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Beyond the Finnegan Scoring System: Novel Assessment and Diagnostic Techniques for the Opioid-Exposed Infant

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Abstract

Infants with in-utero opioid exposure are most commonly assessed using the Finnegan Neonatal Abstinence Scoring System (FNASS) or a modified version of that tool. Traditionally, the purpose of these tools has been to characterize the extent of withdrawal signs to guide the pharmacologic treatment for infants with neonatal opioid withdrawal syndrome (NOWS). In the past decade however, in response to some of the limitations of the FNASS tool, there has been an increasing emphasis on developing novel assessment tools not based on the FNASS in addition to the promotion of non-pharmacologic treatment options as the first line treatment for infants with opioid exposure. Additionally, several prediction tools that may be useful in determining which patients are at high or low risk for receiving pharmacologic therapy have been developed. In this review, we will evaluate the clinical utility of these novel tools and will consider new avenues for future research.

Keywords

Neonatal Abstinence Syndrome, NAS; Neonatal Opioid Withdrawal Syndrome, NOWS; Diagnostic Tools; Assessment

Introduction

In 1975, Dr. Loretta Finnegan and colleagues published the Finnegan Neonatal Abstinence Scoring System (FNASS), the same year two other assessment tools developed by Dr. Lipsitz and Dr. Ostrea were also published.[1–3] These tools described for the first time a way to characterize the signs and severity of neonatal withdrawal from in-utero opioid exposure,

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commonly called neonatal abstinence syndrome (NAS) or neonatal opioid withdrawal syndrome (NOWS). As described in detail by Dr. Kaltenbach in another article in this *Seminars* journal (CITE), the FNASS tool, while originally designed as a standardized scoring system for researchers, has been widely implemented by clinicians and nurses caring for infants at risk for opioid withdrawal to assess the gastrointestinal, neurologic, and autonomic signs of an infant experiencing withdrawal. For the better part of four decades, the FNASS tool, or a modified form of the FNASS has been the most popularly used assessment tool at hospitals around the United States.[4,5] To date, these assessments have been inextricably linked to the pharmacologic management of NAS: initiation of pharmacologic therapy is triggered by FNASS scores greater than or equal to 8 and decreases in medication doses are dependent on whether scores are below 8.

Over the past decade, there has been a growing field of research focused on developing novel assessment and diagnostic techniques to: 1). Enhance the clinical utility of assessment techniques; 2). More objectively characterize infants with NOWS; and 3). Pair assessment tools with non-pharmacologic management of NOWS. In this review, we aim to first present some of the limitations to the widely used FNASS or modified FNASS tools. We also describe techniques that have been developed over the past decade that use novel assessment and diagnostic techniques that are not based on the FNASS tool. When comparisons are available however, we will describe how these tools compare with the FNASS tool. Finally, we will present our recommendations for future areas of research and implementation of novel methods.

Limitations of the Finnegan Scoring System

Despite its broad usage, there are a number of potential limitations with the use of the FNASS tool. While the FNASS tool characterizes in detail 21 signs of neonatal opioid withdrawal, there has been little evaluation of the effectiveness in using the cutoff score of 8 described by Dr. Finnegan and colleagues in their original article to guide the pharmacologic management or weaning strategy of infants with opioid withdrawal symptoms. Currently most institutions using the FNASS have protocols that call for starting or increasing pharmacologic treatment after an infant has received three FNASS scores ≥8 or two scores ≥12.[6] A study by Zimmerman and colleagues demonstrated that infants without in utero opioid exposure rarely reached FNASS scores of 8 or greater.[7] While this finding suggests that a score of 8 may be used to diagnose neonatal opioid withdrawal and differentiate between opioid-exposed and unexposed infants, it does not provide validation for the need for pharmacologic treatment after receiving scores of 8 of more.[8] In one study that evaluated the use of a single score of 9 as a cut off to initiate pharmacologic treatment, Chisamore and colleagues found an overall higher rate of infants required pharmacologic treatment, without a significant change in the overall length of an infant's hospitalization.[9] To our knowledge, there have not been published studies looking at using a cutoff of 7 or lower to initiate pharmacologic management.

In addition, interventions based on FNASS scores can be slow to trigger an increase in treatment in an infant experiencing withdrawal symptoms. As FNASS scores are routinely obtained every 2-4 hours, an infant who is inconsolable due to withdrawal signs would need

to show those signs for more than four hours before three scores could be obtained and any pharmacologic intervention would be initiated. When one institution modified their FNASS protocol, as part of a quality improvement effort, to start pharmacologic treatment after only two scores of 8 or one score of 12 (compared with the usual three scores of 8 or two scores of 12), they found that pharmacologic treatment was initiated earlier, increasing the overall percentage of infants requiring pharmacologic therapy, without decreasing the overall length of stay for infants started on pharmacologic treatment.[10,11]

Next, while non-pharmacologic interventions for infants experiencing opioid withdrawal symptoms such as low stimulation, swaddling, and cuddling are recommended as the first line treatment options for neonatal opioid withdawal[6,12], an accurate FNASS assessment requires the infant to be stimulated and disturbed. For example, to determine if a Moro reflex is exaggerated or if an infant has tremors when disturbed, the infant must be unswaddled and stimulated to obtain an accurate score. The frequency of clinical assessments by front line staff could contribute to an infant's display of withdrawal symptoms during the scoring process.[10]

Another limitation of the FNASS is that it is a lengthy assessment, cataloging 21 signs of withdrawal, but the clinical relevance of certain symptoms is uncertain. The weighting system designed by Finnegan and colleagues in the original scoring tool attempting to classify the severity of certain clinical findings has been widely adopted without validation. For example, sneezing, frequent yawning, and nasal stuffiness are not signs specific to opioid withdrawal, and in any other clinical setting would not trigger a need to initiate pharmacologic treatment. In an evaluation of nineteen clinical elements in a modified form of the FNASS in both opioid exposed and non-opioid exposed newborns, Jones and colleagues found that the combination of three signs: an exaggerated Moro reflex, mild tremors when disturbed, and increased muscle tone, were unique to infants experiencing withdrawal.[13] In another assessment of a modified FNASS tool, Jones and colleagues found that a shortened five-item tool also discriminated well between those infants who received pharmacologic treatment and those who did not.[14] These findings suggest that it may be possible to distinguish between infants with in-utero opioid exposure who have symptoms requiring treatment with a less onerous and more specific tool.

Finally, most infants who are initiated on medication based on elevated FNASS scores are managed with protocols that call for slow, methodical medication weans. This approach has led to a national average length of stay (LOS) for infants with NAS of 19 days, even after improvement efforts to standardize care and reduce the LOS.[15–18] While this weaning process was not described initially by Finnegan and colleagues, the widely adopted protocol emphasizes weaning infants with stable FNASS scores by no more than 10% daily.[6] As a result, an infant who is initiated on pharmacotherapy will likely receive dozens of doses of pharmacologic treatment before being weaned off and prepared for discharge.

Novel Assessment Approaches

1. Eat, Sleep, and Console

In response to some of the clinical limitations of the FNASS tool, in 2014 Dr. Grossman and colleagues developed a new assessment approach at Yale-New Haven Children's Hospital focusing on the functionality of the infant.[19] Investigators aimed to develop a tool that assessed the key functions of a newborn, rather than a characterization of all withdrawal signs, focusing on the infant's ability to: 1). Eat; 2) Sleep; and 3) Be consoled. These bundled three items, termed the ESC approach (Eat, Sleep, Console) were not initially developed as a formal scoring tool, but rather as a foundation for frequent, routine clinical assessments. Specifically, infants were assessed on their ability to breastfeed successfully or eat at least 1oz per feed, their ability to sleep uninterrupted for at least 1 hour, and their ability to be consoled within 10 minutes. If any of those three conditions were not met, a multidisciplinary team huddle convened to optimize treatment options, first focused on escalating non-pharmacologic treatment interventions such as parental presence, swaddling, feeding, and cuddling. If these non-pharmacologic interventions were not successful, pharmacologic management was initiated.

One advantage of the ESC assessment is the ability to perform frequent clinical evaluations as needed based on the infant's presentation. Compared with a formalized scoring tool performed every two- to four-hours, ESC allows for the initiation of interventions quickly. An infant who was found to be inconsolable could receive interventions in as soon as 10 minutes instead of waiting for a scheduled scoring time.

Investigators at Yale initially implemented the ESC approach while continuing to obtain FNASS scores on all opioid exposed infants. Thus, they were able to compare outcomes of infants managed using the ESC compared to those same infants if they had been managed using an approach based on the FNASS. The proportion of infants treated with pharmacotherapy using the ESC approach was 12% compared to 62% who would have been treated with pharmacotherapy using the FNASS approach (those who had three consecutive scores $\geqslant 8$). The average length of stay (LOS) for the infants managed using the ESC tool was 5.9 days. If the Finnegan approach had been used, the estimated average LOS would have been 16 days. There were no adverse events or readmissions reported in this study.[20]

The ESC approach has been successfully implemented at a handful of other institutions, also with significant reductions in medication usage and LOS without reported adverse outcomes. At Boston Medical Center, Dr. Wachman and colleagues implemented an ESC approach to the management of infants with NAS along with an increased focus on non-pharmacologic interventions and a transition from morphine to methadone as first line pharmacologic intervention and noted a 35% decrease in LOS and a 54% reduction in infants treated with pharmacotherapy.[10] At UNC Children's Hospital, Dr. Blount and colleagues implemented the ESC approach along with as needed medication dosing and found a 54% reduction in LOS and a 71% reduction in the proportion of infants treated with morphine.[21]

Recently, Dr. Whalen and colleagues assessed the inter- and intra-rater reliability of the ESC assessment by developing three different objective structured clinical examinations (OSCE's) that were reviewed by 10 teams and a faculty rater who reviewed the scenario independently. All OSCE's were video recorded and reviewed to develop a kappa score, or percent agreement, in each of the three domains of the ESC tool, in addition to soothing support to console infant and calling a team huddle. Identifying inconsolability and need to call a team huddle had the highest inter-rater reliability (kappa of 0.91 and 0.93 respectively), whereas identification of sleeping problems and soothing supports had the lowest inter-rater reliability scores (kappa of 0.7 and 0.6 respectively). The authors proposed to use the findings to consider modifications to the approach where the inter-rater reliability scores were low.[22]

One limitation of the current literature describing the ESC approach is that the ESC assessment was implemented in conjunction with several other interventions as part of a bundled quality improvement project over time. As a result, in the published literature around ESC implementation, it is not possible to tease out whether the significant reductions in pharmacologic treatment are related to the novel functional assessment approach itself or influenced by the other interventions highlighted in these improvement projects. The other efforts combined with ESC at the implementation at the institutions described above include increased non-pharmacologic care for infants with NAS, promotion of alternative feeding options such as a nasogastric tubes for supplementation, transitioning from morphine to methadone as a first line pharmacologic treatment, and using medications as needed rather than a slow weaning process.[10,23]

Finally, as with the FNASS, the ESC assessment is linked to a treatment approach. The ESC was designed in settings that focus heavily on non-pharmacologic interventions as the first-line treatment and its utility in environments that are less conducive to non-pharmacologic interventions, such as care in neonatal intensive care units where parents are not able to be present at the bedside is uncertain.

2. Skin Conductance

Another novel area of investigation has been to explore the skin conductance of opioid-exposed infants, as a measure of activation of the sympathetic nervous system. Dr. Schubach and colleagues evaluated how skin conductance, defined as the number of skin conductance fluctuations per second, is associated with NAS severity.[24] They examined 12 opioid-exposed newborns who received pharmacotherapy and 12 unexposed newborns at nine points during the first six weeks of life. They found significant differences in the skin conductance of term opioid-exposed infants with NAS compared with term non-opioid exposed infants, suggesting that skin conductance could be used to assess the amount of physiologic stress infants are experiencing.

Additionally, Dr. Oji-Mmuo and colleagues looked at skin conductance in 14 infants with in-utero opioid exposure to assess sympathetic activation at 24-48 hours after birth was associated with the use of pharmacologic treatment.[25] They found that infants who received pharmacologic treatment (n=6) had higher mean skin conductance levels, measured as response to a heel stick, than those that did not receive treatment (n=8). Next, Dr. Oji-Mmuo

and colleagues investigated whether skin conductance remained elevated in infants who received pharmacologic treatment for NOWS.[26] Around the time of an infant's discharge, 12 of the initial 14 infants were evaluated again, measuring skin conductance this time as response to an auditory stimulus. They found that skin conductance was higher in the morphine treated group compared with the infants who did not receive pharmacotherapy. This method may provide an objective measure of an infant's physiologic stress prior to, during, or after receiving treatment for NOWS, but requires a potentially invasive intervention and special equipment, which limits its widespread clinical applicability.

3. Infant Pupillary Diameter

In adults, a measure of pupillary diameter is often used to assess the influence of opioids, so Dr. Heil and colleagues sought to evaluate the changes in infant pupil diameter among infants receiving pharmacologic treatment for in-utero opioid exposure and assess the feasibility of measurement to determine opioid effects in infants.[27] Heil and colleagues recruited 10 infants receiving methadone treatment for NOWS and measured the diameter of the pupil and iris at four time points up to 10 hours after dosing. They found a predictable, linear trend of increasing pupil diameter with time from methadone administration and concluded that pupillary diameter could provide an objective measure of opioid exposure. This method may provide insight into assessing the response to medication treatment for infants already receiving pharmacologic treatment for opioid withdrawal symptoms, but has yet to be applied routinely in any clinical settings to our knowledge.

4. Infant Sleep States

There have been several attempts to quantify alterations in sleep state in infants with in-utero opioid exposure and have described an increase in active sleep as compared with quiet sleep compared with non-opioid exposed infants.[28,29] O'Brien and colleagues compared sleep patterns opioid-exposed infants who required pharmacologic treatment for NAS compared to those who did not receive pharmacologic treatment and healthy term controls.[30] Compared with healthy controls, opioid-exposed newborns displayed significantly greater wakeful periods. Additionally, newborns who received pharmacologic treatment were found to have increased signs of sleep deprivation during early treatment, but findings were similar to the non-pharmacologically treated group once symptoms had stabilized. Over the past decade, routine measurement of sleep states has not become routinely integrated into clinical care. However, for institutions using the ESC method described above, measuring sleep states may offer additional quantitative data around alterations in infant sleep patterns.

Predictive Approaches

1. Clinical Prediction Tools

Predicting the severity of withdrawal symptoms by examining maternal and infant characteristics known at birth or shortly after birth has been another area of focus. Dr. Kaltenbach and colleagues performed a secondary analysis of data from a multisite randomized controlled trial of 131 infants exposed to either methadone or buprenorphine in-utero, and looked at maternal and infant factors associated with NAS severity.[31] They found that higher infant birthweight and maternal smoking predicted use of pharmacologic

treatment, whereas type and dose of maternal exposure, exposure to psychotropic medications, method of delivery, and maternal weight did not. Recently, several investigators have developed clinical prediction tools that aim to predict whether an opioid-exposed infant has a low or high risk of receiving pharmacologic therapy based on a set of known maternal and infant characteristics around the time of delivery.

First, Dr. Isemann and colleagues sought to develop a clinical prediction tool that would identify opioid-exposed infants who would go on to receive pharmacologic treatment for NAS. In a two-part retrospective study of 243 infants, they examined type of maternal substance exposure, birth outcomes, and FNASS scores at 36 hours of life.[32] The first period (n=143) was used to develop the clinical prediction tool and the second period (n=121) was used to test the utility of the tool. They looked at a three-symptom measure at 36 hours (increased muscle tone, undisturbed tremors, and excoriation) and a symptom measure plus maternal exposure. In the combination of three-symptom measure plus maternal exposure type, the tool was able to predict that infants with a score of less than or equal to 1 (only one of the three symptoms or high risk maternal exposure types) would not receive pharmacologic treatment with a 94% positive predictive value, and infants with a score greater than or equal to 5 (presence of symptoms plus high risk maternal exposure, with opioid exposure yielding one point and polysubstance exposure yielding two points) would receive pharmacologic treatment with an 86% positive predictive value. The authors conclude that the tool could be particularly useful to optimize management in infants at low risk for receiving pharmacologic treatment at 36 hours.

Next, Dr. Patrick and colleagues used administrative data from the Tennessee Medicaid Program to develop an internally validated clinical prediction tool to determine an infant's risk of receiving a diagnosis of NAS.[33] They included 215,434 maternal-infant dyads (n=109,999 in the development sample and n=105,435 in the validation sample). The final model included infant birthweight, maternal age, cigarette use, Hepatitis C status, opioid type and duration, and exposure to other prescribed maternal medications including: promethazine, fluoxetine, buproprion, sertraline, zolpidem, gabapentin, and benzodiazepines. They found that their final model had a C-index (where 0.5 is equivalent to random chance and 1.0 is perfectly predictive) of 0.76 using their validation sample.

The tools developed by Dr. Isemann and Dr. Patrick hold promise for clinicians interested in identifying patients that are likely at low risk for receiving pharmacologic treatment and potentially tailoring length of clinical observation based on the findings. Currently, the American Academy of Pediatrics recommends that infants be monitored for 4-7 days in the hospital, yet there is minimal data to support these recommendations.[12] It is possible that infants determined to be at low risk for receiving pharmacologic therapy might be safely discharged earlier than 4 days. However, the tools are linked to treatment decisions based on the FNASS or claims data for a diagnosis of NAS, which is not uniformly defined across all institutions (some require pharmacologic treatment for a diagnosis, other institutions include all opioid-exposed infants). To date, these tools have yet to be formally implemented, utilized, and evaluated prospectively in a sample of infants being clinically monitored for withdrawal symptoms, and require additional investigation before being utilized more broadly.

2. Non-invasive assessments

Another category of predictive assessment strategies has focused on the use of non-invasive testing during pregnancy and the intrapartum period including maternal and fetal testing and measuring methadone metabolites from maternal hair samples.

One of the signs in pregnant women that can be impacted by opioid exposure is an alteration in autonomic functioning.[34] Jansson and colleagues have explored how to non-invasively measure autonomic functioning, using vagal tone as a marker, in pregnant women with opioid use disorder. They found that women who exhibited vagal tone lability in response to the administration of methadone gave birth to infants who were more likely to have more severe NAS, as measured using a modified FNASS.[35] Given these findings, the same research group next studied markers of autonomic control in infants. Jansson and colleagues studied 64 infants exposed in-utero to methadone to assess the association of infant heart period and cardiac vagal tone, measured by electrocardiography, on NAS severity within 24-72 hours after birth.[36] They found that infants who had a lower cardiac vagal tone on day of life 1 were more likely to have more severe NAS signs on day of life 3.[36] To date, this measurement tool does not appear to have been implemented for any clinical assessments beyond the initial research study.

Next, a number of studies have attempted to characterize how non-invasive fetal testing parameters are impacted by maternal methadone or buprenorphine,[37,38] but to date only one study has examined the impact of fetal heart rate variability on NOWS severity. Dr. Leeman and colleagues examined 104 pregnant women during the intrapartum period and evaluated how fetal heart tracings were associated with the use of pharmacologic treatment for NOWS.[39] They found that infants who received pharmacologic treatment (n=76) had a slightly higher baseline fetal heart rate (131 v. 126) during active labor, but had no association between fetal heart rate variability or decelerations.

Finally, Dr. Himes and colleagues aimed to determine if the metabolites in maternal hair samples of pregnant women receiving methadone treatment were associated with neonatal outcomes. Twenty-nine women receiving methadone participated in the study who gave a median of 4 hair samples at different times during pregnancy. Himes and colleagues found no dose response relationship between maternal methadone dose and metabolite dose in hair samples. No association was found between the hair segment collected closest to delivery with any measure of NOWS severity including infant FNASS score at birth, time to NOWS onset, duration of NOWS, peak NOWS score, or time to peak score, as measured using the FNASS tool. In the study of fetal heart rate and maternal hair metabolites, there were no significant associations between the non-invasive measurements collected during pregnancy or around the time of delivery and the subsequent severity of NOWS.

To date, there has been limited success in identifying objective maternal measurements that may be clinically useful in determining NOWS severity. Additionally, non-invasive fetal testing and maternal hair sampling requires special equipment and may be more technically difficult to perform. One area of ongoing research includes the assessment of genetic factors that could be contributing to the wide range of NOWS symptomatology in different infants.[40–42] As DNA can be evaluated using saliva samples, there may be clinical utility in

determining specific maternal and infant genetic makeup in the future to non-invasively assess NOWS severity, although these approaches require further investigation and validation.

Research Gaps and Next Steps

The ideal assessment tool for clinicians is one that is short, relatively simple, reliable, valid, and does not require the infant to be disturbed during the evaluation. As the number of infants with in-utero opioid exposure in the United States and around the world continues to rise, additional research and quality improvement efforts to improve and refine the available assessment techniques are important. We have described several novel assessment tools and approaches that have been developed over the past decade that offer new techniques for evaluating the rising number of infants at risk for neonatal opioid withdrawal. However, apart from the ESC approach, the other approaches presented in this review have all relied on either FNASS scoring, or claims data labeling infants as having a diagnosis of NAS for validation. Given some of the limitations of the FNASS tool highlighted above, it is not certain if the findings would have been the same if a different tool or type of assessment and management technique had been utilized.

Additionally, there are a number of confounding factors that may make the assessment and management of opioid-exposed infants today very different than when the original FNASS tool was published over four decades ago. First, many infants exposed to opioids are also exposed to other substances that may cause or exacerbate withdrawal such as nicotine, SSRIs, benzodiazepines, or other illicit drugs.43 Second, recent evidence has demonstrated that intensive non-pharmacologic interventions can significantly reduce length of stay and utilization of pharmacologic therapies, and often are not controlled for in studies assessing NAS severity.[11,44,45]

Next, it is important for clinicians to be able to first accurately diagnose infants experiencing neonatal opioid withdrawal, and then identify the best management approach for each infant. Yet the two most clinically applicable assessment tools, the FNASS and the ESC approach, are both tied to treatment strategies, with the FNASS emphasizing pharmacologic treatment and the ESC prioritizing non-pharmacologic interventions before using pharmacologic treatment. It will be important for future research comparing these two methods to try to distinguish between the ideal method of assessing infants and the best management approach.

Finally, the focus of the tools presented is to either guide the in-hospital treatment or predict the likelihood of pharmacologic treatment in the hospital. The outcomes measured are usually intermediate health care utilization outcomes such as length of stay, length of pharmacologic treatment and proportion of opioid exposed infants treated pharmacologically. To date, a measure of physiologic stress that infants experience during the hospitalization is not routinely assessed, nor are the long-term outcomes related to the utilization of these tools routinely measured. For example, measures evaluating early parental-infant attachment would be informative in assessing the utility of different treatment modalities. These outcomes are more difficult to obtain, but may be of greater

long-term importance to both the infant and the family. Future studies comparing different assessment and management approaches should consider measuring objective markers of infant stress, such as skin conductance or infant cortisol levels, as well as long-term developmental, behavioral and parenting outcomes.

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Practice Points:

- The Finnegan Neonatal Abstinence Scoring System (FNASS) or a shortened version, is the most widely used assessment tool for measuring neonatal opioid withdrawal symptoms
- The FNASS tool is inextricably linked to the pharmacologic management of withdrawal symptoms, despite limited research validating widely accepted cutpoints.
- Novel assessment tools developed in the last decade have focused on optimizing clinical utility, developing prediction tools, and objective measures of withdrawal symptoms

Research Directions:

- To more accurately evaluate currently used and new assessment tools, objective measures should be established. Measures of infant physiologic stress, including skin conductance and cortisol levels may be useful, in addition to longer term infant and dyadic outcomes such as developmental outcomes and parental attachment
- Evaluation of assessment tools should control for practice variation by institution and maternal factors such as polypharmacy exposure