NEONATAL OPIOID WITHDRAWAL (NEONATAL ABSTINENCE SYNDROME) (PASSIVE NEONATAL OPIOID DEPENDENCY

Stephen R. Kandall, MD, FAAP
sk1840@aol.com

General References

- Kandall, S. Substance and Shadow: Women and Addiction in the United States. Harvard U. Press, Cambridge, MA 1996 (Paperback 2001).
- Finnegan, LP and Kandall, S.R. "Maternal and Neonatal Effects of Alcohol and Drugs" in Lowinson, J.H. et. al. (eds). Substance Abuse: A Comprehensive Text Book. (4th ed) Lippincott Williams and Wilkins, Philadelphia, 2005 pp. 805-839 (302 references)
- Finnegan, LP and Kandall, S.R. "Neonatal Abstinence Syndromes" in Yaffe, S.J. and Aranda, J.V. (eds) Neonatal and Pediatric Pharmacology (3rd ed). Williams and Wilkins, Philadelphia, 2005, pp. 848-855
- Finnegan, LP and Kandall, S.R. "Perinatal Substance Use" in Galanter, M. and Kleber, H.D. (eds) Textbook of Substance Abuse Treatment American Psychiatric Publishing, Washington, DC, 2008, pp. 565-580 (4th ed)
- Journal of Addictive Diseases 29:2 (April-June 2010)- "Women, children and addiction." Co-edited by Finnegan, L.P. and Kandall, S.R. (book published in 2011 by Routledge Press, London)

Disclosure Statement

- I have no relevant financial relationships to disclose or conflicts of interest to resolve.

"Opiate" versus "Opioid"

- "opiate" is derived directly from the opium poppy, e.g. opium, morphine
- "opioid" is any substance which acts as an opioid receptor agonist; mimics effects of opiates
- we will deal mainly with the opioids heroin (diacetyl morphine), methadone and buprenorphine (partial mu agonist)

Drugs which produce "neonatal abstinence" ("passive neonatal drug dependency")

- opioids : *opium, *morphine, meperidine (Demerol), methadone, heroin ,oxycodone (Oxycontin), hydrocodone (Vicodin), hydromorphone (Dilaudid), [also extended release (Palladone)], codeine, pentazocine, Fentanyl, [propoxyphene (Darvon)], *buprenorphine
- alcohol, barbiturates, caffeine
- selective serotonin reuptake inhibitors (became available in 1988): citralopram (Celexa), fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), also venlaxafine (Effexor)

Drugs which produce "neonatal abstinence" (cont.)

- Others: tricyclic antidepressants: clomipramine (Anafranil), desipramine (Pertrofan, Norpramin)
- Chlordiazepoxide (Librium). Diazepam (Valium), diphenhydramine (Benadryl), ethchlorvynol (Placidyl), glutethimide (Doriden), hydroxyzine (Atarax), meprobamate (Miltown, Equanil)

Extent and cost (national) of neonatal opioid withdrawal (2009 data)

- Illicit drug use in 16% pregnant teenagers and 7.4% pregnant women aged 18-25
- Overall, about 4.5% of all pregnancies involve illicit drug use
- Neonatal opioid withdrawal diagnosed in 4% (13,539) babies—1 infant/hr
- Hospital charges average $53,400 per baby with opioid withdrawal
- Total cost was $720 million

Methadone vs. Heroin

- heroin short-acting, methadone longer-acting
- heroin not stored; methadone stored in lung, liver, spleen
- about 80% of methadone-exposed neonates show NAS compared to about 60% of heroin-exposed neonates (these figures may be modified by provision of comfort measures)

Methadone vs. Heroin (cont.)

- heroin-associated NAS almost always occurs within 48 hours; methadone- usually within 48 hours but more variable, even "delayed onset"
- Usually self-limited; potentially fatal if undiagnosed
- what determines severity and onset of NAS (assuming no polydrug use)??
  - large geographic variability (MOTHER study)
  - ? maternal dose (total or last trimester)
  - ? individual baby's rate of metabolism (rate of fall)
  - ? minimum level to be reached (0.06 micg/ml)
  - ? gestational age (NAS appears less severe in premies)
  - ? different treatment regimens—comfort care, breastfeeding, rooming in, pharmacotherapy
  - ? different maternal stressors
  - ? genetic influences

Genetics and neonatal opioid withdrawal

- Genes under consideration control:
- -- OPRM1: mu-opioid receptor affecting opioid efficacy, dependence, tolerance
- -- COMT (catechol -o-methyl transferase): key enzyme that metabolizes catecholamines in the CNS; linked to substance abuse
- --single nucleotide polymorphisms

Genetics (cont).

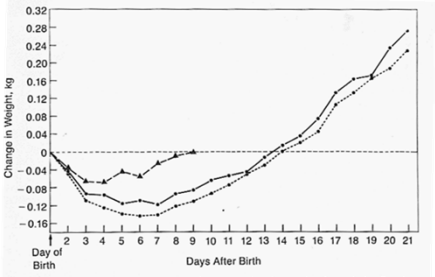
- study at 5 hospitals in Maine and Mass. (2011-2012)
- cohort 86/140 mother-infant dyads on methadone and buprenorphine
- no correlation between maternal Rx dose and NAS
- breastfeeding associated with less need for NAS treatment and length of stay (?drugs in breast milk, ?comfort care)
- cigarette smoking associated with need for increased neonatal treatment
- one nucleotide change in either OPRM1 or COMT genotype led to reduced need for NAS RX and shorter length of stay

Neonatal opioid abstinence (NAS)

- **Opioid receptors most concentrated in CNS and GI systems**
- **1. Central nervous system signs**
  - irritability, high pitched cry, tremors, hypertonia, hyperreflexia
  - dysrhythmic suck-swallow
  - seizures in <5% of methadone-exposed and 1% of heroin-exposed infants (Kandall)—unpredictable, frequently myoclonic, peak at 10 days (range 3-34)
- **2. GI signs**: vomiting and diarrhea
- **3. Respiratory signs**: tachypnea, hyperpnea, respiratory alkalosis, cyanosis, apnea
- **4. Autonomic nervous system signs**: nasal stuffiness, sweating, sneezing, tearing, hyperthermia

Note: vomiting, diarrhea, increased insensible water loss (hyperactivity, tachypnea, sweating) usually leads to excessive weight loss, suboptimal weight gain

Weight-change patterns in NAS (Kandall)



Graphic display of weight-change patterns in untreated and treated patients during first three weeks of life. Dashed line and closed triangles indicates untreated patients (n = 24); solid line and closed circles, patients treated with phenobarbital (n = 43); and dotted line and closed circles, patients treated with paregoric (n = 34).

NAS Scoring System (Lipsitz)—Term Babies

TABLE 4. Neonatal Drug-Withdrawal Scoring System

Signs	Score			
	0	1	2	3
Tremors (muscle activity of limbs)	Normal	Minimally increased when hungry or disturbed	Moderate or marked increase when undisturbed; subside when fed or held snugly	Marked increase or continuous even when undisturbed, going on to seizure-like movements
Irritability (excessive crying)	None	Slightly increased	Moderate to severe when disturbed or hungry	Marked even when undisturbed
Reflexes	Normal	Increased	Markedly increased	
Stools	Normal	Explosive, but normal frequency	Explosive, more than 8 d	
Muscle tone	Normal	Increased	Rigidity	
Skin abrasions	No	Redness of knees and elbows	Breaking of the skin	
Respiratory rate/minute	<55	55–75	76–95	
Repetitive sneezing	No	Yes		
Repetitive yawning	No	Yes		
Vomiting	No	Yes		
Fever	No	Yes		

Reprinted with permission from Lipsitz PJ. *Clin Pediatr.* 1975;14:592–594.

NAS Scoring System (Finnegan)—Term Babies

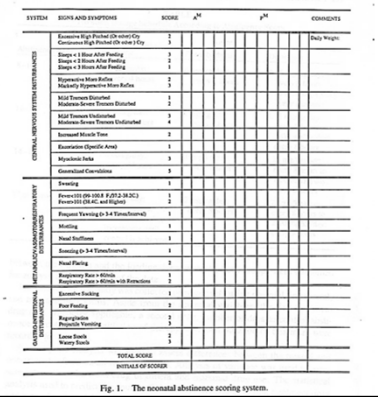


Fig. 1. The neonatal abstinence scoring system.

Use of "Severity Score"

Pros:

- --avoids treatment when comfort care suffices
- --treats infants before they get very ill
- --allows "standardization" of care
- --allows data gathering in uniform way

Cons:

- --"point in time" assessment
- --evaluation is "state-dependent'
- --may have low inter-observer reliability
- --may lead to rigidity of approach

Drug testing

- no overarching federal policy
- testing varies from state-state, city-city, even hospitals within a city
- methodology varies: urine (1-3 days), meconium (second half of pregnancy), umbilical cord tissue (second half of pregnancy), hair (1-6 months)---each has its own merits and drawbacks

**Objective testing and careful maternal history-taking should be non-punitive

Supportive treatment of NAS

- In DR do not use narcan---may precipitate withdrawal
- NICU admission?? Rooming-in??
- experienced, skilled nursing
- careful feeding---voracious appetite, poorly coordinated suck-swallow, risk of aspiration
- increase calories and fluids
- decrease stimulation
- darkened room, pacifier (??water bed)
- observe for signs, especially seizures
- consider other diagnoses such as sepsis, metabolic disorders (hypoglycemia, hypocalcemia), asphyxia, hyperthyroidism, CNS hemorrhage

Swaddling-position controversy

- infants undergoing NAS seem comforted by swaddling and prone position
- essential to "Safe Sleep" campaign is supine positioning without swaddling
- possible strategy: side positioning with light swaddle
- another strategy: use prone position for comfort care, wean baby to supine position prior to discharge

Pharmacotherapy of NAS (cont.)

Not recommended: diazepam, chlorpromazine, (clonidine), (buprenorphine)

Acceptable

- phenobarbital
  --advantages: broad spectrum use; given PO, IM, IV
  --disadvantages: non-specific, long-acting, does not control non- CNS signs, depresses sucking, may depress respirations, poor seizure control

  --regimens:
  (1) begin at 5 mg/kg IM or IV; if unstable, increase by 1 mg/kg/day until stable, then give total dose p.o. divided q8h
  (2) Finnegan: load with 20 mg/kg/day, then maintain at 2-6 mg/kg/day, monitor with blood phenobarbital levels

  --if stable for 4-5 days, reduce dose by 1 mg/kg every 1-2 days using "severity score" as guide

Specific pharmacotherapy of NAS

Acceptable

- methadone---long-acting, harder to titrate, contains 8% ethanol
  --start with 0.05-0.1 mg/kg q6h, increase by 0.05/ dose until stable
  --switch to q 12-24 dose
  --taper by 0.05 mg/kg/d with careful assessment
  --taper by dose, not by frequency of administration
- morphine---alcohol-free morphine sulfate has 0.4 mg/ml.
  --treat with 0.04 mg for mild withdrawal, 0.08 mg for moderate withdrawal, 0.12 mg for more severe withdrawal---titrate dose by severity, wean after 48h . Dose q4h.

Pharmacotherapy of NAS (cont.)

Preferred: short-acting opioid (cooperation with pharmacy)

- Tincture of opium (10mg/ml) in 25-fold dilution
  --gives morphine in dose of 0.4 mg/ml (same as paregoric)
  --dose is 0.1 ml/kg (2 drops/kg) q4h with feeds
  --use severity score to increase, stabilize, and taper dose
  --replaces paregoric (camphorated tincture of opium) at 0.2-0.25 cc q3-4h
  --paregoric contains isoquinolones (anti-spasmodics), camphor (CNS stimulant), alcohol, anise oil, glycerin
  --paregoric also contains 4mg/ml of benzoic acid (may compete for bilirubin binding sites; its oxidation product (benzoyl acohol) may cause acidosis, CNS depression, hypotension, renal failure, seizures, death

Clonidine Treatment of NAS

Theory: alpha 2 adrenergic receptor agonist----stimulates activation of an inhibitory neuron----reduction in sympathetic activity

---can be used alone or with tincture of opium

----advantages are no oversedation (phenobarbital), no respiratory depression (phenobarbital), can be given PO or IV, rapid tapering; some patients prefer non-opioid Rx

---disadvantages are errors in dosing, risk of hypotension and bradycardia (frequent monitoring), not recommended by AAP (legal vulnerability) and not mentioned in proposed WHO guidelines

Clonidine Treatment (continued)

Protocols: low dose, high dose, middle dose

1. Begin clonidine at 0.5-1 microgram/kg PO; titrate over 1-2 days to 3-5 micrograms/kg/day divided q4-6h; taper by 25% of dose every other day as tolerated; maximal dose about 12-20 mcg/kg/day

2. Clonidine IV at 0.5 micrograms/kg/hr (12 micrograms/kg/d; maximal dose 72 mcg/kg/day

3. Clonidine 1 mcg/kg q3h, increase to 2 mcg/kg q3h or add morphine 50 mcg/kg if Severity Score >8; then keep increasing clonidine and/or morphine based on Severity Score and vital signs; maximal clonidine dose is 48-64 mcg/kg/day.

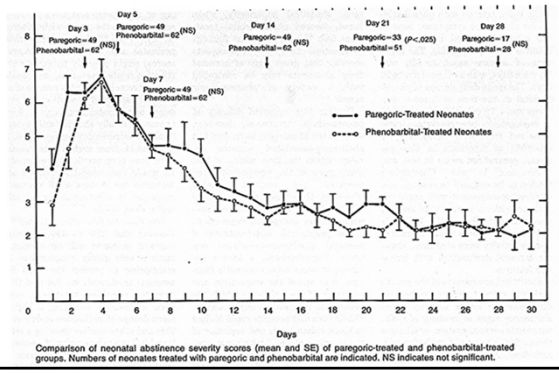
Clonidine Adjunct Treatment for NAS

- Agthe article (Pediatrics, 2009)
- --80 opioid-exposed neonates randomly assigned to dilute tincture of opium + 1 mcg/kg PO q4h of clonidine vs. dilute tincture of opium + placebo
- --clonidine group had shorter LOS (11 v. 15 days), and fewer infants needed higher doses of opium (20% v. 40%)
- --7 in clonidine group needed retreatment
- --60% of mothers took cocaine, 90% smoked; some used benzodiazepines and SSRI drugs

Buprenorphine Treatment of NAS

- Studies by Kraft ---use of a 30% ethanolic suspension of buprenorphine sublingually (SLB) v. standard morphine treatment
- --2008: 13.9 mcg/kg/d divided q8h , dose titrated to maximal dose of 39 mcg/kg/d
- --shorter LORx in SLB group (22 v. 32 days)
- --shorter LOS in SLB group (27 v. 38 days)
- --2011: used 15.9mcg/kg/d divided q8h SLB, titrated to maximal dose of 60 mcg/kg/d
- --shorter LORx in SLB group (23 v. 38 days)
- --shorter LOS in SLB group (32 v. 42 days)

Comparative treatment of NAS (Kandall)



Comparison of neonatal abstinence severity scores (mean and SE) of paregoric-treated and phenobarbital-treated groups. Numbers of neonates treated with paregoric and phenobarbital are indicated. NS indicates not significant.

Cochrane Collaborative analysis of NAS treatment (2010)

- only 9 of 38 studies met criteria for random or quasi-random assignment to treatment
- opiate such as dilute tincture of opium or morphine should be initial therapy
- studies of generally poor quality: usually no random allocation, not blinded, incomplete outcome data; incomplete knowledge of maternal drug-taking pattern (dosages, polysubstance use, timing during pregnancy

NAS-associated seizures

- work-up to consider other causes of neonatal seizures: infection, metabolic disorders, electrolyte and glucose abnormalities, asphyxia, CNS malformations, etc.
- begin opioid, may also begin phenobarbital at 10-20 mg/kg load and 5 mg/kg maintenance pending workup; may include EEG, CT/MRI
- once stable and diagnosis of abstinence established, taper phenobarbital and maintain opioid treatment

Methadone and breastfeeding

- Generally encouraged if baby does not have galactosemia (rare inborn error) and mother (1) is HIV negative; (2) is not taking antiretroviral drugs; (3) is not infected with human T-cell lymphotropic virus Type I or II; (4) does not have active untreated TB; (5) is not on specific anti-cancer treatment; (6) is not on nuclear radiation treatment; (7) is not using or dependent on illicit drugs or is a heavy alcohol consumer

Methadone and breastfeeding

- General therapeutic methadone plasma concentration in patients is about 200-600 nanog/ml
- Methadone levels in breast milk vary extremely widely (21-460 nanog/ml)
- Generally, breast milk: plasma ratio of methadone is 0.29-0.88 (mean 0.42)
- Generally, concentration of methadone in breast milk not related to maternal methadone dose or maternal plasma concentration
- Generally, low level of methadone in breast milk (<0.2mg/day)
- One study: 95 ng/ml of methadone x 475 ml of breast milk/day= 0.05 mg/day
- Average dose of methadone used to treat NAS is 0.05-0.1 mg/kg/q6h = 0.6-1.2 mg/day

Breastfeeding

- -Levels of methadone in breast milk vary widely
- - Generally breast milk levels are 3-10% of maternal weight-adjusted dose
- - Recent AAP guidelines (August 2013)---accurate?
  - a. potential adverse effects of methadone include lethargy, respiratory difficulty, poor weight gain
  - b. buprenorphine with/without naloxone relative contraindication to breast feeding
  - c. abrupt cessation of breast feeding can lead to neonatal withdrawal

Rooming-in

- Fir Square Vancouver, BC---Dr. Ron Abrahams
- Unit provides OB care, detoxification and stabilization for pregnant and postpartum women with problematic substance use
- Protocol includes rooming-in, comprehensive teaching for mother and total care for mother and newborn
- --don't use a "withdrawal score," treat when weight loss exceeds 10% of baby's weight
- --morphine 0.03 mg/kg q3h for 2-3 days, then decrease by 0.02 mg/kg every 2 days

Rooming-In: Fir Square (cont.)

- Major findings:
  - --correlation between maternal methadone dose late in pregnancy and need for neonatal treatment
  - --mean time of neonatal Rx was 17.9 days (range 6-55 days)
  - --rooming-in protocol mitigated the neonatal withdrawal
  - --decrease in NICU admissions, decrease in length of stay, increase in breastfeeding rates, increase in maternal custody
  - Questions:
  - --retrospective (295 women between 2003-2010)
  - --huge amount of polydrug use: 34% used heroin, 23% used alcohol, 59% used crack cocaine, 14% used methamphetamine
  - --labor intensive and expensive program---street outreach, equipped Rx vans, person to person teaching

Buprenorphine

- Generally called an opioid—partial mu agonist
- Derivative of the morphine alkaloid thebaine
- Produces mood elevation , morphine-like effects
- Abuse potential lower than methadone
- Alternative to methadone maintenance
- Poor oral bioavailability, avoid IV use
- Given sublingually as buprenorphine (Subutex) or buprenorphine-naloxone (Suboxone)-----latter generally not used in pregnancy
- Given 3x/week with starting dose 4-8mg/day; final dose usually 24-32mg/day
- Retrospective study of 10 patients on Suboxone---normal growth parameters, only 40% of neonates treated for NAS, mean days of treatment only 6.9 days

Buprenorphine in pregnancy

- FDA –classified as Category C-----potential benefit must justify risk
- no reported teratogeny
- early reports indicate that the NAS is mild with no apparent relation to maternal dose
- NAS appears in 12-72 hrs, peaks at 66-96 hrs
- few reports of delayed or prolonged NAS
- breastfeeding: plasma/milk is 1, but poor bioavailability means that total infant exposure is 10-20% of total ingested

Buprenorphine (cont.)

- MOTHER Study (Maternal Opioid Treatment Human Experimental Research)---NEJM 2010:363:2320-2331
- 8 center international study
- rigorously controlled
- 1074 women screened; only 175 randomized
  - --86 buprenorphine, 89 methadone
  - --58/86 completed study vs. 73/89
  - --better maternal satisfaction with methadone

MOTHER Study –neonatal findings

- 131 infants rigorously examined and monitored
- no difference in number of infants needing treatment for NAS but buprenorphine group needed 89% less morphine than methadone group
- buprenorphine group needed shorter treatment period (4 vs. 10 days) and shorter length of stay (10 vs. 17.5 days) compared to methadone group

Opioid exposure and SIDS

- SIDS is a complex topic; cause(s) not yet known

  --national incidence now <1/1000 live births
  --"Back to Sleep" now part of "Safe Sleep" program

  --Ward (LA 1986-7 data)----unadjusted SIDS rate of 8.7/1000 live births after maternal opioid use

  --Kandall et (NY 1979-89 data)—maternal opioid use associated with 3-fold increase in subsequent SIDS (corrected for race, low maternal age, maternal smoking, and low birthweight)

  --mechanism might be reduced ventilatory response to hypercapnea (Kinney's recent work on lower levels of serotonin and tryptophan hydroxylase in SIDS babies)

Follow-up of opioid-exposed infants

- What do we know about outcomes??
- The short answer: almost nothing
- Why do we know so little??

Follow-up of opioid-exposed infants

- Need to control for maternal lifestyle issues
  - --poverty
  - --homelessness
  - --lack of prenatal and medical care
  - --poor nutrition, vitamin deficiencies
  - --medical illnesses
  - --sexually transmitted diseases, incl. HIV
  - --abuse, battering, poor parenting skills

Follow-up of opioid-exposed infants

- Difficulties in assessing outcome:
  - --changes in drug use patterns over time
  - --variable drug purity from city-city and within cities
  - --concomitant drug use, incl. tobacco and alcohol
  - --hostile, judgmental questioning may obscure drug use
  - --"objective documentation" not uniformly used
  - --"drug-exposed" and "drug-affected" not defined
  - --many studies don't address maternal drug dosages
  - --difficulty in maintaining a cohort group
  - --"organicity" vs. "environmental" effects—parenting, schools, foster care
  - --study numbers very small

Summary of outcome studies

- Studies from Texas (Desmond, Wilson), Detroit (Strauss, Ostrea), Philadelphia (Finnegan, Kaltenbach), New York (Rosen, Johnson, Kandall)
- Conclusion: although most studies are short-term, there are no specific, consistent deficits attributed to intrauterine opiate exposure, including methadone
- Seizure follow-up at 1-2 years (Kandall): normal outcome

Summary

- chronic maternal opioid use during pregnancy is often associated with NAS—proper treatment rests on accurate diagnosis made by non-punitive history-taking, careful clinical observation using a "severity score," and possible drug testing
- methadone-associated withdrawal has a more variable and unpredictable course compared to shorter-acting opioids
- recommended treatment for opioid abstinence is provision of comfort measures, with pharmacotherapy as needed (tincture of opium preferred) under careful observation; other Rx options may be considered
- we will probably see more buprenorphine use—slightly milder NAS, shorter length of stay, but less maternal satisfaction—will they stay in treatment??
- in limited studies, outcome of opioid-exposed infants appears to be relatively normal, even with neonatal abstinence-associated seizures