Aus der Klinik für Neonatologie
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Ausprägung und Therapie des neonatalen Abstinenzsyndroms während der Jahre 2000-2011. Eine monozentrische retrospektive Analyse.

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Vorwort

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Abbreviations

AAP	American Academy of Pediatrics
ABC	Adenosine triphosphate binding cassette
ACOG	American College of Obstetricians and Gynecologists
ANS	Autonomic nervous system
AVSD	Atrioventricular septal defect
BBB	Blood brain barrier
BRCP1	Breast cancer resistance protein 1
CDC	Center for Disease Control
CI	Confidence interval
CNS	Central nervous system
CVK	Charité Campus Virchow-Klinikum
CYP	Cytochrome-P-450-enzymes
CNS	Central nervous system
EEG	Electroencephalography
EDDP	2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine
EMDP	2-ethyl-5-methyl-3,3-diphenylpyrroline
GI	Gastrointestinal
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HDB	High-dose buprenorphine

IUGR	Intrauterine growth restriction
LBW	Low birth weight
LSD	Lysergic acid diethylamide
MANOVA	Multivariate analysis of variance
MDR1	Multidrug resistance protein 1
MMT	Methadone maintenance treatment
MRI	Magnetic resonance imaging
N/A	Not applicable
NAS	Neonatal abstinence syndrome, *Neonatales Abstinenzsyndrom*
N(I)CU	Neonatal (intensive) care unit
OR	Odds ratio
P-gp	Phosphoglycoprotein 1
RCT	Randomized controlled trial
SGA	Small for gestational age
SIDS	Sudden infant death syndrome
SSRI	Serotonin reuptake inhibitor
SSW	*Schwangerschaftswoche*
UGT	Uridine diphosphate glucuronosyltransferase
VEP	Visually evoked potentials

Abstract

Background After exposure to opiates *in utero*, infants display withdrawal symptoms after birth referred to as neonatal abstinence syndrome (NAS). The treatment of this condition typically takes several weeks and comprises both supportive and pharmacological therapy. 4 decades after systematic treatment of NAS was first begun, the preferable treatment strategy is still discussed controversially in current literature.

Methods Medical charts of 366 newborn infants (166 females, 10 twins) with intrauterine exposure to opiates and their 361 mothers at Charité Virchow-Klinikum (CVK) from 2000 to 2011 were reviewed retrospectively.

Results The rate of prematurity (gestational age < 37 $^{0}/_{7}$ weeks) was 20% in this cohort, 32% of our patients were small-for-gestational age (<10th percentile). Among the infants exposed to methadone antenatally (racemic methadone or levomethadone), 70% (195 of 278) required pharmacotherapy for 11 (1-55) days (median; range); among those exposed to buprenorphine 45% (28 of 62) required pharmacotherapy for a median of only 5 (1-20) days ($p = 0.014$). The increased duration of neonatal pharmacotherapy and hospitalization was associated with an increase in the average dosages of maternal methadone. 65% (175 of 268) of infants of mothers who used drugs other than their substitute medication required pharmacological withdrawal treatment compared to 47% (34 of 72) of infants of mothers who did not ($p<0.001$) while the duration of treatment was 10 days in both subgroups. Pharmacotherapy of neonates with phenobarbital (n = 198) was at 9 (1-53) days shorter than treatment with morphine (n = 39) which took 19 (3-55) days ($p < 0.001$). The median duration of pharmacotherapy increased from 5 days in 2000-2004 to 18 days in 2008-2011 ($p < 0.001$). The 11 premature infants below 33 complete weeks of gestation did not require pharmacotherapy for more than 4 days.

Conclusion This thesis indicates 3 factors associated with a shortened duration of neonatal pharmacotherapy for NAS: First, maternal use of buprenorphine, rather than methadone for maintenance therapy during pregnancy. Second, low maternal doses of methadone where buprenorphine is not the substitute. Third, neonatal treatment with phenobarbital rather than morphine, which is now considered standard of care. (In part adopted from (1).)

Zusammenfassung

Hintergrund Nach intrauteriner Opiatexposition zeigen Neugeborene postnatal Entzugssymptome, die als neonatales Abstinenzsyndrom (NAS) bezeichnet werden. Die meist mehrwöchige Therapie dieses Krankheitsbildes beinhaltet supportive sowie medikamentöse Behandlungsansätze. 4 Jahrzehnte nach dem Beginn der systematischen Behandlung des NAS wird in der Literatur weiterhin kontrovers über die optimale Behandlungsstrategie diskutiert.

Methoden Die Patientenakten von 366 intrauterin opiatexponierten Neugeborenen (166 weiblich, 10 Zwillinge) und ihrer 361 Mütter am CVK im Zeitraum von 2000 bis 2011 wurden retrospektiv ausgewertet.

Ergebnisse Der Anteil an Frühgeborenen (<37+0 Schwangerschaftswochen, SSW) betrug 20 %, 32 % der Patienten waren hypotroph (<10.Perzentile). Unter den Methadon (racemisches Methadon oder Levomethadon)-exponierten Neugeborenen wurden 70 % (195 von 278) für 11 (1-55) Tage (Median, Bereich) medikamentös behandelt, unter den Buprenorphin-exponierten Neugeborenen waren es nur 45 % (28 von 62) für 5 (1-20) Tage (p=0,014). Die zunehmende Behandlungs- und Krankenhausaufenthaltsdauer war mit einer zunehmenden durchschnittlichen Tagesdosis der mütterlichen Methadonsubstitution assoziiert. Nach mütterlichem Beikonsum wurden 65 % (175 von 268) der Neugeborenen medikamentös behandelt, ohne Beikonsum waren es 47 % (34 von 72) Neugeborene (p<0,001). Die Behandlungsdauer war in beiden Subgruppen mit 10 Tagen gleich lang. Die medikamentöse Behandlung mit Phenobarbital (n=189) war mit 9 (1-53) Tagen kürzer als die mit Morphin mit 19 (3-55) Tagen (p < 0,001). Die mediane Behandlungsdauer nahm von 5 Tagen im Zeitraum von 2000-2004 bis auf 18 Tage in den Jahren 2007-2011 zu (p < 0,001). Die 11 Frühgeborenen von weniger als 33+0 SSW wurden maximal 4 Tage lang medikamentös behandelt.

Schlussfolgerung Diese Arbeit weist auf 3 Faktoren hin, die mit einer kürzeren medikamentösen Behandlungsdauer des neonatalen Entzugs assoziiert sind: Erstens die maternale Substitutionstherapie mit Buprenorphin während der Schwangerschaft im Vergleich zu Methadon, zweitens die Substitution mit niedrigeren Methadondosierungen, wenn Buprenorphin nicht als Substitution verwendet wird und drittens die medikamentöse Behandlung der Neugeborenen mit Phenobarbital statt Morphin, der aktuellen Standardbehandlung. (Anteilig nach (1).)

1. Introduction

1.1. Background

Opioids are lipophilic substances which readily cross lipid-membranes, such as the blood brain barrier (BBB) or the placenta. In women using opioids during pregnancy, this leads to opioid exposure of the fetus (2). Exposure to any drug during pregnancy potentially affects the placento-fetal unit by one or more of four possible mechanisms: drug-specific teratogenic effects, neurotoxicity affecting the developing neurons and glia cells, placental dysfunction leading to growth restriction and prematurity and the development a tolerance towards the drug. At birth, the exposure to the drug is abruptly discontinued, causing the neonate to experience withdrawal symptoms within the first few days of life. In the case of opioids, the condition is called neonatal abstinence syndrome (NAS) and occurs in 55-94% of exposed infants (3).

Moreover, infants born to drug-dependent mothers are at risk for medical problems and psychosocial difficulties not linked to the opioid exposure itself, but rather to indirect effects of drug use, the mothers' socioeconomic background and the stigmatization of addicts (4). For instance, the consumption of intravenously injectable drugs holds a risk of contracting vertically transmissible diseases, such as human immunodeficiency virus (HIV), hepatitis B (HBV) and C (HCV), via the routes of both needle-sharing and prostitution to finance drugs (4, 5). Furthermore, the adherence to regular antenatal care is lowered among opioid-dependent women (6). Postnatally, children may suffer from frequently changing attachment figures, either by placement into foster families or because of imprisonment of either parent (4). Opioids substitution programs have been shown to mitigate, but not solve, many of these problems (3).

1.2. Epidemiology

Estimates as to the number of children born to opioid addicted mothers in Germany remain vague, mostly due to a high number of unreported cases and lack of central registration. In 2003, a conservative estimate deduced that between 40,000 and 50,000 children live with opiate addicted parents in Germany (4). In the same year, the number of persons using heroin in Germany was approximately 120,000 and 46,200 persons were registered in substitution programs with methadone, levomethadone, buprenorphine and dihydrocodeine (7). Of these, about 1/3 are women, in about 80% in their reproductive age (8). The number of opioid using

persons appears comparatively stable, with 200,000 persons using any illegal intravenously applicable substance, such as opiates, cocaine and stimulants in 2012 (9). The number of patients in substitution programs has meanwhile increased to 76,200 in July 2011 (9). In the United States, an analysis of 299 neonatal intensive care units (NICUs) from 2003 through 2014 by Tolia *et al.* showed that 10,327 neonates were treated for NAS during this ten-year period with a more than six-fold increase of cases from 0.6% to 4.0% of all accumulated NICU days (10).

1.3. Opioid metabolism and pregnancy

In the adult, opioid metabolism may be outlined as follows: the opioid is absorbed into the blood stream via the mucous membranes of the nose, lungs or gastrointestinal (GI) tract or injected intravenously. Diamorphine, or heroin, is deacetylated either in the liver or in the brain to its active metabolites 6-monoacetylmorphine and morphine (11), while methadone and buprenorphine require no additional metabolic transformation. Being lipophilic substances, opioids cross the BBB passively (12). In the brain, opioids bind to the μ(*mu*)- and κ(*kappa*)-opioid receptors and cause euphoria, analgesia and depress respiration (13). Morphine and methadone act as full agonists (13, 14) while buprenorphine is partial opioid μ-agonist and κ-antagonist (15). Opioids are excreted from the body predominantly by hepatic elimination. In phase 1 of hepatic metabolism, methadone is N-demethylated to the pharmacologically inactive 2-ethylidine-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenylpyrroline (EMDP) by cytochrome-P-450-enzymes (CYP), mainly CYP3A4, CYP2B6 and CYP2D6 (12, 14, 16). Buprenorphine is N-dealkylated to norbuprenorphine, another active metabolite, mainly by CYP3A4 and CYP2C8 (16). In phase 2 of hepatic metabolism, morphine, buprenorphine and norbuprenorphine are glucoronidated by uridine diphosphate glucuronosyltransferases (UGTs) before excretion into the bile. UGT2B7 has been identified as the most important enzyme in the glucoronidation of morphine (12), while buprenorphine and norbuprenorphine are chiefly glucoronidated by UGT1A1, UGT1A3 and UGT2B7 (16). Significant interindividual discrepancies regarding expression and activity levels have been noted for both CYP and UGT enzymes (17, 18).

During pregnancy, several physiological changes influence the pharmacokinetics of opioids. Due to an increased maternal plasma volume and thus distribution volume, decreased oral absorption and lowered plasma protein binding lead to lowered maternal opioid blood levels for the same dose administered (15). At the same time, a slower intestinal transit time may

increase intestinal opioid absorption and an increase in fat tissue may cause an accumulation of methadone (19). The expression and activity of maternal CYP and UGT enzymes also changes during pregnancy. The activity of proteins of the CYP3A subfamily, including CYP3A4, has been shown to be increased in pregnant subjects, while CYP2D6 activity is decreased (20). There is also evidence that the activity of UGT1A4 increases during pregnancy whereas the level of UGT2B7 appears to remain unaltered (21).

As pregnancy progresses, the growing placenta plays an increasing role in the metabolism of opioids. Analogous to the BBB, opioids diffuse through the placental membranes without need for active transport proteins. Placental trophoblast cells, however, express enzymes that metabolize and actively eliminate xenobiotics from the fetal blood stream. Among them is the cytochrome-P-450 enzyme CYP 19, also named aromatase, which demethylates methadone to EDDP rendering it inactive (22). CYP 19 also demethylates buprenorphine to norbuprenorphine in the human placenta (23). Adenosine triphosphate binding cassette (ABC) proteins such as phosphoglycoprotein (P-gp), multidrug resistance protein 1 (MDR1) and breast cancer resistance protein 1 (BRCP1) serve as efflux pumps responsible for the elimination of xenobiotics, and thus opioids, from the fetal circulation (24-26).

Within the fetus, opioid metabolism displays some differences to the metabolism seen in adults. The expression and activity of hepatic enzymes has yet to mature. UGT enzymes have been shown to have lower levels of activity in fetal than in adult livers (27). Some CYP enzymes including CYP3A4 have been detected as early as 20 weeks of gestation whereas other CYP enzymes are only expressed later during the pregnancy (15). The fetal BBB also differs from that of the adult with ABCs like P-gp, BRCP1 and MDR1 expressed at several fold different levels (28).

1.4. Effects of intrauterine opioid exposure

1.4.1. Teratogenicity

The incidence of congenital defects after intrauterine opiate exposure appears to play a comparatively minor role. Case control studies show that maternal opioid pain therapy during the first trimester of pregnancy statistically significantly increases the risk of congenital cardiac defects and other birth defects, such as spina bifida and gastroschisis (29, 30). Odds ratios for developing these malformations after opioid exposure were calculated to range from 1.1 to 2.7. As the increase in absolute numbers is minimal, however, the American College of

Obstetricians and Gynecologists (ACOG) concludes that this effect is negligible in the context of opioid-dependent mothers (31).

1.4.2. Neurotoxicity

Regarding neurodevelopment, the effects of opioids have been less thoroughly studied than those of alcohol (32). *In vitro* studies on fetal human microglia and neuron cell cultures show a certain apoptotic effect of morphine via an opioid receptor mechanism on these cells, most markedly on neurons (33). Animal studies have also found differences in phosphorylation patterns of enzymes relevant for neuroplasticity and in the expression of apoptosis inducing proteins in the *hippocampi* of opioid-exposed rats and mice (34, 35). The abilities for spatial learning were also decreased in rat offspring after intrauterine opioid exposure (36). *In vivo*, visually evoked potentials (VEP) of opioid-exposed human neonates show less mature patterns at 4 days of age than non-exposed newborns, suggesting a difference in visual processing (37). At 18 months and 3 years of age, Australian researchers found children who had suffered from NAS to be significantly more likely to have impaired motor, language and cognitive development (38). In a Norwegian prospective study, Moe *et al*. compared 4.5-year-old children who had been exposed primarily to opioids *in utero* and non-exposed children of the same age. Using a multi-scaled psychometric test, this study found the opioid-exposed children to receive normal overall cognitive scores. Their visual-motor and perceptual abilities, however, were significantly weaker than those of the non-exposed children (39). At 11 years of age, magnetic resonance imaging (MRI) showed a decreased volume of several brain areas in follow-up studies of the same children. Prenatal opioid exposure appeared to be most prominently associated with a decreased volume of the putamen, the pallidum and the inferior lateral ventricle (32, 40).

There is evidence, however, that such effects may not only be due to the immediate effect of opioids on the fetal brain. A case-control study by Ornoy *et al.* compared intrauterine opiate-exposed children living in their genetic families, non-exposed children living in social deprivation, non-exposed children without social deprivation and opiate-exposed children who had been adopted by families from a moderate or high socioeconomic class with one another. It suggests that environmental factors may be an even more important influence on neurodevelopment than opioid exposure itself (41) (for more on environmental factors, see “Social and psychological aspects of maternal drug use”).

1.4.3. Intrauterine growth restriction and prematurity

Placental vasoconstriction leads intrauterine growth restriction (IUGR) by limiting the supply of oxygen and nutrients to the fetus (42). This negative outcome is well-known after nicotine, cocaine and selective serotonin reuptake inhibitor (SSRI) use during pregnancy (42, 43). Opioid-exposed neonates are often small for gestational age (SGA) after symmetric IUGR (5, 44). Prematurity has been observed more often than in non-opioid-exposed infants in some cohorts (5), but not in others (43, 44). In the case of heroin, both IUGR and prematurity have been attributed to the opioid alone (31, 43), while in the case of other opioids these observations appear to be at least in part attributable to co-used drugs (44, 45).

1.4.4. Intrauterine and postnatal death after maternal opioid use

Maternal heroin use leads to repeated and abrupt withdrawals for the fetus during pregnancy. This has been described as a risk factor for intrauterine fetal death and still birth (46-48).

An increased rate of the sudden infant death syndrome (SIDS) after maternal opioid use has also been described. While the incidence in the general population ranges between 1.8 and 2.5 per 1000 live births, it is reported to range between 14 and 18 per 1000 live births in prenatally opioid exposed neonates (6, 49).

1.4.5. Co-use of drugs other than opioids and infectious diseases

Frequently, drugs other than the opioid are consumed by opioid-dependent pregnant women. These co-used drugs include both legal, such as alcohol and nicotine, illicit substances, such as cocaine, cannabinoids and amphetamines and neurotropic medication like benzodiazepines and SSRI. Some of these substances, most notably alcohol, are known to be teratogenic and some can also cause or enhance withdrawal symptoms (3, 45, 50, 51).

One other important co-morbidity associated with intravenous drug use is a high prevalence of HBV and HCV as well as HIV. Rohrmeister *et al*. report a prevalence of 30% of HBV, 67% of HCV and 6% of HIV among opioid-dependent mothers. 26% of the women were infected with more than one virus in Vienna between 1995 and 1999 (5).

1.5. Neonatal abstinence syndrome

1.5.1. Clinical presentation

NAS manifests itself neurologically through central nervous system (CNS) signs like tremors, irritability, increased wakefulness, high-pitched crying, hyperactive deep tendon reflexes, exaggerated Moro reflex, seizures, frequent yawning and sneezing. Autonomic nervous system (ANS) signs include increased sweating, nasal stuffiness, fever, hypertonia, temperature instability and mottling. GI symptoms, such as poor feeding, uncoordinated and constant sucking, vomiting and diarrhea resulting in dehydration and poor weight gain, may also occur. Additionally, tachypnea or apnea, and skin excoriations may be present (50, 52).

The typical onset of clinical signs is between the second and third day of life (53), and can be expected within the first week of life (54). In rare cases, the onset of symptoms may be delayed for up to 4 weeks (55).

Differential diagnoses include hyperthyroidism, intracranial hemorrhage, perinatal anoxia, hypoglycemia, hypocalcemia, sepsis and hyperviscosity (52).

1.5.2. Supportive and pharmacological therapy for NAS

The aims of all approaches to therapy for NAS are to reduce withdrawal symptoms to a bearable level for the infant (56), in order to establish stable weight gain, integrate the infant into his or her social environment and to prevent complications such as seizures (3).

Initially, infants beginning to develop NAS should receive so-called “supportive care” regardless of their need for pharmacological intervention. Supportive care includes minimizing environmental stimuli by creating a dark, quiet environment, avoiding auto-stimulation by swaddling the neonate, responding early to signals by the infant, adopting appropriate positioning and comforting techniques. Frequent and small feeds with either human milk or hypercaloric formula to supply as much as 150 to 250 kcal/kg body weight per day in order to minimize hunger and allow for adequate growth should be administered (3). Rooming-in of mother and infant has been shown to reduce the need for pharmacotherapy and the duration of hospital stay (57).

It has become consensus that breastfeeding by the mother should be encouraged (3, 58). Among its well-known benefits, such as passive immunity to infections, some protection

against asthma and obesity and improved early neurodevelopment, the aspect of improved interaction between mother and child is extremely important (59). On top of this, the concentration of methadone appears to be small regardless of the maternal methadone dose (58) and it has been shown that breastfeeding decreases the severity and delays the onset of withdrawal symptoms and decreases the need for pharmacologic therapy (60). Situations where breastfeeding is not recommended are maternal HIV infection (61), if a mother is not in opioid substitution therapy (59) or if there is co-use of intravenously used drugs, benzodiazepines, barbiturates or cocaine.

The American Academy of Pediatrics (AAP) has recommended in 1998 that pharmacological treatment is indicated for infants with confirmed drug exposure and seizures, poor feeding, diarrhea and vomiting resulting in excessive weight loss and dehydration, the inability to sleep and fever unrelated to infection (50). In order to more objectively assess the severity of withdrawal symptoms, the use of scoring systems has been suggested (3), the 2 most important being the Lipsitz tool (62) and the original or modified Finnegan score (63) (see 2.2 Treatment modalities, Table 3). The Finnegan score is considered the more comprehensive of the 2 and is the scoring system most frequently used in clinical studies, while the Lipsitz tool has been recommended as a simpler alternative (3, 50). In both clinical studies and clinical practice these scoring systems are used to begin pharmacological treatment at a given cut-off score and to titrate medication accordingly (3, 64, 65).

If pharmacological therapy is necessary to control withdrawal symptoms, there are 3 main substance groups from which to select an appropriate medication: opioids, sedatives and other CNS receptor agonists or antagonists (Table 1). It has been suggested by several authors to go by the biologically logical approach to use a substance from the group predominantly causing the withdrawal, in other words, to use opioids for opioid-associated NAS and sedatives for benzodiazepine- or alcohol-predominant withdrawal (50, 56). Yet, all 3 groups have been found useful in the pharmacotherapy of opioids-associated withdrawal (66).

Table 1: Substances available for pharmacological treatment of NAS.

	Substance	**Remarks**
Opioids	Morphine - Water-based morphine solutions - Diluted tincture of opium - Paregoric	 Most frequently used substance No longer recommended
	Methadone	Long half-life (approx. 26 h)
	Buprenorphine	Relatively novel in neonatal therapy
Sedatives	Phenobarbital	Long half-life (approx. 3 to 7 days in neonates)
	Diazepam	Long half-life, limited efficacy
Others	Clonidine	Primarily as adjunct therapy
	Chlorpromazine	No longer recommended

Among opioids, morphine solutions are currently the most commonly used medication for NAS (3, 10). Morphine is available as diluted tincture of opium, which contains some ethanol and alkaloids, though less than the below mentioned paregoric, and oral morphine solutions, which are entirely water-based (56). Paregoric was also used in former times, but has been abandoned as it contains potentially toxic substances, such as ethanol, papaverine, noscapine, camphor and benzoic acid (50).

Other opioids that have been tested as treatment for NAS are methadone and, more recently, buprenorphine, both of which have been mainly used as heroin substitution medication (see “Maternal opioid substitution”). Methadone has been shown to be comparable in outcome to the sedatives phenobarbital and diazepam as early as 1977 by Madden *et al*. (67), but its use has not become more wide-spread than 10-20% of infants treated for NAS in the USA (10), possibly due to the long half-life of about 26 hours in neonates and thus risk of accumulation (50). In 2015, a randomized controlled trial (RCT) by Brown *et al*. on 31 neonates with NAS

gave some indication that the treatment duration under methadone may be shorter than under morphine treatment (68). More investigation is needed, however, as their study population consisted of only 31 neonates. Recently, neonatal buprenorphine treatment has become a novel alternative. In 2008, Kraft *et al*. published a pilot-RCT comprising 26 neonates on the subject, showing that it is a safe option as treatment for NAS (69). The follow-up study on 63 neonates with NAS was published in 2017 and demonstrated a shorter duration of pharmacotherapy under buprenorphine rather morphine in this cohort (70).

The more diverse substance group of sedatives includes phenobarbital and diazepam, while clonidine and chlorpromazine have different pharmacological modes of action altogether. Phenobarbital, a barbiturate, has been used to treat neonates with NAS for over 3 decades. In the 1980s, Kaltenbach and Finnegan showed that while treatment failure was seen more frequently under phenobarbital than under morphine, there was no difference between the 2 treatment regiments with regard to neurodevelopmental outcome at 6 months of age (71). Kandall *et al*. published a study that showed that symptoms caused by NAS can be controlled equally well with phenobarbital and paregoric. Borderline significantly more frequent seizures were seen in the group treated with phenobarbital (72). The AAP cautions that phenobarbital does not sufficiently control GI-symptoms and can be accumulated in the infant's body due to its long half-life (50). The most widely noted European study directly comparing morphine and phenobarbital was conducted by Jackson *et al*. and published in 2004. In a double blind RCT which included 75 neonates, the use of morphine lead to a significantly shorter treatment duration than that of phenobarbital. Also, second-line treatment and an admission to the neonatal care unit (NCU) were needed less frequently (64). Since then, morphine has become the gold-standard for the pharmacological treatment of NAS. More recently, in 2014, an Iranian RCT on 60 neonates did not find a difference in treatment duration between infants treated with morphine or phenobarbital for NAS (73).

Diazepam, a benzodiazepine, plays only a minor role in the pharmacological treatment of NAS. It has only been recommended by the AAP with reservations, as neonates are limited in their capacity to metabolize benzodiazepines via the hepatic cytochrome P450 enzyme pathways, resulting in an elimination time of more than one month (56). Additionally, sodium benzoate, which is contained in the parenteral preparation of diazepam, displaces bilirubin from albumin, increasing the risk for jaundice (74). On top of this, diazepam strongly depresses suck and swallow reflexes (75). With regard to effectively controlling symptoms, Madden *et al*., as mentioned above, found no difference in therapeutic response to diazepam compared to

phenobarbital and methadone (67), while Kaltenbach and Finnegan found it to be completely insufficient on its own (71).

Clonidine is a centrally acting alpha-2 adrenergic agonist, which has been primarily used to treat hypertension (76), and subsequently to mitigate opiate and alcohol withdrawal in adults (50, 56). In 2009, Agthe *et al*. demonstrated in an RCT with 80 patients enrolled, that clonidine use in addition to morphine shortens treatment duration by 27% compared to morphine plus placebo. It also appeared to be safe for use in neonatal patients, although hypotension and bradycardia are mentioned as possible side effects to consider (65). 5 years later, a small RCT including 31 neonates by Bada *et al.* demonstrated that clonidine monotherapy may be equal, if not favourable to morphine monotherapy (77).

Chlorpromazine, a phenothiazine and the first antipsychotic drug developed in 1950, has also formerly been used to treat heroin withdrawal in neonates. Kahn *et al*. found that it was not significantly inferior to phenobarbital in 1969 (78), but its use has been discouraged due to prolonged excretion time in neonates, as well as frequent side effects, including cerebellar dysfunction, decreased seizure threshold and hematologic problems (50).

1.6. Maternal opioid substitution

1.6.1. Rationale and substances

Methadone maintenance therapy (MMT) has been the standard of care for opiate-using women in pregnancy since the 1970s (79). Due to its comparatively long half-life of approximately 24 hours (15) it has been noted to reduce the negative effects of repeated heroin withdrawal on the fetus (48). Additionally, it improves the birth weight of the child, possibly by achieving better adherence to obstetrical care by the mother (80). As the orally administered MMT also reduces needle sharing and drug-related prostitution, it leads to less risk of HIV, HBV and HCV infection of both mother and fetus (81). Ziegler *et al*. also found an improved social context, and an improved mother-child-interaction and a significantly increased rate of children discharged to their substituted mothers compared to their unsubstituted counterparts (8). Originally, racemic methadone preparations were used. In more recent years, the prescription of the L-isomer levomethadone has been promoted under the assumption that it causes fewer side effects, such as prolongation of the QT-interval (82).

More recently, buprenorphine has been perceived as a possible alternative substitution medication. In 2006, the first large prospective study comparing MMT to high-dose buprenorphine (HDB) substitution was published by Lejeune *et al*. No major difference in perinatal outcome for both mother and child was found between the traditional MMT-group of 100 mothers-to-be and the HDB substituted group of 159 (83). The “Maternal Opioid Treatment: Human Experimental Research” (MOTHER) study, a multicenter RCT including 131 neonates published in 2010, examined the implications of methadone and buprenorphine substitution during pregnancy in more detail. With regard to maternal outcome, no difference between the 2 modes of substitution was found once again. Looking at neonatal outcome, Jones *et al*. found significantly shorter hospital stays and treatment durations and lower morphine doses in neonates whose mothers had been substituted with buprenorphine rather than methadone (84). Despite these recent findings, the majority of pregnant women in Germany are currently substituted with methadone rather than buprenorphine (85).

1.6.2. Social and psychological aspects of maternal drug use

As mentioned above, the long-term developmental outcome of children of opioid-dependent women strongly depends on social circumstances (8, 41). The socioeconomic status of families with an opioid-using parent is frequently low (41), with high rates of unemployment and mothers often faced with raising their children alone or with changing partners (4, 8). Not few of the families even do not have a home of their own (8, 86).

Other than these general observations, there appear to be some characteristics somewhat more specific for these families. Ziegler *et al.* found that the interaction between mother and child tended to be dysfunctional; especially if the mother was not in an opioid substitution program (8). In the latter case, the negative factors associated with drug procurement also pose stress on the families: Time and money spent, and even prostitution and crime (86). Even if this is not the case, psychological problems are frequently associated with drug use, such as depression and anxiety, with many mothers having grown up with sexual or physical abuse and neglect themselves (4, 86).

All the same, while placing children in foster homes at first glance appears to solve the abovementioned problems and has been shown to be able to improve neurodevelopmental outcome (41), the practice of taking children from their families has its own demerits. Discontinuity of attachment figures has been identified as an important psychological risk factor, yet only a minority of children remains with only one family (4). On the jurisdictional

level, the German Basic Law states the right and duty for parents to care for and educate their own children as one of the key values within the judicial system and assistance with this task is clearly placed before separating children from their parents (87). In a similar ethos, the United Nations Convention on the Rights of the Child obligates all states “to ensure that a child is not separated from his or her parents against their will” (88) as a fundamental right to be observed internationally.

1.7. Objectives

Over the past decades, many studies on NAS have greatly improved both our knowledge about its pathophysiology and patient care. Yet, some controversies still exist. It is consensus that a short duration of withdrawal and required pharmacotherapy is desirable, but the duration of therapy varies greatly between different NICUs with a range of 8 days to more than 80 days (60, 65, 89). Research teams are trying to find treatment schemes leading to shorter treatment durations than the current standard of oral morphine solution (69, 73, 77) while both the number of NAS-affected infants and the duration of pharmacotherapy in the United States of America (USA) keep increasing (10), suggesting that an acceptable solution has not been found to date.

Furthermore, many of the abovementioned studies have been conducted in the USA and thus some of the results and recommendations may, for 2 main reasons, not be directly transferable to the situation in Europe, and Germany. First, the profiles of maternal drug use tend to be different between the 2 settings. Maternal substitution was more frequently performed with buprenorphine in Europe than in the United States (90). While cocaine and SSRI play a major role in the USA (43), they are much less frequently used in the population examined in this study (see “Maternal substitution and drug use patterns”), with opiates predominating the European drug treatment systems (91). Second, a low-tolerance-policy towards users of illicit drugs in the USA (45) may often lead to poor prenatal care and/or less open reporting of drug use during pregnancy, whereas a low-threshold-approach for addiction assistance frequently practiced in Europe (92) may be expected to lead to improved pregnancy outcomes.

In addition, treatment of addicted mothers and their infants remains a rare condition in most perinatal units as a result of a lack of regionalization. Most studies comprise relatively small numbers with the minimum number of patients enrolled being 26 infant-mother pairs (69). Even comparatively large studies include patient numbers of less than 150 (8, 41, 84). The only

marked exception to date is a Cochrane review published in 2010 which meta-analyzes nine studies with a total of 645 neonates (66). Therefore, additional data is frequently called for (68).

1.7.1. Aim of this work

The purpose of this analysis is to describe in some detail the single center experience of treating patients with NAS in a typical urban central European setting. Within Berlin, a certain degree of regionalization is put into practice via the "*Suchtambulanz*" at CVK, an outpatient clinic offering specialized consultation for addicted pregnant women. The primary advantage of this clinic is that it allows an interdisciplinary team including gynecologists, nurses, pediatricians and social workers to start care for the mother-infant-pair early during pregnancy. A secondary advantage lies in the comparatively high numbers of 30-40 opioid-dependent mothers treated each year, making it possible to give a comprehensive review of the majority of Berlin's patients of the past 12 years, and one of the largest populations described to date. Next, it seeks to provide a differentiated analysis of the influence of maternal drug use and substitution, conditions of antenatal care, mode of pharmacologic treatment of the neonate, prematurity and the changes over time on neonatal outcome. Neonatal outcome is regarded in terms of birth data, the course of neonatal abstinence syndrome and the decision about further care providers. Furthermore, the results of this analysis will be compared to the respective current evidence and, as far as possible, explanation for any differences shall be proposed.

2. Methods

2.1. Study design

2.1.1. Inclusion criteria

For this retrospective single center study, the charts of all neonates born in the CVK during the years of 2000-2011 suffering from NAS were analyzed. As such, infants who met the following criteria were considered:

a) Birth to a mother known to have used opiates during their pregnancy from their prenatal care visits to the specialized outpatient clinic (see below)

and

b) diagnosis with neonatal withdrawal syndrome (ICD-10, P96.1) from opiates based on clinical signs in combination with toxicological screening during the postnatal hospital stay.

Neonates who were transferred to other hospitals during the course of the treatment were excluded. Infants who experienced withdrawal exclusively from drugs other than opiates, such as benzodiazepines, were not included in the scope of this work.

2.1.2. Data collection and drug screening

Maternal data was collected prospectively during the women's prenatal care visits to the abovementioned gynecological outpatient clinic specializing in pregnant women with either infectious diseases or drug use. In this setting, a detailed maternal history on drug use during each trimester of pregnancy and maternal urine samples were obtained. It also served to continue, modify or start the substitution with racemic methadone, levomethadone or buprenorphine. Neonatal data was collected retrospectively from archived patient files (Table 2). Co-diagnoses, such as congenital malformations or hyperbilirubinemia were not included in the analysis. Neonatal drug screening by meconium analysis via immunoassay was routinely done since 2003 (93). In prior years, this method was reserved for cases where there were no reliable maternal drug screening tests available. In all, these methods contributed to a detailed knowledge of the illegal substances neonates had been exposed to

in utero. The legal drugs alcohol and nicotine, however, were only noted in the maternal history. Thus, a substantial percentage of unreported use for both substances must be assumed.

Table 2: Data collected from patient files and during prenatal screening consultations.

Maternal data	Age
	Previous pregnancies and live births, whereabouts of other children
	Substitute medication and dosage
	Drugs used in addition to the substitute medication
Neonatal birth biometrics	Gestational age
	Birth weight, body length, frontooccipital head circumference and corresponding percentiles
	Apgar scores (94)
	Perinatal exposition to HIV, HBV and HCV
Course of treatment	Maximum Finnegan score
	Duration of hospitalization
	Initiation and duration of pharmacological therapy
	Initial and secondary mode of treatment if applicable
	Occurrence of seizures as the most severe complication of NAS
Discharge data	Discharge to mother, into a supervised living facility for mothers and children or into foster care
	Assistance by social worker
	Follow-up in pediatric psychiatry

Subsequently, these items were analyzed as described below (see “Statistical analysis”). The “*Jahresauswertung Geburtshilfe 2009*“ by the BQS gGmbH per order of the “*Qualitätsbüro Berlin*” was used to compare our neonatal biometrics to those of the population of our university hospital as well as the general population of all hospitals in Berlin (95).

2.2 Treatment modalities

2.1.3. Interdisciplinary admission

Neonates known to have been exposed to opioids during pregnancy were initially admitted interdisciplinarily on the maternity ward after birth, allowing for as much time for mother and infant to bond as possible. Clinical assessment of the neonate by a pediatrician was carried out once per shift. Once withdrawal symptoms became too severe to manage conservatively, the infant was physically moved to the NCU for pharmacological therapy.

2.2.2 Finnegan score and pharmacological therapy

As a semi-quantitative tool to measure the severity of NAS, the Finnegan score (63), which assesses the abovementioned clinical signs was used (Table 3). It also served to indicate a necessity of pharmacological treatment. Scores were taken once per shift (that is, every 8 hours) initially. If appropriate, for example after a change in medication the interval at which the assessment was done was shortened to 4-hourly or elongated to up to 24 hours.

Table 3: Finnegan score.

Signs and symptoms	Score	Date/Time	Date/Time	Date/Time	Date/Time
High-pitched cry	2				
Continuous high-pitched cry	3				
Sleeps <3 h after feeding	1				
Sleeps <2 h after feeding	2				
Sleeps <1 h after feeding	3				
Hyperactive Moro-reflex	2				
Markedly hyperactive Moro-reflex	3				
Mild tremors if disturbed	1				
Marked tremors if disturbed	2				
Mild tremors even undisturbed	3				
Marked tremors even undisturbed	4				
Increased muscle tone	2				
Skin excoriations	1				
Myoclonic jerks	3				
Generalized seizures	5				
Sweating	1				
Fever 37.2-38.2 °C	1				
Fever >38.2 °C	2				
Frequent yawning (>3-4x/interval)	1				
Mottling	1				
Nasal stuffiness	2				
Frequent sneezing (>3-4x/interval)	1				
Nasal flaring	2				
Respiratory rate >60/min	1				
>60/min with intercostal retractions	2				
Excessive sucking	1				
Poor feeding	2				
Regurgitation	2				
Projectile vomiting	3				
Loose stools	2				
Watery stools	3				
Total score					

Pharmacotherapy was regularly started at Finnegan scores of 12 or higher in 2 consecutive scorings 4 hours apart. The decision to administer either phenobarbital or morphine was based on the current evidence at each time as well as the clinical experience of the attending physician. Phenobarbital was dosed at an initial dose of 10-15 mg/kg, followed by doses of 5 mg/kg/d when necessary, while morphine was started at 0.05 mg/kg 6 times a day and then titrated to achieve Finnegan scores below 12. In line with the results of the RCT by Aghte *et al*. (65), oral clonidine was added to the morphine regime at a dosage of 1-4 µg/kg 6 times a day from 2011 onward. If symptoms could not be sufficiently controlled with the initial choice of medication, escalation of treatment meant that morphine was added to or replaced phenobarbital and vice versa. Pharmacotherapy with morphine was tapered down by 5-10% whenever Finnegan scores were 8 or less for 24 hours and was permanently discontinued when Finnegan scores remained stable below 8 for 48 hours. If clonidine was used, it was reduced by ½ to $^1/_3$ of the dosage and ended 48 to 72 hours after morphine treatment. Phenobarbital treatment was permanently discontinued in one single step with Finnegan scores stable below 8 for 72 hours.

In addition to pharmacological treatment, all children received supportive care as described above (see “Supportive and pharmacological therapy for NAS”). Breastfeeding was encouraged unless the mother co-used benzodiazepines, barbiturates, cocaine or intravenous drugs, was positive for HIV or it was determined that the infant should go into foster care.

The decision whether a child could be discharged into the mother’s home or should be kept in foster care was always made by the youth welfare office in charge. The recommendations made by the hospital staff were, however, taken into close consideration at the helpers’ conferences held.

2.1.4. Periods of different primary pharmacological therapy

Changes in treatment and discharge modalities allowed for the division of the entire period into 3 separate entities. In the period from 2000 to 2004, phenobarbital was used as first-line medication for NAS. In 2005, morphine was introduced as the anti-withdrawal medication of choice, in line with the results of the RCT by Jackson *et al.* (64). However, it was soon noticed that treatment was prolonged under morphine in our setting and phenobarbital was reintroduced as primary pharmacotherapy for NAS. Thus, 2005-2007 was a period during which both lines of treatment were used. In 2008, a systematic follow-up on our patients in the baby and toddler outpatient clinic of the Pediatric Psychiatry department was implemented.

With regard to pharmacotherapy, phenobarbital was far more frequently used than morphine in the period of 2008-2011.

2.2. Statistical analysis

2.2.1. Data subsets

Depending on the type of data analyzed, it was necessary to form useful subgroups (Figure 1). The original number of 378 neonates was reduced by the 12 infants transferred to other hospitals before discharge. The data of all remaining neonates (n=366) was used to describe and evaluate the exposition to HIV, HBV and HCV, the modalities and duration of hospital stays and pharmacotherapy as well as discharge data. For maternal data including drug use, substitution medication and dosage, twin pregnancies were treated as one delivery, rather than 2 different infants, resulting in n=361. As twin pregnancies themselves lead to a lower birth weight and a higher rate of prematurity, the neonatal biometrics regarding birth weight, Apgar score and prematurity were analyzed without the 10 twins' data (n=356).

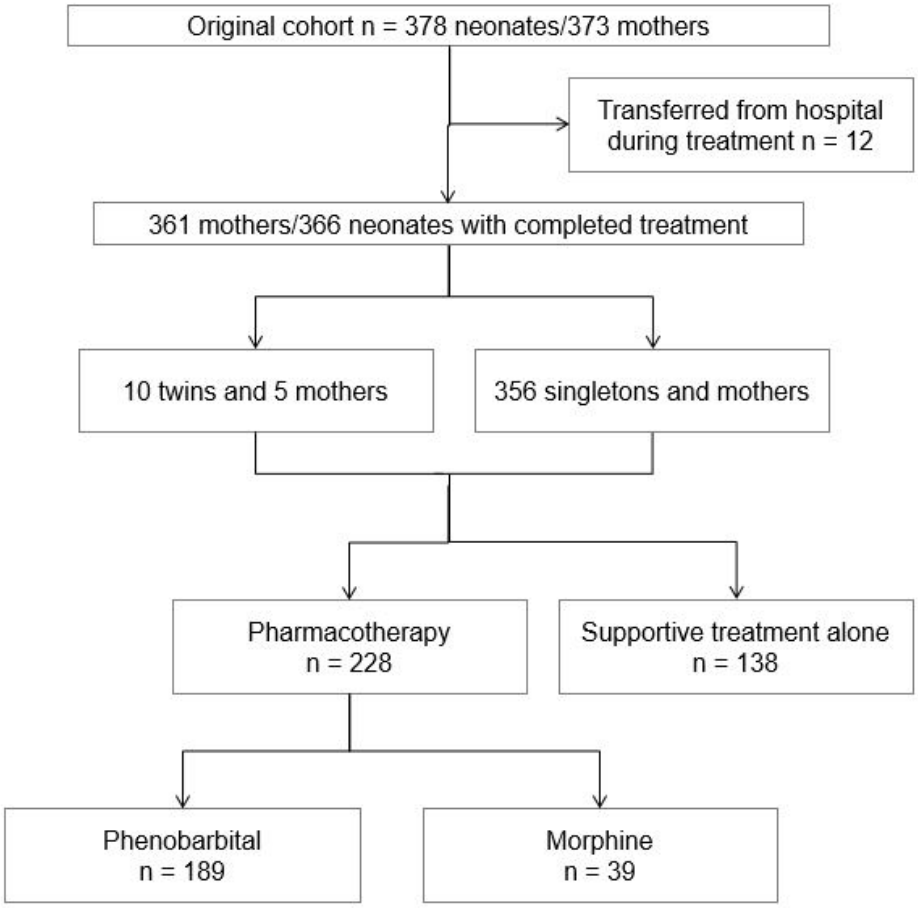

Figure 1: Data subsets.

12 of the original 378 infants were transferred to other hospitals and excluded from the cohort. All neonates (n=366) were taken into account when describing HIV-, HCV- and HBV-exposition, modalities and duration of hospital stay and therapy and discharge data. For each separate mother, pregnancy and delivery (n=361), maternal data including patterns of drug use, the choice of substitution medication and dose as well as their correlation with the duration of pharmacotherapy were recorded. Twins were excluded in the analysis of birth biometrics (n=356). Adopted from (1).

In order to examine the effects of the different choices of opioid substitute, as well as the modes of maternal substitution and drug use patterns, the appropriate subgroups were analyzed in more detail and compared to each other (Figure 7, Figure 10).

For the analysis of the relationship between maternal substitute dosage and the duration of neonatal pharmacotherapy, only deliveries where the maternal dosage at delivery was known could be examined. This was the case for a total of 297 pregnancies; 108

methadone-substituted pregnancies, 136 levomethadone-substituted pregnancies and 53 buprenorphine-substituted pregnancies.

2.2.2. Statistical tests

For the collected data, averages were given for values with a normal distribution, medians for values without normal distribution, percentages were calculated. Averages were presented with the standard deviation, medians with the range of results.

Groups were compared by Mann-Whitney-U test or Kruskal-Wallis test for continuous variables or the chi-square test for categorical variables (Table 4). When the small sample of neonates born prior to 33 $^{0}/_{7}$ weeks of gestation was compared to the entire cohort, Fisher's exact test and the Wilcoxon-signed-rank test for paired variables was used. Multivariate analysis of variance was performed to measure the effect of more than one variable at a time. In all tests, p-values ≤0.05 were considered significant and marked with "*" in tables and figures. Odds ratios (OR) with confidence intervals (CI) are given when appropriate.

Table 4: Statistical tests employed and the comparisons they were applied to.

Statistical test	Application
Chi-square test	Apgar score <7 at 5' and 10', rate of buprenorphine-exposed infants, rate of co-use, rate of HIV exposure, occurrence of seizures, discharge into maternal household
Fisher's exact test	Rate of pharmacotherapy among preterm neonates <33 $^{0}/_{7}$ weeks
Kruskal-Wallis test	Birth weight, gestational age, duration of hospitalization and pharmacotherapy } ≥ 3 groups
Mann-Whitney-U test	Birth weight, gestational age, duration of hospitalization and pharmacotherapy } 2 groups
MANOVA	Effect size of choice of maternal substitute, maternal substitute dosage, neonatal gestational age and choice of pharmacotherapy
Wilcoxon signed rank test	Finnegan scores and duration of therapy among preterm neonates <33 $^{0}/_{7}$ weeks

2.2.3. Computer programs

Computer programs used for statistics and graphs were GraphPad Prism 5 (diagrams, chi-squared test, Fisher's exact test, Kruskal-Wallis test, Mann-Whitney-U test, Wilcoxon signed rank test), Statgraphics Centurion1 Version 16.0 by Statpoint Inc. (MANOVA) and Microsoft Excel 2007 (all other calculations, pie chart).

The monography was written using Microsoft Word 2007 and 2016. Citations were created with the help of EndNote X7 by Clarivate Analytics.

Neonates' birth weight percentiles were calculated using the website "Ped(z) Kinderarzt-Rechner" on the basis of the data of Voigt *et al.* (96, 97).

2.3. Legal and ethical requirements

The "*Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis* " *(*statute set forth by the Charité for securing good scientific practice) was observed (98).

This study was approved by the ethics committee of Charité – Universitätsmedizin Berlin under the designation EA2/029/16 and by the data protection office designated as 137-16.

3. Results

3.1. Population

3.1.1. Patients' characteristics

366 neonates were included in this study. 200 of them were boys and 166 girls. Among them were 5 sets of twins. The median gestational age among the 356 singleton neonates was 38 $^{6}/_{7}$ weeks. 73 singletons (21%) were born prematurely (Table 5). This is significantly more than the Berlin average of 9% preterm infants (OR: 2.608, CI: 1.255 to 5.422) (95). At CVK as a perinatal center level 1 and university hospital, the rate of preterm infants is 16%, which is not different from this study cohort (OR: 1.467, CI: 0.8129 to 2.648). 44 of the 73 premature neonates of this study were born as so called "late-preterm infants" between 35 $^{0}/_{7}$ and 36 $^{6}/_{7}$ weeks of gestation. 24 were born between 32 $^{0}/_{7}$ and 34 $^{6}/_{7}$ weeks, while 3 children were born between 28 $^{0}/_{7}$ and 31 $^{6}/_{7}$ weeks and 2 were born at 27 $^{6}/_{7}$ weeks or younger.

Table 5: Distribution of gestational age of singleton pregnancies in the study population.
The study population is compared to the Berlin-wide average and to the neonates born at CVK; n=356.

	Study population	**CVK**	**Berlin average**
Median gestational age	38 $^{6}/_{7}$ weeks	not applicable (N/A)	N/A
≥ 37 $^{0}/_{7}$ weeks	283 (79%)	84%	91%
< 37 $^{0}/_{7}$ weeks (total)	73 (21%)	16%	9%
32 $^{0}/_{7}$ to 36 $^{6}/_{7}$ weeks	68 (19%)	11%	8%
28 $^{0}/_{7}$ to 31 $^{6}/_{7}$ weeks	3 (0.8%)	2%	1%
< 28 $^{0}/_{7}$ weeks	2 (0.6%)	3%	0.8%

The median birth weight among singletons was 2870 g (min 630 g, max 4400 g). The median birth weight percentile was the 20th percentile. 32% of neonates were born with a weight at or below the 10th percentile, 14% were at or below the 3rd (Figure 2).

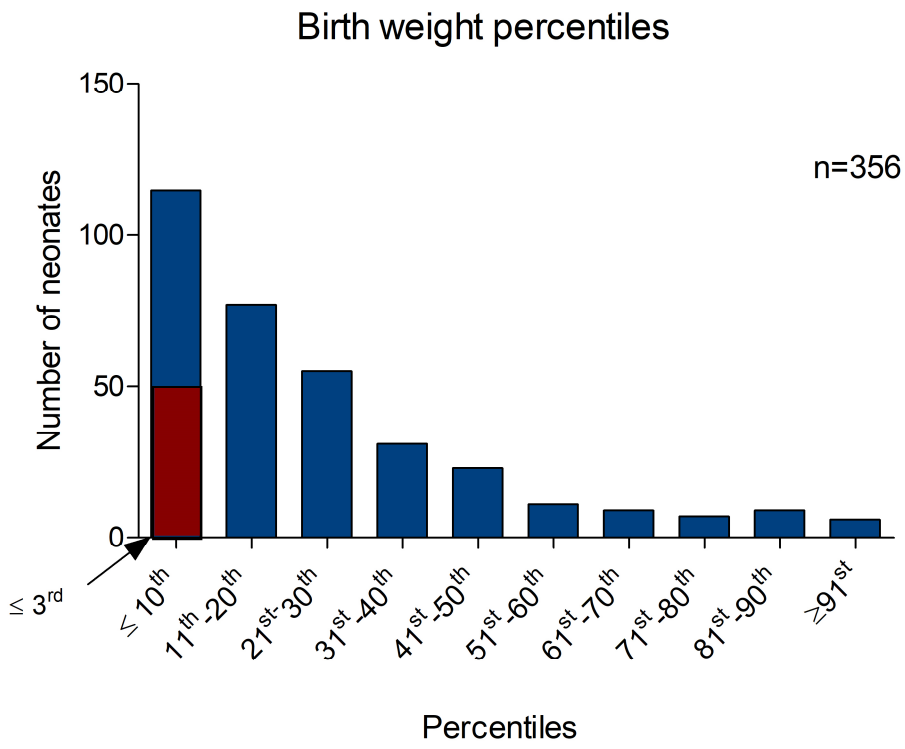

Figure 2: Birth weight percentiles.
Birth weight of singleton children was correlated with the respective percentile in order to account for different gestational age. Blue columns show the number of neonates in each 10-percentile range, the red column signifies neonates born at a weight at or below the 3rd percentile.

Regarding the cardio-respiratory adaptation, an Apgar score of <7 was seen in 11 children (3%) at 5 minutes and 3 children (<1%) at 10 minutes. This is significantly more than the Berlin-wide average of 1.3% (OR 2.421, CI: 1.074 to 5.455) for the 5-minute Apgar score below 7. Compared to the rate of 2.5% observed at CVK, the difference is again not significant (OR 1.243, CI: 0.6053 to 2.554).

3.1.2. Maternal biographic and obstetric information

The 361 mothers were on average 28.3 years (± 5.87) old at the time of delivery. 48% of the women were *primiparae*, 52% had already given birth to at least 1 child (Table 6). The median number of total pregnancies was 2 (minimum 1, maximum 12). Including the delivery of the current infant, the median number of live births was 2 (minimum 1, maximum 7).

20% of mothers reported at least one previous spontaneous abortion, 37% had terminated a pregnancy before. The highest number of spontaneous abortions experienced by 1 woman was 3, that of terminated pregnancies by one woman 10. With regard to siblings, in 28% of cases a minimum of 1 and a maximum of 4 children were already living in the mother's household while in 27% at least 1 child had been put into foster care. In 2% of the cases, the mother had reported that 1 of her children had previously passed away.

Table 6: Maternal history regarding previous pregnancies, deliveries and children.

Reference group		Median	Range
Individual mothers	Number of pregnancies (including the current)	2	1-12
	Number of deliveries (including the current)	2	1-7
	Number of spontaneous abortions	0	0-3
	Number of terminations	0	0-10
	Number of children living within the household	2	0-4
	Number of children living in foster care	0	0-4
		Number	Fraction
Population	Mothers with at least 1 previous delivery	189	52%
	Mothers with at least 1 spontaneous abortion	71	20%
	Mothers with at least 1 previous terminated pregnancy	135	37%
	Mothers with at least 1 child previously passed away	7	2%

One of the co-morbidities associated with drug use is the exposition to HIV, HBV and HCV. 22 neonates (6%) were exposed to HIV. 7 infants (2%) were born to a HBsAg-positive mother, 97 infants (27%) were born to a mother who was HCV-PCR positive. The mothers of 75 infants (21%) exclusively had anti-HCV-antibodies. In the case of 57 children (16%) the HCV-status of the mother was not recorded. HIV-positive opioid-dependent women were regularly delivered by primary cesarean section throughout the study period. HIV-exposed infants

received zidovudin as post-expositional prophylactic antiretroviral therapy. Children with HBsAg-positive mothers were immunized against the virus actively and passively.

3.2. Course of treatment

3.2.1. Duration of hospital stay and treatment, breast feeding

56 neonates (15%) showed only mild symptoms of NAS and remained on the maternity ward with their mothers, while all others were eventually admitted to the NCU. Of those, the longest an infant remained on the maternity ward before requiring transfer to the NCU was 11 days. A total of 138 children (38%) did not receive medication against withdrawal as supportive treatment was sufficient to control withdrawal symptoms (see 1.5.2. Supportive and pharmacological therapy for NAS). The other 228 (62%) were treated pharmacologically. If required, pharmacological treatment was started at a median age of 2 days (minimum 1st, maximum 14th day of life, Figure 3).

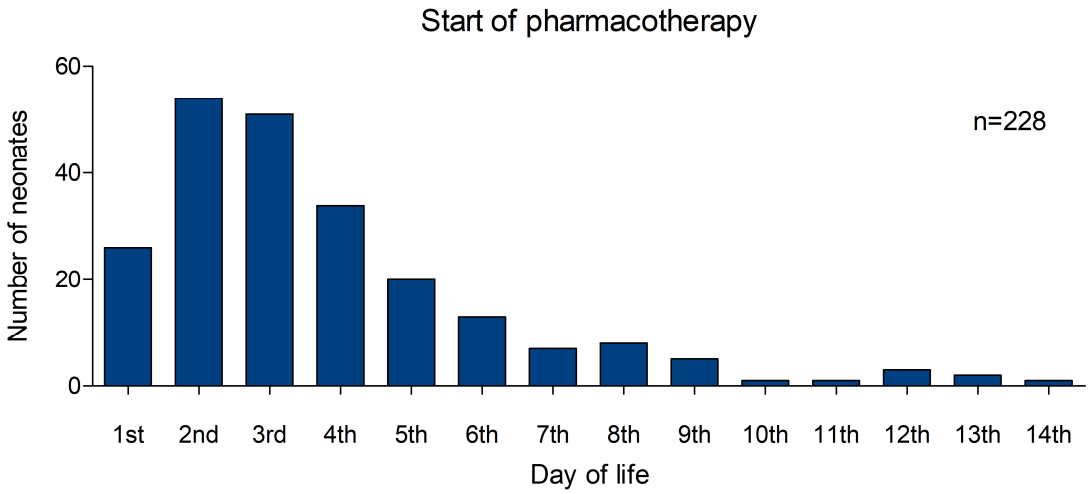

Figure 3: Start of pharmacotherapy.
Each blue column represents the number of infants who required to be started on pharmacotherapy for NAS on each day of life.

The neonates remained in the hospital for median of 14 days (min 2, max 100). Figure 4 shows the maximum Finnegan scores children received during their hospitalization. The median maximum score was 16 (minimum 3, maximum 30). Pharmacological treatment, if necessary, took a median of 10 days (minimum 1, maximum 55).

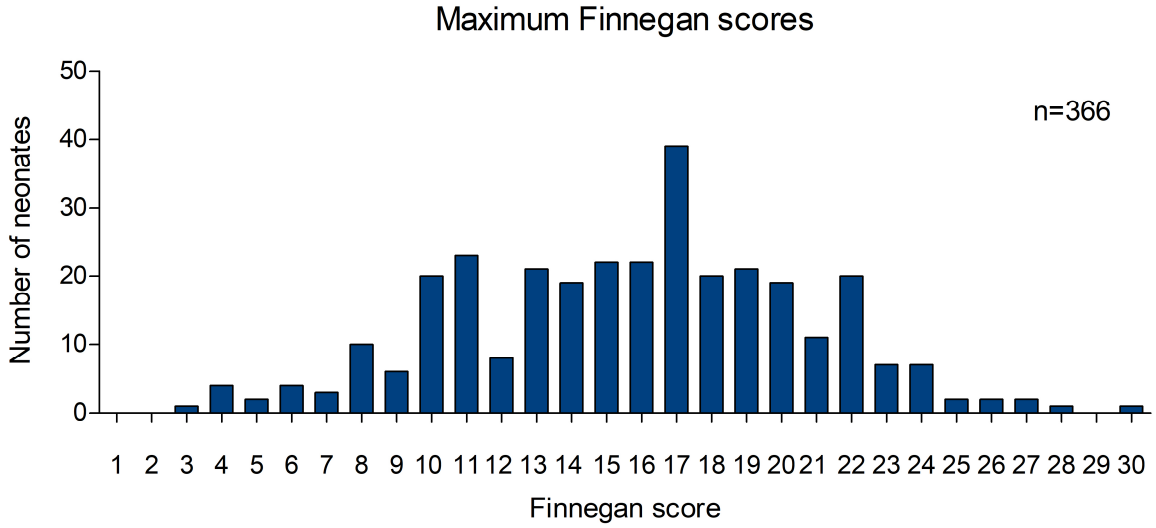

Figure 4: Distribution of maximum Finnegan scores.

Finnegan scores were taken once every 8 hours. The highest score each infant received was noted here. The blue columns represent the number of neonates who received the respective maximum score. A score >12 was used as an indication to start pharmacotherapy, n=366.

At admittance to the NCU, 63 infants (17%) were completely or partly breast-fed. At discharge, the number was 59 infants (16%).

3.2.2. Mode of pharmacological treatment

Among the 228 neonates treated pharmacologically against NAS, in 189 cases the initial medication used was phenobarbital, whereas 39 neonates primarily received morphine (Table 7). The 2 treatment groups were comparable regarding birth weight and gestational age. The median birth weight was 2775 g (minimum 1235 g, maximum 4130 g) in the phenobarbital group and 2890 g (min 1600 g, max 3510 g) in the morphine group (p=0.790). The median gestational age was 38 $^{6}/_{7}$ weeks (minimum 27 $^{3}/_{7}$ weeks, maximum 44 $^{0}/_{7}$ weeks) in the phenobarbital group and 38 $^{5}/_{7}$ weeks (minimum 33 $^{5}/_{7}$ weeks, maximum 42 $^{1}/_{7}$ weeks) in the morphine group (p=0.604). In both groups, pharmacological therapy was started at a median age of 2 days of life and the median highest Finnegan score given was 18 points. The rate of maternal co-use of other drugs was comparable at 87% in the phenobarbital group and 79% in the morphine group (p=0.281). The rate of maternal substitution with buprenorphine

rather than racemic methadone and levomethadone was 12% in the phenobarbital and 15% in the morphine group (p=0.517).

Differences between the 2 treatment groups were seen in the length of both the hospitalization and the pharmacological treatment (Figure 5, Figure 6). Patients initially treated with morphine were hospitalized for a median of 26 days (minimum 7, maximum 58), whereas those who initially received phenobarbital were discharged after a median of 18 days (minimum 3, maximum 60). The period during which the group treated with morphine received medication was also longer at a median of 19 days (minimum 3, maximum 55) compared to 9 days (minimum 1, maximum 53) in the phenobarbital group. These findings are highly significant at p=0.002 and p<0.001 respectively.

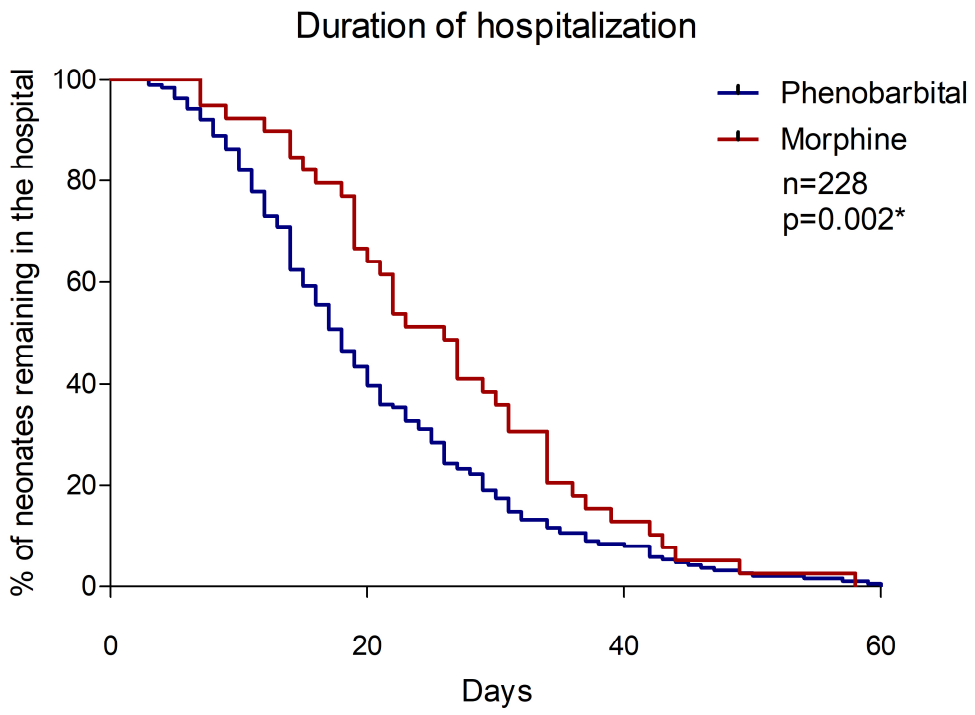

Figure 5: Duration of hospitalization.

Neonates were treated with either phenobarbital or morphine as primary medication. The fraction of children still hospitalized by the number of days in either group was plotted as a Kaplan-Meier-Graph, showing that neonates treated with phenobarbital had significantly shorter hospital stays compared to neonates treated with morphine. Mann-Whitney-U test was performed and the significant difference with p=0.002 was marked *, n=228.

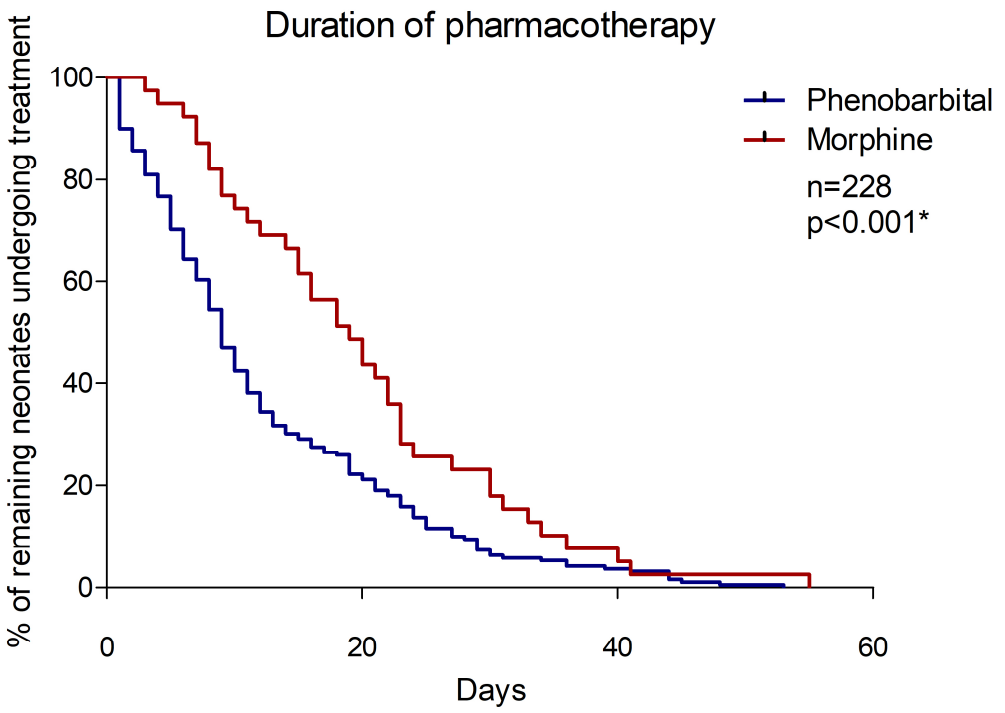

Figure 6: Duration of pharmacotherapy.

Neonates were treated with either phenobarbital or morphine as primary medication. The fraction of children still undergoing pharmacotherapy by number of days in either group was plotted as a Kaplan-Meier-Graph, showing that neonates treated with phenobarbital had shorter durations of pharmacotherapy compared to neonates treated with morphine. Mann-Whitney-U test was performed and the significant difference with $p<0.001$ was marked *, n=228. Adopted from (1).

13 infants (7%) in the phenobarbital group and 2 (5%) in the morphine group suffered seizures, showing no significant difference between the 2 groups (OR 1.366, CI: 0.296 to 6.315). It should be noted that 4 of the 13 seizing children of the phenobarbital group had the seizure prior to the start of treatment and 1 child had a focal seizure diagnosed by electroencephalography (EEG), suggesting an etiology different from opiate withdrawal.

In the phenobarbital group 43 infants (23%) received morphine as a secondary line of treatment as symptoms were not sufficiently controlled with phenobarbital alone. Vice versa, 3 infants (8%) of the morphine group had to be treated with phenobarbital. 6 of the neonates (15%) with morphine as primary treatment additionally received clonidine.

Table 7: Patients characteristics and outcome by choice of neonatal withdrawal medication.
Percentages are based on the number of infants with each agent. Significant differences are marked *. n=228.

	Phenobarbital n=189	**Morphine n=39**	**p-value**
Gestational age, weeks	38 $^{6}/_{7}$ (27 $^{3}/_{7}$ - 44 $^{0}/_{7}$)	38 $^{5}/_{7}$ (33 $^{5}/_{7}$ - 42 $^{1}/_{7}$)	0.790
Birth weight, g	2775 (1235 – 4130)	2890 (1600 - 3510)	0.604
Maternal co-use	87%	79%	0.281
Maternal substitution with buprenorphine	12%	15%	0.517
Median maximum Finnegan score	18	18	0.758
Duration of pharmacotherapy, days	9 (1 - 53)	19 (3 - 55)	<0.001 *
Duration of hospitalization, days	18 (3 - 60)	26 (7 – 58)	0.002 *

3.3. Maternal substitution and drug use patterns

3.3.1. The choice of maternal substitute

A total of 340 mothers (94%) received an opiate substitute during pregnancy. 21 mothers were not on substitution medication at term. In 278 pregnancies (82%) the substituted women were substituted with methadone, either as racemic methadone used in 146 pregnancies (43%), or levomethadone used in 132 pregnancies (39%). During 62 pregnancies (18%) buprenorphine was used as opiate substitute (Figure 7). This distribution is within the typical range for a German setting (9). Among the women substituted with buprenorphine, the rate of co-use of additional drugs was 68%, lower than among the mothers substituted with methadone (79%) and levomethadone (84%, p=0.018).

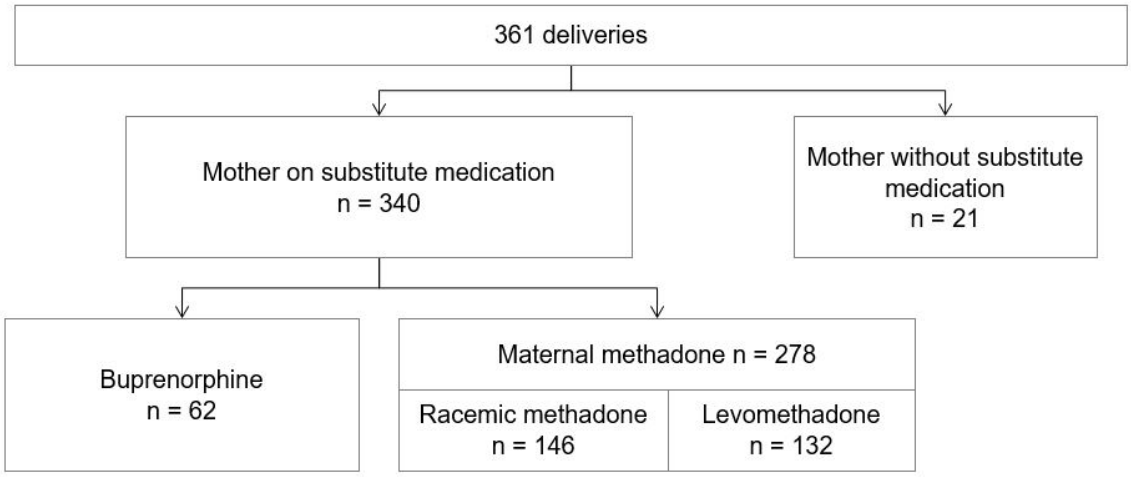

Figure 7: Distribution and choice of maternal substitution medication.

Among the mothers of the 361 separate deliveries, 340 were on substation medication while 21 were not substituted. Among the 340 substituted mothers, 278 were treated with methadone (146 received racemic methadone and 132 took levomethadone for substitution) and 62 were treated with buprenorphine.

The median gestational age was 39 $^{0}/_{7}$ weeks in the racemic methadone group, 38 $^{6}/_{7}$ weeks in the levomethadone group and 38 $^{5}/_{7}$ weeks in the buprenorphine group. Infants born to levomethadone-substituted mothers had a non-significant tendency to be premature. Infants born to buprenorphine-substituted mothers were heavier at birth at a median of 2943 g than infants of methadone-substituted women whose infants weighed 2845 g (p=0.028, Table 8). More importantly, pharmacological therapy was needed less frequently in the buprenorphine group at 45%, compared to 71% and 69% in the racemic methadone or levomethadone group (p<0.001) and was shorter at 5 versus 11 and 10 days (p=0.014, Figure 9). Hospitalization was also shorter at 9 days in the buprenorphine group as opposed to 16 and 17 days in the 2 other groups (p<0.001, Figure 8). Among the infants requiring pharmacotherapy, the percentage of patients treated with morphine rather than phenobarbital was not significantly different between the 3 groups. 16 of the racemic methadone exposed infants (15% of the pharmacotherapy requiring infants in this group), 16 of the levomethadone exposed infants (18% of the pharmacotherapy requiring infants in this group) and 6 of the buprenorphine exposed infants (21% of the pharmacotherapy requiring infants in this group) received morphine as primary medication (p=0.740). Taking into account only the infants treated with phenobarbital as primary medication in each maternal substitute group, the duration of pharmacotherapy remained shorter after buprenorphine exposure. The duration of therapy with phenobarbital

was 5 days after maternal buprenorphine substitution, 10 days after maternal substitution with racemic methadone and 11 days after maternal substitution with levomethadone (p=0.011).

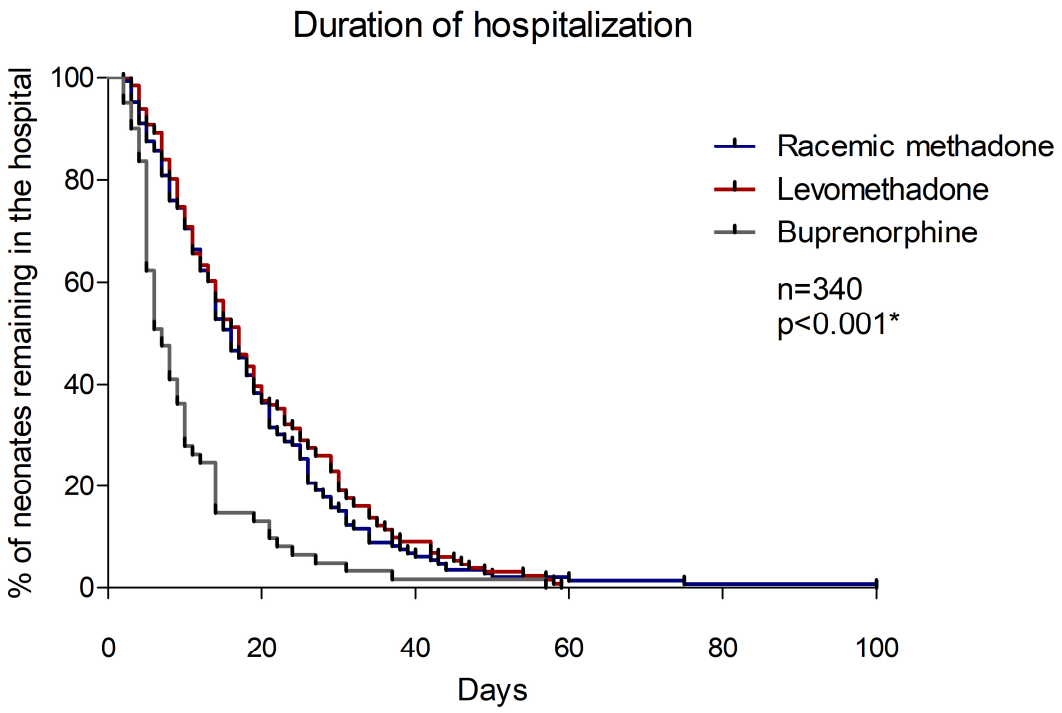

Figure 8: Duration of hospitalization.

The length of hospitalization in days was significantly reduced in neonates whose mothers had been substituted with buprenorphine compared to those whose mothers were treated with racemic methadone or levomethadone, as shown by this Kaplan-Meier-Graph. Kruskal-Wallis test was used and the significant difference with p<0.001 marked *. n=340.

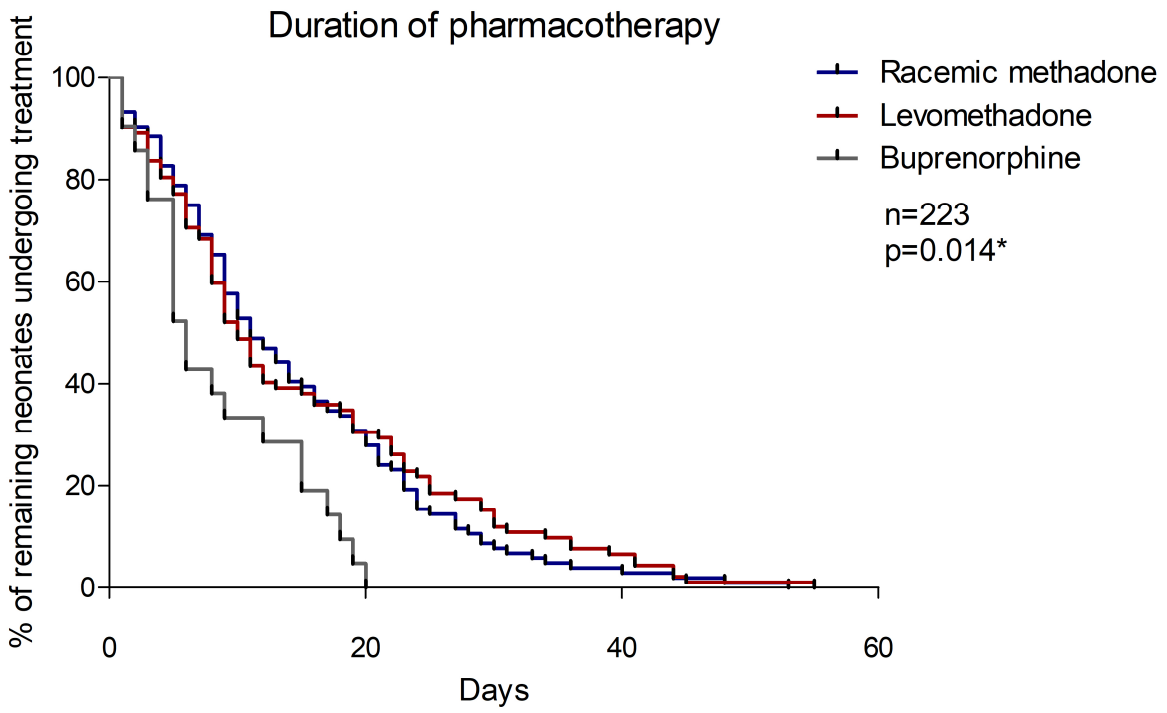

Figure 9: Duration of pharmacotherapy.

The length of treatment in days was significantly reduced in neonates whose mothers had been substituted with buprenorphine compared to those whose mothers were treated with racemic methadone or levomethadone, as shown by this Kaplan-Meier-Graph. Kruskal-Wallis test was used and the statistically significant difference with p=0.014 was marked *. n=223. In part adopted from (1).

The rate of discharge into the maternal household was comparable between all 3 groups at 75% (racemic methadone), 67% (levomethadone) and 77% (buprenorphine) (p=0.194).

Seizures also occurred at a similar incidence: 8 infants (5%) out of the racemic methadone group, 7 infants (7%) out of the levomethadone group and 1 child out of the buprenorphine group (2%) suffered this complication (p= 0.438).

Table 8: Patients' characteristics and outcome by choice of maternal substitution medication.
Percentages are based on the number of women substituted with each agent. In the top line, the methadone group is compared to the buprenorphine group by Mann-Whitney-U or Chi-square test. In the lower line, the groups racemic methadone, levomethadone and buprenorphine are compared to each other by Kruskal Wallis or Chi-squared test. Statistically significant differences are marked *. n=340. Adopted from (1).

	Methadone, n=278		**Buprenorphine, n=62**	**p-value**
	Racemic methadone n=146	**Levomethadone n=132**		
Gestational age, weeks	39 $^{0}/_{7}$		38 $^{4}/_{7}$	0.886
	39 $^{0}/_{7}$	38 $^{6}/_{7}$	38 $^{4}/_{7}$	0.541
Prematurity	59 (21%)		12 (19%)	0.744
	23 (16%)	36 (27%)	12 (19%)	0.586
Birth weight, g	2845 (630-4400)		2943 (860-4140)	0.028 *
	2810 (630-4400)	2880 (1240-4250)	2943 (860-4140)	0.058
Maternal co-use	226 (81%)		42 (68%)	0.018 *
	115 (79%)	111 (84%)	42 (68%)	0.034 *
Need for pharmacotherapy	195 (70%)		28 (45%)	<0.001*
	104 (71%)	91 (69%)	28 (45%)	<0.001 *
Length of pharmacotherapy, days	11 (1-55)		5 (1-20)	0.004 *
	11 (1-53)	10 (1-55)	5 (1-20)	0.014 *
Length of hospital stay, days	16 (2-100)		7 (2-57)	<0.001 *
	16 (2-100)	17 (3-59)	7 (2-57)	<0.001 *
Discharge to mother	197 (71%)		48 (77%)	0.298
	109 (75%)	88 (67%)	48 (77%)	0.194

3.3.2. Stable substitution and co-use of alcohol and illegal substances

Of the 361 deliveries, 340 mothers received opiate substitution while 21 mothers were not on substitution medication. Among the substituted women, 72 were in stable substitution throughout their pregnancy, whereas 268 mothers co-used illegal drugs or alcohol at some point while pregnant (Figure 10).

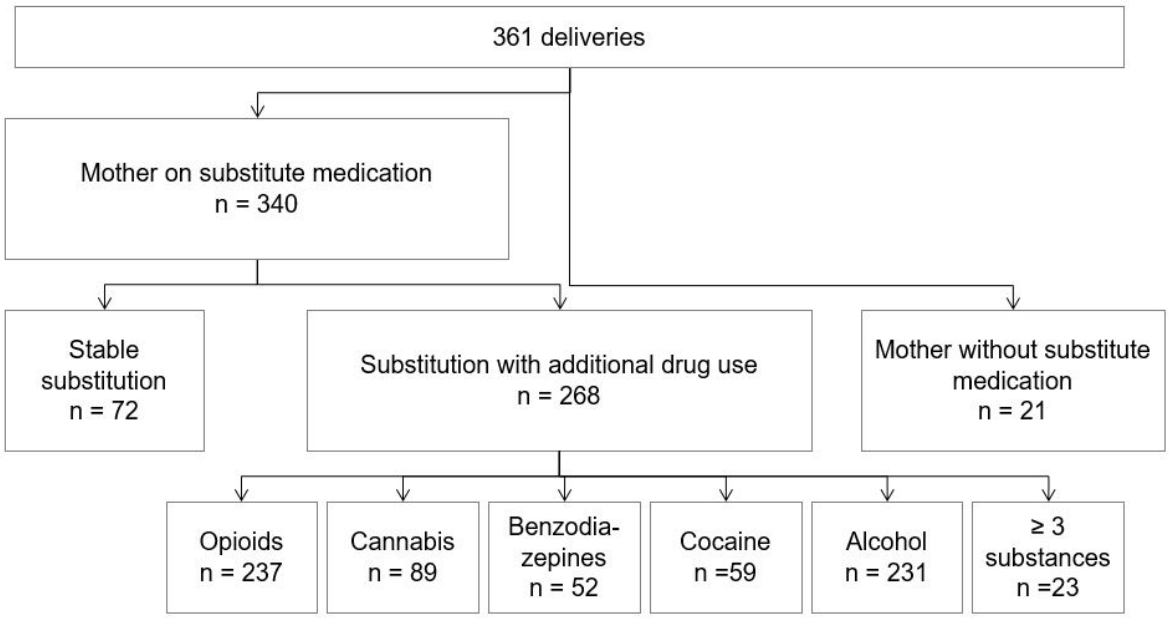

Figure 10: Substitution and co-use.

Out of the substituted women, 72 were “stably substituted” without co-use of alcohol or illegal drugs while 268 women used these substances. Infants of stably substituted mothers were compared to infants of mothers with additional co-use of illegal substances or alcohol and to infants of mothers without any substitute therapy. In 3.3.3 Details of co-use of illegal drugs and alcohol, the infants exposed to other opioids, cannabis, benzodiazepines, cocaine and 3 or more additional substances were compared to the infants of stably substituted mothers.

17% of infants of stably substituted mothers were premature (**Fehler! Verweisquelle konnte nicht gefunden werden.**). The rate of prematurity was 23% in the group with additional drug use and 24% when no substitution medication was used. This difference was not significant (p=0.510).

Newborns of stably substituted mothers weighed a median of 2930 g, with additional drug use the birth weight was 2880 g and 2760 g if the mother was not substituted at all (p=0.268).

In terms of pharmacological therapy, maternal co-use of drugs increased the odds for necessity of pharmacotherapy. Pharmacotherapy was indicated in 65% of neonates whose mothers co-used additional drugs and in 47% if the mother was in stable substitution. It was required in 24% of neonates whose mothers were not substituted (p<0.001). The median duration of pharmacological therapy was 7 days in the group without substitution medication and 10 days necessary in the 2 substituted groups (p=0.223).

The increased rate of pharmacotherapy among infants of co-using substituted mothers also had an effect on the median duration of hospitalization, which was 16 days. In comparison, neonates of stably substituted mothers had hospital stays of a median duration of 13 days, neonates of unsubstituted mothers stayed for 10 days (p=0.026).

Looking at discharge data, 90% of neonates were discharged home to their mothers if the mothers were stably substituted. If the mothers were substituted, but used additional drugs, 73% of neonates were discharged into their mother's care. In 57% of the cases, neonates were discharged into their mothers' household if they were not in any substitution program at all (p<0.001).

3.3.3. Details of co-use of illegal drugs and alcohol

The 268 substituted mothers with additional drug use can be further divided into subgroups according to the substances used other than the substitution medication and nicotine (Figure 11). Opioids other than the prescribed substitute were the most common with 237 women (88% of co-users / 65% of all mothers) taking them at some point during their pregnancy. Cannabis was used by 89 women (33% / 25%), cocaine by 59 (22% / 16%), benzodiazepines by 52 (19% / 14%) and alcohol by 51 (19% / 14%). Antidepressants, amphetamines and LSD played a comparatively minor role. The former 2 were taken by 4 women each (1% / 1%), the latter by only 1 woman (<1% / <1%). Using several substances was common. 23 women (9% / 6%) consumed 3 or more substances other than their substitution medication. Among the unsubstituted mothers, 10 (48% / 3%) used cannabis, benzodiazepine, cocaine and/or alcohol. 4 unsubstituted mothers (19% / 1%) consumed 3 or more illegal substances or alcohol.

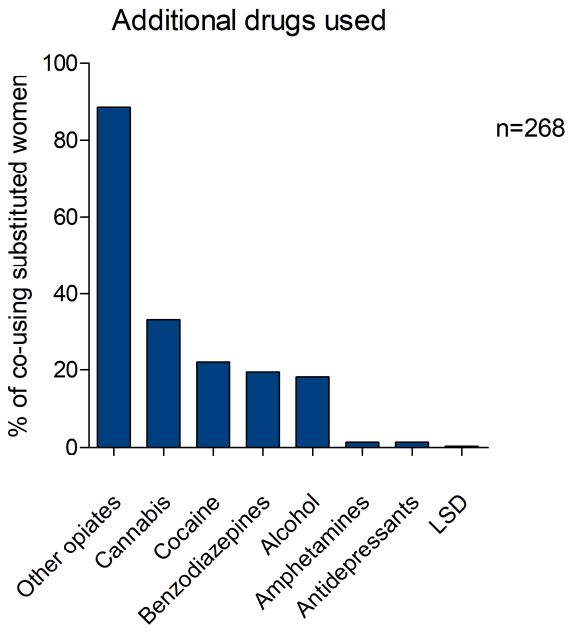

Figure 11: Co-use of illegal drugs and alcohol.

During pregnancy, substituted women were screened for use of drugs other than their substitution medication using interview and urine samples (alcohol was reported by interview only). Additionally, neonatal meconium screening was performed. Columns signify the percentage of co-using substituted women in which each substance was used. In most cases, more than one additional drug was used.

There were no significantly higher rates of premature births after any one specific substance. Prematurity tended to be most prevalent in mothers who had used 3 or more different substances during their pregnancy with 30% of their babies born before 37 complete weeks of gestation (Table 9). The number was also high if the mother used cannabis, in which case 27% of neonates were premature. In both cases, however, the difference between the co-using groups and the stably substituted group was not significant (for the co-use of 3 or more substances: OR 2.188, CI: 0.741-6.461, for cannabis co-use: OR 1.818, CI: 0.837-3.951).

Neonates whose mother had consumed cannabis, cocaine or used 3 or more different substances were lower in birth weight than after stable substitution. Children born after such pregnancies only weighed 2690 g (p=0.009), 2720 g (p=0.013), and 2708 g (p=0.015), respectively.

The rate of pharmacotherapy was increased by 18% in the group of infants of co-using mothers in general compared to infants of stably substituted mothers (see “Stable substitution and co-use of alcohol and illegal substances”). After maternal use of cocaine and 3 or more additional

substances, the rate was highest at 76% (OR for cocaine: 3.592, CI: 1.684 to 7.664) and 78% (OR for ≥ 3 additional substances 4.024, CI: 1.348 to 12.01) respectively. After maternal benzodiazepine and cannabis consumption the risk that pharmacotherapy became necessary was also increased. 69% of neonates required pharmacotherapy in the benzodiazepine group (OR: 2.515, CI: 1.189 to 5.319) and 70% both in the cannabis group (OR: 2.566, CI: 1.344 to 4.901) and in the group of neonates exposed to other opiates than the substitute (OR: 2.721, CI: 1.584 to 4.675).

Pharmacological therapy had a non-significant tendency to be longer than the 10-11 days in all other groups if the mother had used benzodiazepines during pregnancy. In this case, therapy lasted a median of 15 days (p=0.151).

Maternal co-use increased the duration of neonatal hospitalization to 16 days in the opioid group (p=0.023), 17 days in the cocaine (p=0.015) and in the cannabis group (p=0.033), 19 days in the benzodiazepine group (p=0.010) and 21 days in the group with more than 3 additional drugs (p=0.006).

In terms of discharge into the mother's household, the highest rate of 85% was observed if the co-used substance was cocaine rather than other substances (OR: 1.671, CI: 0.5822 to 4.798). This rate was comparable to the infants of stably substituted mothers. If opioids, cannabis or benzodiazepines were used, the percentage of infants discharged home dropped to 63-65% (OR for Opioids: 5.098 CI: 2.236 to 11.620, OR for Cannabis: 5.213, CI: 2.136 to 12.720, OR for Benzodiazepines: 5.346, CI: 2.041 to 14.000), to only 43% if more than 3 different substances were co-used (OR: 12.070, CI: 3.880 to 37.560).: Neonatal outcome parameters after maternal substitution, substitution with co-use of additional drugs and after non-substituted opiate use during pregnancy.

Table 9: Neonatal outcome parameters after maternal substitution, substitution with co-use of additional drugs and after non-substituted opiate use during pregnancy.

Infants of mothers in stable substitution are compared to infants by all mothers with additional drug use and infants by unsubstituted mothers using Kruskal-Wallis test and Chi-squared test. Values of the different subgroups of additional maternal opioid, cannabis, cocaine, benzodiazepine and multisubstance use are in summary compared by Kruskal-Wallis and Chi-squared test and added in grey below. Statistically significant differences are marked *. For detailed comparison between the individual co-use groups and the stable substitution group, see the text above. In part adopted from (1).

	Mother in stable substitution n=72	**Mother substituted with additional drug use n=268**					**Mother not substituted n=21**	**p-value**
		Opioids n=237	**Cannabis n=89**	**Cocaine n=59**	**Benzodia-zepines n=52**	**≥3 additional substances n=23**		
Prematurity	17%			24%			24%	0.510
	17%	46 (19%)	24 (27%)	13 (22%)	10 (19%)	7 (30%)		0.440
Birth weight	2930 g			2880 g			2760 g	0.268
	2930 g	2880 g	2690 g *	2720 g *	2878 g	2708 g *		0.020
Need for pharmaco-therapy	47%			65%			24%	0.005 *
	47%	168 (71%)	62 (70%) *	45 (76%) *	36 (69%) *	18 (78%) *		<0.001 *
Length of pharmaco-therapy	10 days			10 days			7 days	0.223
	10 days	11 days	11 days	10 days	15 days	10 days		0.583
Length of hospital stay	12 days			16 days			11 days	0.003 *
	12 days	16 days *	17 days*	17 days *	19 days *	21 days*		0.028 *
Discharge to mother	92%			72%			57%	<0.001 *
	92%	154 (65%) *	57 (64%) *	50 (85%) *	33 (63%) *	10 (43%) *		<0.001 *

3.4. Discharge data

The majority of the infants on this cohort were discharged into their mother's care. 257 were discharged into their mother's household and 37 went into an assisted living facility together with their mothers (Figure 12). 53 were discharged directly into foster care. 9 infants were discharged to relatives other than their mother.

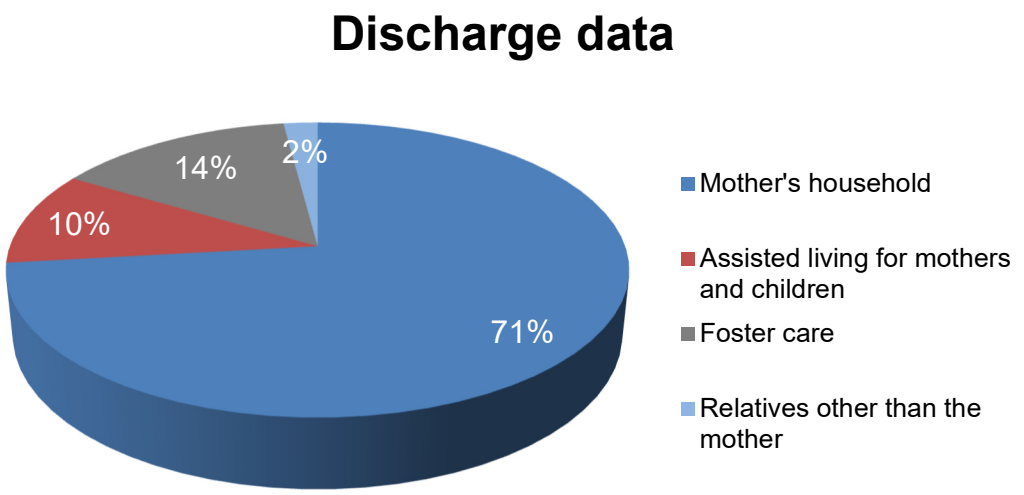

Figure 12: Discharge data.
Patients with NAS were discharged either to the mother's household, into assisted living facilities for mothers and children, into foster care or to other relatives once symptoms had sufficiently subsided and pharmacotherapy was no longer necessary.

In 42% of the cases where children went home with their mothers, special outreach assistance by social workers, so-called "*Familienhilfe*", was either already preexistent or installed before the newborn was discharged from the postnatal hospital stay. Since the introduction of a systematic follow-up by the pediatric psychiatry department in 2007, 74 children of this cohort were included in this scheme.

3.5. Special aspects in preterm children

As described above, 72 singleton children (20%) were born prematurely. Their median duration of pharmacological therapy was 3 days (minimum 0, maximum 44), suggesting a shorter withdrawal for preterm neonates.

Considering the entire spectrum of gestational ages, no correlation between the gestational age and the duration of pharmacotherapy can be shown (p=0.251, Figure 13, also see “Development from 2000 through 2011”). It may be remarked, however, that none of the 11 children born at 33 $^{0}/_{7}$ weeks of gestation or younger received medication for NAS for longer than 4 days.

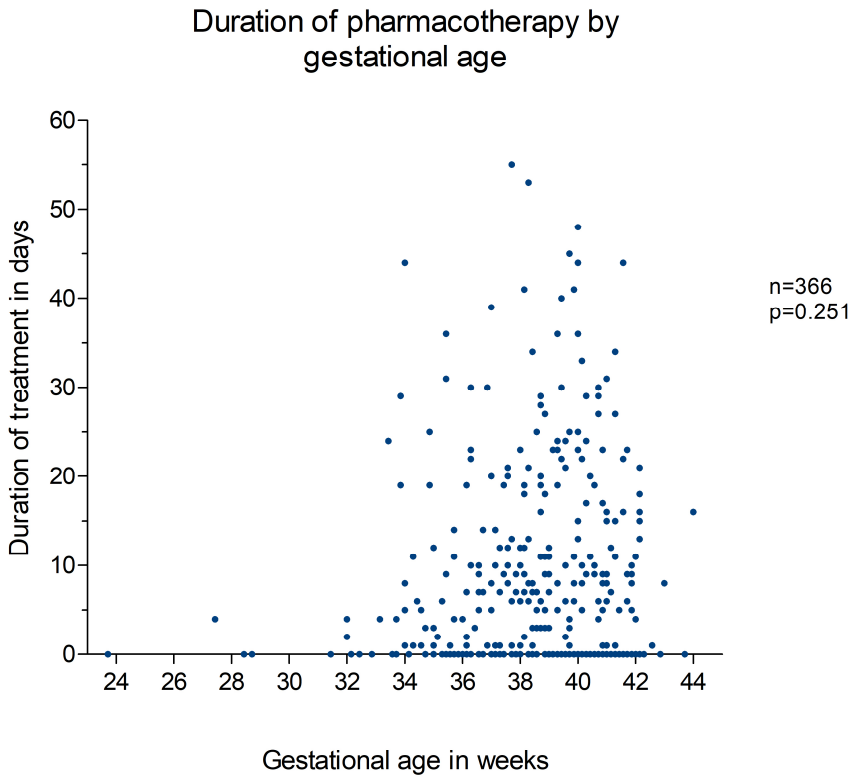

Figure 13: Duration of therapy by gestational age.

For each child the gestational age in weeks is plotted against the duration of therapy in days. Infants who only received supportive care were plotted as 0 days of pharmacotherapy. No immediate correlation between the 2 parameters can be found. Among the children born at 33 weeks of gestation or earlier, however, none was treated for NAS for longer than 4 days.

A total number of 11 neonates were born at or before 33 $^{0}/_{7}$ weeks. Among them were 2 sets of twins. Their median birth weight was 1595 g (min 630 g, max 2310 g), resulting in a median birth weight percentile of 37 (Table 10). 2 of the children were SGA.

These children were hospitalized for their prematurity for a median of 38 days (min 11, max 100). Only 3 of them (27%) received pharmacological therapy for NAS (OR: 0.227, CI: 0.059 to 0.870). The median duration of pharmacotherapy was 4 days (min 2, max 4). With only 3 treated infants, however, this value was not statistically significant (p=0.586). Maximum Finnegan scores were also lower than the rest of the cohort with a median of 13 (min 11, max 15, p=0.036).

Table 10: Neonates born at ≤ 33 $^{0}/_{7}$ weeks of gestation compared to the entire cohort.
Comparison is done regarding birth weight, maximum Finnegan score (Wilcoxon signed rank test), need for (Fisher's exact test) and length of pharmacotherapy (Wilcoxon signed rank test) and length of hospital stay. Statistically significant differences are marked *. Neonates born at ≤ 33 $^{0}/_{7}$ weeks of gestation n=11.

	Neonates ≤ 33 $^{0}/_{7}$ weeks of gestation	**Study population**	**p-value**
Birth weight, g	1595 g (630 g - 2310 g)	2870 g (630 g - 4400 g)	N/A
Birth weight percentile	37th	20th	N/A
Maximum Finnegan score	13 (11 – 15)	16 (3 – 30)	0.036 *
Need for pharmacotherapy	3 (27%)	228 (65%)	0.026 *
Length of pharmacotherapy	4 days (2 – 4 days)	10 days (1 – 55 days)	0.586
Length of hospital stay	38 days (11 – 100 days)	14 days (1 – 55 days)	N/A

3.6. Development from 2000 through 2011

136 neonates were diagnosed with NAS from 2000 to 2004, 100 between 2005 and 2007 and 130 from 2008 to 2011.

The rate of premature births stayed invariably at 21-22% throughout all 3 periods. Concordantly, the median birth weight remained at a stable level; it was 2740 g in 2000-2004, 2900 g in 2005-2007 and finally 2890 g in 2008-2011 (p=0.433).

There was no significant change in the rate of HIV exposure, which was 8% in the first period, 2% in the second and 6% in the third period (p=0.134).

The rate of co-use of additional drugs was continuously high at 83% during 2000-2004 and 79% during 2005-2007 as well as 2008-2011 (p=0.651).

Over the 12-year period there was a non-significant tendency to discharge children into their mother's household less frequently. While the fraction initially was 76% and subsequently 75%, it was 68% during the final four years (p=0.367).

The median number of days of both hospitalization and pharmacological therapy increased during the analyzed interval. The median duration of hospitalization increased from 11 days in 2000-2004 to 17 in 2005-2007 and 19 in 2008-2011 by 8 days (p<0.001, Figure 14). The duration of pharmacotherapy was 5 days in 2000-2004, 13 days in 2005-2007 and 18 days in 2008-2011 (p<0.001). At the same time, the rate of children requiring pharmacotherapy was relatively stable at 65% from 2000-2004, 69% from 2005-2007 and 62% in the years 2008-2011 (p=0.463).

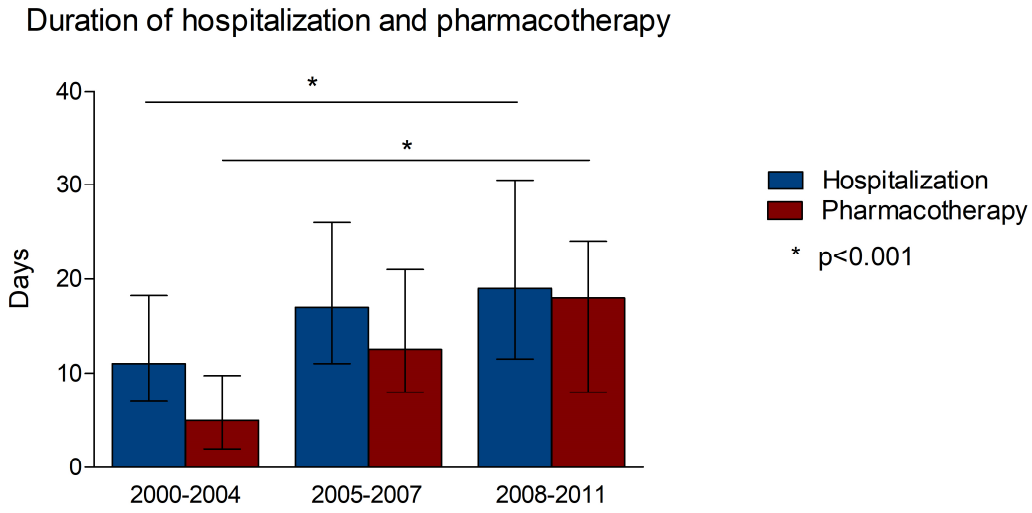

Figure 14: Duration of hospitalization and therapy.

Columns of median with interquartile ranges depict the number of days in both categories for 2000-2004, 2005-2007 and 2008-2011. The median duration of hospitalization increased by 8 days, while the number of therapy-days went up by 13 days. Both the increase in hospitalization and in pharmacotherapy over the 3 periods were tested for statistical significance by Kruskal-Wallis test and significant differences marked *. Regarding hospitalization, n=366, for pharmacotherapy, n=228.

Breaking the development of the duration of hospitalization and pharmacotherapy (Figure 15) down by year, the abovementioned increases remain to be seen. Additionally, a marked increase in the duration of pharmacotherapy is seen in the year 2005. In this year, morphine therapy was introduced, under which the treatment duration was longer than under phenobarbital (see “Mode of pharmacological treatment”). If the infants treated with morphine were not considered, the duration of hospitalization still increased from 11 in 2000-2004 to 16 days in 2008-2011 ($p=0.005$) and the duration of pharmacotherapy went up from 5 to 16 days ($p<0.001$).

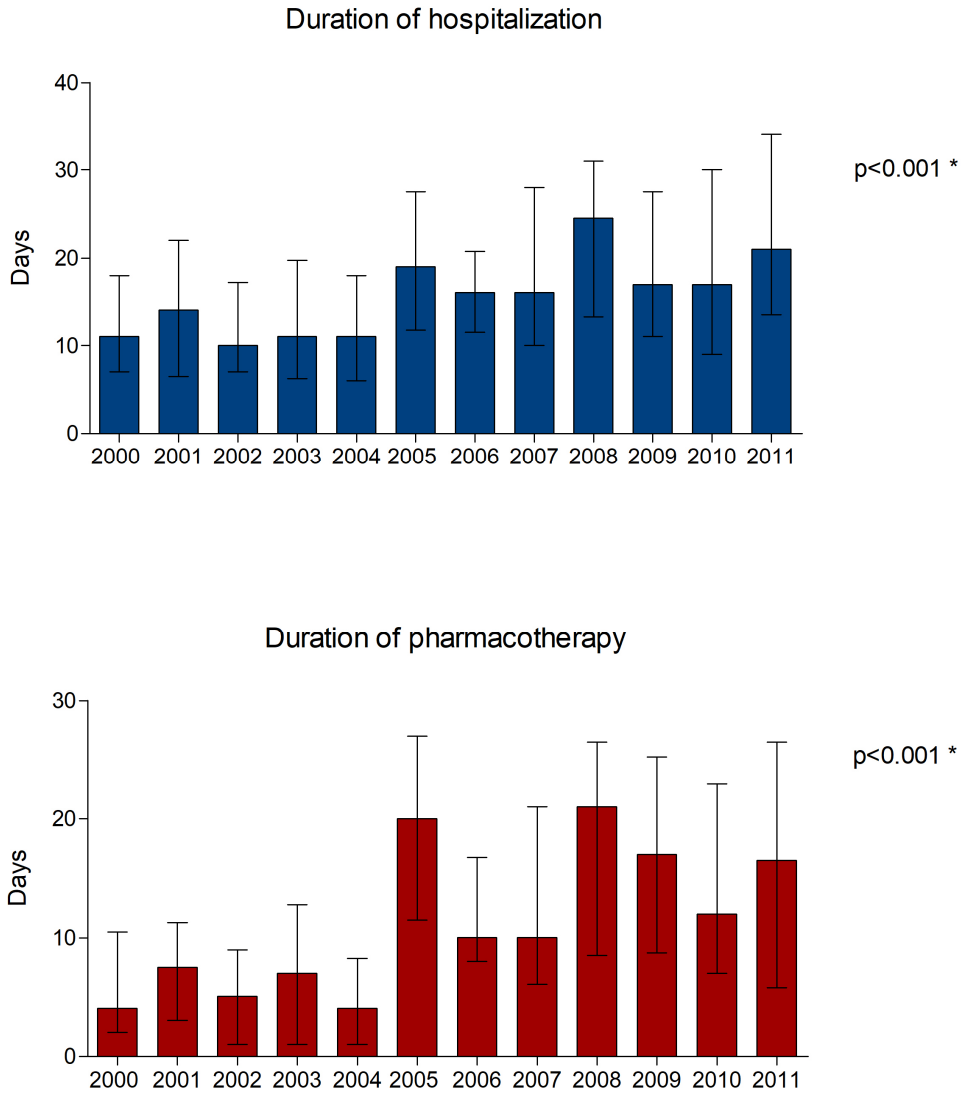

Figure 15: Development of the duration of hospitalization and pharmacotherapy by year.
Columns give the duration of both in median with interquartile ranges. The median duration of hospitalization increased by 10 days from 11 days in 2000 to 21 days 2011, while the duration of pharmacotherapy went up by 13 days from 4 days in 2000 to 17 days in 2011. Statistical significance was tested by Kruskal-Wallis test and the p-values given beside each graph. Statistically significant differences are marked *. Hospitalization, n=366; pharmacotherapy, n=228. Adopted from (1).

Regarding maternal opiate substitution, the dosage of racemic methadone increased from a median daily dose of 13.75 mg to 25 mg (p=0.002, Figure 16) during the analyzed period. Levomethadone doses were increased from 22.5 mg as the initial median dose to 30 mg in

2008-2011 (p=0.020). Buprenorphine was dosed continuously at 4-5.5 mg/day (p=0.811). The percentage of buprenorphine-substituted pregnancies did not increase from 20% in 2000-2004 to 13% in 2005-2007 and 18% in 2008-2011 (p=0.446).

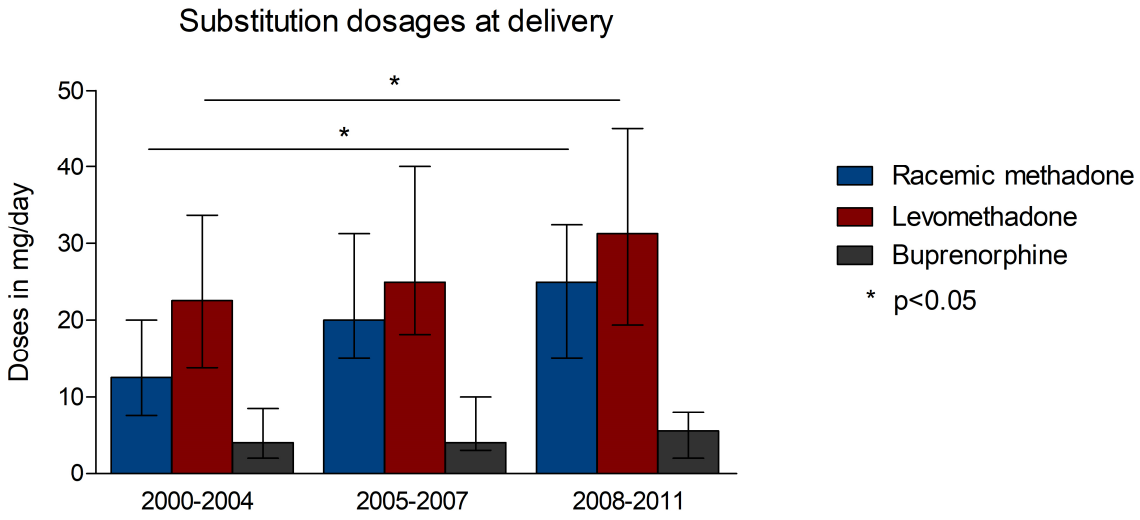

Figure 16: Substitution dose at delivery.

The dosage of racemic methadone, levomethadone and buprenorphine are given as columns of median with the interquartile range. Statistical significance between the 3 periods was tested by Kruskal-Wallis test and significant differences are marked *. The median dose of racemic methadone increased by 11.5 mg from 2000-2004 to 2008-2011 (p=0.002). The median daily dose of levomethadone went up by 7.5 mg (p=0.020). Meanwhile, buprenorphine doses stayed at 4 - 5.5 mg per day throughout (p=0.811). $n_{racemic\ methadone}$=108, $n_{levomethadone}$=136, $n_{buprenorphine}$=53.

Analogous to the increases in duration of pharmacotherapy and hospitalization, the increases in methadone and levomethadone doses remained visible and significant if divided up into the individual years (Figure 17).

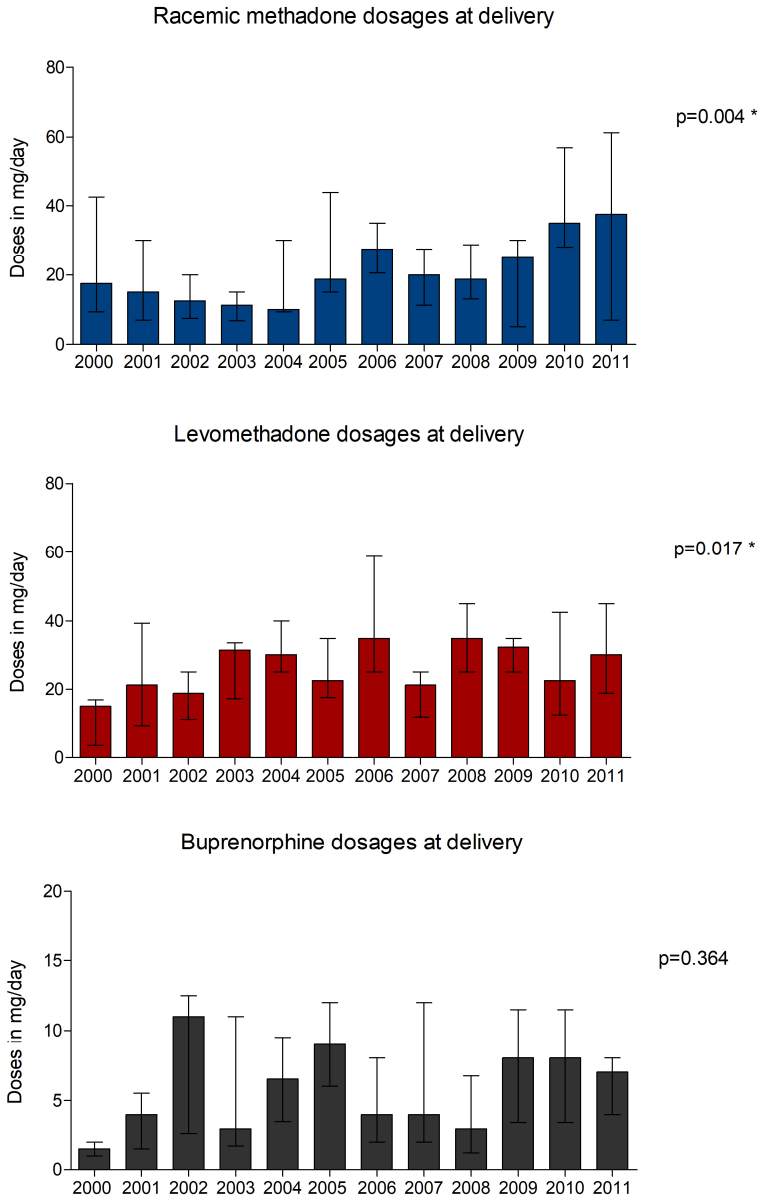

Figure 17: Development of the dosage of racemic methadone, levomethadone and buprenorphine by year. Columns give the doses in median mg/day with interquartile ranges. The median racemic methadone dosage increased from 17.5 mg in 2000 to 35.25 mg in 2011 (p=0.004). The median levomethadone dose was from 15 mg in 2000 and went up to 30 mg in 2011 (p=0.017). The buprenorphine median buprenorphine dose was 1 mg in 2000 and 7 mg in 2011, with no significant increase over the course of the 12 years (p=0.036). Statistical significance was tested by Kruskal-Wallis test and the p-values given beside each graph. Statistically significant differences are marked *. $n_{racemic\ methadone}$=108, $n_{levomethadone}$=136, $n_{buprenorphine}$=53. Adopted from (1).

The correlation between increasing substitute dosages and increasing durations of pharmacotherapy and hospitalization over the 12-year-period analyzed here appears

suggestive of a causal relationship between the two. This conjecture was examined more closely by multivariate analysis of variance for each of the 3 maternal substitutes taking into account whether the neonatal therapy was with phenobarbital or morphine (Table 11). The results of these calculations support that higher maternal dosages of racemic methadone and levomethadone were associated with a longer duration of neonatal therapy (p=0.037 and p<0.001) and hospitalization (p=0.025 and p<0.001). As anticipated by the previous graphs, the buprenorphine dosage did not show a correlation with hospitalization or therapy length (p=0.520 and p=0.511).

Table 11: Effect of different factors regarding the duration of hospitalization and pharmacotherapy.
The contribution of each factor is measured via multivariate analysis of variance and expressed as p-values. The choice of maternal substitute, the choice of neonatal therapy and the dose of maternal substitute were significant, maternal age or gestational age were not. Statistically significant p-values are marked *.

	Main effect	**Covariates**		
	Pharmacotherapy with phenobarbital or morphine	Gestational age	Maternal age	Substitute dose
Duration of hospitalization				
Racemic methadone	0.059	0.076	0.767	0.025 *
Levomethadone	0.003 *	0.244	0.131	<0.001 *
Buprenorphine	0.646	0.878	0.335	0.511
Duration of therapy				
Racemic methadone	0.060	0.064	0.67	0.037 *
Levomethadone	0.002 *	0.332	0.219	<0.001 *
Buprenorphine	0.248	0.353	0.919	0.520

4. Discussion

4.1. Synopsis

The 366 opioid-exposed neonates described in this study had an increased rate of prematurity and low birth weight compared to non-exposed infants. 62% of the study population developed withdrawal symptoms severe enough to require pharmacotherapy for a median of 10 days. After a median of 14 days 71% of all infants were discharged into the maternal household. Subset analysis regarding the rate of and duration of neonatal pharmacotherapy and hospitalization was performed by maternal substitute, maternal co-use, choice of neonatal pharmacotherapy, prematurity and by year. These results are now discussed in the light of current literature. Possible causes for the observations made are deliberated in the following paragraphs.

4.2. Neonatal biometrics and adaptation

4.2.1. Prematurity

The incidence of prematurity was increased to 21% in this cohort of opioid-exposed neonates compared to non-exposed populations in Berlin or at CVK where prematurity was between 9% and 16% (95). Among the premature neonates, however, 59% were born as so called “late-preterm infants” between 35 $^{0}/_{7}$ and 36 $^{6}/_{7}$ weeks of gestation. Merely 7% were born before 32 completed weeks of gestation, allowing for the conclusion that very low gestational age may not be a primary concern with opioid-exposed neonates. Comparing this finding with current literature proves somewhat challenging as most studies on NAS do not further differentiate their preterm subjects by weeks of gestational age (44, 64, 84). Others exclude preterm infants (70) or infants of less than 34 or 35 weeks of gestation (10, 65). 2 significant studies specifically on NAS in premature infants were published by Doberczak *et al*., who compared 34 methadone-exposed preterm infants to 178 term infants prospectively in 1991 (54) and Dysart *et al*. in their retrospective study on 53 preterm and 66 term infants with NAS in 2007 (99). The median gestational age of the preterm infants was 34.3 weeks ± 2.6 weeks in the former (54) and 34.2 weeks with a range from 27–36 weeks in the latter study (99). While not altogether proving the abovementioned conclusion, these numbers and the lack of publications on extreme prematurity after intrauterine opioid exposure appear suggestive of some validity of this statement.

The co-use of other illegal drugs did not significantly increase the risk for prematurity in this cohort. Taking the reverse perspective, however, it may be noted that out of the 5 neonates born at a gestational age of less than 32 weeks, four were exposed to cannabis *in utero.* Burns *et al*. compared almost 2000 opioid exposed neonates and over 400.000 controls in Australia between 2002 and 2006 regarding maternal obstetric and infant perinatal parameters (100). They saw significantly more prematurely born babies among over 2000 neonates exposed to cannabis. Bada *et al*. analyzed 8637 mother-infant-dyads in the USA for risk factors for prematurity and IUGR. In their multicenter study, nicotine use was the strongest substance-based risk factor for prematurity while the risk was just significantly elevated after cocaine use. Alcohol, cannabis or opioids alone were not statistically significant risk factors in that study, although the authors note that the small number of infants exposed to cocaine and opioids in their cohort may have caused an underestimation of the effect of these substances (44). Smoking nicotine was very highly prevalent among the mothers observed in this thesis, making it likely that this confounder was critical to the high number of premature infants in this study.

Among the few very premature infants in this study, the rate and duration of pharmacotherapy was decreased to the extent that no neonate under 33 $^{0}/_{7}$ weeks of gestation was treated against NAS for more than 4 days. The median maximum Finnegan score in this subgroup was only 13 rather than 16 in the entire study cohort. In the abovementioned study, Doberczak *et al.* observed a lower rate of pharmacotherapy preterm than in term neonates by 23%. They also found an apparently less severe manifestation of withdrawal symptoms and a later peak of withdrawal in preterm neonates (54). Dysart *et al*. also noted a lower rate and additionally a shorter duration of pharmacotherapy in premature infants. In their study, the median duration of pharmacotherapy was 19.8 days for preterm and 31.8 days for term infants (99). Several possible reasons for these observations have been postulated: First, the semi-objective NAS score used in the study of Doberczak *et al*. appeared to underscore some withdrawal signs in preterm infants like changes in muscle tone while overscoring others (54). The Finnegan score used in this study likewise includes items preterm infants are unable to exhibit in the same way as term infants like constant high-pitched crying or excessive sucking. Furthermore, it has been shown to increase during the first few weeks of life in non-opiate exposed infants (also see “Limitations”) (101) and it appears likely that it does not appropriately score abstinence syndrome in preterm infants (54, 102). Second, the immature brain, with its relative lack of dendritic ramification and different level of opiate receptor expression, may prevent or lessen the clinical expression of NAS (71, 99). Third, the opioid transfer rate increases towards the

end of the pregnancy as placental membranes thin out towards the end of the pregnancy (25). This effect is further accentuated by the decreased expression of the placental ABC transporter P-gp towards the end of the third trimenon of gestation (also see “Opioid metabolism and pregnancy”). Total intrauterine drug exposure also tends to be lower after a shorter pregnancy (54, 99). Fourth, the neonatal hepatic enzymes, including the N-demethylation depending inactivation of methadone, have not fully matured, leading to a prolonged half-life of methadone and its active metabolites (54, 99). Finally, It should also be noted that a less severe course of NAS cannot predict a lessened effect of the opioid exposure on long-term brain development (54).

4.2.2. Birth weight

A lowered average birth weight was observed in this study’s cohort. 32% of neonates were SGA and the median birth weight percentile was the 20th rather than the 50th which is the median in healthy cohorts. Only very few studies individually calculate birth weight percentiles (68). Most give the median birth weight or rate of infants of low birth weight (LBW) (84, 99). In a cohort that is also known to have an increased rate of prematurity (see “Prematurity”), this method tends to overestimate the degree of growth restriction, as even eutrophic preterm infants may be born with an LBW of less than 2500 g. Therefore, some studies elaborate on the number of SGA or IUGR infants (10, 44). The abovementioned study on risk factors for prematurity and IUGR by Bada *et al*. concludes that opiate exposure may have a borderline significant effect on birth weight, although the influence of nicotine, cocaine and alcohol in excess of one drink per week was much more pronounced (44). Other reviews describe low birth weight as a comorbidity among opioid- and especially among heroin-exposed neonates but do not analyze how much of this effect is due to nicotine use or other confounders (5, 43). As mentioned above, smoking nicotine was very highly prevalent among this study’s infants’ mothers and a strong connection between these 2 circumstances must be considered. In this study, maternal cocaine and cannabis co-use as well as the co-use of 3 or more additional substances significantly decreased neonatal birth weight. Maternal cocaine use is an established risk factor for IUGR (43, 44). Maternal cannabis consumption was not a significant risk factor in Bada *et al.*’s study (44), but has been shown to impede fetal growth in other research (43, 103). Bada *et al.*’s study also demonstrates that the effects of more than one substance can add up to increase the risk for IUGR exponentially, which corresponds well with the significantly lower birth weight among neonates exposed to 3 or more additional

substances (44). Follow-up studies have shown that the majority of children catch up to the normal weight range during the first 3 years of life (38).

4.2.3. Cardiorespiratory adaptation

An impaired cardiorespiratory adaptation, defined by an Apgar score of less than 7 at 5 minutes after birth, was seen in 3% of opioid exposed neonates. This was significantly more frequently than among the infants born in Berlin in 2009 where the rate was 1.3%. This poses the question whether opioid exposed neonates may suffer from opiate induced neonatal depression. Pathophysiologically, opiate induced neonatal depression may be considered unlikely in neonates habituated to opioid exposure unless the dose administered prior to birth was significantly higher than what the infant was adapted to. Burns *et al*. (see “Prematurity”) found similar numbers to this study with respect to neonatal Apgar scores (100). In their cohort, 3.8% of opioid-exposed neonates and 1.6% of non-exposed neonates received an Apgar score of less than 7. Although it was not examined in more detail, one possible explanation might be the much higher percentage of preterm infants both in this cohort (see “Prematurity”) and among the opioid-exposed neonates in the Australian paper, which were 21% and 24% respectively (100). The theory that prematurity, or other neonatal diseases, may have more impact on the adaptation after birth than opioid exposure itself is corroborated by the fact that the rate of impaired cardiorespiratory adaptation seen in the non-opioid-exposed neonates born at CVK is similar to the rate observed in this study. Among all infants born there in 2009, 16% were born prematurely and 2.5% were given a 5 minute Apgar score of less than 7 (95). In summary, after sustained opioid exposure *in utero*, neonates do not appear to have a significantly increased risk for an impaired cardiorespiratory adaptation compared to neonates of equal gestational age.

4.3. Effects on the need for and duration of neonatal pharmacotherapy

Some consensus exists among health care providers and researchers on the topic that a low rate of necessity for and a short duration of pharmacotherapy are desirable objectives in the management of NAS (3, 65). Apart from this consensus, however, there is a great amount of heterogeneity as to the preferable treatment regimen for the affected infants (10). Differences exist in structural and organizational matters, for example whether infants are separated from their mothers or treated in a rooming in setting for part or all of the duration of hospitalization

(54, 57). In terms of pharmacologic agents treat the signs and symptoms of NAS, RCTs or multicentre studies to find an optimal strategy to treat NAS are few. This is due to numerous reasons including a lack of funding and the relatively small number of institutions treating a large enough number of neonates with NAS to conduct an RCT. The few existing RCTs compare other substances to the currently most commonly used drug, morphine (64, 70, 77). Nevertheless, even at its most popular, morphine was only used in 72% of NAS cases in NICUs in the United States in 2013 (10). Even the duration of therapy itself varies greatly from study to study (Figure 18).

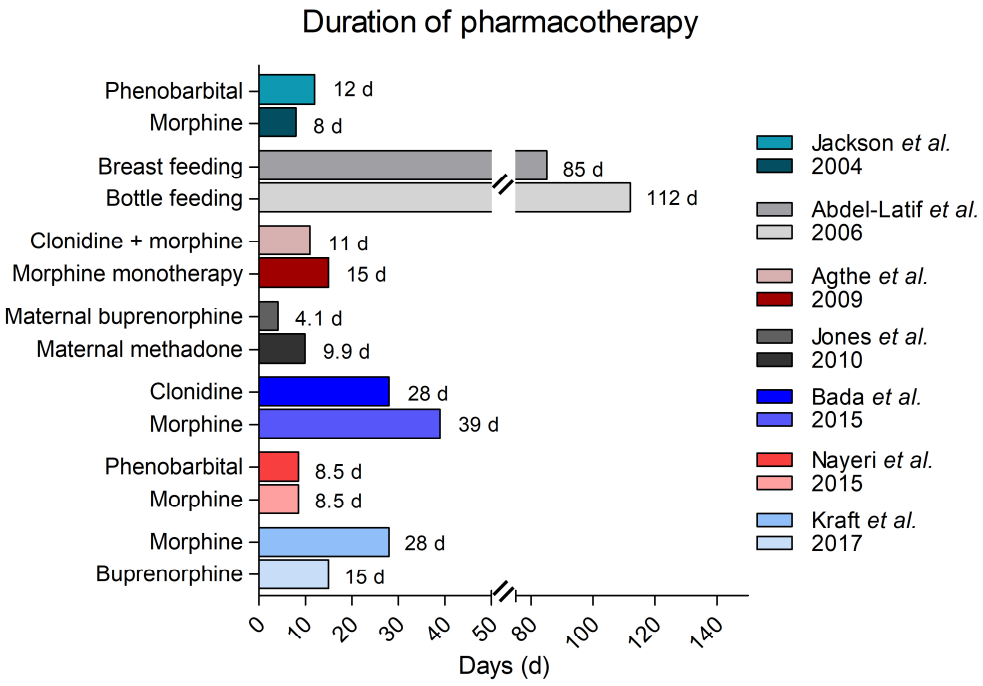

Figure 18: Heterogeneity of the duration of therapy in different studies.

The length of therapy is given in days for the treatment modalities compared in the different studies. Representative studies chosen for this graph were by Jackson *et al.,* 2004 (64), Abdel-Latif *et al.*, 2006 (60), Agthe *et al.*, 2009 (65), Jones *et al*. 2010 (84), Bada *et al.*, 2015 (77), Nayeri *et al.*, 2015 (73) and Kraft *et al.*, 2017 (70).

In this thesis, 2 maternal factors appeared to be associated with a decreased rate of required neonatal pharmacotherapy: The first was maternal substitution free from co-use of drugs other than the maternal substitute; the second was maternal substitution with buprenorphine rather than methadone.

A shorter duration of neonatal pharmacotherapy was seen among the infants of this cohort after using phenobarbital as the neonatal pharmacotherapy rather than morphine, substituting the mothers-to-be with buprenorphine rather than with methadone and using a lower maternal daily dose of methadone if this substitute chosen.

4.3.1. Choice of neonatal pharmacotherapy

In this cohort, pharmacological treatment with phenobarbital rather than morphine with or without added clonidine resulted in a markedly shorter period of hospitalization by 8 days as well as a significantly reduced duration of pharmacotherapy itself by 10 days. At the same time, the incidence of seizures as a major complication of withdrawal was not increased. The only drawback was a more frequent need to switch to a secondary medication as the primary medication appeared to be insufficiently effective. These findings contrast the results of an RCT published in 2004 by Jackson *et al*., which demonstrated a significantly shorter duration of treatment of 41 opioid-exposed infants treated with morphine compared to 34 others who were administered phenobarbital (64). In their study, pharmacotherapy with phenobarbital took 12 days, while morphine treatment took 8 days. This study also observed a trend for a more frequent need for second line medication among phenobarbital treated infants. Another RCT directly comparing phenobarbital and morphine therapy for NAS was conducted by Nayeri *et al*. on 60 opioid-exposed infants in 2015 (73). Their research group found no difference in treatment duration under either medication. The causes for the discrepancy of these findings may lie among the following:

First, the phenobarbital dosing scheme used at CVK includes a loading dose of 10 - 15 mg/kg/d, followed by daily dosages of 5 mg/kg. Nayeri's phenobarbital dosing scheme consisted of a higher loading dose of 20 - 40 mg/kg/d followed by a maintenance dose of 5 - 8 mg/kg/d (73) whereas Jackson's study population received 8 mg/kg/day of phenobarbital with no prior loading dose (64). It has been recommended by various authors that an initial dosage of 10 - 20 mg/kg followed by a lower maintenance dose may be the favourable method of achieving optimal control over neonatal seizures and withdrawal (104-106). It should be noted that in Nayeri *et al*.'s trial, the administration of phenobarbital was done either intravenously or by intramuscular injection. Both routes of parenteral administration pose the risk of infection and cause discomfort in the neonate and are therefore disadvantageous when an oral route is viable.

Second, phenobarbital has a comparatively long half-life of 3 - 7 days in neonates (104), whereas that of morphine solution is only approximately 4 - 9 hours in term infants (13). Thus, after the administration of phenobarbital is discontinued, and treatment by definition is ended, withdrawal symptoms are still suppressed by the sedative for several days. In the dosing scheme employed at CVK, the phenobarbital treatment was terminated abruptly, while in Jackson *et al*.'s double-blinded study, and the RCT by Nayeri *et al.* the dosage was reduced in 10%- or 20%-increments in analogy to the morphine dosing scheme (64, 73). This may have decreased the "benefit" of phenobarbital's long half-life somewhat.

Third, 67% of the neonates of Jackson's phenobarbital treatment group had been exposed to drugs other than opiates, including 44% benzodiazepines, *in utero*, compared to 32% co-use, in other words half the number, in the morphine treatment group (64). Using linear modeling and logistic regression, Jackson *et al*. concluded that this did not independently account for the differences between the 2treatment groups. In our study, neonates of mothers who co-used drugs other than their substitute required pharmacotherapy significantly more often than others and had longer hospital stays and there was a non-significant tendency for a longer treatment duration after benzodiazepine exposure, suggesting that additional classes of drugs may have some effect on the necessity and duration of treatment in general (also see "Maternal co-use of additional drugs"). Nayeri *et al.* excluded benzodiazepine-exposed infants from the study and saw otherwise no significant difference in drug exposure between the 2 treatment groups (73).

Finally, the 2 treatment groups in this retrospective analysis were comparable with regard to gestational age, maternal substitution with buprenorphine and maternal co-use of other drugs (64, 73). In contrast to Jackson's and Nayeri's population, however, it must be taken into account that the allocation to treatment with phenobarbital or morphine was neither randomized nor double-blinded in this study.

The AAP recommends treating infants with a drug of the same class of substance as the one that caused the withdrawal, for instance an opioid for opioid withdrawal (50). In the cohort examined here, there was a significant rate of maternal poly-drug use, but the main concern was always NAS from maternal opioids. There is also some concern about the effect of phenobarbital on long-term neurodevelopment based on research on both animal models and humans (107, 108). At CVK, the management of NAS has shifted to administrating oral morphine solution as a first-line treatment of pharmacotherapy in the years 2010 and 2011 despite the unsatisfactory longer treatment duration. After the double-blinded RCT by Agthe

et al. showing that adding clonidine to oral morphine solution decreases the duration of treatment and cumulative morphine dose in 2009 (65), 6 infants in this study cohort have been treated with clonidine as additional medication, but their number was too small to produce relevant results thus far. Smaller RCTs with 31, 26 and 31 subjects respectively have evaluated the use of clonidine monotherapy, buprenorphine and methadone versus morphine in recent years (68, 69, 77) (also see “Supportive and pharmacological therapy for NAS”). All 3 pilot studies saw a shorter duration of pharmacotherapy under their respective alternative to morphine. Kraft *et al*. have since followed up on their pilot study and published an RCT on 63 neonates suffering from NAS in 2017. In their study, buprenorphine treated infants required only 15 days of pharmacotherapy whereas morphine treated infants received their medication for 28 days with no increase in adverse events (70). Infants exposed to benzodiazepines, preterm infants, neonates of a birth weight lower than 2200 g and infants with concurrent medical conditions like hypoglycemia were excluded from the study but should the reduction in treatment time be reproducible in more inhomogeneous populations, buprenorphine may be a promising treatment option for infants with NAS.

In summary, while oral morphine solution still is the current mainstay of pharmacological NAS therapy (10) and the gold standard all other therapies are tested against, the long treatment duration observed here and in other studies (10, 77) is detrimental to the infants’ health, taxing on health care professionals and disadvantageous for the integration of the affected infants into their social environment. New or rediscovered substances, most notably buprenorphine, may help improve the treatment of NAS significantly. Therefore, more investigation into the subject is warranted.

4.3.2. Maternal substitution and drug use

4.3.2.1. Choice and dosage of maternal substitute medication

The data accumulated here points towards a marked benefit for neonates if their mother had been substituted with buprenorphine during pregnancy. These infants were heavier at birth, required pharmacotherapy 25% less often and for 6 days less and were discharged 9 days faster than their methadone- or levomethadone-exposed counterparts. Lejeune *et al*. report no difference between the methadone and buprenorphine in their prospective observational study on 159 pregnant women (83), whereas the multicenter-RCT MOTHER trial conducted on 175 women by Jones *et al*. found a significant advantage of buprenorphine substitution with shorter durations of treatment and hospitalization as well as a reduced required morphine dose (84).

Some of this beneficial effect may be interpreted from a pharmacological point of view. Buprenorphine has been found to have a low transplacental transfer rate, thus affecting the fetus in smaller doses than other opiates (109). In addition, buprenorphine being a partial opioid receptor agonist, methadone dosages of more than 30 – 40 mg/d or high heroin dosages prior to buprenorphine substitution result in considerable withdrawal and persons substituted with more than 60 mg of methadone are primarily excluded from buprenorphine substitution (110). In Jones *et al*.'s study, post-hoc analysis showed the same bias in favour of buprenorphine if mothers with a methadone dose of more than 100 mg/d were excluded (84). Furthermore, there is indirect evidence that the biological half-life of buprenorphine is longer in neonates than that of morphine (15). The onset of NAS was observed after 72 hours after buprenorphine and after 60 hours after methadone exposure in a double-blinded RCT by Fischer *et al.* including 18 mother-infant-dyads (111). Peak Lipsitz scores were observed after 81 hours after buprenorphine exposure and 66 hours after methadone exposure in the abovementioned RCT by Lejeune *et al*. (83).

Taking into consideration the practical aspects, buprenorphine substitution does appear to have some drawbacks. When switching from methadone or heroin to buprenorphine, some withdrawal is experienced by the substituted patient (110). This not only requires maternal inclination and consent to undergo this transition, but also close monitoring of the fetus in an inpatient setting if the switch is to be made during pregnancy. Another aspect not to be ignored is a certain degree of dissatisfaction with the buprenorphine substitution, leading to potentially more additional heroin use or entire discontinuation of treatment during pregnancy (84). All the same, neither Lejeune nor Jones report adverse maternal or obstetrical effects of buprenorphine substitution (83, 84). In summary, it appears worthwhile to offer buprenorphine substitution to women who wish to get pregnant or even to women of childbearing age in general. It may even be worthwhile to consider switching pregnant women from methadone to buprenorphine (112) if the mother-to-be is sufficiently motivated and it can reasonably be assumed that this will not result in co-use of additional drugs.

With regard to the dosage of the substitute drug, there appeared to be a positive correlation between maternal methadone dose and neonatal duration of pharmacotherapy in our patient sample. To date, literature on the relationship between maternal methadone dose and the severity of neonatal withdrawal yields contradictory results (3). Some authors have found that a lower maternal methadone dose prior to delivery was associated with a reduced incidence or severity of NAS (54, 67, 113, 114), whereas others could not show such a correlation (115-

117). One proposed explanation for this discrepancy is the wide range of daily dosages between the different studies. Studies that showed a relationship between maternal methadone dosage and neonatal withdrawal enrolled women with a methadone dose <50 mg/day, while those that did not find a correlation reported higher doses of 50-100 mg/day (3). At a median daily racemic methadone dose of 20 mg and a median daily levomethadone dose of 25 mg, the mothers in this study fit into the former category. A second possibility is that the interindividual differences in methadone metabolism and thus, serum levels, lead to differences in fetal methadone exposure even with the same dose of methadone administered (3, 118). Polymorphisms of maternal and fetal hepatic CYP enzymes, most notably maternal CYP 3A4 and CYP2B6, placental CYP 19 and ABC transporters eliminating xenobiotics from the fetus and the fetal μ1-opioid-receptor appear to play key roles in this regard (also see "Opioid metabolism and pregnancy" (119)). It should be noted that with increasing plasma volume, placental metabolism of xenobiotics and potentially psychological stress, a higher maternal methadone dose may be required to prevent maternal withdrawal with its known risks for the fetus and the co-use of additional opioids or other drugs (119, 120). As for buprenorphine, other studies have shown no correlation between the maternal total dose or dose prior to delivery and the severity of NAS, in line with the findings of this analysis (83, 121).

4.3.2.2. Maternal co-use of additional drugs

Stable maternal substitution without co-use of drugs other than the substitute and nicotine attenuated the course of NAS among the infants of this study. The necessity for pharmacotherapy was 18% less than if additional drugs were consumed. The duration of hospitalization in the group of infants of stably substituted mothers was shorter by 3 days although the duration of pharmacotherapy was the same. This circumstance may have been partially due directly to the higher rate of pharmacotherapy. It is, however, also possible that some of this additional time in the hospital among co-use group was attributable to a less stable social environment which required more framework to be constructed around the mother-infant-dyad by social workers and even resulted in a 17% lower rate of discharge into the maternal household.

Regarding the specific drugs consumed in addition to the opioid substitute, the rate of pharmacotherapy was highest among infants of mothers who co-used 3 or more additional substances at 78% followed by those of cocaine-using mothers at 76%. One study examining 1185 infants for ANS or CNS symptoms after intrauterine opiate, cocaine and combined opiate and cocaine exposure found that not only do both cocaine and opioids significantly increase

the risk for such symptoms, but the effects of these substances on ANS or CNS symptoms are also cumulative (122). It has been argued that the CNS signs after cocaine exposure are not withdrawal symptoms but result of the detrimental effect of cocaine on the development of the fetal brain (43). In clinical practice, however, it is not possible to differentiate between withdrawal signs and symptoms and the muscular hypertonia or tremors described after cocaine exposure. Thus, infants monitored after opioid exposure using a semi-quantitative scoring tool such as the Finnegan or Lipsitz score will receive higher withdrawal scores. Significant increases in the rate of pharmacotherapy were also seen after maternal cannabis (70%) and benzodiazepine (69%) consumption in this study. Intrauterine benzodiazepine exposure has long been known to cause neonatal withdrawal symptoms (123). Cannabis, on the other hand, is not considered to cause relevant withdrawal symptoms in neonates apart from a mild increase in irritability within 48 to 72 hours after birth (124). It is reasonable to assume that other drugs apart from cannabis may have been a confounder in this instance as 28% of the cannabis-using women also consumed benzodiazepines or cocaine. Another possibility would be an augmentative effect of cannabis on NAS. In an experiment on neonatal rats, it has been shown that cannabis, while not neurotoxic on its own, can severely aggravate ethanol induced neurodegeneration (125). A similar mechanism might very cautiously be speculated for neonatal withdrawal.

It should be noted that even among the mothers defined as “stably substituted” in this study, a very high percentage of mothers was smoking nicotine during at least part of the pregnancy. Previous studies have shown that nicotine not only increases the risk for prematurity and IUGR, but also exacerbates NAS (122), which might explain why the difference in the rate and duration of pharmacotherapy between infants of stably substituted mothers and infants of mothers with additional drug-use was not more pronounced in this study.

It may strike as odd that infants of unsubstituted mothers had a shorter duration of pharmacotherapy and hospitalization than those of substituted women. This circumstance may simply be explained by heroin’s comparatively short half-life (31). The shorter course of NAS is contrasted by the increased risk of intrauterine withdrawal leading to spontaneous abortion or intrauterine death, increased risk of infection with HIV, HBV and HCV and lower adherence to prenatal care programs (see “Rationale and substances”). Under these circumstances, a 3-day cut on the duration of therapy cannot be considered sufficiently important to even consider an unsubstituted pregnancy a viable option.

4.3.3. Conclusions for maternal substitution management

To sum up the above paragraphs, maternal substitution with buprenorphine, substitution free from co-use of other drugs and a lower methadone dosage if this substitute was used lead to less frequent or shorter neonatal pharmacotherapy. It is by no means trivial to reconcile these 3 therapy goals as it has been shown that both buprenorphine substitution and inadequately low methadone dosages may lead to lower adherence to substitution therapy (31, 79, 84). In this case, maternal non-compliance may be either additional drug use by supplementing the substitution treatment with street-bought opioids or other classes of drugs or even discontinuing substitution treatment altogether (31, 84, 120). From the viewpoint of reducing harm to the fetus and neonate, a reasonable approach may be to first reduce or even eliminate additional drug use as far as possible (see “Maternal co-use of additional drugs”). This should first focus on intravenous drug use to reduce the risk of infection with HIV, HBV and HCV. Educating pregnant women about the probability of increasing substitute dosages required during pregnancy (see “Maternal substitution and drug use”) and adjusting maternal treatment accordingly may improve maternal compliance (120). The second step could be to suggest buprenorphine substitution to women of child-bearing age (84) and even to offer switching to buprenorphine during pregnancy under applicable precautions (112). Despite the influence of maternal methadone dosages on the neonatal duration of treatment in this cohort, the reduction of methadone dosages during pregnancy cannot be universally be recommended (see “Maternal substitution and drug use”). As individual women may request such a reduction hoping to reduce the risk for NAS and may resort to performing it independently if not assisted by her substituting physician, it may be reasonable to taper the substitute dose very gradually over the course of weeks and under appropriate monitoring of the fetus via sonography and cardiotocography (120). From the viewpoint of maternal health-care providers, other factors such as maternal preference should also be taken into consideration.

4.4. Development over the study period

Over the 12-year period observed in this work, the infants’ rate of prematurity, median birth weight, rate of HIV exposure, percentage of infants discharged into their mother’s household and the rate of pharmacotherapy remained at constant levels. A considerable increase was discerned in the duration of hospitalization as well as the duration of pharmacotherapy by 8 and 13 days respectively. In the large multi-center study by Tolia *et al*. on 299 NICUs located in the USA, a substantial increase in NICU days attributable to NAS has been seen from 2004

through 2013 (10). In the US cohort, this change is partially caused by a dramatically increased prevalence of opioid pain medication addiction across the general population including women of child-bearing age. A comparable “epidemic” has so far not been noted in Germany, where the majority of the burden of dependence on prescription drugs remains among elderly patients and the substance class of sleep-inducing drugs (9). Concordantly, the incidence of NAS at CVK has remained stable at an average of 31 infants per annum throughout the study period.

Several possible underlying causes for a prolonged course of NAS pertaining to this study’s population have been mentioned in the above paragraphs. Neonatal pharmacotherapy with morphine was introduced in 2005 and a marked increase in the duration of therapy was seen in that year. However, even when all morphine-treated infants were excluded from analysis, the increase in the duration of hospitalization by 5 days and of pharmacotherapy by 11 days remained significant. A second supposable explanation for the phenomenon would be differences in maternal drug use. This point is supported by the circumstance that the dosage of racemic methadone increased by 11.5 mg and that of levomethadone by 7.5 mg. This had a significant influence on the duration of neonatal therapy in this study, although this effect is controversial in current literature (see “Maternal substitution and drug use”). Conversely, the rates of maternal buprenorphine substitution and maternal co-use of additional drugs, both acknowledged influencing variables on the length of neonatal pharmacotherapy have remained the same throughout the years.

Other conceivable causes for the prolonged duration of pharmacotherapy and hospital stays are of a less substance-related nature. Tolia *et al*. suggest that the increasing duration of pharmacotherapy and higher cumulative doses of morphine could be influenced by changes in clinical management of NAS or lack of adherence to standardized protocols as recommended by the AAP (3, 10). While standard operating procedures regarding the treatment of NAS do exist at the CVK, the first-line medication and details concerning supportive care were changed during the study period. This allows for the possibility that some periods of adjustment to new procedures and treatment medication may have had an influence on the duration of pharmacotherapy or hospitalization for some patients. There was, however, no change regarding the indication of starting pharmacotherapy or terminating treatment throughout the study. The possibility that longer hospital stays are, at least in part, caused by social workers appears worth to be taken into consideration. However, the ratio of pharmacotherapy days to days of hospitalization actually increased from 45% to 98% in favour of treatment days. A similar trend was seen in Tolia *et al.*’s study cohort (10), suggesting that

although the evaluation of the infants' social circumstances, installation of a help network or placement in a foster family may be a time-consuming process, this did not routinely delay the infants' discharge. A high percentage of the mothers in this study's cohort had been seen at the "*Suchtambulanz*" at CVK prior to giving birth. In this context, contact to the responsible social workers was regularly established which may have facilitated proceedings after the infant was born. Finally, another aspect worth considering is the reliability of the scoring tool used for the management of neonatal therapy. Austrian researchers have shown that the Finnegan score of non-opioid-exposed infants increases physiologically from during the first 3 days of life, when the 50th percentile is 2 and the 95th percentile 5.5 to the age of 5 to 6 weeks of life when the scores follow a day-night rhythm and the 50th percentile is 5 and the 95th 8 points during daytime (101). Thus, infants treated for NAS longer than others for any one of the above reasons may be treated even longer due to the naturally increasing baseline Finnegan score in healthy babies.

4.5. Limitations

The first and most significant limitation of this study lies within its retrospective design. There was no randomization or blinding regarding the maternal substitute medication or the choice of neonatal pharmacotherapy. The choice of maternal substitution medication was made by the substituting physician, the mother-to-be and the specialized obstetric outpatient clinic. The decision to treat with either phenobarbital or morphine was taken based on the respective current literature and clinical experience, which results in both a higher risk for confounders and a much smaller morphine-treated group compared to the phenobarbital-treated group.

While all illegal drugs were screened for meticulously both via urine samples during the mothers' outpatient visits and via meconium analysis, the legal alcohol and nicotine use were documented via maternal history alone. Especially in the case of alcohol there may have been several unrecorded cases while an extremely high percentage of mothers declared their nicotine smoking during interview.

Rooming-in of mothers with their infants with NAS has been shown to reduce the rate of pharmacotherapy and lead to shorter hospital stays (126). At CVK, infants would typically be primarily admitted to the postpartum ward with their mothers and be transferred to the NCU once pharmacotherapy became necessary. Rooming-in on the NCU was once again possible during the final days before an infant was discharged home with his or her mother but was not routinely done during the course of neonatal treatment. All the same, depending on concurring

diagnoses like prematurity or infection as well as the maternal social situation, this process was not standardized and this study did take into account the proportion of rooming-in with regard to the course of NAS.

Furthermore, the Finnegan score has been developed to diagnose NAS and to measure the severity of NAS in a semi-quantitative way. It has been used as a means to indicate and guide pharmacotherapy by the physicians at CVK as is common practice among researchers and treatment facilities although AAP has noted that an ideal threshold to begin pharmacotherapy has not been established (3).

Studying the infants of substance abusing women, one major area of concern is the long-term social situation and psychosocial development. Apart from the statement where infants were primarily discharged to, no investigation into this question was made within the scope of this thesis. Insights into the long-term development and social environment of opioid-exposed infants are rare and more research into this topic would be advantageous (127).

4.6. Conclusions and outlook

In summary, NAS is a condition of ambiguous nature. Its course is ultimately self-limiting, but it is characterized by severe and potentially life-threatening symptoms such as weight loss and seizures, a long course of treatment and a demanding type of supportive care by parents and nurses alike. As specific to the majority of diseases of the perinatal period, multiple aspects of maternal health and social history and neonatal characteristics have to be taken into consideration. Therefore, close interdisciplinary cooperation between obstetricians, physicians providing opioid substitution therapy, social workers, nurses and pediatricians is necessary to achieve a satisfactory outcome for both mother and infant.

This thesis focuses on the course of NAS with special attention to the factors that influence the need for and duration of neonatal pharmacotherapy. Prematurity and a low birth weight were a common comorbidity in this cohort although part of this effect may be attributed to maternal co-use of drugs other than the substitution medication, especially nicotine. Maternal substitution free from co-use of other drugs, substitution with buprenorphine or a lower methadone dosage if this substitute was used appeared beneficiary for the neonates in this analysis.

In this work, infants treated with phenobarbital had a shorter duration of pharmacotherapy and hospitalization than newborns treated with morphine. Nevertheless, the approach to treat

opioid withdrawal with a sedative drug has been left at CVK and other treatment centers in recent years (10). Considering that the duration of therapy has continued to increase, further investigation into an improved treatment scheme for NAS appears to be the logical consequence. As buprenorphine has been shown to be a promising alternative under controlled RCT conditions (70), testing the substance among the local patient population may be a reasonable next step. Finally, evaluating maternal and neonatal care from the perspective of long-term development would be a relevant complement to the immediate effects evaluated within this thesis.

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Eidesstattliche Versicherung

„Ich, Sonja Karin Scholz, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema „Ausprägung und Therapie des neonatalen Abstinenzsyndroms während der Jahre 2000-2011. Eine monozentrische retrospektive Analyse.“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

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Datum Unterschrift

Publikationsliste und Anteilserklärung

Teilergebnisse der vorliegenden Arbeit wurden im unten genannten Artikel veröffentlicht.

Publikation 1: Mücke S, Nagel M, Siedentopf J, Bührer C, Hüseman D., Neonatal Abstinence Syndrome: Twelve Years of Experience at a Regional Referral Center, Klinische Pädiatrie, Jan. 2017, doi: 10.1055/s-0042-115300.

Beitrag der Doktorandin im Einzelnen:

- Datenerhebung (maternale Daten teilweise durch Frau Soz.-Päd. Nagel erhoben)
- Statistische Analyse der Daten
- Verfassen des Artikels (unterstützt durch Herrn Prof. Bührer)
- Anfertigung der Graphiken
- Revision (in Zusammenarbeit mit Herrn Dr. Hüseman und Herrn Prof. Bührer)

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Unterschrift, Datum und Stempel des betreuenden Hochschullehrers

_____

Unterschrift der Doktorandin

Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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