Aus der Klinik und Poliklinik für Psychiatrie und Psychotherapie der Ludwig-Maximilians-Universität München

Direktor: Prof. Dr. med. Peter J. Falkai

„Safety and Effectiveness of Buprenorphine-Naloxone Sublingual Tablet in the Treatment of Opioid Use Disorder„

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aus Reichenbach/Vogtl.

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Tag der mündlichen Prüfung:	22. Januar 2019

Eidesstattliche Versicherung

Apelt, Sabine M.

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Thema

„Safety and Effectiveness of Buprenorphine-Naloxone Sublingual Tablet in the Treatment of Opioid Use Disorder„

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München, den 20. Juni 2018 Sabine M. Apelt

Vorwort

Seit 1987 wurde primär Methadon in der Therapie opioidabhängiger Patienten in Deutschland eingesetzt. Im Jahr 2002 kam Buprenophin als sublinguale Tablette für die Therapie der Opioidabhängigkeit hinzu und wurde in zahlreichen Studien als sicher und wirksam befunden. Aufgrund des zunehmenden nicht verschreibungsgemäßen Gebrauchs von Buprenorphin, wurde das Kombinationspräparat Buprenorphin-Naloxon entwickelt und 2007 in Deutschland ebenfalls als sublinguale Tablette zugelassen. Nach der Zulassung des Medikamentes mit dem Handelsnamen Suboxone® wurde eine nicht-interventionelle Sicherheitsstudie durchgeführt. Ziel dieser Studie war die Erforschung der Haltequote, der Umstände der Umstellung auf Buprenorphin-Naloxon von einem anderen Substitutionsmittel, der Akzeptanz und Toleranz sowie der Sicherheit des neu zugelassenen Medikamentes an einem breiten Patientenkollektiv in der Routineversorgung in Deutschland.

Die drei für die vorliegende kumulative Dissertation verwendeten wissenschaftlichen Artikel, welche 2013 und 2014 in Peer-Review Fachzeitschriften veröffentlicht wurden, basieren auf den Daten dieser nicht-interventionellen Sicherheitsstudie, die von mir, Sabine M. Apelt, als freie wissenschaftliche Mitarbeiterin konzipiert, durchgeführt und ausgewertet wurde. Die Studie wurde von einem externen wissenschaftlichen Beratergremium unterstützt.

Alle statistischen Analysen wurden von mir, Sabine M. Apelt, mit dem statistischen Programm STATA[1] durchgeführt. Prof. Michael Soyka, Prof. Markus Backmund, Prof. Norbert Scherbaum und Dr. Jörg Gölz waren Teil des wissenschaftlichen Beratergremiums und unterstützten mich bei der Erstellung der folgenden beiden wissenschaftlichen Artikel durch Literaturbesprechung, Ideensammlung, Datenanalysen und Revisionen der Artikelentwürfe:

- S. M. Apelt, N. Scherbaum, J. Gölz, M. Backmund & M. Soyka (2013). Safety, Effectiveness and Tolerance of Buprenorphine-Naloxone in the Treatment of Opioid Dependence: Results from a Nationwide Non-Interventional Study in Routine Care. Pharmacopsychiatry; 46: 94–107
- S. M. Apelt, N. Scherbaum & M. Soyka (2014). Induction and switch to buprenorphine-naloxone in opioid dependence treatment: Predictive value of the first four weeks. Heroin Addict Relat Clin Probl; 16(3): 87-98

Für den dritten in dieser kumulativen Dissertation verwendeten Artikel, unterstützte ich die Autoren mit der Erstellung statistischer Analysen, Literaturbesprechung und Revisionen des Artikelentwurfs:

- M. Soyka, M. Backmund, P. Schmidt & S. Apelt (2014). Buprenorphine-Naloxone Treatment in Opioid Dependence and Risk of Liver Enzyme Elevation: Results from a 12-Month Observational Study. The American Journal on Addictions, 23: 563–569

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[1] Stata Corp. Stata Statistical Software: Release 9. College Station, TX: StataCorp LP; 2005

Table of contents

A. List of abbreviation

ADHD	Attention deficit hyperactivity disorder
ALT	Alanine transaminase
AMP	Adenosine monophosphate
AST	Aspartate transaminase
DAM	Diacetylmorphine
DHC	Dihydrocodeine
EMA	European Medicine Agency
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICD-10	International classification of diseases, 10th edition
IV	Intravenous
MAH	Market authorization holder
6-MAM	6-Monoacetylmorphine
PASS	Post-authorization safety study
OUD	Opioid use disorder
PTSD	Post-traumatic stress disorder
RKI	Robert Koch Institute
RMP	Risk management plan
WHO	World Health Organization

B. List of publications

B.1. In preparation

Apelt, S.M., He, J., Auriacombe, M., Scherbaum, N. & Mankabady, B. (subm, 2018) Analyses of All-Cause Mortality with Buprenorphine/Naloxone in the United Kingdom. Full paper for Pharmacoepidemiology & Drug Safety

Apelt, S.M., Bachellier, J., Polomeni, P., Farah, M. & Mankabady, B. (subm, 2018) A Retrospective Observational Survey of Buprenorphine/Naloxone Use in France. Full paper for Journal of Substance Abuse Treatment

B.2. Original publications

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Apelt, S.M., Bernert, B., Siegert, J., Guenther, A., Bühringer, G., Soyka, M. & Wittchen, H.-U. (2006). How effective is substitution treatment in reducing high risk behavior of opiate addicts in routine care? A 12-month prospective-longitudinal study in patients treated with methadone and buprenorphine. Poster auf der NIDA, Scottsdale, Arizona/USA, 16.-19.06.2006

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C. Aims and outline of the thesis

This thesis aims to gain a better understanding of the clinical conditions and safety of induction and switch to buprenorphine-naloxone in opioid dependent patients from another medication, such as buprenorphine, methadone and levo-methadone, or active street heroin use. To answer the aims of this thesis, data from the nationwide, non-interventional, observational post-authorization safety study (PASS) with buprenorphine-naloxone in routine care with a 12-month observation period was used (described in chapter E.3.).

The aims of the thesis were:

- to evaluate the results from the PASS in patients pre-treated with buprenorphine, methadone, levo-methadone or another maintenance drug after 12 months of treatment with buprenorphine-naloxone under real-life conditions
- to describe retention rates and safety of patients in treatment with buprenorphine-naloxone in routine care
- to assess the circumstances of the switch to buprenorphine-naloxone such as dosing, mode of prescription and subjective effects
- to examine effectiveness, tolerance and acceptance of opioid dependence treatment with buprenorphine-naloxone
- to evaluate the predictive value of the first four weeks of opioid dependence treatment with buprenorphine-naloxone in routine care with regard to positive and negative treatment outcomes
- to assess the risk for liver enzyme elevation in patients in opioid-dependence treatment with buprenorphine-naloxone in routine care

The thesis is based on four chapters:

- Introduction (chapter E)
- Primary analysis of the results from the 12-month nationwide non-interventional safety study on the medication assisted treatment of opioid dependence with buprenorphine-naloxone in routine care in Germany (chapter F)
- Analysis of the first four weeks in the treatment of opioid-dependence after induction or switch to buprenorphine-naloxone and its predictive value for the treatment outcome after 12 months of observation (chapter G)
- Analysis of the development of liver enzymes over 12 months of treatment of opioid-dependence with buprenorphine-naloxone (chapter H)

D. Introduction

D.1. Opioid use disorder

Opioid use disorder (OUD) is a major health and social issue worldwide [1] and can lead to significant somatic and psychiatric complications. In the International Classification of Diseases (ICD-10) the dependence syndrome is described as a physiological, behavioral and cognitive phenomenon. The addicted person grants the drug use a higher priority in life than anything else and feels a strong desire to acquire and consume the drug despite the knowledge of its harmful consequences [2, 3]. Approximately 1.3 million persons are high-risk opioid (mis-)users in Europe. Most of them are using street heroin; a minority misuses prescription opioids such as methadone, buprenorphine or fentanyl [4]. In the beginning the use of opioids might cause feelings of drowsiness, euphoria and relieve of distress, but repeated use will rapidly lead to a physical adaptation to the effects of the drug and to uncontrollable drug consumption [5, 6]. The drug abusing person 1) will experience a physiological state of adaptation to the drug and needs to increase the drug dose and/or reduce intervals between drug consumption because of its loss of effectiveness (tolerance), 2) will have withdrawal symptoms when the drug use is abruptly stopped (physical dependence) and 3) will be developing behavioral patterns of compulsive drug procurement and use (addiction) [5, 7, 8]. At some point the opioid is no longer consumed as positive reinforcer to produce euphoria or relieve distress, but to prevent withdrawal symptoms and dysphoria [5]. Long-term exposure to opioids alters the neurological system of the reward mechanism; it becomes highly sensitive to both the drug effects and the stimuli around the drug-use and causes constant need (craving) for the drug even when no withdrawal symptoms are present [5]. Approximately half of the opioid dependent persons will continue (mis-)using the opioid for the rest of their life with intermittent periods of treatment, imprisonment, abstinence and relapse [2] with high overdose and mortality risks [9]. Therefore opioid addiction is considered a chronic recurring medical disease [5] with a high risk for a fatal outcome.

D.1.1. Opiate vs. opioid

Opiate is the term for all natural psychoactive substances based on raw opium obtained from the seed capsule of the plant papaver somniferum (breadseed or opium poppy) which mainly contains morphine and codeine [10, 11]. Opiates have a long history of medicinal use and non-medicinal abuse worldwide [10].

Opioid is the term for all half synthetic substances based on opium/morphine such as heroin (diacetylmorphine) or thebain such as buprenorphine as well as all fully synthetic substances such as methadone and levo-methadone which have similar pharmacological effects as opiates [10-12]. Opioids were developed to produce more potent analgesics and reduce abuse liability of opiates [10]. Until now there is no opioid which has not been abused at some point.

Both opiates and opioids have a high addictive potential and will eventually lead to tolerance and withdrawal symptoms [11]. The most prominent route of application is intravenous (iv), which is also the highest risk factor for severe morbidity and premature mortality [2].

Throughout the literature the terms opioids and opiates are often used interchangeable (sometimes even misclassified as synonyms) with a more prominent use of the term *opioid* for both groups. In this thesis the term *opioid* is used for harmonization reason.

D.1.2. Agonist vs. antagonist

The term opioid *agonist* is used for substances (body's own or external) which have an affinity with opioid receptors and activate their function. These substances are further distinguished into full and partial agonists. An increased dose of a full agonist increases the effect of the substance and the activity of the receptors. Partial agonists trigger a limited reaction at the receptor even at high dosages. Partial agonists have a partial antagonistic effect because they block the opioid receptors and reduce the potency of a full agonist. Partial agonists can also cause precipitated withdrawal symptoms because they supersede the full agonist from the receptor since they usually have a higher affinity to the same receptor (i.e. buprenorphine). [see 13]

The term opioid *antagonist* is used for substances (body's own or external) which have an affinity with the opioid receptors and block them, but do not activate their receptor function. Competitive antagonists are competing with the agonists for the same bonding spot on the receptor and block the binding potential for the agonist. Non-competitive antagonists bind to another spot at the same receptor and inhibit the receptor function. Agonists can still bind to the receptor but its maximal effects are always reduced due to the presence of the non-competitive antagonist. [see 13]

D.1.3. Opioid receptors

Opioid receptors are molecules on the surface of the cells and in the human body different types of opioid receptors exist [7]. Mainly μ (mu), δ (delta) and κ (kappa) receptors were found to be relevant for opioid drug use disorders [10, 14]; all of them can be further divided into subtypes - μ_1 and μ_2, δ_1 and δ_2, κ_1, κ_2 and κ_3 [10, 15].

Especially the μ receptor is important for the analgesic and addictive effects of opioids and the mediation of drug reinforcement. According to the review from Contet and colleagues [16] this receptor plays a major role in the processes for continued drug use and craving. It provides a high affinity with opioids with abuse potential [10, 17] and is relevant for pain regulation and sensorimotor integration [14]. Moskowitz and colleagues found that μ_1 is responsible for the analgesic effects and μ_2 for respiratory depressant effect [18].

The κ receptor plays a major role in the aversive effects of opioids and seems to be responsible for the negative mediation of behavioral response to opioids and dysphoria [10, 19]. Certain agonists/antagonists can attenuate the rewarding effects of opioids when

attaching to the κ receptor [19]. Hence this receptor is also very important for the development of medications for opioid drug dependence treatment.

The δ receptor seems to have an important role in the rewarding effect of opioids as well as in the development of opioid tolerance and dependence [20]. The activation of this receptor can reduce pain and improve emotional conditions [21]. Yet this receptor has not been in the main focus for studies concerning OUD [21]. While early animal studies with selective δ receptor antagonists provided evidence for reduced development of opioid tolerance and dependence, Pradhan and colleagues [21] noted that its usefulness for opioid drug dependence treatment is still not entirely clear.

D.1.4. Adverse effects and long-term consequences of opioid addiction

In the long-term untreated OUD leads to severe morbidity and increased premature mortality risk [2, 4, 22-26].

Mortality

According to the Drug and Addiction Report [27] in 2010 in total 1,237 persons died from a drug overdose in Germany. Most of those deaths (approximately 70%) were attributed to an overdose of heroin alone or in combination with another drug. In approximately 14% of the death cases, evidence of an overdose by a drug used for medication assisted treatment for opioid dependence such as methadone, levo-methadone or buprenorphine alone or in combination with another illicit drug was found. 214 persons died from the long-term effects of the high risk use of illicit drugs. In the following two years 2011 and 2012 the number of drug-related deaths decreased in Germany. However, since 2013 death cases have been increasing continuously and reached the level of 2010 again in 2015 [4]. According to the latest report by the European Monitoring Center for Drugs and Drug Addiction [4] opioids were involved in 80% of the drug-related death cases with known toxicology. The Drug and Addiction Report from 2017 [11] had to declare another 9% increase of drug-related deaths in 2016. This means that the number of drug related deaths reached the level of 2009. Most of those deaths in 2016 were attributed to opioids alone or in combination with other substances [11].

The reasons for the continued increase of drug-related deaths in Germany are not entirely clear. The „Drug Commissioner of the Federal Government“ in Germany pointed to the increase of polyvalent intoxications with drugs other than opioids such as cocaine (+78% compared to 2015), methamphetamines i.e. Crystal Meth (+2 deaths compared to 2015) and new psychoactive substances including synthetic cannabinoids (+51% compared to 2015) [11]. For the increased number of opioid-related deaths, the „Drug Commissioner“ did not provide an official explanation in the Drug and Addiction Report from 2017 apart from a slight increase of deaths because of intoxications with fentanyl (+9% compared to 2015). During the press conference in 2017, shortly after the release of the Drug and Addiction

Report, the speakers emphasized that an increased quality of the drugs in combination with decreased prices were part of the root cause [28].

Virological and other Infections

Because of high-risk behavior (e.g. needle sharing and unprotected sex with different partners) and unstable social conditions (e.g. homelessness and imprisonment) the risk for virological and other infections is elevated in drug dependent persons [29]. Among patients with iv drug use the prevalence of an infection with the hepatitis C virus (HCV) is more than 50% and of the human immunodeficiency virus (HIV) is below 5% in Europe [29]. Results from the national study DRUCK, conducted by the Robert Koch Institute (RKI) from 2012 until 2016 in Germany, showed a high prevalence of up to 75% for HCV and up to 9% of HIV in drug dependent persons with iv drug use [30]. Older age (≥35) and longer history of iv drug use contributes to an increased risk for viral infections [29, 30]. Alcohol abuse or even dependence worsens the condition in chronic HCV infections resulting in cirrhosis, liver cancer and premature death [29]. Chronic use of opioids generally has an immuno-suppressive effect which can also lead to an increased vulnerability to infections, inflammations and cancer diseases. In persons with iv drug use the risk for severe bacterial infections such as tetanus, botulism and streptococcus is highly elevated [29].

Psychiatric Disorders

Psychiatric disorders are found to be associated with elevated risk for drug abuse and addiction. Especially schizophrenia, bipolar disorders, depression and attention deficit hyperactivity disorder (ADHD) are conditioning factors for drug abuse [5]. Post-traumatic stress disorders (PTSD) were also found to be a high risk factor for drug abuse and dependence [31-33].

Long-term abuse of opioids and its coherent life-style leads to an increased risk for comorbid psychiatric disorders such as anxiety, depression and PTSD as well as cognitive and neurological deficits [1, 22, 33-35].

D.2. Treatment of opioid use disorder

There are different strategies for the treatment of OUD: 1) withdrawal and detoxification, 2) medication assisted treatment with agonists, partial agonists and antagonists and 3) psycho-social therapy. Psychosocial therapy is an important approach in the treatment of OUD, either as a standalone program or in combination with medication assisted treatment [7], but will not be further discussed herein. This thesis is focused on medication assisted treatment.

In Europe approximately 630,000 persons classified as high-risk opioid misusers are currently in therapy; most of them in medication assisted treatment with methadone, levo-methadone or buprenorphine products [4]. In general being in treatment seems to reduce the risk for hospital attendances, morbidity and mortality. In opioid dependent patients who are out of

treatment all cause mortality risk is up to 3.5 times and overdose mortality risk is up to 4.9 times higher compared to patients who are still in treatment [2, 9, 36, 37]. The risk for mortality is particularly high during the first four weeks after leaving treatment [9, 36, 38, 39]. In their retrospective analysis of ambulance service records over a four year period in Australia, Nielsen and colleagues [40] found that methadone or buprenorphine was involved in only 5 cases compared to monthly up to 460 heroin-related cases.

D.2.1. Withdrawal and detoxification

Opioid withdrawal and detoxification is used to bring a patient from opioid dependence to an opioid free state [41] within a short period of time (24 hours to 2 weeks). The medication assisted opioid withdrawal treatment is presently the standard treatment for detoxification [42] and can be done as traditional or rapid/ultra-rapid detoxification using agonistic opioid substitute medicine, such as methadone or buprenorphine, non-opioid medicine, such as clonidine and lofexidine, opioid antagonistic medicine, such as naloxone and naltrexone, or a combination of the above mentioned medications [43-45]. The successful completion of opioid detoxification is a requirement for the start of a weaning off treatment with an opioid antagonist [42].

During the traditional detoxification from heroin with an opioid substitute, the dosage of the substitute, such as methadone or buprenorphine products, will be gradually tapered during several days or weeks until the patient no longer requires any substitute medication to prevent withdrawal symptoms and can then be transferred to opioid antagonist treatment [42, 46, 47]. The duration of this type of detoxification treatment depends on the start dosage of the substitute medication needed to replace the abused opioid [42]. Detoxification with methadone is effective to alleviate withdrawal symptoms. However, the post-detoxification treatment with an opioid antagonist would require up to one week of methadone abstinence to avoid precipitated withdrawal and the relapse rate is very high [43]. Detoxification with buprenorphine is also safe and well tolerated; withdrawal symptoms are resolved faster compared to methadone [45, 47, 48]. The non-opioid approach of the traditional detoxification treatment is conducted by using α_2-adrenergic agonists, such as clonidine and lofexidine, to decrease overactivity of the cyclic adenosine monophosphate (AMP) system in noradrenergic neurons and to reduce opioid withdrawal symptoms [44]. The medication is tapered over a period of 5-10 days until it can be completely stopped [43, 44]. In their outpatient study McCann and colleagues found that clonidine detoxification was more successful for patients whose most recently used drug was any opioid other than heroin, who did not inject the opioid and waited longer after the last dose of their drug of choice before starting detoxification treatment [43]. Compared with the opioid detoxification with α_2-adrenergic agonists alone the combination with an opioid antagonist such as naltrexone seems to be more successful and the resolution of opioid withdrawal symptoms is more rapid [49-51]. A different approach for a successful detoxification is presented by Kosten and O'Connor. They recommended for an optimal outpatient detoxification to start with

buprenorphine, tapering the dose until discontinuation, and switch to lofexidine or clonidine for up to 5 days [44].

The rapid and the ultra-rapid detoxifications are usually done with a combination of α_2-adrenergic agonists and opioid antagonists. In both approaches precipitated withdrawal with an opioid antagonist is used to shorten the time needed for withdrawal [45]. During the rapid opioid detoxification a high dose of clonidine or lofexidine is decreased while the dose of naltrexone or naloxone is increased within 2 to 6 days until no precipitated withdrawal is experienced and the patient can be maintained on naltrexone alone [42, 44, 45, 52]. For the ultra-rapid detoxification the patient is in anesthesia or heavy sedation and receives an opioid antagonist such as naloxone while in intensive care for one day [42, 44, 45]. As post-procedures vary widely internationally [45], in Germany, after retrieval from narcosis or sedation, the patient would receive further opioid antagonist treatment and medication for withdrawal symptoms for about a week before being discharged from the hospital [42]. As Scherbaum and colleagues [42] concluded, ultra-rapid detoxification is only applicable for non-polyvalent opioid dependent persons. Despite 90-100% successful completion of this detoxification treatment, the long-term success of this approach is questionable [42, 45] and there is a high risk for clinical complications as well as mortality [45, 46]. Another ultra-rapid approach was presented by Resnick and colleagues. Patients were given repeated injections of the opioid antagonist naloxone until withdrawal symptoms were no longer induced and the patient was transferred to naltrexone maintenance within 48 hours [53].

During opioid detoxification, withdrawal symptoms (e.g. insomnia, muscle cramps, pain, diarrhea, nausea, vomiting, flu-like symptoms) can be treated with mitigating medications, such as benzodiazepines, nonsteroidal anti-inflammatory drugs or prochlorperazine, as they arise [41, 42, 45].

Almost all authors concluded that long-term success of any type of opioid detoxification is rather doubtful. Short-term detoxification programs alone are not sufficient in preventing deaths and achieving long-term abstinence [26, 54]. After detoxification from the drug and dissipation of withdrawal symptoms, drug addiction does not end [55] as the underlying chronic opioid use disorder is not addressed by detoxification treatment [55]. Therefore detoxification should only be considered a first step in a long-term substance abuse treatment process [46, 55].

D.2.2. Medication assisted treatment

Medication assisted treatment is the most frequent therapy for opioid dependent patients [4]. The main goals are to keep the patient alive, stabilize the patient, prevent withdrawal symptoms, reduce high-risk and health threatening behavior (incl. drug-related crime), enable social re-integration and treatment of co-morbid diseases [1, 24, 56]; thus, prevent or at least reduce drug-related deaths from overdose and drug-use related physical diseases. The drug dependent person is given the chance to reclaim control over his or her life [4, 57].

Medication assisted treatment with maintenance drugs consists of three phases: induction, stabilization and maintenance [4, 6]. The induction phase usually lasts up to one week. During this phase the treating physician will find the minimum dose of the maintenance drug at which the patient no longer experiences withdrawal symptoms as well as uncontrollable craving for opioids and concomitant drug use markedly decreases [7]. The stabilization phase usually lasts one to two month(s). The patient is stabilized in the routine of drug dependence treatment and opioid use further decreases, which shows in an increasing number of negative urine drug screenings [7]. The maintenance phase is the longest period in drug dependence treatment and can last life-long. The patient receives a stable dose of the maintenance drug and is ready for addressing co-morbid diseases as well as psychosocial, family, employment and financial issues [7].

The first four weeks in medication assisted treatment seem to be important for course and outcome of opioid dependence treatment. Some studies reported the highest drop-out rates in the first weeks of therapy [58, 59] especially in patients induced to buprenorphine [60, 61] and patients with positive urine drug screenings for opioids [35, 62]. A high mortality risk after treatment onset has also been reported particularly for patients induced to methadone [9]. A patient is more likely to terminate treatment within the first three months if tested positive for opioids and other illicit drugs [63]. The odds for a successful medication assisted treatment, including complete abstinence, increase with a longer duration of the therapy [59, 64, 65]. Therefore, it is important to monitor the initial response of patients closely after treatment onset [35] and keep them in the treatment beyond the first four weeks.

Medication assisted treatment with antagonists (e.g. naltrexone) is usually done as weaning off treatment after a successful detoxification [42, 66]. Opioid antagonists block the effects of other opioids such as heroin [67]. A purely antagonist treatment for opioid dependent persons is limited because of poor compliance of the patient to the treatment and high drop-out rates [67-69] due to the lack of agonistic effects and continued experience of craving for opioids [7]. The risk for overdose is also increased in case of a relapse to opioid use [7]. Studies showed significantly more successful treatment results when the medication assisted treatment with an antagonist is combined with intensive psychiatric counseling or even psychotherapy [68-70]. Recent trials with sustained-release naltrexone showed promising results concerning medication compliance compared to the oral medication [71], but to date the data is not sufficient to conclude on the effectiveness for opioid dependence treatment [67].

D.2.2.1. Medications for opioid dependence treatment

Methadone

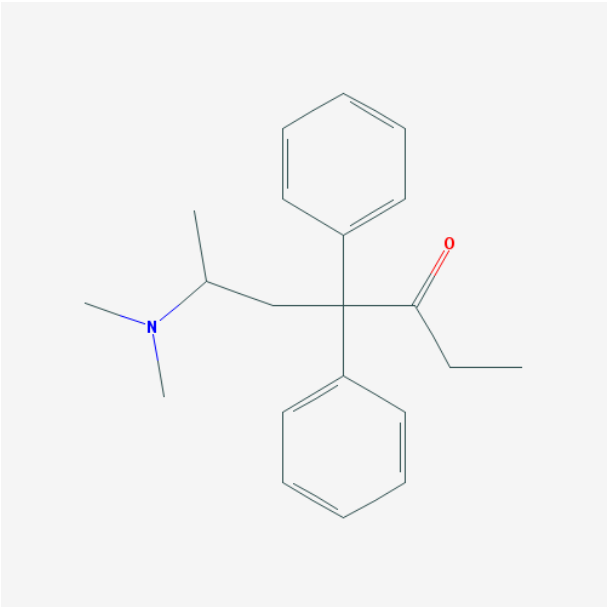

Fig 1: Structural formula of d/l-methadone C21H27NO [72]

Methadone or d/l-methadone is a long acting full μ receptor agonist and a fully synthetic derivate of morphine. Methadone consists of the active R(-)enantiomer levo-methadone and the inactive S(+)enantiomer dextro-methadone [8, 72]. In drug dependence treatment the medication is administered orally as a solution. To effectively suppress withdrawal symptoms, methadone must be administered on a daily basis [73, 74]. After oral administration methadone is detectable in the blood plasma after 30 minutes and reaches its peak at about 4 hours [8]. 90% of the drug is bound to plasma protein with a half-life of approximately 15 to 40 hours [8, 72].

Methadone has a high ratio of oral-to-parenteral potency which reflects the low first-pass metabolism in the liver [8]. It produces adverse effects such as respiratory depression, nausea, dizziness and hypotension [72]. As most opioids methadone is metabolized by the cytochrome P450 3A4 system [72, 73]. Therefore the dose will need to be adjusted in patients undergoing medication treatment for a hepatic disease (e.g. HCV) or HIV as changes in bioavailability and cumulative effects may occur after oral administration of methadone [8, 73].

When inducting a patient to methadone in medication assisted treatment of opioid dependence, it is recommended the patient is no longer intoxicated and does show withdrawal symptoms. The initial dose of maximum 30 mg and a maximum dose of 40 mg on the first day as well as a maintenance dose of 60 to 120 mg per day is recommended. [75].

Because methadone is a full opioid agonist with a complex pharmacokinetic profile it has high potential for misuse and diversion.

Levo-Methadone

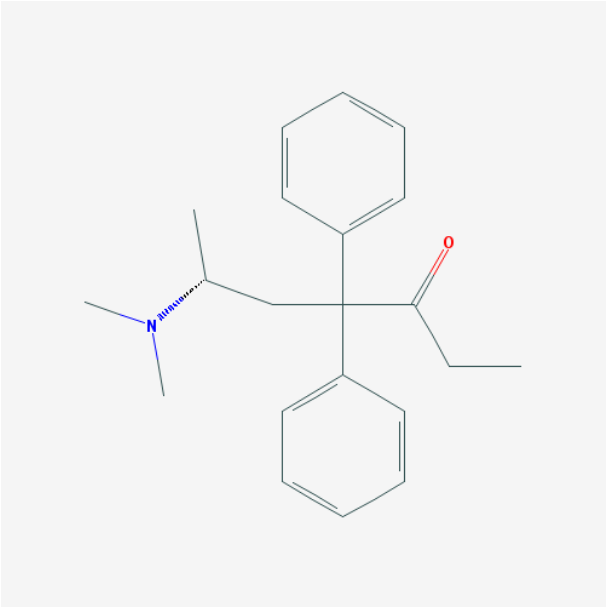

Fig 2: Structural formula of levo-methadone C21H27NO [72]

Levo-methadone is a long acting full μ receptor agonist and fully synthetic derivate of morphine. Levo-methadone consists of the active R(-)enantiomer of d/l-methadone, from which the S(+)enantiomer dextro-methadone is removed. Levo-methadone is approximately twice as effective as d/l-methadone and dosing needs to be considered accordingly. As with methadone it is administered orally as solution and it produces adverse effects such as respiratory depression, nausea, dizziness and hypotension [76]. Plasma bonding, half-life and metabolism are similar to d/l-methadone. The induction dose on should not exceed 20 mg and for maintenance a daily dose between 30 to 60 mg is recommended.[77]

Buprenorphine

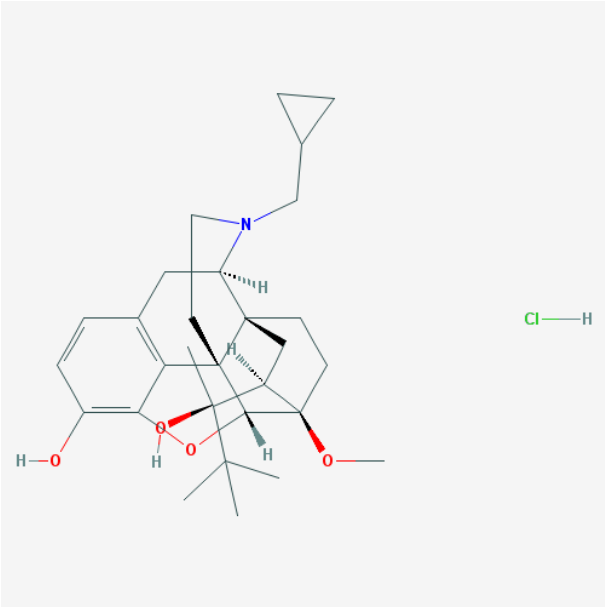

Fig 3: Structural formula of buprenorphine C29H42ClNO4 [72]

Buprenorphine is a semisynthetic partial μ receptor agonist and κ antagonist derivate of thebain and is 20 to 50 times more potent than morphine [7, 8, 78]. For opioid dependence treatment buprenorphine is administered sublingually [7]. Due to its low intrinsic activity at the μ receptor even with full saturation of the receptor system and its dose related ceiling effects on subjective and physiological measures (e.g. euphoric and respiratory depressant effects) [7, 78], buprenorphine has a high safety profile when used as prescribed. After sublingual administration buprenorphine reaches its peak at about 1 to 2 hours [8]. In addition buprenorphine can be administered less than daily (alternate dosing every 2 or 3 days) because of its slow dissociation from the μ receptor and therefore, long lasting effects with higher doses without increased risk [74, 78-81]. Buprenorphine attenuates the effects of other opioids due to its strong bonding to the μ receptor [82, 83] and can be safely used for rapid tapering (7 days) and detoxification [84]. 96% of buprenorphine is bound to the plasma protein with a half-life of about 3 hours, but because of the slow dissociation from the μ receptor, plasma levels of buprenorphine may not be reflected in the clinical effects [8]. Buprenorphine is extensively metabolized in the liver to norbuprenorphine by the cytochrome P450 3A4 system [85]. Other medications also interacting with the same system may enhance or decrease effects of buprenorphine and should be used with caution [7]. Elevated liver enzyme levels for aspartate transaminase (AST) and alanine transaminase (ALT) have been reported during treatment with buprenorphine, especially in patients with a history of hepatitis [86], and when buprenorphine was misused intravenously or in very high doses [87]. Buprenorphine produces adverse effects such as nausea, dizziness and hypotension but not as extensively as a full agonist [7].

When inducting a patient to buprenorphine, the patient needs to be in slight withdrawal from the full agonist to prevent precipitated withdrawal [6]. As a partial agonist on the μ receptor, buprenorphine is also acting like a partial antagonist on the same receptor by superseding the full agonist. For induction to buprenorphine the patient should receive the recommended minimum daily dose and for maintenance a daily dose of 16 mg (range 4 to 24 mg) [6].

Buprenorphine-Naloxone

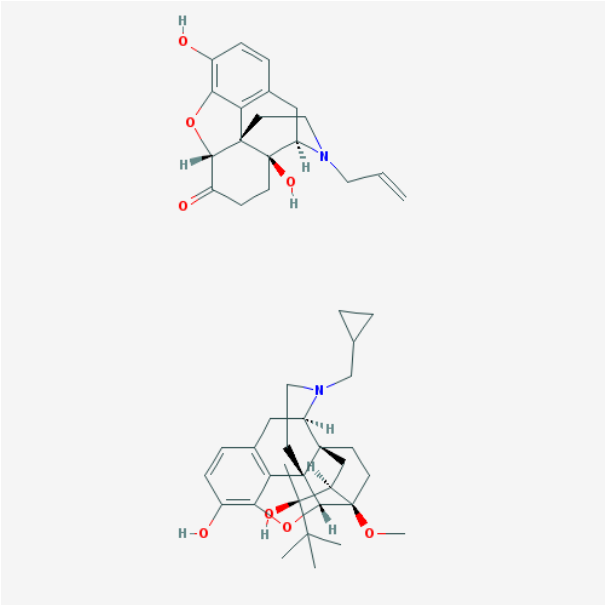

Fig 4: Structural formula of buprenorphine naloxone mixture C48H62N2O8 [72]

Buprenorphine-naloxone is a combination of buprenorphine and the short-acting antagonist naloxone in a 4:1 ratio [88-90]. This combination was developed to minimize the diversion and potential misuse of the medication [88, 91]. The antagonist naloxone has a very low bioavailability (<10%) when administered sublingually [91]. If buprenorphine-naloxone is administered intravenous, it produces antagonistic and bad drug effects (i.e. opioid withdrawal) [89, 91] comparable to the use of naloxone alone. Buprenorphine-naloxone is preferable in drug dependence treatment with buprenorphine, since the antagonist naloxone prevents patients from dissolving the tablet for iv use [6]. Take home prescription could be granted more often because of the reduced risk for diversion and misuse [92] and could increase treatment compliance also in combination with the possibility of alternate dosing [92]. Plasma bonding, half-life, metabolism and side effects are similar to buprenorphine mono-compound.

In Europe buprenorphine-naloxone is only available as sublingual tablet for medication assisted treatment of opioid dependence [90]. Outside of Europe this medication is also approved as sublingual film [93]. The official product description recommends the same daily

dose as with buprenorphine and warns that due to the naloxone portion, the medication should not be used in patients with severe liver problems [90].

Other maintenance drugs

Codeine is a short-acting natural full agonistic content of morphine/opium and dihydrocodeine (DHC) is a short-acting semisynthetic full agonistic derivate of morphine. Both substances require more than one daily dose to prevent withdrawal symptoms due to a „weak" affinity with the μ receptor, a short half-life of 3-4 hours and a duration of action of approximately 6 hours [94-96]. They are metabolized through the cytochrome P450 enzyme CYP2D6 to several compounds including the active metabolite (dihydro-)morphine, which has a 60 times higher affinity with the μ receptor as its parent compound [97]. DHC has a higher portion of the metabolite dihydromorphine and is therefore 3-fold stronger than codeine [96]. Due to the genetic polymorphism of CYP2D6 there is an individual diversity in metabolic profiles, and pharmacological affects vary depending on the speed of codeine/ DHC metabolization [97]. Adverse effects are similar to methadone with more frequent obstipation and upper abdomen ailment [96].

Diamorphine/diacetylmorphine (DAM) is a half-synthetic full-agonistic diacetyl derivate of morphine [72, 94] with a high intrinsic activity at the μ-receptor, especially its metabolite 6-monoacetylmorphine (6-MAM) which is rapidly hydrolyzed after administration of DAM [72, 98, 99]. Because of the short half-life and a duration of action of no more than 4 to 5 hours, the drug needs to be applied at least three times a day [96]. The most common adverse effects are sedation, nausea and vomiting, constipation and sweating including respiratory depression as the most serious adverse effect [72, 96].

D.2.2.2. Medication assisted treatment in Germany

Since July 2002 all physicians working in addiction medicine are obligated to register each patient receiving any medication assisted treatment for opioid dependence in the *Substitutionsregister* [11]. While the number of registered opioid dependent patients in medication assisted treatment continuously increased until 2010 (52,700 in 2003 to 77,400), it remained practically stable until 2015 (77,500) and only slightly increased in 2016 to 78,500 [11].

Until 2002 the majority of opioid dependent patients in medication assisted treatment received methadone, which was first introduced for maintenance treatment in Germany in 1987 [100]. Only in Germany methadone is available in two forms for opioid dependence treatment: d/l-methadone and levo-methadone, also called polamidon [100]. Levo-methadone prescriptions for opioid dependence treatment increased from >16% in 2002 to 33% in 2016. After market approval in 2002 the proportion of patients treated with buprenorphine increased from <10% to >23% in 2016 and includes the combination product buprenorphine-naloxone marketed in Germany in 2006. Codeine/DHC were used

as substitute drugs by heroin addicts since the 1960s [97] and since the 1970s DHC was prescribed as oral solution to a large number of opioid dependent persons due to the strict narcotic regulations for methadone maintenance treatment in Germany at that time [94, 100, 101]. In 1998 the prescription of codeine/DHC had been restricted by law to only exceptional medical cases, e.g. patients intolerant to methadone, because of an increased number of „gray substitution“ (patients did not have to be notified to local health authorities) and an increased number of codeine-related deaths [94]. Prescriptions decreased from 2% in 2002 to 0.3% in 2016 [11]. Since 2010 diamorphine-assisted treatment is available as second-line treatment for a small sub-group of „difficult-to-treat“ opioid dependent patients for whom conventional treatments were not successful [102, 103]. The prescriptions for this last option for medication assisted treatment increased from 0.3% in 2010 to 1% in 2016. [11, 104, 105] .

D.3. Post-authorization safety study (PASS) with buprenorphine-naloxone

After market approval for buprenorphine-naloxone (Suboxone®) in Europe a nationwide non-interventional, post-authorization safety study (PASS) was conducted to evaluate the safety and effectiveness of the medication on a large and representative sample of patients in office based opioid drug dependence treatment in Germany. The study was part of the Risk-Management-Plan (RMP) for buprenorphine-naloxone and a commitment to the European Medicine Agency (EMA). The 12-month PASS was conducted from 2008 to 2010 and included 69 sites and 384 opioid dependent patients (see Figure 4).

Methods and design of the study are extensively described in paper I provided in chapter F.

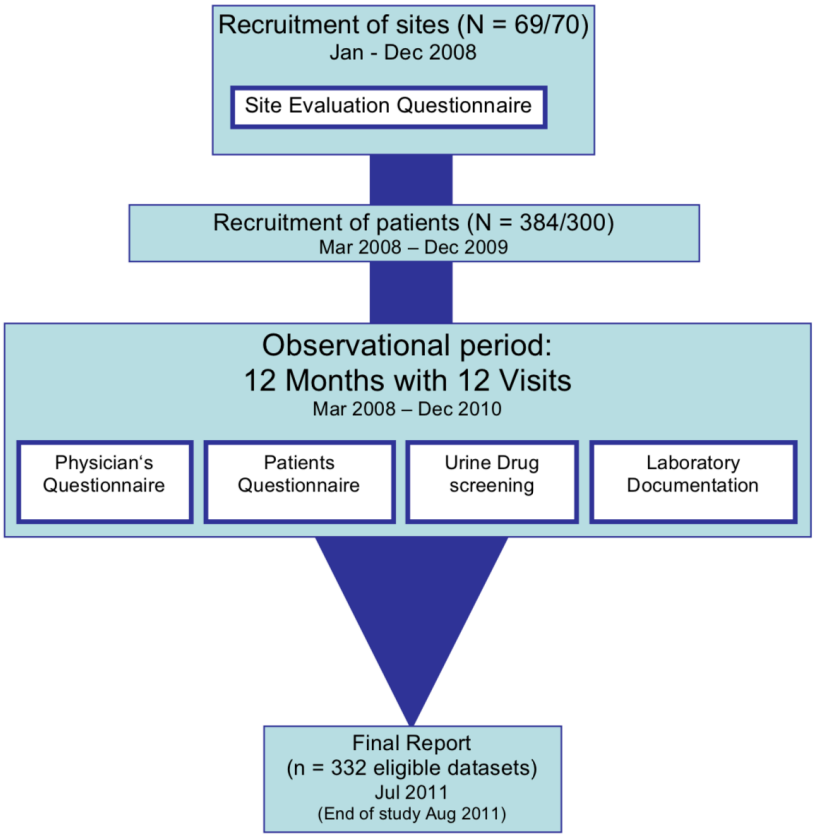

Figure 4: Design of the PASS with buprenorphine-naloxone (paper I)

The majority of the participating physicians were male (83%) and on average 53.4 years of age (SD 7.3, 40-70). Almost 60% of the physicians were working in cities with >100,000 inhabitants, 10% with >50,000 inhabitants, 24% with >10,000 inhabitants and 7% in towns with <10,000 inhabitants. More than half of the physicians (54%) were general practitioners, followed by psychiatrists (19%), internists (15%), medical practitioners (10%) and other fields of specialization (2%). There were no gynecologists or hepatologists participating in the study.

The participating physicians were working in the field of dependence treatment on average for 14 years (SD 6.2, 1-30). Almost 80% of the participating physicians were working office-based in an individual practice (40%), group practice (23%) or shared practice (16%). One physician was working in a drug help facility, one was working in a clinic and two physicians were working in health care centers. The majority of the physicians (84%) were treating >40 opioid dependent patients per day, 14% were treating >10 patients per day and only 2% were treating <10 patients per day. Opioid dependent patients could either receive their medication directly at the site of their treating physician (77%) or at a pharmacy (30%). Virological tests for hepatitis A, B, C and HIV were done on a regular basis by >70% of the physicians. For the treatment of virological infections, patients were transferred to a specialized facility by >65% of the physicians. Concomitant use of illicit drugs was monitored by interview mostly on a weekly basis (63%), by urine drug screening weekly and monthly (34% and 49%, respectively), by urine laboratory test monthly or seldom (32% and 25%, respectively) and by blood tests seldom or never (58% and 24%, respectively). 46% of the participating physicians offered an accompanying psychosocial treatment in their practice. 86% of physicians used a drug help facility and 25% a psychiatrist or psychologist for additional psychosocial treatment.

E. Primary analysis of the results from the 12-month nationwide non-interventional safety study on the treatment of opioid dependence with buprenorphine-naloxone in routine care in Germany (Paper I)

Safety, Effectiveness And Tolerance Of Buprenorphine- Naloxone In The Treatment Of Opioid Dependence: Results From A Nationwide Non-Interventional Study In Routine Care

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Sabine M. Apelt, Norbert Scherbaum, Jörg Gölz, Markus Backmund & Michael Soyka

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This original article had been published by *Pharmacopsychiatry*, a peer-review scientific journal, publishing in the field of medicine, psychiatry and pharmacology in English (impact factor 2013: 2.168). Sabine M. Apelt was as the first author responsible for the concept, literature research, statistical analyses, evaluation of the results and writing the manuscript. Professor Norbert Scherbaum was responsible for literature research and evaluation as well as review of the manuscript. Dr. Jörg Gölz was responsible for patient data and review of the manuscript. Professor Markus Backmund was responsible for literature research and evaluation as well as review of the manuscript. Professor Michael Soyka was responsible for concept and review of the manuscript.

This article provides a detailed description of the methods and design of the non-interventional post-authorization safety study with buprenorphine-naloxone. It describes the characteristics of the study population and answers the primary and secondary objectives of the study.

Safety, Effectiveness and Tolerance of Buprenorphine-Naloxone in the Treatment of Opioid Dependence: Results from a Nationwide Non-Interventional Study in Routine Care

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Key words
- buprenorphine-naloxone
- dependence treatment
- buprenorphine
- naloxone
- opioids
- routine care
- safety

Abstract

Introduction: Buprenorphine is well known in the treatment of opioid dependence. Despite a high safety profile and good tolerance buprenorphine has been subject to misuse and diversion. To reduce misuse the antagonist naloxone was added and the 4:1 combination of buprenorphine-naloxone was launched in Germany in March 2007. On the basis of the results from international clinical trials a non-interventional study was conducted to gather data on safety, effectiveness, retention and acceptability of buprenorphine-naloxone in the treatment of opioid dependent patients in routine care.

Methods: A nationwide multicentre 12-month prospective, non-interventional, post-marketing, surveillance study was carried out with 12 assessment points in N = 384 opioid dependent patients currently in maintenance treatment from N = 69 general practitioners, clinics and outpatient clinics in Germany.

Results: N = 337 data sets were eligible for analysis. The rates of patients with serious and non-serious adverse events were low with 1.2 % and 17.5 %, respectively. No deaths occurred during the observational period and only one hospitalization was documented. Concomitant drug use decreased for all illicit substances. Mental health and quality of life measured with standardized self-assessment questionnaires improved significantly. The 12-month retention rate was 57.1 %. Of the n = 181 patients still in treatment at the end of the observation period, 96.7 % continued treatment with buprenorphine-naloxone.

Conclusion: The findings of the non-interventional study indicate high effectiveness and safety of buprenorphine-naloxone in the treatment of opioid dependence. The medication was well accepted by opioid dependent patients in long-term substitution treatment with substantial reductions of concomitant drug use and measurable improvement in quality of life.

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Introduction

Opioid dependence is a major health and social issue [1,2] and is associated with an excess rate of somatic and psychiatric complications including HIV, hepatitis, depression, suicidality and antisocial behaviour [1,3,4]. Approximately 200 000 persons in Germany have a risky use of illicit substances, excluding cannabis use [5]. Although the number of drug-related deaths continues to decrease still 1237 persons died in 2010 because of drug use, most of them because of heroin overdose (42.8 %), 12.5 % of the deaths were related to methadone/levo-methadone alone or in combination with other drugs and 0.5 % were related to buprenorphine alone or in combination with other drugs [5].

One of the reasons for the lowest number of drug-related deaths in the past 10 years [5] is opioid maintenance treatment which is an established and well-studied approach in opioid dependence and recommended by current treatment guidelines worldwide [6–9]. The main goals of opioid drug dependence treatment are risk and harm reduction, social reintegration, and interruption of the vicious circle of drug use and procurement crime. Furthermore the therapy aims to establish best possible conditions for the treatment of concomitant diseases [10]. Although abstinence is no longer the only primary goal, the long-term target of opioid drug dependence treatment is to support the patients to stop using drugs entirely [10].

In 2010 more than 77 000 of approximately 200 000 opioid-dependent patients in Germany

were registered as currently in maintenance treatment with d/l-methadone (58%), levo-methadone (23%), buprenorphine (19%) and other substitution drugs including diamorphine (0.3%) [7,11]. Both treatments with full opioid agonists (e.g., methadone) and partial agonist/antagonist (buprenorphine) have been found to be effective in reducing substance use and improving somatic, psychiatric as well as social functioning [2,12–14]. However the increasing level of diversion [8,15,16] and the risk of fatal outcomes in opioid maintenance treatment have raised concerns about safety issues in the treatment of opioid dependence.

The combination of the partial mu-agonist/kappa-antagonist buprenorphine with the full mu-antagonist naloxone in a ratio of 4:1 was developed to improve treatment outcomes and to reduce the risk of diversion [17,18]. When the combination is administered sublingually as prescribed, naloxone is inactive because of its low sublingual bioavailability [19] and only the effects of buprenorphine are experienced [16,20] blocking most of the mu-receptors [12]. But when the medication is administered parenterally (intravenous or nasal) the effects of naloxone are experienced for the first 15–90 min [21]. Both buprenorphine and naloxone have a very high bioavailability but naloxone binds more rapidly to the opioid mu-receptors than buprenorphine causing precipitated withdrawal if the user has full agonists in the body [16,18]. Thus the combination of buprenorphine with naloxone is expected to reduce the risk of intravenous or nasal misuse [19]. The combination minimizes the risk of opioid overdose and diversion by making it unattractive for selling [17,21] because of the unpleasant experience directly after parenteral abuse [18,21]. In addition the potential pleasurable effects of buprenorphine are diminished due to the smaller and delayed agonist effects after the subsiding antagonistic effect of naloxone [21].

While a number of randomized clinical trials [2,12,17,22] demonstrated the overall efficacy of buprenorphine-naloxone in the treatment of opioid dependence, to date no non-interventional observational studies on the effectiveness and safety of the novel buprenorphine-naloxone combination reflecting "real world" conditions with a profound and comprehensive assessment both for physicians and patients have been published. Such studies are essential to verify clinical trial results and to receive reliable safety data from routine care treatment. The study was designed to collect comprehensive safety and effectiveness data on a large patient sample in office-based routine opioid drug dependence treatment with buprenorphine-naloxone over a 12-month period (2008–2010).

Methods

Study goals

The primary objectives of the non-interventional study was to describe the retention rate of patients pre-treated with buprenorphine, methadone, levo-methadone or another maintenance drug after 12 months of treatment with buprenorphine-naloxone under real-life conditions and to collect comprehensive safety data during switch to and treatment with buprenorphine-naloxone.

The secondary objectives were to describe the switch to the new medication in terms of dosing, mode of prescription and subjective effects. Data on effectiveness, acceptance and tolerance of opioid dependence treatment with buprenorphine-naloxone should be examined regarding met and unmet needs.

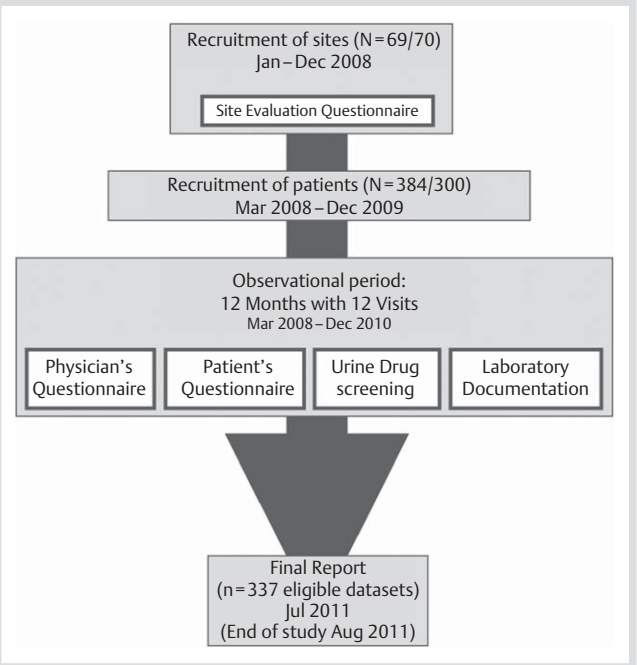

Fig. 1 Design of the non-interventional study with buprenorphine-naloxone.

Study design

The study was a nationwide, prospective 12-month observational, non-interventional, post-authorization safety study (PASS) with patients currently in drug dependence treatment with another medication such as d/l-methadone, levo-methadone or buprenorphine for whom a switch to buprenorphine-naloxone was indicated and planned (**Fig. 1**). A comprehensive paper-based clinical research form was used for data capture. The study was part of the Risk Management Plan (RMP) for the newly marketed product buprenorphine-naloxone (Suboxone®) and therefore a requirement of the European Medicine Agency (EMA). The study is registered with the National Institute of Health (NIH) at ClinicalTrials.gov (NCT00723749).

Study population

From N = 69 physicians working in addiction medicine and qualified pursuant to German Controlled Substances Regulation (Betäubungsmittelverordnung, BtMVV) § 5 (2) (1) (6) and with authorization granted by the Association of Statutory Health Insurance Physicians (Kassenärztliche Vereinigung, KV) N = 384 opioid-dependent patients were enrolled (total population). All patients over 15 years of age who had consented to opioid drug dependence treatment within the scope of medical, social and psychotherapeutic measures, for whom the switch to buprenorphine-naloxone was indicated and planned and who had signed the informed consent form could be included. The participating physicians were not subject to directives in terms of the use of buprenorphine-naloxone and prescribed the medication in the form of a conventional, commercially available product. Therapeutic indications and contraindications for opioid dependence treatment according to the Summary of Product Characterization (SmPC) for buprenorphine-naloxone and national treat-

Points of observation / Method	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12
	Day 0	Day 1	Day 2	Day 3	Day 5	Day 7	Week 2	Week 4	Week 8	Week 12	Month 6	Month 12 or Drop out documentation
Patients informed consent (IC)	X											
Socio-demographics	X										X	X
Addiction/medical history	X											
Drug, alcohol, tobacco use	X										X	X
Vital parameters	X										X	X
Physical examination	X										X	X
Co-morbidities	X	X	X	X	X	X	X	X	X	X	X	X
Co-medications	X	X	X	X	X	X	X	X	X	X	X	X
Urine drug screening	X							X	X	X	X	X
Laboratory screening	X									X	X	X
SF-36 Health Survey	X							X		X		X
OOWS/SOWS	X	X	X	X	X	X	X	X	X	X	X	X
VAS Craving	X	X	X	X	X	X	X	X	X	X	X	X
SCL-90R	X							X		X	X	X
CGI/CGI-I	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE	X	X	X	X	X	X	X	X	X	X	X	X
Dosing, mode of allocation, cost unit		X	X	X	X	X	X	X	X	X	X	X
Course of therapy		X	X	X	X	X	X	X	X	X	X	X
Reason for drop out												X

Fig. 2 Flow chart parameters, methods and time points of observation.

ment guidelines had to be observed when selecting patients for participation in the non-interventional study.

Of this total population n = 47 datasets were excluded from the final analysis. Reasons were treatment not started (only baseline documentation available, n = 18), missing final documentation (month 12 or drop-out, n = 21) and incomplete documentation (no documentation of induction phase and follow-up documentation, n = 8).

The final analysis population of n = 337 eligible datasets contains all patients with written informed consent, as approved by the ethics committee of the Ludwig-Maximilian University in Munich, as well as complete study documentation for at least baseline (day 0), start of treatment with buprenorphine-naloxone (day 1) and the final documentation either as end-of-observation (month 12) or drop-out documentation. For n = 3 patients day 1 documentation was missing and documentation of day 2 of treatment with buprenorphine-naloxone was used instead.

Assessments

Physicians questionnaire (third-party assessment)

The treating physicians informed eligible patients about the purpose of the study, the data collection procedure and the data privacy protection. Only after agreeing to all aspects and signing the informed consent form the baseline assessment, which was conducted before switching the patient to buprenorphine-naloxone, could be commenced.

The physician's questionnaire for evaluation of the patients was a paper-based assessment tool specially developed for the non-interventional study with 45 pages including 12 sections with several standardized instruments to document the following patient parameters: socio-demographics, substance use history, treatment history, co-morbidities, co-medication, concomitant drug use, urine drug screening, main reason for switch to buprenorphine-naloxone, treatment with buprenorphine-naloxone, premature discontinuation before end of observation, effectiveness measures with modified Clinical Global Impression (mCGI), Objective Opiate Withdrawal Scale (OOWS), and safety. It was the physician's decision which treatment data were transferred from the patient's medical chart to the questionnaire.

The CGI [23] is a standard measure for global assessments of illness consisting of 3 different global measures. In the study a modification of the Clinical Global Impression Severity scale (CGI-S) and a modification of the Clinical Global Impression Improvement scale (CGI-I) was used. The OOWS [24] is a standardized scale for measuring the physically observable signs of opiate withdrawal for rating by the physician.

All adverse events (non-serious and serious including adverse drug reactions and pregnancies) were listed as they were spontaneously reported and documented at each visit by the treating physician.

Patients questionnaires (self assessment)

During the 12-month observational period all patients were asked to complete 4 standardized questionnaires in accordance with the schedule of observation points (**Fig. 2**): 1) Short Form 36 – Health Survey (SF-36) [25], a 36-item self-assessment questionnaire to survey the current health status with 2 modified indication specific questions in reference to drug dependence; 2) Subjective Opiate Withdrawal Scale (SOWS) [24], the subjective counterpart of the OOWS is a standardized scale for measuring the intensity of symptoms of opiate withdrawal from the perspective of the patient; 3) revised psychiatric Symptom Check-List (SCL-90R) [26,27], a standardized self-assessment tool to measure subjective impairment due to somatic and psychiatric symptoms; 4) visual analogue scale for craving (VAS Craving), an instrument specially invented for the non-interventional study by the first author containing twelve 100-mm visual analogue scales for the substances alcohol, cannabis, amphetamines, hallucinogens, cocaine, barbiturates, benzodiazepines, opiates, d/l-methadone/levo-methadone, buprenorphine, codeine/DHC and other. Patients were asked to visualize their current craving for each of the listed substances.

Assessment schedule

To ensure eligible and valid data collection for comprehensive evaluation of induction and course of drug dependence treatment with buprenorphine-naloxone compared to baseline data before switch to the new medication, physician's and patient's questionnaires were scheduled for specific time points of observation (**Fig. 2**).

Statistics and analysis

Except for socio-demographics, retention rate, regular end of treatment and safety all comparisons were made between baseline (day 0) and final assessment as regular end of observation (month 12) or premature discontinuation documentation (drop-

out) for the total sample as well as for the analysis groups. Analyses concerning treatment with buprenorphine-naloxone used day 1/start of treatment as baseline measures.
Single and multinomial logistic regression and chi-square tests were used for descriptive correlations between the defined analysis groups, start and end of observation. For numerical parameters, sample statistics, mean and standard deviation, minimum and maximum were calculated. For categorical data, absolute and relative frequencies were calculated. Data generated repeatedly in the course of time were evaluated per observation point. The differences between baseline and final assessment are shown for specific numerical data as absolute and relative difference.
Retention rates were estimated using Kaplan-Meier method and are presented as survival curves and 12-month survival estimates.
The options "not tested" and "no test" were set to missing values. For the option "no change" the status from the previous visit was carried forward.
Statistical significance was defined as p-values < 0.05. Statistical analysis was done with STATA/SE 9 [28].

Measures and specifications

Retention rate: percentage of patients still in drug dependence treatment with buprenorphine-naloxone at the end of the observation period or who completed treatment after achieving a successful therapeutic outcome (regular end of treatment/abstinence).

Safety: percentage of all documented non-serious and serious adverse events including adverse drug reactions, which were coded using MedDRA version 11.1 [29].

Effectiveness: improvement of scores from the standardized instruments mCGI for general health, SCL-90R for mental health, OOWS and SOWS for withdrawal; regular end of treatment (patient abstinent) documented by the treating physician in the final assessment as premature discontinuation documentation was defined as positive treatment outcome and patients were counted as completers.

Quality of life (QoL): improvement of scores from the standardized instrument SF-36 comparing baseline with the final assessment.

Acceptance and tolerance: reduction of concomitant drug use measured by urine drug screening, craving for illicit substances measured by the standardized instrument VAS craving and number of fresh needle marks.

Analysis groups (post-hoc generation)

Completers: patients still in drug dependence treatment with buprenorphine-naloxone at the end of observation (month 12) including patients with dropout reason regular end of treatment (patient abstinent from all illegal drugs including opiate-substitution).

Non-completers: patients with documented premature discontinuation of treatment with buprenorphine-naloxone for any reason other than regular end of treatment (patient abstinent).

Pre-treated: patients with documented current maintenance pharmacotherapy at baseline.

Untreated: patients without any documented previous maintenance pharmacotherapy at baseline [patients with no current maintenance treatment at study entry, but with a history of previous substitution treatment(s) are excluded from analysis between pre-treated and untreated patients].

Buprenorphine: patients in treatment with the mono compound buprenorphine at baseline.

(Levo-)methadone: patients in treatment with d/l-methadone or levo-methadone at baseline.

The term *analysis groups* refers to the above defined groups of completer/non-completer, pre-treated/untreated and buprenorphine/(levo-)methadone.

Results

Data from N = 337 eligible patients was examined.

Patient population

Socio-demographics

Table 1 summarizes patient characteristics at baseline for the total sample and all analysis groups. Most of the patients were male and in their mid-thirties, ranging from 18–62 years, and German nationality. Completers were older, married or living with a partner, working in a full-time job and living in their own flat. Higher rates of the more unfavourable characteristics such as unemployment, being divorced or single and being homeless are found in the group of non-completers.

Addiction history

As shown in **Table 1** N = 244 patients were in maintenance treatment with buprenorphine (66.4%), d/l-methadone (20.9%), levo-methadone (9.8%) or another maintenance drug (2.9%) at baseline. For n = 49 patients the treatment with buprenorphine-naloxone was their first opioid drug dependence treatment and n = 44 patients were previously but not at baseline in maintenance treatment. Most of the participating patients had a long opioid addiction history from almost 14 years on average, ranging from 4 months to 50 years. Patients switched from the mono-compound buprenorphine and pre-treated patients had a significantly longer drug addiction history [patients with no current maintenance treatment at study entry, but with a history of previous substitution treatment(s) are excluded from analysis between pre-treated and untreated patients].
Almost all patients used opioids in their life (94.6%) with no difference within the analysis groups. Non-completers revealed significantly higher rates in the use of benzodiazepines (72.7% vs. 56.5% completer, p = 0.003), cocaine (85.5% vs. 64.9%, p ≤ 0.001), amphetamines (67.2% vs. 36.8%, p ≤ 0.001), hallucinogens (42.5% vs. 25.8%, p = 0.002), codeine (36.1% vs. 18.8%, p = 0.001), barbiturates (29.0% vs. 11.2%, p ≤ 0.001). Pre-treated patients revealed significantly higher rates in the use of cocaine (75.4% vs. 59.6% untreated, p = 0.039), benzodiazepines (64.2% vs. 47.9%, p = 0.035) and codeine (27.4% vs. 10.9%, p = 0.018). Significantly higher rates of life-time cannabis use were found in the group of patients switched from buprenorphine [91.9% vs. 79.7% (levo-)methadone, p = 0.008].

Table 1 Patient's characteristics at baseline.

	Total Sample	Completers	Non-Completers	p	Pre-Treated	Un-Treated	p	Buprenorphine	(Levo-) Methadone	
	337*	195	142		244	49		162	75	p
Age in years [mean (SD)] N = 336	35.1 (8.8)	36 (9.0)	33.9 (8.4)	**0.029**	35.7 (8.8)	32.6 (8.6)	**0.025**	36.8 (8.8)	33.5 (7.8)	**0.006**
Male [n (%)] N = 337	258 (76.6)	154 (79.0)	104 (73.2)	0.220	192 (78.7)	36 (73.5)	0.422	119 (73.5)	66 (88.0)	**0.012**
German nationality [n (%)] N = 336	281 (83.6)	162 (83.1)	119 (84.4)	0.747	196 (80.3)	43 (87.8)	0.221	134 (82.7)	56 (74.7)	0.148
BMI [mean (SD)] N = 332	23.8 (3.9)	24 (3.9)	23.5 (3.9)	0.214	23.9 (3.9)	23.2 (3.9)	0.226	23.9 (4.1)	24 (3.5)	0.911
Marital status [n (%)] N = 334										
– Single	201 (60.2)	108 (56.3)	93 (65.5)	0.088	145 (60.2)	29 (59.2)	0.898	91 (57.2)	47 (62.7)	0.430
– Married/living together	102 (30.6)	69 (35.9)	33 (23.2)	**0.013**	73 (30.3)	16 (32.7)	0.744	49 (30.8)	24 (32.0)	0.855
– Divorced	30 (9.0)	14 (7.3)	16 (11.3)	0.209	23 (9.5)	4 (8.2)	0.762	19 (11.9)	4 (5.3)	0.113
Children [n (%)] N = 331	120 (36.3)	70 (37.0)	50 (35.2)	0.732	90 (37.8)	13 (26.5)	0.134	68 (42.5)	22 (31.0)	0.098
Occupation [n (%)] N = 337										
– Full-time job	77 (22.8)	51 (26.1)	26 (18.3)	0.090	60 (24.6)	8 (16.3)	0.211	49 (30.3)	11 (14.7)	**0.010**
– Part-time job	48 (14.2)	24 (12.3)	24 (16.9)	0.233	40 (16.4)	3 (6.1)	0.064	28 (17.3)	11 (14.7)	0.613
– Unemployed	179 (53.1)	100 (51.3)	79 (55.6)	0.429	122 (50.0)	29 (59.2)	0.240	69 (42.6)	48 (64.0)	**0.002**
Residential status [n (%)] N = 337										
– Own flat	246 (73.0)	150 (76.9)	96 (67.6)	0.057	185 (75.8)	32 (65.3)	0.125	137 (84.6)	45 (60.0)	**<0.001**
– With family/friends	63 (18.7)	35 (17.9)	28 (19.7)	0.681	42 (17.2)	14 (28.6)	0.065	15 (9.3)	23 (30.7)	**<0.001**
– Homeless	5 (1.5)	0 (0.0)	5 (3.5)	**0.008**	3 (1.2)	1 (2.0)	0.655	1 (0.6)	2 (2.7)	0.189
Years of dependence [mean (SD)] N = 311	13.8 (8.7)	14.6 (8.5)	12.8 (8.8)	0.077	14.9 (8.9)	8.5 (6.4)	**<0.001**	15.9 (9.3)	12.7 (6.8)	**0.009**
In maintenance treatment with [n (%)] N = 244										
– Buprenorphine	162 (66.4)	93 (66.4)	69 (66.4)	0.989	162 (66.4)	0 (0.0)		162 (100.0)	0 (0.0)	
– D/l methadone	51 (20.9)	29 (20.7)	22 (21.2)	0.933	51 (20.9)	0 (0.0)		0 (0.0)	51 (68.0)	
– Levo-methadone	24 (9.8)	18 (12.9)	6 (5.8)	0.066	24 (9.8)	0 (0.0)		0 (0.0)	24 (32.0)	
Without prior maintenance treatment [n (%)] N = 337	49 (14.5)	29 (14.9)	20 (14.1)	0.958	0 (0.0)	49 (100.0)		0 (0.0)	0 (0.0)	
≥1 prior detoxification attempt [n (%)] N = 254	209 (82.3)	119 (79.9)	90 (85.7)	0.229	158 (84.5)	15 (55.6)	**<0.001**	105 (83.3)	48 (87.3)	0.500
≥1 prior withdrawal attempt [n (%)] N = 229	142 (62.0)	83 (60.6)	59 (64.1)	0.588	108 (65.1)	8 (30.8)	**0.001**	72 (65.5)	34 (65.4)	0.993
≥1 prior self detoxification attempt [n (%)] N = 197	151 (76.7)	85 (77.3)	66 (75.9)	0.816	105 (75.5)	17 (65.4)	0.279	63 (70.0)	38 (86.4)	**0.039**
Hepatitis C infection [n (%)] N = 335	121 (36.1)	62 (31.8)	59 (42.1)	**0.009**	96 (43.2)	9 (27.3)	0.082	63 (43.2)	30 (43.5)	0.964
HIV infection [n (%)] N = 272	4 (1.2)	2 (1.0)	2 (1.4)	0.637	4 (1.9)	0 (0.0)	0.454	3 (2.2)	0 (0.0)	0.228
Psychiatric comorbidity [n (%)] N = 337	193 (57.3)	106 (54.4)	87 (61.3)	0.195	144 (59.0)	27 (55.1)	0.612	93 (57.4)	47 (62.7)	0.444
Number of psychiatric comorbidities [mean (SD)]	2 (1.5)	1.9 (1.6)	2.1 (1.5)	0.538	2.1 (1.6)	1.4 (0.7)	**0.027**	1.8 (1.4)	2.7 (1.9)	**0.005**

* Eligible datasets

Percentages refer to non-missing total and vary within analysis groups

The average daily dosage for pre-treated d/l-methadone patients was 41.8 ± 37.2 mg (2–160 mg), levo-methadone patients 26.5 ± 17.1 mg (4–60 mg) and buprenorphine patients 7.7 ± 4.3 mg (1–24 mg) at baseline.

Retention rate and drop-out

Retention rate

Of the total eligible patients n = 181 were still in treatment at the end of observation after 12 months of treatment with buprenorphine-naloxone and n = 14 patients terminated their treatment during the observation period because they were rated as abstinent by their treating physician. The 12-month retention rate, analyzed with Kaplan-Meier estimator, was 57.1% for the total analysis population (**Fig. 3**). There were no differences between pre-treated and untreated patients (**Fig. 3**). A slightly higher retention rate was found in (levo-)methadone patients (**Fig. 4**).

Reasons for dropout

N = 142 patient terminated treatment before end of observation. The most frequently documented reasons for drop out were "lost to follow up" (16.7%), "concomitant drug use/relapse" (12.2%), "side effects" (12.2%) and "non-compliance/disciplinary reasons" (10.9%). Significantly more untreated patients (16.7% vs. 4.6% pre-treated, p = 0.033) were rated as abstinent by the treating physician. No deaths occurred during the entire observational period. Only n = 1 hospitalization and n = 3 pregnancies led to premature termination of treatment with buprenorphine-naloxone.

Safety

Safety reporting for non-interventional studies is done according to regulations for routine care practice in Germany. The research forms of this study contained special sheets for documentation of all adverse events and the physician's folder provided reporting forms for serious adverse events but it was the physician's decision if an incident during the observation period required documentation and reporting, respectively. Therefore only non-serious and serious adverse events documented and reported by the treating physician could be included in the analysis. In this paper the adverse events reported were evaluated for the analysis population only.

Serious adverse events (SAE)

For n = 4 (1.2%) of the patients from the analysis population (N = 337) there were n = 4 serious adverse events reported during the complete observational period including 30 days post-study time. The events, listed as system organ class and the term reported by the treating physician (in brackets) were n = 1 psychiatric disorder (hospitalization because of suspected adjustment disorder), n = 1 social circumstances (concomitant drug use), n = 1 surgical and medical procedure (stay in hospital) and n = 1 nervous system disorder (epilepsy). One event was reported with certain correlation to the study drug (concomitant drug use), one with likely correlation (hospitalization because of suspected adjustment disorder), one with unlikely correlation (epilepsy) and one with unknown relation to the study drug (stay in hospital).

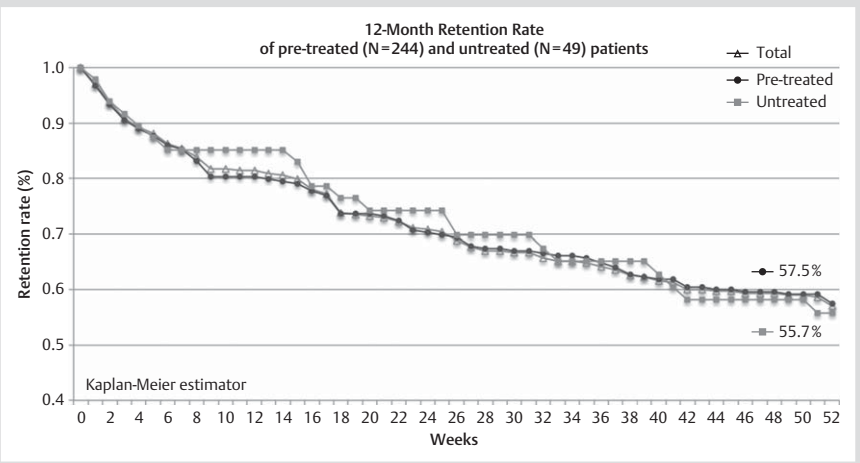

Fig. 3 12-month retention of the total analysis population (N = 337), pre-treated (n = 244) and untreated (n = 49) patients.

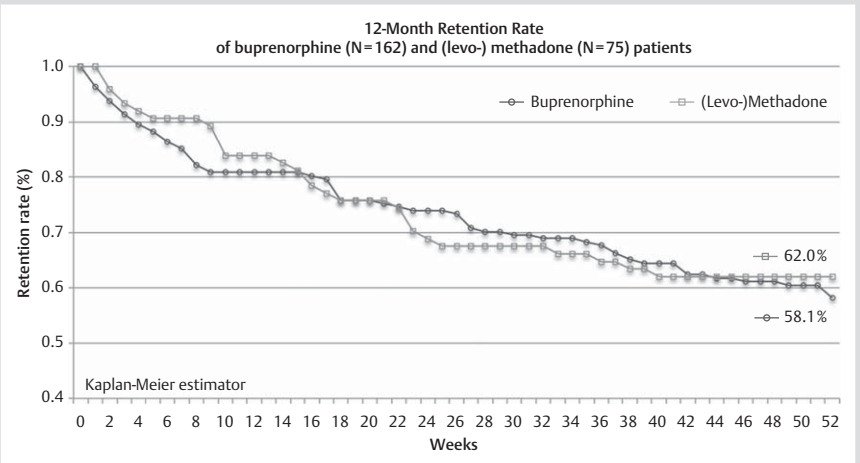

Fig. 4 12-month retention of buprenorphine (n = 162) and (levo-)methadone (n = 75) patients.

No differences within the analysis groups were found in reference to the occurrence of SAEs. No deaths were reported during the study.

Non-serious adverse events (NSAE)

For n = 59 (17.5%) patients n = 141 non-serious adverse events were reported. NSAEs with a threshold of over 5.0% were psychiatric disorders (17.7%), social circumstances (15.6%, most of them concomitant drug use/non-compliance), gastrointestinal disorders (12.8%), infections and infestations (12.8%), nervous system disorders (9.9%) and musculoskeletal and connective tissue disorders (9.2%). 5 of the NSAEs were reported as certainly correlated to the study drug, n = 27 likely related, n = 32 possibly related, n = 67 unlikely related and n = 10 were reported as unknown concerning relation to the study drug. Significantly more non-completers (23.2% vs. 13.3% completers, p = 0.018) and pre-treated patients (20.5% vs. 8.2% untreated, p = 0.042) were reported with non-serious adverse events. No difference was found between buprenorphine and (levo-) methadone patients concerning number of NSAEs.

Treatment with buprenorphine-naloxone

Reason for switch to buprenorphine-naloxone

The main reasons for switching to buprenorphine-naloxone were long-term maintenance treatment with or without abstinence as final goal (28.8%), prior maintenance treatment not successful (21.4%), planned detoxification treatment (17.8%) and prevention of buprenorphine misuse (17.5%). For 11.9% the physicians reported "patient's wish for take home" as reason for the switch to buprenorphine-naloxone.

Dosing of buprenorphine-naloxone

The mean induction dose of buprenorphine-naloxone was 9.2 ± 5.1 mg per day with a maximum of 32.0 mg. This dose slightly increased to 9.6 mg on day 2 and 3 of the treatment with buprenorphine-naloxone and decreased continuously in the course of treatment to 7.7 mg per day. Non-completers received generally higher doses, but those non-completers who were still in treatment at month 6 (n = 37) received virtually the same dose as completers (**Fig. 5**). Patients switched from d/l-methadone or levo-methadone received higher doses of buprenorphine-naloxone than patients switched from the mono-compound buprenorphine (**Fig. 6**). Doses of previous buprenorphine patients did not change during the course of treatment with buprenorphine-naloxone. Interestingly pre-treated and untreated patients' dose of buprenorphine-naloxone did not differ (**Fig. 7**).

Patients rated as abstinent during the observation period (n = 14) were not included in the analyses shown above. Their mean induction dose of buprenorphine-naloxone was 8.5 ± 6.3 mg which decreased rapidly to 7.0 ± 4.7 mg at day 7, 4.6 ± 2.6 mg at week 4 and 2.0 ± 1.6 mg at their final assessment.

Mode of prescription

At the induction day most of the patients (87.1%) received buprenorphine-naloxone on a daily basis at the practice of the treating physician and 8.4% as take-home prescription. All of the take-home prescriptions were documented for pre-treated patients and significantly more for buprenorphine patients (14.4% vs. 5.3% (levo-)methadone, p = 0.043). Take-home prescription increased during treatment with buprenorphine-naloxone and was documented for 25.1% of the patients at the final assessment. Significantly more completers (30.1% vs. 18.3% non-completers, p = 0.014) received take-home at the time of their final assessment.

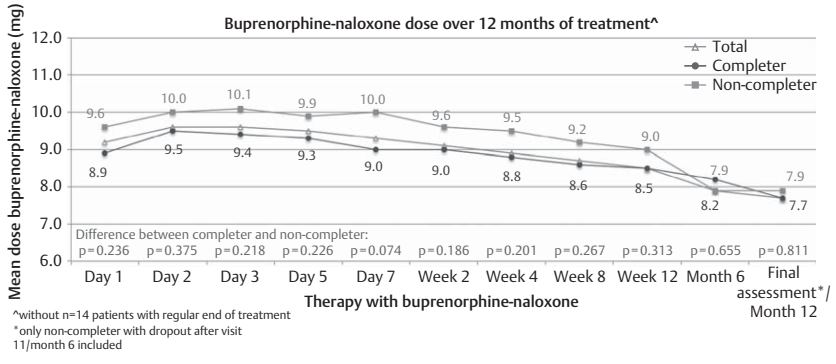

Fig. 5 Mean dose buprenorphine-naloxone (mg/day) for all eligible patients (N = 323), completers (n = 181) and non-completers (n = 142).

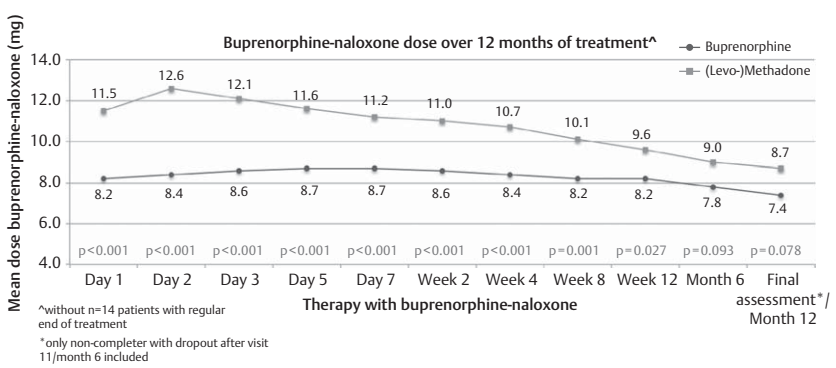

Fig. 6 Mean dose buprenorphine-naloxone (mg/day) for buprenorphine patients (n = 159) and (levo-)methadone patients (n = 73).

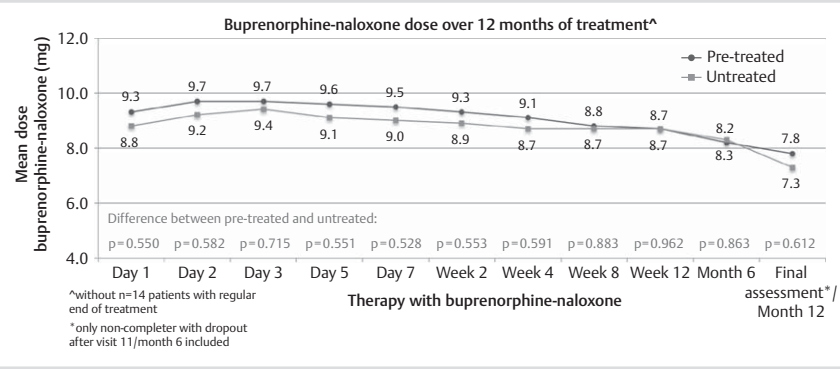

Fig. 7 Mean dose buprenorphine-naloxone (mg/day) for pre-treated (n = 239) and untreated (n = 45) patients.

Quality of life

SF-36

As shown in **Table 2** the scores of the standardized patient questionnaire SF-36 were relatively low at baseline but increased during treatment with buprenorphine-naloxone significantly for all scales. There was no difference between completers and non-completers at baseline except for pain. At the final assessment completers had significantly higher scores in all scales and non-completers revealed no substantial improvement from baseline to final assessment.

Pre-treated patients had higher scores at baseline but at the final assessment untreated patients achieved higher scores in all scales of the SF-36 and significantly for the scales emotional well-being and drug dependence compared to pre-treated patients.

At baseline buprenorphine patients achieved significantly higher rates compared to (levo-)methadone patients but no difference was found at the final assessment. While (levo-)methadone patients improved significantly in all scales, buprenorphine patients showed only for pain, social functioning, emotional role functioning and drug dependence significant improvement from baseline to final assessment.

Effectiveness of the treatment with buprenorphine-naloxone

Mental health

As shown in **Table 3** the mean scores of the SCL-90-R at baseline are higher in all scales for non-completers, untreated and (levo-)methadone patients. All patients achieved a significant improvement of psychiatric distress at their final assessment irrespective of analysis group.

Modified Clinical Global Impression – Severity scale (mCGI-S)

Fig. 8 shows the modified CGI measuring the general health of the patient from the perspective of the physician. The categories were transformed to numeric scores (0 = very good to 5 = extremely bad). There was no difference between completers and non-completers but untreated and (levo-) methadone patients received significantly higher scores at baseline. According to the physicians the general health of all patients improved significantly during treatment with buprenorphine-naloxone except for non-completers. Their general health slightly worsened and the score was significantly higher ($p < 0.001$) at the final assessment compared to completers.

Withdrawal

SOWS: The total score of the subjective opiate withdrawal scale at baseline was 17.2 ± 13.5 and decreased to 5.1 ± 8.4 at final assessment. Non-completers achieved a significantly higher score at baseline (19.0 ± 13.6 vs. 15.9 ± 13.4 completers, $p = 0.043$) and final assessment (11.7 ± 11.7 vs. 3.9 ± 7.0, $p < 0.001$). Untreated patients (20.8 ± 14.7 vs. 14.9 ± 12.5 pre-treated, $p = 0.005$) and (levo-) methadone patients (20.3 ± 13.2 vs. 11.8 ± 10.5 buprenorphine, $p < 0.001$) achieved a significantly higher score at baseline but did not differ from their comparison group at final assessment. All groups, except non-completer, achieved a significant reduction of subjective opiate withdrawal during the treatment with buprenorphine-naloxone.

OOWS: The total score of the objective opiate withdrawal scale reported by the treating physicians was 8.8 ± 8.1 at baseline and decreased significantly to 2.2 ± 4.8 ($p < 0.001$). From the physician's perspective there was no difference between completers and non-completers concerning opiate withdrawal at baseline, but at the final assessment non-completers received a significantly higher score (3.8 ± 6.2 vs. 1.1 ± 3.0 completers, $p < 0.001$). Untreated (12.7 ± 7.4 vs. 7.2 ± 7.6 pre-treated, $p < 0.001$) and (levo-) methadone (11.1 ± 7.7 vs. 4.9 ± 6.3 buprenorphine, $p < 0.001$) patients showed significantly more withdrawal symptoms at baseline. At the end of the observation physicians saw no difference between untreated and pre-treated patients, but in buprenorphine patients they identified more objective withdrawal symptoms [2.2 ± 4.4 vs. 1.1 ± 3.3 (levo-)methadone, $p = 0.050$].

Regular end of treatment

For n = 14 patients the premature discontinuation within the 12-month observation period was the regular end of treatment with buprenorphine-naloxone because they were rated as abstinent by their treating physician (4.2 % of the total eligible patient population). Significantly more patients without prior maintenance treatment became abstinent (8.2 % vs. 2.1 % pre-treated, $p = 0.002$). No difference was found between patients with prior buprenorphine treatment and treatment with (levo-)methadone.

Acceptance and tolerance

Concomitant drug use

According to the results of urine drug screenings (**Table 4**) approximately one-third of the patients had a current use of opioids and cannabis at baseline. Significantly higher rates of

Table 2 SF-36 at baseline and final assessment for all eligible patients (N = 337).

	SF-36 Baseline (BL) vs. Final assessment (FA) Mean (SD)																	
	Physical functioning		Physical role functioning		Pain		General Health		Energy/Fatigue		Social functioning		Emotional role functioning		Emotional well being		Drug dependence	
	BL	FA	BL	FA	BL	FA	BL	FA	BL	FA	BL	FA	BL	FA	BL	FA	BL	FA
Total	79.1 (23.9)	90.1*** (16.5)	28.8 (21.2)	41.7*** (16.7)	55.7 (26.0)	72.8*** (18.0)	48.5 (20.9)	54.4*** (20.8)	43.5 (19.8)	55.9*** (19.3)	58.3 (29.1)	78.1*** (22.5)	51.8 (44.2)	83.7*** (32.2)	49.4 (20.9)	62.6*** (17.9)	53.9 (24.5)	73.8*** (20.1)
Completer	78.9 (24.1)	91.4*** (13.9)	30 (21.2)	43.3*** (15.2)	59.3 (24.3)	74.7*** (15.9)	49 (21.1)	55.8*** (20.9)	43.4 (20.6)	57.6*** (19.0)	59.8 (28.5)	79.6*** (20.7)	55.1 (43.9)	87.0*** (29.2)	49.5 (21.5)	64.4*** (16.9)	55.1 (24.7)	75.4*** (18.3)
Non-completer	79.3 (23.8)	82.8 (26.0)	27 (21.0)	33.1 (21.8)	50.5 (27.5)	62.3 (24.5)	47.7 (20.6)	46.7 (19.1)	43.7 (18.8)	46.2 (18.7)	56.1 (30.0)	69.8 (30.0)	47.2 (44.4)	65.6 (41.5)	49.1 (20.1)	52.7 (20.6)	52.3 (24.4)	65.1 (26.6)
Diff. C vs. NC	p = 0.895	p = 0.009	p = 0.202	p = 0.002	p = 0.003	p < 0.001	p = 0.585	p = 0.031	p = 0.904	p = 0.003	p = 0.265	p = 0.031	p = 0.120	p < 0.001	p = 0.861	p = 0.001	p = 0.305	p = 0.010
Pre-treated	81.2 (22.5)	89.1*** (17.6)	31.8 (20.6)	41.2*** (16.9)	59.9 (24.1)	72.2*** (19.0)	50.8 (21.2)	54.0* (21.4)	46.3 (19.8)	55.5*** (19.2)	61.7 (28.5)	77.0*** (23.5)	56.4 (44.2)	82.2*** (33.4)	52.5 (20.6)	61.8*** (18.4)	56.7 (24.3)	72.4*** (20.8)
Untreated[#]	73.8 (27.9)	93.8* (11.2)	22.8 (20.7)	42.9** (17.9)	43.7 (27.6)	74.7*** (14.2)	42.4 (17.5)	61.8** (18.6)	33.5 (16.4)	63.0*** (18.4)	44.4 (29.3)	83.0*** (17.5)	46.5 (46.1)	95.2** (21.8)	38.9 (18.6)	70.9*** (15.5)	46 (24.9)	82.0*** (17.0)
Diff. PT vs. UT	p = 0.052	p = 0.232	p = 0.008	p = 0.676	p < 0.001	p = 0.557	p = 0.014	p = 0.109	p < 0.001	p = 0.088	p < 0.001	p = 0.258	p = 0.183	p = 0.086	p < 0.001	p = 0.028	p = 0.007	p = 0.041
Buprenorphine	84.8 (19.8)	90.4 (17.1)	35.3 (18.8)	41 (17.3)	62.6 (58.9)	72.8* (19.1)	54.6 (21.8)	55 (23.0)	50.8 (18.8)	55.1 (20.1)	67.3 (28.3)	77.5* (25.2)	64.4 (41.7)	83.2** (33.8)	57 (19.4)	61.7 (19.4)	60.7 (23.6)	73.7** (21.3)
(Levo-) methadone	73.2 (19.8)	88.9*** (13.5)	23.5 (22.2)	42.7*** (14.9)	55.1 (23.6)	74.1*** (14.7)	43.3 (17.5)	52.7*** (18.1)	37.4 (18.7)	57.3*** (16.2)	50 (25.0)	77.8*** (16.6)	38.2 (45.1)	82.3*** (31.3)	43 (20.0)	62.9*** (14.6)	48.9 (23.4)	71.0*** (17.6)
Diff. B vs. LM	p < 0.001	p = 0.602	p < 0.001	p = 0.560	p = 0.029	p = 0.678	p < 0.001	p = 0.531	p < 0.001	p = 0.503	p < 0.001	p = 0.934	p < 0.001	p = 0.882	p < 0.001	p = 0.684	p < 0.001	p = 0.442

Significance level baseline vs. final assessment: * < 0.05; ** < 0.01; *** < 0.001

[#] n = 22 final SF-36 assessments from untreated patients available

Table 3 Changes in psychiatric status: SCL-90-R.

	Psychiatric Status: SCL90-R individual scales Baseline vs. Final assessment Mean sum score (SD)																	
	Somatization		Obsessive-Compulsive		Interpersonal Sensitivity		Depression		Anxiety		Hostility		Phobic Anxiety		Paranoid Ideation		Psychoticism	
	BL	FA	BL	FA	BL	FA	BL	FA	BL	FA	BL	FA	BL	FA	BL	FA	BL	FA
Total	8.7 (8.6)	3.6*** (6.2)	8.2 (7.3)	3.2*** (5.8)	6.1 (6.2)	2.5*** (4.7)	11.8 (10.5)	4.8*** (7.9)	7.2 (7.3)	2.7*** (5.5)	4.8 (4.5)	2.0*** (3.4)	3 (4.4)	1.3*** (3.2)	4 (4.2)	1.5*** (3.0)	4.2 (5.7)	1.6*** (4.1)
Completer	7.9 (8.8)	3.1*** (5.6)	7.5 (7.3)	2.7*** (5.5)	5.8 (6.4)	2.2*** (4.6)	10.9 (10.7)	4.1*** (7.2)	6.5 (7.2)	2.0*** (4.5)	4.4 (4.2)	1.7*** (3.1)	2.7 (4.4)	1.0*** (2.9)	3.8 (4.4)	1.4*** (3.0)	3.7 (5.7)	1.4*** (3.9)
Non-completer	9.7 (8.3)	6.3 (8.2)	9.2 (7.2)	5.7 (6.9)	6.5 (6.0)	4.2* (5.2)	13 (10.1)	8.7 (10.0)	8.2 (7.3)	6.5 (8.1)	5.3 (4.9)	3.6 (5.0)	3.5 (4.3)	2.8 (4.6)	4.2 (4.0)	2.2 (3.1)	4.8 (5.7)	2.9 (4.8)
	p=0.076	p=0.008	p=0.039	p=0.010	p=0.345	p=0.026	p=0.085	p=0.003	p=0.040	p<0.001	p=0.094	p=0.005	p=0.135	p=0.006	p=0.440	p=0.191	p=0.078	p=0.059
Pre-treated	7.8 (8.0)	3.9*** (6.8)	7.5 (6.9)	3.6*** (6.4)	5.9 (6.0)	2.9*** (5.1)	11 (10.0)	5.5*** (8.6)	6.6 (7.1)	3.2*** (6.1)	4.4 (4.3)	2.3*** (3.8)	2.8 (4.1)	1.5*** (3.6)	3.8 (3.9)	1.8*** (3.3)	4.1 (5.4)	2.0*** (4.5)
Untreated	9.8 (10.4)	1.6** (2.2)	9.7 (8.4)	1.2** (1.8)	6.6 (6.7)	1.3** (1.8)	14.3 (12.1)	2.3** (2.9)	8.5 (7.3)	1.0*** (1.1)	5.7 (4.9)	1.0** (1.7)	3.9 (5.2)	0.8 (1.7)	4.4 (4.7)	0.5** (0.9)	4.4 (6.7)	0.5* (1.4)
	p=0.137	p=0.127	p=0.060	p=0.090	p=0.501	p=0.163	p=0.053	p=0.091	p=106	p=0.101	p=0.085	p=0.118	p=0.127	p=0.363	p=0.312	p=0.074	p=0.681	p=0.127
Buprenor-phine	6.6 (6.9)	3.6* (6.0)	6.2 (5.9)	3.2** (6.3)	4.9 (5.3)	2.4*** (5.0)	9.4 (9.3)	5.0*** (8.3)	5.1 (5.6)	2.7* (5.3)	3.5 (3.5)	2.0** (3.4)	2.1 (3.4)	1 (2.8)	3.2 (3.6)	1.6*** (3.2)	3.2 (4.0)	1.4** (3.2)
(Levo-) methadone	9.8 (9.5)	3.5*** (7.0)	10.1 (7.9)	4.0*** (6.3)	7.7 (6.9)	3.3*** (4.8)	14.7 10.7)	5.8*** (8.4)	9.5 (8.4)	3.3*** (6.3)	6.2 (5.0)	2.3*** (3.5)	4.2 (4.8)	2.2*** (4.0)	4.8 (44.4)	2.1*** (3.3)	5.8 (7.2)	2.9*** (5.8)
	p=0.006	p=0.937	p<0.001	p=0.507	p=0.001	p=0.355	p<0.001	p=0.598	p<0.001	p=0.547	p<0.001	p=0.573	p<0.001	p=0.047	p=0.005	p=0.320	p<0.001	p=0.035

Significance level baseline vs. final assessment shown at the FA-value: * <0.05; ** <0.01; *** <0.001

Evaluable assessments at baseline: Total 321; completer 185; non-completer 136; pre-treated 233; untreated 45; buprenorphine 161; (levo-)methadone 66

Evaluable assessments at final assessment: Total 192; completer 162; non-completer 30, pre-treated 150, untreated 21, buprenorphine 100, (levo-) methadone 46

BL: Baseline

FA: Final assessment

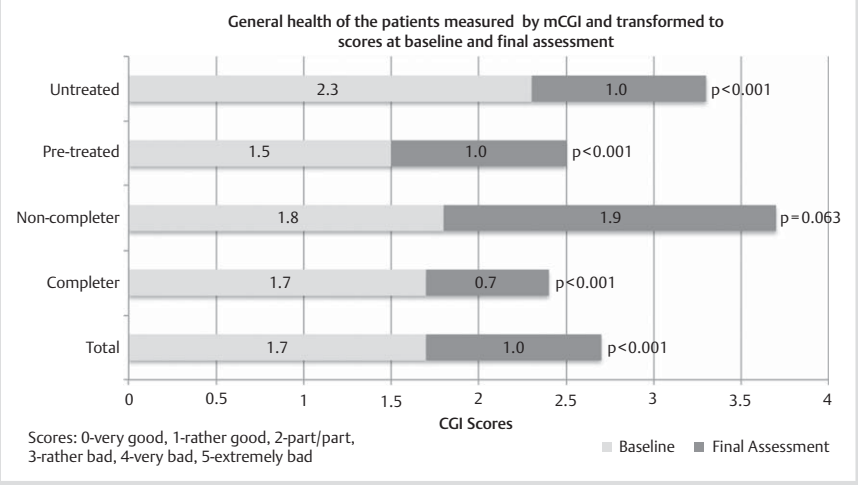

Fig. 8 Modified CGI score at baseline and final assessment for all eligible patients (N = 337).

opioid use were found in non-completers and untreated patients. Significantly more non-completers used cocaine and benzodiazepines, significantly more untreated patients used benzodiazepines and amphetamines and significantly more (levo-) methadone patients used cannabis. During the treatment with buprenorphine-naloxone urine drug screenings revealed a significant reduction of drug use for all illicit substances except barbiturates. Significantly higher rates of opioid use, cocaine, benzodiazepines and amphetamines were found in non-completers compared to completers. Significantly more (levo-)methadone patients were found to be active cannabis users at the final assessment.

Opiate craving (VAS)

Patients reported the highest craving at baseline and the highest decrease of craving during treatment with buprenorphine-naloxone for opiates (32.3 ± 33.2 vs. 7.2 ± 17.3, $p < 0.001$). Non-completers (38.9 ± 35.4 vs. 27.6 ± 30.9 completers, $p = 0.003$) and untreated patients (46.4 ± 37.9 vs. 25.7 ± 29.7 pre-treated, $p < 0.001$) reported a significantly higher total score at baseline, but only non-completers reported a relatively high craving score at the final assessment (24.7 ± 32.5 vs. 4.2 ± 10.5 completers, $p < 0.001$). At the end of the observation untreated patients did not differ from pre-treated patients concerning craving for opiates. There was no difference found between buprenorphine and (levo-)methadone patients at baseline and final assessment. Nevertheless the reduction of craving for opiates was significant for all groups including non-completer.

Fresh needle marks

Physicians documented fresh needle marks for 13.5 % at baseline, for slightly more non-completers (17.3 % vs. 10.8 % completers, $p = 0.086$) and significantly more untreated patients (20.4 % vs. 9.5 % pre-treated, $p = 0.029$). Most of these patients had a positive urine drug screening for opioids (75.6 %).

At the final assessment physicians reported fresh needle marks for n = 10 patients, all of them were non-completers, n = 4 were pre-treated, n = 2 untreated and n = 4 were switched from buprenorphine. Most of these patients had positive drug screenings for opioids (n = 7). Physicians reported no fresh needle marks for (levo-)methadone patients.

Discussion

The results of this non-interventional study underline the overall effectiveness of opioid drug dependence treatment with the 4:1 combination buprenorphine-naloxone. In line with findings in a previous naturalistic study in routine care [30] the 12-month retention rate of patients induced or switched to buprenorphine-naloxone was 55.7–62.0 % depending on previous maintenance treatment. These rates are also in line with results on retention of patients receiving standard methadone treatment [30–32]. No deaths occurred and the very low rate of adverse events emphasizes the high safety profile of buprenorphine-naloxone. Significant improvements in almost all evaluated domains during the 12-month observation period, irrespective of study completion and previous maintenance treatment, verify the effectiveness of the medication found in previous clinical trials [2, 12, 17, 19, 22]. As reported by Wittchen et al. 2008 [30] in their naturalistic study in 2 694 patients, the same proportion of patients (4.2 %) had achieved abstinence during the observational period. Since a certain period (e. g., 5 years) of abstinence is required to reduce the risk of future relapse [3] we recommend a follow-up study to verify the status of patients with documented regular end of treatment because of abstinence.

Compared to international findings on dosing of buprenorphine-naloxone between 16–24 mg/day [33], patients observed in this non-interventional study received lower doses of 10 mg/day on average, which decreased to an average of 8 mg/day at the end of the 12-month observation, irrespective of study completion and previous maintenance treatment. Patients switched from d/l-methadone or l-methadone received significantly higher doses of 11 mg/day on average decreasing until end of study to slightly but non-significantly higher doses of approximately 9 mg/day. Dosing is a critical aspect in the treatment and retention of opioid dependent patients – it is important to alleviate the patient's cravings and withdrawal symptoms. The data of this non-interventional study reveal a significant relation between study completion status and withdrawal symptoms as well as opioid craving scores. Non-completers started with significantly higher subjective opiate withdrawal symptoms and craving which was still significantly higher at the time of their premature discontinuation of treatment with buprenorphine-naloxone. According to the physicians there was no difference concerning objective opiate withdrawal symptoms between non-completers and completers at baseline, but at the final

Table 4 Reduction of drug use during treatment with buprenorphine-naloxone: urine drug screening.

	Drug use: Urine Drug Screening Baseline vs. Final Assessment N (%*)													
	Opioids		Cannabis		Cocaine		Benzodiazepines		Amphetamines		Barbiturates		Tricycl. Antidepr.	
	BL	FA	BL	FA	BL	FA	BL	FA	BL	FA	BL	FA	BL	FA
Total	124 (37.5)	35 (12.8)	83 (32.9)	51 (29.8)	28 (8.5)	17 (6.5)	85 (25.8)	40 (15.2)	14 (5.5)	8 (4.4)	0 (0.0)	1 (1.2)	2 (2.6)	1 (1.7)
Completer	60 (31.6)	3 (1.7)	45 (31.5)	34 (27.4)	6 (3.2)	4 (2.2)	37 (19.4)	17 (9.6)	7 (4.7)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non-completer	64 (45.4)	32 (34.4)	38 (34.9)	17 (36.2)	22 (15.6)	13 (15.5)	48 (35.5)	23 (27.1)	7 (6.6)	7 (12.5)	0 (0.0)	1 (5.6)	2 (6.9)	1 (7.7)
p	0.010	<0.001	0.570	0.264	<0.001	<0.001	0.002	<0.001	0.519	<0.001	n. a.	0.056	0.063	0.058
Pre-treated	55 (23.0)	21 (10.6)	51 (29.0)	42 (31.8)	19 (8.0)	14 (7.1)	51 (21.3)	26 (13.2)	4 (2.3)	4 (3.0)	0 (0.0)	1 (1.5)	1 (1.6)	1 (1.9)
Untreated	35 (72.9)	8 (20.5)	19 (43.2)	5 (20.0)	5 (10.4)	2 (6.3)	17 (36.2)	6 (17.7)	7 (14.9)	3 (10.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
p	<0.001	0.082	0.070	0.237	0.573	0.866	0.029	0.488	<00.001	0.071	n. a.	0.686	0.655	0.732
Buprenorphine	43 (26.9)	15 (11.0)	25 (22.7)	20 (24.4)	14 (8.8)	9 (6.6)	30 (18.6)	18 (13.2)	4 (3.5)	3 (3.4)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)
(Levo-)methadone	11 (15.3)	4 (6.9)	23 (37.7)	21 (42.9)	4 (5.5)	3 (5.3)	17 (23.6)	7 (12.3)	0 (0.0)	1 (2.3)	0 (0.0)	1 (3.2)	0 (0.0)	1 (3.9)
p	0.053	0.383	0.037	0.027	0.379	0.731	0.382	0.857	0.158	0.735	n. a.	0.271	0.362	0.313

*Percentages refer to non-missing totals, which vary for every substance Significance level baseline (BL) vs. final assessment (FA): * <0.05, ** <0.01, *** <0.001

assessment they reported significantly higher objective withdrawal symptoms for non-completers. Completers achieved a significant reduction of subjective opiate withdrawal during the treatment with buprenorphine-naloxone, however the reduction of craving for opiates was significant for all groups including non-completers compared to baseline.

Take-home prescription is an important factor for reintegration into social and occupational life, because it enables the patient to start or stay in employment due to more flexibility in daily routine. 11.9% of all eligible patients wanted to switch to buprenorphine-naloxone for take-home prescription. At start of treatment with buprenorphine-naloxone a minority of patients received take-home prescription (8.4%) and all of these were pre-treated patients. At the end of the observation 25.1% of all observed patients received take-home prescription. The decision for a take-home prescription is discretionary to the treating physician in compliance with §5 (8) BtMVV (Controlled Substances Prescription Regulation). The patient may receive a take-home prescription for up to 7 consecutive days if the patient is in stable maintenance treatment, without relevant concomitant drug use and use of other substances that interact with the maintenance drug and therefore endanger his health [34].

Psychiatric comorbidities are very common in this patient population [35]. At baseline the scores of the SCL-90-R were relatively low with higher rates in all scales for non-completers, untreated patients and (levo-)methadone patients. Apart from non-completers all eligible patients achieved a significant reduction of psychiatric distress at their final assessment. However non-completers did reach lower scores (except for the scale interpersonal sensitivity) at their final assessment. These results are in line with the findings shown by Lieb et al. 2010 [35]. Opioid dependent patients with high scores in psychiatric distress should receive specific care with integrated treatment for both opioid dependence and psychiatric disorder.

The scores of the standardized patient questionnaire SF-36 measuring the quality of life in terms of general health, emotional and social functioning were relatively low at baseline but increased significantly during treatment with buprenorphine-naloxone for all scales. At baseline no difference between completers and non-completers was found, but at the final assessment completers had significantly higher scores and non-completers revealed no substantial improvement during treatment. These findings suggest that the treatment with buprenorphine-naloxone improves the patient's perception of his emotional and social condition and his ability to reintegrate into a functioning social life. Since non-completers obviously did not benefit in this domain there might be other influencing factors, such as dosing, withdrawal and psychiatric comorbidity that need to be explored in order to support special patient groups in the treatment with buprenorphine-naloxone at an early stage.

The results are in line with an Italian longitudinal outpatient survey, which compared the treatment of opioid dependence with buprenorphine-naloxone and methadone [32]. The retention rate was similar in both groups but significant improvements of social life, educational level and concomitant drug use were found in patients treated with buprenorphine-naloxone.

The non-interventional study with buprenorphine-naloxone provides a unique database with comprehensive, reliable and valid data on opioid drug dependence treatment with buprenorphine-naloxone in routine care. However the major limitation is the strict observational nature of the study and the lack of a control group. Confounding factors, which may occur during a non-

interventional study, cannot be controlled in contrast to clinical trials with exact regulations and complete treatment protocol. Thus these uncontrolled confounding factors may influence treatment outcomes. All measures used in this paper were of descriptive quality; effects and correlations need to be interpreted with caution. Since this observational study was part of the Risk-Management-Plan and based on a commitment to the European Medicine Agency (EMA) after market authorization of the product buprenorphine-naloxone, no control group was planned and necessary. Nevertheless this database with its broad range of variables, standardized assessments and parameters describing the course and outcome of the treatment with buprenorphine-naloxone from the physician's and the patient's perspective allows detailed analyses on safety, somatic and psychiatric health as well as subjective and objective effects in reference to special patient groups at different time points. This is the main advantage of this non-interventional study in routine care. In summary, the results indicate high acceptance and tolerance of the treatment accompanied by significant improvements in psychiatric, somatic and social functioning. According to these data buprenorphine-naloxone has an excellent safety profile also in comparison to methadone with a low risk especially for serious intoxications [9]. There are increasing safety concerns for intoxications with opioid prescription drugs, with no corresponding European data. Data from surveillance studies like this may help to better estimate the safety risk associated with the use of opioid maintenance treatment.

Although only pre-treated patients were the target study population some physicians included a small group of untreated patients and they provided encouraging results. The treatment with buprenorphine-naloxone was highly successful for patients without any experience in maintenance treatment with direct transfer from street heroin use to buprenorphine-naloxone treatment.

The characteristics of non-completers need to be analysed further to identify those at risk for negative outcome. Analyses should focus on identifying ways to retain such patients in treatment and heighten their chances for treatment success.

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Essex Pharma GmbH & Reckitt Benckiser Pharmaceuticals conducted this strictly observational, non-interventional study. All physicians received honoraria for the additional effort to document the start and course of the treatment with buprenorphine-naloxone in the comprehensive paper-based clinical research form. The honoraria were in line with the German medical fee schedule (Gebührenordnung für Ärzte, GOÄ) which controls the invoicing of medical attendance outside of the statutory health insurance. All authors contributed to and have approved the final manuscript.

Sabine M. Apelt has a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation. She receives or has in the past 3 years received honoraria from: Schering Plough, Essex Pharma GmbH, MSD SHARP & DOHME GmbH and Reckitt Benckiser Pharmaceuticals. In the past 3 years Norbert Scherbaum received honoraria from Essex Pharma GmbH, Reckitt Benckiser, Molteni and Sanofi-Aventis. Jörg Gölz has no conflict of interest. Markus Backmund has no conflict of interest. For the past 5 years Michael Soyka has received travel grants, unrestricted research funding or has worked as a consultant for Presspharm, Reckitt Benckiser, Lilly, Astra Zeneca, Roche, Essex Pharma GmbH, Lundberg and Sanofi Aventis.

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F. Analysis of the first four weeks in the treatment of opioid-dependence after induction or switch to buprenorphine-naloxone and its predictive value for the treatment outcome after 12 months of observation (Paper II)

Induction And Switch To Buprenorphine-Naloxone In Opioid Dependence Treatment: Predictive Value Of The First Four Weeks

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This article provides a specific description of the methods and design of the non-interventional post-authorization safety study with buprenorphine-naloxone in terms of the first four weeks of treatment. It describes the characteristics of the evaluated patients and assessed the first four weeks of treatment with buprenorphine-naloxone to find predictors for positive and negative treatment outcome after 12 months of observation.

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Induction and switch to buprenorphine-naloxone in opioid dependence treatment: Predictive value of the first four weeks

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Summary

Background: Clinical studies report the highest risk of dropout in the first few weeks of opioid dependence treatment. This secondary analysis of data from a non-interventional study with buprenorphine-naloxone (BNX) aims to evaluate the predictive value of the treatment outcomes after the first four weeks in routine care. **Methods:** Data collected from 69 sites in Germany, came from a multicentre 12-month study involving 337 opioid-dependent patients.
Results: Patients with negative urine screenings for opiates, cocaine or benzodiazepines at screening, a maximum daily dose of 8mg BNX during the first four weeks, significantly lower Global Severity Index (GSI) on the SCL-90-R at day 0 and again at week 4, had a significantly higher chance of being retained in treatment. The patients who switched from d/l-methadone, levo-methadone, buprenorphine or active heroin use showed differences in almost all the parameters that were evaluated. **Conclusion:** The first four weeks of treatment with BNX have a high predictive value for the treatment outcome, especially in terms of urine screening, dosing of BNX and psychiatric distress. But the physician in charge needs to determine if the patient has been pre-treated with d/l-methadone, levo-methadone or buprenorphine, or whether the patient is inducted to BNX directly from heroin, because most of the predictive values seem to be unique for a subgroup of patients only.

Key Words: buprenorphine-naloxone, opioid dependence treatment, predictors of treatment outcome, first weeks of treatment

1. Introduction

Drug dependence therapy with maintenance drugs is an established method for the reduction of criminal behaviour and somatic disorders, including infectious diseases and drug-related deaths, while improving the somatic, mental and social well-being of drug-dependent users [10, 21, 26, 27,28, 32,]. The first goal of maintenance treatment is to stabilize the patient with an adequate dose of the maintenance drug, to prevent withdrawal symptoms, and risky and health-damaging behaviour. An improved status of this kind will give a drug-dependent patient an opportunity to regain control over his/her life [8, 10].

The first four weeks of treatment seem to be extremely important for the general course of opioid dependence treatment. Some clinical studies report the highest risk of dropout and relapse in the first week of opioid dependence treatment [20, 30]. But the longer a patient stays in maintenance treatment, the higher the chances are of accomplishing positive treatment outcomes, including complete abstinence from illicit drug use [11, 23, 24, 30]. To keep the patient in treatment is one of the major challenges of maintenance therapy [6], and is influenced by many factors. Adequate dosing seems to play a major role. Buprenorphine doses of 8 mg/day or less resulted in lower retention rates [12] and higher numbers of positive opioid urine screenings [3]; by contrast, higher doses (12-16mg) resulted in higher chances of

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achieving complete abstinence from opioid drug use [7, 18, 19, 22,]. Thus, an adequate dose of buprenorphine-naloxone is a crucial factor in keeping drug-dependent patients in treatment.

Other predictive variables for high retention and positive treatment outcomes are being older, having a job, having a history of treatment, being cocaine-free at baseline [1, 4, 15, 23, 24, 30], and having cocaine- and heroin-free urine screenings in the first few weeks of treatment [9]. Predictors of negative treatment outcomes include cocaine use and polydrug use at baseline and during treatment [6, 9, 20, 25, 30].

Opioid-dependent drug users show extreme heterogeneity in many of their characteristics [32]. In any case, it can be assumed that, especially in the early phases of treatment, certain characteristics and variables are unique to each patient, and can be used as reliable signals of a positive or negative course and outcome of opioid dependence treatment. These signals, if recognized at an early stage of treatment, could be used to sdjust the treatment plan, and help the patient to be retained and/or reach the ultimate objective of complete abstinence.

Despite several clinical trials with tight assessment schedules for the early weeks of treatment [14, 16, 31], there have been no published multisite, long-term, observational, non-interventional studies in routine care that provide a detailed description of the first four weeks of treatment with buprenorphine-naloxone (BNX), and allow an assessment of the reliability of predictors for positive treatment outcome. Only one single-site, observational cohort study by Stein et al. [30] described the results of 41 opioid-dependent patients treated with buprenorphine-naloxone, with a follow-up of 6 months; their results on retention and its predictive factors reflected those found in clinical trials [30].

This secondary analysis of data from a nationwide, non-interventional, observational study with buprenorphine-naloxone in routine care [2] aims to evaluate the predictive value of the first four weeks for the treatment outcomes.

2. Methods

A detailed description of the study design, goals, population, assessment and measures has been given in Apelt et al. [2].

2.1. Design of the study

The study, conducted from 2008 to 2010, was a nationwide multicentre 12-month prospective, non-interventional, post-marketing safety study with 12 assessment points involving 384 opioid-dependent patients from 69 general practitioners, clinics and outpatient clinics in Germany. Opioid-dependent patients over 15 years of age with written informed consent and for whom the switch to buprenorphine-naloxone (BNX) was indicated and planned were eligible for selection. Therapeutic indications and contraindications of the Summary of Product Characterization (SmPC) for BNX had to be considered. The physician had full responsibility for deciding which patients should be enrolled, how the treatment with BNX was to be implemented and which BNX dosage should be applied. Altogether, 337 data sets were eligible for analysis. A detailed description of the methods used in the study and which datasets were excluded from the final analysis is given in Apelt et al [2].

2.2. Assessment within the first four weeks

The assessment was performed at day 0 before induction into, or a switch to BNX, at days 1, 2, 3, 5 and 7, and at the end of weeks 2 and 4 of treatment with BNX. An extensive clinical research form, completed by the treating physician, and four standardized questionnaires completed by the patients, were used to obtain comprehensive data on sociodemographics, substance use and addiction history, treatment history, comorbidities, co-medication, concomitant drug use, urine drug screening, reason for switching to BNX, details of BNX treatment, premature discontinuation before end of observation, effectiveness, withdrawal, craving, quality of life and safety.

The physician's questionnaire specially developed for the non-interventional study comprised evaluation tools to cover the sections mentioned above, including standardized instruments such as a modified version of the Clinical Global Impression scale (CGI) and the Objective Opiate Withdrawal Scale (OOWS) [17]. The patients' questionnaires were the Short Form 36 – Health Survey (SF-36) [5], the Subjective Opiate Withdrawal Scale (SOWS) [17], the revised psychiatric Symptom Checklist (SCL-90R) [13] and, specially invented for the studyvisual analogue scales for craving [2].

2.3. Aims

The general aim of this evaluation was to find

predictors for treatment outcomes. The predictors specially selected for treatment outcomes were:

- Screening phase (day 0): Gender, age, dose of prior maintenance drug for pre-treated patients, drug screening results, withdrawal and craving, psychiatric status, health-related quality of life.
- Induction phase (days 1 to 7): Withdrawal and craving, dose of BNX.
- Stabilization phase (weeks 2 to 4): Withdrawal and craving, psychiatric status, health-related quality of life, dose of BNX.

2.4. Statistics and Analyses

The following groups were selected and will now be compared:

2.4.1.Retention Status

- Positive Outcome (PO): Patients still in treatment with BNX at the end of observation (month 12) including patients with regular end of treatment before end of observation (patient abstinent) (n = 195)
- Negative Outcome (NO): Patients with documented premature discontinuation of the treatment with BNX for any reason other than regular end of treatment (patient abstinent) before end of observation (month 12) (n = 142). Reasons for premature discontinuations were, for example: "lost to follow up" (16.7%), "concomitant drug use/relapse" (12.2 %), "side effects" (12.2%) and "non-compliance/disciplinary reasons" (10.9%) [2].

2.4.2. Previous Drug:

- MTD: Pre-treated patients switched from d/l-methadone (n = 51).
- L-MTD: Pre-treated patients switched from levo-methadone (n = 24).
- BUP: Pre-treated patients switched from the mono buprenorphine product (n = 162).
- HER: Patients with no current maintenance treatment inducted BNX directly from heroin use (n = 93).

Logistic regressions, analysis of variances or chi-square tests were used to analyse correlations between the defined patient groups and selected predictive parameters. Missing values and "no test" were both defined as positive results. The Kaplan-Meier method was used to estimate retention rates and times. For the determination of group differences in retention rates, the log rank test was used. All statistical analyses were performed using STATA/SE 9.0 [29].

3. Results

3.1. Patient's Characteristics

Table 1 summarizes patients' characteristics at day 0. Predictors of the screening phase for positive treatment outcome (PO) were: older age, stable relationship and own flat, or living with family members. Patients with PO had a longer drug dependence history and pre-treated patients had been significantly longer in their previous maintenance treatment before switching to BNX, especially those who had previously been BUP patients. Fewer withdrawal symptoms and less craving for opiates were further predictors forPO. By contrast, patients with negative treatment outcome (NO) were more likely to be single, homeless, hepatitis C-positive and more severely burdened with psychiatric comorbidity. They reported higher rates for craving and withdrawal at day 0.

3.2 Prior maintenance treatment

The prior treatment status (i.e., whether the patient had been switched from a previous treatment, or had been inducted directly from active heroin use) had no impact on treatment outcome. Conversely, a patient switched from L-MTD had a higher chance of being retained in treatment with BNX for the complete 12 months of observation. A higher last dose of the prior maintenance drug before switching to BNX was a factor predictive for PO in patients switched from MTD and L-MTD.

3.3 Urine drug screening

An overall lower total number of positive drug screenings at day 0 was predictive for PO (2.6±1.7 vs. 3.2±1.7 NO, p=.004, OR 0.83, 95%CI 0.72-0.94), particularly for opiates (33.3% vs. 45.8%, p=.021), cocaine (6.2% vs. 16.2%, p=.003) and benzodiazepines (21.0% vs. 35.9%, p=.002). A significant difference in the total number of positive drug screenings was only found in L-MTD patients (1.4±1.0 PO vs. 4.3±1.9 NO, p<.001, OR 0.23, 95%CI 0.06-0.79).

3.4 Dose of BNX

Patients with NO started with slightly higher

Table 1: Patients' characteristics at baseline.

	Total Sample	PO	NO	
	337*	195	142	p
Age in years [mean (SD)] N = 336	35.1±8.8	36.0±9.0	33.9±8.4	.029
Male [n (%)] N = 337	258 (76.6)	154 (79.0)	104 (73.2)	.220
Marital status [n (%)] N = 334				
- Single	201 (60.2)	108 (56.3)	93 (65.5)	.088
- Married/living with a partner	102 (30.6)	69 (35.9)	33 (23.2)	.013
- Divorced	30 (9.0)	14 (7.3)	16 (11.3)	.209
Occupation [n (%)] N = 337				
- Employed	125 (37.1)	75 (38.5)	50 (35.2)	.542
- Unemployed	179 (53.1)	100 (51.3)	79 (55.6)	.429
Residential status [n (%)] N = 337				
- Own flat/house or living with family	296 (87.8)	177 (90.8)	119 (83.8)	.053
- Homeless	5 (1.5)	0 (0.0)	5 (3.5)	.008
Years of dependence [mean (SD)] N = 311	13.8 (8.7)	14.6 (8.5)	12.8 (8.8)	.077
Currently in substitution treatment [mean (SD] N = 337	244 (72.4)	140 (71.8)	104 (73.2)	.958
Years of current substitution treatment [mean (SD] N = 213	3.8±3.6	4.3±4.0	3.1±3.0	.022
- Buprenorphine	4.2± 3.8	5.0± 4.3	3.0± 2.5	.003
- D/L-Methadone	3.1± 3.1	3.1± 2.8	3.2± 3.6)	.931
- Levo-Methadone	3.3± 3.6	2.7± 3.0	5.0± 4.7	.177
Type of current substitution treatment [n (%)]				
- Buprenorphine	162 (66.4)	93 (66.4)	69 (66.4)	.989
- D/L-Methadone	51 (20.9)	29 (20.7)	22 (21.2)	.933
- Levo-Methadone	24 (9.8)	18 (12.9)	6 (5.8)	.066
Dose of prior substitution treatment [mean (SD)]				
- Buprenorphine (N = 161)	7.7± 4.3	7.2± 4.1	8.4± 4.4	.088
- D/L-Methadone (N = 50)	41.8± 37.2	53.6± 42.4	25.6± 20.1	.007
- Levo-Methadone (N = 23)	26.5± 17.1	31.0± 16.2	10.2± 8.6	.013
Hepatitis C infection [n (%)] N = 335	121 (36.1)	62 (31.8)	59 (42.1)	.009
HIV infection [n (%)] N = 272	4 (1.2)	2 (1.0)	2 (1.4)	.637
Psychiatric comorbidity – physician's assessment [n (%) N = 337	193 (57.3)	106 (54.4)	87 (61.3)	.206
Number of psychiatric comorbidities [mean (SD)] N = 193	2.0± 1.5	1.9± 1.6	2.1± 1.5	.538
Psychiatric Status – SCL90R [mean (SD)]				
- GSI (N = 316)	0.7± 0.6	0.7± 0.6	0.8± 0.6	.051
- PST (N = 321)	37.0± 24.0	34.3± 24.5	40.5±23.1	.023
- PSDI (N = 318)	1.5± 0.5	1.5± 0.5	1.6± 0.5	.161
Withdrawal [mean (SD)]				
- Objective Opiate Withdrawal Scale (N = 337)	8.8± 8.1	8.4± 8.0	9.4± 8.2	.259
- Subjective Opiate Withdrawal Scale (N = 325)	17.2± 13.5	15.9± 13.4	19.0± 13.6	.043
Craving [mean (SD)]				
- Total Score (N = 325)	12.4± 11.1	10.2± 9.6	15.4± 12.3	<.001
- Opiate Craving (N = 323)	32.3± 33.2	27.6± 30.9	38.9± 35.4	.003
Quality of Life – SF36 [mean (SD)]				

* Eligible datasets
PO = Positive Treatment Outcome; NO = Negative Treatment Outcome

doses of BNX on day 1 of treatment. On day 2 the average dose increased in both groups. While the average dose in patients with PO already started to decrease on day 3, in patients with NO the average dose was stable until day 7. In week four both groups reached almost the same average dose of their day of induction.

"Clean" patients were excluded from this analy-

Table 1: Patients' characteristics at baseline.

	Total Sample	PO	NO	
	337*	195	142	p
- Physical Health (N = 324)	52.9± 18.6	54.3± 18.3	51.0± 18.9	.118
- Mental Health (N = 320)	50.8± 24.2	52.0± 25.1	49.0± 22.9	.277
Positive Urine Drug Screening [n (%)]				
- Opiates (N = 331)	124 (37.5)	60 (31.6)	64 (45,4)	.010
- Cocaine (N = 330)	28 (8.5)	6 (3.2)	22 (15.6)	<.001
- Cannabis (N = 252)	83 (32.9)	45 (31.5)	38 (34.9)	.570
- Benzodiazepines (N = 330)	85 (25.8)	37 (19.4)	48 (34.5)	.002
General Health – physician's assessment mean (SD)] N = 335	1.7± 1.0	1.7± 1.0	1.8± 1.0	.384

* Eligible datasets
PO = Positive Treatment Outcome; NO = Negative Treatment Outcome

sis, because their dosing was significantly lower, and it also decreased more rapidly during the first four weeks; it therefore fails to reflect the expected normal course of dosing after induction, or switch to buprenorphine-naloxone.

Figure 1 shows the average dose of BNX during the first four weeks of treatment (N = 323)

If controlled for prior treatment/drug (see Table 2), there is no difference in dosing between PO and NO in patients switched from MTD or HER. Patients with PO switched from L-MTD received slightly lower doses of BNX on day 1 and considerably higher doses at week 4. The switch from BUP to BNX led to an average dose increase of 0.5 mg in both groups. However, BUP patients with PO received significantly lower doses of BNX.

Table 2 shows dosing of BNX by previous drug during the first four weeks of treatment

No significant differences in dosing of BNX within the first four weeks were found concerning regions of Germany. Since only 3 outpatient clinics participated in the study, the type of setting was not analysed as a possible influencing factor.

3.5 Withdrawal

To measure the signs and symptoms of opiate withdrawal, the subjective and objective opiate withdrawal scales (OWS) were used [17]. Lower opiate withdrawal predicted positive treatment outcome (PO). In the objective scale (OOWS) patients with PO received lower scores from day 3 to week 4, and in the subjective scale (SOWS) they achieved lower scores from day 2 to week 4. There were no differenc-

Figure 1. Average dose of BNX during the first four weeks of treatment (N = 323).

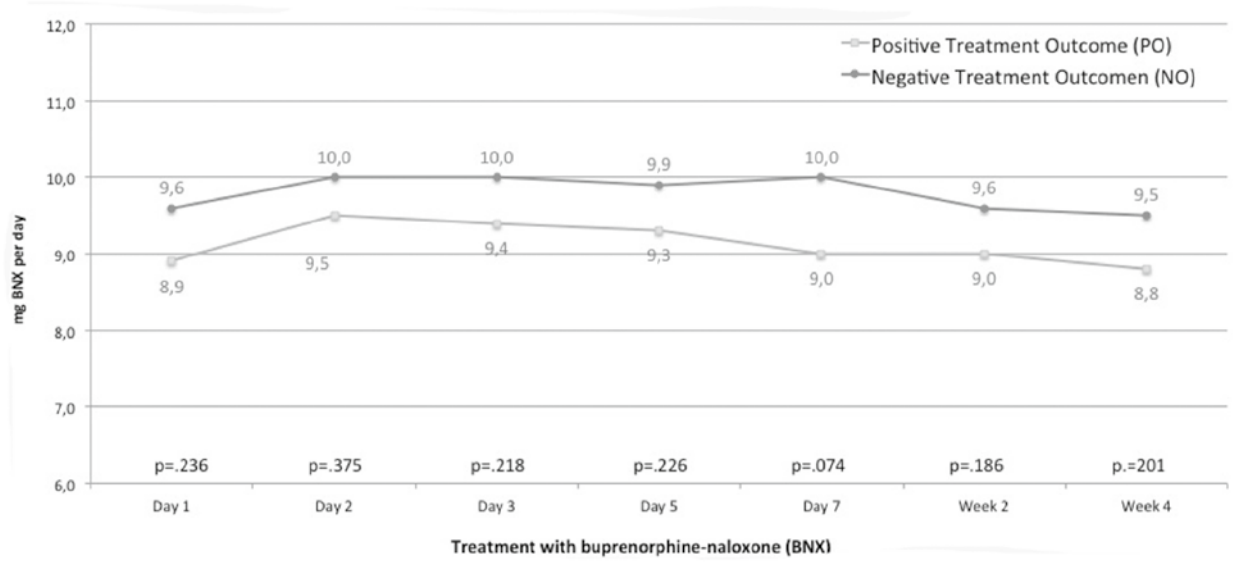


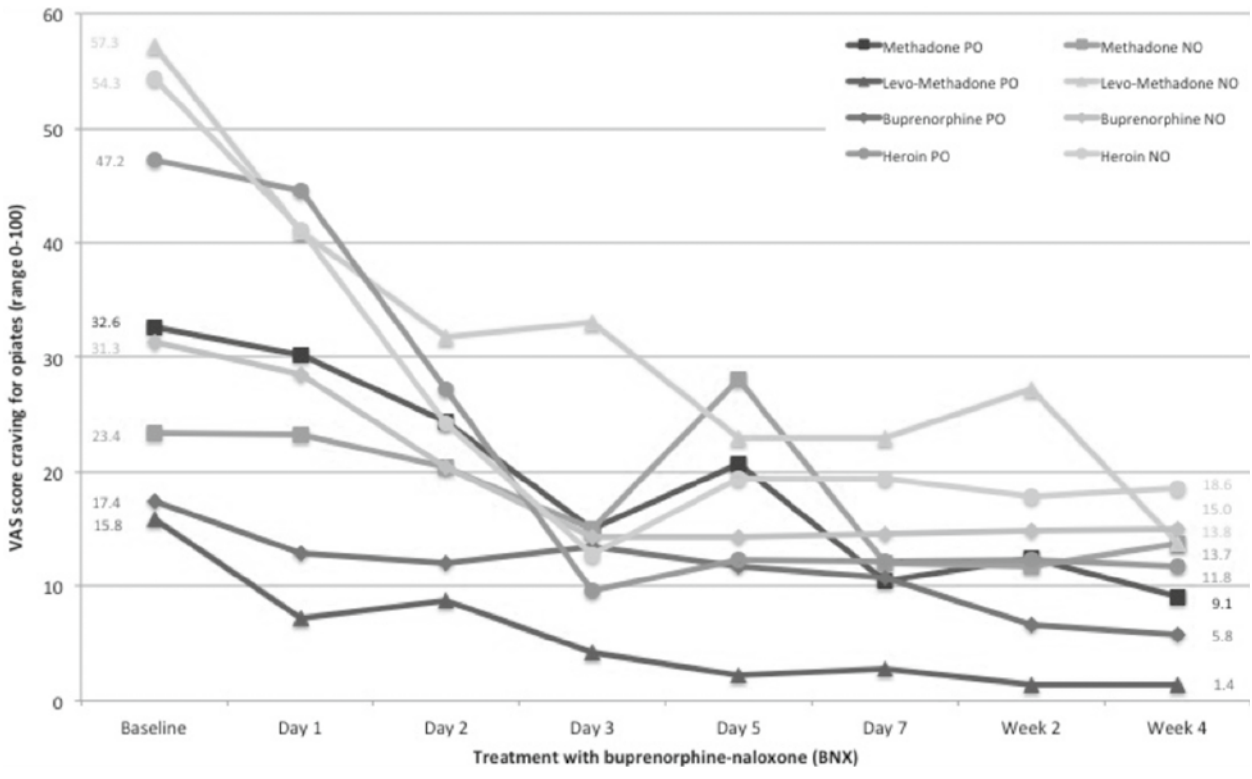
Table 2: Dosing of BNX by previous maintenance treatment and previous drug, during the first four weeks of the study

	MTD (n = 51)			L-MTD (n = 24)			BUP (n = 162)			HER (n = 93)		
	PO	NO	p	PO	NO	p	PO	NO	p	PO	NO	p
Day 1	12.8	12.5	.793	8.2	11.0	.124	7.7	8.9	.066	9.2	8.7	.641
Day 2	13.3	12.8	.793	11.5	12.0	.857	7.8	9.3	.021	9.7	9.5	.855
Day 3	11.9	12.4	.724	12.4	12.0	.900	7.9	9.6	.021	9.6	9.6	.995
Day5	11.4	11.4	.960	12.1	12.0	.964	8.0	9.6	.028	9.4	9.7	.797
Day 7	10.8	10.6	.894	12.1	12.0	.964	7.9	9.9	.008	8.9	9.7	.440
Week 2	11.0	10.3	.450	11.9	10.7	.607	8.0	9.4	.070	8.5	9.7	.199
Week 4	10.6	10.3	.805	12.0	7.5	.083	7.9	9.3	.057	8.3	9.6	.226

MTD: Patients switched from d/l-methadone
L-MTD: Patients switched from levo-methadone
BUP: Patients switched from the mono-compound buprenorphine
HER: Patients inducted directly from heroin use
PO = Positive Treatment Outcome NO = Negative Treatment Outcome

es in withdrawal symptoms between the two groups in prior MTD patients. Prior L-MTD patients with PO showed significantly fewer objective withdrawal symptoms from day 3 to week 4. A similar pattern is found in the SOWS, with significantly lower withdrawal symptoms for patients with PO as early as day 2 of BNX treatment. According to the ratings given by the treating physicians, prior BUP patients with PO showed significantly fewer opiate withdrawal symptoms in the first two weeks of BNX treatment. By week 4, however, the difference was no longer significant compared with BUP patients with NO. The same pattern can be found in the scores from the self-assessment questionnaire SOWS for this group. Prior HER users with PO achieved significantly lower scores for opiate withdrawal between day 7 and week 4 of BNX treatment, but only on the subjective scale. According to physicians, neither group of HER users differed in terms of opiate withdrawal at screening and during the first four weeks of treatment with

Figure 2. Craving for opiates by previous substance



BNX.

3.6 Craving for Opiates

Craving was measured with the self-assessment 100 mm visual analogue scales for 12 substances [2]. Lower craving for opiates predicted PO in all three phases of the first four weeks of treatment with BNX. As shown in Figure 2, the significant difference between PO and NO is only found in patients previously treated with L-MTD or BUP. At screening and in the first two days of treatment with BNX, patients with PO previously treated with MTD experienced higher craving for opiates, but at the end of week 4 these patients experienced marginally lower craving. No differences in terms of craving were found in prior HER users.

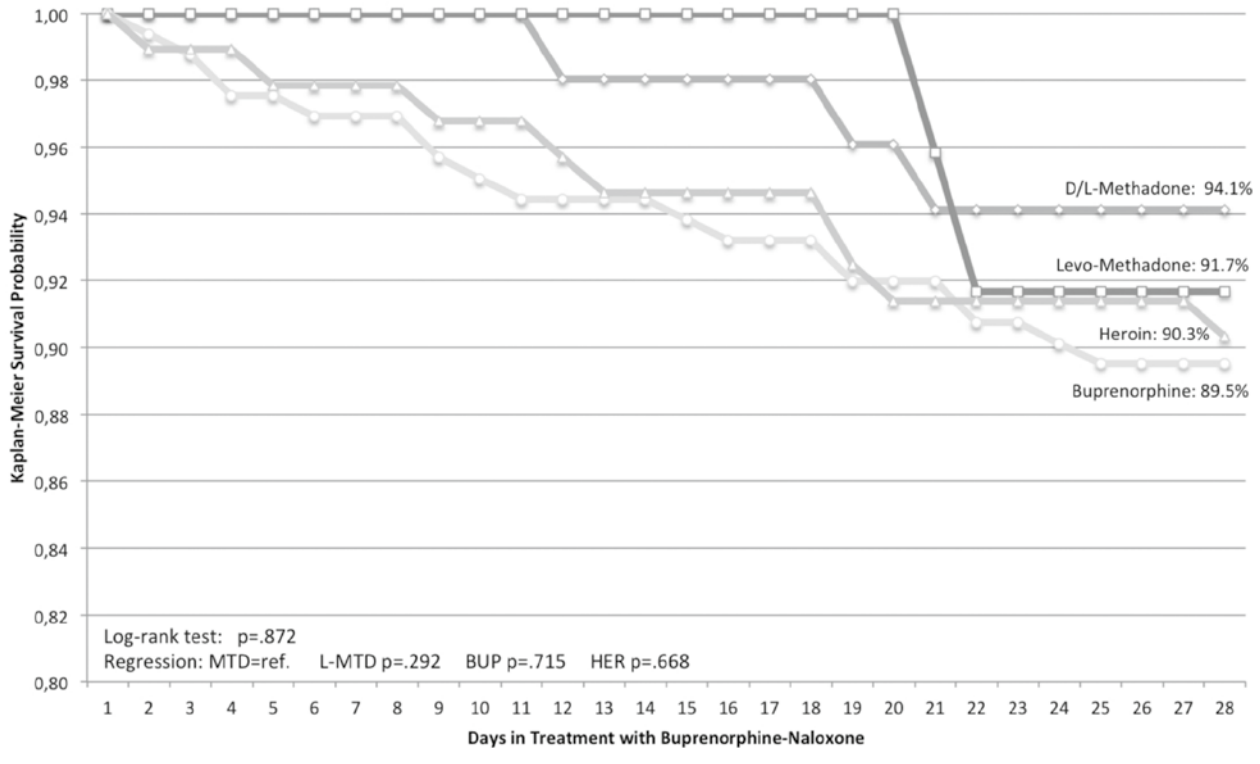
3.7 Psychiatric Distress (SCL-90-R)

The psychiatric distress status was measured with the standardized self-assessment tool SCL-90-R. The Global Severity Index (GSI) is the best indicator for the current extent of overall psychiatric distress [13]. A lower value for this global scale at screening (0.7±0.7 vs. 0.8±0.6 NO, p=.051) and week 4 (0.3±0.4 vs. 0.4±0.5, p=.030) predicted PO. The most severe forms of psychiatric distress were measured in L-MTD patients at screening for both groups (1.1±0.5 PO vs. 0.9±0.3 NO, p=.609) and at week 4 for patients with NO (0.3±0.3 vs. 0.6±0.4, p=.098). The mildest psychiatric distress was measured in BUP patients at screening for both groups (0.5±0.5 vs. 0.7±0.5, p=.004). MTD patients did not differ at screening or at week 4. At screening, prior HER users received scores that were similar to those of patients previously on MTD, with no differences between PO and NO, but at week 4 prior HER users with PO reported significantly milder psychiatric distress (0.3±0.3 vs. 0.5±0.5, p=.025).

3.8 Health-related Quality of Life (SF-36)

The health-related quality of life (QoL) was evaluated with the self-assessment tool SF-36, which measures the subjective core indicators of physical and mental health [5]. No predictive value was found in the two global scales, physical and mental health. In any case, patients with positive treatment outcome (PO) achieved slightly higher scores in both global scales at screening (physical health: 54.3±18.3 PO vs. 51.0±18.9 NO, p=.118; mental health: 52.0±25.1 vs.

Figure 3. Kaplan-Meier Survival Curves by previous Drug



49.0±22.9, p=.277) and at week 4 (physical health: 62.9±13.3 vs. 60.1±14.7, p=.112; mental health: 65.6±20.0 vs. 61.8±20.9, p=.142). No differences at screening or in week 4 were found in patients switched from MTD, L-MTD or HER at screening, or at the end of week 4. But previous BUP patients with PO achieved significantly higher scores at screening (physical health: 62.8±14.4 vs. 54.8±17.6, p=.002; mental health: 64.6±21.7 vs. 53.8±23.7, p=.003). By week 4 the scores were no longer significant (physical health: 66.4±13.4 vs. 62.2±15.1, p=.093; mental health: 71.3±20.0 vs. 65.2±21.8, p=.098).

As itemized within the nine single scales, higher scores in the scales for "physical role functioning" at week 4 (7.2±1.3 PO vs. 6.8±1.5 NO, p=.046), and for "pain" at screening (9.1±2.9 vs. 8.1±3.3, p=003) and week 4 (10.6±1.8 vs. 9.9±5.5, p=.010) predicted a positive treatment outcome (PO).

The extent of improvement between baseline and week 4 was only predictive for L-MTD patients, but, conversely, neither for the total population nor for MTD, BUP or HER. L-MTD patients with PO achieved higher improvement scores in both global scales (physical health: improvement 23.1±11.8 PO vs. 4.3±6.5 NO, p=.008; mental health: improvement 40.2±20.8 vs. 10.8±9.7, p=.015) and again in the single scales for "physical functioning" (4.2±3.0 vs. 0.3±2.1, p=.024), "pain" (3.2±1.7 vs. -0.5±1.9, p=.001), "social functioning" (2.3±1.5 vs. -0.5±1.3, p=.004) and "emotional well-being" (7.4±4.6 vs. 7.8±2.6, p=.033). For BUP patients the only predictive value for PO was found in the scale for "drug dependence" (2.2±6.9 vs. 4.9±8.7, p=.049).

3.9 Retention and dropout

The 4-weeks survival probability for the total population was 89.3%. One quarter (25.4%) of all patients with negative treatment outcome (NO) (n = 142) prematurely terminated treatment with BNX in the first four weeks, including 9 of the group during the first week.

Figure 3 shows the survival probability by previous drug. The highest retention and lowest dropout rate in the first four weeks was found in prior MTD patients (13.6%). 24.6% of patients with NO in prior BUP patients and 23.7% of HER users dropped out of treatment during the first four weeks. Of prior L-MTD patients, 2 out of 6 patients with NO terminated their treatment prematurely during the first 4 weeks. Log-rank test and logistic regression revealed no differences in survival and treatment duration between the four previous drug groups.

Patients with a maximum dose of ≤8 mg per day BNX during the first four weeks stayed significantly longer in treatment compared with patients with at least one dose of >8 mg per day during the first 4 weeks (Log-rank: $\chi 2$ = 3.78, p=.052; two-sample t-test: mean retention 282.0±136.6 days vs. 241.1±149.2 days, t = 2.57, p=.011).

Patients showing no cocaine use at screening stayed significantly longer in treatment than those with positive urine screening for any illicit drug (log-rank χ^2 = 7.06, p=.008). Patients with negative urine screenings for opiates, cocaine and/or benzodiazepines had a significantly longer treatment duration than those with positive test results for all three substances (Log-rank χ^2 = 5.08, p=.024).

4. Discussion

The results of this study proved that opioid-dependent drug users are, indeed, an extremely heterogeneous group [32]. Most of the characteristics evaluated at baseline and during the first four weeks of treatment with buprenorphine-naloxone (BNX) are specific for certain patient groups, especially concerning prior substance and treatment experience. Despite all the individual differences, this evaluation found parameters that can be reliably used as signals to adjust the treatment plan, and influence course and outcome of opioid dependence treatment with BNX.

The major challenge in drug-substitution treatment is to retain patients in treatment [6] and thus enable them to regain control over their lives [8, 10]. The overall 4-week retention rate was 89.3%, irrespective of whether the patient was switched from an ongoing maintenance treatment, or inducted directly from heroin use (HER). As found in previous studies, being older, treatment experienced, and showing no cocaine use at screening predicted higher chances of retention [1, 4, 15, 23, 24, 30]. In this study, employment status at screening had no significant impact on retention, but patients who had their own flat, or were still living at home with their family, seemed to benefit from a more stable living condition. By contrast, homeless patients had practically no chance of a positive treatment outcome.

In previous studies, polydrug use predicted low retention and a high chance of dropout [6, 9, 20, 25, 30]. In this study this criterion only applied to patients switched from levo-methadone (L-MTD). Single negative test results for benzodiazepines, cocaine

or opiates at the screening phase were predictive for positive treatment outcomes in patients switched from BUP and L-MTD. Previous drug use clearly had no impact on retention or on dropout for patients switched from d/l-methadone (MTD) or inducted to BNX from active heroin use.

Contrary to international findings on a positive correlation between higher doses of BNX (12-16mg) and high retention [7, 18, 19, 22], in this study a lower dose of BNX in the first four weeks (≤8 mg) predicted a higher level of retention. The reason might be that patients with a positive treatment outcome (PO) had, in general, a more favourable sociodemographic, medical and addiction history profile than those with a negative outcome (NO). Physicians seem to allocate their patients to a certain induction dose in line with specific patient characteristics such as social circumstances, physical and mental health, withdrawal and craving. The high probability of treatment retention in patients with a maximum dose of 8 mg per day during the first four weeks of treatment with BNX might be explained by the fact that these patients start their therapy from a more favourable level than those who received over 8 mg per day of BNX at least once during the first four weeks. At present this largely unexpected outcome cannot be adequately explained. It follows that this surprising finding calls for further detailed analysis after taking into account the impact of craving, withdrawal, and prior maintenance dose, as well as psychiatric distress, quality of life and other important parameters pertinent to the correlation between BNX dose and retention. In addition, in future studies the concerns of patients over the effects of naloxone in the combination product and the importance of the physician-patient relationship should become a focus of attention.

Parameters assessed in the screening phase (day 0) have a high predictive value and should be studied for treatment planning by physicians. Still more importantly, week 4 of the stabilization phase in BNX treatment seems to play a major role in measuring predictive values for positive treatment outcomes and high chances of retention. Differences between patients with PO and NO were most frequently found in this phase. In particular, scores for psychiatric distress, withdrawal, craving and dosing of BNX differ strongly at week 4, and could therefore be used as signals for operative improvements to the treatment plan. As a result, the physician in charge should test these variables by applying standardized patient questionnaires at the end of the stabilization phase, so as to provide patients, who have rather unfavourable characteristics, their best possible treatment setting.

The predictive value of some of the variables only applied to patients switched from L-MTD, whereas for MTD patients almost none of the variables could be used as predictors at this early stage of BNX treatment. In addition, prior MTD patients and HER users did not differ in their characteristics at baseline, but HER users seemed to draw considerably more benefit from the BNX treatment than MTD patients. These findings support the suitability of BNX as a first-line medication for active heroin users.

One of the limitations of the study might be the absence of a control group. Since the study did not examine the efficacy of BNX, but aimed to evaluate the safety and effectiveness of the switch from an ongoing maintenance treatment to BNX in routine care, this limitation is acceptable. Another limitation is the disproportionate distribution of patients to the prior treatment/drug group. The high predictive value for L-MTD patients might be due to their low number of only 24 patients. Future studies should be conducted with a higher, more evenly distributed number of patients to evaluate the switch from L-MTD, MTD and HER to BNX, and to generate more robust data. Another limitation might be the recruiting process: Only patients who agreed to participate in the study and signed the informed consent form were eligible for inclusion in the 12-month observation period. That leaves open the possibility of a positive selection bias. Patients who refused to participate, as well as those who were excluded from consideration as study candidates by the participating physician were not evaluated, and no comparison with the group of study participants in assessing certain parameters is possible.

The major strength of the study is its authentic reflection of the real life situation in opioid dependence treatment in Germany. It was the sole responsibility of the physician who was in charge to decide which patients should be enrolled, how the treatment with BNX was to be implemented, and what dose of BNX the patients would receive.

5. Conclusions

The first four weeks of BNX treatment after a switch from d/l-methadone, levo-methadone, buprenorphine or active heroin use have a high value in predicting a positive treatment outcome, especially with reference to the parameters: withdrawal, craving and psychiatric distress, to be measured at the screening phase (day 0), and at the end of the stabilization phase (week 4). These values need to be considered

in close conjunction with age, current drug use, social status and treatment experience. For optimal treatment redefinition to raise the patient's chances of being retained and of achieving a positive treatment outcome, the physician in charge needs to take into account whether the patient has been pre-treated with d/l-methadone, levo-methadone or buprenorphine, or whether the patient was inducted into BNX directly from heroin. Many predictive values seem to be unique to a subgroup of patients only.

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Role of the funding source

The original study was part of the Risk Management Plan (RMP) for the newly marketed product buprenorphine-naloxone (Suboxone®) and a requirement of the European Medicine Agency (EMA). The study is registered with the National Institute of Health (NIH) at clinicaltrials.gov (NCT00723749).

Essex Pharma GmbH & Reckitt Benckiser Pharmaceuticals conducted this strictly observational, non-interventional study. All physicians received honoraria for the additional effort to document the start and course of the treatment with buprenorphine-naloxone in the comprehensive paper-based clinical research form. The honoraria were in line with the German medical fee schedule (Gebührenordnung für Ärzte, GOÄ), which controls the invoicing of medical attendance outside of the statutory health insurance.

Contributors

All authors contributed to and have approved the final manuscript.

Conflict of interest

Sabine M. Apelt has a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation. She receives or has in the past 3 years received honoraria from: Schering Plough, Essex Pharma GmbH, MSD SHARP DOHME GmbH and Reckitt Benckiser Pharmaceuticals.

In the past three years Norbert Scherbaum received honoraria from Essex Pharma GmbH, Reckitt Benckiser Pharmaceuticals, Molteni and Sanofi-Aventis.

For the past five years Michael Soyka has received travel grants, unrestricted research funding or has worked as a consultant for Presspharm, Reckitt Benckiser, Lilly, Astra Zeneca, Roche, Essex Pharma GmbH, Lundbeck and Sanofi Aventis.

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G. Analysis of the development of liver enzymes over 12 months of treatment of opioid-dependence with buprenorphine-naloxone (Paper III)

Buprenorphine-Naloxone Treatment In Opioid Dependence And Risk Of Liver Enzyme Elevation: Results From A 12-Month Observational Study

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This original article had been published by *The American Journal on Addictions*, an official journal of the American Academy of Addiction Psychiatry, a peer-review scientific journal, publishing in the field of etiology, prevention, identification, and treatment of substance abuse disorders in English (impact factor 2014: 2.14). Professor Michael Soyka was as the first author responsible for the concept, literature research, evaluation of the results and writing the manuscript. Professor Markus Backmund was responsible for literature research and evaluation as well as review of the manuscript. Dr. Peggy Schmidt was responsible for statistical analyses and review of the manuscript. Sabine M. Apelt was responsible for literature research and evaluation, statistical analyses and review of the manuscript.

This article provides a brief description of the methods, design and study population of the non-interventional post-authorization safety study with buprenorphine-naloxone. It describes laboratory measures in detail with the focus on liver-related values in order to determine possible effects of buprenorphine-naloxone on liver toxicity in routine care.

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Buprenorphine–Naloxone Treatment in Opioid Dependence and Risk of Liver Enzyme Elevation: Results from a 12-Month Observational Study

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Background: Some case series mention possible liver toxicity in opioid-dependent patients under buprenorphine treatment.
Methods: This 12-month prospective observational follow-up study in opioid-dependent patients under buprenorphine–naloxone treatment assessed outcome and safety issues. At baseline, 337 eligible datasets were available; 181 patients completed the 12-month study. Liver enzymes were tested at baseline and after 12, 24, and 52 weeks' treatment.
Results: One to two percent of patients showed mostly discrete elevations of liver enzymes, but no patient met the criteria for drug-induced liver injury. No serious liver-related adverse events occurred, but two non-serious cases of liver enzyme increase were recorded. No patient dropped out of treatment for liver-related disorders.
Conclusion: This study is in line with some recent studies and provides further evidence that buprenorphine–naloxone is relatively safe with respect to liver injury. (Am J Addict 2014;23:563–569)

BACKGROUND

Buprenorphine is an established medication for the treatment of opioid dependence.[1–8] Two forms of buprenorphine are available, both as tablets: One that contains only buprenorphine, and one that combines buprenorphine with the opioid antagonist naloxone in a 4:1 ratio. The American Psychiatric Association (APA)[2] and World Federation of Societies of Biological Psychiatry (WFSBP) guidelines[6] state that buprenorphine is a first-line medication for the treatment of opioid dependence, among others. One advantage of buprenorphine over other opioid agonists may be its relatively low risk for fatal intoxications.[7] Methadone is considered to be safe with respect to liver toxicity.[9]

Other safety issues are of relevance, too. Liver safety in opioid-dependent patients receiving opioid replacement therapy is of particular interest and concern because of the high prevalence of hepatitis C (HCV), which ranges from 64% to 100% in many cohorts.[10–15] In addition, many individuals under opioid replacement therapy are active alcohol drinkers or even alcohol dependent and thus have an increased risk of liver damage.[16]

Drug-induced liver injury (DILI), a spectrum of clinical liver diseases ranging from mild biochemical abnormalities to acute liver failure, is the most frequent reason for the withdrawal of approved drugs from the market. In clinical studies of new drugs, the threshold for considering either more frequent monitoring of blood levels or discontinuing the drug is set at different levels, that is, twice the upper limit of the normal (ULN) reference range (2× ULN), 3× ULN, or 5× ULN.[17] The three common signs of liver toxicity in clinical trials are as follows: (1) A doubling (or more) in the incidence of serum alanine aminotransferase (ALT) elevation >3× ULN; (2) any incidence of serum ALT elevation >8–10× ULN; (3) any incidence of serum ALT elevation >3× ULN accompanied by a serum bilirubin elevation >2× ULN.[18] The classification of DILI is a matter of debate, and an international expert group has proposed threshold criteria for DILI.[18,19]

Population pharmacokinetic analyses indicate that clearance is reduced in subjects with elevated ALT or bilirubin. Therefore, the actions of buprenorphine may be prolonged in subjects with impaired hepatic function.[3,4] Some case reports have described a possible risk of liver-related adverse events with buprenorphine, mainly in patients with HCV.[20–23] The mechanism of injury associated with buprenorphine is unclear (see livertox.nih.gov), but a disruption of mitochondrial

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respiration has been discussed.[20,21] Buprenorphine undergoes extensive first-pass hepatic extraction. Most of the elimination is biliary.

The low doses used and rapid metabolism may account for the apparent relative lack of hepatotoxicity when buprenorphine is used in conventional doses. Because only limited evidence is available on this issue, we conducted a 12-month observational study to assess liver safety in opioid-dependent patients treated with buprenorphine–naloxone.

METHODS

In brief, this was a 12-month non-interventional study on retention rate, outcome, and safety issues in patients switched under real-life conditions to buprenorphine–naloxone after pretreatment with buprenorphine, methadone, or L-methadone. Details are given in Apelt et al.[24] A comprehensive paper-based case report form was used for data capture. The study was part of the Risk Management Plan (RMP) for the newly marketed product buprenorphine–naloxone (Suboxone®) and therefore a requirement of the European Medicine Agency (EMA). The study was registered with the National Institute of Health (NIH) at ClinicalTrials.gov (NCT00723749).

All physicians prescribing buprenorphine–naloxone were obligated to report to the market authorization holder (MAH) any adverse event that occurred during routine treatment. The MAH provided a special form for this purpose that specifically defined "non-serious" and "serious" adverse events: Life-threatening adverse events, including death itself, were to be classified as "serious"; all other adverse events, as non-serious. The physicians were solely responsible for assessing and deciding whether or not an adverse event was related to buprenorphine–naloxone.

Study Population

A total of $N = 384$ opioid-dependent patients were enrolled by 69 physicians working in addiction medicine. The participating physicians prescribed the medication in its conventional, commercially available form. Therapeutic indications and contraindications for opioid dependence treatment according to the Summary of Product Characteristics (SPC) for buprenorphine–naloxone and national treatment guidelines had to be followed when selecting patients for participation in the non-interventional study. "Non-interventional" meant that physicians were free to decide about the clinical management of their patients, without following any study protocol. A total of $n = 47$ patient datasets were excluded from the final analysis; $n = 337$ eligible datasets were included. Details are given in Apelt et al.[24]

The study was approved by the ethics committee of the Ludwig Maximilian University, Munich, Germany.

Assessments

Assessments included a physician and patient questionnaire and various psychometric scales (see Ref.[24]). Liver enzymes were measured at baseline and after 12, 24, and 52 weeks. Normal values were defined as follows: alkaline phosphatase (AP) 40–129 U/L (males), 35–104 U/L (females); glutamic-pyruvic transaminase (GPT; also referred to as ALT) 10–50 U/L; glutamate oxaloacetate transaminase (GOT; also referred to as AST) 10–35 U/L; gamma-glutamyl transpeptidase (GGT) <66 U/L (males), <39 U/L (females). All adverse events (non-serious and serious, including adverse drug reactions and pregnancies) were listed, because they were spontaneously reported and documented at each visit by the treating physician. No central laboratory was used, and each physician sent the material to his preferred laboratory. No cytochrome 450 polymorphisms were measured. No data were reported on consequences in case of changes in liver enzymes, for example, new medications or testing for viral hepatitis. No treatment interventions or assessments were defined, since this was a strictly observational, phase IV study.

DILI was defined according to Abboud and Kaplowitz.[18]

Statistics

This was a descriptive analysis. Since elevations of liver enzymes were very rare (see below), no specific subgroup analysis was performed.

RESULTS

Patients and Outcome

A total of 337 eligible patients were included (258 [76.6%] male), 181 of whom were still in treatment after 12 months. The mean age was 35.1 years (8.8); the mean duration of opioid dependence, 13.8 years (8.7). A total of 121 (36.1%) participants had a history of HCV infection. The mean induction dose of buprenorphine was 9.2 mg.

All patients were German; ethnicity was not reported. Baseline patient characteristics are given in Table 1, and details of enrolment in Figure 1.

A total of 142 patients dropped out before the end of the observation period. No deaths occurred. Four serious adverse events (1.2%) were recorded, none of which was a liver disorder, and 59 non-serious events (15.9%), three of which were liver-associated disorders: One case of HCV infection and two cases of increased liver enzymes. In both cases of increased liver enzymes, treatment was continued, and the treating physician did not see a correlation with buprenorphine/naloxone treatment (on the basis of his or her clinical assumption). No patient dropped out because of a liver disorder or related adverse event.

Liver Enzymes

Mean values for liver enzymes are given in Figures 2–4.

Detailed results are as follows:

AP: One male (117–135 U/L) but no female patient showed mild elevation at week 12 compared to baseline; two male patients (83–176 and 123–150 U/L) and one female patient (123–150), at month 6; three male patients (102–139, 100–146, 110–136 U/I), at month 12.

TABLE 1. Patient Characteristics at Baseline

	Total sample ($N = 337^{*}$)
Age in years [mean (SD)], $N = 336$	35.1 (8.8)
Male [n (%)], $N = 337$	258 (76.6)
German nationality [n (%)], $N = 336$	281 (83.4)
BMI [mean (SD)], $N = 332$	23.8 (3.9)
Marital status [n (%)], $N = 334$	
Single	201 (60.2)
Married/living together	102 (30.6)
Divorced	30 (9.0)
Years of dependence [mean (SD)], $N = 311$	13.8 (8.7)
Maintenance treatment [n (%)], $N = 244$	
Buprenorphine	162 (66.4)
D/L-Methadone	51 (20.9)
L-Methadone	24 (9.8)
Without prior maintenance treatment [n (%)]	49 (16.7)
Hepatitis C infection [n (%)], $N = 335$	121 (36.1)
HIV infection [n (%)], $N = 272$	4 (1.2)

*Eligible datasets.

GPT: Seven male patients (48–61, 37–54, 38–51, 47–52, 31–61, 13–91, 42–88 U/I) but no female patient showed mild elevations at week 12; four male patients (46–51, 22–60, 31–67, 23–81 U/I) and one female patient (19–36 U/I), at month 6. Three male (20–51, 39–96, 38–56 U/I) and two female patients (20–51, 20–85 U/I) showed mild to moderate elevations at month 12.

GOT: Seven male patients (49–51, 32–51, 39–52, 36–58, 22–78, 42–61, 33–54 U/I) but no female patient showed mild to moderate elevations at week 12; three male patients (26–51, 39–57, 35–62 U/I) and one female patient (24–38 U/I), at month 6. Two male patients (41–56, 48–51 U/I) but no female patient showed discrete elevations at month 12.

GGT: Four male patients (57–68, 60–69, 60–75, 61–72 U/I) and one female patient (34–46 U/I) showed discrete elevations at week 12, although these were only just above the upper norm value limit. Three male (42–82, 16–108, 65–71 U/I) and three female patients (25–74, 28–128, 33–42) showed mild elevations at week 24; one male patient (37–68 U/I) and two female patients (24–42, 28–69 U/I), at week 52.

In conclusion, none of the men or women showed an elevation of liver enzymes >3 upper limit over baseline according to the definition of DILI[18] used in this study, and only one women had a >2 elevation compared to baseline.

DISCUSSION AND CONCLUSIONS

This 12-month observational, non-interventional study provided no evidence for a significant risk of liver enzyme elevation or hepatic failure in opioid-dependent patients under treatment with buprenorphine–naloxone. Although 36% of the participants had a history of HCV, no clinically relevant cases of drug-induced liver injury were found in this study. Elevations in liver enzymes were rare (1–2% of patients), mostly within or slightly above the upper normal value, and no patient dropped out of treatment because of a liver-related adverse event. This study differs from the few other studies published so far on this issue in that it was a strictly observational study on safety aspects of buprenorphine treatment, while the other studies were primarily designed to measure liver toxicity[25] or were retrospective.[26]

Concerns about liver toxicity of buprenorphine and the buprenorphine/naloxone combination were raised by some clinical reports of liver injury in patients with hepatitis. Petry et al.[26] found in a retrospective study that patients diagnosed with hepatitis B or C had significant increases in transaminase levels, while patients without hepatitis did not. In addition, hepatotoxicity of buprenorphine has been reported in overdose[27] or intravenous misuse.[28] There are case reports of patients with HCV developing acute hepatitis while misusing their buprenorphine medication i.v.[20,21,23] Herve et al.[29] reported on seven cases of acute cytolytic hepatitis due to buprenorphine. Five out of seven subjects presented with

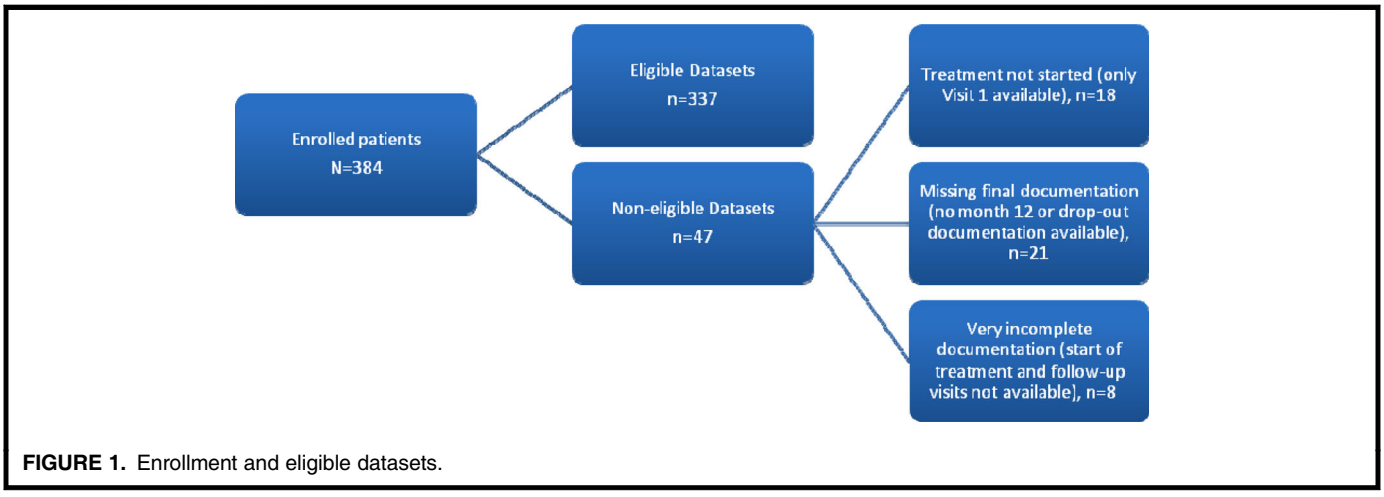

FIGURE 1. Enrollment and eligible datasets.

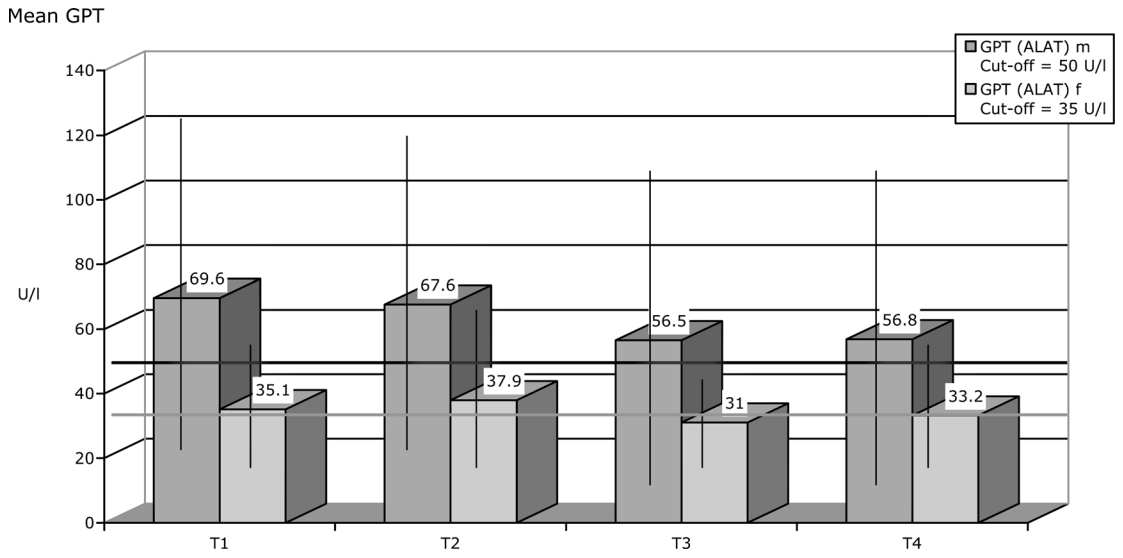

FIGURE 2. Mean GPT values for males (m) and females (f) at T1 (day 0), T2 (week 12), T3 (month 6), and T4 (month 12). The standard deviations (error bar) are shown as vertical lines, the cut-off values as horizontal lines.

acute icteric hepatitis without abdominal pain or fever; there was no evidence for liver failure. Some of the patients described were reexposed to buprenorphine and some remained on a lower dose without further evidence of liver injury. Cytolysis and jaundice resolved rapidly. Bruce and Altice[22] reported a case series of four individuals with acute HCV infection and abnormal liver transaminases. Patients tolerated buprenorphine treatment well and showed improvement in their transaminases during buprenorphine treatment. Despite the small number of reports of buprenorphine treatment being associated with hepatic injury or dysfunction in opioid-dependent patients,[30] these case reports nevertheless led to the recommendation that buprenorphine-treated patients be tested for markers of liver injury at treatment initiation and at intervals thereafter. As a possible explanation for hepatotoxicity of buprenorphine, a disruption of mitochondrial respiration via proton donation by buprenorphine was discussed by Berson et al.,[20,21] on the basis of their animal studies.

The issue of possible liver injury by buprenorphine was more systematically studied in a sample of adolescents

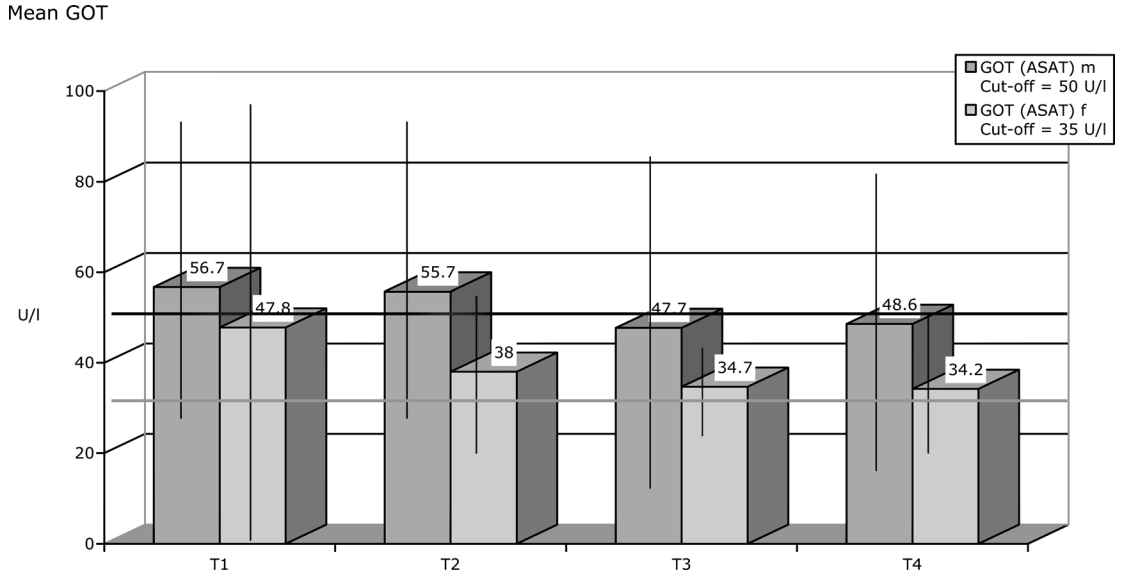

FIGURE 3. Mean GOT values for males (m) and females (f) at T1 (day 0), T2 (week 12), T3 (month 6), and T4 (month 12). The standard deviations (error bar) are shown as vertical lines, the cut-off values as horizontal lines.

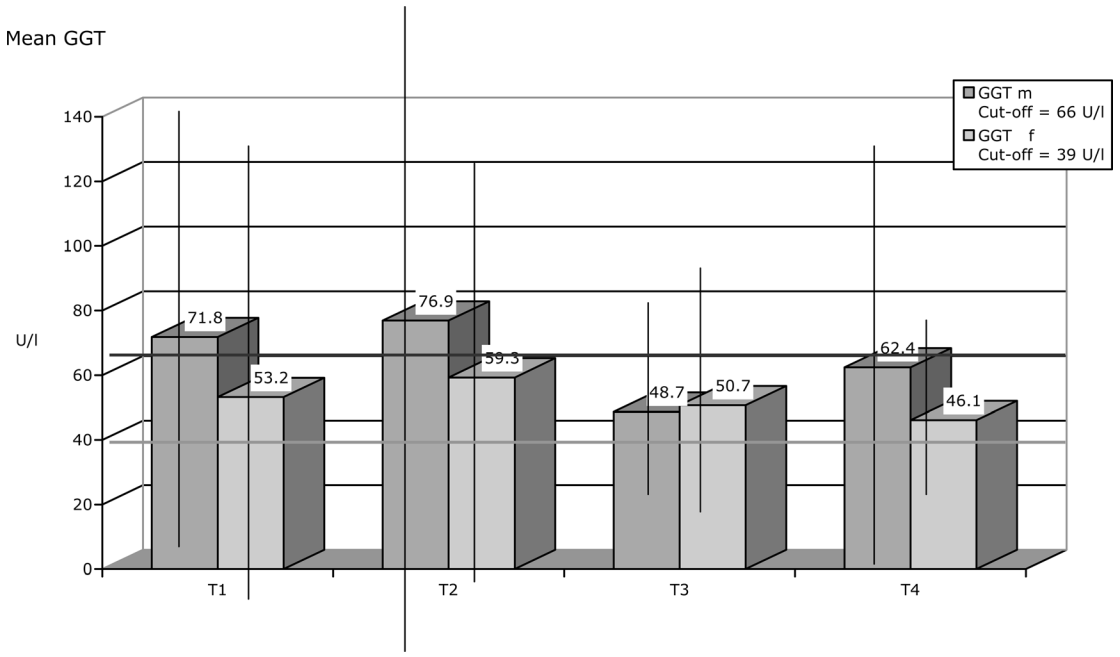

FIGURE 4. Mean GGT values for males (m) and females (f) at T1 (day 0), T2 (week 12), T3 (month 6), and T4 (month 12). The standard deviations (error bar) are shown as vertical lines, the cut-off values as horizontal lines.

receiving buprenorphine.[31] In this study, 152 patients were randomized to 2-week detoxification with buprenorphine–naloxone (detox) or 12 weeks with buprenorphine–naloxone (bup/nx). In 111 patients, at least one set of transaminases were measured. In 8 of the 60 bup/nx and 12 of the 51 detox patients, at least one elevated aspartate aminotransferase (AST) value was measured. HCV status was significantly associated with transaminase abnormalities. Taken together, this exploratory study found no evidence for hepatotoxicity of buprenorphine.

A phase IV hepatic safety study to prove the safety of long-term use of buprenorphine compared to standard care (methadone) was required as part of the FDA approval of buprenorphine products in 2002. Saxon et al.[25] performed a randomized controlled study of 1,269 opioid-dependent, treatment-seeking patients and followed them for 32 weeks. The study was performed by the National Institute on Drug Abuse Trials Network (NIDA) in cooperation with Reckitt Benckiser Pharmaceuticals. A total of 731 participants met "evaluable" criteria, defined as completing 24 weeks of medication and providing at least four blood samples. Participants were randomized to either buprenorphine or methadone. Changes in transaminase levels did not differ by medication condition. Not surprisingly, baseline infection with hepatitis C or B was the only significant predictor for elevation of transaminase levels. Nine buprenorphine and 15 methadone patients showed "extreme" liver test elevations defined as ALT or AST $>10\times$ ULN, total bilirubin >2 mg/dl, direct bilirubin >2 mg/dl, or maximum international normalized ratio >1.5 at any point during the 24 weeks of the study. These patients were more likely than those without extreme elevations to have seroconverted to both hepatitis B and C during study or to have used illicit drugs during the first 8 weeks of treatment. Not surprisingly, baseline infection with hepatitis C or B was the only significant predictor of transaminase levels increasing from low to elevated.

An important study on the effects of buprenorphine–naloxone on hepatic status in HIV-infected opioid-dependent patients was performed by Vergara-Rodriguez et al.[32] A total of 303 HIV-infected patients initiating buprenorphine–naloxone treatment were enrolled. Patients receiving or not receiving the antiretroviral atazanavir were compared. AST and ALT was measured (inclusion criterion: Levels of both AST and ALT $<5\times$ ULN). Buprenorphine–naloxone did not produce measurable hepatic toxicity or pharmacodynamic interaction with atazanavir.

Very recently, McNicholas et al.[30] reported data on liver status and enzymes from the NIDA-sponsored MOTHER study, a double-blind, double-dummy, flexible-dosing study in 175 pregnant women comparing the effects of methadone and buprenorphine on neonatal outcome.[33] ALT, AST, and GGT levels decreased for all subjects across pregnancy. At all measurements, HCV-positive subjects exhibited higher transaminases than HCV-negative subjects, regardless of medication. Both HCV-positive and -negative buprenorphine-maintained participants exhibited lower GGT levels than the methadone-maintained participants ($p < 0.05$). The authors concluded that neither methadone nor buprenorphine appear to have adverse hepatic effects in the treatment of pregnant opioid-dependent women.

No specific pharmacokinetic studies have been conducted on buprenorphine in patients with liver disease.[34] The activity or expression of CYP3A4 may be significantly decreased in patients with liver disease.[35,36] Dose adjustments may be considered. Peyriere et al.[28] reported two cases of acute hepatitis related to i.v. administration of buprenorphine in HCV-infected patients. Surprisingly, viral replication disappeared after acute hepatitis. Patients should be informed about the risk of acute hepatitis associated with intravenous misuse of the drug.

Some limitations of this study must be addressed. First, this was an observational study and no control group was included. The study focused primarily on clinical outcome and safety issues in general, not specifically liver toxicity. Still, the large number of patients studied, long follow-up, and low number of liver enzyme elevations seem to be of clinical relevance. Second, no histological or ultrasound findings were available for analysis.

In conclusion, this prospective, non-interventional study gives further evidence that buprenorphine treatment appears to be safe regarding liver injury in opioid-dependent individuals. Future studies may focus on high-risk individuals with a severe liver disorder, in particular hepatitis C infection, to further explore the possible benefits and risks of buprenorphine–naloxone in such patients.

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Declaration of Interest

Sabine M. Apelt has a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation. She receives or has in the past 3 years received honoraria from: Schering Plough, Essex Pharma GmbH, MSD SHARP & DOHME GmbH, and Reckitt Benckiser Pharmaceuticals. Markus Backmund and Peggy Schmidt do not have a conflict of interest. For the past 5 years, Michael Soyka has received travel grants or unrestricted research funding or has worked as a consultant for Prempharm, Reckitt Benckiser, Lilly, Astra Zeneca, Roche, Essex Pharma, Lundbeck, and Sanofi Aventis.

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H. Summary and conclusion

Chapter F: Primary analysis of the results from the 12-month nation-wide non-interventional safety study on the treatment of opioid dependence with buprenorphine-naloxone in routine care in Germany

69 sites in Germany provided reliable data from 337 eligible patients and helped generating a unique database with the most compact measure schedule and comprehensive assessment tools in medication assisted treatment of opioid use disorders with buprenorphine-naloxone under real-life conditions. Despite the instruction to include only patients from an ongoing medication assisted treatment, physicians also involved 49 patients with no ongoing maintenance treatment and induced them to buprenorphine-naloxone directly from active street heroin use. The evaluation of induction and course of treatment with buprenorphine-naloxone over 12 months provided new insights on dosing and its long-term impact on retention rate and treatment success for pretreated and untreated patients in routine care.

The 12-month retention rate of patients who switched either from an ongoing medication assisted treatment with buprenorphine, methadone or levo-methadone or from active street heroin use was 57.1% and in line with previous naturalistic, observational studies. 4.2% of the patients were rendered abstinent before end of the 12-month observation by their treating physician. There were no deaths and a very low rate of adverse events during the observational period. These findings demonstrated the overall efficacy and high safety profile of buprenorphine-naloxone in the treatment of opioid use disorders in routine care and confirmed findings from clinical studies.

In contrast to international clinical studies with recommended daily dosages of 16-24 mg, the daily doses of buprenorphine-naloxone were much lower with on average 9 mg at start of treatment and 8 mg at end of observation. Subjective withdrawal symptoms and craving for opioids at start of treatment determine course and outcome of the treatment. Patients with premature treatment termination for reasons other than being rated abstinent (non-completers) had higher subjective withdrawal and opioid craving at treatment start than patients still in treatment with buprenorphine-naloxone at the end of the 12-month observational period (completers). One of the reasons could be that the daily dosage of buprenorphine-naloxone was too low for those patients. Take-home prescription increased 3-fold during the 12-month observational period, which was the reason for >10% of the patients for switching to buprenorphine-naloxone.

The study showed (significant) improvement in all domains during the treatment with buprenorphine-naloxone for all analysis groups, except for non-completers, who had no sufficient improvement in quality of life, general health, opioid withdrawal and concomitant drug use. Only concerning opioid craving, which was measured with a self-assessment visual analog scale at all assessment points, data from non-completers revealed a significant decrease between baseline and final assessment. However, craving for opioids and withdrawal

symptoms were significantly higher both at baseline and final assessment compared to those patients still in treatment with buprenorphine-naloxone at the end of the 12 months of observation (completers). For those patients with premature discontinuation of treatment for reasons other than being abstinent (non-completers), one of the most important goals of medication assisted treatment was not fulfilled: to alleviate craving and withdrawal symptoms.

Patients who had switched to buprenorphine-naloxone directly from street heroin use seemed to have the highest benefit from the treatment not only in subjective measures. Significantly more of these patients discontinued treatment with buprenorphine-naloxone prematurely because they were rated as abstinent by their treating physicians. Despite the relatively small number of this group of patients, these encouraging results allow the conclusion, that buprenorphine-naloxone is eligible as first line treatment for opioid use disorders.

Chapter G: Analysis of the first four weeks in the treatment of opioid dependence after induction or switch to buprenorphine-naloxone and its predictive value for the treatment outcome after 12 months of observation

Due to a very tight assessment schedule during the first four weeks (day 0, 1-3, 5, 7, week 2 and 4) the post-authorization safety study provided comprehensive data for a thorough evaluation of induction and stabilization phase in drug dependence treatment with buprenorphine-naloxone. Positive treatment outcome was defined as patients still in treatment at the final assessment (month 12) or rated abstinent. Variables predicting high retention rate and positive treatment outcome were: stable living conditions, being older, treatment experienced, lower withdrawal and craving for opioids, lower concomitant drug use and daily dosages of 8 mg or less of buprenorphine-naloxone during the first four weeks. Negative treatment outcome was defined as patients with premature discontinuation before end of observation for any reason other than being rated abstinent. Variables predicting low retention rate and negative treatment outcome were: unstable living conditions, being hepatitis positive, severe psychiatric comorbidity, higher withdrawal and craving for opioids as well as daily dosages of more than 8 mg buprenorphine-naloxone during the first four weeks. Quality of life, assessed with the standardized self-assessment form SF-36, was the only measure which showed no difference between patients with positive or negative treatment outcome concerning physical and mental health.

The stabilization phase seems to play an important role in predicting treatment outcome. Especially psychiatric distress, withdrawal symptoms, craving for opioids and dose of buprenorphine-naloxone should be measured by the treating physician during this phase in order to redefine treatment parameters to increase patients' probability for high retention and a positive course of treatment. In summary, the study found indeed certain parameters that can be used as predictive signals for treatment course and outcome. Nevertheless many of these values are specific for a subgroup of patients depending on prior substance and treatment experience.

Chapter H: Analysis of the development of liver enzymes over 12 months of treatment of opioid dependence with buprenorphine-naloxone

As a consequence of a high rate of hepatitis C infections and comorbid alcohol misuse or even dependence in opioid dependent patients, liver safety needs to be taken into account during medication assisted treatment. Hepatotoxicity of buprenorphine had been found especially in hepatitis C positive patients and when the medication was used in higher dosages and/or intravenous. In addition, tests had shown prolonged buprenorphine action when certain liver-enzymes were elevated because clearance of the medication was reduced. The post-authorization safety study on drug dependence treatment with buprenorphine-naloxone provided comprehensive laboratory data, assessed at baseline, month 3, 6 and 12, allowing in-depth evaluation of liver-enzyme value changes over time.

121 of the 337 eligible patients (36%) had a history of hepatitis C infection. There were no liver-related serious events and only 3 of the 59 non-serious adverse events were rated as liver-associated disorders – one patient because of a new hepatitis C infection and two patients because of slightly increased liver-enzymes. Treatment with buprenorphine-naloxone was continued in all 3 cases. The analysis of the laboratory parameters revealed no significant risk for liver-enzyme elevation, liver injury or failure during the treatment of opioid dependent patients with buprenorphine-naloxone in routine care. The study provided evidence that buprenorphine-naloxone is a safe medication when applied as prescribed, even in patients with hepatitis C infection.

Conclusion

The findings from the 12-month non-interventional post-authorization safety study of drug dependence treatment with buprenorphine-naloxone provided evidence of its effectiveness and safety in routine care treatment settings. Acceptance and tolerance of buprenorphine-naloxone was high even among patients switching directly from street heroin use. As with other maintenance drugs, the initial response of patients to the treatment impacts course and outcome of the therapy with buprenorphine-naloxone. Early adjustments of certain parameters could help to retain the patient in the treatment and change the course to a positive outcome.

I. Summary/Zusammenfassung

In 2007 buprenorphine-naloxone, a medication for the treatment of opioid use disorder, was launched in Germany. The medication consists of the combination of buprenorphine and naloxone in a 4:1 ratio and was developed because the mono-compound buprenorphine, a well-established medication in opioid dependence therapy, had been subject to diversion and misuse. A non-interventional post-authorization safety study was conducted from 2008 to 2010 to collect comprehensive real-life data on the treatment of opioid dependent patients with buprenorphine-naloxone in Germany. Three major articles, published in international peer-review journals, evaluated data from this study on safety, effectiveness and tolerance, predictive value of the first four weeks as well as risk of liver-enzyme elevation in the treatment of opioid dependent patients with buprenorphine-naloxone.

The findings from these extensive evaluations indicate a high safety profile, a high effectiveness, tolerance and acceptability with substantial improvements in quality of life, mental and physical health. There was no evidence for an increased risk for liver-enzyme elevation even in patients with hepatitis C infections. In the first four weeks specific and general parameters with high predictive value were found that can be used as early signals to adjust the therapy plan in order to positively influence course and outcome of opioid dependence treatment with buprenorphine-naloxone in routine care.

2007 wurde Buprenorphin-Naloxon, ein Medikament für die Behandlung der Opioidabhängigkeit, in Deutschland zugelassen. Das Medikament enthält die Kombination von Buprenorphin und Naloxon in einem Verhältnis von 4:1 und wurde aufgrund zunehmenden Missbrauchs von Buprenorphin, einem gut etablierten Medikament zur Behandlung der Opioidabhängigkeit, entwickelt. Eine nicht-interventionelle Sicherheitsstudie wurde von 2008 bis 2010 durchgeführt, um umfassende Daten zur Routinebehandlung von opioidabhängigen Patienten mit Buprenorphin-Naloxon in Deutschland zu erheben. Drei Hauptartikel, die in internationalen Peer-Review Fachzeitschriften publiziert wurden, analysierten die Daten der Studie hinsichtlich Sicherheit, Effektivität und Toleranz, vorhersagefähiger Variablen der ersten vier Wochen sowie das Risiko für erhöhte Leberenzymwerte in der Behandlung von opioidabhängigen Patienten mit Buprenorphin-Naloxon.

Die Ergebnisse dieser umfangreichen Analysen weisen auf ein hohes Sicherheitsprofil, eine hohe Effektivität, Toleranz und Akzeptanz mit deutlichen Verbesserungen in der Lebensqualität sowie der psychischen und physischen Gesundheit hin. Es zeigten sich keine Anzeichen eines erhöhten Risikos für einen Anstieg der Leberenzymwerte sogar bei Patienten mit einer Hepatitis C Infektion. Die ersten vier Wochen haben einen hohen Vorhersagewert mit spezifischen und generellen Parametern, die als frühzeitige Signale genutzt werden können, um den Behandlungsplan anzupassen und damit Verlauf und Ausgang der Behandlung mit Buprenorphin-Naloxon in der Routinebehandlung positiv zu beeinflussen.

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