

Neonatal Abstinence Syndrome (NAS):

Integrated Best Approaches to Prevention and Treatment

IMPROVING OUTCOMES FOR SUBSTANCE-EXPOSED INFANTS AND FAMILIES
A KANSAS PLAN FOR PREVENTION AND INTERVENTION

August 28, 2017

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DISCLOSURES

I am a consultant to the Maryland Patient Safety Center on a neonatal abstinence collaborative.

I serve as Chair of the FDA Pediatric Advisory Committee.

I have no financial arrangements or affiliations with a commercial entity to disclose.

Any drug therapy I discuss related to NAS is “off label” usage.

CLINICAL FEATURES OF NAS



- Central nervous system hyperirritability
- Autonomic nervous system overactivity
- Gastrointestinal dysfunction
- Sleep disturbances
- Respiratory distress

COMMENTARY ON REPORTING

Babies should not be stigmatized as “addicts”:
behavioral and compulsivity components do not apply.

Rather, they should be considered to be “drug-exposed”.

The phenomena of “tolerance” and “withdrawal” are normal physiologic responses to drug exposure and drug discontinuation.



CLINICAL REPORT

Neonatal Drug Withdrawal

abstract

Maternal use of certain drugs during pregnancy can result in transient neonatal signs consistent with withdrawal or acute toxicity or cause sustained signs consistent with a lasting drug effect. In addition, hospitalized infants who are treated with opioids or benzodiazepines to provide analgesia or sedation may be at risk for manifesting signs of withdrawal. This statement updates information about the clinical presentation of infants exposed to intrauterine drugs and the therapeutic options for treatment of withdrawal and is expanded to include evidence-based approaches to the management of the hospitalized infant who requires weaning from analgesics or sedatives. *Pediatrics* 2012;129:e540–e560

Mark L. Hudak, MD, Rosemarie C. Tan, MD,, PhD, THE COMMITTEE ON DRUGS, and THE COMMITTEE ON FETUS AND NEWBORN

KEY WORDS

opioid, methadone, heroin, fentanyl, benzodiazepine, cocaine, methamphetamine, SSRI, drug withdrawal, neonate, abstinence syndrome

ABBREVIATIONS

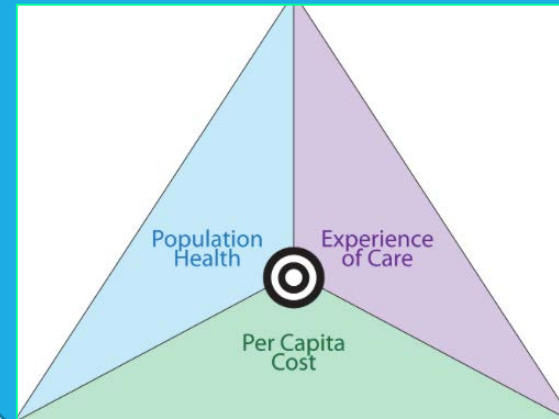
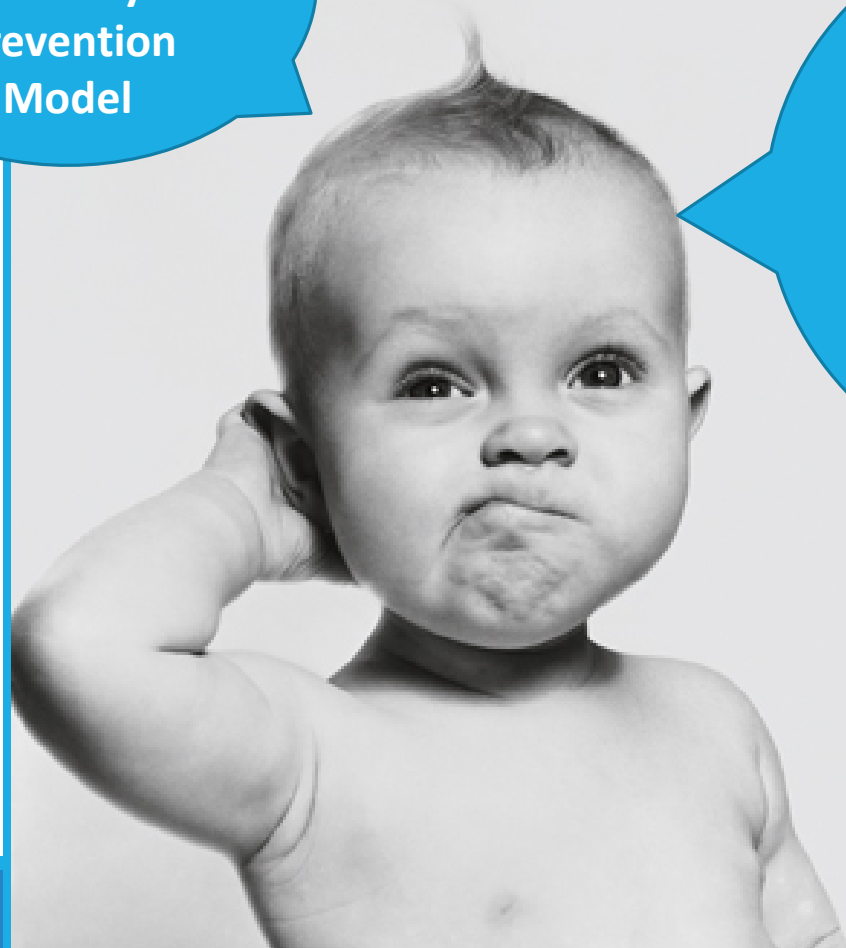
CNS—central nervous system
DTO—diluted tincture of opium
ECMO—extracorporeal membrane oxygenation
FDA—Food and Drug Administration
5-HIAA—5-hydroxyindoleacetic acid
ICD-9—*International Classification of Diseases, Ninth Revision*
NAS—neonatal abstinence syndrome
SSRI—selective serotonin reuptake inhibitor

Highlights From the AAP Clinical Report

1. Consensus protocol for maternal screening for substance abuse and evaluation/management of infants at risk for or with signs of withdrawal.
2. **Emphasis on non-pharmacologic support.**
3. Standardization of assessment of clinical signs.
4. **Caution** about initiating pharmacologic treatment.
5. Optimal threshold score for initiating treatment is unknown.
6. Encouragement of breastfeeding when indicated.
7. Pharmacologic treatment, **when needed**, with opioids. Absolute indications include seizures, feeding intolerance, dehydration/poor weight gain.
8. Duration of in-hospital observation; outpatient follow-up.

What can be done to reduce the burden of NAS in your community?

Primary
Secondary
Tertiary
Prevention
Model



Patrick. *J Pediatr.* 2015.

OVERVIEW OF NAS PREVENTION

OVERVIEW: LEVELS OF PREVENTION OF NAS

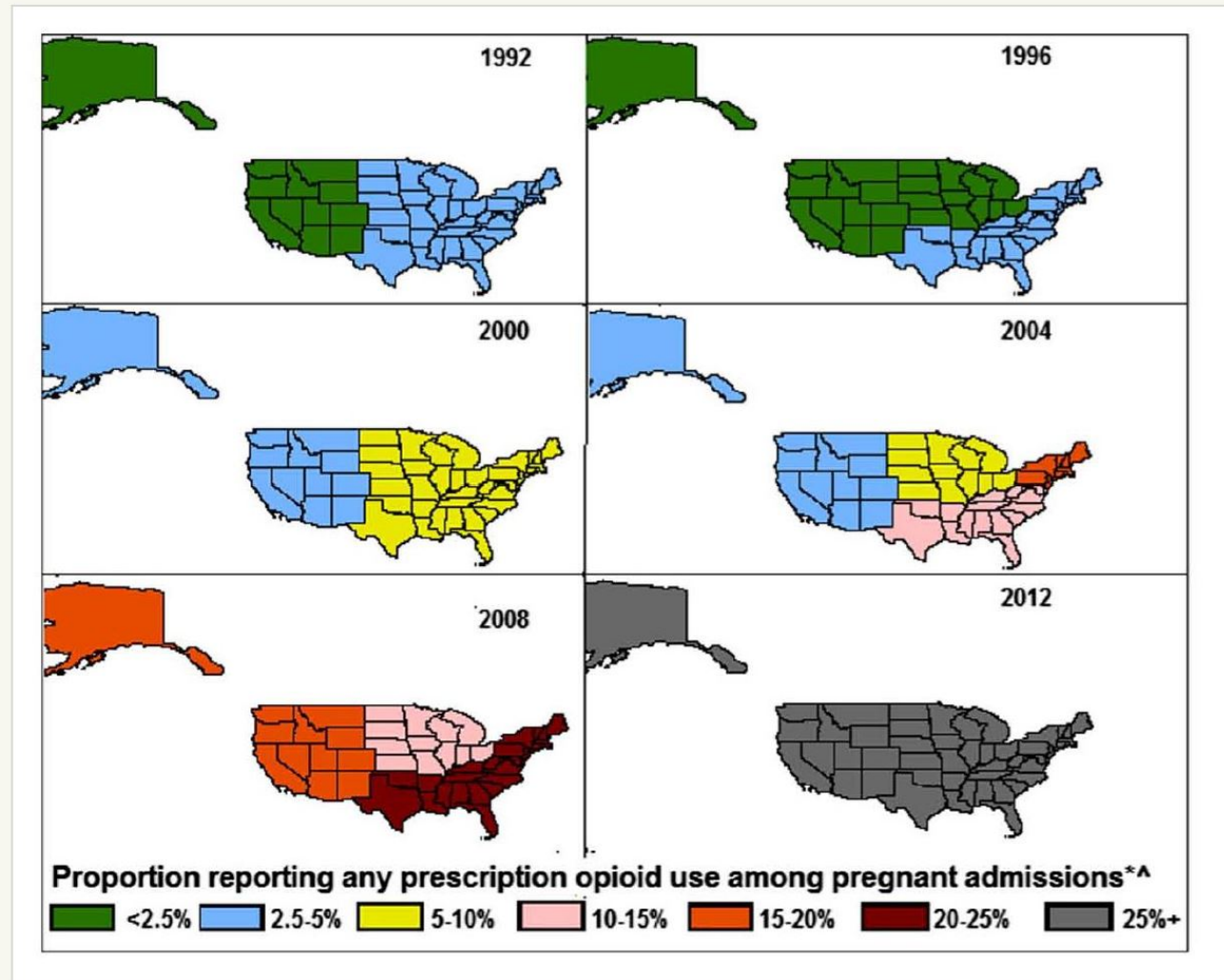
- Primary: Reduce the number of fetuses exposed to opioids
- Secondary: Mitigate risk factors that increase likelihood or severity of NAS in mother/fetus dyads exposed to opioids
- Tertiary: Improve treatment of neonates with or at risk for NAS to reduce length of stay, need for drug treatment, and duration of drug treatment
- Improve parent-infant bonding or outcomes after discharge

EXPANDING BURDEN OF NAS

- Increasing population of fertile women on maintenance opioid therapy
- Marked increase in use/abuse of prescription opioids
- Resurgence of street opioids (heroin) as access to prescription opioids is tightened
- Over 14% of pregnant women with an opioid prescription; over 1% used prescription opioids or heroin illicitly
- High rate of “unintended pregnancy” in women on opioids

National Data: Prescription Opioids During Pregnancy

Proportion Reporting Any Prescription Opioid Use Among Pregnant Admissions



Martin, C.E., et al., Recent trends in treatment admissions for prescription opioid abuse during pregnancy. *Journal of Substance Abuse Treatment* (2014), <http://dx.doi.org/10.1016/j.sat.2014.07.007>

FACTORS FOR RISE IN PRESCRIPTION RX

- Development of extended-release opioids
- Pharmaceutical company promotion
- Higher social acceptability
- Perception of less harm

National Survey on Drug Use and Health 2013-2014

DEPENDENCY OR ABUSE BY U.S. POPULATION

MARIJUANA 4,200,000

PAIN RELIEVERS 1,900,000

Sources for non-medical use (2013)

FRIEND/RELATIVE (free) 53% (5/6 from single MD)

PRESCRIBED BY 1 MD 21%

FRIEND/RELATIVE (bought) 15%

OTHER 4%

DRUG DEALER 4%

PRESCRIBED BY > 1 MD 3%

INTERNET PURCHASE 0.1%

COCAINE 913,000

National Survey on Drug Use and Health 2013-2014

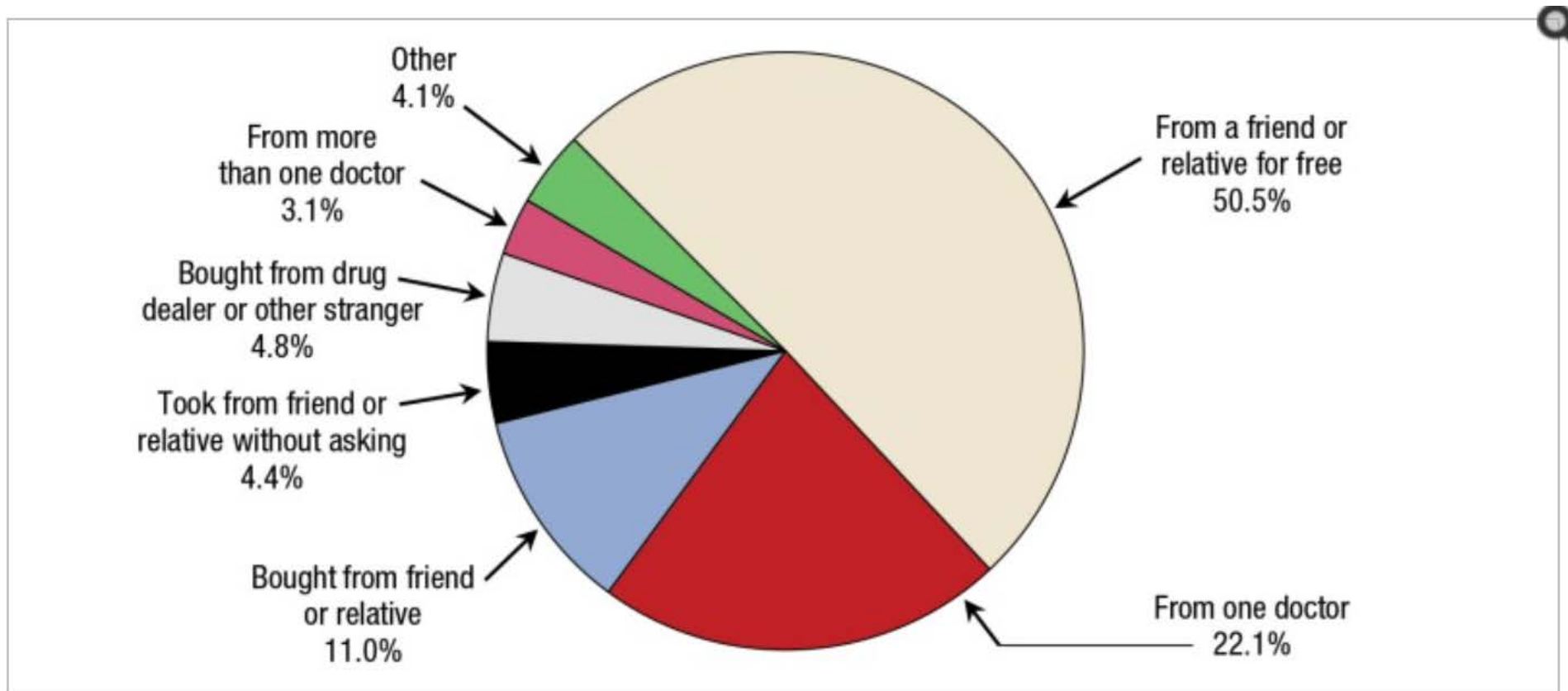


Figure 1 Source of prescription pain relievers for the most recent nonmedical use among past year users aged 12 or older: annual averages, 2013 and 2014

National Survey on Drug Use and Health 2013-2014

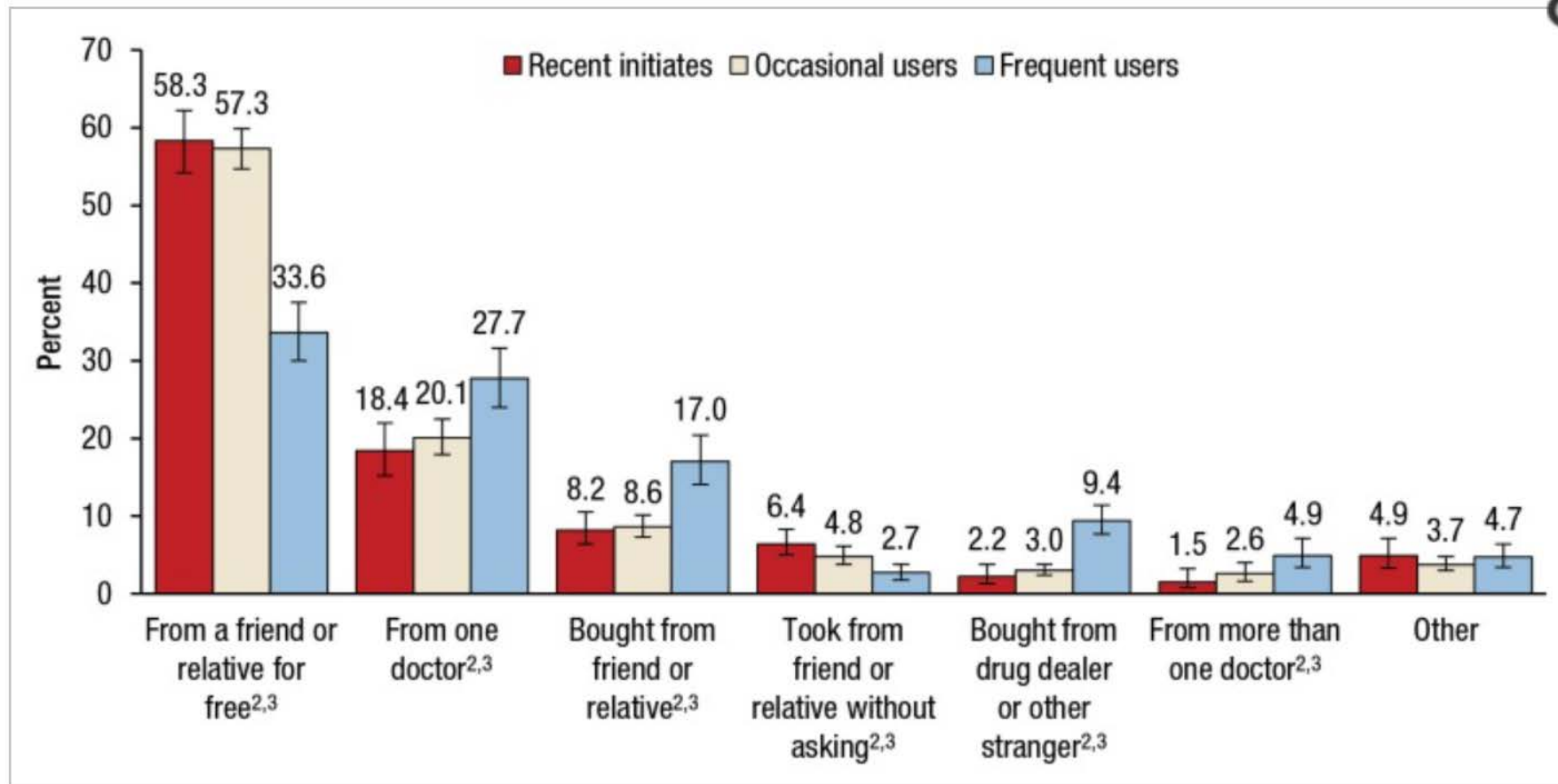


Figure 4 Source of prescription pain relievers for the most recent nonmedical use among past year users aged 12 or older, by type of user: annual averages, 2013 and 2014

NATIONAL TRENDS IN HEROIN ABUSE

Increase in estimated people dependent on heroin from 180,000 in 2007 to 586,000 in 2014

Strong association between nonmedical use of opioids and subsequent past year initiation of heroin

Heroin incidence rates are 19x higher among people who reported prior nonmedical use of pain relievers

Heroin-related overdose deaths have more than quadrupled from 2010 to 2015 (13,000 deaths)

OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary

- Prevent non-medically indicated population opioid use

Secondary

Tertiary

NEW CDC ADVICE ON OPIOIDS AND CHRONIC PAIN

Determining when to initiate or continue opioids for chronic pain (3 points)

Opioid selection, dosage, duration, follow-up and discontinuation (4 points)

- Prescribe immediate release opioids rather than ER/LA options
- Start with lowest effective dose
- Prescribe for expected duration of severe pain (often ≤ 3 days)

Assess risk and address harm of opioid use (5 points)

- No concurrent opioids and benzodiazepines

OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary

- Prevent non-medically indicated population opioid use
- Prevent pregnancy in women on opioids (e.g., LARCs)

Secondary

Tertiary

In the Weeds with Medicaid LARC Policy

CMCS Informational Bulletin

DATE: April 08, 2016

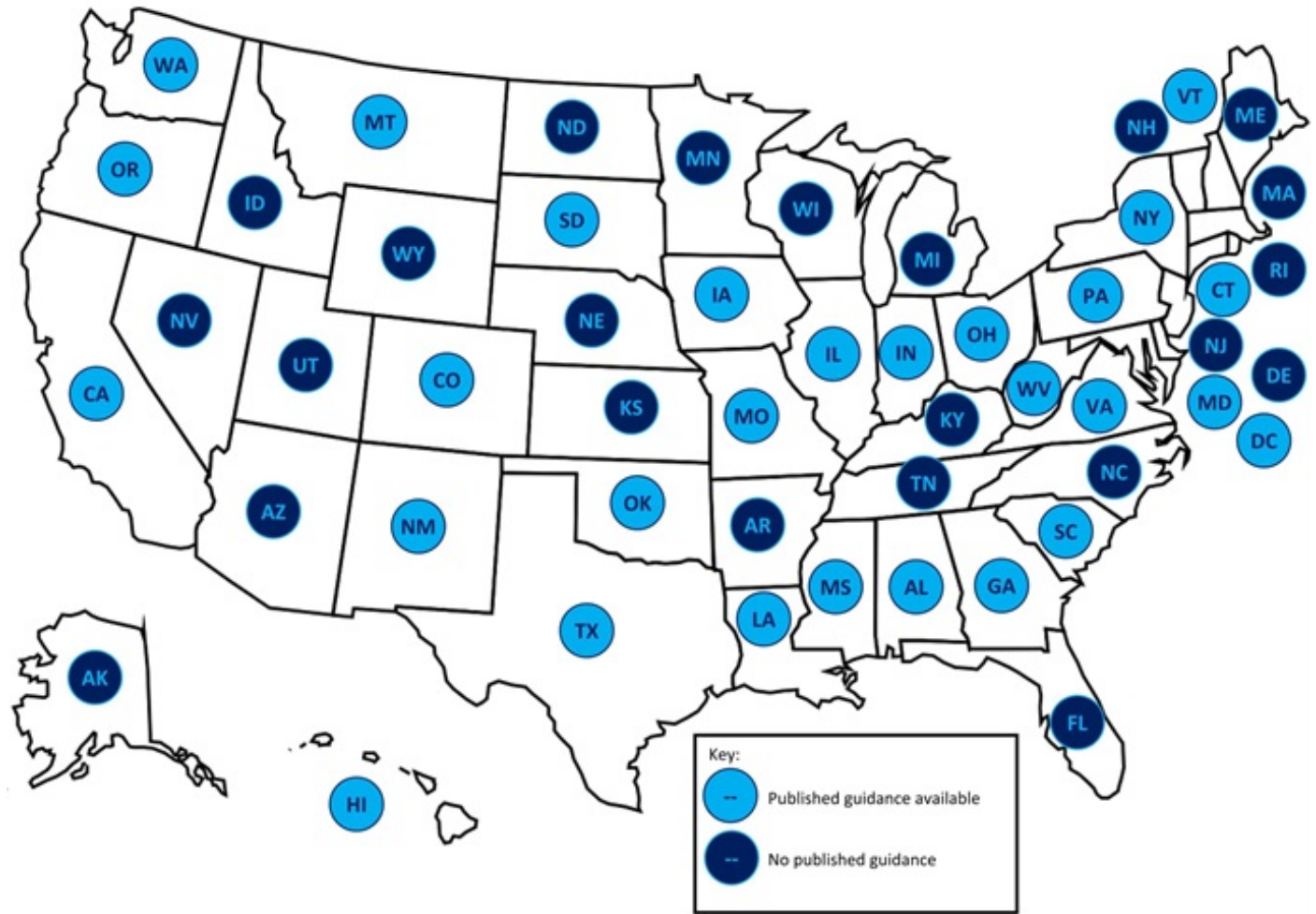
FROM: Vikki Wachino, Director
Center for Medicaid and CHIP Services

SUBJECT: State Medicaid Payment Approaches to Improve Access to Long-Acting Reversible Contraception

Effective for dates of service April 15, 2016 and forward, the Department of Social Services (DSS) will reimburse enrolled hospitals for long-acting reversible contraception (LARC) devices including intrauterine devices (IUD) and subdermal implants when placed immediately postpartum in the inpatient hospital setting.

HCPCS Code	Contraceptive Method
J7300	Intrauterine copper contraceptive (Paragard)
J7301	Levonorgestrel-releasing intrauterine contraceptive system, (Skylark), 13.5 mg
J7302	Levonorgestrel-releasing intrauterine contraceptive system, 52 mg (Mirena)
J7307	Etonogestrel (contraceptive) implant system, including implant and supplies (Implanon, Nexplanon)

Postpartum LARC Medicaid Payments (as of June 2, 2017)



<http://www.acog.org/About-ACOG/ACOG-Departments/Long-Acting-Reversible-Contraception/Immediate-Postpartum-LARC-Medicaid-Reimbursement>

Florida Medicaid 7/1/16

8.2 Specific Criteria

Florida Medicaid reimburses for inpatient hospital services using a DRG methodology, with the exception of:

- Infant and newborn hearing screening
- Intrathecal baclofen therapy pump
- Long-acting reversible contraception
- Transplant services
- Vagus nerve stimulator device

OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary

- Prevent non-medically indicated population opioid use
- Prevent pregnancy in women on opioids (e.g., LARCs)
- ? Supervised medication withdrawal of selected pregnant women

Secondary

Tertiary

NOVEL APPROACHES TO MOTHERS ON OPIOIDS

Narcotic tapering in pregnancy using long-acting morphine

An 18-month prospective cohort study in northwestern Ontario

Year	% opioid-exposed pregnancies	% NAS among opioid-exposed mothers	% total population treated with opioids for NAS
2010	17	29.5	2.5
2013	28	18.1	1.5

NOVEL APPROACHES TO MOTHERS ON OPIOIDS

OBSTETRICS

Detoxification from opiate drugs during pregnancy

Jennifer Bell, MD; Craig V. Towers, MD; Mark D. Hennessy, MD; Callie Heitzman, RN;
Barbara Smith; Katie Chattin

Demographics	Group 1	Group 2	Group 3	Group 4	Total
Number	108	23	77	93	301
Gestational age at detoxification and NICU admission					
Detoxification first trimester, 5–13 wks gestation	10 (9%)	4 (17%)	12 (15%)	2 (2%)	28 (9%)
Detoxification second trimester, 14–27 wks gestation	65 (60%)	10 (43%)	36 (47%)	37 (40%)	148 (49%)
Detoxification third trimester, \geq 28 wks gestation	33 (31%)	9 (39%)	29 (38%)	54 (58%)	125 (42%)
Preterm deliveries prior to 37 wks gestation	21 (19%)	3 (13%)	13 (17%)	16 (17%)	53 (17.6%)
Neonatal intensive care unit admission	32 (30%)	5 (22%)	60 (78%)	22 (24%)	119 (40%)
Pregnancy outcome					
Rate of NAS	20 (18.5%)	4 (17.4%)	54 (70.1%)	16 (17.2%)	94 (31%)
Rate of relapse ^b	25 (23.1%)	4 (17.4%)	57 (74.0%)	21 (22.5%)	107 (36%)

Journal of Addictive Diseases

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/wjad20>

The Perinatal Outcome of Children Born to Women With Substance Dependence Detoxified in Residential Treatment During Pregnancy

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Accepted author version posted online: 09 Apr 2014. Published online: 24 Jun 2014.

Norway Study: 1991-1996 vs. 2004-2008

TABLE 1. Substance Abuse per Trimester in Cohorts 1 and 2

Substance abuse	Cohort 1: Mothers out-patients (n = 78), no. (%)			Cohort 2: Mothers in-patients (n = 21), no. (%)		
	1st Trimester	2nd Trimester	3rd Trimester	1st Trimester	2nd Trimester	3rd Trimester
Opiates	46 (59.0)	45 (57.7)	44 (56.4)	14 (63.6)	6 (27.3)	1 (4.5)
Benzodiazepines	35 (44.9)	37 (47.4)	35 (44.9)	14 (63.6)	5 (22.7)	1 (4.5)
Cannabis	24 (30.8)	23 (29.5)	22 (28.2)	14 (63.6)	4 (18.2)	0 (0)
Amphetamines	13 (16.7)	15 (19.2)	13 (16.7)	13 (59.1)	2 (9.1)	0 (0)
Alcohol	29 (37.7)	26 (33.3)	23 (29.5)	8 (36.4)	1 (4.5)	1 (4.5)
Nicotine daily	78 (100)	—	—	20 (90.1)	20 (90.1)	13 (59.1)
Other substances ^a	13 (16.7)	—	—	5 (22.7)	1 (4.5)	1 (4.5)

^aBarbiturates, cocaine, ecstasy.

Norway Study: Outcomes

TABLE 2. Birth Parameters in Cohorts 1 and 2

Birth Parameters	Cohort 1		Cohort 2	
	Mothers out-patients, <i>n</i> = 78 (45 boys)	Comparison group, <i>n</i> = 58 (35 boys)	Mothers in treatment, <i>n</i> = 22 (12 boys)	Comparison group, <i>n</i> = 30 (18 boys)
Gestational age, ^a mean (SD)	38.3 (2.4)	40.4 (1.4)	39.4 (1.2)	40.0 (1.2)
Birthweight, ^a mean (SD)	3022 (715)	3707 (455)	3293 (428)	3720 (433)
Head circumference, ^a mean (SD)	33.9 (1.9)	35.6 (1.2)	34.8 (1.5)	35.4 (1.2)
Maternal age at delivery, mean (SD)	28.5 (5.4)	29 (3.7)	27.3 (6.0)	33.3 (5.0)
Apgar 1 min, ^b mean (SD)	8.4 (1.3)	—	9.1 (0.4)	—
Apgar 5 min, mean (SD)	9.0 (0.6)	—	9.6 (0.5)	—
Gestational age <37 weeks, no. (%)	20 (25.6)	1 (1.72)	0 (0)	0 (0)
NAS, no. (%)	60 (76.92)	0 (0)	0 (0)	0 (0)

^aBirthweight is given in grams, gestational age in weeks, and head circumference in cm.

^bApgar score was obtained for 62 and 14 infants from the study groups in cohorts 1 and 2, respectively.

NAS = neonatal abstinence syndrome; SD = standard deviation.

OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary

Secondary

- Screen/? test pregnant women for substance use

Tertiary

OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary

Secondary

- Screen/? test pregnant women for substance use
- Incorporate treatment of substance use disorders into prenatal care

Tertiary

OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary

Secondary

- Screen/? test pregnant women for substance use
- Incorporate treatment of substance use disorders into prenatal care
- Optimize maternal OMT (e.g., methadone vs. buprenorphine)

Tertiary

Maternal Opioid Treatment: Human Experimental Research (MOTHER) Study*

2002: FDA approval of buprenorphine (partial μ -opioid receptor agonist, partial κ -opioid receptor antagonist) for males and non-pregnant females

MOTHER: RCT of efficacy of methadone vs. buprenorphine (Subutex): 6 US centers, 1 European center

175 mothers randomized, 131 infants followed to birth (73 methadone, 58 buprenorphine)

Attrition 33% in buprenorphine, 18% in methadone groups

Both drugs are Pregnancy Category C: animal reproductive studies show adverse effect on fetus; no adequate and well-controlled studies in humans; potential benefits may warrant use despite potential risks

METHADONE VS. BUPRENORPHINE

Different panel of presenting signs for NAS

- Higher tremor and hyperactive Moro in M-exposed
- Higher nasal stuffiness, sneezing, loose stools in B-exposed

Severity scores higher in M than B-exposed infants

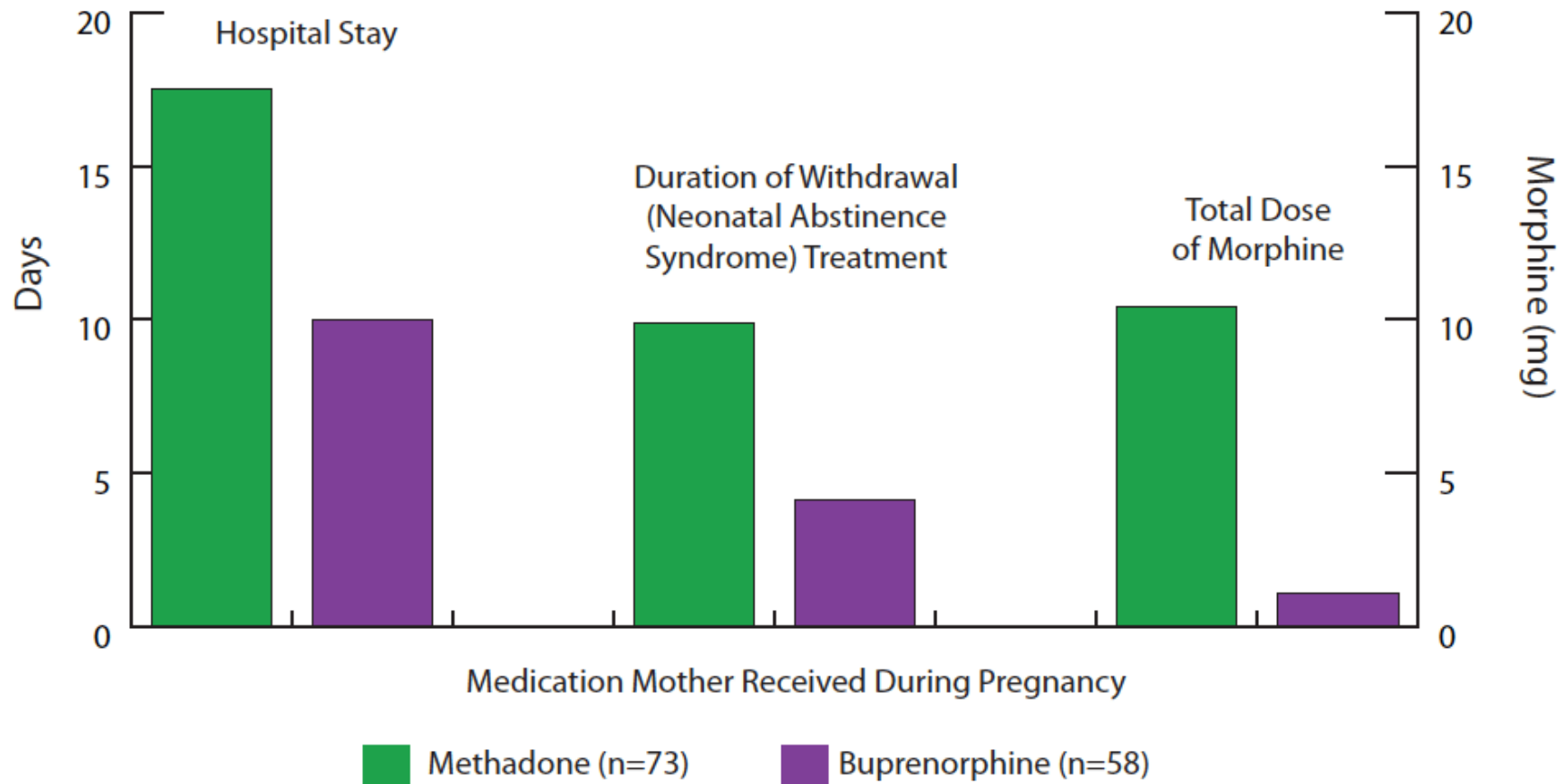
Peak NAS scores occurred later in B-exposed infants

Mean onset of initiation of treatment:

- 36 hours M-exposed
- 59 hours B-exposed

METHADONE VS. BUPRENORPHINE

Mothers' Buprenorphine Treatment During Pregnancy Benefits Infants



OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary

Secondary

- Screen/? test pregnant women for substance use
- Incorporate treatment of substance use disorders into prenatal care
- Optimize maternal OMT (e.g., methadone vs. buprenorphine)
- **Smoking cessation programs**

Tertiary

POTENTIATING FACTORS: SMOKING and SSRIs

TABLE 3 Probability of NAS According to Varying Exposures of Short-Acting Opioids and Maintenance Opioids, Tobacco, and SSRI Use

Variable	Short-Acting (eg, Oxycodone Hydrochloride) 10 mg q6h	Maintenance (eg, Buprenorphine Hydrochloride Tablet) 24 mg q24h
	Probability (95% CI)	Probability (95% CI)
5-wk duration	0.011 (0.008–0.016)	0.132 (0.085–0.199)
No cigarette use, SSRI use	0.023 (0.016–0.034)	0.241 (0.157–0.351)
5 cigarettes/d, no SSRI	0.026 (0.020–0.033)	0.165 (0.123–0.219)
5 cigarettes/d, SSRI	0.053 (0.039–0.071)	0.293 (0.217–0.383)
20 cigarettes/d, no SSRI	0.037 (0.029–0.047)	0.179 (0.137–0.231)
20 cigarettes/d and SSRI use	0.074 (0.056–0.098)	0.314 (0.239–0.399)
25-wk duration	0.048 (0.028–0.081)	0.163 (0.103–0.247)
No cigarette use, SSRI use	0.095 (0.055–0.158)	0.289 (0.188–0.416)
5 cigarettes/d, no SSRI	0.073 (0.045–0.115)	0.172 (0.123–0.236)
5 cigarettes/d, SSRI	0.141 (0.088–0.220)	0.303 (0.218–0.404)
20 cigarettes/d, no SSRI	0.104 (0.068–0.156)	0.216 (0.156–0.291)
20 cigarettes/d and SSRI use	0.196 (0.129–0.285)	0.366 (0.270–0.474)

OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary

- Prevent non-medically indicated population opioid use
- Prevent pregnancy in women on opioids (e.g., LARCs)
- ? Supervised medication withdrawal of selected pregnant women

Secondary

- Screen/? test pregnant women for substance use
- Incorporate treatment of substance use disorders into prenatal care
- Optimize maternal OMT (e.g., methadone vs. buprenorphine)
- Smoking cessation programs
- Prenatal risk assessment

Tertiary

NAS AND MATERNAL OPIOID USE

OPIOID:	PRESCRIPTION OPIOIDS (SA)	HEROIN	BUPRENORPHINE	METHADONE/PRESCRIPTION OPIOIDS (LA)
Half-life in neonates	Short (2-6 hours)	Short (2-6 hours)	Long (24+ hours)	Long (24 hours)
Onset of signs	Not well described, likely < 24-48 hours	Usually < 24 hours	Usually 24-72 hours	Usually 24-48 hours but may be 3-7 days
Severity of signs	Variable	Mild-moderate	Mild-moderate	Moderate-severe
Likelihood of NAS	1-20%, duration and cofactor dependent	50-70%	Intermediate	High (up to 94%)

KEY DETERMINANTS OF INCIDENCE AND SEVERITY OF NAS

Maternal opioid exposure close to delivery

Potentiating factors

- Smoking
- Benzodiazepines
- Selective serotonin reuptake inhibitors
- Marijuana
- ? Alcohol, cocaine, stress

Placental metabolism

Gestational age, infant co-morbidities

Environment of care (physical; caregiver(s))

Efficacy of pharmacologic treatment

Genetics and epigenetics

OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary

Secondary

Tertiary

- Novel drug treatments of pregnant women during labor and babies after birth

OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary

Secondary

Tertiary

- Novel drug treatments of pregnant women during labor and babies after birth
- Optimization of non-pharmacologic support of babies
- Care of families

GOALS OF TREATMENT

Support vital infant functions and development

- Hydration, feeding, growth
- Sleep
- Reasonable comfort, not sedation
- Socialization

Achieve family bonding (integrated care, breastfeeding when possible)

Avoid complications

- Seizures
- Skin breakdown
- Nutritional and sleep disturbances
- Marginalization of social supports

Educate family and marshal post-discharge medical/social support

THERAPEUTIC APPROACH

Initial treatment of infants who develop early signs of withdrawal is directed at minimizing environmental stimuli (both light and sound) by placing the infant in a dark, quiet environment; avoiding autostimulation by careful swaddling; responding early to an infant's signals; adopting appropriate infant positioning and comforting techniques (swaying, rocking); and providing small volumes of hypercaloric formula or human milk to minimize hunger and allow for adequate growth.

The infant needs to be carefully observed to recognize fever, dehydration, or weight loss promptly.

The goals of therapy are to ensure that the infant achieves adequate sleep and nutrition to establish a consistent pattern of weight gain and begins to integrate into a social environment.

THERAPEUTIC APPROACH

Drug therapy is indicated to relieve moderate to severe signs of NAS and to prevent complications such as fever, weight loss, and seizures if an infant does not respond to a committed program of nonpharmacologic support.

Withdrawal from opioids or sedative-hypnotic drugs may be life-threatening, but ultimately, drug withdrawal is a self-limited process. Unnecessary pharmacologic treatment will prolong drug exposure and the duration of hospitalization to the possible detriment of maternal-infant bonding. The only clearly defined benefit of pharmacologic treatment is the short-term amelioration of clinical signs.

NON-PHARMACOLOGIC TREATMENT

Swaddling

C-Position

Vertical rock

Head to toe movement

Percussion

Small frequent high caloric feedings; nursing when indicated

Minimize external environmental stimuli

Introduce stimuli gradually

Intravenous hydration as necessary

SWADDLING

Drug exposed infants have difficulty coordinating breathing and sucking activities, especially when they have excessive muscular activity

Swaddling provides comfort by reducing muscle activity

Allows them the best opportunity to coordinate feeding and breathing

C-POSITION, VERTICAL ROCK

Best employed when baby is frantic and hard to calm

Establish infant in the C-position and hold directly in front of you and turned away.

Slowly and rhythmically rock baby up and down – soothes neurological system.

MINIMIZE EXTERNAL STIMULI

Limit the number of caregivers

Provide calm surroundings

Minimize any loud noise – music and voices should be low volume

Maintain lighting at a low level

Caregiver should have calm presence

Routine is beneficial

EFFECTS OF BREASTFEEDING ON NAS

Malpas 1997:	Decreased LOS by 8 days (NAS rx'ed)
Brown 2011:	Decreased rate of NAS, reduced LOS
McQueen 2011:	Decreased severity, duration of NAS
Pritham 2012:	Decreased LOS by 9 days (methadone)
Welle-Strand 2013:	Decreased LOS, slightly shorter duration of rx, fewer infants requiring rx (methadone-exposed, not buprenorphine-exposed)

WHEN TO BREAST FEED: AAP 2012

Mother adheres to supervised opioid maintenance program

HIV negative

No illicit drugs (marijuana, cocaine, PCP, heroin)

Limited alcohol

No other contraindications

CARE OF FAMILIES

Recognize that mother always feels anxiety and guilt

Show empathy

Project a non-judgmental attitude

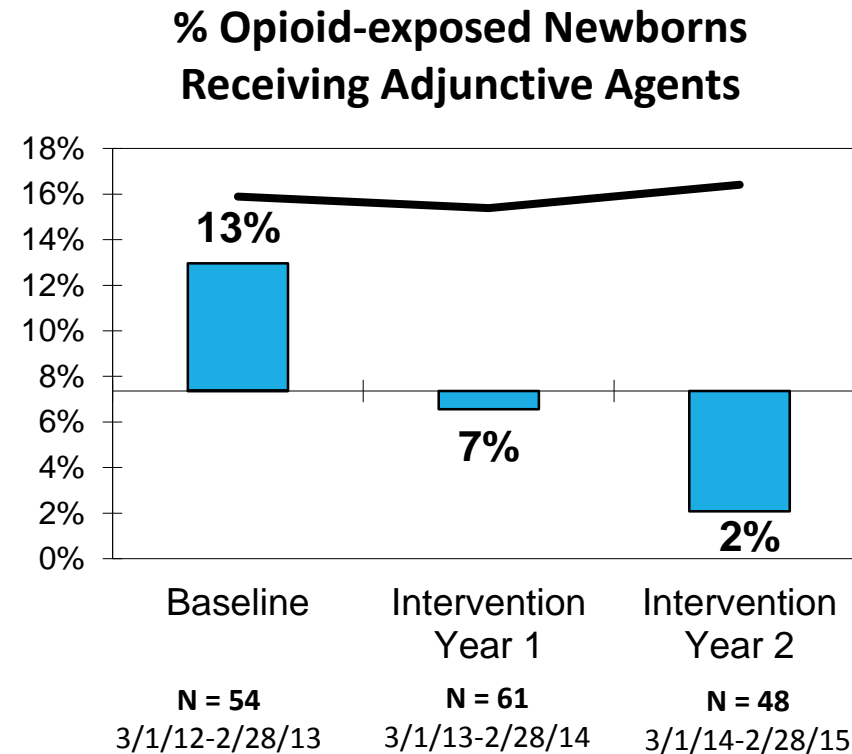
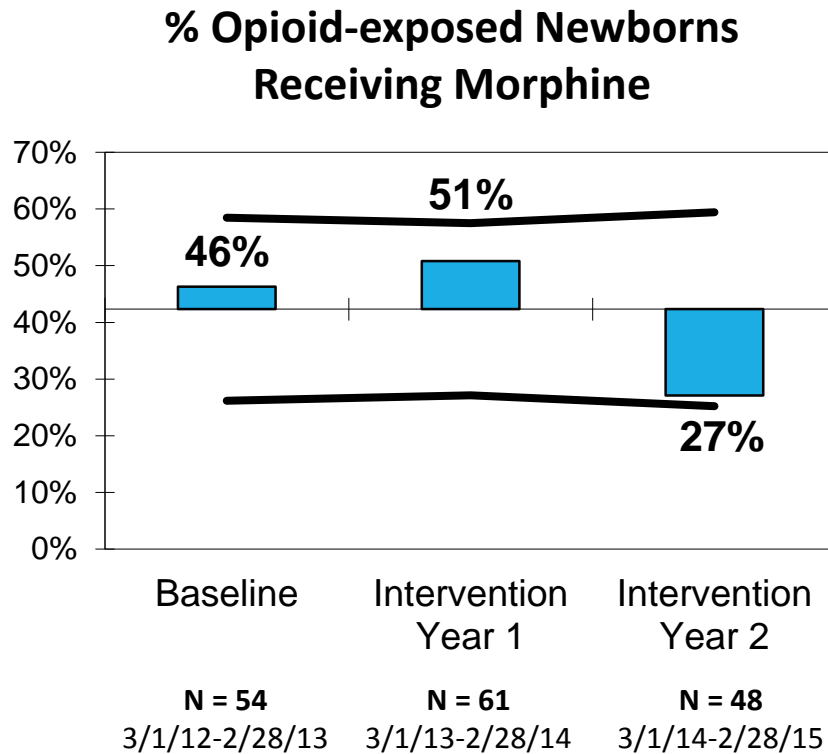
Evaluate maternal (and familial) psychosocial status

Work toward establishing good parental-infant bonding, teach parenting skills, with goals to:

- Avoid later child abuse and neglect
- Promote long-term supportive environment

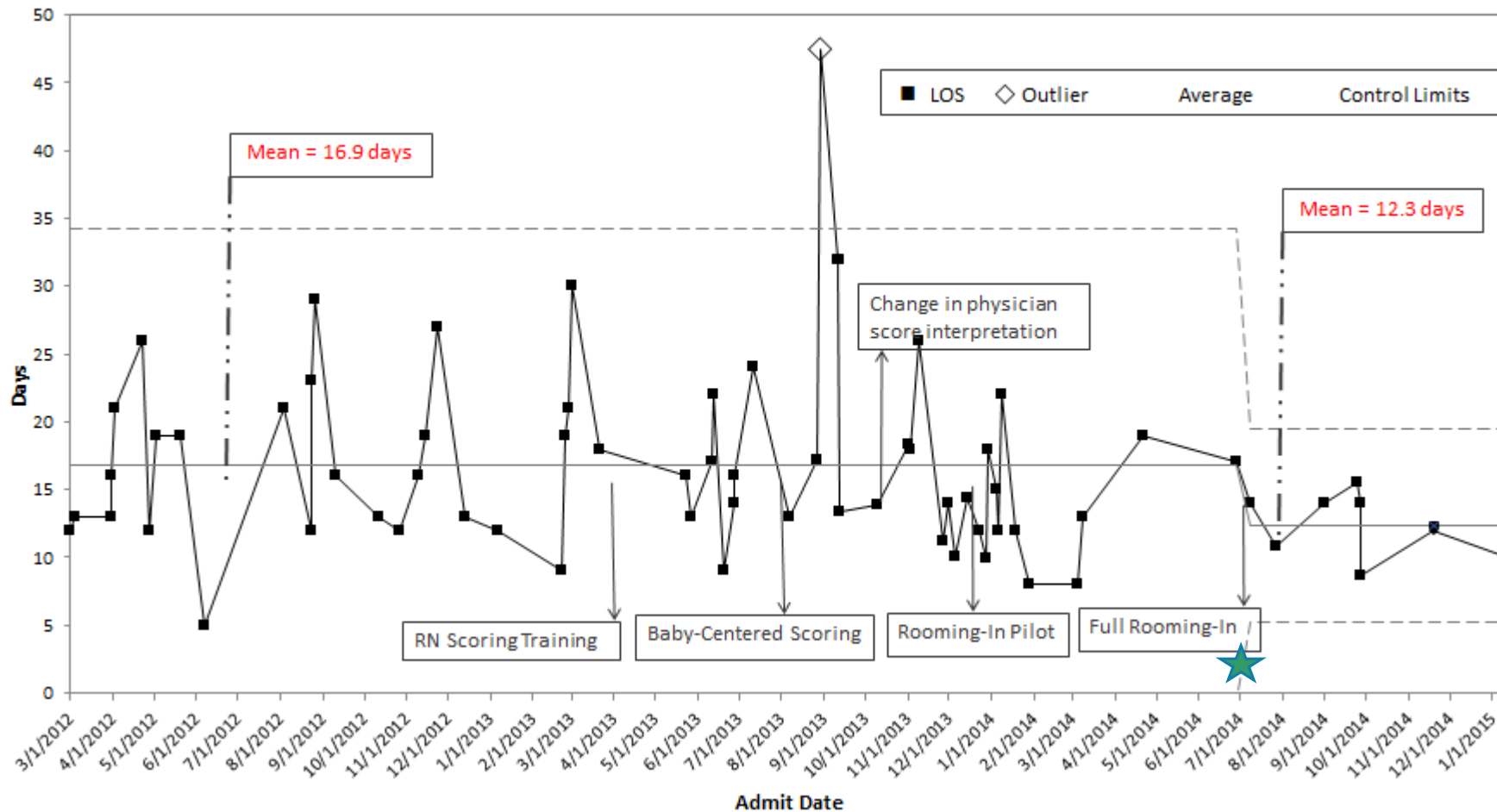
Educate family about resources

DECREASED NEED FOR PHARM RX



N = opioid-exposed infants per year

DECREASED LENGTH OF STAY



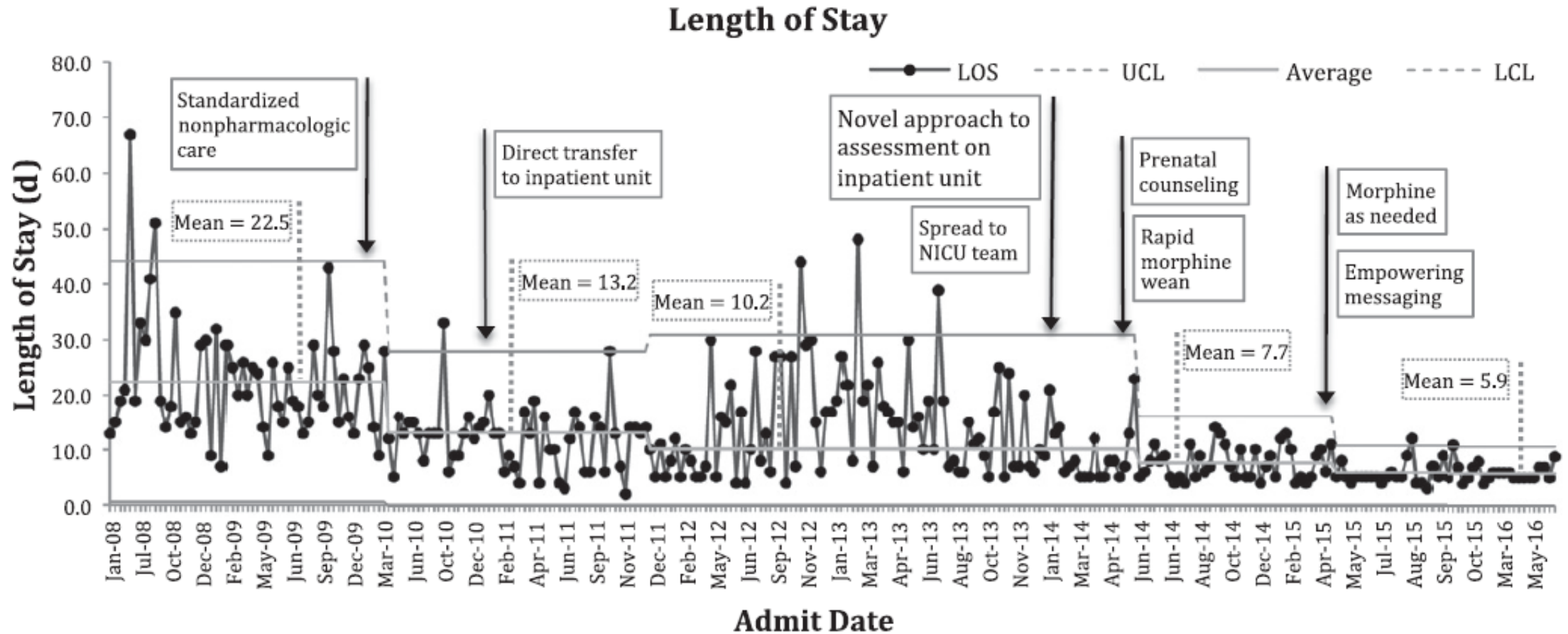
THE YALE INITIATIVE

TABLE 1 Summary of Interventions

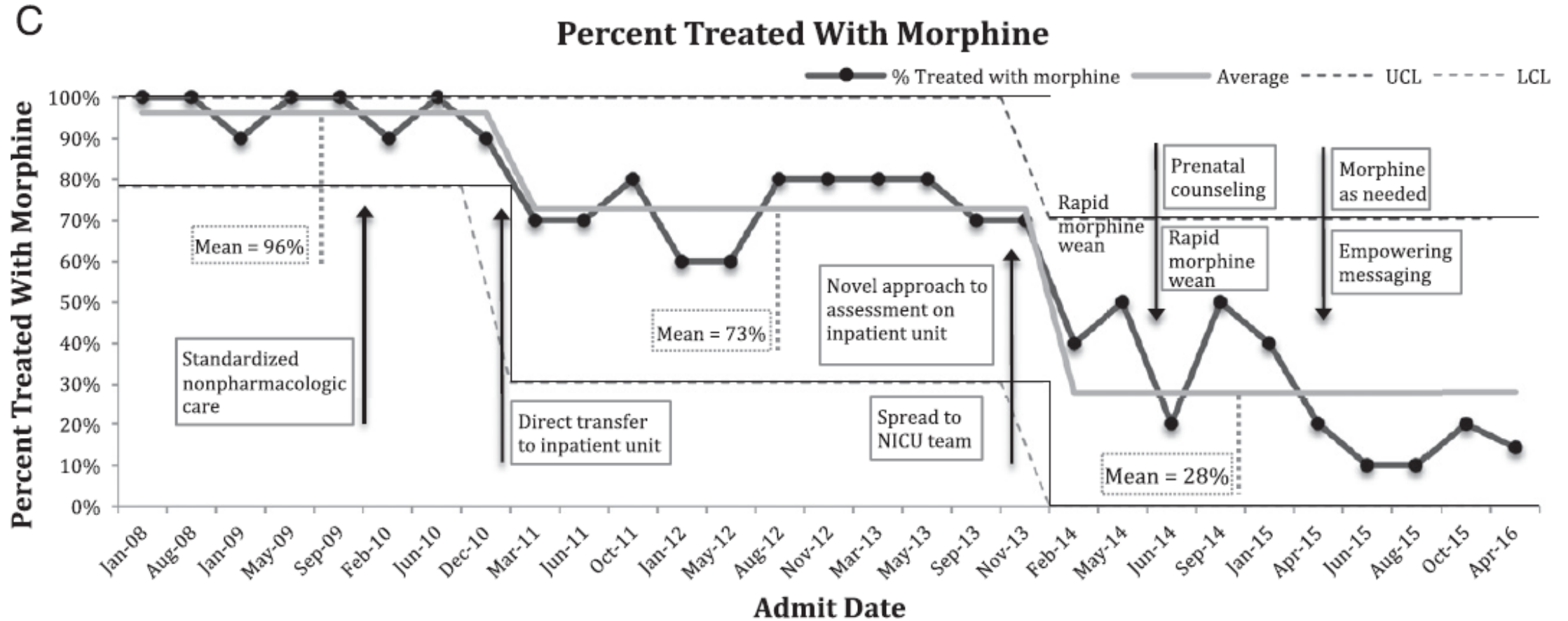
Interventions	Completion Date
Standardized nonpharmacologic care on the inpatient unit	February 2010
Transfer from WBN to the inpatient unit	February 2011
Development of a novel approach to assessment	January 2014
Spread of change concepts to NICU	January 2014
Rapid morphine weans	June 2014
Prenatal counseling of parents	June 2014
Morphine given as needed	May 2015
Empowering messaging to parents	May 2015

THE YALE INITIATIVE

A



THE YALE INITIATIVE



OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary

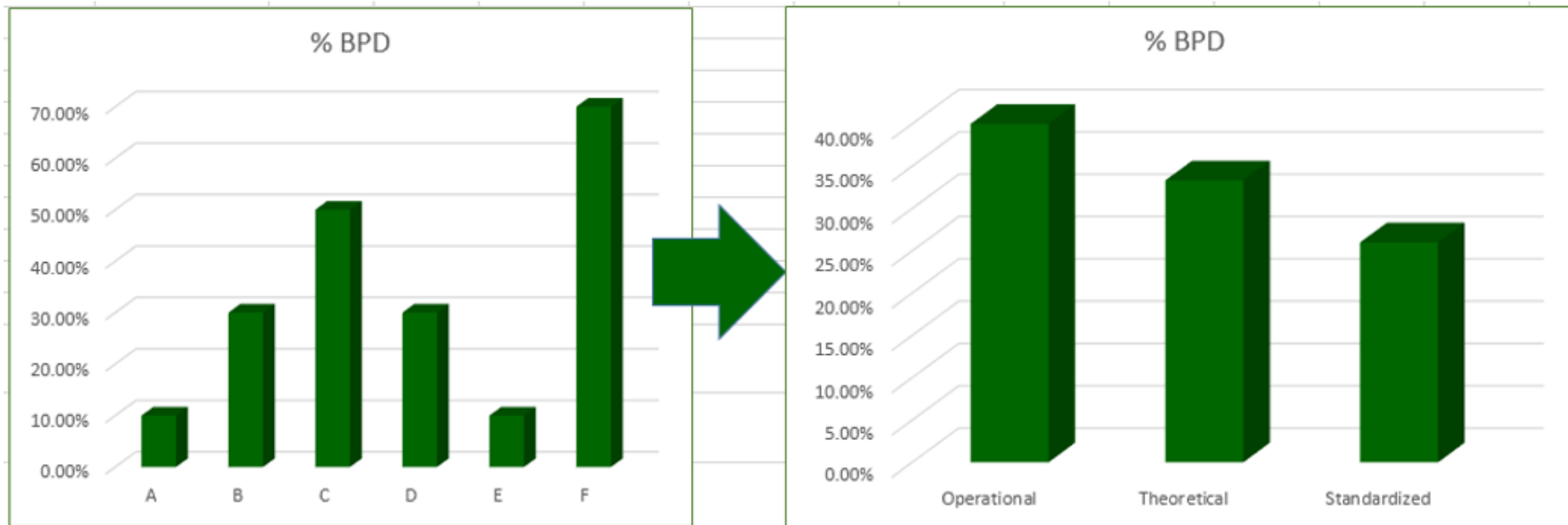
Secondary

Tertiary

- Novel drug treatments of pregnant women during labor and babies after birth
- Optimization of non-pharmacologic support of babies
- Care of families
- **Pharmacologic treatment of babies**

STANDARDIZATION IMPROVES NAS OUTCOMES

- Adoption of a consensus “better” protocol within a unit should achieve better than “mean” results by eliminating practices that have produced outlier results:



- Adoption of a consensus “better” protocol reduces the likelihood of unit operational uncertainties and of individual variability in responses to clinical situations, both of which tend to worsen outcomes (e.g., LOS)

A Multicenter Cohort Study of Treatments and Hospital Outcomes in Neonatal Abstinence Syndrome

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WHAT'S KNOWN ON THIS SUBJECT: Neonatal narcotic abstinence syndrome (NAS) has become more prevalent in the United States. There is no strong evidence base for NAS treatment and thus no consensus regarding NAS management, including the best treatment drug or best taper strategy.



WHAT THIS STUDY ADDS: This study demonstrates that regardless of the initial treatment opioid chosen, use of a standard treatment protocol with stringent weaning guidelines reduces duration of opioid exposure and length of hospital stay for infants with NAS.

- Protocol-based weaning achieved shorter durations of treatment (17.7 vs 32.1 days) and shorter LOS (22.7 vs 32.1 days)
- No differences in treatment duration or LOS between morphine or methadone
- Differences in use of secondary drug may also have been due to differences in protocol specificity

WITHIN OUR WALLS: WHAT WE DO NOT KNOW

- Optimal first-line medication
- Threshold for starting pharmacologic treatment
- Best escalation practice
- Etiology(ies) responsible for “outlier” lengths of stay
- Criteria for adjunctive drug treatment

NAS: TREATMENT ISSUES

Goals of treatment

Non-pharmacologic treatment

Role of breast feeding

Drug therapy: When to start; what drugs to use; how to dose

Care of families

PHARMACOLOGIC PRACTICE

First line drug treatment (U.S. and U.K.): opioid (oral morphine > methadone), but significant use of phenobarbital

Initial dose is usually titrated to Finnegan scores

If signs of NAS are not relieved by maximum dose of single drug, a second drug is added (phenobarbital > clonidine > benzodiazepine)

Dose is weaned by 10-20% every 1-2 days so long as Finnegan scores are generally < 8

ASSESSMENTS AND TREATMENTS

Any assessment instrument that is used to dichotomize treatment vs. non-treatment generates a risk of overtreatment

NAS scores above threshold, although accurate, may have been inflated by environmental stimuli, hunger, and suboptimal caretaker-infant interactions

Accurate scores above treatment threshold may result from factors other than withdrawal

Once initiated, the minimum duration of pharmacologic therapy under most protocols will be 10 days

CURRENT STATE OF EVIDENCE

Most existing trials do not clearly identify the most effective drug class or the most effective drug within a class; many older studies have methodological weaknesses

No trial has critically compared different criteria for initiation of drug therapy

BUT: adherence to a standard protocol reduces the length of hospital stay

OVERVIEW: LEVELS OF PREVENTION OF NAS

Primary

Secondary

Tertiary

- Novel drug treatments of pregnant women during labor and babies after birth
- Optimization of non-pharmacologic support of babies
- Care of families
- Pharmacologic treatment of babies
- **Outpatient management and outcomes**

OUTPATIENT MANAGEMENT

Outpatient management

- Occurs in some areas of the country by necessity
- Literature (Europe and U.S.) documents excessive lengths of outpatient treatment and prolonged use of drugs such as phenobarbital that may have additional long-term morbidity
- Does benefit:risk equation justify potential long-term exposure to drugs as an outpatient over few-several additional days in the hospital
- Requires excellent family selection and close follow-up: it only takes one serious morbidity to dismantle a program

LONG-TERM EFFECTS OF OPIOIDS

Maternal Life Style Study (MLS): NIDA, NIMH, NICHD

- Recruited during 1993-95
- Screened singleton infants > 500 g
- Enrolled 11,811 mother/infant pairs
- Performed maternal interview, meconium collection
- Analyzed:
 - 977 infants exposed to cocaine; 113 exposed to opioids; 92 to both
 - Complicated by other exposures (MJ, tobacco, EtOH)
 - Complicated by other maternal diseases
- Followed-up for 15 years

LONG-TERM EFFECTS OF OPIOIDS

Problems not always evident at 3-5 years of age

By preadolescence:

- Some subtle independent effects of prenatal opioids on behaviors
- Caretaker reports: behavior problem scores worse over time; attention problems

Other influences of equal or greater importance

- Prenatal tobacco, EtOH
- Maternal age and SES
- Maternal lifestyle
- Social environment
- Intrinsic resiliency

EFFECTS OF OPIOIDS ON CHILD

Long term effects – small and variable increase in:

- Behavioral problems

- Attention deficit disorder

- Memory/perception issues

Unknown effects on IQ and executive functioning

OUTCOMES AFTER DISCHARGE

What is known about these babies post discharge?

Experience from New South Wales, Australia, 2000-11

- Higher risk of rehospitalization (OR 1.6)
- Higher risk of death during hospitalization (OR 3.3)
- Higher risk of hospitalization due to assaults (OR 15.2), maltreatment (OR 21.0), poisoning (OR 3.6), mental/behavioral disorders (OR 2.6)
- NAS most important predictor of admissions for maltreatment (OR 4.5) and mental/behavioral disorders (OR 2.3) even after correcting for prematurity, maternal age, and indigenous status