Neonatal Abstinence Syndrome

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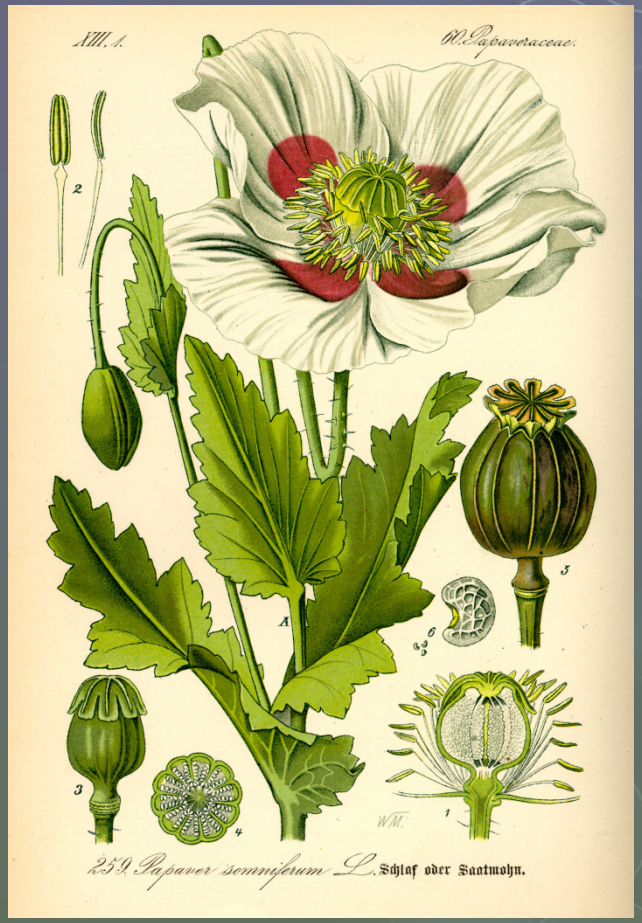
(no financial conflicts to disclose)



Objectives

- Emphasis on opiate/opioid use
- Identify the opioid epidemic and it's affect on newborns
- Outline the current guidelines for screening, identification , confirmation of exposure, and management of infants with NAS
- Identify opportunities for advocacy for the Georgia Perinatal Association

Opioid History

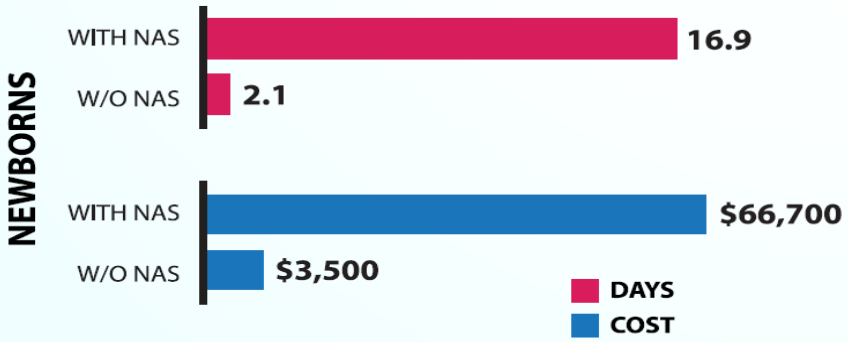
- Opium dates back to 3400 BC
- Opium addiction reports: end of 18th cent
- Morphine isolated in 1804
- Heroin synthesized in 1874
- Oxycodone synthesized in 1917
- Hydrocodone synthesized in 1920

The Perfect Storm

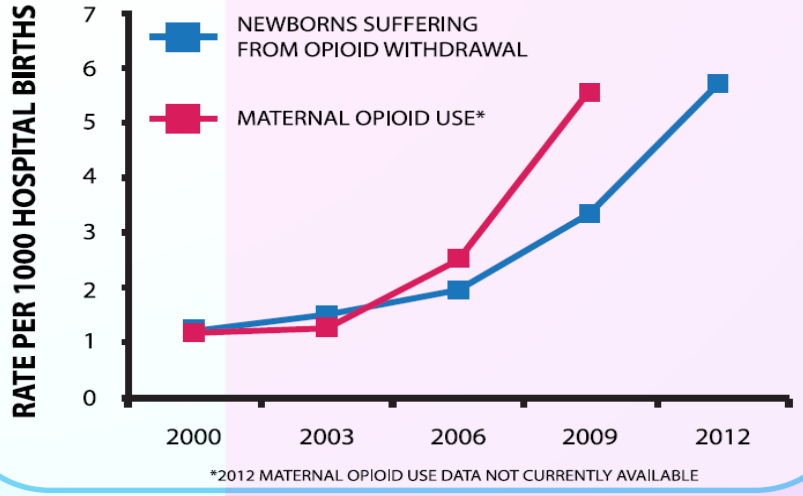
- 1990s Purdue Pharma aggressively marketed OxyContin
- 1996 American Pain Society Campaign & Joint Commission launch "Pain as the 5th Vital Sign"
- 2001 Joint Commission creates care standards for pain managment
- Unregulated Pain Clinics aka "Pill Mills"
- Physician rating becomes popular
  - HCAHPS
  - Healthgrades started in 1998
- In 2010, Purdue Pharma generated $3.1 billion dollars off OxyContin sales alone
- $17 billion in sales 2000-2010

EVERY 25 MINUTES, A BABY IS BORN SUFFERING FROM OPIOID WITHDRAWAL.

AVERAGE LENGTH OR COST OF HOSPITAL STAY



NAS AND MATERNAL OPIOID USE ON THE RISE



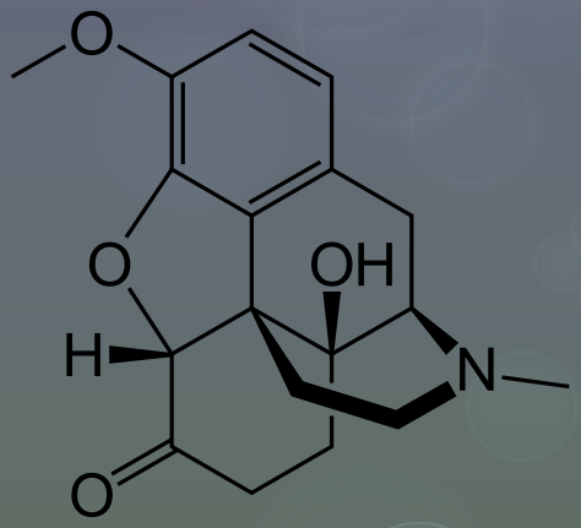
*2012 MATERNAL OPIOID USE DATA NOT CURRENTLY AVAILABLE

NIH National Institute on Drug Abuse

Source: Patrick et. Al., JAMA 2012 , Patrick et. Al., Journal of Perinatology 2015

Short Acting Opioids

- Prescription Pain Meds
  - Codeine (Tylenol 3)
  - Morphine (MS Contin)
  - Oxycodone (OxyContin, Percocet)
  - Hydrocodone (Vicodin)
  - Hydromorphone (Dilaudid)
  - Fentanyl (Duragesic)
- Illicit
  - Heroin
  - Fentanyl



Long Acting Opioids

- Methadone introduced for treatment of opioid addiction in 1964
  - Initially thought to not cause NAS
- Buprenorphine introduced as alternative in U.S. in 2002
  - Also initially thought to be low risk for NAS

Opioid Use in Pregnancy

- 82.5 opioid prescriptions per 100 persons in 2012
- Prescriptions filled by reproductive-aged women per year (2008-2012)
  - 28% of privately insured
  - 39% of Medicaid enrolled women
- 14-22% of pregnant women prescribed opioids
- 1.1% women abused opiates in 2011

Neonatal Abstinence Syndrome

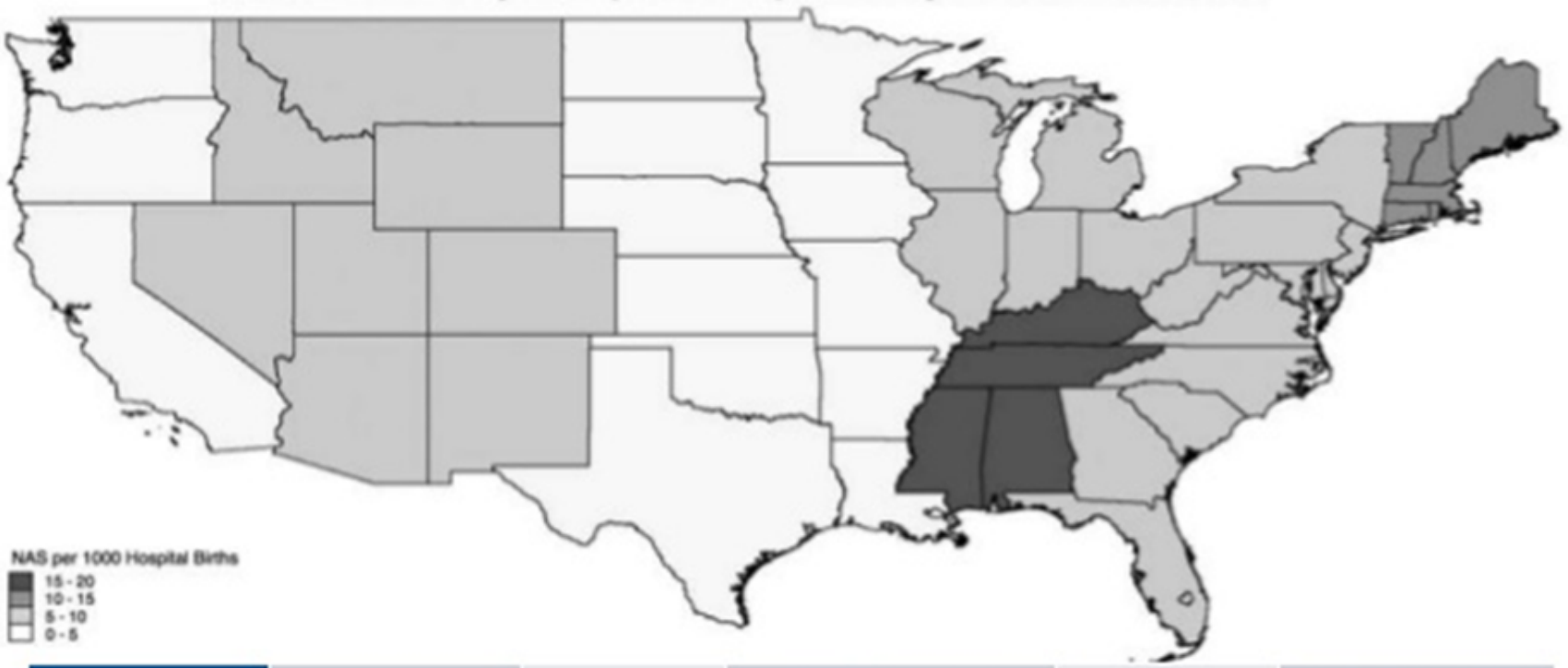
- Historically associated with high mortality
  - About 1903: first reported treatment resulting in survival
  - 1947: successful treatment of seizures from "congenital morphinism"
- Abstinence: "intention to abstain"
  - "Neonatal Withdrawal" is more accurate
- Specifically applies to opioid withdrawal
  - Poly-substance abuse common
  - Scoring system specific for opioid w/d

Incidence of NAS

- 55-94% of newborns born to mothers either addicted to or being treated with opioids.
  - 2-11% develop seizures
- NICU admissions have increased by 10 fold from 2005-2011

Maternal Opiate/Opioid Use and NAS

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



Division	SE Central	New England	NE Central South Atlantic Middle Atlantic	Mountain	NW Central Pacific SW Central
NAS Rate	16.2	13.7	6.8 – 6.9	5.1	2.6 – 3.4

Patrick SW et al. J Perinatol, 2015, in press.

Adverse Infant Outcomes

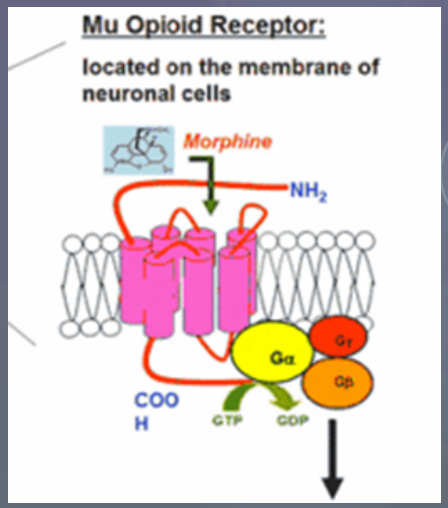
- Low Birth Weight
- Preterm Delivery
- Microcephaly
- Sleep Myoclonus/visual disturbances
- Feeding difficulty/Failure to Thrive
- Jaundice
- Admission to NICU/prolonged hospitalization
  - 17 vs. 2.1 days
  - 23 days if requiring treatment
- Disrupted bonding/maltreatment

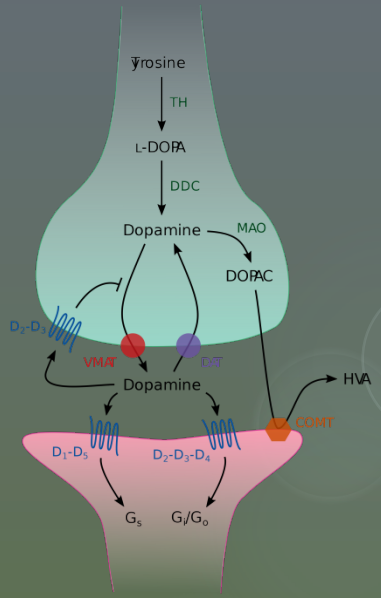
Pathophysiology

- **Opium**: alkaloids from the poppy plant- *Papaver Somniferum.*
- **Opioid**: Naturally occurring, semi-synthetic or synthetic compounds that bind specifically to opioid receptors and share the properties of one or more of the naturally occurring endogenous opioids.
- **Opiate**: Any naturally occurring opioid derived from opium (eg morphine, codeine, heroin).
- **Narcotic**: From the Greek meaning "to numb or deaden". It is often used to denote an opioid but also widely used to describe drugs of addiction and hence includes non-opioid compounds.

Pathophysiology

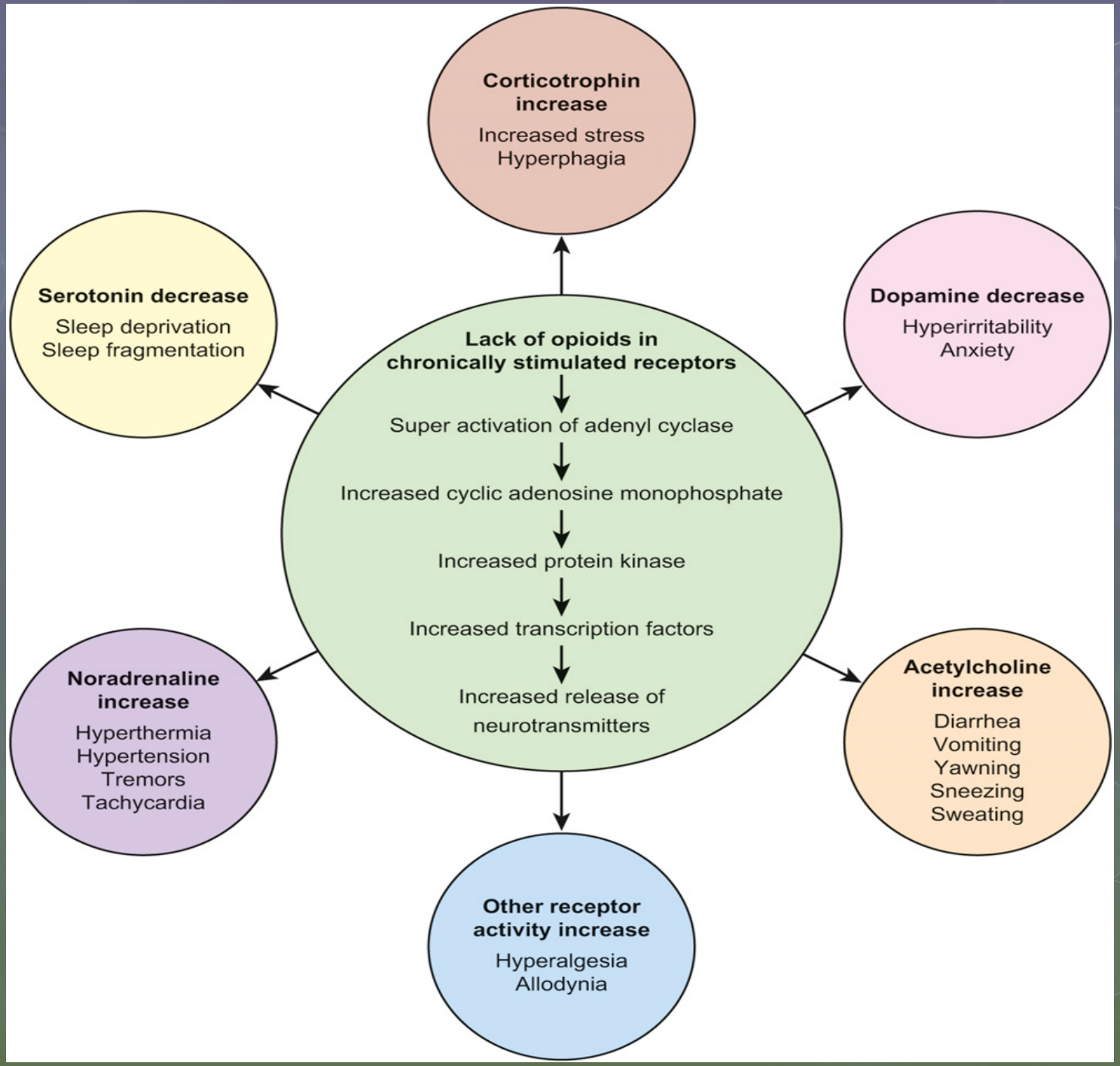
- Opiates
  - Low molecular weight/water soluble
  - Easily transferred through placenta
    - Increased with synthetic opioids
    - Increased as gestation progresses
    - Increased when cocaine/heroin combined
- G protein-coupled receptors
  - μ (mu), ƙ (kappa), δ (sigma)
  - CNS, peripheral nervous system, GI system
  - mu receptors well distributed in neonate





Opioid Dependence

- Endogenous endorphins create a state of equilibrium without chronic use of opioids
- Opioid dependence: frequent and repeated use of opioids leads to structural changes in the brain such that normal brain function requires the presence of opioids.
  - Changes to opioid receptors, messenger enzymes, and kinases
  - Increase in the number of dendritic spines of neurons involved in the "reward pathway"
- Hyper-sensitization of reward pathways dependent on exogenous opioids.
- Permanent structural changes in areas involved in memory, learning, behavior


Corticotrophin increase
Increased stress
Hyperphagia
Serotonin decrease
Sleep deprivation
Sleep fragmentation
Dopamine decrease
Hyperirritability
Anxiety
Lack of opioids in chronically stimulated receptors
Super activation of adenyl cyclase
Increased cyclic adenosine monophosphate
Increased protein kinase
Increased transcription factors
Increased release of neurotransmitters
Noradrenaline increase
Hyperthermia
Hypertension
Tremors
Tachycardia
Acetylcholine increase
Diarrhea
Vomiting
Yawning
Sneezing
Sweating
Other receptor activity increase
Hyperalgesia
Allodynia

Clinical Presentation by Systems

- Autonomic
  - Temperature instability/fever, diaphoresis, sneezing, mottling
- Central/Peripheral Nervous System
  - Irritability, hyper-algesia, tremor, jitteriness, hypertonia, inconsolable crying, high pitched cry, seizures
  - Methadone w/d causes exaggerated tremor/moro/myotonic jerks can mimic seizures
- CV
  - Hypertension, tachycardia
- Respiratory
  - Tachypnea, nasal stuffiness, nasal flaring
- GI
  - Diarrhea, emesis, hyper-phagia (often require 150 kcal/kg/day)
  - Heroin w/d causes exaggerated diarrhea/dehydration

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

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

Factors Affecting Clinical Presentation

- Type of opioid
  - Short vs. long acting opioid
- Timing of last dose
  - Can affect onset in neonate
- Duration of exposure/total accumulation
- Polysubstance
  - Cocaine and methamphetamine cause early symptoms related to CNS irritability
  - Psychotropic drugs (SSRIs, SNRIs) usually cause self limiting w/d
  - Delayed onset with barb/benzo (eg xanax) with opioids

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

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

Identification

- AAP recommendation for hospital discharge
  - 3-7 days
    - Short vs. long acting opioids
  - 5 days likely adequate
- Systematic approach to screening moms
  - Universal vs. targeted screening
    - Recommendations lacking
  - Self-reporting
    - "Relational care": non-judgmental, empathetic, collaborative
    - Punitive legal system reduces self-reporting

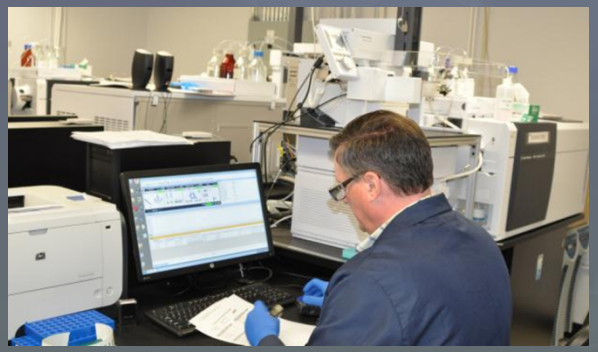
Example of Newborn Screening Criteria

Medical indications for NEWBORN drug testing for possible exposure to illicit drugs *University of Arkansas for Medical Sciences, ANGELS Neonatal Guidelines* [46]
(1) History of maternal drug use or agitated/altered mental status in the mother
(2) No prenatal care
(3) Unexplained placental abruption
(4) Unexplained CNS complications in the newborn (seizures, intracranial hemorrhage)
(5) Symptoms of drug withdrawal in the newborn (tachypnea, hypertonicity, excessive stooling/secretions)
(6) Changes in behavioral state of the newborn (jittery, fussy, lethargic)

Also consider history of IUGR or unexplained CV events in mom or baby.

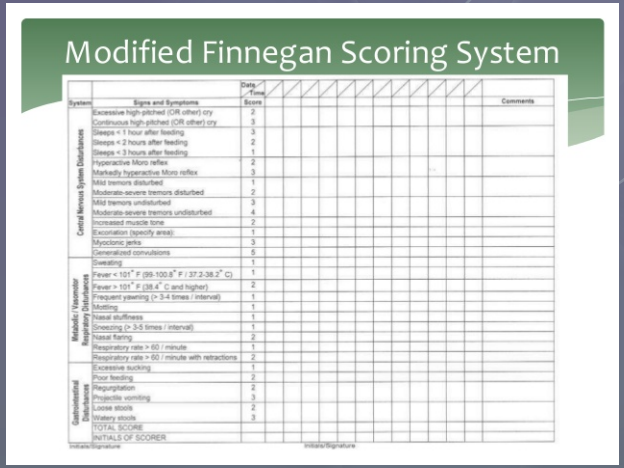
Toxicology Confirmation

- Sensitivity/specificity, detection thresholds, and metabolites create challenges
- Urine
  - First urine specimen most sensitive
  - Detects exposure only in last days of fetal life
- Meconium
  - Detects exposure starting at 20 weeks
  - Avoid contamination with human milk/formula feeds
  - Difficult if meconium passed in-utero
  - Usually as send-out lab
- Cord blood
  - Only detects recent (hours-days) before birth
  - Drugs less concentrated in blood than urine
- Cord tissue
  - As accurate as meconium
  - Can be obtained immediately, shorter turn-around
- Hair
  - Detects exposure from beginning of 3rd trimester
  - 20-50 mg hair cut close to scalp required
  - Samples can be collected for up to 3 months after birth
  - Can estimate exposure period



DPH
Georgia Department of Public Health

Scoring Systems



- Goals
  - Objective treatment threshold
  - Adjusting therapy
  - Facilitate structured weaning
- Modified Finnegan Abstinence Scoring (FNASS)
  - Recommended by AAP
  - 95% of hospitals use this
  - 90% inter-observer reliability rec
    - requires extensive education
- "Alternative treatment approach for neonatal abstinence syndrome may shorten hospital stay", Presented at PAS meeting, May 7, 2017
  - Eat, Sleep, Console (ESC) model
  - Focuses on key withdrawal symptoms
  - Reduced therapy (60% with FNASS vs. 12% with ESC model).

Management

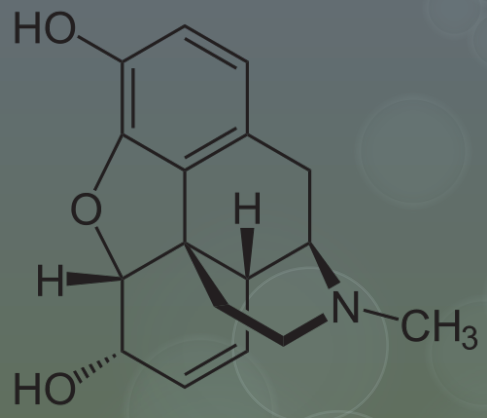
- **<u>Non-pharmacologic Care</u>**
  - **Breastfeed**
  - **Room-in with mom**
  - **Minimal stimulation**
  - **Supportive care**
  - **Avoid NICU**
  - **Avoid pharmacologic therapy**
- Pharmacologic Therapy (**60-80%** of NAS babies need Rx)
  - Morphine
  - Phenobarbital
  - Methadone
  - Buprenorphine
  - Clonidine

Therapeutic Goals

- Prevent seizures, fever
- Maintain normal feeding pattern
  - Prevent FTT, dehydration
- Normal state
  - Promote normal mother-infant bonding
- Pharmacologic management
  - **First line** drug should be opioid
  - Use of a standardized protocol more important than individual opioid used

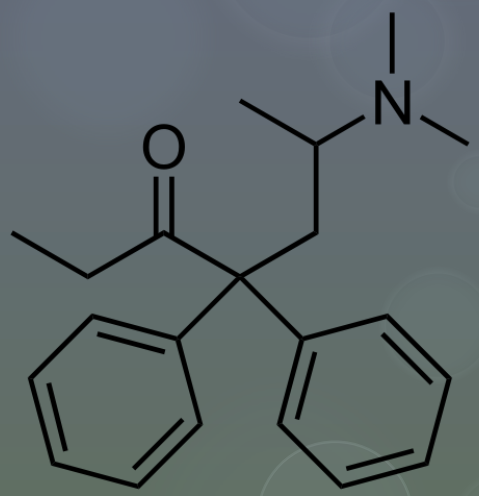
Morphine

- Most commonly used
- Full mu-opioid receptor agonist
- Short half-life
- Benefits
  - Can escalate or de-escalate therapy quickly
  - Reduces diarrhea, risk of seizures
- Risks
  - Respiratory depression/sedation
  - Prolonged hospital stay
- Some considering “as needed dosing”
- Not discharged with prescription

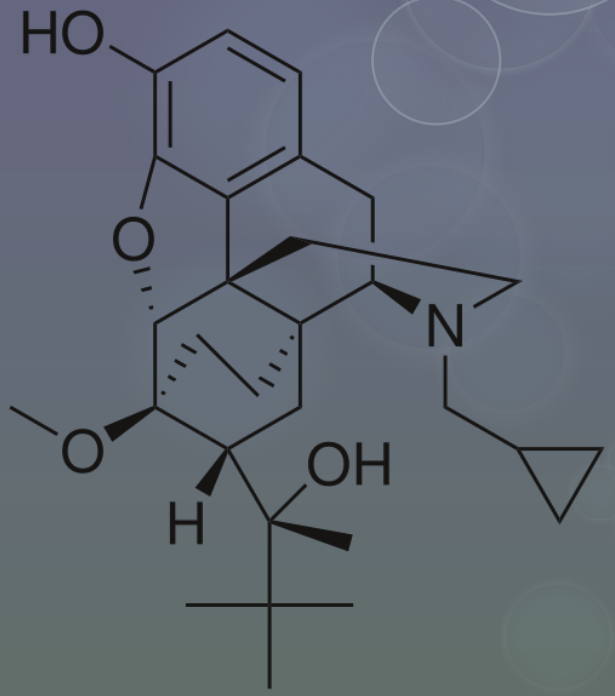


Methadone

- Synthetic full mu-opioid receptor agonist
- Dosed twice daily
- Long half-life: 25-32 hours
  - Harder to titrate dose
- Contains ethanol
- Can be discharged with prescription



Buprenorphine

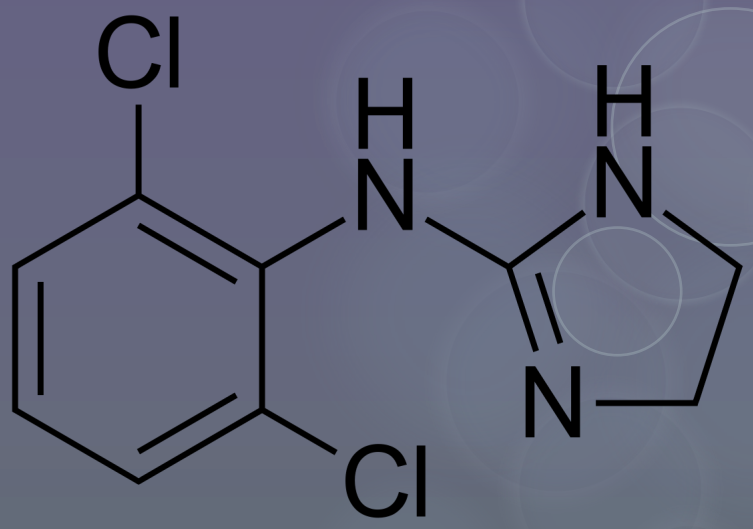


- Partial agonist
- Sublingual administration
- Evidence for shorter hospital stay
  - Promising as first line agent
- Also contains ethanol

Phenobarbital

- Long acting barbiturate
- Not indicated as first line agent for opioid withdrawal
  - Not helpful for GI symptoms
  - CNS depression
  - Impaired suck/swallow
- Used as second line agent in opioid w/d
  - Poly-substance exposure
- First line agent for non-opioid NAS
- Can follow blood levels

Clonidine



- CNS alpha-agonist
  - Reduces sympathetic outflow from brain
- May be as effective as opioid agonists
- Bada, et. al. from University of Kentucky, Pediatrics, Feb 2015
  - Morphine vs. Clonidine (31 babies)
  - Clonidine reduced LOS from 39 to 28 days

Breastfeeding

- AAP recommends breastfeeding when moms on methadone
  - Minimal amount of methadone and buprenorphine in breast milk
  - Not enough to treat NAS
- Oxycodone and hydrocodone concentrates in milk
  - Recommend informing mom's of risk of infant sedation
- Benefits
  - Increased mother-infant bonding
  - Enhanced maternal confidence
  - Possible reduction in incidence of NAS, Rx, and LOS
- Contraindication to breastfeeding
  - Illicit drug use
  - Poly-substance abuse
  - HIV

Supportive Care

- KEY – Nonjudgmental attitude
- Calm environment (quiet & low light)
- Rooming in: ↓Rx, ↓LOT, ↓LOS, ↓Cost
- Education for mother and family
- Skin-Skin time

"Rooming-In to Treat NAS: Improved Family Centered Care at Lower Cost"

- Holmes, AV et. al., PEDIATRICS, June 2016
- Multidisciplinary, QI initiative (VON iNICQ) 2013-2015
- Process changes:
  - Standardize Modified Finnegan Scoring
  - Family feedback
  - Physician interpretation of scoring
    - More emphasis on disruptive symptoms
  - Provider education on addiction science
  - Delayed treatment when co-exposure to both long acting opioids and SSRI's, tobacco, etc.
  - Full rooming-in during observation and treatment
- Outcome
  - Morphine use reduced from 46% to 27%
  - Phenobarbital adjunct use from 13% to 2%
  - LOS reduced from 16.9 to 12.3 days
  - Hospital cost reduced from $19,737 to $8755 per treated infant
  - Hospital cost reduced from $11,000 to $5300 per at-risk infant

"Improving Care for Neonatal Abstinence Syndrome"

- Patrick, SW, et.al., PEDIATRICS May 2016
- Multicenter, multistate collaborative QI
  - VON iNICQ 2012-2014
- 199 centers
- Interventions
  - QI toolkit with list of potentially better practices (PBP's)
  - Internet-based interactive educational webinars
  - Exposure to a "center of innovation"
  - Standardized data collection
  - Coaching and feedback on process improvement efforts
- Results
  - Reduced LOS from 16 to 15 days (p=0.02)
  - Reduced LOT from 21 to 19 days (p=0.02)
  - Reduced number of babies sent home on meds from 39.7% to 26.5%
  - Standardized NAS scoring reduces LOS on average by 3.3 days

Advocacy Opportunities for GPA

- Education of healthcare workers
  - "Relational Care" for encouraging self-reporting
  - Nonjudgmental/empathetic approach to interacting with parents/mothers for in-hospital care
- Non-punitive legal/DHS response
- Non-pharmacologic care
- Rooming-in with parents
  - Avoid NICU
  - Phoebe: peds with CR monitor/oximetry
    - Morphine < 0.4-0.5 mg/kg/day
- Breast-feeding
  - Poly-substance abuse contraindicated

References

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