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Evidence Check

Substance use during pregnancy, birth and the postnatal period

An Evidence Check rapid review brokered by the Sax Institute for NSW Ministry of Health—January 2021

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This report was prepared by: Ju Lee Oei, Syeda Ishra Azim, Evelyn Lee, Stacy Blythe, Kirsten Black, Valsamma Eapen, Nicholas Lintzeris, Karleen Gribble, Hannah Dahlen, Virginia Schmied, Adrian Dunlop, Raghu Lingam, Elizabeth Elliott, Ilan Katz, Lynn Kemp, Robyn Richmond, Deborah Schofield, Sara Clews, Lynette Bown, Keryl De Haan, Melissa Jackson.

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Executive summary

Background

Substance-use issues in pregnancy (SUP) are among the most preventable causes of poor pregnancy outcomes in the world.[1] Based on the principles of Developmental Origins of Health and Disease[2], interventions and therapies to prevent and mitigate the effects of substance use in pregnancy are crucial to ameliorate the consequences of prenatal substance exposure. Preventing harm to the mother and her child, especially in the first 2000 days of life, requires interventions at many time points, as outlined in the framework for the NSW Ministry of Health's policy for keeping families safe beyond the postnatal period.[3]

Purpose of this review

This Evidence Check was commissioned by the NSW Ministry of Health to gather and summarise the latest available evidence for the intervention and treatment of substance use during pregnancy, birth and the postnatal period with reference to four specific questions. The information gathered in this review will be used to update the 2014 NSW Health Clinical Guidelines for the Management of Substance Use during Pregnancy, Birth and the Postnatal Period.

Review questions

This review aimed to address the following specific questions:

Question 1: What interventions are most effective at improving outcomes for women who use substances during pregnancy and their developing fetus during the antenatal period, birth and postnatal period up to 2 years of the child's life?

Question 2: What interventions are most effective at reducing risk of harm in breastfeeding women who use substances?

Question 3: What treatments have been shown to be effective for neonatal substance withdrawal syndromes, including withdrawal from opioids, alcohol, methamphetamines, cocaine, cannabis, benzodiazepines, gabapentinoids and tobacco?

Question 4: What interventions are most effective at preventing the resumption of tobacco smoking and other substance use within the six-month postnatal period?

Key definition

Substance use is defined as the use of alcohol and other drugs, including, but not limited to, opioids, amphetamine-type stimulants (ATS), cocaine, cannabis and inhalants, and prescription medication that can be used legally or illicitly.

Summary of methods

Eight peer-review databases and three grey literature databases were searched individually for literature relevant to each question. Publications were screened against pre-specified inclusion and exclusion criteria (Appendix 2) to determine eligibility. Publications were considered if they were derived from OECD countries and published in English between 2010 and 2020. A total of 477 publications were full-text reviewed. Of these, 470 publications were identified through the search of peer-reviewed literature and 7 were identified through the extensive grey literature search.

Level of evidence (evidence rating) that ranged from I-IV was categorised according to the NHMRC level of evidence (appendix 3, Table 18). The quality of evidence is taken from the NMRC evidence base recommendation where it is classified from excellent to poor, by evaluating evidence base, consistency, clinical impact, generalisability, and applicability (appendix 3, table 19).

From the 477 publications,136 were eligible and included in the review, of which 41 were systematic studies, 28 were randomised controlled trials (NHMRC evidence level II), 2 were non-randomised comparison studies (NHMRC evidence level III-1), 32 were comparative studies with concurrent controls (NHMRC evidence level III-2), and 33 were of level III-3 or lower (single group, pre-post or post-test only).

Key findings

Question 1: What interventions are most effective at improving outcomes for women who use substances during pregnancy and their developing fetus during the antenatal period, birth and postnatal period up to 2 years of the child's life?

A total of 51 studies were identified. Outcomes of interest were categorised as: 1. Pregnancy outcomes (28 studies), 2. Maternal outcomes (15 studies) and 3. Infant (8 studies) outcomes. Most studies between 2010 and 2020 focused on alcohol and opioid-related interventions. There were 11 interventions that examined any drug use (alcohol, opioid, cocaine or any illicit drugs were included in the studies). Pharmacotherapy with maternal buprenorphine, methadone or choline (30 studies), motivational intervention (3 studies) and other psychosocial interventions (18) were associated with

improved pregnancy, infant and maternal outcomes. No studies examined the effects of interventions on health system usage or engagement. No studies assessed specific interventions for improving outcomes after exposure to other substances such as psychostimulants, cannabis or benzodiazepines.

Question 2: What interventions are most effective at reducing risk of harm in breastfeeding women who use substances?

No studies were identified that conducted interventions to reduce the risk of harm in breastfeeding women concerning ongoing substance use on infant long-term outcomes, including neurodevelopment.

Question 3: What treatments have been shown to be effective for neonatal substance withdrawal syndromes, including withdrawal from opioids, alcohol, methamphetamines, cocaine, cannabis, benzodiazepines, gabapentinoids and tobacco?

A total of 66 studies were identified. The definition of 'effectiveness' in the treatment of neonatal withdrawal syndromes was multi-level and included prevention of pharmacotherapy, amelioration of symptoms once pharmacotherapy was commenced and the effects of pharmacotherapy on longer-term outcomes of the infants, including neurodevelopment. All studies between 2010–20 focused on opioid-related Neonatal Abstinence Syndrome (NAS). Rooming-in of the mother with the infant (7 studies), breast milk feeds and/or breastfeeding (11 studies), and other supportive measures (9 studies) reduced the need for pharmacotherapy or duration of pharmacotherapy.[4-28] The optimum type and dose of medication used for opioid-based NAS continues to lack consensus.[29] No study has examined the effects of specific medications on long-term infant outcomes, including neurodevelopment and physical health. There were no studies examining the need or effects of medication and models of care on non-opioid exposure, including methamphetamine, cannabis, cocaine, prescription medications and alcohol.

Question 4: What interventions are most effective at preventing the resumption of tobacco smoking and other substance use within the six-month postnatal period?

A total of 19 studies were identified, all of which addressed smoking cessation. There were no studies examining interventions to prevent the resumption of use of other substances, including opioids or alcohol. Key interventions that were noted to be effective included integrated care models that incorporated psychosocial modifications (behavioural change techniques, motivational interviewing, empowerment techniques), clinician-led counselling (education, telephone interviews), and home visiting by professionals.

Pharmacological interventions were few. Opioid replacement therapies such as methadone and buprenorphine decrease illicit opioid use during pregnancy and improve pregnancy outcomes. Ongoing treatment with opioid replacement therapies should be supported as a means to reduce illicit

substance use beyond the pregnancy, extrapolating from very well-established evidence in non-pregnant adult populations. Even though there are no specific studies in the postnatal population beyond six months after birth, long-term opioid agonist treatment is warranted to decrease the risk of relapse to illicit drug use.[30] There is also the potential for nicotine replacement therapies (NRT) with patches or lozenges to decrease the risk of relapse with smoking. There are no studies of pharmacological interventions to prevent use or relapse of other substances.

There is a lack of high-quality research relating to the economic evaluation of interventions for maternal substance use during pregnancy, birth and the postnatal period. A total of 18 peer-reviewed publications were identified and included in the current review. Most studies were conducted in North America (n=16), one study originated in the UK, and the other was from Germany. No Australian research was identified. Most of the studies adopted a healthcare perspective (n=12) and six studies presented results from a societal viewpoint.

The majority of interventions target opioid use and focus only on short-term inpatient outcomes of infants following in utero exposure to maternal substance use. However, as it is well-established that affected individuals face a lifetime of health, social and economic disadvantage resulting in a significant burden on the healthcare system and social services, it is important that economic evaluation of interventions assess lifetime impact for both mother and infant.[31] The Drummond checklist was used to evaluate the comprehensiveness and methodological rigour of the included studies. Among these studies, six were rated as poor, nine as average and three as good in terms of their methodology underpinning the economic evaluation. Notwithstanding the limitations, included studies suggest that interventions to reduce maternal substance use and improve quality of care for NAS may generally be cost-effective.

Conclusions

This rapid review of studies since 2010 found that women, fetuses and infants exposed to substance use during pregnancy experience short-term perinatal adverse health outcomes, with few of the longer-term adverse health and social outcomes well documented. There is no single intervention that prevents harm to this population, including prevention of death, poor mental and physical health, social and economic vulnerability, and the perpetuation of life-span and intergenerational disadvantage.

Future research must examine interventions specifically designed for women who use substances other than opioids or use multiple substances and consider longer-term outcomes beyond pregnancy and the newborn period. Furthermore, evaluation of entrenched models of care, including important assessment strategies for NAS, should be conducted to ensure mothers and their infants are provided with the best possible evidence-based care designed to optimise long-term health and safety.

Table 1—Summary of evidence and recommendations for improving outcomes for women who use substances during pregnancy and their developing fetus during the antenatal period, birth and postnatal period up to 2 years of the child's life

Intervention	Recommendation	Level of evidence	Quality of evidence
Alcohol			
Computer-delivered brief intervention	Computer-delivered brief intervention effectively reduces alcohol use at one-month follow-up and achieves better neonatal outcomes such as increased birth weight.	**II**	**Grade D: Poor**
Motivational interviewing	Motivational interviewing is effective in reducing alcohol use in pregnancy.	**I**	**Grade C: Satisfactory**
Behavioural change therapy	In pregnant women identified as consuming alcohol (self-reported, scored positive on T-ACE32, TWEAK33 or have alcohol-use disorder), psychosocial interventions appear to increase abstinence rates compared with usual care or no intervention.	**I**	**Grade B: Good**
Family treatment drug court	Family drug treatment court, which uses a multidisciplinary, therapeutic approach, is effective by linking participants to substance dependence and ancillary treatment services and providing close supervision through frequent court appearances, urinalysis, and treatment providers' reports. This has positive outcomes such as reunification, treatment retention and completion.	I	Grade B: Good
Home visits	Studies of home visiting interventions show insufficient evidence to recommend their routine use for women and infants affected by prenatal substance use issues.	I	Grade B: Good
Maternal choline supplementation	Maternal choline supplementation during pregnancy shows promising evidence in improving information processing in 6-month-old infants.	I	Grade C: Satisfactory
Residential withdrawal	Residential withdrawal may have advantages over no treatment to decrease prenatal drug exposure, extend pregnancy duration, increase infant head circumference, and decrease NAS	III	Grade C: Satisfactory

Table 1—Summary of evidence and recommendations for improving outcomes for women who use substances during pregnancy and their developing fetus during the antenatal period, birth and postnatal period up to 2 years of the child's life

Intervention	Recommendation	Level of evidence	Quality of evidence
	risk, without increasing risk of perinatal complications, including miscarriages.		
Comprehensive care models	Comprehensive care models are effective in engaging women earlier in pregnancy, decreasing multiple substance use, retaining custody and retention to care.	III	Grade C: Satisfactory
Opioids			
Buprenorphine	Buprenorphine is the preferred treatment over methadone for opioid use disorder resulting in improvements in maternal and neonatal outcomes.	I	Grade A: Very Good
Methadone	Methadone is an effective treatment for opioid use disorder to improve maternal, fetal and neonatal outcomes.	I	Grade B: Good
Buprenorphine and naloxone	Buprenorphine and naloxone work as effectively as buprenorphine alone. Use of naloxone is not supported in the studies reviewed.	I	Grade C: Satisfactory
Telemedicine	Telemedicine works similarly to in-person treatments in relapse prevention and opioid-use disorders.	III	Grade C: Satisfactory
Psychosocial dyadic interaction	Interventions that focus on mother and child interaction are recommended to reduce maternal hostility, intrusiveness and improve the quality of mother-infant interaction. They also succeed in sustaining high maternal abstinence, treatment retention, and alleviating depressive symptoms.	III	Grade C: Satisfactory
Cocaine			
Contingency management (CM)	CM has potential as an adjunct to other treatments and can help improve maternal compliance with other treatments.	I	Grade C: Satisfactory
Any drug class			

Table 1—Summary of evidence and recommendations for improving outcomes for women who use substances during pregnancy and their developing fetus during the antenatal period, birth and postnatal period up to 2 years of the child's life

Intervention	Recommendation	Level of evidence	Quality of evidence
Psychoeducation and counselling	Psychoeducation and counselling delivered as parental education and leaflets show evidence of significantly improving the mother's and the child's overall social-emotional functioning.	I	Grade B: Good

Table 2—Summary of evidence and recommendations for the management of neonatal abstinence syndrome (in utero exposure to opiods)

Intervention	Recommendation	Level of evidence	Quality of evidence
For prevention of newborn withdrawal or intoxication			
Rooming-in	Rooming-in, i.e. having the infant and mother in the same room post-birth may, if there are no other extenuating risk factors including a child-at-risk issues or health problems in either the mother or infant, significantly decrease the length of stay of both mothers and infants, improve breastfeeding, decrease the need for withdrawal medication and decrease the amount and duration of medication required for NAS.	III	Grade C: Satisfactory
Infant feeding including breastfeeding, breastmilk feeds, and other types of milk feeds, hypercaloric feeds	Breastfeeding is associated with decreased need and duration of pharmacological treatment, shorter hospital stays and decreased severity of NAS for opioid-exposed infants. No studies were identified that examined the feeding method with exposure to non-opioid drugs	III	Grade C: Satisfactory
Withdrawal assessments (Finnegan Neonatal Abstinence Severity Score [FNAS] and Eat, Sleep, Console [ESC])	Compared to FNAS, the ESC approach as first-line treatment was associated with a decreased need for pharmacotherapy and a shorter hospital stay. The FNAS is not validated for non-opioid assessment and does not provide validation for the need for pharmacological treatment.	III	Grade C: Satisfactory

Table 2—Summary of evidence and recommendations for the management of neonatal abstinence syndrome (in utero exposure to opiods)

Intervention	Recommendation	Level of evidence	Quality of evidence
	Existing findings assessing FNAS and ESC were primarily retrospective and used historical controls, which may limit generalisability to other settings.		
Interventions for treating neonatal symptoms from prenatal drug exposure			
Rooming-in	There is consistent evidence supporting rooming-in as an effective strategy for managing NAS by reducing pharmacotherapy and decreasing length of stay. There was no increase in readmission rates with rooming-in compared with those not rooming-in. Further research is needed to assess long-term effects of rooming-in for infant health and development and family bonding.	III	Grade C: Satisfactory
Feeding practice	Emerging evidence shows early initiation of high-calorie feeds may be beneficial to reduce NAS severity in opioid-exposed infants. However, study findings are limited to small numbers and include only infants exposed to methadone, so generalisation is limited.	Ib	Grade C: Satisfactory
Pharmacotherapy	Buprenorphine was associated with significantly shorter treatment lengths for NAS and severity of neonatal substance withdrawal syndromes compared with morphine. There is some evidence that methadone is superior to morphine for treatment of NAS. No high-quality study has been conducted to compare buprenorphine treatment and methadone. Future studies with larger samples should examine the effects of buprenorphine treatment for NAS on neurocognitive outcomes.	Ib	Grade C: Satisfactory
Sedatives	Phenobarbital is considered the adjunct of choice for opioid withdrawal and the preferred second agent for neonates with polysubstance exposure.	Ib	Grade C: Satisfactory

Table 2—Summary of evidence and recommendations for the management of neonatal abstinence syndrome (in utero exposure to opiods)

Intervention	Recommendation	Level of evidence	Quality of evidence
	Existing evidence found phenobarbital as an adjunct resulted in significantly shorter morphine treatment days, inpatient adjunctive therapy, and length of stay compared with clonidine. Further research with larger sample sizes is needed to confirm the findings and assess the long-term effects of adjunctive therapy on infant health and development.		
Inpatient and outpatient or home-based weaning	Outpatient weaning was associated with a shorter hospital stay and higher breastfeeding rates, but there were inconsistent findings on the duration of pharmacotherapy treatment for NAS. Further research is needed to assess weaning protocols on long-term neurodevelopment outcomes of substance-exposed infants.	IIb	Grade C: Satisfactory
Complementary therapies with acupuncture and vibrotactile stimulation	Acupuncture treatment as a complementary therapy was associated with a shorter duration of pharmacotherapy and hospital stay. Further research with larger sample sizes is needed to confirm the findings. Stochastic vibrotactile stimulation may reduce increased neonatal activity associated with NAS. Research on the long-term safety of prolonged stimulation on the developing neonatal brain is required.	Ib	Grade C: Satisfactory
Screening (toxicology)	Evidence suggests biologic specimens such as urine drug screen, hair testing and meconium drug testing of the pregnant woman or newborn can be used to test for the presence of drugs. However, maternal history taken in a neutral and non-judgmental fashion is usually more informative than toxicology screening, which is dependent on technical issues, such as the timing of maternal substance use, the timing of neonatal specimen collection and absence of false positives or negatives.	III	Grade C: Satisfactory

Table 2—Summary of evidence and recommendations for the management of neonatal abstinence syndrome (in utero exposure to opiods)

Intervention	Recommendation	Level of evidence	Quality of evidence
Quality improvement (QI) initiatives	QI initiatives were associated with a decreased need for pharmacotherapy and a shorter hospital stay. Most studies were primarily retrospective and used historical controls, which may limit generalisability to other settings.	III	Grade C: Satisfactory

Table 3: Summary of evidence and recommendations most effective at preventing the resumption of smoking

Intervention	Recommendation	Level of evidence	Quality of evidence
Psychosocial Intervention			
Motivational interviewing	Motivational interviewing shows promise in reducing the resumption of smoking.	I	Grade C: Satisfactory
Nurse-led education intervention	Nurse-led education is effective in reducing the risk of resumption of substance use. The effectiveness increases when combined with other methods such as social and peer support, motivational interviewing, leaflets and usual care.	I	Grade C: Satisfactory
Behavioural change techniques	Effective behavioural change therapies might aim to include the following components that resulted in the reduction of smoking resumption: problem-solving, information about health consequences, information about social and environmental consequences, social support, reduce negative emotions, and instruction on how to perform a behaviour.	I	Grade C: Satisfactory
Pharmacotherapy			
Nicotine replacement therapy (NRT)	NRT patches are effective when administered with behavioural therapy compared with behavioural therapy alone.	III	Grade D: Poor
Progesterone therapy	Progesterone may optimise prevention of smoking relapse. Women given progesterone had	II	Grade D: Poor

Table 3: Summary of evidence and recommendations most effective at preventing the resumption of smoking

Intervention	Recommendation	Level of evidence	Quality of evidence
	more prolonged abstinence, as measured by a negative history and urinary cotinine testing.		

Abbreviations

The following abbreviations are used in this report:

BPN	Buprenorphine
CM	Contingency Management
ESC	Eat, Sleep, Console
FASD	Fetal Alcohol Syndrome
FDA	Food and Drug Administration
FNAS	Finnegan Neonatal Abstinence Severity Score
MI	Motivational Interviewing
MMT	Methadone-maintenance therapy
NAS	Neonatal Abstinence Syndrome
NHMRC	National Health and Medical Research Council
NRT	Nicotine replacement therapy
OECD	Organisation for Economic Co-operation and Development
OMT	Opioid Maintenance Therapy
PuP	Parent under pressure program
QALY	Quality Adjusted Life Years
RCT	Randomised controlled trial
SBIRT	Screening, Brief Intervention, and Referral to Treatment
SUP	Substance use in pregnancy
SURP-P	Substance Use Risk Profile-Pregnancy
T-ACE	Tolerance, Annoyed, Cut down attempts, Eye-opener
TWEAK	Tolerance, Worried, Eye-opener, Amnesia, K/Cut down attempts

Glossary

This list has been adapted from NSW Drug & Alcohol Withdrawal Clinical Practice Guidelines, 2008.

Amphetamines
Synthetic central nervous system stimulants.

Antidepressant
One of a group of psychoactive drugs prescribed for the treatment of depressive disorders. Also used for other conditions such as panic disorder.

Benzodiazepine (BZD)
One of the sedative-hypnotic groups of drugs. Introduced as safer alternatives to barbiturates, they have a general depressant effect that increases with the dose, from sedation to hypnosis to stupor. BZDs have significant potential for dependence. These are also referred to as minor tranquillisers.

Brief intervention
A treatment strategy in which a short-structured therapy is offered (between five minutes and two hours) and typically on a single occasion. Aimed at helping a person to reduce or stop substance use.

Buprenorphine (BPN)
A partial opioid agonist drug used in the treatment of opioid withdrawal and as a maintenance treatment for opioid dependence.

Cannabis
The generic name given to the psychoactive substances found in the plant Cannabis sativa. The main active constituent is delta 9-tetrahydrocannabinol (THC).

Cocaine
A central nervous system stimulant derived from the coca plant, used non-medically to produce euphoria or wakefulness. Often sold as white translucent, crystalline flakes or powder.

Dependence
A state in which drug use has become central to a person's thoughts, emotions and activities. Stopping, or reducing the drug suddenly, can lead to physical withdrawal symptoms.

Depressant
Any substance that suppresses, inhibits or decreases some aspects of central nervous system activity. The main classes of central nervous system depressants are sedatives/hypnotics, opioids and neuroleptics.

Detoxification
Now-outmoded term for managed withdrawal from a drug of dependence, the process by which a person is withdrawn from a psychoactive substance on which they are dependent.

Heroin
Heroin is the most common illicit opioid drug of dependence. It is usually intravenously injected, but it can also be smoked.

Illicit drug
A substance obtained and used illegally for its psychoactive or physical effect.

Intoxication
The condition resulting from use of a psychoactive substance that produces behavioural and/or physical changes.

Meta-analysis
A statistical analysis that combines the results of multiple studies on the same subject, in order to determine overall trends.

Methadone
A long-acting synthetic opioid drug used in maintenance therapy for those who are dependent on opioids (prescribed in oral doses).

Methamphetamine
The most commonly used illicit stimulant, available in powder, base or crystalline (‘ice’) form.

Naloxone
An opioid receptor blocker that reverses the features of opioid intoxication. It is sometimes prescribed for the treatment of opioid overdose.

Naltrexone (NTX)
A specific opioid antagonist similar to naloxone, but more potent and long-acting.

Opiate
One of a group of substances derived from the opium poppy with the ability to induce analgesia, euphoria and, in higher doses, stupor, coma, and respiratory depression.

This term excludes synthetic opioids.

Opioids
The generic term applied to alkaloids from the opium poppy, their synthetic analogues, and similar compounds synthesised within the body.

Overdose
The use of any drugs in such an amount that acute adverse physical or mental effects are produced. A dose that exceeds the individual’s tolerance. Overdose may produce transient or lasting effects, or death.

Pharmacotherapy
The use of prescribed medication to assist in the treatment of dependence. Pharmacotherapies for drug dependence include methadone or buprenorphine as a treatment for heroin dependence and nicotine replacement therapy as a treatment for tobacco dependence.

Polysubstance use
Where a person uses more than one substance, often at the same time or following one another, and usually with the intention of enhancing, potentiating, or counteracting the effects of another substance.

Psychoactive substance
A substance that, when ingested, affects mental processes.

Psychostimulants
A class of drug with stimulatory effects on the central nervous system. The psychostimulants most commonly used illicitly in Australia today are amphetamines, ecstasy and cocaine.

Psychotropic
In the most general sense, a term with the same meaning as “psychoactive” (i.e. affecting the mind or mental processes).

Rehabilitation
The process by which a person recovers from a substance-use disorder to achieve an optimal state of health, psychological functioning and well-being.

Relapse
A return to substance use after a period of abstinence.

Sedative/hypnotic
Any of a group of central nervous system depressants that can relieve anxiety and induce calmness and sleep.

Stimulant
Any agent that activates, enhances, or increases neural activity of the central nervous system. Stimulants include amphetamines, cocaine, caffeine and nicotine.

Substance-use dependence
Defined by the Diagnostic & Statistical Manual of Mental Disorders 5th ed (DSM-5) according to the following criteria: A problematic pattern of substance use, leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring at any time in the same 12–month period:

- Tolerance, as defined by either of the following:
    a. a need for markedly increased amounts of the substance to achieve intoxication or desired effect
    b. a markedly diminished effect with continued use of the same amount of the substance.
- Withdrawal, as manifested by either of the following:
    a. the characteristic withdrawal syndrome for the substance
    b. the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.
- The substance is often taken in larger amounts or over a longer period than was intended
- There is a persistent desire or unsuccessful efforts to cut down or control substance use
- A great deal of time is spent in activities necessary to obtain the substance (e.g. visiting multiple doctors), use the substance (e.g. chain smoking), or recover from its effects
- Craving or a strong desire or urge to use the substance

- Recurrent substance use resulting in a failure to fulfil major role obligations at work, school, or home
- Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance use
- Important social, occupational or recreational activities are given up or reduced because of substance use
- Recurrent substance use in situations in which it is physically hazardous
- Substance use is continued, despite knowledge of having a persistent or recurrent physical or physiological problem that is likely to have been caused or exacerbated by the substance.

Tolerance
A decrease in response to a drug dose that occurs with continued use. Increased doses of the drug are required to achieve the effect originally produced by lower doses.

Withdrawal syndrome
A series of symptoms that develop within hours to a few days following cessation or reduction in use of a drug by an individual with a substance use disorder.

Background

An increasing number of pregnant women and new mothers have substance-use issues.[34] Efforts to address the consequences of substance dependency and addiction are exacerbated by the current COVID-19 pandemic, which has fuelled an increase in substance use, overdoses and deaths in some countries.[35] The exact impact of COVID-19 on Australian women of reproductive age is as yet uncertain[36], but in a 2019 pre-COVID survey of 1445 Australians over 18 years old, the Australian Bureau of Statistics found that 1 in 5 women reported a recent increase in alcohol consumption, compared to 1 in 10 men, citing psychological, economic and other stressors.[37]

If pregnant, substances used by a woman harm not only herself but also her unborn fetus. Substances used by women during pregnancy cross the placental barrier to the fetus, potentially resulting in several adverse outcomes, including teratogenic abnormalities and neonatal withdrawal (Neonatal Abstinence Syndrome (NAS)). Drug and alcohol exposure during pregnancy is the most common preventable cause of child harm, including developmental and cognitive delay, in the world.[38]

Data collected by the National Drug Strategy Household Survey[37], which surveys more than 22,000 Australians over 14 years old and has been conducted every two to three years since 1985, estimates that at least 1 in 4 women continue to drink alcohol after pregnancy, 1 in 9 (11%) smoked, 2.3% used an illicit substance and 1.6% used prescription medications in non-medical ways. Overall, at least 1 in 2 pregnant women (150,000 women a year) report using legal (e.g. alcohol, prescription medications, nicotine) or illegal (e.g. cannabis, heroin, methamphetamines, cocaine, inhalants) substances during pregnancy.[37]

The impact of substances of dependency is not restricted to the direct effects of the drugs. Substance dependency affects all key dimensions of human development and is a problem of global importance. There are many national and international calls for action to increase research, therapeutic strategies and interventions to improve the outcomes of women and children affected by substance use in pregnancy. The US Congress, for example, enacted the NAS Best Practice Act (HR 5927) in 2017 to "*expand, intensify and coordinate research and other activities of the National Institute of Health concerning prenatal opioid exposure and NAS*".[39] The Canadian Centre on Substance Use presented a call to action in 2013 to include wider distribution and understanding of research among care providers and clients, a multidisciplinary approach to treatment, health promotion and prevention, and increased efforts to reduce stigma and discrimination faced by mothers and their families.[40] Australia enacted the first National Drug Strategy in 1985 to prevent harm to Australians from substance-use issues, prioritising young people and families.[41] Recently, the Australian government released the National Fetal Alcohol Spectrum Disorder (FASD) Strategic Action Plan 2018–2028 and a Senate Inquiry is currently underway into effective approaches to prevention, diagnosis and support for Fetal Alcohol Spectrum Disorder.[42]

This review will focus on the following questions:

Question 1: Outcomes to 2 years after the birth

What interventions are most effective at improving outcomes for women who use substances during pregnancy and their developing fetus during the antenatal period, birth and postnatal period up to 2 years of the child's life?

Question 2: Breastfeeding

What interventions are most effective at reducing the risk of harm in breastfeeding women who use substances?

Question 3: Neonatal Abstinence Syndrome

What treatments have been shown to be effective for neonatal substance withdrawal syndromes, including withdrawal from opioids, alcohol, methamphetamines, cocaine, cannabis, benzodiazepines, gabapentinoids and tobacco?

Question 4: Relapse of drug use within 6 months after birth

What interventions are most effective at preventing the resumption of smoking and other substance use within the six-month postnatal period?

Methods

In response to the proposal for the research team, the following method was agreed upon by the researchers and the NSW Ministry of Health. The method followed a systematic review process that was streamlined to allow an expedited review of the evidence related to the review questions. This 'rapid review' method seeks to maintain the rigour of a systematic review, while producing information in a timely manner that is relevant for evidence-informed health policy and practice.[43]

Peer-review literature

Overall summary

The research team selected keywords for the review questions searches in consultation with the Ministry of Health. Eight databases were searched, including Cochrane, Medline and PsycINFO, for each of the three two-part review questions using those keywords for each of the searches. These keywords were also matched to database subject headings where possible. Articles were included if they were from OECD (Organisation for Economic Co-operation and Development) countries, in English and published between 2010 and 2020. As the focus of the review was to report effective interventions that improve outcomes, descriptive studies, protocols and publications that did not assess interventions were excluded.

Method of data extraction and assessment of the quality of evidence

The search yielded 41 systematic reviews and 95 primary studies. Review papers were narratively synthesised for overarching findings related to the research questions. Reference lists were checked for eligible studies to be included in the review (included within the PRISMA diagrams as 'records identified through other sources'). A table was then generated for each research question with included papers after screening, presenting the intervention, results and interpretation of all papers featuring primary studies, and which can be found in tables 4–17 in Appendix 1.

The included studies' quality was assessed using the National Health and Medical Research Council (NHMRC) Levels of Evidence.[44] Studies were categorised according to six levels of evidence. Systematic reviews of randomised controlled trials are considered the highest levels of evidence, followed by randomised controlled trials (RCT), pseudo-randomised controlled trials, comparative studies with concurrent controls, comparative studies without concurrent controls, and lastly, case series studies. A matrix was then used to summarise the quality of the evidence base for each research question. Two researchers categorised the first five studies for each of the research questions. Where categorisation differed, the consensus was obtained through discussion, and a categorisation framework developed. One researcher then categorised the remaining studies.

Grey literature

An internet-based search was undertaken of organisational and government content originating from Australia. Google searches were undertaken using keywords from the three review questions and the suffixes '.org.au' and '.gov.au'. The first 30 resulting sites were scanned for information relevant to the three review questions. Peer-reviewed papers identified through this search were added to the papers identified through database searching and are reported alongside these. Other grey literature (e.g. websites, reports) were narratively synthesised and reported upon separately. We found seven manuscripts from the grey literature, which were included in the review.

Evidence grading

A flowchart of the literature selection process is included in Appendix 2. Figures 1 to 4 depict the selection number for questions 1 to 4, respectively.

Question 1: What interventions are most effective at improving outcomes for women who use substances during pregnancy and their developing fetus during the antenatal period, birth and postnatal period up to 2 years of the child's life?

Out of 120 full-text reviews, 51 met the criteria for inclusion for the review. Of these, 23 were level I reviews (i.e. systematic reviews), 9 were randomised control trials, 1 was a pseudo-randomised controlled trial, and 19 were level III or lower evidence studies. The overall level of evidence was graded at NHMRC evidence grade B. A summary table of the included studies is attached as Appendix 1, Tables 4–9. There were 28 studies identified for pregnancy outcomes (Tables 4–5), 15 for maternal outcomes (Tables 6–7) and 10 for infant outcomes (Tables 8–9). There were 28 studies of interventions for opioid use, 2 for cocaine, 12 for alcohol, and 11 on "*any substance*" use. There were no studies of interventions considering cannabis or amphetamine use. Clinical practice guidelines, as well as two studies on alcohol use and three studies on interventions regarding opioid use from grey literature, were included.

Question 2: What interventions are most effective at reducing risk of harm in breastfeeding women who use substances?

A total of 104 full-text articles were reviewed, but none met the criteria for inclusion. There was also no relevant grey literature.

Question 3: What treatments have been shown to be effective for neonatal substance withdrawal syndromes, including withdrawal from opioids, alcohol, methamphetamines, cocaine, cannabis, benzodiazepines, gabapentinoids and tobacco?

Out of 211 full-text reviews, 66 met the criteria for inclusion. Of these, 13 were level I reviews (i.e. systematic reviews), 9 were RCTs, and 44 were level II or lower evidence studies. The overall level of evidence was graded at NHMRC evidence grade B. A summary table of the included studies is attached in Appendix 1 (Tables 12–13). All studies focused on opioid-related NAS. There were no studies found for NAS due to maternal alcohol, methamphetamine, cocaine, cannabis, benzodiazepine, gabapentinoid, or tobacco use during pregnancy.

Question 4: What interventions are most effective at preventing the resumption of smoking and other substance use within the six-month postnatal period?

Out of 54 full-text reviews,19 were eligible for inclusion. Five were level I systematic reviews and 17 were level II RCTs. A summary table of the included studies is attached in Appendix 1 (Tables 15-16). No eligible studies from the grey literature were identified.

All 19 studies examined interventions for preventing smoking resumption within the specified period. There were no studies regarding interventions to prevent any other substance resumption, including opiates, amphetamines, cocaine, alcohol or cannabis within six months of birth.

Methodological assessment of economic studies

The search strategy returned 1,472 studies. After review of the abstracts, 765 studies were excluded because they did not include an economic evaluation, or were a cost description, commentary or editorial. Of the remaining studies, 18 were eligible for the review. The Drummond 10-point checklist was used in the critical appraisal of the 18 economic studies.[45] For this review, each item was given a possible score of 1 with aggregated results categorised into studies that reflected from an economic appraisal viewpoint, poor quality (scores ranging from 1–3), average quality (scores ranging from 4–7) and good quality (scores ranging from 8–10). This approach has been used in other reviews.[46] Among the 18 studies included in this review, six were rated as poor, nine as average and three as good in terms of their methodology underpinning the economic evaluation. The summary of key characteristics of economic evaluations of interventions included in this review can be found in Appendix 1 (Tables 10, 11, 14 and 17 for question 1 to question 4, respectively).

Findings

Question 1

What interventions are most effective at improving outcomes for women who use substances during pregnancy and their developing fetus during the antenatal period, birth and postnatal period up to 2 years of the child's life?

A total of 23 systematic reviews and 28 primary studies were included in the review of this question.

"*Improving outcomes*" were considered in two timeframes:

1. Outcomes during pregnancy and up to birth.
2. From birth up to 2 years for both the mother and the infant

The outcomes assessed were:

1. Cessation or moderation of substance use
2. Improvement of pregnancy outcomes, including decreasing risk of prematurity (birth before 37 weeks gestation) and low birth weight (infant birth weight below 10th percentile of weight for the population), unexplained fetal death in-utero (stillbirth) and pregnancy-related complications such as antepartum haemorrhage, pre-eclampsia, infection and perinatal hypoxia
3. Infant remaining in maternal care
4. Improvement of maternal health to 2 years postpartum
5. Improving childhood outcomes, including neurocognitive performance and reduction in substantiated child maltreatment up to 2 years of age
6. An economic evaluation of interventions

A. Improvement in pregnancy outcomes in known substance-using mothers

Systematic reviews

A total of 10 systematic reviews explored interventions designed to improve pregnancy and birth outcomes by assisting mothers to cease or moderate substance use, including alcohol, opioids, and any substance that was identified in peer-reviewed literature. There were no systematic reviews that specifically addressed outcomes related to cannabis, amphetamine, cocaine or nicotine use. The summary of the interventions is given below.

1. Alcohol

A scoping review by DeVido et al.[47] summarised evidence behind pharmacological management of alcohol-use disorder and alcohol withdrawal in pregnant women. Screening methods included validated questionnaires that were specifically formulated for pregnant women such as Tolerance, Worried, Eye-opener, Amnesia, K/Cut down attempts (TWEAK)[33], Tolerance, Annoyed, Cut down attempts, Eye-opener (T-ACE) and its revision, the T-ACER3[48], and Substance Use Risk Profile-Pregnancy (SURP-P).[49] TWEAK has been shown to be effective in detecting at-risk drinking in pregnant women[50], T-ACER3 is more effective than T-ACE to identify women whose children had fetal alcohol syndrome.[51] SURP-P can detect a range of substances that may be used besides alcohol.[49]

The review also discussed the effectiveness of three Food and Drug Administration (FDA) approved drugs to treat alcohol-use disorders: naltrexone, disulfiram and acamprosate. Naltrexone, a mu-opioid antagonist, has been shown to reduce the risk of heavy drinking by 83% and drinking days by 4% compared to a placebo. However, none of the studies examined the safety of naltrexone in pregnancy. Disulfiram has a strong deterrent effect (with aversive physical symptoms if alcohol is consumed while taking disulfiram) and reduces the number of drinking days. Acamprosate reduces cravings and heavy drinking days in adults[52] but has not been assessed in clinical trials in pregnancy. Behavioural interventions were also reported, including motivational enhancement therapy, brief interventions, and cognitive behavioural therapies. These are encouraged to supplement routine antenatal care,[53] but there is no evidence to support benefit from any intervention over another.[47]

2. Any substances

Two systematic reviews summarised psychosocial and pharmacological interventions to reduce any substance use during pregnancy. Terplan et al. reported that psychosocial interventions such as counselling, motivational interviewing and case management are effective strategies to reduce alcohol dependency and increase engagement with services. These also decreased the risk of low birth weight, neonatal intensive care unit admissions, and child maltreatment risk. Assessment of pharmacological interventions' effectiveness suggested minimal evidence for the impact of benzodiazepines on alcohol withdrawal and robust evidence that methadone and buprenorphine were effective for treating symptoms secondary to opioid withdrawal.[54] Louw et al.[55] reviewed the effectiveness of CM and motivational interviewing-based (MI) interventions with comprehensive care options (pharmacological treatment such as methadone maintenance, counselling, prenatal care, sexually transmitted disease counselling and testing, transportation, and/or childcare). CM decreased infant length of hospitalisation, but neither CM nor MI improved other outcomes, including rates of pre-term births or maternal overdose beyond other comprehensive care alternatives.

3. Opioids

Four systematic reviews examined the effectiveness of buprenorphine and naloxone, buprenorphine alone, and methadone treatment on pregnancy outcomes. Lund et al.[56] summarised seven studies and found no difference in the need for treatment for NAS, days of infant hospital stay, infant birth outcomes (head circumference, birth weight, pre-term, gestational age, APGAR score) and maternal days of hospitalisation. Klaman et al.[57] and Wilder et al. concluded that women with opioid-use issues could be treated ‘safely’ with methadone or buprenorphine during pregnancy.[56-58] On the other hand, NAS severity and the proportion of infants requiring pharmacological treatment for NAS were highest for infants exposed to methadone, followed by those exposed to buprenorphine and lowest in those exposed to a combination of buprenorphine and naloxone.[59,60]

Primary studies

A total of 18 primary studies were identified in the peer-reviewed literature that explored interventions designed to improve pregnancy and birth outcomes by assisting mothers to cease or moderate alcohol and use of other substances in pregnancy. The summary of the interventions is given below:

1. Alcohol

There were a few primary interventions designed to mitigate the effects of alcohol on pregnancy outcomes.[53] Population screening is extremely important in reducing harm from alcohol use during pregnancy. Still, lack of clinician confidence in the ability to use alcohol and drug screening questionnaires, provide brief interventions, and a lack of belief in interventions' effectiveness were major barriers to use.[61] When considering interventions in women already identified as high-risk drinkers, a phase 1 randomised controlled trial reported promising outcomes for 50 pregnant known risky drinkers who were randomly assigned to either a computer-delivered brief intervention using the T-ACE questionnaire[32] with four items, compared with usual care. Women in both groups self-reported reduced alcohol use at follow-up but mean birth weights of the computer intervention group were significantly higher ($p<0.05$, $d=0.62$).[62]

2. Any substances

Three main modes of intervention were identified as primary interventions for mitigating any substance-use impact on pregnancy outcomes.

2.1 Residential detoxification

A Norwegian comparative retrospective cohort study with concurrent controls by Haabrekke et al. examined women's outcomes when they were detoxified before birth in a residential setting compared to those without access to this treatment. Residential detoxification decreased prenatal drug exposure, extended pregnancy duration, increased infant head circumference and decreased risk of NAS without an increased risk of perinatal complications, including miscarriages.[63] The weakness is the long-time gap (almost a decade) between the control and comparison cohort. The control cohort consisted of children born between 1991–96, while the treatment cohort consisted of infants born between 2004–08.

2.2 Comprehensive care models

Ordean et al.[64] reported on the outcomes of a family medicine-based program at the Toronto Centre for Substance Use in Pregnancy (T-CUP). This comprised of pre-and postnatal medical care, addiction counselling and assistance for complex psychosocial needs. Women enrolled in the program reported earlier pregnancy engagement (19.6 weeks compared to 24–26 weeks), increased stability of housing at delivery (3.3% versus 8.3% with no fixed address) and a small but noticeable decrease in rates of multiple substance use at delivery compared to historical controls. Most infants (74.4%) were discharged home in their mother's care with a significant association between duration of T-CUP care and remaining in maternal care. For example, 1st trimester engagement was associated with retention of care in 94.4% of women compared with 2nd and 3rd trimester engagement (67.8% and 64.3% retention respectively).[64]

2.3 Psychosocial interventions

Lilly et al.[65] described the outcomes of a four-step pilot program, Drug Free Moms and Babies, from the Appalachian region of the US in 2019. This was designed to integrate and evaluate treatment and recovery services for pregnant and postpartum women with substance-use disorders. The first component involved care by a team consisting of – at a minimum – maternity care providers, behavioural health providers, and other community resources. The second component included implementing a Screening, Brief Intervention, and Referral to Treatment (SBIRT) Model, a comprehensive, integrated, evidence-based approach, adapted for a site's unique population and cultural characteristics to identify and treat individuals with substance-use disorders. The third component involved a two-year follow-up, including (but not limited to) peer recovery coaching, ongoing services from staff and participation in social service programs. The fourth component consisted of integration with local and state-wide affiliates and initiatives to address substance-use disorders in pregnancy. This program resulted in a significant reduction in positive urine drug screens for non-prescribed drugs by the end of pregnancy (81% positive in the first trimester to 22% at delivery). It was evaluated to be accessible to the highest risk and most medically underserved populations.[65]

3. Opioids

Pharmacotherapy was the primary intervention used to improve pregnancy outcomes in women using opioids. Studies have reported treatment outcomes with sublingual buprenorphine alone, a combination of buprenorphine with naloxone, and methadone alone. Buprenorphine treatment alone was associated with better pregnancy outcomes and reduced NAS severity compared to methadone in 12 studies.[63,66-76] A combination of buprenorphine and naloxone was examined in three studies, which suggested that this combination could be more effective than buprenorphine alone in reducing NAS severity.[77-79] Nevertheless, methadone is the most commonly used opioid-replacement therapy in the world. Compared to no treatment, methadone maintenance therapy (MMT) significantly improves outcomes, including an increased proportion of infants discharged in their mother's care. This proportion is increased with the addition of an integrated multidisciplinary team model of care[80], regardless of whether the model of care was delivered via telemedicine or in person.[81] The addition of CM (e.g. coupons of escalating value depending on substance use) were found in an Israeli nationwide RCT to provide no additional benefit in improving pregnancy outcomes above treatment with methadone or buprenorphine, including improvement in infant weight.[82]

Evidence grading

According to the NHMRC Levels of Evidence grading, assessment of the quality of evidence is included in Tables 4 and 5, along with citations, interventions, and results of the included studies. The highest level of evidence was graded at Level I. The evidence base, generalisability and applicability of the studies were assessed as high. Grading of evidence leads to the recommendation that the body of evidence provides strong support for the recommendation(s) but care should be taken in their application, which is dependent on the cultural, economic and social contexts.

Grey literature

Grey literature searching identified no reports that provided data relevant to interventions designed to reduce drug use in pregnancy and the post-partum period to 2 years.

B. Improvement in maternal health to 2 years post-partum

Systematic reviews

A total of 6 systematic reviews were identified in the peer-reviewed literature that explored interventions designed to improve pregnancy and birth outcomes by helping mothers cease or moderate drug use, including alcohol, in pregnancy. The summary of the interventions is given below.

1. Alcohol

Two systematic reviews summarised effective behavioural change interventions for reducing alcohol intake by pregnant women. A recent meta-analysis by Gomez et al.[83] reported that the odds of achieving abstinence were 2.31 times higher in intervention groups using informed consequences, social support, goal setting and action-planning strategies, compared with control (usual care) groups. There was also a small but significant decrease in alcohol consumption with intervention. Gilinsky et al.[84] reported eight trials that studied brief interventions, motivational interviewing, self-interviewing with a self-help manual, supportive counselling and basic educational interventions. Of these, brief face-to-face interventions were found to be most effective in maintaining alcohol abstinence during pregnancy compared with usual antenatal care.

2. Any substances

2.2 Psychosocial and multi-intervention models

Two systematic reviews found improved birth outcomes when women participated in community or home-based psychosocial interventions. Multiple interventions – delivered by counselling, education, relapse prevention, and brief interventions together with more formal methods, such as CM, cognitive behavioural and motivational enhancement therapies – were effective either alone or in combination.[85] These interventions improved parenting ability and reduced risk of child maltreatment and substance dependence as measured by self-reporting, urine analysis and blood sampling.[86,87]

3. Cocaine

3.1 Psychosocial interventions

Hull et al. (2010)[88] reported on the efficacy of CM to improve maternal compliance with treatment necessities (e.g. prenatal care, drug use counselling). This was shown to result in a significantly greater duration of cocaine abstinence, a higher proportion of cocaine-negative urine tests and a higher proportion of documented abstinence, compared with a community reinforcement approach and 12-step facilitation interventions.

Primary studies

A total of nine primary studies were identified that explored interventions designed to improve maternal outcomes to two years post-partum by helping mothers cease or moderate substance use, including alcohol, in pregnancy. A summary of the interventions is given below.

1. Alcohol

1.1 Choline and nutritional supplementation

Animal studies suggest that choline supplementation in pregnancy, especially in mothers with risky drinking behaviour and poor nutrition, can improve fetal growth and neurocognitive outcomes. An RCT of heavy drinkers in South Africa compared 2g daily of oral choline with a placebo from antenatal care until delivery. This showed good adherence with the intervention without major side effects, including nausea, diarrhea, vomiting, blood pressure or body odour changes, but choline or any other nutritional supplementation was not shown to improve maternal health or increase abstinence after pregnancy.[89]

1.2 Psycho-social and other therapies

Osterman et al. (2017, 2014)[90,91] reported the positive effect of motivational enhancement therapy on improving overall social-emotional functioning and decreasing prenatal alcohol use in substance-using women. Twomey et al. (2012), reported on improvement in child welfare outcomes with legalised interventions such as court-ordered family treatments. These were marginally effective in the short term, but over time, maternal functioning deteriorated and infant developmental concerns emerged.[92]

2. Any substances

2.1 Psycho-social interventions

A pseudo-randomised controlled trial by Belt (2020)[93] compared mothers from a non-treatment control group with an intervention group, and a comparative study without concurrent controls was assessed by Hildebrandt et al. (2020)[94] Both found that relationship-based case management programs significantly improved overall social-emotional functioning, especially in mother-infant pairs with higher levels of adversity.

3. Opioids

3.1 Pharmacotherapy

Ordean et al. found that primary care-based integrated programs were associated with a significant reduction in use of illicit drugs, prescription opioids, cocaine, marijuana and alcohol.[95] Konijenberg et al.[96] compared mother/child interactions at six months in a group treated with opioid maintenance therapy (OMT) to those without. Both groups of children scored within low-normal ranges of development, but OMT was associated with significantly lower measures on cognitive development and mother-child interaction. Due to the importance of OMT in stabilising maternal substance use, factors other than OMT that influence mother-child interaction and cognitive development need to be considered.[96]

4. Cocaine

4.1 *Psychosocial Intervention*

Schottenfeld et al. compared Contingency Management (CM) with a community reinforcement approach or 12-step facilitation drug counselling for cocaine-dependent pregnant women. Researchers found that CM results in a significantly greater duration of cocaine abstinence, a higher proportion of cocaine-negative urine tests, and a higher proportion of documented abstinence across the 3-, 6-, 9- and 12-month assessments in the CM group compared with community reinforcement and 12-step facilitation drug counselling.[97]

Evidence grading

Assessment of the quality of evidence according to the NHMRC Levels of Evidence grading is included in Tables 6 and 7, along with citations, interventions, and results of the included studies. The evidence base, generalisability and applicability of the studies were assessed as high.

Grey literature

Two articles by Gomez et al. and Gilinsky et al. reported on psychosocial interventions such as informed consequences, social support, goal setting, action-planning strategies and motivational interviewing, which were effective in reducing use of alcohol in pregnancy.[83,84]

C. Improvement in child outcomes, including safety and neurodevelopmental performance, until 2 years

Systematic reviews

A total of 7 systematic reviews were identified in the peer-reviewed literature that explored interventions designed to improve infant outcomes by helping mothers cease or moderate substance use, including alcohol, in pregnancy. The summary of the interventions is below.

1. Alcohol

1.1 Choline Supplementation.

Akison et al.[98] reviewed 189 studies and assessed 22 studies (2 RCTs, 2 prospective cohort studies, and 18 preclinical studies) that met full inclusion/exclusion criteria. Choline interventions were administered at different times relative to alcohol exposure, affecting evaluations of their influence in preventing specific deficits. Preclinical studies showed improvement in epigenetic/molecular changes, and gross motor, memory and executive functions. This suggests that choline supplementation can ameliorate specific behavioural, neurological and cognitive deficits caused by fetal alcohol exposure, but that further clinical trials are needed.[98] Only one clinical study showed significant improvement in information processing in 6-month-old infants from mothers treated with choline during pregnancy.

1.2 Multi-service programs.

Rutman et al.[99] concluded multi-service interventions are effective in reducing alcohol intake and help to prevent fetal alcohol syndrome disorder. These interventions reach vulnerable pregnant/parenting women who face a host of complex circumstances, including substance use, violence, child welfare involvement, and inadequate housing. Still, it is typically the intersection of these issues that prompt women to engage with programs.

2. Any substances

2.1 Home visiting

There is no evidence that home visiting for at least two years after birth improves outcomes (health, social and neurodevelopmental) in vulnerable mother and child. In some high-risk communities, home visiting, even by non-clinical visitors, has the potential to improve educational, social and other outcomes to adulthood and to the next generation. Collectively, there was no significant difference in continued illicit substance use, continued alcohol use or child behavioural problems. Overall, based on this body of evidence, there is currently no conclusive evidence to recommend routine use of home visits for women and infants affected by prenatal substance-use issues.[100]

3. Opioids

3.1 Pharmacotherapy.

Three systematic reviews and meta-analyses have assessed childhood neurodevelopmental outcomes after exposure to prenatal opioids (Lee 2020, Monnelly 2019, Yeoh 2019).[101-103] Collectively, any exposure to prenatal opioids significantly decreases cognitive, motor and language outcomes, evident from as early as six months.[103] Opioid-exposed infants and children also perform more poorly than their non-opioid-exposed peers across various other outcomes, including internalising, externalising and attention behaviours. These problems may persist up to 12 years of age[101] and there is no evidence beyond that to suggest whether these problems persist. Treatment with methadone does not appear to mitigate risk to infants of opioid exposure but currently available data are derived from studies with considerable bias, including lack of blinding, small sample sizes, uncertainties about polysubstance exposure and lack of comparison groups.[102] Besides these studies, a systematic review by Minozzi et al. included four studies. It concluded there were no significant differences between methadone and buprenorphine or slow-release morphine to suggest that one treatment is superior to another for all relevant outcomes. While methadone seems superior in terms of retaining patients in treatment, buprenorphine results in less severe NAS.[104]

Primary studies

Only one primary study was identified in peer-reviewed literature exploring interventions to improve childhood outcomes, including neurocognitive performance and substantiated child harm until two years of age. The summary of the interventions is below.

1. Opioids

1.1 Pharmacotherapy

One study examined the effectiveness of buprenorphine compared with methadone in improving infant outcomes in terms of cognitive development, sensory processing, temperament and language abilities in children. This study also looked at maternal outcomes as the perception of parenting stress, home environment and addiction severity. There were no significant differences in weight, head circumference and height, and overall gains in cognitive development, language abilities, sensory processing and temperament between buprenorphine and methadone treatment groups.[105]

Grey literature

Three systematic reviews are included from the grey literature, which discuss the effect of prenatal methadone and/or buprenorphine as well as other opioids on the childhood neurodevelopmental outcomes after exposure. These studies are included in the above summary.[101-103]

Evidence grading

Assessment of the quality of evidence according to the NHMRC Levels of Evidence grading is included in Tables 8 and 9 with citations, interventions and results of included studies examining infant and child outcomes of interventions designed to decrease substance use in pregnant women. The highest level of evidence was at I, with three systematic reviews and one randomised control trial. The evidence base, generalisability and applicability of the studies were assessed as high.

Economic evaluation of interventions

Systematic reviews

There were no systematic reviews identified.

Primary studies

Five studies provided an economic evaluation of interventions carried out during pregnancy and the first two years of the child's life to improve maternal and child outcomes for women who use substances.[106-110] The types of interventions varied between studies. The most common intervention was individualised therapy, which included cognitive behaviour therapy and behavioural parenting intervention. Only one study compared the cost-effectiveness of medications and detoxification for the management of opioid use during pregnancy.

The outcome measures were highly heterogenous among the studies including the measure of Brief Child Abuse Potential Inventory (BCAP) and cases of fetal alcohol syndrome disorder averted. The review included two studies that compared the aggregate cost of interventions and reported the average or median cost only, e.g. cost per participant. All the studies adopted a healthcare perspective, including two studies that included a broader societal perspective by adding the cost of participants' time in intervention, travel costs, and lifetime cost of care without interventions. All but one study undertook sensitivity analysis to assess the robustness of their findings.

Two studies constructed an analytical decision model to assess the cost-effectiveness of treatment strategies in managing maternal substance use (including alcohol).[108,109] The first study assessed which strategy—methadone, buprenorphine or detoxification using a 14-day buprenorphine taper—was the most cost-effective approach to managing opioid use during pregnancy. The authors found buprenorphine was the dominant strategy (i.e. cost saving and higher quality adjusted life years (QALY)) than methadone or detoxification. The probabilistic sensitivity analysis showed buprenorphine had a 70.5% likelihood of being cost-effective at a willingness-to-pay threshold of US$100,000 per QALY, a commonly used threshold for funding healthcare interventions in the US.[108] Methadone had a 3.9% likelihood and detoxification had a 25.6% likelihood.

Thanh and colleagues assessed the Parent-Child Assistance Program (P-CAP) for women at risk for giving birth to a child with fetal alcohol syndrome. The P-CAP is a three-year home visitation intervention to prevent subsequent drug and alcohol-exposed births by encouraging the use of contraceptives and helping women decrease their use of drugs and alcohol or abstain from them completely. The model estimated that 31 fetal alcohol syndrome disorder cases were prevented with a net monetary benefit of $22 million due to the P-CAP. The results were robust when all inputs were varied by 20%.[109]

Barlow and colleagues conducted a cost-effectiveness analysis of a randomised controlled trial that compared an intensive one-to-one parenting intervention (Parent under pressure programme, PuP) with standard treatment consisting of group family format intervention (standard care). The study showed an incremental cost-effectiveness ratio of £34,095 per QALY and £1004 per unit improvement in the BCAP (Brief Child Abuse Potential Inventory) with PuP.[111] Sensitivity analysis using bootstrapping showed there was a 34.6% and 98% chance that PuP was cost-effective, compared with standard treatment for a willingness-to-pay threshold value of €20,000 per QALY and per unit improvement in the BCAP respectively.[107]

Xu and colleagues reported a nurse-administered motivational enhancement therapy with cognitive behavioural therapy was more costly compared with brief advice by an obstetrical provider for pregnant substance users. However, the total mean cost was comparable between the two groups when the cost of care during the prenatal period and postpartum period (including psychotropic medications) were included. A cost analysis reported overall cost savings with Early Start groups (i.e. women identified as substance users who received a psychological assessment with or without follow-up visits by a program specialist) compared with a screening-positive only group (i.e. identify substance users and receive standard advice from obstetricians to stop using drugs and continued referrals to outside support program).[110]

Evidence grading

The Drummond checklist for methodological quality was applied to the five studies assessing the cost-effectiveness of interventions to improve outcomes for women and who use substances during and after pregnancy of up to 2 years of their child's life. Goler et al and Xu et al were rated as having poorly evaluated analysis due to the provision of limited detail on cost categories and reporting only on mean costs.[107,110] The remaining three studies were rated as being average or good as most criteria of the applicable items were fulfilled in the Drummond checklist.[106,108,109] Table 10 in Appendix 1 lists each study and its evidence grading.

Grey literature

No articles were found.

Question 2

What interventions are most effective at reducing risk of harm in breastfeeding women who use substances?

Breastfeeding protects infants from infectious disease, supports normal growth and development, and promotes maternal bonding and caregiving capacity.[112,113] Infants that are not breastfed are at increased risk of hospitalisation for infectious causes, Sudden Infant Death Syndrome, overweight and obesity, and maternal maltreatment. Cognitive development is also adversely affected by premature cessation of breastfeeding.[112,113] However, any substance taken by the mother has the potential to cross the breastmilk/blood barrier and adversely affect the breastfed infant.[114] Substances can also accumulate in milk with prolonged use. Cannabis, for example, has been detected in milk for up to 6 days after abstinence. The drug(s) involved and the age and health status of the infant affect whether the risks of infant exposure to substances via breastmilk outweigh the positive effect of breastfeeding. There are also concerns that infant harm could occur if the mother were intoxicated and unable to breastfeed safely. Nonetheless, the risks associated with improper reconstitution of infant formula, such as hypo- and hyper-natraemia and over or undernutrition, where mothers are impaired also need to be considered alongside the risks related to poor hygiene.

In mothers with stable substance use, such as those on an opioid-replacement program, breastfeeding is safe and any ingestion of breast-milk significantly decreases the severity of NAS and the need for pharmacological treatment of NAS as well as infant hospitalisation.[115] However, less than 10% of substance-using women breastfeed exclusively on discharge from hospital, citing prolonged infant hospitalisation, lack of support and education, and child protection issues as the main reasons for lactation cessation. Clinicians may also lack knowledge concerning the importance of breastfeeding and how to appropriately weigh the risks associated with maternal substance and, therefore, do not support breastfeeding where it is appropriate.[116] Clinicians have major difficulties promoting breastfeeding in women with substance-use issues, due particularly to a lack of educational support.[116]

Outcomes for this section included assessment of interventions to reduce harm in breastfeeding women using substances in relation to:

1. Reducing harm from breastfeeding, including infant death
2. Increasing duration and incidence of breastfeeding
3. Increasing knowledge of breastfeeding in substance-using mothers.

Systematic reviews

No systematic reviews were identified in peer-reviewed literature that explored interventions designed to reduce harm from breastfeeding and to increase duration, incidence and knowledge of breastfeeding in substance-using mothers.

Primary studies

No primary studies were identified in peer-reviewed literature that explored interventions designed to reduce harm from breastfeeding. In one study, mothers with infants at risk of NAS were given a three-class curriculum to increase breastfeeding education. The education cohort had the largest percentage of exclusively breastfed infants during hospitalisation and at discharge. There was also a significant decrease in length of stay for those infants but there was no intervention specifically designed to "reduce harm from breastfeeding".[8]

Evidence grading

Evidence grading cannot be conducted as there is no relevant existing literature.

Grey literature

The grey literature search did not identify relevant reports that examined interventions designed to reduce harm from breastfeeding in substance-using mothers.

Economic evaluation of interventions

Systematic reviews

No systematic reviews were found.

Primary studies

One study considered outcomes of mothers who roomed-in, with breastfeeding as a secondary outcome and the cost-effectiveness of this intervention from a societal perspective.[117] The study showed that breastfed neonates who roomed-in were least likely to require pharmacotherapy and had the most optimal neurodevelopmental outcomes leading to a favourable cost-saving ratio (i.e. higher QALY at lower costs) based on a willingness-to-pay threshold of US$100,000 per QALY. When probability sensitivity analysis was conducted to account for uncertainty in the model inputs, the rooming-in model is cost-saving in 94.2% of the simulations at a willingness-to-pay of US$100,000 per QALY.[117] Interpretation of this study can be found in Appendix 1 table 11.

Appraisal of methodological quality

The study was assessed as having well-evaluated analysis.

Question 3

What treatments have been shown to be effective for neonatal substance withdrawal syndromes, including withdrawal from

opioids, alcohol, methamphetamines, cocaine, cannabis, benzodiazepines, gabapentinoids and tobacco?

Neonatal substance withdrawal syndrome or Neonatal Abstinence Syndrome (NAS) consists of a collection of clinical signs such as irritability, tremors, and poor feeding and gastrointestinal disturbance caused by an abrupt cessation of maternal substance supply after birth. Although NAS typically occurs following in utero exposure to opioids, maternal use of other prescribed or non-prescribed substances, such as methamphetamines, cocaine, cannabis, benzodiazepines and gabapentinoids, also cause symptoms of infant withdrawal and intoxication. Polysubstance use among substance-using pregnant women has been shown to be more common (>80%) than single-substance use.[118] Nevertheless, for clarity, the direction of this section therefore takes into account the infant's exposure to different primary drugs of exposure including:

1. Opioids (methadone, heroin, prescription opioids, synthetic non-prescription opioids)
2. Stimulants (amphetamine-type substances, cocaine)
3. Sedatives (including benzodiazepines)
4. Alcohol
5. Cannabinoids
6. Nicotine
7. Psychotropic medications (including gabapentinoids, SSRIs and other antidepressants).

We defined "*effectiveness*" in neonatal withdrawal syndromes as:

1. Prevention of withdrawal or intoxication
2. Amelioration of the severity of withdrawal or intoxication
3. Prevention of adverse effects including death, neurodevelopmental delay and longer-term outcomes, including intergenerational substance use
4. Cost-effectiveness of therapy, including infant and maternal length of stay (duration of hospitalisation), re-hospitalisation and quality of life years.

For prevention of newborn withdrawal or intoxication

Systematic reviews

A total of 13 systematic reviews were identified in peer-reviewed literature that explored interventions designed to decrease the severity of newborn withdrawal[29,119-130]. All reviews were based on primary exposure to opioids and none examined prevention of withdrawal or intoxication from non-opioid drugs, including alcohol. One review compared the effectiveness of using sedatives (e.g. phenobarbitone) with supportive care alone for opioid withdrawal[130]. Interventions focused on preventing the need for pharmacological treatment and supportive care that included rooming-in[129], infant feeding[121] (e.g. breastfeeding), hypercaloric feeds and neonatal assessment methods (e.g. the Eat, Sleep and Console [ESC] tool versus the Finnegans score).[123] These found that a combination of rooming-in (i.e. nursing the infant in close proximity to a biological mother or other primary care giver), breastfeeding or breast-milk feeding, and an infant-led withdrawal assessment scale (i.e. the ESC method) significantly decreased the need for withdrawal medication and infant length of hospital stay. McMillan et al. examined six publications on rooming-in. These demonstrated a significant impact of rooming-in for reducing pharmacotherapy and length of stay compared to standard neonatal intensive care. Sensitivity analysis resolved the heterogeneity for the use of pharmacotherapy, significantly

favouring rooming-in.[129] There was no evidence that either rooming-in or ESC improves long-term outcomes, including infant safety, neurocognitive ability and maternal substance use above and beyond other forms of therapies.

Primary studies

A total of 53 primary studies were identified in peer-reviewed literature that explored interventions designed to prevent the need for newborn withdrawal medication and to decrease the severity of withdrawal. Again, there were no studies exploring different treatments for non-opioid drug effects. Primary studies focused on rooming-in, infant feeding methods, including breastfeeding and hypercaloric feeds, and withdrawal assessment scales.

Rooming-in

Seven primary studies were identified in peer-reviewed literature that explored rooming-in (nursing the infant near the mother) in mother/infant opioid-exposed interaction. Rooming-in, if there were no other extenuating risk factors, including child-at-risk issues or health problems in either the mother or infant, significantly decreases the length of stay of both mothers and infants,[23-28,131] improves breastfeeding rates,[23,26,27,131] decreases the need for withdrawal medication[25,27] and decreases the amount and duration of medication required for NAS.[26-28,131] No studies have been conducted to assess the effect on maternal recidivism, substantiated child harm and longer-term neurodevelopmental problems.

Infant feeding

Eleven studies were identified in peer-reviewed literature that explored breastfeeding,[8,13-15,17,18,21] breastmilk feeds[10,12] and other types of milk feeds including donor breast milk,[4] hypercaloric feeds[6] and frequent feeding regimes[12] on preventing the need for withdrawal medication. These studies focused entirely on opioid-exposed babies and there were no studies of the effect of milk feeds on the outcomes of infants after exposure to non-opioid drugs, including methamphetamine, cannabis, alcohol and nicotine. There were case reports (outside of the time range of this review) of adverse events, including death, after breastfeeding by intoxicated mothers[132] or after exposure to drugs such as methamphetamine.[114]

Withdrawal assessments

The proportion of infants medicated for withdrawal may be determined by the type of assessment methods used to determine withdrawal severity. A total of 10 primary studies compared the most widely used assessment methods, the Finnegan Neonatal Abstinence Severity Score (FNAS) to the Eat, Sleep, Console (ESC) method developed by Grossman and colleagues.[4,5,7,9,11,16,19,20,22,133] The ESC, dictated by infant cues and heavily dependent on parental education, reduced infant hospitalisation,[4,5,7] need for withdrawal medication[11,16,20,22] and duration of withdrawal medication[7,19,20,22] without increasing risk of rehospitalisation over the first six months of life.[9,20] However, no assessment method, including the FNAS, has been evaluated for its effect on longer-term outcomes including brain growth and neurodevelopmental outcomes. A large cluster-randomised study (>100 hospitals) in the USA is currently underway to determine the impact of the ESC tool on >3000 opioid exposed infants. No assessment method has been validated for exposure to non-opioid drugs including cannabis, methamphetamine, alcohol, cocaine or psychotropic agents.

Evidence grading

Tables 12 and 13 summarise the level of evidence of the included studies regarding the outcomes of interventions for treatment of NAS according to the NHMRC recommendation grades.[134] As shown in Table 12, the highest level of evidence was Level I. The evidence base, generalisability and applicability of the studies were assessed as medium. Grading of the evidence leads to the recommendation that the 'body of evidence provides support for recommendation(s), but care should be taken in its application'. An assessment of clinical effects was not relevant to the studies as none presented intervention studies of clinical relevance.

Grey literature

Grey literature searching identified no reports that provided data relevant to interventions designed to be effective for preventing neonatal withdrawal symptoms.

Economic analysis

One study assessed the rooming-in and breastfeeding intervention to be dominant (i.e. increased QALYs at a lower cost) over no rooming-in with parents from a societal perspective. Probability sensitivity analysis showed that rooming-in remained a dominant strategy compared to no rooming-in in 94.2% of the simulation at the willingness-to-pay threshold of US$100,000.[135]

Interventions for treating neonatal symptoms from prenatal drug exposure

The treatments assessed for ameliorating symptoms of neonatal withdrawal or intoxication caused by prenatal drug exposure will be categorised as:

1. Supportive care (rooming-in, nursing management, infant feeding)
2. Pharmacotherapy (opioids, sedatives, antihypertensives)
3. Models of care (inpatient, outpatient, home visiting and other programs)
4. Ancillary or non-pharmacological interventions (acupuncture)
5. Assessment methods (Finnegans, Lipsitz, ESC, toxicology).

Summary of evidence

1. Supportive care

1.1 Rooming-in: Evidence Grade I

A recent systematic review and meta-analysis examined the evidence on rooming-in with the mother for infants with NAS.[136] The review examined studies until 2017 and included six studies involving 549 patients (five studies using pre-post assessment and one retrospective analysis) from the US, Canada and Europe. The authors concluded that rooming-in was associated with a decreased need for pharmacological treatment and shortened length of stay. While one study included in the review found a statistically significant increase in breastfeeding at discharge for infants who roomed-in with their mothers,[11] two other studies reported no difference in the rates of breastfeeding between study groups but this was most likely due to the low baseline breast-feeding rates in the studies (<50%).[27,28] None of the

three studies that followed infants for hospital readmission reported a statistically significant increase in readmission for infants who roomed-in with their mothers.[23,24,27] All three studies that assessed the cost of hospital stay reported lower inpatient costs with rooming-in.[11,24,25]

1.2 Nursing management: Evidence Grade I

MacMullen and colleagues reviewed 24 articles on nursing interventions where decreased auditory, visual and tactile stimulation for infants with NAS were implemented in order to diminish stress on hyperactive and sensitive neurological systems. Other interventions, including nursing in a quiet environment, low visual stimulation (e.g. turning the lights off), decreased tactile stimulation and diminished care frequencies, were noted to decrease withdrawal severity and need for medications.[137]

1.3 Infant feeding methods, including breastfeeding and hypercaloric feeds: Evidence Grade I

A systematic review of 25 studies on non-pharmacological interventions found any amount of breast milk feeds or breastfeeding consistently reduced hospital stay and need for pharmacological treatment (range, 7%–44% reduction) but all studies on feeding practices were performed retrospectively.[138] One study randomised infant to standard calorie (20kcal/oz) and high-calorie formula (24kcal/oz). The trial found no significant difference in maximum percentage weight loss, days to regain birth weight, NAS pharmacological treatment rates, or length of hospital stay even though there was a higher mean percentage weight gain per day over the first 21 days of life in infants randomised to the high calorie feeding group.[6]

2. Pharmacotherapy

2.1 Opioids: Evidence Grade I

A recent systematic review and network meta-analysis examined the evidence of different types of medications on NAS due to opioids.[119] The review included 18 randomised controlled trials (RCTs) and suggested that buprenorphine was associated with significantly shorter lengths of treatment and NAS severity compared with morphine. This result, however, was based on only a small number of RCTs with small sample sizes, and heterogeneous methods and study populations. There was also no long-term outcome data (>2 years). Currently, neonatal buprenorphine formulations are not widely available, and this prevents scalability and generalisability of these results. The authors postulated that the benefits of buprenorphine may have been due to the long half-life of buprenorphine compared to morphine, as this may have decreased infant drug fluctuations leading to exacerbation of infant withdrawal symptoms. Future studies should examine the effect of NAS buprenorphine treatment on neurocognitive outcomes.[139]

Two agents used as adjuncts are the centrally acting alpha-2 adrenergic agonist clonidine and the GABA agonist phenobarbital. There have been a number of small studies that have compared clonidine to phenobarbital as an adjunct to treatment of opioid-related NAS but the optimum approach as to the best adjunctive treatment for neonatal opioid withdrawal remains uncertain.[122,140,141]

2.2 Sedatives: Evidence Grade I

Phenobarbital has traditionally been the adjunct treatment of choice for opioid withdrawal and remains the preferred second agent for neonates with polysubstance exposure. Previous

studies have shown that phenobarbital does not directly address the pathophysiology of withdrawal, but when used as an adjunct, it consistently reduces the duration of opioid therapy and the length of hospital stay,[130] especially in infants that failed initial treatment with morphine. The long-term implications of phenobarbitone, considering its negative effect on neuronal survival and differentiation, remains to be evaluated.[141]

3. Models of care

3.1 Inpatient v outpatient management, Evidence Grade I

For decades, most infants requiring medication for NAS were hospitalised as inpatients for the duration of their treatment, primarily because of concerns about administering restricted agents (e.g. morphine) by socially vulnerable caregivers. In 2001, Oei et al. described the outcomes of infants who were managed as outpatients for NAS. Compared with infants who completed NAS treatment as inpatients, outpatient weaning significantly decreased hospitalisation for mothers (7.8 vs 4.8 days) and infants (14.8 vs 8.7 days) with a 92% compliance with clinic attendance and no major medication errors.[142] Few studies assessing outpatient management for NAS showed favourable neonatal outcomes.[143-145] For example, six studies reviewed by Murphy-Oikonen et al (2019) showed that outpatient management significantly reduced length of hospital stay ranging from 7.3 days to 18.9 days. This led to considerable cost savings through decreased length of hospital stay and the findings were consistent regardless of the pharmacological agent used to wean (methadone, morphine) and the healthcare provider regimen for follow-up.[146]

However, existing studies showed outpatient NAS treatment results in significantly increased duration of exposure to pharmacological agents. In two of the four studies, infants who received home weaning required a longer duration of pharmacological treatment compared with in-hospital treatment management even though no difference was found in the cumulative dosage of morphine between the inpatient and outpatient groups in the included studies.[145,147-149]

4. Ancillary or non-pharmacological interventions

4.1 Acupuncture: Evidence grade II

Few studies have reported on the use of ancillary interventions such as acupuncture, including auricular acupuncture for treatment of NAS.[150-154] Acupuncture exerts its effects by modulating neural blood flow and neurotransmitter (including endorphin and serotonin) activity. Various modalities, including laser, tactile and auricular acupuncture have been assessed in small studies for preventing need for NAS medication and/or the duration of therapy. Acupuncture may be a promising adjunct to other preventive NAS strategies such as breastfeeding and further investigation on a large scale is warranted.

5. Assessment methods

5.1 Finnegans: Evidence Grade III

The Finnegan Neonatal Abstinence Scoring System (FNAS) developed by Loretta Finnegan and colleagues in 1975 is the most common model of care for assessing withdrawal severity after prenatal drug exposure. Most institutions using the FNAS have protocols that call for

starting or increasing pharmacological treatment after an infant has received three FNAS scores ≥8 or two scores ≥12 but the evidence or benefit behind this is uncertain.[155]

5.2. Eat, Sleep, Console model: Evidence Grade III.

The FNAS is not validated for non-opioid assessment. A recent study by Zimmerman and colleagues demonstrated that healthy-term infants rarely exceeded FNAS scores of eight.[156] There is also an argument that scoring does not provide validation for the need for pharmacological treatment as the original Finnegans Score[155] was based on a series of narcotic-exposed infants who were nursed in a nursery, bottle-fed and treated with a variety of medications, including phenobarbitone, tincture of opium and paregoric, which are not first-line medications today. Wachman et al assessed the outcomes of pharmacotherapy and length of hospital stay associated with the Eat, Sleep, Console (ESC) model and noted that implementation of a structured ESC model, which emphasises education of clinicians and carers as well as implementing non-pharmacological care as first-line treatment, resulted in a decrease in pharmacotherapy and length of stay without an increase in short-term adverse events compared with infants in the pre-intervention period.[138] Existing studies assessing the outcome of a structured ESC model have found beneficial outcomes on infants with NAS.[157-161] Another study that assessed the treatment of infants with NAS in community hospitals compared to academic hospitals using standardised management protocol has also shown favourable outcomes in infants with NAS.[162] Nevertheless, like the FNAS, evaluation of the effects of ESC and other assessment methods on the long-term outcomes of infants with NAS needs to be determined.

5.3 Screening (toxicology): Evidence Grade I

Evidence suggests that when biological specimens of the pregnant woman or newborn infant are tested for the presence of drugs, the rate of positive results is higher than the rate of maternal self-reported substance use.[163] Biological infant specimens that can be tested for drugs include meconium, hair, cord blood, and urine but the benefits of these tests on treatment of the infant are uncertain. There is evidence that detailed, non-punitive and open histories from the mother are more informative than neonatal toxicology screens, which rely on timing of maternal drug use, timing of neonatal specimen collection and absence of false positives or negatives.[164]

Economic evaluation of intervention for treatment of neonatal withdrawal syndromes

Systematic reviews

There were no systematic reviews found.

Primary studies

Apart from Avram et al., who conducted a decision-analytic analysis to assess the cost-effectiveness of rooming-in for NAS, the remaining nine studies assessed the cost of interventions for neonatal substance withdrawal syndromes by comparing them with standard care for NAS or with a historical control group (i.e. prior to intervention). For these studies, only mean costs of intervention were reported.[4,11,19,24,25,135,144,145,165,166]

These nine studies adopted a healthcare perspective and direct medical costs were estimated from hospital records and medical databases. The outcomes between studies were similar, including cost associated with hospitalisation and a reduced length of stay as a result of intervention. None of the studies conducted a sensitivity analysis.

For example, the study by Holmes and colleagues reported the intervention to standardised scoring, rooming-in, and environmental and pharmacological management of NAS was associated with a lower average hospital cost for all infants treated for NAS compared with prior to intervention.[24] Two other studies[25,135] that compared mothers or parents or other caregivers for rooming-in and not rooming-in showed similar outcomes.[4,135,145] Compared with neonates who completed their morphine wean as inpatients, neonates who completed their morphine wean at home had fewer readmissions for continued withdrawal resulting in substantial in-hospital cost savings.

Appraisal of methodological quality

The Drummond checklist was applied to the 10 studies assessing the cost effectiveness of interventions for NAS. All but one study by Avram et al. were rated as having a poorly evaluated analysis as only mean costs were reported. Table 14 in Appendix 1 lists each study and its quality rating.

Question 4

What interventions are most effective at preventing the resumption of smoking and other substance use within the six-month postnatal period?

Smoking

We only found interventions that aimed to prevent the resumption of smoking. We did not find any studies that looked specifically at the resumption of opioid, cannabis, cocaine or amphetamines within the six-month postnatal period.

Systematic reviews

Five systematic reviews were included in this review. Three examined nurse-led interventions, one examined behavioural technique, and the fifth examined a multiple intervention approaches with NRT, patch/gum and behavioural interventions.

1. Psychosocial interventions

1.1 Behavioural change techniques (BCT): Evidence Grade Level I

Brown et al[167] summarised 32 trials of behavioural change techniques to maintain smoking abstinence or to promote cessation along with maintenance of abstinence. A total of 93 individual BCTs were identified, of which six showed long-term effectiveness of sustained

smoking abstinence program for more than six months post-partum in at least two studies. These BCTs were problem-solving, information about health consequences, information about social and environmental consequences, social support, reduce negative emotions, and instruction on how to perform a behaviour.

1.2 Nurse-led counselling: Evidence Grade Level I

Nurse-led counselling was reported in three systematic reviews. One focused on addressing second-hand smoke and concluded that more comprehensive second-hand smoking interventions are needed.[168] Two systematic reviews examined tele-counselling via nurses and neither showed any enhanced benefits compared with face-to-face counselling. The studies kept standard care as a control. The intervention group received standard care and tele-counselling, which consisted of telephone outreach from nurses using standardised questions to assess signs and symptoms of labour, motivational interviewing, and strategies to maintain smoking cessation. Some of the studies included in the review also provided peer support, newsletters and relapse prevention kits. Overall, the effectiveness of interventions increased when a combination of methods was used.[169,170]

5. Pharmacological therapies

2.1 NRT patch/lozenge

Su et al.[171] conducted a systematic review of pharmacological therapies. NRT was used as an intervention to help women maintain abstinence from smoking. One of the studies showed positive nicotine replacement therapy results when used with cognitive behavioural therapy compared with cognitive behavioural therapy alone. The other study found NRT patches not to be useful. None of the studies, including pharmacological, behavioural and incentives-based interventions, consistently maintained abstinence in the longer term after birth.

Primary studies

Fourteen studies were eligible for inclusion, of which 10 were RCTs, one a pseudo-randomised controlled trial and three were studies with no concurrent controls. The effective interventions were motivational interviewing, nurse-led psychosocial intervention and progesterone therapy.

6. Psychosocial interventions

1.1 Motivational Interviewing and Empowerment techniques

Five studies with level II and level III evidence showed mixed results. Three of them (Hannover et al., Stotts et al. and Suplee et al.)[172-174] had negative results while Reitzel et al. and French et al.[175,176] showed promising results. Two of these effective studies used Motivational Interviewing developed by Miller & Rollnick (2002)[177] and relapse prevention by Marlatt and Gordon (1980)[178] to counsel participants.

1.2 Nurse-led psychosocial interventions

Seven individual studies reporting nurse-led interventions were eligible. The interventions included weekly encouragement to remain smoke-free and routine breastfeeding support, educational booklets and nurse-delivered smoking abstinence intervention monthly postpartum incentives. These interventions were provided as face-to-face, in-hospital

counselling sessions at birth and were followed by telephone counselling. Overall, nurse-led counselling was effective against a resumption of smoking within the six-month postnatal period, but there was no evidence of longer-term abstinence.[179-186]

1.2 Behavioural change techniques

Levine et al. examined the effectiveness of a cognitive behavioural intervention that focused on women's postpartum concerns about mood, stress and weight, or a supportive, time and attention-controlled comparison. The intervention began after delivery and continued for six months postpartum. Both interventions were effective and related to sustained abstinence.[181]

7. Pharmacological therapies

2.1 Progesterone therapy

Only one pilot study (evidence Level II) examined the effects of progesterone on maternal smoking.[187] Progesterone is a neuroactive steroid that is active in cognitive functioning and stress reduction and reward responses. Abstinence was measured within seven days post-birth but not beyond.

Grey literature

One article discussed effective models for postpartum smoking resumption prevention for women who stopped smoking while pregnant. The intervention began during pregnancy, continued postpartum, and addressed pregnancy and contextual parenting factors in women's lives. The model was based on motivational theory and included patient assessments, development of risk profiles, triage of women to different intervention intensity levels, and matching intervention strategies to women's risk profiles. However, the intervention was not evaluated.[188]

Evidence grading

The level of evidence according to the NHMRC is included in tables 15 and 16 along with citations, interventions and results of included studies resumption of smoking in the postnatal period. The highest level of evidence was at I, with five systematic reviews, 10 randomised control trial and four studies with level III or lower. The evidence base, generalisability and applicability of the studies were assessed as medium.

Economic evaluation of interventions

Systematic reviews

There were no systematic reviews found.

Primary studies

Three studies reported the cost of interventions to prevent the resumption of smoking and other substance use during the postnatal period from a healthcare perspective.[189-191] However, only one

study assessed the cost-effectiveness of motivational interviewing and usual care (i.e. discuss patient smoking and provide a pamphlet describing ways to deal with nicotine withdrawal symptoms) to encourage cessation and prevent the resumption of smoking and other substance use in low-income pregnant women. The model showed that usual care was the dominant strategy for cessation while motivation interviewing was more effective than usual care at an estimated $628 per QALY.[190]

Appraisal of methodological quality

The Drummond checklist was applied to the three studies assessing the cost-effectiveness of interventions to prevent the resumption of smoking and other substance use within the six-month postnatal period. The studies by Xu et al. and Ruger et al. were rated as having poorly evaluated analysis as mean cost was reported.[189-191] More information on the studies can be found in Appendix 1, Table 17.

Gaps in research

This review yielded useful information but also identified a wide range of gaps in the evidence around interventions for substance use in pregnancy. The key areas that require further research are:

1. Improving identification of substance-use in pregnancy through greater understanding of effective screening strategies and enhanced engagement

The first step in the provision of appropriate treatment is to determine the amount and frequency of any substances used and whether a substance use disorder is present. Expanding the knowledge of whether and under what conditions screening and relevant interventions can be effective, including appropriate antenatal histories, biological monitoring and understanding of the cost-effectiveness of screening procedures in routine clinical practice is needed.[192] There is also a need for greater understanding of the true prevalence of substance use in pregnancy and what factors enhance disclosure. Significant barriers still remain, including lack of patient and clinician education, a culture of stigma and discrimination by health providers and broader society, and a lack of participation and engagement by parents in much-needed research, treatment and rehabilitation services.[193] More nuanced clinical outcomes need to be developed in concert with consumers—beyond concepts of ‘long-term parental abstinence’—that better reflect relationships between parental substance use and subsequent parental and childhood harms. The lack of information on the effects of antenatal interventions on longer-term outcomes, including substance use and childhood development and behaviour, appears to be a major gap that needs to be addressed.

2. Impact of psychosocial interventions on longer-term outcomes

The short-term benefits of brief interventions such as motivational interviewing is promising for those with mild substance-use disorders, but further research is required to examine responses to those who do not respond to such interventions (e.g. stepped care approaches). Further research is required to examine transnational dimensions of such research, including workforce issues, resources

and effects on longer-term outcomes. Multidisciplinary CM, although effective in quasi-research settings, is rarely routinely adopted or translated into routine clinical practice due to heavy resource needs, lack of funding and societal concerns.[194] Large-scale intervention analyses, including the effects of interventions on specific niche and cultural groups, are needed, along with robust cost-effectiveness analyses.[195]

3. Pharmacotherapy

While there is good evidence for pharmacotherapeutic management of opioid dependence in pregnancy, there is little data on the safety or efficacy of pharmacological interventions for mothers with other substance-use disorders – most notably alcohol, stimulants and cannabis.[47,55-58,67,196,197] We need to improve the evidence base to inform women with alcohol-use disorders in pregnancy about the best and safest strategies for management of withdrawal and reduction of alcohol use and the process of sustaining abstinence following birth. There is also very limited evidence for use of pharmacotherapy in other types of substance use, including methamphetamine, cannabis and cocaine. Further understanding of the best ways to manage withdrawal from stimulants, benzodiazepines, cannabis and alcohol in pregnant women is needed along with risks and benefits of such medications. Further research is required to evaluate the safety and effectiveness in pregnancy of emerging medications used to treat methamphetamine or cannabis use disorders (e.g. lisdexamfetamine, NAC, nabiximols).

4. Breastfeeding

There was no research that examined which interventions increase exclusivity and duration of breastfeeding in the context of maternal substance-use disorders. However, it is well recognised that successful establishment and continuation of exclusive breastfeeding is supported where infants remain in close proximity and that breastfeeding is undermined when they are separated. Infants and substance-using mothers are often separated in hospital and after discharge because of reasons associated with infant medical treatment, maternal incarceration or child protection concerns. Breastfeeding success for substance-using mothers and their infants will be maximised where mothers and infants room-in in hospital and remain together after discharge. Drug rehabilitation programs and prisons should enable mothers and infants remaining together while women are in their facilities. Premature cessation of breastfeeding may negatively affect both the mother's and infant's future health, including mental health, intelligence and physical health.[198] There is also the need to improve education of end-users, including parents, foster carers, child-protection workers and clinicians on the benefits and risks of breastfeeding for substance-using mothers.[198]

5. NAS medications

There is a lack of information on the effect of NAS medications on long-term infant neurodevelopmental outcomes. All intervention studies focus on short-term outcomes, especially on length of infant hospitalisation, hospital readmissions within the first six months of life and child-at-risk issues.[196,197,199-202] One study assessed the neurobehavioural performance of infants treated with morphine compared with clonidine at one-year follow-up.[203] There are no dose effectiveness studies or studies on the effect of assessment or screening procedures on the need for infant NAS medications. Furthermore, almost all intervention studies are opioid-centric with almost no information

or data on the effects of non-opioid substances on the infant, including amphetamine-type substances.[119,204]

6. Postpartum reductions of substance use

There was only limited evidence that assessed the effectiveness of interventions in reducing relapse to heavy and prolonged substance use within six months of delivery apart from smoking. Smoking-cessation interventions included psychological counselling-based interventions using behaviour change techniques such as motivational interviewing. Early results from a single study showed promising results in the use of progesterone to decrease smoking and nicotine replacement therapies but none of the studies showed scalability or longer-term (>6 months) impact.[179,180]

7. Economic impact

The review has highlighted the current gaps in the economic evaluation of interventions to improve the outcomes of women who used substances during and after pregnancy and their affected infants. First, very few studies conducted an economic evaluation alongside randomised trials. Randomised controlled trials are the gold standard of clinical evidence. By conducting economic evaluations with randomised trials, it will better help understand the resources used and the potential cost-effectiveness of strategies to avert substance use and subsequent economic and social savings.[205] Most of the studies have been conducted in North America, which may limit applicability to Australia and other OECD countries.[205] It is necessary to include a broader measurement of outcomes such as budget impact analysis and equity measurement that are more relevant to the health system and policy makers. Furthermore, as the negative effects of maternal substance use on the health and development of affected children and families are likely to be significant, this suggests costs are likely to be high and accumulate over a lifetime. Therefore, all studies need to consider the cost of the whole-of-life approach to substance use rather than the short-term outcomes.

Discussion

Question 1: What interventions are most effective at improving outcomes for women who use substances during pregnancy and their developing fetus during the antenatal period, birth and postnatal period up to 2 years of the child's life?

While it appears to be clear that all pregnant women should be screened for substance use at the first prenatal visit, the evidence is unclear as to how this is best achieved routinely in healthcare settings, or what appropriate responses to identifying substance use in pregnancy should be. Interventions that may be effective in those without a substance-use disorder (e.g. brief advice, education) are not often effective in those with a moderate or severe substance-use disorder. Indeed, the evidence for interventions to manage substance-use disorders other than opioid dependence is patchy. Research supporting methadone and buprenorphine and/or buprenorphine-naloxone for treating opioid-use disorders in pregnancy is established but should not be used as frontline treatment without other interventions, such as behavioural therapies. A range of behavioural and psychosocial interventions have been trialled but there is a lack of consistency in the complexity, methods and measured outcomes, and a lack of clarity about which program components are likely to improve outcomes. Future research is needed to determine how best to screen and engage women in antenatal care in ways that protect patient autonomy and minimise discrimination and stigmatisation. The best and most cost-effective model of care that optimises outcomes for women, their infants and their families is still to be determined. Studies should identify the most efficient and cost-effective infrastructure and staffing requirements necessary to provide the best pregnancy outcomes. More information on long-term maternal and neonatal outcomes would help inform health service policy makers by identifying the most cost-effective interventions.

Question 2: What interventions are most effective at reducing risk of harm in breastfeeding women who use substances?

This review aimed to identify which interventions were most effective in reducing risk of harm in breastfeeding women who use substances. We identified a large amount of literature in relation to breastfeeding and maternal substance use, but the majority of this literature explores or discusses the effects of breastfeeding on either maternal or infant outcomes. There is a need for research on which interventions will reduce risk of harm to breastfeeding mothers who use substances.

Breastfeeding by substance-using women presents challenges to decision making. Women who use substances during pregnancy, and their infants who are exposed to these substances, are known to experience poorer health outcomes than the general population. Exclusive breastfeeding for the first six months of an infant's life, with ongoing breastfeeding up to the infant's second birthday is known to have positive mental and physical health benefits for both infants and mothers.[206] Breastfeeding also supports maternal caregiving capacity and a large, 15-year prospective study of Australian mothers and infants found breastfeeding to be a protective factor against child maltreatment.[207]

It could be argued that the promotion of breastfeeding among this population is an intervention with the potential to improve outcomes, thereby reducing risk. This was the logic that led to the inclusion of one systematic review summarising interventions to support breastfeeding in the context of maternal opioid use. Research on supporting breastfeeding in general populations may apply to substance-using mothers.[208] Certainly, breastfeeding in the context of continued maternal substance use is a complicated issue. Determining whether the risks outweigh the benefits can be difficult for both the mother and healthcare clinicians. There are some studies reporting on women's decision making in relation to breastfeeding, which could be deemed as risk reduction.[209] There are also studies that explore women's experiences of breastfeeding while receiving treatment for opioid addiction.[210] However, these studies are exploratory and did not test specific interventions.

There is an obvious lack of research evidence to guide decision making in relation to breastfeeding and maternal substance use. As a result, the Academy of Breastfeeding Medicine suggests that in most cases, breastfeeding is contraindicated for women who are using substances[211] but there is enough evidence that infants of women receiving treatment for opioid dependence (e.g. methadone, buprenorphine) who are breastfed experience a reduction in the severity and duration of withdrawal symptoms. As such, breastfeeding should be encouraged in this context.

Maternal substance use is considered a significant risk factor for child maltreatment, and can result in the infant being separated from the mother and placed into out-of-home care.[212] Unfortunately, the infant's separation from the mother and subsequent placement into out-of-home care often results in the cessation of breastfeeding, depriving both the infant and mother of the multiple benefits of breastfeeding.[198] As previously noted, current consensus indicates that breastfeeding is generally contraindicated for mothers using substances, with the exception of those mothers receiving treatment for opioid dependence or for mothers who used legal substances such as tobacco and alcohol.[208] Opioid use interferes with oxytocin production and can make the establishment and maintenance of breastfeeding challenging. There are studies that investigate the use of oxytocin for the promotion of lactation[213], but not in relation to women being treated for opioid dependence. Given opioid treatment is the one context currently considered 'safe' for breastfeeding, investigation of the use of oxytocin to assist in lactation may be warranted.

Given the multiple health benefits of human milk, and the current consensus for women using substances (other than treatment for opioid dependence) to not breastfeed their infants, it is surprising there is no research on the use of donor milk. The use of donor milk could potentially provide the infant with many of the health benefits[214] while reducing risk of harm. Upon searching, only one protocol (dated 2014) for a clinical trial using donor milk for infants experiencing neonatal withdrawal syndrome was identified but no study results were identified.[215]

Question 3: What treatments have been shown to be effective for neonatal substance withdrawal syndromes, including withdrawal from opioids, alcohol, methamphetamines, cocaine, cannabis, benzodiazepines, gabapentinoids and tobacco?

The interventions for neonatal substance withdrawal syndrome (NAS) have predominantly been opioid-centric, focusing on pharmacotherapy for withdrawal from maternal opioids and on assessment methods based on narcotic-exposed infants.[11,155] However, with the widespread use of other substances, including alcohol, stimulants (amphetamines, cocaine, MDMA), cannabis and sedatives

(benzodiazepines), and polysubstance use, a greater understanding of the long-term consequences of prenatal substance exposure, and interventions to prevent and treat NAS related to other substances, is required.

The effectiveness of intervention implies that intervention is needed for an established condition. In NAS, the primary aim is to prevent the development of symptoms severe enough to warrant pharmacotherapy. Subsequently, focus then moves towards ameliorating the severity of withdrawal and then the prevention of longer-term effects that are not tangible during the newborn period, including death, neurodevelopmental delay, behavioural problems and other behaviours like substance use. There is also very little in terms of the cost-effectiveness of any NAS interventions except for rooming-in strategies (see section 5, economic evaluation).[216]
There are no intervention studies for preventing or treating NAS or infant intoxication in non-opioid exposure. Breastfeeding is not recommended in methamphetamine-using or cocaine-using mothers as there have been reports of infant death after acute use.[114] The types of medications used for infant withdrawal should be receptor-based, i.e. withdrawal from opioids should be treated with opioids and other drugs by sedatives. Recently, the alpha-2 blocker clonidine has been used increasingly either as the sole or adjunct therapy for severe opioid-associated NAS, but again its effect on longer-term outcomes is unknown.

Multiple opioids are used for treating infants with NAS from maternal opioids, including morphine, methadone and buprenorphine. There are no dose-finding studies, and the doses for NAS treatment vary as much as 200-fold between institutions.[217] The majority of institutions use morphine as the first-line therapy with the addition of phenobarbitone or clonidine if the infant is unresponsive.[218] There is no evidence about weaning or escalation regimes, and duration of treatment can vary from a few days to more than a few months.[119] Methadone is approved by the American Food and Drug Administration for NAS treatment and buprenorphine is used in some US institutions as a long-acting alternative to morphine.[218] For all three opioids, there is no information about the type of dosing regime, the duration of treatment or the effects of medication on long-term outcomes for the infant.

Sedatives, such as phenobarbitone and clonidine, are also used as adjuncts for opioid-based NAS or as sole agents for non-opioid withdrawal. The implication of treatment with these agents on long-term outcomes, again for neurodevelopment, is unknown. Inpatient management of the withdrawing infant is now proposed as the standard of care for Australian institutions, but whether resources allow for this model of care is uncertain. Home visiting programs and family integrated care programs are designed to ensure safety of the family after hospital discharge. None have been evaluated for their effect on infant outcomes after treatment for NAS.

The only ancillary intervention noted is acupuncture.[219] This exerts its effects by modulating neural blood flow and neurotransmitter (including endorphin and serotonin) activity. Various modalities, including laser, tactile and auricular acupuncture have been assessed in small studies for preventing the need for NAS medication and/or the duration of therapy. Acupuncture may be a promising adjunct to other preventive NAS strategies, such as breastfeeding, and further investigation on a large scale is warranted.

Question 4: What interventions are most effective at preventing the resumption of smoking and other substance use within the six-month postnatal period?

The review found limited evidence for interventions that promoted long-term abstinence. The most commonly used interventions, and which appear to be most effective, include a combination of psychosocial interventions, such as behavioural change techniques, motivational interviewing and empowerment techniques, nurse-led counselling, progesterone therapy, and NRT patches/lozenges. There was some evidence of the efficacy of motivational interviewing, but results are mixed and larger-scale randomised controlled trials for preventing the resumption of smoking and other substances with longer follow-up is required.

Applicability

This review was based on studies published in English from Organisation for Economic Co-operation and Development (OECD) countries, with select and specific populations. The findings apply to Australia and can be used as an evidence base for further studies and to develop policies in substance dependence and use in pregnancy and postnatal period.

Conclusion

This review identified significant evidence gaps for interventions to improve outcomes of mothers and infants affected by substance-use disorders. This includes a lack of evidence regarding epidemiology of substance use in pregnancy, as well as a paucity of information regarding the long-term outcomes of both mothers and infants. In addition, the effects of screening tools, assessment methods and treatment strategies for both the mother and infant need to be evaluated and placed into context with the developing child and not only of a newborn infant. Finally, the individual and societal repercussions of models of care must be assessed to ensure best economic, health and societal outcomes.

In conclusion, the review highlights the importance of generating new evidence in this area and the necessity to rapidly adapt practice and policy. Current therapeutic regimes are stagnated and do not consider the agility in which substance use changes, based on availability and cost. The need to incorporate stakeholder input in planning, research, policy development and practice is also crucial to ensure rapid, effective and economical translation of any knowledge. Finally, an integrated system of care is required, in which the focus extends beyond pregnancy and the immediate newborn period to ensure that this very large and vulnerable group of mothers and infants have the best possible outcomes.[220]

Appendices

Appendix 1—Tables

Table 4—Systematic reviews for improvement in pregnancy outcomes in known substance-using mothers (n=10)

Drug	Study	Intervention/Subject area	Results/Findings	Interpretation
Alcohol	DeVido et al. 2015. Alcohol use disorders in pregnancy	Pharmacological interventions, behavioural interventions, motivational enhancement therapy, brief interventions and cognitive behavioural therapies	A summary of effective interventions for alcohol-use disorders in pregnancy: pharmacological interventions, behavioural interventions, motivational enhancement therapy, brief interventions and cognitive behavioural therapies.	This study is an overview of interventions available for alcohol use in pregnancy. Motivational enhancement therapy, brief interventions and cognitive behavioural therapies are all effective.
Any substances	Louw et al. 2018. Substance use in pregnancy: The medical challenge	Psychoeducation, counselling, motivational interviewing techniques, detoxification (to identify the women using alcohol heavily), nicotine replacement therapy, medication-assisted	Psychosocial interventions: Counselling, motivational interviewing and case management are effective for alcohol dependency. Pharmacological intervention: Benzodiazepines used for alcohol withdrawal are limited and conflicting.	Summarised psychosocial intervention for alcohol use (counselling, motivational interviewing and case management) and pharmacological intervention for alcohol (benzodiazepine)

Table 4—Systematic reviews for improvement in pregnancy outcomes in known substance-using mothers (n=10)

Drug	Study	Intervention/Subject area	Results/Findings	Interpretation
		withdrawal from opioids and routine screening	Methadone and buprenorphine are both effective for opioid withdrawal.	and opioid (methadone and buprenorphine).
Any substances	Terplan et al. 2015. Psychosocial interventions for pregnant women in outpatient illicit drug treatment programs compared to other interventions	Contingency management (CM), motivational interviewing (MI)	CM groups decreased hospital stay for neonates.	Both CM and MI did not change pre-term birth rates or maternal toxicity rates when used with other comprehensive care options.
Opioid	Brogly et al. 2014. Prenatal buprenorphine versus methadone exposure and neonatal outcomes: systematic review and meta-analysis	Buprenorphine	Buprenorphine-exposed neonates had a higher mean gestational age and greater weight, length and head circumference at birth than methadone maintenance therapy.	Buprenorphine may result in better short-term outcomes for the newborn infant than methadone.
Opioid	Jones et al. 2012. Methadone and buprenorphine for the management of opioid dependence in pregnancy	Buprenorphine	Buprenorphine resulted in less fetal cardiac and movement suppression, less severe NAS than methadone.	Buprenorphine was associated with less severe NAS relative to methadone.
Opioid	Jones et al. 2012. Buprenorphine treatment of opioid-dependent pregnant women: a comprehensive review	Buprenorphine	Maternal treatment with buprenorphine was associated with reduced physiologic suppression of fetal heart rate and reduced NAS severity.	Buprenorphine produces a less severe NAS than methadone, but there is still a role for methadone in treating opioid dependence during pregnancy.

Table 4—Systematic reviews for improvement in pregnancy outcomes in known substance-using mothers (n=10)

Drug	Study	Intervention/Subject area	Results/Findings	Interpretation
Opioid	Klaman et al. 2017. Treating Women Who Are Pregnant and Parenting for Opioid Use Disorder and the Concurrent Care of Their Infants and Children: Literature Review to Support National Guidance	Pharmacological therapy: Methadone and buprenorphine treatment	Women with opioid-use disorder can be treated safely with methadone or buprenorphine during pregnancy. On average, buprenorphine-receiving women decreased their daily ibuprofen dose, whereas methadone receiving women increased their daily ibuprofen dose.	Buprenorphine and methadone are effective at treating opioid-use disorder. Among these two, buprenorphine also helped to reduce ibuprofen intake compared to methadone.
Opioid	Lund et al. 2013. A comparison of buprenorphine + naloxone to buprenorphine and methadone in the treatment of opioid dependence during pregnancy: Maternal and neonatal outcomes	Pharmacotherapy: Buprenorphine and naloxone	Summary statistics of seven previous studies were collected, and same outcomes were compared for 10 women in each of those studies. The study found no significant differences in maternal outcomes for buprenorphine plus naloxone than buprenorphine, methadone, or methadone-assisted withdrawal.	There was no difference between buprenorphine and naloxone duo treatment compared to buprenorphine alone, methadone or methadone-assisted withdrawal.
Opioid	Wilder et al. 2015. Pharmacological management of opioid-use disorder in pregnant women	Pharmacotherapy: Methadone and buprenorphine	Both buprenorphine and methadone treatment improve maternal, fetal and neonatal outcomes with a lower incidence of preterm birth and less suppression of fetal heart rate acceleration compared to no treatment.	There may be an increasing move towards buprenorphine over methadone for treating opioid-dependent pregnant women.
Opioid	Zedler et al. 2016. Buprenorphine compared with methadone to treat pregnant women with opioid-use disorder:	Buprenorphine	Buprenorphine treatment of maternal opioid-use disorder during pregnancy was not associated with greater harms than methadone treatment. Moderately strong	There is an increasing move towards buprenorphine over methadone.

Table 4—Systematic reviews for improvement in pregnancy outcomes in known substance-using mothers (n=10)

Drug	Study	Intervention/Subject area	Results/Findings	Interpretation
	a systematic review and meta-analysis of safety in the mother, fetus and child		evidence indicated a lower risk of preterm birth, greater birth weight and larger head circumference with buprenorphine.	

Table 5— Primary studies for improvement in pregnancy outcomes in known substance-using mothers (n=18)

Drug	Study	Level	Intervention	Results/Findings	Interpretation
Alcohol	Tzilos et al. 2011. A randomized phase I trial of a brief computer-delivered intervention for alcohol use during pregnancy	II – A randomised controlled trial	Computer-delivered brief intervention	Computer-delivered brief interventions were compared with assessment only. Both groups significantly reduced their self-reported alcohol use at follow-up. Still, the mean birth weight of infants born to women in the intervention group was significantly higher than that for infants of women in the control group.	Women who attended computer-delivered brief interventions delivered infants with higher birth weights than that of the control group.
Any substances	Haabrekke et al. 2014.The perinatal outcome of children born to women with substance dependence detoxified in residential treatment	III-2 – A comparative study with concurrent controls	Substance dependence detoxified in residential buprenorphine treatment	Infants born to mothers in residential detoxification treatment experience less prenatal drug exposure and show better perinatal outcomes on gestational age and head circumference and	Detoxification in residential treatment can be a preferred treatment form for many pregnant women struggling with drug dependence problems and

Table 5— Primary studies for improvement in pregnancy outcomes in known substance-using mothers (n=18)

Drug	Study	Level	Intervention	Results/Findings	Interpretation
	during pregnancy			no NAS, compared with the infants in the earlier cohort whose mothers did not receive residential treatment. No miscarriages, complications or morbidities were associated with residential detoxification treatment.	should possibly be used more often to ensure the best possible perinatal outcome for these children.
Any substances	Lilly et al. 2019. Drug Free Moms and Babies: Qualitative and quantitative program evaluation results from a rural Appalachian state	IV – Case series with either post-test or pre-test/post-test outcomes	Drug Free Moms and Babies (DFMB) pilot program consisted of maternity care and behavioural health providers and community resources Screening, Brief Intervention, and Referral to Treatment (SBIRT) Model, a two-year follow-up, including (but not limited to) peer recovery coaching, ongoing services from DFMB staff, and participation in social service programs. The fourth component required integration with	The pilot program results suggest that the DFMB program was associated with reduced substance use among participants.	Intervention program with multiple components which integrate and evaluate treatment and recovery services for pregnant and postpartum women with substance use disorders are effective in reducing substance use

Table 5— Primary studies for improvement in pregnancy outcomes in known substance-using mothers (n=18)

Drug	Study	Level	Intervention	Results/Findings	Interpretation
			local and state-wide initiates to address SUD in pregnancy		
Any substances	Ordean et al.2011. Comprehensive treatment program for pregnant substance users in a family medicine clinic	III-3 – A comparative study without concurrent controls	Primary care programs based on integrated care models, which incorporated comprehensive addiction and obstetric care	Pregnant substance-using women have reduced substance use outcomes when they receive comprehensive care in a family medicine setting.	Integrated care programs have been associated with significant decreases in substance use in pregnant opioid-dependent women.
Opioid	Bandstra et al. 2012. Maternal Opioid Treatment: Human Experimental Research (MOTHER) Study: maternal, fetal and neonatal outcomes from secondary analyses	II – A randomised controlled trial	Buprenorphine	Buprenorphine-exposed neonates required significantly less morphine to treat NAS and treatment duration was reduced compared with methadone-exposed neonates.	Buprenorphine may improve short-term neonatal outcomes compared to methadone.
Opioid	Buckley et. al. 2013. Predictors of neonatal outcomes amongst a methadone- and/or heroin-dependent population	III-2 – A comparative study with concurrent controls	Methadone Maintenance treatment	Methadone treatment was compared to a heroin-dependent population not treated with methadone. Women using methadone only were more likely to retain custody of their child at hospital discharge compared with those who used both methadone	Methadone treatment was beneficial in predicting the discharge custody status of the neonate. Women who continue to use heroin should not be denied methadone treatment for fear of worse

Table 5— Primary studies for improvement in pregnancy outcomes in known substance-using mothers (n=18)

Drug	Study	Level	Intervention	Results/Findings	Interpretation
				and heroin or only heroin. There was no difference in low birth weights, rate of prematurity or NAS among the groups.	neonatal outcomes.
Opioid	Cochran et al. 2018. Optimizing Pregnancy Treatment Interventions for Moms (OPTI-Mom): A Pilot Study	III-3 – A comparative study without concurrent controls	Patient Navigation Intervention (strength-based case management and motivational interviewing)	Women in the patient navigation program had improved prenatal care, improvement in abstinence from illicit opioids and other substance use, lower levels of depression and enhancements in general health	Patient Navigation is a feasible adjunctive intervention that promises health improvements and service engagement among women in opioid-dependence treatment program.
Opioid	Guille et al. 2020. Treatment of Opioid Use Disorder in Pregnant Women via Telemedicine	III-2 – A comparative study with concurrent controls	Opioid use disorder treatment via telemedicine	There were no statistically significant differences in retention rates in treatment between women receiving treatment via telemedicine vs in person (80.4% vs 92.7%). These findings were also apparent in newborns with NAS (telemedicine: 45.4% vs in person: 63.2%).	Tele-medicine works similarly to in-person treatments in relapse prevention and NAS. This may be useful for the management of clients in remote areas.
Opioid	Gawronski et al. 2013. Neonatal outcomes following in utero exposure to buprenorphine/naloxone or methadone	III-3 – A comparative study without concurrent controls	Buprenorphine/naloxone and methadone treatment	NAS occurred less frequently among infants of mothers treated with buprenorphine/naloxone than those treated with methadone. There was a trend toward shorter	No apparent significant adverse neonatal outcomes were detected following treatment with either

Table 5— Primary studies for improvement in pregnancy outcomes in known substance-using mothers (n=18)

Drug	Study	Level	Intervention	Results/Findings	Interpretation
				treatment duration and lower cumulative dosages of methadone among buprenorphine/naloxone–exposed infants.	buprenorphine/naloxone or methadone maintenance medication.
Opioid	Haabrekke et. al. 2014.The perinatal outcome of children born to women with substance dependence detoxified in residential treatment during pregnancy	III-2 – A comparative study with concurrent controls	Residential withdrawal program	Residential withdrawal programs decreased prenatal drug exposure, leading to better perinatal outcomes, including head circumference and no NAS. No miscarriages, complications, or morbidities were noted with residential withdrawal treatment.	Withdrawal treatments in residential may help pregnant drug-dependent women
Opioid	Mullins et al. 2020. Buprenorphine and Naloxone Versus Buprenorphine for Opioid Use Disorder in Pregnancy: A Cohort Study	III-2 – A comparative study with concurrent controls	Combination of buprenorphine and naloxone v buprenorphine alone	The combined product, relative to the mono-product, was associated with lower odds of neonatal abstinence syndrome: odds ratio (OR) 0.453 (95% confidence interval [CI] 0.253–0.813; P = 0.008).	Compared with buprenorphine monotherapy, the combination of buprenorphine and naloxone was an acceptable alternative pharmacological treatment for opioid use disorder during pregnancy.

Table 5— Primary studies for improvement in pregnancy outcomes in known substance-using mothers (n=18)

Drug	Study	Level	Intervention	Results/Findings	Interpretation
Opioid	Lacroix et al. 2011. Buprenorphine versus methadone in pregnant opioid-dependent women: a prospective multicentre study	III-2 – A comparative study with concurrent controls	Buprenorphine	The study did not observe more frequent malformations or NAS cases in the buprenorphine group than in the methadone-treated group.	Buprenorphine appears to be as safe as methadone for short-term outcomes of the infant.
Opioid	Nguyen et al. 2018. Treating women with opioid use disorder during pregnancy in Appalachia: Initial neonatal outcomes following buprenorphine + naloxone exposure	III-3 – A comparative study without concurrent controls without a parallel control group)	Buprenorphine + naloxone	Gestational age, birth weight, 5-minute Apgar scores and growth parameters were within normal limits for infants whose mothers were treated with buprenorphine and naloxone. The need for pharmacological treatment of NAS was also reduced.	Buprenorphine and naloxone treatment is associated with increased pregnancy duration and better neonatal outcomes.
Opioid	Nechansk Ã¡ et al. 2018. Neonatal outcomes after fetal exposure to methadone and buprenorphine: national registry studies from the Czech Republic and Norway	III-3 – A comparative study without concurrent controls	Buprenorphine	Two national cohorts of women receiving opioid maintenance treatment during pregnancy showed small but not statistically significant differences in neonatal outcomes favouring buprenorphine compared with methadone.	Buprenorphine may improve short term neonatal outcomes compared to methadone

Table 5— Primary studies for improvement in pregnancy outcomes in known substance-using mothers (n=18)

Drug	Study	Level	Intervention	Results/Findings	Interpretation
Opioid	Peles et al. 2017. Newborn birthweight of pregnant women on methadone or buprenorphine maintenance treatment: A national contingency management approach trial	III-2 – A comparative study with concurrent controls	Contingency management	Newborn birth-weight was comparable among the two study arms indicating no advantage with the contingency management approach	Contingency management and methadone did not improve neonatal outcomes compared to methadone alone
Opioid	O'Connor et al. 2011. Observational study of buprenorphine treatment of opioid-dependent pregnant women in a family medicine residency: reports on maternal and infant outcomes	IV – Case series with either post-test or pre-test/post-test outcomes	Buprenorphine	No relationship between the dose of maternal buprenorphine and infant birth weight.	Buprenorphine dose increase did not impact on infant birth weight.
Opioid	Salisbury et. al. 2012. Fetal assessment before and after dosing with buprenorphine or methadone	II – A randomised controlled trial	Buprenorphine	Buprenorphine compared with methadone appeared to result in less suppression of mean fetal heart rate, fetal heart rate reactivity.	Buprenorphine is associated with better fetal physiological parameters compared to methadone.

Table 5— Primary studies for improvement in pregnancy outcomes in known substance-using mothers (n=18)

Drug	Study	Level	Intervention	Results/Findings	Interpretation
Opioid	Unger et al. 2011. Randomized controlled trials in pregnancy: scientific and ethical aspects. Exposure to different opioid medications during pregnancy in an intra-individual comparison	II – A randomised controlled trial	Buprenorphine or methadone	Both medications were effective and safe in reducing illicit opioid relapse and decreasing the risk of preterm labour, but buprenorphine-exposure was associated with reduced NAS severity	Buprenorphine may improve short term neonatal outcomes including NAS compared to methadone

Table 6—Systematic reviews for improvement in maternal outcomes in known substance-using mothers up to 2 years postnatal (n=6)

Drug	Study	Intervention	Results/Findings	Interpretation
Alcohol	Gilinsky et al. 2011. Interventions delivered during antenatal care to reduce alcohol consumption during pregnancy: A systematic review	Interventions included brief interventions, MI, a self-help manual, face-to-face brief intervention, supportive counselling, high-feedback ultrasound and basic educational interventions	Eight trials were included in the review, including six RCTs and two non-RCTs. There was some evidence that single-session face-to-face brief interventions resulted in positive effects on the maintenance of alcohol abstinence during pregnancy. Women choosing abstinence as their drinking goals and heavier-drinking women who participated with a partner were more likely to abstain at follow-up.	Among the different interventions, single-session face-to-face brief interventions resulted in positive effects on the maintenance of alcohol abstinence during pregnancy.

Table 6—Systematic reviews for improvement in maternal outcomes in known substance-using mothers up to 2 years postnatal (n=6)

Drug	Study	Intervention	Results/Findings	Interpretation
Alcohol	Gomez et al. 2020. Are psychosocial interventions effective in reducing alcohol consumption during pregnancy and motherhood? A systematic review and meta-analysis	Behavioural change therapy	Twenty-four studies were included, and data from six studies were pooled. Most common Behavioural Change Therapies included information about consequences, social support, goal setting and action planning. In pregnant women identified as consuming alcohol, psychosocial interventions appeared to increase abstinence rates and reduce drinking compared with usual care or no intervention.	Behavioural Change Therapies may reduce alcohol consumption in mothers with dependent children. It is unclear which behaviour change techniques are contributing to these effects.
Cocaine	Hull et al. 2010. Treatment of cocaine abuse during pregnancy: Translating research to clinical practice	Contingency management (CM)	CM has potential, as it can be used as an adjunct to other treatments and can improve maternal compliance with necessary treatment. Besides CM, screening and brief intervention and computer-directed screening and brief intervention are also helpful for prevention and intervention.	CM has potential, as it can be used as an adjunct to other treatments and can help improve maternal compliance with necessary treatment such as prenatal care and drug dependence counselling.
Any substances	Madgula et al. 2011. Illicit substance use in pregnancy: Effects and management	Counselling, education, relapse prevention and brief intervention to more formal methods, such as CM therapy, CBT and MET	Management of drug dependency requires multidisciplinary intervention. Psychosocial interventions such as CM and cognitive behavioural therapy have been useful in reducing stimulant misuse and improving engagement and compliance. Benzodiazepines and methadone are effective treatments for drug dependency.	Management requires a coordinated, multidisciplinary approach of both pharmacological and psychosocial intervention to ensure individualised care.

Table 6—Systematic reviews for improvement in maternal outcomes in known substance-using mothers up to 2 years postnatal (n=6)

Drug	Study	Intervention	Results/Findings	Interpretation
Any substances	Smedslund et al. 2011. Motivational interviewing for substance abuse	Motivational enhancement therapy (MET)	There were no significant differences between MET and treatment as usual for either follow-up post-intervention, or short or medium follow-up. MET was better than assessment and feedback for medium follow-up. There were no differences in short-term outcomes.	Motivational interviewing helps reduce the use of substances when compared with people who have not received any treatment. However, active treatment is as effective as motivational interviewing.
Any substances	West et al. 2020. Systematic Review of Community- and Home-Based Interventions to Support Parenting and Reduce Risk of Child Maltreatment Among Families with Substance-Exposed Newborns	Community and home-based parenting interventions: Psychoeducation, case management, recovery support	Twelve studies were included. Five studies showed positive effects of community and home-based interventions including psychoeducation, child-focused developmental services, emotional treatment and case management on at least one parenting or child maltreatment outcome.	Community and home-based parenting interventions consisting of psychoeducation, case management and recovery support help reduce child maltreatment outcomes.

Table 7— Primary studies for improvement in maternal outcomes in known substance-using mothers up to 2 years postnatal (n=9)

Drug	Study	Level	Intervention	Results/Findings	Interpretation
Alcohol	Jacobson et al. 2018. Feasibility and Acceptability of Maternal Choline Supplementation in Heavy-Drinking Pregnant Women: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial	II – A randomised controlled trial	Supplementing oral dose of 2g choline until delivery	A choline supplementation program with very heavy drinkers during pregnancy is feasible even among highly disadvantaged and poorly educated women. Adherence rate was good to excellent.	A choline supplementation program with very heavy drinkers during pregnancy is feasible even among highly disadvantaged and poorly educated women.
Alcohol	Osterman et al. 2017. Efficacy of motivational enhancement therapy to decrease alcohol and illicit-substance use in pregnant substance users reporting baseline alcohol use	II – A randomised controlled trial	Motivational enhancement therapy (MET)	MET for pregnant substance users decreased alcohol and illicit-substance use over time relative to usual treatment.	The intervention provides preliminary support for the use of MET to decrease prenatal alcohol use in substance-using women.
Alcohol	Osterman et al. 2014. Single-session motivational intervention to decrease alcohol use during pregnancy	II – A randomised controlled trial	Motivational Interviewing (MI) intervention	Although MI was not effective in decreasing alcohol use, low levels of reported alcohol use by the women at baseline left little room for improvement due to the intervention.	MI not found to be effective in decreasing alcohol use.

Table 7— Primary studies for improvement in maternal outcomes in known substance-using mothers up to 2 years postnatal (n=9)

Drug	Study	Level	Intervention	Results/Findings	Interpretation
Alcohol	Twomey et al. 2010. After Family Treatment Drug Court: Maternal, Infant, and Permanency Outcomes	III-3 – A comparative study without concurrent controls	Family treatment drug court (FTDC)	FTDC used the multidisciplinary, therapeutic approach that linked participants to substance dependence and ancillary treatment services and provided close supervision. The majority of families experienced positive child welfare outcomes, but maternal functioning deteriorated and infant developmental concerns were identified over time.	The long-term benefits of FTDC are questionable.
Any substances	Belt et al. 2012. Psychotherapy groups and individual support to enhance mental health and early dyadic interaction among drug-abusing mothers	III-1 – A pseudo-randomised controlled trial	Psychotherapy groups and individual support	This shows success in sustaining high maternal abstinence, treatment retention, and alleviating depressive symptoms through psychological and individual support to enhance mental health. The findings are discussed in relation to preventing negative transgenerational interaction patterns in the high-risk dyads.	Psychotherapy groups and individual support positively affect drug abstinence and treatment retention, and alleviate depressive symptoms.
Any substances	Hildebrandt et al. 2020. Predictors and moderators of improved social-emotional functioning in mothers with substance-use disorders and their young children enrolled in a relationship-based case	III-3 – A comparative study without concurrent controls	Relationship-based case management program (Parent-Child Assistance Program), relational theory, motivational interviewing, and harm-reduction	Dyads in both treatment groups improved in overall social-emotional functioning as assessed by the Functional Emotional Assessment Scale (FEAS).	Relational theory, motivational interviewing and harm-reduction principles help in improving mother and child socio-emotional functioning.

Table 7— Primary studies for improvement in maternal outcomes in known substance-using mothers up to 2 years postnatal (n=9)

Drug	Study	Level	Intervention	Results/Findings	Interpretation
	management program		principles		
Opioid	Konijnenberg et al. 2016. Mother-child interaction and cognitive development in children prenatally exposed to methadone or buprenorphine	III-3 – A comparative study without concurrent controls	Psycho-social (dyadic interaction)	Reduction in opioid maintenance treatment, maternal depression, and parenting stress and infant developmental status and sensory-integrative functions were observed in the study.	Language-related cognitive skills may be more related to mother-child interaction. Higher cognitive functions requiring precise control over sensorimotor responses may be more sensitive to other factors such as prenatal opioid maintenance therapy exposure.
Opioid	Ordean et al. 2013. Integrated care for pregnant women on methadone maintenance treatment: Canadian primary care cohort study	III-2 – A comparative study with concurrent controls	Methadone Maintenance Therapy	Participants in opioid maintenance had a significant reduction in illicit drugs, prescription opioids, cocaine, cannabis and alcohol use.	Methadone maintenance therapy is associated with significant decreases in substance use in opioid-dependent pregnant women.
Cocaine	Schottenfeld et al. 2011. Contingency management with community reinforcement approach or twelve-step facilitation drug counselling for cocaine dependent	II – A randomised controlled trial	Contingency management (CM)	Significantly greater duration of cocaine abstinence, a higher proportion of cocaine-negative urine tests, and a higher proportion of documented abstinence across the 3-, 6-, 9- and 12-month assessments in the CM group compared with a	CM is efficient for cocaine dependence management alone.

Table 7— Primary studies for improvement in maternal outcomes in known substance-using mothers up to 2 years postnatal (n=9)

Drug	Study	Level	Intervention	Results/Findings	Interpretation
	pregnant women or women with young children			community reinforcement approach and 12-step facilitation drug counselling.	

Table 8— Systematic reviews for improvement in infant outcomes in known substance-using mothers up to 2 years postnatal (n=7)

Drug	Study	Intervention	Results/Findings	Interpretation
Alcohol	Gilinsky et al. 2011. Interventions delivered during antenatal care to reduce alcohol consumption during pregnancy: A systematic review	Interventions included brief interventions, MI, a self-help manual, face-to-face brief intervention, supportive counselling, high-feedback ultrasound and basic educational interventions	Eight trials were included in the review, including six RCTs and two non-RCTs. There was some evidence that single-session face-to-face brief interventions resulted in positive effects on the maintenance of alcohol abstinence during pregnancy. Women choosing abstinence as their drinking goals and heavier-drinking women who participated with a partner were more likely to abstain at follow-up.	Among the different interventions, single-session face-to-face brief interventions resulted in positive effects on the maintenance of alcohol abstinence during pregnancy.
Alcohol	Akison et al. 2018. Effect of Choline Supplementation on Neurological, Cognitive, and Behavioural Outcomes in Offspring Arising from Alcohol Exposure During Development: A	Maternal choline supplementation	Only one clinical study showed significant improvement in information processing in 6-month-old infants from mothers treated with choline during pregnancy. Choline interventions were administered at different times relative to alcohol exposure, affecting their success to prevent specific outcome deficits.	Choline supplementation may help improve child cognitive and behavioural outcomes

Table 8— Systematic reviews for improvement in infant outcomes in known substance-using mothers up to 2 years postnatal (n=7)

Drug	Study	Intervention	Results/Findings	Interpretation
	Quantitative Systematic Review of Clinical and Preclinical Studies			
Alcohol	Rutman et al. 2019. National evaluation of Canadian multi-service FASD prevention programs: Interim findings from the co-creating evidence study	Multi-service prevention programs	These interventions reach vulnerable pregnant/parenting women who face a host of complex circumstances, including substance use, violence, child welfare involvement and inadequate housing. Still, it is typically the intersection of these issues that prompt women to engage with programs.	Multi-service interventions are effective in reducing alcohol intake and help prevent fetal alcohol syndrome disorder.
Alcohol	Turnbull et al. 2012. Home visits during pregnancy and after birth for women with an alcohol or drug problem	Home visits that commenced during pregnancy and/or after birth by teams or individuals consisting of doctors, nurses, social workers, counsellors or trained lay people	Seven studies were included in the review to summarise the effectiveness of home visits. There was no significant difference in continued illicit substance use, continued alcohol use, failure to enrol in a drug treatment program, not breastfeeding at six months, incomplete six-month infant vaccination, child behavioural problems, infants not in the care of the biological mother, non-accidental injury and non-voluntary foster care. Individual studies reported a significant reduction in involvement with child protective services and failure to use postpartum contraception.	Insufficient evidence to recommend the routine use of home visits for pregnant or postpartum women with a drug or alcohol problem.
Opioid	Lee et al. 2020. Neurodevelopmental Outcomes of Children Born to Opioid-Dependent	Prenatal opioid exposure	Opioid-exposed infants and children also performed more poorly than their non-opioid-exposed peers across other outcomes such as internalising (standardised mean difference (SMD)=0.42),	Opioid-exposed infants and children also performed more poorly than their non-opioid-exposed peers in

Table 8— Systematic reviews for improvement in infant outcomes in known substance-using mothers up to 2 years postnatal (n=7)

Drug	Study	Intervention	Results/Findings	Interpretation
	Mothers: A Systematic Review and Meta-Analysis		externalising (SMD=0.66), and attention problems (SMD=0.72) up to 12 years of age.	neurodevelopmental assessments
Opioid	Minozzi et al. 2013. Maintenance agonist treatments for opiate-dependent pregnant women	Pharmacotherapy	Four studies were included. There were no significant differences between methadone and buprenorphine or slow-release morphine, suggesting that no one treatment is superior to another for all relevant outcomes. While methadone seems superior in terms of retaining patients in treatment, buprenorphine results in less severe NAS.	Methadone and buprenorphine both work equally well as treatments for opioid-dependent pregnant women, but buprenorphine may reduce NAS severity.
Opioid	Monnelly et al. 2018. Childhood neurodevelopment after prescription of maintenance methadone for opioid dependency in pregnancy: a systematic review and meta-analysis	Methadone	Forty-one studies were included, and data from eight studies were used in meta-analysis. Among methadone-exposed children, there were poorer Mental Development Index, psychomotor Development Index, visual outcomes and behavioural scores.	Treatment with methadone does not mitigate the risk of neurodevelopmental problems.
Opioid	Yeoh et al. 2019. Cognitive and Motor Outcomes of Children with Prenatal Opioid Exposure: A Systematic Review and Meta-analysis	Prenatal opioid exposure	Collectively, any exposure to prenatal opioids significantly decreased cognitive, motor and language outcomes, evident from as early as 6 months.	Prenatal opioid use decreased cognitive, motor and language outcomes of infants.

Table 9— Primary studies for improvement in infant outcomes in known substance-using mothers up to 2 years postnatal (n=1)

Drug	Study	Level	Intervention	Results/Findings	Interpretation
Opioid	Kaltenbach et al. 2018. Prenatal exposure to methadone or buprenorphine: Early childhood developmental outcomes	II – A randomised controlled trial	Buprenorphine	Changes over time occurred for child outcomes, including expected child increases in weight, height and head circumference, and overall gains in cognitive development, language abilities, sensory processing and temperament. For mothers, significant changes over time in parenting stress suggested increasing difficulties with their children, notably seen in increasing parenting stress and an increasingly enriched home environment.	Buprenorphine is an effective treatment to treat opioid-dependent pregnant women.

Table 10— Studies for the cost effectiveness for the improvement in pregnancy, maternal and infant outcomes in known substance-using mothers up to 2 years postnatal (n=5)

Author, (Year)	Aim of study	Intervention (s) evaluated	Key findings	Interpretation	Quality rating
Barlow et al. 2019. A randomized controlled trial and economic evaluation of the	To evaluate the effectiveness and cost-effectiveness of the Parents under Pressure (PuP) program with parents currently engaged	Intensive one-on-one parenting program (PuP)	The incremental cost-effectiveness ratio (ICER) per quality-adjusted life-years (QALY) gained, and a unit improvement in brief child-abuse potential inventory (BCAP) were estimated to be £34,000 and £1004	PuP involving one-on-one intensive parenting program is cost-effective compared to standard treatment (group format) from a societal perspective.	6

Table 10— Studies for the cost effectiveness for the improvement in pregnancy, maternal and infant outcomes in known substance-using mothers up to 2 years postnatal (n=5)

Author, (Year)	Aim of study	Intervention (s) evaluated	Key findings	Interpretation	Quality rating
Parents Under Pressure program for parents in substance abuse treatment	in community-based substance abuse treatment		respectively. The probability of the PuP program providing value for money is 34.6% and 98.0% if the cost-effectiveness threshold is ≤£20,000 for an additional QALY and improvement in BCAP respectively.		
Goler et al. 2012. Early start: a cost-beneficial perinatal substance abuse program	To conduct a cost–benefit analysis of Early Start, an integrated prenatal intervention program for stopping substance use in pregnancy	Screened-assessed-followed group: Pregnant women who were screened positive (by questionnaire with or without positive urine toxicology) were referred to an Early Start specialist who conducts an in-depth psychosocial assessment where all women will receive education on stopping substance use and brief intervention and	Compared with the screened-assessed-followed and the screened-assessed groups, the screened-positive-only group incurred an additional $7000 adjusted total mean costs (i.e. maternal and infant combined healthcare services costs) and an additional $9000 higher compared with the control group. The implementation of the Early Start program for pregnant women resulted in an overall cost savings of $23,160,694 or $20,813,594 over 3.5 years, or $5,946,741 annualised.	The Early Start program with at least one follow-up visit resulted in an overall cost-saving compared to women who screened but were not followed up.	4

Table 10— Studies for the cost effectiveness for the improvement in pregnancy, maternal and infant outcomes in known substance-using mothers up to 2 years postnatal (n=5)

Author, (Year)	Aim of study	Intervention (s) evaluated	Key findings	Interpretation	Quality rating
		follow-up care visits with routine prenatal care appointments			
Premkumar et al. 2019. Methadone, Buprenorphine, or Detoxification for Management of Perinatal Opioid Use Disorder: A Cost-Effectiveness Analysis	To assess which non-residential treatment – methadone, buprenorphine, or detoxification treatment – is the most cost-effective approach to the management of opioid-use disorder during pregnancy	Pharmacotherapy (buprenorphine or methadone)	Buprenorphine is a dominant strategy (i.e. results in lower costs and higher number of QALYs) when compared with methadone or detoxification. Use of buprenorphine was associated with a cost savings of $8827 per person compared to methadone and $23,647 per person with detoxification. The probabilistic sensitivity analysis showed buprenorphine remains the cost-effective strategy in 70.5% of 100,000 simulations compared to 3.9% with methadone and 25.6% with detoxification.	Buprenorphine is the dominant strategy for management of perinatal opioid-use disorder compared with methadone or detoxification from a healthcare perspective.	8
Thanh et al. 2015. An economic evaluation of the	To evaluate the cost-effectiveness and net monetary benefits of Parent–Child Assistance	Parent-Child Assistance Program (P-CAP) involves three years of	The model estimated that 31 cases of fetal alcohol syndrome disorder (FASD) among 366 women were prevented as a result of the 3-year	P-CAP model is cost-effective compared to standard program for women who use substances, including alcohol, from a societal	8

Table 10— Studies for the cost effectiveness for the improvement in pregnancy, maternal and infant outcomes in known substance-using mothers up to 2 years postnatal (n=5)

Author, (Year)	Aim of study	Intervention (s) evaluated	Key findings	Interpretation	Quality rating
parent-child assistance program for preventing fetal alcohol spectrum disorder in Alberta, Canada	Program to prevent alcohol-exposed births for women with heavy alcohol consumption	receiving home visitation/case management harm reduction mentorship model	P-CAP intervention. The incremental cost per prevented case is $97,000 (range $72,000–$153,000) at a net monetary benefit of $22 million (range $13 million–$31 million). Compared to the incremental lifetime cost per case of FASD ($800,000), the results indicates that P-CAP intervention is cost effective and the net monetary benefit is significant.	perspective.	
Xu et al. 2014. Costs of a motivational enhancement therapy coupled with cognitive behavioural therapy versus brief advice for pregnant substance users	To compare costs of a nurse-administered behavioural intervention for pregnant substance users that integrated motivational enhancement therapy with cognitive behavioural therapy (MET-CBT) to brief advice (BA) administered by an obstetrical provider	Nurse-administered behavioural intervention for pregnant substance users that integrated motivational enhancement therapy with cognitive behavioural therapy	From the societal perspective, the total costs (including participants' time cost) for the two interventions were $120,483 and $27,199 respectively, resulting in a per participant cost of $1469 (95% CI: $1422–$1514) and $316 (95% CI: $302–$330), respectively.	Nurse-administered behavioural intervention for pregnant substance users that integrated motivational enhancement therapy with cognitive behavioural therapy incurred lower average cost per participant compared to brief advice by an obstetrical provider from a societal perspective.	5

Table 11— Studies for the cost effectiveness of breastfeeding intervention study (n=1)

Author, (Year)	Aim of study	Intervention (s) evaluated	Key findings	Interpretation	Quality rating
Avram et al. 2020. A Cost-Effectiveness Analysis of Rooming-in and Breastfeeding in Neonatal Opioid Withdrawal	To investigate the costs and outcomes associated with rooming-in and infant feeding status to determine the optimal management strategy of neonatal opioid withdrawal	Non-pharmacological interventions using rooming-in and breastfeeding	Rooming-in and breastfeeding is the dominant strategy (i.e. less costly and higher QALYs) resulting in a cost-savings of $509.7 million and an additional 12,333 QALYs. Based on a cost-effectiveness threshold of $100,000 per QALY, the rooming-in and breastfeeding model was cost-effective. The Monte Carlo simulation of 10,000 trials found rooming-in was cost-effective in 94.2% of the runs.	Rooming-in model is cost-effective compared to no rooming-in from a societal perspective.	8

Table 12—Systematic reviews for the treatment of neonatal substance withdrawal syndrome (n=13)

Study	Intervention	Results/Findings	Interpretation
Disher et al. 2019. Pharmacological Treatments for NAS: A Systematic	Pharmacological treatment for NAS	Eighteen studies included. Compared with other pharmacological therapies (clonidine, diluted tincture of opium and clonidine, diluted tincture of opium, morphine, methadone, and phenobarbital),	Buprenorphine is superior compared to morphine.

Table 12—Systematic reviews for the treatment of neonatal substance withdrawal syndrome (n=13)

Study	Intervention	Results/Findings	Interpretation
Review and Network Meta-analysis		buprenorphine is associated with shorter hospital length of stay (LOS) and duration of pharmacotherapy for NAS. Morphine and phenobarbital monotherapies were the lowest-ranked opioid for length of treatment and LOS. Research is needed to compare buprenorphine and morphine for NAS.	The reviewers cautioned about small samples, small number of RCTs, heterogeneous methods and lack of long-term outcome and suggest caution in interpreting evidence.
Lee et al. 2019. Comparative effectiveness of opioid replacement agents for neonatal opioid withdrawal syndrome: a systematic review and meta-analysis	Pharmacological treatment for NAS	Eleven studies were included. Meta-analysis showed no significant difference in the length of treatment (LOT) or length of stay (LOS) between methadone and morphine treatment. However, the use of adjunct drugs was significantly higher with the use of morphine. Buprenorphine was associated with shorter length of treatment and hospital stay compared with morphine but no significant difference in use of adjunct treatment. High-quality research is needed to examine the safety and long-term child development outcomes of pharmacotherapy for NAS beyond the initial birth hospitalisation.	Methadone and buprenorphine may achieve better short-term outcomes compared with morphine.
MacVicar et al. 2019. Systematic mixed-study	Supportive care	Fourteen studies were included. The overall findings found non-pharmaceutical management (consolation therapy, rooming-in of mother and	Providing and optimising non-pharmacological management for infants at risk of NAS improves outcomes.

Table 12—Systematic reviews for the treatment of neonatal substance withdrawal syndrome (n=13)

Study	Intervention	Results/Findings	Interpretation
review of nonpharmacological management of NAS		baby) and family integrated care was associated with a reduced need for pharmacotherapy and a shorter hospital stay. Other complementary therapies of acupuncture, infant massage, vibrotactile stimulation and Reiki were assessed, and none reported adverse effect. The review highlighted the need to educate practitioners about substance-use disorders and interventions for NAS.	The reviewers cautioned the generalisation of study findings to other healthcare settings and contexts.
Slowiczek et al. 2018. Morphine and Methadone for NAS: A Systematic review	Pharmacological treatment for NAS	Five studies. Conflicting results on length of stay (LOS) and length of treatment (LOT) across studies to draw a meaningful conclusion. For example, LOT ranged between 7.46 and 22.9 days for infants receiving morphine compared with 13.9 to 38.08 days for those receiving methadone, while mean LOS ranged between 21.5 and 44.23 days. Adverse effects were not described as outcomes in any of the studies. The use of adjunct therapy differs among studies with some studies reporting a combination of methadone or morphine with clonidine, clonazepam or phenobarbital. High-quality research is needed to determine the comparative efficacy of morphine and methadone.	Limited evidence on the comparative efficacy of morphine and methadone for NAS.

Table 12—Systematic reviews for the treatment of neonatal substance withdrawal syndrome (n=13)

Study	Intervention	Results/Findings	Interpretation
Wachman et al. 2018. Neonatal Abstinence Syndrome: Advances in Diagnosis and Treatment	Pharmacotherapy and nonpharmacological treatment for NAS	Fifty-three studies were included. The overall findings showed that although non-pharmacological interventions such as rooming-in, breastfeeding and feeding practice are associated with a decreased need for pharmacological treatment and result in shorter hospitalisations, interventions in these studies are heterogeneous and retrospective. High-quality research to support the evidence is needed. Eleven studies examined pharmacological treatment for NAS. Evidence on which medication is most effective for NAS is inconclusive and limited.	The Eat, Sleep and Console approach was associated with lower rates of pharmacological treatment for NAS. Non-pharmacological interventions such as rooming-in and breastfeeding were associated with improved neonatal outcomes (shorter hospital stay and duration for pharmacological treatment for NAS). Buprenorphine is associated with improved neonatal outcomes (shorter hospital stay and duration for pharmacological treatment for NAS).
Xiao et al. 2019. Methadone versus morphine treatment outcomes in neonatal abstinence syndrome: A meta-analysis	Pharmacological treatment for NAS	Five studies were included. A pooled analysis of three studies found no significant difference between morphine and methadone treatment on opioid treatment days. Meta-analysis of two studies found no significant difference in the opioid treatment days, length of stay or duration of treatment between morphine and methadone treatment.	No evidence supports the use of morphine or methadone therapy to improve neonatal outcomes (length of stay and duration of treatment).
McQueen et al. 2019. Systematic Review of Newborn Feeding Method and Outcomes Related to Neonatal Abstinence Syndrome	Feeding method	Eight studies were included. The review found that breastfeeding was associated with a decreased incidence and duration of pharmacological treatment, shorter hospital length of stay, and decreased severity of NAS for infants exposed to methadone compared with formula-fed infants.	Breastfeeding improves neonatal outcomes compared to formula-fed infants exposed to methadone.

Table 12—Systematic reviews for the treatment of neonatal substance withdrawal syndrome (n=13)

Study	Intervention	Results/Findings	Interpretation
		The evidence on the association between newborn feeding method and NAS among newborns exposed to buprenorphine was unclear.	
Murphy-Oikonen et al. 2018. Outpatient pharmacological weaning for neonatal abstinence syndrome: a systematic review	Inpatient and outpatient management	Six studies were included. All studies identified that outpatient weaning for select infants was associated with shorter hospitalisation than infants weaned in-hospital only and may be potentially effective in reducing associated healthcare costs. However, the duration of pharmacological treatment was longer in the outpatient weaning groups in the majority of the studies. Research on long-term effects of pharmacological treatment on infant development outcomes are needed.	Outpatient weaning may be beneficial compared to weaning in-hospital only for infants with NAS, but reviewers cautioned on the longer duration of treatment with outpatient weaning.
Mangat et al. 2019. Pharmacological and non-pharmacological treatments for the Neonatal Abstinence Syndrome (NAS)	Pharmacological and non-pharmacological treatment for NAS	Although this is a narrative review of both pharmacological and non-pharmacological therapies, this review provided a useful overview of non-opioid adjunct therapy such as clonidine and phenobarbital. Although phenobarbital is more commonly used than clonidine due to added efficacy in circumstances of polysubstance exposure, there remains a lack of evidence on the best adjunct therapy or regimen for NAS. When clonidine is compared with morphine as the primary treatment, clonidine has shorter median	Clonidine has a shorter median length of treatment compared with morphine.

Table 12—Systematic reviews for the treatment of neonatal substance withdrawal syndrome (n=13)

Study	Intervention	Results/Findings	Interpretation
		length of treatment (28 days compared to 39). The results are limited by its small sample size.	
Osborn et al. 2010. Opiate treatment for opiate withdrawal in newborn infants	Pharmacological treatment for NAS	Nine studies included. Meta-analysis of four studies comparing opiate and phenobarbitone found no significant difference in treatment failure (i.e. failure to reduce a standardised score of NAS to clinically 'safe' level or use of additional pharmacological treatments for control of NAS in the neonatal period) but opiate treatment may reduce incidences of seizures. When compared to diazepam, opiates reduced the incidence of treatment failure. Compared to supportive care only, opiates may reduce time to regain birth weight and duration of supportive care but increase duration of hospital stay. No evidence on treatment failure. However, this is based on the results of only one study.	Opiates such as morphine or dilute tincture of opium may be used as initial treatment for opiate withdrawal in newborn infants.
Osborn et al. 2010. Sedatives for opiate withdrawal in newborn infants	Pharmacological treatment for NAS	Seven studies were included. Individual studies in this review found the use of phenobarbitone compared to supportive care alone reduces the amount of time an infant needs supportive care, is better than diazepam at preventing treatment failure, and reduces the severity of withdrawal in infants treated with an opiate. In infants treated with an opiate, the addition of a sedative (phenobarbitone or clonidine) may reduce withdrawal severity, although safety and efficacy	Phenobarbitone is the preferred adjunct of choice to ameliorate symptoms in infants with NAS.

Table 12—Systematic reviews for the treatment of neonatal substance withdrawal syndrome (n=13)

Study	Intervention	Results/Findings	Interpretation
		need confirming. Overall studies included in the review are of poor quality. The safety and long-term effects of use of phenobarbitone on an infant's development have not been determined.	
MacMillan et al. 2018. Association of Rooming-in With Outcomes for Neonatal Abstinence Syndrome A Systematic Review and Meta-analysis	Rooming-in	Six studies were included. Rooming-in is associated with reduced need for pharmacotherapy and length of stay compared with those cared for in neonatal intensive care units. No evidence that rooming-in was associated with a significant increase in hospital readmission. No reported adverse effects with rooming-in.	Rooming-in is recommended as a preferred inpatient care model for NAS.
MacMullen et al. 2014. Evidence-Based Interventions for Neonatal Abstinence Syndrome	Nursing management	Twenty-four articles and three internet sites for guidelines and a book were included. Current literature suggests the beneficial use of supportive interventions, including swaddling, gentle awakening and a quiet environment to minimise the physiologic effect of central and autonomic system dysfunction. High-calorie formula is recommended in several studies with small frequent feeds to aid in tolerating feeding and improving digestion.	Supportive interventions are recommended to minimise the physiologic effects of NAS and promotes more effective mothering. Small frequent feeding is recommended to assist in tolerating feeding and improve digestion.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
Bada et al. 2014. Morphine Versus Clonidine for Neonatal Abstinence Syndrome	II – A randomised controlled trial	Pharmacotherapy	The morphine group had a longer duration of treatment compared with the clonidine group (median: 39 vs 28 days; p=0.02). Neurobehavioral performance was comparable between the two groups except for mean lethargy score, which was higher in the clonidine group than the morphine group (5.13 vs 3.6, p=0.03). One-year motor, cognitive and language scores did not differ between two groups. More research is needed to confirm the findings and examine the long-term effect of treatment on health and development in infant with NAS.	Clonidine may be a favourable alternative to morphine as a single-drug therapy for short-term NAS but long-term outcomes need to be examined.
Brusseau et al. 2019. Clonidine versus phenobarbital as adjunctive therapy for neonatal abstinence syndrome	II – A randomised controlled trial	Pharmacotherapy	The clonidine group had a longer duration of treatment (34.4 days vs 25.5 days, p=0.026), higher average time from initiation of adjunctive therapy until discharge (33.8 vs 22 days, p=0.042), and longer length of hospital stay (41.8 vs 31 days, p=0.018) compared to the phenobarbital group. Six of 14 infants (42.9%) in the clonidine group experienced adverse events	Compared to clonidine, phenobarbital as an adjunctive therapy is more effective for improving short-term outcomes (in terms of shorter duration of morphine therapy, inpatient adjunctive days and length of stay) in infants who failed their first-line treatment.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
			compared to none in the phenobarbital group. A comparable proportion of infants required triple therapy in both groups (morphine, phenobarbital and clonidine).	
Bogen et al. 2018. Randomized Clinical Trial of Standard- Versus High-Calorie Formula for Methadone-Exposed Infants: A Feasibility Study	II – A randomised controlled trial	Supportive care: Infant feeding methods – hypercaloric feeds	No significant difference in days to weight nadir, maximum per cent weight loss, days to return to birth weight, and percentage weight change per day (days 3 to 14) between infants in the high-calorie formula group and standard calorie group. However, the high-calorie group had a significant per cent weight gained per day when assessed to 21 days.	Early initiation of high-calorie formula improves weight gain patterns for infants with in-utero exposure to methadone.
Brown et al. 2015. Methadone versus morphine for treatment of neonatal abstinence syndrome: A prospective randomized clinical trial	II – A randomised controlled trial	Pharmacotherapy	Methadone-treated infants had a shorter duration of opioid treatment for NAS compared with morphine treated infants (median days, 14 vs 21, p=0.008).	Methadone reduces duration of withdrawal treatment compared with morphine.
Davis et al. 2018. Comparison of Safety and Efficacy of Methadone vs Morphine	II – A randomised controlled trial	Pharmacotherapy	The study used a novel approach of determining treatment doses based on infant weight and NAS severity, as assessed by Finnegan scores, to assess	Methadone for NAS improves short-term neonatal outcomes compared with morphine.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
for Treatment of Neonatal Abstinence Syndrome			the outcomes of safety and efficacy between infants who received methadone and infants who received morphine for NAS treatment. Methadone was associated with a significant reduction in median length of stay and length of treatment compared with morphine. There was a non-significant difference in the use of phenobarbital between the two groups. Both groups had an equal number of adverse events. The study found maternal cigarette smoking to be associated with a need for higher doses of opioids and longer length of stay and treatment for NAS.	
Kraft et al. 2017. Buprenorphine for the Treatment of the Neonatal Abstinence Syndrome	II – A randomised controlled trial	Pharmacotherapy	This study compared sublingual buprenorphine and oral morphine for NAS. Sublingual buprenorphine for NAS resulted in shorter median duration of treatment (15 days vs 28 days, $p<0.001$) and median length of hospital stay (21 days vs 33 days, $p<0.001$) compared with morphine.	Sublingual buprenorphine was more effective compared with oral morphine in reducing duration of treatment and length of stay.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
			Adjunctive phenobarbital was administered in 5 of 33 infants (15%) in the buprenorphine group and in 7 of 30 infants (23%) in the morphine group (p=0.36). Rates of adverse events were similar in the two groups.	
Raith et al. 2015. Laser Acupuncture for Neonatal Abstinence Syndrome: A Randomized Controlled Trial	II – A randomised controlled trial	Ancillary or non-pharmacological interventions	The study compared acupuncture (acupuncture and pharmacological therapy of morphine and phenobarbital) and control group (pharmacological therapy alone) for NAS. The acupuncture group had significantly shorter median drug treatment duration (28 days vs 39 days, p=0.019) and shorter length of hospital stay (35 vs 50 days, p=0=0.048) compared with the control group. Further research with larger samples is needed to confirm the findings.	There is evidence that adjuvant laser acupuncture is an effective adjunct in a multimodal therapy program for NAS.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
Schwartz et al. 2011. Auricular acupressure augmentation of standard medical management of the neonatal narcotic abstinence syndrome	II – A randomised controlled trial	Ancillary or non-pharmacological interventions	The study examined the safety and potential efficacy of auricular acupressure augmentation for treatment of infants compared with standard medical management (pharmacological treatment with support from diluted deodorised tincture of opium [DTO] or phenobarbital) for NAS. No significant difference in outcomes in terms of length of stay or amount of pharmacological support to control NAS symptoms in infants who received acupressure and standard management. The median length of stay was (22.4 days vs 22.6 days) and 86.5% vs 76.9% required DTO in the control group and treatment group, respectively.	The study suggests the potential benefits of acupuncture-based interventions for NAS.
Bhatt-Mehta et al. 2014. Effectiveness of a Clinical Pathway With Methadone Treatment Protocol for Treatment of Neonatal Abstinence Syndrome Following In Utero	III-3 – A comparative study without concurrent controls	Pharmacotherapy	In this retrospective observational study to assess the effectiveness of methadone for NAS, 57 of 60 patients (95%) initiated methadone treatment according to a predefined clinical treatment pathway. This pathway incorporates screening for NAS, supportive care and systematic	The study found that despite strict adherence to clinical pathways, there were substantial variabilities in neonatal outcomes (length of stay and treatment duration) suggesting other contributory factors for the observed variability.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
Drug Exposure to Substances of Abuse			methadone dosing escalating and de-escalating based on withdrawal scores. Despite adherence to protocol, the study found deviation from the protocol at 48 and 72 hours of treatment with approximately 59% and 13% of the patients still on methadone at more than the prescribed amount to control neonatal abstinence syndrome. The mean ± standard deviation of the total methadone exposure was 1.99 ± 1.63 mg/kg, length of treatment was 11.66 ± 9.02 days, and total hospital length of stay was 22.43 ± 29.3 days, suggesting significant variability in response. Length of stay (LOS) was shorter for infants whose mothers were prescribed methadone or buprenorphine during pregnancy compared with those who did not receive such treatment. This suggests that in-utero treatment compared with no treatment leads to quicker mother-infant bonding opportunities and transition to the home	

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
			environment, both of which have been identified as significant factors in the neurodevelopment of the neonate. Both birth weight and gestation age were not significant contributors to the LOS.	
DeAtley et al. 2017. Evaluation of the Effectiveness of Two Morphine Protocols to Treat Neonatal Abstinence Syndrome in a Level II Nursery in a Community Hospital	III-2 – A comparative study with concurrent controls	Model of care	The study assessed the effect of length of stay and treatment duration and pre-post implementation of different dosing protocols of morphine therapy for NAS. In the protocol 1 group, neonates received an initial dose of morphine of 0.04mg/kg administered orally every 4 hours. Under protocol 2, neonates received an initial dose of morphine of 0.06mg/kg administered orally every 3 hours. The study found comparable average length of stay (28.65 vs 21 days) and average duration of treatment (18.3 vs 25.4 days) between the two morphine protocol groups.	Despite the lack of statistical differences, the study findings showed potential benefits in morphine protocol of an initial dose of morphine 0.06mg/kg administered orally every 3 hours for improving neonatal outcomes.
Hall et al 2015. Cohort analysis of a pharmacokinetic-modelled	III-3 – A comparative study without concurrent	Model of care	This retrospective cohort study assessed the implementation of a stringent protocol (i.e. completed opioid weaning as	Implementation of a stringent weaning protocol (complete weaning as inpatient) decreased

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
methadone weaning optimization for neonatal abstinence syndrome	controls		inpatients and compliance with outlined weaning phases guidelines). The study reported a shorter duration of opioid treatment (23.0 vs 34.0 days, p<0.001) and length of inpatient hospital stay (23.7 vs 31.6 days, p<0.001) with the strict protocol compared with standard protocol. There was also a significantly lower rate of adjunctive therapy in the strict protocol group compared with the standard group.	length of stay and duration of treatment.
Howard et al. 2017. Impact of parental presence at infants' bedside on neonatal abstinence syndrome	III-3 – A comparative study without concurrent controls	Supportive care, rooming-in	The retrospective single-centre study examined parental presence and NAS outcomes. The study found 100% parental presence was associated with shorter length of stay (by 9 days, p<0.01) and duration of treatment (by 8 days of infant opioid therapy, p<.001) compared with when a parent was not present. Parental presence was associated with decreased NAS severity after adjusting for rate of breastfeeding.	Greater parental presence resulted in beneficial effects on neonatal outcomes (reduced NAS score and duration of treatment).

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
Isemann et al. 2011. Maternal and neonatal factors impacting response to methadone therapy in infants treated for neonatal abstinence syndrome	III-2 – A comparative study with concurrent controls	Supportive care: Infant feeding methods including breastfeeding and hypercaloric feeds	This retrospective study used medical chart records to examine maternal and neonatal factors affecting responses to pharmacotherapy for NAS. Maternal breast milk (MBM) was associated with a shorter median duration of methadone therapy in pre-term and term infants. Compared with formula-led infants, ingestion of MBM was associated with shorter length of stay (median 12.5 vs 18.5 days, p=0.001). Compared with infants managed with methadone alone, infants that required adjunctive therapy with phenobarbital had longer LOS (median 24.5 vs 13.0 days, p<.001) and were born from mothers on higher doses of methadone (median 90 vs 60, p=0.04).	The findings suggest that feeding with maternal breastmilk improves response to pharmacotherapy for NAS.
Isemann et al, 2017. Early Prediction Tool to Identify the Need for Pharmacotherapy in Infants at Risk of	III-3 – A comparative study without concurrent controls	Assessment methods	This retrospective study examined the validity of a predictive tool to predict the need for pharmacological treatment for NAS within 2 days of birth.	The study findings suggest the potential use of predictive tool as part of the care management protocol.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
Neonatal Abstinence Syndrome			An NAS prediction tool combining three clinical signs with and without category of opioid exposure showed high positive predictive values for requiring or not requiring pharmacotherapy.	
MacVicar et al. 2018. Breastfeeding and the substance-exposed mother and baby	III-2 – A comparative study with concurrent controls	Supportive care: Infant feeding methods, including breastfeeding and hypercaloric feeds	The study used a mixed method including an RCT to assess the feasibility of intervention programs including breastfeeding advice, promotion of maternal self-efficacy through encouragement and provision of neonatal self-consolation techniques within a low-stimuli environment. Infants in the intervention group were less likely to require pharmacotherapy (30% vs 100%) and were discharged earlier than formula-fed infants (10.8 and 30.0 days, respectively). P-value not provided. The study findings were limited by a small sample size (N=14 infants).	The findings highlight the feasibility of tailored breastfeeding support to promote and support breastfeeding among substance-using mothers.
McQueen et al. 2011.The impact of infant feeding method on neonatal abstinence scores of	III-2 – A comparative study with concurrent	Supportive care: Infant feeding methods, including	This retrospective study assessed feeding method for infants exposed to methadone in-utero.	Breastfeeding may offer beneficial outcomes for infants exposed in-utero to methadone.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
methadone-exposed infants	controls	breastfeeding and hypercaloric feeds	Infants who were predominantly breastfed had significantly fewer NAS scores done and lower mean scores suggesting decreased severity and duration of NAS symptoms compared with infants who were combination fed or predominantly formula fed. The study findings were limited by a small sample size (n=28 mothers).	
O-Connor et al. 2013. Breastfeeding rates and the relationship between breastfeeding and neonatal abstinence syndrome in women maintained on buprenorphine during pregnancy	III-2 – A comparative study with concurrent controls	Supportive care: Infant feeding methods, including breastfeeding and hypercaloric feeds	This retrospective chart review assessed whether breastfeeding improves outcomes. Though not statistically significant, breastfed infants were less likely to require pharmacological treatment (23.1% vs 30.0%, p=0.56) and had shorter length of stay (7.08 vs 6.60 days, p=0.35) compared to non-breastfed infants.	Breastfeeding may reduce severity of NAS.
Oji-Mmuo et al. 2018. Heightened sympathetic arousal is demonstrated by skin conductance responsivity to auditory stimuli in a small cohort of	III-2 – A comparative study with concurrent controls	Ancillary or non-pharmacological interventions	This prospective single-centre study assessed the utility of skin conductance (SC), an objective tool used for physiologic measurement of pain and sympathetic arousal in NAS.	The findings suggest a potential use of SC in clinical setting to assess infant condition after pharmacotherapy to determine the need for ongoing care post-discharge.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
neonates with opiate withdrawal			Infants who were morphine treated (MT) had a significantly higher skin conductance responsivity to an auditory stimulus (basal, EDR/seconds and mean of peaks) near discharge ($p<0.05$) and longer length of stay 32 vs 7 days ($p<0.05$) compared to the non-MT group. The mean + standard error peak morphine dose was 0.85 + 0.20mg/kg/day in the MT group.	
Pritham et al. 2012. Opioid Dependency in Pregnancy and Length of Stay for Neonatal Abstinence Syndrome	III-3 – A comparative study without concurrent controls	Supportive care: Infant feeding methods, including breastfeeding and hypercaloric feeds	This retrospective study examined opioid replacement therapy in pregnancy and its effect on neonatal outcomes. Infants who received exclusive breastmilk had 3.3 fewer days of stay than mixed (breastfed and formula-fed) infants and 6.6 fewer days than formula only [adjusted coefficient -3.323 (standard error 1.69), p=0.05] Maternal methadone and concomitant in-utero exposure to benzodiazepines increased length of stay for neonates.	Maternal concomitant use of benzodiazepines may worsen neonatal withdrawal outcomes and increase length of stay. Breastfeeding was associated with improved neonatal outcomes and infant attachment/ bonding.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
Short et al. 2016. The association between breastfeeding and length of hospital stay among infants diagnosed with neonatal abstinence syndrome: A population-based study of in-hospital births.	III-2 – A comparative study with concurrent controls	Supportive care: Infant feeding methods, including breastfeeding and hypercaloric feeds	This retrospective study assessed the association between breastfeeding and length of stay among infants with NAS. Length of hospitalisation was reduced by 9.4% in the breastfed group compared with the non-breastfed group (median 10 days vs 12 days respectively). There was a significant inverse relationship between breastfeeding and length of stay (B=−0.085, p=0.008) after controlling for covariates.	Breastfeeding was associated with improved neonatal outcomes (length of stay).
Smirk et al. 2014. Home-based detoxification for neonatal abstinence syndrome reduces length of hospital admission without prolonging treatment.	III-2 – A comparative study with concurrent controls	Model of care - inpatient and outpatient management	Home-based detoxification reduced hospital stays (18.9 vs 39.6, p<0.001) and increased breastfeeding at discharge (45% vs 22%, p=0.022) compared with standard inpatient care. Comparable outcomes on total dose morphine and treatment with phenobarbitone in both groups.	The finding suggests a beneficial effect with home-based detoxification for some selected infants without prolonged exposure to opiates.
Welle-Strand et al. 2013. Breastfeeding reduces the need for withdrawal treatment in opioid-exposed infants	III-2 – A comparative study with concurrent controls	Supportive care: Infant feeding methods, including breastfeeding and	The study assessed the rate of breastfeeding among women in opioid maintenance treatment and effect on neonatal outcomes.	The findings suggest breastfeeding may have a beneficial effect on inpatient outcomes for NAS.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
		hypercaloric feeds	Breastfed infants had a significantly lower incidence of NAS needing pharmacological treatment (53% vs 80%, p<0.05) and shorter duration of pharmacological NAS treatment (28.6 ± 19.1 vs 46.7 ± 26.3, p<0.05) than non-breastfed infants, respectively.	
Zuzarte et al. 2017. Vibrotactile stimulation: A non-pharmacological intervention for opioid-exposed newborns	III-2 – A comparative study with concurrent controls	Ancillary or non-pharmacological interventions	The prospective single-centre study examined the therapeutic potential of stochastic vibrotactile stimulation as a complementary non-pharmacological intervention for NAS. Stochastic vibrotactile stimulation (SVS) reduced prolonged movement activity by 14% and improved cardiac (2.6 beats/min) and respiratory function (5.6 breaths/min) compared with non-SVS intervention in opioid-exposed newborns diagnosed with NAS. No adverse effects associated with SVS. More research on safety and efficacy of SVS is needed.	SVS may provide an effective complementary non-pharmacological intervention for NAS.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
Chisamore et al. 2016. A Comparison of Morphine Delivery in Neonatal Opioid Withdrawal	III-3 – A comparative study without concurrent controls	Pharmacotherapy	This is a retrospective study to compare weight-based protocol and symptom-only protocol on neonatal outcomes. The symptom-only model was more likely to receive morphine (OR 7.0, 95% CI: 3.4-14.5, p<0.001) and a significantly higher LOS compared to those in the weight-based model (15 days vs 6 days, p<0.001).	Chisamore et al. 2016. A Comparison of Morphine Delivery in Neonatal Opioid Withdrawal
Crook et al. 2017. Prenatal Breastfeeding Education: Impact on infants with neonatal abstinence syndrome	III-3 – A comparative study without concurrent controls	Supportive care: Infant feeding methods, including breastfeeding and hypercaloric feeds	The pre-post intervention study assessed the rates of breastfeeding following implementation of a Quality improvement (QI) initiative that promotes, protects and supports breastfeeding for mother at risk of having infants with NAS. Implementation following QI initiatives reduced average length of stay: Baseline 18.8 days compared to 13.1 days (BFS cohort) and 10.4 days (BFS plus breastfeeding education) (p<0.001) and decreased need for pharmacological treatment: Baseline 67.3% vs 53.9% (BFS) and 34.8% (BFS + education), p<0.001.	Breastfeeding education and support for mothers at risk of delivering an infant with NAS to promote breastfeeding rates and decrease need for pharmacological treatment.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
Crook et al. 2017. Prenatal Breastfeeding Education: Impact on infants with neonatal abstinence syndrome	III-3 – A comparative study without concurrent controls	Supportive care: Infant feeding methods, including breastfeeding and hypercaloric feeds	The pre-post intervention study assessed the rates of breastfeeding following implementation of a Quality improvement (QI) initiative that promotes, protects and supports breastfeeding for mother at risk of having infants with NAS. Implementation following QI initiatives reduced average length of stay: Baseline 18.8 days compared to 13.1 days (BFS cohort) and 10.4 days (BFS plus breastfeeding education) ($p<0.001$) and decreased need for pharmacological treatment: Baseline 67.3% vs 53.9% (BFS) and 34.8% (BFS + education), $p<0.001$.	The findings show clonidine has a beneficial effect on inpatient outcomes for NAS and could potentially act as an alternate treatment for NAS.
Esmaeili et al. 2010. Treatment of neonatal abstinence syndrome with clonidine and chloral hydrate	III-2 – A comparative study with concurrent controls	Pharmacotherapy	This is a retrospective study to assess a treatment regime with either clonidine or tapering dosages of morphine. The duration of treatment and length of stay were significantly shorter (median 14 days vs 35 days, median 32 vs 44 days, respectively) in the clonidine group compared with the morphine group. In addition, patients in the clonidine group had significantly fewer withdrawal symptoms.	The findings show clonidine has a beneficial effect on inpatient outcomes for NAS and could potentially act as an alternate treatment for NAS.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
Favara et al. 2019. Maternal breast milk feeding and length of treatment in infants with neonatal abstinence syndrome	III-3 – A comparative study without concurrent controls	Supportive care: Infant feeding methods, including breastfeeding and hypercaloric feeds	This is a retrospective study that compared outcomes of infants who received any amount of breastmilk and infants who were exclusively formula-fed. Median length of pharmacological treatment was significantly lower in infants who received any breastmilk (BM) (14 days) compared with “no BM” group (17 days, p=0.04). Similarly, median length of hospitalisation was significantly reduced in “any BM” group (19 days vs 20 days), which remained significant after adjustment for confounders (p=0.01). There was no difference in hospital readmission rates.	Any amount of breastmilk was associated with better inpatients outcomes (hospital stay and treatment duration) compared to formula only for NAS.
Gullickson et al (2018) Comparison of outcomes between morphine and concomitant morphine and clonidine treatments for neonatal abstinence syndrome	III-2 – A comparative study with concurrent controls	Pharmacotherapy	This is a retrospective cohort study that assessed outcomes of infants after treatment with morphine and clonidine and a morphine-only regime for NAS. Compared to infants who received morphine alone (n=22), infants who received morphine and clonidine (n=100) had significantly longer length of treatment	The combination of morphine and clonidine was associated with significantly longer length of treatment and higher peak morphine dose compared with morphine alone.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
			(mean 11.3 days vs 19.7 days, p<0.01) and a higher average peak morphine (0.14mg/kg g3h vs 0.10mg/kg q3h), p=0.04).	
Hall et al. 2015. Cohort analysis of a pharmacokinetic-modelled methadone weaning optimization for neonatal abstinence syndrome	III-3 – A comparative study without concurrent controls	Pharmacotherapy	This is a pre-post cohort study to assess outcomes using optimised methadone weaning protocol – pharmacokinetic modelling and standard methadone weaning. Newborn infants treated with the revised methadone protocol had a shorter duration of treatment (13.1 vs 16.4 days, p<0.001) and length of inpatient stay (18.3 vs 21.7 days, p<0.001) compared with standard protocol methadone protocol. There were comparable outcomes on total methadone dose and rate of adjunctive therapy with phenobarbital in both protocol groups.	The study shows the use of pharmacokinetic modelling may decrease treatment duration with methadone for NAS.
Janssen et al. 2012. Auricular acupuncture for chemically dependent pregnant women: a	II – A randomised controlled trial	Ancillary or non-pharmacological interventions Acupuncture	This is a randomised trial that compared acupuncture treatment with usual care for NAS.	Despite the nonsignificant results, acupuncture may provide a safe and feasible treatment to help mothers reduce their dosage of

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
randomized controlled trial of the NADA protocol.			Among newborns of women who were compliant with the acupuncture regime, there was a nonsignificant reduction of 2.1 and 1.5 days in length of treatment for neonatal abstinence syndrome compared with the non-compliant and control groups.	methadone to mitigate the severity of NAS among newborns.
Wachman et al. 2020. A quality improvement initiative to implement the eat, sleep, console neonatal opioid withdrawal syndrome care tool in Massachusetts' PNQIN collaborative	III-3 – A comparative study without concurrent controls	Model of care: Eat, Sleep, Console	This is a pre-post cohort study to assess neonatal outcomes following Quality Improvement (QI) initiatives. Using QI methodology led to decreased risk of NICU admission (OR 0.51, 95% CI 0.38–0.69), more infants receiving skin-to-skin (OR 2.20, 95% CI 1.54, 3.14) and their mother's milk at discharge (OR 1.34, 95% CI 1.03, 1.73), lower rates of pharmacotherapy (OR 0.35, 95% CI 0.26, 0.46) and secondary agent use (OR 0.23, 95% CI 0.12, 0.44). There was also shorter length of stay (RR 0.79, 95% CI 0.76, 0.82), opioid treatment days (RR 0.80, 95% CI 0.75, 0.86) and lower readmission rates in post intervention (0.4% vs 1.6%, p<0.03). There were no adverse events.	The findings show a beneficial effect of QI initiatives on inpatient outcomes for NAS.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
Backes et al. 2012. Neonatal abstinence syndrome: transitioning methadone-treated infants from an inpatient to an outpatient setting	III-2 – A comparative study with concurrent controls	Model of care: inpatient and outpatient management	This is a retrospective study to compare safety and efficacy of a traditional inpatient-only approach with combined inpatient and outpatient weaning strategy for NAS. The combined approach resulted in shorter length of stay (13 vs 25 days, p<0.0001), longer duration of methadone treatment (37 vs 21 days, p<0.001) and comparable cumulative methadone dosage (3.6 vs 3.1, p=0.42) compared with traditional inpatient setting.	Combined inpatient and outpatient treatment program was associated with improved inpatient outcomes compared to traditional inpatient approach.
Chau et al. 2016. Outpatient Management of Neonatal Abstinence Syndrome: A Quality Improvement Project	III-3 – A comparative study without concurrent controls	Model of care	This pre-post cohort study assessed outcomes following the implementation of an outpatient program (comprehensive discharge planning, a focused electronic health record template, management guidelines and parent/provider education) to standardise quality of care for NAS. The outpatient pharmacological management used methadone only. Results showed comparable total outpatient days on methadone and cumulative methadone dose. Parents had better understanding of NAS (71% vs	The findings suggest that an outpatient program to wean infants from NAS medications can be safe and associated with clinician and patient compliance.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
			100%, p=0.009) and providers had increased comfort with outpatient management (24% vs 67%, p<0.001) and education of parents (48% vs 82%, p=0.001) following intervention.	
Friedman et al. 2018. Pharmacological treatment of infants with neonatal abstinence syndrome in community hospitals compared to academic medical centres	III-2 – A comparative study with concurrent controls (i.e. non-randomised experimental trials, cohort studies, case-control studies, interrupted time series studies with a control group)	Model of care	This is a cohort study to compare inpatient outcomes using standardised NAS management in community hospitals vs academic centres. No statistical difference in the outcomes (length of stay, timing of initiation of treatment) between community setting and academic centres, suggesting the value of management in both care settings.	The findings showed a consistency of outcomes between community and hospital care settings and suggest that community interventions could benefit from standardised management protocols.
Grossman et al (2018). A Novel Approach to Assessing Infants With Neonatal Abstinence Syndrome	III-3 – A comparative study without concurrent controls	Model of care: Eat, Sleep, Console	This is a retrospective study that assessed the utility of Finnegan NAS scoring system versus the Eat, Sleep, Console (ESC) approach for NAS. The ESC approach resulted in morphine initiation for 6 infants (12%) compared with 31 infants (62%) who would have had	The findings show that the ESC approach may reduce pharmacological treatment for NAS and reduce inpatient stays.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
			morphine initiated using the FNAS approach (p<0.001). Morphine was initiated or increased on 8 patient days using the ESC approach (2.7%) compared with 76 patient days (25.7%) with the FNAS approach (p<0.001).	
Holmes et al. 2016. Rooming-in to treat neonatal abstinence syndrome: improved family-centred care at lower cost	III-3 – A comparative study without concurrent controls	Supportive care: rooming-in	This is a pre-post cohort study to assess Quality improvement initiatives that standardised protocol and promoted rooming-in on inpatient outcomes. Post intervention showed that the proportion of infants requiring morphine declined from 46% baseline to 27% during intervention. The average length of stay for pharmacologically treated NAS decreased from 16.9 to 12.3 days (p value not reported) and those not requiring pharmacological treatment remain unchanged (4.2–4.4 days, p=0.33).	The study findings highlighted the beneficial effect of a coordinated standardised program on inpatient outcomes for NAS.
Kelly et al. 2015. Oral morphine weaning for neonatal abstinence syndrome at home	III-2 – A comparative study with concurrent	Model of care - inpatient and	This is a retrospective study to assess safety and effectiveness of outpatient oral morphine weaning.	Oral morphine at home resulted in fewer returns to hospital for continued withdrawal management but there is no evidence of

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
compared with in-hospital: an observational cohort study	controls	outpatient management	Neonates who weaned at home had shorter days in NICU (median days: 16 vs 22, p=0.04), fewer admissions to hospital for withdrawal treatment (2% vs 14%, p=0.04) but were on oral morphine for longer (p<0.001) and were more likely to have had phenobarbital/clonidine and/or clonazepam in NICU (31% vs 4%, p<0.01) compared to infants treated as inpatients.	increased effectiveness of inpatient weaning.
Lee et al. 2015. Neonatal Abstinence Syndrome: Influence of a Combined Inpatient/Outpatient Methadone Treatment Regimen on the Average Length of Stay of a Medicaid NICU Population	III-2 – A comparative study with concurrent controls	Model of care - inpatient and outpatient management	This is a retrospective study to examine factors that influenced length of stay for NAS. Neonates treated with methadone alone and discharged to complete outpatient treatment had significant shorter average length of stay (11.4 vs 25.1 days, p<0.001) compared to methadone.	The findings showed a beneficial effect of a combined inpatient/outpatient regimen with methadone on average length of stay and hospital costs.
Saiki et al. 2010. Neonatal abstinence syndrome – postnatal ward versus neonatal unit management	III-2 – A comparative study with concurrent controls	Supportive care: rooming-in	This is a pre-post study to assess the inpatient outcomes of infants who were cared on the postnatal ward with their mother (Group B) compared with neonatal units (Group A).	The findings suggest a beneficial effect of caring for infants with NAS on the postnatal ward on their inpatient outcomes.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
			The mean duration of treatment (12.7 days vs 7.3 days) and length of hospital stay (19.8 vs 15.9 days) were longer in Group A (i.e. infants admitted to neonatal unit for assessment and treatment) compared with Group B (postnatal ward). There was no difference in the rates of discharge home with the biological mother. None of the infants required readmission to hospital in the two months after discharge from the maternity hospital.	
Asti et al. 2015. A Quality Improvement Project to Reduce Length of Stay for Neonatal Abstinence Syndrome	III-3 – A comparative study without concurrent controls	Model of care	This is a pre-post retrospective study to assess the quality improvement in patient outcomes for NAS. The average length of stay reduced from 36 days (baseline) to 18 days.	A standardised protocol is important for reducing length of infant hospitalisation after NAS.
Blount et al. 2019. Reduction in Length of Stay and Morphine Use for NAS With the "Eat, Sleep, Console" Method	III-3 – A comparative study without concurrent controls	Model of care: Eat, Sleep, Console	This is a pre-post retrospective study to assess the quality improvement initiatives with Eat, Sleep, Console (ESC) approach on inpatient outcomes for NAS. The average length of stay decreased from a baseline of 10.3 days to 4.9 days during the intervention period. The	ESC may decrease length of stay and need for morphine treatment with NAS.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
			proportion of infants treated with morphine decreased from 92% at baseline to 19% post-intervention.	
Burnette et al. 2019. The effect of standardizing treatment when managing neonatal abstinence syndrome	III-3 – A comparative study without concurrent controls	Model of care	This is a prospective cohort study to standardise a strict NAS weaning treatment protocol. The length of stay (LOS) for the 17 months prior to the initiation of this protocol was 23.31 (±6.2) days (233 neonates). The LOS in the 13 months after protocol initiation was 18.17 (±5.1) days (162 neonates). This was a reduction of 5.14 days in LOS (95% CI 4.0–6.3 days, p<0.0001).	The findings show the beneficial effect of a standardised NAS treatment protocol on inpatient outcomes.
Achilies, J S et al. 2019. A quality improvement initiative to improve the care of infants born exposed to opioids by implementing the eat, sleep, console assessment tool	III-3 – A comparative study without concurrent controls	Model of care: Eat, Sleep, Console	This is a pre-post retrospective study to assess the Quality improvement initiatives with Eat Sleep Console (ESC) approach on inpatient outcomes for NAS. Post-intervention of qualitative improvement methods resulted in a lower total cumulative dose of opioids in methadone equivalents (1.3mg vs 6.6mg, p <.001) and shorter lengths of stay (10.9 vs 18.7days, p<.0005).	The findings show the beneficial effect of ESC approach on inpatient outcomes

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
Dodds et al. 2019. Successful Implementation of the Eat Sleep Console Model of Care for Infants with NAS in a Community Hospital.	III-3 – A comparative study without concurrent controls	Model of care: Eat, Sleep, Console	This is a pre-post retrospective study that assessed the quality improvement initiatives with the Eat Sleep Console (ESC) approach on inpatient outcomes for NAS in a community hospital. Following implementation of the ESC care model, average length of stay decreased from 11.77 to 5.94 days (p=0.0003) cumulative amount of morphine used per stay decreased from 2.25 to 0.45 mg/kg (79% reduction, p=0.001). None of affected infants was readmitted or transferred for NAS-related complications.	The findings show the beneficial effect of ESC approach on inpatient outcomes
Paralam et al. 2019. Improving care for infants with neonatal abstinence syndrome: a multicentre, community hospital–based study	III-3 – A comparative study without concurrent controls	Model of care: Eat, Sleep, Console	This is a pre-post retrospective study that assessed the quality improvement initiatives with the Eat, Sleep, Console (ESC) approach on inpatient outcomes for NAS. Using QI methodology led to a decrease in length of stay from baseline 9.0 to 6.2 days (32% reduction) and scheduled morphine use (57% to 23%). No p-values were reported.	The findings show the beneficial effect of QI initiative with the Eat, Sleep, Console (ESC) approach on inpatient outcomes.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
Wachman et al. 2018. Quality improvement initiative to improve inpatient outcomes for Neonatal Abstinence Syndrome	III-3 – A comparative study without concurrent controls	Model of care: Eat, Sleep, Console	This is a pre-post retrospective study that assessed the quality improvement initiatives with the Eat, Sleep, Console (ESC) approach on inpatient outcomes for NAS. Quality improvement interventions were associated with decreased proportions of pharmacologically treated infants from 87.1% to 40.0% (p<0.0001), a decrease in adjunctive agent use from 33.6% to 2.4% (p<0.0001), decreased mean length of stay for opioid-exposed infants from 17.4 days (95% CI 15.8–19.0) to 11.3 days (95% CI 10.0–12.6) (p<0.0001), decreased length of stay of all drug-exposed infants from 17.5 days (95% CI 15.8–19.1) to 11.6 days (95% CI 10.1, 13.1), and decreased opioid treatment days for pharmacologically treated infants from a mean of 16.2 (95% CI 14.5–17.9) to 12.	ESC decreased length of infant inpatient stay and treatment for NAS.
Abrahams et al. 2010. An evaluation of rooming-in among substance-exposed newborns in British Columbia	III-2 – A comparative study with concurrent controls	Supportive care: rooming-in	This is a retrospective study that compared the inpatient outcomes between traditional standard care model and an interdisciplinary rooming-in care model.	The study shows the beneficial effect of rooming-in as a safe model of care for infants with NAS.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
			Compared to standard care, rooming-in was associated with a decrease in admissions to NICU (OR 0.68 95% CI 0.51–0.92, p=0.01), shorter NICU length of stay for the term infant (1.1 day ± 3.1 vs 3.1 ± 8.3, p<0.001), increased likelihood of breastfeeding, either exclusively or in combination with formula, during hospital stay (OR 2.11, 95% CI 1.61–2.77, p<0.001) and increased likelihood of discharge with mother (OR 1.63 95% CI 1.22–2.19, p=0.001). No significant differences in breastfeeding status at discharge were noted.	
Hünseler et al. 2013. Neonatal opiate withdrawal and rooming-in: a retrospective analysis of a single centre experience	III-2 – A comparative study with concurrent controls	Supportive care: rooming-in	This is a retrospective study that assessed inpatient outcomes for NAS with rooming-in. Rooming-in was associated with shorted length of hospital stay (median 33.0 vs. 41.5 days, p=0.077) and lower median hospital costs (€9547 vs €14,486, p=0.014) compared to not rooming-in. The duration of NAS medications was also shorter in infants who were roomed-in (27 days vs 32.5, p=0.043).	The study shows the beneficial effect of rooming-in on short-term infant inpatient outcomes.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
Newman et al. 2015. Rooming-in care for infants of opioid-dependent mothers: Implementation and evaluation at a tertiary care hospital	III-2 – A comparative study with concurrent controls	Supportive care: roomng-in	This is a prospective study designed to assess inpatient outcomes with rooming-in. Compared to infants admitted directly to NICU, fewer neonates in the rooming-in group required pharmacotherapy (83.3% vs 14.3%, p<.0001). They also had significantly shorter mean [SD] length of stay (7.9 [7.8] days vs 24.8 [15.6] days, p<0.001).	The study shows the beneficial effect of rooming-in on inpatient outcomes.
Cree et al. 2019. A Hospital-Level Intervention to Improve Outcomes of Opioid Exposed Newborns	III-3 – A comparative study without concurrent controls	Model of care: Eat, Sleep, Console	This is a pre-post retrospective study that assessed inpatient outcomes following implementation of quality improvement initiatives. Implementation of non-pharmacological intervention reduced NICU admission from 100% to 7.5% (p<.001), decreased average NICU length of stay from 8.2 days to 0.2 days (p<0.001) and total length of stay from 14 days to 10.1 days (p=0.032). No statistical difference in pharmacological treatment. Among those newborns started on pharmacological treatment, length of treatment decreased significantly from 15.68 to 9.71 days (p=0.023).	The findings show the beneficial effect of quality improvement initiatives with rooming-in model on inpatient outcomes.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
McKnight, et al. 2016. Rooming-in for infants at risk of neonatal abstinence syndrome	III-2 – A comparative study with concurrent controls	Supportive care: rooming-in	Rooming-in was associated with a reduced need for pharmacological treatment and shorter length of stay. (No access to full text).	The study shows the beneficial effect of rooming-in on inpatient outcomes.
Walsh et al. 2018. Ohio Perinatal Quality Collaborative Improves Care of Neonatal Narcotic Abstinence Syndrome	III-3 – A comparative study without concurrent controls	Model of care	The pre-post study assessed inpatient outcomes following implementation of quality improvement initiatives. Compared to baseline results, intervention was associated with decreased length of treatment (13.4 to 12.0 days) and length of stay (18.3 to 17 days)	The findings show the beneficial effect of quality improvement initiatives on inpatient outcomes.
Grossman, et al. 2017. A novel approach to assessing infants with neonatal abstinence syndrome	III-3 – A comparative study without concurrent controls	Model of care: Eat, Sleep, Console	The pre-post study assessed inpatient outcomes following implementation of quality improvement initiatives. Compared to standard treatment, interventions to improve standardised non-pharmacological interventions were associated with decreased average length of stay (22.4 to 5.9 days, p<0.001) and proportions of infants treated with morphine, from 98% to 14% (p<0.001) resulting in cost savings of $10,289 (from $44,824) (p<.001). The proportion of	The findings show the beneficial effect of quality improvement initiatives on inpatient outcomes.

Table 13—Primary studies for the treatment of NAS (n=53)

First author, year,	NHMRC Levels of evidence/Study design	Intervention	Results/Findings	Interpretation
			infants who were breastfed increased from 20% to 45% (p=0.01) following intervention. Fewer infants were admitted directly to NICU (p<0.001).	

Table 14— Economic evaluation of intervention for treatment of neonatal withdrawal syndromes (n=10)

Authors (Year)	Aim of study	Intervention (s) evaluated	Key findings/recommendation	Interpretation	Quality rating
Grossman et al. 2017. An initiative to improve the quality of care of infants with neonatal abstinence syndrome	To assess the outcomes (average length of stay, proportion of infants treated with morphine and total cost of hospitalisation) of an intervention to standardise non-pharmacological care coupled with an empowering message to parents, development of a novel	Standardised non-pharmacological care; prenatal counselling; empower messages to parents; simplified assessment of infants; rapid morphine weans; morphine given as needed; transferred nursery to inpatient unit; focused educational session to staff.	Compared to pre-intervention, the proportion of infants treated with morphine decreased from 98% to 14% (p<0.001) and the average cost of hospitalisation decreased from $44,824 to $10,289 (p<0.001).	Qualitative improvement initiatives that standardised non-pharmacological care reduces cost of hospitalisation per patient.	2

Table 14— Economic evaluation of intervention for treatment of neonatal withdrawal syndromes (n=10)

Authors (Year)	Aim of study	Intervention (s) evaluated	Key findings/recommendation	Interpretation	Quality rating
	approach to assessment, administration of morphine on an as-needed basis, and transfer of infants directly to the inpatient unit, bypassing the NICU.				
Holmes et al. 2016. Rooming-in to treat neonatal abstinence syndrome: improved family-centred care at lower cost	To assess the outcomes of a coordinated program for neonatal abstinence syndrome including standardised protocols for scoring, medications and weaning, and a calm rooming-in environment to improve family-centred care.	Trained nurses in modified Finnegan scoring, ensured scoring only after on-demand feeds during skin to-skin care, and standardised physician score interpretation, provided prenatal family education, increased family involvement in symptom monitoring and non-pharmacological treatment, and treated otherwise healthy infants on the inpatient paediatric unit instead of in the NICU.	Compared to pre-intervention, the proportion of infants treated with morphine decreased from 46% to 27% ($p<0.001$) and the average hospital cost per treated infant decreased from $19,737 to $8755 and cost per at-risk infant fell from $11,000 to $5300 ($p<0.01$).	Qualitative improvement initiatives that standardised non-pharmacological care reduces cost of hospitalisation per patient.	3

Table 14— Economic evaluation of intervention for treatment of neonatal withdrawal syndromes (n=10)

Authors (Year)	Aim of study	Intervention (s) evaluated	Key findings/recommendation	Interpretation	Quality rating
Millren et al. 2018. Hospital variation in neonatal abstinence syndrome incidence, treatment modalities, resource use, and costs across paediatric hospitals in the United States, 2013 to 2016	To examine the number of infants with NAS admitted to paediatric hospitals, hospital variation in pharmacological treatment, and the effect of treatment on resource use during neonatal hospitalisation, including length of stay, readmission, and cost-of-living adjusted hospital costs.	To compared outcomes and cost for those treated pharmacologically (i.e. opioids, opioid agonists, barbiturates or benzodiazepines)	Adjusted total costs for pharmacologically treated neonates were more than double compared to other neonates with NAS ($44,720 vs $20,708, p<0.01). Compared with neonates without NAS, neonates with NAS cost $34,000 more per admission and stayed a cumulative excess of 52,000 hospital bed days, representing a cumulative cost burden of $111 million during 2013–16	Pharmacologically treated infants with NAS incurred higher hospitalisation costs compared to other infants with NAS due to longer length of stay and treatment duration.	4
Wachman et al. 2018. Neonatal abstinence syndrome: advances in diagnosis and treatment	To describe the outcomes of a comprehensive Quality Improvement program that focused on non-pharmacological care, function-based assessments, and methadone	Plan to do study act (PDSA) cycle methodology: Cycle 1: Non-pharmacological care bundle, change in prenatal/parental messaging and Finnegan symptoms prioritisation. Cycle 2: Staff Q1 Project education, transition to	Parental presence at the bedside increased from a mean of 55.6% to 75.8% (p<0.001). Mean cuddler presence was 4.4% in the post-intervention group, increasing total care giver presence to 80%. Average hospital charges decreased from $31,825 to	Qualitative improvement initiatives that standardised non-pharmacological care improves neonatal outcomes thereby reduces cost of hospitalisation per patient.	4

Table 14— Economic evaluation of intervention for treatment of neonatal withdrawal syndromes (n=10)

Authors (Year)	Aim of study	Intervention (s) evaluated	Key findings/recommendation	Interpretation	Quality rating
		methadone with no treatment in the first 24 hours of life. Cycle 3: Function-based eating, sleeping, and consoling and Cuddler program.	$20,668 per infant during the intervention period (p<0.001).		
Avram et al. 2020. A Cost-Effectiveness Analysis of Rooming-in and Breastfeeding in Neonatal Opioid Withdrawal.	To investigate the costs and outcomes associated with rooming and infant feeding status to determine the optimal management strategy of neonatal opioid withdrawal.	Non-pharmacological interventions using rooming-in and breastfeeding.	Rooming-in and breastfeeding is the dominant strategy (i.e. less costly and higher QALYs) resulting in a cost-savings of $509.7 million and additional 12,333 QALYs. Based on a cost-effectiveness threshold of $100,000 per QALY, rooming-in and breastfeeding model was cost-effective. The Monte Carlo simulation of 10,000 trials found rooming-in was cost-effective in 94.2% of the trials.	Rooming-in is the dominant strategy from a societal perspective.	8
Achilles et al. 2019. A quality improvement initiative to improve the care of infants	To examine outcomes of quality improvement methodology compared to preintervention period.	Quality Improvement methodology to conduct plan-do-study-act cycles. Interventions included prenatal	Compared with the baseline group, the postintervention group had lower total cumulative dose in methadone equivalents (p<0.0001) and	Qualitative improvement initiatives that standardised no-npharmacological care reduces cost of	4

Table 14— Economic evaluation of intervention for treatment of neonatal withdrawal syndromes (n=10)

Authors (Year)	Aim of study	Intervention (s) evaluated	Key findings/recommendation	Interpretation	Quality rating
born exposed to opioids by implementing the eat, sleep, console assessment tool.		education, family engagement, non-pharmacological treatments, morphine as needed, and the eat, sleep, console assessment tool.	shorter length of stay (10.9 days vs 18.7 days; p<0.0005). While not statistically significant, total direct costs were lower in the post intervention group ($11,936 vs $15,039; p<0.18).	hospitalisation per patient.	
Devlin et al. 2017. Decreasing total medication exposure and length of stay while completing withdrawal for neonatal abstinence syndrome during the neonatal hospital stay.	To examine outcomes of a modified NAS protocol (P2) where morphine is offered every 3 hours and used clonidine as adjuvant therapy compared to protocol (P1) that provides morphine every 4 hours and used phenobarbital as adjuvant therapy.	A modified NAS protocol (P2) where morphine is offered every 3 hours and used clonidine as adjuvant therapy.	Compared to P1, modified protocol P2 led to a decrease in the length of stay by 9 days resulting in a corresponding decrease in hospital cost of $27,090 per patient.	Qualitative improvement initiatives that standardised non-pharmacological care reduces cost of hospitalisation per patient.	2
Hünseler et al. 2013. Neonatal opiate withdrawal and rooming-in: a retrospective	To compare clinical outcomes and average between parental rooming-in and not	Parental rooming-in	The study showed the length of hospital stay was shorter for new-born infants who were roomed-in with parents compared to infants not	Parental rooming-in reduces hospital cost as a result of shorter length of stay.	3

Table 14— Economic evaluation of intervention for treatment of neonatal withdrawal syndromes (n=10)

Authors (Year)	Aim of study	Intervention (s) evaluated	Key findings/recommendation	Interpretation	Quality rating
analysis of a single centre experience.	rooming-in intervention.		roomed-in (median 33.0 vs 41.5, p=0.077) resulting in a lower median cost of hospital stay of €9547 (€7024–€16,135) vs €14,486 (€9479–€19,352) respectively.		
Kelly et al. 2015. Oral morphine weaning for neonatal abstinence syndrome at home compared with in-hospital: an observational cohort study.	To assess the safety and effectiveness of managing NAS at home with oral morphine and cost savings from continuing oral morphine waning post hospital discharge.	Neonates are discharged with complete oral morphine tapering at home. Parents were encouraged to continue with other non-pharmacological interventions, included minimising lighting and stimulation, speaking softly, swaddling, and applying ointment cream (nystatin, zinc oxide) to the perianal area following frequent stools.	Compared to hospital weaning, neonates treated at home remained on morphine for more days but resulted in fewer readmissions for continued withdrawal thereby leading to a cost savings of $560,200 per neonate, suggesting that a slower tapered wean may be advantageous in managing NAS.	Oral morphine at home results in cost savings from a healthcare perspective.	3

Table 14— Economic evaluation of intervention for treatment of neonatal withdrawal syndromes (n=10)

Authors (Year)	Aim of study	Intervention (s) evaluated	Key findings/recommendation	Interpretation	Quality rating
Lee et al. 2015. Neonatal Abstinence Syndrome: Influence of a Combined Inpatient/Outpatient Methadone Treatment Regimen on the Average Length of Stay of a Medicaid NICU Population.	To compare outcomes (average length of stay and associated cost) between neonates treated with a combined inpatient/outpatient methadone regimen and neonates treated with morphine (with or without adjunctive medication) as an inpatient.	Neonates treated with a combined inpatient/outpatient methadone regimen	Analysis of the medication used for treatment revealed infants who were treated with a combined inpatient/outpatient regimen with methadone had an average length of stay of 11.4 days compared to 25.1 days for infants who were treated entirely as inpatients ($p<0.001$), a 55% reduction in average length of stay and a cost savings of $396 million per year (in 2009).	Outpatient weaning for infants with NAS reduces hospital costs as a result of shorter length of stay.	2

Table 15—Systematic reviews for effective intervention at preventing the resumption of smoking (n=5)

First Author. Year. Title	NHMRC Levels of evidence/Study design	Interventions	Results/Findings	Interpretation
Ashford et al. 2009. Postpartum smoking relapse and secondhand	I – A systematic review of Level II studies	Educational intervention addressing second-hand smoking in the home (Booklet, personalised letter, relapse	Nurse- and paediatrician-led interventions resulted in lower relapse rates.	More comprehensive educational second-hand smoking interventions are required.

Table 15—Systematic reviews for effective intervention at preventing the resumption of smoking (n=5)

First Author. Year. Title	NHMRC Levels of evidence/Study design	Interventions	Results/Findings	Interpretation
smoke.		prevention kit, three prepartum telephone counselling sessions, postpartum telephone counselling)		
Brown et al. 2019. A systematic review of behaviour change techniques within interventions to prevent return to smoking postpartum.	I – A systematic review of Level II studies	Behavioural Change Therapies	Six BCTs were promising to enhance the effectiveness of interventions to maintain smoking abstinence, problem solving, information about health consequences, information about social and environmental consequences, social support, reduce negative emotions, and instruction on how to perform.	To maximise effectiveness of behavioural change therapies, six themes can be included: problem solving, information about health consequences, information about social and environmental consequences, social support, reduce negative emotions, and instruction on how to perform a behaviour.
Dennis et al. 2008. A systematic review of telephone support for women during pregnancy and the early postpartum period.	I – A systematic review of Level II studies	Telephone Intervention: counselling session by trained nurse	This systematic review summarises the results of 14 trials. In general, telephone support may prevent smoking relapse, reduce the risk of low birth weight, increase breastfeeding duration and exclusivity, and decrease depression.	Telephone support was able to reduce smoking, prevent relapse and decrease preterm birth, low birth weight and postpartum depressive symptomatology.
Levitt et al. 2007.	I – A systematic	Nurse-led face-to-face advice	Five studies were included in the	No benefits of face-to-face advice and

Table 15—Systematic reviews for effective intervention at preventing the resumption of smoking (n=5)

First Author. Year. Title	NHMRC Levels of evidence/Study design	Interventions	Results/Findings	Interpretation
Systematic review of the literature on postpartum care: Effectiveness of interventions for smoking relapse prevention, cessation, and reduction in postpartum women.	review of Level II studies	and telephone counselling.	review. The studies showed no statistically significant benefits of advice materials and counselling interventions in hospital, paediatricians' offices, or child health centres on relapse prevention, cessation rates, or smoking reduction in the postpartum period.	telephone counselling on relapse prevention, cessation rates, or smoking reduction in the postpartum period.
Su et al. 2013. Maintenance of smoking cessation in the postpartum period: Which interventions work best in the long-term?	I – A systematic review of Level II studies	Pharmacological: NRT patch/gum/lozenge (n=2), behavioural (n=27); Relapse prevention booklets tailored to stage of change mailed until 8 months postpartum or smoking cessation booklets not customised to stage, social support; Depression-focused intervention; Midwives brief counselling; behavioural therapy; Telephone counselling; Psychotherapy; Cash Incentive	Thirty-two studies were included in the review. The majority of interventions reviewed showed a statistically significant difference in quit rates by the end of pregnancy for nonspontaneous smokers, and these interventions were not effective in long-term (9-12 months) relapse prevention. However, intervention groups still had higher rates of quitting during pregnancy that was sustained for longer periods postpartum	The interventions were effective for a short-term (5-8 month) postpartum period.

Table 16—Primary studies for effective intervention at preventing the resumption of smoking (n=14)

Citation	NHMRC Levels of evidence/Study Design	Interventions	Results/Findings	Interpretation
McBride et al.1999. Prevention of relapse in women who quit smoking during pregnancy	II – A randomised controlled trial.	Self-help booklet only (booklet-only group), booklet plus prepartum intervention (prepartum group), or booklet plus prepartum and postpartum intervention (pre/post group).	The intervention increased abstinence of smoking postpartum.	Interventions for pregnant smokers that include relapse prevention assistance in the early postpartum period may delay, but not prevent, a postpartum return to smoking.
Stotts et al. 2002. One-to-one: a motivational intervention for resistant pregnant smokers	II – A randomised controlled trial.	Motivational Interviewing (MI)	Women who received all pieces of the intervention were more likely to quit or reduce smoking in their last trimester and the early postpartum period at higher rates than their control counterparts.	MI is effective in reducing smoking in pregnancy.
Suplee et al. 2005. The importance of providing smoking relapse counselling during the postpartum hospitalization	II – A randomised controlled trial.	A brief counselling session using empowerment techniques, motivational interviewing, identification of stressors and individual coping strategies, and educational materials.	Fifty-two per cent of women relapsed to smoking by the second week postdelivery. There was no difference in relapse rate between the intervention and the control group.	Postpartum interventions are not effective in smoking relapse prevention. Nurses should also address smoking behaviours each trimester and before postpartum hospital discharge.
Reitzel et al. 2010. Preventing postpartum smoking relapse	II – A randomised controlled trial.	Motivation and Problem-Solving (MAPS) treatment	MAPS was more effective than usual care in the prevention of postpartum relapse. A promising intervention for	Motivation and Problem-Solving (MAPS) treatment is effective in

Table 16—Primary studies for effective intervention at preventing the resumption of smoking (n=14)

Citation	NHMRC Levels of evidence/Study Design	Interventions	Results/Findings	Interpretation
among diverse low-income women: a randomized clinical trial			postpartum smoking relapse prevention among low-income women. MAPS treatment effect was stronger among women who smoked more cigarettes per day.	preventing postpartum relapse.
Hannover et al. 2009. Smoking cessation and relapse prevention for postpartum women: Results from a randomized controlled trial at 6, 12, 18 and 24 months	III-1 – A pseudo-randomised controlled trial.	Motivational Interviewing (MI) and two scheduled telephone booster sessions 4 and 12 weeks after counselling.	No effect regarding relapse prevention. Inspecting repeated 4-week point prevalence abstinence rates revealed a statistically significant difference at 6 months follow-up, but not at 12, 18 or 24 months.	Motivation Interviewing intervention was effective to prevent relapse only for the 6 months past partum.
French et al. 2007. Staying smoke free: An intervention to prevent postpartum relapse	III-2 – A comparative study with concurrent controls (interrupted time series studies with a control group).	A motivational interviewing brief intervention during postpartum hospitalisation, a home visit, and two follow-up phone calls.	Over a 1- to 2-month period, the pilot study demonstrated a doubling of the proportion of women who remained smoke-free at 3 and 6 months following a brief nurse-delivered intervention based on the US Public Health Service clinical practice guideline.	Motivational interviewing, home visit and follow-up phone calls together were effective in improving the rate of persistent postpartum smoke-free status for women who quit smoking during pregnancy
Phillips et al. 2012. Prevention of postpartum smoking	II – A randomised controlled trial.	Weekly encouragement to remain smoke-free and routine breastfeeding	There was a significant decrease in smoking relapse rate at 8 weeks postpartum in the intervention group	Weekly encouragement in NICU effectively reduced self-reported smoking status of mothers, CO-

Table 16—Primary studies for effective intervention at preventing the resumption of smoking (n=14)

Citation	NHMRC Levels of evidence/Study Design	Interventions	Results/Findings	Interpretation
relapse in mothers of infants in the neonatal intensive care unit		support.	compared with the control group (81% vs 46%, p<0.001). Interventions to support mother-infant bonding during a newborn's hospitalisation in the NICU are associated with reduced rates of smoking relapse and prolonged breastfeeding duration during the first 8 weeks postpartum.	oximetry and salivary cotinine levels.
Levine et al. 2016. Preventing Postpartum Smoking Relapse: A Randomized Clinical Trial	II – A randomised controlled trial.	Nurse-delivered postpartum-adapted, behavioural smoking abstinence intervention	No difference in abstinence and time to relapse were observed in the developed intervention.	The intervention was not effective in preventing postpartum abstinence or relapse.
Johnson et al. 2000. Preventing smoking relapse in postpartum women	II – A randomised controlled trial.	Nurses provided face-to-face, in-hospital counselling sessions at birth, followed by telephone counselling.	Smoking abstinence in the treatment group was 38% and 27% in the control group. The treatment also reported less daily smoking when compared to the treatment group (48% vs 34%)	Those who received treatment were less likely to relapse and had reduced daily smoking compared to the control group. The intervention was not effective in the long term.
Pbert et al. 2004. A Community Health Centre Smoking-Cessation Intervention for Pregnant and	II – A randomised controlled trial.	Counselling and office system intervention which established program boards to coordinate the transfer of documentation	There was a statistically significant difference in 30-day abstinence rates between the intervention (26%) and usual care (12%) This effect remained at one month postpartum but was lost at 3-	Interventions that were delivered by healthcare providers during routine prenatal care increased smoking abstinence. When the intervention was extended into

Table 16—Primary studies for effective intervention at preventing the resumption of smoking (n=14)

Citation	NHMRC Levels of evidence/Study Design	Interventions	Results/Findings	Interpretation
Postpartum Women		among clinics, including periodic meetings with representatives from all clinics.	and 6-month postpartum follow-ups.	postpartum, it did not affect relapse.
Gadomski et al. 2011. Effectiveness of a combined prenatal and postpartum smoking cessation program	III-2 – A comparative study with concurrent controls (i.e., non-randomised experimental).	Prenatal and postpartum smoking cessation counselling, biomarker, random saliva cotinine testing and a monthly postpartum incentive.	Counselling program was effective in increasing abstinence at six months postpartum, lower baseline carbon monoxide level and attending more prenatal sessions.	Prenatal and postpartum smoking cessation counselling, biomarker, random saliva cotinine testing and a monthly postpartum incentive was effective in increasing smoking abstinence at six months postpartum.
Pollak et al. 2016. Efficacy of a Nurse-Delivered Intervention to Prevent and Delay Postpartum Return to Smoking: The Quit for Two Trial	III-2 – A comparative study with concurrent controls (non-randomised experimental trials).	A nurse-delivered smoking abstinence intervention, one relapse prevention booklet from the series.	High rate of biochemically validated abstinence at 12 months postpartum. Among women at low risk of returning to smoking, the crude abstinence rate was significantly higher in the control arm (46%) than in the intervention arm (33%). Among women at high risk of returning to smoking, the crude abstinence rate was slightly lower but not different in the control arm (31%) than in the intervention arm (37%).	A nurse-delivered smoking abstinence intervention program was effective in lowering the risk of returning to smoking.
Severson et al. 1997.	II – A randomised	Counselling in paediatric	The intervention reduced smoking (5.9%	Counselling delivered during

Table 16—Primary studies for effective intervention at preventing the resumption of smoking (n=14)

Citation	NHMRC Levels of evidence/Study Design	Interventions	Results/Findings	Interpretation
Reducing maternal smoking and relapse: long-term evaluation of a paediatric intervention	controlled trial.	well care visits	vs 2.7%) and relapse (55% vs 45%) at 6-month follow-up, but logistic regression analysis at 12 months revealed no significant treatment effect.	paediatric healthcare visits is effective in reducing smoking and relapse.
Allen et al. 2016. Progesterone and Postpartum Smoking Relapse: A Pilot Double-Blind Placebo-Controlled Randomized Trial	II – A randomised controlled trial.	Progesterone therapy	The pilot study was effective. The randomised trail findings support the feasibility, trial retention, and acceptability of progesterone treatment among postpartum women/smokers.	Progesterone therapy seems to be effective in reducing postpartum relapse.

Table 17— Cost effectiveness study for the intervention at preventing the resumption of smoking (n=3)

Authors	Aim of study	Intervention (s) evaluated	Key findings/recommendation	Interpretation	Quality rating
Ruger et al. 2009. Measuring the costs of outreach motivational interviewing for	Measure the cost of outreach motivational interviewing and usual care for cessation and relapse prevention	Motivational intervention (MI) comprised of a monthly visit from a public health nurse until one month post-partum.	Cost of MI intervention is $311.80 per participant compared to $4.82 per participant for usual care.	Cost per participant is higher in intervention using motivational interviewing compared to usual care of providing a	4

Table 17— Cost effectiveness study for the intervention at preventing the resumption of smoking (n=3)

Authors	Aim of study	Intervention (s) evaluated	Key findings/recommendation	Interpretation	Quality rating
smoking cessation and relapse prevention among low-income pregnant women.	during and after pregnancy for low-income pregnant women.	The MI sessions: 1) educated clients about the effects of smoking on mothers, fetuses, and newborns; 2) helped clients evaluate their smoking behaviour; 3) helped increase self-efficacy for smoking cessation and abstinence; 4) provided information on reducing exposure to environmental tobacco smoke and set goals on changes in smoking; and 5) provided feedback about household nicotine levels.		pamphlet on ways to deal with nicotine withdrawal symptoms for low-income pregnant women from a societal perspective.	
Ruger et al. 2007. Cost-effectiveness of motivational interviewing for smoking cessation and relapse prevention among	To assess the economic impact of a behavioural intervention that integrated motivational enhancement therapy with cognitive	Mothers assigned to Motivational interviewing (MI) received an average of three home visits designed to deliver a specific program for smoking intervention	Usual care was the dominant strategy for cessation as it was less costly with higher QALY gained compared to MI. The ICER for MI for relapse prevention was estimated to be $851/LY saved and	For cessation, usual care (UC) of providing up to five minutes intervention is less costly and more effective compared to motivational interviewing. For prevention of relapse,	6

Table 17— Cost effectiveness study for the intervention at preventing the resumption of smoking (n=3)

Authors	Aim of study	Intervention (s) evaluated	Key findings/recommendation	Interpretation	Quality rating
low-income pregnant women: a randomized controlled trial.	behavioural therapy (MET-CBT) for treatment of substance use in pregnancy, in comparison with brief advice.	versus usual care. The intervention consisted of a five-minute module that outlined the harmful effects of smoking during and after pregnancy and also provided self-help materials.	$628/QALY gained, compared to usual care.	motivational interviewing is cost effective compared to UC. UC was the dominant strategy for cessation as it was less costly with higher QALY gained compared to MI. The ICER for MI for relapse prevention was estimated to be $851/LY saved and $628/QALY gained, compared to UC.	
Xu et al. 2017. Economic evaluation of a behavioural intervention versus brief advice for substance use treatment in pregnant women: results from a randomized controlled trial.	To assess the economic evaluation of an innovative intervention integrating motivational enhancement therapy with cognitive behavioural therapy (MET-CBT) with brief advice for women with substance-use disorders.	One-on-one motivational enhancement therapy with cognitive behavioural therapy (MET-CBT) at prenatal visits and optional booster visit after delivery.	Although MI had higher intervention cost compared to brief advice, the overall medical costs of up to three months postpartum were comparable between the two groups (median total cost = $26,993 per participant for MET-CBT versus $27,831 per participant for brief advice, p=0.90).	The study found comparable cost (in terms of cost per participant) between the MI and usual care. Although MI had a higher intervention cost compared to brief advice, the overall medical costs of up to three months postpartum were comparable between the two groups (median total cost = $26,993/participant	6

Table 17— Cost effectiveness study for the intervention at preventing the resumption of smoking (n=3)

Authors	Aim of study	Intervention (s) evaluated	Key findings/recommendation	Interpretation	Quality rating
				for MET-CBT versus $27,831/participant for brief advice, p=0.90).	

Appendix 2 — PRISMA flowchart

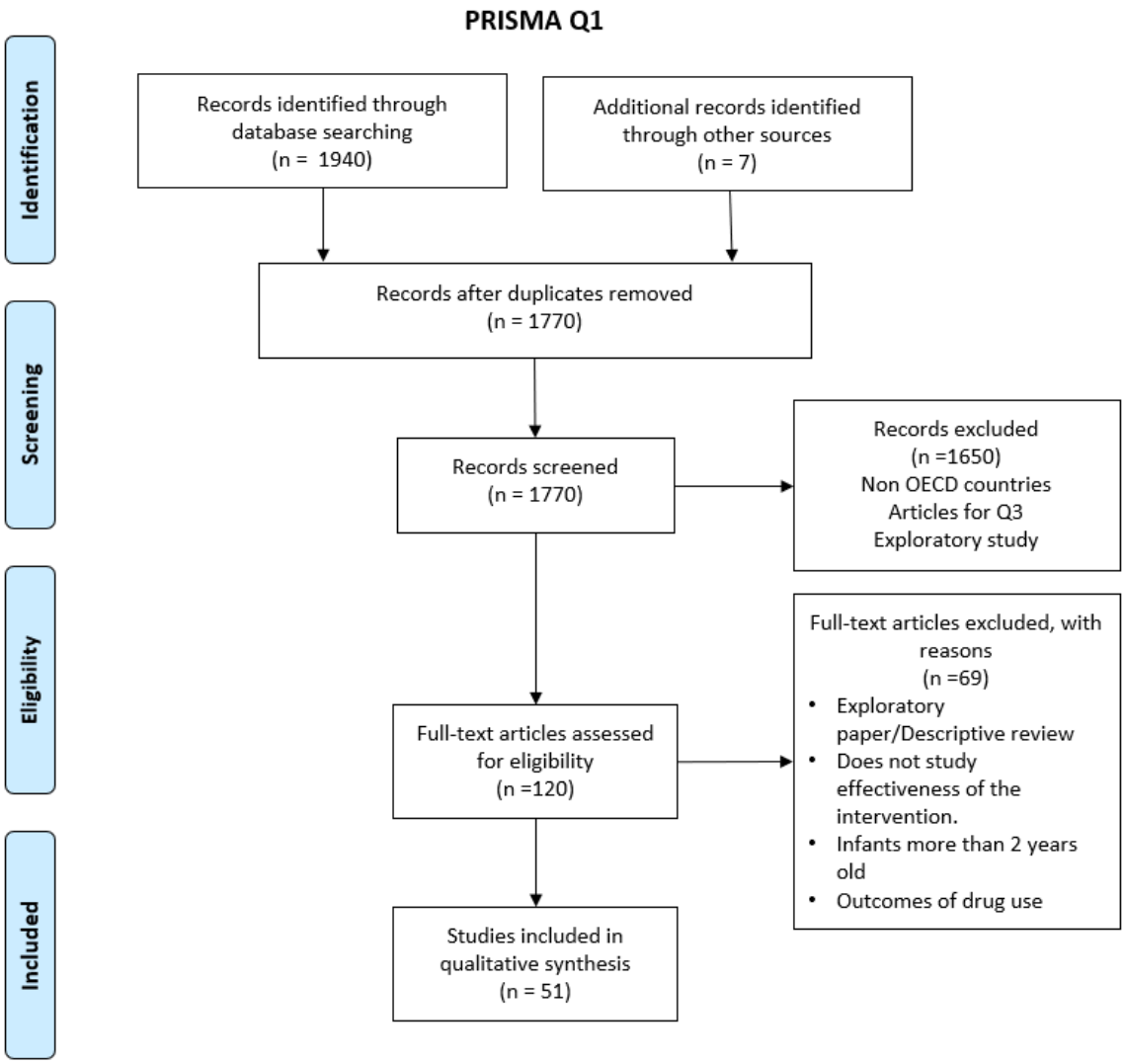

Figure 1—Prisma Chart for Q1: What interventions are most effective at improving outcomes for women who use substances during pregnancy and their developing fetus during the antenatal period, birth and postnatal period up to 2 years of the child's life?

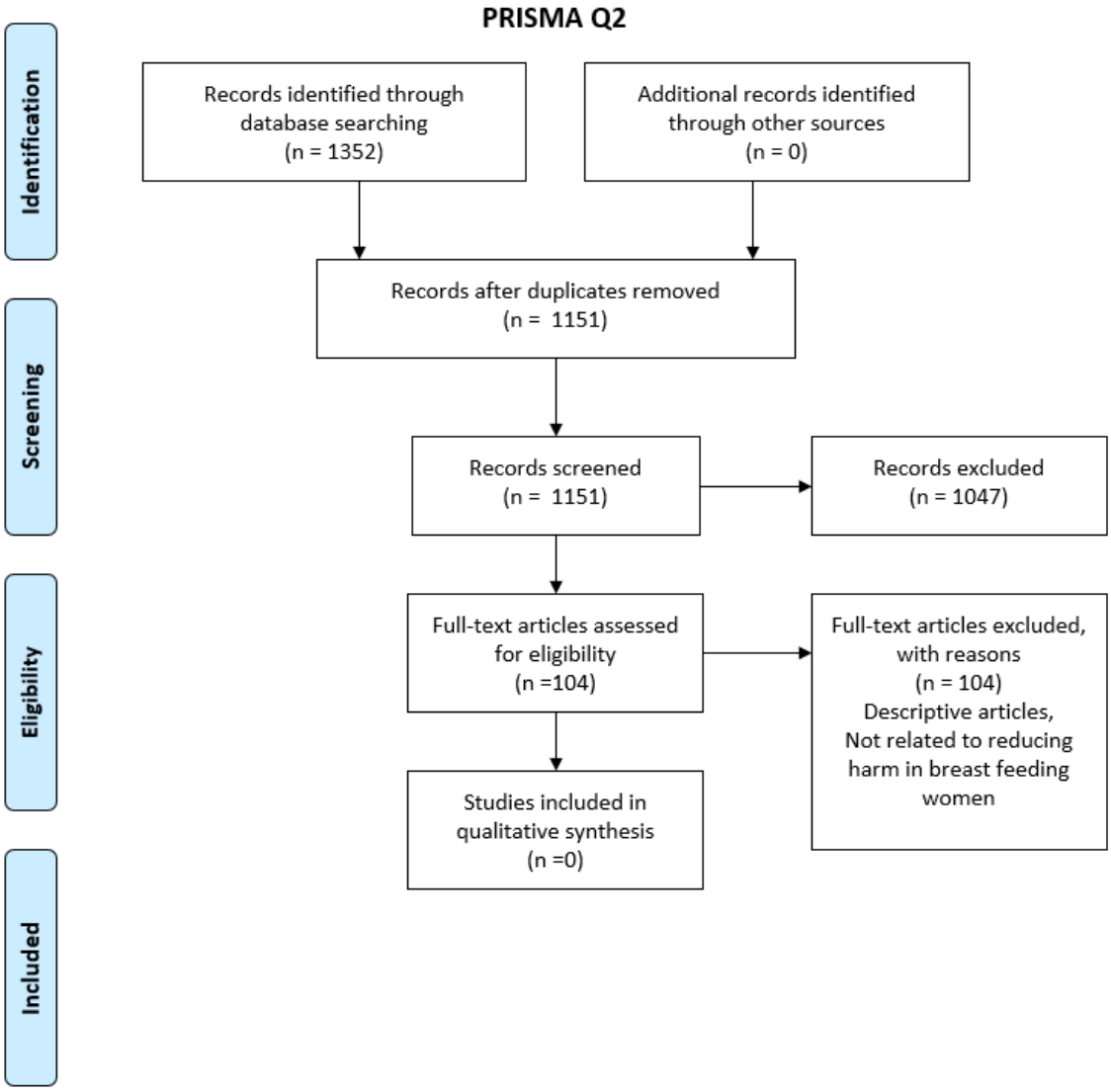

Figure 2—Prisma Chart for Q2: What interventions are most effective at reducing risk of harm in breastfeeding women who use substances?

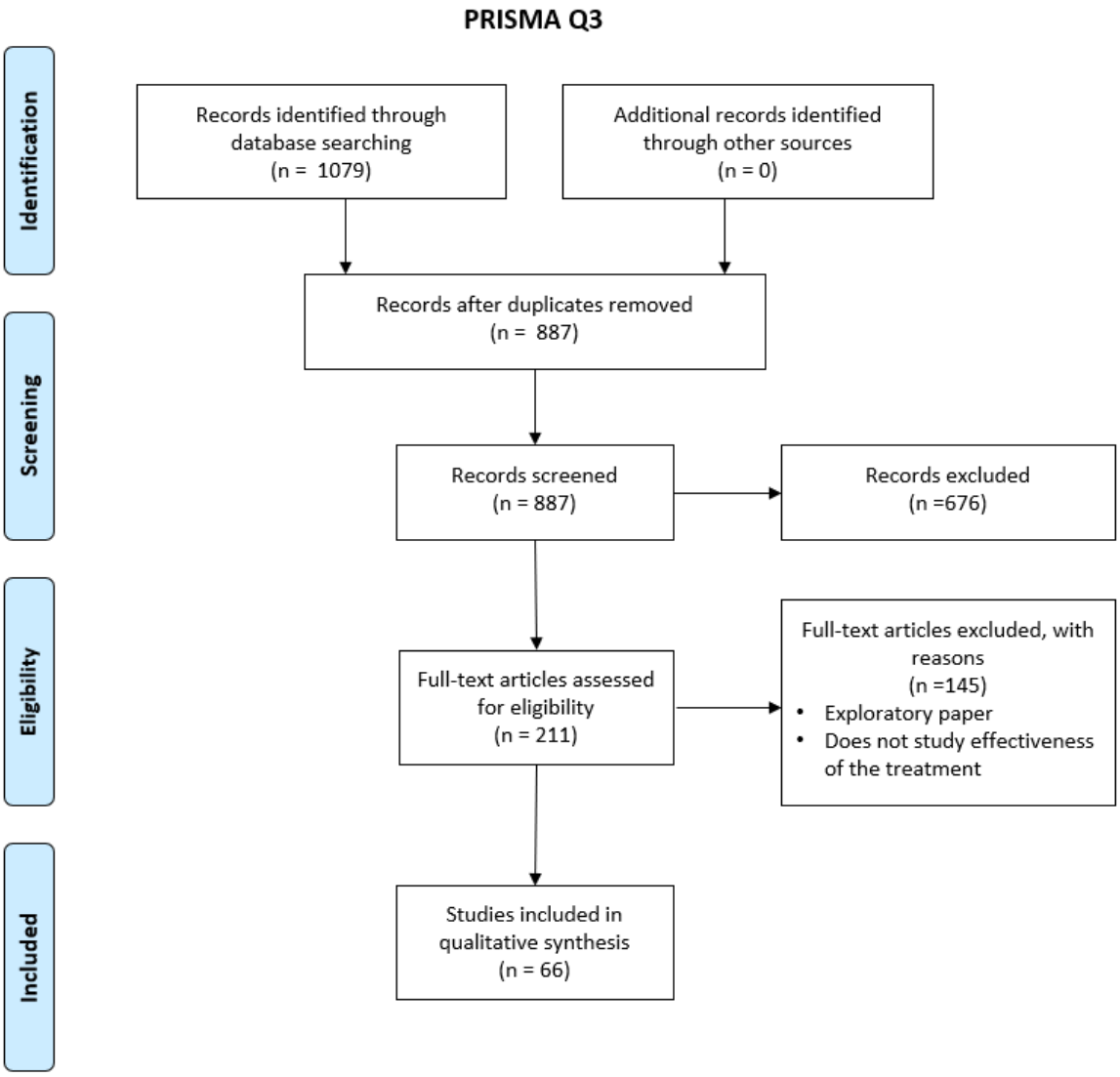

Figure 3—Prisma Chart for Q3: What treatments have been shown to be effective for neonatal substance withdrawal syndromes, including withdrawal from opioids, alcohol, methamphetamines, cocaine, cannabis, benzodiazepines, gabapentinoids and tobacco?

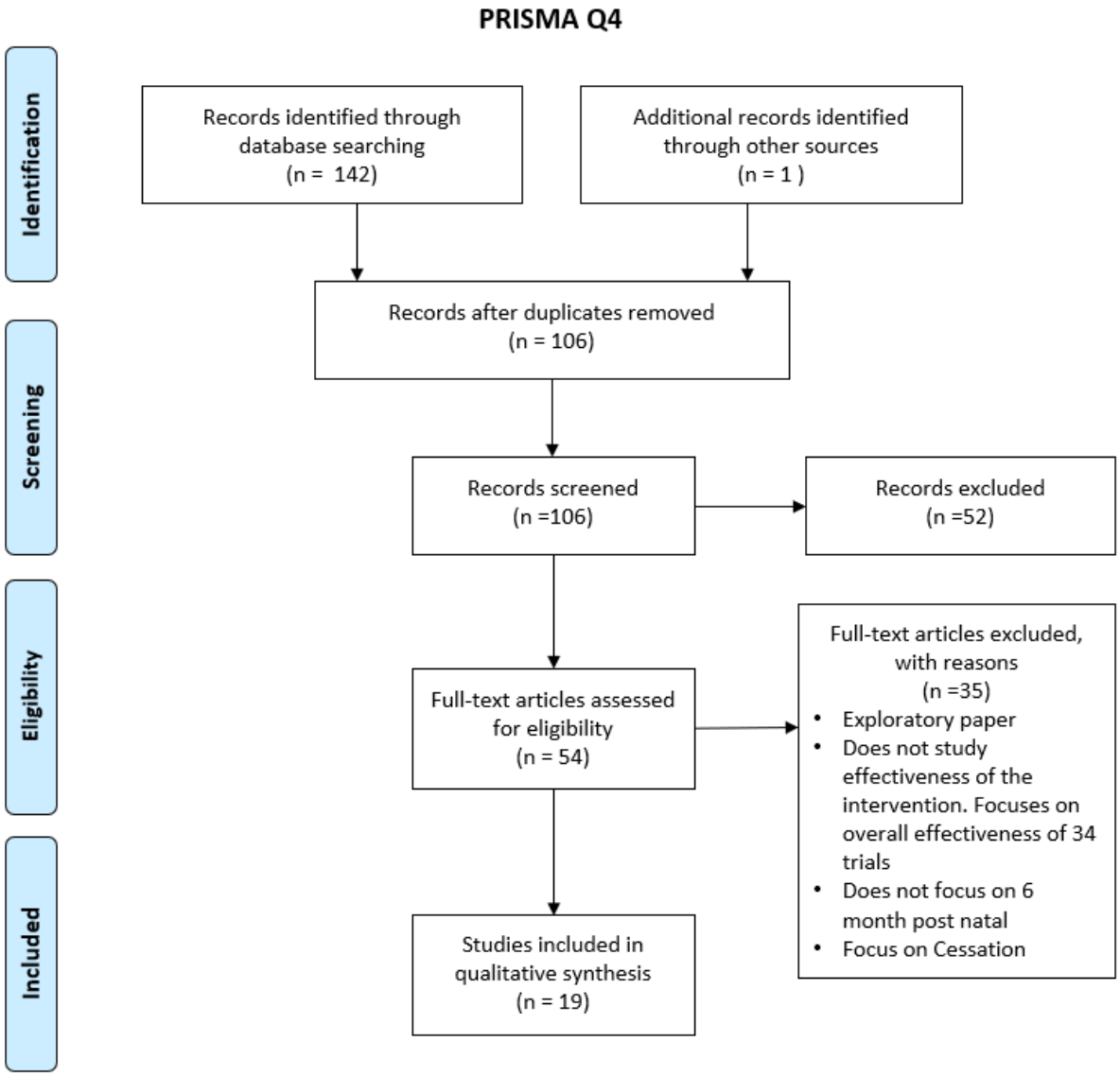

Figure 4: Prisma Chart for Q4: What interventions are most effective at preventing the resumption of smoking and other substance use within the six-month postnatal period?

Appendix 3 — NHMRC Level of Evidence and evidence base

Table 18—NHMRC level of evidence

Level of Evidence	Study Design
I	A systematic review of Level II studies
II	A randomised controlled trial
III-**1**	A pseudo-randomised controlled trial (i.e., alternate allocation or some other method)
III-**2**	A comparative study with concurrent controls (i.e. non-randomised experimental trials, cohort studies, case-control studies, interrupted time series studies with a control group)
III-**3**	A comparative study without concurrent controls (i.e. historical control study, two or more single arm studies, interrupted time series studies without a parallel control group)
IV	Case series with either post-test or pre-test/post-test outcomes

Table 19—NHMRC matrix to summarise evidence base

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence base[A]	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a systematic review or multiple level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency[B]	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population in question	population/s studied in the body of evidence are similar to the target population in question	population/s studied in body of evidence differ to target population in question but it is clinically sensible to apply this evidence to target population	population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian context	applicable to Australian context with few caveats	probably applicable to Australian context with some caveats	not applicable to Australian context

[A] Level of evidence determined from the NHMRC evidence hierarchy as in Table 1.

[B] If there is only one study, rank this component as 'not applicable'.

Appendix 4— Search strategy

Search strategy for Substance use during pregnancy, birth, and the postnatal period

The following databases were included:

Database	Grey literature
Medline	Campbell
Medline Epub ahead of print and in-process & other non-indexed	SAMHSA's National Registry of Evidence-based Programs and Practices (NREPP)
Embase	Analysis and Policy Observatory (APO)
CINAHL	CrimeSolutions
Cochrane Library	Research trial registry
Emcare	Google
PsycINFO	
Scopus	

Question 1: What interventions are most effective at improving outcomes for women who use substances during pregnancy and their developing fetus during the antenatal period, birth and postnatal period up to 2 years of the child's life?

Intervention AND	Intervention OR Program Evaluation OR Counselling OR Stress OR Psychological OR Pharmacotherapy OR Drug Therapy OR Psycho-social OR Case Management OR Drug Therapy OR Combination OR Psychoeducation OR Health Engagement OR Health system.mp. OR Systematic Review OR Randomized Controlled Trials as Topic OR pseudo-randomised controlled trial OR non-randomised experimental trials.mp. OR Case-Control Studies OR Case series OR Cohort Studies
Outcome AND	Pregnancy Outcome OR Treatment Outcome OR Health Services OR Harm Reduction OR child well being.mp. or Child Welfare OR Recidivism OR exp Child Development OR Delivery of Health Care OR Pregnancy, High-Risk OR health system service OR Risk Reduction Behaviour OR Health Services, Indigenous OR Delivery of Health Care OR health system OR Social Determinants of Health OR health engagement.mp. OR Health Utilization
Substance use AND	exp Substance-Related Disorders OR Alcohols OR Analgesics, Opioid OR Cannabis OR Cannabinoids OR Benzodiazepines OR amphetamine stimulants OR Cocaine-Related Disorders/ or Cocaine/ OR Cocaine Smoking OR Crack Cocaine OR inhalant OR Inhalant Abuse OR amphetamines/ OR amphetamine OR p-chloroamphetamine OR methamphetamine OR n-methyl-3,4-methylenedioxyamphetamine OR Buprenorphine OR Methadone OR Drug dependence OR Drug abuse OR gabapentinoids.mp. OR oxycodone OR SSRI
Pregnancy, Birth, postnatal, child up to 2 years	Pregnancy OR maternal-fetal exchange OR pregnancy in adolescence OR pregnancy outcome OR pregnancy, high-risk OR pregnancy, multiple OR pregnancy, unplanned OR pregnancy, unwanted OR Parturition OR Postnatal care OR postnatal period OR postnatal period OR Infant OR infant, newborn OR infant OR Fetus OR Fetal Development

Question 2: What interventions are most effective at reducing risk of harm in breastfeeding women who use substances?

Intervention AND	Intervention OR Program Evaluation OR Counselling OR Stress OR Psychological OR Pharmacotherapy OR Drug Therapy OR Psycho-social OR Case Management OR Drug Therapy OR Combination OR Psychoeducation OR Health Engagement OR Health system.mp. OR Systematic Review OR Randomized Controlled Trials as Topic OR pseudo-randomised controlled trial OR non-randomised experimental trials.mp. OR Case-Control Studies OR Case series OR Cohort Studies
Outcome AND	Pregnancy Outcome OR Treatment Outcome OR Health Services OR Harm Reduction OR child well being.mp. or Child Welfare OR Recidivism OR exp Child Development OR Delivery of Health Care OR Pregnancy, High-Risk OR health system service OR Risk Reduction Behavior OR Health Services, Indigenous OR Delivery of Health Care OR health system OR Social Determinants of Health
Substance use AND	exp Substance-Related Disorders OR Alcohols OR Analgesics, Opioid OR Cannabis OR Cannabinoids OR Benzodiazepines OR amphetamine stimulants OR Cocaine-Related Disorders/ or Cocaine/ OR Cocaine Smoking OR Crack Cocaine OR inhalant OR Inhalant Abuse OR amphetamines/ OR amphetamine OR p-chloroamphetamine OR methamphetamine OR n-methyl-3,4-methylenedioxyamphetamine OR Labor, Obstetric OR Labor, Induced OR Labor Onset OR Buprenorphine OR Methadone OR Drug dependence OR Drug abuse OR gabapentinoids.mp. OR oxycodone
Breast feeding Woman	Lactation OR Breast Feeding OR lactating woman OR breastfeeding women OR breast-feeding woman

Question 3: What treatments have been shown to be effective for neonatal substance withdrawal syndromes, including withdrawal from opioids, alcohol, methamphetamines, cocaine, cannabis, benzodiazepines, gabapentinoids and tobacco?

Intervention AND	Intervention OR Program Evaluation OR Psychological OR Pharmacotherapy OR Drug Therapy OR Psycho-social OR Case Management OR Drug Therapy OR Combination OR Systematic Review OR Randomized Controlled Trials as Topic OR pseudo-randomised controlled trial OR non-randomised experimental trials.mp. OR Case-Control Studies OR Case series OR Cohort Studies
Neonatal AND	Neonatal Intensive Care OR neonatal OR newborn OR Newborn Infant OR Infant
Substance use AND	exp Substance-Related Disorders OR Alcohols OR Analgesics, Opioid OR Cannabis OR Cannabinoids OR Benzodiazepines OR amphetamine stimulants OR Cocaine-Related Disorders/ or Cocaine/ OR Cocaine Smoking OR Crack Cocaine OR inhalant OR Inhalant Abuse OR amphetamines/ OR amphetamine OR p-chloroamphetamine OR methamphetamine OR n-methyl-3,4-methylenedioxyamphetamine OR Buprenorphine OR Methadone OR Drug dependence OR Drug abuse OR NPS.mp. OR New psychoactive substances.mp. Tobacco Use OR Tobacco Use Cessation OR Tobacco Use Disorder OR Tobacco Use Cessation Devices OR Tobacco, Smokeless OR Tobacco OR Smoking OR Non-Tobacco Products OR Tobacco Smoking OR Pipe Smoking OR Smoking Cessation OR Cigar Smoking OR Smoking OR Smoking Water Pipes OR Smoking Pipes OR Marijuana Smoking OR Cigarette Smoking OR Cocaine Smoking OR NPS.mp. OR New psychoactive substances.mp. OR gabapentinoids.mp. OR oxycodone
Neonatal substance withdrawal syndromes	Neonatal Abstinence Syndrome OR Substance Withdrawal Syndrome OR substance withdrawal OR Neonatal Abstinence Syndrome

Question 4: What interventions are most effective at preventing the resumption of smoking and other substance use within the six-month postnatal period?

Intervention AND	Intervention OR Program Evaluation OR Counselling OR Stress OR Psychological OR Pharmacotherapy OR Drug Therapy OR Psycho-social OR Case Management OR Drug Therapy OR Combination OR Psychoeducation OR Health Engagement OR Health system.mp. OR Systematic Review OR Randomized Controlled Trials as Topic OR pseudo-randomised controlled trial OR non-randomised experimental trials.mp. OR Case-Control Studies OR Case series OR Cohort Studies
Resumption AND	Resumption OR resume OR resum* OR Relapse
Substance use AND	exp Substance-Related Disorders OR Alcohols OR Analgesics, Opioid OR Cannabis OR Cannabinoids OR Benzodiazepines OR amphetamine stimulants OR Cocaine-Related Disorders/ or Cocaine/ OR Cocaine Smoking OR Crack Cocaine OR inhalant OR Inhalant Abuse OR amphetamines/ OR amphetamine OR p-chloroamphetamine OR methamphetamine OR n-methyl-3,4-methylenedioxyamphetamine OR Labor, Obstetric OR Labor, Induced OR Labor Onset OR Buprenorphine OR Methadone OR Drug dependence OR Drug abuse OR Tobacco Use OR Tobacco Use Cessation OR Tobacco Use Disorder OR Tobacco Use Cessation Devices OR Tobacco, Smokeless OR Tobacco OR Smoking OR Non-Tobacco Products OR Tobacco Smoking OR Pipe Smoking OR Smoking Cessation OR Cigar Smoking OR Smoking OR Smoking Water Pipes OR Smoking Pipes OR Marijuana Smoking OR Cigarette Smoking OR Cocaine Smoking OR NPS.mp. OR New psychoactive substances.mp. OR gabapentinoids.mp.
Postnatal	post natal.mp. OR Postnatal Care OR postnatal period.mp. OR postnatal.mp. OR postnatal period.mp.

Eligibility criteria:

Studies were included if they met the following inclusion criteria:

- Treatment or intervention study
- Published between
  - 2010 and September 2020 (Question 1-3)
  - All time for Question 4
- Programs based in OECD countries.

Study selection:

We will search the data base with the above words. Titles and abstract will be screened to look for appropriate literature based on the eligibility criteria. After screening title and abstract, we will then screen full text to include the most relevant articles that will meet the eligibility criteria.

Data extraction:

The following outcome table will be filled to extract data from each selected study:

Study title	
Author	Outcomes
Year of publication and country	Measured (how measured, tools used)
Drug Type	Years of intervention
NHMRC Levels of evidence/Study Design	Setting
Population/Participants/Sample	Results
Interventions/methods	Sub Population Differences
Comparator	

Quality assessment:

According to the NHMRC level of evidence we will rank studies from level I (systematic review of randomised controlled trials) to Level IV (case series with post-test or pre/post-test outcomes).

Economic Analysis Method:

MeSH for cost aspect of substance use in pregnancy.

Concept	**Population**	**Substance use**	**Alcohol use**	**Economics; cost**
MeSH terms	exp Pregnancy/infant/ or infant.mp. /Fetus/ or fetus.mp/ Neonatal Abstinence Syndrome/ or neonatal.mp.	substance-related disorders.mp. or exp Substance-Related Disorders/	*Ethanol/ or Prenatal Exposure Delayed Effects/ or Pregnancy/ or *Female/ or *Alcohol Drinking/	*Economics, Nursing/ or *Economics, Behavioral/ or *Economics, Pharmaceutical/ or *Economics/ or *Economics, Medical/ or economic.mp. or *Economics, Hospital
				exp "Costs and Cost Analysis"/

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