Opioid Dependence During Pregnancy: Balancing Risk/Benefit

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Conflicts: None

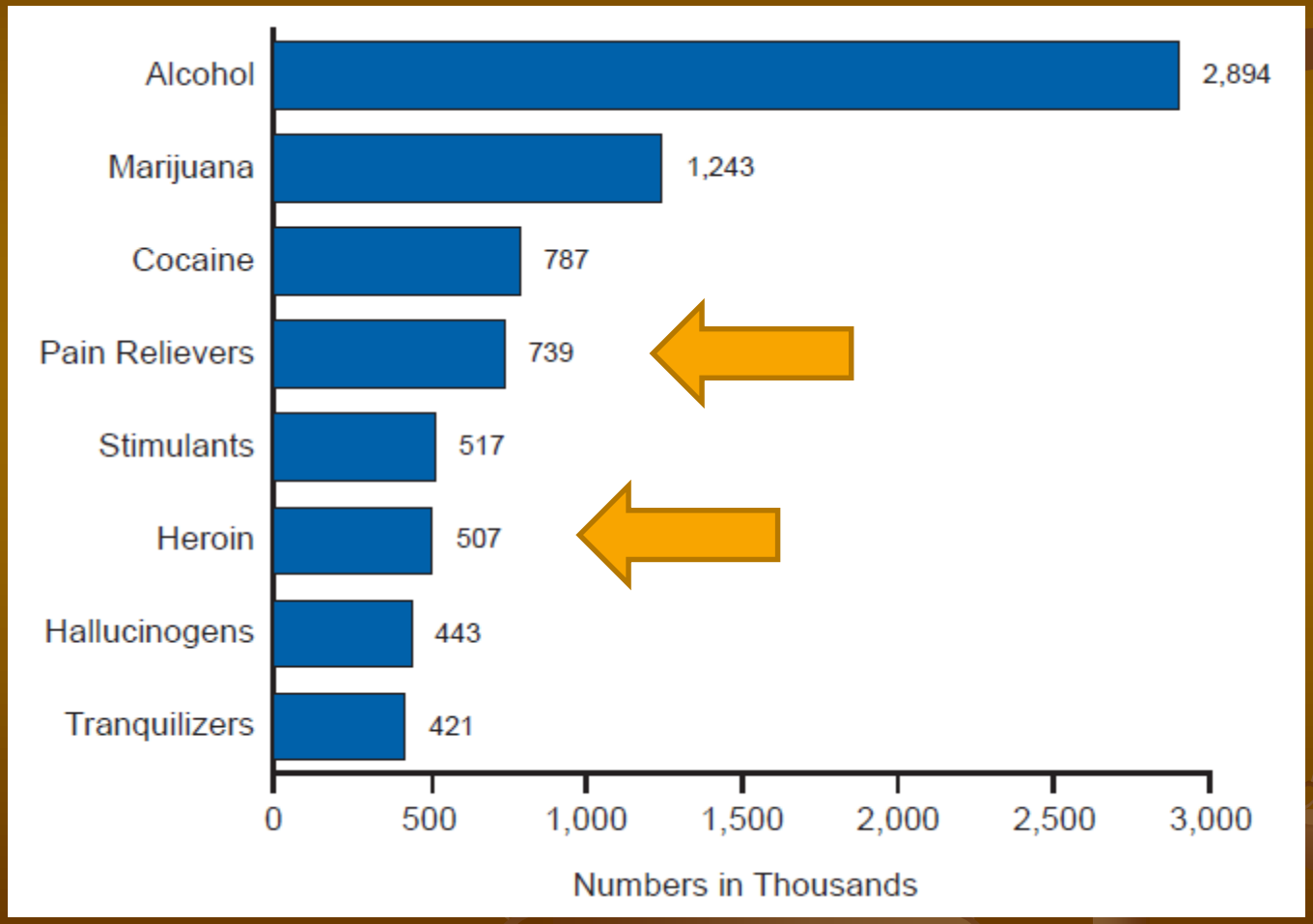
Outline

I. Epidemiology of opioid dependence in pregnancy
II. Complications and treatment benefits
III. MOTHER RCT in pregnant women: buprenorphine *vs* methadone
IV. Implications

Opioid Dependence in Pregnancy: Heroin

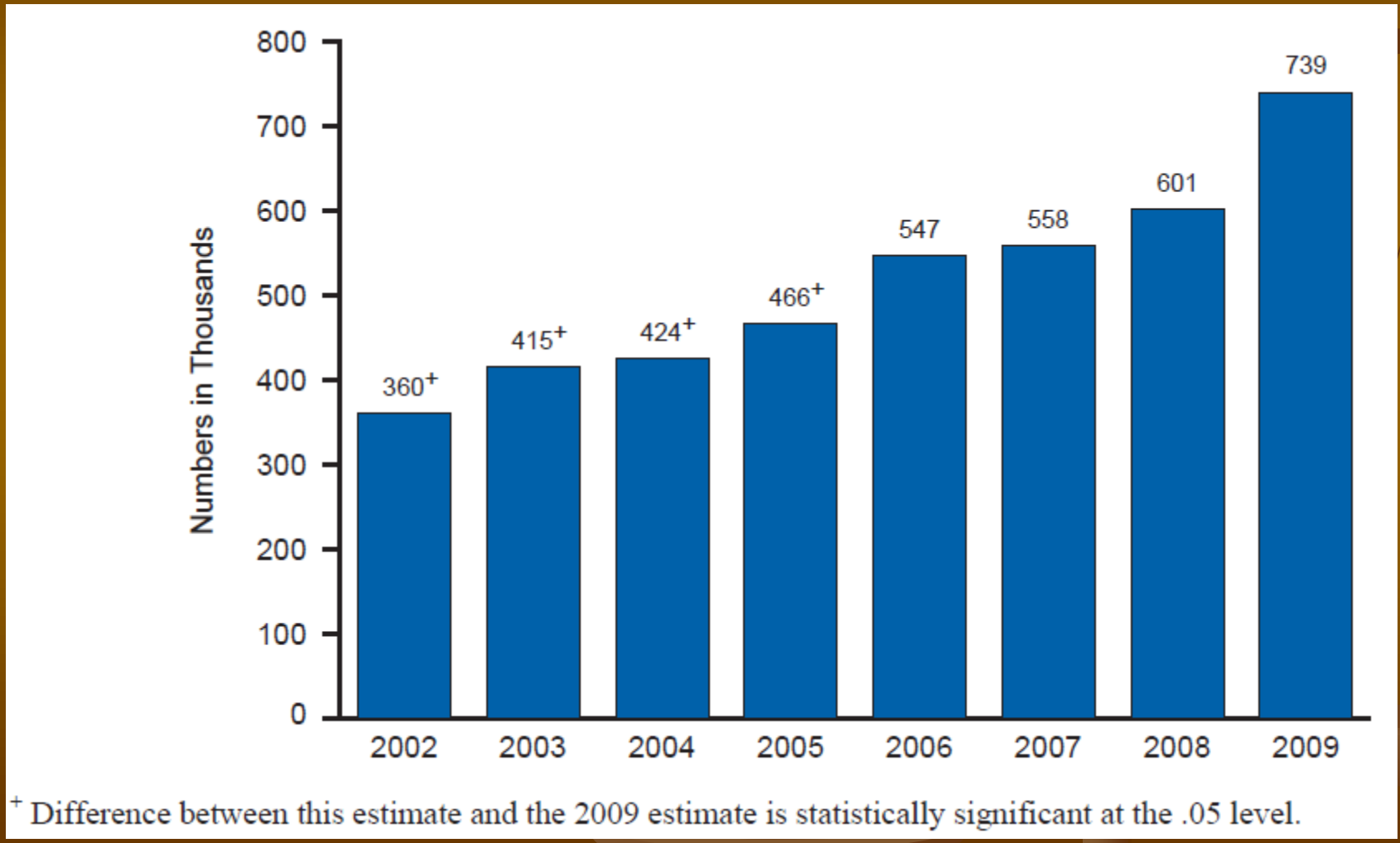
- The magnitude of the problem is unreliably ascertained and likely under-reported
- Estimated 53,400 U.S. babies were exposed to opioids (mostly heroin via intravenous route) in 1992
- 114,000 new heroin users in U.S. in 2008
- 15% of pregnant women in addiction treatment had heroin dependence in 2008 (unchanged over previous decade)

Drug Use Problems Treated in US (≥12 yrs, 2009)



SAMHSA, *Results from the 2009 National Survey on Drug Use and Health*, 2010

Addiction Treatment (Pain Relievers) in Past Year (≥12 yrs, 2009)

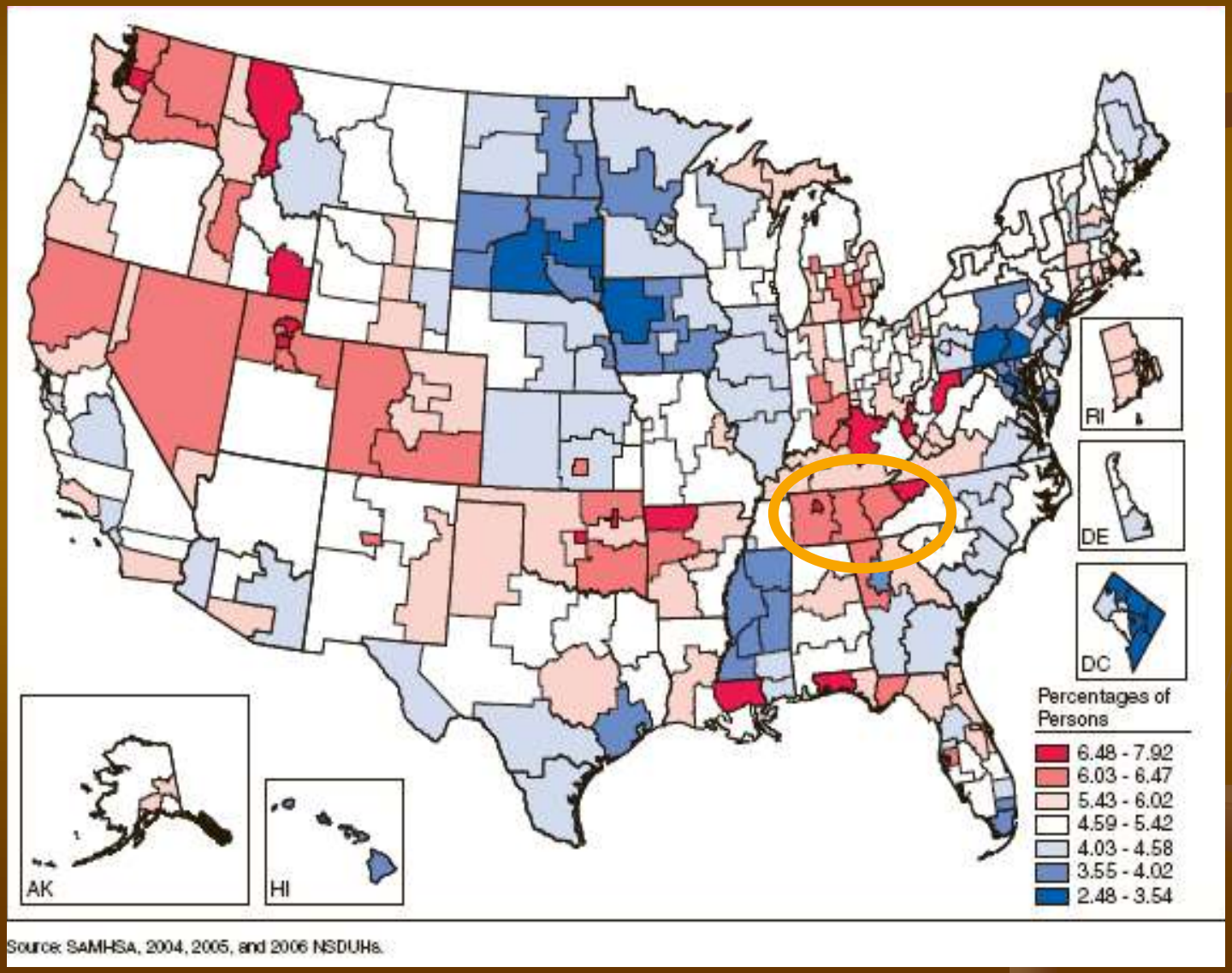


SAMHSA, *Results from the 2009 National Survey on Drug Use and Health,* 2010

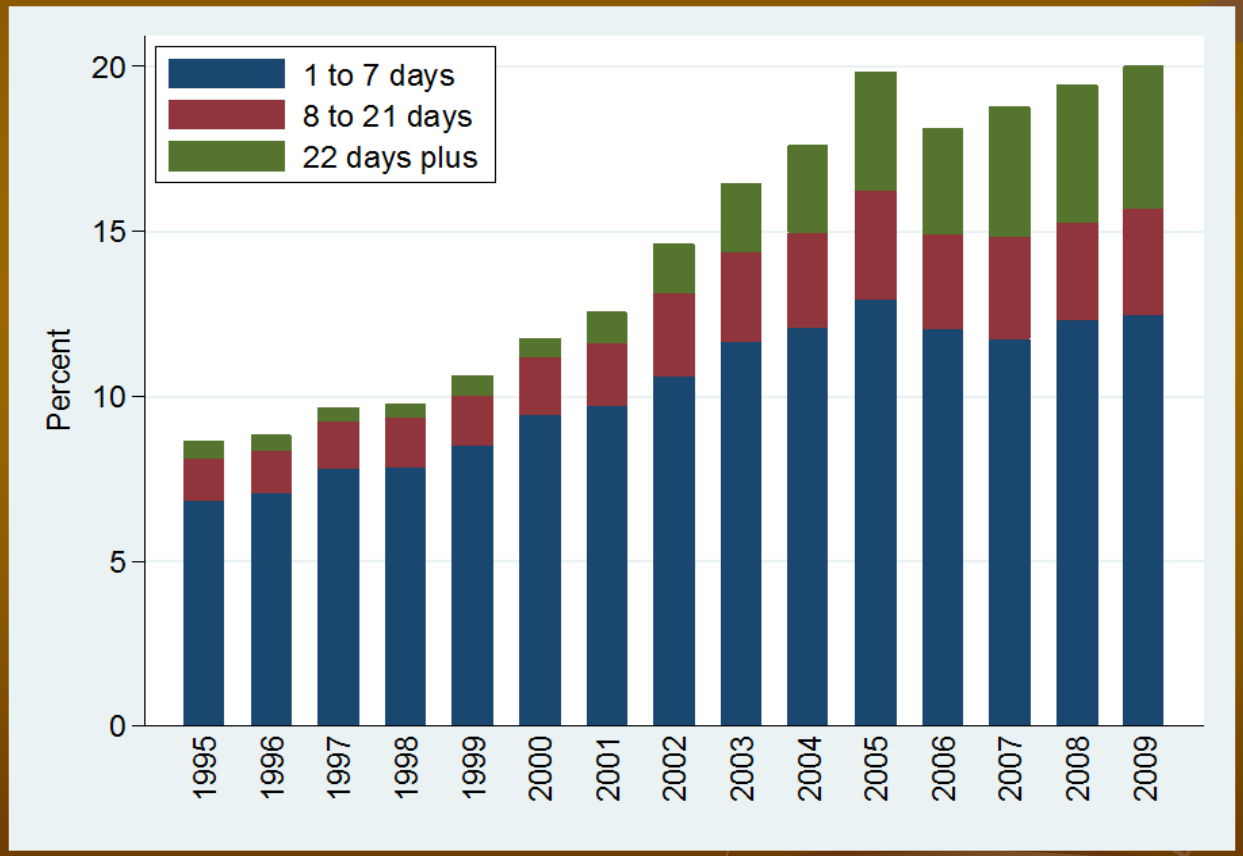
Opioid Dependence in Pregnancy: Nonmedical Prescription Analgesics

- 2.4 million new nonmedical prescription analgesic users in U.S. in 2003
- Treatment admissions for prescription opioid dependence increased five-fold (1% to 5%) during 1997-2007
- Only ~10% of the 23.5 million persons (age ≥12 yrs.) who need addiction treatment in U.S., actually receive it
- *A very large number of the women in OB care have unrecognized opioid (especially, analgesic) dependence needing treatment*

Nonmedical Use of Pain Relievers in Past Year (≥12 yrs, 2004-06)



Proportion of Pregnancies among TNCare Enrollees with First Trimester Opioid Use



Ratio: 2009 to 1995 (exposure duration)

-1 to 7 days:
12.45/6.85 = 1.82

-8 to 21 days:
3.26/1.25 = 2.61

-22 days plus:
4.30/0.53 = 8.17

Epstein et al., 2011

Rev Saúde Pública 2009;43(1):140-46

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Use of analgesics in adults with pain complaints: prevalence and associated factors, Turkey

Uso de analgésicos por adultos com queixas de dor: prevalência e fatores associados, Turquia

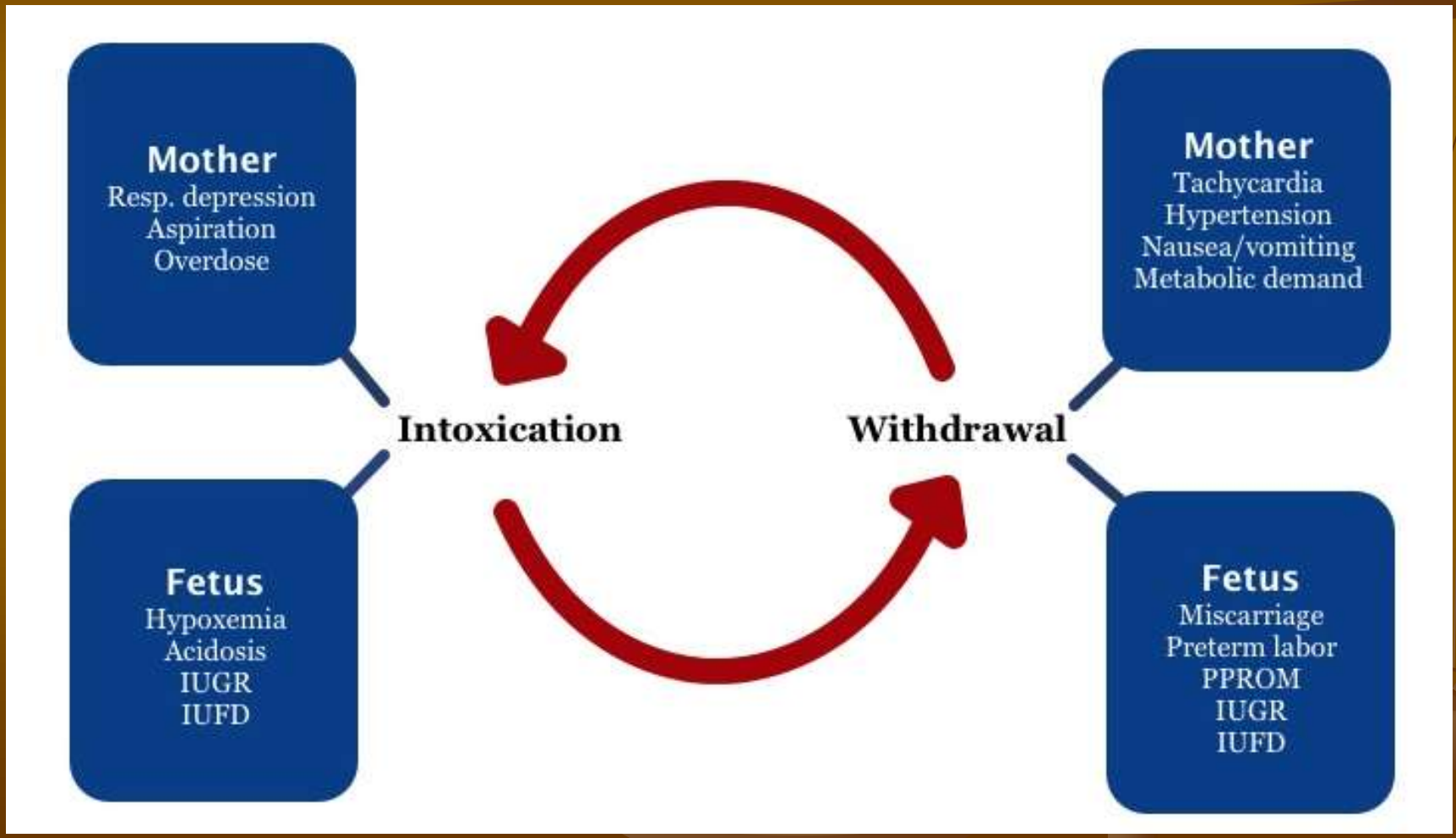
RESULTS: The prevalence of analgesic use was 73.1%, and it was higher in females (75.7%; $p<0.05$), in subjects 45-54 years (81.4%; $p<0.05$), in subjects in rural areas (74.6%; $p<0.05$), in subjects in northern region (84.3%; $p<0.05$), in illiterate subjects (79.1%; $p>0.05$), and in subjects of lower socioeconomic status (74.1%; $p>0.05$). One in ten of the participants used non-prescription analgesics. Non-prescription analgesics were more prevalent among the 55-65 age groups (18.1%; $p<0.05$), among female (11.6%; $p>0.05$), among the urban population (10.7%; $p>0.05$), and in subjects of lower middle socioeconomic status (13.2%; $p<0.05$). Logistic regression showed statistically significant ORs only for age groups, duration of education, socioeconomic status, and demographic regions ($p<0.05$).

CONCLUSIONS: The results showed that the prevalence of analgesic use and prescription analgesic use is high in Turkey, and their use is related to sociodemographic characteristics.

Management of Opioid Dependence in Pregnancy

- Treatment recommendations for opioid dependence in pregnancy have been derived from studies of *heroin-dependent* women
- Progressively increasing proportions of opioid-dependent women are addicted to non-medically prescribed analgesics
- Doctors may find it particularly challenging to identify and manage these women
- *How do the presentation, clinical course, and complications of these forms of opioid dependence compare with each other?*

Repeated Opioid Intoxication and Withdrawal during Pregnancy



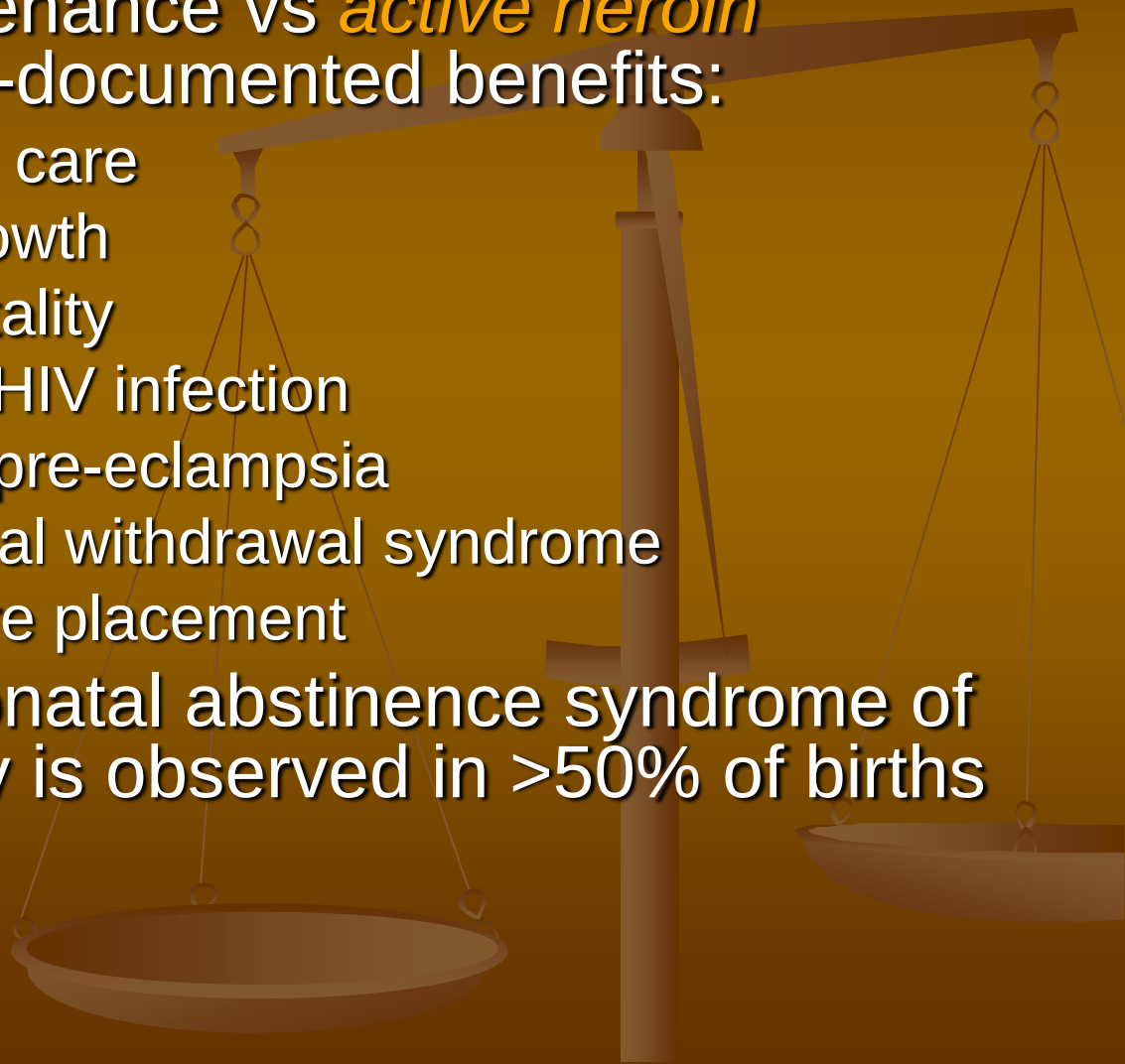
Complications of Opioid Dependence in Pregnancy

- Overdose/intrauterine withdrawal*
- First trimester spontaneous abortion
- Meconium staining
- Ante-partum hemorrhage
- Premature delivery
- Low birth weight
- Maternal/neonatal infection
- Neonatal abstinence syndrome*

* *Primarily* influenced by opioid pharmacological actions, not poor prenatal care/self-neglect

Opioid Dependence in Pregnancy: Benefits of Agonist Treatment

- Methadone maintenance vs *active heroin addiction* has well-documented benefits:
  - improved prenatal care
  - increased fetal growth
  - reduced fetal mortality
  - decreased risk of HIV infection
  - decreased risk of pre-eclampsia
  - decreased neonatal withdrawal syndrome
  - reduced foster care placement
- Nevertheless, neonatal abstinence syndrome of significant severity is observed in >50% of births



Do Benefits of Agonist Treatment Apply to Prescription Opioid Dependence?

- Not fully established if benefits of methadone maintenance during pregnancy demonstrated in heroin dependent women may extrapolate to *non-medically prescribed opioid analgesics*
- Recent research in non-pregnant individuals treated with buprenorphine for prescription opioid dependence has shown repeated relapses as buprenorphine discontinued
- Differences in complications can probably be attributed to intravenous route of administration (heroin)
- Support, structure, prenatal obstetrical oversight, and opioid maintenance delivered in a *comprehensive treatment program* are likely beneficial compared to the stressful and chaotic lifestyle associated with *active addiction to either heroin or prescription opioids*

Opioid Agonist Medications

- Methadone recognized as the standard of care in pregnancy for >40 years; discontinuation can cause significant neonatal abstinence syndrome (NAS)
- Buprenorphine recognized as highly effective for treatment of opioid dependence with less severe withdrawal; use in pregnancy relatively recent
- Less NAS with buprenorphine?


Methadone

Buprenorphine

- Opioid partial agonist at MOR; antagonist at KOR
- Schedule III (methadone is Schedule II)
- Buprenorphine treatment modalities available through "Qualifying Physicians" (DATA, 2000):
  - Office based treatment
    - Primary Care
    - Specialty (e.g.: Infectious Disease, Obstetrics/Gynecology, Psychiatry)
    - Substance abuse treatment clinics
  - Methadone maintenance programs

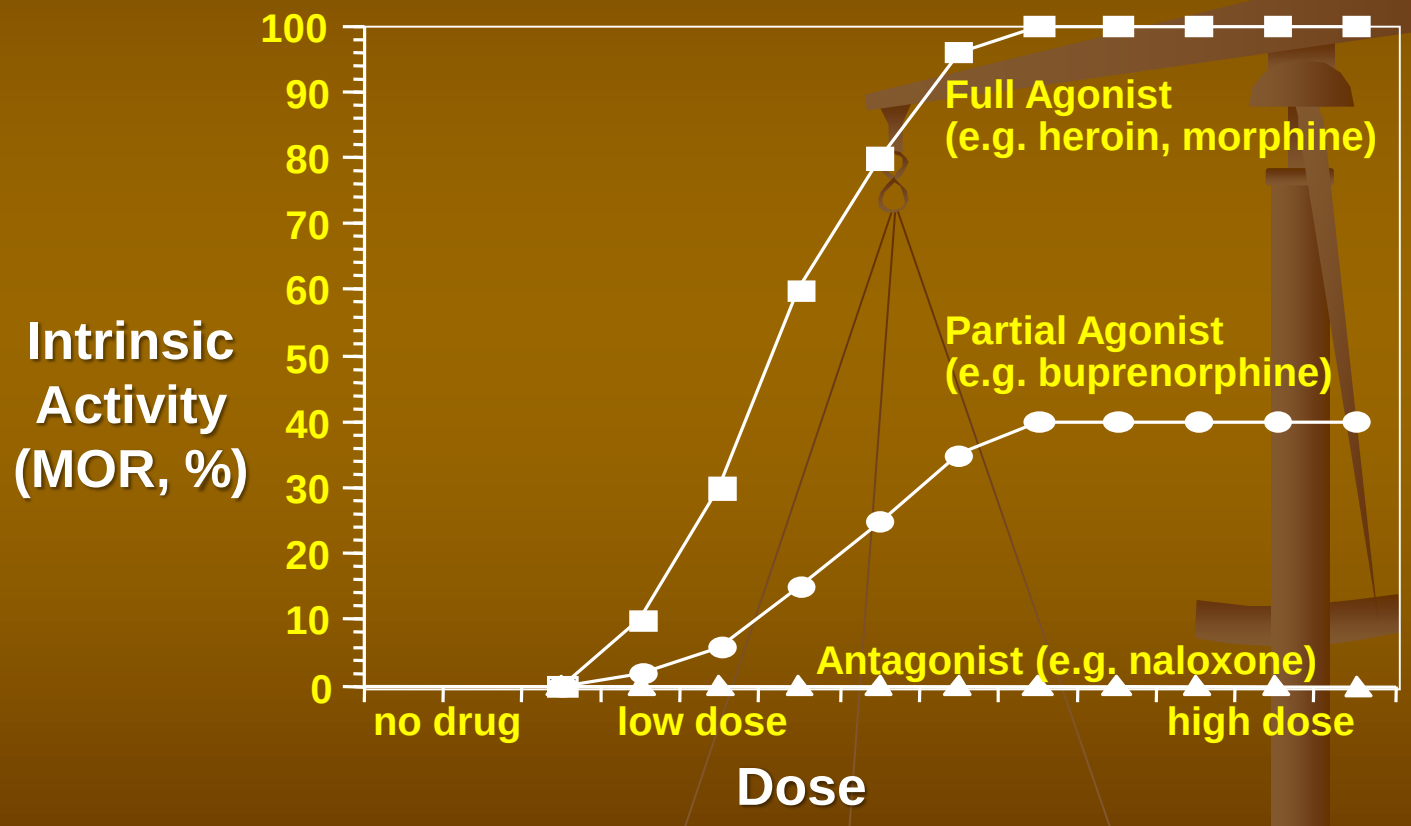
Buprenorphine has high binding affinity at MOR

- **AFFINITY** is the strength with which a drug physically binds to a receptor, but receptor affinity (strong or weak) is NOT the same as receptor **ACTIVATION** (efficacy)
- The affinity of buprenorphine is very strong and it **DISPLACES** full agonists like heroin and methadone (acts like an antagonist)

Buprenorphine dissociates very slowly from MOR binding site

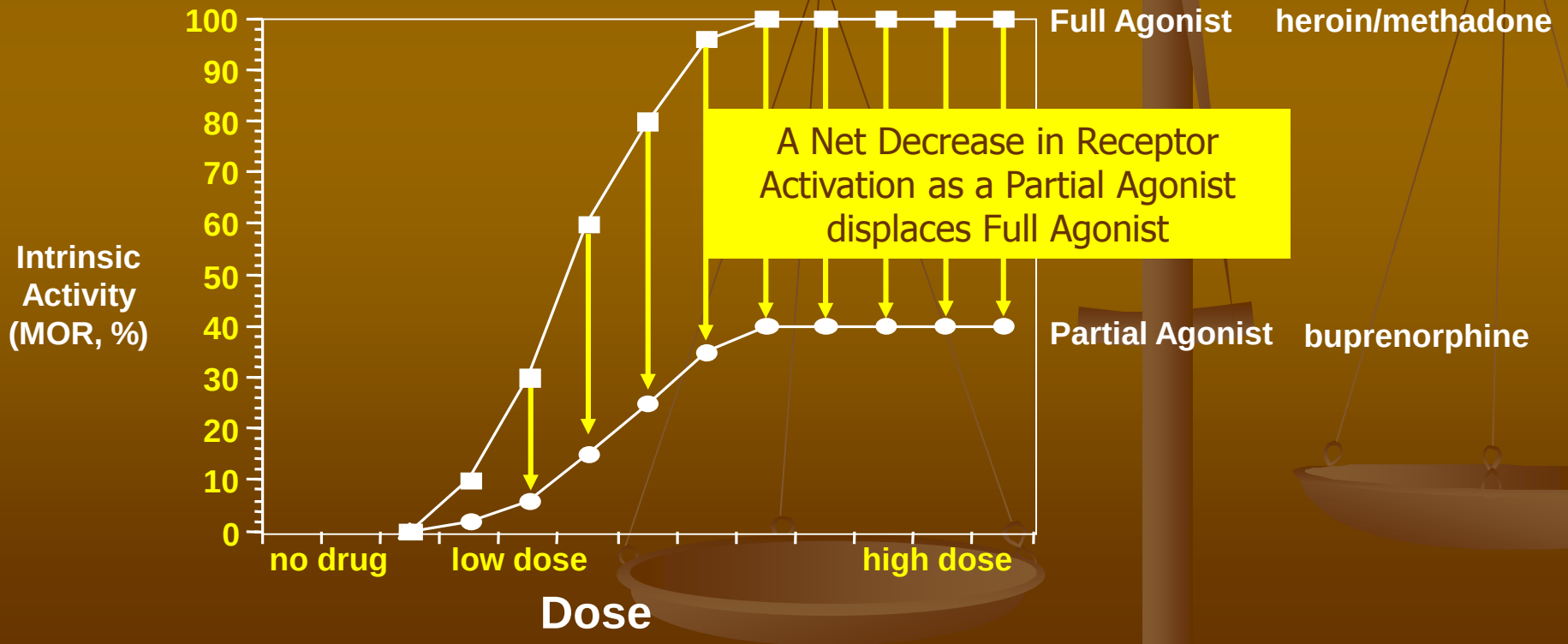
- **DISSOCIATION** is the rate at which a drug disengages or uncouples from the receptor after activation
  - Dissociation rate of buprenorphine is relatively slow
  - Therefore, buprenorphine occupies the receptor for a long time and thereby blocks agonists (e.g., heroin or methadone) from binding

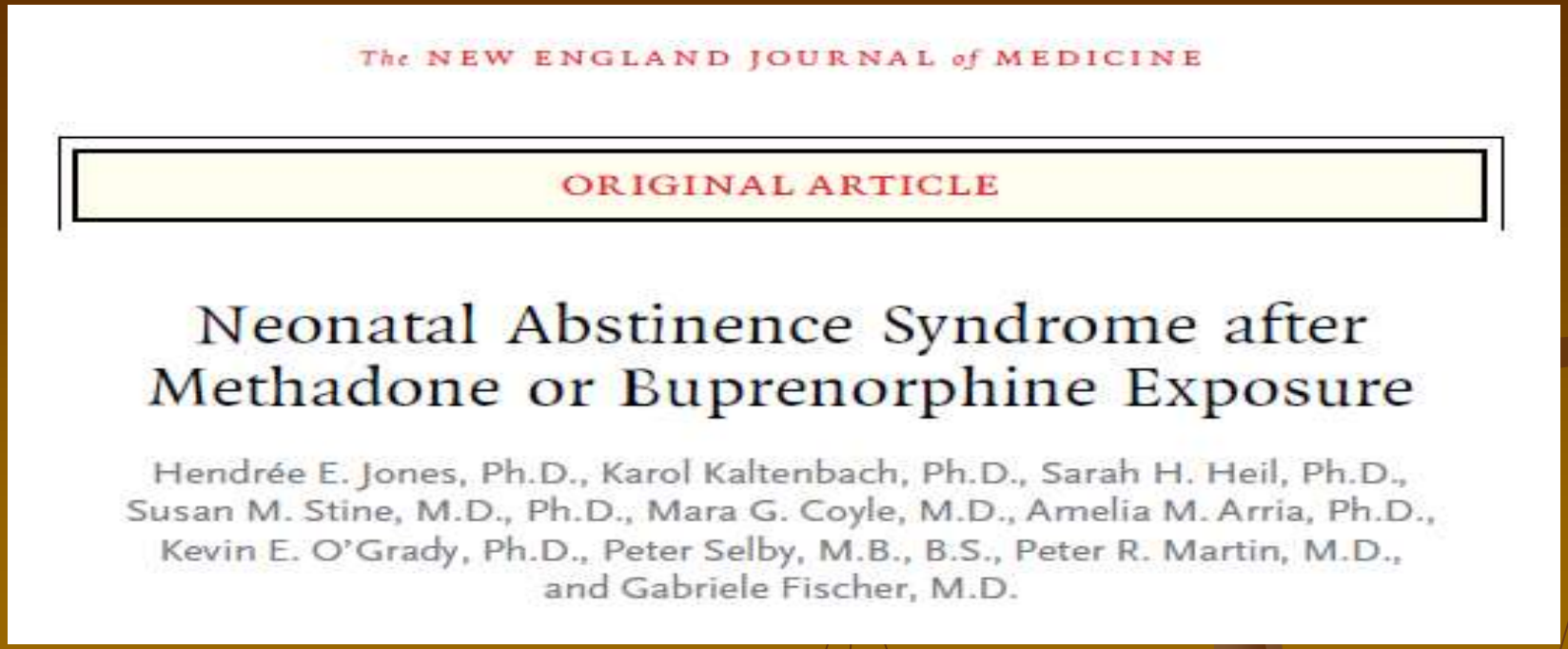
Buprenorphine is a partial (~50% activity) agonist at MOR



Pharmacology of Full *vs* Partial Agonists

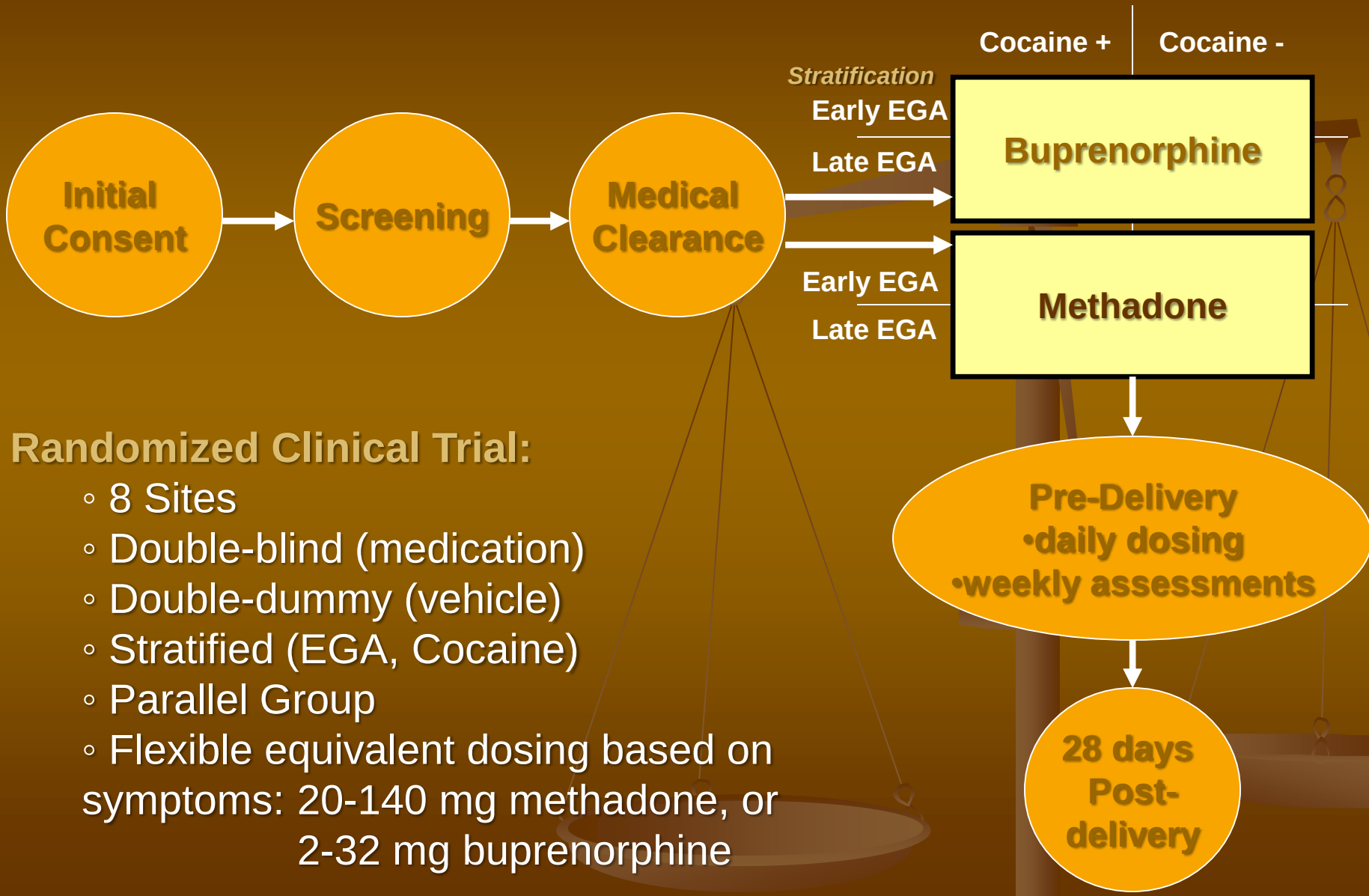
- Buprenorphine can precipitate withdrawal if it displaces a full agonist from MOR because it only partially (~50%) activates the receptor, therefore resulting in a net decrease in activation





Objective: To compare, for the first time, in opioid-dependent women, maternal and neonatal outcomes of treatment with buprenorphine or methadone throughout pregnancy in an international multi-center randomized, controlled, double-blind/double-dummy clinical trial.

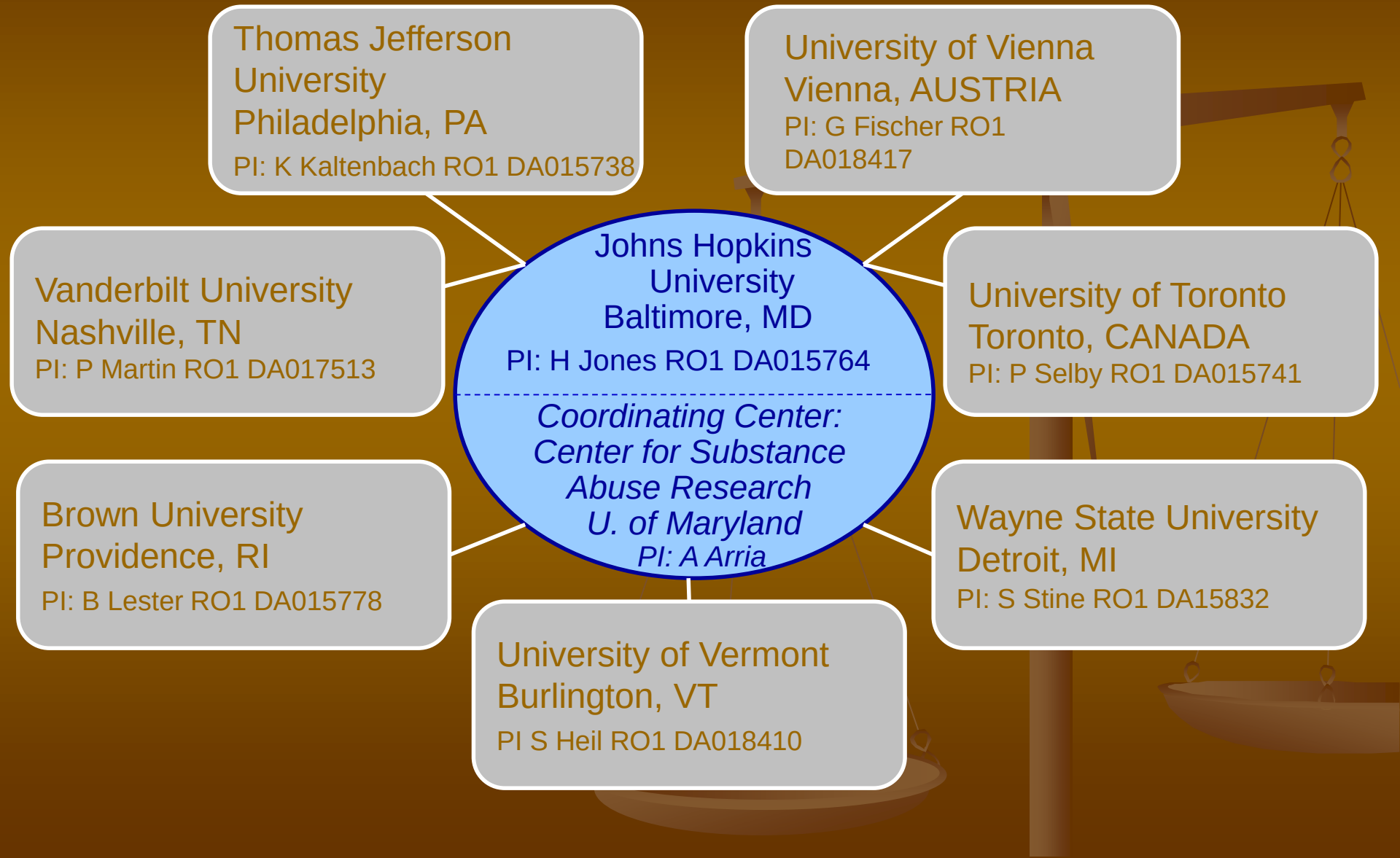
MOTHER Study: Experimental Design



Randomized Clinical Trial:

- 8 Sites
- Double-blind (medication)
- Double-dummy (vehicle)
- Stratified (EGA, Cocaine)
- Parallel Group
- Flexible equivalent dosing based on symptoms: 20-140 mg methadone, or 2-32 mg buprenorphine

MOTHER Study: Clinical Sites



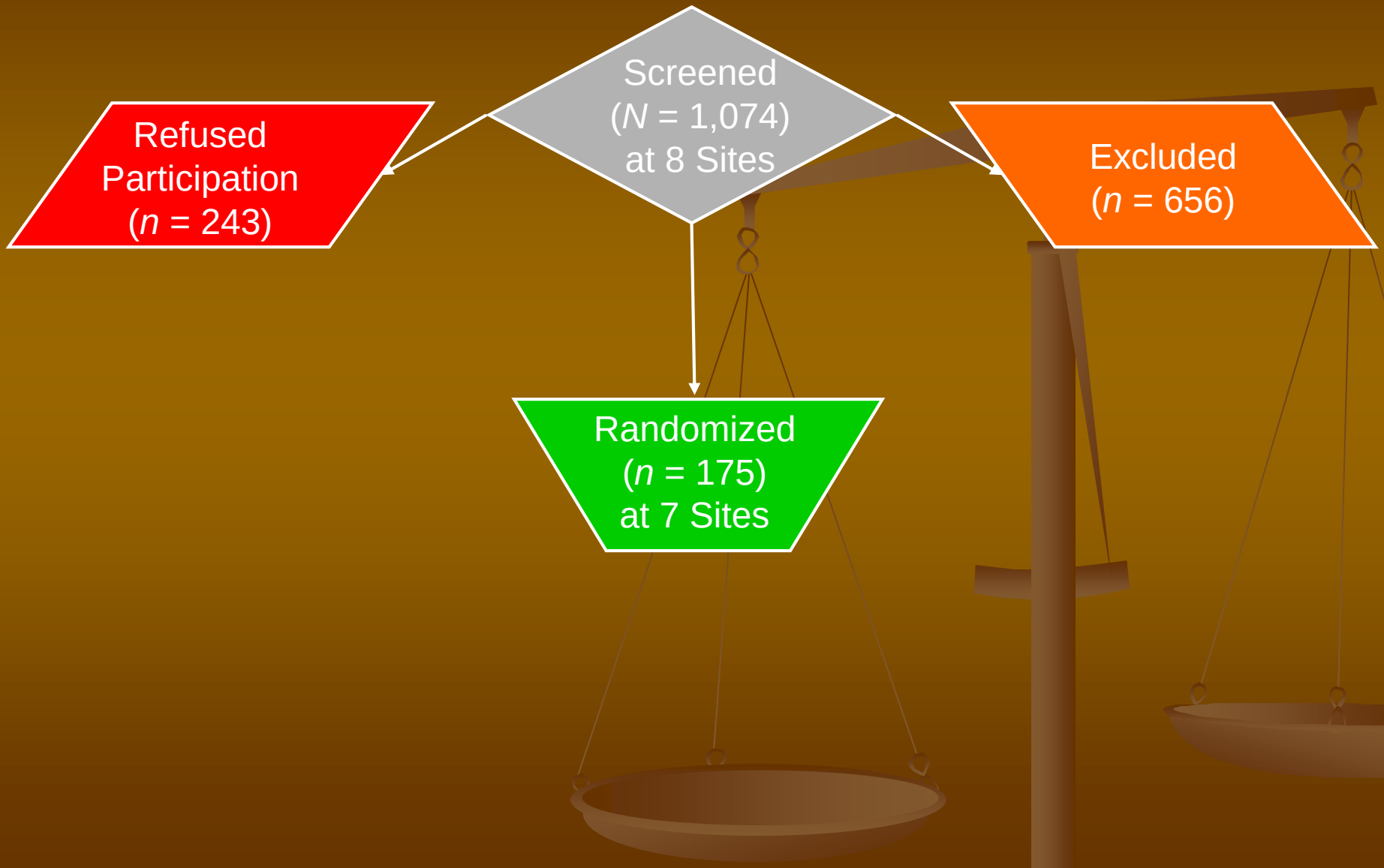
MOTHER: Inclusion/Exclusion Criteria

- 18-40 years of age
- Gestational age 6-30 weeks
- Opioid-dependent (DSM-IV, SCID I)
- Opioid-positive urine
- No alcohol or benzodiazepines
- Single-fetus pregnancy
- Plan to deliver at site hospital

MOTHER Experimental Design Comprehensive Care

- Vouchers (progressively increasing $-value gift certificates) contingent upon drug-negative urine and breathalyzer results and compliance with treatment program
- Addiction counseling and education about healthy pregnancy and preparation for parenting, relationships
- Prenatal obstetric services and medical, psychiatric care

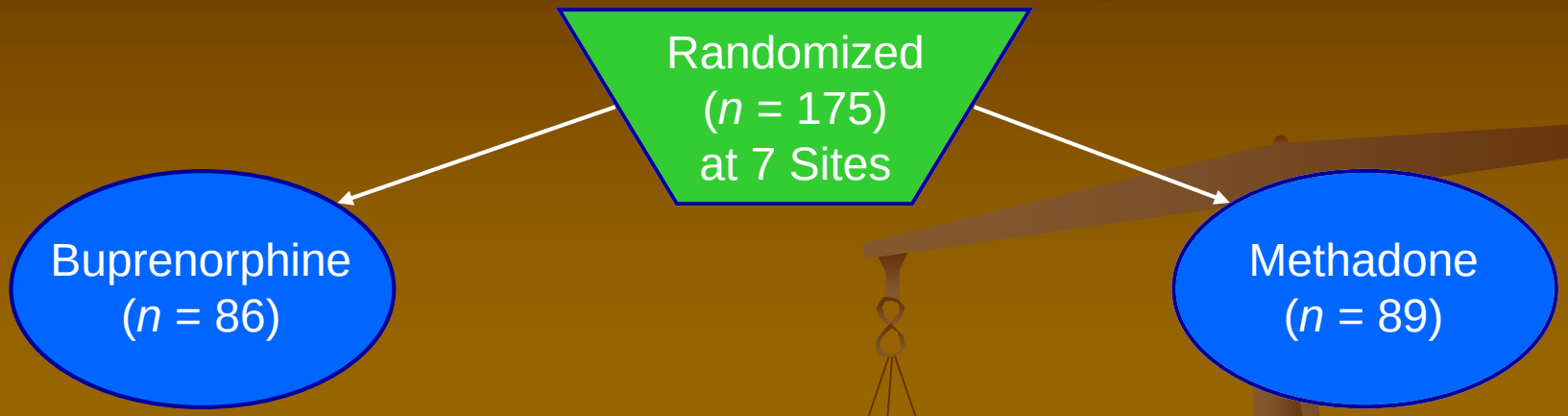
CONSORT Diagram



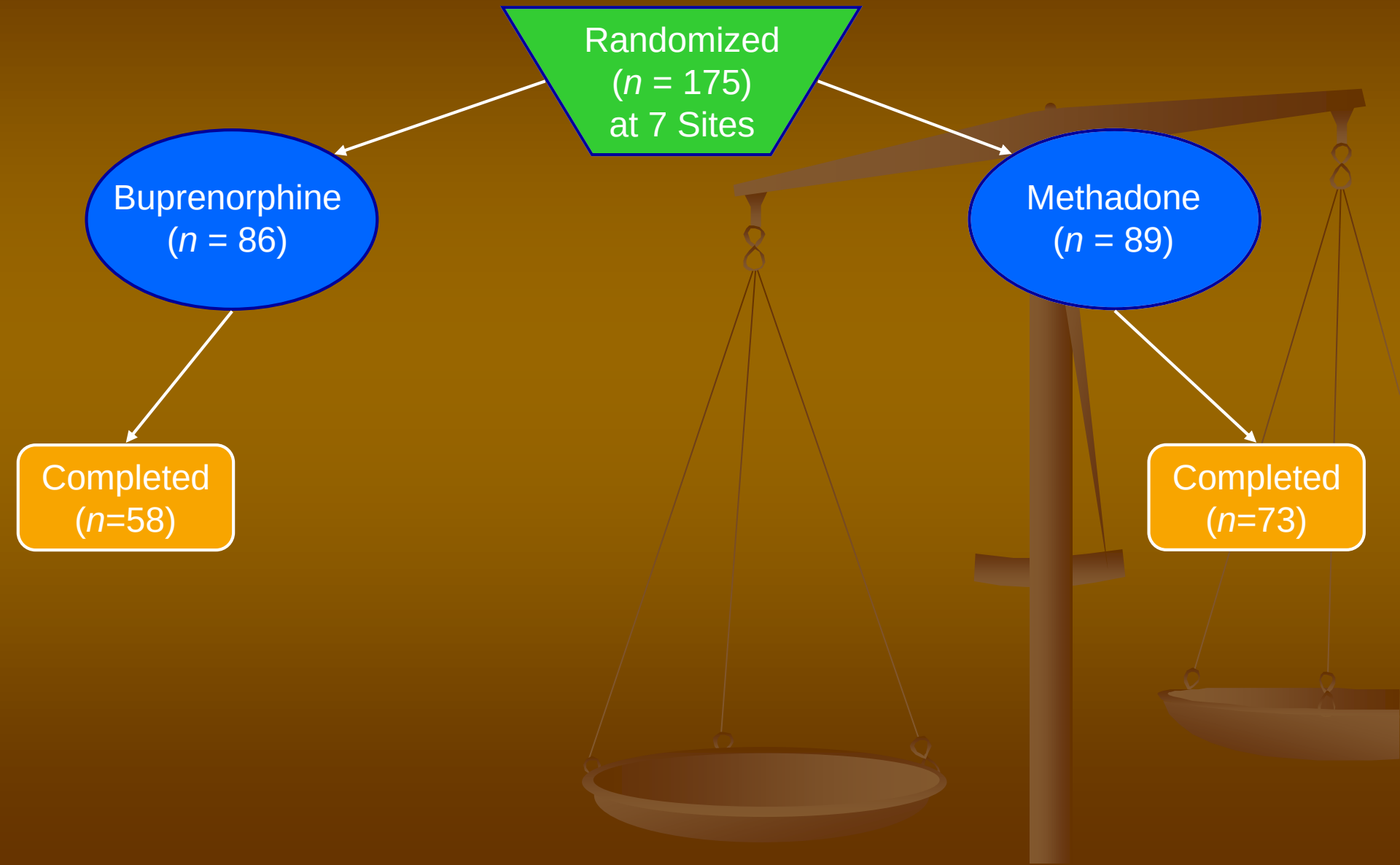
CONSORT Diagram

Randomized
(*n* = 175)
at 7 Sites

CONSORT Diagram



CONSORT Diagram



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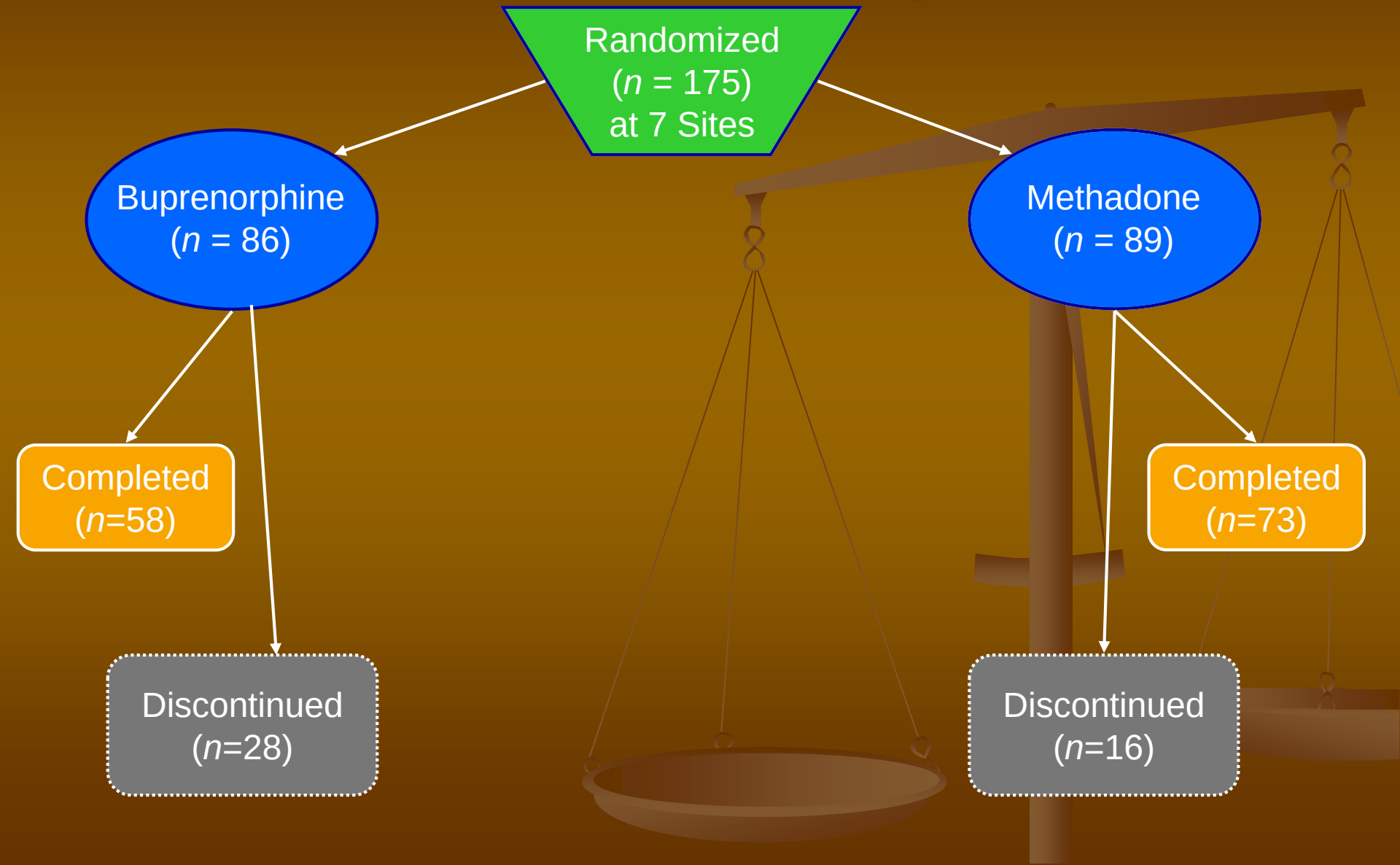

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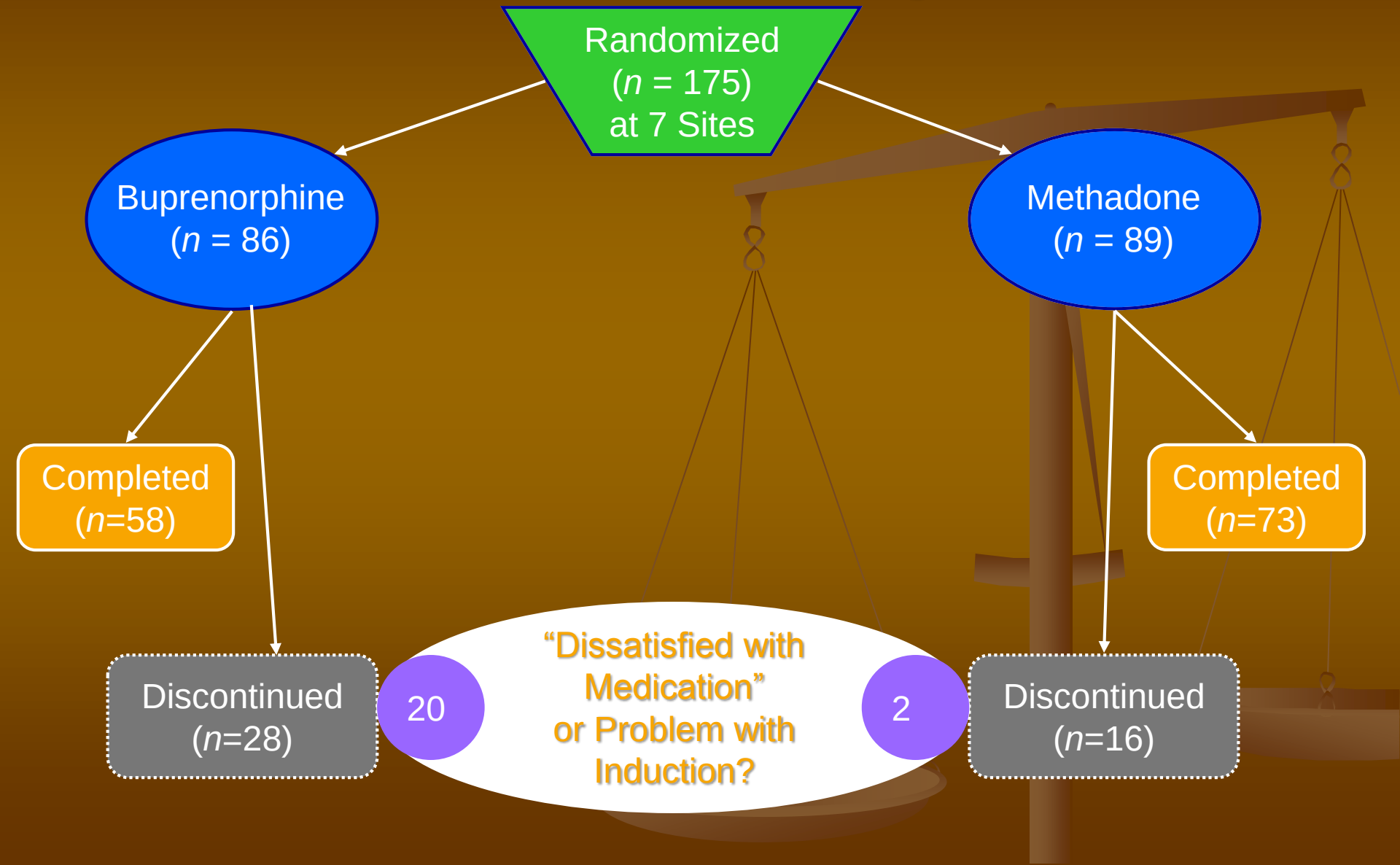
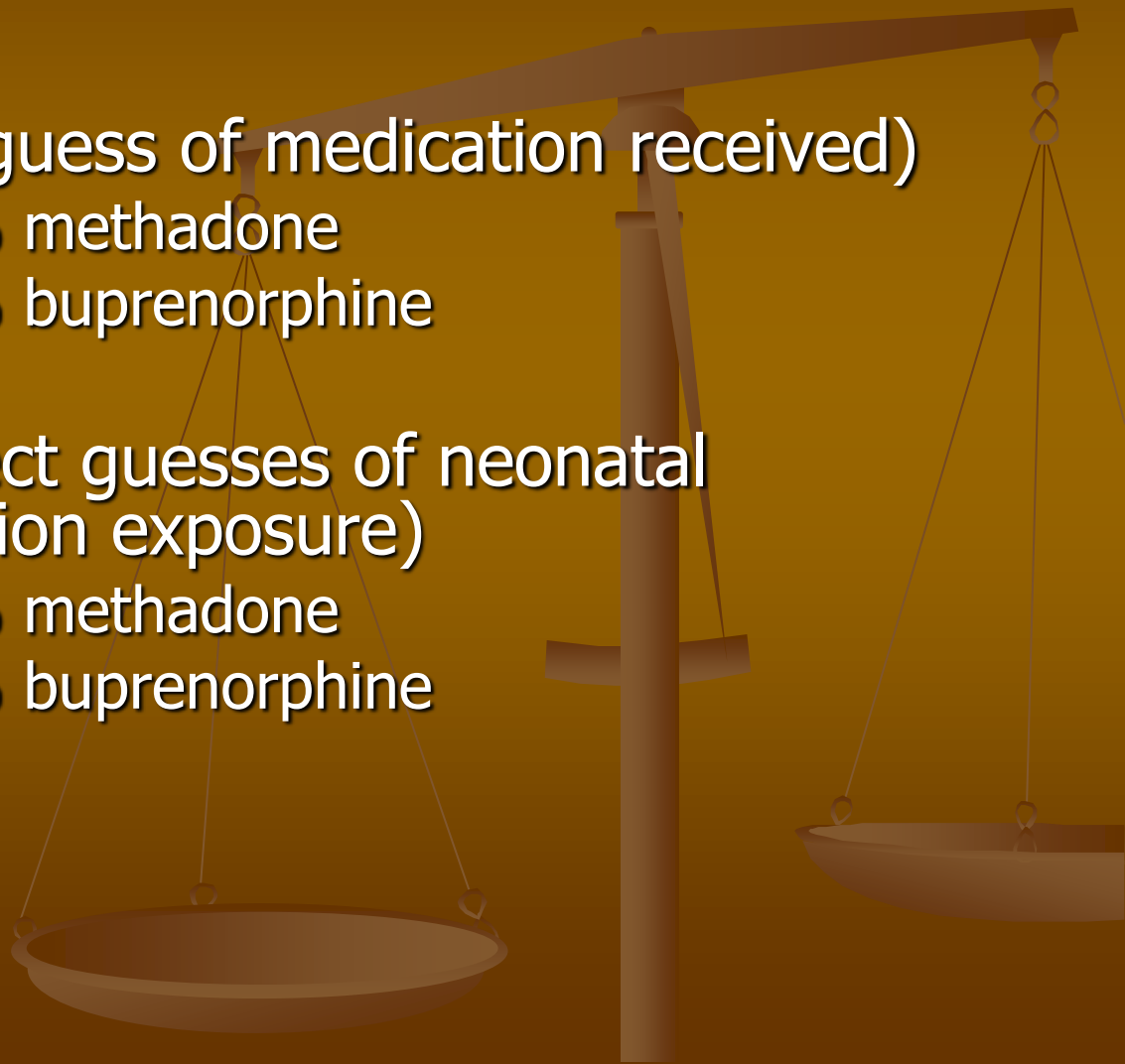


Baseline Characteristics: Completers

	Total Sample (*N*=131) % or Mean (*SE*)	Methadone (*n*=73) % or Mean (*SE*)	Buprenorphine (*n*=58) % or Mean (*SE*)	*p*
Maternal age in years	26.6 (.5)	27.7 (.7)	25.3 (.7)	.014
Race				.263
White	87.8%	84.9%	91.4%	
Black	9.2%	13.7%	3.4%	
Other	3.1%	1.4%	5.2%	
Years of education	11.3 (.2)	11.3 (.3)	11.3 (.2)	.912
Employed	16.0%	13.7%	19.0%	.414
Legal Status (uninvolved)	83.2%	79.5%	87.9%	.197
Estimated weeks of gestational age at study entry	18.7 (.5)	18.7 (.8)	18.7 (.7)	.938

Site was a blocking factor in all analyses; Bonferroni's principle was used to set family-wise α = .0045.

Blind Satisfactorily Protected



- Patients (correct guess of medication received)
  - 24.7% methadone
  - 51.7% buprenorphine
- NAS Raters (correct guesses of neonatal medication exposure)
  - 39.7% methadone
  - 44.8% buprenorphine

Neonatal Abstinence Syndrome

- Neurologic excitability
  - irritability, hyperactivity, sleep disturbance
- Gastrointestinal dysfunction
  - uncoordinated sucking/ swallowing, vomiting
- Autonomic Signs
  - fever, sweating, nasal stuffiness

Finnegan & Kaltenbach, 1992

Primary Outcomes

Primary Outcomes	Methadone Mean (*SE*)	Buprenorphine Mean (*SE*)	Odds Ratio *(Confidence Interval)*	*p*
Treated for NAS [Yes]	{57%}	{47%}	.65 (.24, 1.76)	.26
NAS peak score	12.76 (.56)	11.03 (.62)		.04
Total amount of morphine for NAS (mg)	*10.40 (2.56)*	*1.11 (.65)*		*.00000012*
Days of infant hospital stay	*17.46 (1.52)*	*9.99 (1.24)*		*.00012*
Head circumference (cm)	33.03 (.25)	33.81 (.27)		.03

Notes. Significant results are in italics. Site was blocking factor in all analyses. The O'Brien-Fleming α spending function resulted in $\alpha = .0091$ for the inferential tests of the Medication Condition effect for the 5 primary outcome measures at the conclusion of the trial.

Secondary Neonatal Outcomes

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)*		*.0005*
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

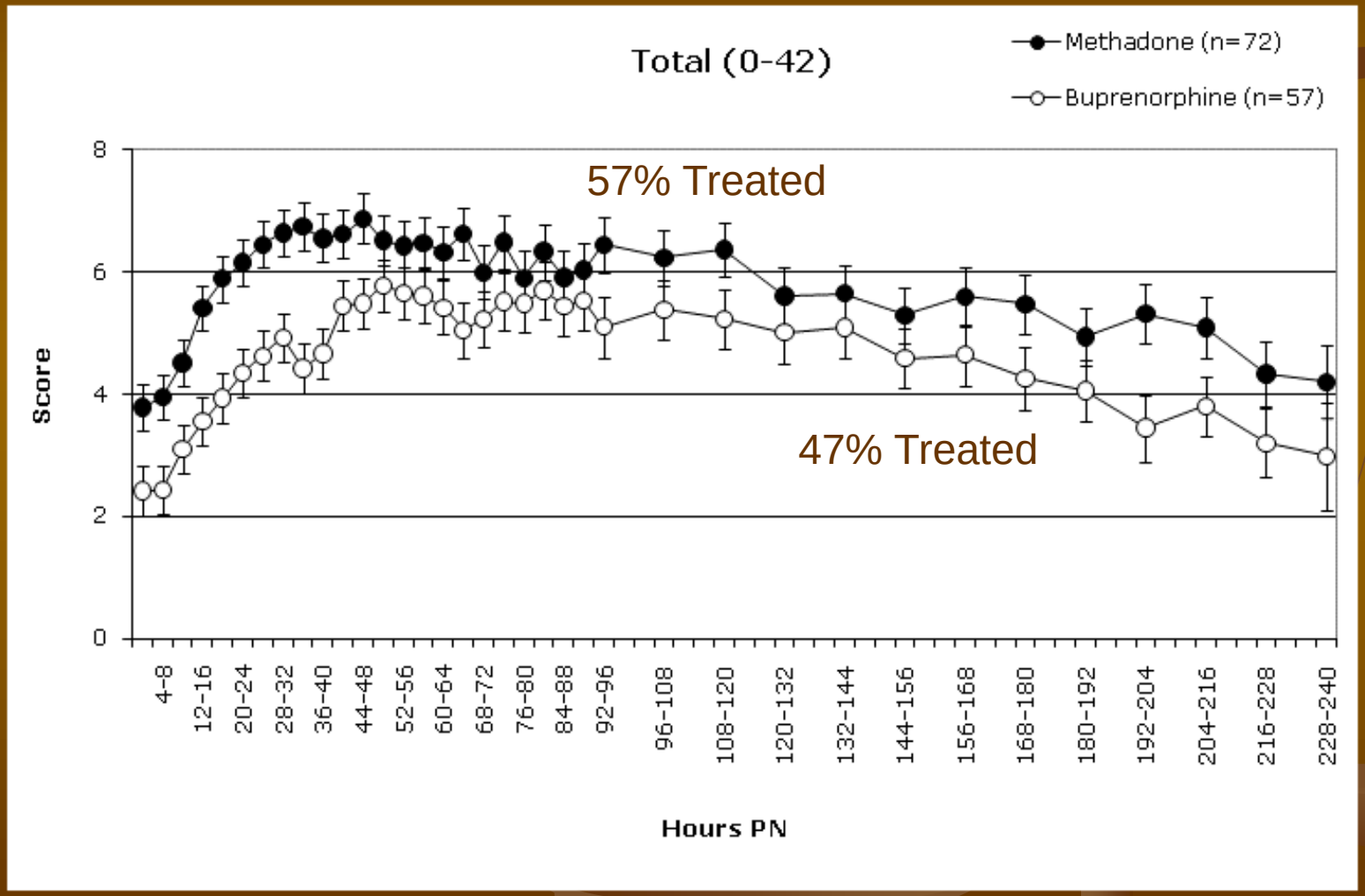
Note. Significant results are in italics. Bonferroni's principle was used to set familywise α =.003125 (nominal α = .05/16) for the secondary outcome measures.

Secondary Maternal Outcomes

Secondary Maternal Outcomes	Methadone Mean (*SE*)	Buprenorphine Mean (*SE*)	Odds Ratio *(Confidence Interval)*	*p*
Medication dose at delivery (mg)	78.20 (3.95)	16.15 (.86)		*NA*
Premature Discontinuance [Yes]	{18%}	{33%}	2.61 (1.26, 5.60)	.02
Drug screen at delivery [Positive]	{15%}	{9%}	1.92 (.34, 10.86)	.27
Medical complications at delivery [Yes]	{51%}	{31%}	.45 (.21, .92)	.03
Normal presentation [Yes]	{86%}	{95%}	.31 (.04, 2.41)	.09
Cesarean section [Yes]	{37%}	{29%}	.62 (.20, 1.99)	.23
Maternal weight gain (kg)	8.59 (.96)	8.26 (.86)		.80
Number of prenatal obstetrical visits	8.80 (.45)	8.69 (.41)		.86
Amount of voucher money earned for drug-negative tests (US $)	1,570.6 (121.7)	1,391.4 (123.6)		.30

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

NAS Scores in Neonates Exposed to Buprenorphine or Methadone



Heil et al, Addiction (in press)

Secondary Analyses of Maternal Psychiatric Symptoms

- Prevalence of co-occurring other psychiatric disorders among opioid-dependent pregnant women?
- Does presence of psychopathology at study entry predict retention in treatment?
- *What are the implications of co-occurring psychopathology for treatment of opioid-maintained pregnant women?*

Co-occurring Other Psychiatric Diagnoses (MINI) among MOTHER Participants (n=174)*

Co-occurring (Putative) Disorder	Prevalence (%)
Major Depressive Disorder	32
Dysthymia	31
Hyperthymia	39
Generalized Anxiety Disorder	40
Panic Disorder	26
Agoraphobia	22
Social Phobia	16
Post-Traumatic Stress Disorder	16
Obsessive Compulsive Disorder	3
Bulimia	<1

*Benningfield et al., Am J Addict. 19:316-421, 2010

Addiction Severity Index Composite Scores by MINI Diagnoses*

Psychiatric symptoms	ASI composite scores*													
	Medical		Employment		Alcohol		Drugs		Legal		Family/ social		Psychological	
	X	*p*	X	*p*	X	*p*	X	*p*	X	*p*	X	*p*	X	*p*
MDD														
Yes ($n = 56$)	**.35**	**.007**	.83	.973	.01	.464	**.33**	**<.001**	.12	.702	**.38**	**.001**	**.36**	**<.001**
No ($n = 118$)	**.22**		.79		.01		**.28**		.13		**.27**		**.14**	
GAD														
Yes ($n = 69$)	.29	.125	.79	.192	.01	.923	**.31**	**.003**	.13	.325	**.39**	**<.001**	**.33**	**<.001**
No ($n = 105$)	.24		.81		.01		**.29**		.12		**.25**		**.13**	
Hypomania														
Yes ($n = 67$)	**.31**	**.023**	**.79**	**.013**	.00	.250	**.31**	**.011**	.14	.245	**.37**	**.003**	**.32**	**<.001**
No ($n = 107$)	**.22**		**.81**		.01		**.29**		.12		**.26**		**.14**	
Dysthymia														
Yes ($n = 55$)	.31	.155	.83	.130	.01	.020	**.33**	**<.001**	.13	.298	**.41**	**<.001**	**.36**	**<.001**
No ($n = 119$)	.23		.79		.01		**.29**		.12		**.26**		**.14**	

*Benningfield et al., Am J Addict. 19:316-421, 2010

Co-occurring Depression and Anxiety (MINI): Likelihood of Drop-out from MOTHER Study*

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	Random	1.093	.420	6.767	1	.009	2.982	1.309	6.794
	Depres	-1.324	.569	5.420	1	.020	.266	.087	.811
	Dysthmia	.092	.530	.030	1	.862	1.096	.388	3.095
	Suicide	.162	.707	.052	1	.819	1.176	.294	4.703
	Hypomani	-.487	.553	.776	1	.378	.615	.208	1.816
	Panic	-.309	.562	.303	1	.582	.734	.244	2.208
	Agorapho	-.529	.611	.752	1	.386	.589	.178	1.949
	SAnxiety	.659	.644	1.046	1	.307	1.932	.547	6.827
	Obcomp	-.987	1.343	.540	1	.462	.373	.027	5.184
	PTSD	.753	.621	1.468	1	.226	2.123	.628	7.171
	Bulimia	-1.637	.975	2.820	1	.093	.195	.029	1.315
	Genanxi	1.962	.500	15.367	1	.000	7.110	2.667	18.959
	Constant	-3.079	.778	15.676	1	.000	.046		

a. Variable(s) entered on step 1: Depres, Dysthmia, Suicide, Hypomani, Panic, Agorapho, SAnxiety, Obcomp, PTSD, Bulimia, Genanxi.

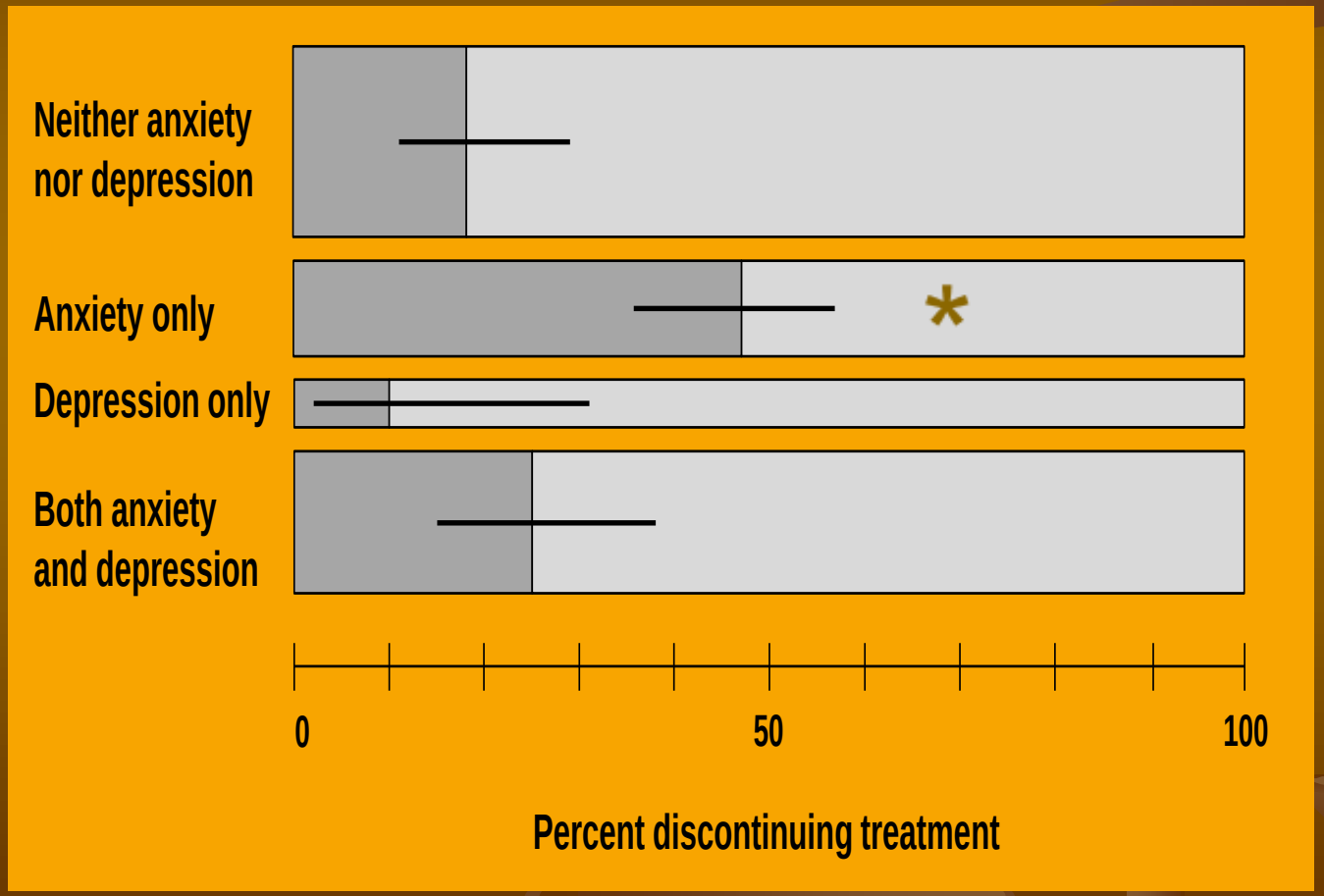
*Benningfield et al. (in press)

Co-occurring Depression, Anxiety, or Both (MINI) among MOTHER Participants (N=175)*

Co-occurring (Putative) Disorder	Prevalence (%)
Depression (Major Depressive Disorder, Dysthymia, Suicide)	10.9
Anxiety (Generalized Anxiety, Panic, Agoraphobia, Social Phobia, Post-Traumatic Stress, Obsessive-Compulsive Disorders)	19.4
Both Depression and Anxiety	32.0

*Benningfield et al. (in press)

Co-occurring Anxiety (MINI): Greatest Determinant of Premature Drop-out



Implications for Clinical Practice

- Depressed women in opioid maintenance are less likely to drop out of treatment, perhaps due to a *significant "antidepressant" effect* of opioid agonists
- Women with anxiety are much more likely to drop out of opioid maintenance; they may need *individualized psychotherapeutic interventions or additional pharmacotherapy* to assist retention
- Differential effects of methadone and buprenorphine on depressive/anxiety symptoms in this population would be important to determine in future research

Management of Depression in Pregnancy

- Ten percent or more of pregnant (approx 40% opioid dependent) women have clinical depression
- Relapse rates of depression high if treatment stopped
- There are significant fetal complications associated with untreated maternal depression *per se*
- Data are lacking on the best way to manage depression in pregnant (even non-opioid dependent) women
- Pressing need to compare SSRIs with other treatments to determine which are the safest, the most effective, and the best tolerated by pregnant women
- *Personalized treatment that optimizes risk/benefit with informed consent is the goal*

J L Mills, *N Engl J Med 2006 354: 636-638*

SSRI Exposure in Third Trimester: Poor Neonatal Adaptation Syndrome

- Jitteriness
- Poor muscle tone
- Weak or absent cry
- Respiratory distress (with other causes ruled out)
  - Typically starts within 3 days after birth
  - Occasionally requires respiratory support
  - Self-limited
- Hypoglycemia
- Low Apgar score
- Seizures

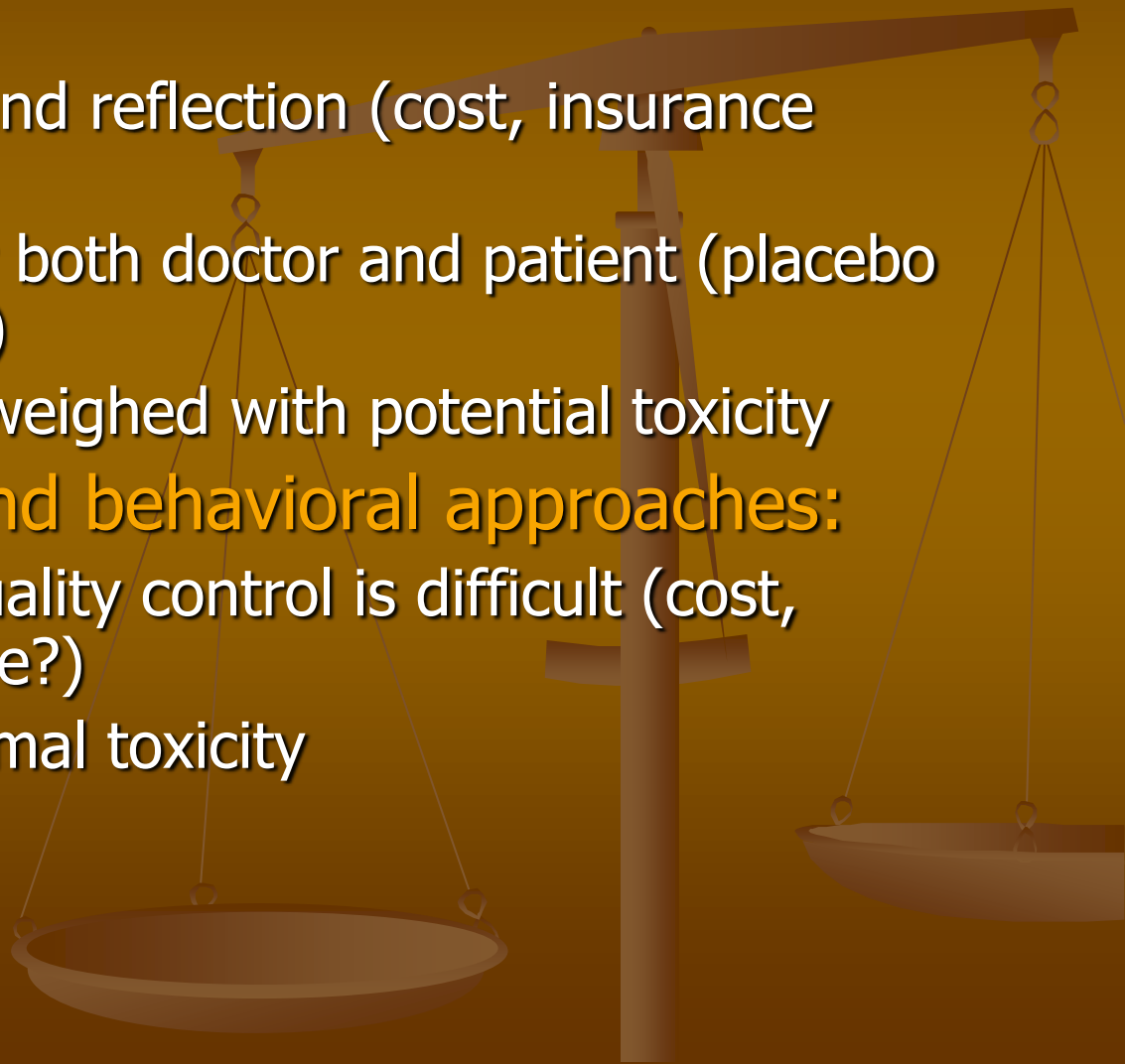
Koren, G. et al. CMAJ 2005;172:1457-1459

Treatment of Depression/Anxiety in Pregnant Opioid Addicts

- Diagnosis of depression/anxiety is confounded by similarities with the signs and symptoms of pregnancy and opioid dependence
- Medication choice for depression/anxiety in these women should be significantly modified:
  - *Pregnancy*—minimize exposure of fetus to any medications unless absolutely necessary
  - *Co-occurring opioid dependence*—opioid agonists can have significant beneficial effects on mood

Risk/Benefit Ratio is Altered in Pregnancy

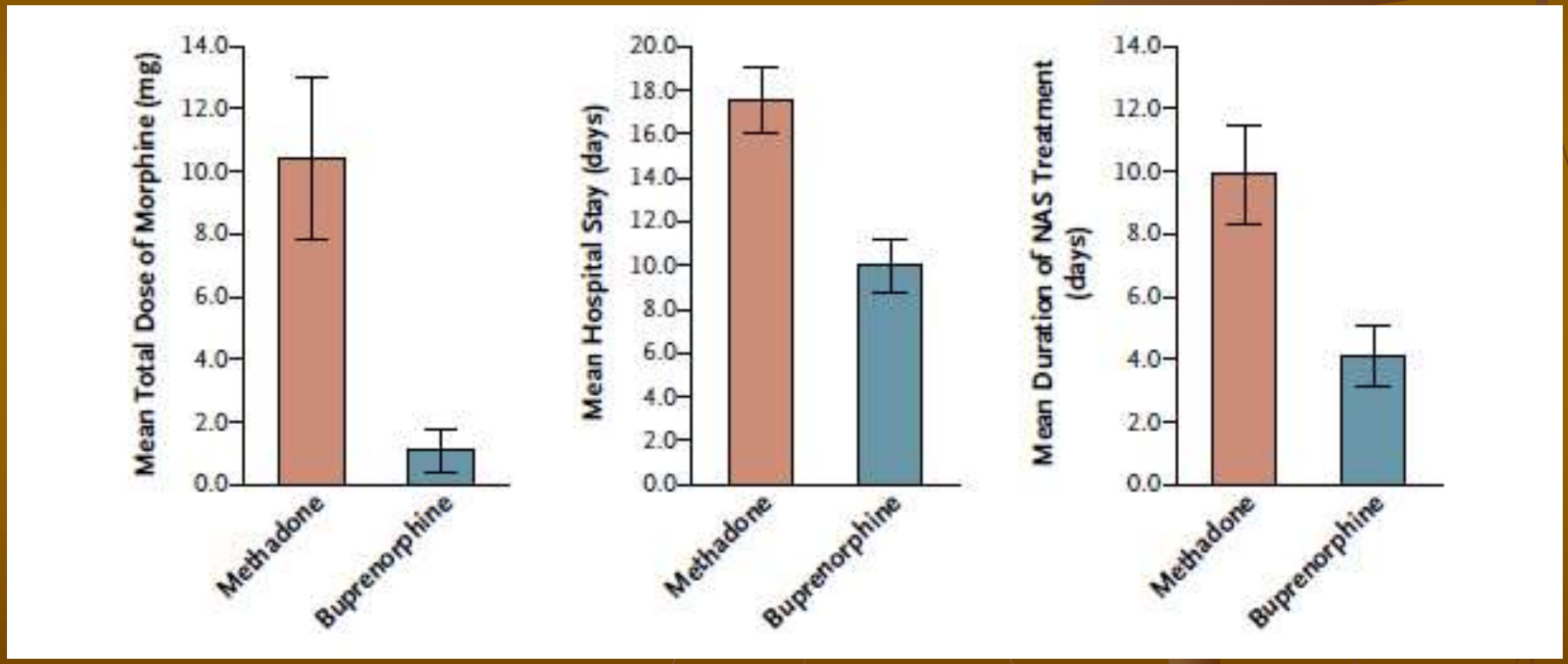
- Medications:
  - less time, effort, and reflection (cost, insurance coverage?)
  - symbolic value for both doctor and patient (placebo effect is profound)
  - benefits must be weighed with potential toxicity
- Psychotherapy and behavioral approaches:
  - labor intensive, quality control is difficult (cost, insurance coverage?)
  - benefits with minimal toxicity



Opioid Dependence during Pregnancy: Recommendations for Pharmacotherapy

- Medications (beyond *adequate* opioid substitution) may *not* be needed in many moderately depressed/anxious women with access to good behavioral treatment/monitoring
- For severely depressed/anxious patients, or those with previous episodes with significant complications, cautious antidepressant prescription may be indicated
- Targeting anxiety may be particularly important in treatment of opioid dependent patients

Major Findings of MOTHER Study: Morphine Dose, Length of Hospital Stay, and Treatment Duration for NAS



Jones et al, N Engl J Med 2010 Dec 9;363(24):2320-31.

Summary of Obstetrical Outcomes in MOTHER Study

- Methadone and buprenorphine produced similar obstetric outcomes in the context of comprehensive care, except:
  - Buprenorphine treatment resulted in less suppression of fetal heart rate, fetal heart rate reactivity, and the biophysical profile score after medication dosing
  - Methadone maintenance was associated with a higher incidence of preterm labor and a significantly higher percentage of respiratory distress in neonates

Salisbury et al, Addiction (in press)

Clinical Implications

- In summary, the safety and efficacy of opioid maintenance treatment during pregnancy must be judged in the context of *other services provided by a comprehensive treatment program* rather than the administered medication *per se*
- Buprenorphine is not inferior to methadone, the standard of care for heroin dependence in pregnancy for >40 yrs; but it may be preferable in terms of some pregnancy outcome measures
- Safe buprenorphine induction of actively using opioid dependent pregnant women is challenging and should not routinely be attempted

Early Fetal Exposure to Opioids

- Reports of teratogenic effects of first trimester opioid exposure must now be added to our risk/benefit considerations:
  - FDA guidelines do not currently recommend avoiding use of prescription opioids during pregnancy
  - Ex vivo and animal studies suggest the possibility of teratogenic effects
  - First trimester exposure associated with significant increase in major cardiac and neural tube defects and trend towards increase in major CNS defects (CDC National Birth Defects Prevention Study, Broussard et al., 2011)
  - Magnitude of necessary fetal exposure undetermined

Changing Face of Opioid Dependence in the U.S.

Newly Born and Withdrawing From Painkillers—NY Times, April 9, 2011

The MOTHER Team