Substance Abuse

• Substance abuse during pregnancy is a serious problem

• Intrauterine exposure to drugs may lead to neonatal intoxication or withdrawal depending on the substance, extent of exposure and timing of exposure in relation to delivery.

Incidence

• 2010 National Survey on Drug Use and Health:
  • 4.4% of pregnant women ages 15-44 years of age report using illicit drugs

• 2011 US Birthrate: 4,000,000
• ~176,000 Neonates in the US prenatally exposed to illicit drugs
Break down by age: 2010

- 15-17 yr = 16.2%
- 18-25 yr = 7.4%
- 26-44 yr = 1.9%

Comparison to Previous Studies

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996-1998</td>
<td>2.8%</td>
</tr>
<tr>
<td>2000-2001</td>
<td>3.7%</td>
</tr>
<tr>
<td>2004-2005</td>
<td>3.9%</td>
</tr>
<tr>
<td>2007-2008</td>
<td>5.1%</td>
</tr>
<tr>
<td>2008-2009</td>
<td>4.5%</td>
</tr>
<tr>
<td>2009-2010</td>
<td>4.4%</td>
</tr>
</tbody>
</table>

Infants with ICD-9 codes of neonatal withdrawal nationally

- 7,653 in 1995
- 11,937 in 2008
Exposure

- Sedatives or opiates
  - heroin
  - methadone

- Stimulants
  - cocaine
  - methamphetamine

- Psychoactive
  - Marijuana

- Hallucinogens
  - PCP

Exposure

SSRI's (Selective Serotonin Reuptake inhibitors)
- Fluoxetine (Prozac)
- Citalopram (Celexa)
- Escitalopram (Lexapro)
- Paroxetine (Paxil)
- Sertraline (Zoloft)
- Fluvoxamine (Luvox)

- Passive dependence develops in neonates exposed in utero to addictive illicit drugs.

- At delivery, discontinuation of the illicit drug from the maternal circulation can lead to a constellation of withdrawal symptoms known as the Neonatal Abstinence Syndrome (NAS) or Neonatal Drug Withdrawal.
Antenatal Risk for Infants
- Blood borne and sexually transmitted diseases (Hep B & C, HIV)
- Miscarriage
- Pregnancy induced hypertension
- Placental abruption
- Preterm rupture of membranes
- Intrauterine growth restriction

Intrapartum Risk for Infants
- Include
  - Preterm birth
  - Prolonged labor
  - Precipitous birth
  - Stillbirth
- Related to:
  - Intrauterine asphyxia
  - Neonatal hyperactivity

Postnatal Risk for Infants
- Low Apgar scores
- Respiratory distress
- Low birth weight
- Small for gestational age
- Failure to thrive
- Congenital abnormalities
- Increased risk of SIDS
Clinical Manifestations

- Newborns who withdraw from opioids present with a well recognized constellation of symptoms known as the Neonatal Abstinence Syndrome (NAS)

NAS

A generalized disorder characterized by:
1. Central nervous system hyper-irritability
2. Gastro-intestinal dysfunction
3. Respiratory distress
4. Vague autonomic symptoms

Finnegan and Weiner 1993

- Occurs in 60% of infants born to mothers of opiate addiction
- Occurs in 75% of infants born to mothers taking methadone
- Chance of withdrawal may be dose related
- Long term addiction and shorter interval between the last dose and delivery increases chance of withdrawal
**Pathophysiology of NAS withdrawal**

- Complex and not fully understood
- One theory involves cAMP (responsible for signal transduction)
- Initial activation of the opioid receptor strongly inhibits adenyl cyclase that prevents production of cAMP.
- After subsequent repeated exposure, the inhibition becomes weaker due to increased production of adenyl cyclase.
- After removal of the opioid, the inhibition of adenyl cyclase is reversed, which causes over-production of cAMP.
- The flux of cAMP is a suspect for the intense withdrawal symptoms.

**Central Nervous System**

- Decreased duration of sleep between feedings
- Frequent yawning and sneezing
- Tremors
- Irritability
- Increased wakefulness
- High pitched cry
- Increased muscle tone
- Hyperactive reflexes
- Seizures (2-11%)
- Skin excoriation due to excessive rubbing

**Gastrointestinal dysfunction**

- Poor feeding
- Poor weight gain
- Uncoordinated suck
- Constant sucking
- Vomiting
- Loose or watery stools
- Dehydration
Respiratory Distress

- Increased RR
- Nasal flaring
- Nasal stuffiness
- Sneezing

Autonomic/Metabolic

- Fever
- Increased sweating
- Mottling of the skin
- Temperature instability
- Mild elevation of BP

Frequency of symptoms of opiate withdrawal

| Percentage   | Jitteriness | Intability | Hyperactivity | Hypertonicity | Decreased sleep | Shill cry | Excessive suck | Poor feeding | Vomiting | Diarrhea | Sneezing | Tachypnea | Sweating | Fever | Seizures |
|--------------|-------------|------------|---------------|---------------|-----------------|----------|---------------|--------------|----------|----------|----------|----------|----------|--------|---------|----------|
| 75-100%      | Poor feeding| Vomiting   | Diarrhea      | Sneezing      | Tachypnea       | Sweating | Fever         | Poor feeding| Vomiting | Diarrhea | Sneezing | Tachypnea | Sweating | Fever  | Seizures |
| 25-75%       | Poor feeding| Vomiting   | Diarrhea      | Sneezing      | Tachypnea       | Sweating | Fever         | Poor feeding| Vomiting | Diarrhea | Sneezing | Tachypnea | Sweating | Fever  | Seizures |
| <25%         | Poor feeding| Vomiting   | Diarrhea      | Sneezing      | Tachypnea       | Sweating | Fever         | Poor feeding| Vomiting | Diarrhea | Sneezing | Tachypnea | Sweating | Fever  | Seizures |
| Rare         | Poor feeding| Vomiting   | Diarrhea      | Sneezing      | Tachypnea       | Sweating | Fever         | Poor feeding| Vomiting | Diarrhea | Sneezing | Tachypnea | Sweating | Fever  | Seizures |
Withdrawal associated Seizures

- Primarily myoclonic
- Responds to opiates
- Carry no increased risk of poor outcome
- Based on the depression of NE and Dopamine observed in methadone exposure in animal models
- Speculated to be attributable to lowered levels of neurotransmitters

Opioid

- Clinically important neonatal withdrawal most commonly results from intrauterine opioid exposure
- Substances with morphine-like activity
- Opiate subclass-including Morphine, codeine, Heroin, and Methadone
- Readily crosses placenta

Heroin

- Symptoms appear early (within hours) and abate relatively quickly
- 60-90% experience symptoms
  - Hypertonia 70%
  - Hyperactive moro 43%
  - Loose stools 22%
  - Excessive suck 22%
Methadone

- Opiate analgesic
- Works as a substitute for opiate drugs of abuse
- Used to prevent withdrawal symptoms in patients addicted to opiates and are enrolled in a treatment program

Methadone: Advantages

- Minimizes opioid craving
- Blocks heroin induced euphoria
- Reduces relapse
- Reduces unsafe behavior
- Promotes optimization of
  - prenatal care
  - general maternal physical health
  - mental health

Methadone: Disadvantages

- Unlikely successful detoxification after delivery
- More severe and prolonged course of NAS
Methadone
- Methadone withdrawal can occur up to 2 weeks after birth but most likely occurs within the first 96 hrs.
  - Avid tissue binding results in a more gradual and slow release of the drug, delaying the onset and prolonging the duration of withdrawal symptoms.
- Recent data has shown that co-exposure of Methadone with nicotine increases the severity and duration of neonatal withdrawal
- ~75% experience withdrawal, ~50% require tx

Studies conflict on correlation between methadone dose and withdrawal symptoms in infant (incidence likely directly related to rate of elimination in newborn)
- Recommendation to reduce methadone dose in pregnancy likely harmful to mother as volume of distribution increases during pregnancy

Buprenorphine
- Semi-synthetic opioid used to treat opioid addiction
- Similar to methadone
- Better outcomes/less relapse
- Easily tapered for detox
- Less withdrawal in newborns
- Approved for use with non-pregnant women
Stimulants

- Cocaine
- Amphetamines
- Methamphetamines

Problems Associated with Maternal Stimulant Use

- Neurobehavioral abnormalities
  - hyper-arousal
  - physiologic stress

- Compared to opiate exposed infants
  - less symptomatic
  - shorter duration

Stimulants

- Exposure to stimulants has not been clearly defined
- Many studies assessed behavior using scoring systems that were designed to evaluate opioid withdrawal
- Abnormalities may reflect drug effect rather than withdrawal (cocaine detected in neonate urine as long as 7 days after delivery)
Stimulants

- Adverse effects due to intoxication, not withdrawal
- Pronounced symptoms immediately after birth that gradually abate over several hours
- Nearly all experience symptoms
- Only small percentage require treatment

Cocaine

<table>
<thead>
<tr>
<th>Sign</th>
<th>Percent (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertonia</td>
<td>91</td>
</tr>
<tr>
<td>Hyperactive moro reflex</td>
<td>32</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>21</td>
</tr>
<tr>
<td>Loose stools</td>
<td>18</td>
</tr>
<tr>
<td>Decreased sleep</td>
<td>15</td>
</tr>
<tr>
<td>Excessive suck</td>
<td>12</td>
</tr>
<tr>
<td>Nasal stuffiness</td>
<td>6</td>
</tr>
<tr>
<td>Poor feeding</td>
<td>0</td>
</tr>
</tbody>
</table>


Cocaine

- Higher incidence of abnormal auditory brainstem responses and EEGs (Tan-Laxa 2004)
- By 19 days: heavily exposed
  - More excitable
  - Poor state regulation
- No published studies have carefully evaluated pharmacologic treatment of infants with signs attributable to prenatal cocaine exposure
**Methamphetamines**

- Overall rates are low compared to cocaine
- Rates have decreased between 2006 and 2008
- Increased risk for
  - Preterm birth
  - Placental abruption
  - Fetal distress
  - IUGR

One study: 4% of infants expose to meth treated for drug withdrawal (not able to exclude concomitant abuse of other drugs) Smith 2003

Reports of long term adverse neurotoxic effects of meth exposed infants:
- Behavior - emotional reactivity, anxious/depressed
- Cognitive skills
- Physical dexterity

Billing 1988, Cernerud 1996

**Other Drugs**

- PCP
- SSRI: Selective Serotonin Reuptake Inhibitor
PCP
- Hallucinogen
- Disturbs normal development of neural activity in fetus
- Premature birth, respiratory distress
- Withdrawal: tremor, lethargy, hypertonicity, sleep problems
- Currently no antagonist for treatment
- 1 year F/U attachment behavior abnl

SSRI
- Antidepressant
- Pronounced symptoms within 1-2 days
- Abate over several days
- 30-60% experience symptoms
- None required specific medical treatment
- No indication of long term problems

SSRI
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-pitched cry</td>
<td>18</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>21</td>
</tr>
<tr>
<td>Exaggerated Moro reflex</td>
<td>3</td>
</tr>
<tr>
<td>Tremor</td>
<td>37</td>
</tr>
<tr>
<td>Hypertonicity or myoclonus</td>
<td>14</td>
</tr>
<tr>
<td>Convulsions</td>
<td>2</td>
</tr>
<tr>
<td>Sweating</td>
<td>1</td>
</tr>
<tr>
<td>Fever</td>
<td>3</td>
</tr>
<tr>
<td>Autonomic nervous system</td>
<td>4</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>12</td>
</tr>
<tr>
<td>GI disturbance</td>
<td>34</td>
</tr>
</tbody>
</table>
**SSRI**

- Some say symptoms represent a withdrawal phenomenon, others have hypothesized that they reflect serotonergic hyperstimulation.
- Small study: short term course of chlorpromazine provided relief of symptoms (Nordeng 2001).

**SSRI Treatment**

- Infants born to mothers with untreated depression are at higher risk for adverse neonatal outcomes than those born to non-depressed mothers (Zackerman 1990, Misri 2004).

**Neonatal Drug Withdrawal**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>0-1 day</td>
<td>3-6 days</td>
<td>5-7 days</td>
<td>Mild</td>
</tr>
<tr>
<td>Heroin</td>
<td>0-3 days</td>
<td>3 days</td>
<td>2-4 weeks</td>
<td>Mild-Mod</td>
</tr>
<tr>
<td>Methadone</td>
<td>0-3 days</td>
<td>7-10 days</td>
<td>2-6 months</td>
<td>Mild-Sev</td>
</tr>
<tr>
<td>PCP</td>
<td>0-3 days</td>
<td>5-7 days</td>
<td>4-6 months</td>
<td>Mod-Sev</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>0-3 days</td>
<td>3-5 days</td>
<td>--</td>
<td>Mild-Mod</td>
</tr>
<tr>
<td>Cocaine</td>
<td>0-3 days</td>
<td>3-5 days</td>
<td>1-2 months</td>
<td>Mild-Mod</td>
</tr>
<tr>
<td>SSRI</td>
<td>0-1 days</td>
<td>1 day</td>
<td>1-2 weeks</td>
<td>Mild-Sev</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>2 days</td>
<td>3 days</td>
<td>--</td>
<td>Mild-Sev</td>
</tr>
</tbody>
</table>

- If 1 week or longer between last maternal opioid use and delivery, incidence of withdrawal is relatively low.
Specific System of Care
- Identify Infants at Risk
- Diagnose
- NAS management
- Other considerations
- Long term follow-up

Common Indications for Toxicology Testing in the Neonate
- History of drug or alcohol abuse in the past 6 years
- < 3 prenatal visits
- Maternal history of STD’s
- Unexplained IUGR or SGA
- Placental abruption
- Atypical infant behavior
- Maternal drug screen positive

Diagnosis
- Drug use in pregnancy
  - Self reported through interview
  - Identified only 40-60% of pregnant women with a positive urine test for drugs (Magura 1996)
- Testing of newborns
  - Urine drug screen – most commonly used
  - Meconium testing
  - Hair
  - Umbilical cord testing
  - Amniotic fluid-in development
Urine Drug Screen

- Sensitivity 52%
- No consent needed to obtain
- Mother should be aware of testing
- Be sensitive to the rights of the patient to privacy as well as potential for adverse effects (employment, insurance, personal relationships if confidentiality of results are lost)
- Finite amount of time after ingestion that drug can be detected in urine

UDS: Length of time results may be positive

<table>
<thead>
<tr>
<th>Substance</th>
<th>Adult</th>
<th>Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cocaine</td>
<td>24-48hr</td>
<td>2-4 days</td>
</tr>
<tr>
<td>Meth</td>
<td></td>
<td>2-4 days</td>
</tr>
<tr>
<td>Marijuana</td>
<td>7d-1mn</td>
<td>20+ days</td>
</tr>
<tr>
<td>Heroin</td>
<td>24 hr</td>
<td>2-3 days</td>
</tr>
<tr>
<td>Methadone</td>
<td>2-3 d</td>
<td>10 days</td>
</tr>
<tr>
<td>PCP</td>
<td>1-8 d</td>
<td>6-8 days</td>
</tr>
</tbody>
</table>

Meconium Testing

- Sensitivity of 88%  Specificity 94.6%
- Can identify substances mother used throughout the 3rd trimester
- Best method for detecting drug exposure during pregnancy with a specificity of 94.6%
- Limited amount of time to collect
- May take days to 2 weeks for results
Hair Analysis
- Can detect drug exposure from the last 3 months of pregnancy and up to 2 to 3 months post birth
- Method is expensive and not readily available.
- Need maternal acceptability of this method as it requires a 1.5cm hair sample of both the mother and baby
- 2 days for results after labs receives

Umbilical Cord Testing
- Results similar to meconium
- 6-8 inches of umbilical cord tissue
- Likely detection window up to 20 wks

Completing the Evaluation
- Rule out other potential causes of jitteriness and irritability
  - Hypoglycemia
  - Hypocalcemia
  - Hypomagnesemia
  - Sepsis
  - Meningitis
**Initial Lab work-up**
- CBC with diff, consider bld clx and other cultures, lytes, Ca, Mg, Glucose
- Urine tox screen or meconium tox screen
  - H/O drug or alcohol abuse in past 5 yr
  - <3 prenatal visits
  - Maternal H/O STD
  - Unexplained IUGR/SGA
  - Placental abruption
  - Atypical infant behavior
  - Maternal drug screen positive

**Initial Lab work-up**
- Confirm maternal hepatitis and HIV status and treat accordingly
  - HIV: decrease transmission by 2/3
  - Hep B: 95% prevented

**NAS Assessment**
- Finnegan
- Lipsitz
- Neonatal Narcotic Withdrawal Index
- Neonatal Withdrawal Inventory
**Modified Finnegans Neonatal Abstinence Scoring System**

- Predominant tool used in US
- More comprehensive
- Assigns cumulative score based on interval observation of 21 items

**NAS scoring**

- Scoring of an infant with proven or suspected in utero opiate/drug exposure begins at two hours of age and scoring is repeated every 3-4 hr.
- If the infant’s total score is eight or greater, the assessment should be repeated every 2 hrs until a score of seven or less is obtained over a 24 hr period.
- When a total score of seven or less is obtained, every 3-4 hrs scoring can be resumed.
**NAS scoring**
- All symptoms occurring within two or four hours are scored, so the score represents the entire scoring period, not just a single point in time
- If the infant does not require pharmacologic treatment by 72 hrs of age, scoring may be discontinued. If symptoms or questionable symptoms reoccur, NAS scoring may be reinstituted

**Principles of NAS management**
- Accurate observation and assessment (NAS scoring)
- Supportive Care
  - Environment of care (quiet, dark)
  - Therapeutic handling (swaddling)
  - Symptomatic care
- Pharmacological Intervention

**Supportive Care**
- 40% of Infants who have symptoms of drug withdrawal can be treated without medication
- Decrease Sensory Stimulation
  - Both light and sound
- Slow movement, gentle touch
  - Holding, rocking, swaddling
  - No Bouncy seats or fast rocking
**Supportive Care**

- Small frequent feeds
- Monitor weight and readjust dietary intake – may need smaller volumes with 24 cal/oz breast milk or formula  
  * May need 150-250 cal/kg/day
- Breast feeding by mothers who continue to use methadone is safe
- Skin care – frequent diaper changes, diaper dermatitis treatment

**Pharmacological Intervention**

- Initiation of drug therapy is based on clinical signs: seizures, degree of weight loss, diarrhea, fever, tachypnea.
- Initiated for NAS scoring of:  
  * 3 consecutive scores ≥8 or  
  * 3 consecutive scores averaging ≥8 or  
  * 2 consecutive score ≥12

**Drugs used to control symptoms**

- Methadone
- Morphine
- Phenobarbital
- Tincture of opium
- Paregoric
- Diazepam
- Newer  
  - Buprenorphine  
  - Clonidine
Morphine
- Oral administration
- Inhibition of bowel motility
- Low level sedation
- Effective in treating seizures
- May require large doses
- Contains alcohol
- More frequent administration (q3-4h)
- Superior to Phenobarbital in RCT

Methadone
- Synthetic opiate agonist
- Contains 8% alcohol (markedly less than paregoric)
- Long half life (26 hrs)
- Beneficial in maintaining a “steady state” and reducing “peaks and valleys”
- Retrospective studies find equivalence to Morphine
- Potential Q-T prolongation in first 2 days

Tincture of Opium
- Active ingredient is morphine
- Contains a 25 fold higher concentration of morphine than oral morphine solution
- Need diluted form
- Increased risk of drug error and overdose
- Less stable than Morphine
- 19% alcohol
Paregoric
- No longer recommended
- High concentration of alcohol (45%)
- Half life 4 hrs
- Contains variable conc. of other opioids
- Toxic additives
  - Comphor (CNS stimulant)
  - Anise oil
  - Benzoic acid

Phenobarbital
- Non-specific CNS depression
- Controls irritability and insomnia
- Little to no effect on GI symptoms
- Does not stop seizures
- Large dose required to achieve desired effects
- Toxicity/efficacy levels are quite close – need to monitor blood levels
- Contains 10-14% alcohol

Diazepam
- Safe rapid suppression of symptoms
- Interferes with sucking reflex
- Marked sedation
- Contraindicated in pt. with hyperbilirubinemia
- Contains 10% alcohol
- Elimination may continue for more than 4 weeks
- Questionable efficacy
- Because of disadvantages and lack of efficacy, diazepam should not be considered in the treatment of NAS
**Chlorpromazine**
- Decreases CNS symptoms
- Very efficacious for GI symptoms
- Contraindicated in NB with elevated bilirubin
- Prolonged excretion (reported to be as long as 18 months)
- Was used extensively in the 1970’s for treatment of NAS. However, it is rarely used today given the problems with excretion and hyperbilirubinemia

**Buprenorphine**
- Commercially available as sublingual tablets given once daily
- Half life ~20 +/- 8 hrs
- Length of treatment and LOS were significantly shorter compared to morphine vs no significant reduction
- Alcohol content 30%
- Additional studies needed

**Clonidine**
- Suspension not commercially available
- Must be prepared from crushed tablets or from epidural injection formulation
- As an adjunct therapy appears to be safe and effective (length of therapy was 27% shorter for the clonidine/DTO group
- Pharmacokinetics is limited
- No adverse effects observed
- Cessation can result in a rebound of autonomic activity
Choosing an agent

- If pharmacologic management is chosen, a drug from the same class as that causing withdrawal is preferred
  - Opioids may be more appropriate to treat NAS due to opioid exposure
  - Sedatives may be more appropriate for NAS due to non-opioid or NAS poly-drug exposure
- Recommend a single agent be used when possible

Dosing schedules

- If interested in specific dosing schedules for Morphine or Methadone please contact via email:
  - glenn_barber@ssmhc.com
  - mary_hope@ssmhc.com

Pharmacologic Treatment Caveats

- Morphine dosage typically decreased by 10-20% per day based on NAS scores
- Methadone dosage decreased not more than every other day due to long half life
- If scores are high may need to consider a "rescue dose" and then increase routine dosage
- Monitor infant off pharmaco-therapy for 48 hours before considering discharge from hospital
Other Considerations

- Consultations
  - Social Service
  - OT, PT, Nutritionist
- Discharge Readiness
  - Parent education
  - Home nursing visits
- Infant Protection issues
  - State child protective services

Follow-up

- PMD
  - PE, immunizations, anticipatory guidance
- State Child Protective Services
- Developmental
- Early Intervention

Long Term Outcome

- Developmental effects difficult to evaluate
  - Poly drug use – it is difficult to isolate the effects of any one drug
  - Confounding variables
    - Environmental
    - Dysfunctional caregivers
Long Term F/U of Methadone
- Early infancy: elevated SBP lasting for approximately 12 weeks
- Group followed by Rosen & Johnson
  - First 36 months – more abnormalities in motor and language development

Long Term F/U of Methadone
- 37-84 months – no difference in ht or wt, generally healthy
  - As the children approach school age differences between the 2 groups are diminishing
  - Trend toward lower scores in receptive Language
  - Also higher number of referral for behavioral and academic problems

Take Home Points
1. Develop a protocol for screening
2. Standardize plan for evaluation and treatment
3. Be aware of other diagnosis
4. Initial approach non-pharmacologic
5. Signs of withdrawal can be scored using published assessment tool
Take Home Points

6. Optimal threshold score for starting pharmacologic treatment is unknown
7. Breast feeding/breast milk encouraged
8. Evaluate other causes of seizures
9. Limited evidence from controlled trials supports use of Morphine and Methadone for treatment

Take Home Points

10. Growing evidence suggests that oral clonidine is also effective but further prospective trials are warranted
11. Severity of withdrawal has not been shown to be associated with differences in long term outcome
12. If known exposure, need close f/u the first week

Take Home Points

13. We still have significant gaps in knowledge concerning the optimal treatment strategy
Care for the baby with NAS

- difficult challenge
- Much yet to be learned
- As health care providers it is our responsibility to facilitate the development of comprehensive coordinated, family centered care.