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NEONATAL ABSTINENCE SYNDROME (NAS) AKA NEWBORN DRUG WITHDRAWAL:THE NEWARK EXPERIENCE

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Neonatal Abstinence Syndrome (NAS): DEFINITIONs

- NAS are signs and symptoms in the Newborn infant that results from sudden discontinuation of fetal exposure to substances that were USED or ABUSED by the mother during pregnancy

- Substances may be LICIT or ILLICIT

SUBSTANCES ASSOCIATED WITH NAS

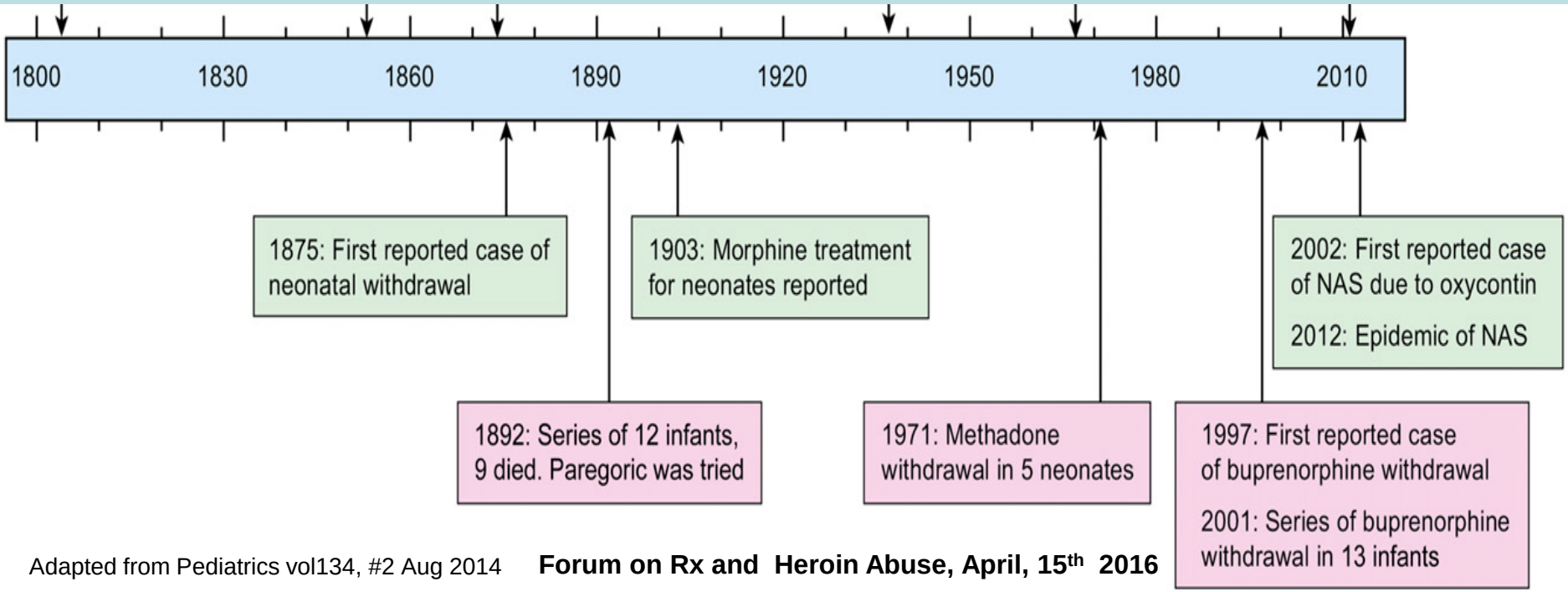
Opioids

- Morphine
- Methadone
- Heroin
- Buprenorphine
- Prescription pain medications (Vicodin, Oxycontin, Percocet)

Non Opioids

- Psychotropic medications such as antidepressants including SSRIs, SSNRIs, TCAs, anti anxiety drugs such as Benzodiazepines
- Methamphetamines
- Inhalants

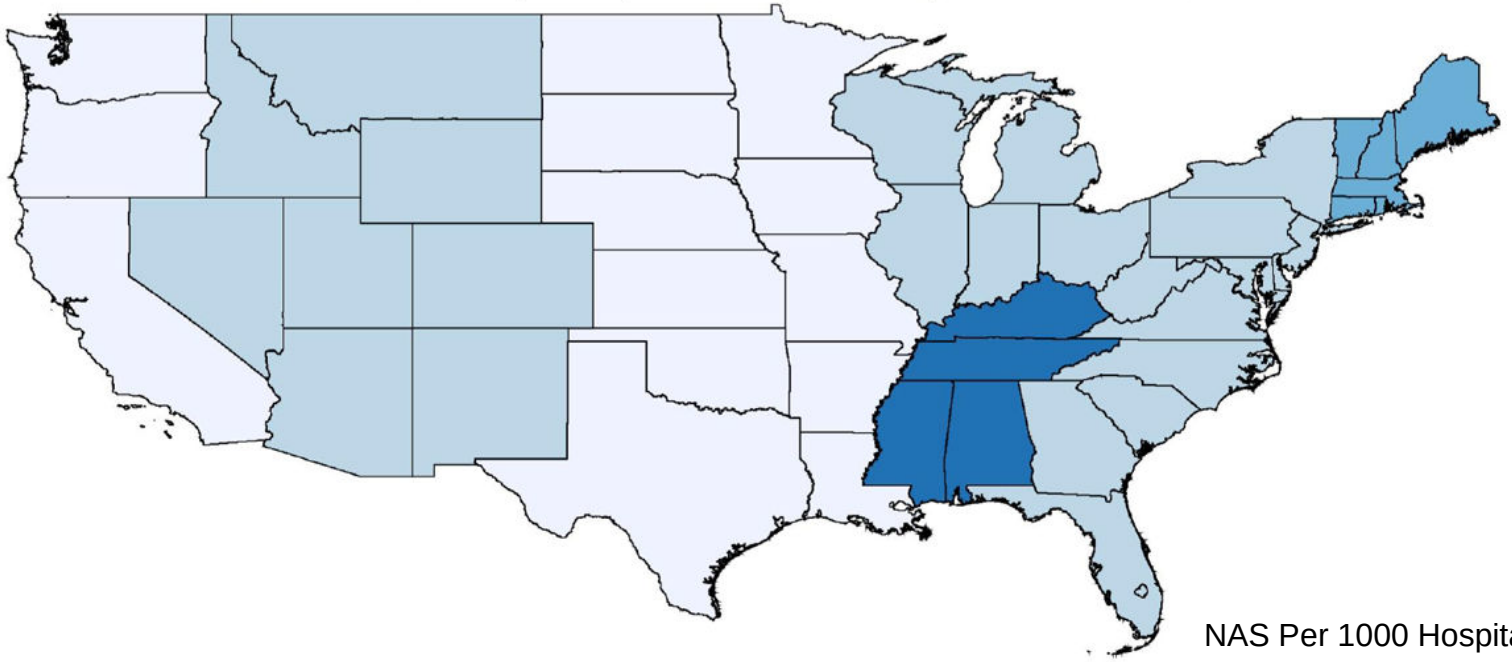
Historical Overview



Adapted from Pediatrics vol134, #2 Aug 2014

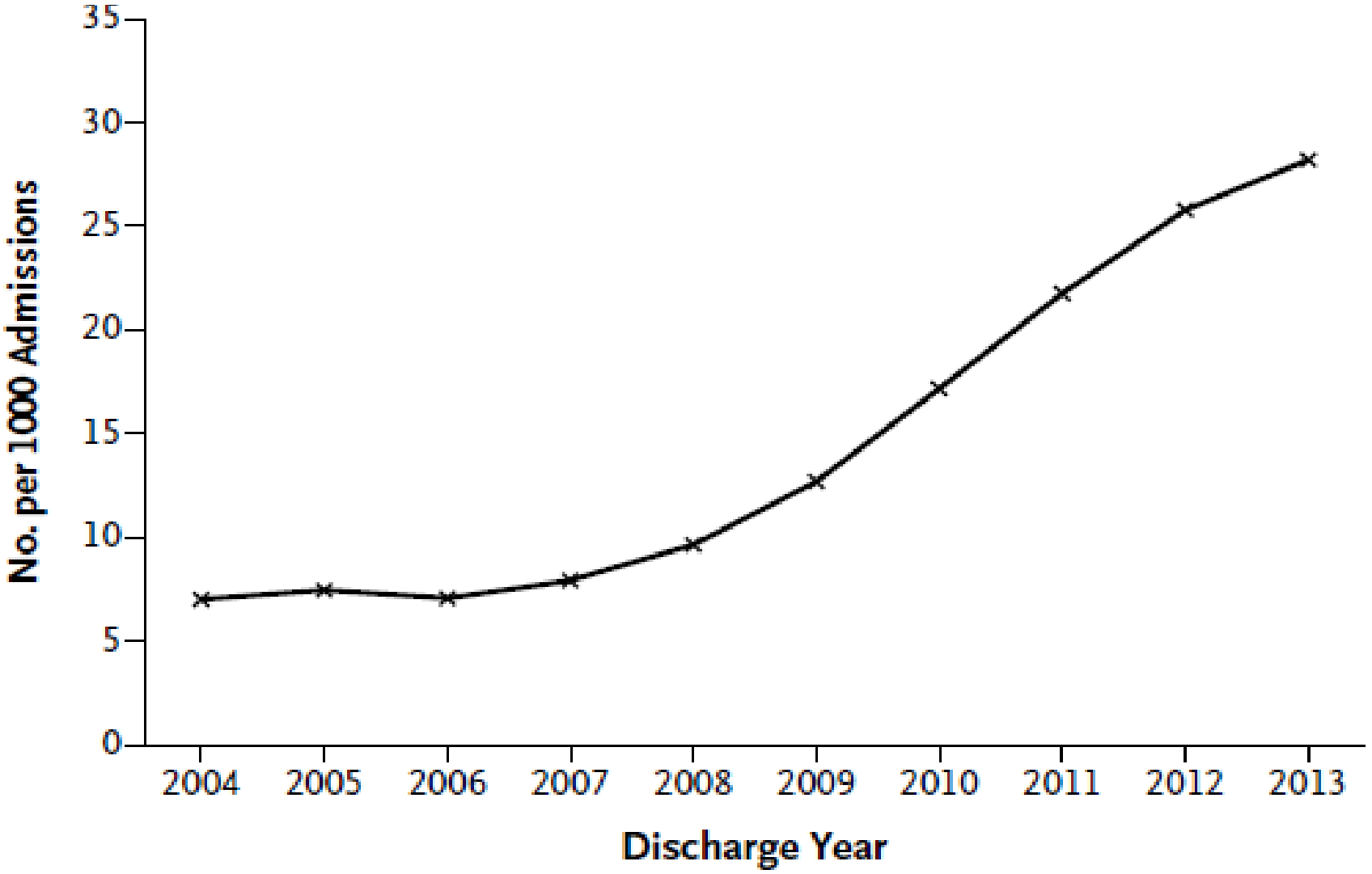
EPIDEMIOLOGY

Neonatal Abstinence Syndrome per 1000 Hospital Births by US Census Division, 2012



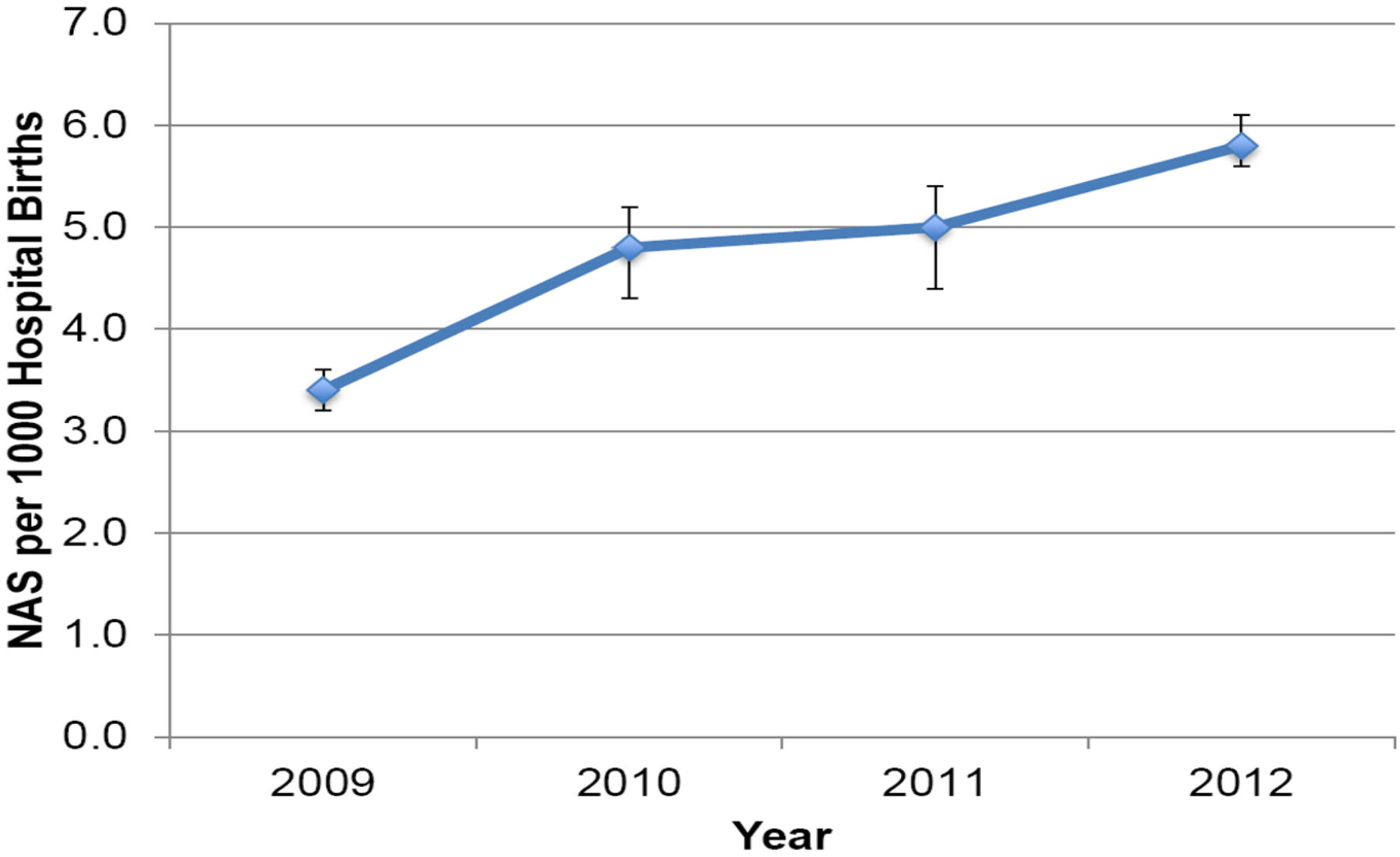
US Census Division	NAS Rate per 1000 Births (95% CI)
New England	13.7 (12.5-14.5)
Middle Atlantic	6.8 (5.9-7.6)
East North Central	6.9 (6.0-7.8)
West North Central	3.4 (3.0-3.8)
South Atlantic	6.9 (6.3-7.4)
East South Central	16.2 (12.4-18.9)
West South Central	2.6 (2.3-2.9)
Mountain	5.1

Admissions for the Neonatal Abstinence Syndrome - US



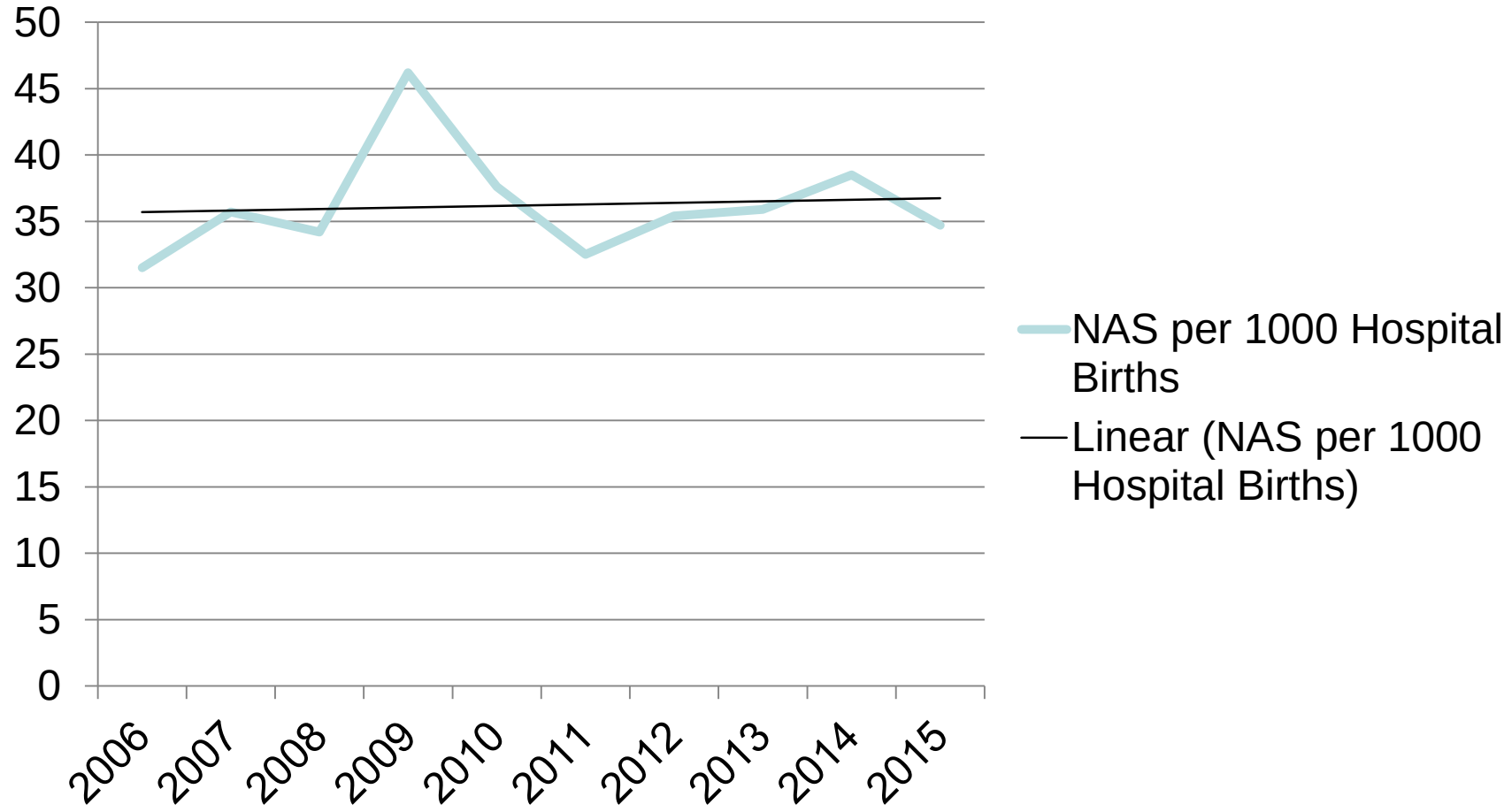
Spitzer et al NEJM 2015

Incidence of NAS per 1000 Hospital Births in the US, 2009- 2012

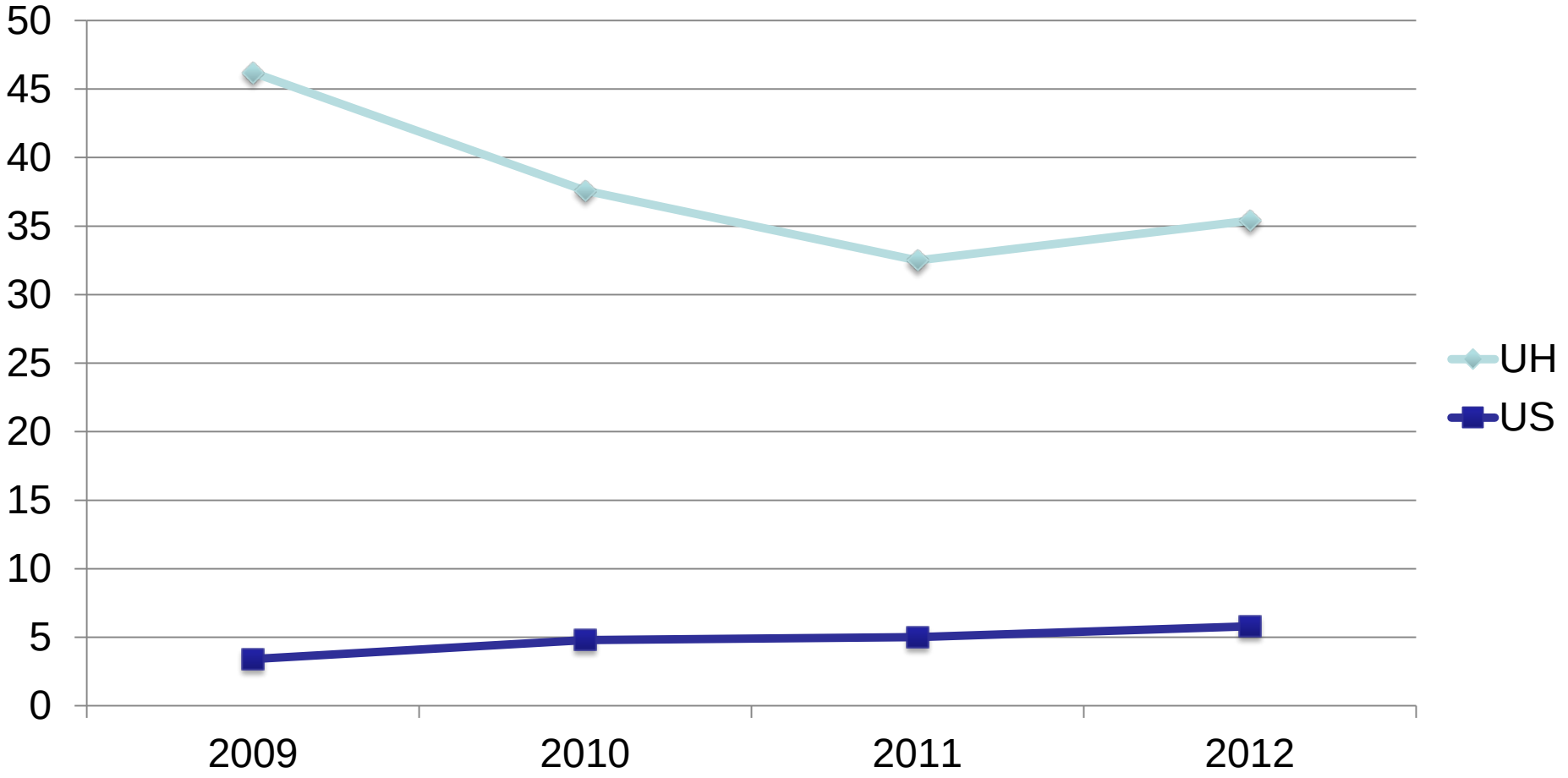


S Patrick et al. J Perinatol Aug 2015

Incidence of Neonatal Abstinence Syndrome per 1000 Hospital Births at University Hospital, Newark, NJ



Incidence of Neonatal Abstinence Syndrome per 1000 Hospital Births UH vs. US



- **PATHOPHYSIOLOGY**

DRUGS AND DEVELOPING FETAL BRAIN

Gestational exposure to licit and illicit drug is the most common preventable cause of environmentally induced developmental delay of infants in USA.

DRUG TERATOLOGY

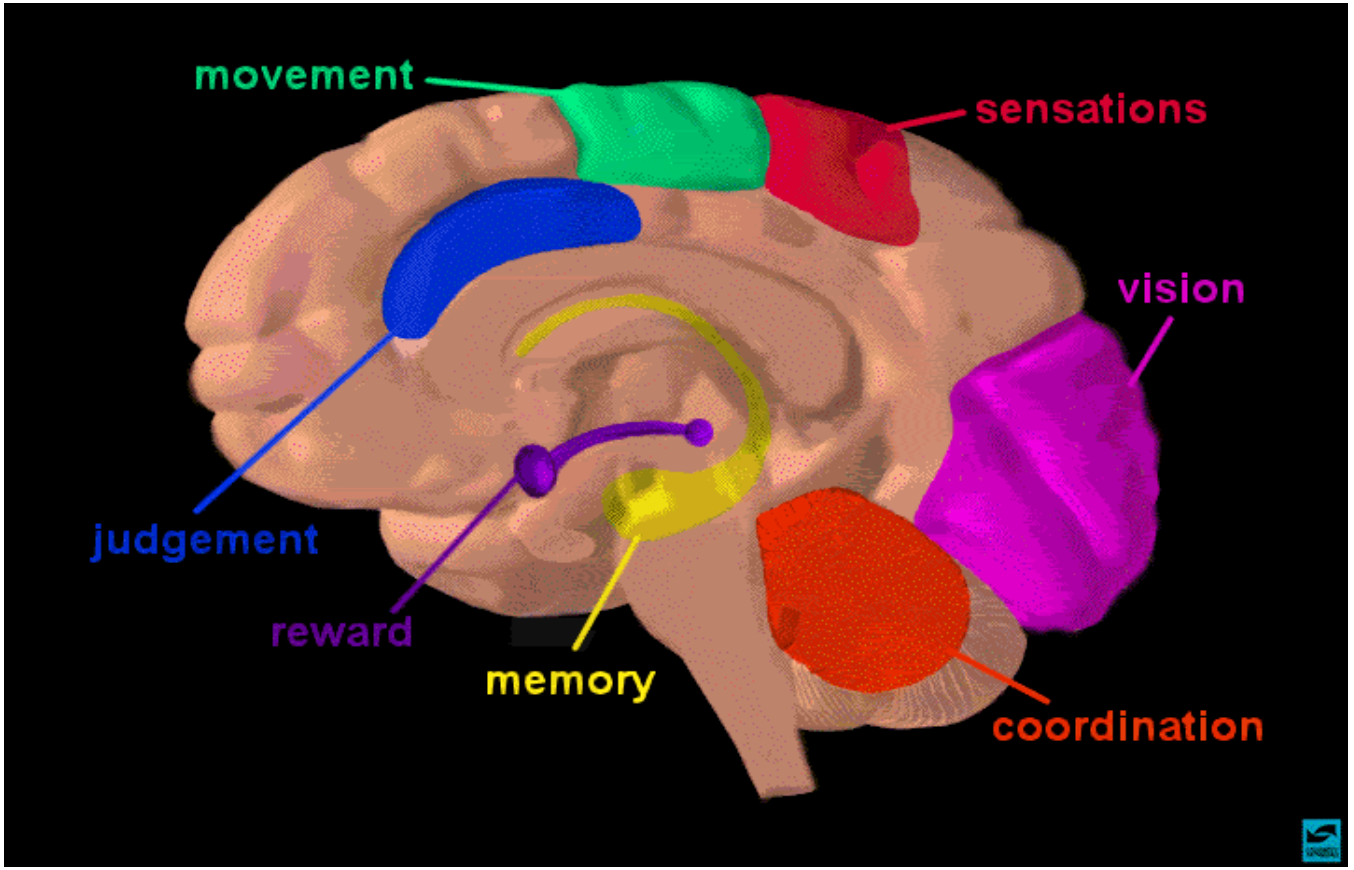
- **Fetal Brain :** intrauterine drug exposure can disturb the normal brain circuitry and neuronal communication leading to molecular **malformation.**
- **Adult brain :** alteration of normally formed adult brain homeostasis at neural circuit and neuro-chemical level leading to the **maladaption** or **deformation** of the brain.

DRUG TERATOLOGY

- Cytogenesis and cell migration begins from 28 days post conception till first half of gestation.
- Brain growth and differentiation begins from second half of pregnancy till childhood and consist of progressive and regressive events.

BRAIN REWARD SYSTEM

- Reward: behaviors producing pleasurable feelings provides positive reinforcement and repetition of same behaviors
- Natural rewards are eating, drinking, procreating and nurturing
- Artificial rewards are drugs


movement
sensations
vision
judgement
reward
memory
coordination

REWARD PATHWAY

- Shared by all drugs of abuse
- Consist of VTA, NA and PFC
- Excitatory neurotransmitters DA, NE, 5-HT
- Inhibitory neurotransmitter GABA
- Intracellular events involving calcium, potassium, G- protein, PKA, gene- transcription

MATERNAL SCREENING

- Maternal Screening
  - History, Self Report
    - Unreliable, depends on patient and interviewer
    - Canadian Study
      - Neonatal urine testing indicates 27% of mothers did not admit to substances detected in the infant.
      - 24% of meconium screens detected additional substances other than what the mothers admitted to.
  - Suspicion (Risk Factors)
    - Gravida 4 or more
    - No or late prenatal care
    - Previous children not living with mother
    - History of CPS involvement
    - Abruption
    - Physical injuries
    - History of chronic pain
    - STDs, Other risky behavior
    - Disorientation, confusion during interviews
  - Maternal urine or hair testing

MATERNAL COMPLICATIONS

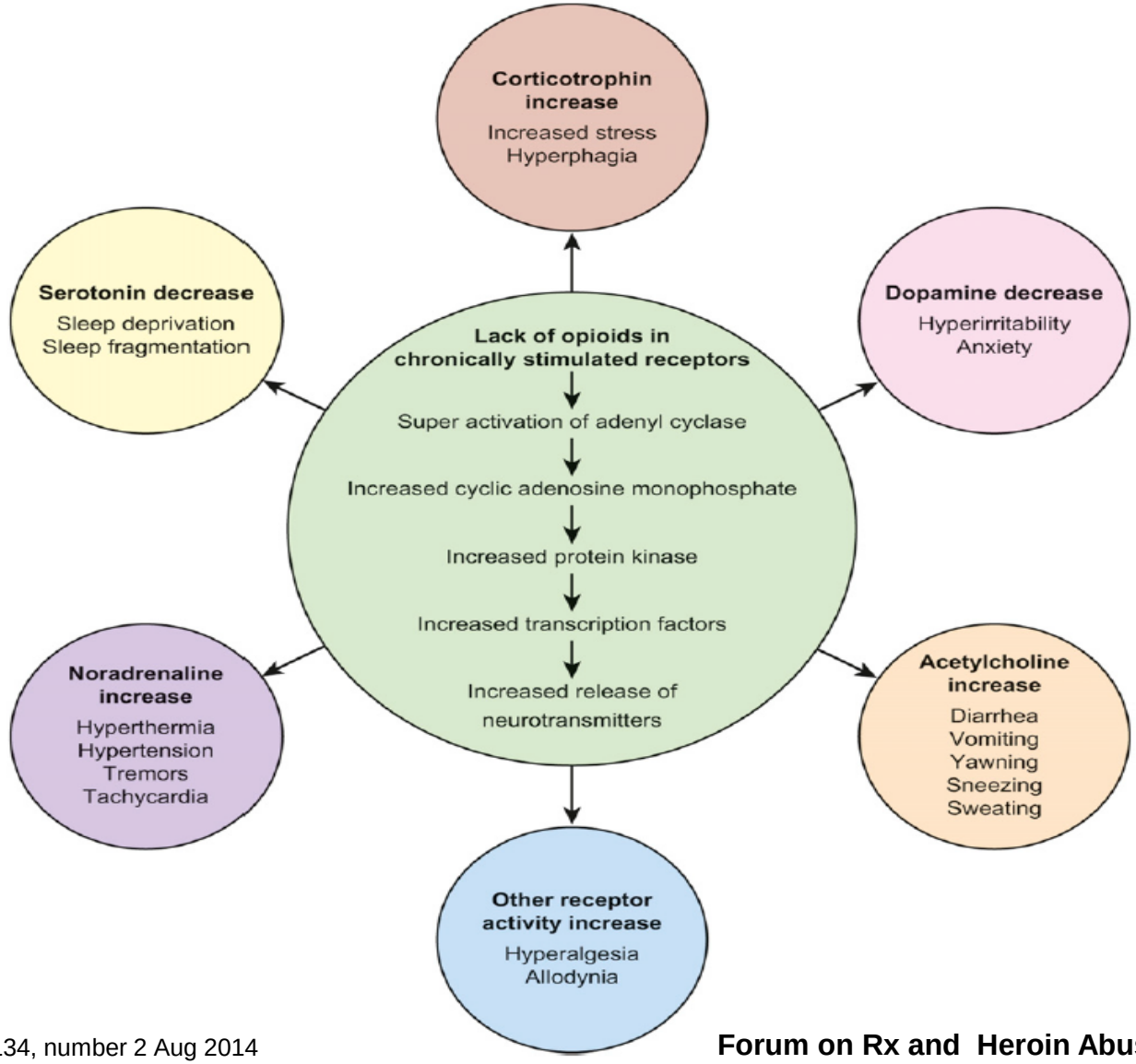
- Poor prenatal care
- Preterm delivery
- Spontaneous abortion
- Prenatal death
- Abruptio placentae
- PPROM
- Breech presentation
- Intrapartum analgesia
- STD's
- Extrauterine pregnancy
- Malnutrition
- IUGR
- Psychiatric problems
- PIH
- Outside delivery
- Uterine rupture
- Systemic complications

** arrhythmia, seizures, sudden death, multiorgan failure, hypertension, ischemic visceral damage.

NEONATAL COMPLICATIONS

- Prematurity
- Perinatal depression
- Growth retardation
- NDWS
- Infection
- Ischemic organ injury
- Hypertension
- Arrhythmia
- Seizures
- SIDS
- Poor state control
- Congenital anomaly

CLINICAL PRESENTATION



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SIGNS OF DRUG WITHDRAWAL BY SYSTEMS

- CNS dysfunction
  - High-pitched cry
  - Restlessness
  - Hyperactive reflexes
  - Jitteriness
  - Tremors
  - Hypertonia
  - Myoclonic Jerks
  - Seizure
- Metabolic and Vasomotor Disturbance
  - Sweating
  - Fever
  - Mottling
  - Yawning
- GI Dysfunction
  - Excessive Sucking
  - Poor Feeding
  - Hyperphagia
  - Vomiting
  - Loose Stools
  - Severe diaper rash
- Respiratory Symptoms
  - Sneezing
  - Nasal Flaring
  - Tachypnea
  - Apnea
- Other
  - Abrasions
  - Excoriations

ASSESSMENT OF NAS

- Finnegan
  - Assessment of 21 common symptoms of NAS with weighted scores for each symptom
    - Pharmacotherapy after score of 8
    - Most commonly used form
  - Considered too complex by some
- Ostrea
  - 6 item simple scale (yes/no)
    - No guidelines for pharmacotherapy
  - Does not allow for summing of multiple symptoms
    - Little attention to autonomic symptoms. Focus on seizure control and adequate nutrition/growth.
      - "If he is laying there waving his hands around we give him flags to hold"
- Lipsitz
- Neonatal Withdrawal Inventory
- Neonatal Narcotic Withdrawal Index
- Neonatal Brazelton Neurobehavioral Scales (NBAS)
- Neonatal Network Neurobehavioral Scales (NNNS)

TABLE 2 Risk Factors for Increasing Severity and/or Intensity of NAS

Definite	Probable
Term[97,98,108]	Male gender[112,113]
Good birth weight[97,109]	Methadone[45,46]
Polydrug abuse[106,107, 110]	Smoking[97,109,114]
Combination with benzodiazepines[97,111]	Combination with SSRIs[97,109,115]
μ-opioid receptor (OPRM1 118 AA) positive[105]	
Catechol-O-methyltransferase (COMT 158 AA) positive[105]	

TABLE 1 Onset, Duration, and Frequency of NAS Caused by Various Substances

Drug	Onset, h	Frequency, %	Duration, d
Opioids			
Heroin	24–48	40–80[27]	8–10
Methadone	48–72	13–94[37]	Up to 30 or more
Buprenorphine	36–60	22–67[46,48]	Up to 28 or more
Prescription opioid medications	36–72	5–20[56,60]	10–30
Nonopioids			
SSRIs	24–48	20–30[64]	2–6
TCAs	24–48	20–50[64]	2–6
Methamphetamines	24	2–49[101]	7–10
Inhalants	24–48	48[70]	2–7

Kocherlakota. Pediatrics July 2014

NEONATAL SCREENING

- Infant Screening
  - Urine Drug Screen
    - Detects recent exposure
  - Meconium Drug Screen
    - Detects prolonged or not recent exposure
      - Beyond 20 weeks gestation
    - Expanded opiate testing required to detect oxycodone, propoxyphene and methadone
    - May not be available
      - Early passage (fetal stress), limited or delayed passage (very preterm)
  - Universal Screening?
    - Regulations, privacy?
- Other tests
  - Umbilical cord tissue
    - Easy, noninvasive, quick, long window of exposure detection
    - Specialized testing
  - Neonatal hair
    - Present on the fetus after 6 months of gestation
    - Can be used during the first 3 months of life

TABLE 3 Urinary Screening for Various Drugs and Approximate Duration of Detection in the Neonate[116,118–120]

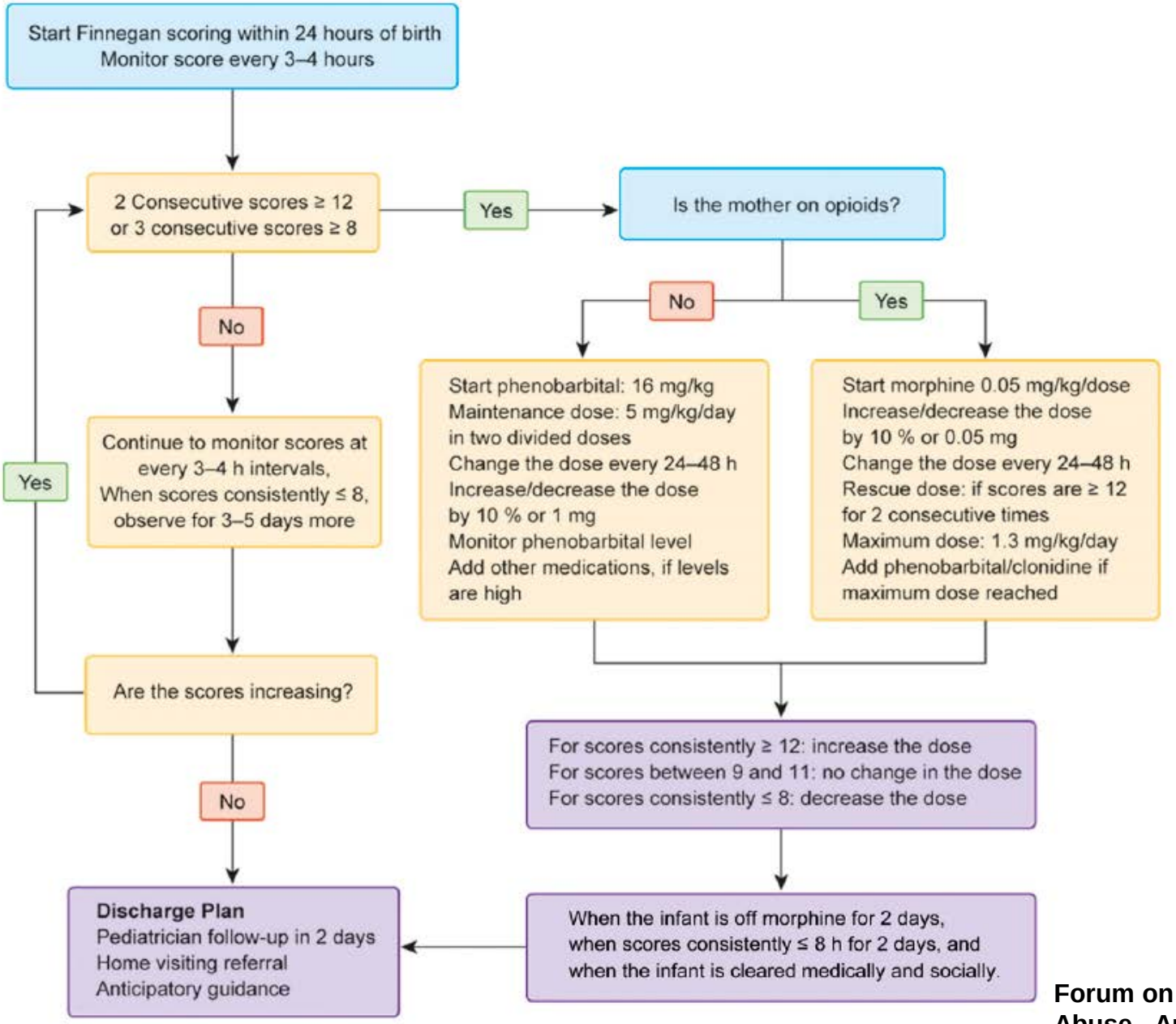
Substance	Compound/Metabolite/Usage	Duration of Detectability
Alcohol[123]	Ethanol	Few h
	Fatty acid ethyl esters	Up to 5 d
	Ethyl glucuronide	Up to 30 h
	Ethyl sulfate	
Amphetamines	Amphetamine	1–2 d
	Methamphetamine	1–2 d
Barbiturate	Short acting	<2 d
	Long acting	1–7 d
Benzodiazepines	Short acting	1–7 d
	Long acting	Up to 30 d
Cocaine	Cocaine	6–8 h
	Metabolites	2–5 d
		(up to 10–22 d with heavy use)
Marijuana	Single use	1–3 d
	Moderate use	5–7 d
	Heavy	up to 10 d
	Chronic heavy use	up to 30 d
Opiates	Heroin, morphine, codeine	1–2 d
	Hydromorphone, oxycodone	2–4 d
	Methadone	2–3 d
	Methadone metabolite	Up to 6 d
	Buprenorphine[125]	2–3 d
	Buprenorphine	2–3 d
	Norbuprenorphine	
Phencyclidine		1 to 8 d

SAMPLE POSITIVITY REPORT-Meconium (4th Quarter 2015)

Drug	UH, Newark	USA
Amphetamine	-	+++
Cocaine	+	+
Opiates	+	+++++
PCP	-	-
Cannabinoids	+	++++
Methadone	+	+
0xycodone	-	+
Barbiturates	-	+
Buprenorphine	-	+++
Fatty Acid Ethyl Esters(Alcohol)	++++	++++
Tramadol	-	+
Meperidine	-	+

MANAGEMENT

- Goals
  - Treat with drug from same class as exposure
  - Minimize symptoms
  - Promote appropriate growth and weight gain
  - Promote care-taker:child interaction
- Concerns about multiple exposures and "therapeutic" sedation effects.
- Optimal regimen has not been established.
  - Considerable heterogeneity in the diagnosis and treatment.
- Only clearly defined benefit of pharmacologic treatment is the short-term amelioration of clinical signs.
  - Unknown if long-term morbidity is changed by pharmacotherapy.



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Non-Pharmacologic Care (Active maternal participation)	Pharmacologic Therapy
First option, less expensive and less controversial	Morphine
Gentle Handling	Methadone
Demand Feeding	
Careful avoidance of waking the sleeping infant	Phenobarbital
Swaddling	
Minimal stimulation (dim light, low noise)	Clonidine
Frequent feeds (high caloric formula and thickened feeds)	
Kangaroo care	Buprenorphine
Music and massage therapy	
Non insertive acupuncture	Sucrose
Holding, cuddling and manual rocking	

TABLE 4 Pharmacological Treatment Options for NAS

Medication	Mechanism of Action	Dose	Advantages	Disadvantages
Morphine	Natural μ-receptor agonist	0.05–0.2 mg/kg/dose q 3–4 h Increase by 0.05 mg/kg Maximum dose: 1.3 mg/kg/day[141]	No alcohol Short half-life (9 h)	Sedation Apnea Constipation Frequent dosing
Methadone	Synthetic complete μ-receptor agonist N-methyl-d-aspartate antagonist	0.05–0.1 mg/kg/dose q 12 h, increase by 0.05 mg/kg q 48 h Maximum dose: 1 mg/kg/d[21]	Long half-life (26 h) 12 hourly doses	Longer duration of treatment Alcohol 8% Frequent follow-up needed (Variable half-life)
Phenobarbital	γ-amino butyric acid agonist	Loading dose: 16 mg/kg Maintenance dose: 1–4 mg/kg/dose q12 h[150]	Long half-life (45–100 h) Monitor level	Possible hyperactivity High treatment failure Alcohol 15% Drug-drug interactions Sedation
Clonidine	α-adrenergic receptor agonist	Initial dose: 0.5–1 μg/kg, followed by 0.5–1.25 μg/kg per dose q 4–6 h[153]	Nonnarcotic antagonist No sedation No alcohol Long half-life (44–72 h) Monitor level	Hypotension Abrupt discontinuation may cause rapid rise of blood pressure and heart rate
Buprenorphine	Semi-synthetic partial μ-receptor agonist, κ-receptor antagonist	Dose: 4–5 μg/kg/dose q 8 h Maximum dose: 60 μg/kg/d[152]	Sublingual route Half-life (12 h)	Alcohol 30% Adjuvant medications required

BREAST FEEDING RECOMMENDATIONS

- Continued exposure to maternal drugs of abuse
  - Little transmission to breastmilk
  - Helps control the symptoms of NAS
  - What if mother is in a program with close monitoring?
- Contraindicated if continued use of THC or other illicit substances.

SAMPLE ACROSS THE U.S

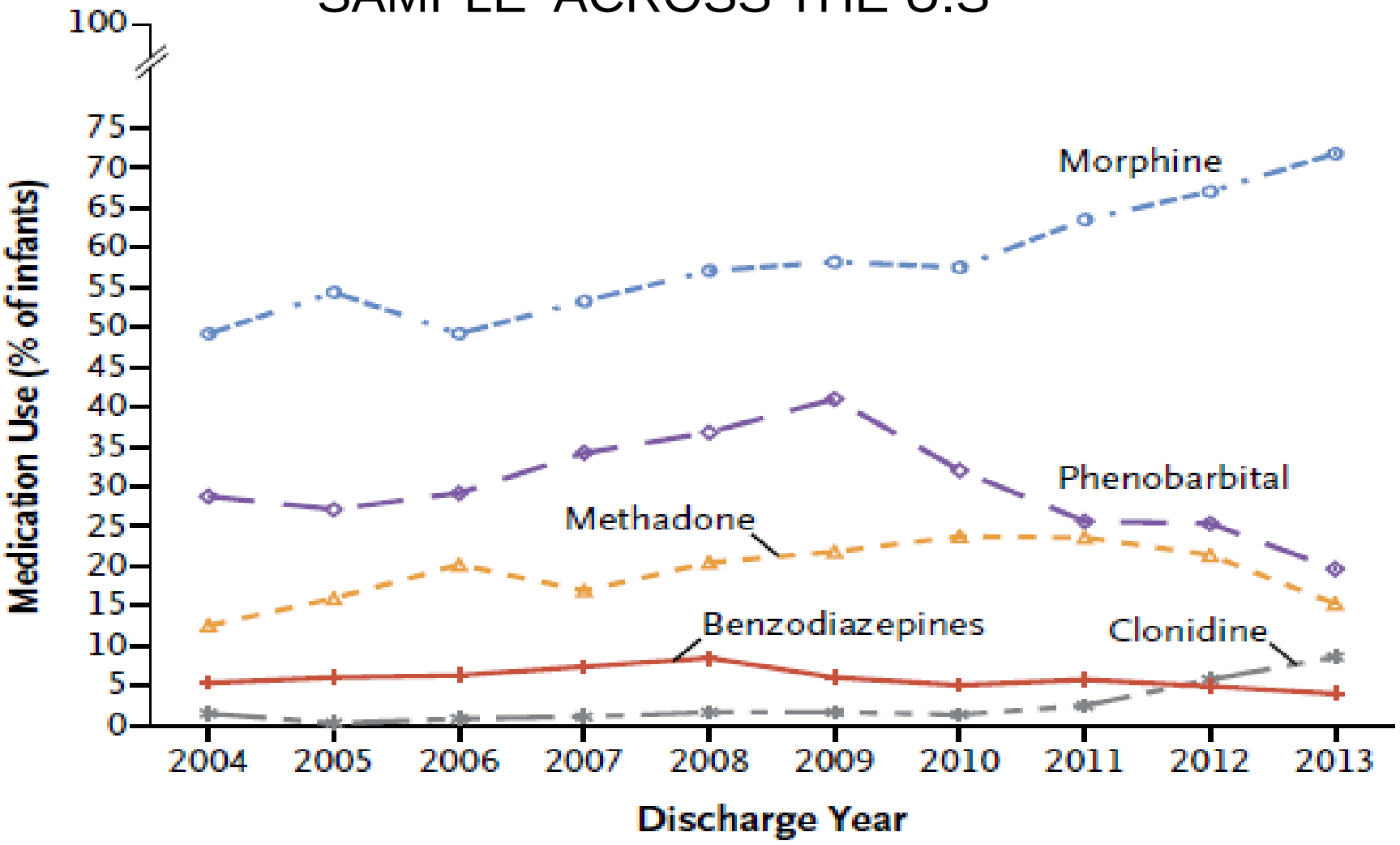

Figure 3. Medication Use in Infants with the Neonatal Abstinence Syndrome.

Spitzer et al NEJM May, 2015

OUTCOMES

- Poor scores in the areas of attention, memory, information processing, representational play, responsiveness and attachment
- Lower scores than the population means
- Presence of confounding variables
- Effect of cumulative risk factor
- Child-care giver interaction
- Intervention services targeting the cumulative risk factors

OUTCOMES

- Increased risk of SIDS:
  - 3.7 times increased risk in methadone exposed infants
  - 2.3 times increased risk in cocaine exposed infants
    - Prolonged QT in adults, Sleep habits
- Increased Risk of Abuse
  - Substance abuse is a risk factor in 80% of child abuse cases.
  - No published data, but intuition suggests infants with NAS may be at higher risk
- Seizures:
  - 2-11% incidence of seizures in infants withdrawing from opiates*
  - Withdrawal associated seizures do not carry increased risk of poor outcome.

PUBLIC HEALTH INTERVENTIONS

- State role in public health response to NAS to decrease the number of babies affected
- What are the funding sources
- NAS as reportable disease, all exposures vs symptomatic
- Mandatory Prenatal screening and treatment
- Neonatal screening Universal vs Targeted
- Educational and Intervention Program, public and physicians
- Statewide enrollment in Quality Collaborative i.e. VON
- Guideline for Screening and Treatment
- Prescription Drug Monitoring Program variable requirements
- Drug take back program
- Guideline for prescribing

PUBLIC HEALTH INTERVENTIONS

- Hospital charges for NAS increased from $732M to $1.5B from year 2009 to year 2012
- Treatment program for pregnant drug abuser
- Post discharge policy for NAS affected infants
- Post discharge follow up programs for NAS affected infants
- Maternal-Neonatal toxicology report and relationship with child abuse
- “Every dollar of prevention saves five times that amount in treatment and other cost to society”