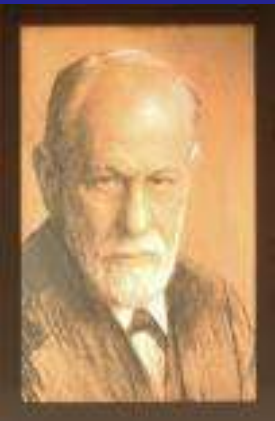
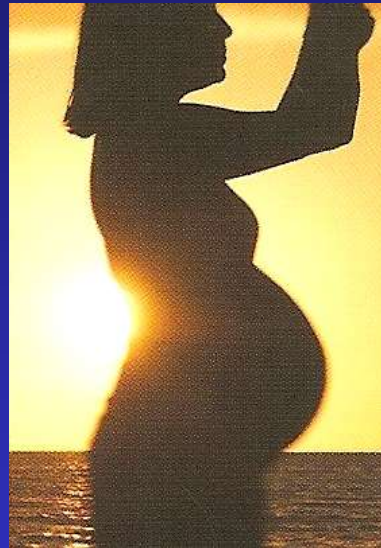


Creating Synergy Conference

3rd - 5th November, Wollongong

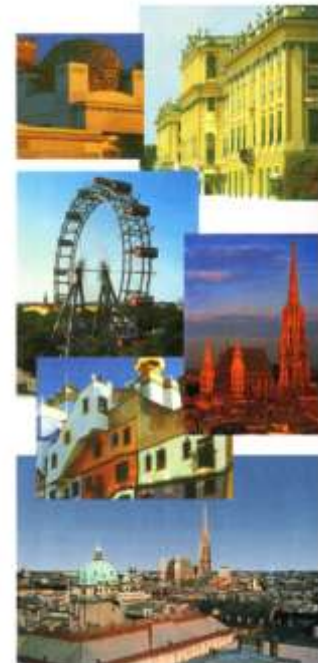


MEDICAL UNIVERSITY VIENNA

ADDICTION CLINIC

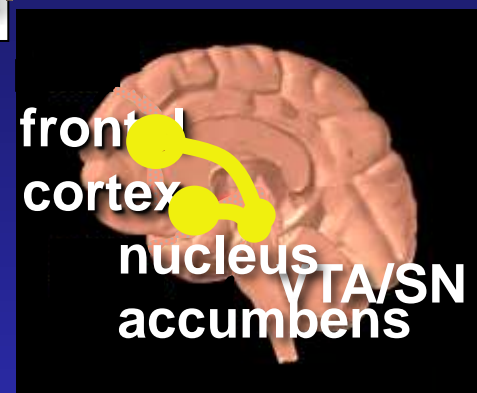
Gabriele Fischer MD PhD

Gabriele.fischer@meduniwien.ac.at



Structure

- General aspects
- Co-morbidities
- Influence of substances & drugs
- Who are responsible care-providers ?
- Focus on opioids
- Pharmacological treatment during pregnancy
- Heterogeneity of research reports in NAS
- Relevance of non-pharmacological intervention
- „MOTHER STUDY“
- Preliminary out look of developmental factors



- Biological abnormalities
 - Behavioral deviations
- Translational research

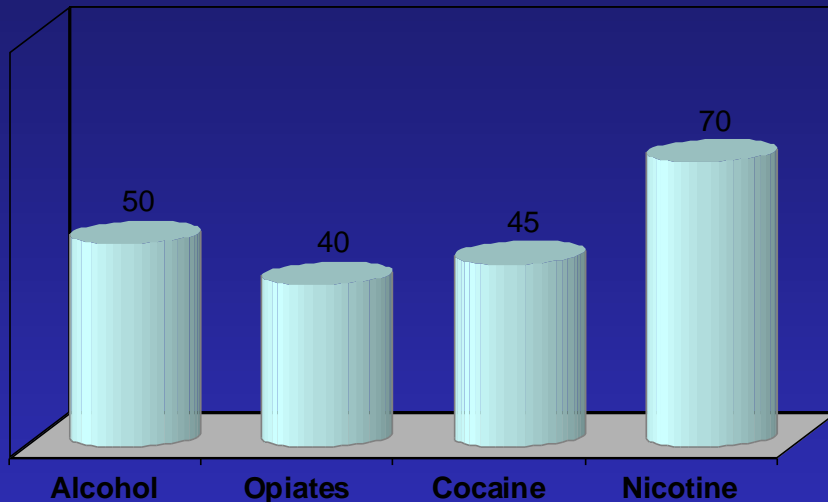
- Addiction behaviour is changing its phenotypes
- Addiction is a chronic relapsing disorder: *Science* 1999
- Stigma
- How to be a good enough mother -
 - Who defines that ?



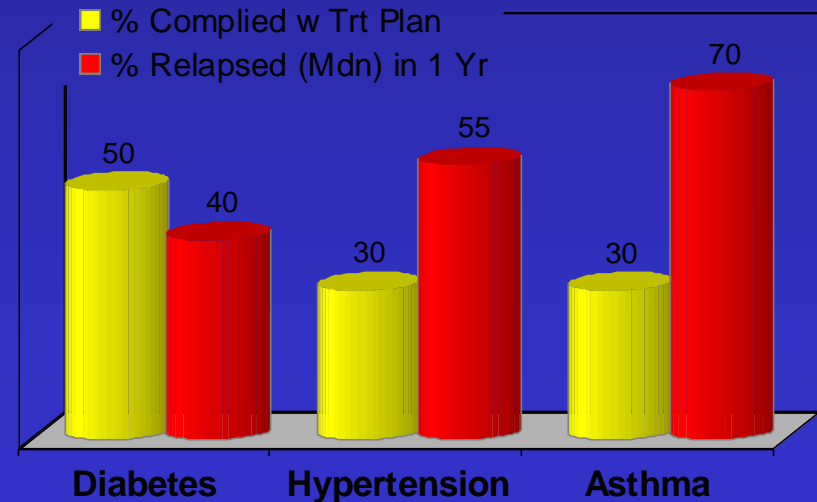
Addiction is a chronic relapsing disorder

Science 1999

Relapse Rates following treatment

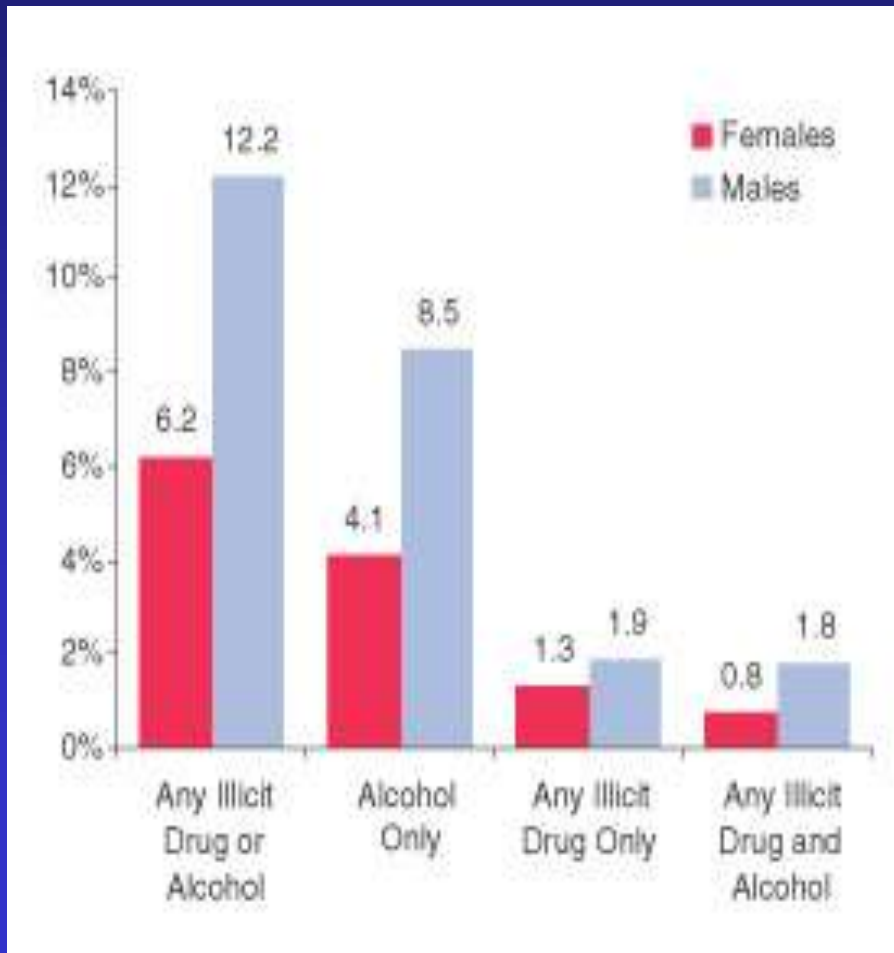


Comparative Rates for Treatment Compliance & Relapse



O'Brien & McLellan, 1996, The Lancet

Gender differences in prevalence



- 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

Pregnancy & Addiction



Issues



1. Neonate
2. Pregnant woman -“pamper“ as long as they are pregnant
3. Childrens development ?? „normal“ controls ?

• Woman

- Psychiatric & somatic comorbidity: diagnosis & treatment
 - Genetic loading ?
 - Trauma ?
 - Depression/anxiety disorder ?
 - ADHD ?
 - Plasmalevels ? Drug/drug interaction - QT-time ?
 - Hepatitis C- treatment - after delivery?



• Partners

- Other children: foster care/live with biological mothers
- „New“ unexperienced mother - assistance in child care ?
- Reintegration - working ?? Kindergarden assistance
- Assistance for children with abnormal developmental features

Psychiatric Comorbidity 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.

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 cannot be supported any more!*

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)

Nicotine

- Double-blind, placebo-controlled study with nicotine (2 mg by inhaler) to investigate changes in cognitive performance
- Nicotine did not improve attention and memory; exposure to stress increased anxiety and aggression in **women**, which were blocked through nicotine, but not in men
- **Smoking in women correlated to stress situation.**

File et al., Int J Neuropsychopharmacology, 2001

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 (Lag Reid 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

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



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

Management of pregnant illicit drug misusers

Council of Europe

1998:ISBN: 92-871-3784-6



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



Training - Teaching programs for interdisciplinary groups



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

Opioid dependence



Background of Pregnancy & Opioid Addiction

- >30% of opioid dependent women are in child-bearing age
- Improved treatment through ↑ opioid maintenance options
- Constant ↑ numbers of patients maintained on opioids
- Opioids are not teratogenic
- **However:**
 - *Alcohol - fetal alcohol syndrome- and cocaine* are teratogenic
 - ? *Benzodiazepines* linked to increased orofacial malformation and prolonged neonatal abstinence syndrome (NAS)
 - Watch *nicotine* dependence – low weight for gestational age, preterm delivery, FTS (fetal tobacco syndrome)
 - Consider the influence of changing hormonal state (enzyme induction) and *other psychopharmacological* medication interaction in regard to metabolism and QT-time

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, 2005)
 - This translates into more than 57.000 heroin- or pain reliever-exposed pregnancies each year in the US
- 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)

Problems Related To Opioid Exposure During Pregnancy

MOTHER

- Continuation of **heroin consumption**
 - Expose woman to extended risk of violence
 - No involvement in medical care
 - High risk for preterm labour and multiple substance abuse
 - Limited chance of assistance to provide a living environment for a family
- >50% have a co-dependent partner
- Women have high psychiatric co-morbidity
 - >60% anxiety disorder & depression
 - Diagnosis & Treatment
 - Watch: drug-drug interactions; also: Persistent pulmonary hypertension (PPHN) in newborns exposed *in utero* to SSRIs (Chambers et al., 2006)

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

- 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
- Heterogenous reports – retrospective, observational, controlled
- Heterogenous approach regarding treatment of NAS – phenobarbiturates/oral morphine solution

Neonatal Abstinence Syndrome (NAS)

Medline research between 1998 – 2006:

84 citations and **44** publications

- Newborn appears normal at birth
 - Symptoms appear 10 – 72 hrs (may not appear until day 5)
- Symptoms
 - CNS irritability
 - Respiratory distress
 - Vagal autonomic symptoms
 - Gastrointestinal dysfunction
- Measured by « *Finnegan* (modified ?) « or Lipsitz scores
- *Consistent finding: Around 40 % of neonates exposed to either methadone or buprenorphine have no NAS (no concomitant use).*



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 ?

Methadone & Buprenorphine Benefits and Disadvantages in pregnancy



Medication

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



- **Buprenorphine:**
 - Long experience (around 1990)
 - Increase coverage
 - Sublingual tablets



- We talk about treatment & not a “religion” (eg industry)

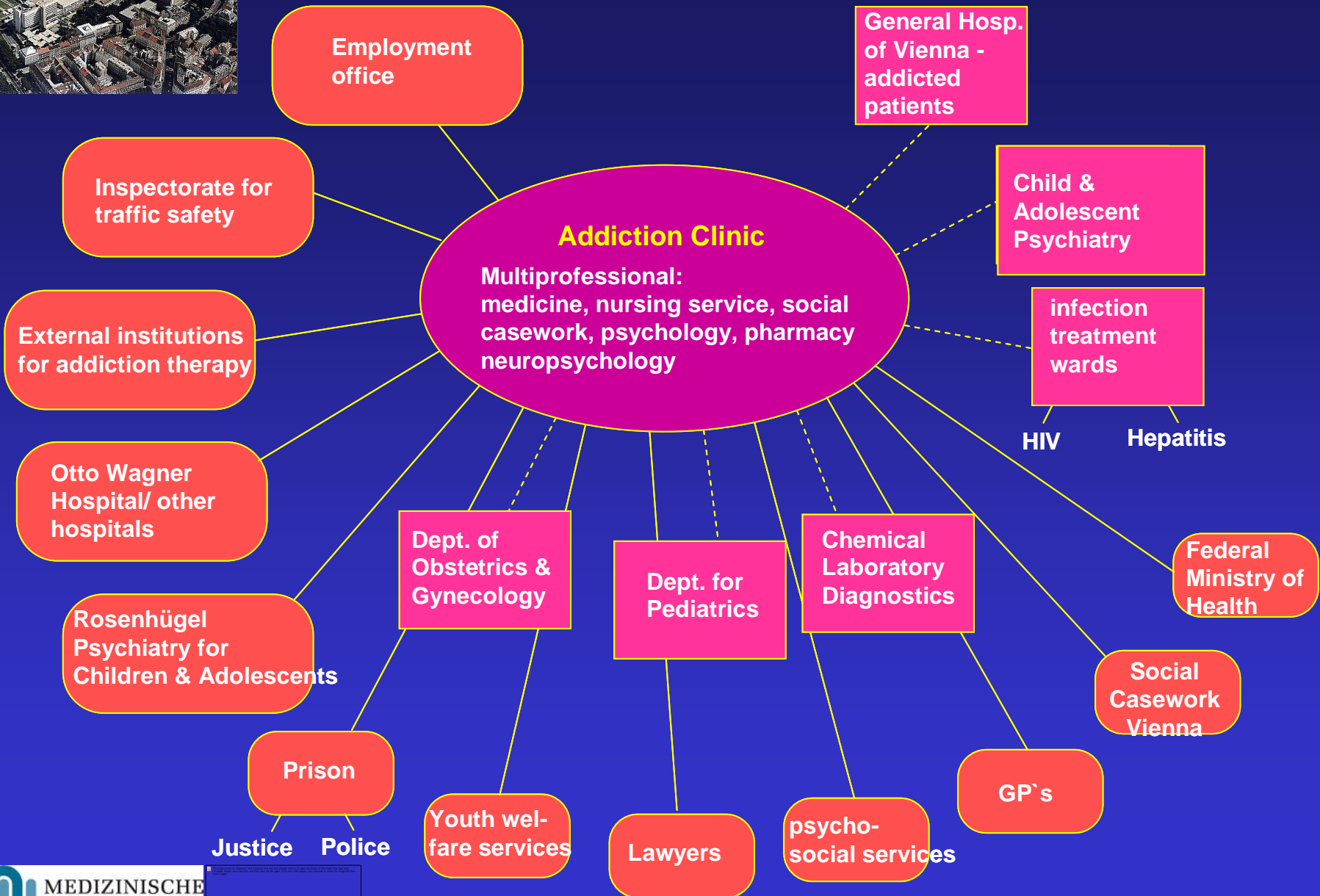
Background



- Research controlled studies
 - Open label studies
 - Field observations
 - Case reports
-
- Influences other than medication: **setting**
 - Other medical disorders have a variety on medication
 - Legislation – opioid medication is differently regulated than any other medication
 - ?? „double - morality“ ??



NATIONAL NETWORK OF THE ADDICTION CLINIC



Buprenorphine and NAS

- Prospective open-label controlled studies of prenatal buprenorphine exposure showed mild-to-no NAS (21% of neonates requiring short-term medication)^{1–2}
- 66% of neonates prenatally exposed to buprenorphine required medication to treat NAS³
- Review of all available prenatal data: 60% of buprenorphine-exposed neonates require treatment for NAS compared to 60–87% of methadone-exposed infants⁴
- Differing and contradictory results regarding medication differences on NAS outcomes^{5–9}

1) Fischer *et al.* *Addiction*. 2000; 95:239–244. 2) Schindler *et al.* *Addiction*. 2003; 98:103–110. 3) Hytinantti *et al.* *Acta Paediatr*. 2008; 97:1040–1044. 4) Johnson *et al.* *Drug Alcohol Depend*. 2003; 70:S87–S101. 5) Lejeune *et al.* *Drug Alcohol Depend*. 2006; 82:250–257. 6) Bakstad *et al.* *Eur Addict Res*. 2009; 15:128–134. 7) Kakko *et al.* *Drug Alcohol Depend*. 2008; 96:69–78. 8) Fischer *et al.* *Addiction*. 2006; 101:275–281. 9) Jones *et al.* *Drug Alcohol Depend*. 2005; 79:1–10.

FREQUENCY OF NAS & APPLIED TREATMENT

n = 53 neonates

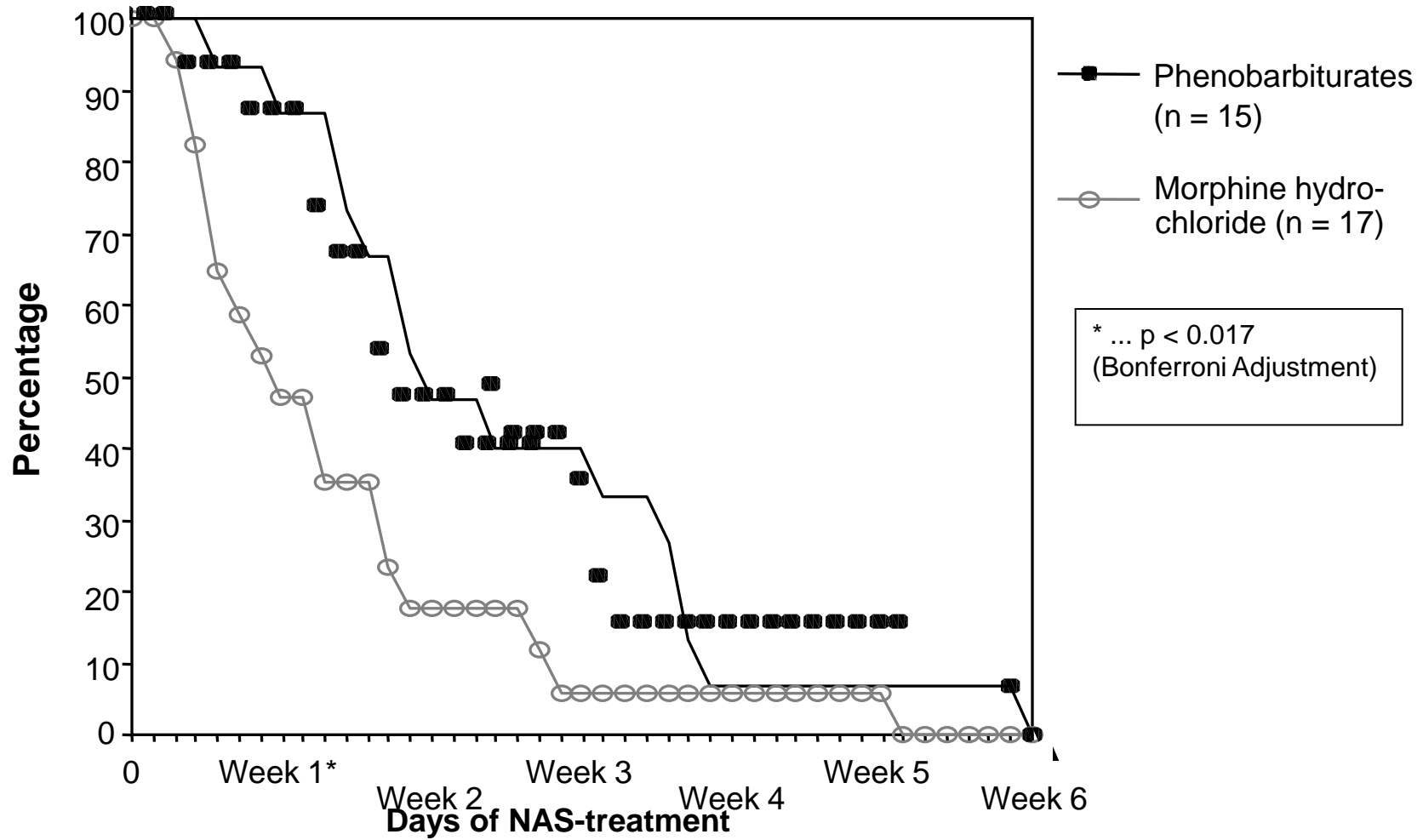
	Applied detoxification treatment in neonates (n = 32)		No detoxification treatment (n = 21)
	Phenobarbiturates	Morphine hydrochloride	
Number of patients (n = 53)	15 (28,3%)	17 (32,1%)	21 (39,6%)
Methadone maintenance (n = 22) (mean dose: 47 mg)	5 (22,8%)	10 (45,4%)	7 (31,8%)
Slow release morphine maintenance (n = 17) (mean dose: 400 mg)	10 (58,8%)	4 (23,5%)	3 (14,3%)
Buprenorphine maintenance (n = 14) (mean dose: 7 mg)	0 (0,0%)	3 (17,6%)	11 (82,4%)

Drug & Alcohol Dependence 87 (2007) 131-138

Ebner N., Rohrmeister K., Winklbaaur 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

Ebner N., Rohrmeister K., Winklbaaur B., Baewert A., Jagsch R., Peternell A., Thau K., Fischer G.



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 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)

- SRM: 32 h post delivery
- methadone: 34 h post delivery
- buprenorphine: 58 h post delivery

„Mother“- Study

NIH1R01 DA018417

Addiction Clinic (Medical University of Vienna)

double-blind, double-dummy Study
in opioid-dependent pregnant patients under standardized
psycho-social care



Addiction Clinic

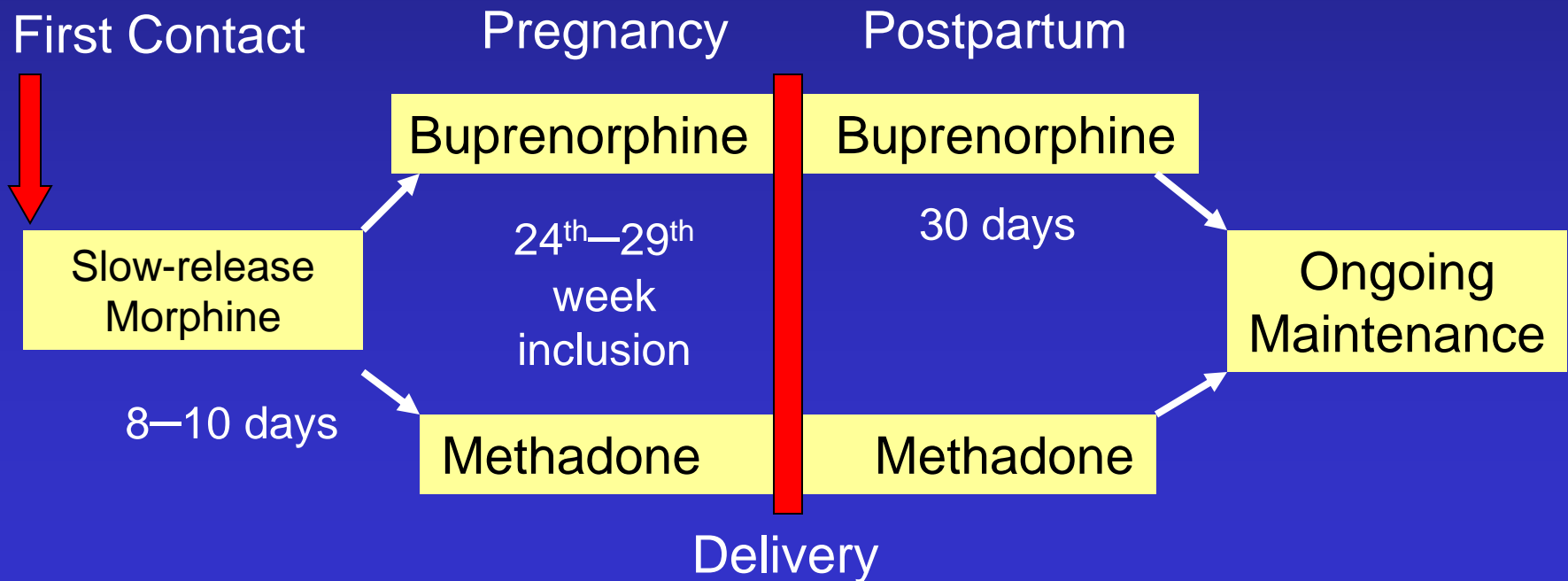
Multi-professional:

Medicine, nursing care,
social casework, psychology,
pharmacological treatment,
neuropsychology
psychotherapy

Methadone Versus Buprenorphine In Pregnant Addicts: Study Design

(Fischer et al. *Addiction*, 2006)

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



Buprenorphine vs. Methadone in the treatment of pregnant opioid-dependent patients: Effects on NAS

- Double-blind (both staff and patients), Double-dummy
- Two study groups: methadone or buprenorphine
- Study included contingency management
- Flexible dosing regimen:

Methadone	20 – 100 mg
Buprenorphine	4 – 24 mg

- Main research questions:
 - Treatment effect on Neonatal Abstinence Syndrome (NAS)
 - Length of hospital stay (LOS)



BREASTFEEDING



YES

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

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

Limitations:

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

Summary

MULTIDISCIPLINARY & INTERDISCIPLINARY

Opioid Maintenance keeps women in treatment:

- Pregnancy counselling
- Multi-professional approach is wanted
- Breast feeding should be encouraged
- Detoxification – limited success
- Methadone & buprenorphine are both safe
- Dose increase may be required (twice daily in methadone)
- Contingency management might reduce illicit drug use
- In the *MOTHER study* quite some site differences might be revealed

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

Neonatal abstinence syndrome (NAS): Postnatal ward versus neonatal unit management

**Tolulope Saiki, Silke Lee,
Simon Hannam, Anne Greenough**

Eur J Pediatr (2010) 169; 95-98

Aim of the study

- To test that hypothesis that caring for infants with NAS **with their mothers on the postnatal ward** rather than admit them to the **neonatal unit** would **reduce treatment duration and length of hospital stay** by comparing the outcomes of the infants cared for before and after the change in policy

Methods

- **Type of drugs abused** was divided into three groups:
 - Methadone alone
 - Methadone plus other drugs
 - Drugs other than methadone
- **Assessments**
 - four hourly intervals
 - River's scoring system
 - **Group A:** scored above four-> **neonatal unit** for further assessment and treatment if required, neonates remained on the neonatal unit throughout the duration of their treatment
 - **Group B:** Infants remained on the **postnatal ward with their mother**, regardless of whether they were receiving treatment for NAS
- **Treatment: morphine drops**

Neonatal outcomes by time period

Group A – neonatal ward

Group B – postpartal ward with mothers

Results	Group A (2002-2005)	Group B (2006-2007)	p
N	42	18	
Infants requiring treatment	19 (45%)	2 (11%)	0.012
Duration of treatment (days)	12.7 (0) (0-55)	7.3 (0) (0-65)	0.05
Duration of hospital stay (days)	19.8 (12.5) (3-65)	15.9 (6) (0-74)	0.012
Discharged home with mother	25 (60%)	13 (67%)	0.264

Data are demonstrated as number (%) or mean (median) (range);

- No infant in either group was readmitted within the next 2 months

ADDICTION

PREGNANCY

Methadone dose and neonatal abstinence

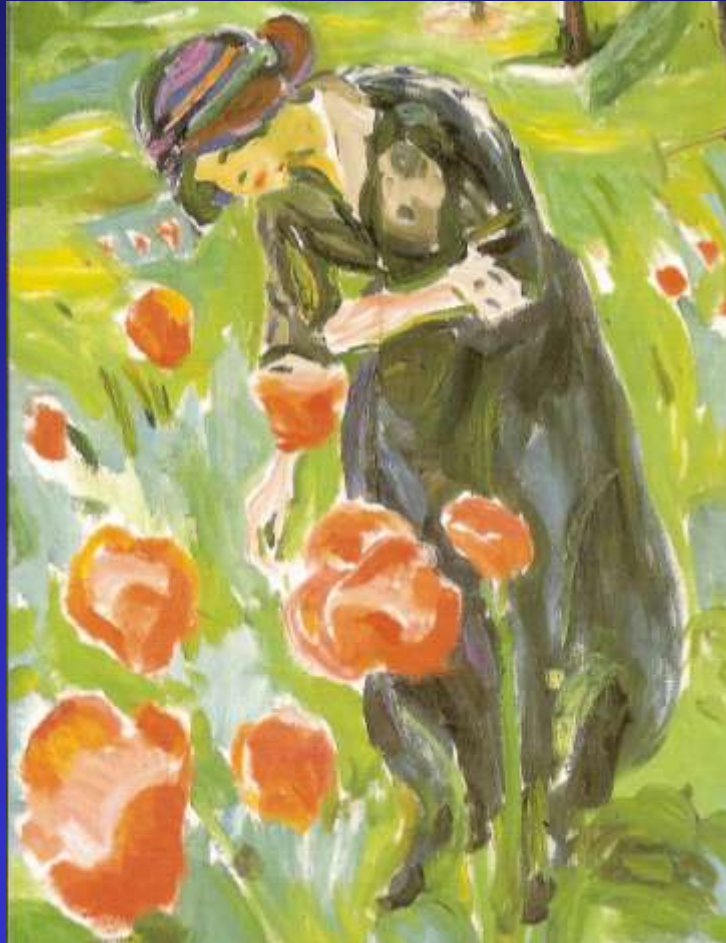
Syndrome — systematic review and meta-analysis.

Cleary BJ, Donnelly J, Strawbridge J, Gallagher PJ, Fahey T,
Clarke M & Murphy DJ.:
Current issue

**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.**

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

Thank you for your attention...



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

Developmental and neurocognitive development in children following intrauterine opioid exposure

Andjela Baewert

Gabriele Fischer

Supported by Austrian National Bank

(Project No. 12763)

Consequences of Opioid Exposure

- Deficits in cognitive and psychomotoric development
- Limited arithmetic ability
- Delayed language development
- Learning and behavioral problems
- Attention-Deficit Hyperactivity Disorder (ADHD)

Aims of the Study

Pregnant women in opioid maintenance between 1997-2003

- **Primary aim (children: age 6-11):**
- to examine the **effects of intrauterine exposure** to Methadone, Slow-Release Oral Morphines (SROM) and Buprenorphine regarding
 - IQ, work memory and executive functions
 - Social and emotional status (e.g. depression, anxiety)
- **Secondary aim (mothers: in treatment between 1997 – 2003):**
to examine to **long-term effects of opioid maintenance therapy** in women over a period of 6-11 years, considering
 - Current psychiatric diagnoses
 - Current substance use/abuse
 - Life quality
 - Subjective health status

Acknowledgements

Grant Support

*Austrian (ÖNB 9669 , Science foundation),
NIDA MOTHER 1R01 DA018417-01*

*Schering Plough (educational grant to the Medical
University Vienna – for pilot study)*

Medical University Vienna

*Staff at Departments of Psychiatry, Gynecology,
Pediatrics, Laboratory-medicine, Pharmacy*

..... & my research staff