verbal IQ [56]. Nearly all of our patients were daily smokers. Thus, verbal IQ differences in these patients may not to be primarily premorbid.

Conclusion

Both methadone and buprenorphine/naloxone-treated OST patients show deficits in working memory and verbal list learning during the early phase of their treatment. Deficits in attention may be seen only in methadone-treated patients and their impairments may be dose-dependent. Verbal memory deficit may be more extensive in methadone- than in buprenorphine/naloxone-treated patients. Thus, this study further shows that in clinical samples, in which recent benzodiazepine use and benzodiazepine comedication as well as other psychoactive medications are common, methadone-treated patients have more cognitive deficits than buprenorphine- or buprenorphine/naloxone-treated patients. Buprenorphine/naloxone may preserve cognitive function in early OST better than methadone, at least when benzodiazepine comedication is used. Longitudinal studies are warranted to investigate whether this advantage is permanent or is restricted to early OST

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

PR planned and performed cognitive testing and statistical analysis. He wrote the first version of the manuscript and prepared the final manuscript. HA and MS conceived the idea of this study and advised in manuscript preparation. HK and KW participated in the design of the study and in manuscript preparation. CF carried out psychiatric investigations. All authors read and accepted the final manuscript.

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II

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Memory function in opioid-dependent patients treated with methadone or buprenorphine along with benzodiazepine: longitudinal change in comparison to healthy individuals

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Abstract

Background: Opioid-substitution treatment (OST) for opioid dependence (OD) has proven effective in retaining patients in treatment and reducing illegal opiate abuse and crime. Consequently, the World Health Organization (WHO) has listed the opioid agonists methadone and buprenorphine as essential drugs for OD that should be available worldwide. In many areas of the world, OD is often associated with concomitant benzodiazepine (BZD) dependence and abuse, which complicates treatment. However, possible changes in the cognitive functioning of these patients are not well-known. The present study is the first to examine longitudinal stability of memory function in OST patients with BZD use, thus providing a new tool for health policy authorities in evaluating the usefulness of OST.

Methods: Within the first two months (T1) and between 6–9 months (T2) after OST admission, we followed the working memory, immediate verbal memory, and memory consolidation of 13 methadone- and 15 buprenorphine- or buprenorphine/naloxone-treated patients with BZD dependence or abuse disorder. The results were compared to those of fifteen normal comparison participants. All participants also completed a self-reported memory complaint questionnaire on both occasions.

Results: Both patient groups performed statistically significantly worse than normal comparison participants in working memory at time points T1 and T2. In immediate verbal memory, as measured by list learning at T1, patients scored lower than normal comparison participants. Both patient groups reported significantly more subjective memory problems than normal comparison participants. Patients with more memory complaints recalled fewer items at T2 from the verbal list they had learned at T1 than those patients with fewer memory complaints. The significance of the main analyses remained nearly the same when the statistical tests were performed without buprenorphine-only patients leaving 12 patients to buprenorphine/naloxone group.

Conclusion: Working memory may be persistently affected in OST patients with BZD use. A high number of memory complaints among OST patients with BZD use may indicate memory consolidation impairment. These findings show that recovery of memory function in OD patients treated along with BZDs takes time, and their memory complaints may have practical relevance.

Introduction

Opioid-substitution treatment with the full mu opioid receptor agonist methadone or the partial agonist buprenorphine is the most effective treatment for OD [1,2]. Follow-up studies of OST patients have shown consistently high retention in OST, fewer crimes, reduction in substance abuse, and improved health [3,4]. However, the psychosocial recovery of OD patients during treatment is still controversial. It has been stated that while opioid abuse and other problem behavior reduces during the OST, there is little research-based evidence for improvement if patient-centered indicators of quality of life are used [5]. While this critique underestimates the importance of reduction of the health hazards of OD, it also shows the shortage studies using objective measures of psychological functions. In order to meet this challenge, studying memory function of OD patients is an important element, because the patients often complain poor memory [6,7]. Therefore, in this longitudinal study memory function of OST patients was evaluated by tests and subjective memory questionnaire. Because in Finland most OD patients are prescribed benzodiazepines or abuse them from illegal sources [7,8], we examined memory function of this clinically relevant majority.

Some studies have shown substantial memory deficits among OD patients in methadone treatment even after years of treatment [9,10]. Also, buprenorphine-treated patients may show poor memory function [11,12]. However, only two studies have examined the longitudinal stability of memory function during OST. In the seminal longitudinal study by Grevert et al., the memory performance of OST patients, of whom about one third tested positive for other drugs of abuse during the tests, was assessed three times within the first three months of treatment [13]. No baseline or subsequent differences between the methadone patients and a comparison group were seen in objective or subjective memory function. No significant correlations were seen between drug screen status and memory test results. However, as the patients performed the tests immediately before or after the methadone dose, that is, when their plasma concentration is known to be at the lowest level, short-term negative effects of high methadone concentrations may have been missed. In a more recent study by Gruber et al., the tests were done a few hours after the methadone dose [14]. The patients' memory performance was tested first within the first few weeks of OST and again after two months of treatment. Although 65% of the patients tested positive for any illicit use at the first test and 76% at the second test, the results showed a statistically significant improvement in verbal list learning among patients.

In our previous study, we found that both methadone- and buprenorphine/naloxone-treated patients in early OST performed worse than normal comparison participants on a working memory task [15]. The verbal memory deficit was more pronounced in methadone-treated patients than in buprenorphine/naloxone-treated patients. Although the results partially favored buprenorphine/naloxone-treated patients, BZD co-medication that was common in both patient groups, may have affected the results. There are no longitudinal studies comparing the effects of OST drugs while patients use BZDs. However, there is some evidence for acute negative effects of opioid agonists on working memory in drug-naïve healthy volunteers and for chronic negative effects in pain patients [16,17]. The negative effects of BZDs on working memory and long-term memory are better – known, vary from small to moderate, and may last several months after cessation of use [18]. Of special interest is the study of Lintzeris et al., which found that in comparison to a placebo condition, methadone dose alone, or buprenorphine dose in combination with BZD diazepam impairs verbal recall in OST patients [19]. Given these findings suggesting memory deficits in OST patients using BZDs, we did a follow-up study of memory function in OD patients treated with methadone or buprenorphine (including buprenorphine/naloxone) along with BZDs. In order to control for the effects of repeated testing, a comparison group performed similar tests. Working memory, immediate verbal memory, and memory consolidation were examined. The participants also completed the Memory Complaint Questionnaire, which assesses subjective memory function [20].

We hypothesized that working memory function in both OST patient groups treated along with BZDs would be impaired relative to normal comparison participants in the first testing (T1) and would not show improvement. Second, we hypothesized that immediate verbal memory would be impaired relative to normal comparison participants at T1 and would not show improvement in OST patients also using BZDs. Third, we hypothesized that memory consolidation would be impaired in OST patients. Finally, we hypothesized that among OST patients subjective and objective memory function would correlate negatively.

Methods

The study participants with OD were volunteers admitted for standard OST in the addiction clinics of the Helsinki area. Normal comparison participants were recruited from adult education centers and by word of mouth. All participants included in the study were between 18 – 50 years of age and native Finnish speakers. For OST patients, additional inclusion criteria were OD diagnosis, BZD dependence or abuse diagnosis, start of OST during the last two months, and treatment of OD with methadone, buprenorphine, or buprenorphine/naloxone. We excluded participants with uncontrolled polysubstance abuse, acute alcohol abuse, or acute axis I psychiatric mor-

bidity other than substance abuse related. We also excluded participants with severe brain injury, chronic neurological disease, history of other than substance-induced psychoses, epileptic seizures, human immunodeficiency virus (HIV) infection, pregnancy, or primary cognitive deficit. For these purposes, psychiatric interviews by clinical psychiatrist were conducted for all participants, and diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) were applied [21,22].

Each OST participant eligible for our study was screened by urine sample for substance abuse on the day of testing and at least once in the preceding month. One third of normal comparison participants were chosen at random for screening for drug of abuse. Participants showing signs of current intoxication, ongoing binge on any substance of abuse, and those with any extra psychoactive drug dose within 24 h were all excluded. According to these criteria 13 methadone- and 15 buprenorphine/naloxone- or buprenorphine-treated patients and 15 normal comparison participants could be studied twice. This represents 59% of volunteer methadone patients at T1, 52% of buprenorphine patients (including both products), and 79% of normal comparison participants. Eight volunteer patients were excluded from the study based on their substance abuse before the test. Fourteen eligible patients and four normal comparison participants dropped out of the study between T1 and T2. At T1, 23% of the methadone patients and 40% of the buprenorphine patients were tested in inpatient settings. At T2, none of the methadone patients and 13% of the buprenorphine patients were tested in inpatient settings.

Ethics

The study was approved by the independent Hospital District of Helsinki and Uusimaa Ethical Committee (permission 90/2001). The study was conducted in accordance with the 1964 Declaration of Helsinki. All patients were required to be able to read and understand the patient information sheet and sign the informed consent form. All participants were free to discontinue participation in the study whenever they wanted. The participants were reimbursed with € 40 if they attended all study visits.

Procedure

Cognitive testing was done three to six hours after administration of the opioid-substitution drug. During this time the drug plasma concentration is at its peak [23]. At T1, the methadone patients were given, under supervision on the morning of the test day, a mean dose of 72.9 mg (*SD* = 35.2) of liquid methadone, range 35 – 150 mg. At T2, the respective values for methadone were 125.7 mg (*SD* = 35.8), range 70 – 180 mg. At T1, the buprenorphine patients were given, under supervision on the morning of the test day, a mean dose of 17.3 mg (*SD* = 3.6) of sublingual buprenorphine, range 12 – 24 mg. At T2, the respective values were 22.7 mg (*SD* = 2.9), range 16 – 28 mg. Rise of the dose was statistically significant in both groups (Wilcoxon's Signed Ranks test, exact (2-sided) $p = 0.001$ in both groups). In the buprenorphine group, 80% of the patients were given buprenorphine/naloxone; thus, they were also given sublingual naloxone in a ratio of 1:4 together with their buprenorphine dose. Several studies have shown that among OD individuals sublingual naloxone has minimal if any interference with the opioid agonist effects of the buprenorphine [24-26]. Other prescribed psychoactive medications were given to the patients according to their clinical dose regimen. Table 1 describes the BZDs and their doses used within the 24-hour period before the tests. In order to compare the BZD doses of the groups, all BZDs were converted to diazepam equivalent doses according to their known clinical potency [27]. Temazepam and midazolam doses were halved in order to account for their use as hypnotics on the night before testing. After this conversion, no statistically significant difference existed between the patient groups in their mean estimated diazepam equivalent dose at T1 or T2. There was no significant change between the T1 and T2 BZD doses within the groups. The diazepam equivalent dose at T1 was on average 26.2 mg (*SD* = 18.5) in the methadone group and at T2 26.5 (*SD* = 10.0); in the buprenorphine group, the respective values were 27.7 (*SD* = 24.1) and 21.0 (*SD* = 11.1). In other types of psychoactive drugs there were no statistically significant changes between the test points.

Memory tests

Working memory refers to the limited capacity short-term store that temporarily maintains information, which is lost without rehearsal [28]. It was assessed by the Letter-Number-Sequencing task from the Wechsler Memory Scale-third version (WMS-III) and by the computerized version of the Paced Auditory Serial Addition Task (PASAT) from the FORAMENRehab software package [29-31].

Immediate verbal memory refers to immediate storage of verbally presented items in those situations that exceed the capacity of sensory-specific working memory stores. Typical examples of immediate verbal memory measures include recall of a list or story. Immediate verbal memory is thought to rely on both working and long-term memory stores. This concurrent activation of two memory stores has recently been experimentally confirmed [32]. Immediate verbal memory was assessed by two verbal memory tasks, a list learning and a story recall task: the Memory for Persons Data and The Logical Memory [29,33]. Both tasks were presented in modified versions. The details of these tasks are presented in our previous study [15].

Table 1: Co-medications among patients used within the last 24 h before testing at T1 and T2

	Methadone (*n* = 13)		**Buprenorphine or Buprenorphine/Naloxone (*n* = 15)**	
	Proportion of patients	**Dose, range**	**Proportion of patients**	**Dose, range**
Antidepressants (any), T1/T2	**54%/46%**		**40%/53%**	
Citalopram T1	8%	40 mg	-	-
Citalopram T2	-	-	13%	10 mg
Escitalopram T1	8%	5 mg	-	-
Escitalopram T2	8%	10 mg	-	-
Doxepine T1	-	-	13%	75 – 100 mg
Doxepine T2	8%	50 mg	20%	25 – 100 mg
Fluoxetine T1	15%	20 – 30 mg	-	-
Fluoxetine T2	8%	40 mg	-	-
Milnacipran T1	-	-	-	-
Milnacipran T2	-	-	7%	50 mg
Mirtazapine T1	25%	15 – 30 mg	-	-
Mirtazapine T2	25%	30 mg	7%	30 mg
Paroxetine T1	8%	50 mg	7%	50 mg
Paroxetine T2	-	-	13%	40 mg
Sertraline T1	-	-	7%	50 mg
Sertraline T2	-	-	7%	50 mg
Trimipramine T1	-	-	-	-
Trimipramine T2	8%	150 mg	-	-
Venlafaxine T1	-	-	13%	75 mg
Venlafaxine T2	-	-	7%	75 mg
Anxiolytics, sedatives and hypnotics: Benzodiazepines (any), T1/T2	**87%/100%**		**93%/100%**	
Alpratzolam T1	-	-	13%	1 – 2 mg
Alpratzolam T2	-	-	13%	1 – 2 mg
Clonazepam T1	-	-	13%	2 – 5 mg
Clonazepam T2	-	-	-	-
Diazepam T1	46%	10 – 55 mg	47%	10 – 40 mg
Diazepam T2	38%	15 – 30 mg	67%	5 – 30 mg
Oxazepam T1	31%	60 – 120 mg	33%	30 – 90 mg
Oxazepam T2	46%	15 – 60 mg	20%	55 – 60 mg
MidazolamT1[a]	-	-	-	-
MidazolamT2[a]	-	-	7%	30 mg
Temazepam T1[a]	31%	20 mg	13%	20 mg
Temazepam T2[a]	15%	20 – 40 mg	13%	20 – 40 mg

Table 1: Co-medications among patients used within the last 24 h before testing at T1 and T2 *(Continued)*

Non-benzodiazepine hypnotics (any), T1/T2	**15%/8%**		**20%/7%**	
Zolpidem T1[a]	-	-	-	-
Zolpidem T2[a]	8%	10 mg	7%	10 mg
Zopiclone T1[a]	15%	7.5 mg	20%	7.5 – 15 mg
Zopiclone T2[a]	8%	7.5 mg	7%	7.5 mg
Neuroleptics (any), T1/T2[b]	**20%/8%**		**7%/7%**	
Levomepromazine T1	-	-	-	-
Levomepromazine T2	8%	50 mg	-	-
Quetiapine T1	20%	50 – 300 mg	7%	300 mg
Quetiapine T2	-	-	7%	150 mg
Rispiderone T1	-	-	-	-
Rispiderone T2	8%	-	-	-
Substance abuse withdrawal symptom or (non-opioid) pain relievers (any), T1/T2	**42%/25%**		**40%/13%**	
Disulfiram T2	-	-	-	-
Disulfiram T2	8%	600 mg	-	-
Hydroxyzine T1	25%	25 – 200 mg	27%	75 – 200 mg
Hydroxyzine T2	8%	50 mg	7%	100 mg
Ibuprofen T1	8%	600 mg	7%	400 mg
Ibuprofen T2	-	-	7%	600 mg
Lofexidine T1	8%	0,2 mg	20%	0.2 – 0.6 mg
Lofexidine T2	-	-	-	-
Metoclopramide T1	8%	10 mg	-	-
Metoclopramide T2	-	-	-	-
Naproxen T1	8%	500 mg	-	-
Naproxen T2	-	-	-	-
Propranol T1	8%	20 mg	-	-
Propranol T2	-	-	-	-
Valproate T1	8%	1000 mg	20%	500 – 1000 mg
Valproate T2	-	-	7%	100 mg

[a] Used as a hypnotic on the night before testing.
[b] Used for anxiolysis.

Memory consolidation refers to the storage and consolidation of memory traces. Early memory consolidation lasts from minutes to hours and late memory consolidation from weeks to years; these rely partly on separate neural processes [34,35]. Early memory consolidation was assessed by the percentage of the Logical Memory and Memory for Persons Data items successfully recalled by free recall after a short delay (30 min). Late memory consolidation was assessed by free recall of the Memory for Persons Data items at T2, which occurred after at least four and on average six, months after initial learning. Participants were further asked to rate the certainty of their answers after the long delay. This may give additional information about the memory processes the participants are employing [36]. If the participant gave the right answer, it was asked if he/she was certain that he/she actually remembered the answer or if he/she only felt he/she knew the answer but was not certain about it. In the case of "felt" or no answer, three nearly identical alternatives were given, one of them being correct. After the participant gave his/her choice, he/she was asked if he/she remembered, felt, or just guessed the answer.

Subjective memory functioning was assessed by the Finnish version of the Memory Complaint Questionnaire, the MCQ [20]. In the MCQ, the participant is asked how his/her memory now functions compared to when he/she was younger. Several answers are given, using a Likert-type scale, describing how well memory functions in everyday tasks (remembering persons, things, news, shopping list items, etc.). A high score indicates subjective memory impairment.

Statistical Analysis

Overall group differences in memory performance at T1 and T2 were tested for statistical significance using multiple planned analysis of covariance (ANCOVA) with years of education and verbal IQ estimate as covariates. Although there were no statistically significant differences between the groups in the verbal IQ, it was used as a covariate because it is known to affect memory performance in tasks with verbal content [37]. ANCOVA was followed, when appropriate, by pairwise group comparisons using normal comparison group as a reference group. The Holm's sequential Bonferroni procedure was used to control for Type I error across the pairwise comparisons [38]. In all analyses, statistical significance was set at 0.05 (two-tailed). In the Memory for Persons Data, the data were highly skewed due to a ceiling effect in the initial learning and recall at T1. At T2, the Memory for Persons Data for delayed recall was skewed because of small variance. Because of these violations of the assumptions of parametric testing, we analyzed these conditions by Kruskal-Wallis ANOVAs, which were followed, when appropriate, by pairwise Mann-Whitney *U* tests. In order to confirm the validity of combining buprenorphine/naloxone and buprenorphine-only patients, the ANCOVAs and ANOVAs were also performed with buprenorphine/naloxone patients (n = 12). The cross-sectional MCQ scores and the MCQ T2 differences between high vs. low score groups were analyzed by *t*-tests or Mann-Whitney *U* tests. Correlations between the MCQ values and cognitive variables were analyzed by Pearson's product moment correlation or Spearman's rho correlations depending on the normality of the variables. Correlations of at least .35 will be reported. The statistical significance of correlations was determined by using the Holm-Bonferroni procedure.

Longitudinal changes were analyzed by repeated measures ANCOVA using education and VIQ as a covariates and the comparison group as a reference group. All statistical analyses were performed using SPSS statistical software, version 15.0, with the exception of the effect size calculations. For this purpose, an effect size calculator provided by Durham University, UK was employed [39,40]; and the Cohen's d values were corrected by Hedge's correction for small sample bias.

Results

Study demographics

Table 2 shows the comparisons of demographic variables of each group. The group difference in verbal intelligence (Verbal IQ) was statistically non-significant even though the comparison group had more education than the patient groups. There were no significant differences between the OST groups in history of substance abuse, duration of OST, or the prevalence of psychiatric co-morbidity. Personality disorder diagnoses were common in both patient groups. Buprenorphine was the main opioid of abuse before the OST admission in both groups. Among patients, no major change in the number of non-opioid substances abused during the recent month before the T1 or T2 testing was seen during the study period.

Group comparisons at T1

In Table 3, an overview of unadjusted memory test results at both test points is presented together with statistical comparisons for years of education and verbal IQ adjusted values, whenever adjusting was possible. In working memory tests, the methadone patients were inferior to controls in the PASAT, but in the Letter-Number Sequencing the group difference remained non-significant. The buprenorphine patients were inferior to normal comparison participants on the both of the working memory tests. In immediate verbal memory as measured by the first learning trial of the Memory for Persons Data, both patient groups performed significantly worse than normal comparison group. In early memory consolidation as measured by short-term retention of percentages of the Logical Memory and the Memory for Persons Data items, no significant group differences emerged. The statistical significance of the analyses remained the same when the analyses outlined in the Table 3 were done with buprenorphine/naloxone patients (n = 12) instead of combining the buprenorphine-only and buprenorphine/naloxone patients. Statistically significant values of overall group effects were, in order, The Letter-Number Sequencing, The PASAT, the first trial of the Memory for Persons Data, and the MCQ (F (2, 35) = 3.63, p = 0.009; F (2, 35) = 9.57, $p < 0.001$; X^2 (2, N = 40) = 7.99, exact p = 0.018; X^2, (2, N = 40) = 11.83, exact p = 0.004). After this, pairwise analyses between the buprenorphine/naloxone and normal comparison groups were performed. In the Letter-Number Sequencing the pairwise group comparison was statistically non-significant (t (26) = 2.67, p = 0.065). In the PASAT and in the first trial of the Memory Persons Data, the buprenorphine/naloxone group showed worse performance than the normal comparison group (t (26) = 4.71, p = 0.00; Mann-Whitney U = 45.50, exact p = 0.028, respectively). In the MCQ, the buprenorphine/naloxone patients reported more memory complaints than the comparison participants (Mann-Whitney U = 26.00, exact p = 0.004).

Table 2: Group demographics

	Methadone (*n* = 13)	**Buprenorphine or Buprenorphine/Naloxone (*n* = 15)**	**Normal Comparison (*n* = 15)**	**Group comparison *p*-values[a]**
Age, mean of years at T1 (*SD*)	29.2 (6.8)	27.7 (6.8)	28.7 (9.6)	M vs. BN, $p = 0.99$ M vs. NC, $p = 0.99$ BN vs. NC, $p = 0.99$
Sex: females/males	7/6	4/11	8/7	M vs. BN, $p = 0.14$ M vs. NC, $p = 0.98$ BN vs. NC, $p = 0.14$
Verbal intelligence, Mean[b] (*SD*)	100.6 (11.4)	99.4 (9.3)	104.1 (9.6)	M vs. BN, $p = 0.99$ M vs. NC, $p = 0.74$ BN vs. NC, $p = 0.63$
Education, mean of years (*SD*)	10.1 (1.2)	10.5 (2.0)	12.6 (1.3)	M vs. BN, $p = 0.54$ M < NC***, $p < 0.001$ BN < NC**, $p = 0.006$
Opioid of abuse used within last month at T1				
Buprenorphine	85%	100%	-	M vs. BN, $p = 0.48$[c]
Heroin	15%	0%		
Other substances of abuse used within last month at T1 and T2				
Alcohol (heavy use)[d]	15%/15%	13%/7%	7%/7%	M vs. BN vs. NC (T1/T2), $p = 0.99$[c]/0.99[c]
Amphetamine	8%/8%	13%/7%	-	M vs. BN vs. NC (T1/T2) $p = 0.99$[c]/0.99[c]
Benzodiazepine, any Use	100%/100%	100%/100%	0%/0%	M & BN > NC*** (T1/T2), $p < 0.001$[c]/$p < 0.001$[c]
Benzodiazepine, extra doses	38%/38%	42%/33%	-	M vs. BN (T1/T2), $p = 0.62$/$p = 0.78$[c]
Cannabis	31%/31%	40%/27%	-	M vs. BN (T1/T2), $p = 0.83$[c]/0.84[c]
Nicotine (daily use)	100%/100%	100%/100%	33%/33%	M & BN > NC*** (T1/T2), $p < 0.001$[c]/$p < 0.001$[c]
Duration of OST in the day of testing at T1, Mean of days (*SD*)	21 (14)	19 (12)	-	M vs. BN, $p = 0.69$
Duration of OST on the day of testing at T2, Mean of days (*SD*)	213 (25)	224 (17)	-	M vs. BN, $p = 0.15$
Participants with other dependence or abuse diagnosis at T1				
Alcohol	0%	0%	0%	M vs. BN vs. NC, $p = 0.99$[c]
Amphetamine	0%	0%	-	M vs. BN, $p = 0.99$[c]
Benzodiazepine	100%	100%	-	M vs. BN, $p = 0.99$[c]
Cannabis	15%	20%	-	M vs. BN, $p = 0.99$
Nicotine	100%	100%	33%	M vs. BN, $p = 0.99$[c] M vs. NC, $p = 0.13$[c] BN vs. NC, $p = 0.12$[c]
Participants with any DSM-IV axis I diagnosis at T1	15%	20%	0%	M vs. BN, $p = 0.99$[c] M vs. NC, $p = 0.21$[c] BN vs. NC, $p = 0.22$[c]

Table 2: Group demographics *(Continued)*

Participants with any personality disorder diagnosis (DSM-IV axis II) at T1	54%	59%	0%	M vs. BN, $p = 0.99$[c] M > NC**, $p = 0.003$[c] BN > NC**, $p = 0.002$[c]
Duration of opioid abuse at T1, Mean of years (*SD*)	11.4 (5.5)	9.0 (2.9)	-	M vs. BN, $p = 0.26$
Duration of any substance abuse at T1, Mean of years (*SD*)	15.0 (5.1)	13.4 (5.2)	-	M vs. BN, $p = 0.37$

[a] Based on pairwise group comparisons with analysis of variance (ANOVA) or chi-squared test.
[b] Estimation based on the WAIS-R Vocabulary score.
[c] Fisher's Exact Test (2-tailed).
[d] Alcohol use was considered heavy if it was at least a mean of 16 portions weekly for females and 24 portions weekly for males. One portion was defined as 12 g of alcohol.
BN = buprenorphine or buprenorphine/naloxone, M = methadone, NC = Normal comparison.
*** = statistically significant at level $p < 0.001$. ** = statistically significant at level $p < 0.01$. * = statistically significant at level $p < 0.05$.

Group comparisons at T2

At T2, both patient groups were inferior to normal comparison group in working memory tests. In immediate verbal memory assessed by the immediate recall of the Logical Memory items, no significant group differences were seen. In early memory consolidation assessed by the Logical Memory short-term retention percentage, group differences were not significant. In late memory consolidation assessed by the Memory for Persons Data free recall or recognition retention percentages after at least four months' delay, there were no group differences. Again, dropping buprenorphine-only patients from the buprenorphine group did not change the statistical significance of the overall ANOVAs or ANCOVAs. Significance values of overall group effects were, in order, the Letter-Number Sequencing, The PASAT, and the MCQ ($F(2, 35) = 3.82$, $p = 0.032$, ($F(2, 35) = 7.52$, $p = 0.02$, (X^2, (2, $N = 40$) = 15.91, exact $p < 0.001$). Pairwise comparisons between the buprenorphine/naloxone and normal comparison groups favored the comparison group in both working memory tasks: the Letter-Number Sequencing and The PASAT, respectively ($t(26) = 2.21$, $p = 0.03$; $t(26) = 3.33$, $p = 0.002$). In the MCQ, the buprenorphine/naloxone patients reported more memory complaints the normal comparison participants (Mann-Whitney $U = 29.50$, exact $p = 0.004$).

Interestingly, total "black-outs" in long delay free recall were rare. Only one methadone patient, two buprenorphine patients, and one comparison participant could not recall any items from the Memory for Persons Data in this condition. From Figure 1, which shows lines for cumulative percentages, it can be seen that about 50% of the normal comparison participants and buprenorphine patients could recall at least 4 items out of 15 correctly, while the corresponding score was 2 items among the methadone patients. When asked about the certainty of their answers, the patients were non-significantly more certain than the normal comparison participants that they actually remembered, not just felt, the correct answers they gave. On average, methadone-treated patients said that they surely remembered a mean of 64.1% of their correct free recall answers (*SD* = 38.8). In the buprenorphine group the corresponding figure was 67.2% (*SD* = 24.1) and in the normal comparison group 45.5% (*SD* = 31.3). In the same vein, there were no significant group differences in certainty of recognized correct answers (data not shown). Both patient groups again reported significantly more memory complaints in the MCQ.

Correlations between subjective and objective memory functions among the patients

The highest correlation between subjective MCQ score and the objective memory tests completed by the OST patients at T1 was – .38 for the Logical Memory retention percent after short delay (30 min). However, after correction for multiple comparisons, this moderate correlation was statistically non-significant. The correlation between the MCQ score at T1 and the long delay free recall of the Memory for Persons Data items at T2, that is, at least four months after initial learning, was – .58 and statistically significant, $p = 0.028$. This relationship is depicted in Figure 1. At T2, two moderate correlations between subjective MCQ score at T2 and objective memory performance of the patients were seen: – .40 for long delay free recall of the Memory for Persons Data items and – .39 for the PASAT. However, after correction for multiple comparisons these were no longer statistically significant. In order to explore how the OST patients with high MCQ scores at the stabilized phase (T2) are different from those with low MCQ scores, the patient group was divided into high vs. low memory complaints groups using the T2 MCQ median score as the cut-off. Patients with scores of 26 or more at T2 made up the high memory complaints group

Table 3: Group comparisons of memory functions at T1 and T2

Domain or Test	Methadone (*n* = 13)	Buprenorphine or Buprenorphine/ Naloxone (*n* = 15)	Normal Comparison (*n* = 15)	Group effect	Statistical comparisons between normal comparison and patient groups using years of education and VIQ adjusted scores, whenever possible[b]	Effect sizes, whenever possible
	M (SD)	*M (SD)*	*M (SD)*			
Working memory, raw scores						
WMS-III Letter-Number Sequencing at T1	9.6 (2.3)	8.4 (2.3)	11.7 (3.2)	F (2, 38) = 4.57 p = 0.017*	t(27) = 1..84, p = 0.074, M vs. NC = *ns* $t(29)$ = 3.02, p = 0.008, NC > BN **	d = 0.68 d = 1.01
WMS-III Letter-Number Sequencing at T2	8.6 (2.1)	9.2 (2.3)	11.6 (2.9)	F *(2, 38)* = 4.19, p = 0.023*	t(27) = 2.76, p = 0.018, NC > M* t (29) = 2.39, p = 0.022, NC > BN *	d = 1.05 d = 0.83
PASAT at T1	31.4 (9.2)	31.8 (10.7)[a]	46.7 (9.4)	F *(2, 38)* = 9.84 p = 0.001***	t(27) = 4.19, p < 0.001, NC > M ***	d = 1.43
PASAT at T2	31.6 (8.6)	34.1 (8.4)	46.0 (8.7)[a]	F *(2, 38)* = 7.15 p = 0.002**	t(29) = 3.70, p < 0.001, NC > BN*** t(27) = 3.47, p = 0.002, NC > M** t(29) = 3.32, p = 0.002, NC > BN**	d = 1.54 d = 1.42 d = 1.24
Immediate verbal memory, raw scores						
Memory for Persons Data, first trial at T1	10.7 (2.6)	10.8 (2.5)	13.0 (1.5)	χ^2(2, N = 43) = 8.91 p = 0.012*	U = 43.0, p = 0.011, NC > M* U = 51.5, p = 0.020, NC > BN*	-
Memory for Persons Data, sum of last two trials (T1)	14.9 (0.2)	14.6 (0.7)	14.9 (0.2)	χ^2 (2, N = 43) = 2.75 p = 0.25	-	-
WMS-III Logical Memory, immediate free recall (T1)	12.9 (2.4)	15.1 (4.3)	16.3 (3.6)	F *(2, 38)* = 1.90, p = 0.16	-	-
WMS-III Logical Memory, immediate free recall (T2)	14.2 (3.1)	14.1 (3.3)	16.3 (3.1)	F *(2, 38)* = 1.25, p = 0.30	-	-
Memory consolidation, percentages						
WMS-III Logical Memory, free recall after short-delay (30 min) (T1)	91.4 (15.3)	91.7 (14.0)	87.5 (13.1)	F *(2, 38)* = 0.64, p = 0.94	-	-

Table 3: Group comparisons of memory functions at T1 and T2 *(Continued)*

WMS-III Logical Memory, free recall after short (30 min) delay (T2)	87.1 (14.4)	93 .8 (17.1)	98.3 (14.1)	F (2, 38) = 1.28, p = 0.29	-	-
Memory for Persons Data, free recall after short delay (30 min) (T1)	92.8 (7.9)	98.2 (6.1)	98.7 (3.1)	$\chi^2(2, N = 43)$ = 4.48 p = 0.11	-	-
Memory for Persons Data, free recall after long delay (4 – 8 mo) (T2)	22.1 (18.1)	29.8 (23.2)	32.4 (22.1)	$\chi^2(2, N = 43)$ = 1.54 p = 0.46	-	-
Memory for Persons Data, recognition after long delay (4 – 8 mo) (T2)	79.6 (10.6)	82.1 (12.9)	81.3 (10.7)	F (2, 38) = 0.60 p = 0.55	-	-
Memory complaints, raw score						
The Memory Complaint Questionnaire (T1)	26.6 (5.7)	26.0 (5.4)	20.4 (2.5)	$\chi^2(2, N = 43)$ = 11.25	U = 39.0, p = 0.012, NC < M*	-
				p = 0.004**	U = 40.0, p = 0.008, NC < BN **	-
The Memory Complaint Questionnaire (T2)	25.6 (3.2)	24.5 (6.7)	20.4 (1.5)	χ^2 (2, N = 43) = 14.04	U = 16.5, p < 0.001, NC < M***	
				p = 0.001***	U = 49.0, p = 0.015, NC < BN *	

Note: PASAT = Paced Auditory Serial Addition Task;
WMS-III = Wechsler Memory Scale-third version.
BN = buprenorphine or buprenorphine/naloxone, M = methadone, NC = Normal comparison.
[a] = Missing value of one participant was substituted by carry-over value from the first test.
*** = statistically significant at level p < 0.001, ** = statistically significant at level p < 0.01, * = statistically significant at level p < 0.05, *ns* = non-significant.

(n = 14) and those with scores up to 25 the low memory complaints group (n = 14). There were no statistically significant differences between the high and low memory complaint groups in demographics, substance abuse history, or treatment or medication variables. For cognitive variables, there were no significant differences between the groups except on the measure of Memory for Persons Data free recall, on which the respective means for the high and low groups were 16.7% (SD = 16.7) and 35.7% (SD = 21.0); (t (27) = 2.66, p = 0.013). As can be seen from Figure 2, most of the patients classified as high memory complainers at T2 already had high MCQ scores at T1. Seventy-one percent of the high memory complainers at T2 complained of memory problems at T1 matching or exceeding the MCQ high memory complaints cut-off score of 26.

Longitudinal changes

In the first working memory task, the Letter-Number Sequencing, methadone-treated patients' performance seemed to deteriorate from T1 to T2 as shown by a decrease in their raw scores. On the other hand, they seemed to improve in immediate verbal memory performance. Opposite trends were seen in the buprenorphine group. However, no significant group by time interactions emerged.

Discussion

The main finding of this longitudinal study is the persistence of the working memory deficit in OD patients treated with methadone or buprenorphine along with BZDs. At T1, the buprenorphine patients were inferior to normal comparison participants in both working memory tests; and the methadone patients performed worse than normal comparison participants at the second working memory task, the PASAT. At T2, both patient groups were impaired relative to a normal comparison group on both working memory tests. The working memory tests used in this study have both been used also earlier in opioid-related neuropsychological studies. In an earlier study by Verdejo-Garcia et al., minimum 15 days abstinent heroin abusers outperformed methadone-treated OST patients

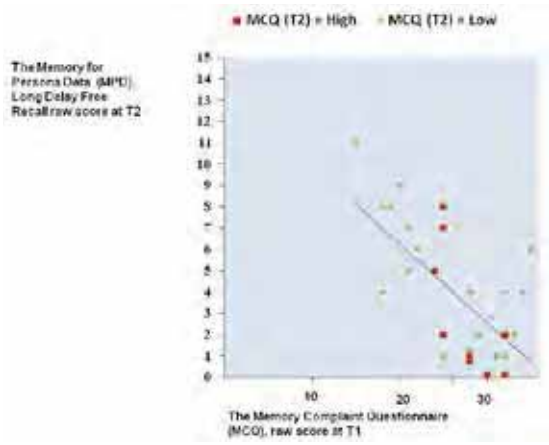

Figure 1
Correlation percentage of the Memory for Persons Data, delayed recall (T2) scores by group.

on our first working memory measure, the Letter-Number Sequencing [41]. In a study by Mintzer and Stitzer, methadone-treated OST patients performed worse than a well-matched normal comparison group on a two-back working memory task closely resembling the PASAT [42]. The evidence for opioid agonist effects is not, however, unambiguous because in both of these studies, the OST patients had a previous history of using other substances of abuse, including BZDs. On the other hand, in a study by Sjögren et al., pain patients treated with pain drugs other than opioids outperformed non-addicted opioid-treated pain patients on the PASAT [17]. In the same vein, a recent study showed that the opioid agonist morphine negatively affects working memory performance in healthy volunteers [16]. Although pure OST drug effects on working memory seem possible, the effects of OST drugs, alone or in combination with BZDs, on working memory can only be reliably examined if OST patients with and without a history of BZD use can be compared.

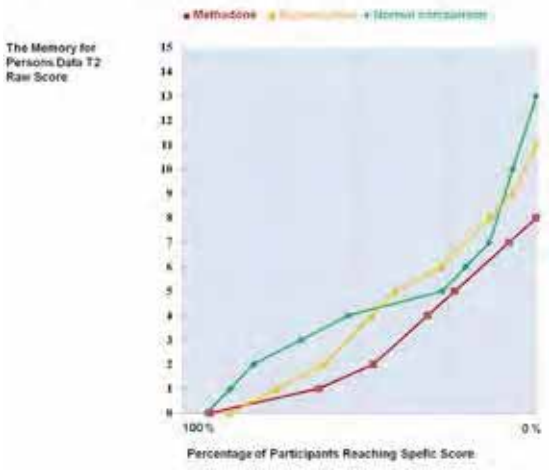

Figure 2
Cumulative percentage of the Memory for Persons Data, delayed recall (T2) scores by group.

Our hypothesis of impaired performance in immediate verbal memory was partially confirmed as both patient groups were impaired at T1 in the first trial of a list learning task, the Memory for Persons Data. This finding is in line with earlier studies showing similar deficits among methadone patients [9,43]. However, the stability of this deficit in verbal list learning remains to be studied because the Memory for Persons Data learning task was not repeated at T2. Of note here is the study of Gruber et al. concerning an earlier treatment phase than was investigated in our study [14]. In their study methadone-treated patients' verbal list learning performance, improved between the first testing performed after a mean of two weeks of OST and the second after two months of treatment. However, a control group was lacking in their study. Although alternate test forms were used, practice effect in repeated verbal memory testing cannot be ruled out [44]. Thus, the evidence for early improvement of memory function is not strong.

Buprenorphine patients with concurrent BZD medication showed inferior list learning during early OST (T1). This finding is in line with a recent study by Soyka et al. in which buprenorphine patients without other dependencies were also inferior to normal comparison participants in verbal learning [45]. In a recent study by Loeber et al. no significant correlation was found between buprenorphine dose and verbal list learning performance [46]. On the other hand, Lintzeris et al. have reported that buprenorphine in combination with the BZD diazepam impairs delayed verbal memory more than buprenorphine given alone [19]. In sum, further studies of the possible "pure" buprenorphine effects or the additive negative effects of buprenorphine and BZDs on immediate verbal memory are needed.

Memory consolidation was examined by short- and long-term retention percentages. No significant group differences between patient groups and normal comparison group were observed in any condition. This is surprising because mu opioid receptor agonists and BZDs are known to negatively affect memory consolidation [47-50], However, our study is the first to study memory consolidation up to late memory consolidation that starts few hours after event occurrence [34,35]. Further studies are needed

to examine if the observation of no memory consolidation impairment among OD patients is due to development of tolerance to negative effects of these drugs. There is some evidence for tolerance to methadone's long-term effects on episodic memory [51]. Tolerance for episodic memory impairing effects of BZDs, in general, are small [52], but among young individuals development of tolerance has been reported [53]. The second possible explanation for no memory consolidation impairment is that negative effects of opioids given along with BZDs may be hard to detect without a change in drug status. This means a change from a relatively highly drugged state to a low or non-drugged state or reverse. It has been reported that state change from BZD drug to placebo condition may negatively affect on memory retrieval in comparison to continuous BZD condition [54].

Analyses of long-term memory consolidation showed that among OST patients those with high memory complaints at T2 performed worse than those with low memory complaints in late memory consolidation assessed by free recall of the Memory for Persons Data items after a mean delay of six months. Of note here is the observation that there were no significant differences between high and low memory complainers on any background or other cognitive variables.

Self-rated memory problems were elevated among OD patients treated along with BZDs at both test points. Thus the patients feel that in regards to memory function their quality of life does not improve during the OST. Although OD patients often have both subjective and objective memory problems, few studies have addressed the relationship between subjective and objective memory function among patients with substance abuse problems [13,55,56]. In these studies patients' memory complaints have had small, if any, associations with their objective memory performance. In our study, though, moderate relationships were seen between subjective memory complaints and objective memory test performance, especially in late memory consolidation. Unfortunately, late memory consolidation deficit is not easily captured by standard neuropsychological assessment.

Methodological innovations to assess long-term memory consolidation in clinical settings are needed.

Treatment and policy implications

Working memory function is considered a gateway for problem solving in new situations, which requires fluid intelligence and executive function. Thus, when working memory capacity is low, practical reasoning tends to result in instant firm decisions that are based on readily available salient observations [57,58]. Among OST patients this may mean that individuals with low working memory capacity readily associate their negative sentiments with the common belief that their OST medication is "insufficient". They may feel overwhelmed if asked to consider the counterexamples that co-occurrence of medication and negative sentiments may be coincidental or that negative drug effects may be short-lived in comparison to the positive effects that will show up later.

An OST patient who is using BZD medication and who has working memory impairment may show excellent memory in one instance and very poor memory in another. The variability of a patient's performance level in rehabilitation settings or at work or school may cause confusion in the clinic and the community. To minimize this, adequate examinations should be performed, and information should be provided to the patient and his/her treatment team more frequently than is currently the case.

The results indicate that memory deficits in OST patients with current or recent BZD use are rather stable at least during the first six months of their treatment. It is possible that this is associated with OST drugs and BZDs given legally to the OD patients. However, this does not mean that OST would be harmful for the recovery of OD patients. OD patients entering OST are, in general, so stuck in the addiction, that a abstinence oriented treatment program with no opioid or BZD agonists is a realistic alternative only in rare cases [1,4]. Both treatment alternatives are needed, but OST should be seen as the mainstream option.

Limitations

Comparing a clinical sample of OST patients who use BZDs and other psychoactive medications against normal comparison participants imposes several limitations. Some of the patients (see Table 2), but none of the comparison participants were abusing illicit drugs. This is clear confounding factor that is difficult to eliminate when evaluating performances in memory tests. The same applies to other psychoactive medications that were legally given to some of the patients but none of the comparison participants. Thus, our results cannot be generalized to OD patients without psychoactive medications who have achieved long-term abstinence from any illicit use of drugs. Psychiatric comorbidity that included Axis I and Axis II disorders was common among patients and absent among comparison participants. A recent study by Prosser et al [59] examined correlates of cognitive function in a relatively large sample of opioid dependent patients (n = 56). It was found that personality pathology accounted for a greater portion of the variance in cognitive performance than any of the variables of drug use history. However, the only memory variable included in their analyses was immediate visual memory.

The mean opioid agonist doses given to our patients changed between test points, while the mean BZD doses

and illegal substance abuse remained rather stable. The methadone dose increased from a mean of 73 mg at T1 to 126 mg at T2. The buprenorphine dose increased from a mean of 17 mg at T1 to 23 mg at T2. Thus, dose change and time factors are both affecting the results, and with our study design, separating these effects is not possible. The buprenorphine group included both buprenorphine-only and buprenorphine/naloxone patients. This was partially a practical issue because the majority of buprenorphine patients in Finland have been transferred to buprenorphine-naloxone combination medication. There is no evidence that sublingual naloxone exhibits opioid antagonist activity or would interfere with the opioid agonist effects of buprenorphine [26,60]. However, because there are no studies directly comparing buprenorphine-only and buprenorphine/naloxone patients, combining these patients can be considered a limitation of our study. The list learning task (the Memory for Persons Data) was not repeated at T2, which poses a limitation for the analyses of immediate verbal memory. Psychoactive drugs, such as short-acting non-BZDs, neuroleptics, or opioid withdrawal relievers, were given to both patient groups in order to alleviate opioid withdrawal symptoms or to treat psychiatric comorbidity. The possible interactions of OST medications with these medications warrant further studies with larger sample sizes. Recent-month drug screens were considered important because it is known that long-term use of benzodiazepines or cannabis may have a negative impact on cognitive function even weeks after cessation of use [18,61]. However, our data cannot determine the precise doses used during the recent month, nor does the data cover full time span of the follow-up. Thus, the results do not reflect "pure" drug effects of OST drugs and BZDs. On the other hand, no major differences between the substance abuse profiles of methadone and buprenorphine patients were seen. OD patients may differ from the general population already in their premorbid cognitive functioning [62]. Screening for premorbid conduct or attention deficit disorder could possibly reveal interactions with current cognitive functions among OST patients [63,64]. However, retrospective assessment of these has low reliability in the absence of longitudinal records [65]; therefore, these assessments were not done in our study. Finally, our sample size was relatively small, and therefore type 2 errors cannot be excluded.

Conclusion

OD patients treated with methadone or buprenorphine along with BZDs showed substantial deficits in working memory both during beginning of the treatment, and after six months of treatment. Given the previously stated limitations of this study, we conclude that OD patients taking opioid agonist drugs and BZDs score worse than normal comparison persons in tests of memory during first six months of their OST. Thus, it is possible that the working memory deficit observed among these patients might be relatively permanent. An immediate verbal memory deficit may also be seen among them. Surprisingly, there were no significant memory consolidation differences between the patient groups and normal comparison group. On the other hand, OST patients reported subjective memory problems that were associated with poor late memory consolidation. This has obvious functional relevance for the patients. Therefore, we propose that the relationship between subjective and objective memory function should be taken into account in longitudinal studies of substance abuse treatment and clinical practice.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PR planned and performed cognitive testing and statistical analysis. He wrote the first version of the manuscript and prepared the final manuscript. HA conceived the idea of the study and advised in manuscript preparation. HK participated in the design of the study and in manuscript preparation. CF carried out psychiatric investigations. All authors prepared, read and accepted the final manuscript.

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III

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Cognitive functioning in opioid-dependent patients treated with buprenorphine, methadone, and other psychoactive medications: stability and correlates

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RESEARCH ARTICLE Open Access

Cognitive functioning in opioid-dependent patients treated with buprenorphine, methadone, and other psychoactive medications: stability and correlates

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Abstract

Background: In many but not in all neuropsychological studies buprenorphine-treated opioid-dependent patients have shown fewer cognitive deficits than patients treated with methadone. In order to examine if hypothesized cognitive advantage of buprenorphine in relation to methadone is seen in clinical patients we did a neuropsychological follow-up study in unselected sample of buprenorphine- vs. methadone-treated patients.

Methods: In part I of the study fourteen buprenorphine-treated and 12 methadone-treated patients were tested by cognitive tests within two months (T1), 6-9 months (T2), and 12 - 17 months (T3) from the start of opioid substitution treatment. Fourteen healthy controls were examined at similar intervals. Benzodiazepine and other psychoactive comedications were common among the patients. Test results were analyzed with repeated measures analysis of variance and planned contrasts. In part II of the study the patient sample was extended to include 36 patients at T2 and T3. Correlations between cognitive functioning and medication, substance abuse, or demographic variables were then analyzed.

Results: In part I methadone patients were inferior to healthy controls tests in all tests measuring attention, working memory, or verbal memory. Buprenorphine patients were inferior to healthy controls in the first working memory task, the Paced Auditory Serial Addition Task and verbal memory. In the second working memory task, the Letter-Number Sequencing, their performance improved between T2 and T3. In part II only group membership (buprenorphine vs. methadone) correlated significantly with attention performance and improvement in the Letter-Number Sequencing. High frequency of substance abuse in the past month was associated with poor performance in the Letter-Number Sequencing.

Conclusions: The results underline the differences between non-randomized and randomized studies comparing cognitive performance in opioid substitution treated patients (fewer deficits in buprenorphine patients vs. no difference between buprenorphine and methadone patients, respectively). Possible reasons for this are discussed.

Background

Opioid agonists buprenorphine and methadone prevent opioid withdrawal symptoms and reduce craving for opioids [1,2]. Both drugs are used in opioid substitution treatment (OST), also known as opioid maintenance treatment. OST has proven effective in reducing illicit drug use, somatic diseases, mortality, and social or mental health problems in opioid-dependent patients [3,4]. Cognitive effects of OST drugs have been examined in clinical and experimental studies, but the results have been mixed. Studies comparing OST patients against healthy controls have, in general, shown cognitive impairment among patients [5-8]. Yet, it has not been proven that the impairment would be specifically related to opioid substitution drugs [5,9,10]. In non-randomized studies, however, buprenorphine-treated

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opioid-dependent patients have performed better than methadone patients in several cognitive tests [7,11-13].

It is important to know if the possible cognitive differences between unselected buprenorphine vs. methadone patients are stabile during the treatment and what are the correlates of cognitive performance. Therefore, we compared cognitive performance of buprenorphine and methadone patients against healthy controls thrice (T1 - T3) during the first year in the OST by (part I of the study). In part II we analyzed correlates of cognitive performance in patients after six (T2) and twelve (T3) months in treatment by using extended patient pool. The present study is an extension to our previous studies [7,14].

Part I: Stability

Opioid and dopamine systems in the brain have important interactions, and current opioid drug use may negatively affect cognitive functioning, especially working memory [15-17]. However, Pirastu et al. have presented evidence that buprenorphine as being a partial mu opioid agonist and kappa opioid receptor antagonist may improve cognitive performance after long-term opioid abuse. According to them methadone as being a full mu opioid agonist may lack properties for supporting normal cognitive function [18]. Also, there is evidence that adverse interactive effects benzodiazepines (BZD) and opioid substitution drugs on cognitive performance are greater for methadone than buprenorphine [19,20]. Therefore, we hypothesized that patients treated with buprenorphine combined in most cases with BZD and other comedications would show greater cognitive improvement in long-term treatment in comparison to methadone-treated ones.

Part II: correlates

In the part II of the study the patient sample was extended to include additional patients examined at all test points, but whose data were excluded at T1. After this, data from 36 patients could be analyzed at T2 and T3. We hypothesized that there would be negative correlations between medication variables (opioid agonist dose, BZD dose, and the number of psychoactive drugs) and cognitive performance in opioid-dependent patients treated either with buprenorphine or methadone. In addition, we hypothesized that those with the highest opioid dose would have higher BZD doses, because BZDs have been associated with craving for higher opioid dose [21]. The negative effects of methadone and buprenorphine on cognition are dose-dependent in healthy volunteers, although little is known about the development of tolerance [22,23]. It is known that BZDs have negative effects on memory performance in opioid substitution treated patients, and these effects are stronger for methadone than for buprenorphine [24]. Little is known about possible effects of polypharmacy on cognition in opioid-agonist treated patients. However, in other patient populations, those patients treated with several drugs perform worse in cognitive tests than patients treated with single drug [25-27].

Negative correlations were also hypothesized between cognitive performance and frequency of substance abuse in the past month, benzodiazepine dosage, the number of other psychoactive drugs, early onset of substance abuse, early-onset mental health or behavioral problems, opioid-related overdoses, and duration of lifetime alcohol abuse. In our sample recent alcohol and/or cannabis abuse were common, and these negatively affect cognitive function [28-31]. Early onset substance abuse and childhood mental health or behavioral problems have been associated with poor adult cognitive functioning among individuals with substance abuse problems [32-35]. High number of opioid-related overdoses, lifetime alcohol abuse, and low level of education have all been associated with poor cognitive performance among opioid-dependent patients [5,36,37]. Verbal intelligence (IQ) and years of education were hypothesized to correlate positively with memory performance.

Methods

All participants included in the study were between 18 - 50 years of age and participated voluntarily. Inclusion criteria for patients were opioid dependence and BZD dependence or abuse according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), treatment of opioid dependence with methadone, buprenorphine, or buprenorphine/naloxone. We excluded participants with uncontrolled polysubstance abuse, acute alcohol abuse, or acute axis I psychiatric morbidity according to DSM-IV other than substance abuse disorders. Full description of our inclusion and exclusion criteria is given in our previous report [7].

In order to screen for substance abuse an urine sample was collected from each patient on each day of testing and at least once in the preceding week. Each healthy control participant was screened for substance abuse once during the study period. In addition, we interviewed all participants about their past month and lifetime substance use by using the European Addiction Severity Index as a basis for further inquiry [38]. If any indication of intoxication was observed, we excluded them. Breath alcohol testing was used when considered necessary. Participants who had used within 24 h alcohol more than four/five drinks (females/males, respectively) or significant as-needed benzodiazepine dose (5 mg or more as diazepam equivalent dose) were excluded as well. The study protocol was accepted by the Ethics Committee of Helsinki University Central Hospital. We

obtained a written informed consent according to the Declaration of Helsinki from all participants, and paid them € 60 if they attended all study visits.

Part I participants

Participants who were eligible for T1-T3 follow-up (sample I) represent 42% (14/35) of the all buprenorphine patients tested at T1, 55% (12/22) of the methadone patients and 78% (14/18) of the healthy controls, respectively. To test whether the follow-up completers of either group were significantly different from the non-completers of that group, we compared these groups by independent samples *t*-tests, chi-square tests, or Mann-Whitney *U*-tests (p-value = 0.05). No statistically significant differences emerged in demographic, medication or cognitive variables. Because there were few follow-up non-completers (n = 4) among the potential healthy controls, these comparisons were not made in healthy controls.

When the groups were compared on demographic variables with analysis of variance (ANOVA) or chi-square-test (Table 1) there were no statistically significant differences in age, sex, or estimated premorbid intelligence. Healthy controls had completed more years in education than either one of the patient groups. Because BZD use on prescription was very common, their doses were converted to diazepam equivalent doses according to the conversion tables given by Nelson and Chouinard [39]. Temazepam doses were halved in order to account for their use as hypnotics on the night before testing. Substance abuse in the past month was estimated as frequency of use. Because accurate number of the days of abuse was hard to obtain we dichotomized the frequency of the past month substance abuse into two categories. The first category was labeled as low to moderate use, and it included abstinence or substance abuse up to two days a week. The second category was labeled as high frequency group and included all the participants with substance use of three days a week or more. This classification was based on the findings showing that mean three days of substance use a week is one of the threshold values for getting into serious substance abuse problems [40,41]. In the buprenorphine group, 79% of the patients were given buprenorphine/naloxone at all test points. Thus, they were also given sublingual naloxone in the ratio 1:4 combined with their buprenorphine dose. When the tablet is taken sublingually the absorption of naloxone is low and eliminates within first hours [42]. It has been concluded that naloxone has minimal, if any effect, on the bioavailability or pharmacokinetics of buprenorphine [43,44]. Also, buprenorphine and buprenorphine/naloxone have similar physiological effects [43]. On the basis of these findings, we combined patients using either one of the buprenorphine compounds. Table 2 shows medication characteristics of the sample I within the last 24 h before testing. Both patient groups used more psychoactive medications than healthy controls.

Part II participants

Sample II (n = 36) included 51% of all the buprenorphine-treated and 59% of methadone-treated patients who entered the follow-up at T1. The methadone group included also five patients who were tested without opioid medication at T1, but who then started methadone treatment within few days after the testing. Thus, all patients were tested after minimum 6 (T2) and 12 months (T3) of OST. They had been tested at start of their treatment, but were excluded from the part I sample. Substance abuse history variables included in the analyses were onset ages of any substance and opioid abuse, years of heavy alcohol use, and the number of self-reported opioid-related overdoses. Whenever possible, the data was checked using medical reports. It turned out that no reliable information about the number of opioid-related overdoses could be obtained. Therefore this variable was excluded from the analyses. Current substance abuse variables were frequency of substance abuse in the past month (low vs. high) and drug screen result (positive vs. negative). Medication drug use variables that were examined included opioid substitution drug (buprenorphine vs. methadone), benzodiazepine dose (diazepam equivalent), and the number of other psychoactive drugs other than opioid substitution drug. Demographic variables included in the analyses were age, sex, years of education, early neurobehavioral problems, and verbal IQ. Data about childhood mental health or behavioral problems was gathered using the Childhood Behavioral Checklist as a basis for interview, and medical reports were used, whenever possible [45]. Those participants who had had treatment or referral to special services due to mental health or behavioral problems before the onset of substance abuse were rated as early-onset neurobehavioral problem group (31%). If significant change was seen in cognitive performance then change (T3 - T2) in that that variable, as well in medication, and substance use changes were analyzed. Medication and substance abuse change variables were made more reliable by dichotomizing the data. Change in opioid drug dose between T2 and T3 was dichotomized as steady or reduced dose group (58%) or higher dose group (42%). Change in BZD dose between T2 and T2 was grouped respectively. The majority of the patients belonged to steady or reduced BZD dose group (83%), and the rest (17%) had higher BZD dose at T3. All those who reduced their frequency of substance abuse as indicated by the shift from the high frequency group to low to moderate frequency group were put into group of reduced substance abuse.

Table 1 Group demographics in sample I

	Buprenorphine (n = 14)	Methadone (n = 12)	Healthy control (n = 14)	Group comparison *p*-values
Age (*M* ± *SD*)	30 ± 7	31 ± 8	29 ± 10	*ns*
Sex (female/male)	36%/64%	50%/50%	50%/50%	*ns*
Intelligence[a] (*M* ± *SD*)	101 ± 11	98 ± 9	105 ± 8	*ns*
Education, years	10 ± 2	10 ± 1	13 ± 1	BN & M < HC ***
Main opioid of abuse used within last month at T1 (%)				
Buprenorphine	93%	83%?	-	*ns*[b]
Heroin	7%	17%	-	*ns*[b]
Days in opioid substitution treatment at test (*M* ± *SD*)				
T1	21 ± 15	20 ± 14	-	*ns*[b]
T2	210 ± 20	200 ± 28	-	*ns*[b]
T3	414 ± 46	405 ± 31	-	*ns*[b]
Examined in inpatient settings %				
T1	21%	25%	-	*ns*[b]
T2	7%	0%	-	*ns*[b]
T3	7%	8%	-	*ns*[b]
Participants with high frequency of use of any substance of abuse [c] %				
T1	86%	67%	14%	BN > HC ***; M > HC *
T2	29%	42%	7%	*ns* ; *ns*
T3	36%	33%	7%	*ns* ; *ns*
	T2 < T1**	T3 < T1*		
	T3 < T1*			
Participants with the past month extra doses of any opioid [d], %				
T1	86%	92%	-	*ns*[b]
T2	29%	33%	-	*ns*[b]
T3	36%	33%	-	*ns*[b]
	T2 < T1**	T2 < T1**		
	T3 < T1*	T3 < T1**		
Participants with the past month nicotine use (daily)				
T1	100%	100%	36%	BN & M > HC ***
T2	100%	100%	36%	BN & M > HC ***
T3	100%	93%	29%	BN > HC **; M > HC ***

Note. BN = buprenorphine patients, HC = healthy control group, and M = methadone patients.

[a] Estimation based on the vocabulary and picture completion subtests of the Wechsler Adult Intelligence Scale - Revised (WAIS-R) [67].

[b] Tested only between patient groups.

[c] High frequency = three or more days a week. Alcohol use was taken into account if it was at least mean weekly 16 portions (12 g) for females and 24 portions for males or binge drinking occurred on any day.

[d] Extra doses of any non-prescribed opioid use during the recent month seen in drugs screens or admitted by the patients.

> = superior than, *** = statistically significant at level $p < 0.001$. ** = statistically significant at level $p < 0.01$. * = statistically significant at level $p < 0.05$.

This group included also the patients who belonged to the low to moderate frequency group at both time points, totaling 58% of the patients. The rest were put into group of non-reduced substance abuse (42%). Change in the number of psychoactive drugs was dichotomized similarly. All those with less psychoactive drugs at T3 in comparison to T2 or no other psychoactive prescribed drugs than opioid drug at both time points were put in the group of reduced use of psychoactive drugs (42%). The rest were put into group of non-reduced use of psychoactive drugs (58%). Table 3 presents the demographic characteristics of the sample II. In the buprenorphine group, 78% of the patients were given buprenorphine/naloxone at all test points. Table 4 shows other medication characteristics of the sample II within the last 24 h before testing.

Procedure

Cognitive tests were administered between three to six hours after opioid substitution drug had been given.

Table 2 Medications given to participants within the last 24 h before testing in sample I

	Buprenorphine (n = 14)	Methadone (n = 12)	Healthy control (n = 14)	Group or time point comparison *p*-values
Opioid agonist drug, dose				
Buprenorphine (*M* ± *SD*; (range))				
T1	16 ± 3 mg (12 - 24 mg)	-	-	-
T2	20 ± 5 mg (14 - 28 mg)	-	-	T2 > T1**
T3	21 ± 6 mg (6 - 28 mg)	-	-	T3 > T1**
Methadone (*M* ± *SD*;(range))				
T1	-	71 ± 39 mg (30 - 135 mg)	-	-
T2	-	127 ± 36 mg (80 - 180 mg)	-	T2 > T1 ***
T3	-	135 ± 34 mg (75 - 180 mg)	-	T3 > T1 ***
Participants treated with BZD medication			'	
T1	79%	100%	0%	BN & M > HC ***
BZD dose at T1 (*M* ± *SD*)	20 ± 17 mg	21 ± 11 mg	-	*ns* [a]
T2	71%	100%	0%	BN & M > HC ***
BZD dose at T2 (*M* ± *SD*)	16 ± 11 mg	22 ± 11 mg	-	*ns* [a]
T3	64%	100%	0%	BN & M > HC ***
BZD dose at T3 (*M* ± *SD*)	13 ± 12 mg	22 ± 9. mg	-	BN < M *
Number of other medications with possible cognitive effects [b] (*M* ± *SD* (range))				
T1	1.9 ± 1.1 (0 - 4)	3.0 ± 1.3 (0 - 5)	0.2 ± 0.4 (0 - 1)	BN & M > HC ***; M > BN *
T2	1.9 ± 1.2 (0 - 3)	2.3 ± 0.8 (1 - 4)	0.2 ± 0.4 (0 -1)	BN & M > HC ***
T3	1.8 ± 1.3 (0 -4)	2.2 ± 1.0 (1 -4)	0.2 ± 0.4 (0 -1)	BN & M > HC ***

[a] Tested only between patient groups.

[b] These included antidepressants, neuroleptics (used with anxiolytic indications), non-benzodiazepine hypnotics, and substance abuse withdrawal symptom or (non-opioid) pain relievers. There were no significant differences between time points within the groups in medication variables.

> = superior than, *** = statistically significant at level $p < 0.001$. ** = statistically significant at level $p < 0.01$. * = statistically significant at level $p < 0.05$.

Attention was assessed by two tests from the Test for Attentional Performance (TAP) [46]. In the Alertness test, the participant was instructed to respond to visual stimuli by pressing a response key as quickly as possible. The stimuli were presented without or with auditory warning signal. The condition without warning signal is a simple reaction time task reflecting tonic alertness. The condition with auditory warning signal reflects both tonic and phasic alertness. In the Go/NoGo test, the participant was instructed to respond only to two out of five alternative stimuli. Thus, selective attention and executive control of action was assessed.

Working memory was assessed by two tests. In the Letter-Number Sequencing task from the Wechsler Memory Scale - III the participant was instructed to repeat letters and numbers in specific order [47]. In the Paced Auditory Serial Addition Task (PASAT) the participant was instructed to add two consecutive numbers from an auditory series of digit [48]. A new digit was presented after every 1.6 seconds. Both tests are thought to tap complex working memory because simultaneous storage and manipulation of the material is needed.

Verbal memory was assessed by the Logical Memory from the Wechsler Memory Scale - III. However, only

Table 3 Group demographics in sample II

	Buprenorphine or Buprenorphine/ Naloxone (*n* = 18)	Methadone (*n* = 18)	Group or time point comparison *p*-values
Age, years at T1 (*M* ± *SD*)	30 ± 8	32 ± 8	*ns*
Sex: females/males, %	28/72%	33/67%	*ns*
Verbal IQ [a] (*M* ± *SD*)	101 ± 8	100 ± 11	*ns*
Education, years (*M* ± *SD*)	10 ± 2	11 ± 1	*ns*
Participants with early neurobehavioral problems %	33%	28%	*ns*
Examined in inpatient settings %			
T2	6%	6%	*ns*
T3	11%	11%	*ns*
Participants with high frequency use of any substance of abuse % [b]			
T2	44%	39%	*ns*
T3	44%	44%	*ns*
Participants with recent month extra doses of any opioid % [c]			
T2	36%	36%	*ns*
T3	36%	43%	*ns*
Nicotine, participants using daily, %			
T2	100%	100%	*ns*
T3	100%	100%	*ns*
Days in opioid substitution treatment at test (*M* ± *SD*)			
T2	211 ± 19	196 ± 27	*ns*
T3	411 ± 43	405 ± 29	*ns*
Age of onset, any substance abuse (*M* ± *SD*)	16 ± 4	15 ± 3	*ns*
Age of onset, opioid abuse (*M* ± *SD*)	19 ± 5	19 ± 4	*ns*
Participants with lifetime alcohol abuse	72%	83%	*ns*
Years of any substance abuse at T1 (*M* ± *SD*)	15 ± 7	17 ± 7	*ns*
Years of alcohol abuse at T1 (*M* ± *SD*)	3 ± 4	3 ± 3	*ns*[b]
Years of opioid abuse at T1, years (*M* ± *SD*)	10 ± 7	12 ± 7	*ns*

[a] Estimation based on the WAIS-R Vocabulary score.

[b] High frequency = three or more days a week Alcohol use was considered heavy if it was at least mean weekly 16 portions for females and 24 portions for males. One portion was defined as 12 g of alcohol.

[c] Non-prescribed doses of opioids during the recent month seen in drugs screens or admitted by the patient.

one story was presented. A full description of the tasks is given in our previous report [7].

Statistical analyses: stability of function

Longitudinal changes in cognitive function were examined by repeated-measures analysis of variance (ANOVA) using general linear model approach. Group was used as between-subjects factor and time as within-subjects factor. Before the analyses normality assumptions of cognitive variables were examined by Shapiro-Wilk's test and homogeneity of variance by Levene's test. The data were also screened for outlying values. On the basis of these procedures, reaction time and the PASAT scores were subjected to log transformations before further analyses, and the Go/NoGo errors were examined by non-parametric Kruskal-Wallis ANOVA. Sphericity assumption was tested by Mauchly's test, and when appropriate, analyses of effects were interpreted using Huynh-Feldt correction. The effects of demographic variables on cognitive performance were tested as covariates. Only significant covariates were retained in the model. Statistically significant between groups effects were followed by planned contrast using healthy controls as a reference group. Significant time effects we

Table 4 Medications given to participants within the last 24 h before testing in sample II

	Buprenorphine or Buprenorphine/ Naloxone (*n* = 18)	Methadone (*n* = 18)	Group or time point comparison *p*-values
Opioid drug, dose (*M* ± *SD* (range))			
T2	22 ± 5 mg (10 - 28 mg)	-	T2 vs. T3, *ns*
T3	21 ± 6 mg (6 - 30 mg)	-	
T2	-	119. ± 33 mg (80 - 180 mg)	T2 vs. T3, *ns*
T3	-	129 ± 33 mg (75 - 180 mg)	
Participants using BZD medication			
T2/T3	78%/67%	89%/94%	*ns/ns*
BZD dose at T2 (*M* ± *SD* (range))	20 ± 16 mg (0 - 60 mg)	21 ± 16 mg (0 - 70 mg)	T2 vs. T3, *ns* *ns*
BZD dose at T3 (*M* ± *SD* (range))	16 ± 14 mg (0 - 40 mg)	20 ± 10 mg (0 - 40 mg)	*ns* T2 vs. T3, *ns*
Number of other medications with possible cognitive effects [a]			
T2/T3 (*M* ± *SD* ; (range))	1.8 ± 1.1 (0 - 3)	2.2 ± 0.7 (1 -4)	*ns*
	1.9 ± 1.4 (0 - 4)	2.0 ± 1.0 (1 - 4)	*ns*
			T2 vs. T3, *ns*

These included antidepressants, neuroleptics (used with anxiolytic indications), non-benzodiazepine hypnotics, and substance abuse withdrawal symptom or (non-opioid) pain relievers.

C = controls, M = methadone, BN = buprenorphine or buprenorphine/naloxone

> = superior than, *** = statistically significant at level $p < 0.001$. ** = statistically significant at level $p < 0.01$. * = statistically significant at level $p < 0.05$.

examined using repeated contrast (T2 vs. T1 and T3 vs. T2). When a significant group by time interaction effect was noted, it was examined further by combining previous contrasts (healthy control vs. buprenorphine group * T2 vs. T1, healthy control vs. buprenorphine group * T3 vs. T2; and healthy control vs. methadone group, respectively). All statistical analyses were done by SPSS statistical software, version 15.0, with an exception of the effect size calculations. These were done by an effect size calculator provided by Durham University, UK [49]. For the effect size estimation we pooled the samples and corrected the values by Hedge's correction for small sample bias.

Statistical analyses: correlates of cognitive functioning

Cognitive tests selected for the analyses were the same as in the part I, except that the PASAT was excluded from the second set of analyses. Improvement in the PASAT is shown to be related to practice effect [50]. This makes it problematic to analyze the correlates of this measure in repeated testing. In order to reduce the number of cognitive variables correlations between the variables analyzed, and whenever justified, domain-wise cognitive sum scores for T2 and T3 performances were formed. T2 performance was used as a reference point in T3 summed scores. Analysis of correlation is sensitive for the effects of outliers. Therefore, visual inspections of scatter plots were used to check the linearity of the relationship between variables and the role of possible outliers. Then correlations between cognitive variables we analyzed by the Pearson product moment method. As expected there were high positive correlations between all reaction time measures at both test points (range .52 - .86); whereas correlations between reaction time measures and other cognitive measures ranged from zero to moderate (-.38 as highest). Therefore, a mean composite score called attention performance was calculated after converting the test scores into z-scores. The working memory measure, the Letter-Number Sequencing task, showed only low to moderate correlations with other measures (.38 as highest) and therefore it was not combined with other measures. The verbal memory measures, immediate and delayed recall of the Logical Memory, correlated strongly at both test points (.80 at T2 and .91 at T3). Therefore, a mean sum score called verbal memory was formed after z-score conversion. Then group differences in cognitive function were examined by repeated-measures analysis of variance

(ANOVA) using general linear model approach. Group was used as between-subjects factor and time as within-subjects factor. After this all significant or three highest correlates of each cognitive variable were further examined by checking for intercorrelations between these variables and other variables of interest. Also, medication variables were checked for significant intercorrelations. The sample size did not allow for multiple regression analysis. Instead three highest correlations for each cognitive domain were investigated with analyses of semipartial correlations. Correlations between .10 - .19 were considered to show low association and .20 - 29 mild association. Only some of these are reported. Correlations between, .30 - .49 were considered to show moderate association, .50 - 69 substantial and those .70 or above a strong association [51].

Results

Stability of cognitive functioning in sample I

The pattern of means in Table 5 identifies change over time in cognitive performance in each group. There were statistically significant overall group differences in all attention and memory measures. As apparent from the Table 5, the methadone-treated patient group constantly lagged behind the healthy control group in the TAP reaction time tests measuring alertness and selective attention. Planned contrasts confirmed that the healthy controls outperformed the methadone group in these measures (p = 0.002 for the TAP tonic alertness/simple reaction time; p = 0.002 for the TAP phasic alertness/reaction time with-auditory-warning-signal; and p = 0.001 for the TAP Go/NoGo reaction time/selective attention). There were neither significant time nor group by time interaction effects in these measures. Errors in the Go/NoGo task were rare in all groups, and no significant between groups differences were observed. In both working memory measures there was an overall group effect. In the PASAT the planned contrast revealed that both patient groups performed *overall* worse than the healthy controls at the level of p = 0.001. In the Letter-Number Sequencing the values were p = 0.016, for healthy controls vs. buprenorphine patients and p = 0.008 for healthy controls vs. methadone patients. However, because there was also time effect (the PASAT), or a group by time interaction effect (the Letter-Number Sequencing) in these measures, further analyses are needed before the final interpretation. In the PASAT the improvement in overall performance between T1 and T2 turned out to be non-significant, but the overall improvement between T2 and T3 was significant, p = 0.01. As apparent from Figure 1, the source of group by time interaction in the Letter-Number Sequencing was due to differences between the groups between T2 and T3. This was confirmed by a planned contrast which showed improved performance in the buprenorphine patients between T2 and T3 relative to healthy control group, p = 0.017. Effect size of the T2 - T3 improvement in the buprenorphine group, as measured by Cohen's **d**, was 0.77. In verbal memory, there was a significant overall group effect both in immediate and delayed condition of the Logical Memory. Both patient groups performed worse than the healthy controls in the immediate Logical Memory, p = 0.029 for the buprenorphine group; and p = 0.007 for the methadone group. In the delayed Logical Memory the values were p = 0.005, and p = 0.028, respectively.

Cognitive functioning in sample II

The cognitive group comparisons in the part II (T2 - T3) sample brought results that were in line with the part I sample analyses. Buprenorphine patients outperformed methadone patients in the combined attention performance (p = 0.004), and no significant time or group by time effect were seen. In working memory as measured by the Letter-Number Sequencing there was a main effect of time (p = 0.01) and a significant group by time interaction, (p = 0.04) indicating again that improvement in this measure was due to enhanced performance in the buprenorphine patients between T2 and T3. In the combined verbal memory measure there were no significant differences between groups, time effect, or group by time interaction.

Correlations between medication variables and non-cognitive variables in sample II

At T2, buprenorphine dose correlated substantially with BZD dose (.62, p = 0.006) and moderately with the number of psychoactive drugs (.40, *ns*). In the methadone group, respective values were (.47, *ns;* and .58, p = 0.013). At T3, buprenorphine dose correlated at moderate level with BZD dose (.33, *ns*) and at very low level with the number of psychoactive drugs (.10, *ns*). In the methadone group respective values were mild (.25, ns; and .20, ns). In general, buprenorphine or methadone doses did not show significant correlations with substance abuse or demographic variables. As an exception buprenorphine dose correlated negatively with years of alcohol abuse, at T2 the value was -.56 (p = 0.016) and at T3 -.64 (p = 0.004). In the methadone group, no significant correlations emerged. Other significant correlations between medication variables and other non-cognitive variables of interest are presented in Table 6. It can be noted that high BZD dose was associated with high frequency of substance abuse in the past month and younger age at both time points.

Table 5 Group comparisons of cognitive performances using repeated measures ANOVA in sample I

TAP Tonic Alertness/simple reaction time (ms)				
T1	232 ± 25	261 ± 21	238 ± 22	**Group, $p = 0.002$**
T2	236 ± 18	263 ± 21	233 ± 21[a]	Time, *ns*
T3	242 ± 25	267 ± 36	241 ± 25	Group × Time, *ns*
TAP Phasic Alertness/ reaction time with warning signal (ms)				
T1	227 ± 24	244 ± 20	226 ± 21	**Group, $p = 0.005$**
T2	229 ± 21	255 ± 28	224 ± 21 [a]	Time, *ns*
T3	229 ± 19	254 ± 45	225 ± 22	Group × Time, *ns*
TAP Go-NoGo reaction time (ms)				
T1	490 ± 50	548 ± 74	460 ± 41	**Group, $p = 0.001$**
T2	480 ± 42	548 ± 104	443 ± 72 [a]	**Group, $p = 0.002$**
T3	493 ± 43	529 ± 63	462 ± 47	**Age, $p = 0.022$**
				Time, *ns*
				Group × Time, *ns*
TAP Go-NoGo errors				
T1	1.1 ± 1.3	0.7 ± 0.6	0.5 ± 0.5	*ns*
T2	0.5 ± 0.7	1.0 ± 0.9	0.5 ± 0.8 [a]	*ns*
T3	0.6 ± 0.8	0.5 ± 1.0	0.2 ± 0.4	*ns*
The Letter-Number Sequencing				
T1	8.4 ± 2.2	9.3 ± 2.4	11.8 ± 3.4	**Group, $p = 0.009$**
T2	8.8 ± 2.2	8.5 ± 2.3	11.6 ± 3.0	Time, *ns*
T3	10.6 ± 2.2	8.8 ± 2.4	11.2 ± 3.2	**Group × Time, $p = 0.007$**
The PASAT				
T1	32.4 ± 10.5	31.0 ± 8.5	46.3 ± 9.7	**Group, $p = 0.001$**
T2	35.0 ± 6.8	33.4 ± 10.1	45.8 ± 9.0 [a]	**Time, $p = 0.013$**
T3	35.8 ± 10.0	34.9 ± 11.0	49.8 ± 8.4	Group × Time, *ns*
Logical memory, immediate				
T1	12.8 ± 2.6	14.9 ± 4.5	15.9 ± 3.3	**Group, $p = 0.016$**
T2	13.8 ± 3.1	14.8 ± 3.7	16.3 ± 3.2	Time, *ns*
T3	15.5 ± 4.1	14.3 ± 4.3	17.9 ± 2.9	Group × Time, *ns*
Logical memory, delayed				
T1	11.8 ± 3.0	13.1 ± 4.0	13.9 ± 4.0	**Group, $p = 0.013$**
T2	12.0 ± 4.0	13.7 ± 4.0	15.6 ± 3.1	Time, *ns*
T3	12.4 ± 4.1	11.8 ± 4.7	15.9 ± 3.6	Group × Time, *ns*

Bold indicates statistically significant effects.

[a] One missing value was replaced by the carry-over value from the preceding testing point.

Correlates of cognitive performances in sample II

As shown in Table 7, the only significant correlate for attention performance at both test points was the opioid substitution drug group. High frequency of substance abuse correlated negatively with the Letter-Number Sequencing performance at both time points. Figures 2 and 3 depict this association. It can be noted from these Figures that the association between working memory performance and frequency of substance abuse in the past month is similar in both groups. The T2 negative correlation remained significant after controlling for two next highest correlates. The T3 correlation dropped to non-significant level after controlling for two next highest correlates (-.18). At T3, high benzodiazepine dose correlated negatively with the Letter-Number Sequencing performance. After controlling for the two other highest correlates, this association was no longer significant (-.22). In further analysis no evidence in support of high association between BZD dose and the Letter-Number Sequencing performance was seen, because T2 correlation between these variables was at zero level (.02). Belonging to the buprenorphine group was the only variable that correlated significantly (.34) with change of the Letter-Number Sequencing performance. After controlling for two other highest correlates, this association was no longer significant.

The number of psychoactive drugs correlated positively with verbal memory performances at both testing points. At T3, the positive association with the number of psychoactive drugs reached significant level after two other

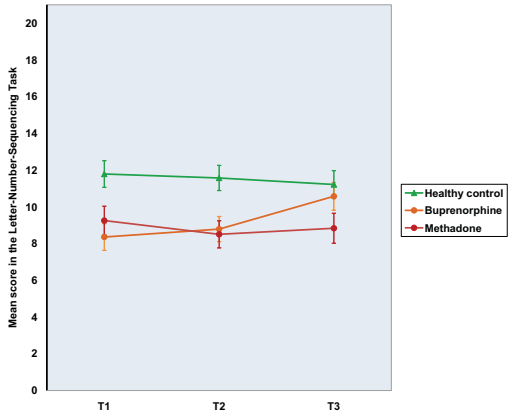

Figure 1 Group performances in the Letter-Number Sequencing Task during the study period in sample I.

correlates were taken into account. At T2, there was a negative association with the highly frequent past month substance abuse and verbal memory performance. After controlling for two other highest this correlation dropped to non-significant level (.28). Furthermore, at T3 the correlation between highly frequent substance abuse in the past month and verbal memory was very low and to the opposite direction (-.08).

Correlations between opioid substitution drug dose and cognitive performances opioid drug doses could be examined only group-wise (n = 18 in both groups). None of the correlations reached statistical significance. Because there was a significant group by time interaction in the Letter-Number Sequencing indicating specific improvement in this task in the buprenorphine group, correlates for the improvement in the buprenorphine group were examined. No significant correlates for the change score emerged.

Discussion

This study was designed to evaluate stability and correlates of cognitive functioning in unselected buprenorphine- vs. methadone treated opioid-dependent patients during the first year in OST. The main findings are the following. Buprenorphine-treated opioid-dependent patients do not show deficits in attention, improve in one of the working memory tests, the Letter-Number Sequencing, but they show stable deficits in the other working memory test, the PASAT, and verbal memory. Methadone-treated opioid-dependent patients show stabile cognitive deficits in attention, working memory, and verbal memory. When correlates of cognitive performances are analyzed 6 and 12 after the start of the OST drug type (buprenorphine vs. methadone) is moderately associated with attention performance. Highly frequent substance abuse in the past month is negatively associated with performance in the Letter-Number Sequencing. The number of other psychoactive drugs and verbal IQ both show mild positive correlation with verbal memory.

Stability of buprenorphine patients' cognitive function during the first year in treatment

Our observation of no reaction time deficits in buprenorphine-treated opioid-dependent patients in relation to healthy controls is in accordance with the idea that some of the negative effects of buprenorphine on cognition disappear after the development of tolerance. Most patients had abused buprenorphine before the treatment (Table 1). Further studies are needed to examine if buprenorphine patients' normal performance in attention tests is related to the development of tolerance only, or if a population selection process is affecting performance in patient samples.

Our finding of partial recovery of working memory function in buprenorphine-treated patients during the OST is in line with the idea of Spiga et al. [52]. The idea is supported by observations by Pirastu et al. showing that buprenorphine patients outperform methadone patients in spatial working memory [18]. They suggest that buprenorphine could preserve working memory function better than methadone because of its antagonism on kappa opioid receptor, which then affects prefrontal dopamine tone known to be important for working memory. This reasoning, however, does not explain why the improvement in working memory in our study took place between 6 and 12 months in the treatment.

Table 6 Significant correlations between medication variables and other non-cognitive variables in sample II

Medication variables	Substance abuse variables	Demographic variables
Benzodiazepine dose (T2)	Frequency of substance abuse in the past month **.36 (p = 0.033)**	Age **-.34 (p = 0.040)**
Benzodiazepine dose (T3)	Frequency of substance abuse in the past month **.50 (p = 0.002)**	Age **-.33 (p = 0.048)**
Number of other psychoactive drugs (T2)		
Number of other psychoactive drugs (T3)	Years of opioid abuse **-.37 (p = 0.028)**	

Table 7 Highest correlations between cognitive and non-cognitive variables in sample II

Domain or test	Medication variables	Substance abuse variables	Demographic variables	Significant correlations after controlling for two other correlates
Attention (T2)	Opioid substitution drug **.48 (p = 0.003)** Number of other psychoactive drugs (T2) .24	Opioid abuse onset age .25		Opioid substitution drug **.46, (p = 0.004)**
Attention (T3)	Opioid substitution drug **.37 (p = .024)**	Opioid abuse onset age .28	Age .26	Opioid substitution drug **.37, (p = 0.021)**
The Letter-Number Sequencing Task (T2)	Number of other psychoactive drugs .25	Frequency of substance abuse in the past month **-49 (p= .002)**	Verbal IQ .29	Frequency of substance abuse in the past month **-44 (p = .005)**
The Letter-Number Sequencing Task (T3)	Benzodiazepine dose **.-38**	Frequency of substance abuse in the past month **.-34 (p = .044)** Years of opioid abuse .28		
Change score in the Letter-Number Sequencing Task (T3 - T2)	Opioid substitution drug **.34 (p = .039)**		Change in the opioid agonist dose -.33 Change in the number of psychoactive drugs -.24	
Verbal memory (T2)	Number of other psychoactive drugs (T2) .25	Frequency of substance abuse in the past month **-. 34 (p = .044)**	Verbal IQ .28	
Verbal memory (T3)	Number of other psychoactive drugs (T3) .31		Verbal IQ .32 Years of education .27	Number of other psychoactive drugs **.34 (p = .035)**

Bold indicates statistically significant correlation.

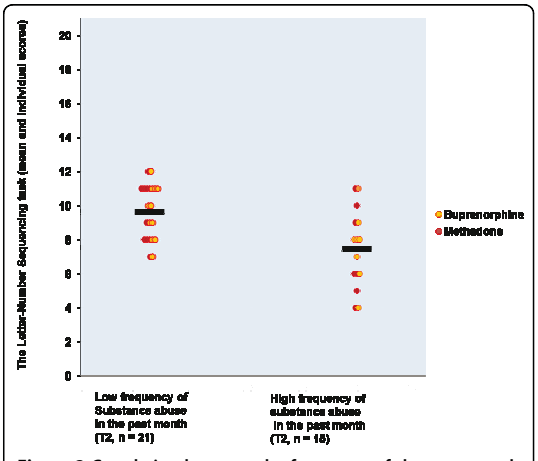

Figure 2 Correlation between the frequency of the past month substance abuse and the performance in the Letter-Number Sequencing at T2 in sample II.

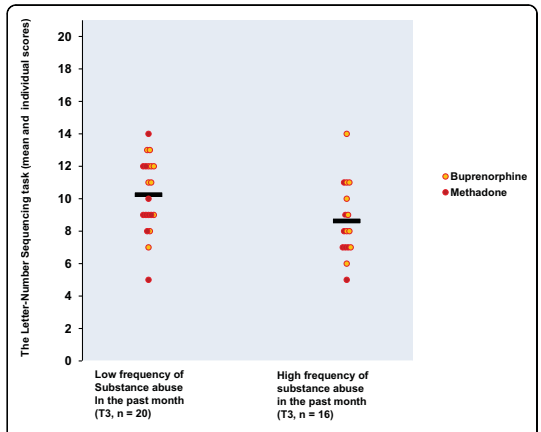

Figure 3 Correlation between the frequency of the past month substance abuse and the performance in the Letter-Number Sequencing at T3 in sample II.

In the other working memory measure, the PASAT, both patient groups are inferior to healthy controls while all groups show improvement during the study period. Improvement that is seen in all groups is a normal finding when the PASAT is administered, and most likely reflects practice effect [50]. The result of no specific improvement in the buprenorphine patients in this measure may be related to the finding that also several other cognitive processes than working memory are needed for good performance in the PASAT [53].

In verbal memory buprenorphine-treated patients perform worse than healthy controls during the whole follow-up. Buprenorphine dose given to our patients was relative high (range mean 16 mg (T1) - 21 mg (T3)). High dose of buprenorphine (32 mg) have been associated with verbal memory impairment [54]. In addition, in recent study by Messinis et al. buprenorphine-treated opioid-dependent patients with a fairly low mean dose of buprenorphine (7 mg) performed worse than healthy controls in verbal memory. Abstinent opioid-dependent patients treated with mu opioid antagonist naltrexone showed no significant difference relative to healthy controls. In sum, buprenorphine may negatively affect verbal memory, although evidence is still insufficient.

Stability of methadone patients' cognitive function during the first year in treatment

In this study, methadone patients show cognitive deficits in all domains studied: attention, working memory and verbal memory. Not all studies, however, have shown attention deficits among them. Gordon found that methadone-treated opioid-dependent patients outperformed controls in simple visual and visual multiple choice reaction times [55]. Curran et al. found that 3 h after methadone dose opioid-dependent patients in methadone-aided opioid withdrawal actually had faster simple reaction times than before the dose [56]. On the other hand, in the Lintzeris et al study high dose of methadone (150% of normal dose) was associated with slower reaction times in OST patients [20]. Thus, the issue whether methadone dose prolongs reaction times in opioid-dependent patients is not fully resolved.

We found a stabile working memory deficit in both complex working memory measures, the Letter-Number Sequencing and the PASAT, in methadone patients. In early study Gritz et al. found no deficit in methadone patients in "simple" working memory test, the Digit Span from the Wechsler scales, in which the items needs to repeated without organizing them [57]. However, in a more recent study Darke et al. found medium effect size difference between methadone patients and healthy controls in the same test [5]. Interestingly, in abstinent opioid-dependent patients "simple" working memory seems to be spared while complex working memory performance is impaired [58,59]. Thus, it would be informative to compare methadone patients against abstinent opioid-dependent patients using both simple and complex working memory measures.

Methadone patients were inferior to healthy controls in verbal memory. Also, in the Darke et al. study opioid-dependent patients treated with methadone for a minimum 5 months were impaired relative to healthy controls in verbal memory [5]. However, in the Curran et al. study opioid-dependent patients treated with methadone for a minimum 6 months were given their normal dose, 33% increased dose, or placebo linctus; and then tested 3-4 after the dose. No significant treatment effect was seen, and the authors conclude that single doses of methadone are devoid of verbal memory effects among long-term methadone users. Thus, negative effect of methadone on verbal memory is not well-confirmed.

Correlates of cognitive functioning in opioid substitution treated patients

The most consistent finding of analyses of correlates of cognitive functioning after 6 (T2) or 12 months (T3) in treatment is that belonging to the methadone group negatively associates with attention performance. However, as stated earlier in randomized or well-controlled studies methadone patients, in general, have performed at equal level than buprenorphine ones in tests measuring attention. Thus, it is possible that patient selection or other medication or substance abuse factor is affecting the results in non-randomized studies, in which methadone patients perform worse than buprenorphine patients.

We hypothesized that the number of prescribed psychoactive drugs given to the patients would show negative correlations with performance in cognitive tests. Our results, however, show three mild to moderate *positive* correlations between the number of psychoactive drugs and verbal memory. Thus, the results do not confirm the hypothesis that the number of psychoactive drugs as such would correlate negatively with cognitive performance in OST patients. We hypothesized that those with the high opioid substitution drug dose would have higher BZD doses. The results were in line with this hypothesis. Benzodiazepine use was very common in both patient groups, and experimental studies have shown that benzodiazepines, when given in combination with opioid substitution drug may affect negatively attention or verbal memory functioning [24]. Therefore, we hypothesized that a negative correlation between the BZD dose and cognitive measures would be seen. Although one moderate negative correlation between working memory measures and BZD dose is seen in our clinical sample, this does not remain significant when

two other correlates are taken into account. In sum, substantial differences between test points and many significant intercorrelations show that relationships between medication variables and cognitive performance are not easily discovered in clinical sample studies.

High frequency of substance abuse in the past month was negatively associated with the working memory measure with executive function component, the Letter-Number Sequencing, at both test points. This finding is line with studies reporting negative association between working memory and recent substance abuse, possibly affecting fluid intelligence in general [31,58,60]. In addition, frequency of substance abuse in the past month correlates positively with BZD dose at both test points (.36 - .50), and BZD dose correlated negatively with the T2 Letter-Number Sequencing performance. Furthermore, the opioid substitution drug doses show moderate or substantial correlations with the BZD doses. There is temptation to suggest an association between the past month frequent substance abuse, high opioid agonist dose, high BZD dose, and impaired working memory performance. Yet, our data do not allow controlling for all these intercorrelations.

The hypothesis of negative effect of lifetime substance abuse on cognitive performance was examined using substance abuse onset ages and durations of abuse as correlates for cognitive performance. Some negative correlations emerged, but these were moderate at best.

Demographic variables have been shown to be important correlates for cognitive performance in opioid-dependent patients [10,36,37]. In our study, the only consistent finding is the positive correlation between Verbal IQ measured by the vocabulary test and verbal memory. This relationship is not surprising because vocabulary and verbal memory correlate moderately in normal and clinical populations [61,62].

Limitations

The main limitation of part I of this study is the fact that, while the opioid-dependent patient groups were comparable to each other in variables of interest, our healthy comparison group had hardly any medication or substance abuse. Although these differences relate to the 'dark side' of addiction [63] they limit the specificity of our results. Some of the cognitive deficits seen in patients may be premorbid or related to early-onset substance abuse [64,65]. In order to examine these questions analyses of correlations were done in extended population in part II of our study.

Because of high drop-out rate in our study we could not use statistical methods to test causal relationships in part II. On the other hand, comparison of correlations from two testing points gives possibility to evaluate their reliability and consistency. In case of prescription opioid drug, drug screen do not show extra doses. Thus, it is possible that opioid doses are not fully accurate. While much is known about the pharmacological comparisons between different BZDs, the values of BZD equivalent doses are approximations instead of precise values [39]. Alcohol use estimates may not be fully accurate. These estimates were based on information given by the participants. Breath alcohol analyzer or other objective test was used only when considered necessary. Finally, our results do not imply that functional capacity of an opioid-dependent patient could be determined on the basis of his/her drug group. Instead, validation of cognitive test battery to a functional task, for instance driving a car, as well as exploration of non-cognitive factors is needed [66]. Only then individual assessment of the functional capacity can be made.

Conclusions

In conclusion, our results show again that in non-randomized clinical studies buprenorphine patients tend to perform better than methadone patients. The results do not support the idea that there would be substantial negative associations with medication variables and cognitive performance among patients in OST. A longitudinal study of opioid substitution treated patients who switch from buprenorphine to methadone or vice versa would be ideal in detecting cognitive effects of these drugs and the roles of other clinical variables.

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Authors' contributions

PR planned and performed cognitive testing and statistical analysis. He wrote the first version of the manuscript and prepared the final manuscript. HA conceived the idea of the study and advised in manuscript preparation. HK participated in the design of the study and in manuscript preparation. CF carried out psychiatric investigations. All authors prepared, read and accepted the final manuscript.

Competing interests

Pekka Rapeli has given a paid lecture in training organized by Schering-Plough, the former manufacturer of buprenorphine.

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IV

SUBSTANCE ABUSE TREATMENT, PREVENTION, AND POLICY

RESEARCH Open Access

Do drug treatment variables predict cognitive performance in multidrug-treated opioid-dependent patients? A regression analysis study

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Abstract

Background: Cognitive deficits and multiple psychoactive drug regimens are both common in patients treated for opioid-dependence. Therefore, we examined whether the cognitive performance of patients in opioid-substitution treatment (OST) is associated with their drug treatment variables.

Methods: Opioid-dependent patients (N = 104) who were treated either with buprenorphine or methadone (n = 52 in both groups) were given attention, working memory, verbal, and visual memory tests after they had been a minimum of six months in treatment. Group-wise results were analysed by analysis of variance. Predictors of cognitive performance were examined by hierarchical regression analysis.

Results: Buprenorphine-treated patients performed statistically significantly better in a simple reaction time test than methadone-treated ones. No other significant differences between groups in cognitive performance were found. In each OST drug group, approximately 10% of the attention performance could be predicted by drug treatment variables. Use of benzodiazepine medication predicted about 10% of performance variance in working memory. Treatment with more than one other psychoactive drug (than opioid or BZD) and frequent substance abuse during the past month predicted about 20% of verbal memory performance.

Conclusions: Although this study does not prove a causal relationship between multiple prescription drug use and poor cognitive functioning, the results are relevant for psychosocial recovery, vocational rehabilitation, and psychological treatment of OST patients. Especially for patients with BZD treatment, other treatment options should be actively sought.

Keywords: Opioid-dependence, Opioid agonist therapy, Pharmacotherapy, Psychotropic drugs, Neurocognitive performance, Neuropsychological testing

Background

Opioid abuse affects about 0.4% of the world's population in the age range of 15–64 years [1]. Many of them are dependent on opioids and fail to complete opioid withdrawal. Standard treatment for these individuals is opioid substitution treatment (OST), also known as opioid maintenance treatment. However, opioid-dependence is often complicated with psychiatric comorbidity. In epidemiological studies, the joint lifetime prevalence of opioid dependence and non-substance-use psychiatric disorders has ranged from almost 50% up to 90%, while the current prevalence of mood, anxiety, or personality disorders is also high [2-4]. Consequently, polypharmacy with psychoactive medication is a common practice in OST [5-9]. While several studies have examined the cognitive performance differences between buprenorphine- vs. methadone-treated opioid-dependent patients [10-14], few studies have examined the possible role of other psychoactive medications on the cognitive functioning of

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these patients. Thus, the results of current studies may not be fully appropriate for multidrug-treated patients. However, studies concentrating on this patient group would be important because opioid-dependent patients who are treated with multiple drugs tend to have lower quality of life than those who only use an opioid agonist drug [15]. A recent study concerning cannabis-dependent individuals found that even relatively subtle cognitive deficits that were seen in test performance can be verified by those who know the affected individual well [16]. Furthermore, at least for BZDs, even prescription drug use has been shown to be associated with serious health and safety risks [17,18]. Thus, if a drug treatment variable is negatively associated with cognitive performance in OST patients this may have practical relevance.

Earlier we have reported that opioid-dependent patients treated with buprenorphine/naloxone along with BZDs do not show attention deficit as measured by reaction time tasks, but their working memory and verbal memory performance is worse than that of healthy controls, at least for the first six months in treatment [19]. Patients treated with methadone along with BZDs show deficits in attention, working memory, and verbal memory. In our later study, OST drug group membership (buprenorphine vs. methadone) correlated significantly with attention performance and improvement in the Letter-Number Sequencing. Recent high-frequency substance abuse was associated with poor performance in working memory. Although the effects of the other two highest correlates were controlled for, many other variables could not be taken into account.

Our major aim in the current study was to examine the predictive power of drug treatment variables on specific cognitive performance measures in a naturalistic sample of multidrug-treated opioid-dependent patients. There is some evidence that short-term use of high dose methadone and BZD diazepam affects negatively on simple reaction times in opioid-dependent patients, but in buprenorphine patients only high diazepam dose affects negatively on reaction times [20,21]. Therefore, we hypothesized that in buprenorphine patients, BZD treatment (use vs. non-use or dose) but not buprenorphine treatment variables (dose) would be negatively associated with attention performance; while in methadone patients both methadone and BZD treatment variables would affect negatively on attention performance as measured by reaction times. There is preliminary evidence that buprenorphine may preserve working memory performance better than methadone [22,23]. Thus, we hypothesized that having buprenorphine as the OST drug would predict good working memory performance among opioid-dependent patients. It has been shown that long-term use of BZD drugs is associated with a wide range of cognitive deficits [24]. Sedative and anticholinergic effects have been reported for various psychiatric drugs [25,26]. Consequently, patients treated with several psychoactive drugs typically perform worse in cognitive tests than patients treated with a single drug [27,28]. We therefore hypothesized that being on a BZD drug or on a high number of prescribed psychoactive drugs (other than opioid or BZD) would predict poor cognitive performance in all measures among opioid-dependent patients treated with buprenorphine or methadone.

Methods

The study participants were volunteer opioid-dependent patients admitted for OST in the addiction clinics of the greater Helsinki or Tampere area. Further inclusion criteria were the following: aged 18–50 years, native Finnish speaker, opioid-dependence diagnosis, and minimum six months in OST with methadone, buprenorphine, or buprenorphine/naloxone. Exclusion criteria were the following: uncontrolled polysubstance abuse, acute alcohol abuse, or acute axis I psychiatric disorder (e.g. acute phase of major depression, suicidality, hypomania, mania, or psychosis), initiation of new psychoactive drugs within the past week, severe brain injury, chronic neurological disease, history of other than substance-induced psychoses, epileptic seizures, human immunodeficiency virus (HIV) infection, pregnancy, or primary cognitive deficit (estimated IQ less than 85). To ensure study eligibility, the clinical psychiatric interview SCID I was conducted for each participant, and diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) were applied [29]. Estimation of IQ was done by the neuropsychologist and it was based on the vocabulary subtest of the Wechsler Adult Intelligence Scale – Revised (WAIS-R) [30].

Each participant was screened for substance abuse by urine sample on the day of testing and at least once in the preceding month using the Nano5 test (from Ferle Produkter AB; Helsingborg, Sweden). Participants showing signs of current intoxication or binging on any substance of abuse and those having extra psychoactive drug doses within the last 24 h were all excluded. Also, those showing a positive drug screen for non-prescribed opioids or BZDs were excluded. The study included 104 OST patients, with 29% of them coming from the longitudinal sample used in the previous studies [5,13]. The rest were new long-term treated opioid-dependent patients. As shown in Table 1, buprenorphine-treated patients were statistically significantly younger than methadone ones, otherwise there were no significant demographic differences between buprenorphine- vs. methadone-treated patients.

The study was approved by both the independent Ethical Committee of the Hospital District of Helsinki and Uusimaa (permission 90/2001) and the A-Clinic

Table 1 Group demographics

	Buprenorphine (n = 52)	Methadone (n = 52)	Group comparisons[a]
Age (*M* ± *SD*)	31 ± 7	35 ± 8	BN < M, $p = .007$**
Sex, female/male	18/34	20/32	$p = .84$
	35%/65%	38%/62%	
Verbal intelligence[b] (*M* ± *SD*)	100 ± 10	101 ± 10	$p = .44$
Education, patients with primary education/any secondary education	35/17	34/18	$p = 1.00$
	67%/33%	65%/35%	
Substance abuse onset age, years (M ± SD)	16 ± 3	15 ± 2	$p = .17$
Patients with early onset of substance abuse[c]	15	23	$p = .31$
	29%	44%	
Duration of OST, months (*M* ± *SD*)	14 ± 7	17 ± 10	$p = .08$
Patients with more than 12 month in OST	30	33	$p = .69$
	57%	63%	
Number of cognitive testing			
patients with one testing	34 (65%)	40 (77%)	$p = .28$
patients with two or three testing	18 (35%)	12 (23%)	
Patients with high-frequency substance abuse in the previous month[d]	18	22	$p = .55$
	35%	42%	
Patients with positive drug screen at test	13	13	$p = 1.00$
	25%	25%	
Patients with the past month daily nicotine use	52	51%	$p = .50$
	100%	98%	

Note. *BN* = buprenorphine patients, *M* = methadone patients.
[a]Tested with *t*-test or Fisher's Exact Test.
[b]Estimation based on the vocabulary subtest of the Wechsler Adult Intelligence Scale – Revised (WAIS-R) [30].
[c]Considered as early up to 14 years of age.
[d]Considered as high when three or more days a week. Alcohol use was taken into account if it was at least mean weekly 16 portions (12 g) for females and 24 portions for males or binge drinking occurred on any day.
**$p < 0.01$.

Foundation. The study was conducted in accordance with the 1964 Declaration of Helsinki. All participants were able to read and understand the patient information sheet, and signed the informed consent form. The participants were free to discontinue participation in the study whenever they wanted. They were paid €20 if they attended all study visits.

Procedure

The patients were tested with cognitive measures between three to six hours after the administration of the opioid substitution drug. In the buprenorphine group, 54% of the patients were given buprenorphine/naloxone. Thus, they received a dose of naloxone in the ratio of 1:4 combined with their buprenorphine dose. When the tablet is given sublingually the absorption of naloxone is low and eliminates within the first hours [31]. It has been shown that naloxone has minimal, if any effect, on the bioavailability or pharmacokinetics of buprenorphine [32,33]. Therefore, we combined patients using either one of the buprenorphine compounds. Benzodiazepine doses of oxazepam were converted to a diazepam equivalent dose in the ratio of 3:1 [34]. Table 2 describes the psychoactive medications used by the participants in the 24-hour period before the testing. Medication doses were compared by using the Mann–Whitney *U* test. Medication frequencies were compared using the chi-square test.

Statistical analyses

Group-wise comparisons of cognitive performance between buprenorphine and methadone patients were done by an analysis of variance (ANOVA). As our verbal and visual memory tests lacked age-corrected norm values and there was a significant difference between the patient groups on age, an analysis of covariance (ANCOVA) was used when testing these parameters. In all group-wise comparisons, the normality assumptions of the cognitive variables were first examined by Shapiro-Wilk's test and the homogeneity of variance by the Levene's test. When appropriate, analyses of the main effects were interpreted using the Welch correction for heterogeneous variances. The data were also screened for outlying values. There was strong positive

Table 2 Medications given to patients within the last 24 h before testing in sample I

	Buprenorphine (n = 52)	Methadone (n = 52)	Group comparison *p*-values
Opioid agonist drug (*M* ± *SD*)	20 ± 6 mg	–	–
Buprenorphine (*M* ± *SD*)	–	113 ± 49 mg	
Patients using any psychoactive medication, other than opioid	42 (81%)	43 (83%)	$p = 1.00$
Patients using any BDZ drug	37 (71%)	38 (73%)	$p = 1.00$
diazepam	29 (56%)	24 (46%)	$p = .43$
oxazepam	8 (15%)	14 (27%)	$p = .15$
Benzodiazepine, diazepam equivalent dose (*M* ± *SD*)	22 ± 10 mg	21 ± 10 mg	$p = 0.77$
The number psychoactive drugs, other than opioid or BZD[a]			
(*M* ± *SD*)	1.2 ± 1.2	1.2 ± 1.2	$p = .81$
0, no. patients (%)	18 (35%)	19 (36%)	$p = 1.00$
1 no. patients (%)	19 (37%)	13 (25%)	$p = .29$
2 no. patients (%)	9 (17%)	13 (25%)	$p = .47$
3 no. patients (%)	2 (4%)	5 (10%)	$p = .44$
4 or more no. patients (%)	4 (7%)	2 (4%)	$p = .68$
Patients using psychoactive drug, other than opioid or BZD			
Any drug[b]	34 (65%)	33 (63%)	$p = 1.00$
Anticonvulsants	6 (12%)	5 (10%)	$p = 1.00$
Antidepressants	22 (42%)	13 (25%)	$p = .096$
Antihistamines	6 (12%)	10 (19%)	$p = .42$
Neuroleptics	7 (13%)	9 (17%)	$p = .79$
Non-Benzodiazepine hypnotics	16 (31%)	19 (37%)	$p = .68$
Non-opioid pain killers	4 (8%)	6 (12%)	$p = .74$

[a]Tested with *t*-test or Fisher's Exact Test.
[b]These included anticonvulsants (used as mood stabilizers), antidepressants, neuroleptics (used with anxiolytic indications), non-benzodiazepine hypnotics, and non-opioid pain killers.

correlation (.78) between the alertness task conditions; hence in order to reduce the number of dependent variables in the regression analysis, these measures were combined by standardizing the values and pooling them.

The assumption of a linear relationship between the dependent variable and predictors was checked by plotting the data (LOWESS curves) and by a lack of fit test. In order to ascertain the linearity between the dependent variable and predictors, many of the predictors were transformed into dichotomous ordinal variables. Buprenorphine doses up to 16 mg were considered as low dose and higher values as high. This was done because the dose-dependence of buprenorphine pharmacodynamics is not linear [33]. BZD doses were considered as low if lower than 20 mg and higher if 20 mg or above. The number of prescribed psychoactive drugs, other than OST or BZD drug, was considered as low up to one drug, and high if two or more other drugs. Duration of OST was considered as short if between six and twelve months, and long if above this. Substance abuse in the previous month was dichotomized as high vs. low frequency of abuse. Abstinence or substance abuse up to two days a week was considered as low-frequency substance abuse, and values above this as high-frequency substance abuse. This was based on findings showing that a mean three days of substance abuse a week is associated with a worsening of psychosocial and cognitive problems [35-37]. Substance abuse age of onset was considered as early onset up to 14 years of age, and as late onset age if 15 years of age or higher. This was based on findings showing that substance abuse onset before 15 years is especially hazardous to psychosocial and cognitive development [38]. Education was considered as low if no other than primary education had been completed, and as high if any secondary education had been completed. Homogeneity of error variance (homoscedasticity) was confirmed graphically by plotting the standardized residual against the predicted values. Independence of errors was checked using the Durbin-Watson test. Normality of residuals was checked by normality plots and using the Shapiro-Wilk's test. Because our main interest was to examine drug treatment variables

as predictors of cognitive performance, we employed multiple sequential/hierarchical linear regression analysis. First, the full model was examined as follows. Demographic variables, substance abuse variables, and the number of tests (one vs. more than one), were first entered into the model as control variables. Demographic variables included sex, level of education, and age if the test values were not age-corrected initially. Substance abuse variables included age of onset of substance abuse and frequency of substance abuse in the past month. Control variables were retained in the subsequent reduced model only if they gave a statistically significant ($p < 0.05$) contribution to the full model as a block or individually. The number of tests was also checked for the direction of association, with a positive association indicating a practice effect of repeated testing. Drug treatment variables included opioid drug type (buprenorphine vs. methadone), BZD treatment (yes vs. no), the number of psychoactive drugs (other than opioid or BZD drugs), and duration of OST. All drug treatment variables were entered sequentially into the reduced model. Unless otherwise stated, explained variance (R^2) is reported as an adjusted value, and the regression coefficient as a standardized value (beta). All statistical analyses were done by SPSS statistical software, version 20.0, with the exception of effect size calculations, which were done by an effect size calculator devised by Durham University, UK [39]. Effect size estimations were corrected by Hedge's correction for sample size bias.

Cognitive tests

Attention was assessed by two tasks from the Test for Attentional Performance (TAP) [40]. In the Alertness task, the participant is instructed to respond to visual stimuli by pressing a response key as quickly as possible. The stimuli are presented without and with an auditory warning signal. The 'without' condition is a simple reaction time task reflecting tonic alertness. The 'with-auditory-warning-signal' condition reflects both tonic and phasic alertness. Age corrected values were used in analyzing reaction time results.

Working memory was assessed by the Letter-Number Sequencing task from the Wechsler Memory Scale-III. In this test the participant is instructed to repeat letters and numbers in specific order [41]. Age corrected values were used.

Verbal memory was assessed by the Logical Memory from the Wechsler Memory Scale-III [41]. However, only immediate recall was tested and one story used. For those participants tested repeatedly a different story was given than previously. **Visual memory** was assessed by the Benton Visual Retention Test [42].

Results

Group comparisons

Buprenorphine-treated patients showed statistically significantly faster simple reaction times in comparison to methadone-treated ones (the 'without warning signal' condition of the alertness test; ($F(1, 100) = 7.54$, $p = 0.028$). No other significant differences emerged. (All test results shown as an Additional file 1).

Predictors of attention performance

When control variables were first entered into the full model they could predict only 1.3% of the performance variance (2.8% in the sample) of the combined alertness measure. In contrast, drug treatment variables as a block could predict an additional 6.3% (9.7% in the sample). The increment of drug treatment variables as a block significantly improved the model ($F(4, 93) = 2.59$, $p = 0.041$), but the full model remained statistically non-significant ($p = 0.12$). None of the individual predictors turned out to be significant in the full model. When the reduced model including only the drug treatment variables was tested, the OST drug group turned out to be the only significant predictor in the model (beta = .20, $t(97) = 2.09$, $p = 0.040$). The reduced model was significant (R^2 (adjusted) = .056, $F(4, 97) = 2.51$, $p = 0.047$).

In order to examine the hypothesis that reaction times are predicted by different drug treatment variables in buprenorphine- vs. methadone-treated patients, the reduced model including drug treatment variables was used. As shown in Table 3, in the buprenorphine group, being on BZD drug treatment was the only significant predictor in the model. In the methadone group, the high number of other psychoactive drugs was the best and only significant predictor in the model. Adding methadone dose to the model made it significant, although the negative association of methadone dose was not independently significant.

Predictors of working memory performance

The full model including control variables predicted 8.2% of the variance (16.4% in the sample). The model as a whole was significant ($F(8, 93) = 2.28$, $p = 0.028$). None of the control variables as a block or individually gave a significant contribution to the model. Consequently the control variables predicted a very low proportion of the variance (−2.5%). In contrast, the drug treatment variables as a block significantly improved the full model ($F(4, 93) = 4.13$, $p = 0.004$) predicting 11.7% of the variance above the control variables. Therefore, the control variables were removed from the model. As shown in Table 4, treatment with a BZD drug was negatively associated with working memory performance while being more than one year in OST was positively

Table 3 Hierarchical regression results for combined reaction times in the Alertness test by opioid drug group

Buprenorphine-treated patients (n = 51)				
Predictors in the reduced model	**Step1 Beta (*t*-test)[a,b]**	**Step2 Beta (*t*-test)**	**Step3 Beta (*t*-test)**	**Step4 Beta (*t*-test)**
Drug treatment variables				
BZD treatment (yes vs. no)	.34	.36	.37	.38
	$t(49) = 2.51$	$t(48) = 2.64$	$t(47) = 2.60$	$t(46) = 2.60$
	$p = 0.015$*	$p = 0.011$*	$p = 0.012$*	$p = 0.013$*
Buprenorphine dose (high vs. low)[c]		-.16	-.17	-.19
The number of psychoactive drugs, other than opioid or BZD (high vs. low)[d]			.05	.05
Duration of OST (long vs. short)[e]				-.05
R^2 (adjusted)	.096	.103	.084	.069
Model (ANOVA)[a]	$F(1,49) = 6.29$	$F(2,48) = 3.88$	$F(3,47) = 2.58$	$p = 0.12$
	$p = 0.015$*	$p = 0.027$*	$p = 0.065$#	
Change (ANOVA)[a]		$p = 0.24$	$p = 0.76$	$p = 0.71$
Methadone-treated patients (n = 51)				
Predictors in the reduced model	**Step1 Beta (*t*-test)[a,b]**	**Step2 Beta (*t*-test)**	**Step3[f] Beta (*t*-test)**	
Drug treatment variables				
The number of psychoactive drugs, other than opioid or BZD (high vs. low)	.27 #	.30 *	.31 *	
	$t(49) = 1.92$	$t(48) = 2.21$	$t(47) = 2.09$	
	$p = 0.060$#	$p = 0.032$*	$p = 0.042$*	
Methadone dose BZD treatment (yes vs. no)		.26 #	.26 #	
		$t(48) = 1.88$	$t(47) = 1.86$	
		$p = 0.066$#	$p = 0.069$#	
			-.02	
R^2 (adjusted)	.051	.098	.073	
Model (ANOVA)[a]	$F(1,49) = 3.71$	$F(2,48) = 3.72$	$F(3,47) = 2.43$	
	$p = 0.060$#	$p = 0.032$*	$p = 0.077$ #	
Change (ANOVA)[a]		0.066 #	0.90	

[a]Only *p*-value shown when $p \geq 0.10$.
[b]Signs of beta values are reversed so that positive values refer to slowing of reaction times.
[c]Considered as low up to 16 mg.
[d]Considered as low up to one drug.
[e]Considered as short when between six and twelve months.
[f]Step 4 is not shown because 'the duration of OST' variable correlated strongly (.61) with methadone dose producing a multicollinearity condition, and on a theoretical basis it was excluded from the analyses.
*$p < 0.05$. #$p < 0.10$.

associated with working memory performance. The BZD drug treatment effect was significant but the duration of the treatment effect only approached significance. Finally, the predictive power of the drug treatment variables including the BZD variables (type or dose) on working memory performance was tested using the group including only patients with BZD in their drug regimen (n = 75). However, this model had very low predictive power on working memory (– 0.6%) and was statistically non-significant ($p = 0.48$).

Predictors of memory performance

When repeated testing was entered as the first variable of the full model, it was significantly associated with verbal memory performance (beta = .36, t (93) = 3.49, $p = 0.0007$). Therefore, in order to eliminate the significant effect of repeated testing from the model, a model including only patients tested once was formed (n = 74). Because demographic variables had minimal effect in the initial full model (data not shown), this block was dropped from the next model. Thus, the model included substance abuse variables and drug treatment variables. Because age of onset of substance abuse (early vs. late) showed a non-significant effect in the model, it was dropped from the final model. As shown in Table 5, high-frequency substance abuse and a high number of other psychoactive drugs (other than opioid or BZD drug) were the only individual

Table 4 Hierarchical regression results for working memory (n = 102)

Predictors in the reduced model	Step 1 Beta (*t*-test)[a]	Step 2 Beta (*t*-test)	Step 3 Beta (*t*-test)	Step 4 Beta (*t*-test)
Drug treatment variables				
BZD treatment (yes vs. no)	-.34	-.30	-.28	-.28
	$t(100) = 3.56$	$t(99) = 3.14$	. $t(98) = 2.83$	$t(97) = 2.81$
	$p = 0.0006$ ***	$p = 0.002$ **	$p = 0.006$ *	$p = 0.006$ *
Duration of OST (long vs. short)[b]		.17	.17	.16
		$t(99) = 1.81$	$t(98) = 1.72$	$t(97) = 1.69$
		$p = 0.074$ #	$p = 0.088$ #	$p = 0.094$ #
The number of psychoactive drugs, other than opioid or BZD (high vs. low)[c]			-.06	.07
OST drug type (buprenorphine vs. methadone)				-.03
R^2 (adjusted)	.104	.124	.119	.100
Model (ANOVA)[a]	$F(1,100) = 12.68$	$F(2,99) = 8.12$	$F(3,98) = 5.52$	$F(4,97) = 4.12$
	$p = 0.0006$ ***	p =0.0006 ***	$p = 0.002$ **	$p = 0.004$ **
Change (ANOVA)[a]		F (1,99) = 3.26		
		$p = 0.074$#	$p = 0.52$	$p = 0.76$

[a]Only *p*-value shown when $p \geq 0.10$.
[b]Considered as short when between six and twelve months.
[c]Considered as low up to one drug.
***$p < 0.00$. **$p < 0.01$. *$p < 0.05$. #$p < 0.10$.

significant predictors of verbal memory performance, both of which were associated negatively with verbal memory performance.

The full or reduced model predicting visual memory showed only low and non-significant values for all predictors. Thus, the predictive power of the models remained non-significant (p = 0.33 and p = 0.85, respectively).

Discussion

The aim of the study was to examine the predictive power of drug treatment variables on specific cognitive

Table 5 Hierarchical regression results for verbal memory (n = 74)

Predictors in the reduced model	Step 1 Beta (*t*-test)[a]	Step 2 Beta (*t*-test)	Step 3 Beta (*t*-test)	Step 4 Beta (*t*-test)	Step 5 Beta (*t*-test)
Substance abuse variable					
Frequency of the previous month substance abuse (high vs. low)[b]	-.35	-.34 **	-.36 **	-.35 **	-.36 **
	$t(72) = 3.17$	$t(71) = 3.24$	$t(70) = 3.34$	$t(69) = 3.22$	$t(68) = 3.15$
	$p = 0.002$**	$p = 0.002$**	$p = 0.0013$**	$p = 0.002$**	$p = 0.002$**
Drug treatment variables The number of psychoactive drugs, other than opioid or BZD (high vs. low)[c]		-.32	-.35	-.35	-.35 **
		$t(71) = 3.06$	$t(70) = 3.15$	$t(69) = 3.13$	$t68) = 2.99$
		$p = 0.003$**	$p = 0.002$**	$p = 0.003$**	$p = 0.004$**
BZD treatment (yes vs. no)			.10	.10	10
OST drug type (buprenorphine vs. methadone)				-.03	-.03
Duration of OST (long vs. short)[d]					.01
R^2 (adjusted)	.110	.203	.199	.189	.177
Model (ANOVA)	$F(1,72) = 10.02$	$F(2,71) = 10.28$	$F(3,70) = 7.06$	$F(4,69) = 5.24$	$F(5,68) = 4.14$
	$p = 0.002$**	$p = 0.0001$***	$p = 0.0003$ ***	p =0.001***	p =0.002 *
Change (ANOVA)[a]		$F(1,71) = 9.37$			
		$p = 0.003$ **	$p = 0.40$	$p = 0.79$	$p = 0.91$

[a]Only *p*-value shown when $p \geq 0.10$.
[b]Considered as high when three or more days a week. Alcohol use was taken into account if it was at least mean weekly 16 portions (12 g) for females and 24 portions for males or binge drinking occurred on any day.
[c]Considered as low up to one drug.
[d]Considered as short when between six and twelve months.
***p <0.001. **$p < 0.01$. *$p < 0.05$. #$p < 0.10$.

performance measures in multidrug-treated opioid-dependent patients. Also, we were interested in finding out which of the possible significant associations turn out as hypothesized. All patients had been in OST for at least six months, and there were no major changes in their drug regimen within the last week prior to the study. Being on methadone-treatment predicted a rather low, though statistically significant proportion (about 5%) of attention performance as measured by combined reaction times in alertness tests. When opioid drug groups were analyzed separately about 10% of attention performance variance could be explained in both groups, but the predictors were different. Being on BZD drug treatment predicted about 10% of working memory performance. Having more than one other psychoactive drug (than an opioid or BZD drug) was negatively associated with verbal memory performance. Also, recent high-frequency substance abuse was negatively associated with verbal memory performance. Together these factors predicted about 20% of verbal memory performance variance.

Drug treatment variables as predictors of attention performance

In buprenorphine patients co-treatment with a BZD drug was negatively associated with attention performance, but buprenorphine dose had no significant effect. This is in line with an experimental study showing that BZD diazepam in combination with buprenorphine affects negatively on reaction time, and the effect is independent of the buprenorphine dose administered [21]. In methadone patients the interpretation is more complex. The highest predictor of slower reaction time in methadone patients was treatment with more than one other psychoactive drug than methadone or BZD (beta .31). As hypothesized, there was a positive slope between methadone dose and the combined reaction time (.26) among methadone-treated patients. It is known that rapid elevation of methadone dose reduces peripheral blood oxygen saturation even among patients highly tolerant to methadone [43]. Oxygen saturation reduction has been associated with specific reaction time deficit with relative sparing of other cognitive functions [44]. Specific to methadone it has been shown by Lintzeris et al. that when a higher than normal (150%) dose of methadone is given to methadone-treated opioid-dependent patients, reductions in oxygen saturation and reaction time can be detected [21]. In sum, our results give support to our hypotheses that among buprenorphine patients, co-treatment with a BZD drug is associated negatively with attention performance. Methadone treatment, especially when done together with other psychoactive drugs, can be negatively associated with attention performance. Of note here is the timing of the possible opioid agonist effects: the drug plasma concentration peaks between 0.5–4 h after the dose for buprenorphine and 2–6 h for methadone [31,45-47].

Drug treatment variables as predictors of working memory performance

Our hypothesis of an advantage for buprenorphine in working performance was not supported by the analyses. Instead, treatment with a BZD drug was negatively associated with working memory performance (Table 4). When we analyzed the possible associations of BZD drug type or dose, no significant associations were found, and the model had very low predictive power. Thus, we could not link the working performance with BZD parameters. According to the meta-analysis, BZDs in general have small or medium sized negative effects on working memory functioning as measured by Cohen's d [24]. Although diazepam and oxazepam are probably the most widely used BZDs, few studies have examined their effects on a complex working memory measure like Letter-Number Sequencing. One study found that 5 mg of diazepam did not affect performance in the complex working memory measure, the n-back task, although it reduced frontal brain activation [48]. It is known that high BZD doses have a general sedative effect and thus have the potential to affect cognitive function, but the development of tolerance may outweigh these effects [49]. Notably, we observed that more than one year in OST was positively, although weakly associated with working memory performance (beta = .16). This observation is in line with our previous observation that working memory improves in buprenorphine patients between six and twelve months into OST [22].

Drug treatment variables as predictors of memory performance

The high number of other psychoactive drugs (than opioid and BZD) and recent high- frequency substance abuse together predicted 20% of immediate verbal memory performance variance as measured by a story recall task. There is some evidence that verbal memory is more sensitive than other cognitive domains to the negative effects of multiple psychoactive drugs. This observation, however, may be specific to elderly patients and anticholinergic drugs [50]. Even less is known about the possible memory effects of psychoactive drug burden (as measured by the number of drugs) in combination with opioid agonists. In our recent longitudinal study, both buprenorphine- and methadone-treated patients lagged behind healthy controls in verbal memory performance as measured by story recall [22]. Surprisingly, when we extended the sample in the second part of our earlier study, the difference to healthy controls disappeared. Also, the correlation between the number of psychoactive

drugs and verbal memory was positive, not negative, as in the current study. In sum, although our finding of a negative verbal memory effect of more than one psychoactive drug is in concert with our hypothesis, the specificity of this finding cannot be shown with our data. The finding that recent high-frequency substance abuse predicted poor verbal memory is in accordance with studies showing that recent frequent substance abuse impairs verbal memory performance [51,52].

Implications

The results of this study suggest that cognitive impairment in opioid-dependent patients is more common when the patient is prescribed additional psychoactive drugs. It is also likely, although not confirmed by our study, that at least long-term BZD medication independently predicts cognitive impairment among multidrug-treated opioid-dependent patients. Fortunately, during OST many patients become more open to discussion about medication side-effects. Patients may agree that slower reaction times, associated in our study with co-medication differently in buprenorphine- vs. methadone-treated patients, can be disadvantageous in vehicle driving and many sport activities. For instance there is evidence OST patients being disproportionately involved in road traffic crashes accidents [53,54]. Working memory deficits, associated in our study with BZD co-medication, are known to impair reading comprehension, learning, and reasoning [55]. BZDs interfere with affective learning which is important in therapy [56]. Thus, combining BZD medication with psychological treatment may actually be detrimental to the long-term outcome of the treatment. The finding that one fifth of story recall performance variance was explained by two variables (high number of psychoactive drugs other than opioid or BZD drug; and high-frequency substance abuse in the previous month) is also relevant information. The optimal functioning of verbal memory is a useful resource in everyday life, work, or education [57]. All these facts may give the patient and prescriber a good reason to consider non-pharmacological treatment choices in place of polypharmacy. In some cases a realistic choice, for the time being, is to change cognitively harmful drugs like BZDs and tricyclic antidepressants for ones that are less harmful to cognition [58,59].

Limitations

The distribution of the drug treatment variables, except opioid drug groups, was unplanned, and turned out to be highly skewed for some variables. As dichotomizations were used for these variables this reduces the statistical power of the analyses [60]. Therefore our findings about drug treatment effects are preliminary. Also, data about opioid and BZD doses may not be fully accurate, because drug screens do not detect extra doses of prescription drugs. Thus, our results do not confirm a causal association between drug treatment variables and cognitive performance. Patients with a higher number of prescribed drugs may have premorbid cognitive deficits that explain the associations found. On the other hand, longitudinal studies of patient groups other than OST patients have shown that discontinuation of a BZD drug regimen is followed by slow improvement in cognitive function and quality of life but no negative effects on sleep [61-64]. Our results support the idea that this could also be possible in opioid-dependent patients as well. There has been progress in the classification of psychoactive drugs by their interaction potential with buprenorphine or methadone [5,58] Alternatively, the recently formed drug burden index could be a promising tool for reducing the number of drug treatment variables in clinical studies [65]. These tools were found, however, to be unsuitable for our purposes. Negative cognitive effects of psychoactive drugs usually diminish during long-term use, and there may be differences in this between attention and memory effects [22,59,66,67]. If we had had data on length of drug use this would have been an important variable in analysing drug treatment effects. Our regression analyses were restricted only to the main effects of variables. Perhaps interactions between the variables could have explained more of the variation in cognitive performance. This was not considered appropriate given the high number of variables. Repeated testing of a third of patients is a potential confounder in the results, although after an interval of six months between testing times, as was the case in our study, the effects of repeated testing are trivial or non-existent for most measures [68,69]. In our study the verbal memory test, the Logical Memory test, was an exception, and this was taken into account in the analyses. Inclusion of psychiatric control variables, as used by Loeber et al. or Prosser et al. when studying cognitive performance in opioid-dependent patients, would probably have raised the predictive power of the analyses [70,71], and consequently the specificity of the findings.

Conclusions

While the causal direction of effects cannot be assured with these data, the results agree with the idea that specific prescription drug treatment variables may predict poor cognitive performance in OST patients. Improvement in quality of life, successful psychological treatment, and work or education participation are common goals in OST programs, each of which are associated with good cognitive functioning. Our results suggest that psychoactive polypharmacy may be contradictory to these goals. This should give treatment practitioners and

policy makers one more reason to monitor the rationality of polypharmacy in OST.

Additional file

Additional file 1: Group comparisons of cognitive performances.

Competing interests

Pekka Rapeli has given a paid lecture in training organized by Schering-Plough, the former manufacturer of buprenorphine.

Authors' contributions

PR planned and performed the cognitive testing and statistical analyses. He wrote the first version of the manuscript and prepared the final manuscript. HA conceived the idea of the study and advised in manuscript preparation. HK participated in the design of the study and in manuscript preparation. CF carried out psychiatric investigations. All authors have read and accepted the final manuscript.

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Research Article Open Access

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

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Abstract

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

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

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

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

Keywords: Opioid-substitution therapy; Psychoactive drugs; Tranquilizers; Drug-related driving impairment; Traffic safety

Abbreviations: BMI: Body Mass Index; BZD: Benzodiazepine; GABA: Gamma-Aminobutyric Acid; MMT: Methadone Maintenance Treatment; OMT: Opioid Maintenance Treatment

Introduction

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

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

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

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

Material and methods

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

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

Research ethics

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

Procedure

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

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

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

[1]Tested by Fisher's Exact Test
[2]BZD equivalent doses [28].
[3]These included anticonvulsants and lithium.

Table 1: Group comparisons on demographic and treatment variables.

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

On-road driving assessment

On-road driving assessment was done by the same licensed driving instructor for each participant. The one-hour driving test using a car took place in city traffic during normal day- time instead of rush hours. The test included various car driving tasks typically done in driving evaluations devised for neurological patients [28]. This evaluation was meant for driving a car for non-professional purposes [29]. The driving instructor completed two formal evaluation sheets. Driving errors were classified as nonhazardous vs. hazardous errors. An error was classified as a hazardous one, if it exposed anyone on the road to a potential risk. The marking of the errors was done according to the manual developed by the Finnish Vehicle Administration [30]. In addition driving instructor gave a performance score for 11 driving domains. The scoring was done as follows: 5=definitely strong, 4=strong, 3=either strong or weak, 2=weak and 1=definitely weak [27]. Driving domains which were evaluated included the following: awareness of other vehicles and road users, appropriate adjustment of speed, signaling one's intentions, predictability, correctness of driving lines, understanding correct driving order, e.g., at intersections, junctions, roundabouts, ability to follow traffic lights and traffic signs, distance to other vehicles and obstacles , vehicle handling and vehicle control, independence and ability to map out one's driving, ability to anticipate events in traffic, and concentration on driving. Finally, an overall safety assessment was done using four levels [31]. The highest level of safety was 'safe driver in all conditions' meaning that she/he was considered as being a safe driver in all places and any road conditions. The next best level was 'safe driver in normal conditions' meaning that she/he was considered as a safe driver in all places but good road conditions were essential for safe driving. Third level was 'safe driver only in the best conditions' meaning that she/he was considered as a safe drive only in familiar places and in good road conditions. The last level was 'unsafe driver' meaning that driving was considered unsafe in all places and road conditions. According to the Finnish driving regulations drivers belonging to the classes 'safe drivers in all conditions' or 'in normal conditions' are considered fit to drive a car.

Medical examinations

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

Driving-related cognitive tests

Cognitive examinations done by a neuropsychologist included the Determination, Peripheral Perception, Signal Detection, Stroop Interference, and Tachistoscopic Traffic Perception tests from the computer-aided Vienna Test System [32-36]. The purpose of the Determination test is to measure 'Resilience of Attention and reaction speed under conditions of sensory stress'. The examinee is instructed to identify color or sound stimuli and react to them pressing correspondent response button using a response panel. Adaptive version S1 was used. The number of correct reactions was chosen as the variable of interest as it has been shown to have specific predictive value for driving ability [37].

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

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

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

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

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

Statistical analyses

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

Results

Sample characteristics

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

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

[1]Tested by Fisher's Exact Test
[2]n=9

Table 2: Group comparisons on driving variables.

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

On-road driving

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

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

Medical examinations and cognitive-driving related tests

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

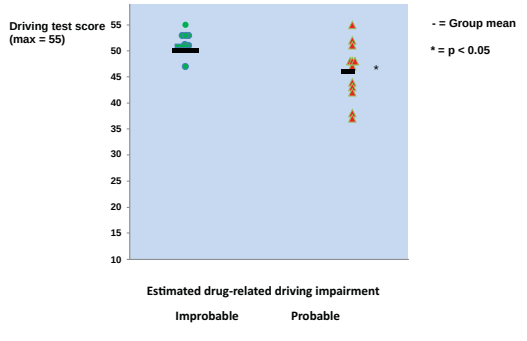

Figure 1: The relationship between medication groups and on-road driving test score.

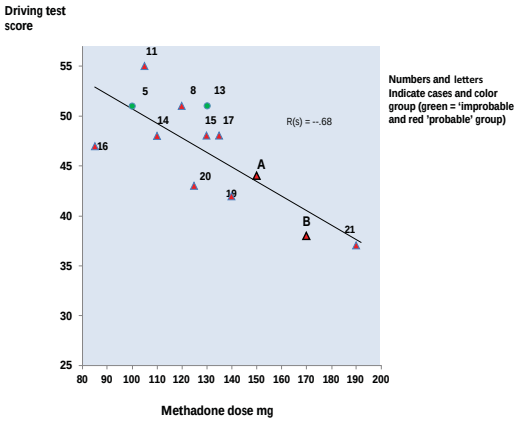

Figure 2: Correlation between methadone dose and driving test score.

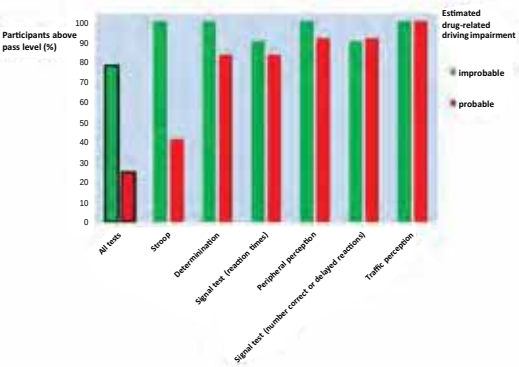

Figure 3: Percentage of passed driving-related cognitive tests by group.

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

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

Case A: When A came to driving test he was 47 years old. He had been in methadone maintenance treatment for 4 years, current dose 150 mg. In addition he was prescribed BZD oxazepam 90 mg a day (30 mg every 8 h) as an anxiolytic. In the evening he took a third prescribed medicine, tricyclic antidepressant doxepine 100 mg, as a somnolent and antidepressant. His depression, however, was considered as being in partial remission. A had obtained a driver's license 20 years ago, and he said that he had driven since then 'a huge amount of kilometers both home and abroad', all non-professional driving. In a medical inspection he was considered fit to drive. During the four years in MMT, A had gained 35 kg weight. His BMI index was 36.2, which is considered as obese according to the World Health Organization classification, but this was not considered as health problem affecting driving fitness.

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

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

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

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

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

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

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

Discussion

This study was planned to examine driving fitness of stable OMT patients. All included patients had been at least one year in treatment and were tested negative in drug screens for substance abuse at least for one month. As expected more than half of the patients in the sample were currently using some other psychoactive prescription drug too. The main finding in our case-series of 22 OMT patients is that all expect one of the patients was found fit to drive according to an on-road driving test which followed official guidelines used for all drivers in Finland. In order to assess the association between co-medications and driving fitness, the patients were divided into two groups according to their probability of drug-related driving impairment. The analyses showed that the patients with 'probable drug-related driving impairment' scored lower than other patients in the sum of on-road driving tests and in two out of six driving-related cognitive tests.

Patients with improbable drug-related driving impairment

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

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

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

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

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

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

Patients with probable drug-related driving impairment

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

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

The European research-based recommendation of driving assessment for patients treated with drugs states that each OMT patient's driving fitness should be individually evaluated, and in cases of other prescription drugs, tests of cognitive performance are recommended, especially for elder patients [51]. Although significant information about driving fitness of the patient can be inferred from her/his medication and cognitive performance, also other information needs to be taken into account. To illustrate this detailed information of two cases were reported in the results section. The first case (middle-aged patient A) has methadone 150 mg, oxazepam 90 mg, and doxepin 100 mg in his drug regimen. The driving impairing effect of each of these drugs is well-known for drug naïve individuals [52,53]. Yet, individual variation of drug effects is large and most of the patients using these drugs will eventually become tolerant for the negative effects on driving [54]. In the case of A it can be noted that his doses for all drugs were relatively high, and it is possible that full tolerance for the day-time sedative effects of these may not have developed. In accordance with this idea two studies have reported that higher methadone dose is associated with longer reaction times in tasks measuring alertness or vigilance [55,56]. Furthermore, tricyclic antidepressant doxepin has potential for long-term negative effects on driving-related cognitive testing [50]. In medical examination of A nothing was found that would be make him unfit to drive. A, however, belongs to the minority of methadone-treated patients that had gained a lot of weight during the MMT. There is no consensus if this is a pharmacological side-effect of methadone or solely related to life-style changes among patients [57,58]. Case A complained daytime drowsiness as well, which is a common side effect of full opioid agonists [59]. It is known that methadone shows large interindividual variability both in pharmacokinetics and pharmacodynamics [60-62]. Thus, it is possible that A gets more side-effects from his drug regimen than OMT patients in general. In spite of this, A was considered fit to drive. It is likely that his long driving experience gave him some advantage in on-road assessment. Anyhow, his case illustrates that a methadone patient who is treated with three psychotropic medications can be considered fit to drive a car for non-professional purposes.

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

Strengths and limitations of the current study

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

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

Conclusions

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

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