Systematic mixed study review of non-pharmacological management of neonatal abstinence syndrome

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ABSTRACT

Background: Neonatal abstinence syndrome is a multi-system disorder resulting from exposure to maternal addictive substance use in pregnancy. Withdrawal is characterized by neonatal tremors, feeding difficulties and sleep disruption. The aim of this systematic review is to explore the non-pharmacological management of infants at risk of neonatal abstinence syndrome following prenatal exposure.

Methods: A systematic mixed study review was conducted. A search of CINAHL, MEDLINE, AMED, PsycArticles, PsycInfo and Web of Science was performed for relevant articles published between January 2007 and June 2018. Quantitative and qualitative data were extracted, and thematic analysis undertaken. The findings were synthesized as a narrative summary.

Results: Fourteen studies were included in the review of which nine were quality improvement initiatives and five explored complementary therapies. The most common components of non-pharmacological management were consolation therapy and rooming-in of mother and baby. Implementation strategies incorporated family integrated care and practitioner training in the evaluation of neonatal withdrawal. When non-pharmacological management was applied there was a reduction in the need for pharmacotherapy and a shorter hospital stay for neonates. Potential barriers to effective management included unreliable assessment tools, judgemental practitioner attitudes and limited breastfeeding promotion.
Conclusion: Providing and optimizing non-pharmacological management for the infant at risk of neonatal abstinence syndrome improves outcomes by reducing their length of hospital stay and the need for pharmacotherapy.

Keywords: ‘neonatal abstinence syndrome’, 'non-pharmacological care', 'mixed study review’

INTRODUCTION

Neonatal abstinence syndrome (NAS) is a multisystem disorder of adverse neuro-behaviour \( ^{(1)} \). It results from the exposure of the fetus to maternal use of illicit or prescription addictive substances during pregnancy. Following the abrupt discontinuation of these compounds at birth the neonate is placed at risk of withdrawal symptoms. The severity of the withdrawal process is variable but it is characterized by tremors, feeding difficulties and inconsolability with the potential of respiratory distress, seizures and death if left untreated \( ^{(2)} \).

The documented prevalence of NAS varies significantly between institutions and the number of neonates at risk of withdrawal is difficult to predict \( ^{(3)} \). This stems from a number of factors including the hesitancy of women to self-report their illicit substance use due to its illegal nature, a fear of stigma and child custody concerns \( ^{(2)} \). Furthermore, not all exposed neonates will demonstrate signs of withdrawal leading to under diagnosis \( ^{(4)} \). Recent data, however, indicates an increasing incidence of substance use in pregnancy with the number of infants at risk of NAS estimated at 2–6/1000 per live births \( ^{(3, 5)} \).
Current guidelines recommend in-hospital observation and non-pharmacological or 
supportive management for infants at risk of NAS (6). The aim of this is to alleviate 
the severity and escalation of withdrawal symptoms in order to support the infant to 
 maintain adequate hydration, nutrition and rest. Supportive management 
incorporates consolation strategies of swaddling, non-nutritive sucking and skin-to-
skin contact; minimizing environmental stimuli from light, noise and activity, and 
breastfeeding promotion (2,7).

When non-pharmacological measures are insufficient to contain withdrawal 
severity, pharmacotherapy of an opiate and sedation medication is recommended 
(8,9). While pharmacotherapy will ease the withdrawal severity, there are 
disadvantages associated with it use. The long-term impact of medication on the 
neonate is unknown and the gradual weaning process results in a lengthy hospital 
stay. This prolonged separation of mother and infant brings the potential of disrupted 
bonding (6) and the increased period of hospitalization incurs significant health care 
costs (10).

Effective non-pharmacological care offers a clear benefit of minimizing the need for 
pharmacotherapy. Yet despite existing evidence, provision of non-pharmacological 
care is primarily based on practitioner experience or local conditions and its 
implementation within clinical practice is reported as variable (11,12). Previous 
research also suggests that the diversity of outcome measures used to evaluate 
NAS management may have impeded the synthesis of evidence and limited its 
 widespread adoption (4).

Given the increasing prevalence of substance use in pregnancy and the adverse 
impact for the neonate and family it is important to forward our understanding of non-
pharmacological management in order to optimize outcomes. The purpose of this
review is to explore the non-pharmacological management of infants at risk of neonatal abstinence syndrome following in utero exposure to addictive substances.

METHODS

A systematic mixed studies review using a convergent qualitative synthesis was conducted (13). The aim of a convergent design is to fully explore the same topic by integrating both quantitative and qualitative data. The search strategy was devised by a specialist librarian and online electronic databases CINAHL, MEDLINE, AMED, PsycArticles, PsycInfo and Web of Science were searched for peer reviewed articles available in English. An initial time span of 10 years, January 2007 to October 2017, was chosen to identify current practice, and this was updated in June 2018. The search was conducted by two independent reviewers and the search strategy used a combination of the following keywords and terms: ‘neonatal abstinence syndrome’ OR (withdrawal) (substance* or drug or opioid or opiate) AND (infant* or newborn or baby or neonat* or toddler). A manual search of reference lists of included studies was also conducted to identify any relevant studies that may have been missed.

The search strategy was intended to return a breadth of studies before applying key definitions, inclusion and exclusion criteria to the studies. For the purpose of this review key definitions were determined for NAS expression and management strategies. Infants deemed at risk of NAS and those with a diagnosis of NAS due to intrauterine exposure were included. Exposure to addictive substances included opiate substitution medication or known illicit addictive substances in pregnancy verified by toxicology or maternal report. Exposure to alcohol and infants with
iatrogenic exposure in the postnatal period were excluded. Publications were considered for inclusion if they were primary research and reported individual non-pharmacological strategies or a combination of strategies within a quality improvement initiative. Quality improvement initiatives with pharmacotherapy as an adjunct to non-pharmacological management were included. Studies with the focus on pharmacotherapy or the impact of infant feeding on NAS were excluded.

Data analysis and extraction

The search strategy returned 14 studies as relevant to the review. Data abstraction included details and frequency of the individual strategies employed, how the strategy was implemented, and the outcomes used in the evaluation process (Table 1). The frequency of each strategy was noted. Secondly, qualitative findings were read, reread and revisited as necessary to ensure representation of evidence. As a convergent qualitative synthesis, the qualitative findings were initially extracted as guided by the quantitative data categories (13). Further emergent themes were identified, and consensus reached on their inclusion through discussion between the authors. The qualitative and quantitative findings were integrated as overarching themes and sub-themes.

Quality appraisal

Due to the heterogeneity of the identified studies two quality appraisal tools were used. The quality improvement studies and three cohort studies were independently assessed for quality appraisal and risk of bias using the Quality Improvement Minimum Quality Criteria Set (14). The cohort studies were assessed as quality
improvements as they provided a package of non-pharmacological strategies in addition to their primary focus of rooming-in of the mother and infant. The remaining studies included a number of study designs and therefore these were appraised using the Mixed Methods Appraisal Tool Version 11 (15). This tool can assess studies of different research designs with previous work supporting its content validity, efficiency and reliability (16).

RESULTS

The search identified a total of 1422 citations and title screening excluded 1062. Of the 360 titles returned, abstract review excluded 251 studies. Full text screening of the remaining 109 studies excluded 95 studies, with agreement reached through discussion between authors. A total of 14 studies remained and were included in the review (Figure 1).

The included studies all originated in high resource countries including the United States of America (n=9) (17,18, 19,20,21,22,23,24,25), Canada (n=3) (26, 27,28), Austria (n=1) (29) and the United Kingdom (n=1) (30). The quality improvement and cohort studies were appraised as fair to good methodologically, with all meeting a minimum of eight of the 16 quality content domains (Table 2). The remaining five studies included an RCT (29) case series (18, 25), cohort study (22) and a phenomenology study (20). A common study limitation of these was the variability of the study populations (Table 3).

Thematic analysis revealed three main themes with sub themes. These were 1) non-pharmacological management strategies including rooming-in, consolation
therapy and complementary therapies, 2) implementation of non-pharmacological management derived from supporting family integrated care and health care professional training, 3) evaluation of NAS management including outcome measures and the use of NAS scoring systems to evaluate and guide management.

Non-pharmacological management strategies

Frequently adopted non-pharmacological strategies included consolation therapy and rooming-in of mother and baby. Optimizing consolation therapies was introduced by five quality improvement initiatives (19, 21, 23, 24, 28). All of the studies promoted environmental measures to minimize external stimuli of ambient noise and light. Parental presence was encouraged to console the infant or volunteers were used when parents were unavailable. Wachman et al. (23) and Grossman et al. (19) both emphasised consolation therapy rather than initiating pharmacotherapy when withdrawal symptoms escalated. Walsh et al. (24) and Wachman et al. (23) promoted breastfeeding but Grossman et al. (19) only supported breastfeeding if there were no medical contraindications. Walsh et al. (24) recommended low lactose formula when breastfeeding was contraindicated but noted that despite provision of support measures increasing from 37.1% to 59.4%, there was a reluctance by practitioners to give low lactose formula or expressed breastmilk to infants.

Rooming-in was the focus of 4 studies (26, 27, 28, 30) and was an integral part of all of the quality improvements. It was found to decrease the need for, and duration of, pharmacotherapy. Abrahams (26, 27) reported increased breastfeeding initiation following rooming-in and mothers were more likely to retain infant custody. When
compared with regional data Abrahams (27) noted a longer hospitalization for the rooming-in cohort but this was contradicted by Saiki et al. (30) and Newman et al. (28) who both reported a shorter length of hospital stay.

Complementary therapies of acupuncture, infant massage, vibrotactile stimulation and Reiki were less common and mainly used as part of feasibility studies. No adverse events were associated with non-insertion acupuncture and infants were considered to be less restless after sessions and for some there was a noted improvement in feeding quality (18). Laser acupuncture resulted in shorter duration of pharmacotherapy although no difference was noted in peak NAS scores (29). Infant massage sessions were described by the majority of women as a positive experience enjoyed by both themselves and their baby and were valued as an opportunity to bond (20). The infant seemed to be calmed by the massage which in turn relaxed the mother, however this was not sustained once the session ended. Despite this, mothers reported that undertaking the massage empowered them as a parent as it gave them a ‘tool’ to aid their infant’s recovery. Stochastic vibrotactile stimulation reduced neonatal activity with no adverse effects. However, the long-term safety of prolonged stimulation on the developing neonatal brain is unsubstantiated thus limiting the potential of this treatment (25). Radziewicz et al. (22) found no adverse effects during Reiki sessions and noted a slight decrease in mean NAS scores.
Implementation of non-pharmacological management

Implementing and optimizing the standard of non-pharmacological management focussed on both formal and informal care givers. This included supporting family integrated care, the use of volunteer care givers and health care professional training. In total eight studies implemented measures to support family integrated care with parents as the primary care givers. These included parental education, encouraging direct care delivery and facilitating bedside presence. Newman et al. (28) surveyed rooming-in participants regarding their educational and support needs. Participants rated ‘how well was the (rooming-in) program explained’ as mean 4.7/5, and ‘did you feel well prepared to care for your baby’ as mean 4.8/5. Whether they felt supported by practitioners was dependent on the professional discipline and ranged from mean 3.5 (nursing staff) to 4.9 (doctors). Positive verbatim comments included,

“We felt we could ask any questions and would receive the best information possible” and “I had a great experience and felt very supported”.

Negative aspects of management included lack of practitioner understanding and disparities between assessors when evaluating NAS severity,

“Nurses to have better understanding of addiction and methadone”, and “I wish nurses would’ve left us alone more- I didn’t like that they all scored different”.

MacVicar & Kelly
Non-pharmacological management of NAS
Most studies placed the focus of parental education on identifying signs of NAS and the appropriate and timely implementation of consolation strategies. Wachman et al. (24) introduced parental messaging to inform parents that continued bedside presence was expected and facilitated this by arranging local methadone dispensing and nominating additional caregivers to assist parents. Volunteer ‘cuddlers’ were appointed to console neonates when parents were unavailable. One study encouraged practitioners to partner with a substance-exposed family to deliver parental education and foster family involvement (24).

To enable practitioners to effectively implement non-pharmacological management professional training needs and behaviours focussed on improving inter-professional practices, enhancing communication, fostering a team approach and eliminating judgemental attitudes towards families. Practitioner understanding of substance use disorders and NAS was highlighted as an area for development by the majority of quality improvement studies. Asti et al. (17) established an NAS taskforce to facilitate learning and champion change while Wachman et al. (23) disseminated new practices with multidisciplinary conferences and in-person and on-line education. Three studies (21, 24, 28) targeted changing negative practitioner behaviours, attitudes and distrust towards those with a substance use disorder. This included sessions on substance use as a chronic illness, how to work with families in addiction, non-judgemental behaviours and trauma informed care. Walsh et al. (24) introduced collaborative learning sessions with in-recovery mothers sharing their personal stories.
Evaluation of NAS management

The outcomes measured to evaluate NAS severity and management effectiveness included length of hospital stay, aspects of pharmacotherapy and withdrawal presentation. NAS scoring systems were predominantly used when assessing pharmacotherapy although these were also found as a barrier to effective management.

Length of hospital stay was the most commonly recorded outcome measure in ten studies with all noting a reduction in stay. Nine studies considered the need for, and duration of, pharmacotherapy and all saw a decreased need for medications although individual studies evaluated this using differing statistical methods. NAS presentation as an outcome included the range and severity of withdrawal symptoms with Abrahams\(^{(26,27)}\) noting the only difference between cohorts was less episodes of vomiting for neonates who roomed-in.

NAS scoring systems were predominantly used when assessing pharmacotherapy although these were also found as a barrier to effective management. All studies employed an NAS scoring system to assess withdrawal severity and guide pharmacotherapy initiation and weaning. Initially all six quality improvements used Finnegan scoring system\(^{(31)}\) as their standard NAS assessment tool, however four studies found that practitioner training was required to standardize scoring and interpretation\(^{(17, 19, 21, 23)}\). Asti et al.\(^{(17)}\) required an extensive and prolonged educational program to embed the assessment guidance into clinical practice before a decrease in length of neonatal stay occurred. Grossman et al.\(^{(19)}\) decided not to use the Finnegan scoring system and developed their own approach, the ‘Eat, Sleep, Console’ assessment tool. This simplified the assessment process based on
three parameters, the infant’s ability to eat and maintain hydration, sleep pattern, and be consoled. There was a noted reduction in length of stay after its implementation. Wachman et al. (23) initially used Finnegan scoring training then adopted the ‘Eat, Sleep, Console’ assessment and shared decision making for pharmacotherapy initiation and weaning. Holmes et al. (21) conducted family interviews to explore views on NAS assessment and incorporated these into the improvement process. This highlighted that infants were being woken or removed from the parents for assessment and given points for crying when they were hungry. Implementation of ‘infant-centred scoring’, when assessment was only undertaken when infants were skin-to-skin with carer, and a policy of on-demand feeding was introduced. Physicians also practiced a standardized approach to score interpretation with less reliance on numerical value and greater emphasis on quality of feeding, weight gain, inconsolability and sleep.

DISCUSSION

This review of 14 studies exploring the non-pharmacological management of infants at risk of NAS found that the most frequently employed strategies were consolation therapies, rooming-in of mother and baby and family integrated care. Underpinning these strategies were training programs for practitioners and parents to enhance efficacy and implementation uniformity. Common barriers included practitioner judgemental attitudes and distrust that parents would not meet the responsibilities of family integrated care; reluctance to promote breastfeeding; and the unreliability in the use of existing NAS scoring tools. The main outcomes measured were pharmacotherapy and length of hospital stay. The integrated findings demonstrated
that providing or optimizing non-pharmacological management resulted in a lesser need for pharmacotherapy and shorter duration of hospitalization for neonates.

We found that quality improvement initiatives were the most popular method of implementing or improving compliance of non-pharmacological management. Quality improvement cycles offer a number of benefits when implementing change (32). Their reactive nature allows prompt identification of barriers and the process of continual reassessment allows strategies to be tailored to the specific challenges and local context. However, this can also be a limitation for transferability and replication of the quality improvement to other settings and impacts on the strength of the evidence to influence practice. It is suggested that stakeholders should exercise caution when considering the direct application of a quality improvement project to their clinical setting and a baseline needs assessment is recommended.

A number of the quality initiatives encouraged family integrated care and equipped parents to deliver consolation therapy. Involving families in shared care and decision making can reduce parental stress, facilitate family attachment and improve practitioner/parent relations (33). Valuing parents as direct care givers has been shown to positively impact on self-efficacy and promote parenting skills (34). Previous research identifies that a negative influence on maternal perceptions of self-worth is the feeling of guilt and responsibility associated with substance use in pregnancy (35). This review, however, highlighted that family integrated care was not wholly endorsed and was met with resistance by some practitioners. Several studies noted practitioner distrust of parental commitment to meet infant care needs and parents reported feeling judged by health care personnel. There is an acknowledged culture of stigmatisation towards those with a substance use disorder within the maternity
setting and this can impede the development of a collaborative relationship between practitioners and families \cite{12, 36}. The promotion and acceptance of new practices revolves around changing behaviours and attitudes. In this review it was recognized that embedding respectful care was a priority to both support and empower the families while influencing practitioner perceptions of substance use disorders.

Breastfeeding and the provision of breastmilk containing substitution medication is well-evidenced as a supportive practice which improves neonatal outcomes and increases maternal satisfaction \cite{6, 35}. In the review only three quality initiatives encouraged breastfeeding and there was suboptimal practitioner compliance to giving expressed breast milk when mothers were not present. Health care professionals need to be aware of evidence-based breastfeeding contraindications and the current safety profile of addictive substances in breastmilk to confidently and accurately advise women on breastfeeding, and to advocate on their behalf. Fundamental to the success of breastfeeding is maternal education on its specific benefits to alleviate neonatal withdrawal, support to initiate and establish lactation and the acceptance to express and discard milk after illicit substance use \cite{6}.

The most frequently reported outcomes measures were the need for pharmacotherapy and length of hospital stay. Pharmacotherapy was guided by NAS assessment tools and the review identified the poor application and subjectivity of the Finnegan scoring system as a barrier to progressing infants for discharge home. A number of the studies discontinued use of the Finnegan score and adopted a simplified system based on three parameters of eat, sleep, console. Within the
neonatal literature it has been queried whether the Finnegan score is still a suitable assessment tool given that the drug profile of intrauterine exposure has changed significantly since its development in 1975 \(^{(1,6)}\). Using the duration of hospital stay as an appropriate outcome measure for an infant at risk of NAS is also debatable. Length of stay varies significantly between centres due to factors not related to NAS, including social and maternal issues and institutional discharge policies. Outpatient and at-home weaning programs may shorten in-hospital duration but can prolong duration of pharmacotherapy \(^{(37)}\). Without a consensus on what are the predominant NAS outcomes, and how to define and assess these, comparison of research studies will remain problematic and impede our understanding and treatment of NAS.

**Strengths and Limitations**

A key strength of our review is the integration of mixed studies into a comprehensive account of current non-pharmacological management. This provides evidence on an aspect of NAS care which has long been neglected or poorly applied.

A number of limitations should be acknowledged when interpreting the study findings. The review was restricted to English language only which may have reduced the number of retrieved, and potentially relevant, studies. The heterogeneity of the sources did not allow meta-analysis of the findings and resulted in a narrative review. Some of the study populations included all neonates exposed to intrauterine addictive substances without taking account of different gestations, type and length of exposure or infant feeding method. All of these factors can influence the expression of NAS and may impact the outcomes assessed. However, this variability is representational of clinical practice and frequently information of substance
exposure is limited with the interaction between polysubstance use unknown and unpredictable.

CONCLUSIONS

Non-pharmacological management has been a neglected aspect of NAS care, and the current plethora of quality improvement initiatives and complementary therapies are timely and welcome. Whilst the quality improvements demonstrate improved outcomes the review cannot draw an overall conclusion of the applicability of individual initiatives due to the limitations noted. Quality improvements are context driven and may be uniquely tailored to their setting therefore their applicability should be considered in relation to a local needs assessment. Recommendations for clinical practice include implementation of family integrated care, targeted practitioner education program on non-judgemental attitudes and the promotion and support of breastfeeding for women with a substance use disorder. Future research should focus on defining core outcome measures for NAS assessment to allow studies to be synthesized and thus forward our understanding to enhance and improve outcomes.

References


Table 1: Characteristics of included studies of non-pharmacological management of neonatal abstinence syndrome.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Method</th>
<th>Participants</th>
<th>Intervention &amp; Implementation</th>
<th>Findings/outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrahams et al.</td>
<td>(26)</td>
<td>Canada</td>
<td>Retrospective cohort review</td>
<td>Intervention: n=32 maternal addiction service &amp; rooming-in</td>
<td>- rooming-in&lt;br&gt;- maternal education on infant care and signs of NAS</td>
<td>Intervention decreased pharmacotherapy v comparison ([RR] 0.40, 95%[CI] 0.20 to 0.78) and control ([RR] 0.39, 95%[CI] 0.20 to 0.75). Intervention group shortest length of stay. Intervention increased maternal custody of infant v control ([RR] 1.52, 95%[CI] 1.15 to 2.53) v comparison ([RR] 2.23, 95%[CI] 1.43 to 3.98).</td>
</tr>
<tr>
<td></td>
<td>(27)</td>
<td>Canada</td>
<td>Retrospective cohort review</td>
<td>Intervention: n=355 NAS infants rooming-in control: n=597 NAS infants</td>
<td>- rooming-in&lt;br&gt;- maternal education on infant care and signs of NAS</td>
<td>Intervention decreased odds of NICU admission, increased breastfeeding initiation but not sustained at discharge, no difference in NAS severity, increased maternal custody. Length of stay intervention mean 21 v control 11 days.</td>
</tr>
<tr>
<td>Asti et al.</td>
<td>(17)</td>
<td>USA</td>
<td>Quality improvement</td>
<td>Baseline n=23 Total n=92 NAS infants</td>
<td>- multidisciplinary taskforce&lt;br&gt;- standardize assessment and pharmacotherapy protocol</td>
<td>Length of stay reduced from 36 to 18 days and no readmissions for NAS within 30 days.</td>
</tr>
<tr>
<td>Filippelli et al.</td>
<td>(18)</td>
<td>USA</td>
<td>Retrospective case series</td>
<td>n=54 NAS infants with 92 sessions in total</td>
<td>Non-insertion acupuncture</td>
<td>Restless infants calmed during session. No adverse events of changed vital signs, bruising, rash. 8 infants ‘better feeding’ or increased calorific intake.</td>
</tr>
<tr>
<td>Grossman et al.</td>
<td>(19)</td>
<td>USA</td>
<td>Quality improvement</td>
<td>n=287 NAS infants</td>
<td>- optimize non-pharmacological care&lt;br&gt;- family integrated care&lt;br&gt;- standardize assessment and pharmacotherapy protocol</td>
<td>Length of stay decreased from 22.4 to 5.9 days, morphine use decreased 98% to 14% and hospital cost decreased post intervention.</td>
</tr>
<tr>
<td>Hahn et al.</td>
<td>(20)</td>
<td>USA</td>
<td>Phenomenology study with thematic analysis. n=8 mother and infant dyad.</td>
<td>Infant massage&lt;br&gt;Mother trained to perform infant massage</td>
<td>Maternal empowerment, sessions encouraged enjoyment and bonding, mother and infant experienced sessions as calm and comforting.</td>
<td></td>
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<tr>
<td>Holmes et al.</td>
<td>(21)</td>
<td>USA</td>
<td>Quality improvement</td>
<td>N=207 NAS infants</td>
<td>- optimize non-pharmacological care&lt;br&gt;- family integrated care&lt;br&gt;- rooming-in&lt;br&gt;- standardize assessment and pharmacotherapy protocol&lt;br&gt;- volunteer baby carers</td>
<td>Morphine decrease 46% to 27%, phenobarbital decreased 13% to 2%. Length of stay 16.9 days to 12.3 days and costs reduced.</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Country</td>
<td>Participants</td>
<td>Interventions</td>
<td>Outcomes</td>
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</table>
| Newman et al. | Quality improvement     | Canada  | Pre-intervention n= 24, Intervention n=21 | - parental education non-pharmacological care  
- low stimuli room  
- assessment scoring training  
- community support | Pharmacotherapy reduced 83.3% to 14.3%, length of stay reduced 25 to 8 days. Breastfeeding initiation 78% and 86% duration 2.5 months. Maternal questionnaire-n=14/21, 100% satisfaction and rooming-in rated favourably. |
| Radziewicz et al. | Pilot cohort study       | USA     | n=14 infant pharmacotherapy, n= 16 non-treated infants | Reiki sessions | No adverse events during reiki: heart rate statistically significant decrease, oxygen no change, mean NAS score no change. |
| Raith et al.  | RCT                     | Austria | Total n=28 NAS infants, Intervention n=14 / control n=14 | Laser acupuncture | Intervention shorter median duration of pharmacotherapy and reduced length of stay. |
| Saiki et al.  | Retrospective cohort study | UK     | Intervention n=18 infants, Control n=42 infants in NICU | Rooming-in | Intervention reduced pharmacotherapy 11% v 45% and reduced duration mean 7.3 v 12.7 days, shorter length of stay mean 15.9 v 19.8 days. |
| Wachman et al. | Quality improvement     | USA     | n=240 NAS infants | - optimize non-pharmacological care  
- family integrated care  
- rooming-in  
- standardize assessment and pharmacotherapy protocol  
- Eat, Sleep, Console assessment  
- cuddler programme | Total length of stay reduced mean 17.5 days v 11.6 days and pharmacotherapy reduced mean 17.4 days to 11.3 days |
| Walsh et al.  | Quality improvement     | USA     | Intervention: n=3266 NAS infants. | - optimize non-pharmacological care  
- family integrated care  
- rooming-in  
- promote breastfeeding  
- standardize assessment and pharmacotherapy protocol  
- trauma informed care | Pharmacotherapy decreased 33.8 days to 21.3 days and length of stay decreased 13.4 days to 12 days. |
| Zuzarte et al. | Prospective within subject case series | USA   | N=26 NAS infants | Stochastic vibrotactile stimulation- 1 session per infant | Fewer movements and 35% reduced activity, respiratory rate stabilised, reduced heart rate, no adverse effect on oxygen saturation or temperature |
Table 2: Appraisal of Quality Improvement studies using the Quality Improvement-Minimum Quality Criteria Set (14)

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* MacVicar & Kelly
* Non-pharmacological management of NAS
Table 3: Appraisal of studies using the Mixed Methods Appraisal Tool (15)

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<tr>
<td><strong>Screening questions</strong></td>
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<tr>
<td>Are there clear qualitative and/or quantitative research objective?</td>
<td>Y</td>
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<tr>
<td>Do the collected data allow address the research objective?</td>
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<td><strong>Qualitative</strong></td>
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<td>1.1. Are the sources of qualitative data relevant to address the research objective?</td>
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<td>1.2. Is the process for analysing qualitative data relevant to address research objective?</td>
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<td>1.3. Is appropriate consideration given to how findings relate to the context in which the data were collected?</td>
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<tr>
<td>1.4. Is appropriate consideration given to how findings relate to researchers’ influence</td>
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<td><strong>Quantitative randomized controlled (trials)</strong></td>
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<tr>
<td>2.1. Is there a clear description of the randomization/sequence generation?</td>
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<td>2.2. Is there a clear description of the allocation concealment?</td>
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<td>2.3. Are there complete outcome data (80% or above)?</td>
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<td>2.4. Is there low withdrawal/drop-out (below 20%)?</td>
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<td>Y</td>
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<td><strong>Quantitative descriptive</strong></td>
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<td>4.1. Is the sampling strategy relevant to address the quantitative research question?</td>
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<td>Y</td>
</tr>
<tr>
<td>4.2. Is the sample representative of the population understudy?</td>
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<tr>
<td>4.3. Are measurements appropriate (clear origin, validity known, standard instrument)?</td>
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<td>4.4. Is there an acceptable response rate (60% or above)?</td>
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