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Does the Presentation of Neonatal Abstinence Syndrome Symptoms Differ Among Infants Based on Exposure Substance?

by

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Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

INTRODUCTION: Neonatal abstinence syndrome (NAS) is one of the primary negative effects of substance use during pregnancy. Neonatal abstinence syndrome refers to a generalized disorder observed in infants experiencing opiate withdrawal. Signs and symptoms of NAS include yawning, sneezing, sweating, stuffy nose, mottling, fever and increased secretion of tears, and often the development of tremors, high pitched cry, increased muscle tone and irritability. The modified Finnegan scoring tool is widely used to assess NAS and guide NAS treatment. However, the emphasis is usually on the total score. Little is known about which symptoms (individual items) on the modified Finnegan Scoring Tool are the most commonly observed among infants presenting with NAS and whether they differ based on type of substance exposure. Similarly, little is known whether the severity of NAS differs based on the type of substance exposure. Thus, the purpose of this study was to evaluate whether the presentation of NAS symptoms, severity of NAS and neonatal outcomes differ among infants based on the substances they were exposed to *in utero*. METHODS: A retrospective chart review was conducted collecting data from infant and maternal health records (over a one year period) from a tertiary care hospital. ANALYSIS: Descriptive statistics, Chi-Square and One-way Analysis of Variance (ANOVA) using the Student-Newman-Keul (SNK) post hoc comparisons were conducted to determine whether significant differences existed between groups on outcome variables based on exposure substance. RESULTS: Data were collected on 131 infant/mother pairs. Infants were categorized by exposure substance into one of four groups; methadone only, methadone and other substances, single non-methadone, and poly non-methadone. Three symptoms (increased muscle tone, tremors when

disturbed and fever between 37.2°C and 38.3°C) were identified as the most common symptoms observed across all four groups of infants. Two symptoms (generalized convulsions, fever ≥38.4°C) were never observed in any of the four groups, and ten symptoms were seen at a frequency of less than 5% in any of the groups. No clear significant differences were found between the four groups on the relative frequency of symptom observation. However, infants exposed to methadone (solely or in addition to other substances) experienced more severe NAS compared to infants not exposed to methadone. This was demonstrated by the significantly higher peak scores, longer time from onset of symptoms to peak score, larger number of infants requiring pharmacological treatment, longer length of treatment and longer lengths of stay in hospital. No significant differences among the four groups were found for any of the neonatal outcomes including term, weight, length, head circumference, and one minute and five minute Apgar scores. CONCLUSION: Infants exposed to methadone (alone or with other substances) experienced more severe NAS after delivery than did those exposed to substances other than methadone. Further evaluation of and a possible reduction in the number of items on the modified Finnegan scoring tool is needed as many items were rarely if ever observed, regardless of the substance exposure. There are varying findings in the literature regarding differences in birth outcomes based on substance exposure, further investigation is justified.

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Table of Contents

List of Figures

List of Tables

List of Abbreviations

AAP	American Academy of Pediatrics
ANS	Autonomic Nervous System
ANOVA	Analysis of Variance
Cm	Centimeter
CNS	Central Nervous System
g	Grams
Hrs	Hours
MMT	Methadone Maintenance Therapy
NAS	Neonatal Abstinence Syndrome
NICU	Neonatal Intensive Care Unit
NIDA	National Institute on Drug Abuse
PCMCH	Provincial Council for Maternal and Child Health
PHAC	Public Health Agency of Canada
RNAO	Registered Nurses' Association of Ontario
SNK	Student-Newman-Keul
SNRI	Selective Norepinephrine Reuptake Inhibitor
SPSS	Statistical Package for the Social Science
SSRI	Selective Serotonin Reuptake Inhibitor
TCPS	Tri-Council Policy Statement

Introduction

Illicit drug use and prescription drug abuse is a public health concern in Canada. While the Canadian Alcohol and Drug Use Monitoring Survey (2010) indicated that in most categories, substance use has remained constant or decreased slightly over the past six years (Health Canada, 2011) the rates are still alarming. For example, the results of the 2010 survey indicated that 11% of Canadians aged 15 and older used substances in the last 12 months. The rates for males are double that of females, and the rate of substance use among youth (15 – 24 years of age) is three times that of adults (25 years and older). Between 2002 and 2005 there was a 24% increase in the proportion of street drug users that were using prescription opioids non-medically (Popova, Patra, Mohapatra, Fischer & Rehm, 2009). The estimates of drug use established from self-reporting are estimated to be 3 to 3.5 times lower than the true value (Chen, Fang, Shyu, & Lin, 2006). Ontario had the lowest prevalence of illicit drug use out of all the provinces in Canada in 2010; 8.2% compared to the highest at 14.1% in the Nova Scotia (Health Canada, 2011). Substance use in northwestern Ontario is higher than the Ontario average; particularly in the student aged population (grades 7 – 12) (Sieswerda, Starkes, & Adlaf, 2007). For example, northwestern Ontario students reported higher use rates of cannabis (31.7% vs. 26.5%), hallucinogens (11.7% vs. 6.7%), methamphetamine (4.5% vs. 2.2%), OxyContin (4.5% vs. 1%) and cocaine (6% vs. 4.4%) (Sieswerda, Starkes, & Adlaf, 2007). Substances that are used in this region range from tobacco and alcohol to cocaine, heroin, methamphetamines, opiates, tranquilizers and stimulants (Adlaf & Paglia-Boak, 2005; Sieswerda et al., 2007).

Substance use has many negative effects on the individual, family and society. In adolescents, poor academic performance, acting out, dropping out of school, mood disorders, violence, committing crimes, infectious diseases and unplanned pregnancies are some of the effects that are identified (Catalano, White, Fleming & Haggerty, 2011; National Institute on Drug Abuse [NIDA], 2010). Adults with substance abuse problems, who often began to use in adolescence, may have memory and cognitive problems, are more likely to be unemployed and have poor health (Catalano et al., 2011; NIDA, 2010). Often poor social behaviours are developed, affecting performance at work and personal relationships (NIDA, 2010). Medical consequences of substance use include cardiovascular and respiratory diseases, stroke, cancer, changes in neurons and brain circuits, mental illness and severely compromised long-term health of the brain, and gastrointestinal and liver disorders (Keaney et al., 2011; NIDA, 2010). Substance abuse among parents may harm their children's well-being and development as these households are often chaotic and stressful; substance abuse can be an intergenerational problem (NIDA, 2010). Parenting can be a stressful job that appears to be even more stressful for substance abusing women (Kelley, 1992; Kelley, 1998). This perceived higher amount of stress and increased potential for child abuse can be associated with environmental risk factors for parenting problems and negative child outcomes (Nair, Schuler, Black, Kettinger & Harrington, 2003). Adolescents who have family members (specifically caregivers) that use substances are at an increased risk of using and becoming dependent on illicit substances (Kilpatrick et al., 2000).

The use of illicit substances during pregnancy is also a concern. The Canadian Maternity Experience Survey for 2006-2007 reported that

approximately 7% of women indicated using illicit substances within 3 months of knowing they were pregnant and approximately 1% continued to use throughout the pregnancy (Public Health Agency of Canada [PHAC], 2009). However, gathering accurate data is challenging because of the unwillingness of many women to disclose drug use likely due to the illegal and social undesirability of this activity during pregnancy (Bell & Harvey-Dodds, 2008; PHAC, 2009). Discrepancy between maternal self-reporting and meconium and neonatal urine screening has been documented in numerous studies (Chen, Fang, Shyu, & Lin, 2006; Eyler, Behnke, Wobie, Garvan, & Tebbett, 2005; Murphy-Oikonen, Montelpare, Southon, Bertoldo & Persichino, 2010). Chen, Fang, Shyu, and Lin (2006), estimate that the true prevalence of substance use is 3 to 3.5 times higher than what is reported through self-report. Eyler and associates (2005) found that 17% of mothers who had denied substance use during pregnancy had a biological specimen obtained (infant or maternal) that tested positive for substances. Murphy-Oikonen and colleagues (2010) detected a maternal failure to report rate of 24% to 27%. While the occurrence of substance abuse during pregnancy is less than that of the overall population, it is still significant (Wong, Ordean, & Kahan, 2011).

Many negative outcomes associated with substance abuse during pregnancy are similar to those during the non-perinatal period including problems with cognitive functioning (thinking clearly, paying attention, remembering), violence, and poor social behaviours (NIDA, 2010). Also, pregnant substance abusing women often receive less prenatal care including gynecologic exams and ultrasounds during pregnancy, than non-using pregnant women (Vucinovic et al., 2008). Maternal substance use during pregnancy has specific

effects on the fetus including higher rates of prematurity and growth retardation resulting in small for gestational age babies, deficits in behaviour, attention and cognition, neonatal morbidity and mortality, as well as neonatal abstinence syndrome (NAS) (Fergusson, Horwood, Northstone & ALSPAC Study Team, 2002; Hurd et al., 2005; NIDA, 2010; Vucinovic et al., 2008). Infants born prematurely and small for gestational age have been found to have significantly lower percent body fat and higher blood pressure than full-term infants (Willemsen, de Kort, van der Kaay, & Hokken-Koelega, 2008). Premature infants may also be at higher risk of symptoms of ADHD, problems with social competence and adaptive functioning as children compared to children who were born at full-term (Chapieski & Evankovich, 1997). Low birth weight has been associated with an increased risk of neurological soft signs (deviations in motor, sensory, and integrative functions), these soft signs have been associated with an increased risk for subnormal IQ, and learning disorders, and issues internalizing and externalizing problems as children (Breslau, Chilcoat, Johnson, Andreski, & Lucia, 2000).

Infants exposed to opioid substances *in utero* may exhibit NAS, whereby they display central nervous, gastrointestinal and respiratory dysfunction (Kassim & Greenough, 2006; Wong, Ordean & Kahan, 2011). Neonatal abstinence syndrome refers to a generalized disorder observed in infants experiencing opiate withdrawal. Signs and symptoms of NAS include yawning, sneezing, sweating, stuffy nose, mottling, fever and increased secretion of tears, and often the development of tremors, high pitched cry, increased muscle tone and irritability (Kaltenbach & Finnegan, 1986). This is a complex disorder which is widely variable with different symptoms being exhibited at various times by each infant (Jansson, 2008). While NAS refers to opioid withdrawal, infants withdrawing from

other substances including barbiturates, benzodiazepines, and selective serotonin reuptake inhibitors (SSRIs), exhibit similar symptoms as are observed in NAS (Blumenthal & Lindsay, 1977; Levinson-Castiel, Merlob, Linder, Sirota & Klinger, 2006; Nordeng, Linemann, Perminov & Reikvam, 2001; Sanz, De-las-Cuevas, Kiuru, Bate & Edwards, 2005; Sutton & Hinderliter, 1990).

Not only do infants exposed to illicit substances experience NAS, infants exposed to the treatments for opioid addictions (methadone and buprenorphine) also experience NAS (Jones, Kaltenbach et al., 2010; Lim, Prasad, Samuels, Gardner, & Cordero, 2009; Ludlow, Evans, & Hulse, 2004). Methadone is the most commonly used substance in opioid maintenance treatment (van den Brink & Haasen, 2006). According to the SOGC, MMT is the gold standard treatment for opioid dependency in pregnancy (Wong, Ordean & Kahan, 2011). During pregnancy MMT has well documented benefits for both mother and infant (McCarthy, Leamon, Parr & Anania, 2005). Maternal benefits include reduction in withdrawal, cravings for other substances, unpredictable use of opioids and risk of relapse; recovery from illicit drug use; improved health and compliance with prenatal care; and better preparation for parenthood (Centre for Addiction and Mental Health [CAMH], 2007; Finnegan, 2000; Jansson, et al., 2008; McCarthy, Leamon, Parr & Anania, 2005). Methadone also decreases the risk of obstetrical complications including preterm labour, spontaneous abortion and miscarriage (Registered Nurses' Association of Ontario [RNAO], 2009). Benefits for infants stem from the reduction in use and cravings for other substances which reduces fetal exposure to repeated cycles of withdrawal; improved compliance with prenatal care which results in fewer fetal and neonatal complications such as premature births, low birth weight and neonatal mortality; and better preparation

for parenthood which leads to increased health and safety of the infant (CAMH, 2007; Finnegan, 2000; Jansson et al., 2008; McCarthy, Leamon, Parr & Anania, 2005; Ordean, 2012). The use of methadone also protects both mother and infant from the risk of infection associated with unsafe injection drug use (i.e. HIV, Hepatitis) (CAMH, 2007; Jansson, et al., 2008; RNAO, 2009).

Despite the well-known benefits of MMT, studies evaluating NAS among methadone exposed infants have reported that compared to other treatment methods (buprenorphine or morphine), the onset of NAS symptoms is later and they have longer lengths of stay in hospital, thereby separating mother and newborn (Ebner et al., 2007; Jones, Kaltenbach et al., 2010; Serane & Kurian, 2008). As well, more of the methadone-exposed infants required treatment compared to buprenorphine-exposed newborns, but significantly fewer than those exposed to morphine (Ebner et al., 2007; Jones, Kaltenbach et al., 2010).

Johnson, Greenough and Gerada (2003) assessed age at NAS symptom onset, duration of treatment and length of neonatal unit stay of forty-one infants by opioid exposure (methadone, methadone and others [other substances], and substances other than methadone). They found that the median age at onset of symptoms did not differ among the three groups. While the duration of treatment and the duration of hospital stay were longest in the methadone plus other substances group, significant differences were only found between the methadone plus other substances group and the non-methadone group (duration of treatment $p = 0.03$; duration of hospital stay $p = 0.02$). Both duration of treatment and length of stay were not found to be significantly different between the methadone group and the other groups (p-value not provided). Limitations of this study include its small sample size ($n = 41$), which resulted in small uneven group

sizes (methadone only, n = 14; methadone plus other substances, n = 17; non-methadone, n = 10). Also, the sample was taken from medical records over a ten year period, and halfway through this time frame the method of pharmacological treatment changed from prescribed chlorpromazine to prescribed morphine. Thus, there is the possibility that the differences in treatment could affect the outcomes evaluated.

When assessing NAS diverse tools may be used including the Finnegan, the Lipsitz, the Reilly pain scale, the River's scoring system, the Ostrea and self-designed hospital tools (American Academy of Pediatrics, 1998; Crocetti, Amin & Jansson, 2007; Johnson, Greenough & Gerada, 2003). The original Finnegan neonatal abstinence scoring system was developed in 1975 in an effort to improve the method for the assessment of NAS, as related to narcotic withdrawal, and for evaluating therapeutic methods (Finnegan, Connaughton, Kron & Emich, 1975). The scoring system was made up of 32 items spanning 20 observable symptoms reflecting central nervous system stimulation. The scoring value of each symptom is based on its potential for medically negative effects. These values range from 1 to 5, one having the least potential for adverse effects and 5 having the highest potential for adverse effects (Finnegan et al., 1975). Inter-rater reliability was tested among four pairs of nurses, each pair scoring one individual infant (Finnegan et al., 1975). This scoring system was found to be highly reliable among multiple nursery staff, with the inter-rater reliability coefficient (type of coefficient not specified) in each pair ranging from 0.75 to 0.96, with a mean coefficient of 0.82, all coefficients were statistically significant ($p < 0.005$) (Finnegan et al., 1975). This system was also found to be valuable in assessing the

symptomatology before, during and after therapeutic interventions were implemented (Finnegan et al., 1975).

The Finnegan Scoring Tool is still the most commonly used abstinence scoring tool used to assess NAS in the United States (used by 56% - 65% of institutions) (Crocetti, Amin, & Jansson, 2007). Various studies indicate that this tool can be used to assess the presence and severity of symptoms as well as to guide decisions about the need for NAS treatment and dosage alterations (Kassim & Greenough, 2006; Sarkar & Donn, 2006; Zimmermann-Baer, Nötzli, Rentsch & Bucher, 2010). Though the Finnegan is still the most widely used scoring tool, and is the assessment tool recommended for use by the Provincial Council for Maternal and Child Health (PCMCH) (2012), Sarkar and Donn (2006) found that many institutions using the Finnegan scoring system are actually using a modified version of the original. When reviewing the modified Finnegan scoring tool it became evident that there are slight variations of the modified Finnegan and not one modified and validated tool. For example, one version of the modified Finnegan tool has an item termed “failure to thrive” and does not include “high-pitched cry” (Choo, Huestis, Schroeder, Shin & Jones, 2004) while others do not have “failure to thrive” and include “high-pitched cry” (McQueen, Murphy-Oikonen, Gerlach & Montelpare, 2011; Zimmermann-Baer et al., 2010).

While the Finnegan Scoring Tool provides information on both individual symptoms and total scores, it is the total scores that are most frequently reported. Minimal information is available on the individual items scores and which items (symptoms) if any are most frequently observed and which items are infrequently observed. For example, are certain symptoms such as high pitched cry, tremors, yawning, *etcetera*, more common in the presentation of NAS and are there other

symptoms that are rarely observed? It would be valuable to know whether all 30 items are useful in identifying NAS or whether there are subsets of items that may identify the same outcomes. One study was identified which evaluated individual symptom items of the modified Finnegan (Choo, Huestis, Schroeder, Shin and Jones, 2004). They compared the single items on a modified Finnegan as a function of tobacco exposure among 29 methadone maintained mother/infant dyads. In this study infants were divided into two groups based on maternal smoking; low smoking (≤10 cigarettes/day; n=16) and high smoking (≥ 20 cigarettes/day; n=13), they did not evaluate a middle group (10 – 20 cigarettes/day). They found that disturbed tremors, increased muscle tone and hyperactive Moro reflex were the most frequently observed items in both the low and high smoking groups. They also noted that generalized seizures and failure to thrive were not reported at all, with yawning and vomiting observed in less than 1% of the infants in this study.

There is also limited information about whether individual symptoms are similar or different in relation to the type of substance exposure. The most commonly observed symptoms of NAS in infants exposed to opiates and opioid maintenance substances are high-pitch cry, short sleep after feeding, tremors, poor sucking, hyper-reflexibility, increased muscle tone, vomiting, sneezing, and increased respiratory rate (Ebner et al., 2007; Serane & Kurian, 2008; Zimmermann-Baer et al., 2010). Bada, Bauer and colleagues (2002) also completed a study analyzing central and autonomic nervous system (CNS & ANS) symptoms among opiate exposed (n = 100), cocaine exposed (n = 717) and opiate and cocaine exposed (n = 92) infants. They found that jitteriness, tremors and irritability were the most commonly observed symptoms. These symptoms were

found in >5% of non-exposed infants, >12% of infants exposed to cocaine, >20% of infants exposed to opiates and >40% of infants exposed to both cocaine and opiates. High pitched cry was the next most frequently observed symptom, found in approximately 3% of infants exposed to cocaine, 12% of infants exposed to opiates and 15% of infants exposed to both substances. However, as this study evaluated general CNS/ANS symptoms based on the New Ballard scoring tool not a Finnegan scoring tool, direct comparisons cannot be made. These studies provide valuable information on individual symptoms of the modified Finnegan when exposed to methadone and NAS symptom differences between opioids and cocaine based on another scoring system. Still little is known about whether the presentation of symptoms is similar or different between infants exposed to methadone as part of methadone maintenance treatment and other substances. No studies were identified that have specifically evaluated the individual symptoms on a modified Finnegan scoring tool between infants exposed to methadone and those exposed to other substances and whether they are similar or different.

It has been proposed that NAS symptoms and their severity vary by substance, frequency, quantity and length of exposure (Ebner et al., 2007; Serane & Kurian, 2008). Similarly, specific to methadone, the development of NAS and its duration have been identified as related to maternal methadone dosage with higher dosages associated with increased severity of symptoms (Dryden, Young, Hepburn & Mactier, 2009; Lim et al., 2009; Wouldes & Woodward, 2010). The dosage of methadone has also been associated with symptom onset, length of treatment, and length of hospital stay with higher dosages being associated with later onset, longer length of treatment and longer hospital stays (Dryden et al.,

2009; Lim et al., 2009; Serane & Kurian, 2008; Wouldes & Woodward, 2010). However, others have found no evidence that the timing, duration or amount of maternal methadone exposure is associated with the risk of needing treatment for NAS or longer hospitalization (Kuschel, Austerberry, Cornwell, Couch & Rowley, 2004; McCarthy, Leamon, Parr, & Anania, 2005; McCarthy, Leamon, Stenson & Biles, 2008). Further evaluation of onset of symptoms, peak score, length of time from onset of symptoms to peak score, length of treatment and length of hospital stay based on substance exposure is required.

Research on neonatal outcomes and *in utero* substance exposure is also inconsistent. Some studies indicate that birth weight, length and head circumference of infants exposed to illicit substances *in utero* are lower than those of healthy unexposed infants (Burns, Mattick, & Cooke, 2006; Dryden et al., 2009). Others found that there is limited or no differences in birth weight, length, head circumference and gestational age at birth between exposed and unexposed infants (Ebner et al., 2007; Simmat-Durand, Lejeune, & Gourarier, 2009). Studies have also found infants exposed to methadone having smaller head circumferences, lower birth weights and being small for gestational age (Dryden et al., 2009; Lim, Prasad, Samuels, Gardner, & Cordero, 2009).

There have also been some studies on exposure to cocaine, marijuana, opioid and amphetamine substance exposure and neonatal outcomes. Smith and colleagues (2006) found that infants exposed to methamphetamines had lower birth weights, were more frequently small for gestational age and were born earlier than non-exposed infants. Ludlow, Evans, and Hulse (2004) found that compared to infants exposed to opiate substances, amphetamine exposed neonates were less frequently small for gestational age and less frequently

admitted to NICUs but were more likely to have Apgar scores <7 and spend more time in special care nurseries. Fergusson and colleagues (2002) stated that frequent cannabis use during pregnancy may be associated with decreases in birth weight compared to infants not exposed to cannabis. Burns, Mattick and Cooke (2006) evaluated outcomes of neonates exposed to opioids, stimulants, cannabis and those that were not exposed. They found that those exposed to opioids were the most likely to be born premature, have Apgar scores <7 and spend more than 14 days in hospital. Other than those exposed to cannabis, the opioid group also had the highest percentage that were small for gestational age. Bada, Das and colleagues (2002) evaluated birth outcomes in infants exposed to cocaine compared to those not exposed to cocaine. They found that cocaine exposure was associated with a decrease in birth weight as well as length and head circumference. Exposure to opiates in addition to cocaine had a significant effect on birth weight (lower birth weights than those not additionally exposed to opiates).

This review of the literature has identified several gaps in the evidence regarding neonatal outcomes as a result of substance exposure *in utero*. In particular, little is known about which NAS symptoms are the most commonly observed among infants presenting with NAS and whether they differ based on substance exposure. Also, there is varying information regarding the presentation of NAS, including age at onset of symptoms, need for pharmacological treatment, time to peak score, *etcetera,* and if they differ based on substance exposure. Similarly, whether outcomes such as Apgar scores, birth weight, head circumference, *etcetera*, differ based on substance exposure is also unclear. Given that the evidence is limited, the purpose of this study is to evaluate whether the

type of substance exposure (methadone, methadone and other substances, a single non-methadone substance or poly non-methadone substance use) affects the presentation of NAS symptoms and neonatal outcomes.

Research Questions

(1) Do the individual symptoms of NAS differ among infants based on their exposure substance? (e.g., are there some symptoms that are always observed versus never or seldom observed?)

(2) Does the presentation of NAS (e.g., onset of symptoms, peak scores, time to peak score) differ among infants based on their substance exposure?

(3) Do neonatal outcomes (e.g., birth weight, length, head circumference, Apgar scores) differ among infants based on their substance exposure?

Methodology

Study Design

This study was a retrospective review of birth records from a tertiary care hospital in northwestern Ontario. The sample included all infant records and corresponding maternal medical records meeting the study eligibility criteria from September 1, 2010 to August 31, 2011. Inclusion in this study required that infants (1) had documented NAS scores using the modified Finnegan scoring tool and (2) had a record (maternal self-report, urine and/or meconium screening) of exposure to a substance (illicit drug and/or prescribed methadone). Exclusion from the study included: (1) multiple births and/or (2) transfers to other facilities due to serious medical conditions.

Definition of Variables

Neonatal abstinence syndrome. For the purpose of this study, an infant was categorized as having NAS if he/she had been exposed to a substance(s) *in utero* and had recorded NAS scores in their chart on the modified Finnegan scoring tool.

Substance exposure. Substance in this study was defined as any drug that may lead to neonatal abstinence syndrome. Antenatal opioid exposure, including methadone, morphine, heroin, buprenorphine, oxycodone and codeine has been known to cause NAS (Wong, Ordean & Kahan, 2011). Withdrawal from other substances including barbiturates, benzodiazepines, and selective serotonin reuptake inhibitors (SSRIs), manifests with similar symptoms as NAS (Blumenthal & Lindsay, 1977; Levinson-Castiel, Merlob, Linder, Sirota & Klinger, 2006; Nordeng, Linemann, Perminov & Reikvam, 2001; Sanz, De-las-Cuevas, Kiuru, Bate & Edwards, 2005; Sutton & Hinderliter, 1990). Tobacco and alcohol use

during pregnancy were recorded separately as they were important variables for describing the sample but were not an evaluated outcome in this study.

The primary method used to determine substance exposure was maternal self-report (the mother identifying that she had used specific substances during pregnancy). Infant urine screen results were also used to determine exposure substance. The time frame that substances can be detected in urine varies depending on the substance; typical detection time is within 72 hours with a few substances being detected after that length of time (Verstraete, 2004). Meconium drug screen results were used to determine exposure substance only when there was no record of maternal self-report, no record of urine screen or if the results of the urine screen were negative. Meconium screening results were used as the last method for identifying substance exposure. While meconium screening is very accurate, it detects substances used as early as the second trimester of pregnancy (Ostrea et al., 2001). Therefore, it is possible that a woman who has not used substances in weeks or even months could have an infant with a positive meconium drug screen.

All substances were recorded from mother and/or infant records (e.g., percocet, marijuana, valium) with the exposure substances further categorized based on the seven classifications common in hospital urine test kits; opiates, barbiturates, tricyclics, methadone, cannabinoids, cocaine and benzodiazepines. Some infants were tested for additional substances not included in these classifications; these were also recorded in the data for this study, including Selective Serotonin Reuptake Inhibitors (SSRIs), Selective Norepinephrine Reuptake Inhibitors (SNRIs), ritalin and antipsychotics.

Symptomatology of NAS. Symptomatology of NAS refers to the presence of individual symptoms using the modified Finnegan scoring tool (Appendix A). In this study the symptomatology of NAS was evaluated using the relative frequency of observed symptoms over three time frames. The three time frames were (1) onset of symptoms to the time of peak score, (2) onset of symptoms to the initiation of pharmacological treatment, and (3) onset of symptoms to 72 hours of recorded NAS symptom observation.

Presentation of NAS. Presentation of NAS refers to how the syndrome presents as measured by six variables. These variables include, (1) the onset of symptoms (number of hours from birth to first presentation of NAS symptoms), (2) peak NAS scores (highest total score on the modified Finnegan scoring tool before weaning of pharmacological treatment), (3) time to peak (number of hours from onset of symptoms to when the highest total score is reached), (4) type of treatment (pharmacological or non pharmacological), (5) length of treatment (number of hours from initiation of pharmacological treatment to discontinuation) and (6) length of hospital stay (number of days from birth to discharge).

Neonatal outcomes. Neonatal outcomes refer to objective measures of the neonate recorded at birth. Outcomes included gestational age, Apgar scores at 1 and 5 minutes, weight, length and head circumference.

Sample

Setting and sample size. The tertiary care centre is the sole provider of maternal-infant care in the area and the referral hospital for the catchment area. The selected site had a birth rate of approximately 1500 babies for the year 2010-2011. It was estimated by a hospital manager at this facility that approximately 12% of infants born at this institution experience NAS. Based on this estimate

and the birth rate it was anticipated that approximately 180 infants would experience NAS yearly. Given the inclusion/exclusion criteria and this estimate it was proposed that a sample size of 100-150 infant/mother pairs would be feasible.

Procedure

Upon university and hospital ethics approval, request to access infants' electronic and paper health records and matching maternal electronic health records was submitted to the Health Records Department. From this request, Health Records created a list of records matching the inclusion/exclusion criteria. These records were assessed for eligibility in the study. Data were extracted from the charts by the student investigator and documented on the data collection form (see Appendix B) on site at the hospital. The data collection form was designed based on the outcomes identified in the literature and the information available in medical records at this tertiary care hospital. Completed data forms were taken to Lakehead University and entered into Excel data spreadsheets.

Consent

As this was a retrospective chart review consent from participants was not obtained as is consistent with the Tri-council policy statement version 2 (TCPS 2) (2010). Researchers are not required to seek consent from individuals for the secondary use of non-identifiable information. When secondary data includes identifiable information, the TCPS 2 indicates that consent may be waived if (1) the identifiable information is essential to the research, (2) the use of this information is unlikely to adversely affect the welfare of those whom the information pertains to, (3) the researchers take appropriate measures to protect the privacy of the individuals whose information is being used, (4) the researchers

will comply with any previously known preferences of the individual, (5) it is impossible or impracticable to seek consent, and (6) the researchers have obtained all other necessary permission for the secondary use of the information. No identifiable information (i.e., names, address, health record number, health insurance number, or maternal birth date) was collected for this research study. The researchers believed that it was impractical to obtain consent for this research study based on the nature of the research topic. To contact mothers whose infants experienced NAS due to maternal substance use may have caused unnecessary psychological harm to the mother. This harm could have been in the form of causing them to relive any feelings of guilt or judgement due to their substance use and the negative effects it may have had on their child. It was also possible that the infants may not have been in the care of their biological mother which could have then created more negative emotions for the mother when contacted for consent. It was possible that many of the mothers may also have moved as unstable housing has been associated with substance use (Bebout, Drake, Xie, McHugo & Harris, 1997). Due to the small number of records that met the inclusion/exclusion criteria, being unable to contact mothers to get consent (relocation, phone disconnected, change in contact information, etc.) could have affected the validity of study findings. As there were no identifying characteristics included in the data collected for this study, the research involved no more than minimal risk as defined by the TCPS 2 and waiving the consent procedure was unlikely to have negative effects on the welfare of those whose health information was to be accessed.

Summary of Measures

Demographic variables. To describe the sample, demographic information collected included maternal age at delivery, maternal smoking status, gender of the newborn and the type of maternal substance use. As this was a chart review many socio-demographic variables such as income, education, and culture were not included nor was the amount of maternal substance use as they were not consistently recorded in medical records.

Group categories. Infants were categorized into one of four groups based on their substance exposure. These groups were: (1) "methadone"; infants exposed to prescribed methadone only, (2) "methadone and other"; infants exposed to prescribed methadone and other substances, (3) "single non-methadone"; infants exposed to one single substance category other than methadone, and (4) "poly non-methadone"; infants exposed to more than one non-methadone substance.

Modified Finnegan scoring tool. The modified Finnegan scoring tool was used to assess NAS symptomatology and the presentation of NAS. The modified Finnegan scoring tool used at this tertiary care hospital was a 30 item tool whereby items (symptoms) are grouped together based on the body system that is affected (Central Nervous System, Metabolic, Vasomotor, Respiratory, and Gastrointestinal). Each symptom has a specific value between 1 and 5; if the symptom is not apparent then no score is given. If a symptom is identified it is assigned the designated value (See Appendix A). For example, a high pitched cry is assigned a score of 2, whereas a continuous high pitched cry is assigned a score of 3; tremors when disturbed are assigned a score of 1 while moderate/severe tremors when undisturbed are given a score of 4. Higher scores

indicate a greater potential for clinically adverse effects (Finnegan et al., 1975). Based on the specific values assigned to each symptom on the modified Finnegan scoring tool, the minimum total score that can be given is 0 and the maximum total score is 44 (McQueen et al., 2011). Three consecutive scores of 8 or greater suggests NAS symptoms requiring pharmacological treatment. All infants, regardless of the type of substance of exposure are assessed using this tool and treated accordingly.

NAS Symptomatology. The primary goal of this research was to identify whether or not there are differences in the appearance of NAS symptoms among infants based on substance exposure. This was evaluated primarily by assessing NAS Symptomatology (the assessment of individual symptoms from the modified Finnegan scoring tool). All individual item scores and total scores on the modified Finnegan scoring tool were recorded on the data collection sheet. The symptomatology of NAS was evaluated by the relative frequency that each individual symptom was observed for each infant at three main time periods. These time periods were onset of symptoms to (1) the peak of withdrawal (highest total score on the modified Finnegan before weaning of morphine), (2) the initiation of pharmacological treatment and (3) 72 hours of recorded NAS symptom observation. Relative frequency was defined as the number of times a symptom was observed divided by the total number of times the infant was evaluated using the modified Finnegan scoring tool. The total score for each group of symptoms (Central Nervous System, Metabolic, Vasomotor, Respiratory, and Gastrointestinal) was also evaluated at the time of peak score for each infant.

Presentation of NAS. The presentation of NAS was evaluated using six variables. These variables were (1) the onset of symptoms (number of hours from

birth to first presentation of NAS symptoms), (2) peak NAS scores (highest total score on the modified Finnegan scoring tool before weaning of pharmacological treatment), (3) time to peak (number of hours from onset of symptoms to when the highest total score is reached), (4) type of treatment (pharmacological or no pharmacological), (5) length of treatment (number of hours from initiation of pharmacological treatment to discontinuation) and (6) length of hospital stay (number of days from birth to discharge).

Neonatal outcomes. The secondary objective of this study was to examine neonatal birth outcomes among the four groups of infants. The neonatal outcomes data collected in this study included gestational age (number of weeks gestation) at birth, birth weight, length, head circumference and Apgar scores. Apgar scores are based on the Apgar scoring system and include 5 assessments (heart rate, respiratory effort, muscle tone, reflex irritability and skin colour) and can range from 0 to 10. Newborns are assessed at 1 and 5 minutes after birth (Ladewig, London, Moberly & Olds, 2002).

Data Management

The student investigator was responsible for: (1) contacting health records regarding required charts, (2) extracting data from health records and (3) entering data into a computer based program for analysis. All computer files were password protected and saved to a USB key. All hard-copy, study-related materials were stored in a locked filing cabinet. No identifying participant information such as names, addresses or hospital record numbers were recorded. The data will remain in a locked filing cabinet at Lakehead University for five years following completion of the study as per University policy.

Data audit. Prior to analysis, data collected for this study were double-checked by a Master's prepared professional for accuracy and errors. In order to audit the data, a random number generator was used to select a sample of the files of data (n = 28, 20.4%). Each file included (1) a data spreadsheet, (2) a modified Finnegan scoring spreadsheet, (3) relative frequency spreadsheets, and (4) time calculations. The data spreadsheet consisted of 41 variables for each infant/mother pair. The modified Finnegan scoring spreadsheet included 30 symptoms and the indication for initiation of treatment, first wean of pharmacological treatment, peak score, and 72 hours of recorded NAS symptom observation. Each file had three relative frequency calculations spreadsheets (one for each time period); these spreadsheets included the relative frequencies for each symptom. There were four time calculations (onset of symptoms, time to peak, length of pharmacological treatment and length of hospital stay) for each infant. A total of six errors were found during the audit. Due to this minimal amount of errors identified through the audit of 20% of the data, it was felt that no further data needed to be audited. During the analysis phase, four additional errors were identified. All errors found through the audit and analysis process were fixed accordingly.

Analysis

The data set was analyzed using the Statistical Package for the Social Science (SPSS) version 19. Descriptive statistics, Chi-square test and One-way Analysis of Variance (ANOVA), followed by Student-Newman-Keul post hoc comparisons (SNK) with the significance level of $p = 0.05$ were used to analyze the data collected in this study.

Demographics of sample. The sample was described using frequencies, measures of central tendency (mean), and measures of dispersion (standard deviation).

Primary outcome variables. Relative frequencies were chosen as the appropriate measure for the individual NAS symptoms due to the fact that the frequency and duration of NAS scoring differed among infants. Therefore the number of times each infant was assessed using the modified Finnegan scoring tool varies due to the frequency at which they are assessed as well as the length of time they are assessed for. The inconsistency in the number of scores obtained for each infant made using the mean frequency of symptom observation less appropriate for this study. Relative frequencies of each individual item (symptom) on the modified Finnegan scoring tool were calculated. This was done by dividing the number of times a symptom was observed by the total number of times the infant was assessed using the modified Finnegan scoring tool. The relative frequency of symptom observation was assessed over three periods of time, (1) from onset of symptoms to the peak score, (2) from the onset of symptoms until the initiation of pharmacological treatment, and (3) from the onset of symptoms until 72 hours of recorded NAS symptom observation. The frequencies of symptoms exhibited in each exposure group were compared using mean tables. One-way Analysis of Variance (ANOVA) calculations were used to compare the four exposure groups on (1) symptomatology of NAS, (2) symptom category scores at time of peak score, and (3) the NAS presentation variables, other than the requirement of pharmacological treatment. With each ANOVA, Post Hoc analysis using the Student-Newman-Keuls (SNK) test was completed. The need for

pharmacological treatment was compared between groups using Chi-square analysis.

Secondary outcome variables. The neonatal outcomes of birth length, weight, head circumference and 1 and 5 minute Apgar scores were compared between groups using ANOVA with SNK post hoc comparisons. The number of term infants between groups was compared using Chi-square analysis.

Benefits

There is no direct benefit to the participants in this study. This research may benefit the scientific community by contributing to the body of knowledge surrounding substance use during pregnancy and the associated infant outcomes. In particular, this study will provide valuable information regarding the presentation of NAS symptoms, the presentation of NAS (eg. Onset of symptoms, length of hospital stay and type of treatment required), and neonatal outcomes related to different exposure substances. Investigating the presentation of NAS by drug type and identifying the differences in symptom appearance (if found) by exposure substance may help to benefit the newborn through early identification and therefore early and appropriate treatment. Early identification of NAS in emergency departments based on the most commonly found individual symptoms would also be beneficial. The results of this study could provide supporting evidence for possible modifications to the current modified Finnegan scoring tool if individual items are found to never or seldom be observed. The elimination of symptoms that are very rarely or never seen could benefit the nursing staff and infants by reducing the time it takes to score each infant, as infants with NAS are assessed every 2 to 8 hours. The frequency of scoring is dependent on the scores that are recorded; when higher scores are observed the frequency of assessment

is increased. (Ebner et al., 2007; Jansson, DiPietro, Elko & Velez, 2010; Jones, Kaltenbach et al., 2010; Lim et al., 2009). Additionally, this study will provide information about the prevalence and type of drug use during pregnancy in northwestern Ontario among this cohort. All of this information may be relevant to health care professionals working with childbearing women.

Results

Sample

The total number of live births at the acute care hospital during the study period (Figure 1) was 1502. The number of infant/mother pairs identified by the Health Records department who matched the inclusion criteria was 137. Therefore, approximately 9% of infants at this hospital during the study period exhibited symptoms of NAS. The medical records for these infants and mothers were further assessed for eligibility. Of the 137 record pairs a total of 6 (4%) were excluded from analysis. Five of these records were excluded due to a lack of /or unclear substance exposure and one due to missing information related to NAS symptomatology. Thus, the final sample for this study was comprised of 131 infant/mother pairs.

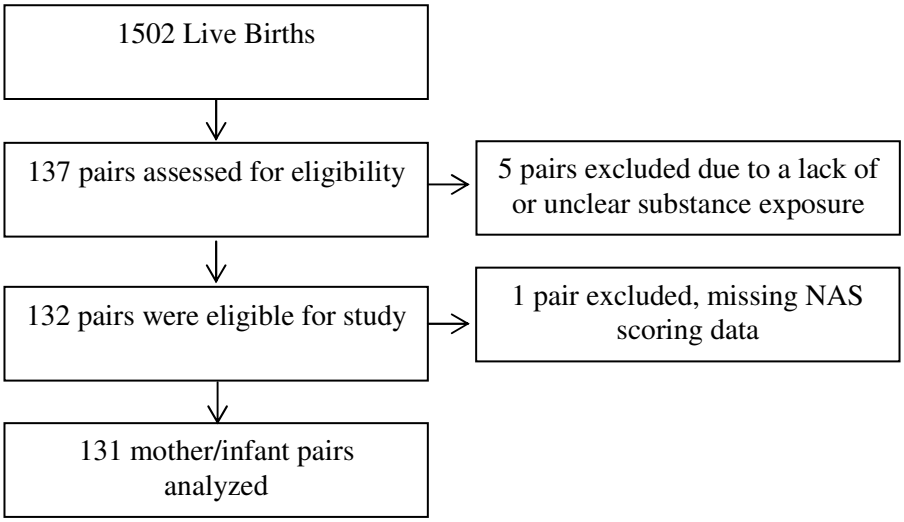

Figure 1: Schema of Study Sample

Demographic Data

The average age of the mother at time of delivery was 25.6 (SD = 5.4) years and the majority (n = 110, 83.3%) were smokers (see Table 1). Twenty four mothers (18.2%) had some level of alcohol consumption during this pregnancy. The majority of infants were delivered vaginally (n = 109, 82.6%) at term (≥37 weeks gestation) (n = 124, 93.9%) with slightly more than half being male (n = 71, 53.8%) (Table 2). Congruent with the majority being term infants, the mean body length (M = 50.1, SD = 2.9), weight (M = 3349.6, SD = 559.3), head circumference (M = 34.3, SD = 1.6) were within the normal ranges. More than 85% of the infants in the study had Apgar scores of eight or higher at both one and five minutes after birth. A total of 103 (78.6%) infants were admitted to the Neonatal Intensive Care Unit (NICU) and 95 (72.5%) received pharmacological treatment for NAS.

Table 1: Maternal Demographics

Characteristic	*Result*
Age (years)	M = 25.6 (SD = 5.4)
Smoking	n = 110 (83.3%)
<10/day	n = 56 (50.9%)
10 – 20/day	n = 25 (22.7%)
>20/day	n = 1 (0.9%)
Number not recorded	n = 28 (25.5%)
Alcohol use	n = 24 (18.2%)

Table 2: Infant Demographics

Characteristic	*Result*
Sex	
Male	n = 71 (53.8%)
Female	n = 61 (46.2%)
Delivery	
Vaginal	n = 109 (82.6%)
Caesarean	n = 23 (17.4%)
Length (cm)	M = 50.1 (SD = 2.9)
Weight (g)	M = 3349.6 (SD = 559.3)
Head Circumference (cm)	M = 34.3 (SD = 1.6)
Apgar Scores (≥8)	
One Minute	n = 115 (87.1%)
Five Minute	n = 129 (97.7%)

Substance Exposure

Infants were exposed to a variety of substances *in utero* including opiates, methadone, benzodiazepines, barbiturates, cocaine, cannabinoids, tricyclics, Selective Serotonin Reuptake Inhibitors (SSRIs), Selective Norepinephrine Reuptake Inhibitors (SNRIs), ritalin and antipsychotics. The substances that infants were most commonly exposed to were opiates (n = 77, 58.3%), methadone (n = 71, 53.8%) and cannabinoids (n = 31, 23.5%) (Figure 2).

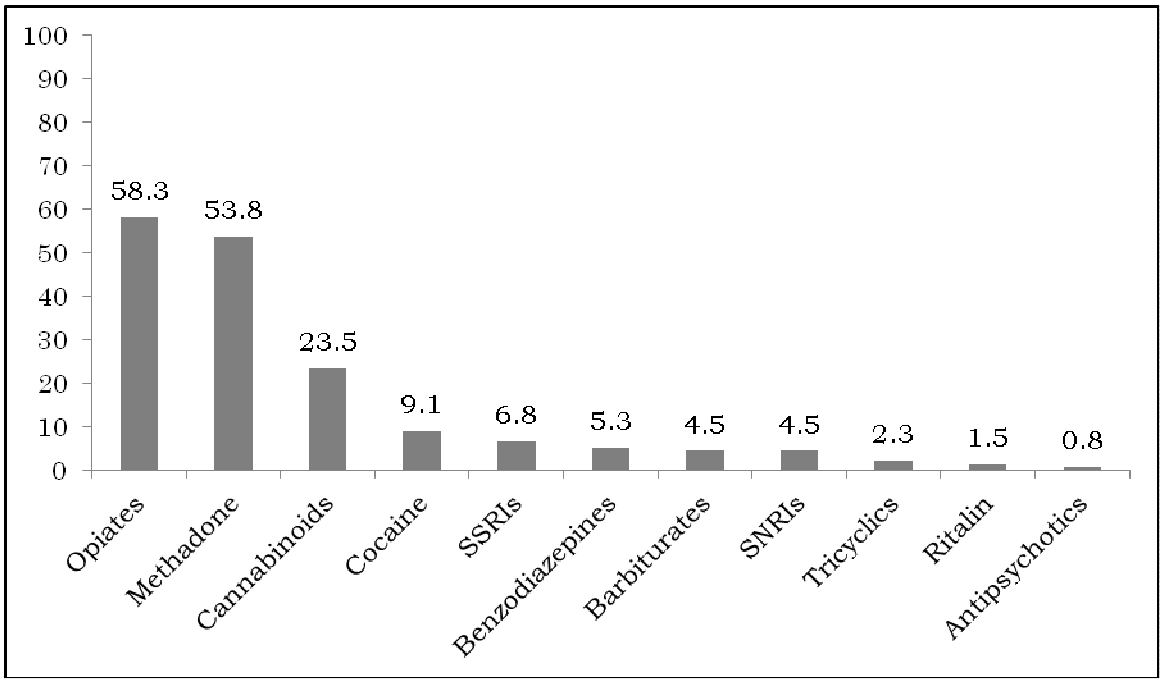

Figure 2: Infant Substance Exposure (% of infants exposed)

Group Categories

Each infant was categorized into one of four groups based on the substance(s) they were exposed to *in utero*. The "methadone" group (n = 30) consisted of infants exposed only to methadone (Table 3). The "methadone and other" group (n = 40) were exposed to methadone and another substance(s). The other substances included opiates, benzodiazepines, barbiturates, cocaine,

cannabinoids, SSRIs, SNRIs, ritalin and antipsychotics; the most common being opiates (n = 22, 53.7%) and cannabinoids (n = 18, 43.9%). Infants in the "single non-methadone" group (n = 41) were exposed to a single substance that was not methadone. The majority of this group (n = 39, 95.1%) were exposed to opiates. The "poly non-methadone" group (n = 20) consisted of infants exposed to two or more substances that were not methadone. The substances that these infants were exposed to included opiates, benzodiazepines, barbiturates, cocaine, cannabinoids, SSRIs, SNRIs, and tricyclics. The substance exposures that were most common for this group were opiates (n = 16, 80%), cannabinoids (n = 12, 60%) and cocaine (n = 5, 25%).

Table 3: Substance Exposure within Substance Groups (% within group)

Exposure Substance	*Methadone (n = 30)*	*Methadone and Other (n = 40)*	*Single Non-Methadone (n = 41)*	*Poly Non-Methadone (n = 20)*
Methadone	100%	100%		
Opiates		53.7%	95.1%	80%
Cannabinoids		43.9%	2.4%	60%
Cocaine		17.1%		25%
SSRIs		17.1%		10%
Barbiturates		7.3%		15%
Tricyclics				15%
Benzodiazepines		9.8%	2.4%	10%
SNRIs		9.8%		10%
Ritalin		4.9%		
Antipsychotics		2.4%		

Symptomatology of NAS

The primary research question for this retrospective chart review was to identify whether or not the individual symptoms of NAS differed among infants based on substance exposure. The individual symptoms of NAS were assessed using the relative frequency of observation for each symptom over three periods of time; (1) from onset of symptoms to the peak score (n = 131), (2) from the onset of symptoms until the initiation of pharmacological treatment (n = 96) and (3) from

the onset of symptoms until 72 hours of scoring (n = 117). It is noteworthy that the total size of the sample included in each of these time frames varied as not all infants received pharmacological treatment and not all were observed for 72 hours or longer after the onset of symptoms.

Onset to peak score. The frequency of symptom observation from onset of symptoms to peak score (see Table 4) indicates that the three most frequently observed symptoms for infants in the "methadone" group were increased muscle tone (M = 73.48, SD = 25.69), tremors when disturbed (M = 49.69, SD = 29.82) and a fever between 37.2˚C and 38.3˚C (M = 46.42, SD = 27.91). The three least frequently observed symptoms for this group were continuous high-pitched cry (M = 0.27, SD = 1.10), nasal flaring (M = 0.42, SD = 2.28) and respiratory rate greater than 60/minute plus retractions (M = 0.50, SD = 1.92). During this time period, the infants in the "methadone" group never exhibited the symptoms of myoclonic jerks, generalized convulsions or fever of 38.4˚C or greater.

The "methadone and other" group most frequently exhibited the symptoms of increased muscle tone (M = 74.72, SD = 24.69), fever between 37.2˚C and 38.3˚C (M = 54.25, SD = 25.68), and respiratory rate of greater than 60/minute (M = 38.63, SD = 30.62). The least frequently exhibited symptoms were myoclonic jerks (M = 0.11, SD = 0.72), frequent yawning (M = 0.21, SD = 1.32), and continuous high-pitched cry (M = 0.90, SD = 3.22). This group never exhibited the symptoms of generalized convulsions, fever of 38.4˚C or greater, mottling, or projectile vomiting.

The three most frequently observed symptoms in the "single non-methadone" group were increased muscle tone (M = 64.34, SD = 32.36), fever between 37.2˚C and 38.3˚C (M = 49.48, SD = 28.20) and tremors when disturbed

(M = 42.44, SD = 32.00). The three least frequently observed symptoms for this group included markedly hyperactive Moro-reflex (M = 0.81, SD = 5.21), mottling (M = 1.00, SD = 5.31) and nasal flaring (M = 1.40, SD = 6.01). There were five symptoms that were never observed; excoriation, myoclonic jerks, generalized convulsions, fever of 38.4˚C or greater, and projectile vomiting.

Infants in the "poly non-methadone" group most frequently exhibited the symptoms of increased muscle tone (M = 68.81, SD = 31.38), fever between 37.2˚C and 38.3˚C (M = 39.23, SD = 25.39) and tremors when disturbed (M = 36.73, SD = 33.03). They rarely exhibited projectile vomiting (M = 0.33, SD = 1.49), and frequent yawning (M = 0.71, SD = 3.19). This group never exhibited continuous high-pitched cry, markedly hyperactive Moro-reflex, excoriation, myoclonic jerks, generalized convulsions, fever of 38.4˚C or greater, mottling or nasal flaring.

One-way Analysis of Variance (ANOVA) was used to analyze the relative frequencies of each individual symptom within each time period to determine whether or not there were differences among the groups. Significant differences among groups were further examined using Student-Newman-Keuls (SNK) post hoc comparisons (see Table 7). Analysis of the relative frequencies from onset to peak score showed that there was a significant difference among groups for only two variables: (1) moderate/severe tremors undisturbed, $F(3, 127) = 3.42$, $p = 0.019$ and (2) nasal stuffiness, $F(3, 127) = 3.16$, $p = 0.027$. However, using the SNK, no difference was found.

Table 4: Relative Frequency of Symptom Observation From Onset to Peak Score*

Symptom	Methadone M(SD)	Methadone and Other M(SD)	Single Non-Methadone M(SD)	Poly Non-Methadone M(SD)
High-pitched Cry	36.38(31.75)	35.15(33.66)	29.07(35.96)	27.36(35.11)
Continuous High-pitched Cry	--0.27(1.10)--	--0.90(3.22)--	1.95(6.68)	^^0.00(0.00)^^
Sleeps <1 Hour After Feeding	7.74(12.19)	10.49(14.75	16.37(28.38)	5.27(7.73)
Sleeps <2 Hours After Feeding	13.51(18.61)	13.77(15.30)	11.90(16.36)	13.52(24.97)
Sleeps <3 Hours After Feeding	17.59(16.92)	13.60(20.39)	9.38(11.61)	18.02(23.42)
Hyperactive Moro-Reflex	14.50(25.86)	22.50(23.35)	13.87(21.65)	18.04(23.28)
Markedly Hyperactive Moro-Reflex	0.83(4.56)	4.06(11.79)	--0.81(5.21)--	^^0.00(0.00)^^
Tremors Disturbed	++49.69(29.82)++	37.86(29.70)	++42.44(32.00)++	++36.73(33.03)++
Mild Tremors Undisturbed	24.66(27.93)	28.61(25.79)	29.07(32.93)	28.21(26.95)
Moderate/Severe Tremors Undisturbed	8.10(16.33)	25.61(29.04)	11.04(27.37)	9.86(25.20)
Increased Muscle Tone	++73.48(25.69)++	++74.72(24.69)++	++64.34(32.36)++	++68.81(31.38)++
Excoriation	0.60(3.28)	1.37(4.35)	^^0.00(0.00)^^	^^0.00(0.00)^^
Myoclonic Jerks	^^0.00(0.00)^^	--0.11(0.72)--	^^0.00(0.00)^^	^^0.00(0.00)^^
Generalized Convulsions	^^00.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^
Sweating	12.81(25.85)	9.05(13.19)	6.41(17.73)	5.34(15.36)
Fever 37.2°C – 38.3°C	++46.42(27.91)++	++54.25(25.68)++	++49.48(28.20)++	++39.23(25.38)++
Fever ≥ 38.4°C	^^0.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^
Frequent Yawning (>4x/interval)	0.61(2.43)	--0.21(1.32)--	1.71(6.19)	--0.71(3.19)--
Mottling	3.56(18.26)	^^0.00(0.00)^^	--1.00(5.31)--	^^0.00(0.00)^^
Nasal Stuffiness	14.90(20.97)	9.18(17.48)	23.84(30.07)	9.73(20.19)
Frequent Sneezing (>4x/interval)	17.96(21.26)	19.10(23005)	13.28(19.17)	8.75(12.08)
Nasal Flaring	--0.42(2.28)--	3.42(13.21)	--1.40(6.01)--	^^0.00(0.00)^^
Respiratory Rate > 60/min	27.06(22.48)	++38.63(30.62)++	34.56(34.55)	21.44(22.39)
Respiratory Rate >60/min plus Retractions	--0.050(1.92)--	1.52(5.58)	2.74(15.69)	4.76(16.82)
Excessive Sucking	23.41(25.59)	18.23(28.52)	21.65(27.62)	7.92(15.17)
Poor Feeding	18.13(24.17)	26.92(31.32)	21.85(29.03)	12.60(19.44)
Regurgitation	12.14(16.61)	16.44(24.92)	13.63(18.56)	9.83(24.02)
Projectile Vomiting	3.97(18.39)	^^0.00(0.00)^^	^^0.00(0.00)^^	--0.33(1.49)--
Loose Stools	5.95(9.57)	10.69(19.98)	7.56(12.00)	6.25(12.91)
Watery Stools	1.35(4.11)	1.09(3.07)	4.58(9.31)	4.17(14.94)

*Percent of times each symptom was observed during the time specified; n=131
(++) Most frequently observed (--) Least frequently observed (^^) Never observed

Onset to initiation of pharmacological treatment. During this time period, the "methadone" group most frequently exhibited the symptoms of increased muscle tone (M = 76.02, SD = 24.73), tremors when disturbed (M = 53.80, SD = 33.58) and fever between 37.2˚C and 38.3˚C (M = 48.57, SD = 21.69) (see Table 5). Infants in this group rarely exhibited the symptoms of watery stools (M = 0.60, SD = 2.10), frequent yawning (M = 0.60, SD = 2.92) and continuous high-pitched cry (M = 0.83, SD = 4.08). The symptoms that were never observed in this group were excoriation, myoclonic jerks, generalized convulsions, fever of 38.4˚C or greater, or nasal flaring.

The "methadone and other" group most frequently exhibited the symptoms of increased muscle tone (M = 78.11, SD = 22.55), fever between 37.2˚C and 38.3˚C (M = 53.33, SD = 26.37) and high-pitched cry (M = 42.98, SD = 32.00). The three least frequently observed symptoms were frequent yawning (M = 0.28, SD = 1.58), continuous high-pitched cry (M = 0.67, SD = 2.69), and watery stools (M = 0.69, SD = 2.84). This group did not exhibit the symptoms of myoclonic jerks, generalized convulsions, mottling and projectile vomiting.

Increased muscle tone (M = 75.51, SD = 25.18), fever between 37.2˚C and 38.3˚C (M = 50.81, SD = 20.33), and tremors when disturbed (M = 46.49, SD = 27.22) were the three most frequently observed symptoms for the "single non-methadone" group. Excoriation (M = 0.23, SD = 1.24), nasal flaring (M = 0.69, SD = 3.71) and markedly hyperactive Moro-reflex (M = 1.15, SD = 6.19) were the three least frequently observed symptoms. The five symptoms that were never observed in this group were myoclonic jerks, generalized convulsions, fever of 38.4˚C or greater, mottling and projectile vomiting.

Table 5: Relative Frequency of Symptom Observation From Onset to Initiation of Treatment*

Symptom	Methadone M(SD)	Methadone and Other M(SD)	Single Non-Methadone M(SD)	Poly Non-Methadone M(SD)
High-pitched Cry	37.60(28.61)	++42.98(32.00)++	37.26(31.28)	40.99(36.84)
Continuous High-pitched Cry	--0.83(4.08)--	--0.67(2.69)--	3.04(8.270	^^0.00(0.00)^^
Sleeps <1 Hour After Feeding	8.31(10.57)	10.33(12.32)	15.50(20.48)	8.10(11.62)
Sleeps <2 Hours After Feeding	16.85(21.57)	15.33(14.30)	15.12(14.84)	9.36(12.67)
Sleeps <3 Hours After Feeding	16.79(16.79)	13.74(17.82)	14.58(11.75)	21.14(20.46)
Hyperactive Moro-Reflex	16.33(19.47)	24.11(23.48)	14.20(17.70)	22.32(28.14)
Markedly Hyperactive Moro-Reflex	1.67(8.17)	4.44(13009)	--1.15(6.19)--	^^0.00(0.00)^^
Tremors Disturbed	++53.80(33.58)++	33.34(29.58)	++46.49(27.22)++	++45.19(27.91)++
Mild Tremors Undisturbed	24.80(29.10)	30.55(21.45)	36.46(29.20)	36.24(22.12)
Moderate/Severe Tremors Undisturbed	7.31(17.80)	29.53(26.31)	4.29(10.53)	--7.22(16.57)--
Increased Muscle Tone	++76.02(24.73)++	++78.11(22.55)++	++75.51(25.18)++	++85.20(16.51)++
Excoriation	^^0.00(0.00)^^	1.79(5.40)	--0.23(1.24)--	^^0.00(0.00)^^
Myoclonic Jerks	^^0.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^
Generalized Convulsions	^^0.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^
Sweating	13.98(28.04)	11.75(17.52)	5.90(10.88)	8.78(18.53)
Fever 37.2°C – 38.3°C	++48.57(21.69)++	++53.33(26.37)++	++50.81(20.33)++	++49.65(17.21)++
Fever ≥ 38.4°C	^^0.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^
Frequent Yawning (>4x/interval)	--0.60(2.92)--	--0.28(1.58)--	1.82(4.80)	^^0.00(0.00)^^
Mottling	1.43(4.91)	^^0.00(0.00)^^	^^0.00(0.00)^^	--1.43(4.52)--
Nasal Stuffiness	12.87(18.46)	13.13(18.97)	18.61(20.88)	10.43(23.03)
Frequent Sneezing (>4x/interval)	17.96(12.62)	16.12(18.10)	15.22(15.15)	7.97(10.03)
Nasal Flaring	^^0.00(0.00)^^	1.43(5.80)	--0.69(3.71)--	^^0.00(0.00)^^
Respiratory Rate > 60/min	33.14(21.31)	36.37(27.89)	37.83(26.27)	35.89(31.01)
Respiratory Rate >60/min plus Retractions	1.07(3.80)	4.31(17.92)	3.79(18.60)	9.17(23.39)
Excessive Sucking	22.73(22.01)	17.04(23.03)	24.98(23.93)	12.67(13.20)
Poor Feeding	16.98(22.40)	25.86(28.49)	22.90(27.22)	16.65(19.22)
Regurgitation	15.37(20.03)	16.40(25.33)	16.90(18.64)	9.47(12.06)
Projectile Vomiting	1.29(4.38)	^^0.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^
Loose Stools	4.19(7.18)	9.12(18.97)	8.83(13.76)	11.52(15.81)
Watery Stools	--0.60(2.10)--	--0.69(2.84)--	4.73(7.75)	--5.50(12.52)--

*Percent of times each symptom was observed during the time specified; n=96
(++) Most frequently observed (--) Least frequently observed (^^) Never observed

Increased muscle tone (M = 85.20, SD = 16.51), fever between 37.2˚C and 38.3˚C (M = 49.65, SD = 17.21), and tremors when disturbed (M = 45.19, SD = 27.91) were also the three most frequently observed symptoms for the "poly non-methadone" group. The three least frequently observed symptoms were mottling (M = 1.43, SD = 4.52), watery stools (M = 5.50, SD = 12.52) and moderate/severe tremors when undisturbed (M = 7.22, SD = 16.57). This group had nine symptoms that were not observed; continuous high-pitched cry, markedly hyperactive Moro-reflex, excoriation, myoclonic jerks, generalized convulsions, fever of 38.4˚C or greater, frequent yawning, nasal flaring and projectile vomiting.

The One-way ANOVA for the relative frequencies of each individual symptom for the onset to initiation of pharmacological treatment (Table 7) indicated that there was a significant difference among groups for moderate/severe tremors undisturbed, $F(3,92) = 10.7$, $p < 0.001$, and watery stool, $F(3,92) = 3.8$, $p = 0.013$. The SNK comparison showed that at the significance level of 0.05, the "methadone and other" group exhibited moderate/severe tremors undisturbed significantly more often than the other three groups, with no significant differences found between the other three groups. It also showed no significant difference among the groups for the symptom of watery stool.

Onset to 72 hours of observation. The "methadone" group most often exhibited the symptoms of increased muscle tone (M = 73.62, SD = 25.34), tremors when disturbed (M = 52.79, SD = 22.23), and fever between 37.2˚C and 38.3˚C (M = 44.05, SD = 18.23) (Table 6). Symptoms that were seldomly observed in

Table 6: Relative Frequency of Symptom Observation From Onset to 72 hours of Recorded NAS Observation *

Symptom	Methadone M(SD)	Methadone and Other M(SD)	Single Non-Methadone M(SD)	Poly Non-Methadone M(SD)
High-pitched Cry	34.45(27.55)	37.55(30.23)	30.74(29.78)	29.43(27.29)
Continuous High-pitched Cry	--0.34(1.23)--	--0.37(1.29)--	1.07(2.86)	^^0.00(0.00)^^
Sleeps <1 Hour After Feeding	5.85(7.67)	4.49(6.69)	7.05(8.18)	3.90(6.12)
Sleeps <2 Hours After Feeding	11.69(10.62)	8.52(7.85)	11.12(9.28)	6.54(8.69)
Sleeps <3 Hours After Feeding	21.05(13.31)	14.19(13.47)	13.66(8.24)	15.41(15.48)
Hyperactive Moro-Reflex	9.45(10.14)	22.81(23.04)	7.76(10.80)	21.94(26.88)
Markedly Hyperactive Moro-Reflex	--0.31(1.64)--	1.57(2.93)	--0.27(1.59)--	--0.27(1.03)--
Tremors Disturbed	++52.79(22.23)++	++48.82(22.12)++	++44.79(21.54)++	++41.32(17.48)++
Mild Tremors Undisturbed	23.52(21.76)	23.87(16.94)	24.49(18.89)	26.42(15.01)
Moderate/Severe Tremors Undisturbed	6.38(11.98)	18.75(20.68)	2.71(6.18)	5.32(8.79)
Increased Muscle Tone	++73.62(25.34)++	++80.98(16.26)++	++61.98(22.56)++	++75.35(20.40)++
Excoriation	^^0.00(0.00)^^	4.21(10.02)	0.53(1.90)	1.11(4.30)
Myoclonic Jerks	^^0.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^
Generalized Convulsions	^^0.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^
Sweating	12.69(18.69)	9.62(14.80)	4.67(8.61)	4.98(10.45)
Fever 37.2°C – 38.3°C	++44.05(18.23)++	++44.48(18.89)++	++37.49(16.08)++	++33.78(12.87)++
Fever ≥ 38.4°C	^^0.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^	^^0.00(0.00)^^
Frequent Yawning (>4x/interval)	0.73(2.29)	--0.13(0.77)--	0.98(2.34)	--0.32(1.23)--
Mottling	--0.37(1.35)--	^^0.00(0.00)^^	--0.32(1.34)--	0.81(2.17)
Nasal Stuffiness	14.03(18.43)	10.07(14.34)	16.44(18.11)	13.40(20.92)
Frequent Sneezing (>4x/interval)	13.37(11.14)	13.32(14.14)	11.70(11.19)	10.60(12.70)
Nasal Flaring	^^0.00(0.00)^^	--1.14(3.53)--	0.79(3.28)	0.33(1.29)
Respiratory Rate > 60/min	25.46(17.10)	29.63(21.89)	26.21(19.88)	26.13(20.30)
Respiratory Rate >60/min plus Retractions	0.49(1.44)	2.31(6.41)	1.43(6.44)	1.84(4.66)
Excessive Sucking	17.43(18.34)	16.05(18.77)	18.93(17.55)	17.28(17.01)
Poor Feeding	20.42(21.44)	27.79(24.35)	17.98(24.17)	21.93(24.79)
Regurgitation	11.41(11.65)	11.15(13.13)	9.39(10.44)	6.62(7.03)
Projectile Vomiting	--0.37(1.35)--	^^0.00(0.00)^^	--0.20(1.19)--	--0.27(1.03)--
Loose Stools	10.17(10.47)	13.88(13.24)	13.04(11.75)	10.77(12.97)
Watery Stools	1.40(3.49)	4.64(8.99)	4.39(7.70)	2.54(7.21)

*Percent of times each symptom was observed during the time specified; n=117
(++) Most frequently observed (--) Least frequently observed (^^) Never observed

this group included markedly hyperactive Moro-reflex (M = 0.31, SD = 1.64), continuous high-pitched cry (M = 0.37, SD = 1.35) and mottling (M = 0.37, SD = 1.35) and projectile vomiting (M = 0.37, SD = 1.35). This group did not exhibit the symptoms of excoriation, myoclonic jerks, generalized convulsions or nasal flaring.

The "methadone and other" group had the same three most frequently observed symptoms as the "methadone" group; increased muscle tone (M = 80.93, SD = 16.26), tremors when disturbed (M = 48.82, SD = 22.12), and fever between 37.2˚C and 38.3˚C (M = 44.48, SD = 18.89). Seldomly observed symptoms included frequent yawning (M = 0.13, SD = 0.77), continuous high-pitched cry (M = 0.37, SD = 1.29), and nasal flaring (M = 1.14, SD = 3.53). This group never exhibited the following symptoms; myoclonic jerks, generalized convulsions, fever of 38.4˚C or greater, mottling, or projectile vomiting.

Again, increased muscle tone (M = 61.98, SD = 22.56), tremors when disturbed (M = 44.79, SD = 21.54) and fever between 37.2˚C and 38.3˚C (M = 37.49, SD = 16.08) were the three most frequently observed symptoms for the "single non-methadone" group. The least frequently observed symptoms were projectile vomiting (M = 0.20, SD = 1.19), markedly hyperactive Moro-reflex (M = 0.27, SD = 1.59), and mottling (M = 0.32, SD = 1.34). The symptoms that were never exhibited by this group were myoclonic jerks, generalized convulsions, and fever of 38.4˚C or greater.

The "poly non-methadone" group most frequently exhibited symptoms of increased muscle tone (M = 75.35, SD = 20.40), tremors when disturbed (M = 41.32, SD = 14.48) and fever between 37.2˚C and 38.3˚C (M = 33.78,

SD = 12.97). The most seldom observed symptoms were markedly hyperactive Moro-reflex (M = 0.27, SD = 1.03), projectile vomiting (M = 0.27, SD=1.03), and frequent yawning (M = 0.32, SD = 1.23). This group did not exhibit the symptoms of continuous high-pitched cry, myoclonic jerks, generalized convulsions, or fever of 38.4˚C or greater.

The One-way ANOVA for the relative frequencies of individual symptoms from onset to 72 hours of scoring (Table 7) show that there was a significant difference among the groups on the symptoms of hyperactive Moro-reflex, $F(3,113) = 5.96$, $p = 0.001$, markedly hyperactive Moro-reflex, $F(3,113) = 3.26$, $p = 0.024$, moderate/severe tremors undisturbed, $F(3,113) = 9.25$, $p < 0.001$, increased muscle tone, $F(3,113) = 5.10$, $p = 0.002$, and excoriation, $F(3,113) = 3.45$, $p = 0.019$. Using the SNK comparison a significant difference ($p = 0.05$) was found among the groups for three of the individual symptoms. Infants in the "methadone and other" and the "poly non-methadone" groups exhibited a hyperactive Moro-reflex significantly more often than those in the other two groups. The infants in the "methadone and other" group also had undisturbed moderate/severe tremors significantly more often than the other three groups. Also, the "methadone and other" group demonstrated increased muscle tone significantly more often than the "single non-methadone" group. No significant differences were found between the "methadone and other" group or the "single non-methadone" group compared to the other two groups on this symptom.

Overall. The three most commonly observed symptoms in all four groups overall were increased muscle tone, tremors when disturbed and fever between 37.2˚C and 38.3˚C (Table 8). These symptoms were observed in all groups at a frequency greater than 65% of the time for increased muscle tone and greater

Table 7: Symptoms Significantly Different between Groups at Each Time Period

Symptom	*Onset to Peak*	*Onset to Initiation of Treatment*	*Onset to 72 Hours of Observation*
High-pitched Cry			
Continuous High-pitched Cry			
Sleeps <1 hour After Feeding			
Sleeps <2 hours After Feeding			
Sleeps < 3 hours After Feeding			
Hyperactive Moro-reflex[b]			*** ^
Markedly Hyperactive Moro-reflex			*
Tremors Disturbed			
Mild Tremors Undisturbed			
Moderate/Severe Tremors Undisturbed[a]	*	*** ^	*** ^
Increased Muscle Tone[c]			** ^
Excoriation			*
Myoclonic Jerks			
Generalized Convulsions			
Sweating			
Fever 37.2˚C – 38.3˚C			
Fever ≥ 38.4˚C			
Frequent Yawning (>4x/interval)			
Mottling			
Nasal Stuffiness	*		
Frequent Sneezing (>4x/interval)			
Nasal Flaring			
Respiratory Rate >60/min			
Respiratory Rate >60/min + Retractions			
Excessive Sucking			
Poor Feeding			
Regurgitation			
Projectile Vomiting			
Loose Stools			
Watery Stools		*	

* p </= 0.05 (ANOVA) ^ Significant based on SNK comparison at p=0.05

** p </= 0.01(ANOVA)

*** p </= 0.001(ANOVA)

[a] "methadone and other" group exhibited this symptom significantly more often than the other three groups at during both time frames

[b] the "methadone and other" and "poly non-methadone" groups exhibited this symptom significantly more often than the other two groups

[c] "methadone and other" group exhibited this symptom significantly more often than the other three groups

than 40% of the time for the other two symptoms. Myoclonic jerks were not exhibited by infants in the "methadone", "single non-methadone" or the "poly non-methadone" groups and were observed in the "methadone and other" group at a frequency of less than 5%. Mottling and projectile vomiting were not exhibited by infants in the "methadone and other" group, both were observed less than 5% of the time in all of the other three groups. In the "poly non-methadone" group had

Table 8: Frequency of Symptom Observation for all Time Periods

Symptom	*Methadone*	*Methadone and Other*	*Single Non-Methadone*	*Poly Non-Methadone*
High-pitched Cry				
Continuous High-pitched Cry	--	--	--	^^
Sleeps <1 hour After Feeding				
Sleeps <2 hours After Feeding				
Sleeps < 3 hours After Feeding				
Hyperactive Moro-reflex				
Markedly Hyperactive Moro-reflex	--	--	--	--
Tremors Disturbed	++	++	++	++
Mild Tremors Undisturbed				
Moderate/Severe Tremors Undisturbed				
Increased Muscle Tone	++	++	++	++
Excoriation	--	--	--	--
Myoclonic Jerks	^^	--	^^	^^
Generalized Convulsions	^^	^^	^^	^^
Sweating				
Fever 37.2˚C – 38.3˚C	++	++	++	++
Fever ≥ 38.4˚C	^^	^^	^^	^^
Frequent Yawning (>4x/interval)	--	--	--	--
Mottling	--	^^	--	--
Nasal Stuffiness				
Frequent Sneezing (>4x/interval)				
Nasal Flaring	--	--	--	--
Respiratory Rate >60/min				
Respiratory Rate >60/min plus Retractions	--	--	--	--
Excessive Sucking				
Poor Feeding				
Regurgitation				
Projectile Vomiting	--	^^	--	--
Loose Stools				
Watery Stools	--	--	--	--

(++) most frequent (>40%) (--) least frequent (<5%) (^^) never observed

one additional symptom that was never exhibited, continuous high-pitched cry, which was observed less than 5% of the time in the other three groups. There were ten symptoms that were observed less than 5% of the time for the entire sample (Table 9). Generalized convulsions and fever ≥38.4°C were not once exhibited by this sample.

Table 9: Frequency of Symptom Observation for Entire Sample

Symptom	*Whole Sample*
High-pitched Cry	
Continuous High-pitched Cry	--
Sleeps <1 hour After Feeding	
Sleeps <2 hours After Feeding	
Sleeps < 3 hours After Feeding	
Hyperactive Moro-reflex	
Markedly Hyperactive Moro-reflex	--
Tremors Disturbed	++
Mild Tremors Undisturbed	
Moderate/Severe Tremors Undisturbed	
Increased Muscle Tone	++
Excoriation	--
Myoclonic Jerks	--
Generalized Convulsions	^^
Sweating	
Fever 37.2˚C – 38.3˚C	++
Fever ≥ 38.4˚C	^^
Frequent Yawning (>4x/interval)	--
Mottling	--
Nasal Stuffiness	
Frequent Sneezing (>4x/interval)	
Nasal Flaring	--
Respiratory Rate >60/min	
Respiratory Rate >60/min + Retractions	--
Excessive Sucking	
Poor Feeding	
Regurgitation	
Projectile Vomiting	--
Loose Stools	
Watery Stools	--

(++) most frequent (>40%) (--) least frequent (<5%) (^^) never observed

Analysis among groups was also conducted using the category of symptoms on the modified Finnegan scoring tool (see Appendix B) (Central Nervous System [CNS], metabolic, vasomotor, respiratory, and gastrointestinal) as opposed to individual symptoms (see Table 10). The ANOVA showed that the groups of infants differed significantly in the category of CNS symptoms, $F(3,127) = 3.99$, $p = 0.009$. Post hoc analysis using the SNK test indicated that the "methadone and other" group (M = 9.3, SD = 2.3) had significantly higher scores in the CNS category than did the "single non-methadone" (M = 7.7, SD = 2.6) and "poly non-methadone" (M = 7.5, SD = 2.4) groups. However, no significant differences were found between the "methadone" group and the other three groups. Significant differences were not found among the groups regarding the metabolic symptoms, vasomotor symptoms, respiratory symptoms or the gastrointestinal symptoms.

Table 10: Symptom Category Scores at Time of Peak within Groups

Symptom Category	*Methadone*	*Methadone and Other*	*Single Non-Methadone*	*Poly Non-Methadone*	*p*
CNS*	M = 8.1 SD = 2.3	M = 9.3[a] SD = 2.3	M = 7.7[a] SD = 2.6	M = 7.5[a] SD = 2.4	0.009
Metabolic	M = 1.0 SD = 0.64	M = 0.72 SD = 0.64	M = 0.76 SD = 0.58	M = 0.65 SD = 0.67	0.186
Vasomotor	M = 0.57 SD = 0.63	M = 0.53 SD = 0.64	M = 0.51 SD = 0.6	M = 0.5 SD = 0.6	0.980
Respiratory	M = 0.53 SD = 0.57	M = 0.78 SD = 0.73	M = 0.68 SD = 0.69	M = 0.4 SD = 0.6	0.164
Gastrointestinal	M = 2.1 SD = 1.4	M = 2.1 SD = 1.7	M = 2.2 SD = 1.6	M = 1.4 SD = 1.4	0.206

* Found significant by ANOVA and SNK

[a] Methadone and other group had significantly higher scores in this category than the two non-methadone groups

Presentation of NAS

The second research question of this study was to identify if the presentation and treatment of NAS differed among infants based on exposure substance. The six variables of NAS presentation were (1) age at onset of symptoms, (2) peak score, (3) time from onset to peak score, (4) pharmacological treatment, (5) length of pharmacological treatment and (6) length of hospital stay.

The presentation of NAS in the entire sample is illustrated in Table 11. Means, standard deviations, Chi-Square and One-way ANOVA were used to compare the six variables of NAS presentation among the four groups of infants (Table 12). Age at onset of symptoms was similar among the four groups, with the average age at onset ranging from 8.3 to 11.1 hours for all groups. The One-way ANOVA found that age at onset of symptoms was not significantly different among the four groups.

Table 11: Presentation of NAS

Variable	*Result*
Age at Symptom Onset (hrs)	M = 9.6 (SD = 12.1)
Time from Onset to Peak of Symptoms (hrs)	M = 34.3(SD = 28.7)
Peak Score	M = 12.2 (SD = 3.2)
Pharmacological Treatment	n = 95 (72.5%)
Length of Pharmacological Treatment (days)	M = 11.4 (SD = 10.4)
Length of Hospital Stay (days)	M = 14.4 (SD = 9.2)

The average peak score for the four groups ranged from 10.35 to 13.43. The “poly non-methadone” group had the lowest average peak score at 10.35 with the “methadone and other” group having the highest average peak score at 13.43. Peak score was significantly different among the four groups, $F(3,127) = 4.55$, $p = 0.005$; post hoc analysis showed that at the significance level of 0.05, the peak score was significantly less in the “poly non-methadone” group (M = 10.4,

SD = 3.4) than in the "methadone" (M = 12.3, SD = 2.5) and "methadone and other" (M = 13.4, SD = 2.9) groups, but was not significantly different from the "single non-methadone" group (M = 11.9, SD = 3.5).

Table 12: NAS Presentation Outcomes within Groups

NAS Presentation Outcomes	*Methadone Only*	*Methadone and Other*	*Single Non-Methadone*	*Poly Non-Methadone*	*p*
Age at Symptom Onset (hrs)	M = 8.3 SD = 6.3	M = 8.6 SD = 13.7	M = 10.7 SD = 14.2	M = 11.1 SD = 10.7	0.734
Peak Score*[a]	M = 12.3 SD = 2.5	M = 13.4 SD = 2.9	M = 11.9 SD = 3.5	M = 10.4 SD = 3.4	0.005
Time from Onset to Peak of Symptoms (hrs)*[b]	M = 55.1 SD = 40.2	M = 30.0 SD = 22.3	M = 28.5 SD = 21.2	M = 23.4 SD = 16.2	<0.001
Pharmacological Treatment (% received Rx)*[c]	80	82.5	68.3	50	0.040
Length of Pharmacological Treatment (days)*[d]	M = 13.8 SD = 8.5	M = 15.1 SD = 11.6	M = 7.3 SD = 6.1	M = 7.2 SD = 8.6	<0.001
Length of Hospital Stay (days)*[e]	M = 17.5 SD = 7.3	M = 17.9 SD = 11.2	M = 11.1 SD = 6.4	M = 9.5 SD = 7.4	<0.001

* Found significant through ANOVA and SNK or Chi-Square
[a] Peak score was significantly lower in poly non-methadone group compared to the two methadone groups
[b] Methadone group took significantly longer to peak than the other three groups
[c] Need for pharmacological treatment was significantly higher in methadone exposed groups
[d] Methadone groups were treated significantly longer than other two groups
[e] Methadone groups had significantly longer hospital stays than other two groups

Time to peak score varied among the four groups. The average time from onset of symptoms to peak score ranged from 23.4 to 55.1 hours after onset. The "poly non-methadone" group had the lowest average time to peak score at 23.4 hours; the highest average time to peak score was seen in the "methadone" group at 55.1 hours after onset. One-way ANOVA analysis indicated time to peak score was significant, $F(3,127) = 8.28$, $p < 0.001$; SNK post hoc indicated that at the level of 0.05 the "methadone" group (M = 55.1, SD = 40.2) took significantly longer to peak than did the other three groups.

The percentage of infants in each group that received pharmacological treatment widely varied. The need for pharmacological treatment was significantly related to the substance group, X^2 (131, df = 3) = 8.30, p = 0.04. The "methadone" and "methadone and other" groups had similar proportions of the group receiving pharmacological treatment (80% and 82.5% respectively). In contrast only 68.3% of those in the "single non-methadone" group received pharmacological treatment, while only 50% of the "poly non-methadone" group received pharmacological treatment.

There was variation in the length of time that infants in each group were treated pharmacologically. The "poly non-methadone" group was treated pharmacologically for the shortest period of time at 7.2 days. The "methadone and other" group received pharmacological treatment for the longest amount of time at 15.1 days, over twice the length of time of the "poly non-methadone group". The length of pharmacological treatment was found to be significant, F(3,128) = 7.38, p < 0.001); the "methadone" (M = 13.8, SD = 8.5) and "methadone and other" (M = 15.1, SD = 11.6) groups had significantly longer lengths of treatment compared to the "single non-methadone" (M = 7.3, SD = 6.1) and the "poly non-methadone" (M = 7.2, SD = 8.6) groups.

The groups varied on the length of hospital stay. The "methadone and other" group had the longest hospital stay at 17.9 days. The shortest hospital stay was observed in the "poly non-methadone" group at 9.5 days, just over half the length of stay of the "methadone and other" group. Length of hospital stay was significant, F(3,128) = 7.99, p < 0.001; the infants in the "single non-methadone" (M = 11.1, SD = 6.4) and "poly non-methadone" (M = 9.5, SD = 7.4) groups had significantly shorter hospital stays than did the infants in the "methadone"

(M = 17.5, SD = 7.3) and "methadone and other" (M = 17.9, SD = 11.2) groups.

Neonatal Outcomes

The final research question for this study examined whether neonatal outcomes differed (term, weight, length, head circumference, and one minute and five minute Apgar scores) among infants based on their substance exposure. All four groups were similar across all six neonatal outcomes (see Table 13). In particular, infants were primarily term, with an average weight, length and head circumference within the normal parameters for term infants. All groups had 80% or more of their one minute Apgar scores being 8 or higher. At five minutes, the majority (≥95%) of Apgar scores were 8 or higher. The One-way ANOVA showed that there were no significant differences among the four groups on weight, length, head circumference, and one and five minute Apgar scores. Chi-Square analysis showed that there was no difference between the four groups when looking at whether the infants were term gestation when they were born.

Table13: Neonatal Outcomes within Groups

Neonatal Outcomes	*Methadone Only*	*Methadone and Other*	*Single Non-Methadone*	*Poly Non-Methadone*	*p*
Term (%)	93.3%	92.5%	97.6%	90%	0.650
Weight (g)	M = 3380.9 SD = 631.6	M = 3232.3 SD = 606.6	M = 3446.6 SD = 481.1	M = 3343.9 SD = 484.4	0.069
Length (cm)	M = 50.6 SD = 2.6	M = 49.1 SD = 3.3	M = 50.6 SD = 2.4	M = 50.3 SD = 2.9	0.338
Head Circumference (cm)	M = 34.0 SD = 1.6	M = 34.0 SD = 1.9	M = 34.6 SD = 1.4	M = 34.4 SD = 1.5	0.662
1 min Apgar (≥8)	80%	87.8%	90.2%	90%	0.134
5 min Apgar (≥8)	96.7%	95.2%	100%	100%	0.265

Discussion

This study was designed to answer three questions. The first question was whether individual NAS symptoms (e.g. cry, tremors, temperature) differed based on substance exposure, and the findings failed to show clear, significant differences among the four substance exposure groups. The second question was whether the presentation of NAS (e.g. onset of symptoms, peak scores, length of stay) differed among infants based on their substance exposure. The findings showed that the presentation of NAS was significantly more severe among infants exposed to methadone alone and methadone and other substances. The third question was whether neonatal outcomes (e.g., birth weight, length, head circumference and Apgar scores) differed among infants based on their substance exposure. No significant differences were found on any of the neonatal outcomes.

Presentation of NAS

In terms of the presentation of NAS, infants exposed to methadone (solely or in addition to other substances) experienced significantly higher peak scores, longer time from onset of symptoms to peak of score, a higher rate of pharmacological treatment, longer length of treatment time and longer lengths of stay in hospital compared to infants exposed to substances other than methadone.

The average age at onset of symptoms was in the early neonatal period (<12 hours after birth) with the “methadone” group being the first to develop symptoms. However, there was a wide range with some infants developing symptoms as late as 85.8 hours after birth. While the age of onset was not significantly different between groups, the variability in age of onset of symptoms may be clinically relevant. Generally length of stays in Canada for mother and

newborn are 48 hours, though early discharge is common if all criteria for early discharge are met (Cargill & Martel, 2007). Therefore, if the onset of NAS symptoms is typically within 12 hours, symptoms of NAS should be evident for most infants prior to discharge. However, it is important to recognize that there are some infants who develop symptoms later than the average and that further assessment for NAS may be warranted. Given the variability of onset of symptoms in this study, it is of interest that a survey conducted to assess the care practices of substance-exposed infants in Canadian hospitals found only 6% had discharge protocols specific to NAS (Marcellus, 2002). However, the specific information contained in these discharge protocols was not identified. Therefore, it is unknown if care facilities teach parents/caregivers to monitor for symptoms of NAS and when to seek help if infants develop symptoms after discharge. As public health nurses may be one of the first contacts with new families after discharge it is equally important that they have adequate training and assessment regarding NAS. Further investigation into the best practices of discharge, follow-up and parent teaching protocols in regards to infants with NAS is warranted.

Various ages of onset have similarly been reported in the literature. Johnson, Greenough and Gerada (2003) indicated that infants exposed to methadone *in utero* developed symptoms within the first day after birth, those exposed to non-methadone opioids also experienced symptoms during day one of life, while infants exposed to methadone plus other substances took longer to develop symptoms, averaging two days after birth. In contrast to the findings in the current study, Serane and Kurian (2008) and Ebner and colleagues (2007) found the average age of onset of symptoms for infants exposed to both methadone and other substances to be much later at 26 (range 6 - 63) and 57.5

(SD = 37.5) hours after birth, respectively. Differences in age of onset findings may be attributable to the differences in sample size and methods for identifying NAS. The current study had a total sample size of 131 infants, whereas the other three studies had sample sizes ranging from 32 to 53 infants. Two out of the three studies also used a modified version of the Finnegan Scoring Tool while the third used the River's system which consists only of ten signs/symptoms for identifying NAS. The hospital from which the sample for the current study was taken has a protocol in place for standardized identification of at-risk infants. This protocol outlines criteria for screening infants who are at risk of developing NAS (Murphy-Oikonen, et al., 2010). After implementation of this protocol the number of infants screened for NAS increased by 29%, indicating that having a screening protocol in place enhances the detection of infants who have had substance exposure (Murphy-Oikonen, et al., 2010). The fact that this protocol is in place may contribute to the early identification of NAS in this sample.

The average peak score ranged from 10.4 to 13.4. The peak score for the "methadone" and the "methadone and other" groups were significantly higher than the "poly non-methadone group". Two studies found similar results with peak scores between 11 and 12.8 for infants exposed to methadone/methadone plus other substances (Jones, Kaltenbach et al., 2010; Velez, Jansson, Schroeder & Williams, 2009). It has also been found that infants exposed to opioids during pregnancy and no methadone had a much lower average peak score of 5.1 (Jones, Harrow et al., 2010).

By comparison, a study evaluating infants not exposed to substances *in utero* found the median peak score to be 2, though there have been some infants scoring between 1 and 11 in the first three days after birth (Zimmermann-Baer,

Nötzli, Rentsch & Bucher, 2010). Another study found that over the first two days after birth, infants who were not exposed to substances during pregnancy had an average peak score of 0.9, with peak scores ranging from 0 – 5 (Jones, Harrow et al., 2010). Godding and colleagues (2004) found that infants not exposed to illicit substances *in utero* but were exposed to maternal smoking scored an average of 3.8 to 4.7 on the Finnegan scoring tool over the first four days of life. Infants exposed to maternal smoking scored significantly higher than newborns who were not exposed on days 1 ($p = 0.05$), 2 ($p = 0.002$) and 4 ($p = 0.007$) (Godding, et al., 2004). Therefore peak score could be affected by maternal smoking status.

The "methadone" group also took significantly longer to peak than did the other three groups at 55.1 hours after onset (SD = 40.2). This is similar to additional studies which found that scores for infants exposed to methadone/methadone and other substances peaked on the second and third days of life (Jansson, DiPietro, Elko & Velez, 2010; Velez, Jansson, Schroeder & Williams, 2009). Though they have similar findings, neither of those studies looked specifically at the time frame between onset of symptoms and peak score. The fact that the "methadone" group took longer to peak is consistent with research that suggests that withdrawal will occur later for substances that have a longer half-life (American Academy of Pediatrics [AAP], 1998). In the early neonatal period, the level of methadone in the infant's system is similar to that of its mother, afterwards the concentration slowly decreases based on its long elimination half-life (~26 hours), which contributes to the delay in NAS development observed in methadone exposed infants (AAP, 1998; Glastein, Garcia-Bournissen, Finklestein, & Koren, 2008).

Another possible explanation for the differences in time to peak score could be level of smoking. The current study had a high percentage of women who smoked during pregnancy (83.3%). Fifty percent of those who smoked indicated smoking < 10 cigarettes per day, 22% smoked between 10 and 20 cigarettes per day, 1% smoked more than 20 per day and 25% did not indicate the amount. Choo and colleagues (2004), found that the level of maternal smoking affected the infant's time to peak score, with those infants exposed to ≥20 cigarettes per day taking significantly longer to peak than those exposed to ≤10 cigarettes per day ($p = 0.025$).

Significantly more infants exposed to methadone required pharmacological treatment than those exposed to other substances. In particular, approximately 80% of the infants exposed to methadone/methadone and other substances required pharmacological treatment in comparison to half of those not exposed to methadone. There are various findings in the literature regarding substance exposure and the need for pharmacological treatment. Johnson, Greenough and Gerada (2003) found high rates of infants requiring pharmacological treatment with the methadone exposed infants requiring treatment more so than the infants exposed to other substances (100% of those exposed to methadone, 88% of those exposed to methadone and other substances and 70% of those exposed to opioids other than methadone). Similarly, other studies found that 75% to 87% of infants exposed to methadone/methadone and other substances received treatment for NAS (Jansson, DiPietro, Elko and Velez, 2010; Lim et al., 2009). However, some studies identified lower numbers of methadone/methadone and other exposed infants requiring pharmacologic treatment ranging between 45% and 68% (Dryden, Young, Hepburn & Mactier, 2009; Ebner et al., 2007; Velez, Jansson,

Schroeder & Williams, 2009). Some of the variability in the literature may be attributable to differences in sample size, ranging from 41 to 437, as well as the different methods used for identifying severity of NAS requiring pharmacological treatment and different treatment thresholds, as currently there is no one standard threshold (O'Grady, Hopewell, & White, 2009). The current study used the modified Finnegan scoring tool, had a sample of 131 infants, treatment was initiated after three consecutive scores of ≥8 and 80% of infants exposed to methadone / methadone and other substances required pharmacological treatment. Johnson, Greenough and Gerada (2003) used the River's system, had 41 infants in their sample, initiated pharmacological treatment when infants scored >3/10 on two consecutive occasions and had 88% of infants exposed to methadone plus other substances and 100% of infants exposed to methadone who required pharmacological treatment. Whereas, Dryden, Young, Hepburn and Mactier (2009) had the largest sample (437), used the Lipsitz scoring tool initiating treatment at two consecutive scores of ≥5, and had only 45.5% of infants requiring pharmacological treatment.

Infants in the "methadone" and "methadone and other" groups received pharmacological treatment for significantly more time than infants not exposed to methadone (13.8 – 15.1 days). There have been studies that support these findings, indicating that infants exposed to methadone/ methadone and other substances were treated on average between 11 and 14 days (Dryden, Young, Hepburn & Mactier, 2009; Jansson, DiPietro, Elko & Velez, 2010; Velez, Jansson, Schroeder & Williams, 2009). In a separate study infants exposed to methadone/methadone and other substances required a shorter treatment (9.9 days) (Jones, Kaltenbach et al., 2010). However, Johnson, Greenough and Gerada

(2003) found that infants exposed to methadone/ methadone and other substances required treatment for a longer period of time than what was found in the current study (25.5 – 37 days compared to 13.8 – 15.1 days). It is possible that these inconsistencies are due to variations in the weaning protocols between the hospitals in each study.

All of the previously mentioned studies, including the current study used morphine as the treatment substance when pharmacological treatment was required (Dryden, Young, Hepburn & Mactier, 2009; Jansson, DiPietro, Elko & Velez, 2010; Johnson, Greenough & Gerada, 2003; Jones, Kaltenbach, et al., 2010; Velez, Jansson, Schroeder & Williams, 2009). In the study by Johnson, Greenough and Gerada, (2003), infants treated during the first half of the study were treated with chlorpromazine. Both the current study and that by Dryden, Young, Hepburn and Mactier (2009), used a second treatment substance, phenobarbital, if required. Weaning protocols were not described in all studies.

The “methadone group” and the “methadone and other group” had significantly longer hospital stays than did the other two groups (17.5 -18 days). The literature on length of hospital stay varies in findings; similar to the current study, Jones, Kaltenbach and colleagues (2010) found that infants exposed to methadone/ methadone and other substances had an average length of stay of 17.5 (SD = 1.5) days. Some studies have found that infants exposed to methadone/ methadone and other substances had shorter lengths of stay than was found in the current study (8 - 12 days) (Dryden, Young, Hepburn & Mactier, 2009; Jansson, Dipietro, Elko & Velez, 2010). Alternatively, much longer length of stay has also been reported. Johnson, Greenough and Gerada (2003) found that infants exposed to methadone and those exposed to methadone and other

substances had average lengths of stay of 29 and 41 days respectively. Lim and colleagues (2009) also found longer hospital stays for infants exposed to methadone ranging from 19 to 28 days. The differences found among studies regarding length of treatment could be due to differences in sample size (41 – 437), treatment substances (morphine, phenobarbital, chlorpromazine, or methadone) and/or treatment and weaning protocols. For example, the study with the smallest sample, used the River's system for identifying NAS, treatment was initiated when the infant scored > 3/10 on two or more consecutive occasions, infants were treated with either chloropromazine or morphine and the median length of hospital stay for those exposed to methadone was 29 days compared to those exposed to methadone and other substances, 41 days (Johnson, Greenough & Gerada, 2003). The study with the largest sample size used the Lipsitz scoring tool, infants were treated pharmacologically if they scored ≥5 on two consecutive occasions, treatment medications were morphine followed by phenobarbitone if required and the median length of hospital stay was 13 days (Dryden, Young, Hepburn & Mactier, 2009). The current study had 131 infants, used the modified Finnegan scoring tool, infants were pharmacologically treated if they scored ≥ 8 on three consecutive occasions or >12 on a single occasion, treatment substances were morphine followed by phenobarbital if needed and the average length of stay in hospital for those exposed to methadone only was 17.5 and methadone and other substances was 18 days.

Overall the findings regarding the presentation of NAS symptoms demonstrated that infants exposed to methadone (solely or in addition to other substances) experienced significantly higher peak scores, longer time from onset of symptoms to peak of score, a larger number of infants requiring

pharmacological treatment, longer length of treatment time and longer lengths of stay in hospital. These findings are not overly surprising given previous research and the long half-life of methadone (~26 hours). Research suggests that the longer the half-life of the substance, the later the withdrawal will occur (American Academy of Pediatrics [AAP], 1998). The clinical implications of these data are that while methadone has been identified as the gold standard for the treatment of opioid dependency during pregnancy (Wong, Ordean & Kahan, 2011) there are negative implications to the neonate. Infants who have been exposed to substances *in utero*, particularly those who have been exposed to multiple substances including methadone will take longer to present with symptoms and even longer to reach the peak of withdrawal. This should be taken into consideration when discharging infants from hospital as in some cases the severity of their NAS may not have peaked. When infants withdrawal outside of medical facilities, it can be very serious as narcotic withdrawal may be life-threatening and NAS symptoms can results in significant morbidity (AAP, 1998; Jansson, Velez, & Harrow, 2009). Early discharge can put these infants at greater risk of morbidity, a fragile maternal-child relationship, with the potential for infant abuse, maternal relapse, developmental delays, and behaviour and learning problems into childhood (Finnegan, 2000; Jansson, Velez, & Harrow, 2009). It is important that parents know the effects that substance use has on the health outcomes of their unborn child. It is recommended that this information be provided during the prenatal period if at all possible so that parents are aware of what may happened and the role that they along with the healthcare team have in supporting their infant (PCMCH, 2012). One way that this could happen is to include this information in prenatal counselling, prenatal classes and/or

substance use support programs. It would also be beneficial to include education regarding monitoring for NAS symptoms and when to get help when discharged from the hospital. This knowledge might also help parents to be better prepared for the stage of withdrawal after birth. It is also important for public health practitioners to be aware of the signs and symptoms of NAS so they are able to identify NAS during visits and better support parents of NAS infants. The PCMCH (2012), recommends that a professional home visitor, such as a high-risk public health nurse, is provided to continue to address risk factors and support the family after discharge. Protocols should also be in place to assist public health nurse's decision making should they experience an infant with NAS symptoms.

Despite the potential negative effects on the infant (NAS), methadone maintenance therapy has been associated with longer adherence to treatment and decreased relapse into drug use (Jones, Kaltenbach et al., 2010; Wong, Ordean & Kahan, 2011). Women on methadone tend to have fewer drug cravings, fewer episodes of withdrawal that can have negative effects on the fetus, and have a reduction in drug-seeking and risk-taking behaviours (Finnegan, 2000). Thus, the benefits of MMT during pregnancy are believed to outweigh the risks.

One potential intervention that may decrease the infant's NAS symptoms is breastfeeding. Researchers have studied the effect of feeding method (breastfeeding, formula feeding and combination feeding) on NAS symptoms among infants exposed to methadone *in utero* (Abdel-Latif et al., 2006; Ballard, 2002; Jansson et al., 2008; McQueen, Murphy-Oikonen, Gerlach & Montelpare, 2011). They found that breastfed infants compared to formula and/or combination (breast and formula) fed infants experienced less severe NAS symptoms, less need for pharmacological treatment and shorter lengths of

hospital stay (Abdel-Latif et al., 2006; Ballard, 2002; Jansson et al., 2008; McQueen, Murphy-Oikonen, Gerlach & Montelpare, 2011). It is speculated that the small amount of methadone in the mother's milk may have a weaning effect. As such, mothers who are stable on MMT, have no contraindications for breastfeeding and wish to breastfeed their infants should be encouraged to do so (McQueen, Murphy-Oikonen, Gerlach & Montelpare, 2011; The Academy of Breastfeeding Medicine Protocol Committee, 2009). The benefits of breastfeeding and the potential benefit for those experiencing NAS far outweigh any theoretical minimal risks (Abdel-Latif et al., 2006; Glastein, Garcia-Bournissen, Finklestein, & Koren, 2008; Jansson et al., 2008; McQueen, Murphy-Oikonen, Gerlach & Montelpare, 2011). Frequently women in MMT programs are discouraged from breastfeeding by the practitioners monitoring the at-risk infants (Jansson et al., 2008). Often the reasons for discouragement are prejudices of the practitioner, unclear guidelines regarding lactation among women on MMT, and the paucity of research in the area (Jansson et al., 2008). The best practice guidelines for Supporting Clients on Methadone Maintenance treatment provided by the Registered Nurses Association of Ontario (RNAO) (2009) recommends that nurses support parenting practices including breastfeeding. The PCMCH (2012) also support breastfeeding as safe and preferable for mothers maintained on methadone, provided there are no contraindications. Therefore, in the postpartum period both clinical and public health practitioners should be encouraging and supporting a mother to breastfeed.

While methadone is the standard of treatment for opioid dependency during pregnancy, there is an alternative treatment substance called buprenorphine. Methadone is a full opioid receptor agonist that with higher doses

continues to have an increasing effect (Srivastaca & Kahan, 2006; Wong, Ordean & Kahan, 2011). Whereas, buprenorphine has a long half-life similar to methadone, yet is a partial opioid receptor agonist, which has less risk for overdose than methadone, but has a ceiling effect (Srivastaca & Kahan, 2006; Wong, Ordean & Kahan, 2011). The use of buprenorphine during pregnancy has shown neonatal birth outcomes similar to those of methadone exposed pregnancies, both of which are comparable to those of non-exposed infants (Ebner et al., 2007). Infants exposed to buprenorphine during pregnancy have an earlier onset of symptoms, peak sooner, have lower mean NAS scores, have a shorter duration of symptoms, require pharmacological treatment less, receive pharmacological treatment for NAS for a shorter period of time, and spend less time in hospital when compared to infants born to women maintained on methadone (Enber et al., 2007; Gaalema et al., 2012; Jones, Kaltenbach et al., 2010; Lejeune, Simmat-Durand, Gourarier, Aubisson, & the Groupe d'Etudes Grossesse et Addictions, 2006). Even with the improved NAS outcomes, buprenorphine is not widely used as the treatment of choice during pregnancy, because there is minimal research on the long-term effects of exposure *in utero*, the adherence to treatment is not as high as with methadone and there is limited availability of the drug in some countries (Jones, Kaltenbach et al., 2010; Wong, Ordean & Kahan, 2011). The availability of buprenorphine in Canada is limited; the only readily available product is a combination of buprenorphine and naloxone, for which there is little information on the safety of use during pregnancy (Wong, Ordean & Kahan, 2011).

Symptomatology of NAS

Making comparisons between the present study and the general literature was difficult regarding the symptomatology of NAS as the outcomes were evaluated at different time periods. In the present study, NAS symptoms were evaluated over three time periods, (1) onset of symptoms to peak score (2) onset of symptoms to initiation of pharmacological treatment, and (3) onset of symptoms to 72 hours of NAS symptom observation. No other studies in the literature looked at these specific time frames. Comparisons are made based on the outcomes overall.

Increased muscle tone, tremors when disturbed and having a fever between 37.2˚C and 38.3˚C were the most commonly observed symptoms on the modified Finnegan, regardless of substance exposure. Alternately, generalized convulsions and having a fever of 38.4˚C or greater were not observed in any of the infants in the present study. Choo and colleagues (2004) found similar results, when looking at infants exposed to methadone, with tremors when disturbed and increased muscle tone being the most frequently observed symptoms followed by hyperactive Moro reflex. They similarly identified generalized seizures having never been exhibited. Additionally, the current study found that several symptoms were infrequently observed (<5% of the time) or only observed in one group. These symptoms were continuous high-pitched cry, markedly hyperactive Moro-reflex, excoriation, myoclonic jerks, frequent yawning (>4x/interval), mottling, nasal flaring, respiratory rate >60/min plus retractions, projectile vomiting and watery stool. Studies looking at infants exposed to opiate treatment substances, cocaine and/or opiates, had similar findings, in that the most common symptoms observed were increased muscle tone and tremors, with

additional frequently observed symptoms including irritable cry, tachypnea and sleeplessness (Bada, Bauer et al., 2002; Serane & Kurian, 2008). The symptoms that were observed five percent of the time or less in the current study were observed at similar rates in other studies (Bada, Bauer et al., 2002; Choo et al., 2004; Serane & Kurian, 2008). Uncommon symptoms were also similar including excessive sucking, nasal stuffiness, sneezing and seizures (Bada, Bauer et al., 2002; Serane & Kurian, 2008).

There were some symptoms that were not common in the current study that were evident in other studies. In particular, as the severity of NAS increased, symptoms including poor feeding, regurgitation, fist sucking and excoriation were identified (Bada, Bauer et al., 2002; Ebner, et al., 2007; Serane & Kurian, 2008). In the current study, poor feeding and regurgitation were not in the top three most commonly observed symptoms, or in the group of symptoms observed less than 5% of the time. They were observed between 10% and 27% of the time. Fist sucking was not a symptom included on the modified Finnegan that was used for the current study yet was observed as one of the most prominent symptoms in a study by Ebner and colleagues (2007). Similarly, excoriation was in the least observed symptoms in the current study, yet Serane and Kurian (2008) found it to be a symptom that came to the forefront as the severity of the syndrome increased. This could indicate that these symptoms are important indicators of NAS in severe cases. Perhaps the cases observed in the current study were not as severe as those observed in the previously mentioned studies as treatment is initiated early to minimize infant distress. It is also possible that there is subjectivity to some of these symptoms, particularly poor feeding, regurgitation and projectile vomiting. Thus, there may be some variability among institutions in

terms of their scoring. Many infants do have difficulty latching and many do spit up; one person may interpret this as normal where another may observe it as a symptom of poor feeding or regurgitation relative to NAS. As there is the potential that items are being scored differently among institutions, future research studies on the symptomatology of NAS should consider a multisite study.

Infants not exposed to substances *in utero* may exhibit some of the symptoms on the modified Finnegan at birth including high-pitched cry, sleeping for short periods after eating, vomiting and sneezing (Zimmermann-Baer, Nötzli, Rentsch & Bucher, 2010). Jitteriness/tremors, irritability and high pitched cry were the most frequently observed symptoms in both infants that were not exposed and those who were exposed (cocaine and/or opioids) (Bada, Bauer et al., 2002). Also, many of the symptoms rarely observed in infants with NAS, as indicated by this study, are very rarely seen in the non-exposed infants including excoriation, myoclonic jerks, sweating, frequent yawning, mottling and tachypnea (Zimmermann-Baer et al., 2010). Therefore, it is possible that some of the infants experiencing these symptoms may not be experiencing NAS, but are exhibiting the symptoms for some other reason.

Prenatal exposure to nicotine as well as alcohol can result in withdrawal symptoms, some of which are similar to those observed in infants experiencing NAS. Some of these symptoms include worse self-regulation and greater need for handling, increased irritability, increased muscle tone, tremors, high-pitched cry and sleeplessness (Coles, Smith, Fernhoff, & Falek, 1985; Schaefer, 1962; Stroud, Paster, Goodwin et al., 2009; Stroud, Paster, Papandonatos, et al., 2009). As women in the current study had a high rate of maternal smoking (83.3%) and alcohol use at some point during pregnancy (18.2%), it is possible that these two

factors could have had an effect on NAS symptoms. Additional research is required regarding the effects of smoking and/or alcohol use on NAS symptoms among substance exposed infants.

In addition to analyzing individual scores, total scores for each category of symptoms on the modified Finnegan scoring tool (Central Nervous System [CNS], metabolic, vasomotor, respiratory, and gastrointestinal) at the time of peak score were also analyzed. It was found that the groups differed significantly in the CNS symptom category. The "methadone and other" group had significantly higher scores in this category compared to the "single non-methadone" and the "poly non-methadone" groups, indicating that at the peak of symptoms, this category of symptoms was significantly more severe in the "methadone and other" group compared to the two groups not exposed to methadone.

The findings from the current study suggest that regardless of substance exposure infants presented with similar symptoms. This may be clinically significant in that assessment tools may not need to differ based on substance exposure. Further validation of the Finnegan scoring tool for assessing infants withdrawing from substances other than opiates is required, as the Finnegan scoring tool was designed to assess NAS after *in utero* exposure to opioids. Findings also suggest that the modified Finnegan scoring tool may be too long, and further evaluation possibly reducing the number of items is warranted. There are symptoms that were never exhibited by any infant in this study as well as many symptoms that were observed very rarely. Many of the latter symptoms are seen at a comparable rate in non-exposed infants (Zimmermann-Baer, Nötzli, Rentsch & Bucher, 2010), indicating that they may not be a NAS symptom and not needed in this assessment tool. Jones, Harrow and colleagues (2010)

explained that using a three-item index (a screening tool), consisting of hyperactive Moro reflex, mild tremors when undisturbed and increased muscle tone, is useful in discriminating between infants who have been exposed to opioids and those that are not exposed. Having a short version (i.e., a three-item index based on the most frequently observed items) could help to quickly identify those infants who require further assessment. Also, having a shorter scoring tool would be beneficial in that it may decrease the time it takes health care providers to assess for NAS. Having a short version or list of most frequently observed symptoms may also allow public health practitioners to quickly identify infants who may need further assessment in a medical setting.

Neonatal Outcomes

There were no significant differences found in neonatal outcomes among the four groups. More than 90% of the infants in the current study were born at term. Birth weight differences among the four groups averaged a total of 200 grams; birth weights for all groups were within the appropriate weight for term non-exposed infants (Kramer et al., 2001). The largest difference among the four groups in length at birth was 1.5 cm, all of which were within the 49-53 cm norm for non-exposed infants (Dietitians of Canada, 2010). Normal head circumference at birth for non-exposed infants is 34 - 35cm; all groups had head circumference averages within this range (Dietitians of Canada, 2010). Between 80% and 90% of the infants in each group had 1 minute Apgar scores of 8 or higher, while 95% - 100% off all infants had scores of 8 or greater at 5 minutes; Apgar scores between 7 and 10 at 5 minutes are considered normal (AAP, 2006). Jansson, DiPietro, Elko and Velez (2010), found similar birth outcomes in infants of opioid addicted mothers who were in comprehensive, multidisciplinary treatment during

pregnancy, but with a slightly lower average birth weight than the current study, while other studies found no significant differences in birth outcomes when comparing infants exposed to different treatment substances (methadone, morphine or buprenorphine) during pregnancy (Ebner et al., 2007; Jones, Kaltenbach et al., 2010). Adverse infant outcomes are influenced by maternal substance use, maternal prenatal care and maternal complications. Infants of mothers who receive methadone and regular prenatal care commonly have decreased incidence of preterm birth, lower birth weights and other complications (Finnegan, 2000).

There are varying findings in the literature. Some studies have found similar birth weights, gestational age and Apgar scores for infants exposed to methadone as was found in the current study (Lim et al., 2009; Velez, Jansson, Schroeder & Williams, 2009). Other findings indicate that infants exposed to methadone *in utero* are born earlier, have lower birth weights and lengths than what was found in this study (Jones, Kaltenbach et al., 2010; Lim et al., 2009). Also contrary to the finding of the current study, for infants exposed to multiple substances and a treatment substance either methadone or buprenorphine birth outcomes were not all consistent with norms for non-exposed infants; birth weight was lower and almost 40% of infants were <10th percentile for length at birth (Lejeune et al., 2006). Some of the literature indicates that exposed infants (cocaine, opiates, or both) tend to present with significantly lower gestational age, length, birth weight and head circumferences than non-exposed infants and that mothers taking methadone, regardless of whether they also take other substances have higher birth weight infants than mothers who take non-methadone opioids (Bada, Bauer et al., 2002; Johnson, Greenough & Gerada, 2003).

The current study did not examine the dosage (amount and frequency of exposure) of the substances that the infants were exposed to, which has been found to contribute to differences in birth outcomes in the literature (Wouldes & Woodward, 2010). Another possible variable that contributed to the results found in this study was the high number of mothers receiving methadone (53.4% of the sample). Perhaps the mothers with the most severe substance use history, whose infants may have been most at risk for adverse outcomes, are getting methadone treatment. It is also possible that this sample did not include infants that have experienced prolonged or high dosage substance use.

Limitations

Limitations of this study include that it was a retrospective chart review that relied upon the availability, accuracy and consistency of information recorded in the infant and maternal health records at the time of birth and treatment. A prospective study would have allowed for a more detailed drug exposure to be obtained such as the dosage, the frequency of use, when the drug was started and/ or discontinued *etcetera*. Similarly, the method for determining substance exposure was inconsistent at times. Maternal self-report was listed for the majority of the mothers. However, self-report for substance use is estimated to be 3 to 3.5 times less than the true rate (Chen, Fang, Shyu, & Lin, 2006). Therefore it is possible that there was failure to report substance use by the mother, which also leads to the possibility that there were infants who may have been exposed in utero that were not included in this study. This is a limitation of many studies evaluating substance use and not solely to this study. However, urine screening and/or meconium analysis was available for some infants. This helped to limit the number of infants who were exposed to substances in utero

and did not have maternal reporting of substance. This study also did not examine the dosage of substances that infants were exposed to or length of exposure, both of which according to research may contribute to prematurity, longer hospital stays, increased need for pharmacological treatment for NAS, later onset of NAS symptoms and increased severity of NAS symptoms (Dryden, Young, Hepburn & Mactier, 2009; Lim et al., 2009; Serane & Kurian, 2008; Wouldes & Woodward, 2010). Also, maternal smoking was not addressed in this study and could be a confounding variable effecting which symptoms are observed, the peak scores, and time from onset of symptoms to peak score (Choo et al., 2004; Godding et al., 2004; Stroud, Paster, Goodwin et al., 2009; Stroud, Paster, Papandonatos et al., 2009).

Comparability of study findings to the general literature was also difficult due to the diverse tools being used to assess NAS, the protocols for initiation and weaning of pharmacological treatment, the timing of outcome measures as well as sample size. Additionally, symptoms of NAS exhibited by infants may be scored differently among practitioners due to the subjectivity of some of the items on the Modified Finnegan scoring tool.

Direction for Future Research

Future efforts should be made to develop protocols for discharge when substance use during pregnancy is known or suspected as some infants may develop NAS symptoms or the NAS symptoms may peak after discharge. If asymptomatic substance exposed infants are discharged home, standardized protocols are required so that parents may be able to identify symptoms of NAS and seek appropriate treatment if necessary.

More research should be conducted to determine whether there is any one tool that should be recommended to assess NAS based on psychometric properties. This may assist to establish a consistent widely used assessment tool, to allow for more accurate comparisons across the literature. Additionally, evidence from this study suggests that the modified Finnegan scoring tool should be further evaluated and item reduction may be considered as many symptoms were not observed among infants in our study, a multisite study would be recommended. The removal of some items on the tool may help to make it less complex and more practical for use in every day practice. Should the tool be shortened, assessment of inter-rater reliability of the tool would also be imperative.

The effects that different substances used to treat NAS have on the presentation of the syndrome is another avenue for potential research. More information is needed in regards to NAS symptomatology and neonatal outcomes. For example, not all methadone exposed infants required treatment in this study. It would be beneficial to know what factors influence the severity of NAS among methadone exposed infants. Also, further analysis of maternal smoking in addition to substance use and the effects on the neonate is important. Finally, further research on drugs to treat opioid addiction and outcomes on the neonate and long term effect is required.

Summary

Overall the findings regarding the presentation of NAS symptoms demonstrated that infants exposed to methadone (solely or in addition to other substances) experienced significantly more severe NAS, based on their peak scores, time from onset of symptoms to peak of score, number of infants requiring

pharmacological treatment, length of treatment time and lengths of stay in hospital. Infants who have been exposed to substances *in utero*, particularly those who have been exposed to multiple substances including methadone will take longer to present with symptoms and even longer to reach the peak of withdrawal. The length of time it may take for infants to present with symptoms as well as to reach the peak of withdrawal should be taken into consideration when discharging infants from hospital as the implications of infant's withdrawing at home can be severe. While methadone is the standard of treatment during pregnancy, further evaluation of alternative opioid dependence treatments and their effects on the neonate, should be conducted.

The most commonly observed symptoms on the modified Finnegan, regardless of substance exposure, were increased muscle tone, tremors when disturbed and having a fever between 37.2˚C and 38.3˚C. Two symptoms were never observed and there were ten symptoms that were observed less than 5% of the time across the entire sample for this study. Many of the latter symptoms are observed at a comparable rate in non-addicted infants (Zimmermann-Baer, Nötzli, Rentsch & Bucher, 2010), indicating that they may not be a NAS symptom and not needed in this assessment tool. At the peak of withdrawal, the CNS category of symptoms was significantly more severe in the "methadone and other" group compared to the two groups not exposed to methadone. The number of items that were infrequently or never observed supports the potential for the number of items on the scoring tool to be reduced. For any changes made to the modified Finnegan scoring tool, psychometric testing would be required.

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Appendix A

Modified Finnegan Scoring Tool

Day:		Evaluation of Symptoms / Time of evaluation											
Symptom	Value												
CNS Symptoms													
High-pitched cry	2												
Continuous high-pitched cry	3												
Sleeps <1h after feeding	3												
Sleeps <2h after feeding	2												
Sleeps <3h after feeding	1												
Hyperactive Moro reflex	2												
Markedly hyperactive Moro reflex	3												
Tremors disturbed	2												
Mild tremors undisturbed	3												
Moderate/severe tremors undisturbed	4												
Increased muscle tone	2												
Excoriation (specify area)	1												
Myoclonic jerks	3												
Generalized convulsions	5												
Metabolic Symptoms													
Sweating	1												
Fever 37.2˚C – 38.3˚C	1												
Fever ≥ 38.4˚C	2												
Frequent Yawning >4x/interval	1												
Mottling	1												
Vasomotor Symptoms													
Nasal stuffiness	1												
Frequent sneezing >4x/interval	1												
Respiratory Symptoms													
Nasal Flaring	2												
Respiratory rate >60/min	1												
Respiratory rate >60/min + retractions	2												
Gastrointestinal Symptoms													
Excessive sucking	1												
Poor feeding	1												
Regurgitation	2												
Projectile vomiting	3												
Loose stools	2												
Watery stools	3												
Total score (0-44)													

Appendix B

NAS Data Collection Sheet

Research ID Number _____ Newborn DOB (d/m/y)_____

Time of Delivery_____ Sex _____ Birth weight _____ Length _____

Head circumference _____ Gestational age at birth _____

Date of Discharge _____ Time of Discharge _____

1 minute Apgar score _____ 5 minute Apgar score _____

Maternal Data

Age (in years) _____ Reported smoking YES NO number/day _____

Reported alcohol/substance use YES NO Substance type _____

NAS Related Data

Age at onset of NAS symptoms _____(hours) Peak Finnegan score_____

Time to peak _____(hours) Type of treatment _____

Date and time of initiation _____

Date and time of discontinuation _____

Length of treatment _____(hours) Length of stay in hospital _____(hours)

NICU admission: YES NO Reason for admission _____

Exposure substance:

Urine screening _____

Meconium screening _____

CNS total score at peak of withdrawal _____

Metabolic total score at peak of withdrawal _____

Vasomotor total score at peak of withdrawal _____

Respiratory total score at peak of withdrawal _____

Gastrointestinal total score at peak of withdrawal _____