THS – BIARRITZ 2011

MEDIZINISCHE UNIVERSITÄT WIEN

Opioid dependent pregnant women

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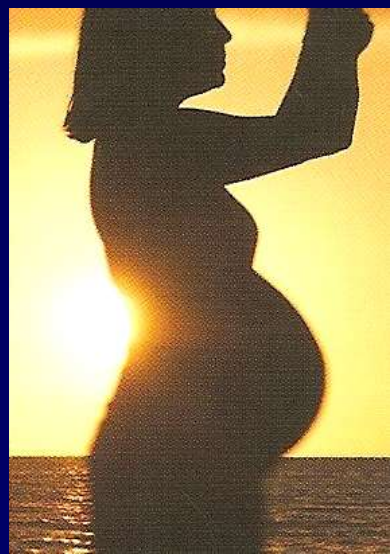


National Institute on Drug Abuse:
R01DA018417
EU- grants & ÖNB grant

www.nature.com/nature
Vol 465 | Issue no. 7299 | 10 June 2010

Putting gender on the agenda

(Editorial)

“ Medicine as it is currently applied to women is less evidence-based than that being applied to men.”

- How to deal with the most fundamental sex difference: Pregnancy ?
  - Pregnant women get ill, and sick women get pregnant...
  - Entering pregnant women in clinical trials is problematic – for ethical reasons — the result is that physicians prescribe drugs whose effects during pregnancy are poorly known.
  - One possible solution: systematic retrospective data collection from women who had no choice but to take an unproven drug while they were pregnant.

- Drug regulators should ensure that physicians and the public alike are aware of sex-based differences in drug reactions and dosages.
- Medical-school accrediting bodies should impress the importance of training physicians in how disease symptoms and drug responses can differ by sex.
- More women into the senior ranks of science?
- The research community can take a number of steps to address this problem.
  - ↗ Journals can insist that authors document the sex of animals in published papers
  - ↗ Funding agencies should demand that researchers justify sex inequities in grant proposals

- These may be the first steps in the direction of ***truly personalized*** medicine —
  what, after all, is more personal than sex.

Importance of a strong ethical framework

The concept of the fetus as a patient plays an essential role in the ethically justified design and conduct of pharmacologic treatment & research in pregnant women (development of medication)

McCullough L.B., Coverdale J.H., Chervenak F.A. (2005). A comprehensive ethical framework for responsibly designing and conducting pharmacologic research that involves regnant women. American Journal of Obstetrics and Gynecology, 193, 901-97.

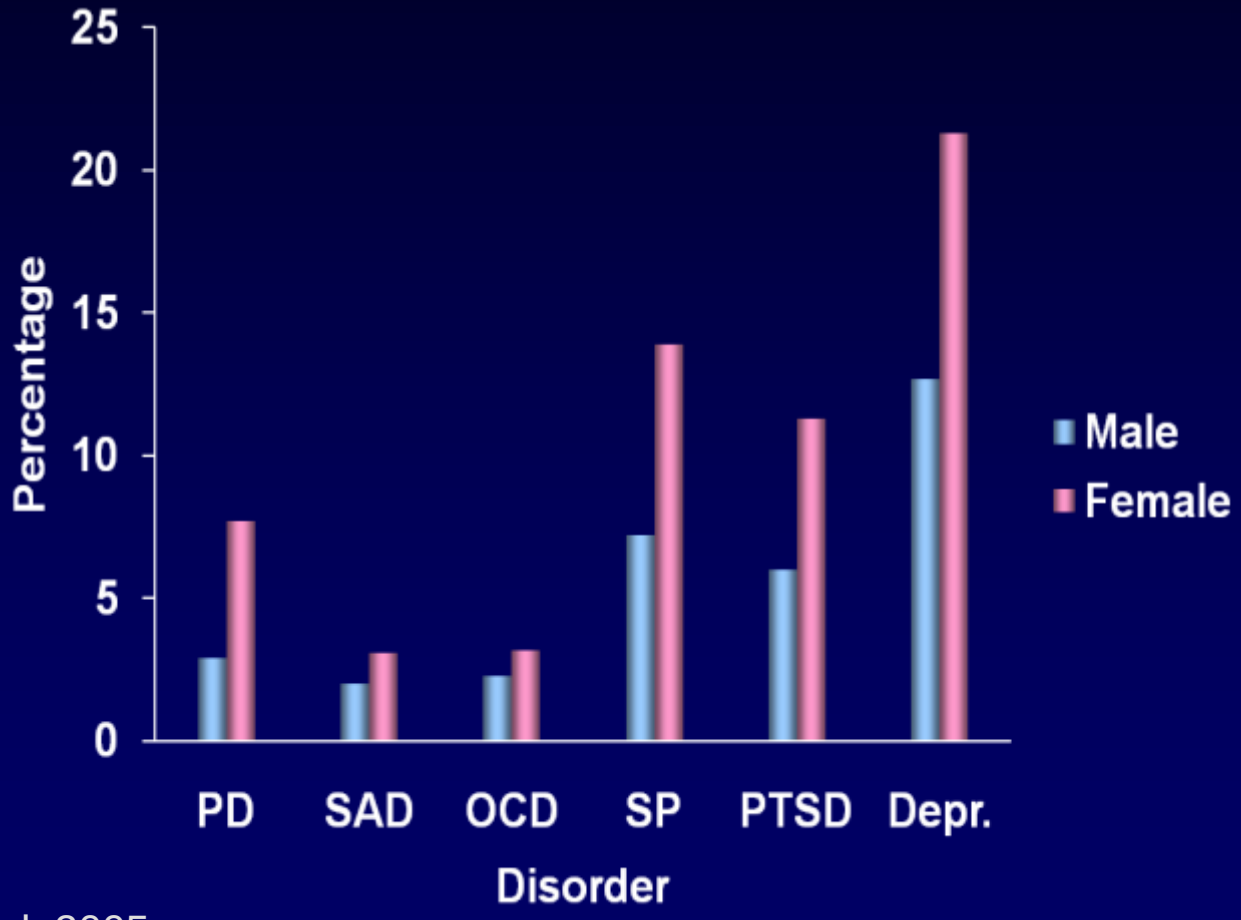
Enrolling pregnant women in research

- Women who gave birth annually
  - 4 million women in US
  - 131 million worldwide
    - 64% in the U.S. are given prescriptions for medications for chronic medical or acute problems during pregnancy (excluding vitamins and minerals)
- Risks of research on pregnant women and fetus can be minimized
  - Regard benefits to a fetal patient & Informed consent
- If pregnant women are generally excluded
  - No benefits
- **Pregnant women -> different pharmacokinetics**
  - Problems due to lack of data
    - incorrect dosing
    - ineffective subtherapeutic treatment
    - Drug resistance

Goldkind S.F., Sahin L., Gallauresi B. (2010). Enrolling Pregnant Women in Research – Lessons from the H1N1 Influenza Pandemic. ***The New England Journal of Medicine, 362, 2241-2243.***

Pregnancy

Sex and mood disorders: prevalence



Wittchen et al, 2005.

Co-morbidity

- **Epidemiological Data: Around 53% of individuals diagnosed with drug dependence also had another psychiatric diagnosis** (Regier et al; JAMA 1990; Kessler et al; Arch Gen Psychiatry, 1994)
  - Follow-up: 20% of individuals with substance use disorders had symptoms of a mood disorder, 17% symptoms of an anxiety disorder (Grant et al; Arch Gen Psychiatry, 2004)
- **Mood or anxiety disorders in opioid dependent pregnant** women showed a **negative effect on treatment outcomes** (Fitzsimons et al; J Subst Abuse Treat, 2007)
  - Depressed women were more likely tested positive for drugs during treatment
  - Babies born to women with mood disorders stayed longer in the neonatal intensive care unit (related to pharmacological medication)
- **Prevalence of psychiatric disorders during pregnancy is not well established**
  - M**ajor depression** during pregnancy is estimated between 7-16% higher risk occurring later in pregnancy (Bennett et al; Obstetrics & Gynecology 2004)
  - **Bipolar disorder** occurs much less frequently in the general population with a lifetime prevalence of 1%, but has a high rate of comorbidity with substance use disorders

Co-occurring Psychiatric Symptoms are Associated with Increased Psychological, Social & Medical Impairment in Opioid Dependent Pregnant Women

Benningfield, M.M., Arria, A.M., Kaltenbach, K., Heil, S.H., Stine, S.M., Coyle, M.G., Fischer, G., Jones, H.E., Martin, P.R.

AM J Addict, 2010, 19(5): 416-421.

Co-occurring Psychiatric Symptoms are Associated with Increased Psychological, Social & Medical Impairment in Opioid Dependent Pregnant Women

- Assessment of prevalence of co-occurring psychiatric symptoms in an expanded sample & exploration of the relationship between psychiatric symptoms, severity of drug use & drug related problems

- **Cross-sectional data**
  - **n = 174 opioid dependent pregnant women** (18 - 41 yrs)
  - Part of: Maternal Opioid Treatment: Human Experimental Research **(MOTHER)** study

- **Inclusion criteria**
  - DSM-IV diagnose for current opioid dependence
  - Single pregnancy
  - No pending law case with the risk of imprisonment
- Exclusion criteria
  - Major psychiatric or somatic disorder
  - Any other substance dependence except nicotine & cannabis use

Benningfield, M.M., Arria, A.M., Kaltenbach, K., Heil, S.H., Stine, S.M., Coyle, M.G., Fischer, G., Jones, H.E., Martin, P.R. Co-occurring Psychiatric Symptoms are Associated with Increased Psychological, Social and Medical Impairment in Opioid Dependent Pregnant Women. AM J Addict, 2010, 19(5): 416-421.

Sample Characteristics (N=174)

Demographics	Mean (SD)
Age (years)	**27.3 (5.9)**
Estimated Gestational Age (weeks)	17.1 (6.3)
Education completed (years)	11.4 (2.0)
Race/Ethnicity:	**n (%)**
- Caucasian	145 (83.3)
- Black	24 (13.8)
- Other	5 (2.9)
Marital status:	
- Never married	125 (71.8)
- Married	22 (12.6)
- Widowed	3 (1.7)
- Divorced	12 (6.9)
- Separated	12 (6.9)
Employed	**23 (13.2)**

Demographics	Mean (SD)
Legal status:	
- No Legal Issues	140 (80.5)
- Parole	4 (2.3)
- Probation	24 (13.8)
- Impending trial	3 (1.7)
- Unknown/Other	3 (1.7)
Site:	
- Baltimore	33 (19.0)
- Burlington	30 (17.2)
- Detroit	19 (10.9)
- Philadelphia	30 (17.2)
- Providence	4 (2.3)
- Nashville	17 (9.8)
- Vienna	**41 (23.6)**

Benningfield, M.M., Arria, A.M., Kaltenbach, K., Heil, S.H., Stine, S.M., Coyle, M.G., Fischer, G., Jones, H.E., Martin, P.R. Co-occurring Psychiatric Symptoms are Associated with Increased Psychological, Social and Medical Impairment in Opioid Dependent Pregnant Women. AM J Addict. 2010; 19(5): 416-421.

Prevalence of psychiatric comorbidity

Psychiatric Symptoms	In%
One or more psychiatric diagnosis	**64,6**
Major Depression (MDD)	32
Dysthymia	31
Hypomanic episode	39
Anxiety disorders	
- Generalized anxiety disorder (GAD)	40
- Panic disorder	26
- Agoraphobia	22
Social Phobia	16
Post-traumatic Stress Disorder (PTSP)	16
Obsessive–compulsive disorder (OCD)	3
Bulimia	<1

Symtoms at some point in the past 30 days	In %
Depressive symptoms	48.6
Anxiety symptoms	40.0
Suicial thinking	12.6

-> A large majority of the sample showed symptoms of a co-occurring psychiatric illness

Benningfield, M.M., Arria, A.M., Kaltenbach, K., Heil, S.H., Stine, S.M., Coyle, M.G., Fischer, G., Jones, H.E., Martin, P.R. Co-occurring Psychiatric Symptoms are Associated with Increased Psychological, Social and Medical Impairment in Opioid Dependent Pregnant Women. AM J Addict, 2010, 19(5): 416-421.

ASI Composite Scores by Diagnoses

P values for Psychiatric Symptoms	Medical	Employment	Alcohol	Drugs	Legal	/Social	Psychological
MDD	**.007**	.973	.464	**<.001**	.702	**.001**	**<.001**
GAD	.125	.192	.923	**.003**	.325	**<.001**	**<.001**
Hypomania	**.023**	**.013**	.250	**.011**	.245	**.003**	**<.001**
Dysthymia	.155	.130	.020	**<.001**	.298	**<.001**	**<.001**
Panic Disorder	**.031**	**.002**	.593	.210	.441	**<.001**	**<.001**
Agoraphobia	.060	**<.001**	.798	.098	.465	**<.001**	**<.001**
Social Phobia	**<.001**	.406	.269	.121	.452	**.009**	**<.001**
PTSD	.072	.421	.821	**.005**	.618	**<.001**	**<.001**
Suicidality	.147	.430	.792	**.001**	.251	**.020**	**<.001**
Bulimia	.271	.373	.093	.075	.203	**<.001**	**<.001**
OCD	.985	**.017**	.483	.162	.569	**.051**	**<.001**

-> Women who endorsed co-occurring psychiatric symptoms showed severe impairment on the ASI

Benningfield, M.M., Arria, A.M., Kaltenbach, K., Heil, S.H., Stine, S.M., Coyle, M.G., Fischer, G., Jones, H.E., Martin, P.R. Co-occurring Psychiatric Symptoms are Associated with Increased Psychological, Social and Medical Impairment in Opioid Dependent Pregnant Women. AM J Addict, 2010, 19(5): 416-421.

Conclusion

- ***Findings highlight the importance of evaluating & treating co-occurring psychiatric illness in opioid dependent women during pregnancy***

- ***Unawarness of psychiatric co-morbidity yields often to***
  - ***Ongoing drug consumption (licit & illicit)***
  - ***Use of benzodiazepines (often prescribed)***
  - ***Negative influences on the course of pregnancy and related outcome***

Benzodiazepines

- *Categoriy D: There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective)*

SSRI use in pregnancy

- Retrospective, case-control epidemiological study to assess association between exposure to SSRI during late pregnancy and persistent pulmonary hypertension of the newborn (PPHN)

- Interviews within six months after delivery

- Selective Serotonin-Reuptake Inhibitors and Risk of Persistent Pulmonary Hypertension of the Newborn
  Chambers CD et al.
  N Engl J Med 2006;354:578-87

- Paroxetine FDA 2005 birth defects

Edvard Munch (1918-1919) “Women With Poppies”

Background on pregnancy & dependence

- >30% of opioid-dependent women are of child-bearing age;
- Estimated 30,000 pregnant women in Europe use opioids each year
- >50% have a co-dependent partner
- Improved treatment through ↑ opioid maintenance options
- Constantly ↑ numbers of patients maintained on opioids
- Opioids are not teratogenic
- ***However:***
  - ↗ Alcohol and cocaine are teratogenic
  - ↗ Benzodiazepines may be linked to ↑ orofacial malformation and prolonged neonatal abstinence syndrome (NAS)
  - ↗ Watch nicotine dependence → low weight for gestational age, preterm delivery, fetal tobacco syndrome (FTS)
  - ↗ Consider the influence of other psychopharmacological medication (eg antidepressants or atypical neuroleptic)
  - ↗ Drug–drug interaction (eg QT interval)

1) Winklbaur *et al*. Eur Addict Res. 2009;15(3):150–156. 2) Sanz *et al*. Lancet. 2005; 365:482–487.

Pregnancy and opioid dependence

- **Detoxification** would be ideal goal
  - ↗ Almost impossible to achieve without relapses and risk of destabilization during pregnancy

- Most experience with ***methadone*** and ↑ buprenorphine
  - ↗ Keeps women in medical treatment
  - ↗ ↑ retention
  - ↗ ↓ illicit consumption
- No registration studies available but many publications on the benefits during pregnancy
- Many “wrong“ conclusions drawn (eg outcomes being a direct consequence of opioid medication)
- Still heterogenous approach of NAS medication – morphine should be the drug of choice[1–3]

1) Winklbaur B et al. 2008. 2) Jones et al. 2008. 3)Fischer et al., 2000.

Neonatal Abstinence Syndrom (NAS)

- CNS hyperirritability and dysfunction of the autonomic nervous system, GI tract, and respiratory system[1]
- NAS is a treatable consequence of the abrupt discontinuation of opioid exposure at delivery[3]
- Methadone associated NAS often requires prolonged hospitalization, medication and monitoring[2]
- Buprenorphine leads to weaker NAS[7]
- Majority of studies report about no sign. correlation of mean dosing at delivery & intensity nor frequency of NAS
- NAS is also related to non-opioid exposure (eg antidepressants), neuroleptics and tobacco (FTS)[7]
- Heterogeneity in applied instruments and treatment[4]

1) Finnegan & Kaltenbach. Neonatal abstinence syndrome. In Primary Pediatric Care (Second Edition). Eds. Hoekelman *et al*. 1367–78 (St. Louis: Mosby, 1992). 2) Jones *et al*. Am J Addict. 2008; 17:372–386. 3) Winklbaur *et al*. Addiction. 2008; 103:1429–1440. 4) Kaltenbach *et al*. Ob Gyn Clinics in North Am. 1998; 25:139–151. 5) Kandall *et al*. Pediatrics. 1976; 58:681–685. 6) Finnegan. J Psychoactive Drugs. 1991; 23:191–201. 7) Winklbaur *et al*. Eur Addict Res. 2009; 15(3):150–156.

We talk about treatment & not a "religion"

- **Methadone:**
  - Long & most experience (1965)
  - World wide high coverage
  - Solution
    - Polamidon (Germany)

- **Buprenorphine:**
  - Long experience (around 1995)
  - Increased coverage
  - Subliqual tablets

Methadone

Oral slow release - morphine (SROM) vs methadone in pregnancy

Fischer et al., 1999
Addiction 94 (2), 231-238

- 100% retention
- Both substances are safe and well tolerated
- Healthy neonates, no significant differences
- Both induce a NAS - no difference in intensity and duration of NAS (mean 16 days)

- **But:** Significant lower concomitant consumption of heroin and benzodiazepines in SR-morphine-group

- **Limitations:**
  - SR-morphine was given twice a day in contrast to methadone once a day
  - Use of phenobarbiturates in the treatment of NAS

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 opioid doses in 53 mothers at delivery & intensity of NAS (Finnegan - scoring):
  - methadone: r = 0.170, p = 0.474
  - slow-release morphine: r = -0.012, p = 0.967
  - buprenorphine: r = 0.360, p = 0.206
- Significant less 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
- Mean onset of NAS in others (**after last medication**):
  - Methadone group: 60 hrs
  - Buprenorphine group: 72 hrs

Methadone vs. Buprenorphine - „state of the art“ therapy ?

• Methadone enhances maternal and neonatal outcomes relative to no treatment or medication-assisted withdrawal [6, 10,11]

• Methadone *combined with comprehensive care* during pregnancy is associated with positive maternal and infant outcomes [6, 11-13]

• Buprenorphine has been shown to be effective in the treatment of opioid dependence [15]

• Buprenorphine has lower intrinsic receptor efficacy (i.e., less receptor-activation than a full mu-opioid agonist) and results in a less-than-maximal opioid effect (i.e., a ceiling/plateau effect) [16] which can be related to a weaker NAS

6. Winklbaur, B., *et al.* 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. *Addiction* **103**, 1429-1440 (2008).
10. Jones, H.E., O'Grady, K.E., Malfi, D., & Tuten, M. Methadone maintenance vs. methadone taper during pregnancy: Maternal and neonatal outcomes. *Am J Addict* **17,** 372-386 (2008).
11. Kaltenbach, K., Berghella, V., & Finnegan, L. Opioid dependence during pregnancy: Effects and management. *Ob Gyn Clinics in North Am* **25**, 139–151 (1998).
12. Kandall, S.R.,*et al*. Differential effects of maternal heroin and methadone use on birth weight. *Pediatrics* **58**, 681–85 (1976).
13. Finnegan, L.P. Treatment issues for opioid-dependent women during the perinatal period. *J Psychoactive Drugs* **23**, 191–201 (1991).2. Connaughton, J.F., Reeser, D. & Finnegan, L.F. Pregnancy complicated by drug addiction. In: *Perinatal Medicine: Management of the High Risk Fetus and Neonate,* ed. R. Bolognese & R.H. Schwartz, 259-272. (Baltimore, Williams & Wilkins,1977).
15. Mattick, R.P., Kimber, J., Breen, C., & Davoli, M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2008 Apr 16;(2):CD002207.
16. Walsh, S.L., Preston, K.L., Bigelow, G.E., & Stitzer, M.L. Acute administration of buprenorphine in humans: Partial agonist and blockade effects. *Pharmacol Exp Ther* **274,** 361-372 (1995)

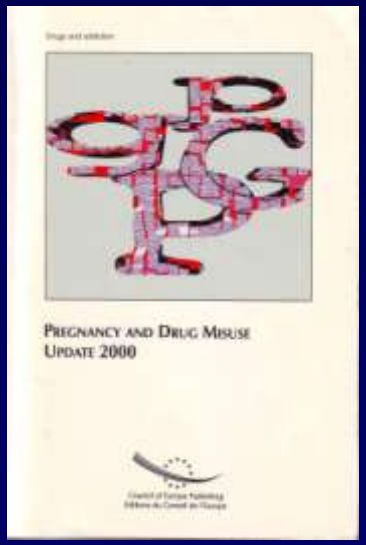
REVIEW ARTICLE

The Opioid Dependent Mother and Newborn Dyad: Nonpharmacologic Care

Martha Velez, MD, and Lauren M. Jansson, MD

J Addict Med • Volume 2, Number 3, September 2008

Council of Europe
1998:ISBN: 92-871-3784-6



NATIONAL NETWORK OF THE ADDICTION CLINIC

Employment office

General Hosp. of Vienna - addicted patients

Inspectorate for traffic safety

Child & Adolescent Psychiatry

Addiction Clinic

Multiprofessional:
medicine, nursing service, social casework, psychology, pharmacy neuropsychology

External institutions for addiction therapy

infection treatment wards

HIV

Hepatitis

Otto Wagner Hospital/ other hospitals

Dept. of Obstetrics & Gynecology

Dept. for Pediatrics

Chemical Laboratory Diagnostics

Federal Ministry of Health

Rosenhügel Psychiatry for Children & Adolescents

Social Casework Vienna

Prison

Justice

Police

Youth wel-fare services

Lawyers

psycho-social services

GP`s

Gabriele Fischer 2009

Euro Addict Res 1998 (4) 32 – 36.

Buprenorphine maintenance in pregnant opiate addicts

Fischer, Etzersdorfer, Eder, Jagsch, Langer, Weninger

RESEARCH REPORT

Addiction, 2003

Neonatal outcome following buprenorphine maintenance during conception and throughout pregnancy

Shird Dieter Schindler[1], Harald Eder[1], Romana Ortner[1], Klaudia Rohrmeister[2], Martin Langer[3] & Gabriele Fischer[1]

RESEARCH REPORT

doi:10.1111/j.1360-0443.2006.01321.x

Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study

Gabriele Fischer[1], Romana Ortner[1], Klaudia Rohrmeister[2], Reinhold Jagsch[4], Andjela Baewert[1], Martin Langer[3] & Harald Aschauer[1]

Buprenorphine in pregnancy:relevant facts

- Most data from French „naturalistic retrospective studies“
  - Results: buprenorphine safety in pregnancy & conception

Jernite et al, 1999; Lejeune et al, 2001; Gourarier et al, 2002; Lacroix et al, 2004; Lejeune et al, 2006, Lejeune C et al. Drug Alcohol Depend. 2006; 20;82(3):250-7, Simmat- Durand L et al. Eur J Obstet Gynecol Reprod Biol. 2009; 142(2):119-23.

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

- Prospective trials with standardised study design in women & 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

- RCTs: methadone & buprenorphine; double-blind, double-dummy
  - Jones et al, DAD 2005 ; Fischer et al, Addiction 2006
- Multisite double-blind double-dummy comparison: Bup vs Meth „MOTHER“

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2286 THIS WEEK AT NEJM.ORG

- 6 US Sites
  - leading site = Johns Hopkins
- 1 Canadian (Toronto)
- 1 European (Vienna)

ORIGINAL ARTICLE

Neonatal Abstinence Syndrome after Methadone or Buprenorphine Exposure

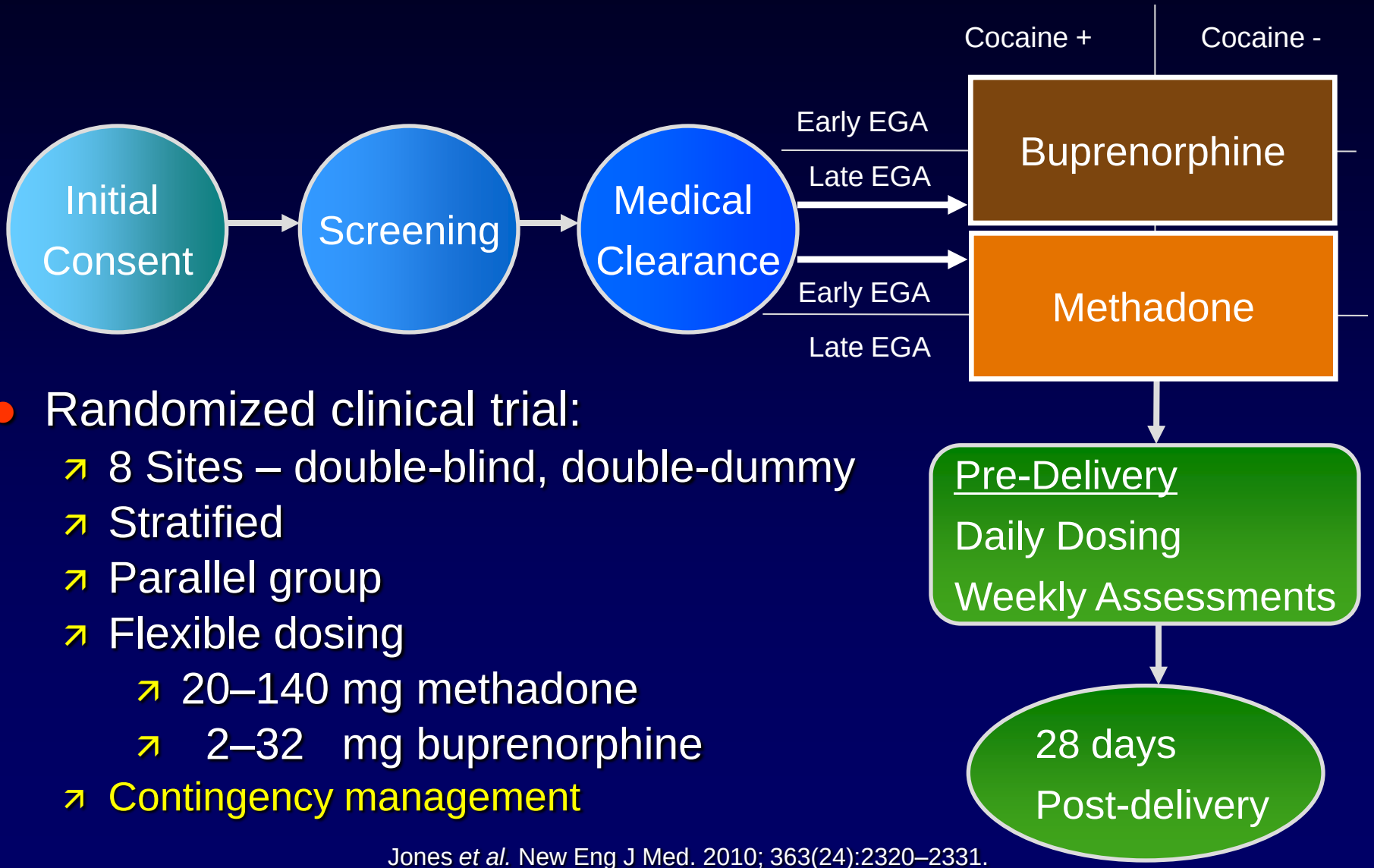
Hendrée E. Jones, Ph.D., Karol Kaltenbach, Ph.D., Sarah H. Heil, Ph.D., Susan M. Stine, M.D., Ph.D., Mara G. Coyle, M.D., Amelia M. Arria, Ph.D., Kevin E. O'Grady, Ph.D., Peter Selby, M.B., B.S., Peter R. Martin, M.D., and Gabriele Fischer, M.D.

„ Mother Study“:

Maternal Opioid Treatment: Human Experimental Research

R01 NHI DA018417-01

MOTHER Experimental Design



- Randomized clinical trial:
  - 8 Sites – double-blind, double-dummy
  - Stratified
  - Parallel group
  - Flexible dosing
    - 20–140 mg methadone
    - 2–32 mg buprenorphine
  - Contingency management

Jones *et al.* New Eng J Med. 2010; 363(24):2320–2331.

MOTHER - Procedure

- While receiving rapid-release-morphinesulfate to prevent withdrawal, participants completed a comprehensive screening assessment battery characterizing their obstetrical, medical, and psychiatric health
- Randomization to methadone or buprenorphine and transitioned to double-blind, double-dummy, study medication administered daily with sublingual tablets (buprenorphine or placebo) followed by oral liquid (methadone or placebo)
- Flexible dose range of 2 to 32 mg of buprenorphine (Subutex) and 20 to 140 mg of methadone was used
- To reduce concomitant drug use: monetary vouchers for providing urine samples thrice weekly that tested negative for opioids and other illicit drugs
- Using a modified Finnegan Scale, all neonates were repeatedly evaluated for NAS for a minimum of 10 days by trained staff
- During the first post-partum month, participants were offered a choice of treatment options which depended upon local availability

NAS - Primary Outcomes

Selection of *a priori* five primary outcome measures:

1) Treated for NAS
2) NAS peak score (?)
3) Total amount of morphine
4) Days of infant hospital stay (?)
5) Head circumference

St***atistics:*** Bonferroni was used to set α= 0.1 (nominal α=.05/5), but end-of-trial α was .0091 for each primary outcome measure***.***

Secondary outcomes

key indicators of neonatal and maternal health and well-being

Secondary Neonatal Outcomes

1) Days medicated for NAS
2) Birthweight
3) Infant length (?)
4) Pre-term (< 37 weeks) birth
5) Gestational age at delivery
6) Apgar score at 1 minute (?)
7) Apgar score at 5 minutes (?)

Secondary Maternal Outcomes

1) Cesarean section (?)
2) Maternal weight gain
3) Non-normal presentation Anesthesia during delivery
4) Drug screen at delivery (?)
5) Medical complications at delivery
6) Discontinued from study
7) Amount of voucher money earned for drug-negative tests
8) Number of prenatal obstetrical visits

Bonferroni's principle was likewise used to set familywise α=.003125 (nominal α=.05/16) for the secondary outcome measures

Concomitant variables

1) number of days of study medication

2) average daily number of cigarettes smoked during study enrollment

3) percent of cocaine-positive urine toxicology

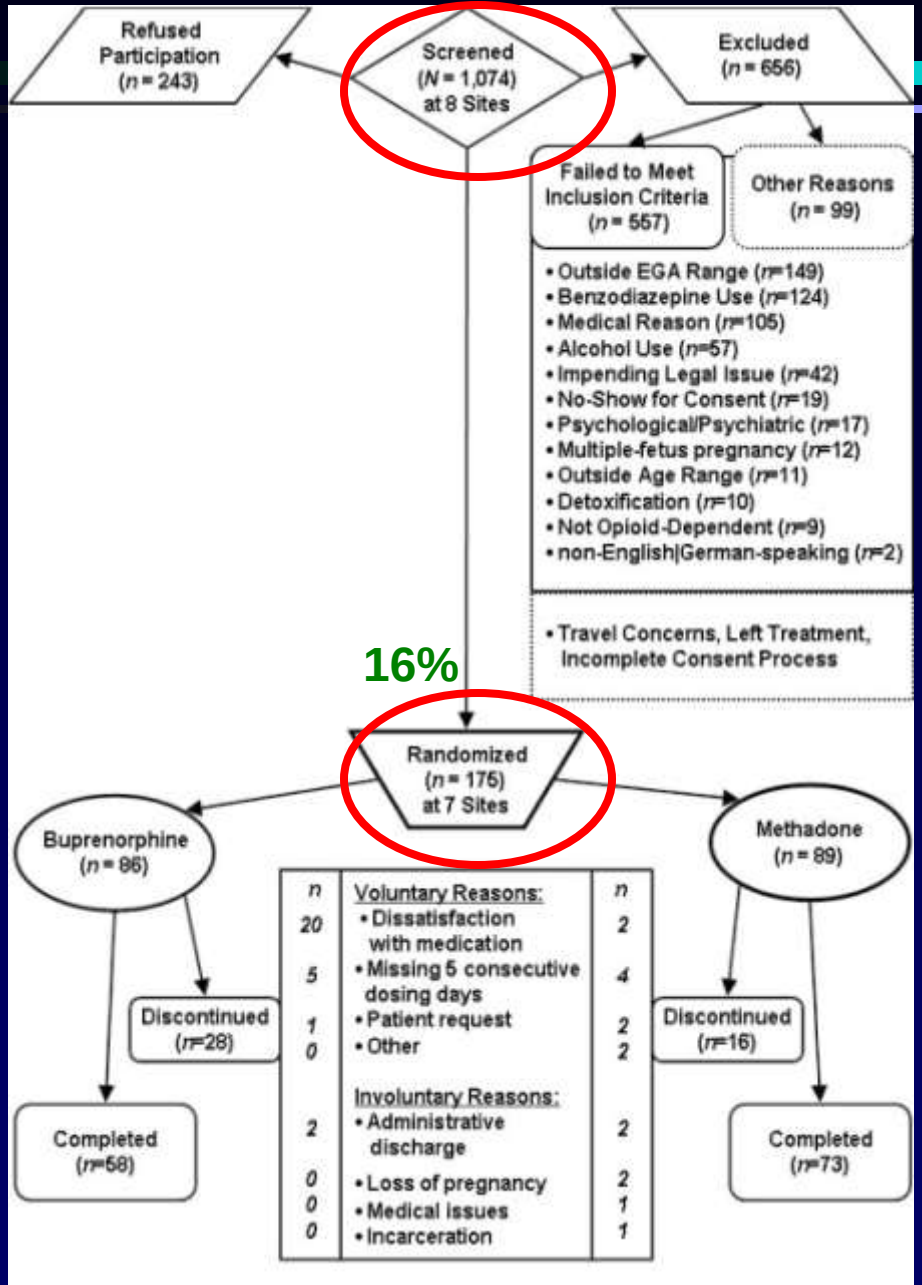
4) exposure (yes vs. no) to serotonin specific reuptake inhibitor (SSRI) medications during study enrollment

5) number of prenatal obstetrical visits during study enrollment

6) estimated gestational age at delivery (except when estimated gestational age at delivery was the outcome measure)

7) maternal urine toxicology results (positive vs. negative) in the 28 days prior to delivery (in coherence with NAS)

Recruitment – 7 centers recruited

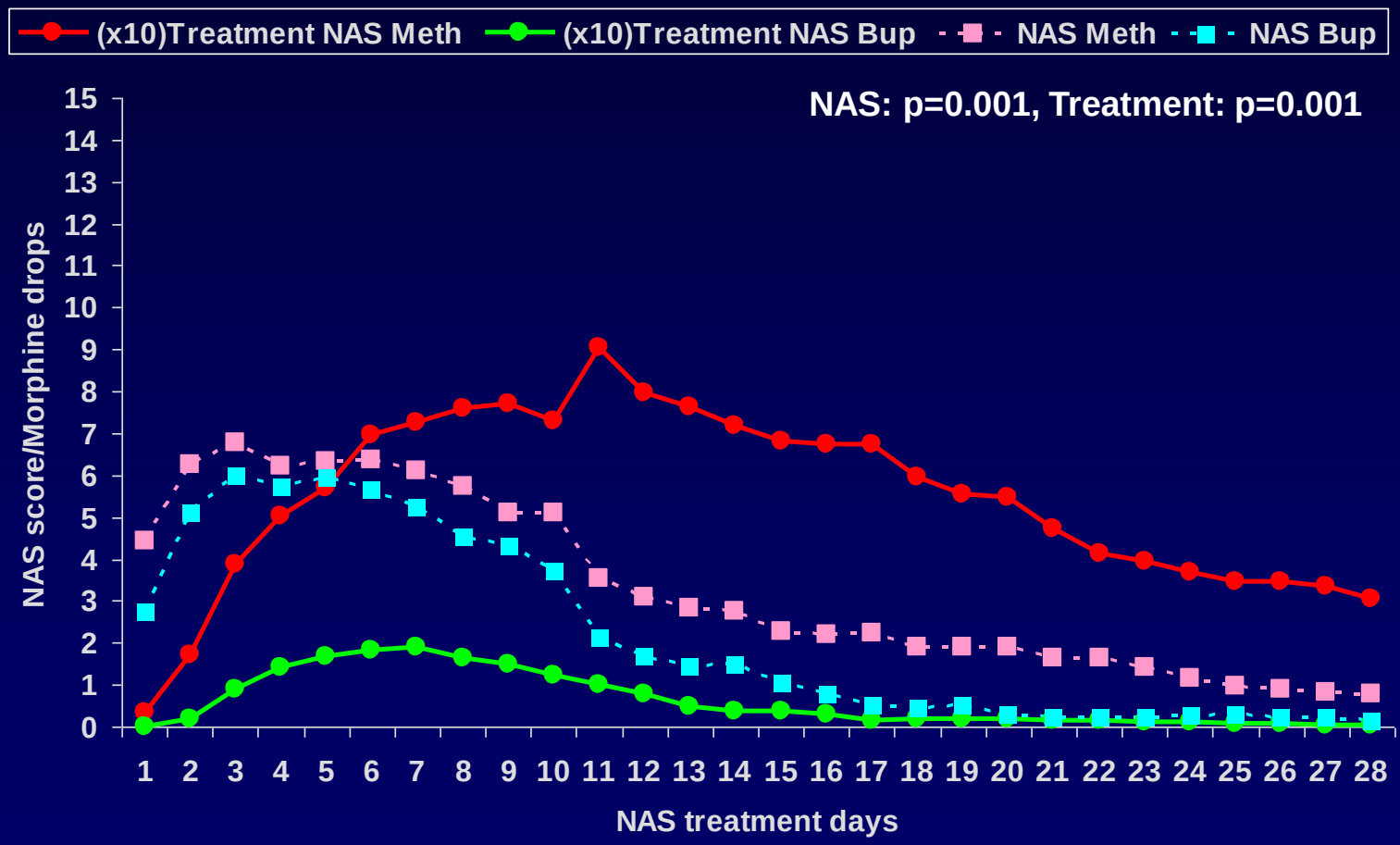


2 fixed-effect factors in all analyses: *medication (bup vs meth)* and *site* [US Urban (Baltimore, Philadelphia, Detroit, Providence,) *v. US Rural (Burlington, Nashville) vs European (Vienna)*

- **131 completers (12% of screened population)**
- no relevant differences on demographics between medication groups

Course and treatment of NAS

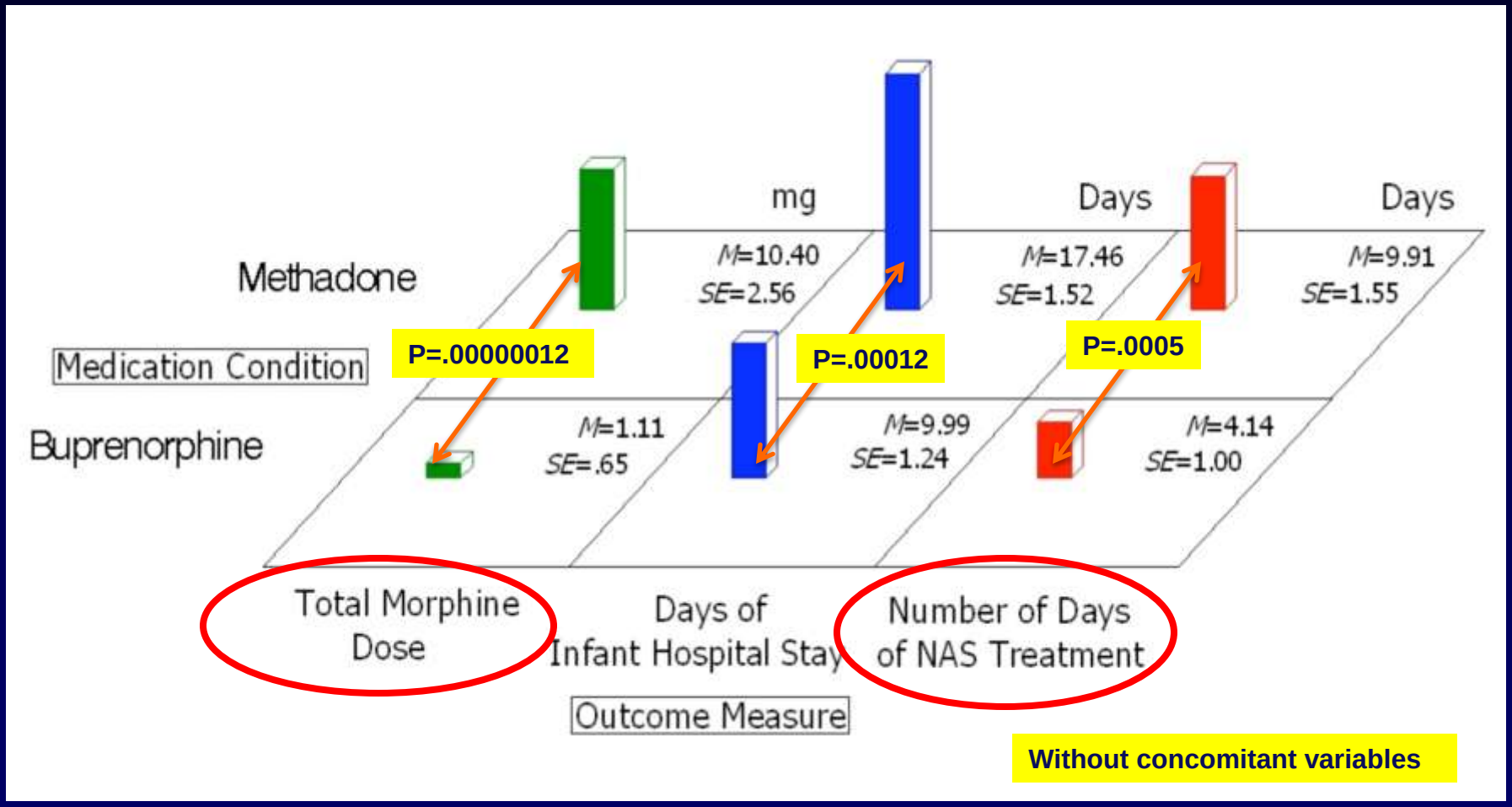
- Total sample: 131
- Treatment: 68 (52%) - 57% meth vs 47% bup / p = 0.26



Secondary Neonatal Outcomes	Methadone Mean (*SE*)	Buprenorphine Mean (*SE*)	Odds Ratio (*Confidence Interval*)	*p*
Days medicated for NAS	*9.91 (1.55)*	*4.14 (1.00)*		*<.0031 25*
Birthweight (gm)	2878.46 (66.27)	3093.66 (72.61)		.83
Infant length (cm)	47.83 (.47)	49.83 (.52)		.0049
Pre-term (<37 weeks) birth [Yes]	{19%}	{7%}	.33 (.06, 1.98)	.069
Gestational age at delivery (weeks)	37.94 (.28)	39.06 (.31)		.0069
Apgar score at 1 minute	8.03 (.19)	8.08 (.21)		.87
Apgar score at 5 minutes	8.95 (.12)	9.03 (.13)		.69

Note. Significant results are in italics. Bonferroni's principle was used to set familywise α =.003125 (nominal α = .05/16) for the secondary outcome measures.

Total Morphine Dose, Days of Infant Hospital Stay, and Number of Days of NAS Treatment



Results:
Medication Condition Differences (sign.)

Outcome Measures	without concomitant variables			with concomitant variables		
Total N = 131	Methadone n = 73	Buprnorphine n = 58	P-Value	Methadone n = 73	Buprenorphine n = 58	P-Value
Primary Outcomes						
Total amount of morphine for NAS in mgs., *mean (SE)*	10.40 (2.56)	1.11 (.65)	< .0001	10.30 (2.50)	1.05 (.57)	< .0001
Days of infant hospital stay, *mean (SE)*	17.46 (1.52)	9.99 (1.24)	.00012	16.88 (1.67)	2.35 (.13)	.0015
Secondary Neonatal Outcomes						
Days medicated for NAS, *mean (SE)*	9.91 (1.55)	4.14 (1.00)	.0005	11.03 (2.16)	4.29 (1.14)	.0005

Characteristics of Non-Completers (N = 44)

	Methadone n = 16	Buprenorphine n = 28	P-Value
Days remained in the study, *mean (SD, range)*	35.1 (35.2, 4 - 155)	8.6 (17.2, 0 - 80)	.002
doses at the time of drop-out in mgs., *mean (SD, range)*	87.3 (21.8, 41.3 - 133.2)	14.3 (5.9, 3.0 - 30.0)	---
dissatisfaction with the medication as reason for leaving, *% of drop-outs, (n)*	12.5 (2)	71.4 (20)	<.001

Discussion drop-out Buprenorphine induction related

- buprenorphine induction too slow
- maximum buprenorphine dose too low
- individual variation in absorption of sublingual buprenorphine tablets
- abruptly ceasing buprenorphine may be more comfortable for patients than ceasing methadone due to buprenorphine's milder withdrawal
- buprenorphine may provide less agonist effects than methadone to mitigate cravings and withdrawal
- ***Influence on site differences***

Summary facts of total „Mother“ sample

- 175 (16%) randomized
- 131 (12%) completed
  - ↗ 44 drop-outs
    - 16 meth vs 28 bup
- 131 neonates investigated
  - ↗ 55.7% meth (n = 73) vs 44.3% bup (n = 58) / p = 0.293
- 68 NAS to treat (52% of sample)
  - ↗ 57% meth vs 47% bup / p = 0.26

- Total amount of morphine for NAS (mg)
  - ↗ 10.40 meth vs 1.11 bup / p <.0091
- Days medicated for NAS
  - ↗ 9.91 meth vs 4.14 bup / p <.003125

Jones *et al.* New Eng J Med. 2010; 363(24):2320–2331.

„Contingency – Management“

(except THC & nicotine) – Vienna site

(drop out: 10%)

Total amount of money dispensed	72. 911 ,- €
Mean amount of money earned per mother	1. 696 ,- € (Range: 28 - 3. 089,-)
Mean duration of study participation	22,1 Wochen (Range 6 - 40, SD = 6.3)
Mean gestational age at delivery in weeks	38.4 - *15% < 37 SSW* (Range 29-42, SD = 2.40)

Higgins S. & Petry N. 1999. Contingencymanagement. Incentivesforsobriety. *Alcohol Res Health 23* (2): 122-127.

Higgins S. et al. 2004. Clinical implicationsofreinforcementas a determinantofsubstanceusedisorders. *AnnuRevPsychol 55*: 431-461.

Costs of preterm deliveries in UK in €/ infant

	Preterm delivery (< 37 weeks)	Early preterm delivery (< 33 weeks)	Very early preterm delivery (< 28 weeks)
Prevalence of live births	7.17	1.71	0.48
Costs for delivery	443,-	974,-	2.425,-
Costs for neonatal care	28.993,-	79.447,-	116.230,-
Costs for inpatient treatment until age of 18 yrs	29.762,-	81.152,-	120.495,-
Costs for outpatient treatment until age of 18 yrs	761,-	1.104,-	2.187,-
Costs for medical and social care until age of 18 yrs	30.775,-	83.015,-	124.913,-
TOTAL	90.734,-	245.692,-	466.250,-

Mangham et al. 2009. The Cost of Preterm Birth Throughout Childhood in England and Wales. *Pediatrics* 123: e312-327

Addiction

CASE SERIES

doi:10.1111/j.1360-0443.2011.03440.x

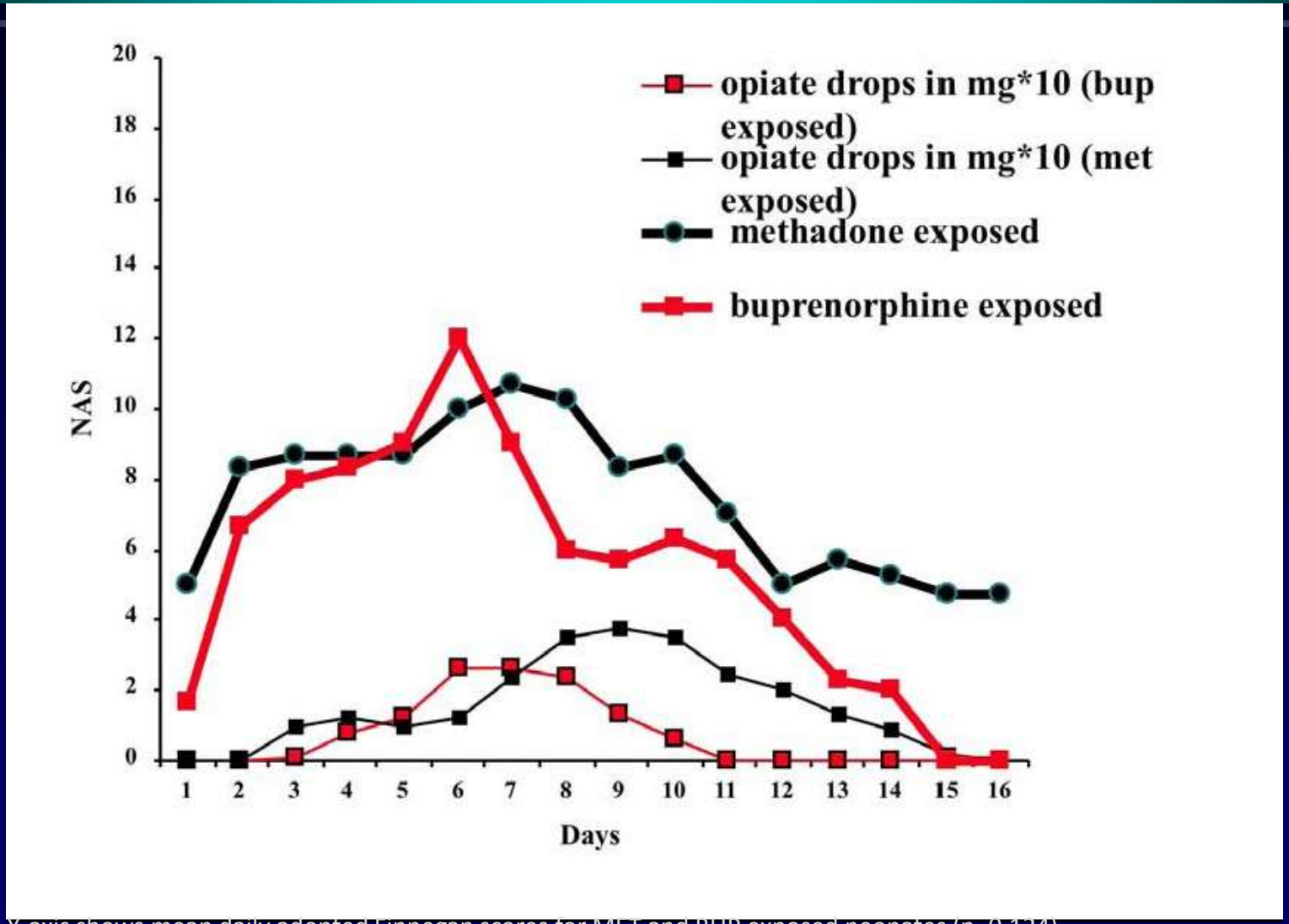
Randomized controlled trials in pregnancy: scientific and ethical aspects. Exposure to different opioid medications during pregnancy in an intra-individual comparison

Annemarie Unger[1], Reinhold Jagsch[2], Hendree Jones[3], Amelia Arria[4], Harald Leitich[5], Klaudia Rohrmeister[6], Constantin Aschauer[1], Berndadette Winklbaur[1], Andjela Bäwert[1] & Gabriele Fischer[1]

Results: sample characteristics

	MOTHER 1		MOTHER 2		MOTHER 3	
	Baby 1	Baby 2	Baby 1	Baby 2	Baby 1	Baby 2
Medication exposure	METHADONE	BUPRENORPHINE	METHADONE	BUPRENORPHINE	BUPRENORPHINE	METHADONE
Mother's age (years)	25	26	24	25	34	35
Estimated gestational age at study entry (weeks)	14	28	15	23	15	21
Parity	1	2	2	3	5	6
Number of study days	192	93	194	136	211	141
Voucher sum (EUR)	2201	766	2227	892	2310	1344
Cigarettes per day	15	15	10	20	20	20
Prior medication	300 mg SROM	50mg MET	50mg SROM	40mg MET	8mg BUP	18mg BUP
Morphine dose at induction	250mg	300mg	65mg	180mg	240mg	540mg
Dose at delivery	90mg	16mg	40mg	8mg	16mg	115mg
Dose 10 days post partum	90mg	10mg	40mg	8mg	14mg	100mg
Pos. urine screens	18.3%	7.9%	15.6%	21.8%	11.7%	11.8%
NAS medication (total amount)	3.15g	0g	0.68g	1.44g	1.80g	3.48g
NAS medication treatment	12 days	0 days	5 days	6 days	8 days	10 days
Birth weight	3510g	3110g	3190g	2890g	2680g	2940g
Birth length	49cm	50cm	52cm	49cm	52cm	50cm
Head circumference	35cm	34cm	34cm	33cm	36cm	33cm
EGA at birth	268 days	263 days	276 days	264 days	287 days	266 days

Time course of NAS over 16 days following birth



Y-axis shows mean daily adopted Finnegan scores for MET and BUP exposed neonates (p=0.124)
Lower curves show NAS treatment with morphine drops for MET and BUP exposed neonates (p=0.394)
X-axis shows days of NAS assessment/treatment.

HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2011; **26**: 412–421.
Published online 8 August 2011 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hup.1224

Impact of treatment approach on maternal and neonatal outcome in pregnant opioid-maintained women

Verena Metz[1]*, Reinhold Jagsch[2], Nina Ebner[3], Johanna Würzl[1], Anna Pribasnig[1], Constantin Aschauer[1] and Gabriele Fischer[1]

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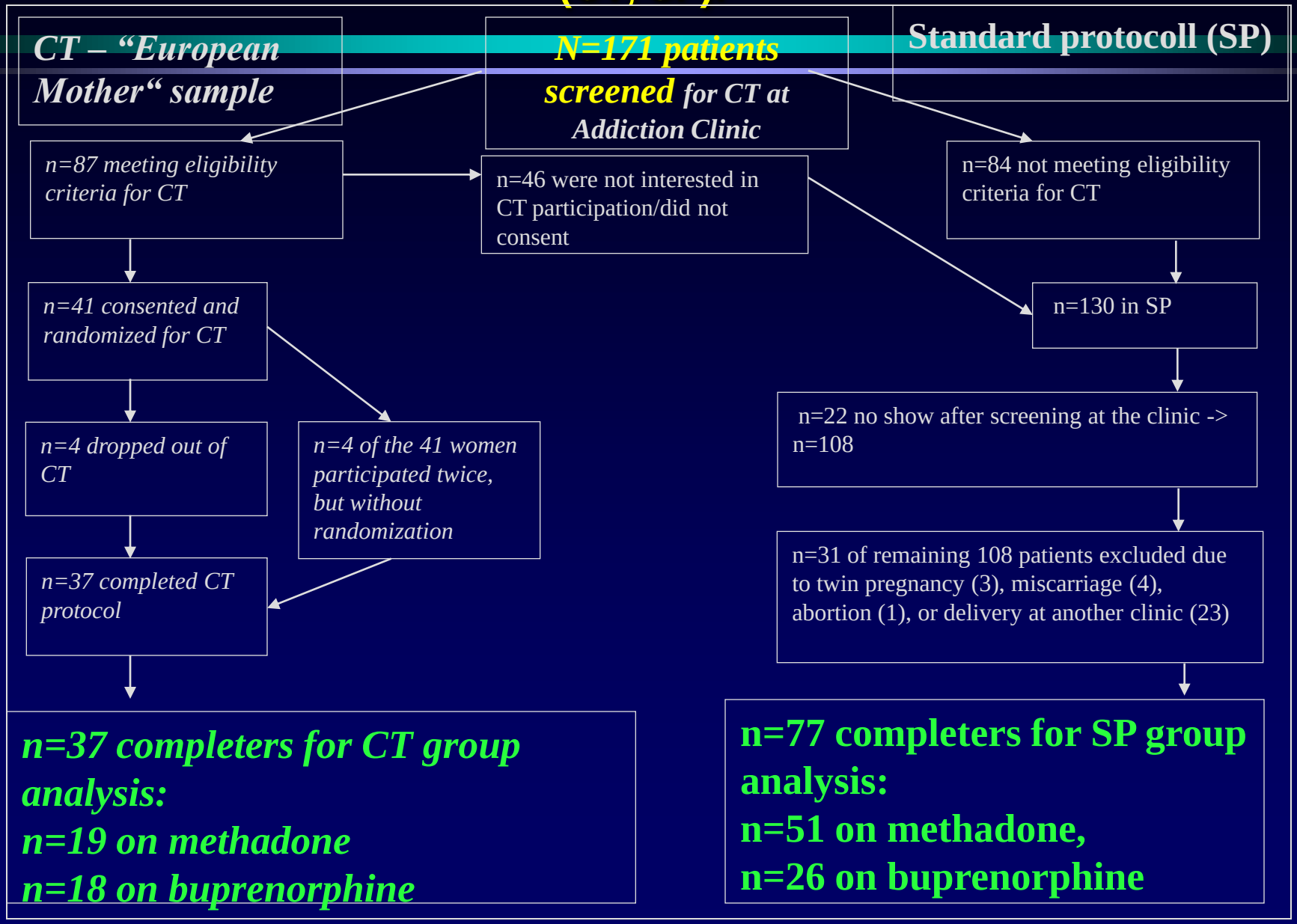
[3]*Department of Child and Adolescent Psychiatry, Medical University of Vienna, Vienna, Austria*

Screening, randomization, and treatment completion of both groups (CT, SP).



Methods: Procedures

- **Clinical trial (CT- „Mother“) procedures**
  - Randomization to opioid medication (buprenorphine/ methadone)
  - Daily visits until 28 days postpartum with medication intake under supervision
  - Supervised urine toxicology 3 times a week (combined with contingency management)
  - Delivery and 10 days postpartum inpatient stay required (rooming-in with infants)
  - NAS: assessment and treatment by blinded staff
    - Pharmacological treatment initiated when mod. Finnegan score ≥9
    - ***Morphine drops (0.05% morphine HCl) dosed according to NAS score***
    - ***Supportive care measures***

- **Standard protocol (SP) procedures:**
  - Opioid medication and frequency of visits individually determined
  - Supervised urine toxicology on average twice a week
  - Delivery and discharge upon medical indication
  - NAS: assessment and treatment by the same staff, but not blinded
    - Pharmacological treatment initiated when mod. Finnegan score >10
    - ***Morphine drops dosed according to body weight and NAS score***
    - ***Separate ward for children***

Methods: Statistics

- Outcome measures
  - Concomitant consumption of opioids, benzodiazepines and cocaine during last trimester
  - Gestational age (GA) at birth (preterm/ fullterm birth)
  - Demographic neonatal data
  - NAS data (morphine required, duration of treatment and length of stay in hospital)
  - Number of daily smoked cigarettes
  - Mode of delivery (vaginal / C-section / vacuum / forceps)
  - Parity
  - Maternal opioid medication and dose at delivery and association with neonatal parameters
- Statistical analyses
  - Chi-square tests for categorical data
  - T-tests for independent samples for continuous data
  - Two-way ANOVA in case of combination of maternal and neonatal outcome variables, with „opioid medication“ and „treatment approach“ as independent variables
  - $P<.05$ considered significant

Maternal characteristics

	SP (n=77)		CT (n=37)	
	Methadone (n=51)	Buprenorphine (n=26)	Methadone (n=19)	Buprenorphine (n=18)
Age at delivery (years)	23.94 (4.51)	24.81 (5.25)	26.37 (5.89)	23.78 (4.48)
Parity	1.55 (0.83)	1.38 (0.75)	1.63 (0.76)	1.61 (1.09)
Treatment entry (pregnancy weeks)	18.56 (7.70)	20.67 (8.94)	20.47 (7.16)	21.12 (5.99)
Cigarettes/ day during last trimester	11.24 (6.67)	10.81 (6.54)	12.53 (5.96)	13.89 (5.81)
Medication dose at delivery (mg)	74.16 (39.26)	9.85 (6.24)	63.68 (36.09)	13.44 (6.28)

No significant differences between SP and CT

Percentages of patients with concomitant consumption during last trimester of pregnancy

Urine toxicologies positive for	SP		CT		χ^2 MET	P MET	χ^2 BUP	P BUP
	MET	BUP	MET	BUP				
Opioids	36%	19%	33%	30%	0.007	0.932	0.416	0.706
Cocaine	7%	9%	14%	10%	1.239	0.355	0.178	1.000
Benzodiazepines	34%	18%	14%	20%	2.178	0.140	0.016	1.000
Any substance	52%	23%	47%	33%	0.132	0.717	0.559	0.498

Urine toxicologies positive for	SP (n=77)	CT (n=37)	X^2	P
Opioids	30%	32%	0.056	0.812
Cocaine	8%	11%	0.311	0.719
Benzodiazepines	29%	16%	2.039	0.153
Any substance	42%	41%	0.026	0.871

No significant differences between SP and CT

Neonatal characteristics

	SP (n=77)		CT (n=37)		χ^2 MET	P MET	χ^2 BUP	P BUP
	MET (n=55)	BUP (n=26)	MET (n=19)	BUP (n=18)				
Sex: male	25 (49%)	13 (50%)	10 (53%)	7 (39%)	0.072	0.788	0.530	0.467
Fullterm births	45 (88%)	25 (96%)	16 (84%)	17 (94%)	0.200	0.696	0.072	1.000
Vaginal delivery	34 (67%)	17 (65%)	8 (42%)	11 (61%)	3.480	0.062	0.084	0.772
APGAR 1 (<8)	4 (8.2%)	0 (0.0%)	1 (5.3%)	0 (0.0%)	0.169	1.000	-	-
APGAR 5 (<9)	3 (6.1%)	0 (0.0%)	1 (5.3%)	1 (6.0%)	0.018	1.000	1.422	0.419
NAS treatment	31 (65%)	15 (58%)	13 (68%)	15 (83%)	0.089	0.766	3.223	0.073

No significant differences between SP and CT

Demographic birth data & NAS parameters

sign (α=0.05) regarding SP vs. CT; P OM sign regarding medication MET vs. BUP, P IA sign of interaction between TR and OM

	SP (n=77)		CT (n=37)		P TR	*P OM*	P IA
	MET (n=51)	BUP (n=26)	MET (n=19)	BUP (n=18)			
GA (weeks)	38.59 (1.92)	39.65 (1.62)	38.37 (2.17)	39.72 (2.37)	0.851	***0.003****	0.722
Weight (g)	2729 (510)	3151 (542)	2862 (403)	2967 (504)	0.800	***0.011****	0.124
Length (cm)	48.26 (3.30)	50.23 (3.28)	48.66 (2.65)	49.11 (2.65)	0.572	0.059	0.236
Head circ. (cm)	32.93 (1.72)	33.56 (1.75)	33.61 (1.70)	33.61 (1.97)	0.319	0.383	0.392
Total morphine dose (mg)	21.61 (26.64)	4.30 (7.30)	5.18 (6.94)	2.02 (1.71)	**0.014***	***0.008****	0.0061
Duration of NAS treatment (mean days)	21.25 (21.22)	6.62 (8.07)	9.53 (9.14)	7.33 (4.46)	**0.079**	***0.008****	**0.048***
Length of hospital stay (mean days)	29.36 (17.94)	13.92 (7.33)	16.74 (6.78)	13.67 (2.63)	**0.015***	***0.001****	**0.019***

Summary of results

- CT group: strict selection process –“evidence-based“
- SP group: reflecting the „real world situation“

- No significant differences regarding major maternal characteristics or concomitant consumption of other substances despite contingency management in the CT group

- No significant differences in demographic birth data, but
  - **clearly superior results regarding NAS parameters (morphine dose/NAS treatment) in the CT group**

- No significant associations between opioid medication dose at time of delivery and NAS parameters, but
  - **Significantly better results** for children exposed intrauterally to **buprenorphine** throughout pregnancy **in gestational age at birth, birth weight, and all tested NAS parameters**

Limitations & conclusions

- A-priori existing differences between patients in CT and SP
- Staff in SP group not blinded

- Beneficial treatment procedures in the CT group:
  - Rooming-in of neonates with mothers after delivery
  - Additional supportive care measures for NAS treatment
  - More intense care for mothers

- Buprenorphine and methadone were both safe and efficient for mothers and children
  - Buprenorphine shows consistantly superior results in NAS parameters

- Succesfully implemented beneficial CT procedures should be considered for integration into standard care

European Journal of Pain
in press (Hoeflich et al)

Peripartum pain management in opioid dependent women

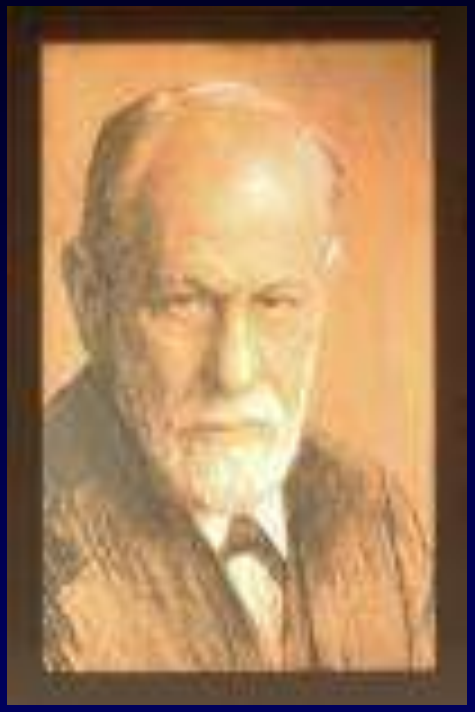
Following cesarean delivery opioid maintained women received significantly less opioid analgesics (day of delivery p = 0.038; day 1: p = 0.02), NSAIDs were administered more frequently than to the comparison group during cesarean section and postpartum.

Opioid group: „european mother sample“ vs healthy controlls

Sigmund Freud

The major question, which I am unable to answer despite my 30 years of studying the female sole:

„ What wants a woman ?“



6.5.1856 - 3.9.1939

Londa Schiebinger (1993):

Has feminism changed science ??

- *22 071 men (0 females!) participated in clinical trials concerning myocardiac infarction prophylaxis →*

<u>Now we know</u> : aspirin is not effective in women in preventing mycard infarction. NEJM, 2005

The size and burden of mental disorders and other disorders of the brain in Europe 2010

Wittchen, Jacobi et al. European Neuropsychopharmacology, 21:9 (655-679) September 2011

38.2% of the EU population suffers from a mental disorder.

This corresponds to 164.8million persons affected (adjusted for age & comorbidity)

The most frequent disorders are

- anxiety disorders (14.0%)
- insomnia (7.0%)
- major depression (6.9%)
- somatoform (6.3%)
- ***alcohol and drug dependence (>4%)***
- ADHD (5%) in the young
- dementia (1–30%, depending on age)