



International Neonatal Consortium

Second Annual Neonatal Scientific Workshop at the EMA

Welcome

September 12th – 13th, 2016



Agenda – September 12th, Afternoon



1:00 - 2:15 p.m.	Session II: INC Workgroup Updates RON PORTMAN, INC CO-DIRECTOR (NOVARTIS)
2:15 – 3:00 p.m.	Session III: <i>Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome</i> JOHN VAN DEN ANKER (CHILDREN'S NATIONAL HEALTH SYSTEM/U-BASEL CHILDREN'S HOSPITAL) & JON DAVIS, INC CO-DIRECTOR (TUFTS UNIVERSITY), CO-CHAIRS
3:00 - 3:30 p.m.	COFFEE BREAK
3:30 – 5:00 p.m.	Session III Panel
5:00 p.m.	<i>Concluding Remarks for Day 1</i> JON DAVIS (TUFTS UNIVERSITY), INC CO-DIRECTOR
6:30 p.m.	NETWORKING DINNER AT THE PEARSON ROOM 16-19 Canada Square, Canary Wharf

Agenda – Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome



2:15 – 3:00 p.m.

Session III: *Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome*

JOHN VAN DEN ANKER (CHILDREN'S NATIONAL HEALTH SYSTEM/U-BASEL CHILDREN'S HOSPITAL) &
JON DAVIS, INC CO-DIRECTOR (TUFTS UNIVERSITY), CO-CHAIRS

The Opioid Epidemic and Neonatal Abstinence Syndrome

STEPHEN PATRICK (VANDERBILT UNIVERSITY)

The Use of Narcotics for Sedation or Analgesia

JACOB ARANDA (UNIVERSITY HOSPITAL – BROOKLYN)

3:00 – 3:30 p.m.

COFFEE BREAK

3:30 – 5:00 p.m.

SESSION III PANEL

Agenda – Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome



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SESSION III PANEL



International Neonatal Consortium

Prescription Opioid Use in Pregnancy and Neonatal Abstinence Syndrome

Stephen W. Patrick, MD, MPH, MS
Vanderbilt University School of Medicine
International Neonatal Consortium
September 12, 2016



History

History



Trends in
Opioid Use



NAS



Research
Gaps

ADDICTION RARE IN PATIENTS TREATED WITH NARCOTICS

To the Editor: Recently, we examined our current files to determine the incidence of narcotic addiction in 39,946 hospitalized medical patients¹ who were monitored consecutively. Although there were 11,882 patients who received at least one narcotic preparation, there were only four cases of reasonably well documented addiction in patients who had no history of addiction. The addiction was considered major in only one instance. The drugs implicated were meperidine in two patients,² Percodan in one, and hydromorphone in one. We conclude that despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction.

JANE PORTER
HERSHEL JICK, M.D.
Boston Collaborative Drug
Surveillance Program
Boston University Medical Center

Waltham, MA 02154

1. Jick H, Miettinen OS, Shapiro S, Lewis GP, Siskind Y, Slone D. Comprehensive drug surveillance. *JAMA*. 1970; 213:1455-60.
2. Miller RR, Jick H. Clinical effects of meperidine in hospitalized medical patients. *J Clin Pharmacol*. 1978; 18:180-8.

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1996

- American Pain Society “Pain as the 5th Vital Sign Campaign”

1998

- Federation of State Medical Boards published "Model Guidelines for the Use of Controlled Substances for the Treatment of Pain."

2003

- *The New York Times* reports tripling of young adults (18-25) abusing opioid pain relievers. DEA and FDA create task force to crack down on internet sales of opioids.

2007

- Maker of OxyContin, Purdue Pharma, plead guilty to “criminal charges that they misled regulators, doctors and patients about the drug’s risk of addiction and its potential to be abused.” Results in a \$600M settlement.

2000+

- Rapid expansion of opioid use in the US

Trends in Opioid Use

History



Trends in
Opioid Use

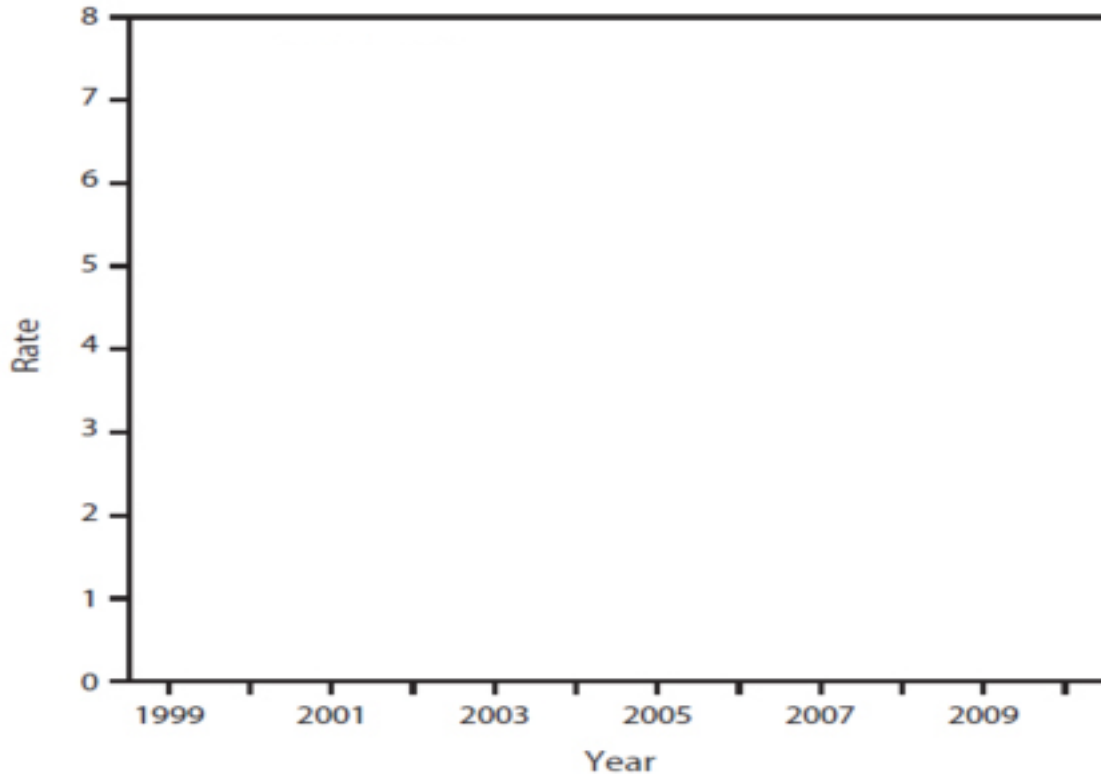


NAS



Research
Gaps

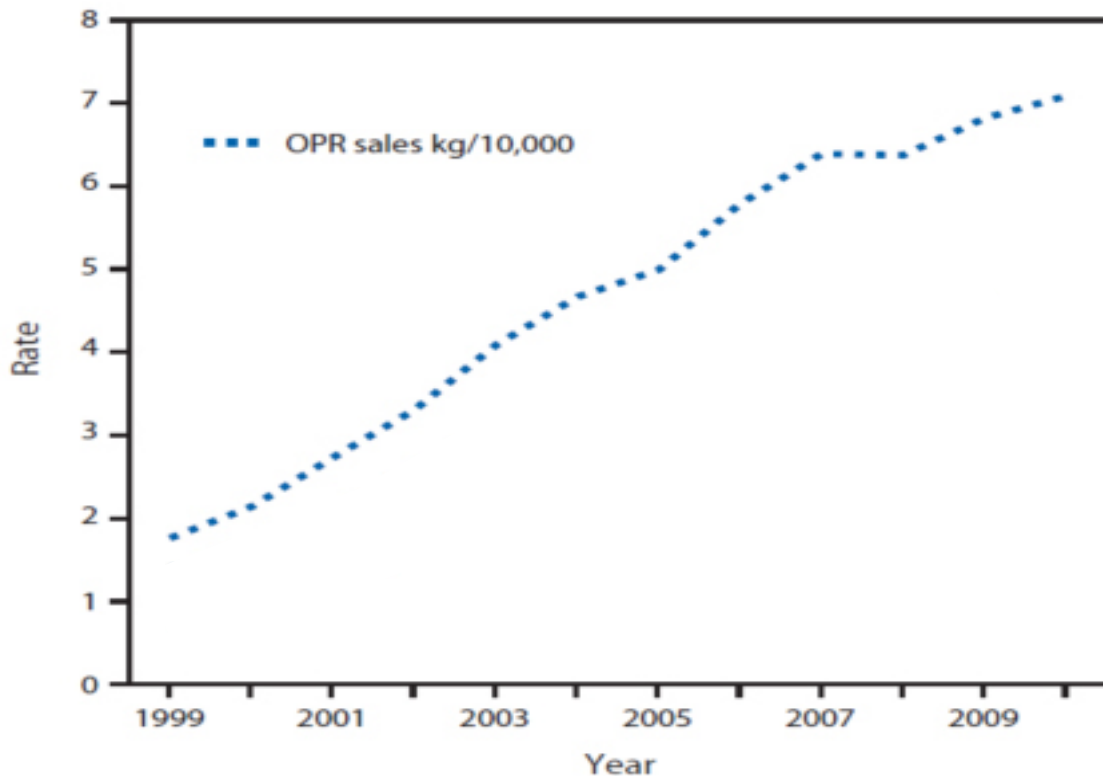
Rates of Opioid Pain Reliever (OPR) Overdose Death, OPR Treatment Admissions, and Kilograms of OPR Sold



United States, 1999–2010

Age-adjusted rates per 100,000 population for OPR deaths, crude rates per 10,000 population for OPR abuse treatment admissions, and crude rates per 10,000 population for kilograms of OPR sold.

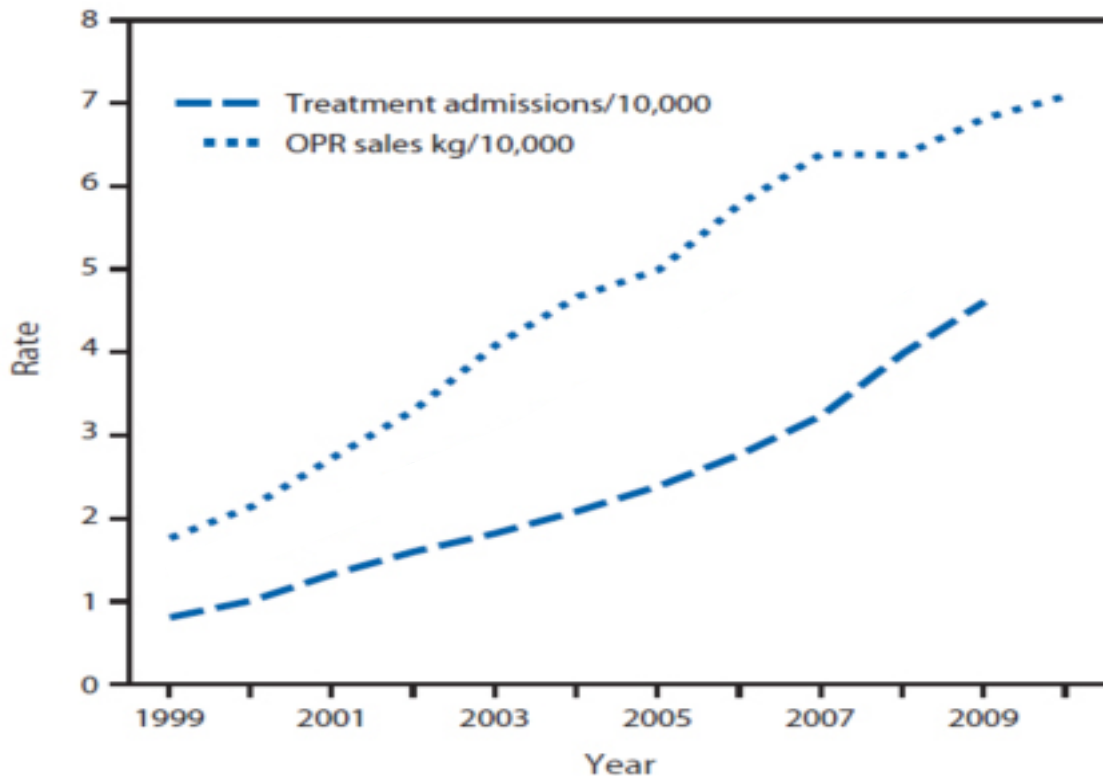
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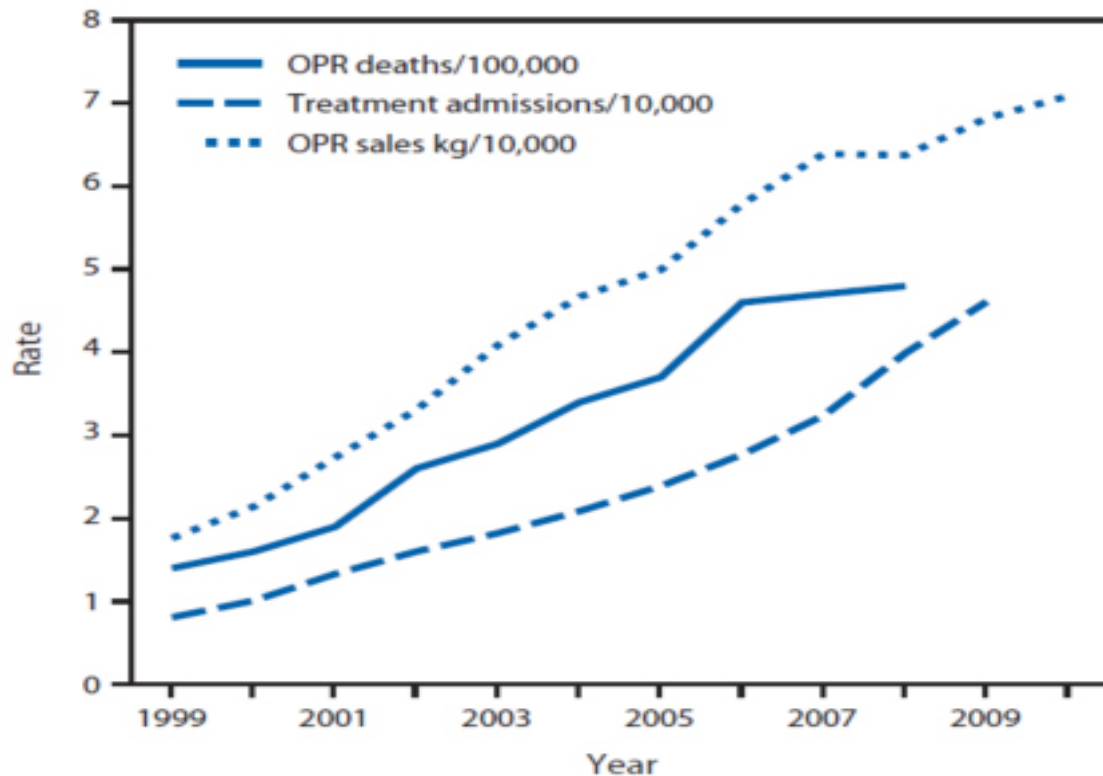
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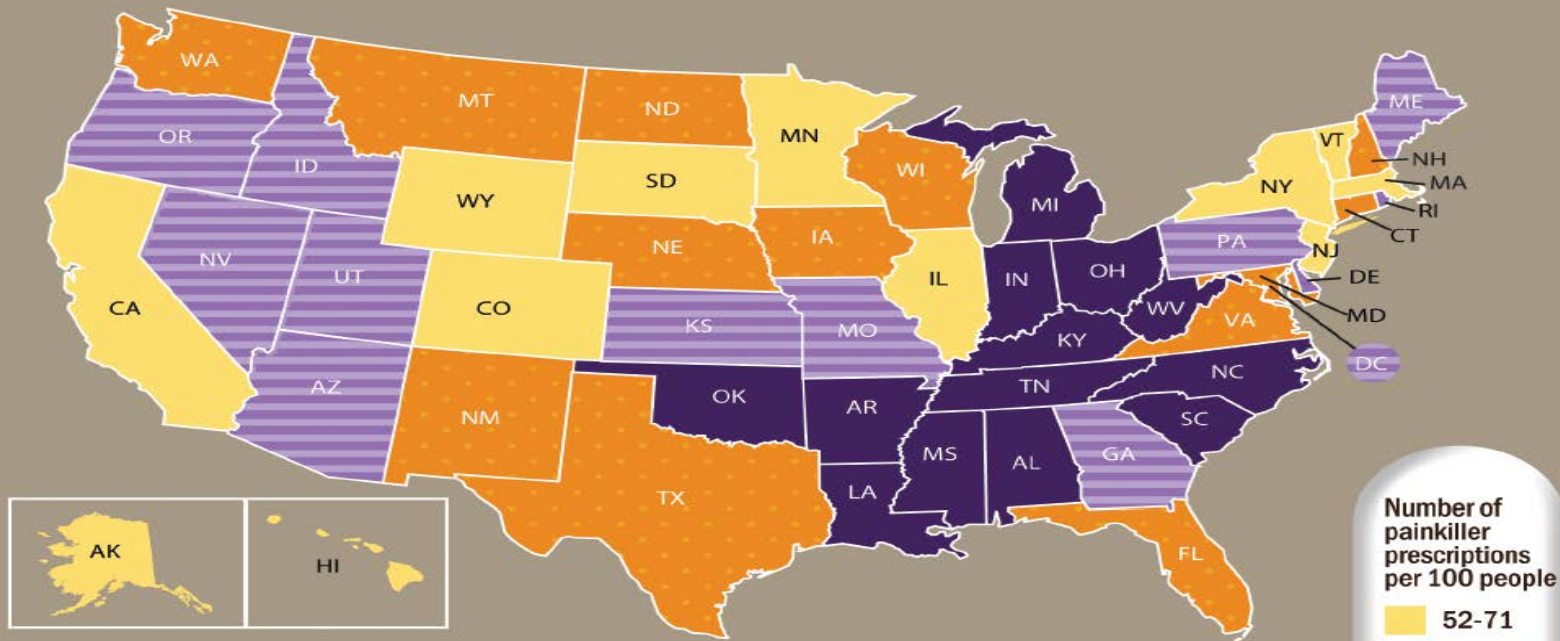
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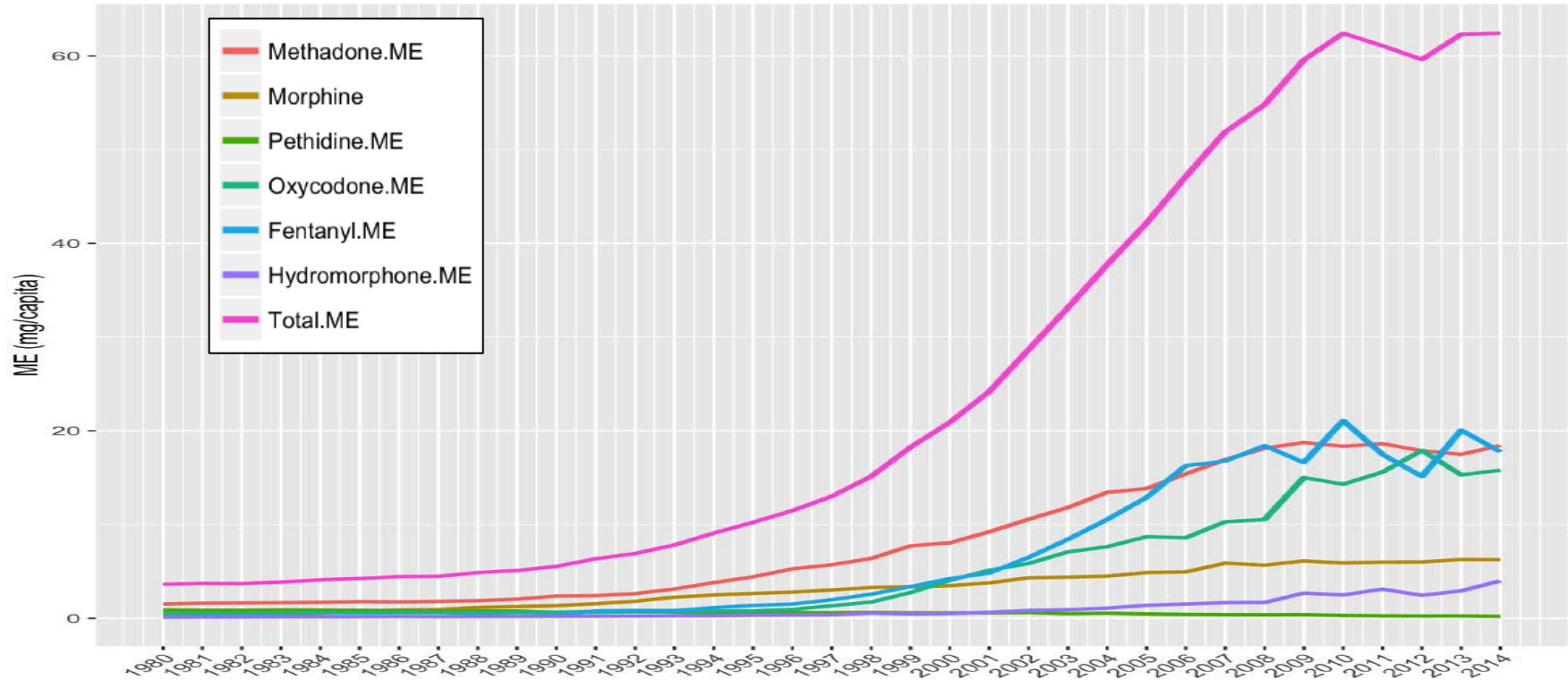
Some states have more painkiller prescriptions per person than others.

Opioid Pain Relievers in the US

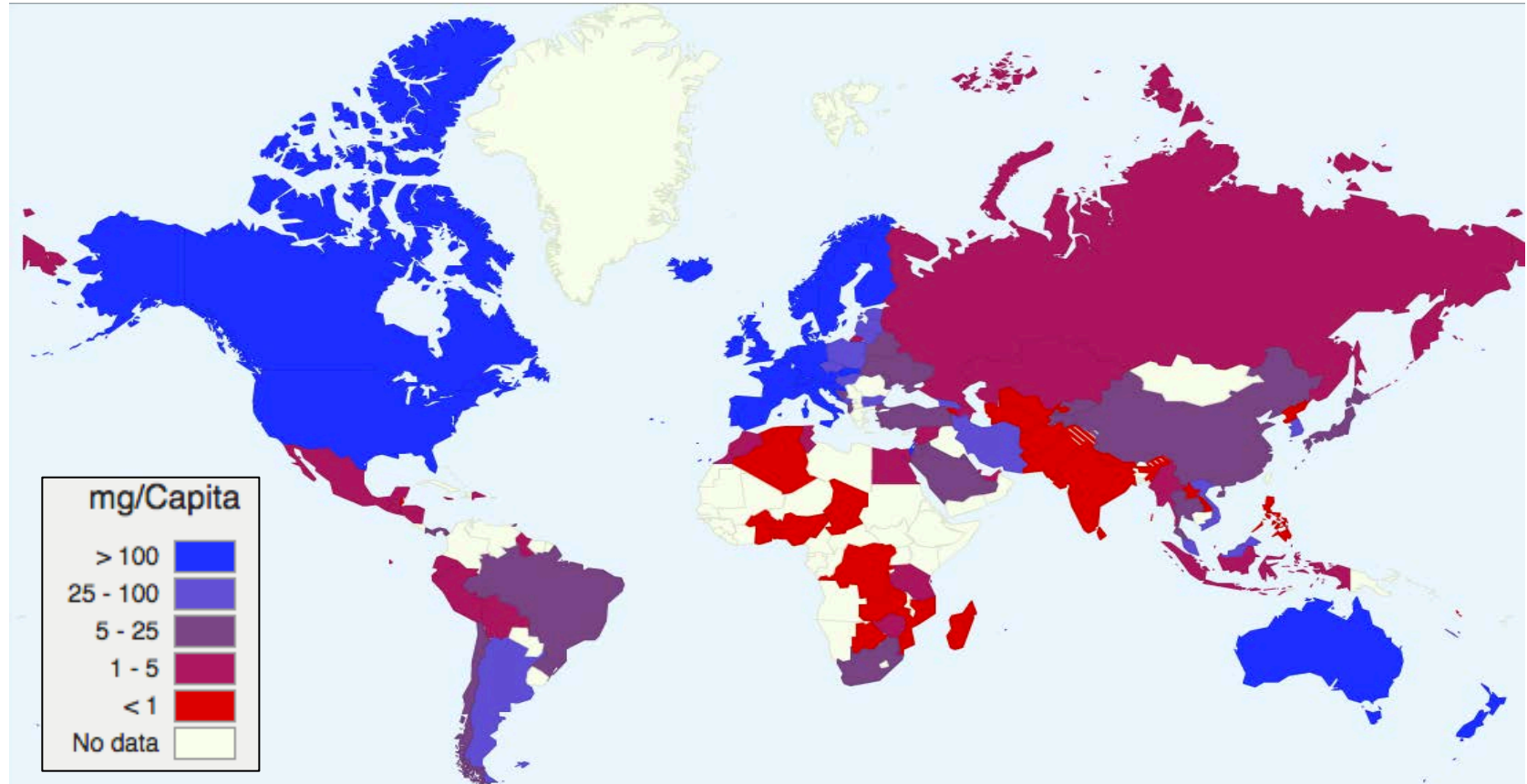
- Prescriptions grew 4-fold over last decade
- Now account for more overdose deaths than cocaine and heroin combined
- More deaths than car accidents
- In 2012, enough OPR were prescribed to give every adult in the US one prescription
- Heroin use and overdoses increasing

Source: Centers for Disease Control and Prevention

Global Opioid Consumption Morphine Equivalence (ME) (mg/capita)



Global Opioid Consumption Morphine Equivalence (ME) (mg/capita) by Country, 2014



NAS

History



Trends in
Opioid Use



NAS



Research
Gaps

What is NAS?

- A withdrawal syndrome experienced by drug exposed newborns after birth
- Generally follows opioid exposure, though other drugs have been implicated
 - Alcohol, benzodiazepines (valium, etc.), barbiturates (phenobarbital, etc.)
- 40-80% of heroin and methadone exposed newborns develop NAS
 - ~5% of those exposed to opioid pain relievers



- GI
 - Poor feeding/vomiting/loose stools
 - Leading to dehydration and poor weight gain
- CNS
 - Tremors/hypertonia
 - Irritability/decreased sleep
 - Exaggerated reflexes (e.g. moro)
 - Seizures
- Autonomic activation
 - Tachypnea
 - Yawning
 - Dilated pupils

- Not every exposed newborn has withdrawal
- Exposure: history, maternal drug screens (urine), infant drug screens (urine, umbilical cord, meconium)
- Diagnosis made based on scoring system of newborn signs of withdrawal

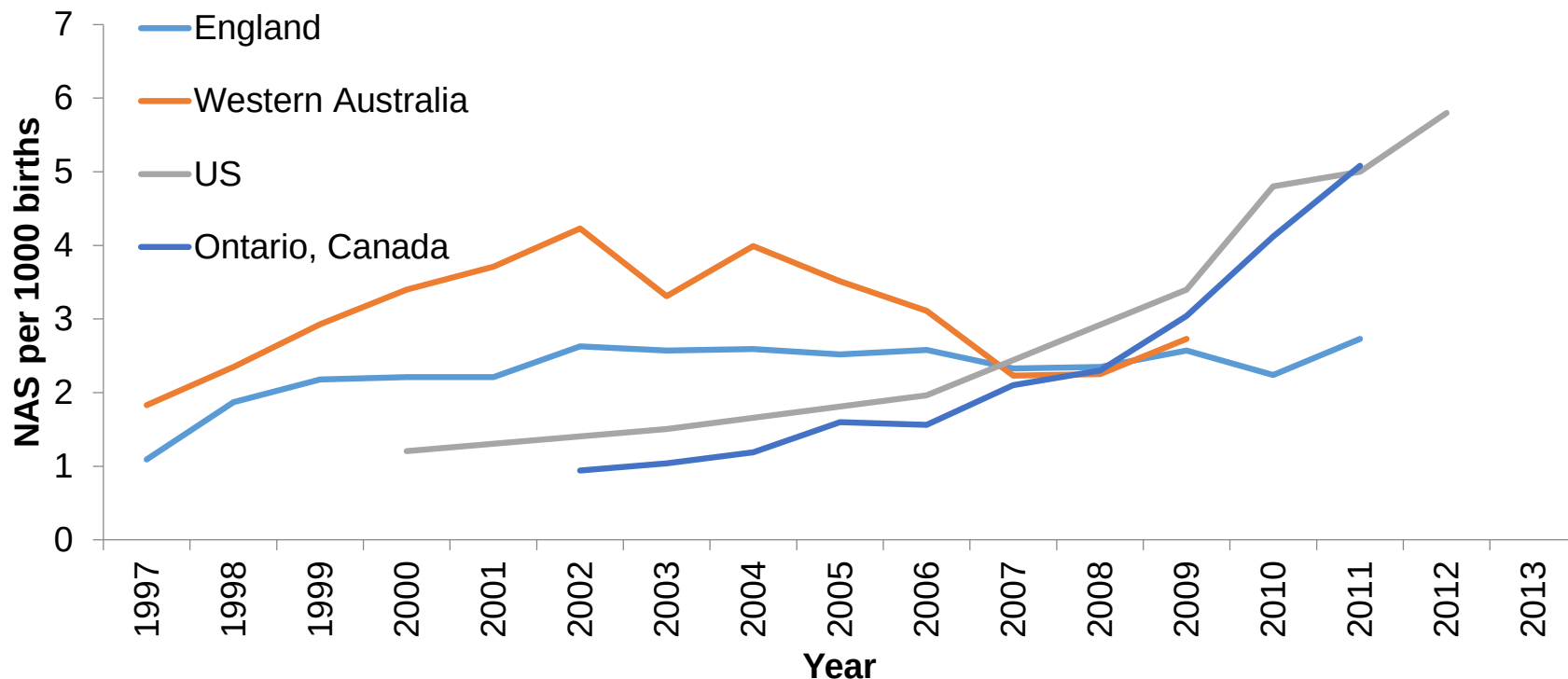
SYSTEM	SIGN	SCORE			
Central nervous system disturbances			Gastrointestinal disturbances	Excessive sucking	1
	High pitch/excessive cry	2		Poor feeding*	2
	Continuous (high pitched) cry	3		Regurgitation*	2
	Sleeps less than 1 hour after feeds	3		Projectile vomiting	3
	Sleeps less than 2 hours after feeds	2		Loose stools	2
	Sleeps less than 3 hours after feeds	1	Watery stools	3	
	Hyperactive Moro reflex	2	Respiratory/vasomotor disturbances	Sweating	1
	Markedly hyperactive Moro reflex	3		Fever 37.3 to 38.3°C	1
	Mild tremors disturbed*	1		Fever 38.4°C and above	2
	Mod/severe tremors disturbed*	2		Frequent yawning (> 3 – 4 in ½ hr)	1
	Mild tremors undisturbed*	3		Mottling	1
	Mod/severe tremors undisturbed*	4		Nasal stuffiness	1
	Increased muscle tone	2		Sneezing (> 3 – 4 in ½ hr)	2
	Excoriation*	1		Nasal flaring	1
	Myoclonic jerks	3		Respiratory rate > 60/min	1
	Generalised convulsions	5		Respiratory rate > 60/min and retractions	2

Zimmermann-Baer U. Finnegan neonatal abstinence scoring system: normal values for first 3 days and weeks 5-6 in non-addicted infants. *Addiction* (Abingdon, England). 2010;105(3):524-528.

- Scoring Tools
 - Have not undergone rigorous instrument development
 - Significant inter-rater reliability challenges
- Scoring Cut-point Threshold
- Scoring Context
 - Never tested in preterm infants
 - Tested on pure opiate-exposed population
 - Currently poly-substance exposure is the norm
 - Finnegan paper = average LOS was 6 days . . .

- Goal of treatment to “control” withdrawal, minimizing complications (e.g. seizure)
- Non-pharmacologic intervention (e.g. environmental controls, etc)
- Involves using opioids (morphine, methadone) and slowing weaning dose

Global NAS, 1997-2013

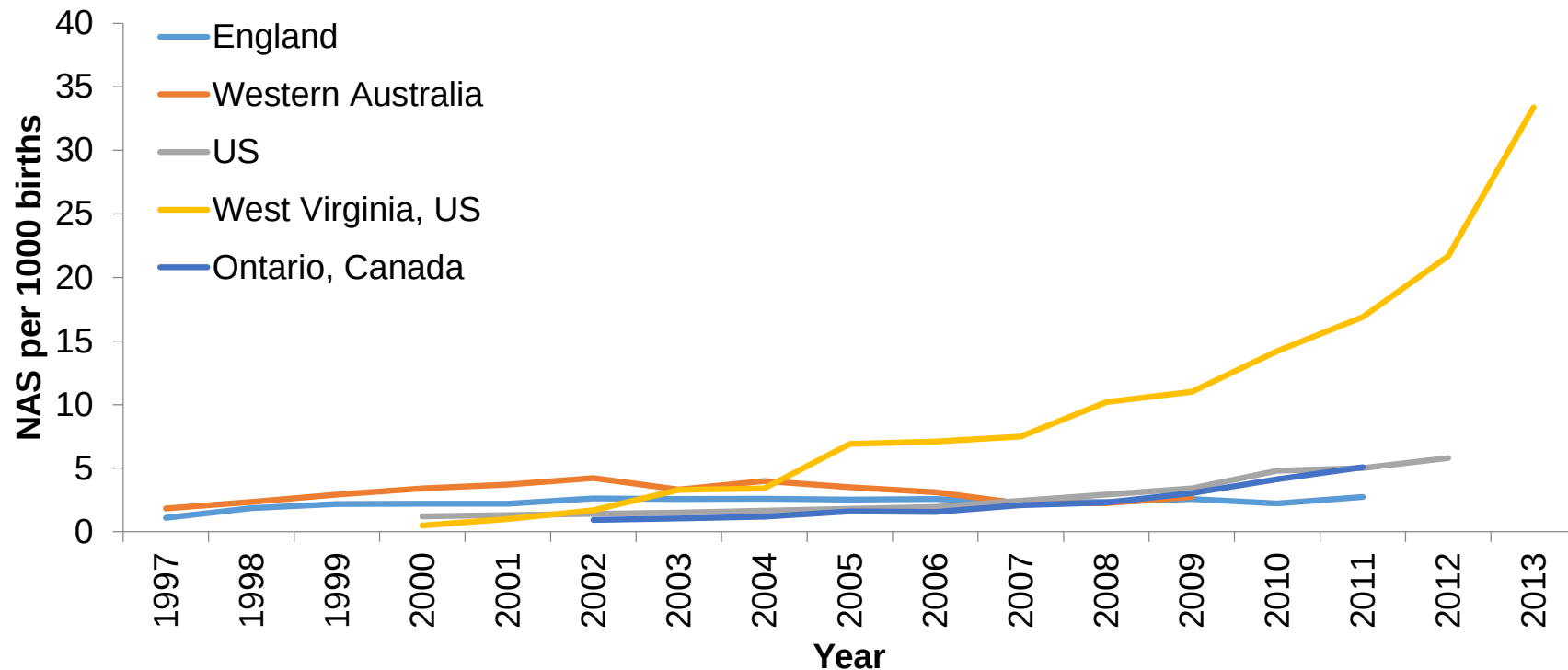


Davies H, Gilbert R, Johnson K, et al. Neonatal drug withdrawal syndrome: cross-country comparison using hospital administrative data in England, the USA, Western Australia and Ontario, Canada. *Arch Dis Child Fetal Neonatal Ed.* 2016;101(1):F26-30.

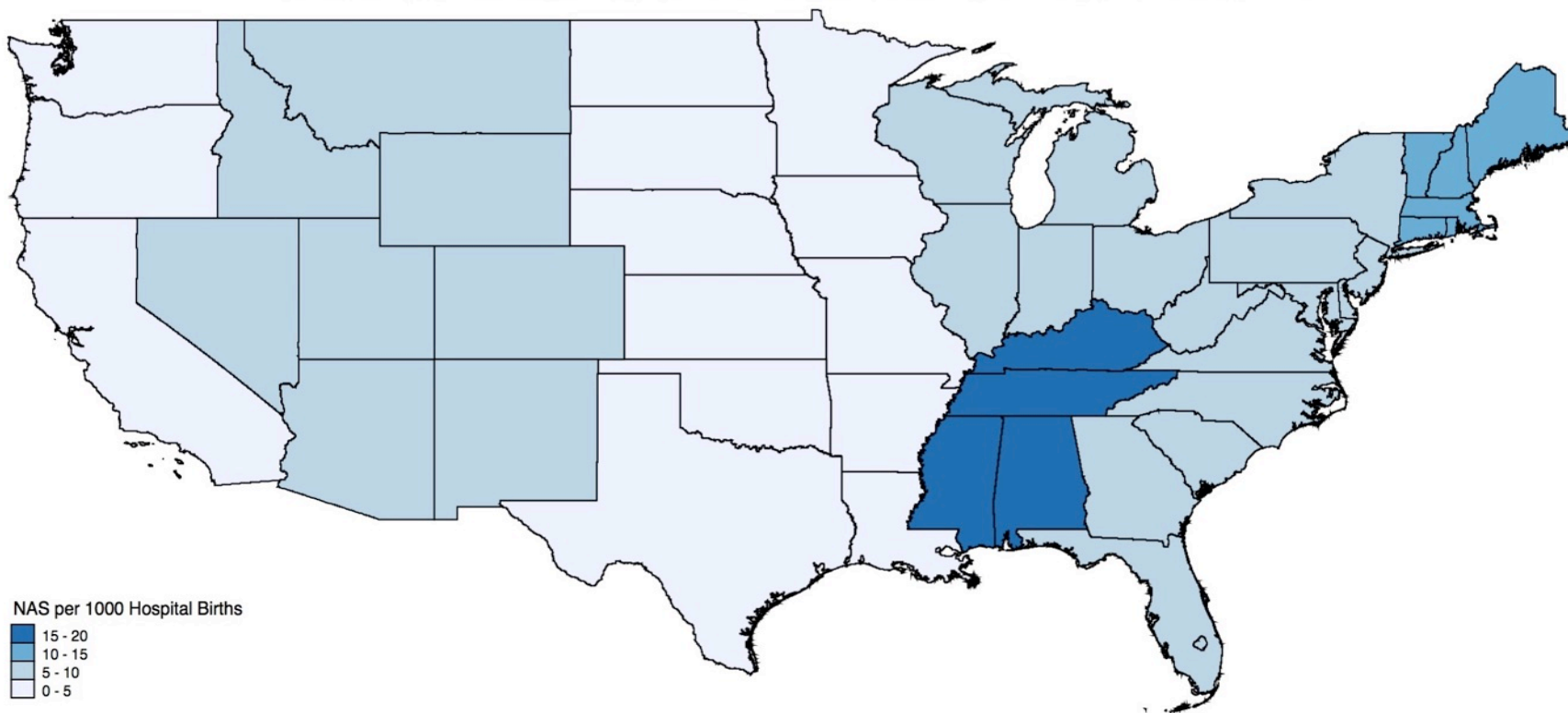
Patrick SW, et. al. Neonatal Abstinence Syndrome and Associated Healthcare Expenditures – United States, 2000-2009. *JAMA.* 2012 May 9;307(18):1934-40.

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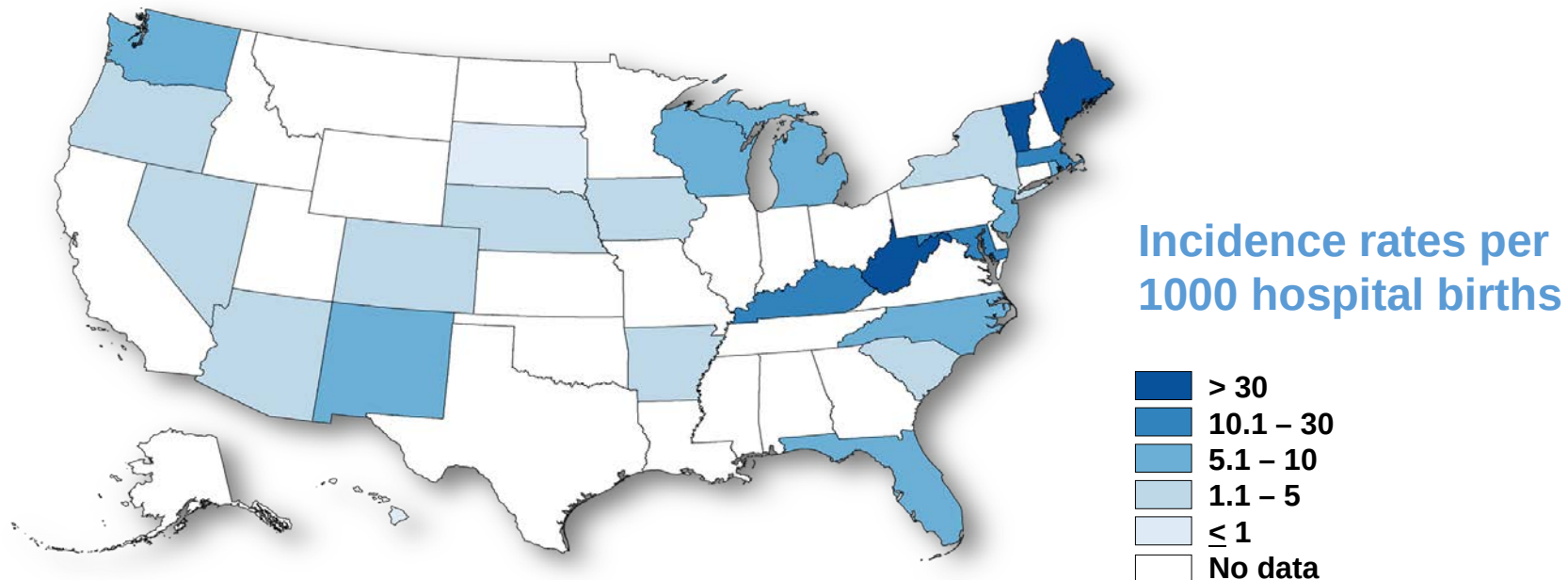


NAS by US Geographic Division, 2012



Patrick SW, Davis MM, Lehman CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. J Perinatol. Apr 30 2015.

NAS in 28 US States, 2013



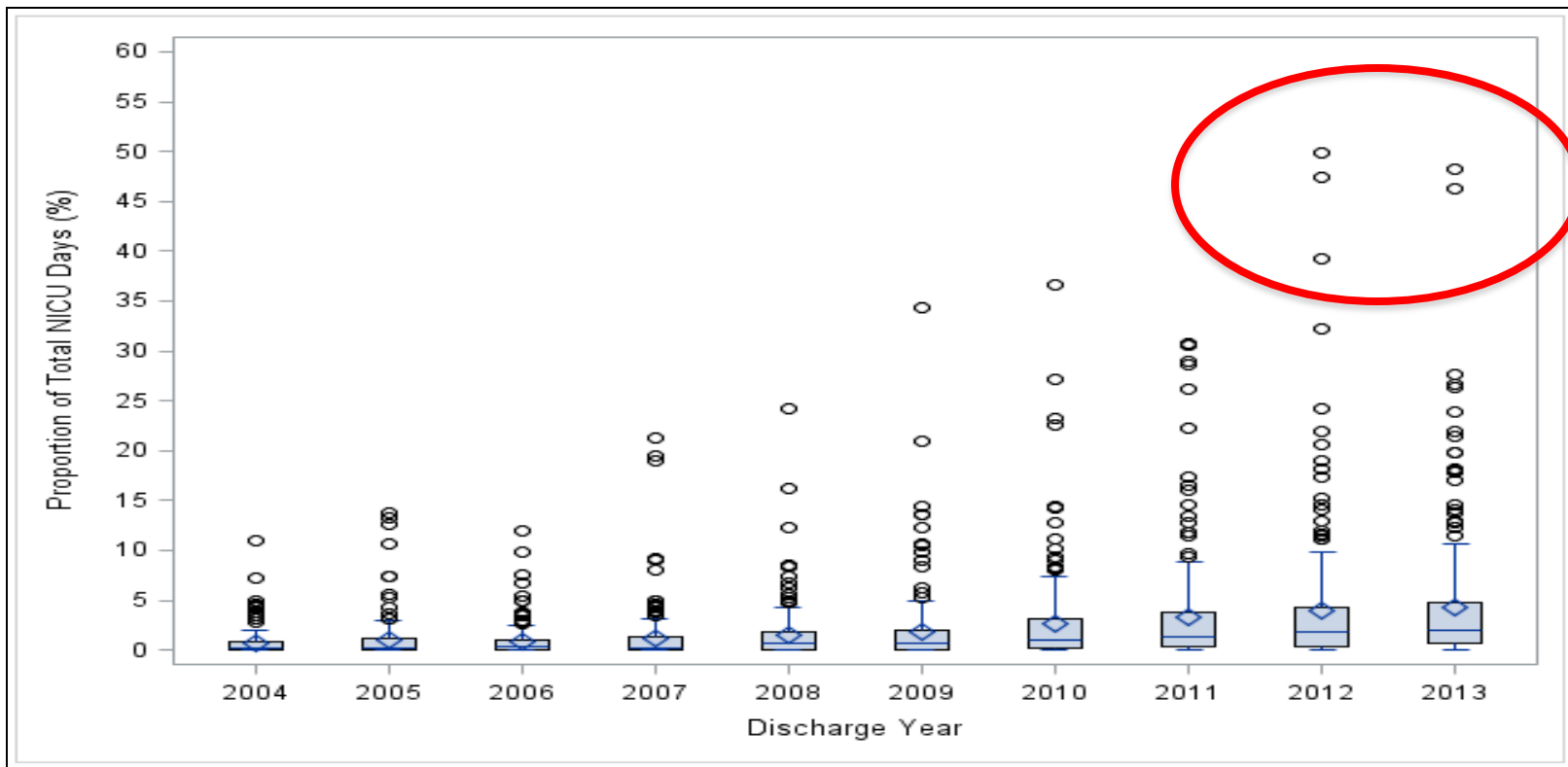
Ko JY, Patrick SW, Tong VT, Patel R, Lind JN, Barfield WD. Incidence of Neonatal Abstinence Syndrome - 28 States, 1999-2013. MMWR Morb Mortal Wkly Rep. 2016;65(31):799-802.

Mean LOS and Hospital Charges for NAS, 2009-2012

	2009	2010	2011	2012
Mean LOS (day)	22.7	22.9	22.8	23.0
Mean Charges* (2012 US\$)	\$75,700	\$80,500	\$87,700	\$93,400

* $p < 0.001$

Proportion of NICU Days, By NICU (N=299)



Tolia VN, Patrick SW, Bennett MM, et al. Increasing Incidence of the Neonatal Abstinence Syndrome in U.S. Neonatal ICUs. *N Engl J Med*. 2015;372(22):2118-2126.

Total Hospital Charges for NAS, 2009-2012

	2009	2010	2011	2012
Medicaid*	\$560M	\$870M	\$900M	\$1.2B
Private Payer*	\$130M	\$170M	\$210M	\$200M
Self Pay*	\$20M	\$40M	\$30M	\$40M
Other Payer*	\$14M	\$30M	\$30M	\$30M
Total Charges*	\$730M	\$1.1B	\$1.2B	\$1.5B

Patrick SW, Davis MM, Lehmann CU, Cooper WO. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *J Perinatol.* 2015;35(8):650-655.

Research Gaps

History



Trends in
Opioid Use

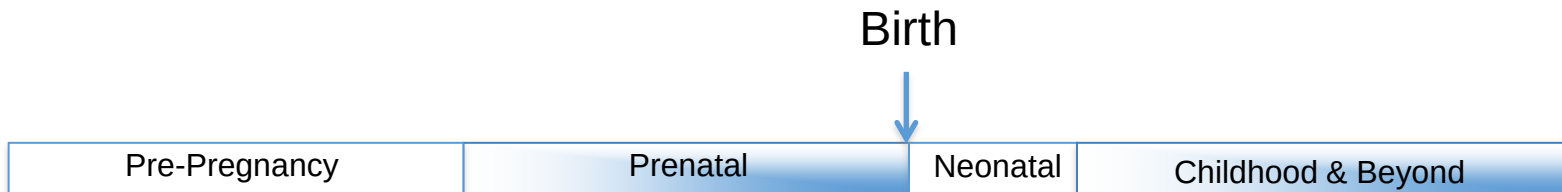


NAS



Research
Gaps

Research Across the Continuum



Where are the intervention points? How can we improve research and data?



United States Government Accountability Office

Report to Congressional Requesters

February 2015

PRENATAL DRUG USE AND NEWBORN HEALTH

Federal Efforts Need Better Planning and Coordination

GAO Cited Research Gaps



Research gap	Number that cited gap
Treatment of prenatal opioid use, including medication-assisted treatment	13
Long-term effects of prenatal opioid exposure in children	12
Treatment of NAS	11
Screening and diagnosing of NAS	10
Understanding of NAS and severity of NAS	10
Appropriate research methods or available data (i.e., studies of appropriate size and applied research)	7
Knowledge of best practices in opioid prescribing	5
Prevention, including prevention of substance use disorders or pregnancy in women with opioid use disorders	4
Screening for prenatal opioid use	2
Understanding prenatal opioid use	2

Source: GAO. | GAO-15-203

- Specifics noted –
 - Treatment of opioid use disorders in pregnant women – universal screening?
 - Best practices for MAT; barriers to treatment
 - Subjectivity and labor intensiveness of Finnegan NAS Tool
 - Treatment of NAS
 - Effectiveness of different drugs
 - Long-term outcomes of opioid-exposed infants

- Barriers to research
 - Identifying and retaining pregnant women
 - Low numbers; high drop out rates
 - Reluctance to participate due to possible criminal repercussions
 - Polysubstance use
 - Variation in expression of NAS
 - Need for large numbers
 - Funding
 - Capacity (multidisciplinary teams needed)

- Standardization/structure for international research efforts
- What is NAS/NOWS?
 - Gold standard definition
 - Objective means for diagnosis, validated
- Relevant outcomes
 - Not limited to utilization (e.g. length of stay, not family centered, does not take post-discharge outcomes into account)
 - Standardized outcomes for site/international comparisons

- Opioid use and NAS are not new, but challenges with recent surges
- Opioid use and NAS are international problems, with particularly high rates in North American, Europe and Australia
- A coordinated, international agenda will facilitate better research and more effective coordination ultimately improving outcomes for this vulnerable population

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Vanderbilt

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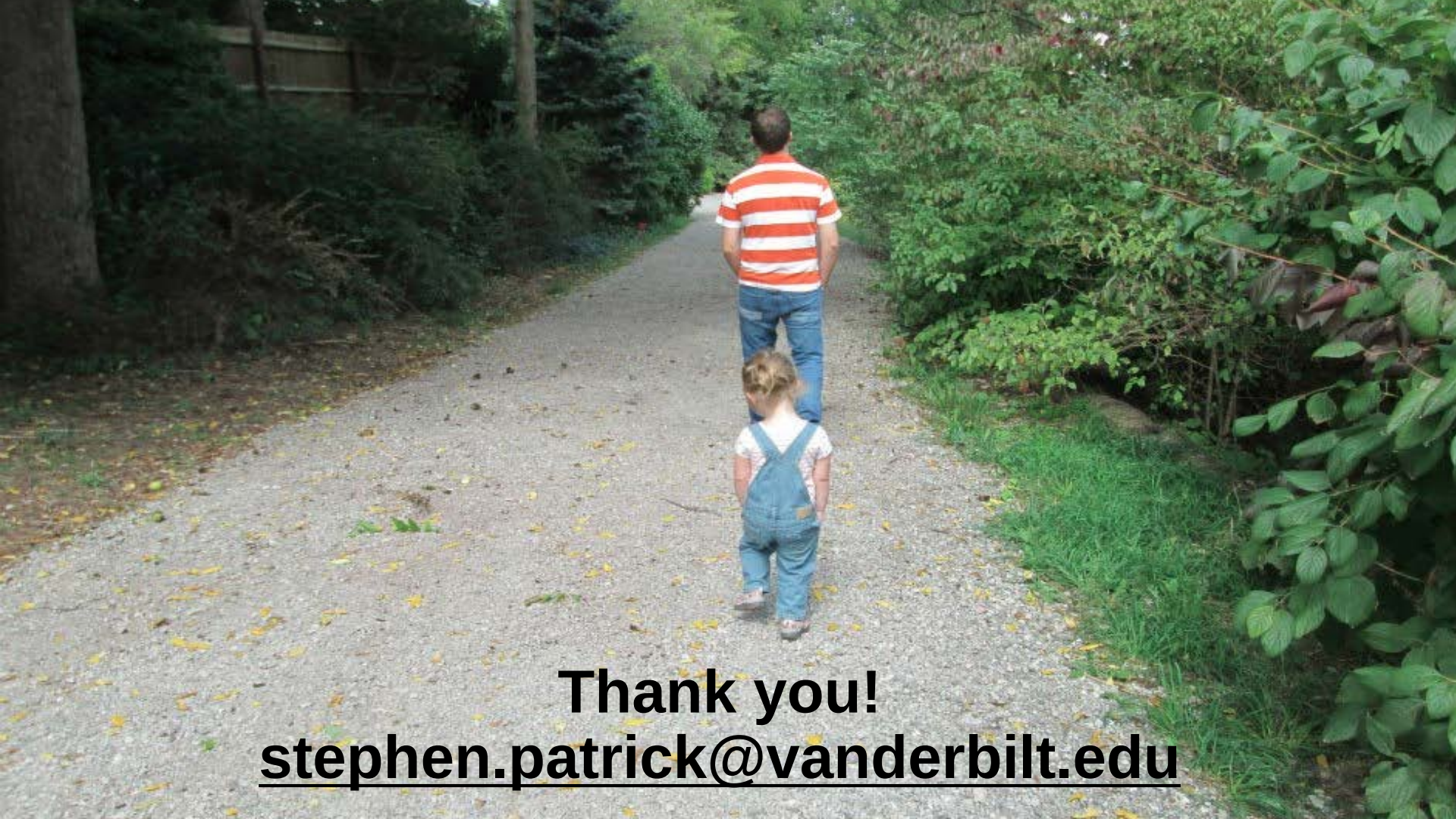
Robert Wood Johnson Foundation Clinical Scholars Program

Tennessee Department of Health/HRSA

National Institutes of Health - 5KL2TR000446-08

National Institute on Drug Abuse - K23DA038720

National Institute on Drug Abuse Loan Repayment Program



Thank you!
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Prescribing and NAS

- Study from our group - >110,000 TN births
 - >31,000 women prescribed opioids (96% short-acting)
 - More likely to have co-occurring psychiatric diagnoses
- 2/3 of infants with NAS, mother with legal Rx
 - Smoking increased risk of NAS
 - Higher dose of immediate release increased risk of NAS
 - Dose of maintenance drugs did not change risk
 - 1:50, Short-acting opioid cost: infant cost

Agenda – Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome



2:15 – 3:00 p.m.

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3:00 – 3:30 p.m.

COFFEE BREAK

3:30 – 5:00 p.m.

SESSION III PANEL

Analgesia and Sedation in the Newborn

J.V. Aranda, MD, PhD, FRCPC, FAAP

***Professor and Director of Neonatology and the
U54 New York Pediatric Developmental Pharmacol Res Center
State University of New York Downstate Medical Center
Brooklyn, New York, NY***

Email: *jaranda@downstate.edu*

Scope

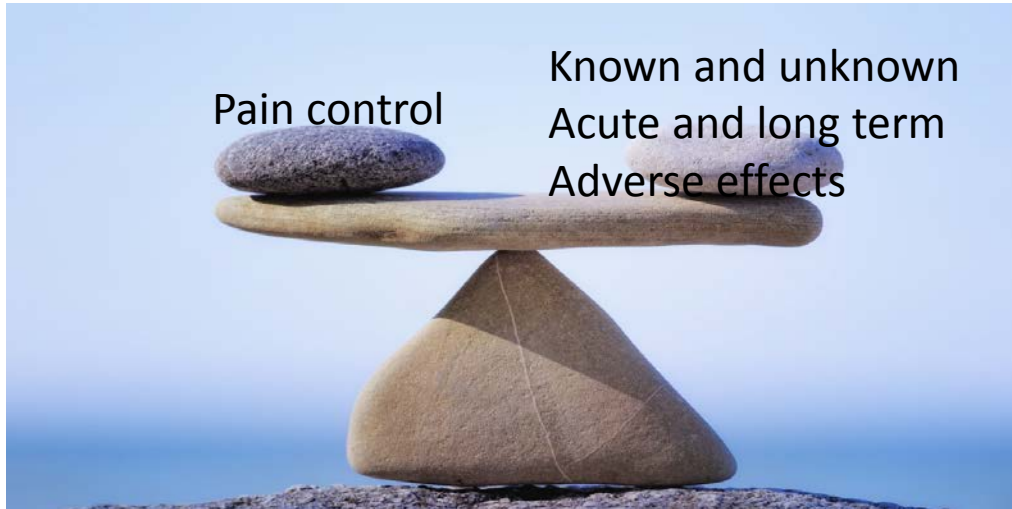
1. Use of analgesics and sedation in NICUs
2. Outcome of unrelieved pain and treatments
3. Pain assessment and quantification in Newborns
4. Opiates
5. Sedatives
6. NSAIDs
7. GAPS in knowledge: Pharmacotherapy of Pain and Stress in newborns
8. Questions and Comments along the way

Basic Principles - Neonatal Pain

- Newborns can feel pain
- Humane and Ethical IMPERATIVE to provide comfort and relieve pain in a vulnerable, non-verbal population
- Increased pain sensitivity due to immature pain modulatory mechanisms
- Prolonged hyperalgesia following tissue injury
- Acute physiologic and behavioral responses to painful stimuli

Analgesia and Sedation Practices in NICUs

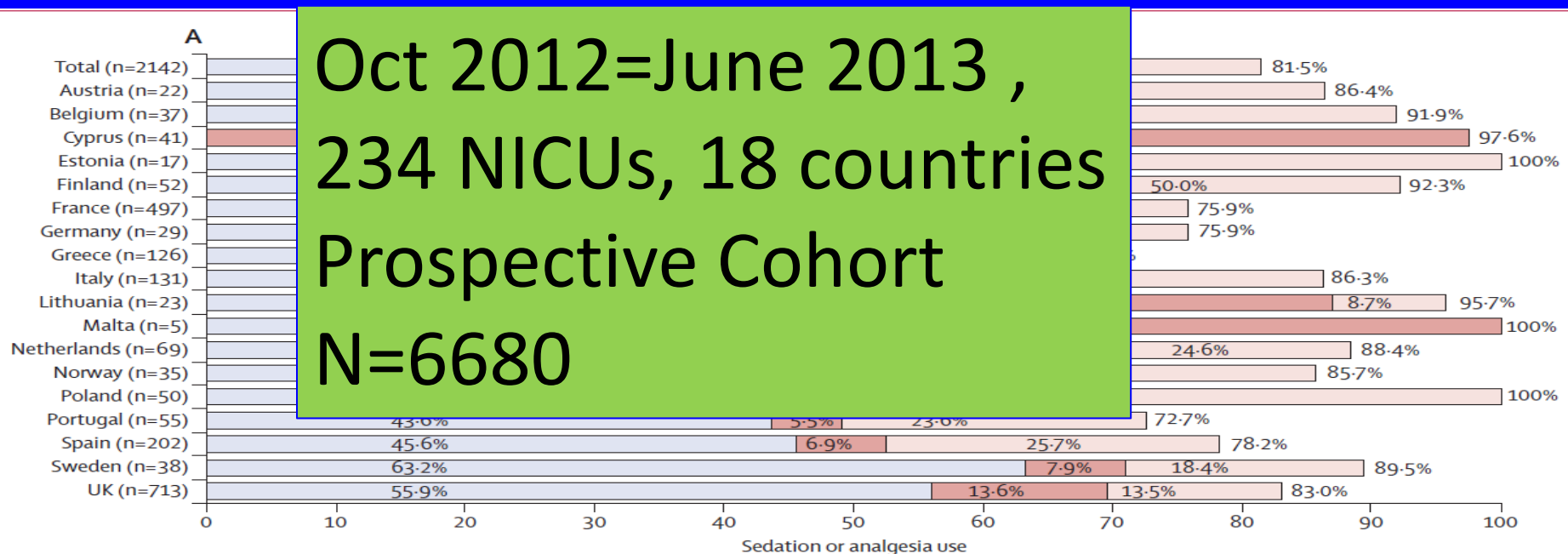
Wide variation occur in NICU's and Countries



Sedation and analgesia practices in neonatal intensive care units (EUROPAIN): results from a prospective cohort study

Lancet Respir Med 2015; 3: 796–812

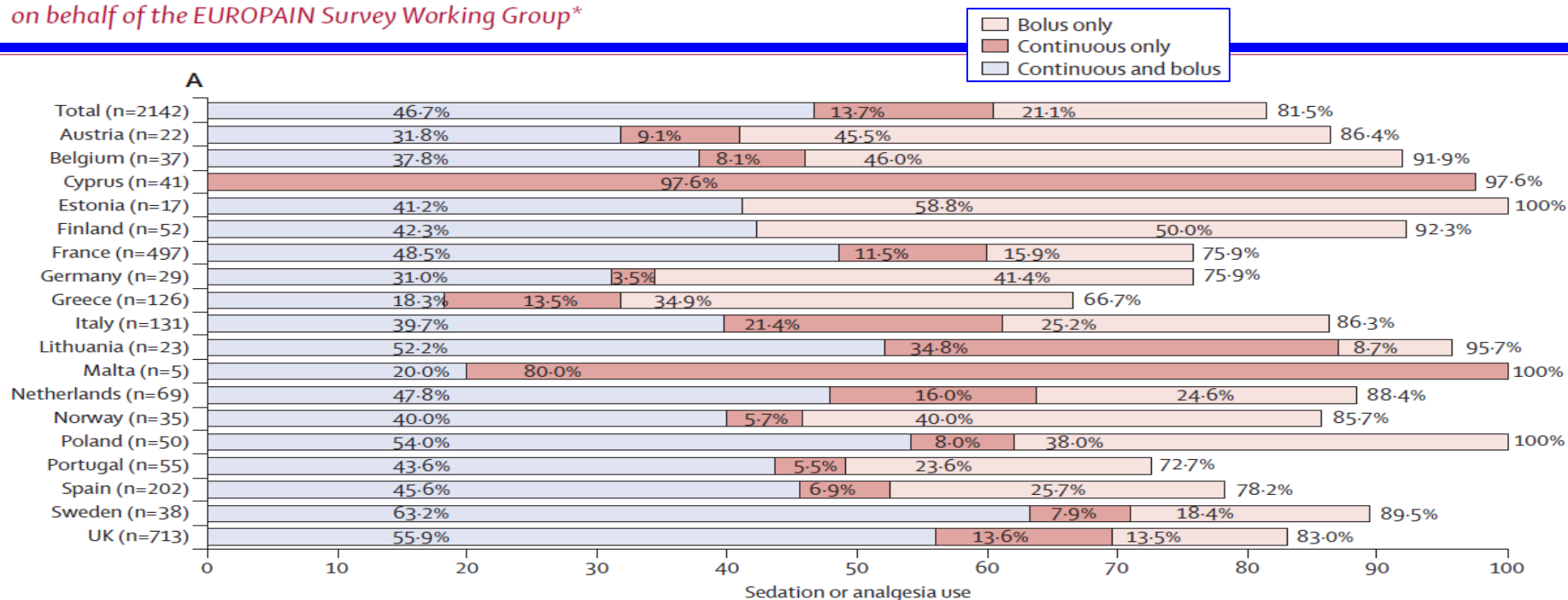
Ricardo Carbajal, Mats Eriksson, Emilie Courtois, Elaine Boyle, Alejandro Avila-Alvarez, Randi Dovland Andersen, Kosmas Sarafidis, Tarja Polkki, Cristina Matos, Paola Lago, Thalia Papadouri, Simon Attard Montalto, Mari-Liis Ilmoja, Sinno Simons, Rasa Tameliene, Bart van Overmeire, Angelika Berger, Anna Dobrzanska, Michael Schroth, Lena Bergqvist, Hugo Lagercrantz, Kanwaljeet J S Anand, on behalf of the EUROPAIN Survey Working Group*

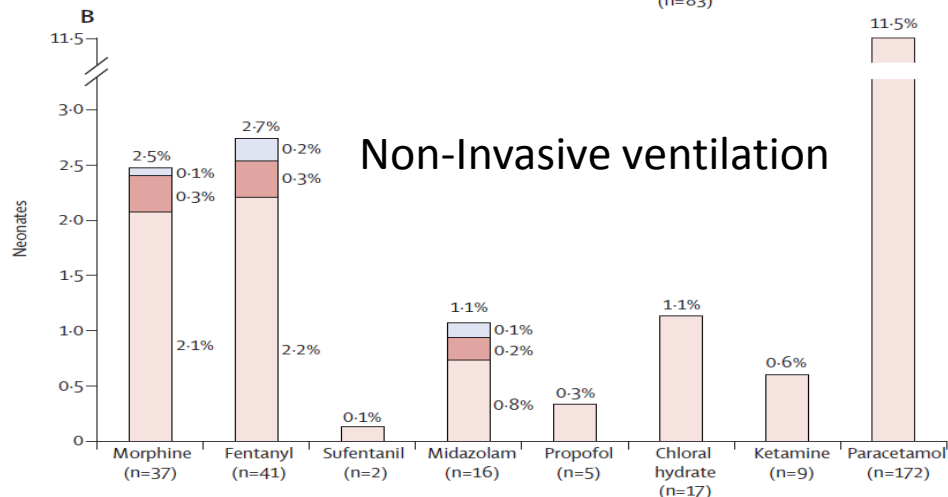
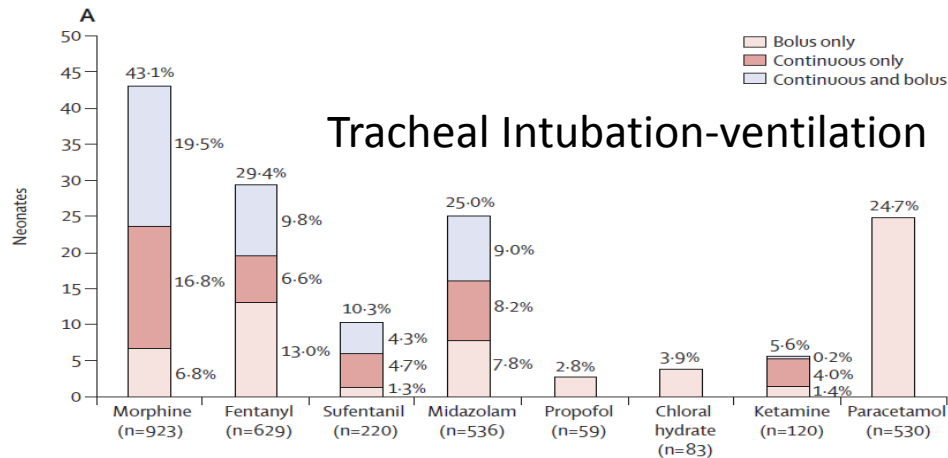


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Lancet Respir Med 2015;

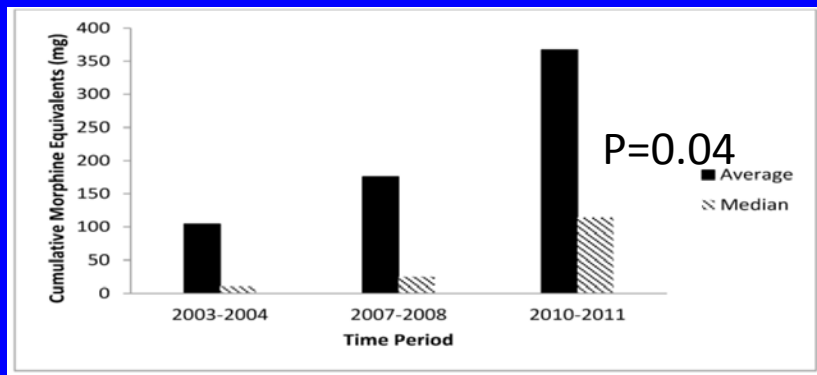
Other Drugs	Total (n=2064)	Tracheal Vent (n=1139)
Paracetamol	326(16%)	229 (20%)
Ibuprofen	15 (1%)	14 (1%)
Local anesthetics	8 (<1%)	7 (1%)
Others	2(<1%)	2 (<1%)
Nueromus-cular blockers	259 (13%)	259 (23%)
Pain scale use	1136 (55%)	682(60%)
Withdrawal syndrome	15 (1%)	13 (1%)

Questions-Comments

- Establish Priority
- Which drug should we study first and why?
- If your decision is already made up, what, how and why did you choose the drug?

Increasing opiate use and increased iatrogenic withdrawal in NICU

Lewis et al: J Opioid Manag 2015: 11:305-312



Opiate	Morphine: Opiate Equivalence ratio
Morphine	1:1 (IV or po)
Fentanyl	20:1 (IV)
Hydromorphone	5:1 (IV)
Methadone	10:1 (IV and po)
DTO (Diluted tincture of Opium)	0.4:1 (always po)

Drug exposure Mean(SD)	2003-2004 N=22	2007-2008 N=14	2010-2011 N=28	p
Days –Continuous opiate infusion	15.2(27.3)	17.0(13.8)	21.6 (22.3)	0.094
Days -paralytics	1.5(2.1)	1.8 (5.0)	3.4 (4.7)	0.434
Days-benzodiazepine	13.3 (34.8)	15.4 (17.2)	18.8 (25.5)	0.305
Required weaning-N(%)	11 (53%)	10(71%)	23 (82%)	0.068
Discharge Dx-NAS: N(%)	2(9%)	5(36%)	14 (50%)	0.012

NICU Iatrogenic withdrawal

- 15/30 newborn survivors treated for CDH with ECMO (2003 to 2005)
- 5/15 weaned at home (telephone contact once a week.)
- Weaning at home took 11, 42, 107, 173, and 180 days.
- [Ista E et al: J Opioid Manag. 2010 Jan-Feb;6\(1\):55-62.](#)

How soon do addiction and tolerance develop in newborns?

- Tolerance and withdrawal noted after 3 days of opiate therapy
- Fentanyl dose doubles within 5 days in ECMO babies to obtain similar pharmacologic effect

QUESTION

- Would alternating Opiates with other analgesics eg NSAIDs, propofol etc decrease risk of addiction or tolerance ???

Pharmacologic Control of Pain in Newborn

- 1. NSAIDS: Paracetamol, ibuprofen, Ketorolac**
- 2. Sedatives: Benzodiazepines, Midazolam, Diazepam**
- 3. Opiates: Morphine , Fentanyl, Sufentanil, codeine, Alfentanil , Remifentanil**
- 4. Recent: ketamine, propofol, dexmedetomidine**
- 5. Local Anesthetics - EMLA , Lidocaine, Prilocaine**
- 6. Sucrose**

Pain in Newborns – Assessment

Outcome tools for analgesia studies

- > 40 Pain Scores: (multidimensional: physiologic,behavioral)
- Commonly used Scoring tools (validated for gest. Age)
 1. Premature Infant Pain Profile –PIPP; (Stevens B Clin J Pain 1996)
Revised –PIPP-R (Stevens Clin J Pain 2014)
 2. Neonatal Pain Sedation Scale –N-PASS (Hummell P J Perinatol 2008)
 3. Neonatal Facial Coding System-NFCS (Grunau Pain 1998)
 4. Behavioral Infant Pain Profile -BIPP (Holsti Pain 2007)
 5. Doleur Aiguë du Nouveau-né-DAN (Carbajal Arch Pediatr 1997)

Pain in newborns "surrogate biomarkers" for analgesia evaluation

- Near infra-red spectroscopy
- Amplitude integrated EEG
- Functional MRI
- Heart rate variability
- Skin conductance
- Skin blood flow
- Crying – spectrographic and power spectrum
- Biochemical/hormonal – catecholamines, cortisol, glucagon, beta-endorphins

Morphine

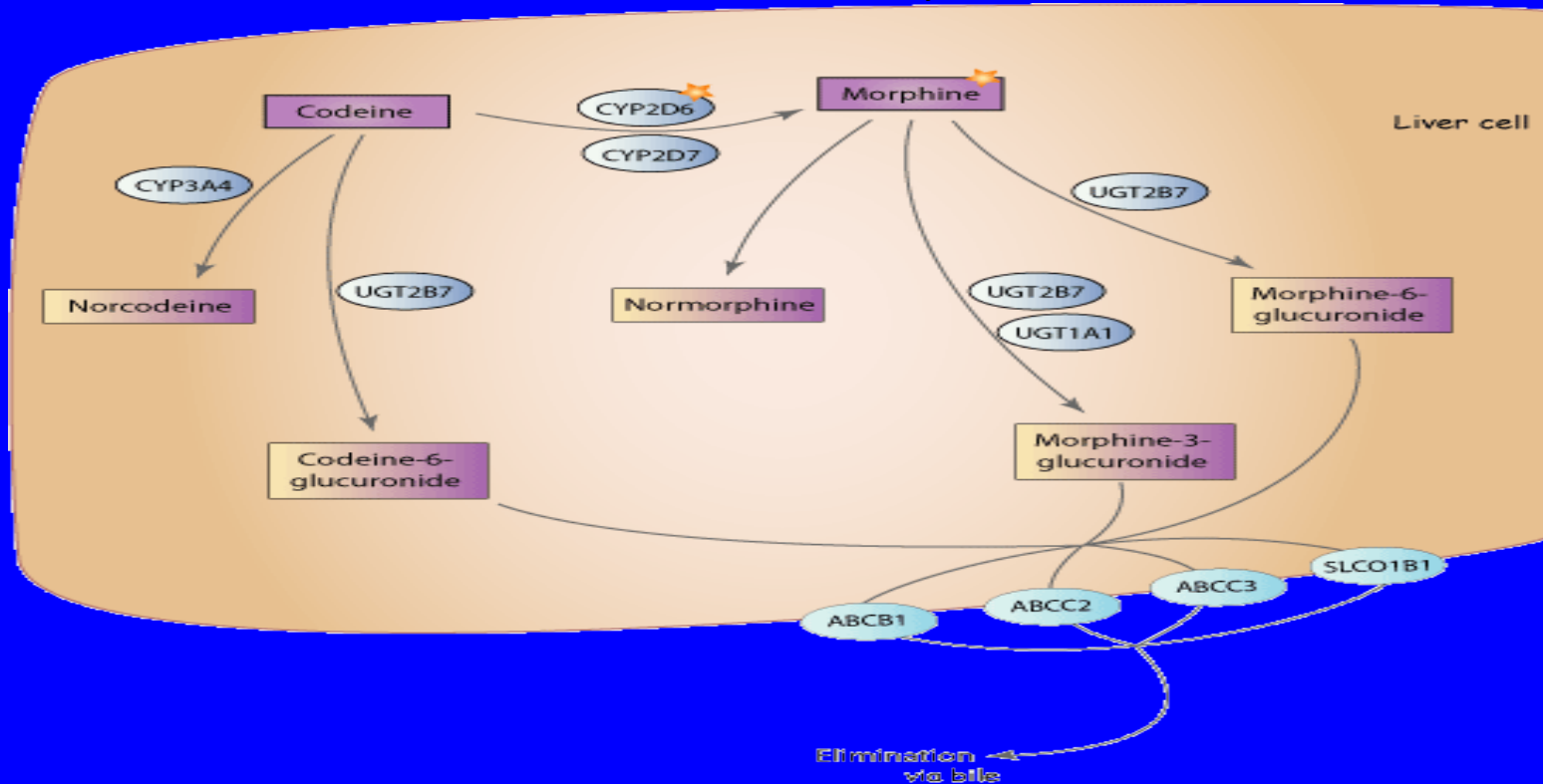
- Preferred use in ventilated newborns in part due to respiratory depressant effect
- Plasma $t_{1/2}$ 6-8 to 7.3 hrs (term)(Lynn 1987, Koren 1985, Choonara 1992, McGuinness 1989, Bouwmeester NJ, 2003,2004
< 10 hrs (preterm) (Bhat 1990)

Acute Adverse effects: Hypotension, Seizures,
Histamine release - - Bronchospasm

Metabolic pathway of morphine and codeine

[http:// www.pharmgkb.org/search/pathway/codeine-morphine/codeineMorphine-pk.jsp#](http://www.pharmgkb.org/search/pathway/codeine-morphine/codeineMorphine-pk.jsp#)

accessed Feb 19,2012



Morphine

- Pop PK derived non-linear morphine Loading dose : 100 microgm/kg ; maintenance dose of 5 $\mu\text{g}/\text{kg}^{1.5}/\text{h}$, with a 50 % dose reduction in neonates with a postnatal age (PNA) <10 days (Krekels 2014)
- *Polymorphisms : OPRM1 118A>G (asn⁴⁰asp), COMT 472G>A (val¹⁵⁸met) and ARRB2 8622C>T and OPRM1/COMT – increased rescue morphine doses*
- UGT2B7 polymorphisms alters morphine PK (Matic ,Pharmacogenomics 2014)

COMMENT

- PHARMACOGENOMICS SHOULD BE A COMPULSARY COMPONENT OF ANY DRUG DEVELOPMENT STUDY
- WHAT ARE THE RELATIVE CONTRIBUTIONS OF GENOMICS, PK/PD, METABOLISM, DISEASE STATE AND CULTURAL AND DEMOGRAPHIC FACTORS IN THE FINAL OBSERVED DRUG RESPONSE???
- RECEPTOR SENSITIVITY?

Morphine in mechanical ventilation

> 7 Neonatal Clinical Trials

	NEOPAIN (Anand 2004)	Dutch Trial (Simon 2005)
Design	Double Blind RCT	Double Blind RCT
Sample Size	898	150
Gestational Age	23-32 weeks	25-32 weeks
Morphine Dose (mcg)	100 mcg/kg +10 -30 mcg/kg/hr	100 mcg + 10 mcg/kg/hr
Control	Placebo	Placebo

Morphine in Ventilated Preterm Neonates

- Primary Outcomes from the NEOPAIN Trial
(Composite of neonatal death, severe IVH or PVL)
- Anand KJS et al - Lancet 363: 1673-1682, May 22,2004
- 898 newborns; (23-26 wks,27-29, 30-32 wks)
- 12 US centers, 4 Euro centers

Morphine in ventilated newborns- Anand et al Lancet May 22,2004

Data summary:

- No difference in primary outcomes (25.7% vs 27.4%) neonatal deaths (10.5% vs 12.9%); severe IVH (10.7% vs 13.4%) or PVL (9.3% vs 7.4%)
- Morphine: decreased pain scores ($p=.002$) HR($p=0.004$) RR($p<0.045$) but
- Increased hypotension ($p<0.01$) prolonged vent ($p(0.034)$,feeding intolerance ($p=0.045$)

Morphine in mechanically ventilated newborns (Anand Lancet 2004)

- **Open label morphine:**

Morphine group 202 /449 (45.3%)

Placebo group 240/449 (54.2%, $p < 0.008$)

Open label morphine:

primary outcomes (23.6% vs 14.0%); $p = .03$

severe IVH (16.2% vs 4.3% $p = 0.04$)

Within Placebo group:

Open label morphine:

primary outcome (34.5% vs 14.9%);

death (13.8 vs 6.9% $p = 0.02$)

severe IVH (17.2% vs 3.1% $p < 0.001$) PVL (13.2% vs 4.8% $p = 0.006$)

Long Term Outcome: Morphine

- **Five year:** Dutch Cohort:
Lower IQ in morphine group n=49: 94 ± 14.5 vs 100 ± 12.9 placebo, n=41 , Visual analysis IQ subtest negatively ($p < 0.05$) to morphine exposure. (deGraaf J, et al *Pain*. 2011 Jun;152(6):13)
- **Eight to Nine Year** Follow-up: 43 morphine; 46 placebo: *Valkenburg J Pain* 2015 :16:926-933 & *deGraff et al Pain* 2013; 154:449-458
 - Neurological exam normal in 29 (76%) morphine and in 25 (61%) control $p = 0.14$ (NS); No difference in Head Circumference
 - IQ : placebo: 101(SD 18) vs 99(19) morphine; $p = 0.63$ (NS)
 - Quantitative sensory testing (QST)- no difference between groups
 - Fewer problems with daily executive functions (eg: organizing) in morphine $p < 0.04$

Long term outcome -Morphine

Royal Melbourne Study (Steinhorn R et al [J Pediatr](#). 2015 May;166:1200-1207.)

233 prems < 30 weeks gest; 57 had morphine; 176 no morphine:

- At term: MRI Morphine group had cortical gray matter with smaller orbitofrontal (pleft=0.002, pright=0.01) and subgenual (pleft=0.01, pright=0.02) volumes bilaterally. Had decreased tone (p=0.01)
- At 2 years: BSID-II Cognitive (MDI), motor(PDI) speech: no difference; but morphine group had more behavioral dysregulation (p<0.007)
- At 7 years: MRI findings , brain volumes similar in both groups.
Morphine and no-morphine groups performed similarly on measures of IQ (WASI), motor function (MABC-2), executive function (BRIEF), and behavior (SDQ).
Morphine group: Higher scores in basic educational skills (WRAT 4)p=0.008. which persisted across subgroup tests of reading (p=0.002) and spelling (p=0.001).

Long Term Outcome-Morphine

Neopain Cohort:

Five to Seven Year: Morphine=14; Placebo=5:

Morphine group: smaller head circumference ,
longer response latencies, more social problems

Ferguson SA, Neurotoxicol Teratol. 2012 Jan-Feb;34(1):47-55

Examples of Mechanisms in Neuronal damage or protection

VEGF Signaling Genes at P14

(Values are fold change from RA saline control)

Genes of Interest	Retro/Sal RA	Sal/Caff RA	Retro/Caff RA	Sal/Sal O ₂	Retro/Sal O ₂	Sal/Caff O ₂	Retro/Caff O ₂
VEGF A	1.7±0.03	1.4±0.09	1.2±0.47	2.1±0.07	-1.0±0.99	1.5±0.12	1.4±0.07
VEGFR-1	1.4±0.17	2.1±0.01	-1.2±0.99	2.3±0.07	-1.0±0.99	-1.4±0.45	12.8±0.13
VEGFR-2	-1.6±0.24	-1.0±0.71	-2.0±0.14	-1.4±0.37	-2.5±0.1	-1.8±0.18	-2.3±0.09
VEGFR-3	1.8±0.45	2.0±0.35	1.1±0.98	-1.4±0.43	1.3±0.87	-1.0±0.75	19.0±0.13
NP-1	1.4±0.13	1.1±0.55	-1.0±0.94	-6.8±0.09	-1.2±0.49	-1.2±0.45	2.6±0.13
NP-2	1.3±0.22	1.6±0.01	-1.0±0.74	1.2±0.4	-1.1±0.55	-1.2±0.38	5.6±0.13
HIF1α	1.0±0.96	-1.1±0.69	-1.5±0.21	1.0±0.73	-1.8±0.36	-1.0±0.92	-1.6±0.17

Neuropilin-1 and 2 are transmembrane proteins- coreceptor tyrosine kinase for VEGF and Semaphorins ; plays versatile roles in angiogenesis, axon guidance, cell survival, migration, and invasion and repulsive axon guidance

VEGFR3: lymphatic endothelial cell development, modulated by NP2, NOTCH signaling

SEDATION IN NEWBORNS

Indication: Stress (any sources: intubation, pain – procedural, acute, post-operative, chronic)

Drugs:

Midazolam

Diazepam

Lorazepam

Benzodiazepines- Midazolam

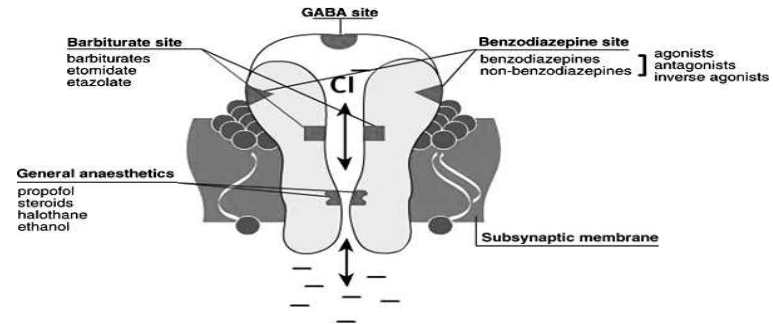
Benzodiazepines potentiate GABAergic neurotransmission by promoting postsynaptic receptor opening (GABA-A receptor), increased conductance to chloride ions, membrane hyperpolarization and neuronal inhibition.

Pharmacologic uses: sedative, hypnotic, anxiolytic, anticonvulsant, and muscle relaxant properties.

Benzodiazepines:

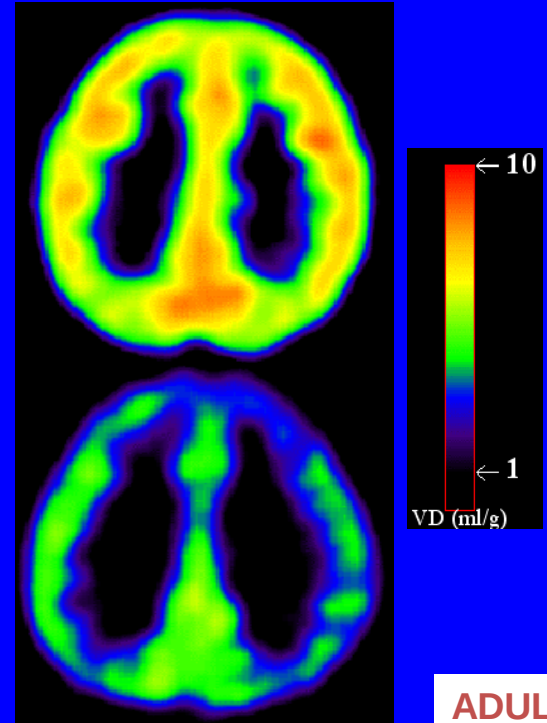
- [Midazolam](#)
- Diazepam
- Lorazepam

Depolarising (excitatory) in newborn. Transition to Hyperpolarizing (inhibitory) Postnatally.

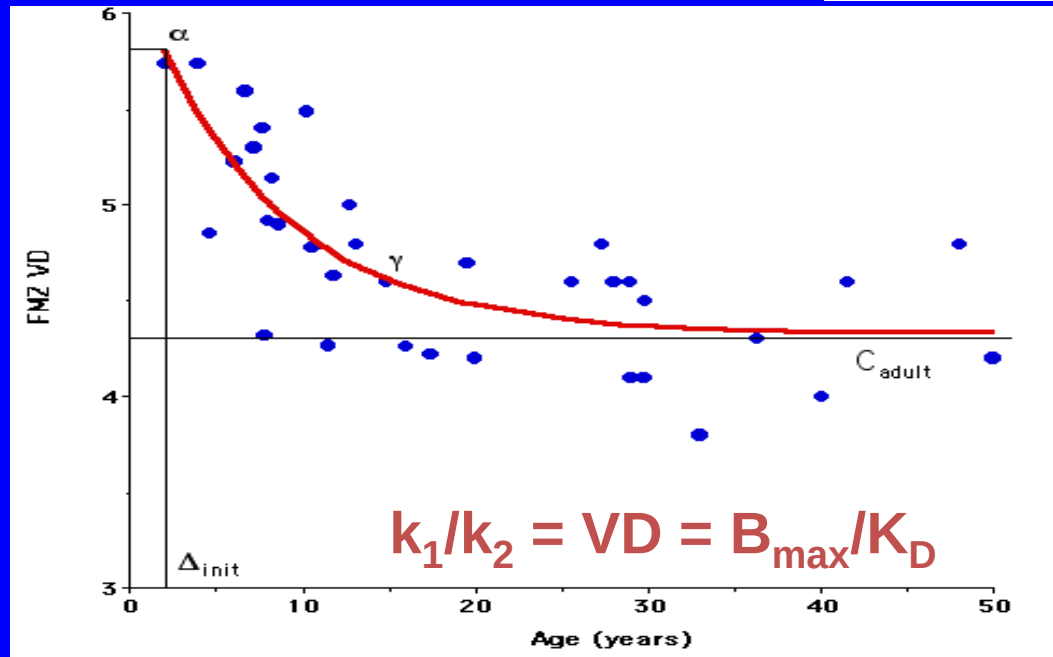


GABA_A RECEPTORS USING [C-11]FMZ PET HIGHER IN INFANTS THAN ADULTS

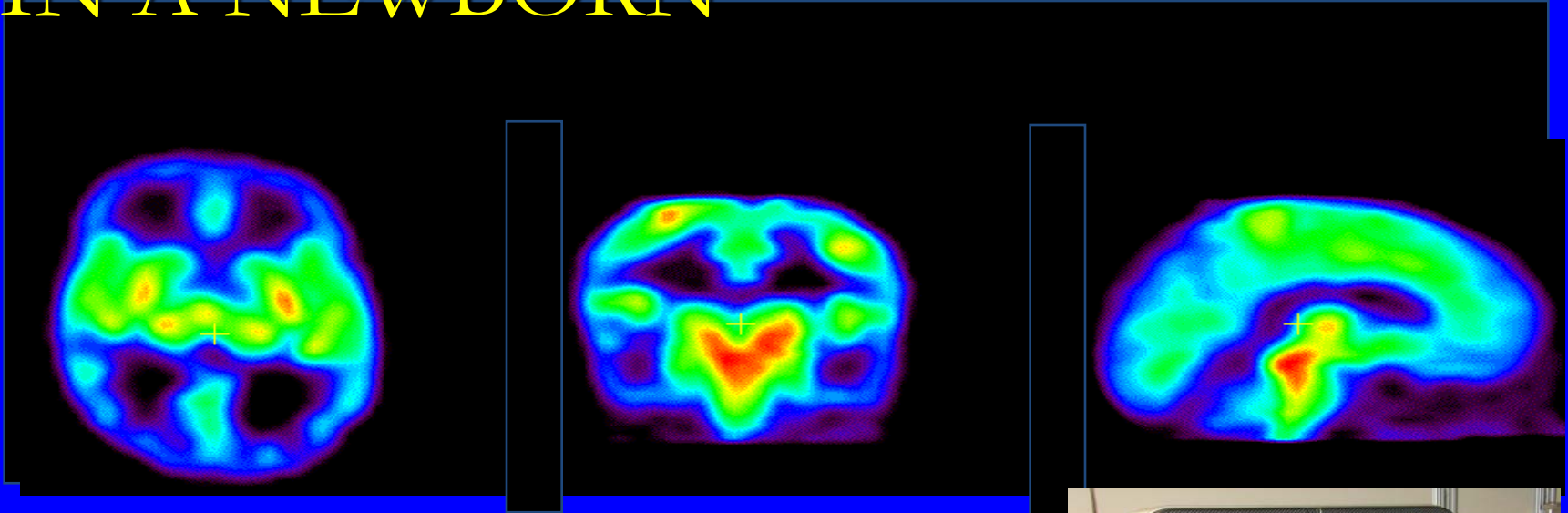
AGE 6 YEARS



ADULT



GABA_A RECEPTOR DISTRIBUTION IN A NEWBORN



**Newborn MICRO-PET SCANNER
WSU-NIH/PPRU(PI- Aranda)**



Midazolam

Imidazobenzodiazepine: anxiolytic, sedative, muscle relaxant and anticonvulsant

Absorption 30% - oral and 50% with nasal administration.

Rapid and extensive distribution, Highly protein bound (97%) .

Hepatic metabolism to active and inactive derivatives, major metabolite (1-hydroxymidazolam) has shorter $t_{1/2}$

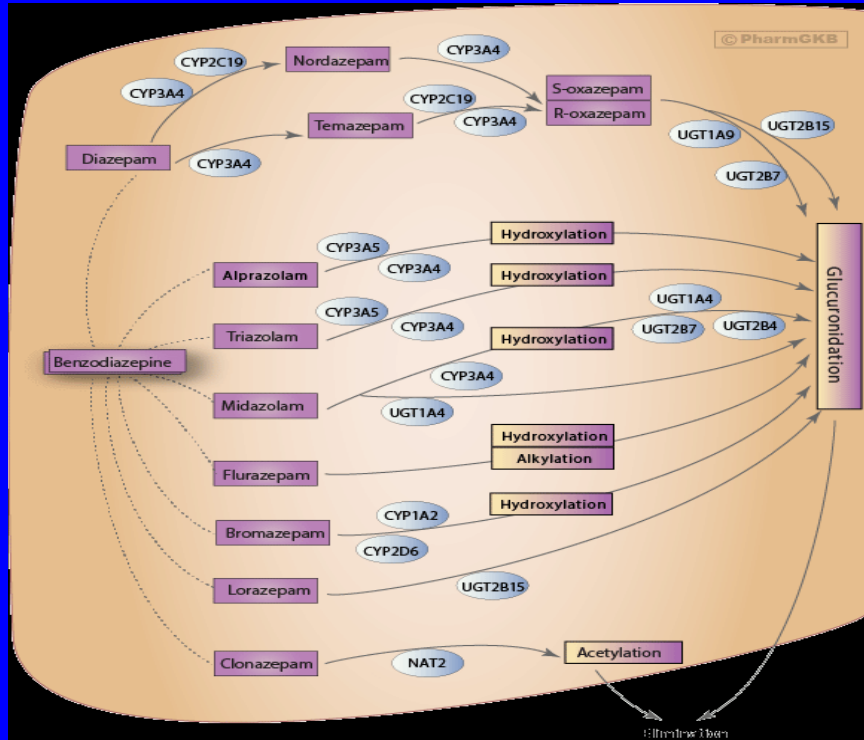
impaired by poor hepatic perfusion . Very slow elimination via the kidneys.

Elimination half-life variable (6-7 hours in term infants , longer in less mature infants), major metabolite (1-hydroxymidazolam) has shorter $t_{1/2}$

Rapid onset of action (<3 minutes) and peak sedative action <20 minutes after IV administration. Anticonvulsant action may be more rapid.

The IV preparation has a pH of 3.

Midazolam



Imidazobenzodiazepine: anxiolytic, sedative, muscle relaxant and anticonvulsant

Absorption 30% - oral and 50% with nasal administration.

Rapid and extensive distribution, Highly protein bound (97%)

Hepatic metabolism : CYP3A4. major metabolite (1-hydroxymidazolam) has shorter $t_{1/2}$

Elimination half-life variable (6-7 hours in term infants , longer in premature infants), major metabolite (1-hydroxymidazolam) has shorter $t_{1/2}$

Drug clearance Not affected by hypothermia unless there is decreased liver and renal function. (Welsing 2013)

Rapid onset of action (<3 minutes) and peak sedative action <20 minutes after IV administration.

Anticonvulsant action may be more rapid.

IV Midazolam in newborns

IV Midazolam : 6 randomized controlled trials

- McCarver-May 1996 : single bolus dose
- Kawakami 1998: anesthetic induction
- Parkinson 1997: included newborns up to 15 years of age.

Anand 1999 n=67, 24-32 weeks gestation

Arya 2001, n= 33, < 2000 grams

Jacqz-Aigrain 1994, n= 48 ; 32.1 + 2.8 weeks

Primary Outcome: 5-item behavioural scale

- facial expression,
- Sucking continuous motor activity,
- excitability
- response to stimulation,
- excessive flexing
- physiological measures of sedation level
Eg: heart rate, blood pressure

Ng et al, Cochrane 2012:
NO effectiveness of
midazolam infusion (n= 146)
NO effect on morbidities
(IVH)

MIDAZOLAM CO-ADMISTERED WITH MORPHINE

Midazolam: Adverse Effects

- Hypotension , decreased cardiac output, particularly when used with fentanyl.
- Respiratory depression and apnoea.
- Hypotonia.
- Seizures or seizure-like activity following rapid bolus administration
- Cerebral blood flow velocities may decrease transiently after midazolam boluses, reflecting reduction in blood pressure

MIDAZOLAM : MRI , BAYLEY III AT 18 MONTHS FOLLOW-UP

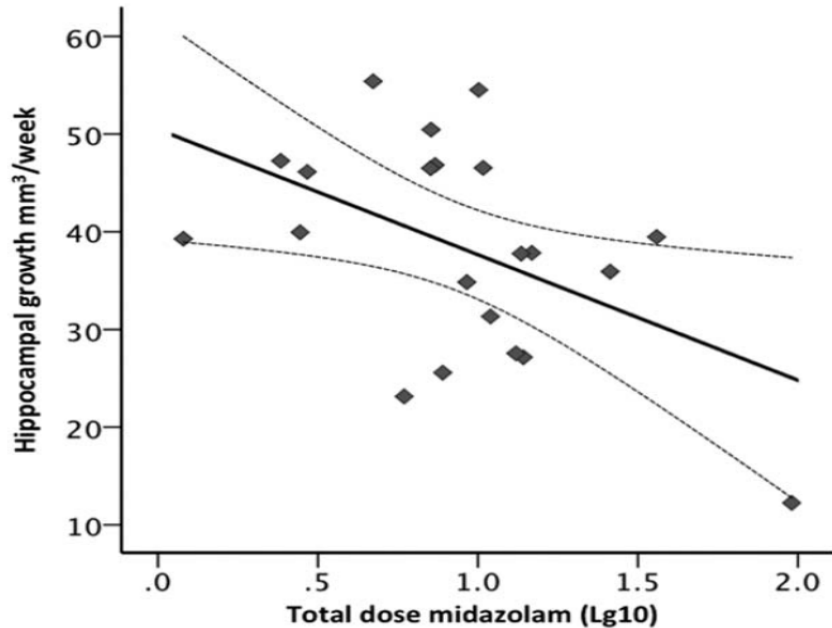


FIGURE 2: Average hippocampal growth (in mm³/wk) in relation to the average dose of midazolam (log10) in neonates exposed to midazolam. Error bars represent the standard deviation of the mean.

138 preterms, 24-32 weeks, MRI at 32 weeks and at 40 weeks. Cognitive Scores at 18 months) by Bayley III directly associated with Hippocampus volume (p=0.003) but negatively related to midazolam dose (p 0.03)

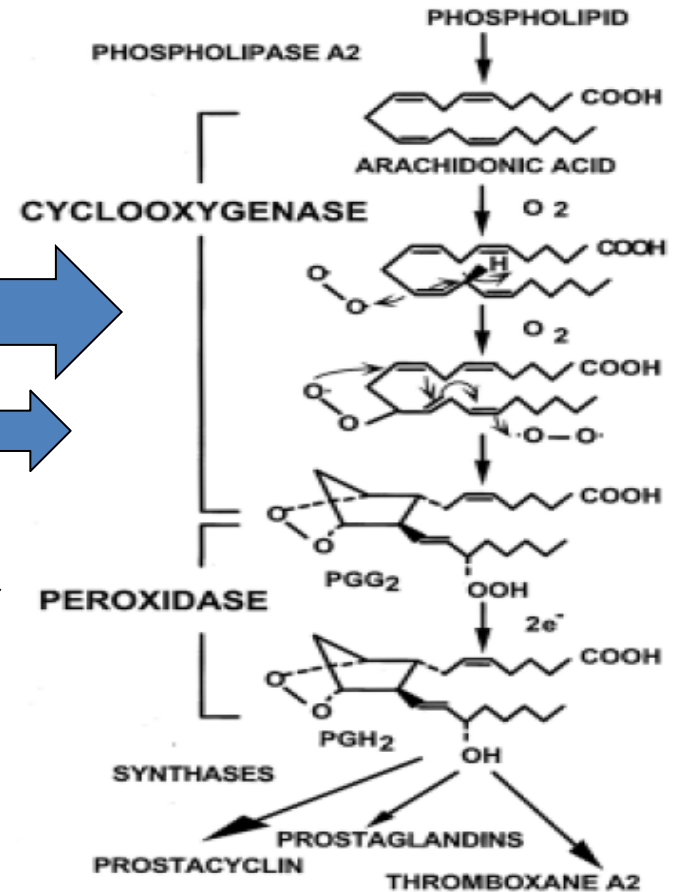
(Duerden Ann Neurol 2016: 79:548)

Biosynthesis of prostanoids

Smith W et al Annu Rev Biochem 2000

Indomethacin
Ibuprofen
Ketorolac

PARACETAMOL
(acetaminophen)



NSAIDs IN NEWBORNS

Standard of Care:

- 1 Closure of Patent Ductus arteriosus- Indomethacin ,
ibuprofen, paracetamol
2. Prevention of Intraventricular hemorrhage-
Indomethacin
3. Analgesia and Opiate Sparing Effect:
Paracetamol, ibuprofen

Potential indication:

4. Prevention of ROP

Paracetamol: Metabolism and Excretion

In adults:

Paracetamol: almost exclusively metabolized by liver then excreted into urine,

- paracetamol glucuronide (47–62%)
- paracetamol sulphate (25–36%)
- paracetamol (oxidized by cytochrome P450 (CYP2E1) into 3-hydroxy-paracetamol and the toxic metabolite NAPQI or N-acetyl-p-benzoquinone-imine = (8-10%)
- unchanged paracetamol in urine (1-4%)

NAPQI- conjugated by glutathione to urinary excreted non-toxic thiol metabolites (cysteine, mercapturate, methylthioparacetamol and methanesulfinylparacetamol)

Toxicity occurs if glutathione is depleted resulting in conjugation of NAPQI with hepatocellular proteins leading to centrilobular liver necrosis.

Plasma Protein Binding:

Acetaminophen: 20%;

Indomethacin: 97.8% (Ghuman J J Mol Biol 2005)

Ibuprofen : 95% (cord blood) (Aranda JV Acta Pediatr 1997)

Ketorolac : 97-99%: (Gravenstein J Clin Anesth 1998)

Bucarechi F et al: Acute liver failure in a term neonate after repeated paracetamol administration. [Rev Paul Pediatr](#). 2014 Mar;32(1):144-8.

Gaps in Knowledge and Summary

- Age-related pharmacodynamic differences that will affect dose and the impact of active metabolites on response are not quantified.
- PK/PD Data on the Periviable Preterm (23-26 weeks) not available. Dosing guidelines in this population are needed.
- Neonatal transition from stimulatory (depolarising) to inhibitory (hyperpolarizing) GABA-A receptor is not known
- Morphine at “low doses” may produce early adverse neurodevelopmental damage which appears to resolve by 8-9 years. High dose may produce more lasting damage.
- Relative contributions of pharmacogenomics, PK/PD and demographic characteristics to individual analgesic/sedative drug responses in neonate remains unexplored.
- Of the dozen NSAID, which is the most effective and safe drug.
- Opiate sparing effects of NSAIDs

Gaps in Knowledge and Summary

CHALLENGES IN ANALGESIC DEVELOPMENT IN NEWBORNS:

1. Quantitative Measures for Pain (Severity to Match Intervention)
2. Valid Outcome measures (Which morbidities, or surrogates)
3. Studies on the Periviable Newborn : 23 to 25 weeks
4. Appropriate Duration of Long term follow up
5. Age and maturation of drug metabolism, clearances and development of rational dose guidelines
6. Linking imaging technologies and morphology to function and neurodevelopmental evaluations
7. Physiologic based PK/PD modeling
8. Pharmacogenomic studies as a requisite component of clinical drug development
9. Technologies and feasible methods of studying receptor function in newborn babies

- THANK YOU
- QUESTIONS?

Agenda – Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome



2:15 – 3:00 p.m.

Session III: *Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome*

JOHN VAN DEN ANKER (CHILDREN'S NATIONAL HEALTH SYSTEM/U-BASEL CHILDREN'S HOSPITAL) &
JON DAVIS, INC CO-DIRECTOR (TUFTS UNIVERSITY), CO-CHAIRS

3:00 – 3:30 p.m.

COFFEE BREAK

3:30 – 5:00 p.m.

Session III Panel:

JACOB ARANDA (U HOSPITAL – BROOKLYN)

GERRI BAER (FDA)

ANNE GREENOUGH (KING'S COLLEGE LONDON)

WALTER KRAFT (THOMAS JEFFERSON UNIVERSITY)

STEPHEN PATRICK (VANDERBILT UNIVERSITY)

MERRAN THOMSON (HILLINGDON HOSPITAL NHS TRUST, CHIESI)

ROBERT WARD (UNIVERSITY OF UTAH)

MAREK MIGDAL (PDCO)

NAS - the UK experience

Anne Greenough

Professor of Neonatology & Clinical Respiratory Physiology
King's College London School of Medicine

How common is the problem in the UK?

- Approximately one in a thousand women in Great Britain is dependent on opiates, the majority are of child bearing age.

Singleton Office for National Statistics 2001

- Between 250,000 and 300,000 children of problem drug abusers in the UK

Advisory Council on the Misuse of Drugs 2003

- Anonymous screening of women attending two inner city London antenatal clinics:

Number screened	1000	807
One of more illicit substances	10.6%	15.6%
Opiates (inc methadone)	1.7%	1.4%
Cannabis	8.5%	14.5%

Farkas et al BJOG, Sherwood EJP

Cross country comparison

- NAS rates increased from 1997 to 2011
- Rates stabilised in the 2000s in England and West Australia, but rose steeply in the USA and Ontario
- 2011 prevalence rates per 1000 live births
 - 2.7 in England and Western Australia
 - 3.6 in the USA
 - 5.1 in Ontario

Socio-clinical profile

- 168 mother-infant pairs (Swansea, Wales)
- 97.4% also smoked (52% >10/day)
- 85.4% unemployed
- 91% unmarried
- 61.3% polydrug exposure
- Methadone, heroin, cannabis and benzodiazepines
- 30% Hepatitis C positive

Goel et al Eur J Pediatr 2011

Duration of neonatal unit stay

Mean duration 22 days – on average 3 cots per day occupied

Coghlan et al Irish Medical J 1999

Length of stay - methadone 29 days and methadone + other substances 41 days

Johnson et al Addiction 2003

Reducing neonatal stay:

- Management on the postnatal ward

Saiki et al EJ Ped 2009

- Discharge home on medication (29% of units)
 - 58% medication administered in the community

Grady et al ADC 2009

SIDS and substance abuse

- Meta-analysis of ten studies demonstrated SIDS risk is not specific to intrauterine cocaine exposure,
- Risk of SIDS - 3-10 times higher than the general population
- 32 infants dying suddenly and unexpectedly in the first 28 days after birth
 - 12 (37.5%) methadone and/or other substance misuse
 - all had multiple risk factors for SIDS – smoking, prematurity and inappropriate sleeping place

Cohen et al Acta Paed 2015

Substance abuse and respiratory control

- Infants of substance misusing mothers (SMM) have a dampened response to hypercarbia
 - in the perinatal period (Ali et al 2014)
 - which is greater at peak age for SIDS (Ali 2016)
- Neonates have a biphasic response to hypoxia
 - infants of SMM had a greater increase and then a greater decline in minute ventilation

Ali et al ADC 2106

Slope of ventilatory response to hypercarbia

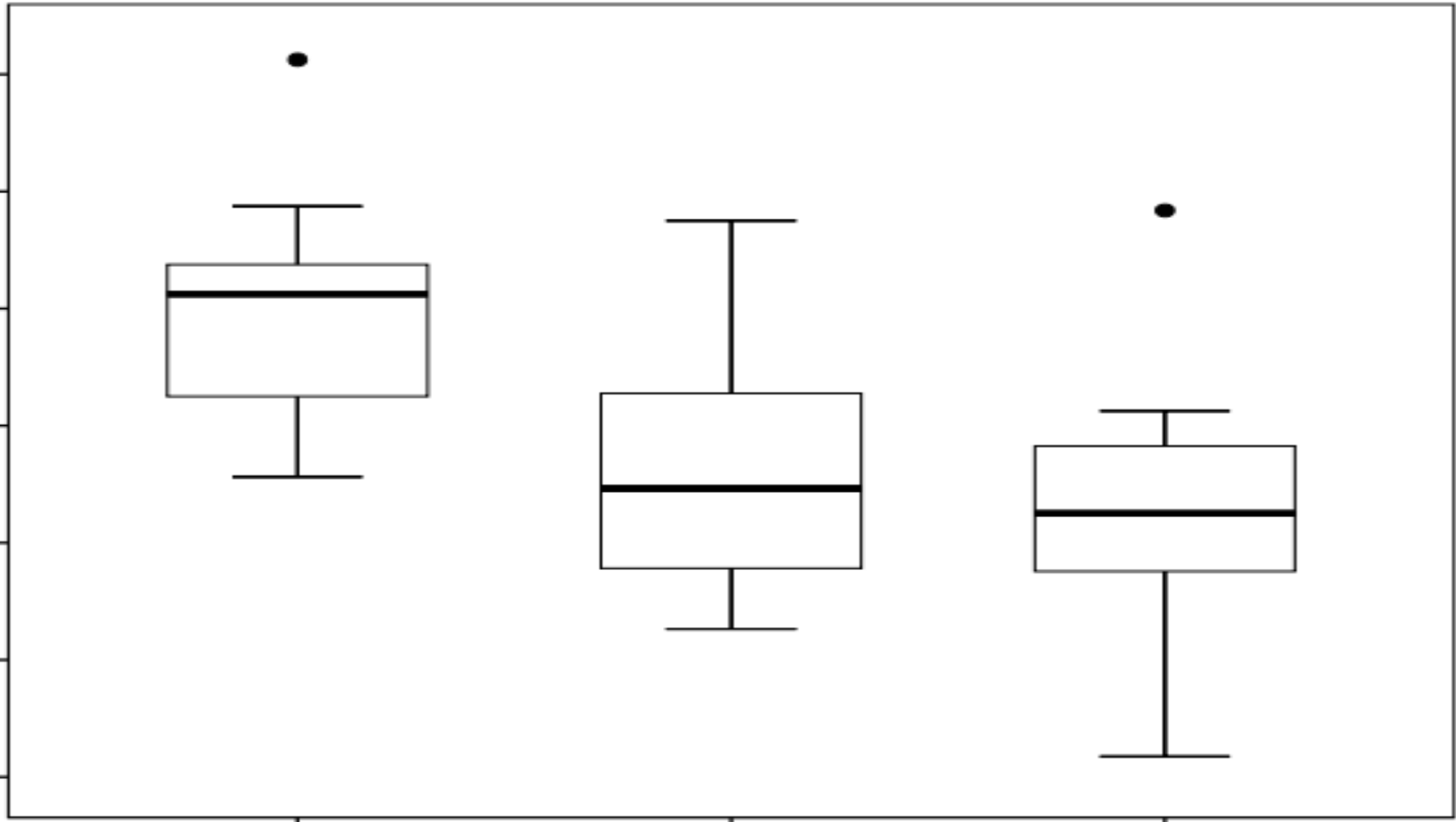
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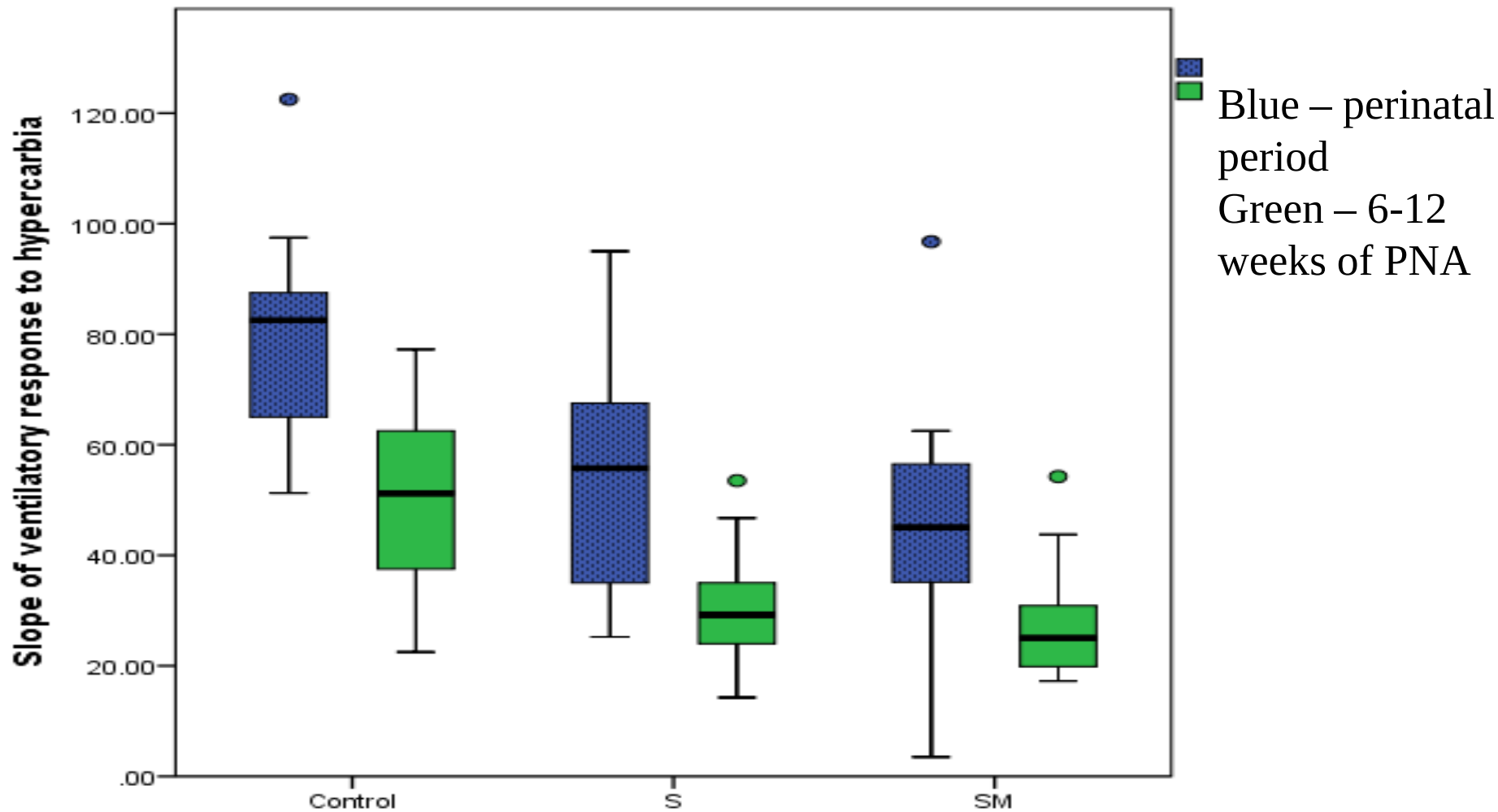
Control

S

SM

Ali et al Ann Am Thoracic Soc 2014





My perspective on UK priorities

- Better methods of diagnosing and recording all infants affected by substance misuse (ICD codes likely to detect only a proportion).
- Identifying effective treatments for those affected by polydrug exposure (currently morphine is widely used).
- Evaluation of “non neonatal unit” care
- Can the adverse effect on infant respiratory control be reduced by changes in antenatal medication?

Panel III

“Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome”

Merran Thomson

Many challenges to overcome including:

- New disease area for pharma and FDA
- Lack of evidence based practice (RCTs etc.)
- Diverse clinical practice
- ? Standard of care
 - Who to treat?
 - When to treat?
 - What to treat with?
- Health and social care attitude and processes

Can a regulatory drug development be successful?

Challenges - new drug development in NAS

1. Patient population
2. Scoring tool
3. Comparator therapy
4. Primary outcome measure
5. Long term follow up
6. Different regulatory processes for inpatient and community prescribed drugs

The “real world” vs “ideal study” population

- Babies with NAS are often born into families with social/psychiatric challenges
 - Consent and long term follow up challenging
- Mothers’ polysubstance use
 - opioids plus nicotine, alcohol, psychotropic medications etc.
- Variable access to / and practice within drug rehab programs
 - Influences maternal behaviour including antenatal care etc.
- Social service / foster care
 - Restrictions on trial participation and follow up between / within states

Must develop treatment for the “real world” heterogonous population → collaborative working across several agencies etc.

Finnegan Neonatal Abstinence Scoring (FNAS) Tool

- Most commonly used psychometric assessment tool
- Key decision making tool used to:
 - ✓ Diagnose NAS
 - ✓ Assess need for treatment
 - ✓ Escalate, wean and stop treatment
 - ✓ Add adjunct therapy

BUT

- complex, intra / inter observer variability, repeated training etc.

Will regulators recognise this as a validated score?

Challenge 3 – Comparator drug

What should this be?

- No regulatory approved drug
- Placebo controlled trials – unethical
- ? Excipients
- ? Standard of care - morphine most commonly used drug
- ? Efficacy and safety

Adjunct therapy

- No regulatory approved drug
- Placebo controlled trials – unethical
- ? Excipients
- ? Standard of care - phenobarbital most commonly used drug
- ? Efficacy and safety

Challenge 4 – Primary outcome

Should measure the efficacy of the drug

- Length of treatment
- Secondary outcome measures
 - Length of stay
 - Need for adjunct therapy
 - Safety

Challenge 5 – Long term follow up

- Comparator population
 - ? NAS babies
 - ? Normal controls
 - 12months / 2 years / 5 years
 - ? Achievable
 - ? Payment
 - ? Incentives
- ? What to test – validated and standardised assessment

Modeling, Dose Optimization, and Clinical Endpoints in NAS

Walter Kraft, MD
(Thomas Jefferson University
Philadelphia, PA)

The past

Empirically derived dose

Variability

- Scoring instrument
- Consistency of scoring
- Varied protocols

No PK data

Case series and small RCTs

Practitioner focused

Common clinical endpoints in NAS trials

- Length of treatment
- Length of hospitalization
- Use of adjunctive rescue medication
- Total dose of opioid

Pharmacokinetics of Oral Methadone in the Treatment of Neonatal Abstinence Syndrome: A Pilot Study

Jason R. Wiles, MD¹, Barbara Isemann, RPh², Tomoyuki Mizuno, PhD³, Meredith E. Tabangin, MPH⁴, Laura P. Ward, MD^{1,5}, Henry Akinbi, MD^{1,5}, and Alexander A. Vinks, PharmD, PhD^{3,5}

Objective To characterize the population pharmacokinetics of oral methadone in neonates requiring pharmacologic treatment of neonatal abstinence syndrome and to develop a pharmacokinetic (PK) model toward an evidence-based treatment protocol.

Study design Based on a methadone dosing protocol, serum concentrations of methadone and its metabolites were assessed by high performance liquid chromatography-tandem mass spectrometry from dried blood spots. Population PK analysis was performed to determine the volume of distribution and clearance of oral methadone. Methadone plasma concentration-time profiles were simulated from the deduced PK model to optimize the dosing regimen.

Results There was substantial interindividual variability in methadone concentrations. Blood concentrations of methadone were best described by a 1-compartment model with first-order absorption. The population mean estimates (coefficient of variation percentage) for oral clearance and volume of distribution were 8.94 (103%) L/h/70 kg and 177 (133%) L/70 kg, respectively. Optimized dosing strategies were developed based on the simulated PK profiles. We suggest a starting dose of 0.1 mg/kg per dose every 6 hours for most patients requiring pharmacologic treatment of neonatal abstinence syndrome followed by an expedited weaning phase.

Conclusions The proposed dosing regimen may reduce the cumulative dose of opioid and shorten the length of hospitalization. Future studies should aim to validate the simulated dosing schemes with clinical data and expand our understanding of the between-patient PK variability. (*J Pediatr* 2015; ■: ■-■).

Trial registration ClinicalTrials.gov: NCT01754324.

Table I. Oral methadone dosing scheme

Taper step	Dose (mg/kg)	Frequency	Number of doses
1	0.05	q6	×4
1A*	0.1	q6	×4
1B*	0.075	q6	×4
1C*	0.05	q6	×4
2	0.04	q6	×4
3	0.03	q6	×4
4	0.02	q6	×4
5	0.02	q8	×3
6	0.02	q12	×4
7	0.01	q12	×4
8	0.01	q24	×2

Time
0-48 hrs

AUC
(ng·h/mL)

Median

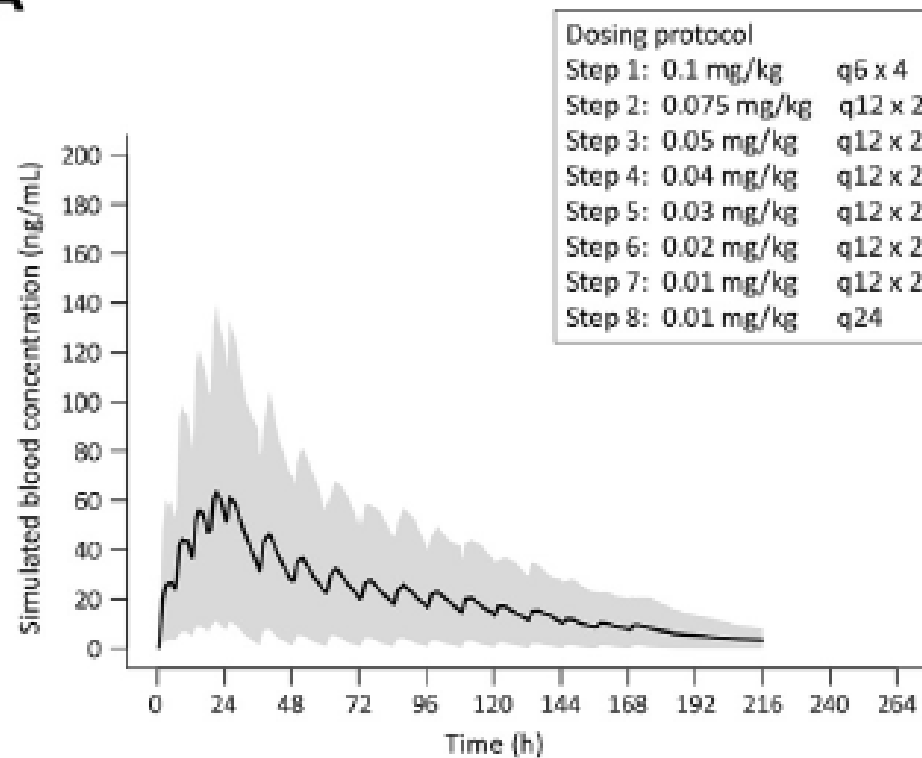
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1061

Simulated Dosing

A



AUC₀₋₂₄
(ng·h/mL)

985

SD

1020

Cohort Analysis of a Pharmacokinetic-Modeled Methadone Weaning Optimization for Neonatal Abstinence Syndrome

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Objective To evaluate neonatal abstinence syndrome (NAS) treatment outcomes achieved using an optimized methadone weaning protocol developed using pharmacokinetic (PK) modeling compared with standard methadone weaning.

Study design This pre-post cohort study evaluated 360 infants who completed pharmacologic treatment for NAS with methadone as inpatients at 1 of 6 nurseries in southwest Ohio between January 2012 and March 2015. Infants were initially treated with a standard methadone weaning protocol ($n = 267$). Beginning in July 2014, infants were treated with a revised methadone weaning protocol developed using PK modeling ($n = 93$). Linear mixed models were used to calculate adjusted mean primary outcomes, including total duration of methadone treatment, total administered methadone dosage, and length of inpatient hospital stay, which were compared between weaning protocols. The use of adjunctive therapy for NAS treatment was examined as a secondary outcome.

Results Infants who received NAS treatment with the revised protocol experienced a shorter duration of methadone treatment (13.1 vs 16.4 days: $P < .001$) and shorter duration of inpatient treatment (18.3 vs 21.7 days: $P < .001$)

Table IV. Hospital outcomes comparing those treated with standard vs the revised methadone weaning protocol

Outcome	Standard methadone ($n = 267$)	Revised methadone ($n = 93$)	P value
Days of methadone treatment, mean, (95% CI)*	16.4 (15.2-17.5)	13.1 (11.4-14.9)	<.001
Length of stay, mean, (95% CI) [†]	21.7 (20.4-23.0)	18.3 (16.2-20.3)	<.001
Total methadone dose, mg/kg, (95% CI) [‡]	0.52 (0.42-0.62)	0.52 (0.39-0.64)	.97
Received adjunct therapy	25.5%	22.6%	.68

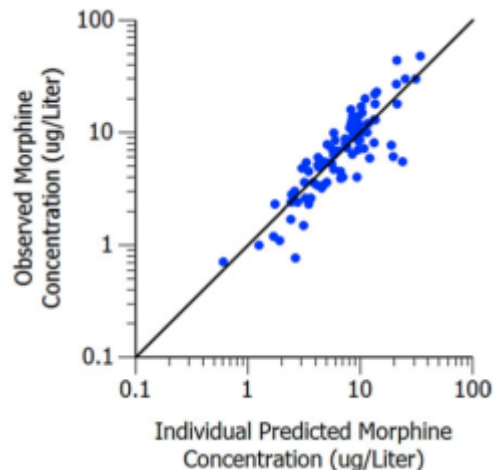
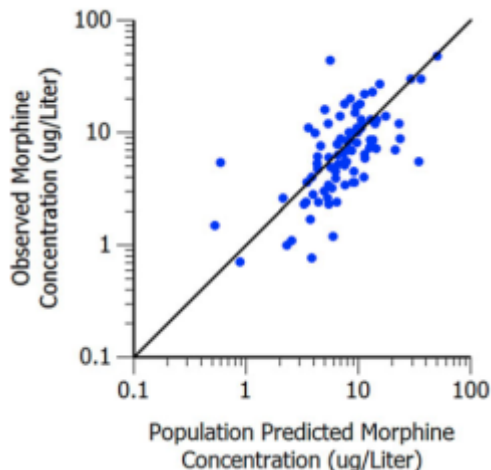
Mechanistic Population Pharmacokinetics of Morphine in Neonates With Abstinence Syndrome After Oral Administration of Diluted Tincture of Opium

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 2016, 0(0) 1–10
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 Clinical Pharmacology
 DOI: 10.1002/jcph.696

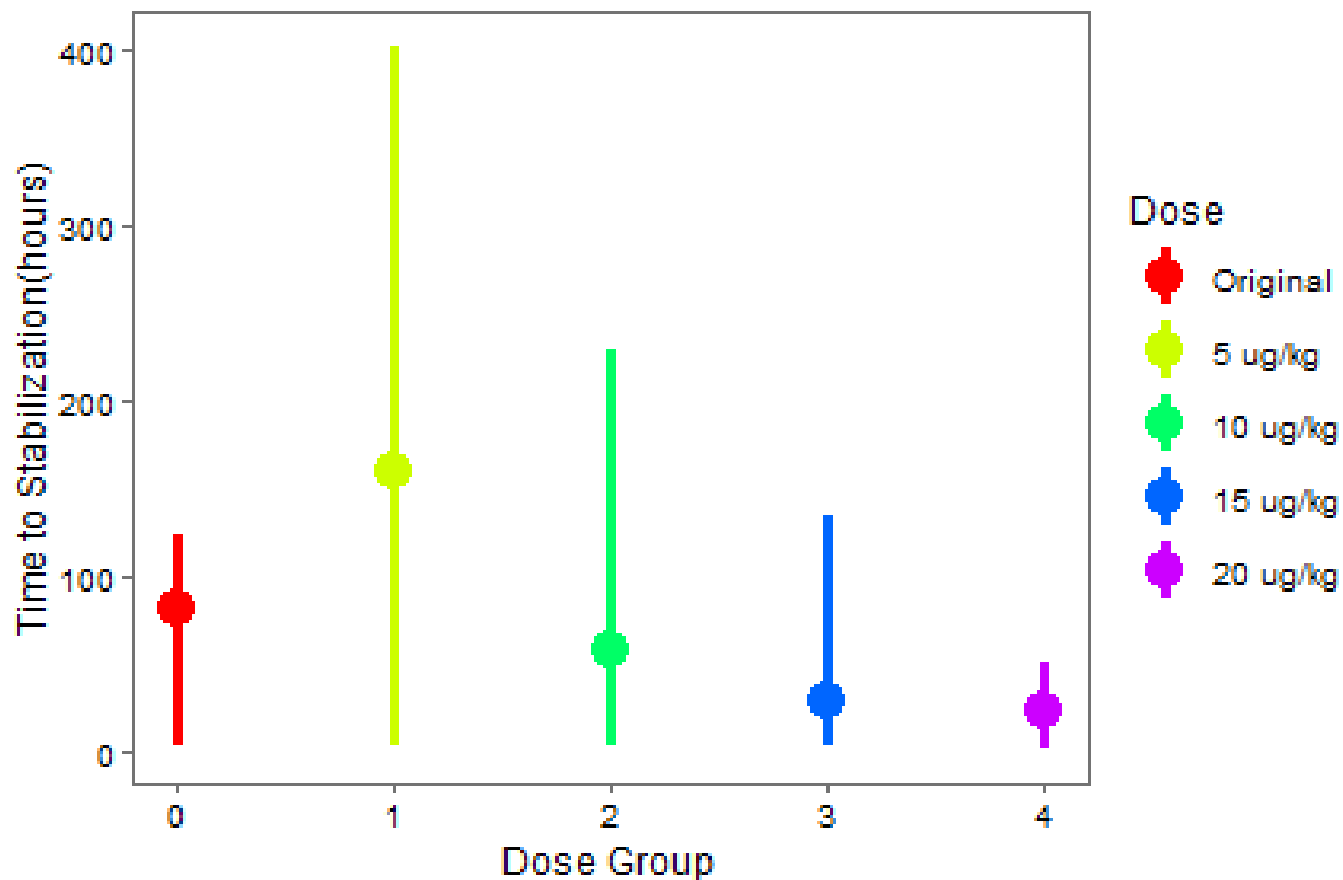
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 MBA, FCP¹, and Vijay Ivaturi, MS, PhD¹

Abstract

Conducting and analyzing clinical trials in vulnerable neonates are extremely challenging. The aim of this analysis pharmacokinetics (PK) model using data collected during a randomized control trial in neonates with abstinence morphine structural PK model after intravenous (IV) administration from previously published work was utilized. A scaling method with physiological consideration was used to extrapolate a PK profile from adults to pediatric bioavailability were estimated in NAS after oral administration of diluted tincture of opium (DTO). Goodness of fit, prediction distribution error and bootstrap method were performed for model evaluation. We successfully extrapolated PK parameters to pediatrics after IV administration. The estimated first-order absorption rate constant and bioavailability were used in the model. Model evaluations showed that the model can accurately and precisely describe the observed data. The population PK model for morphine after oral administration of DTO is reasonable and acceptable; therefore, it can be used to describe the integration of the previous population PK knowledge as prior information successfully overcomes the log neonate population.



Modeled time to stabilization



The present and future

Model based dosing

Standardized protocols

PK driven model refinement

Randomized controlled trials AND pragmatic trials

Multi-disciplinary approach

When to start pharmacologic treatment

Non-pharmacologic

- Minimize stimuli
- Breastfeeding
- Rooming in
- Swaddling

Pharmacologic

?

NAS areas of research interest

- PK driven dosing
 - Time to stabilization
 - Therapeutic target
 - Optimizing weaning
- Improving the Finnegan
- Opioid
 - Best opioid?
 - Weight or symptom based regimens
- Adjuncts
 - Phenobarbital vs clonidine
 - When to start, when to stop?
- Operationalizing pharmacogenetics



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Can We Reduce Opioid Treatment of NAS?

Robert M. Ward, MD, FAAP, FCP
Professor Emeritus, University of Utah

Family-Centered Care Reduces Treatment, Shortens Stays

- Dartmouth multidisciplinary QI PDSA (plan-do-study-act) cycle-NAS
- Rooming-in skin to skin care 24/7, family & volunteers Psychiatry educated staff in how to work with substance abuse patients
- Delayed start of pharmacotherapy for 24 to 36 hrs when effects of SSRI's, nicotine, and long acting opioids may confound NAS scores
- Change & standardize physician interpretation of scores with less emphasis on starting/increasing treatment with scores >8
 - Less emphasis on tremors, yawning, sneezing
 - More emphasis on crying, feeding, sleeping, diarrhea, emesis, fever, weight loss
- Nurses trained to standardize modified Finnegan scoring & retested
- Begin prenatal education classes at substance abuse treatment programs in response to parent request

Holmes et al. Pediatrics. 2016;137(6):e20152929

Family-Centered Care Reduces Treatment, Shortens Stays

- 163 newborns enrolled from 3/2012 to 3/2015 with several PDSA cycles
- NAS cores did not change throughout the study, but---
- Morphine treatment decreased from 46% to 27%; total dose decreased from 13.7 mg to 6.6 mg
- LOS decreased from 16.9 to 12.3 days for newborns requiring opioid treatment; No change for those not needing treatment (4.2-4.4 days)
- Hospital costs for newborns needing pharmacologic treatment decreased from \$19,737 to \$8755
- No adverse events; no increased readmissions; no readmissions for NAS

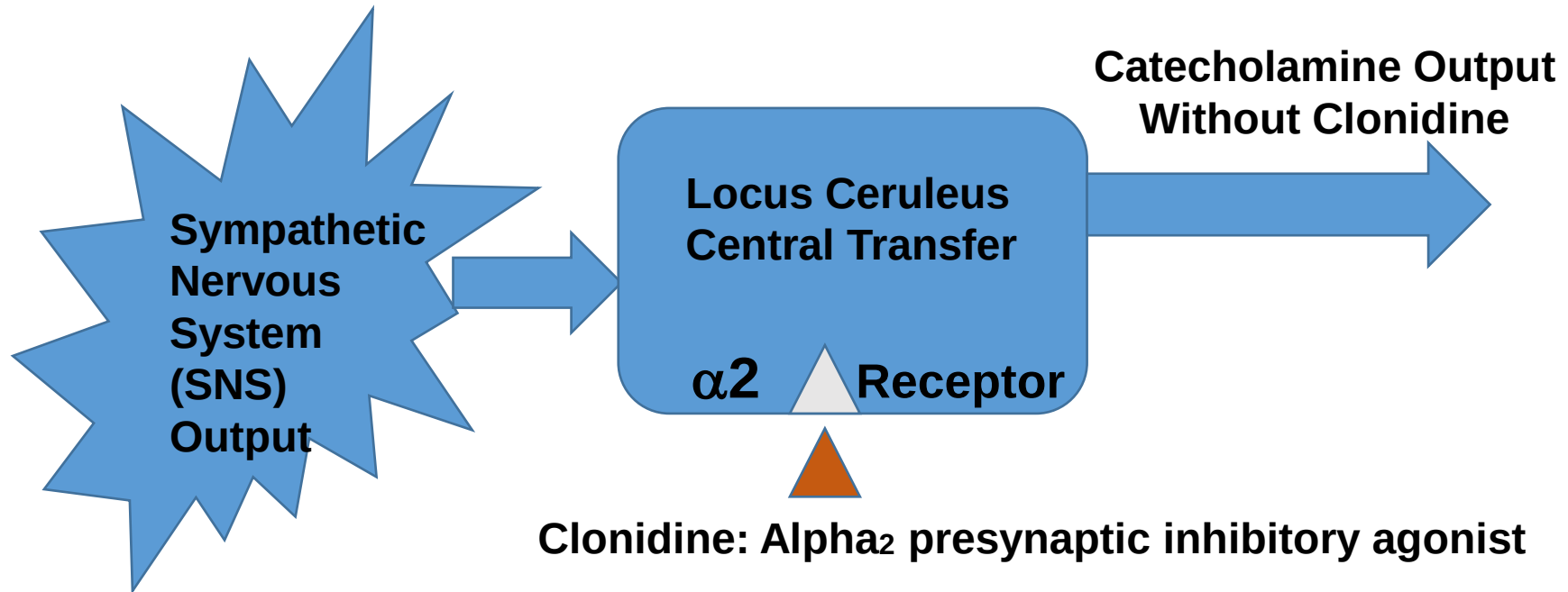
Holmes et al. Pediatrics. 2016;137(6):e20152929

- 6 Ohio children's hospitals covering 20 hospitals established 6 different NAS protocols
 - 6 protocols established guidelines for NAS identification and initiation of Rx
 - 3 also had strict weaning protocols
- Not every physician followed the protocol
 - 417 treated by a protocol, 130 did not follow a protocol
- Protocol guided treatment shortened duration of opioid treatment (32.1 to 17.7 days ($p = 0.0001$); shortened hospital stay (32.1 to 22.7 days, $p = 0.004$).
- No difference in LOS between treatment with methadone and morphine

[Pediatrics 2014;134:e527–e534](#)

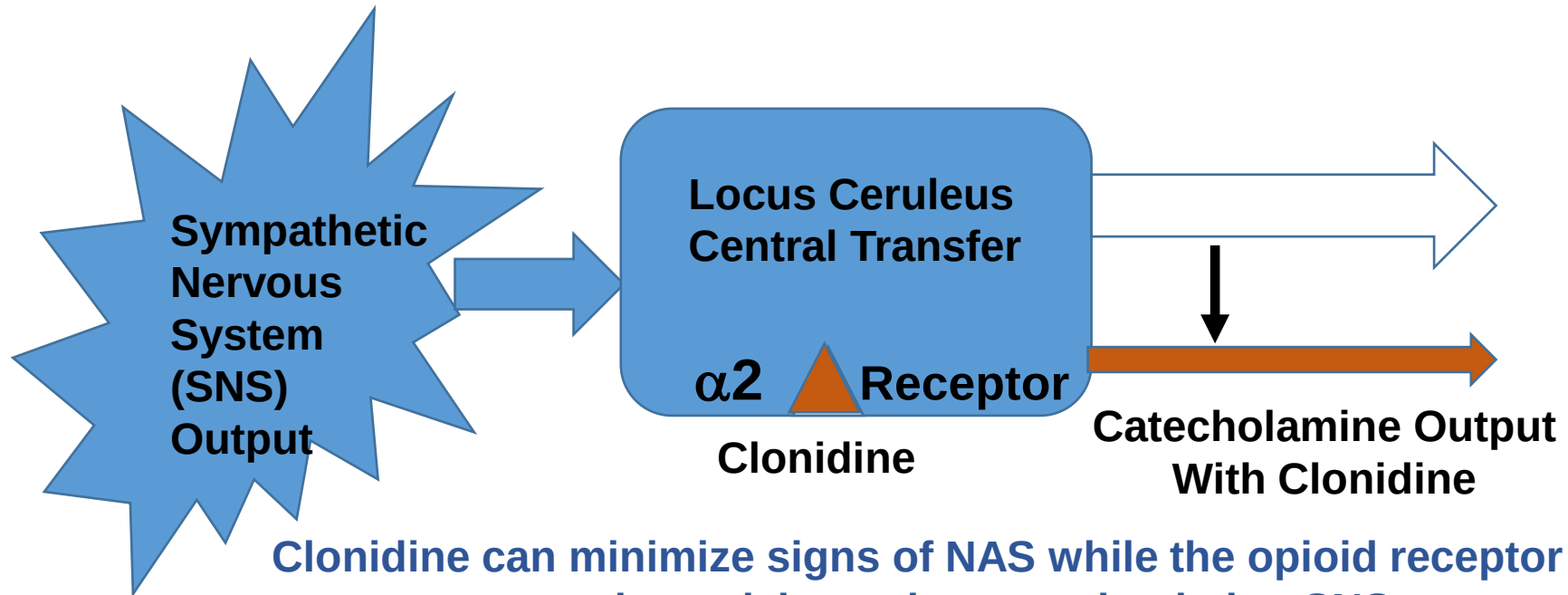
Clonidine to Reduce Opioid Treatment of NAS

**Dependent Opioid Receptor
Without Adequate Opioid**



Clonidine to Reduce Opioid Treatment of NAS

**Dependent Opioid Receptor
Without Adequate Opioid**



Clonidine can minimize signs of NAS while the opioid receptor reverts to normal reactivity and stops stimulating SNS output

- Ondansetron: Serotonin (5-HT)_{3a} receptor antagonist
- Ondansetron: blocks narcotic withdrawal in rat & man (Peltz lab-Stanford)
 - (*Pharmacogenet Genomics*. 2009;19:193)
- Ondansetron pK pregnant women and neonates:
 - *Clin Pharmacol Ther*. 2015;97:167-76
- RCT: Pregnant women from methadone maintenance program dosed in labor to reach fetal concentration to prevent NAS & continue treatment of newborns; enrolling now; blinded; no results
- NAS TREATMENT WITHOUT NARCOTICS MAY SOON BE POSSIBLE

Voting Slide – Neonatal Abstinence Syndrome



Considering both impact and feasibility, which of the following projects is your **first** choice?

1. To develop a gold standard definition of neonatal abstinence syndrome and/or neonatal opioid withdrawal syndrome based upon objective, validated tools.
2. To develop standardized outcome and process measures for NAS/NOWS to be utilized in clinical trials.
3. To understand the impact of non-pharmacologic treatment in optimizing outcomes for women and infants impacted by the opioid use disorder and NAS, including rooming in, soothing techniques and breastfeeding in addition to and independent of various pharmacotherapies for NAS.
4. To develop a gold standard treatment protocol and standardized medication of choice for severe NAS, address the variability of dosing/drugs, and include defining the safety and role of adjunctive treatments, particularly phenobarbital
5. To understand the predictors of NAS, both genomic and pharmacologic
6. “Walk-in Option A” (offered up by audience)
7. None of the above

Voting Slide – Neonatal Abstinence Syndrome

Considering both impact and feasibility, which of the following projects is your **second** choice?

1. To develop a gold standard definition of neonatal abstinence syndrome and/or neonatal opioid withdrawal syndrome based upon objective, validated tools.
2. To develop standardized outcome and process measures for NAS/NOWS to be utilized in clinical trials.
3. To understand the impact of non-pharmacologic treatment in optimizing outcomes for women and infants impacted by the opioid use disorder and NAS, including rooming in, soothing techniques and breastfeeding in addition to and independent of various pharmacotherapies for NAS.
4. To develop a gold standard treatment protocol and standardized medication of choice for severe NAS, address the variability of dosing/drugs, and include defining the safety and role of adjunctive treatments, particularly phenobarbital
5. To understand the predictors of NAS, both genomic and pharmacologic
6. “Walk-in Option A” (offered up by audience)
7. None of the above

Agenda – September 12th, Afternoon



- 1:00 - 2:15 p.m. **Session II: INC Workgroup Updates**
MARK TURNER, INC CO-DIRECTOR (UNIVERSITY OF LIVERPOOL)
- 2:15 – 3:00 p.m. **Session III: *Use of Narcotics for Sedation, Analgesia, or Treatment of Neonatal Abstinence Syndrome***
JOHN VAN DEN ANKER (CHILDREN'S NATIONAL HEALTH SYSTEM/U-BASEL CHILDREN'S HOSPITAL) & JON DAVIS, INC CO-DIRECTOR (TUFTS UNIVERSITY), CO-CHAIRS
- 3:00 - 3:30 p.m. COFFEE BREAK
- 3:30 – 5:00 p.m. **Session III Panel**
- 5:00 p.m. ***Concluding Remarks for Day 1***
JON DAVIS (TUFTS UNIVERSITY), INC CO-DIRECTOR
- 6:30 p.m. **NETWORKING DINNER AT THE PEARSON ROOM**
16-19 Canada Square, Canary Wharf



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Thank you!