

TREATMENT OF OPIOID DEPENDENCE DURING PREGNANCY: challenges and perspectives for health care providers with an emphasis on pharmacotherapy



Gabriele Fischer

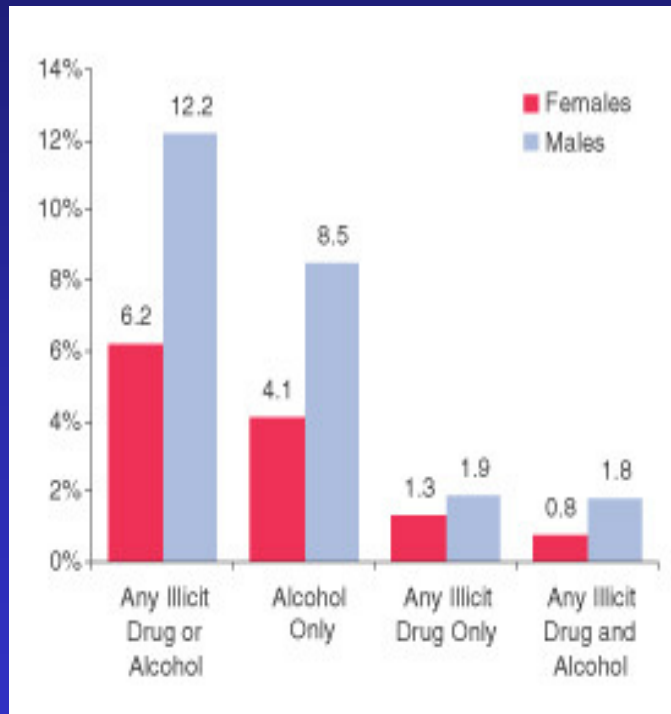
ADDICTION CLINIC

www.sucht-addiction.info

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Gender Gap



- Percentages of past year dependence on or abuse of alcohol or any illicit drug among persons aged 12 or older, by gender: 2003

- Males-to-females ratios of prevalence are narrowing

In Pregnancy, Treatment Professionals Must
be Cognizant of the Fact that they are
Treating Two Individuals with Particular
Considerations for Each One



Management of pregnant illicit drug misusers

Council of Europe

1998:ISBN: 92-871-3784-6



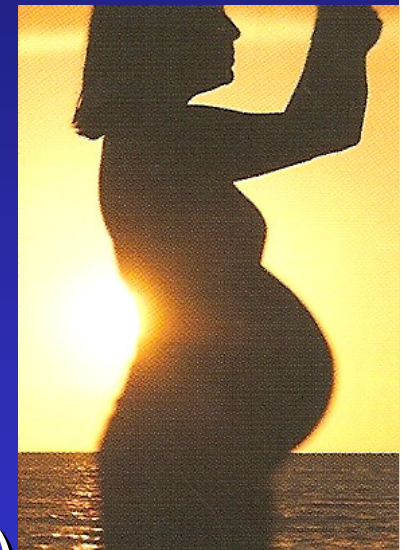
- Out-Reach Services
- Medical treatment
- Psychological assistance
- Psychosocial treatment
- Evaluation of target group
- Training program



Training - Teaching programs for interdisciplinary groups



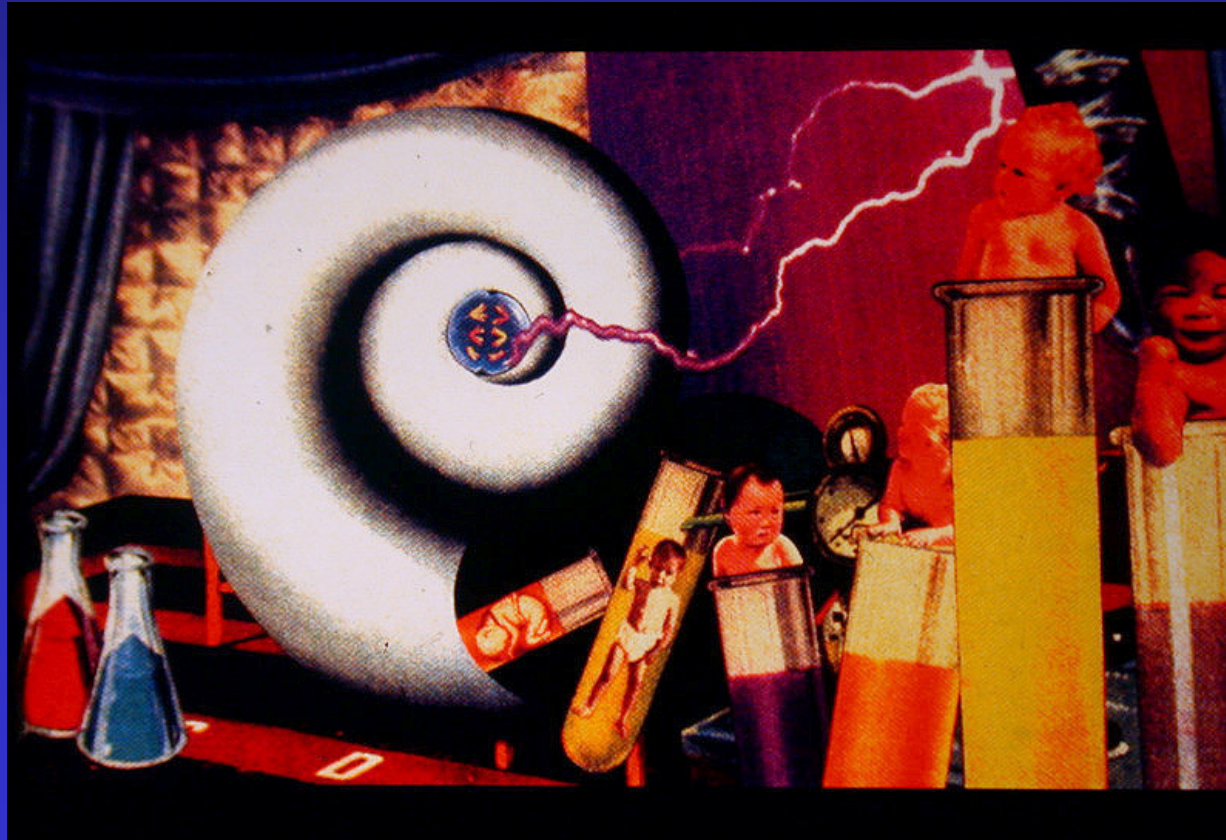
- social workers
- obstetricians
- mid-wives
- nurses
- general practitioners
- psychiatrists (psychiatric co-morbidity)
- pediatricians
- anesthesiologists
- health authorities /welfare systems



Pregnancy and Opioid Addiction

Treating pregnant women dependent on opioids is not the same as treating pregnancy and opioid dependence: a knowledge synthesis for better treatment for women and neonates.

Winklbaur B, Kopf N, Ebner N, Jung E, Thau K. & Fischer G.
Addiction 103: 1429-1440 (2008)



Opioid-dependence during Pregnancy



- 27% of pregnant women reporting illicit drug use; they report the use of heroin or non-medical use of pain-relievers (Substance Abuse and Mental Health Services Administration US, 2005)
- 39,6% use analgesics during pregnancy (Headley et al. and the ALSPAC Study team. Medication use during pregnancy: data from the Avon Longitudinal Study of Parents and Children. Eur J Clin Pharmacology 60: 355-361; 2004)
 - 62,3% use analgesics during pregnancy (Lacroix et al., Prescription of drugs during pregnancy in France. Lancet 356:1735-1736; 2000)

Prevalence of psychiatric disorders (Lifetime M-CIDI/DSM IV) in general population, n=4181

<i>DSM-IV-diagnosis</i> (in %)	♂	♀
Psychiatric disorder as consequence of medical disease:	1.8	2.7
<i>Psychiatr. disorders in relation to substance use disorder:</i>	15.6	4.2
Alcoholdependence:	14.4	2.6
Schizophrenia incl. other psychotic disorder:	4.1	5.0
Unipolar depression:	11.2	23.3
Bipolar disorder:	0.8	1.2
Panic disorder:	2.2	5.5
Pain-disorder:	<u>7.8</u>	<u>17.8</u>
Eating disorder:	0.3	1.3

Jacobi et al., Psychological Medicine 2004, 34, 1-15

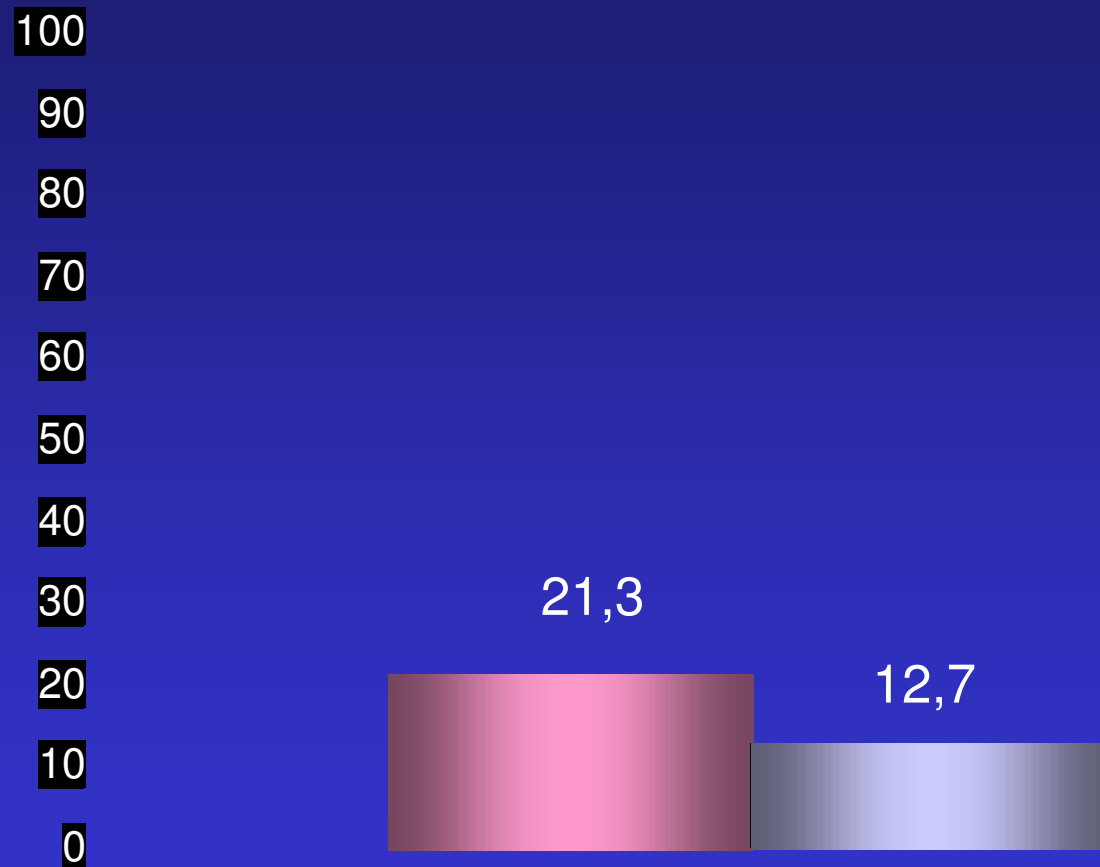
Psychiatric Comorbidity of Adolescents in Substance Abuse Treatment & Matched Controls*

	SA Patients	Controls
Depression	36.3%	4.2%
Anxiety Disorder	16.3%	2.3%
ADHD	17.2%	3.0%
Conduct Disorder	19.3%	1.2%
Conduct Disorder (w/ODD)	27.3%	2.3%
Any Psychiatric Diagnosis	55.5%	9.0%

* All $p < .001$

Sterling S, Weisner C. Chemical dependency and psychiatric services for adolescents in private managed care: Implications for outcomes. *Alcohol Clin Exper Res.* 2005;25(5):801-9.

Depression: prevalence ♀ : ♂



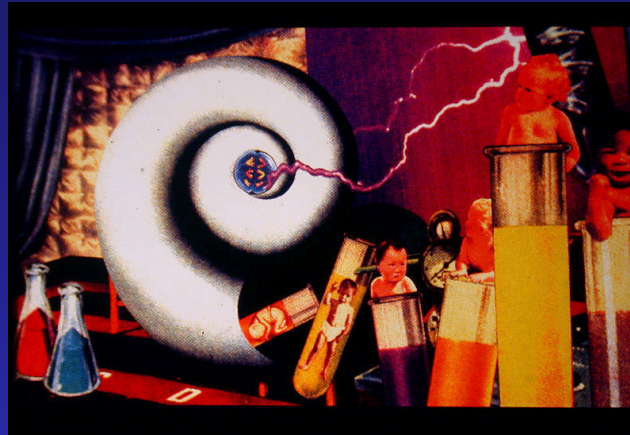
Psychiatric comorbidity

- High prevalence of affective disorder symptoms in pregnant substance dependent women - frequently prescribed psychotropic drugs
- Anxiety exists regarding to safety of medication among patients and healthcare providers (Einarson et al., 2005)
→ Selective Serotonin Reuptake Inhibitors (SSRIs) prescribed and administered *in utero*: Occurrence of a neonatal behavioral syndrome (Moses-Kolko et al., 2005)

SSRIs in pregnancy

- Fluoxetine is better investigated than Paroxetine, Sertraline and Fluvoxamine
- Controversial outcome in publications regarding to Fluoxetine and miscarriage (Chambers et al., 1996; Baum and Misri, 1996)
 - Neonates exposed to SSRIs in the third trimester of pregnancy are at higher risk for developing neonatal complications (Nordeng et al., 2005)
 - Persistent pulmonary hypertension (PPHN) in newborns exposed *in utero* to SSRIs (Chambers et al 2006).
- Paroxetine no longer recommended

Pregnancy & Addiction



Nicotine

- More than 20% of pregnant women in the general population smoke during pregnancy (Narayanan et al., 2002)
- Estimates indicate 90% of drug-dependent women are heavy smokers (US Department of Health and Human Services, 1996; King, 1997)
- Consequences for the neonate include lower birth weight, deceleration of fetal growth, fetal hypoxia, Fetal Tobacco Syndrome (FTS), higher risk for the occurrence of Sudden Infant Death Syndrome (SIDS) (Shah et al., 2000; Mitchell, 1995; Kirchengast et al., 2003; Choo et al., 2004)

The Issue of Birth Measurements

Is it Methadone or alcohol and tobacco?

- Magnitude of observed outcomes for illicit drugs cannot compare to that of confirmed adverse growth, health and developmental risks of alcohol and tobacco;

Most MM women use tobacco and many drink alcohol

- Alcohol associated with *Fetal Alcohol Spectrum Disorders*
- Prenatal tobacco use associated with growth restriction and later developmental problems as a result of nicotine disruption of CNS development

Striessguth, AP. Et al. Am J Obstet Gynecol. 2002; Slotkin, TA. J Pharmacol Exp Ther 1998; Weitzman, M. et al. Neurotoxicol Terat 2002

Benzodiazepines

- Slow detoxification is required to avoid preterm labour or worsening of psychiatric symptoms (Swortfiguer et al., 2005; Eberhard-Gran et al., 2005)
- Neonates of mothers with benzodiazepine use during pregnancy develop NAS with a prolonged course (Lagreid et al., 1992; Coghlan et al., 1999)

Benzodiazepines

- ❑ Benzodiazepines are still administered in pregnancy to avoid prescribing opioids or to be able to decrease opioid-doses
- ❑ Increasing results regarding the teratogenicity of benzodiazepines have been reported - oro-facial malformations (Eros et al., 2002)
- ❑ Adverse affects of an untreated maternal „mood disorder“ must be balanced against possible adverse effects of neonatal exposure to benzodiazepines (Eberhard-Gran et al., 2005)

Cocaine

- United Nations Office on Drugs and Crime (UNODC) reports increasing figures for Europe, Asia and Australia in prevalence of cocaine use : prevalence between 0.1% and 2.7% (World Drug Report, 2005)
- No proven medication for effective pharmacological treatment
- Cocaine abuse during **pregnancy** may lead to complications like preterm labour, cerebral ischemia, malignant hypertension, stroke and sudden death in the pregnant women (Vascia et al., 2002; Brownlow et al., 2002; Egred et al., 2005)
- **Post-partum** the neonate may develop an NAS including the symptoms irritability, lethargy, increased appetite, yawning, sneezing, higher sleep requirement, foetal tachycardia and hypertension

Basic Knowledge

- 50% of pregnancies unplanned
(UK, Taylor et al. The Bethlem and Maudsley prescribing guidelines, 1999)
- 96 % of pregnant women report taking medications during pregnancy (Refuerzo et al., 2005)
 - High prevalence of co-occurred psychiatric disorders
 - Mostly affective disorders (antianxiety & antidepressive medication)
- No prospective controlled comparison studies in any pharmacological treatment during pregnancy
- Retrospective evidence about medication recommendation (eg antidepressive medication)
- “Real field” observations are important

Pregnancy And Opioid Addiction



- Detoxification ideal goal
 - Almost impossible to achieve without relapses and risk of destabilisation during pregnancy
- Most experience with **methadone**
 - Keeps women in medical treatment
 - ↑ retention
 - ↓ illicit consumption
- No registration studies available - but many publications on the benefits of methadone maintenance treatment during pregnancy
- Many “wrong” conclusions were drawn - outcomes being a direct consequence of methadone medication, which might not be the case

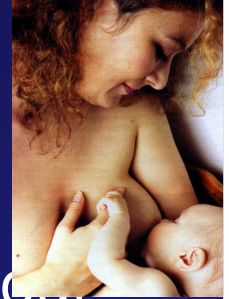
Problems Related To Opioid Exposure During Pregnancy

CHILD/NAS

- 55–94% of IU exposed neonates show signs of NAS
- 60–87% require treatment
- *Children born to methadone maintained mothers:*
 - Mean treatment duration 10 – 30 days:
 - No correlation between doses at delivery, intensity and duration of NAS
- Increasing results in **intrauterine exposure to buprenorphine**
- Heterogenous reports – retrospective, observational, controlled
- Heterogenous approach regarding treatment of NAS – phenobarbiturates/oral morphine solution



What are we measuring ?



- Many publications are retrospectively - no information about the medication & substance abuse during pregnancy
 - NAS reports „related“ to methadone ??? - This doesn't seem to be justified
 - The only good references are prospectively followed + in consideration of nicotine consumption
 - Are preterm deliveries separately investigated from term deliveries ?
 - Many „Finnegan“ versions + different medications applied
 - Do publications differentiate between breastfeeding & bottle nursing ?
- Do we have any information about pharmacodynamics & pharmacokinetics of medication in neonates ?

Neonatal outcome of 58 infants exposed to maternal buprenorphine in utero

(Hytinantti et al, Acta Paediatrica 2008)

Study Design

- Prospective design (2001-2005, Helsinki University Central Hospital)
- 58 buprenorphine-using pregnant women in supervised sublingual replacement therapy
- Antenatal treatment by an obstetrician -> assessment of foetal bioprofile and growth every 4 weeks
- Psychiatric support and counselling offered
- Measurement of urinary buprenorphine and norbuprenorphine concentrations in mothers prior to delivery and in infants during first 3 days of life
- Postnatal assessment („Finnegan Score“ every 2h) and treatment of NAS (Finnegan Score ≥ 8)

Maternal Parameters

Median age	24 years
Median duration of opioid use	7 years
Initiation of buprenorphine replacement therapy (mean)	13.5 weeks (of pregnancy)
Median buprenorphine dose/day	<u>5 mg</u>
Tobacco smokers	54 (100%)
Infections	
HIV-positive	1 (2%)
Hepatitis C-positive	43 (80%)
Hepatitis B-positive	2 (4%)

Neonates I – birth parameters

Sex (n=58)	32 male/ 26 female
Mean gestational age at birth	39.7 weeks
Mean birth weight	3267 g
Mean birth length	49.1 cm
Head circumference	34.4 cm
Preterm infants	n=3
Vaginal deliveries	n=45
Developmental anomalies	n=2

Neonates II - postnatal assessment

<u>Infants requiring NAS treatment</u>	<u>n=38 (66%)</u>
Length of hospital stay	25 ±19 days
Duration of morphine treatment	20 ±10 days
Mean time frame beginning of morphine hydrochloride treatment	2.4±1.1 days
Mean initial dose of morphine	0.34 mg/kg/day
Urine samples (except BUP)	N = 21 (36%) infants
Benzodiazepines	n=19
Amphetamine	n=2
Ephedrine	n=1
Tramadol hydrochloride	n=1

Buprenorphine during pregnancy

- Buprenorphine has been broadly available for treatment of opioid dependence
- More pregnancies occurring during buprenorphine maintenance (including at conception)
- Other women receive treatment initiation during pregnancy
- Scientific literature includes data of > 600 neonates exposed to buprenorphine prenatally
 - 61% NAS
 - 50% requiring treatment (>40% confounded by illicit drug use)
- Combination product (buprenorphine/naloxone) should not be administered in pregnancy - switch from Suboxone[®] to Subutex[®] 1 : 1.
 - Therefore family-planning counselling

Buprenorphine: Observational Data

- Most data on buprenorphine use in pregnancy = French publications:
 - „naturalistic retrospective studies“
- Results: safety of buprenorphine use during pregnancy and conception
 - Jernite et al, 1999
 - Lejeune et al, 2001
 - Gourarier et al, 2002
 - Lacroix et al, 2004
 - Lejeune et al, 2006

Buprenorphine: Prospective Studies

Marc Reisinger 1996, 162:261: Poster at CPDD with the report on four women maintained on buprenorphine (1 mg) during pregnancy

- Three prospective trials with *standardised study design* in women and neonates, *controlled for concomitant consumption by structured urinalysis*:
 - Fischer et al, 2000: n=15; mean doses 7 mg; NAS 2 days (n=3)
 - Johnson et al, 2001: n=3; mean doses 10/12 mg; no NAS to treat
 - Schindler et al, 2003: n=4; at conception; dose range 4-16mg; no NAS
- Two RCTs comparing methadone & buprenorphine in a double-blind, double-dummy design during pregnancy
 - Jones et al, DAD 2005
 - Fischer et al, Addiction 2006



PREGNANCY AND ADDICTION

Vienna

Inter,- & multidisciplinary

GP'S

ADDICTION CLINIC

visits: 1-7 times a week
group psychotherapy/weekly
psychosocial care/psycho-
education/casemanagement

Child Welfare
Institution

Video
Interaction
Analysis

Gynaecology

- 6 times prenatal
- delivery

Internal medicine

- EKG, infectious
disease

Neonatology

- NAS-Treatment

Child Neurology

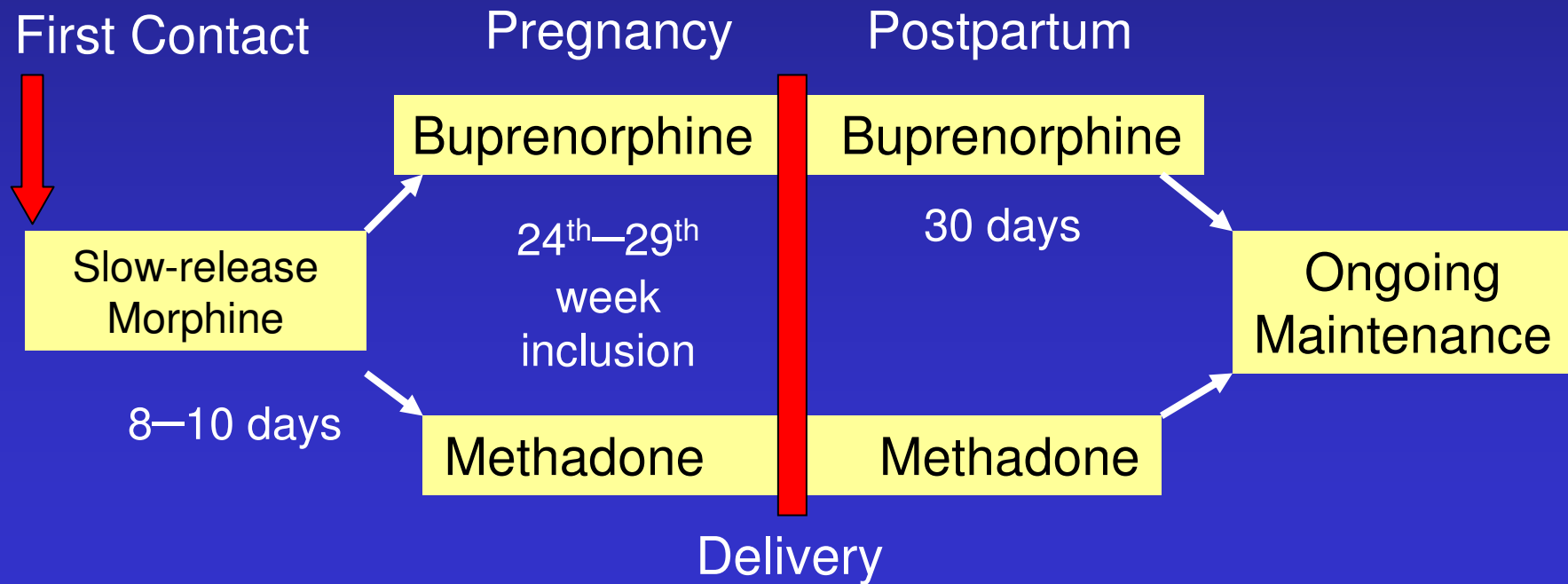
- 4 examinations
during 1st year
- 2 examinations
during following
year

Lawyer

Methadone Versus Buprenorphine In Pregnant Addicts: Study Design

(Fischer et al. *Addiction*, 2006)

Double-blind, double-dummy comparison study in pregnant addicts



Methadone v buprenorphine in pregnancy

- *Main research questions:*

- Retention rate
- Additional consumption
- NAS 

- NAS ratings made under “blind” conditions

- Daily attendance of patients until 4 weeks postpartum

- No urine results during pregnancy – no contingency management

- 26% of screened pat. included in study over 3 year enrolment

- Exclusions based on: severe polydrug abuse, refusal of daily clinic visit, past 29th week of pregnancy, already on methadone, pregnancy complications, abortion

Dosing Schedule

- Induction period (3 day inpatient admission):
 - Between 24th–29th week
- Dosing: Methadone Buprenorphine
- Level 1: 40 mg 8 mg
- Level 2: 55 mg 12 mg
- Level 3: 70 mg 16 mg
- Level 4: 85 mg 20 mg
- Level 5: 100 mg 24 mg

Demographics In Women (N=18)

		Percent
Opioid- dependent Partner	Yes	46.2%
	No	53.8%
Hepatitis Status	Hepatitis – A	5.6%
	Hepatitis – B	11.1%
	Hepatitis – C	55.6%
	Hepatitis – comb	16.7%

Data Comparison In Neonates

4 drop outs: 3 methadone (1 stillbirth), 1 buprenorphine

	Methadone n=6	Buprenorphine n=8	<i>p</i>
n (%)	6 (43%)	8 (57%)	
Wk of delivery	37.5	38.4	0.513
Weight (g)	2689	2923	0.550
Length (cm)	48.2	48.6	0.818
Head circumference (cm)	32.2	31.9	0.835
Preterm births	3	2	

- Birth weight on preterm deliveries: 2200 g (1750–2750 g)
- Birth weight on term deliveries: 3171 g (2450–4040 g)

No significant difference between treatment groups

NAS

- Rating and treatment (every 4 hrs – ‘blinded’)
 - Finnegan score: Max: 45 pts/treatment higher than 10
 - Oral morphine-hydrochloride/based on body weight and score intensity
- Three neonates in each group did not require NAS treatment
- Mean onset of NAS in others (after last medication):
 - Methadone group: 60 hrs
 - Buprenorphine group: 72 hrs
- Duration of treatment in days (mean \pm SD, range)
 - Methadone group: 5,3 \pm 1,5 [4; 7]
 - Buprenorphine group: 4,8 \pm 2,9 [1; 8]



Results

- Long screening period + limited inclusion: strict design
- 78% completion rate
- 65% term deliveries
- One serious AE: one IU death (week 39/methadone)
- Mean maintenance dosage (mg):
 - methadone day 5: 47.5 [40;55] and delivery: 52.5 [40;85]
 - buprenorphine day 5: 13.5 [8;20] and delivery: 14.0 [8;20]
- ↑ concomitant opioid consumption in buprenorphine group (two more patients)
- 43% no NAS to treat (score <11)
- No significant difference in demographic parameters

Conclusion

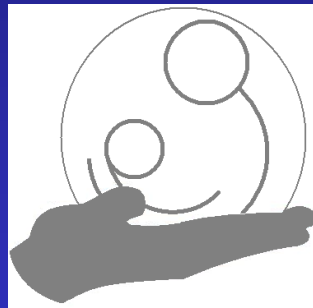
- Despite considerable concomitant consumption, short duration of NAS treatment duration in *both groups (5 d)*
- Dose increase may be clinically indicated even when the patient is reluctant to increase
- Voucher based studies may increase clean urines, benzodiazepine and concomitant opioid use
- Evidence – structured research may not reflect ‘**real world**’ situation
- Further multicentre trials should be undertaken

Mother Study

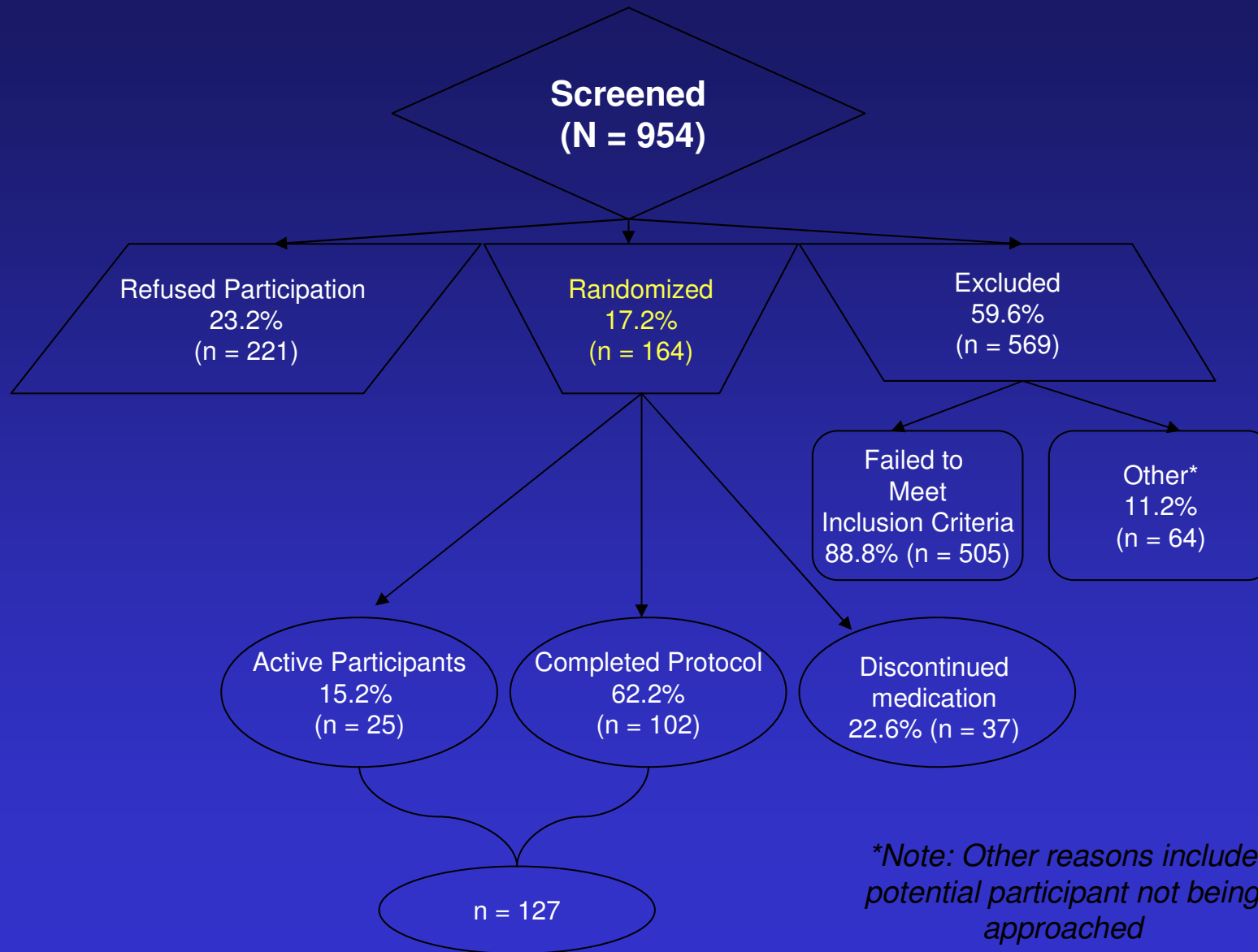
MOTHER 1R01 DA018417-01

double-blind, double-dummy comparison of buprenorphine/methadone with contingency management

- 5 US Sites
- 1 Canadian
- 1 European

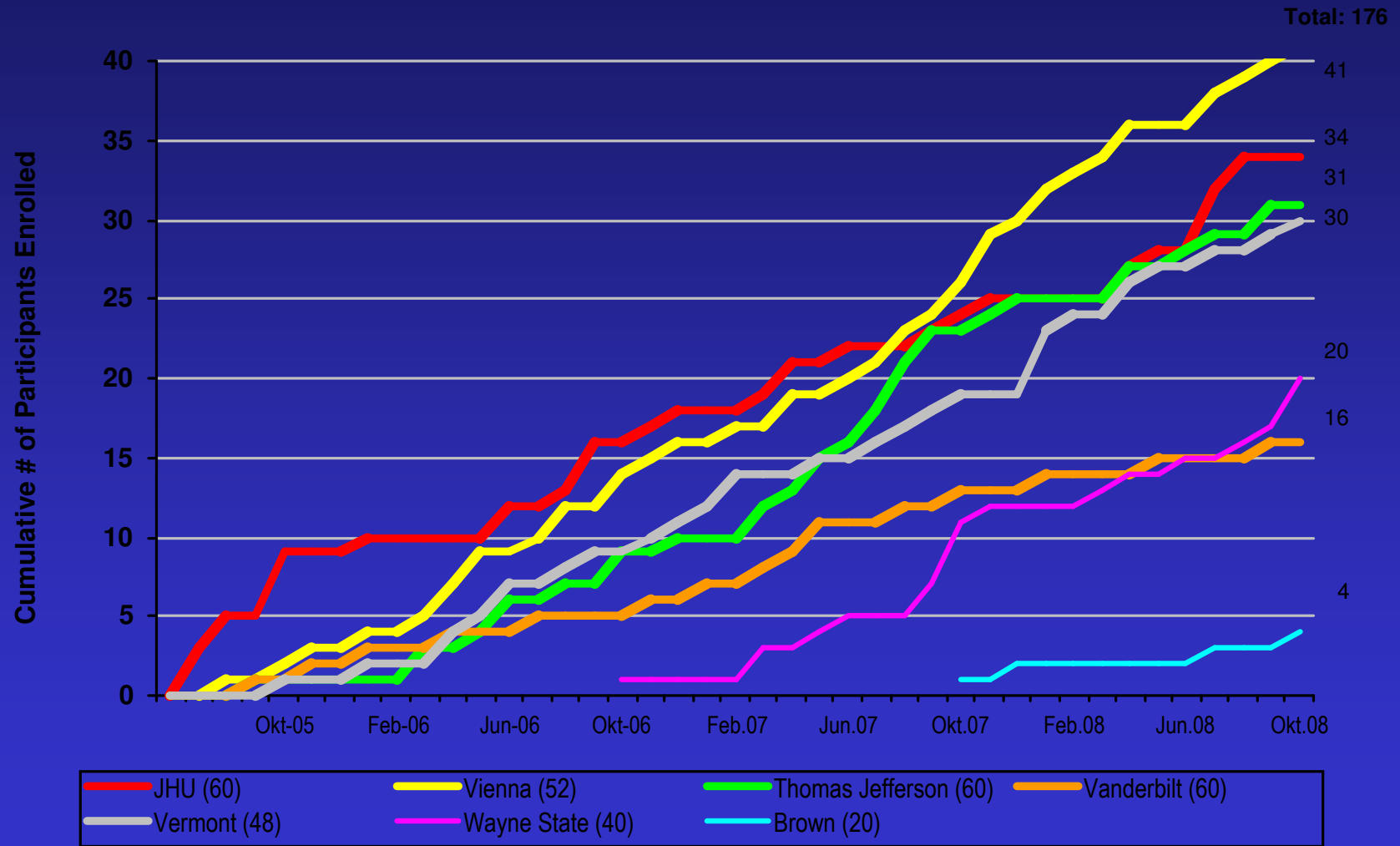


MOTHER STUDY PROGRESS



Subject Enrollment to date by Site 10/22/08

(Toronto not included)

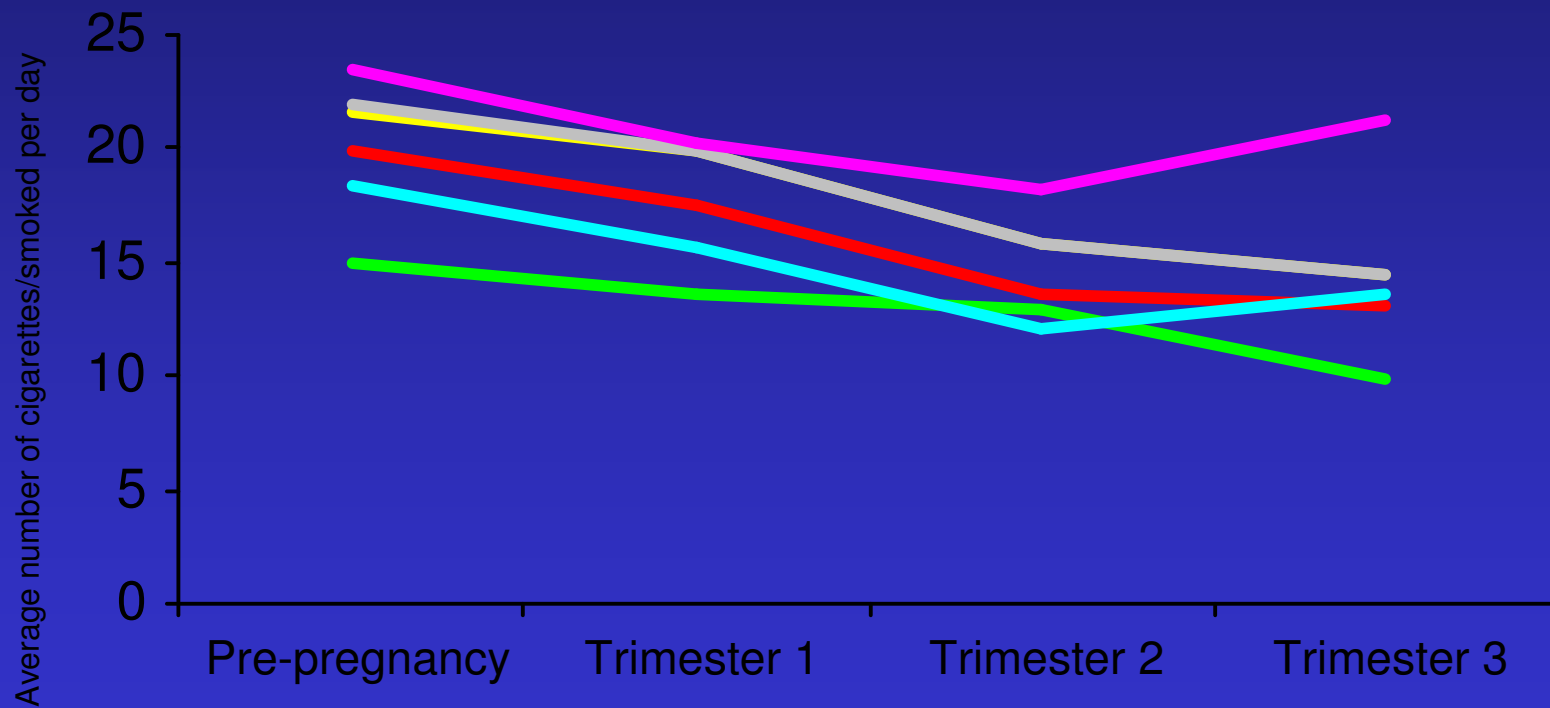


Estimated quotas are in parentheses for each site

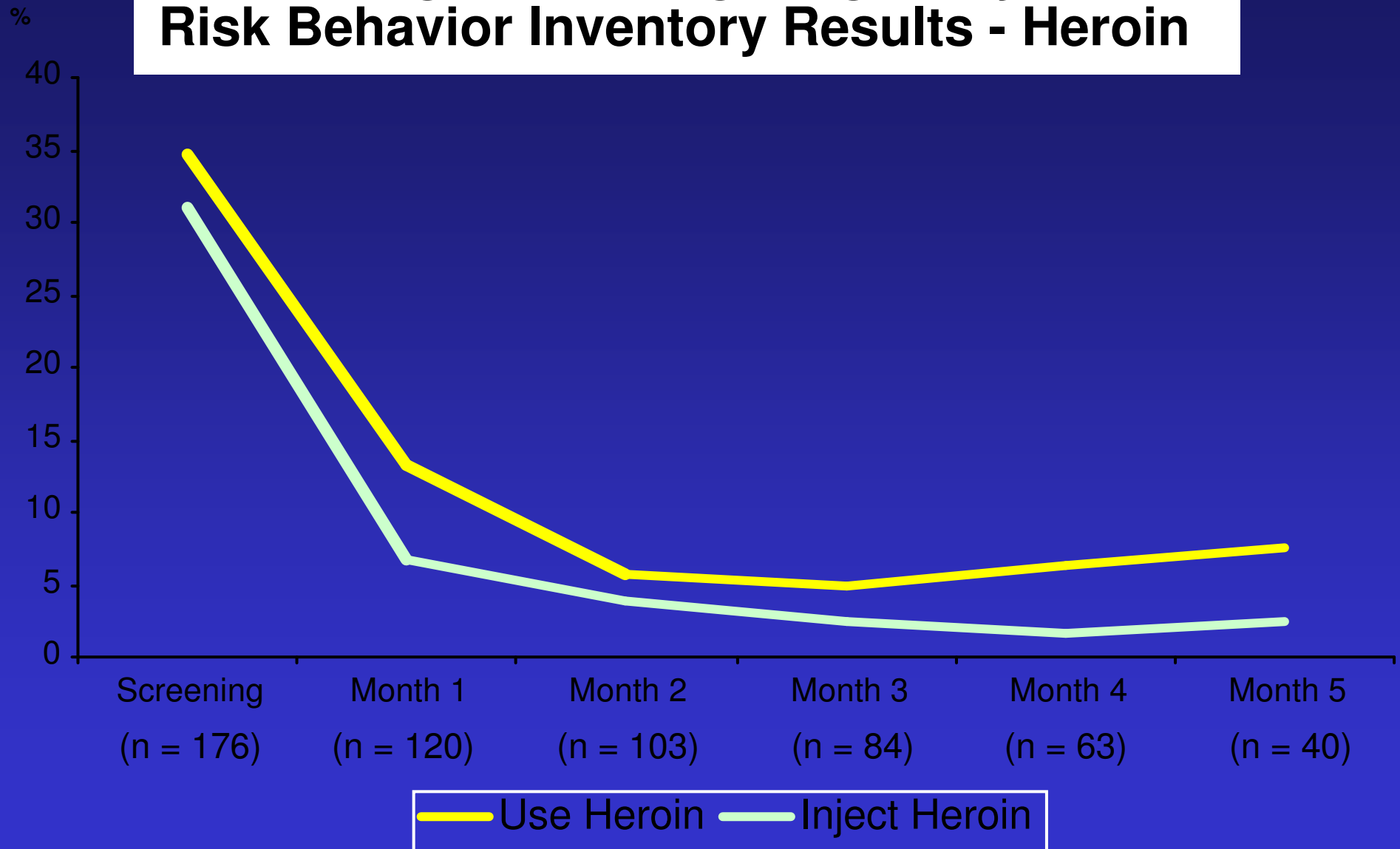
Maternal Characteristics	Randomized Patients (n = 164)	Non-randomized Patients (n = 790)
Mean Age	27.48	28.30
Mean EGA at Study Entry	17.27	n/a
Race		
White	83.5%	71.0%
Non White	16.5%	29.0%
Marital Status (% married)	12.9%	9.8%
Employment Status		
Employed	12.9%	10.1%
Unemployed	85.3%	88.2%
Educational Level (Mean)	11.31	11.08
Prior Treatment History		
% Ever Received Treatment	91.5%	91.8%
% In Current Treatment	72.6	87.2%
# Times Prescribed Methadone	1.17	1.70
# Times Prescribed Buprenorphine	0.64	0.71
Drug Use in 30 Days Prior to Screening		
Opioid	81.7%	84.5%
Cocaine	36.0%	43.9%
Current Smoker	93.3%	n/a
Mean gestational age at delivery (wks)	38.44 Range 29-42 SD = 2.40	n/a

Tobacco Use during Pregnancy among Smokers

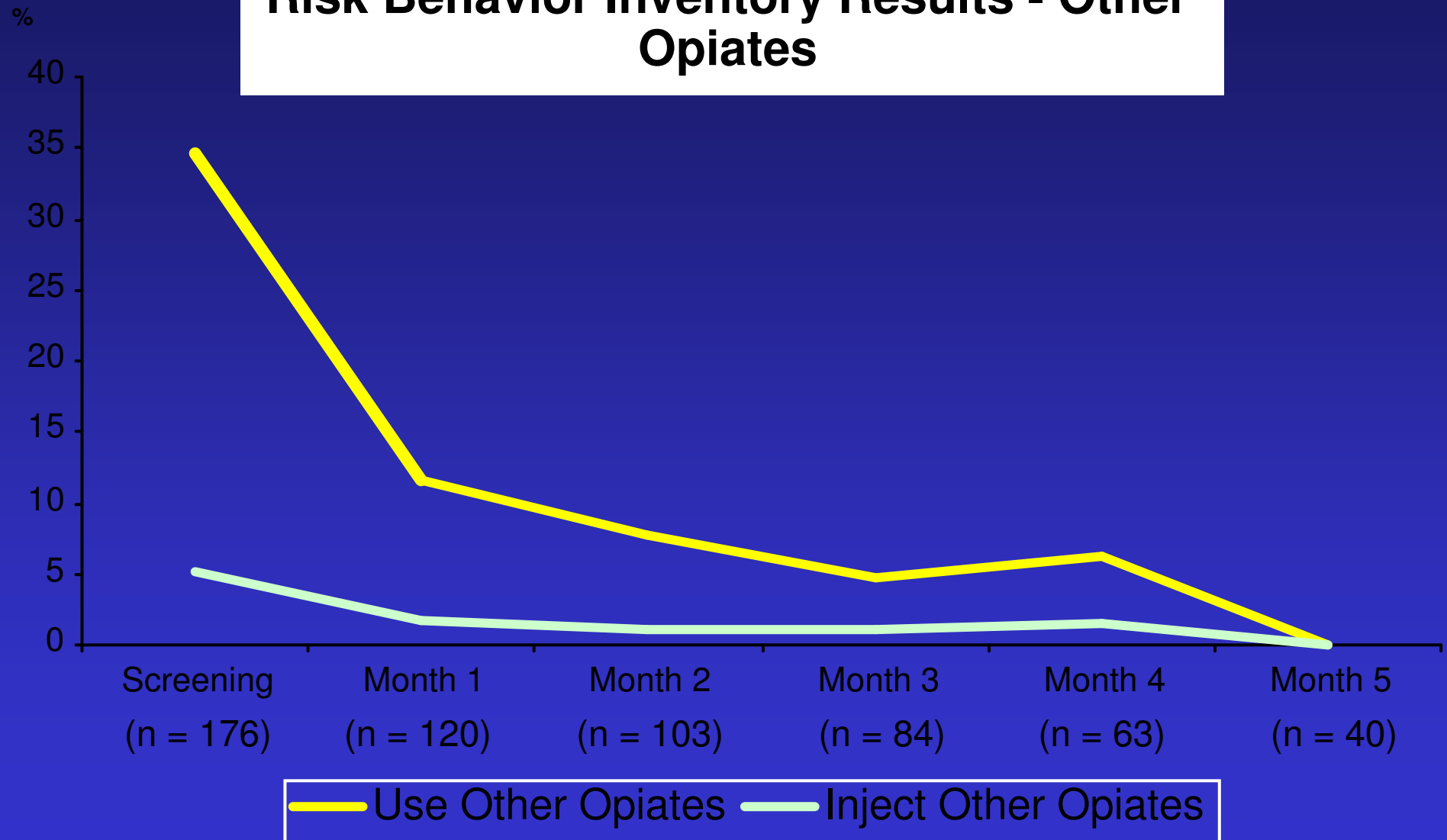
— Total — JHU — TJU — Vermont — Vienna — Vanderbilt



Drug Use during Pregnancy: Risk Behavior Inventory Results - Heroin



Drug Use during Pregnancy: Risk Behavior Inventory Results - Other Opiates



DOSES OF SYNTHETIC OPIOIDS AND INTENSITY OF NAS

*Management of neonatal abstinence syndrome in neonates born to opioid
maintained women;*

Ebner et al., DAD 87 (2007) 131

No significant correlation between mean daily doses of opioid in the 53 mothers (clean urines!) at delivery and intensity of NAS (Finnegan-scoring) could be found for either substances:

– methadone: $r = 0.170, p = 0.474$

– slow-release morphine: $r = -0.012, p = 0.967$

– buprenorphine: $r = 0.360, p = 0.206$

Significant lower occurrence of NAS in buprenorphine group $p=0.002$

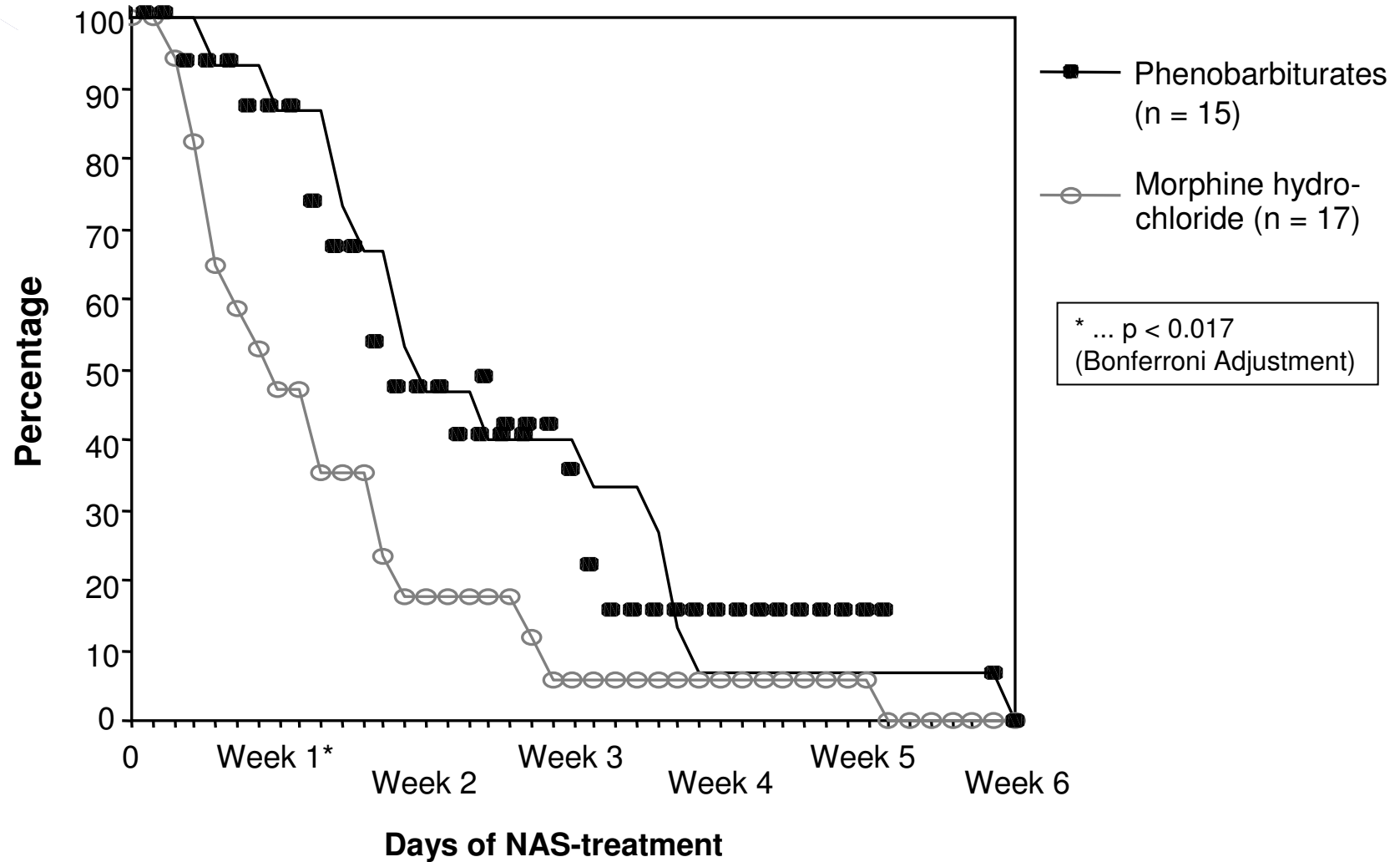
Onset of NAS after delivery (mean)

–SROM: 32 h post delivery

–methadone: 34 h post delivery

–buprenorphine: 58 h post delivery

Ebner N., Rohrmeister K., Winklbaur B., Baewert A., Jagsch R., Peternell A., Thau K., Fischer G. Management of neonatal abstinence syndrome in neonates born to opioid maintained women. Drug & Alcohol Dependence 87 (2007) 131-138



Prospective randomised comparative study of the effect of buprenorphine, methadone and heroin on the course of pregnancy, birthweight of newborns, early postpartum adaptation and course of the neonatal abstinence syndrome (NAS) in women followed up in the outpatient department

Binder & Vavrinková, *Neuroendocrinology Letters* 2008

→ *No information about urinetoxicology*

Demographics

	Heroin (n=47)	Buprenorphine (n= 38)	Methadone (n=32)
mean age	26.6 (22-29)	25.4 (23-28)	26.8 (23-29)
Duration of addiction (years)	4.2 (3-5)	3.9 (3-5)	4.4 (4-5)
No. of visits in Perinatal Care Unit	5.8 (5-7)	6.4 (5-7)	7.2 (5-10)

Birth - outcome

*p =0.003 (heroin-BUP),
p =0.007 (BUP-MET)

	Heroin (47)	Buprenorphine (38)	Methadone (32)
Premature labours (week 34-37)	14 (29.8%)	10 (26.8%)	7 (21.8%)
Birthweight* (g)	2601	3050	2900
Apgar score 1,5, 10 min.	8.9/9.5/9.8	8.4/9.3/9.7	8.7/9.3/9.6
Cesarean rate	4 (8.5%)	3 (7.9%)	2 (6.2%)

Results - NAS

- Duration of necessary treatment:
heroin (11 days) < BUP (11-12 days) < MET (30 days)
 - BUP-MET $p < 0.000001$
 - heroin-MET $p < 0.000001$
 - BUP-heroin not significant
- Severity of symptoms (Finnegan Score)
MET (17.5) < heroin (11) < BUP (8.2)
 - BUP-MET $p < 0.000001$
 - heroin-MET $p < 0.000001$
 - BUP-heroin not significant

Sublingual Buprenorphine for Treatment of NAS: A Randomized Trial

W.K. Kraft, MD^a, E. Gibson, MD^{b,c}, K. Dysart, MD^{b,c}, V.S. Damle, MS^{b,c}, J.L. LaRusso, DO^a, J.S. Greenspan, MD^{b,c}, D.E. Moody, PhD^d, K. Kaltenbach, PhD^b and M.E. Ehrlich, MD^{b,c,e}

Pediatrics 2008
122: (3) - 0601-0607

NAS - Treatment

Buprenorphine has never been administered to neonates with opioid abstinence syndrome

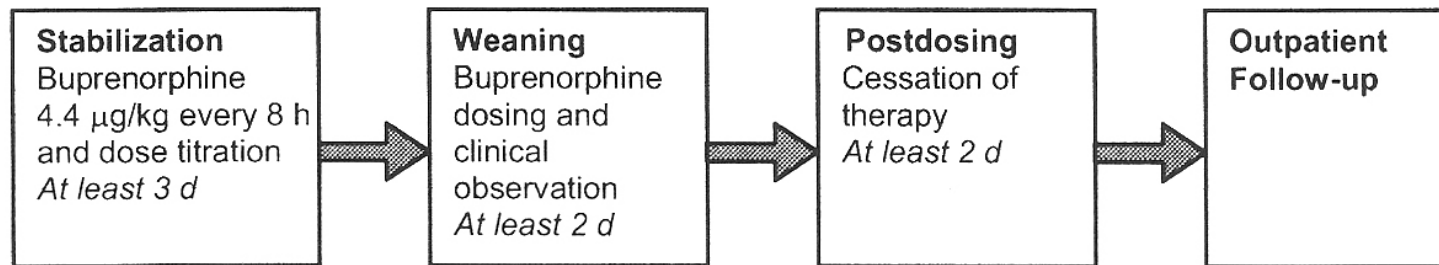
- Standard:

- Morphine in the form of neonatal opium solution (NOS)

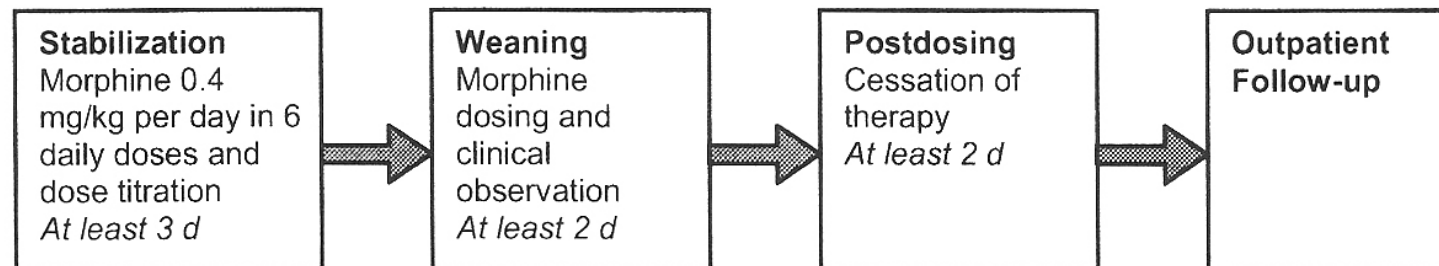
→ Exploration of the efficacy of Buprenorphine sublingually
(Buprenorphine 0.4 μg g/kg every 8 heures)
compared with standard-of-care treatment with NOS
(Morphine 0.4mg/kg per day in 6 daily doses)
- length of treatment
- length of stay

Dose Progression

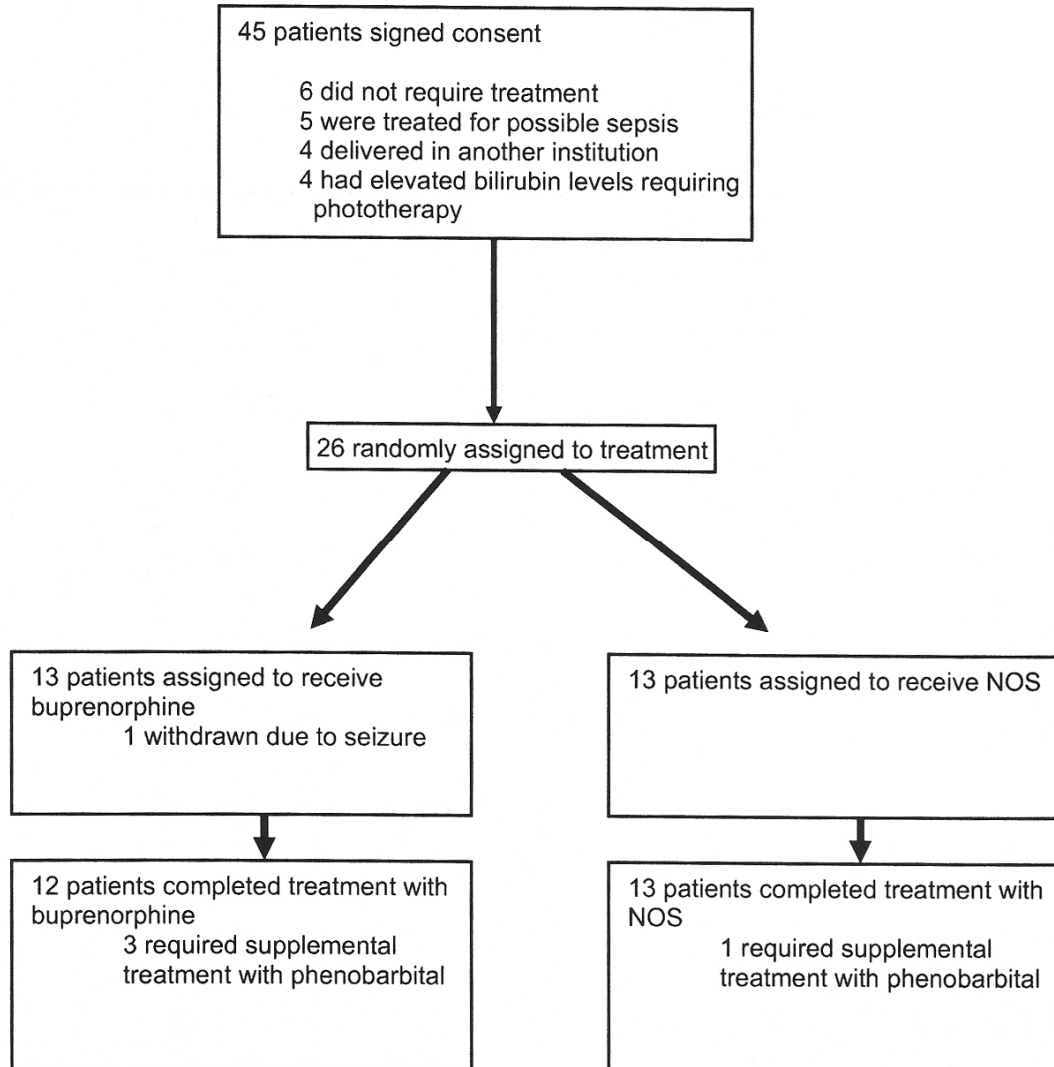
The dose progression for the buprenorphine arm



The dose progression for the morphine (in the form of NOS) arm



Disposition of enrolled Patients



- Single-site
- Open-label trial
- Conducted between IV / 2005 and I/ 2008
- NAS: modified Finnegan Scale

Demographic Data

Characteristic	NOS	Buprenorphine	P
N	13	13	
Gender			
Male	7	10	
Female	6	3	
Onset of treatment after birth (mean, SD) (days)	2.8 (1.6)	2.5 (1.1)	.4
Gestational age (mean) (week)	38.7	39.3	.9
Birth weight (gramm)	3020	2985	.97
1-min Apgar score (mean)	8.2	7.3	.2
5-min Apgar score (mean)	8.8	8.5	.3

Efficacy - Results

- No significant difference between the clinical outcome variables length of treatment and length of stay
- Trend toward lower values in the Buprenorphine group

Parameter	Buprenorphine	NOS	p
n	12	13	
Length of treatment (days)	22	32	.077
Length of stay (days)	27	38	.068

Conclusion

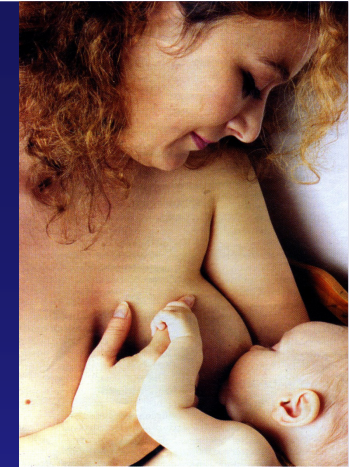
Treatment of NAS with sublingual Buprenorphine is feasible and has an acceptable safety margin

There is a suggestion of improved efficacy in terms of length of stay and length of treatment

→ Suggestions need to be confirmed in further studies & *buprenorphine administration in neonates after intrauterine buprenorphine exposure*



BREASTFEEDING



YES

If no concomitant consumption or other stable medication than methadone or buprenorphine is taken

- *small concentration of opioids is detectable in breastmilk - but it will not treat sufficiently NAS*
- *Special care in weaning of neonates*

Limitations:

- *HIV*
- *Hepatitis C - decision depending on viral load by pediatrician*

Summary

MULTIDISCIPLINARY & INTERDISCIPLINARY

Opioid Maintenance keeps women in treatment:

- Pregnancy counselling
- Multi-professional approach is wanted
- Dose increase may be required (twice daily with methadone)
- Breast feeding should be encouraged
- Detoxification – limited success
- Contingency management might reduce illicit drug use

MORE RESEARCH

- Carefully interpretation of literature:
 - Comorbidity of pregnant women
 - Nicotine influence
 - Concomitant medication
 - Conclusion towards methadone/buprenorphine without structured information (urinetoxiology) during pregnancy
 - How is NAS evaluated - which treatment applied

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