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Neonatal Abstinence Syndrome: A Targeted Review for Pharmacists

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This knowledge-based activity is targeted for all pharmacists and is acceptable for .5 hour (.05 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-14-192-H01-P

Objectives

After completion of this program, the reader should be able to:

1. Explain the etiology, patient presentation and diagnosis of neonatal abstinence syndrome (NAS).
2. Describe perceived complications of NAS.
3. Describe nonpharmacologic treatment options for treating NAS.
4. List pharmacologic treatment options for opioid exposed NAS, as well as benefits and limitations for each medication.
5. Identify several ways that a pharmacist can impact the care of a patient with NAS.

Abstract

Neonatal abstinence syndrome (NAS) is a disease that impacts drug-exposed infants and describes an array of issues that arise in newborns just hours after birth. Patient presentation and disease symptomatology vary widely based upon the specific substance utilized by the mother while pregnant and duration of exposure. Treatment is dependent on which symptoms are present and, assuming an opioid-derived abstinence syndrome, is based primarily on opioid supplementation to prevent symptoms of withdrawal. Treatment of non-opioid derived abstinence syndrome is often slightly more complex and involves the use of different agents depending on the drug of exposure. Due to the intricate nature of treating NAS, a team of health care professionals, including a pharmacist, should oversee management of the disease state. Pharmacists in both the inpatient and outpatient settings are in important locations to prevent and/or positively impact the outcomes for NAS.

Disease Overview

Neonatal abstinence syndrome (NAS) is a condition that affects drug-exposed infants and encompasses a group of problems that occur in a newborn exposed to illicit or prescription drugs prior to birth.[1,2] Of those children born each year, 3 percent are exposed to illicit or prescription drugs in utero, with 55 to 94 percent of drug-exposed infants displaying symptoms at birth.[2] The disruptive symptomatology of this condition is due to the neonate becoming dependent on substances that cross the placental barrier in utero.[1] Most newborns with NAS will show signs of withdrawal 24 to 48 hours after birth; unfortunately, there is no known way to detect NAS prior to birth.[3]

Patient Presentation

Symptoms of NAS are most commonly due to *in utero* opioid exposure. However, there are a multitude of other implicated medications, including amphetamines, barbiturates, benzodiazepines, cocaine and marijuana, that could also cause NAS.[1] Drug withdrawal symptoms are dependent on various factors such as the type of drug used, the mother's ability to metabolize medications, the amount of drug used and the duration of use.[1] Such factors lead to varying severity of presentation in neonates, including neurological excitability, autonomic dysfunctions, and gastrointestinal (GI) irritability.[4] Examples of such symptoms consist of blotchy skin, diarrhea, consistent crying, fever, hyperactive reflexes, increase in muscle tone, irritability, rapid breathing, seizures, sleep issues, difficulty in weight gain, sweating, tremors and vomiting.[1] Additional signs of NAS include cyanosis, jaundice, hypothermia, electrolyte abnormalities, renal impairment and atrial septum defects.

Diagnosis

Health care providers (most often nurses) can utilize several assessment-based systems in order to determine whether the neonate is displaying withdrawal symptoms. Tools often utilized for analysis include the Finnegan NAS scoring system, a toxicology screening of bowel movements, looking for meconium, and urinalysis.[1] The Finnegan NAS scoring system is an objective evaluation of the central nervous system (CNS), metabolic, motor, respiratory and GI disturbances in children with suspected NAS, assigning numeric values. Those newborns with a score of greater than or equal to eight on two or more Finnegan NAS scoring system evaluations four hours apart should receive immediate treatment for withdrawal symptoms. Those newborns displaying a high objective measurement of GI disturbances are recommended to have a toxicology screening of bowel movements as well as a urinalysis.[5]

Complications

Complications of NAS include birth defects, premature birth, low birth weight, small head circumference, failure to thrive and sudden infant death syndrome (SIDS). Due to the wide variety in prenatal exposure to the drug, duration, and total exposure dose, long-term effects are not well characterized. Withdrawal symptoms can be controlled and resolved, but

damage resulting in birth defects will likely lead to a permanent decrease in quality of life for the child.[1,6] Specific long-term effects on quality of life include poor school performance and learning disabilities.[3] While NAS can cause long-term reduced quality of life, most neonates born with NAS can experience complete symptom resolution with pharmacological agents and will not experience long-term complications.[6]

Treatment Considerations

There are many different treatment options for NAS, and treatment selection is based upon what drug the newborn was exposed to and, as a result, the presentation of symptoms. NAS can be caused by either opioid exposure or non-opioid exposure as mentioned previously. Symptoms caused by opioid exposure fall into three main categories: neurological, gastrointestinal and autonomic.[1,2] According to a study done by Rosen and Pippenger, the most common symptoms that occur in neonates with NAS are tremor, hypertonicity and irritability, all occurring at rates of 86 percent.[7] The least common symptoms cited were diarrhea (14%) and fever (17%).[7] Specific treatment options that target each grouping of symptoms often overlap and a mixture of all three types of symptoms are seen.[8]

The first type of treatment that all NAS newborns receive (both opioid exposed and non-opioid exposed infants) is nonpharmacologic, which is the preferred intervention when possible.[9] Nonpharmacologic treatment is centered on calming the newborn, and consists of methods such as swaddling, rocking, providing minimal sensory or environmental stimulation, maintaining the newborn's temperature, maintaining a consistent feeding schedule and using breast milk if possible.[9] One caution with breast-feeding includes the fact that drugs can be passed to the newborn through breast milk. Therefore, if the mother is still using illicit or prescription drugs that are excreted in breast milk, the risks of further drug dependence outweigh the benefits of breast-feeding.[10] Additionally, due to the potential dehydration, vomiting and diarrhea that may occur with NAS, another important aspect of nonpharmacologic therapy is to maintain intravenous (IV) hydration in the neonate.[9]

Pharmacologic treatment is initiated based upon scores from the Finnegan NAS scoring system as mentioned previously. Pharmacologic treatments generally fall into two separate categories: opioids and non-opioids.[9] Opioids are the main cause of NAS; as a result, this is the area of focus for pharmacologic treatment. For opioid-exposed newborns with NAS, treatment options include opium tincture, morphine, methadone and buprenorphine (see Table 1 for administration directions).[9] While all these options are opioids themselves, they are used to wean the infant off opioids slowly while trying to minimize withdrawal symptoms. Previously, opium tincture was the agent of choice, but it has fallen out of favor as morphine has gained prominence. Currently, morphine is the most commonly used opioid treatment option given to the symptomatic newborn after birth.[9]

An alternative to morphine is methadone. Methadone is also the recommended agent by the U.S. Department of Health and Human Services to give to the mother during pregnancy to help both the mother and child. Their guidelines state that methadone maintenance should be the first-line option for opioid-dependent women during pregnancy, and that morphine should be given to opioid addicted women during pregnancy only if methadone is not available. These guidelines also state that opioid detoxification should not be ad-

Table 1. Benefits and Limitations of NAS Treatment Options.[12,13]

Medication	Benefits	Limitations
Morphine	Most studied Proven efficacy	Frequent dosing Long withdrawal period
Methadone	Less frequent dosing Approved for use in pregnancy Appear to be the safest	Difficult to wean State and federal regulations
Buprenorphine	Less frequent dosing Less respiratory depression (compared to morphine and methadone) Less abuse potential	Ceiling effect Higher failure rates (compared to morphine and methadone) Least studied
Opium tincture	Well studied Proven efficacy	Contains alcohol and alkaloids Frequent dosing

ministered to every pregnant woman due to the high risk of relapse seen when opioids are the initial drug of abuse.[10] Buprenorphine in NAS treatment is currently being researched. It is primarily used in adults to treat withdrawal symptoms, but also has potential in neonates. In a study done by Fischer and colleagues, mothers were maintained with buprenorphine during pregnancy, although neonates were treated with morphine after birth. Out of the 15 opioid-dependent pregnant women included in the study, NAS was absent in eight of the neonates, mild in four neonates, and moderate in three neonates.[10] Buprenorphine was well tolerated by both mother and fetus during pregnancy, but because there have been no large trials done with buprenorphine in neonates, it is still not recommended as a first-line treatment for NAS.[11] Figure 1 provides an example treatment algorithm of the type that may commonly be developed at an institutional

Figure 1. Example Treatment Algorithm for NAS

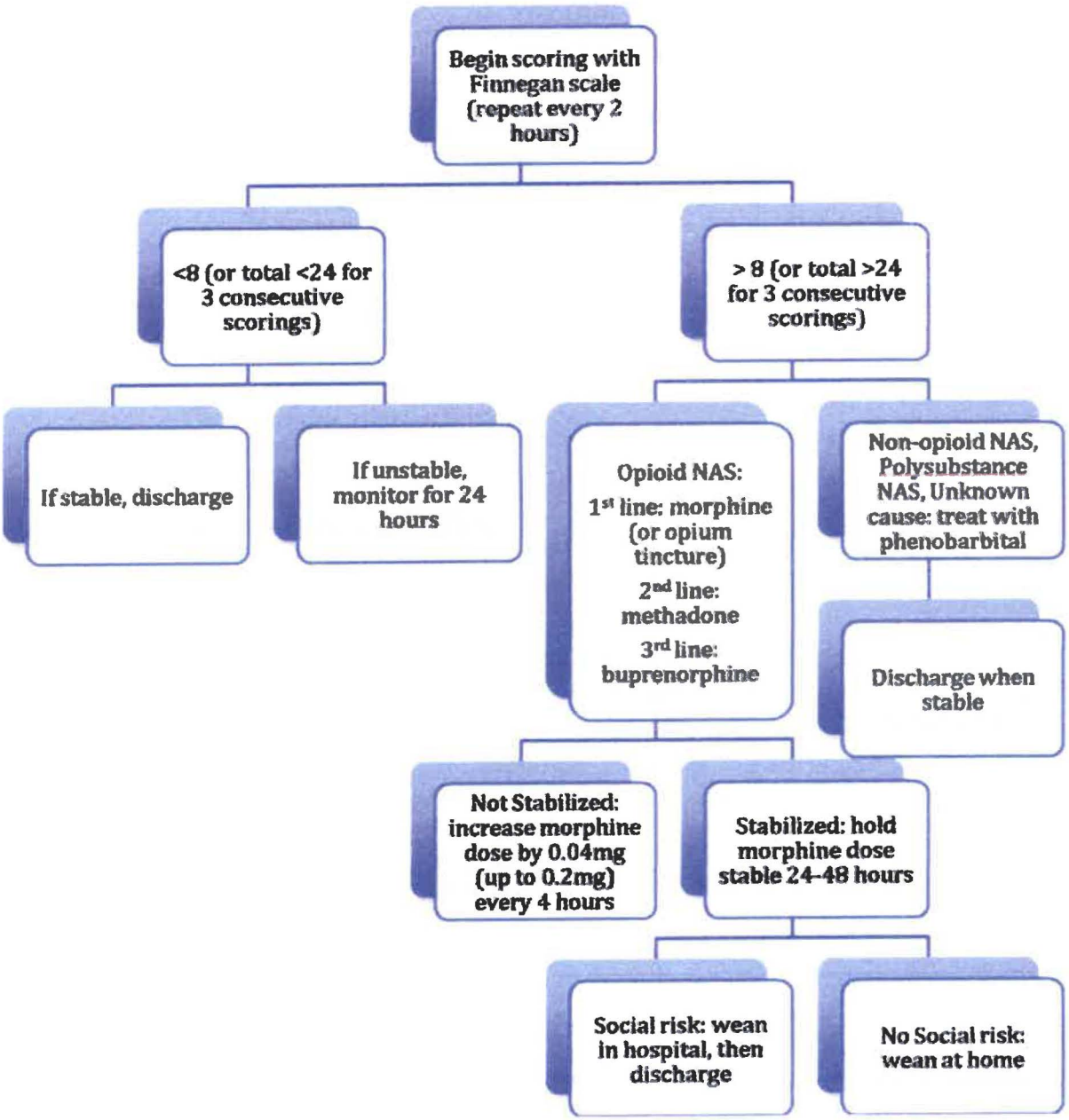

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Table 2. Common Dose, Administration, and Taper Duration for NAS Treatment Options.[4,14,15]

Medication	Dose	Route of administration	Taper duration
Morphine	0.04mg/kg/dose (max 0.2mg/kg/dose) for 2-3 days	Oral	2 to 7 days
Methadone	0.5mg/kg/day in divided doses q8h	Oral, IV	1 to 1.5 months
Buprenorphine (limited data)	5.3mcg/kg/dose q8h for 3 days	Sublingual	unspecified
Opium tincture	0.04mg/kg/dose q3-4hr for 3-5 days	Oral	2 to 4 weeks

level to treat NAS.[A,B]

The second category of pharmacologic treatment includes non-opioid treatments that are intended to provide symptomatic relief.[12] Non-opioid treatments for symptomatic relief of NAS have traditionally included two sedatives (phenobarbital or diazepam), an antiemetic (chlorpromazine) and an antihypertensive (clonidine). Phenobarbital is used to treat the hyperactive behavior that may accompany opioid withdrawal and is used preferentially over diazepam.[12] Clonidine is used to inhibit sympathetic nervous system output; therefore, it decreases the autonomic side effects seen in opioid withdrawal such as tachycardia, hypertension, restlessness, and diarrhea.[16] Chlorpromazine has been used in the past as an antiemetic if necessary; however, it has limited usefulness due to adverse reactions such as hypothermia and a decrease in the seizure threshold. It is important to avoid this decrease in seizure threshold because seizures are a common manifestation of opioid withdrawal.[17] Non-opioid treatment options should be considered for relief only if opioid withdrawal effects become too severe.

Ultimately, there are several challenges that pharmacists face when evaluating treatment options for NAS. One challenge is the lack of randomized controlled trials regarding optimal detoxification in neonates. Given that immediate treatment is required in neonates, as long as there are therapies and drug options that work, few trials will be conducted to discover if other alternatives would be superior. Another challenge in treating NAS is maternal adherence to treatment. In cases of accidental and illicit drug consumption during pregnancy, a change in maternal drug usage will most likely be seen if it is discovered that the newborn has NAS. These mothers are typically more adherent to infant treatment if the newborn has NAS. However in cases of illicit drug use where the mother does not adhere to any sort of treatment during pregnancy, the neonate may face difficulties once discharged from the hospital.[10]

Role of the Pharmacist

Neonatal abstinence syndrome is a complex disease state that impairs the quality of life of an extremely vulnerable patient population. Ultimately, the management of this disease state should be overseen by a team of health care professionals, including a pharmacist, who work together dynamically to achieve optimal patient outcomes. As a medication and pharmacology expert, the pharmacist is in a unique position to positively impact NAS patient outcomes. More specifically, the pharmacist can make recommendations regarding drug therapy choices, play a critical role in the education of both the health care providers and the affected families, aid in the development of system-wide protocol for the treatment of NAS and help to inform the public on the implications of substance abuse during pregnancy. This wide array of interventions allows the pharmacist to substantially impact patient care in both the community and inpatient setting.

The community pharmacist is in an ideal position with regard to the education of the public. Pharmacists are dispensing more opioid products now than in the past. According to the National Institute on Drug Abuse, 210 million opioid prescriptions were dispensed by community pharmacies in 2010, up from 131 million in the year 2000.[18] Along with this fact, legal substances (such as opioids) have replaced illicit substances (such as heroin or cocaine) as the most common cause of fatal drug poisoning in the United States.[19] In fact, data suggest that in 2005, oxycodone usurped all illicit drugs in the category of nonmedical abuse; the most blatant reason for this shift being ease of access.[20] One major study suggests that the rate of maternal opioid abuse increased fivefold between 2000, and 2009, while the rate of NAS diagnosis has increased threefold in the same timeframe.[21]

In an effort to prevent the circumstances that precipitate NAS, the community pharmacist should remain vigilant in the fight against opioid abuse. Pharmacists should be on the

alert for patients who consistently claim lost prescriptions, emergency department prescriptions, display opioid-seeking behavior and those who refuse and are unwilling to alter their treatment.[20] Many states have developed integrated databases that allow for tracking an individual's history with drugs that possess a high abuse potential.[22] In particular, if these behaviors are witnessed in a pregnant female, the pharmacist should take it upon himself/herself to provide a robust education to the patient about the potential implications of this behavior on the unborn child.[20] One way to ensure that counseling reaches the patient in a time-appropriate manner is to target education and counseling to individuals coming to the pharmacy to purchase prenatal vitamins.

One critical population to monitor is pregnant women with mental health issues. One study showed that over the span of one year, 45 percent of children born with NAS were born to a female parent with psychiatric illness.[23] Studies show that use of antidepressants while pregnant have not been found to damage development of the fetus, whereas noncompliance with antidepressants are linked to increased substance abuse and therefore development of NAS in the child. As pharmacists, the opportunity exists to educate patients about medication adherence and to ensure patients are taking their medications properly.[24]

In addition to prevention of the disease state in the community, the pharmacist should be involved at an institution level to develop a protocol for the treatment of NAS. Due to the diverse symptomatology associated with NAS, in addition to the lack of high quality evidence regarding treatment, it is important to establish a thorough protocol.[13] This protocol should then be referenced by physicians and pharmacists alike throughout the treatment process in order to ensure consistent treatment for each patient. By utilizing a standard protocol throughout the system, it becomes much easier to identify specific ways to improve overall levels of care to achieve improved outcomes over time. Unfortunately, this system-by-system approach to NAS protocols makes it even more difficult to come to an overall consensus on how to optimally treat the disease state.

Furthermore, once treating individual patients for NAS, the pharmacist should make it a priority to offer counseling services to the affected families.[25] Always be sure to put aside personal opinion and approach the situation as a professional. Mothers, in particular, are in critical need of education and must be informed of proper treatment and care techniques. Additionally, NAS prevention education should still be given in order to protect against NAS in future pregnancies and any issues that could present themselves during breast-feeding.[25] Due to this fact, family counseling should be a priority for pharmacists not just in the treatment of NAS but for all major pediatric conditions.

Finally, the pharmacist should be a strong resource for the health care team regarding proper pharmacologic management of NAS. As previously noted, the treatment for NAS can often be quite complex and is heavily dependent on several factors that differ in individual pregnancies. Given the current lack of high quality evidence regarding the treatment of NAS, it is critical that the pharmacist continue to be cognizant of advances in the field of neonatology and be willing and able to discuss new findings with all members of the health care team, particularly the primary prescribers. Ultimately, the pharmacist should be a critical force in providing information for the health care team as a whole.

Conclusion

NAS describes an array of issues that present in newborns soon after birth. Ultimately, symptomatology will vary widely based upon the specific substance utilized by the mother while pregnant and duration of exposure. Clinically, treatment is essentially divided based upon an opioid-derived abstinence syndrome versus a non-opioid derived abstinence syndrome. Treatment is focused on providing supplemental pharmacologic agonist effects for the source of the withdrawal. Due to the intricate nature of treating NAS, management of the disease state should be overseen by a team of health care professionals, including a pharmacist. Both clinical pharmacists in the inpatient setting and community pharmacists in the outpatient setting are in uniquely strategic locations to prevent and/or positively impact the outcomes for NAS.

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Assessment Questions

1. After birth, most newborn babies will show signs of withdrawal within
   A. 2 to 4 hours
   B. 12 to 24 hours
   C. 24 to 48 hours

2. Neonatal abstinence syndrome (NAS) is most closely related to maternal use of:
   A. Alcohol
   B. Illicit substances
   C. Prescription medications
   D. Both a and b
   E. Both b and c

3. Initial screening of NAS includes use of:
   A. Finnegan scoring system
   B. Urinalysis
   C. GI toxicology screening

4. Complications of NAS include all of the following except:
   A. Failure to thrive
   B. High birth weight
   C. Small head circumference
   D. Sudden infant death syndrome (SIDS)

5. True or False? Neonates with NAS only show symptoms from one of the three categories of symptoms: neurological, gastrointestinal, or autonomic.
   A. True
   B. False

6. Nonpharmacologic treatment options include
   A. Swaddling
   B. Maintaining a consistent temperature
   C. Giving a consistent feeding schedule
   D. All of the above

7. What is the correct first-line treatment and dose for newborns with NAS?
   A. Morphine 0.04 mg/kg/dose
   B. Morphine 0.4 mg/kg/dose
   C. Buprenorphine 5.3 mcg/kg/dose
   D. Opium tincture 0.4 mg/kg/dose

8. Which of the following is a benefit of buprenorphine for treating newborns with NAS?
   A. It is well-studied
   B. It is the drug of choice in pregnant women
   C. It has a ceiling effect
   D. It has a low abuse potential

9. Which of the following describes a major role that community pharmacists can have regarding NAS?
   A. Refusing to dispense addictive medications to pregnant women
   B. Targeting education to women purchasing prenatal vitamins
   C. Helping to promote control of mental disorders through medication compliance
   D. Two of the above
   E. All of the above

10. Which of the following describes a major role that inpatient pharmacists can have regarding NAS?
    A. Focus only on the patient when providing counseling
    B. Help to develop an institution-specific protocol for treating NAS
    C. Avoid pain control medications in pregnant women
    D. Two of the above
    E. All of the above

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UAN: 0048-0000-14-192-H01-P CEUs: .05

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Program Content:	Strongly Disagree				Strongly Agree
The program objectives were clear.	1	2	3	4	5
The program met the stated goals and objectives:					
Explain the etiology, patient presentation and diagnosis of neonatal abstinence syndrome (NAS).	1	2	3	4	5
Describe perceived complications of NAS.	1	2	3	4	5
Describe nonpharmacologic treatment options for treating NAS.	1	2	3	4	5
List pharmacologic treatment options for opioid exposed NAS, as well as benefits and limitations for each medication.	1	2	3	4	5
Identify several ways that a pharmacist can impact the care of a patient with NAS.	1	2	3	4	5
The program met your educational needs.	1	2	3	4	5
Content of the program was interesting.	1	2	3	4	5
Material presented was relevant to my practice.	1	2	3	4	5

Comments/Suggestions for future programs:

Thank you!

Answers to Assessment Questions—Please Circle Your Answer

1. **A B C**
2. **A B C D E**
3. **A B C**
4. **A B C D**
5. **A B**
6. **A B C D**
7. **A B C D**
8. **A B C D**
9. **A B C D E**
10. **A B C D E**

Any questions/comments regarding this continuing education program can be directed to Lauren Hamman, Advanced Administrative Assistant for the Office of Continuing Education (email: l-hamman@onu.edu, phone 419-772-2280).

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