Thesis title:

A retrospective cohort Study Exploring Existing Sedation, Analgesia and Withdrawal management in a Paediatric Intensive Care Unit (PICU):

The SEESAW study

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Statement

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Abstract

Purpose

Paediatric Intensive Care Unit (PICU) patients are at risk of developing withdrawal when high doses of opioid analgesics and sedatives are stopped or tapered too rapidly. The primary aim of the study was to explore the factors associated with the increased incidence of withdrawal in order to better understand the extent of the problem. The secondary aim was to analyse if the presence of withdrawal syndrome was associated with clinical complications or delayed recovery.

Methods

The retrospective chart audit examined the medical records of 120 mechanically ventilated infants and children that were admitted to the PICU within a tertiary children's hospital from 2015 to 2017. The patients were selected if exposed to at least 24 hours of continuous opioid or sedative infusion. The presence of withdrawal syndrome was assessed retrospectively using the Sophia Observation of withdrawal Symptoms (SOS) scale. The retrospective cohort study provided a means to report on the natural course of untreated and under-treated withdrawal. A multivariate regression model analysed variables associated with withdrawal.

Results

Overall, the incidence of withdrawal in the study cohort was 61% (73/120). This included 45 patients that had been diagnosed with withdrawal by the clinical team and 28 that were undiagnosed.

Patients that received fentanyl were more likely to develop withdrawal compared to patients that received morphine (RR 1.5, 95% CI 0.96-2.20). However, the mean infusion rate was significantly (3.4 times) higher for fentanyl, accounting for the difference. The mean opioid infusion rate and infusion duration were both associated with withdrawal to varying degrees. High mean infusion rates of 3 mcg/kg/hr fentanyl and 80 mcg/kg/hr morphine were 80% predictive of precipitating withdrawal. Dose tapering characteristics were analysed and demonstrated that the patients that developed withdrawal were typically tapered from a dose of 3 mcg/kg/hr fentanyl over 0-24 hours.

Patients with withdrawal symptoms had significantly higher rates (24/73 vs 4/47) of severe clinical deterioration within 72 hours of opioid dose tapering (OR 5.8, 95% CI 1.8-18.5, p = 0.003). Severe clinical deterioration included seizures, aspiration events, life-threatening arrhythmias, hypoglycaemia, and respiratory failure that required intubation or mechanical ventilation. Comparing outcomes, patients with withdrawal had prolonged PICU (8.0 vs 4.7 days, p = 0.001) and hospital (23 vs 14 days, p = 0.003) length of stay.

Conclusion

The SEESAW study demonstrated that significantly higher mean infusion rates of fentanyl were administered to patients in PICU, compared to morphine. The incidence of withdrawal was predominantly fentanyl dose-driven. Using the retrospective SOS scale results, the presence of withdrawal was associated with increased clinical complications and delayed recovery.

Chapter 1: Introduction

1.1 Introduction

This thesis reports on the SEESAW study, a retrospective cohort study exploring existing sedation, analgesic and withdrawal management in a Paediatric Intensive Care Unit (PICU). The single centre study retrospectively examined the medical records of mechanically ventilated infants and children within the PICU at the Women's and Children's Hospital in Adelaide, South Australia over a two year period. The purpose of the study was to describe the factors that increased the incidence of withdrawal symptoms and analyse if the presence of withdrawal increased the risk of clinical complications and delayed the patient's recovery.

This chapter identifies the problem and the research question and how the study intended to answer it.

1.2 Context of the study

Within the PICU, sedation and analgesia are routinely used to minimise the pain and discomfort associated with a patient's illness, injuries or surgical procedures, and reduce the discomfort, anxiety and distress associated with invasive treatments such as intubation and mechanical ventilation. The goal is to achieve optimal levels of comfort and sedation for each patient while minimising unwanted side effects and complications. Withdrawal is one such complication. Withdrawal occurs when the patient develops physiological dependence on persistent use of an opioid or sedative medication, and is manifested when the medication is abruptly withdrawn or weaned too rapidly (Franck et al, 2012). Unrecognised and untreated withdrawal is associated with clinical complications, increased hospital length of stay (LOS) and increased mortality (Franck, Naughton & Winter 2004).

The reason for undertaking the research was to further investigate the clinical practice finding that patients transferred from PICU to the ward had sometimes developed withdrawal syndrome but it was not being routinely screened for, nor treated. This study would be a scoping study to improve understanding of the incidence and extent of the problem.

1.2.1 Iatrogenic withdrawal syndrome in PICU

In PICU, common analgesic and sedative agents associated with withdrawal symptoms include opioids, benzodiazepines and the alpha$_2$ adrenergic agonists (The Hospital for Sick Children, 2012). This list is not exhaustive since most sedatives have the potential for associated withdrawal syndromes. In many ways, withdrawal is less a complication and more a likely outcome as a result of prolonged administration of the medication and then abrupt cessation.

Opioid withdrawal has distinct clinical features. Typically, withdrawal syndrome affects three organ systems: the central nervous system (CNS), the sympathetic nervous system and the gastro-intestinal (GIT) system (Cramton & Gruchala, 2013). Signs and symptoms of CNS irritation include irritability, (grimacing or crying in infants), muscle spasms and aches, tremors, poor sleep pattern, anxiety, hallucinations, dilated pupils and seizures. Sympathetic hyperactivity signs include tachycardia, hypertension, tachypnoea, fever, sweating, goose bumps, increased secretions, yawning, and hiccups. Signs and symptoms of GIT disturbance include nausea, gagging, vomiting, abdominal pain, uncoordinated suck or swallow and diarrhoea (Franck et al, 2004; Ista et al 2013).

The difference between opioid and benzodiazepine withdrawal is difficult to identify and measure due to their overlapping signs and symptoms (Amigoni et al, 2017). However, it has been suggested that GIT symptoms are more evident in opioid withdrawal (Harris et al, 2016).

Specific features of alpha$_2$ adrenergic agonist withdrawal include rebound hypertension, tachycardia and neurological symptoms such as unequal pupils, agitation, irritability, delirium, difficulty speaking and swallowing (Miller, Allen & Johnson, 2010).

Withdrawal syndrome can have a detrimental impact on a patient. The acute sympathetic and central nervous system effects of withdrawal include mild symptoms of tremors, restlessness and anxiety; moderate symptoms such as tachycardia, fever, hypertension, sleeplessness and agitation; and severe symptoms such as delirium or seizures (Birchley, 2009). Persistent diarrhoea and vomiting can lead to poor nutrition and dehydration (Fisher, 2010), or skin breakdown with significant ongoing suffering in the vulnerable patient. Tachycardia, tachypnoea, fever and hypertension will usually lead to multiple unnecessary tests and specialist referrals, with fluid boluses and medications prescribed (Fisher, 2010). At a broader level, these clinical complications will delay recovery and increase a patient's length of stay (Franck, Naughton & Winter, 2004).

In the paediatric critical care context, withdrawal occurs a result of the opioid and sedative medications administered to patients in PICU, and hence is also termed iatrogenic withdrawal syndrome. The next section presents some background regarding analgesia and sedation in PICU.

1.2.2 Analgesic and sedative use in PICU

To provide sedation and analgesia to patients in PICU, administration of short acting opioid analgesics (e.g. morphine, fentanyl) and sedatives (e.g. midazolam, dexmedetomidine, and propofol) via continuous intravenous infusion are preferred. This is because the dose can be titrated to a steady state or bolus can be administered to cover breakthrough pain, agitation or procedures (Harris et al, 2016; Playfor et al, 2006; Kudchadkar, Yaster & Punjabi, 2014).

Opioids are strong analgesics with sedative qualities at high doses (Bryant & Knights, 2011) and are the most common analgesic used in PICU (Playfor et al, 2006). Benzodiazepine sedation (i.e. midazolam) is used widely in combination with opioids to reduce distress, agitation and anxiety in the intubated and ventilated patient (Kudchadkar, Yaster & Punjabi, 2014). Alpha$_2$ (α_2) adrenergic agonists such as dexmedetomidine have demonstrated comparable sedative and anxiolytic effects to midazolam for PICU patients and offer an alternative with less respiratory depression (Ista, Tibboel & van Dijk, 2015). Propofol is a rapid acting hypnotic sedative with no analgesic effects used mainly as an anaesthetic induction agent (Bryant & Knights, 2011). In PICU the use of propofol for sedation is usually restricted to short term infusions for less than 48 hours due to the risk of propofol infusion syndrome (PRIS), a life threatening complication in children (Kruessel et al, 2012).

1.2.3 What are the benefits of analgesia and sedation?

The benefits of sedation and analgesia for children in PICU are pain relief and comfort during their invasive intensive care treatment and to assist in their recovery. In their sentinel study, Anand et al (1987) introduced opioid analgesia to infants undergoing cardiac surgery, compared to the (then) usual practice of muscle relaxants alone and demonstrated a reduction in complication rates and mortality. Subsequent research elaborated on the biochemical features, describing how pain stimulates the release of stress hormones and leads to tachycardia, hypertension and a persistent catabolic state which interferes with the body's immune system and delays healing (Anand, 1993; Epstein & Breslow, 1999). The subsequent routine provision of opioid analgesia in NICU and PICU was based largely on this research.

The physiological benefits of analgesia and sedation to a critically ill child that are measurable at the bedside include a decrease in metabolic demands and decrease in oxygen consumption (Lewis et al, 1994; Barr et al, 2013). PICU patients with specific diseases benefit from the decrease in intracranial pressure or effects on pulmonary vascular resistance (Birchley, 2009). Effective pain management also improves tolerance to movement, chest physio, deep breathing and coughing, which are important for recovery (Vet et al, 2016; Saliskar and Kudchadkar, 2015).

When agitated and distressed, a child is at risk of pulling out invasive tubes and monitoring devices (Harris et al, 2016). Accidental extubation is a life threatening complication for a critically ill child (Ista et al, 2013). For an intubated patient, agitation also leads to increased secretions and an increased need for suctioning. The vigorous movement of the endotracheal tube (ETT) (e.g. from head thrashing) increases the need for ETT retaping and increases the risk of airway trauma and subsequent stridor post extubation (Grant et al, 2012).

In general, pain and distress have a negative impact on the mind and body (Simons & MacDonald, 2006; Harris et al 2016). Opioid analgesia can benefit a PICU patient by reducing pain and the associated stress response, which in turn reduces the rate of complications and mortality (Anand et al, 1987). Sedating a patient while also administering opioids in PICU will also reduce the agitation, anxiety and distress

associated with being intubated and ventilated, which in turn will reduce complications such as accidental extubation. The addition of a sedative means a lower opioid dose will be required to achieve patient comfort (Playfor et al, 2006).

1.2.4 What are the risks of analgesia and sedation?

There are clear risk factors related to providing analgesia and sedation to a PICU patient, which highlights the need for balance in its administration and management (Cramton & Gruchala, 2013). The main principle is the greater the dose of opioid or sedation, the more likely that the patient will be exposed to side effects of the medication (Best, Boullata & Curley, 2015). Since the mechanically ventilated child is exposed to higher doses of opioids than those prescribed for non-ventilated children, there is an increased risk of side effects occurring.

The most common side effects of opioid medication (at any dose) include: slower gut motility, nausea and constipation (Galinkin & Koh, 2018). Other side effects include itchiness, urinary retention and drowsiness (Bryant & Knights, 2011). In high doses, the sedative effects of opioids are increased, and in the non-ventilated patient an opioid overdose can be life threatening due to respiratory depression (Bryant & Knights, 2011) and cardiac suppression effects such as hypotension and bradycardia (Galinkin & Koh, 2014). Another high dose opioid side effect is muscle rigidity (particularly chest wall rigidity with fentanyl), which leads to ventilation difficulties and clinical instability, even in the intubated and ventilated patient (Anand et al, 2010). Less common, high doses of opioids can produce “paradoxical” hyperalgesia (increased pain), a tachyphylaxis that results in even benign stimuli to be perceived as pain (Anand et al, 2010; Lee et al, 2011).

Tolerance and dependence are common with prolonged use of opioids (Nicholls & Schaffner, 2016). Development of tolerance to the analgesic and sedative effects of opioids requires an increased dose to achieve the desired effect (Galinkin & Koh, 2014). Physiological dependence is a neuronal adaptation whereby removing the drug leads to a withdrawal syndrome (Anand et al, 2010).

Sedative use in ICU has come under scrutiny after a number of studies reported that over-sedation was commonly occurring (Ostermann et al, 2000). Prolonged deep sedation is associated with complications such as ventilator-associated pneumonia (VAP) and pressure areas (Grant, Balas & Curley, 2012).

Muscle relaxants may be used in the care of clinically unstable patients within PICU, at times due to difficulties in managing sedation (Martin et al, 2001; Jenkins et al 2007). The paralysed patient has a higher incidence of developing complications of deep sedation such as ventilator associated pneumonia and pressure areas, along with residual muscle weakness (Hughes, McGrane & Pandharipande, 2012).

1.2.5 Current trends in PICU sedation and analgesia management

The current trend in ICU is for the provision of "analgo-sedation", which implies either (1) analgesia-first sedation: where an opioid is used first to ensure adequate analgesia is achieved before adding a sedative to reach a sedative goal, or (2) analgesia-based sedation where an opioid is used instead of a sedative to reach a sedative goal (Devlin et al, 2018). Further to this, there is evidence that the implementation of "protocolized" or "goal directed" sedation reduces a patient's sedation requirements, duration of mechanical ventilation and length of stay (Barr et al, 2013, Devlin et al, 2018). To achieve this, a target range of the sedation score is set and regular assessment of the patient's sedation level is suggested to prevent both excessive and inadequate sedation (Barr et al, 2013; Playfor et al, 2006).

It is recognised that there are added challenges in paediatrics (Playfor et al, 2006). There is a higher risk of distress and agitation related to developmental age (Ayasrah, 2018). Some critically ill children are difficult to sedate, due to their age or condition. Further, there are cases when a critically ill or injured patient may require targeted heavy sedation, e.g. due to acute traumatic brain injury (Barr et al, 2013).

The aforementioned principle of ensuring adequate analgesia is dependent on regular pain assessment. Self-report of pain provides the most accurate measure (Playfor et al, 2006) and underlies the value of communication with an awake patient. Pain assessment is thus challenging in PICU when communication is diminished due to factors such as developmental age, illness, injury, intubation and ventilation, and when sedated. Pain assessment in the infant or preverbal child is inherently difficult and is reliant on behavioural cues (Harris et al, 2016). Pain assessment in the critically ill intubated and ventilated patient is similarly difficult. A common problem cited is the sedated patient may still be uncomfortable and experiencing pain (Ayasrah, 2018). These factors make PICU patients highly vulnerable. Recognising these difficulties, the assessment of pain and sedation levels may be enhanced by the use of standardised assessment tools that are age appropriate and validated for use in PICU (Harris et al, 2016).

Pain frequently results in distress, but distress may have other causes than pain (Harris et al, 2016). Attention to the patient's comfort includes addressing environmental and physical factors such as breathing difficulty, ventilator dys-synchrony, temperature, noise, light, positioning, hygiene, toileting, feeding, hydration, nausea; and psychological factors such as promoting normal patterns of sleep / rest, facilitating communication, parental support and temporal orientation (Playfor et al, 2006).

After reviewing the underlying principles of optimal analgesia and sedation management, it is evident that there are conflicting targets. There are both benefits and risks of sedation to consider. On the one hand, sedation is required in the ventilated patient to enhance comfort, promote adequate rest and keep the patient safe. On the other hand, there are benefits for the patient to be awake, self-ventilating, moving spontaneously and communicating. Clinical stability often

dictates the level of sedation targeted, but there is also more complexity than this. There is an art to it.

The usual pattern of recovery from critical illness or injury involves weaning from life-sustaining treatment and invasive interventions such as intubation and mechanical ventilation. The sedation and opioid analgesics are weaned off in parallel with this. The patient is at risk for developing withdrawal when opioid and sedative doses are tapered or stopped (Anand et al, 2010). Withdrawal has been reported to manifest within 2 to 72 hours after a rapid decrease in dose (Duceppe et al, 2018).

From the results of a meta-analysis of withdrawal incidence in this patient population, an estimated 10-34% of all PICU patients are at risk for developing withdrawal, and for those exposed to greater than 5 days of opioids and benzodiazepines, the risk is between 50% and 100% (Best et al, 2016). Withdrawal is a significant problem for PICU patients.

These patients, often unable to communicate their pain, discomfort, anxiety and fear, are at great risk of delayed recognition of withdrawal syndrome (Harris et al, 2016). There is beginning evidence that unrecognised and untreated withdrawal in infants and children is associated with clinical complications, increased hospital length of stay and increased mortality (Franck, Naughton & Winter 2004; de Silva et al, 2016). However, knowledge gaps in this area continue to limit our understanding of the clinical impact of withdrawal on patient outcomes.

1.3 Research problem

The research problem was based on the observation by the author (a PICU liaison nurse consultant) that a number of patients had signs and symptoms of withdrawal after transfer from PICU to the ward. Common symptoms that the author identified as part of a withdrawal syndrome were sleeplessness, agitation, poor feeding, rigidity and tremors. Haemodynamic symptoms of tachycardia, hypertension, fever and tachypnoea were present in varying degrees. One infant developed seizure-like twitching. The author noted that the PICU handover had not mentioned withdrawal assessment in these patients. The ward nurse had not recognised the symptoms as indicators of withdrawal.

The role of the PICU liaison nurse consultant includes teaching on the run and using critical care knowledge to bridge the gap between PICU and the wards. In this case knowledge of withdrawal and its management proved useful. It was evident that a significant barrier to providing timely rescue treatment for the patient's withdrawal was the lack of resources to guide ward clinicians.

Essentially, the problem was that many infants and children transferred from PICU to the ward were at risk of developing withdrawal, but the syndrome was not being recognised once patients were transferred to the general ward setting. Additional factors which impacted on management of withdrawal outside of PICU were: the PICU guideline for opioid dose tapering and withdrawal management did not cover

treatment for suspected benzodiazepine withdrawal, a neonatal withdrawal assessment score was being used that was not validated for use in paediatrics, and some patients were exhibiting signs of withdrawal despite receiving sedation for less than five days, which was uncommon according to the guideline.

While reviewing the literature for evidence to update the withdrawal management guidelines, it became apparent that there were gaps in the existing evidence regarding withdrawal in paediatric critical care with regard to (1) the specific antecedent sedation and analgesia practices that influence its occurrence, (2) how to prevent withdrawal in PICU patients, and (3) how to manage withdrawal after it is identified.

1.4 Purpose of the study

The purpose of the SEESAW study was to describe the factors that were associated with increased incidence of opioid and sedative withdrawal syndrome in PICU patients and then to analyse if the presence of withdrawal increased the rate of clinical complications or delayed the patient's recovery.

1.5 Research questions and statement of the hypotheses

Research questions:
(1) Which factors in the sedation and analgesic management within PICU are associated with an increased incidence of withdrawal?
(2) Is withdrawal associated with poor outcomes for the patient, such as increased clinical complications or prolonged length of stay (LOS) in hospital?

The hypotheses:

(1) There is a risk of developing clinically significant withdrawal symptoms when high dose opioids or sedatives are administered for a duration less than 5 days (i.e. The risk is not limited to when opioids or sedatives are administered for greater than 5 days as previously thought)
(2) The incidence of withdrawal is proportional to the dose and duration of opioid or sedative.
(3) Untreated withdrawal is associated with increased clinical complications.

1.6 Aim and objectives

The aim of the study was to collect and analyse health information relating to sedation and opioid analgesia management of infants and children within the PICU and post PICU, with a specific focus on analysing factors that influenced the incidence of withdrawal in order to inform future practice in the prevention and management of withdrawal.

The objectives of the study were defined as

(1) Determine if the incidence and severity of withdrawal is associated with medication factors such as:
   a. Medication type,
   b. Opioid dose and duration,
   c. Sedative dose and duration,
   d. Method and length of tapering, and
   e. Withdrawal rescue treatment.

(2) Determine if withdrawal impacts on the patient's recovery, as measured by:
   a. Clinical complications, and
   b. LOS in hospital.

1.7 Significance of the study

This study adds to previous research that has reported on the incidence of withdrawal for PICU patients (Fisher et al, 2013; de Silva et al, 2016; Amigoni et al, 2016). The significance of this study, or what this study adds is (1) it is the first withdrawal research presented from an Australian PICU context; (2) it addresses the problem of withdrawal assessment and management in both the PICU and post PICU patient; and (3) the results could contribute towards developing new strategies for the prevention and management of withdrawal in PICU and post PICU, improving understanding and guiding practice in this area.

1.8 Assumptions

The risk of withdrawal increases when a threshold dose of opioid or sedative is exceeded, with the risk of withdrawal increasing the higher the dose and duration. The study was designed to capture and report on the threshold dose and duration. It was assumed that patients receiving sedation for less than 24 hours were not at risk for developing withdrawal (Anand et al, 2010).

PICU patients represent a heterogeneous population due to the variations in age, diagnoses and critical illness severity. This presents a challenge for study of these patients (Wolf et al, 2014). Further, PICU nursing ratios differ worldwide. As such, the variability in PICU patient acuity and nursing ratios may independently account for variation in outcomes for patients and research results.

1.9 Definitions of terms

Alpha$_2$ adrenergic receptor agonists are a class of sympathomimetic agents that act primarily in the CNS to suppress sympathetic neuronal firing (Bryant & Knights, 2011). Uses include antihypertensive, sedative, and adjunct analgesic.

Dexmedetomidine by continuous IV infusion is used in intensive care for sedation. Clonidine is also used to reduce symptoms of opioid withdrawal that are due to sympathetic hyperactivity (Bryant & Knights, 2011).

Benzodiazepines act via effects on the inhibitory GABA neurotransmitter in the CNS to produce anxiolytic, sedative, amnesic, anticonvulsant and muscle relaxant effects (Bryant & Knights, 2011) (E.g. Midazolam, Diazepam). Midazolam is used widely for procedural sedation and for continuous sedation in intensive care, typically via continuous IV infusion. Diazepam is also used for treatment of alcohol, barbiturate and benzodiazepine withdrawal to suppress acute agitation, tremors and other symptoms (Bryant & Knights, 2011).

Opioid analgesics (E.g. Morphine, Fentanyl) have potent analgesic qualities and are used widely for the treatment of moderate to severe pain. Although the mechanism of action is still not completely clear, opioids cause their effects by mimicking the actions of endorphins and encephalins on opioid receptors. Stimulation of opioid receptors at the spinal level inhibits the release of substance P (a pain messenger), plus 'closes the gate' in the dorsal horn to inhibit afferent transmission and decrease neurotransmitter release, which leads to opioid analgesia. Stimulation of opioid receptors in the CNS alters the perception of pain and emotional response to it (i.e. producing euphoria) (Bryant & Knights, 2011; Anand et al, 2010).

Opioid-induced hyperalgesia (or tachyphylaxis) is the rapid loss of analgesic effects of an opioid medication due to exhaustion of the mechanisms for synaptic neurotransmitter suppression, with activation of antagonistic signalling systems and subsequent increased release of excitatory neurotransmitters (Velayudhan, Bellingham & Morley-Forster, 2014). The effect for the patient is increased pain and also pain from non-noxious stimuli (Anand et al, 2010; Lee et al, 2011).

Physiological Dependence is a state of neuronal adaptation after prolonged exposure to a drug such that removing the drug precipitates a withdrawal syndrome that is characteristic for that particular drug (Galinkin & Koh, 2014).

Tolerance is the decreasing clinical effects of a drug after repeated exposure to it, requiring escalating doses to achieve the desired clinical effect (e.g. achieving analgesia or sedation) (Anand et al, 2010; Galinkin & Koh, 2014).

1.10 Conclusion

PICU patients may receive high dose opioid and/or sedation infusions while intubated and ventilated, putting them at risk for developing withdrawal within the 2 to 72 hours after the opioid and/or sedative medication is rapidly reduced or stopped. The current opioid weaning and withdrawal guidelines provided instruction for dose tapering and screening for withdrawal syndrome if the duration of infusion exceeds five days. The research problem was that withdrawal syndrome was not being recognised or treated in patients that developed symptoms outside of PICU.

The aim of the SEESAW study was to collect and analyse health information relating to sedation and opioid analgesia management of PICU patients, in order to analyse factors that were associated with the development of withdrawal syndrome. The results of the study will inform future practice to improve the recognition, prevention and management of withdrawal.

Chapter 2: Literature Review

2.1 Introduction

Withdrawal Syndrome has been well described in the PICU since the 1990s (Tobias, 2000; Katz, Kelly & Hsi, 1994). Franck, Naughton and Winter (2004) were among the first to highlight the significance of the problem of opioid and benzodiazepine withdrawal for critically ill children, reporting on their prospective repeated measures study after implementing a new guideline for sedation tapering and a withdrawal assessment tool. The symptoms and severity of withdrawal were described, along with a discussion of the difficulties experienced during sedation tapering, which included poor compliance from staff and failure of the prescribed treatment for withdrawal symptoms. Research in the area has made a lot of progress in 15 years, but continues to be hampered by attitudinal obstacles and ongoing difficulties with withdrawal prevention and management.

This chapter provides a critical review of the last decade of withdrawal research, including breakthroughs, barriers, and ongoing knowledge gaps.

2.2 Withdrawal assessment

Accurate assessment is essential to identify withdrawal and to monitor the effectiveness of interventions (Harris et al, 2016). A number of studies have focussed on the development and validation of withdrawal assessment tools for use in paediatric patients (Franck, Naughton & Winter, 2004; Franck et al, 2008; Ista et al 2013). The first withdrawal assessment tool was developed for neonatal abstinence syndrome, to assess and treat infants born of opiate dependant mothers. The Neonatal Abstinence Scale (NAS) was validated for the assessment of withdrawal symptom severity in neonates up to 28 days old (Finnegan, 1990).

Since then, separate teams of researchers from two continents have developed withdrawal assessment scales and subsequently validated these for use in PICU patients. The Withdrawal Assessment Tool (WAT-1) was developed by Franck et al (2008) in North America, shortly followed by the Sophia Observation of withdrawal Symptoms Scale (SOS scale), developed by Ista et al (2013) in Europe. The WAT-1 is a 0-12 point scale that defines clinically significant withdrawal as a score of 3 or greater, and the SOS scale is a 0-15 point scale that defines clinically significant withdrawal as a score of 4 or greater. These withdrawal assessment scores both have high sensitivity to assess the severity of iatrogenic withdrawal, and high specificity to differentiate withdrawal from other reasons for agitation and/or sympathetic activation in paediatric patients (Franck et al, 2012; Ista et al, 2013).

2.3 Withdrawal incidence in PICU

Following validation of the paediatric withdrawal assessment tools, the number of studies reporting on withdrawal incidence in PICU increased dramatically. Whether

this trend represents a true increase in the incidence of withdrawal in PICU over the past decade is unclear, but plausible. Galinkin and Koh (2014) reported that the frequency of opioid prescription for children had doubled in the past decade in the USA. In their review, Cramton and Gruchala (2013) noted the more liberal use of opioids and benzodiazepines in PICU and suggested it was related to an increased awareness of the need for adequate pain control and sedation in critically ill children.

2.3.1 Duration of opioid or sedative exposure

There is consensus among researchers that the risk of developing withdrawal is greater the longer the duration of opioid and sedative administration, with the incidence of withdrawal reported to approach 100% after 9 days of continuous infusion of opioids and sedatives in PICU (Katz et al, 1994; Best et al, 2015).

The majority of studies have focussed on the incidence of withdrawal after 5 days or more of continuous sedative infusion in PICU (de Silva et al, 2016), reporting the incidence of withdrawal for opioids 45-64% (Fisher et al, 2013; Amigoni et al, 2016), benzodiazepines 17 - 37% (de Silva et al, 2016; Amigoni et al, 2014), and alpha$_2$ adrenergic agonists 37 - 60% (Lardieri et al, 2015) after this time period is reached.

A number of recent studies have included ICU patients in the lower risk group, i.e. 3 days or more of continuous opioid or sedative exposure, and the withdrawal incidence for this group is 17-22% (Wang et al, 2017; de Silva, 2016). Notably, Wang et al (2017) reported on the incidence in adult ICU. A recent systematic review concluded that iatrogenic withdrawal appears to be a frequent syndrome in critical care patients receiving regular opioids and/or benzodiazepines for 3 days or more (Duceppe et al, 2018).

Comparing continuous to intermittent administration of opioid analgesia, a randomised trial demonstrated no significant differences between 0 to 3 year old children randomised to intravenous morphine via continuous infusion or intermittent dosing for post-operative analgesia (Bouwmeester et al, 2001).

2.4 Risk factors for withdrawal

2.4.1 Dose of opioid or sedative

A recent systematic review of the risk factors for iatrogenic withdrawal syndrome in PICU confirmed that the risk of withdrawal increases when higher doses of opioids and benzodiazepines are administered (Best et al, 2015).

A number of systematic reviews and multi-centre studies have reported on dose thresholds associated with development of withdrawal syndrome (see table 1). Cumulative doses of 1.2 to 2.5mg/kg of fentanyl and 44 to 70 mg/kg of midazolam were predictive for development of withdrawal syndrome (Best et al, 2016). Putting this into perspective, a cumulative dose of 1.2mg/kg of fentanyl is equivalent to 5mcg/kg/hr fentanyl for 10 days. For midazolam, 200mcg/kg/hr infused for 10 days

equals a cumulative dose of 48mg/kg. In essence, these are very high doses. However, researchers report withdrawal syndrome was not limited to patients above these threshold doses, and was frequently observed in patients who received much lower doses (Amigoni et al 2016). Further research is required to determine the therapeutic range of opioid and midazolam doses with minimal risk of developing withdrawal syndrome.

Table 1: Fentanyl and Midazolam Dose thresholds reported in previous studies.

Medication	Dose threshold that predicted Withdrawal	Author/s	Type of study
Fentanyl	Cumulative dose 1.2 - 2.5mg/kg	Best et al, 2016	Systematic review
	Cumulative dose 1.6mg/kg	Arnold et al, 1990	Prospective observational study
	Cumulative dose of 2mg/kg	American Academy of Paediatrics (AAP), 2013	Systematic review
	Cumulative dose 2.5mg/kg	Amigoni et al, 2016	Prospective observational study
Midazolam	Cumulative dose 44 mg/kg	Amigoni et al, 2014	Prospective observational study
	Cumulative dose 60 mg/kg	Best et al, 2016	Systematic review
	Cumulative dose 65mg/kg	Amigoni et al, 2016	Prospective observational study
	Cumulative dose 70mg/kg	deSilva et al, 2016	Prospective observational study
	Peak infusion rate 200-420 mcg/kg/hr	Amigoni et al, 2014	Prospective observational study
	Mean infusion rate 300mcg/kg/hr	Best et al, 2016	Systematic review
	Mean infusion rate 350mcg/kg/hr	deSilva et al, 2016	Prospective observational study

2.4.2 Opioid or sedative type

Multiple studies have reported that fentanyl is associated with increased withdrawal when compared to morphine (Franck, Naughton & Winter, 2004; Amigoni et al, 2016). The proposed mechanism for this is that fentanyl has a relatively short half-life of 30 – 60 minutes, but with continuous administration of high doses there is accumulation in peripheral compartments that leads to rapid tolerance and later withdrawal (Playfor et al, 2006). Fentanyl was recently reported to be the most prescribed opioid in North American PICUs (Kudchadkar, Yaster & Punjabi, 2014).

A number of single centre studies reported that midazolam was associated with withdrawal in their PICU (Amigoni et al, 2014; de Silva et al, 2016). According to a recent survey of PICU intensivists, midazolam remains the most common sedative used in PICUs worldwide (Kudchadkar, Yaster & Punjabi, 2014).

There is considerable variability in how opioid and benzodiazepine medications are used with regard to doses, duration of treatment, and the concomitant use of adjunct analgesics and sedatives. More detailed analysis is required to understand this better.

2.4.3 Number of sedative classes used

The use of additional sedative classes was proposed as a method to reduce the development of tolerance and withdrawal, with sedatives such as dexmedetomidine and propofol added or substituted via continuous infusion (Tobias, 2006; Sheridan et al, 2003). These sedatives offered viable alternatives to midazolam. Research has since demonstrated that each of these sedatives could also precipitate withdrawal (Miller, Allen & Johnson, 2010; Lardieri et al, 2015). Conversely, withdrawal incidence increased with the number of sedatives used per patient (Ista et al, 2013; Best et al, 2016).

2.4.4 Patient factors

A large multi-centre study in the USA (Best et al, 2016) used multivariate analysis to identify patient factors that increased the risk for withdrawal. Patients less than one year old and those with pre-existing cognitive impairment were more likely to develop withdrawal (Best et al, 2016). However, an Italian multi-centre study did not reproduce these results in their population (Amigoni, 2016). The USA study was larger and restricted to patients ventilated for respiratory failure, and in comparison there was increased heterogeneity in the Italian PICU patient population studied.

2.4.5 Method of tapering

Gradual tapering of IV infusions involves decreasing by a percentage at specified intervals. Changing to oral/enteral medications is another method of dose tapering.

Some studies reported withdrawal symptoms continued despite implementation of a weaning schedule (Chui et al, 2017). Katz, Kelly & Hsi (1994) examined the occurrence of withdrawal syndrome in children undergoing an opioid taper (50% reduction each day for two days then discontinuation on day three) and the emergence of withdrawal symptoms in this patient group was very high. Since then, it is suggested dose tapering should be more gradual to minimise the emergence of withdrawal (Chui et al, 2017). Best et al (2016) compared patients weaned by less than or greater than 20% of their opioid dose daily and noted a difference of 46% versus 85% respectively in the incidence of subsequent withdrawal. Successful implementation reportedly relies on monitoring of withdrawal symptoms and may require the speed of tapering to be adjusted or intermittent rescue provided (Franck et al, 2011).

2.5 Treatment of withdrawal

There is conflicting information in the literature about how best to treat withdrawal, with a lack of high quality evidence regarding the optimal regimen for dose tapering

(American Academy of Paediatrics, 2014). Experts suggest treating withdrawal with administration of the specific medication (e.g. opioid or sedative) responsible for the withdrawal and then gradually decreasing the dose every 24 – 48 hours (known as dose tapering or weaning) (Cramton & Gruchala, 2013). However, prescriber references are limited and further research is required to address this.

2.5.1 Medications used in the treatment of withdrawal

Methadone is a common agent used to treat opioid withdrawal in the community and has been trialled extensively in children, however researchers report variable responses to treatment and the optimal tapering regime remains unclear (Bowens et al, 2011; Chui et al, 2017; Best et al, 2016). One study compared high and low doses over a 10 day taper with poor results (Bowens et al, 2011), whilst another study compared methadone tapering over 5 or 10 days with no difference (Berens et al, 2006), and yet another study compared speed of tapering between 10% and 20% daily and reported 87% incidence of breakthrough withdrawal symptoms (Cramton & Gruchala, 2013). The variability in results suggests methadone dosing is difficult due to significant patient-to-patient differences in bioavailability, and expert guidance is recommended to assist with conversion doses (Robertson et al, 2000).

Clonidine is an alpha$_2$ adrenergic agonist that has been used widely to treat opioid withdrawal symptoms in PICU patients. The current evidence to support the use of clonidine in the prevention and treatment of opioid withdrawal in ICU is limited to case reports and small retrospective studies with concurrent other medications (e.g. opioids or sedatives) and variable dosing schemes (Honey, Miller & Johnson, 2009). In 2009, a systematic review noted the low grade of evidence and suggested clonidine as a second-line adjunct to longer acting opioids (Honey, Miller & Johnson, 2009). In their prospective study, Amigoni et al (2016) reported a higher incidence of withdrawal in patients treated pre-emptively with clonidine, contributing to doubt regarding clonidine's role in preventing withdrawal. The contribution of clonidine to successful weaning remains unclear (Best et al, 2016).

There were no studies comparing use of other long acting opioids such as enteral morphine for treatment of opioid withdrawal, or enteral diazepam for treatment of benzodiazepine withdrawal. More studies in this area are required (Best et al, 2016).

2.6 Impact of withdrawal on outcomes

An ongoing barrier that limits tapering of opioid and sedative medications to prevent withdrawal is the concern that the side effects of the opioids and sedatives for the patient are worse than the suffering and clinical consequences associated with withdrawal.

From the bedside, it is evident that withdrawal syndrome causes patient suffering as a result of sleeplessness, feed intolerance and central nervous system agitation. However, withdrawal is often thought of as distressing, but ultimately not life threatening (Hanna & Swetter, 2017). Research in this area has begun to challenge this view. A number of case reports have described serious clinical complications

arising from untreated opiate withdrawal, which included seizures, aspiration pneumonia, oesophageal wall tear/rupture, rhabdomyolysis, acute kidney injury, Takotsubo cardiomyopathy, cardiac arrhythmias (Hanna & Swetter, 2017; Olson et al, 2017). Notably, the case reports did include one death (Hanna & Swetter, 2017).

On a broader scale, iatrogenic withdrawal syndrome has been associated with prolonged ventilation, and prolonged length of stay (Franck et al, 2008; Ista et al, 2013). In their multi-centre Italian study, Amigoni et al (2016) found the patients with withdrawal had an increased duration of ventilation, PICU and hospital length of stay (LOS). However, these results were difficult to interpret because it could not be ascertained if it is the patient's condition that best predicts these outcomes, necessitating prolonged analgesic and sedative treatment, or if the analgesic and sedative treatment protocols and weaning protocols are what prolongs the ventilation and LOS, independent of the patient's underlying condition (Amigoni et al, 2016).

The prospective study of withdrawal incidence improves the early detection of withdrawal and thereby lessens the chance of withdrawal being untreated.

2.7 Prevention of withdrawal

Prevention of iatrogenic withdrawal syndrome could be more important than early prediction (Ista & van Dijk, 2015). There is a call for research to address opioid and sedative medication modelling for a variety of PICU patient conditions and duration of treatment to determine the optimal doses (Ista & van Dijk, 2015).

A number of studies (Kress, 2000; Barr et al, 2013) have focussed on strategies to reduce excessive doses of opioids and sedatives with daily sedation interruption (DSI) proposed as a method to reduce the amount of sedative being administered and therefore reduce the time that the patient requires ventilation. Many single centre prospective studies reported reduced ventilator hours and ICU LOS (Kress et al, 2000; Girard et al, 2008), which increased the uptake of this practice. However, a systematic review by Burry et al (2014) of DSI in adult ICU concluded that overall were no reduction in ventilation hours and no benefit to the patient. It was noted that the re-intubation rate and subsequent ventilated period were not reported in the original studies (Burry et al, 2014). Further, a large prospective paediatric study compared DSI to continuous sedation and found there was no change in ventilation hours but there was increased mortality in the DSI group (Vet et al, 2016). In the recent update of the adult ICU sedation guidelines, the change in focus is apparent, i.e. away from DSI towards goal directed (protocolized) sedation (DAS taskforce, 2015).

A significant driving pressure for rapid weaning of sedation is to reduce ventilation hours and PICU length of stay (Barr et al 2013). However, what the DSI research has demonstrated is that these outcome measures have limited value for the child if their risk of clinical complications and mortality is increased. The period of time while the patient is "waking up" to enable assessment or extubation is difficult to

navigate at times. Agitation levels can fluctuate dramatically. The sudden cessation of high dose opioids and sedation to enable rapid weaning from ventilation increases the risk of clinical complications such as aspiration pneumonia, pulmonary oedema, air leaks, and re-intubation (Grant et al, 2012). These factors impact on the patient's recovery and LOS. The impact of acute withdrawal on these events is unclear, but agitation can precipitate significant clinical deterioration in the vulnerable PICU patient.

2.8 Guidelines for Sedation, Analgesia and Withdrawal in PICU

A guideline can be a driving force for improving quality and clinical outcomes (Abdouni et al, 2016). In their pre and post implementation study, Neunhoeffer et al (2015) demonstrated that the implementation of a nurse-driven protocol for sedation, analgesia and withdrawal in their PICU reduced the incidence of withdrawal syndrome from 23.6% to 12.8%. For the past decade, a number of studies (Keogh, Long & Horn, 2015; Dreyfus et al, 2017) have reported on benefits gained from the local implementation of sedation and analgesia guidelines based on the "Consensus clinical practice guidelines for the provision of sedation and analgesia in critically ill children" developed by the UK Paediatric Intensive Care Society (Playfor et al, 2006).

Interestingly, a survey of Paediatric Intensivists in 2014 suggested that only 27% reported having written sedation and analgesia guidelines in their PICU and concluded there is continued variability in physician practices worldwide (Kudchadkar, Yaster & Punjabi, 2014). Withdrawal guidelines are even less common. Physicians that do not adhere to the 2006 guidelines reported a complexity of patient variables within PICU and the need to tailor treatment on an individual basis (Kudchadkar, Yaster & Punjabi, 2014). In a survey of Australian PICUs, 4 (of 8) used pain and sedation assessment scores (Long, Horn & Keogh, 2005). Further understanding of current practices regarding sedation, analgesia and withdrawal in PICU may bridge this gap.

Exploring the impact on the patient's long-term recovery, a recent systematic review reported an incidence of 17 – 34 % of post-traumatic stress disorder (PTSD) in adults one year after intensive care unit discharge (Parker et al, 2015). In children aged 7-12 years, the incidence of PTSD after admission to PICU has been reported at 28% (Colville, Kelly & Pierce, 2008). The development of PTSD is linked to memories of pain or distressing events. Franck et al (2004) conducted follow up interviews with child survivors, and reported that memories of the pain and distress experienced in PICU contributed to ongoing emotional suffering which was manifested as fear, anxiety and an increased sensitivity to pain. These results provide a salient reminder of the invasive, distressing and painful situations (which includes withdrawal syndrome) that are the norm in PICU and how they may impact on the patient in a vulnerable position.

2.9 Conclusion

Research has confirmed the high incidence of withdrawal in PICU patients. However, there is a paucity of high quality evidence regarding the prevention and treatment of withdrawal. Further research in this area is needed to better identify the critically ill children at risk of withdrawal and analyse the consequences of delayed or under-treatment of withdrawal. In order to prevent withdrawal and improve management, the antecedent sedation and analgesia practices in PICU are a necessary part of the analysis. Improved withdrawal management guidelines are required to guide dose tapering and rescue treatment and prevent complications (American Academy of Paediatrics, 2013).

The proposed research project aims to explore the local context of withdrawal in order to improve understanding of sedation and analgesia practices in PICU and other factors that influence withdrawal. The results will inform the development of guidelines for the prevention and treatment of withdrawal in PICU in order to improve practice in this area.

Chapter 3: Methods

3.1 Introduction

This chapter outlines the research design and methods used in the study. The study elements presented include the population being studied, inclusion and exclusion criteria, sampling strategies, the study setting, the data collection methods, ethical considerations, issues of validity and reliability, and the statistical analysis used.

The main objectives of the study were to determine the incidence of withdrawal after exposure to variable doses and durations of opioid analgesics and/or sedatives and to analyse the relative risk of clinical complications for patients that developed withdrawal syndrome.

3.2 Description of research design

The research design was a single centre retrospective cohort study using a retrospective chart audit.

A retrospective cohort study is classed as an observational study method that is analytical because it assesses the relationship between a study factor (exposure) and an outcome (Buttner & Muller, 2011). Therefore, a cohort study was ideal for analysing risk factors for withdrawal syndrome and determining incidence in the natural setting.

A retrospective chart audit was an appropriate research method to answer the research question with the minimal risk to participants or inconvenience to clinical staff. It was also achievable in the timeframe for the master's research thesis. However, the most important factor in considering the validity of conducting a retrospective chart audit is whether the data required could be obtained from the patient's medical records. The initial assessment was that the quality and completeness of the documentation in the medical records regarding sedatives, analgesics and withdrawal was adequate for the purpose of the study.

A limitation of the retrospective chart audit is that it relies on the completeness of documentation as the only source of data, and the documentation in the medical record was not written for the purpose of research (Vassar & Holzmann, 2013). In retrospective chart reviews, there are a number of threats to validity and potential sources of bias (Schneider et al, 2016). Missing data could potentially reduce the validity of the study (Panacek, 2007). Further, the quality of retrospective data is inferior to data recorded prospectively since it is filtered by the clinician's initial interpretation of events rather than the data being collected from the actual events (Buttner & Muller, 2011). However, a well-designed study can address these

concerns and enhance the validity, reproducibility and overall quality of data collected from medical records (Panacek, 2007).

3.3 Setting

The setting for the study was a 13 bed combined Paediatric Intensive Care Unit and High Dependency Unit (without cardiac surgery or ECMO) located within an Australian metropolitan (200 bed) tertiary paediatric hospital.

Best, Boullata & Curley (2015) conducted a systematic review of withdrawal studies in PICU patients and recommended that authors provide a description of PICU staffing characteristics to enable comparison of system factors. The staffing characteristics of the PICU studied were 100% registered nurses, and of these, 70% had paediatric critical care qualifications (one year paediatric critical care nursing certificate or two year graduate diploma). A 1:1 nurse to patient ratio was the norm for all intubated patients and two clinicians were routinely present for all endotracheal tube (ETT) suction. The ETT securement method was either bilateral trouser leg tapes over a silk or cotton tie, or an ETT securement device for oral ETTs in older children. Minimal patient restraints were used throughout the hospital, restricted to mittens, infant swaddling, and splints for protection of invasive lines.

3.4 Population

The target population, or cohort, was the group of patients who were at risk of developing withdrawal, but were free from withdrawal at the time of enrolment.

3.4.1 Inclusion criteria

The inclusion criteria for selection was defined as paediatric patients (0 to 17 years of age) who were admitted to PICU within the retrospective study period, were intubated and mechanically ventilated, and received continuous intravenous opioid analgesia and/or sedation for greater than 24 hours.

3.4.2 Exclusion criteria

Patients were excluded from selection if (1) control of seizures was the primary reason for admission (a confounding variable due to the use of benzodiazepines in this case for seizure control rather than sedation), (2) the patient had a tracheostomy on admission to PICU (these patients have a different PICU course because they are not intubated or extubated), (3) the patient was previously exposed to opioids or sedatives for greater than 42 days prior to recruitment (introducing an additional confounding variable of opioid tolerance and dependence prior to admission), and (4) the patient had received continuous infusion of opioids and/or sedation for greater than 42 days in PICU without extubation or dose tapering during that time.

3.5 Sampling strategies

3.5.1 Sample size calculation

Statistical advice was sought during the study design phase to ensure the sample size was sufficient to give the study adequate power to perform the statistical analysis.
When regression analysis is being used to determine the association between variables, Peduzzi et al's (1996) work suggests using the event per variable (EPV) rule for sample size, which recommends an EPV of 10 or greater. This translates to a sample size of 10 (or greater) per independent variable. For the SEESAW study, the dependent variables were binary withdrawal present – yes/no. The independent variables were patient factors (age, severity of illness, reason for admission), medication duration, dose, type, tapering method, rescue medication type, and clinical complications. To analyse 5 independent variables for each dependent arm, a sample size of at least 100 would be required.

Another method of sample size calculation can be used for cross sectional studies to estimate prevalence (Buttner & Muller, 2011). The formula is:

$$\text{Sample size} = n = \frac{z^2 \times p(1-p)}{d^2}$$

z is for statistical confidence. With the confidence interval set at 95%, z = 1.96.
p is the expected, hypothesized prevalence, If unsure assume 50%, p = 0.05. This will give the largest sample size estimate. The prevalence of withdrawal in the study cohort is predicted to vary with duration of therapy 13 – 24% at 3 days (Dreyfus et al, 2017; Neunhoeffer et al, 2015), 50 – 64% at 5 days (Best et al, 2016; Amigoni et al 2016).
d describes the intended precision. If d = 0.01 this means +/- 10% precision

$$\text{The sample size calculation} = n = \frac{1.96^2 \times 0.5(1-0.5)}{0.01^2} = 96.04$$

Schneider and Whitehead (2016) suggest sample size calculation should take into account previous similar studies. For withdrawal studies, sample sizes of 113 – 368 (Amigoni et al, 2016; Best et al, 2016) have used regression analysis and obtained statistically significant results.

An adjustment, i.e. increase, was added for the retrospective chart audit design, to account for missing data. The final sample size calculation was to aim for a minimum of 120 – 160, dependent on available time and resources.

3.5.2 Sampling strategies

To estimate the timeframe required to achieve a sample size of 120 - 160 from the target population, PICU data was obtained from the published Australian and New Zealand Paediatric Intensive Care (ANZPIC) registry report (2015). In 2015, WCH PICU had 570 admissions with 182 (32%) patients intubated and mechanically ventilated. 96 patients had a PICU length of stay greater than 3 days. Accounting for patients with multiple admissions (each patient would only be eligible for inclusion in the study once) and exclusion criteria, this equals approximately 80 patients per year available for recruitment. Therefore the proposed retrospective study period was set for 2.5 years, between 1/7/2015 and 31/12/2017.

A convenience sampling strategy was employed, with planned enrolment of subjects (i.e. medical records) chronologically from the start of the study period until 120 - 160 patient records were enrolled.

It was recognised that random sampling would require a much larger retrospective study period, i.e. 5 years, to achieve the sample size. Therefore, although random sampling was feasible, it would introduce risks of increased variability in practice over time, and would limit the ability to interpret the results as a single cohort.

3.5.3 Patient selection

To find the target population, a list of patients with the criteria: intubated and ventilated for greater than 24 hours within the study period was filtered from the local ANZPIC registry database. The medical record files were then obtained to assess each for eligibility using the inclusion and exclusion criteria.

The principal investigator kept a confidential record of each subject enrolled in the study with the name, date of birth, medical record number and date of admission to PICU and allocated research subject number. The purpose of the allocation list was to track the number of subjects and ensure each patient was enrolled in the study only once.

A total of 120 subjects were enrolled chronologically from PICU admissions within the retrospective study period from 1/7/2015 – 31/12/2017. Patient enrolment was stopped when the time available for data collection was reached, ending the retrospective study period on 31/7/2017, i.e. after collecting data from the study period spanning 2.1 years.

3.6 Data collection

The starting point for data collection was from the time of endotracheal intubation. The end point for data collection was 72 hours after the last dose of opioid or sedative medication, on discharge from hospital, or after 42 days of data collection

(which ever occurred first). The data collection encompassed the total opioid and sedation infusion period, the tapering period and 3 days after cessation. The reasoning was that withdrawal symptoms are most prevalent in the 72 hours following rapid weaning or cessation of an opioid or sedative medication (Ista et al, 2013; Franck et al, 2012).

The data collected was based on the study objectives and proposed outcome measurements.

Patient demographic factors were collected to describe the study population in order to determine if it is representative of the wider PICU population, and to detect potential confounders. The patient demographic information included: age, diagnoses, reason for PICU admission, severity of illness, and if the patient had surgery during their PICU admission.

The time periods recorded were:

(1) Hospital admission and discharge, i.e. hospital LOS;
(2) PICU admission and discharge, i.e. PICU LOS;
(3) ETT intubation and extubation, to record total intubation hours;
(4) When continuous IV infusion of opioid and/or sedatives started and stopped, for accurate dose and duration calculations; and
(5) When tapering of opioids and sedatives started and stopped.

It was important to collect data relating to intubation and mechanically ventilation, since the weaning of ventilation and extubation is reliant on tapering of sedation.

The medication data was primarily focussed on the opioid and sedative infusions administered and the dose tapering that followed. It was also important to collect information regarding any potential confounders. Therefore information was collected regarding adjunct analgesics and sedatives, muscle relaxants, anti-emetics.

The medication data collected included:

- Opioid and sedative type
- Opioid and sedative daily dose
- Number of boluses of opioids and sedatives
- Reasons for boluses
- Dose tapering data
- Adjunct analgesics
- Adjunct sedatives
- Muscle relaxants
- Anti-emetics
- Agitation rescue
- Enteral medications

The patient assessment data collected included:

- Target sedation level (documented by the PICU Medical Officer)

- Agitation
- Over-sedation
- Poor Feeding / Feed intolerance
- SOS Withdrawal symptoms
- Withdrawal assessment scores (NAS)
- 'Withdrawal' documented by clinicians

The assessment of withdrawal was the primary aim, however agitation, sedation and pain assessment are closely linked. They were potential confounders in the assessment of withdrawal. In addition, the data related to the assessment of pain and sedation provides context for the medication data. Baseline pain and sedation scores were not available. In contrast, there was good available data in relation to events; therefore the reasons for boluses were recorded to provide information about why increased opioid and sedative doses were given for some patients, i.e. for patient agitation.

The quality of a patient's analgesia and sedation may be defined in a number of ways, such as a targeted range of a validated pain and/or sedation score, like the COMFORT score. Neunhoeffer et al (2015) used a COMFORT – B score (Boerlage et al, 2015) target range of 12 – 18 to indicate adequate analgesia and sedation in their prospective before and after protocol implementation study. Grant, Balas & Curley (2013) define episodes of prolonged agitation (SBS sedation score > 0) as sedation failure. In the SEESAW study the data collection was simplified to record episodes of agitation and over-sedation that were documented by the clinical team.

Finally, clinical complications were recorded to analyse if the presence of withdrawal syndrome impacted on the patient's recovery, by the association with increased incidence of clinical complications.

Complications recorded included:

- Accidental extubation (ETT)
- Any other invasive tube dislodged
- Post extubation stridor
- Failed extubation
- Unplanned readmission to PICU (within 72 hours)
- Clinical deterioration (within 72 hours of dose tapering)
- Pressure Areas

3.6.1 Data collection form

The data collection form (Appendix A) was developed specifically for the study by the principal investigator based on the focus of the research. In the planning stage the form was trialled by two PICU registered nurses using the medical records of four ventilated patients in PICU, and adapted based on the clinical feedback received. The clinical relevance of the data collection form was further evaluated by a group of

clinical experts (PICU intensivists and nursing clinicians) gathered for the Department of Paediatric Critical Care Medicine (DPCCM) research meeting.

3.6.2 Withdrawal assessment

The dependent variable in the SEESAW study was the presence or absence of withdrawal syndrome. A strategy was developed for retrospective withdrawal assessment.

Two withdrawal symptom assessment scales have been validated for use in infants and children, the Withdrawal Assessment Tool (WAT-1) (Franck et al, 2008) and the Sophia Observation withdrawal Symptoms scale (SOS) (Ista et al, 2008). In addition, the Finnegan Neonatal Abstinence Scale (NAS) is validated for use in neonates up to 28 days corrected gestational age (Finnegan, 1990).

The withdrawal assessment score being used in PICU during the study period was the Finnegan Neonatal Abstinence Scale (NAS) (Appendix B). A 0-21 point score, the NAS guideline directed four hourly assessments if the patient received opioids for more than five days and intervention is suggested for a score of eight or greater (Finnegan, 1990). Validated for use in neonates, the validity of the NAS when used to assess for withdrawal in older infants and children is unknown.

The WAT-1 (Franck et al, 2012) and SOS (Ista et al, 2013) are both validated scores for the assessment of iatrogenic withdrawal syndrome in paediatrics and in critically ill children. The scores are very similar, containing a list of common withdrawal symptoms that include autonomic, neurological and gastrointestinal symptoms. Both have a scale of increasing withdrawal symptoms (WAT-1 0-12 and SOS 0-15) and both scores advise the practitioner to consider treatment of withdrawal when a threshold score is reached (i.e. score of 3 or 4 respectively). However, there are differences in the scoring method. The WAT-1 requires the concomitant use of the SBS sedation scale (Curley et al, 2006) to assess the patient prospectively at a single point in time, pre and post a stimulus (Franck et al, 2012). In contrast, the SOS instructs the clinician to document the presence of symptoms from the retrospective 4-8 hour period (Ista et al, 2013).

The WAT-1 and the SOS were tested at the bedside of two patients with suspected withdrawal by a PICU registered nurse and the author. Both were relatively easy to use. The SOS (Appendix C) was identified as the most appropriate paediatric withdrawal assessment score for retrospective use in the SEESAW study, due to its established validity in retrospective assessment. To enable accurate and consistent data collection, the individual symptoms of the SOS were embedded into the data collection form.

The SOS was used retrospectively to record individual withdrawal symptoms that were documented in the medical record each shift (split into 12 hour day and night shifts). The total SOS score was recorded for each shift. As per the SOS instructions (Ista et al, 2013), clinically significant withdrawal is to be considered when the SOS

total is 4 or greater. In practice, the patient would then be re-assessed by the clinical team to determine if the elevated SOS score was related to pain, withdrawal or an underlying clinical reason. To replicate this retrospectively, the following criteria were used to determine if the symptoms were not specific for withdrawal (e.g. tachycardia, tachypnoea and agitation without tremors, other motor disturbances, nor GIT symptoms) and another cause for the symptoms was identified (e.g. if the patient's agitation was resolved following non-opioid analgesia, the result was recorded as withdrawal negative).

In the SEESAW study, the presence or absence of withdrawal syndrome was then recorded in the results in three ways:

1. There was a reference to the patient having signs and/or symptoms of "withdrawal" in the medical record entry by a nurse or doctor. Recorded as 'clinical withdrawal positive';
2. There was a prospective withdrawal score (NAS) completed and the total score was 8 or greater. Recorded as 'NAS positive'
3. There were symptoms of withdrawal documented in the medical record, and the retrospective SOS score total for one shift was 4 or greater (as defined in the previous paragraph). Recorded as 'SOS ≥ 4 withdrawal positive'.

3.6.3 Pilot study

In preparation for the research study, a pilot study was conducted to test the data collection form using a sample of 16 patient records. The purpose of the pilot study was to evaluate the data collection tool, with respect to the time frame for data extraction and the ability of the investigator to identify the outcome variables from the information available retrospectively in the medical records. It provided an opportunity for final modifications to the study protocol and the data collection form.

The results of the pilot study were evaluated:

1) The data extraction took 1 to 4 hours per subject, depending on the duration of opioid and sedative infusions. The time allocated for data collection was extended to accommodate this.

2) The data collection form was modified and the procedure manual was further developed to address the identified weaknesses and improve the speed of data collected, whilst maintaining accuracy and consistency.

3) Further exclusion criteria were identified:
   a) Patients that were transferred to another PICU prior to sedation tapering; and
   b) Patients that died or were palliated within 7 days without sedation tapering.

   The reason for excluding these patients was because their opioid or sedative/s were not tapered and therefore were no longer in the population "at risk" of withdrawal.

4) Completeness of data. The objective data such as dates and times and medication doses were of high quality. Reasons for opioid or sedation infusion boluses were documented with moderate quality, with some missing data. The documentation relating to the clinical assessment of pain and sedation were subjective descriptions rather than scores, which limited the reproducibility and use for this study. Scores to describe withdrawal assessment were used more frequently, providing quality data when present, but were missing at times. Agitation episodes were frequently recorded but not counted. Agitation and withdrawal rescue were well documented. In summary, overall, the data from the pilot study was evaluated to be of sufficient quality and completeness to provide valid and reliable results.

3.6.4 Data gathering

After receiving HREC approval, the data collection for the retrospective chart audit commenced in May 2018 with the pilot study and was completed in January 2019. The data was extracted from the medical records primarily by the principal investigator with assistance from two PICU liaison nurses (i.e. with similar experience level).

To maintain consistency and accuracy throughout the data extraction process, the principal investigator developed a data collection procedure manual, which outlined the procedures for data collection (Appendix D). For example, the procedure manual outlined where to find specific data (e.g. medical and nursing entries, withdrawal chart, observation chart and fluid balance chart for documentation of withdrawal signs and symptoms), how to record it (e.g. tick if symptom present), and provided codes to categorise the data recorded (e.g. codes for each medication used for agitation or withdrawal rescue). The 2 nurses were then trained to extract the data from the medical records using the data collection form. Emphasis was placed on the essential requirement to maintain an observational and descriptive perspective, relaying the information documented, without any assumptions or insertion of own clinical opinions (Eder et al, 2005). To evaluate the inter-rater reliability of the SOS scale assessments, the retrospective SOS scale was repeated independently by the primary investigator and compared with the SOS scale completed by the 2 research assistants, for 4 patient records. There was agreement regarding presence or absence of withdrawal between the data collectors. The primary researcher completed 95% of the total data collected.

The data was extracted and documented manually using paper forms and then entered into a computer database (Microsoft Excel). This allowed for a second data checking. Every effort was made to ensure the data was complete, such as going back and re-checking and searching subsequent medical record volumes for missing data. This resulted in high quality data regarding times, dates and medications. It was recognised that the medical records contained incomplete data regarding regular pain, sedation and withdrawal assessment. In comparison, agitation and over-sedation episodes were well documented. The retrospective withdrawal

assessment by the data abstractors using the SOS scale was implemented to overcome this.

3.7 Ethical Considerations

A research proposal for the SEESAW study was submitted to the Women's and Children's Hospital Network (WCHN) Human Research Ethics Committee (HREC) (Appendix E) and approval was granted in May 2018. Secondary acceptance of ethical approval and indemnity insurance was then sought and obtained from the University of Adelaide Research Ethics Secretariat and Legal & Risk Office (Appendix E). Access to ANZPIC registry data was requested via the national ANZPIC registry database manager and approval was granted.

After receiving WCHN HREC approval, permission was sought to access patient medical records for audit purposes with approval granted by the WCHN medical records manager. Access to confidential patient medical records was restricted to WCHN employees, in accordance with Section 93 of the 'Health Care Act' (2008), and the 'Code of Ethics for the South Australian Public Sector' (2015).

The requirement for seeking participant consent was waived. To explain why, the process of seeking of consent from parents of children who were admitted to PICU in the previous three years was considered impractical and outweighed the benefit of informed consent in this study. It was argued that informed consent was not required because the research involved the collection of data from existing retrospective patient records. Since the retrospective events being described and analysed have already happened, the research was considered to have minimal risk of harm or inconvenience to the participants involved. Further, anonymity of participants was maintained due to the data being de-identified following recruitment, which mitigated the remaining risk.

The recruitment process involved allocation of a research subject number, to ensure the data was de-identified. Anonymity was achieved because no information that could identify an individual patient was documented on the data collection form or reported in the results. All information collected was treated in a confidential manner. The hard copies of data collection records were stored in a secure area (locked filing cabinet) that could only be accessed by the primary investigator and the electronic data such as computer databases and data analysis files were stored securely using password protection.

3.8 Issues of validity and reliability

Data quality is the largest threat to validity when using retrospective medical records as the primary source of data. The quality of the data is reliant on the quality of the records. For the SEESAW study, there was high quality data available for patient demographic information, times and dates of events and the objective data relating to medications and doses. The clinical records also contained detailed daily information regarding any clinical complications and significant changes. The data

relating to withdrawal symptoms contained enough information to reliably use the findings, particularly in relation to heart rate, respiratory rate, fever, agitation, anxiety, inconsolable crying, sleeplessness, hallucinations, vomiting and diarrhoea. The more subtle symptoms such as grimacing, tremors, motor disturbances, and increased muscle tension were not routinely reported, and their report was limited to documentation (1) by PICU clinicians, (2) if the withdrawal score was being used or (3) to describe why withdrawal was suspected.

Use of validated instruments to measure the variables of interest improves the validity of the study (Schneider et al, 2016). The Sophia Observation of withdrawal Symptoms (SOS) scale has been validated as an instrument for screening benzodiazepine and opioid withdrawal in paediatric critical care patients (Ista et al, 2013; Chiu et al, 2017; Harris et al, 2016). The SOS scale was used to retrospectively assess for the presence of withdrawal in the SEESAW study, which was in keeping with the designed application of the instrument.

Blinding of the data abstractors to the research question is recommended as a method to reduce the risk of subjective bias (Panacek, 2007). This was not achievable is this study due to the nature of the study problem, i.e. that withdrawal symptoms were often unrecognised by clinicians when the patient was not already being monitored with a withdrawal score or on a tapering plan. It was also not achievable to blind the abstractors to the medication doses because the medical and nursing notes contained this information.

3.9 Statistical Analysis

Descriptive statistics were used to describe the data distribution, e.g. to compare the proportions, percentage, mean, standard deviation, median and inter-quartile range between variables of interest. In the PICU population studied, there were outliers that skewed the data, largely due to a few patients with an extended ventilation period and prolonged length of stay. Since the data were not normally distributed, non-parametric tests were used to determine the statistical significance of the results.

Inferential statistics using uni-variable analysis, e.g. chi-square, mann-whitney U test, risk ratio, and contingency table analysis, were employed to determine if there was an association between the presence or absence of withdrawal (binary dependent variable) and opioid/sedative type, average infusion rate, peak daily infusion rate, cumulative dose, duration, tapering method, and clinical complications (independent variables). This was followed by multivariate analysis, specifically logistic regression, to determine the strength of the relationship between contributory factors.

Both STATA and the IBM SPSS statistics programs were used to assist the statistical analysis. The confidence interval of 95% was set with a p value of 5% ($p = 0.05$).

3.10 Conclusion

This chapter outlined the research design and methods used in the SEESAW study. Using a retrospective cohort study design, a retrospective chart audit was employed to determine the incidence of withdrawal within in the cohort. The withdrawal-screening tool used for retrospective data collection was the Sophia Observation of withdrawal Symptoms (SOS) scale. The data collection focussed on (1) the opioid analgesic and sedative medications administered, (2) the presence of withdrawal symptoms and clinical deterioration during the tapering period and 72 hours after medications were ceased, and (3) patient outcome measures. The retrospective study design provided the opportunity to observe the clinical course of untreated withdrawal syndrome in the natural setting.

Chapter 4: Results

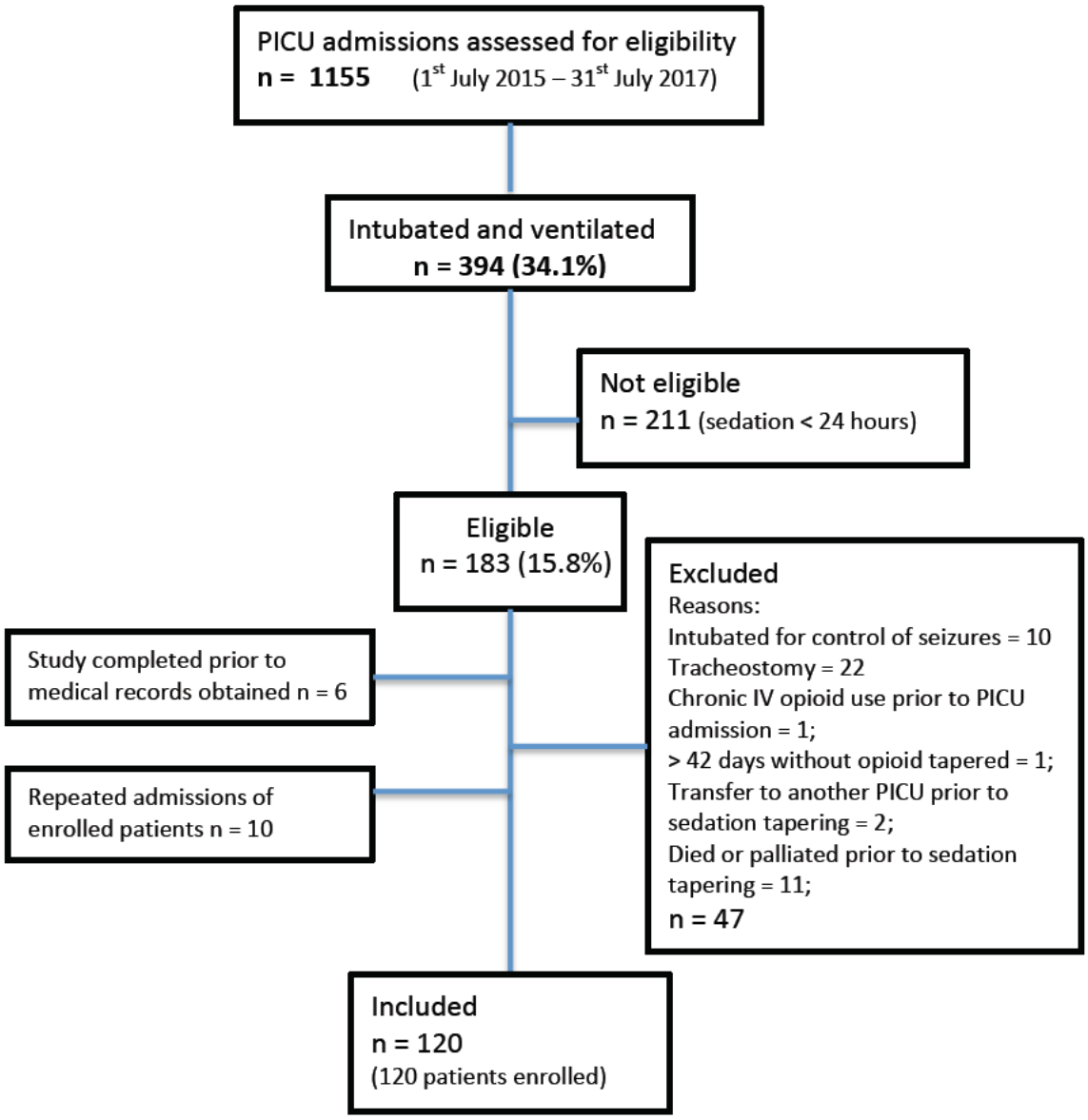
4.1 Introduction

This chapter reports on the results of the data analysis. In keeping with the SEESAW study's aims, the results provide an in depth analysis of the factors that increased the incidence of withdrawal in the study cohort and then compared the outcomes of patients who developed withdrawal to those who did not.

4.2 Patient selection

A total of 120 patients were enrolled in the study, selected from patients admitted to the PICU within the retrospective study period spanning 2.1 years (Figure 1).

Figure 1: Consort diagram showing PICU admissions, study eligibility and final numbers included / excluded



4.3 Demographic characteristics

The baseline characteristics of the cohort were examined. Where available, comparison was made to data from the 2016 ANZPIC registry report, which contains pooled data from all Australian and New Zealand PICUs and was considered representative of the PICU population from which the cohort was selected (Table 2).

Table 2: Demographic Characteristics of Enrolled Patients

Characteristics of Enrolled Patients	**N = 120**		
Variables	Number	%	ANZPIC* (2016)
Gender - male	71	59.2%	57.1%
Age			
• < 1 month	40	33.3%	9.2%
• 1 – 12 months	32	26.7%	27.9%
• 1 – 4 years	19	15.8%	28.1%
• 5 – 11 years	16	13.3%	
• 12 – 17 years	13	10.8%	
Age (years)	mean 2.98	median 0.33 (4 months)	
PICU diagnostic categories:			
Respiratory	60	50%	25.3%
• Bronchiolitis	15	13%	16.7%
• Pneumonia	6	5%	7.5%
• Congenital Diaphragmatic Hernia (CDH)	15	13%	
• Acute Respiratory Distress Syndrome (ARDS)	2	2%	
Cardiac	12	10%	24.8%
Neurological	14	12%	7.0%
• Traumatic Brain Injury	4		
Sepsis/GIT/Renal	27	23%	
Trauma/Burns/Analgesia	7	6%	4.2%
• Burns	4		
Surgery	60	50%	
Duration of Intubation (days)	Mean 8.8	Median (IQR) 4.0 (2.3-5.9)	Median 1.0 **WCH PICU
PICU LOS (days)	Mean 12.1	Median (IQR) 6.4 (4.0-10.0)	Median 3.1 **WCH PICU
Hospital LOS (days)	Mean 38.1	Median (IQR) 20 (11.8-34.0)	
Paediatric Index of Mortality (PIM)	Mean	Median (IQR)	Median
• PIM2 score (%)	6.25	3.08 (0.98-6.27)	
• PIM3 score (%)	5.43	3.19 (0.88-5.97)	1.35**WCH PICU
PICU Outcomes			
• Ward	114	95%	95.6%
• Transferred to another PICU	4	3.3%	1.5%
• Died in PICU	2	1.6%	2.5%

*Notes: *The Australian & New Zealand Paediatric Intensive Care (ANZPIC) registry report (2016) contains pooled data from 28 hospitals. **Hospital specific data for the Women's and Children's Hospital PICU was calculated for duration of intubation and length of stay (LOS) in 2016.*

The study cohort contained 59.2% males, which was similar to the PICU population reported in the ANZPIC registry (ANZPIC, 2016), which reported 57.1% males. However, the age group was younger in the cohort, with a significantly higher representation of patients less than one month old (33.3% versus 9.2%). The most common diagnostic category in the cohort was respiratory (50%), followed by sepsis/GIT/renal (23%), neurological (12%), cardiac (10%), then trauma/burns/analgesia (6%). This represented a higher proportion of respiratory and lower proportion of cardiac patients. The reason for the low percentage of cardiac patients in the cohort can be explained because the majority of cardiac patients were transferred to another PICU for cardiac surgery prior to sedation weaning, excluding them from the study. 50% of the patients in the cohort had a surgical procedure preceding or during their PICU stay.

The duration of intubation demonstrated a skewed data set, due to an outlier with a prolonged duration of intubation and mechanical ventilation. The median duration of intubation was 4.0 days, with an interquartile range (IQR) of 2.3 to 5.9 days. The baseline PICU length of stay (LOS) and hospital LOS data for the cohort were similarly skewed. The median PICU LOS was 6.4 days (IQR 4.0-10.0), and the median hospital LOS was 20 days (IQR 11.8-34.0). When compared to all PICU admissions in 2016, the cohort were intubated longer (median 4.0 versus 1.0 day), had a longer PICU LOS (median 6.4 versus 3.1 days), and an increased Paediatric Index of Mortality (PIM3) (median 3.19 versus 1.35). These results suggest the cohort represents a relatively sicker group of PICU patients.

4.4 Incidence of withdrawal syndrome

The research problem was that many patients transferred from PICU to the ward were at risk for developing withdrawal syndrome but these patients were not routinely being screened for withdrawal symptoms. There was a written PICU guideline for opioid tapering and withdrawal assessment. As per the guideline, patients that received high dose opioids or opioids for five days were to be tapered and have withdrawal assessment once per shift. The Finnegan Neonatal Abstinence Score (NAS) was the withdrawal assessment tool used by the clinical team prospectively. In the cohort studied, there were 55 patients that received opioids for at least five days. The results showed that in practice the NAS was used in 34 patients, representing 62% adherence to the guideline.

From the chart audit, the clinical team had documented and treated for withdrawal syndrome in 46 of the 120 patients (38%), termed ‘clinical withdrawal’ in table 3. However, 86 of the 120 patients (i.e. the majority of patients) did not have a withdrawal assessment score completed by the clinical team. To determine the “true” incidence of withdrawal syndrome, the researcher applied a retrospective withdrawal assessment tool, using the observations and symptoms documented in the medical records. The validity of the Sophia Observation of withdrawal Symptoms (SOS) scale for the retrospective assessment of withdrawal syndrome in PICU patients has previously been established (Ista et al, 2013). The SOS scale was applied

retrospectively to define the presence of withdrawal syndrome in the cohort. The retrospective SOS scale results demonstrated that clinically significant symptoms of withdrawal syndrome were present in 73 of 120 patients (61%), defined by SOS ≥ 4 (as per criteria outlined in 3.6.2). Therefore, the retrospective SOS scale results found 28 (possible) missed cases of withdrawal syndrome that were not screened for withdrawal by the clinical team.

Table 3: Incidence of Withdrawal Syndrome using the SOS scale

	SOS Withdrawal +ve	SOS Withdrawal -ve	Total
Clinical withdrawal +ve	45	1	46
Clinical withdrawal -ve	28	46	74
Incidence of withdrawal syndrome	73	47	

Notes: Clinical withdrawal +ve = withdrawal syndrome was documented in the medical record by the clinical team; SOS withdrawal +ve = SOS ≥ 4 (criteria in 3.6.2) SOS = Sophia Observation of withdrawal Symptoms scale (Appendix C).

The sensitivity and specificity were calculated for the clinical team's withdrawal screening, using the results obtained from the SOS withdrawal assessment scores. Compared to the retrospective SOS score, the clinical team's diagnosis of withdrawal syndrome had a sensitivity of 61.8% and a specificity of 97.9%. The positive predictive value (PPV) was 97.8% that a patient had withdrawal syndrome when there was documentation by a clinician. However, the negative predictive value (NPV) was only 62% that a patient without any documentation regarding withdrawal did not have withdrawal syndrome.

The incidence of withdrawal syndrome in the SEESAW study cohort was 61% (73 of 120 patients) as defined by the SOS score results. This included 45 cases of withdrawal syndrome that had been identified by the clinical team and 28 cases of withdrawal syndrome that were undiagnosed. After obtaining the primary result, the next part of the analysis involved comparing patients with SOS withdrawal present to those without withdrawal syndrome, to determine which factors (independent variables) were associated with the development of withdrawal syndrome.

4.5 Univariate analysis of medication factors associated with withdrawal syndrome

4.5.1 Prescribing patterns

Examining the medications administered during the study period, fentanyl and morphine were the only opioids delivered by continuous infusion. Fentanyl was the most commonly prescribed opioid (72 vs 44 patients). Looking at prescribing patterns for sedative infusions, midazolam was most frequently administered (84 patients), with dexmedetomidine and propofol both used less often (15 and 16 patients respectively). The combinations of medications administered in the cohort included 25 patients that received an opioid infusion with no sedative, 3 patients

that received a sedative infusion with no opioid, 71 patients received an opioid infusion plus one sedative infusion, and 20 patients received two or more sedative classes in addition to an opioid.

Table 4: Proportions of patients receiving various opioid analgesics and sedative combinations, comparing incidence of withdrawal

	Total	Withdrawal present	Withdrawal absent	diff	p value
N (%)	120	73 (61%)	47 (39%)		
Opioid < 24 hours	4	0	4	- 4	
Opioid ≥ 24 hours	116	73 (63%)	43 (37%)	+ 30	
Opioid only	25	12 (48%)	13 (52%)	- 1	
One Opioid (≥ 24 hours continuous infusion)					
morphine	33	15 (45%)	18 (55%)	- 3	
fentanyl	59	39 (66%)	20 (34%)	+ 19	RR 1.5 (CI 0.96-2.2) p = 0.07
Single (sub-total)	92				
Two opioids rotated (≥ 24 hours continuous infusion)					
Both opioids (morphine and fentanyl)	24	19 (79%)	5 (21%)	+ 14	
By primary opioid type, includes one and two opioids					
morphine	44	24 (55%)	20 (45%)	+ 4	
fentanyl	72	49 (68%)	23 (32%)	+ 26	
Sedative only	3	0	3 (100%)	- 3	
Sedative combinations (≥ 24 hours continuous infusion)					
midazolam	84	58 (69%)	26 (31%)	+ 32	
midazolam only	1	0	1 (100%)	- 1	
midazolam + morphine	29	14 (48%)	15 (52%)	- 1	
midazolam + fentanyl	35	29 (83%)	6 (17%)	+ 23	
midazolam + both opioids	19	15 (79%)	4 (21%)	+ 11	
dexmedetomidine	15	10 (67%)	5 (33%)	+ 5	
propofol	16	9 (56%)	7 (44%)	+ 2	
By number of sedatives (≥ 24 hours continuous infusion)					
Opioid + 1 sedative	**71**	**47 (66%)**	**24 (34%)**	+ 23	
midazolam	64	44 (69%)	20 (31%)	+ 24	
dexmedetomidine	2	2 (100%)	0	+ 2	
propofol	5	1 (20%)	4 (80%)	- 3	
Opioid + 2 sedatives	**19**	**14 (74%)**	**5 (26%)**	+ 9	
Opioid + 3 sedatives	**1**	**1 (100%)**	**0**	+ 1	
Muscle relaxed	47	38 (81%)	9 (19%)	+ 29	

Notes: N = absolute number, RR = relative risk, CI = 95% confidence interval, p = level of statistical significance. Data was included for analysis if the medication was administered continuously for ≥ 24 hours. One patient received a combination of analgesic and sedatives but no single medication was administered for ≥ 24 hours. When two opioids were rotated, the 'Primary opioid' was defined by the opioid with the highest dose administered in PICU.

4.5.2 Opioid type

The univariate results compared opiate types administered, finding an association between fentanyl and the subsequent development of withdrawal syndrome. 39 of 59 patients (66%) that received fentanyl developed withdrawal, compared to 15 of 33 (45%) that received morphine (see table 4). Comparing patients that received fentanyl to those that received morphine (but not both), the relative risk (RR) of developing withdrawal was 1.5 (95% CI 0.96-2.20) for patients that received fentanyl (Appendix F. Table 15).

4.5.3 Sedative classes

When comparing the type of sedative infusion administered and the subsequent development of withdrawal syndrome, 58 of 84 patients (69%) that received midazolam developed withdrawal, compared to 10 of 15 (67%) that received dexmedetomidine, and 9 of 16 (56%) that received Propofol (see table 4). However, these differences were not statistically significant (Appendix F. Table 16).

4.5.4 Opioid and sedative combinations

Examining the combinations of opioid and sedatives, table 4 shows the incidence of withdrawal increased as the number of sedative classes per patient increased. 47 of 71 patients (66%) that received an opioid infusion plus one sedative infusion developed withdrawal syndrome, compared to 14 of 19 (74%) that received two sedative classes in addition to an opioid, and 1 of 1 (100%) that received three sedative classes. Similarly, the incidence of withdrawal increased with the number of opioids used. 59% of patients that received one opioid developed withdrawal, compared to 79% of patients that received both fentanyl and morphine (on rotation, not concomitantly).

4.5.5 Opioid dose and duration

The initial univariate analysis compared the medians of the two groups using the Mann-Whitney U test, defined by the binary dependent variable, withdrawal present or absent. The average (mean) opioid infusion rate, the peak opioid daily infusion rate, and the cumulative opioid dose were all increased in the withdrawal present group, and these results were all statistically significant (see table 5). Patients that developed withdrawal had received opioids for a median 6.2 days (IQR 3.8-11.9 days) compared to a median of 2.9 days (IQR 2.0-4.7 days) in patients that did not develop withdrawal ($p = 0.001$) (see table 5).

The preliminary results showed that patients with withdrawal had received higher doses of opioids and for a longer duration.

Table 5: Opioid doses and duration comparison for patients with clinically significant withdrawal present and withdrawal absent.

By primary opioid	Total	Withdrawal present	Withdrawal absent	Mann-Whitney U test
morphine	N = 44	N = 24 (54%)	N = 20	
Average infusion rate (mcg/kg/hr)	30 (19.3-49.9)	41 (25.1-72.3)	22 (17.2-30.3)	p = 0.015* U=373,z=2.4,r=0.36
	*Fentanyl equiv***	*0.6** (0.4-1.1)*	*0.3** (0.2-0.4)*	
Peak daily infusion rate (mcg/kg/hr)	43 (25.7-96.9)	78 (31.5-96.9)	32 (20.7-50.6)	p = 0.001* U=402,z=3.1,r=0.47
	*Fentanyl equiv***	*1.2** (0.5-1.5)*	*0.5** (0.3-0.8)*	
Cumulative dose (mg/kg)	3.0 (1.2-9.3)	6.8 (3.3-13.8)	1.7 (0.7-2.6)	p = 0.001* U=448,z=4.1,r=0.62
	*Fentanyl equiv***	*0.1** (0.05-0.2)*	*0.03**(0.01-0.04)*	
DURATION (days)		4.9 (3.9-9.1)	3.3 (1.7-3.7)	p = 0.001*
fentanyl	N = 72	N = 49 (67%)	N = 23	
Average infusion rate (mcg/kg/hr)	1.9 (1.0-2.8)	2.0 (1.5-3.0)	1.0 (0.8-2.1)	p = 0.006* U=822,z=2.7,r=0.32
Peak infusion rate (mcg/kg/hr)	3.3 (2.1-5.0)	3.7 (2.6-4.8)	1.9 (1.1-2.8)	p = 0.002* U=912,z=3.9,r=0.46
Cumulative dose (mg/kg)	0.2 (0.1-0.5)	0.3 (0.1-0.5)	0.1 (0.05-0.1)	p = 0.001* U=983,z=4.6,r=0.54
DURATION (days)		5.4 (3.3-9.6)	2.4 (2.0-4.7)	p = 0.002*
All opioids	N = 116	N = 73	N = 43	
DURATION (days)	Median (IQR)	6.2 (3.8-11.9)	2.9 (2.0-4.7)	p = 0.001*

*Notes: Reported as: Median (IQR); IQR = interquartile range; N = number of patients in each group; Non-parametric comparison of medians using Mann-Whitney U test; *statistical significance level = p < 0.05; U = Mann Whitney U value, z =standardised test statistic, r = effect size, where 0.1 = small, 0.3 = medium, 0.5 = large (Cohen, 1988).*
***To calculate and compare opioid doses, morphine was converted to the fentanyl equivalent dose. Morphine and Fentanyl dose equivalence formula used: Morphine (mcg) x 0.015 = fentanyl (mcg) equivalent dose (Franck, Naughton & Winter, 2004; Faculty of Pain Medicine, 2015).*

4.5.6 Sedative dose and duration

The patients that received a sedative by continuous infusion for at least 24 hours were similarly analysed using the Mann-Whitney U test, comparing the medians between the withdrawal present and absent groups. For patients that received midazolam, the average (mean) infusion rate (41 vs 24 mcg/kg/hr), the peak daily infusion rate (63 vs 32 mcg/kg/hr), and the cumulative dose (4.1 vs 1.1 mg/kg) were all increased in the withdrawal present group, and these results were statistically significant (see table 6). Comparing the duration of the midazolam infusion between the two groups, this was similarly increased in the withdrawal present group

(median 4.0 vs 2.2 days) (p = 0.001). The results demonstrated that patients with withdrawal had received a higher dose of midazolam and for a longer duration.

Table 6: Sedative doses and duration comparison for patients with clinically significant withdrawal present and withdrawal absent.

	Total	Withdrawal present	Withdrawal absent	p value
midazolam (>= 24 hours infusion)	**N = 84**	**N = 58 (70%)**	**N = 26 (30%)**	
Mean infusion rate (mcg/kg/hr)	31 (20-52)	41 (26-60)	24 (14.5-32)	p = 0.001* U=1099,z=3.5,r=0.4
Peak infusion rate (mcg/kg/hr)	48 (28-80)	63 (31-89)	32 (21-51)	p = 0.002* U=1047,z=3.0,r=0.3
Cumulative dose (mg/kg)	2.5 (1.4-7.1)	4.1 (1.9-7.4)	1.1 (0.6-1.7)	p = 0.001* U=1234,z=4.9,r=0.5
DURATION (days)	3.5 (2.2-5.8)	4.0 (2.2-6.3)	2.2 (1.0-3.1)	p = 0.001* U=1123,z=3.8,r=0.4
dexmedetomidine (>= 24 hours infusion)	**N = 15**	**N = 10 (67%)**	**N = 5 (33%)**	
Average infusion rate (mcg/kg/hr)	0.8 (0.5-1.2)	0.6 (0.5-1.0)	1.2 (0.6-1.4)	p = 0.18
Cumulative dose (mg/kg)	41 (17-96)	41 (14-96)	41 (19-314)	p = 0.66
DURATION (days)	2.2 (1.7-4.0)	2.6 (1.9-4.0)	1.6 (1.2-10.0)	p = 0.23
CLONIDINE TAPERING	N = 17	N = 14	N = 3	
PROPOFOL (>= 24 hours infusion)	**N = 16**	**N = 9 (56%)**	**N = 7 (44%)**	
Average infusion rate (mg/kg/hr)	2.0 (1.5-2.6)	1.6 (1.0-2.2)	2.4 (1.9-2.9)	p = 0.04*
Cumulative dose (mg/kg)	75 (61-109)	70 (44-101)	90 (64-141)	p = 0.38
DURATION (days)	1.8 (1.6-2.2)	2.0 (1.1-2.7)	1.6 (1.2-2.1)	p = 0.57
Clonidine (IV intermittent or enteral)				**RR**
yes	N = 55	N = 43 (78%)	N = 12 (22%)	RR 1.7 CI 1.3-2.3
no	N = 65	N = 30 (46%)	N = 35 (54%)	

*Notes: Reported as: Median (IQR); IQR = interquartile range; N = number of patients in each group; Non-parametric comparison of medians using Mann-Whitney U test; *statistical significance level = p < 0.05; U = Mann Whitney U value, z =standardised test statistic, r = effect size, where 0.1 = small, 0.3 = medium, 0.5 = large (Cohen, 1988); RR = relative risk, CI = 95% Confidence Interval.*

The small number of patients in the cohort that received dexmedetomidine or propofol via infusion for at least 24 hours limited the statistical analysis of these sedative groups. Looking at doses, there was no difference when the dexmedetomidine doses were compared between the two groups. This result is consistent with the prescribing guidelines for dexmedetomidine and the narrow therapeutic range. An interesting finding was that patients with withdrawal had received a lower average infusion rate of propofol than patients without withdrawal

(median 1.6 vs 2.4 mcg/kg/hr), which was statistically significant (p = 0.04) (see table 6). Finally, patients with withdrawal had received all sedative classes for longer, however this was not statistically significant for dexmedetomidine or propofol.

Table 7: Descriptive Comparison of differing duration groups of continuous opioid and sedative combinations and their incidence of withdrawal

DURATION		Opioids	Midazolam	Alpha 2 adrenergic agonist	Propofol
1 - < 3 days	N (total)	31	31	10	15
N (%) withdrawal positive		11 (35%)	15 (50%)	7 (70%)	8 (41%)
3 - < 5 days	N	30	29	2	1
N (%) withdrawal positive		19 (63%)	22 (76%)	1 (50%)	1 (100%)
5 - < 9 days	N	24	14	2	0
N (%) withdrawal positive		17 (71%)	13 (93%)	2 (100%)	0
>= 9 days	N	31	10	1	0
N (%) withdrawal positive		27 (87%)	9 (90%)	0	0
Total	N	116	84	15	16
N (%) withdrawal positive		73 (64%)	58 (70%)	11 (67%)	9 (56%)

The table demonstrates that incidence of withdrawal increased as the duration increased, and this was consistent for all opioids and sedative combinations. The proportions of withdrawal in patients in the sedative groups are difficult to interpret because of the opioid combination effect – and the opioid durations often exceeded the sedative durations

4.5.7 Comparison of withdrawal incidence for various opioid infusion durations

Table 7 demonstrates the increase in withdrawal incidence as the duration of opioid infusion increases. Interestingly, for patients that received less than 5 days of opioids, the incidence of withdrawal was 49%. In patients that received opioids for 5 days or greater, the incidence of withdrawal was 80%.

4.6 Multivariate analysis of medication factors associated with withdrawal syndrome

4.6.1 Opioid type, dose and duration

Logistic regression was used to analyse the variables of opioid type (morphine or fentanyl), mean infusion rate, peak infusion rate and duration of opioid infusion, for their association with incidence of withdrawal. To enable multivariate analysis, fentanyl doses were converted to morphine equivalent doses (table 8). In the preliminary modelling it was evident that, once converted, the mean infusion rate was significantly higher for fentanyl than morphine (135 mcg/kg/hr compared to 39 mcg/kg/hr or 3.4 times higher than the mean morphine infusion rate).

Table 8(a): Comparison of fentanyl and morphine doses

Opioid = Fentanyl

Variable	Obs	Mean	Std. Dev.	Min	Max
Mean infusion rate	73	**135.1322**	85.27887	22.17877	494.7775

Opioid = Morphine

Variable	Obs	Mean	Std. Dev.	Min	Max
Mean infusion rate	46	**38.52463**	28.91004	7.593031	172.7553

Notes: Mean infusion rate = mcg/kg/hr; Conversion factor = fentanyl x 66 = morphine equivalent dose. (135mcg/kg/hr morphine = 2.0mcg/kg/hr fentanyl)

Table 8(b): Multivariate analysis of opioid type, dose and duration using logistic regression

Withdrawal	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Mean infusion rate	1.015061	.0047123	3.22	0.001	1.005867	1.02434
Infusion duration	1.089856	.0338147	2.77	0.006	1.025555	1.158188
Morphine(Baseline)						
Fentanyl	.4986443	.2793203	-1.24	**0.214**	.1663344	1.494856
_cons	.3388527	.1393264	-2.63	0.008	.1513636	.7585782

Notes: In the table: variable labels, their Odds ratio, standard errors, the z-statistic, associated p-values, and the 95% confidence interval of the variables.
To explain the model, the results indicate the following:

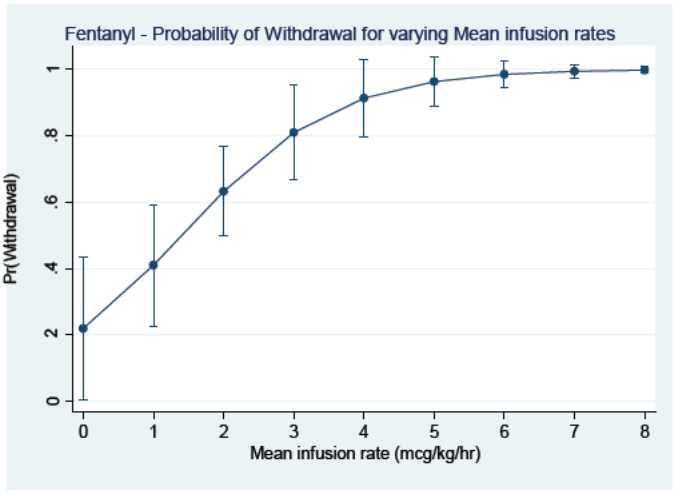
1. *For every 1unit increase in the mean infusion rate, the odds of a withdrawal incidence increased by 1.02.*
2. *For every 1day increase in the infusion duration, the odds of a withdrawal incidence increased by 1.09.*

Both these results were statistically significant. In conclusion mean infusion rate and Infusion duration are all associated with an increased incidence of withdrawal to varying degrees.

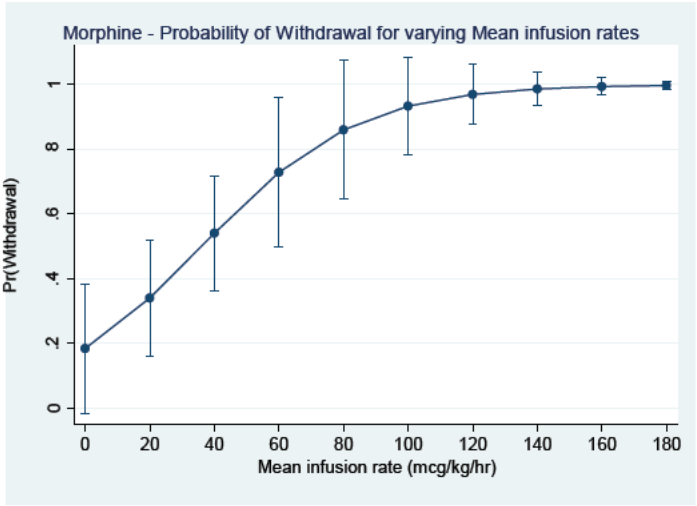
The results from multivariate analysis concluded that the mean opioid infusion rate and the duration of opioid infusion were the variables associated with increased incidence of withdrawal to varying degrees. Therefore, the type of opioid (fentanyl or morphine) was not statistically significant when adjusted for the other variables. To explain, this was due to the fact that a patient on fentanyl was likely to have a high mean infusion rate compared to a patient on morphine. Any effect on the incidence of withdrawal by fentanyl was accounted for by the mean infusion rate (table 8).

4.6.2 Opioid dose

Figure 2: The probability of Withdrawal for varying Mean Opioid infusion rates



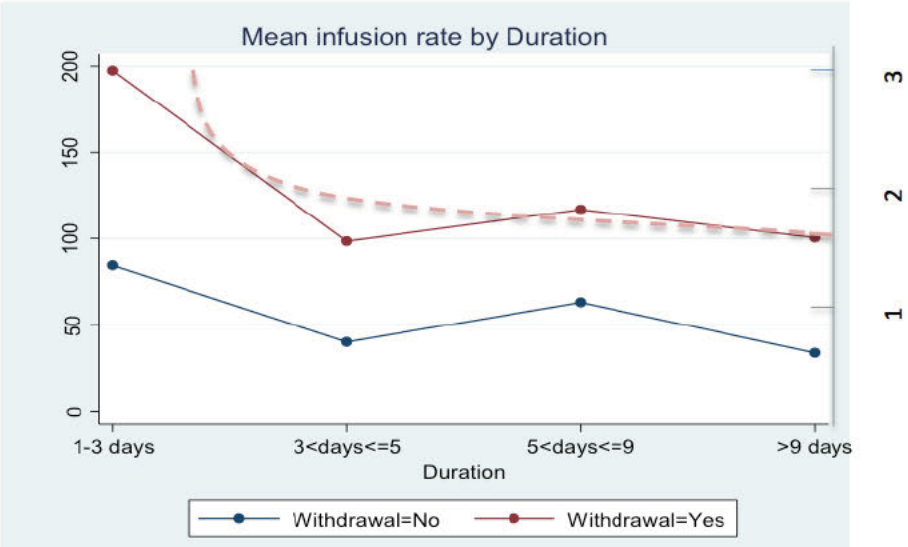
Notes: The graph illustrates that as the mean infusion rate of fentanyl increases, the probability of withdrawal increases. The duration was held constant at 5 days. At a mean infusion rate of 1.5 mcg/kg/hr, the probability of withdrawal is 50%.



Notes: The graph illustrates that as the mean infusion rate of morphine increases, the probability of withdrawal increases. The duration was held constant at 5 days. At a mean infusion rate of 40 mcg/kg/hr, the probability of withdrawal is greater than 50%.

Logistic regression was used to model the probability of withdrawal at increasing mean infusion rates of fentanyl and morphine (see figure 2). The results demonstrated that the probability of developing withdrawal increases when the mean infusion rate increases. The risk of withdrawal reached 50% at a mean infusion rate of 1.5mcg/kg/hr fentanyl and 40mcg/kg/hr morphine. Critical values of 3mcg/kg/hr fentanyl and 80mcg/kg/hr morphine were identified as being greater than 80% predictive of developing withdrawal. Mean infusion rates higher than this approached 100% probability of developing withdrawal.

Figure 3: Opioid mean infusion rates for differing infusion durations, comparing withdrawal positive and negative patients



Notes: Fentanyl converted to Morphine equivalent doses to enable comparison (I.e. Fentanyl dose multiplied by 66) Unit = mcg/kg/hour. The graph demonstrates that the mean opioid infusion rate associated with withdrawal was 3 mcg/kg/hr fentanyl for duration 1 - 3 days. The mean opioid infusion associated with withdrawal decreased as the duration of infusion increased beyond 3 days, as illustrated by the dashed line. Patients that had fentanyl < 1.5 mcg/kg/hr for 1- 3 days or < 1.1 mcg/kg/hr for any duration did not develop withdrawal.

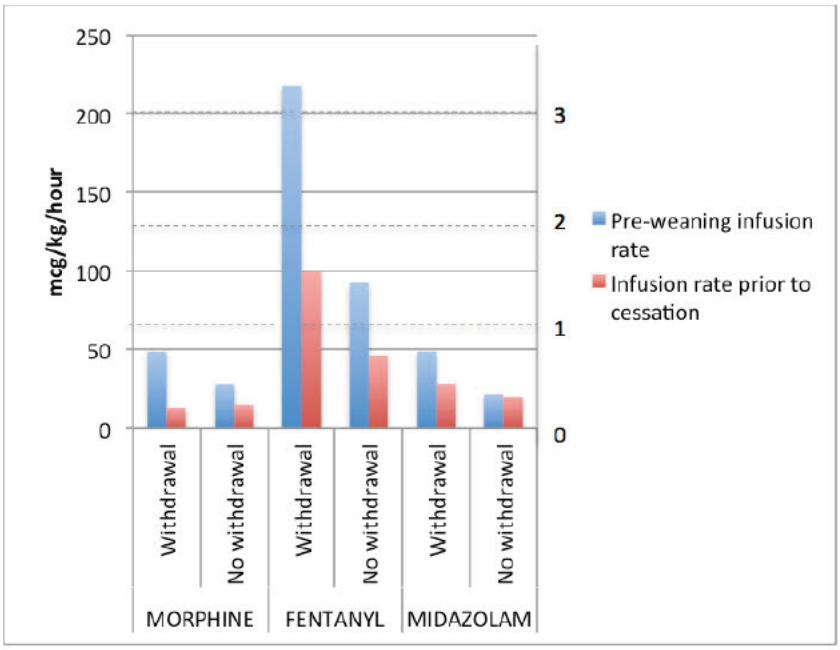
The relationship between dose and duration was further analysed by comparing the mean infusion rates associated with withdrawal for each duration period (1-3 days, 3-5 days, 5-9 days, >9days). The descriptive results (in figure 3) demonstrated that administration of very high mean infusion rates of fentanyl (3 mcg/kg/hr) was associated with development of withdrawal syndrome in patients that had received opioids for less than 3 days. Logistic regression modelling of durations demonstrated that fentanyl was associated with withdrawal at shorter durations than morphine, and at 5 days there was 70% versus 50% incidence of withdrawal (see appendix G).

4.6.3 Midazolam dose and duration

Midazolam was added to the multivariate model in order to determine if there was an association between midazolam and an increased incidence of withdrawal. The multivariate results in this case were inconclusive and difficult to interpret, due to the varying dose combinations of opioids and midazolam received by each patient and the differing durations of each medication. When modelled with morphine there was an association with midazolam's mean infusion rate increasing, but when modelled with fentanyl, there was an association with increased duration of the midazolam infusion. A larger sample size of patients would be required to further understand the effects of dose and duration of midazolam, on the incidence of withdrawal.

4.7 Dose tapering characteristics

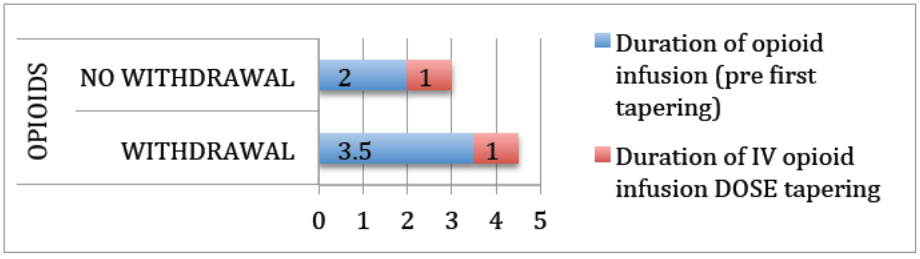
Figure 4: Analysis of dose tapering characteristics of first attempt, comparing the pre-tapering and final infusion rates of opioids and sedatives



Notes: Opioids converted to Morphine equivalent doses to enable comparison.
The graph displays morphine and midazolam mean infusion rates on the left vertical axis and fentanyl mean infusion rate on the right vertical axis.

Exploring the characteristics of the first attempt at opioid dose tapering in the cohort, the patients that developed withdrawal had a higher pre-weaning infusion rate (I.e. 50 mcg/kg/hr morphine and 3 mcg/kg/hr fentanyl, compared to 28 and 1.4 mcg/kg/hr respectively) (figure 4). Despite the higher mean infusion rate prior to tapering, the time spent tapering the dose (1 day) was similar in both groups (figure 5). In the withdrawal group, high doses were typically tapered by 50% initially then stopped over an average tapering period of 24 hours. In the group that developed withdrawal, 30% (22 patients) had their opioid infusion stopped without tapering.

Figure 5: FIRST attempt at opioid dose tapering, showing Duration spent tapering the infusion dose



The graph illustrates the duration (in days) of the opioid infusion showing the proportion of time spent tapering the opioid dose. The dose tapering period was constant in both groups.

For many of the patients in the cohort, the first attempt at opioid and sedative dose tapering was an unstable period. The primary aim of treatment during this period was the weaning of mechanical ventilation and extubation in a timely manner to reduce the patient's time on the ventilator. What the retrospective data showed, however, was that 18 patients failed extubation and required re-intubation. 17 of the patients that failed extubation had clinically significant withdrawal symptoms.

There were 28 patients that had a second opioid dose tapering period, 24 of these were in the withdrawal syndrome group, including 18 patients that were diagnosed with clinical withdrawal by the clinical team. The second dose tapering period was much slower, particularly for the withdrawal group (7.9 compared to 4.0 days) (see figure 6). Following diagnosis of withdrawal syndrome, dose tapering was typically achieved by smaller dose increments of 10% per day.

Figure 6: SECOND attempt at opioid dose tapering, showing Duration spent tapering the infusion dose

The second dose tapering period was much slower, particularly for the withdrawal group.

4.8 Patient factors associated with withdrawal

The chi-squared test and Mann-Whitney U test were used to compare several patient demographic and diagnostic variables for their association with withdrawal. Gender, age and most diagnostic categories did not have an association with withdrawal (see table 9). The main result was that the patients with a higher PIM 3 score (I.e. higher mortality risk, sicker patients) were more likely to have withdrawal. Patients in the sepsis/GIT/renal category were the only diagnostic group that had a statistically significant association with withdrawal ($p = 0.046$).

Table 9: Patient variables associated with withdrawal

Patient Variables		Total cohort	Withdrawal positive	Withdrawal negative	P value
TOTAL	N	**120**	**73**	**47**	
Gender - female	N (%)	49	35 (71%)	14 (29%)	
Gender - male		71	38 (54%)	33 (46%)	0.059
Age (years)	Median	0.3	0.4	0.2	0.348
PICU diagnostic categories					
Respiratory	N (%)	60	33 (55%)	27 (45%)	0.152
Cardiac		12	8 (67%)	4 (33%)	0.69
Neurological		14	7 (50%)	7 (50%)	0.556
Sepsis/GIT/Renal		**27**	**21 (78%)**	**6 (22%)**	**0.046**
Trauma/Burns/Analgesia		7	4 (57%)	3 (43%)	0.814
Surgery					
Yes	N (%)	60	35 (58%)	25 (42%)	
No		60	38 (63%)	22 (37%)	
Paediatric Index of Mortality (PIM 3 score)	**Median (IQR)**	**3.2 (0.9-6.0)**	**3.8 (1.2-6.6)**	**1.3 (0.8-4.7)**	**0.026**

Notes: chi-square tests and Mann-Whitney U test results comparing several patient demographic and diagnostic variables for their association with Withdrawal.

4.9 Impact of withdrawal on patient recovery

4.9.1 Relationship between withdrawal and outcome measures

Kapplar Meier analysis was used to determine the relationship between withdrawal and outcome measures (appendix G). There was no effect on mortality rates. However, withdrawal did significantly delay the patient's recovery. Patients with withdrawal syndrome were intubated longer (4.7 compared to 2.9 days), had a longer PICU length of stay (8.0 compared to 4.7 days) and stayed in hospital longer (23.3 compared to 13.9 days) and these results were all statistically significant (table 10).

Earlier, it was established that patients with higher PIM3 scores (indicating higher mortality risk) and patients with sepsis/GIT/renal diagnoses were more likely to develop withdrawal. Therefore, it follows that patient diagnosis and mortality risk were likely also influencing the length of stay. Cox regression was used to analyse the relative influence of each of the variables: sepsis/GIT/renal diagnostic group, severity of illness (PIM 3 score) and withdrawal on hospital length of stay. Withdrawal was the only variable tested that had a statistically significant influence on hospital length of stay (appendix G). Therefore, taking into account that the sicker patients had more withdrawal, the results suggest that withdrawal had an independent influence on prolonging hospital length of stay.

It should be noted, there may be other factors outside of the three tested that may affect hospital length of stay.

Table 10: Patient Outcomes

OUTCOMES		Total cohort	Withdrawal positive	Withdrawal negative	Difference	P value
SOS score	Mean		5.8	3.3	+ 2.5	
SOS score ≥ 4 (days)	Mean		3.7 days			
Duration of Intubation (days)	Median (IQR)	4.0 (2.3-5.9)	4.7 (3.2-8.8)	2.9 (2.0-3.9)	+ 1.8	p = 0.0003
PICU LOS (days)		6.4 (4.0-10.0)	8.0 (5.5-15.1)	4.7 (3.4-6.7)	+ 3.3	p = 0.0001
Hospital LOS (days)		20 (11.8-34)	23.3 (13.6-38)	13.9 (7.2-27)	+ 9.4	p = 0.003
PICU Outcome						
Ward	N	114	70	44		
Transferred to another PICU	N	4	2	2		
Died in PICU	N (%)	2	1	1		p = 0.742
Hospital Outcome						
Deceased	N (%)	4	2	2		p = 0.549

Statistical significance of outcomes using Kappler Meier analysis, log rank test for equality and chi-squared test (appendix G). Statistical significance level = $p < 0.05$

4.9.2 Withdrawal and clinical deterioration

There was a high incidence of clinical deterioration within 72 hours of sedation being tapered, highlighting this was an unstable period for many patients. This is understandable, considering that many patients were also being weaned from mechanical ventilation and extubated during this time. 91 of the 120 patients had at least one clinical deterioration episode during this period. The incidence of clinical deterioration was higher in patients with withdrawal, 90% of patients with withdrawal syndrome had at least one physiological marker of clinical deterioration recorded, compared to 53% incidence of clinical deterioration in the patients without withdrawal (table 11).

Next, the clinical deterioration was stratified according to severity: i.e. 'mild' if physiological signs were evident, but resolved without treatment; 'moderate' if the clinical deterioration resulted in a change in treatment; and 'severe' if there was organ failure and/or emergency management provided (see table 11). 28 patients had a severe clinical deterioration and 24 of these patients also had symptoms suggestive of withdrawal. The results of logistic regression analysis demonstrated that patients with withdrawal were 5.8 times more likely to have a severe clinical deterioration (OR 5.8, CI 1.8-18.5, p = 0.003) (see appendix G).

Table 11: Association between withdrawal and clinical deterioration within 72 hours of sedation being tapered

		CLINICAL DETERIORATION WITHIN 72 HRS of sedation being tapered		CLINICAL DETERIORATION severity			Logistic regression p value
	Total	NO	YES	MILD	MOD	SEVERE	
Withdrawal negative	47	22	**25 (53%)**	15	6	**4 (16%)**	
Withdrawal positive	73	7	**66 (90%)**	30	12	**24 (36%)**	0.003
TOTAL	120	**29**	**91 (76%)**	**45**	**18**	**28 (23%)**	

CLINICAL DETERIORATION severity	Definition	Examples (Number of patients)
MILD	Clinical deterioration with concern regarding vital signs or symptoms, required medical review +/- investigations, but no change in management	Tachypnoea, increased work of breathing (30) Bradycardia (6) Tachycardia (3) Fever (2) Hypertension (18) Mottled (2)
MODERATE	Clinical deterioration that required medical review and a change in management	Tachypnoea, increased work of breathing with increased oxygen requirement, nasal high flow or cpap commenced (14) Hypertension + antihypertensive (6) Hypotension, hypovolaemic (1) Over-sedated (1) Delirium (1) Abdominal distension (1) Fluid overload (1)
SEVERE	Severe clinical deterioration requiring emergency management	Respiratory Failure, requiring intubation or assisted ventilation (17) Aspiration event, poor airway clearance (3) Abdominal sepsis (1) Cardiogenic shock (3) Hypoglycaemia (1) Life threatening arrhythmia (3) Seizure (no previous history of seizures) (9)

Examining the types of clinical deterioration in the withdrawal group, respiratory failure that required intubation and/or assisted ventilation was the most common severe clinical deterioration, 9 patients had seizures, with no previous history of seizures and 2 patients had serious aspiration events.

To determine the impact of withdrawal on the patient's recovery, adverse events that occurred within 72 hours of the sedation being tapered were analysed for their association with the presence of withdrawal symptoms (table 12). 17 of the 18

patients that failed extubation also had clinically significant withdrawal symptoms identified, and this result was statistically significant (p = 0.001).

Table 12: Adverse events within 72 hours of sedation being tapered

Adverse event	TOTAL	Withdrawal positive	Withdrawal negative	Chi^2 p value
1. Accidental ETT extubation	5	5	0	
2. Any tube dislodged (not ETT)	18	12	6	0.398
3. Post extubation stridor	20	11	9	0.532
4. Failed extubation	**18**	**17**	**1**	**0.001**
5. Unplanned re-admission to PICU within 72 hours	7	6	1	
6. Pressure Areas	13	10	3	0.366
Total	81	61	20	

ETT = endotracheal tube. Extubation = ETT removed. Failed extubation = patient was re-intubated due to respiratory failure within 48 hours. Results of chi squared test, statistical significance level = p < 0.05. Failed extubation was the only adverse event that had a statistically significant association with withdrawal.

4.9.3 Agitation and over-sedation

Looking at the measures of analgesia and sedation adequacy in the total cohort of patients studied, 77% of patients had 'agitation' documented during their period of intubation on an average of 3.5 days/patient and 8% of patients were documented to be 'over-sedated' on an average of 1.4 days. From earlier analyses, the patients that developed withdrawal syndrome had a higher mean opioid infusion rate than the patients that did not develop withdrawal. Interestingly, the patients that received the higher opioid doses had more agitated days per patient (mean 4.8 compared to 2.8 days/patient) and a smaller proportion was reported to be over-sedated (table 13).

Table 13: Agitation and Over-sedation days

Analgesia and sedation factors		Total cohort	Withdrawal positive	Withdrawal negative	Difference
		120	73	47	
Agitated days I & V	N Patients (%) Mean days/pt	93 (77%) 3.5	57 (78%) 4.8	36 (76%) 2.8	+ 2% + 2.0
Agitated days Post Extubation	N Patients (%) Mean days/pt	80 (66%)	52 (71%) 4.5	28 (60%) 2.0	+ 11% + 2.5
Over-sedated days	N Patients (%) Mean days/pt	10 (8%) 1.4	5 (6.8%) 1.4	5 (10.9%) 1.4	- 4.1% 0

4.9.4 Impact of GIT symptoms of withdrawal

Opioid withdrawal is characterised by gastrointestinal symptoms such as nausea, vomiting, abdominal pain, diarrhoea, and uncoordinated suck/swallow that can lead to poor oral intake and enteral feed intolerance (Ista et al, 2009). Reporting on the incidence of feeding difficulties in the cohort, a higher proportion (76% vs 57%) of patients with withdrawal syndrome had poor oral intake or enteral feed intolerance post extubation and this persisted for a longer period (mean 5.5 vs 2.7 days) (see table 14). The documented reasons for the poor oral intake included 'uncoordinated suck' and 'refusing oral intake'. Diarrhoea was another common problem for patients with withdrawal, and 6 patients had persistent diarrhoea that resulted in skin breakdown.

Table 14: Feeding difficulties post extubation

Feeding difficulties		**Total**	**Withdrawal positive**	**Withdrawal negative**	**Difference**
Poor oral intake / enteral feed intolerance (days)	N Patients (%) Mean days/pt	82 (68%)	56 (76%) 5.5	26 (57%) 2.7	+ 19% + 2.8 days
Diarrhoea > 5 days with skin breakdown		7	6	1	

Notes: poor oral intake = oral feeding being attempted but only very low oral intake achieved; enteral feed intolerance = enteral feeds held for 12 hours or more due to vomiting, large aspirates or abdominal distension.

4.10 Enteral and intermittent IV medications used in the prevention and management of withdrawal

4.10.1 Adjunct analgesics

The most common adjunct analgesic received by patients during the study period was paracetamol by intermittent IV or enteral dosing. There was a high variability in the frequency of doses, with regular 6 hourly doses commonly prescribed for patients that were admitted to PICU following elective surgery, and prn doses commonly prescribed in other patients. Other adjunct analgesics used less frequently were ketamine (via continuous IV infusion), tramadol, non-steroidal anti-inflammatory drugs (NSAIDs) and gabapentin.

4.10.2 Prescribing patterns of enteral and intermittent IV taper medications

The prescribing patterns of enteral medications used in opioid and sedative dose tapering were tabulated to enable comparison (table 15). Enteral opioids were administered to 44 of 116 (38%) patients that received opioids for greater than 24 hours. This rate was marginally higher for post-operative patients (25/60 (42%) vs 19/60 (32%)). Enteral diazepam was administered to 29/84 (35%) of patients that received midazolam for greater than 24 hours. Clonidine was administered in

combination with an enteral opioid and/or diazepam in 36 patients and as a sole agent in 19 patients.

56 (77%) of patients with withdrawal symptoms were prescribed an enteral opioid, diazepam and/or clonidine. The most commonly prescribed medication to reduce a patient's withdrawal symptoms was clonidine (43), followed by enteral opioids (33), diazepam (23), chloral hydrate (20) and various anticonvulsant medications (see table 15). Comparing enteral opioids, diazepam and clonidine, there was no difference in the duration of therapy, with all medications administered for an average of 10 days/patient.

Table 15: Summary of enteral and intermittent IV medications administered during analgesic and sedative tapering

TAPER MEDICATIONS		Withdrawal present	Withdrawal absent	Total
		73	47	120
ENTERAL OPIOID	N patients	**33**	11	**44**
	Mean days/patient	**10.8**	5.9	
	Continued > 42 days or on discharge	7	0	
Enteral Opioid type	morphine	13	1	14
	methadone	9	1	10
	oxycodone	16	8	24
	oxycontin	2	2	4
ENTERAL BENZODIAZEPINE				
DIAZEPAM	N patients	**24**	5	**29**
	Mean days/patient	**10.0**	16.6	
	Continued > 42 days or on discharge	2	1	
CLONIDINE	N	**43**	12	**55**
	Mean days/patient	**10.7**	4.6	
	Continued > 42 days or on discharge	1	0	
CHLORAL HYDRATE	N	**20**	3	**23**

4.10.3 Complications of withdrawal treatment

One of the barriers to the successful prevention and management of withdrawal in PICU patients is the concern regarding the safety of prescribing opioid and benzodiazepine medications for non-intubated patients, and particularly for ward patients outside of PICU. In the SEESAW study cohort, the side effects of medications used to treat withdrawal were associated with clinical deterioration in only 5 patients. Exploring these in more detail, 4 patients receiving clonidine had bradycardia, and 1 patient receiving methadone, diazepam and clonidine was over-sedated, with subsequent poor secretion clearance.

4.11 Conclusion

The researcher applied a retrospective withdrawal assessment tool, the SOS scale, using the documented symptoms in patient's medical records. The incidence of withdrawal syndrome in the SEESAW study cohort was 61% (73 of 120 patients) as defined by the SOS score ≥ 4. This included 45 cases of withdrawal syndrome that had been identified by the clinical team and 28 cases of withdrawal syndrome that were undiagnosed. Using the SOS scale results, the groups were split into withdrawal positive and withdrawal negative for statistical analysis.

The first research question was: which factors in the sedation and analgesic management within PICU are associated with an increased incidence of withdrawal? The univariate results showed patients that received fentanyl were more likely to develop withdrawal syndrome than patients that received morphine (RR 1.5 CI 0.96-2.20). However, multivariate analysis showed the effect was dose related. In the cohort studied, the average dose for fentanyl was 3.4 times higher than the average morphine dose. Mean daily infusion rate and duration were the factors influencing withdrawal to varying degrees. Modelling of the relationship showed that patients that received a mean infusion rate of 3 mcg/kg/hr fentanyl or 80 mcg/kg/hr morphine had an 80% risk of withdrawal, largely accounting for those that developed withdrawal after opioids for 1-3 days. After 3 days of opioids, the dose threshold decreased, and a mean infusion rate greater than 1.5 mcg/kg/hr fentanyl or 40 mcg/kg/hr morphine were associated with withdrawal.

In support of hypothesis one, the incidence of withdrawal in the cohort was 49% for patients that had received opioids for less than 5 days. Therefore, there is a risk of developing withdrawal when high doses of opioids are administered for less than 5 days. In support of hypothesis two, the incidence of withdrawal increased as duration of the continuous opioid or sedative increased. Similarly the incidence of withdrawal increased as the mean opioid infusion rate increased. However, with regard to the influence of sedative dose on the incidence of withdrawal, there was insufficient data to support the hypothesis.

The second research question was: is withdrawal associated with poor outcomes for the patient, such as increased clinical complications or prolonged length of stay (LOS) in hospital? Comparing outcomes, the presence of withdrawal was associated with delayed recovery, demonstrated by prolonged PICU and hospital LOS. Patients with higher PIM3 scores (sicker patients) and patients in the sepsis/GIT/renal diagnostic group had higher rates of withdrawal, which likely contributed to increased LOS indirectly, but multivariate analysis revealed withdrawal had an independent influence on LOS. Patients with withdrawal were also 5.8 times more likely to have a severe clinical deterioration (OR 5.8, CI 1.8-18.5, p = 0.003). Therefore, hypothesis three, that untreated withdrawal is associated with increased clinical complications, was supported by the results.

Chapter 5: Discussion

5.1 Introduction

The final chapter provides a discussion of the major findings from the SEESAW study and their significance to clinical practice.

5.2 Restatement of the research problem

The research problem was that more patients transferred from PICU to the ward were at risk for developing withdrawal syndrome but it was not being routinely screened for, nor treated. In addition, some patients had clinically significant withdrawal syndrome, despite having received opioids for less than 5 days, which was uncommon according to the hospital guideline. Outside of PICU, there was limited clinical experience regarding the treatment of withdrawal, and this new 'earlier' withdrawal was puzzling.

A review of the literature found research has expanded in the area, particularly in the assessment of withdrawal using validated withdrawal assessment tools. Of interest, recent studies reported that the incidence of withdrawal in PICU patients had increased in patients that received opioids or sedatives for less than 5 days (de Silva et al, 2016; Duceppe et al, 2018). This highlighted that there were ongoing knowledge gaps in the field regarding the prevention and management of withdrawal syndrome in PICU patients, which would benefit from further study.

The purpose of the SEESAW study was to describe the factors that were associated with increased incidence of withdrawal syndrome in PICU patients and then to analyse if the presence of withdrawal increased the rate of clinical complications or delayed the patient's recovery.

5.3 Summary description of procedures

Using a retrospective cohort study design, the researchers examined the medical records of 120 mechanically ventilated infants and children that were admitted to PICU over a period spanning 2.1 years, from July 1st 2015 until July 31st 2017. The patients were selected based on the inclusion criteria (exposure) of at least 24 hours of continuous opioid or sedative infusion.

The retrospective chart audit provided a mechanism for focussed observation and analysis of the natural setting. This included the natural history of untreated or under-treated withdrawal.

Data collection included the details of all analgesic and sedative medications administered, patient factors, and relevant time periods of intubation, PICU LOS and hospital discharge. Daily records included total opioid / sedation infusion boluses,

agitation episodes, over-sedation, any adverse events, and clinical deterioration details.

All patients were scored once per shift using the "SOS scale", a validated retrospective withdrawal assessment tool, based on the symptoms documented in patient's medical records. The highest SOS score was recorded daily. Clinically significant withdrawal syndrome was defined by SOS ≥ 4 (criteria outlined in 3.6.2). Based on the retrospective SOS ≥ 4 score results, the patients were sorted into two groups of 'withdrawal positive' and 'withdrawal negative' to determine the incidence of withdrawal in the cohort and enable further analysis.

5.4 Major Findings and their significance to clinical practice

5.4.1 Withdrawal Assessment

There was a written PICU guideline for opioid tapering and withdrawal assessment. As per the guideline, patients that received high dose opioids or opioids for five days were meant to have a withdrawal assessment (using the Finnegan NAS score) once per shift. In the cohort studied, 55 patients had received opioids for at least five days, but in practice the NAS was used in 34 patients, representing 62% adherence to the guideline.

After the SOS scale was applied retrospectively, the incidence of withdrawal syndrome in the SEESAW study cohort was 61% (73 of 120 patients) as defined by the SOS score results. This included 45 cases of withdrawal syndrome that had been identified by the clinical team and 28 cases of withdrawal syndrome that were undiagnosed.

Exploring potential barriers to withdrawal assessment within the cohort studied, the NAS withdrawal score (Finnegan, 1990) was designed specifically to assess for withdrawal in neonates, therefore the lack of an appropriate withdrawal assessment tool for older infants and children may have influenced the clinician's decision to use the score. Implementation of a validated paediatric withdrawal assessment tool (e.g. WAT-1 or SOS scale) has the potential to improve the recognition of withdrawal in paediatric patients within PICU and on the general wards.

5.4.2 Withdrawal syndrome incidence, clinical complications and delayed recovery

The retrospective chart audit provided a mechanism for focussed observation and analysis of the natural setting. This included the natural history of untreated or under-treated withdrawal.

The primary outcome of the study was that iatrogenic opioid and sedative withdrawal syndrome had an incidence of 61% within the PICU cohort studied. Putting this into a broader perspective, the incidence of withdrawal represented approximately 6.3% of all PICU admissions during the study period and 18.5% of all mechanically ventilated patients.

Analysing patient outcomes, the presence of withdrawal was associated with delayed recovery, demonstrated by prolonged intubation time, PICU LOS, and hospital LOS. These findings were similar to results from a previous Italian study that showed patients with withdrawal syndrome had increased LOS (Amigoni et al, 2016). Patient factors such as higher PIM3 scores (sicker patients) and sepsis/GIT/renal diagnostic group had higher rates of withdrawal, which likely contributed to the increased LOS indirectly, as in the Italian study. As a point of difference, the multivariate analysis in the SEESAW study revealed withdrawal had an independent influence on hospital LOS when compared to patient's severity of illness. Caution is still required when interpreting, because there could be yet another factor influencing the results that was not being measured.

The retrospective cohort design provided the opportunity to study the natural history of under-treated and untreated withdrawal and the consequences for the patient. The results suggested that patients with withdrawal were 5.8 times more likely to have a severe clinical deterioration (OR 5.8, CI 1.8-18.5, p = 0.003) including a significantly higher risk of failed extubation. Respiratory failure that required re-intubation and/or assisted ventilation was the most common severe clinical deterioration, occurring in 17 patients. The mechanism for respiratory failure is unclear, however it is plausible that the rapid tapering of high dose opioids and/or sedatives prior to extubation may have contributed to the patient's clinical instability.

A previous link between opioid withdrawal and respiratory distress was found in a case series report by Tobias (1997), which described two paediatric patients with stridor and respiratory distress post extubation. Not uncommon, except these patients had no evidence of airway trauma or oedema and the symptoms completely resolved when the opioid infusion was restarted (Tobias, 1997).

Further examining the severe clinical deterioration events in the withdrawal group, nine patients had one or more seizures despite no previous history of seizures. This result supports findings from early studies of babies born to opioid-dependent mothers, with seizures reported in 2-11% of newborns with opioid withdrawal (Zelson, Rubio & Wasserman, 1971; Kandall & Gartner, 1974; Herzlinger, Kandall & Vaughan, 1977). In paediatrics, seizure-like choreoathetoid movements that persisted for up to four weeks were reported in a case series of children after their fentanyl infusion was discontinued (Lane et al, 1991). Exploring how medications used in the treatment of withdrawal can affect outcomes, a systematic review compared enteral opioids to other sedatives for the treatment of opioid withdrawal in newborn infants, and found opioids were more effective in preventing seizures (Osborn, Jeffery & Cole, 2010).

These findings have significance for clinical practice, because the early recognition and treatment of withdrawal syndrome could prevent complications for the patient and decrease their LOS.

5.4.3 Pain as a potential confounding influence

Pain could also be a factor that contributed to clinical instability. There are many symptoms that overlap making it difficult to differentiate pain and withdrawal syndrome retrospectively. Given that only 38% of the patients that had an opioid infusion in PICU were tapered to enteral opioids, the majority of patients in the SEESAW study were not given step-down analgesics, other than paracetamol. These figures suggest that untreated pain may have contributed to the high withdrawal scores and the associated clinical instability.

There is strong evidence that pain negatively affects critically ill patients (Anand, 1993; Lewis et al, 1994). Lewis et al (1994) conducted a systematic review of analgesic treatment on the physiological consequences of acute pain, and reported that adequate analgesia through the use of local anaesthetics and opioids postoperatively generally results in improved cardiovascular function, decreased pulmonary morbidity and mortality, earlier ambulation, and decreased likelihood of deep vein thrombosis. Subsequent research has supported these findings, including a prospective pre and post implementation study that found the implementation of an assessment-driven and standardized pain management protocol improved ICU outcomes (Skrobik et al, 2010).

Opioid tapering (using enteral or intermittent IV dosing) is required for treatment of pain as much as for prevention of withdrawal. In order to distinguish between pain and withdrawal, concomitant pain assessment is recommended.

5.4.4 Effect of GIT withdrawal symptoms on the patient's recovery

Feeding difficulties post extubation were common in the PICU patient cohort studied. The results suggested that more patients with clinically significant withdrawal symptoms had feeding difficulties than patients without withdrawal symptoms (56/73 vs 26/47) and this delayed the establishment of feeds for an average 2.7 days per patient. Evidence to support the association between poor feeding and withdrawal included specific symptoms such as 'uncoordinated suck', a common symptom described in neonatal abstinence syndrome (Finnegan, 1990; Tobias, 2000).

Two multicentre studies in adult ICUs reported that feed intolerance was associated with poor clinical outcomes and prolonged ICU LOS (Gungabissoon et al, 2015; Blaser et al, 2014). The SEESAW study results are consistent with these findings, since patients with withdrawal had both increased feeding difficulties and prolonged LOS. In their review of feeding intolerance within the PICU, Tume & Valla (2018) comment that despite being a commonly cited problem, feeding intolerance in PICU is not well managed and urge clinicians to investigate causes (such as withdrawal syndrome) that may respond to treatment.

Osborne, Jeffery and Cole (2010) reported that the administration of enteral opioids (compared to control) was associated with faster weight gain for neonates with opiate withdrawal, however LOS in hospital was not reduced. Further research is

required in paediatrics to determine if tapering opioids more gradually using IV or enteral routes decreases feeding difficulties and reduces LOS.

5.4.5 What is Clonidine's role?

In the SEESAW study cohort, clonidine was the most commonly prescribed treatment for withdrawal, including 19 patients treated with clonidine as a sole agent. Recent results from multi-centre studies have questioned the effectiveness of clonidine in managing opioid withdrawal syndrome in PICU patients (Best et al, 2016; Amigioni et al, 2016). In the SEESAW study, there was a high incidence of feeding difficulties observed in patients with withdrawal syndrome. It is possible that using clonidine alone to suppress CNS agitation and the autonomic symptoms of opioid or benzodiazepine withdrawal could be only partially treating the syndrome. As a point of interest, clonidine does not reduce feeding difficulties and may even exacerbate these problems since nausea, vomiting, loss of appetite and abdominal pain are all common side effects for patients treated with clonidine (Bryant & Knights, 2011).

Examining the opioid and benzodiazepine tapering guidelines from Franck, Naughton & Winter (2004), the first step is to taper the opioids and sedatives gradually after initiating a withdrawal assessment tool every 4-6 hours. The use of clonidine is suggested for breakthrough withdrawal symptoms as an adjunct to opioid and benzodiazepine tapering (Nicholls & Schaffner, 2016).

5.4.6 Incidence of withdrawal in patients that received opioids for less than 5 days duration

The incidence of withdrawal increased as the duration of opioid infusion increased. However, the median duration of patients with withdrawal of 6.2 days does not give the full story. Looking closer, there was a 49% incidence of withdrawal in patients that received continuous opioids for less than 5 days. Previous research over the past five years (de Silva, 2016; Fisher et al, 2013; Amigoni et al, 2016) has similarly demonstrated an increase in the incidence of withdrawal in patients receiving opioids for less than 5 days. The mounting evidence suggests it is no longer uncommon. The next question is why?

5.4.7 Factors associated with increased Incidence of withdrawal

Initial univariate results showed that patients that received fentanyl were more likely to develop withdrawal syndrome than patients that received morphine (RR 1.5 CI 0.96-2.20). However, multivariate analysis showed the effect was likely dose related. Comparing mean daily infusion rates, the average dose for fentanyl was 3.4 times higher than the average morphine dose. The patients that developed withdrawal received an average mean daily infusion rate of 2.0 mcg/kg/hr fentanyl or 41 mcg/kg/hr morphine. However, similar to the opioid duration, this does not provide the full story.

5.4.8 Opioid dose modelling

A number of authors have provided instructions to guide opioid tapering in order to prevent withdrawal (Nichols & Shaffer, 2016; Tobias, 2000; De Silva et al, 2016; Franck et al, 2008; The Hospital for Sick Children, 2012). An ongoing problem in practice, however, is the lack of a definition of the "high dose" of opioid that is likely to elicit withdrawal symptoms in patients that received opioids for less than 5 days.

To improve understanding in this area, opioid dose modelling was attempted, by modelling the probability of withdrawal at varying mean daily infusion rates, with a fixed duration (5 days). A separate model was developed for fentanyl and morphine.

Using the fentanyl model, administration of fentanyl at 3 mcg/kg/hr was highly predictive of withdrawal (> 80%), and accounted for the majority of patients that developed withdrawal after only 1-3 days. For fentanyl infusions greater than 3 days, there was a 50% risk of withdrawal at 1.5 mcg/kg/hr, and 60% risk at 2 mcg/kg/hr. Therefore, what the dose modelling demonstrated was the "high dose" associated with withdrawal was also related to the duration, with 3 mcg/kg/hr highly predictive for any duration and 1.5 mcg/kg/hr was 50% predictive for developing withdrawal after 3 days duration. Conversely, patients receiving up to 1.1 mcg/kg/hr fentanyl rarely developed withdrawal.

Using the morphine model, administration of 80 mcg/kg/hr was highly predictive of withdrawal (> 80%) at any duration and 50 mcg/kg/hr is associated with 60% risk of withdrawal for a duration of greater than 5 days. Looking at safe doses, mean doses below 40 mcg/kg/hr morphine were rarely associated with withdrawal.

5.4.9 Dose tapering characteristics

The dose tapering characteristics were analysed for the first and second sedation weaning attempts. Patients that developed withdrawal typically had their infusion either stopped suddenly or tapered quickly. The most common dose prior to the first taper was fentanyl 3mcg/kg/hr, weaned over 0 – 24 hours. It was likely that the speed of dose tapering both contributed to patient clinical instability and precipitated withdrawal syndrome. The ventilation weaning strategies and preparation for extubation had a marked influence on sedation weaning.

Patients that required a second dose tapering attempt were typically weaned slowly, at a rate of 10 – 20% per day, which was tolerated without clinical deterioration.

5.4.10 Fentanyl and withdrawal

An association between fentanyl and withdrawal has been previously described and the trend for an increase in withdrawal correlates with an increased use of fentanyl in PICUs worldwide (Kudchadkar et al, 2014). A recent review by Casamento and Bellomo (2019) compared fentanyl to morphine, and concluded there are no clear benefits of fentanyl over morphine. Morphine's histamine release, sedation and respiratory depression are regularly cited (Hughes, McGrane & Pandharipande,

2012), but clinical research has demonstrated that both drugs have similar side effects (Nada & Alabdulkareem, 2018). Fentanyl has a faster onset of action and shorter elimination half-life (Playfor et al, 2006), which is an advantage when a single dose is given. However, administration of fentanyl via continuous infusion leads to a prolonged (context-sensitive) half-life, which does not happen with continuous administration of morphine (Casamento & Bellomo, 2019). Fentanyl is preferred in patients with renal impairment, but at reduced doses due to drug accumulation (Casamento & Bellomo, 2019). Further, fentanyl in high doses is associated with muscle rigidity particularly affecting the chest wall (Tobias, 2000), which is more a contra-indication.

5.4.11 Fentanyl doses – a clue to unravel the mystery

There is a degree of mystery surrounding the relative potency of fentanyl compared to morphine, leading to ongoing confusion amongst PICU clinicians. Most drug references state that fentanyl is "100 x more potent" than morphine (Ostermann et al, 2000), but this refers to a single IV dose (morphine 100-200 mcg/kg vs fentanyl 1-2 mcg/kg). When administered by continuous infusion the conversion of morphine equivalence is "66 x fentanyl dose" (Faculty of Pain Medicine, 2015; Franck et al, 2004). This was the formula used in this study to enable comparison between the 2 opioids, but is strangely not readily available to clinicians. At the Women's and Children's Hospital, the Acute Pain Service has simplified the calculation to "morphine = 50 x fentanyl dose" when prescribing opioid infusions for ward patients, which enables simple mental calculation at the bedside (an extremely important quality for a dangerous drug).

The confusion is not helped by the convention for two different concentrations for fentanyl infusions, the choice depending on whether the patient is mechanically ventilated or not, I.e. 50mcg/kg per 50mls (mechanically ventilated) or 10mcg/kg per 50mls (all other patients). The problem with all of this conflicting information is that currently most PICU clinicians are very confused about what the conversion really is. Taking a recent poll of PICU nurses, most thought the conversion was "10 x fentanyl dose". This finally provided context and an explanation for why patients in the study cohort had their infusion of 2 or 3mcg/kg/hr fentanyl stopped without tapering (thinking it was a low dose) or monitoring for withdrawal. It was also common practice for fentanyl infusions in the study to be routinely titrated in increments of 1mcg/kg/hr fentanyl, which is equivalent to 50 - 66mcg/kg morphine. In comparison, morphine is titrated in 10 mcg/kg/hr increments.

5.4.12 Analgo-sedation

The prevention of excessive doses of sedatives was the motivation for the analgo-sedation trend. A number of authors highlighted that using a sedative to treat pain works poorly, in effect sedating the patient excessively to reduce distress rather than properly addressing pain (Playfor, 2008; Simons & McDonald, 2006). Hence, their advice was to provide adequate opioid analgesia to ensure pain is treated and to keep sedation light. However, another interpretation of analgo-sedation is the

prescription of opioid analgesia (usually fentanyl) in high doses in order to provide analgesia and deep sedation (Farkas, 2016). The problem is that use of opioids in this way exposes the patient to toxic doses that increase the adverse effects and incidence of withdrawal (Anand et al, 2010; Farkas, 2016). It is time to question the benefit.

For the SEESAW study patients, analgo-sedation was being practised, characterized by high doses of fentanyl and minimal use of sedatives. However, despite high doses of opioids, 77% of patients had documented agitation episodes on an average of 3.5 days/patient. It is possible that increased side effects, such as nausea, urinary retention, pruritus, or chest wall muscle rigidity could have played a part. The patients were also at risk of developing hyperalgesia, a condition that occurs when high dose opioids overwhelm the receptors, leading to the enhanced sensation of pain from stimuli (Lee et al, 2011). Any of these side effects have the potential to cause distress for the patient and are far from the original goal of maintaining patient comfort.

5.4.13 Sedatives

During the SEESAW study, the average midazolam infusion rate was 31 mcg/kg/hr, which is low compared to other PICUs. Midazolam mean infusion rates of 200 - 420 mcg/kg/hr were reportedly associated with increased withdrawal in one PICU (Amigoni et al, 2014). This comparison of extremes demonstrates the wide variation in sedation and analgesia practices. From a local perspective, there is room to increase the use of sedatives (such as midazolam, dexmedetomidine or propofol) as an adjunct to opioid analgesia, in order to pre-emptively reduce excessive doses of fentanyl. This is supported by recent clinical guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility and sleep disruption in Adult ICU, which states: “concomitant use of an opioid and sedative infusion results in decreased opioid administration” (Devlin, 2018).

5.5 Study Limitations

The findings of the SEESAW study must be interpreted with caution because of the limitations of the methods. Firstly, the potential confounders (such as severity of illness) were addressed, but it should be noted that there could be other factors influencing the results, apart from those analysed. Secondly, the retrospective withdrawal assessment using the SOS scale was dependent on the available documentation in the medical record, and there is potential for missing data. For example, pain and sedation scores were not routinely documented in the PICU studied. A strategy for differentiating pain and withdrawal was implemented, however untreated pain may have contributed to increased withdrawal scores or influenced the results. Thirdly, the SOS scores may have been influenced by observer bias because the same person collected the medication data and performed the SOS withdrawal score. There were plans for a nurse with a similar experience level to independently repeat the SOS withdrawal scores for a random sample from the

cohort post-hoc, for the purpose of testing the inter-rater reliability of the SOS score results. However, it could not be achieved within the available timeframe.

5.6 Recommendations for future research

At the local PICU level, the priority is to implement strategies to improve the early recognition and management of withdrawal. Research surrounding this could include a Prospective Pre and Post Implementation study of a goal-directed Analgesia, Sedation and Withdrawal Protocol, using validated paediatric scores to assess the PICU patient's pain, sedation and withdrawal.

Considering the common use of opioids in PICU, there is a lack of research comparing different opioids and dose ranges. A prospective randomized, controlled trial (RCT) comparing morphine and fentanyl, or low versus high doses of fentanyl in PICU would be a good start.

There are a number of enteral tapering options that could be evaluated prospectively for their effectiveness, for example:

- Development of guidelines for opioid analgesic step-down
- Comparison of enteral morphine versus enteral morphine plus clonidine for opioid withdrawal

A next logical step would be a study that is focussed on modelling midazolam doses using mean infusion rates and the probability of withdrawal at various doses, including a "safe" therapeutic dose range.

Finally, a priority for the PICU community is to establish a PICU analgesia and sedation clinical network in order to share ideas and combine research efforts.

5.7 Recommendations for practice

From a local perspective, the aim of the SEESAW study was to gain further understanding regarding the factors influencing withdrawal, and to inform the development of a guideline for the prevention and management of withdrawal syndrome. It is apparent from the results, improving the early recognition and treatment of withdrawal is the key to prevent clinical complications and decrease LOS.

Protocolized / goal-directed sedation (to a specific pain and sedation score range) offers a solution for better monitoring of pain and sedation levels in PICU. There is evidence that nurse driven protocols may offer improvements for patients such as reduced pain/agitation and decreased opioid and sedative doses. Advantages include consistency in prescribing, and an algorithm can be developed to assist with decision making regarding dose increases and decreases.

Fentanyl doses were found to be 3.4 times higher than morphine equivalent doses and this was the factor identified to be closely associated with the development of opioid withdrawal. Clearer guidelines for opioid equivalence and dosing for fentanyl are required.

5.7.1 Treatment of withdrawal

Given the high incidence of withdrawal in PICU, and risks of delayed recognition and treatment, a structured strategy for prevention and management of withdrawal is needed. In order to optimally prevent and treat withdrawal, the guidelines developed by Ista et al (2015) were updated to propose the following reasonable practices:

1. Establish weaning protocols.
    i. When dosage or duration thresholds are exceeded:
        (1) Fentanyl high doses > 1.5 mcg/kg/hr;
        (2) Duration > 3 days
    ii. Tapering schedule for IV continuous infusions
    iii. Guide for conversion of IV to enteral medications
2. Selection of a rescue protocol for withdrawal symptoms.
    i. Prn "rescue" medication (can be intermittent IV or enteral)
3. Assessment for withdrawal
    i. Use withdrawal assessment tools validated for use in PICU
    ii. Begin when dose tapering commences

5.8 Conclusion

The retrospective chart audit provided a mechanism for focussed observation and analysis of the natural setting. This included the natural history of untreated or under-treated withdrawal. The results demonstrated that the presence of withdrawal syndrome was associated with increased clinical complications and delayed recovery for patients. The results will be used to inform local practice and develop strategies for the early recognition and management of withdrawal, such as implementing a validated paediatric withdrawal assessment tool and reviewing the tapering methods for opioid analgesics and sedatives.

Of particular interest, multivariate analysis revealed that fentanyl was routinely administered to mechanically ventilated patients in much higher doses than morphine. High mean opioid infusion rates were associated with development of withdrawal. The opioid dose modelling could potentially be used in practice to guide dose tapering and withdrawal screening. Further prospective research is required to determine the relative effectiveness of lower mean infusion rates of fentanyl when caring for mechanically ventilated patients in PICU.

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Appendix A: SEESAW Data collection form

SEESAW data collection tool – version 3

Data Collection Form – PICU sedation and withdrawal study - page 1 (Demographic data)			
Participant number	__ __ __		MR volume/s _____
Gender	Male	Female	
Age			
Diagnosis			
Reason for admission to PICU			
WCH hospital admission episode	Admission Date Time	Discharge Date Time	
Hospital discharge code	Home	Transferred to another hospital	Deceased
PICU/PHDU admission episode -1	Admission Date Time	Discharge Date Time	
PICU/PHDU discharge code - 1	Ward transfer	Transferred to another hospital	Deceased
Multiple PICU/PHDU episodes during the study period?	PICU Admit - 2 Date time	PICU Discharge - 2 Date time	Yes – how many? No
	PICU Admit - 3 Date time	PICU Discharge - 3 Date time	
Endotracheal Intubation (location)	Start (1) (2) (3) (4)	Finish (1) (2) (3) (4)	ANZPIC intubation hours
Opioid or sedative exposure prior to this PICU admission	Yes	No	If yes, specify details: Medication Dose/50ml Mls delivered Start / stop dates + times

Data Collection Form – PICU sedation and withdrawal study - page 2 (Medications)								
Participant number __ __ __	Day	Day	Day	Day	Day	Day	Day	Notes / Totals
Date								
Weight								
Opioid medication type								**Record times infusion started and stopped**
Dose (mg in 50ml)								
Infusion rate (ml/hr)								
Bolus doses/day								Total number of boluses
Total infusion/day (ml)								
procedural doses								(additional to infusion)
Sedative medication (1)								**Record times infusion started and stopped**
Dose (mg in 50ml)								
Infusion rate (ml/hr)								
Bolus doses/day								Total number of boluses
Total infusion/day (ml)								
procedural doses								(additional to infusion)
Sedative medication (2)								**Record times infusion started and stopped**
Dose (mg in 50ml)								
Infusion rate (ml/hr)								
Bolus doses/day								Total number of boluses
Total infusion/day (ml)								
procedural doses								(additional to infusion)
Adjunct infusion								**Record times infusion started and stopped**
Infusion rate (ml/hr.)								
Bolus doses/day								
Total infusion/day (ml)								
Other analgesics Paracetamol (P) NSAIDS (NS); Tramadol (T); Gabapentin (G)								**Record number of doses**
Other sedatives Chloral hydrate (CH)								
Anti-emetic								
Muscle relaxant								Number of doses
Tapering commenced?								Record time
Method of tapering used IV/oral, type and % decrease								
Morphine/Methadone/Oxy								circle
Diazepam								Regular / prn
Clonidine								

Data Collection Form – PICU sedation and withdrawal study - page 3 (Assessment)															
Participant number __ __ __	Day		Day		Day		Day		Day		Day		Day		Notes / Totals
Date															
Surgery															Tick
Chest drain															Tick
Invasive procedures															list
Intubated & Ventilated															Tick & Record time intub /extub page 1
Ventilation details															
Weaning ventilation															
Planning for extubation															
Night / Day shift	N / Day		N / D		N / D		N / D		N / D		N / D		N / D		
PICU MO or APS - Sedation target															
Pain															pain score + description
Sedation / Activity Level															sedation score + description (see abbreviations)
Sleep															
Reason for boluses															Use codes from KEY
Episodes of agitation															Tick if present
Over-sedation															
Hypertension															
Seizure															
Feeding details															0-Nil, 1-minimal, 2-grading up, 3-full oral intake
Poor Feeding / intolerance															y/n describe
"Withdrawal" documented															
Withdrawal (FNAS) score															Current PICU score
Rescue for agitation or withdrawal															Use codes from KEY Record all
Retrospective SOS score:															total
• Tachycardia															15% above baseline
• Tachypnoea															15% above baseline
• Fever															38.3 and above
• Sweating															
• Grimacing															frequent yawning /sneezing/hiccups
• Agitation															irritable/restless/ agitated/ fidgety
• Inconsolable crying															unable to distract or console
• Anxiety															panicky/scared /withdrawn
• Tremors															spontaneous or with movement
• Motor disturbance															muscle jerks / twitching
• Increased muscle tension															clenched fists / toes, or limbs stiff
• Sleeplessness															less than 1 hour at a stretch
• Hallucinations															
• Vomiting															x1 in 4 hour period
• Diarrhoea															
notes															

Data Collection Form – PICU sedation and withdrawal study - page 4 (complications)							
Participant number	Day	Day	Day	Day	Day	Day	Day
Date							
Unplanned ETT extubation							
Failed extubation							
Post extubation stridor							
Unplanned removal of any invasive tube							
Re-admission to PICU/PHDU within 72 hours							
Pressure area							
Clinical deterioration : 1) Tachycardia 2) Bradycardia 3) Hypertension 4) Hypotension 5) Fever > 37.5 6) Poor perfusion / mottled 7) Tachypnoea 8) Low respiratory rate 9) Apnoea 10) Respiratory distress 11) Hypoxaemia – SaO2 less than 90% 12) Aspiration 13) Seizures **14) Death** **15)** Other **(Record details)**							

KEY

Reason for boluses:

A	Painful procedures / dressings / suction / physio	**F.**	Clinically unstable :
B	Care interventions i.e. turns/nappy change		**i.** High ICP
C	Fighting / splinting against the ventilator		**ii.** Tachycardic
D	Agitated / restless		**iii.** Hypotensive
E	Pain		**iv.** Hypertensive
			v. Hypoxaemic
			vi. Low ventilated tidal volumes
			vii. Tachypnoeic

Rescue used for agitation or withdrawal: (record all)

1	Panadol	10	Chloral hydrate
2	Increase IV opioid infusion rate	11	PRN clonidine
3	IV opioid bolus	12	Start regular clonidine
4	PRN Oral opioid medication	13	IV sedation bolus
5	regular Oral opioid medication	14	Increase IV sedation infusion rate
6	PRN adjunct analgesia - tramadol	15	PRN Oral diazepam
7	ketamine	16	regular diazepam
8	comfort measures	17	Muscle relaxed
9	Reduce dose tapering	18	Other

Appendix B: Finnegan Neonatal Abstinence Scale (NAS)

PAEDIATRIC AND NEONATAL DRUG WITHDRAWAL SCORING SYSTEM	*PATIENT LABEL* UR NO: SURNAME: GIVEN NAMES: D.O.B: SEX:

NO.	SIGNS	SCORE			
		0	1	2	3
1	Tremors (muscle activity of limbs)	Normal	Minimally increased when hungry or disturbed	Moderate or marked increase when undisturbed– subside when fed or held snugly	Marked increase or continuous even when undisturbed, going onto seizure-like movements
2	Irritability (excessive crying) Confusion	None	Slightly increased	Moderate to severe when disturbed or hungry	Marked even when undisturbed
3	Reflexes	Normal	Increased	Markedly increased	***weaning protocol**
4	Stools	Normal frequency	Explosive, but normal	Explosive, more than 8/day	Commenced on: Date:
5	Muscle tone	Normal	Increased	Rigidity	Time:
6	Skin abrasions	No	Redness of knees & elbows	Breaking of the skin	Starting Dose:
7	Respiratory	<55	55-75	76 and above	
8	Repetitive sneezing	No	Yes	**SCORE EVERY 2 TO 4 HOURS CONSIDER INTERVENTION IF SCORE CONSISTENTLY >8**	
9	Repetitive yawning	No	Yes		
10	Vomiting/nause	No	Yes		
11	Fever/sweating	No	Yes		

DATE & TIME / SIGN NUMBER													
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													
11													
TOTAL													

Appendix C: SOS - Sophia Observation withdrawal Symptoms – scale

SOS – Sophia Observation of withdrawal Symptoms scale

Start SOS withdrawal scoring from the first day of dose tapering (weaning) in patients who have received opioids +/- sedation (Benzodiazepines or alpha 2 adrenergic agonists):

- by infusion at high doses: Fentanyl > 1.5 mcg/kg/hr, Morphine > 40 mcg/kg/hr, or Midazolam > 60 mcg/kg/hr ; or
- by infusion for > 3 days

Continue scoring until 72 hours after the last dose.
Score 4 hourly routinely, if symptomatic (SOS ≥4), score hourly until resolved. Stretch to 8 hourly if scoring consistently 0 - 1.

Instructions:

Evaluate for the previous 4 – 8 hour period (or since last SOS score).
Tick box if symptom present.
If SOS withdrawal score is ≥4, then iatrogenic withdrawal syndrome is possible – inform M.O. and consider rescue +/- re-evaluate tapering plan for opioids and sedatives.

	Date											
	Time											
	AUTONOMIC DYSFUNCTION											
1	Tachycardia *15% above baseline*											
2	Tachypnoea *15% above baseline*											
3	Fever *> 38.3 C*											
4	Sweating											
	CENTRAL NERVOUS SYSTEM IRRITABILITY											
5	Agitation *irritable, restless, agitated or fidgety*											
6	Anxiety *eyes wide open & eyebrows raised, or behaviour is panicky or withdrawn*											
7	Tremors *spontaneous, with movement, or in response to stimuli*											
8	Motor disturbance *Any muscle twitching or jerking – ie. involuntary movement of forearms, lower legs, face, head.*											
9	Increased muscle tension *Clenched fists or tense legs / toes*											
10	Inconsolable Crying (>5 minutes) *Consoling/ reassurance / offering food or distraction (includes silent crying if intubated)*											
11	Grimacing											
12	Sleeplessness *only sleeps for short periods up to1 hour at a stretch*											
13	Hallucinations *Child seems to see hear or feel things that are not there*											
	GASTRO-INTESTINAL DYSFUNCTION											
14	Vomiting / gagging											
15	Diarrhoea											
	Count ticked boxes (0-15) TOTAL											

(Ista E, de Hoop N, Tibboel D, Duivenvoorden & Van Dijk M, 2013)

Appendix D: PROCEDURE MANUAL

SEESAW study – Data collection

INSTRUCTIONS for data collection

1. Obtain casenotes for auditing:

- The casenotes, which are ready for auditing, are being stored in the CN's office in the trolley near the door.
- When the data collection is completed for a set of casenotes, please leave them aside for Katrina (CN's office - in the tray near the computer/filing cabinet)
- Kat will complete a final check, and then the casenotes will be returned to the trolley next to Lynn McDonald's desk.

2. Check the master list from ANZPIC database for the name and corresponding PICU admission. Tick on the left side of the name.

3. Check the admission summary for details that may indicate if the patient can be included or excluded from the study:

PICU admission is within the retrospective study period = 1/7/2015 to 31/12/2017

Inclusion criteria:

- Paediatric patients 0 – 18 years
- Intubated and ventilated
- Opioid Analgesia and/or sedation for 24 hours or more

Exclusion criteria

- If control of seizures is the primary reason for admission.
- Tracheostomy – if the trachy was present on admission or was inserted prior to weaning from analgesia/sedation.
- > 42 days opioid/sedation prior to enrolment / PICU admission date.

4. Complete the "Patient Enrolment record"

- Enrolled (yes or no) based on the inclusion/exclusion criteria.
- If no – record the reason for exclusion
- If yes – allocate a study participant number. Check the study allocation number list to allocate the next in the series.
- Use the study participant number on the data collection form.
- Document the medical record volume number.

Data collection

- Start the data collection from the time of ETT intubation.
    - Record the date & time intubated and extubated
    - If prior to PICU, check the pre-hospital or pre-PICU information to find this.
- Stop at 72 hours after the last dose of opioid or sedative medication.
    - Maximum of 42 days;
    - Stop if the patient dies or the decision to withdraw life-sustaining treatment is made (may be excluded from statistical analysis of withdrawal prevalence if this prevented sedative tapering);
    - Stop when the patient is transferred to another hospital or discharged (may be excluded from statistical analysis of withdrawal prevalence if this prevented assessment during sedative tapering).

Demographic data – page 1

Gender – male / female (circle)
Age
Diagnosis – record acute and chronic conditions

- Eg. Bronchiolitis, RSV +ve.

Reason for admission to PICU/PHDU (may be the same as the diagnosis in many cases)

- E.g. Respiratory failure.

WCH hospital admission episode = record admission and discharge date and time
Hospital Discharge code – Home / Died / Transferred to another hospital (up/down transfer)

- Circle correct response

PICU/PHDU admission episode = record PICU/PHDU admission and discharge date and time
PICU/PHDU discharge code – Ward / Died / Transferred to another hospital (up/down transfer)

- Circle correct response

Endotracheal intubation = record date and time of intubation and extubation
Opioid or sedative exposure prior to this PICU admission

- If yes, provide details:
- For data before intubation, record the medications that the patient was prescribed prior to intubation (eg. Current medications = Methadone 10 mg BD).
- For data after intubation, be specific: (Eg. Medstar: propofol 5mg for intubation, fentanyl @ 2mcg/kg/hr for 2 hours during transport).
- If admitted to another hospital and intubated for a number of days, then this data should be entered in the daily records, starting from the first day of intubation

The right hand column is not completed during data entry. These values will be calculated when the data is entered into the XL Database:

LOS – in days
Intubated days

Medications – page 2

Record dose (IV infusions):

- Morphine = mg in 50ml
- Fentanyl = mcg in 50 ml
- Midazolam = mg in 50ml
- Dexmedetomidine = mcg in 50ml
- Ketamine = mg in 50 ml
- Propofol = 10mg/ml neat solution

(if different than this – record information so that mg/ml or mcg/ml can be worked out)
Record the total number of boluses per day (mls per bolus – not required)
Record the total infused = mls per day

- If the dose (syringe concentration) was changed during the day –
    - record the time of the change
    - record the mls infused of each concentration

Record any procedural doses (that were not accounted for in the infusion total above, e.g. separate IV doses given for intubation, in OT)

For entering into the XL database only:

- *Calculate the total daily dose (mg)*
- *Calculate the total daily dose per kg (mcg/kg/day) = divide the total daily dose (in mcg) by weight*
- *Calculate the mean daily dose (mcg/kg/hr) = divide the above value by 24 (or by the total hours delivered if less than 24)*

Record other analgesics and sedative adjuncts used (each day). Record number of doses, and if prn or regular.

- Paracetamol
- NSAIDS
- Gabapentin
- Tramadol
- Chloral Hydrate

DOSE TAPERING

Record dose tapering method = oral / IV
Record the oral medication used and dose (e.g. oral morphine 0.5mg 6/24)

- Morphine
- Methadone
- Ms contin (oxycontin)
- oxycodone
- Diazepam
- Clonidine

Record percentage of dose tapering and timing (every day – alternate days – every 2nd day)

ASSESSMENT – page 3

Record the medical plan for sedation / analgesia, if there is one documented.

Record the sedation assessment from the "CNS" or "neuro" section in the nursing and/or medical documentation for both night / day shift, if available.
Use only abbreviations provided.
If there were 2 day shifts record both.

If a pain score or sedation score is used record the lowest and highest number recorded.

For the boluses, record (1) the number of boluses per day and (2) any reason provided that the bolus/es were given. Use the KEY provided (on page 4 of the data collection tool). There may be more than one:
KEY:

A. Painful procedures / suction / physio / dressings
B. Care interventions ie. nappy changes
C. Fighting / splinting against the ventilator
D. Agitated / restless
E. Pain
F. Clinically unstable
    i. High ICP
    ii Tachycardic
    iii Hypotensive
    iv Hypertensive
    v Hypoxaemic
    vi Low ventilated tidal volumes
    vii Tachypnoeic

Abbreviations List:

abbreviation	for
Fent	Fentanyl
Morph	Morphine
Midaz	Midazolam
M&M	Morphine & Midazolam
prop	Propofol
ket	ketamine
CH	Chloral hydrate
dexmed	Dexmedetomidine
P	paracetamol
G	gabapentin
T	tramadol
NGT	Nasogastric tube
FD	Free drainage
sed	sedated
OpEs	opens eyes
MsLs	Moves limbs
spont	spontaneously
wi	with
intvn	interventions
sett	settled
btw	between
approp	appropriate
tol	tolerated

Withdrawal assessment

Withdrawal assessment: record all 3

1. The PICU withdrawal score - 'Paediatric and Neonatal Drug Withdrawal Scoring System' (FNAS score) was used -

- Record lowest and highest score per shift.
- If FNAS score not documented, leave blank.
- If FNAS score 0, record "0"

2. Reference to the patient experiencing 'withdrawal' was documented in the patient's medical record,

- Tick "withdrawal" documented

3. The withdrawal symptoms as documented using the 'Sophia Observation of Withdrawal Symptoms (SOS) scale':

- Tick for all symptoms present in one shift
- Once per Day and once per night shift
- Start when tapering of opioids / sedatives commenced and continue until 72 hours after the last dose of opioids / sedatives are tapered

Record the SOS score by ticking the boxes if any of the symptoms are present. This is fully dependent on the information provided in the observation chart and case-note entries. Only use the information documented. Do not add your own opinion.

Record the details of the "Rescue" used for agitation or withdrawal

Rescue used for agitation or withdrawal: (record all)

1	Panadol	10	Chloral hydrate
2	Increase IV opioid infusion rate	11	PRN clonidine
3	IV opioid bolus	12	Start regular clonidine
4	PRN Oral opioid medication	13	IV sedation bolus
5	regular Oral opioid medication	14	Increase IV sedation infusion rate
6	PRN adjunct analgesia - tramadol	15	PRN Oral diazepam
7	ketamine	16	regular diazepam
8	comfort measures	17	Muscle relaxed
9	Reduce dose tapering	18	Other

During the opioid/sedative infusion period and dose tapering thereafter, record if there are documented episodes of:

- Pain
- Agitation
- Seizures
- Hypertension
- Over-sedation – i.e. Heavily sedated / unresponsive
- Poor feeding / feeding intolerance
- Oral intake

Sedation-related complications – page 4

Were any of these Complications present? (Tick)

1. Unplanned ETT extubation
2. Failed extubation
3. Post extubation stridor
4. Unplanned removal of any invasive tube
5. Re-admission to PICU/PHDU within 72 hours (unplanned)
6. Clinical deterioration
    a) Tachycardia
    b) Bradycardia
    c) Hypertension
    d) Hypotension
    e) Fever
    f) Poor perfusion / mottled
    g) Tachypnoea
    h) Apnoea
    i) Low respiratory rate
    j) Respiratory distress
    k) Hypoxaemia – SaO2 less than 92%
    l) Increased oxygen
    m) Aspiration
    n) Seizures
    o) death
    p) Other
7. Pressure area

Record details the clinical deterioration here, along with any extra information that is relevant for each day but could not be filled in elsewhere.
E.g. Hypoxaemia ticked, notes = SaO2 to 80s

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3rd May 2018

Ms K Welbing
Dept of Paediatric Critical Care Medicine
WCHN

Dear Ms Welbing

Re: The SeeSAW study. A retrospective cohort Study Exploring Existing Sedation, Analgesia and Withdrawal management in a Paediatric Intensive Care Unit (PICU). Audit 1018A/5/2021.

The above audit application was considered by the WCHN Human Research Ethics Committee at its meeting on 2nd May 2018. The Committee considered that the public interest in the study outweighed any privacy concerns and approved the audit.

Approval is given for three years only. If the audit is more prolonged than this, an extension request should be submitted unless there are significant modifications, in which case a new submission may be required. Please note the expiry date in the title above and include it in any future communications. If a report is written on the above audit, please provide a copy to the Committee.

Please note that the WCHN HREC does not in general provide approval for non-WCHN staff or students to have access to identifiable patient information without patient consent. If now, or in the future, and **following specific WCHN HREC approval**, the audit involves students or non-WCHN staff, the following institutional requirements must be met:

a. **Department for Communities and Social Inclusion (DCSI) *Child related employment screening.*** The DCSI *Child related employment screening* are to be provided to the WCHN Human Resources Department for verification (telephone 81617249 for further information) and copies forwarded to the Ethics Committee. Applications for a DCSI Record Check are lodged through the Australia Post Office, the below link has more details:
http://www.dcsi.sa.gov.au/services/screening/what-kind-of-screening-do-I-need

b. **Confidentiality Agreements**. If the project involves patients/clients/staff of WCHN or their personal information, signed Confidentiality Agreements are to be provided for all students and non WCHN staff to the Committee who will be involved in the project. Please refer to
http://www.wch.sa.gov.au/research/committees/humanethics/ConfidentialityAgreement.html

Where non-WCHN staff or students are involved in the audit, that person or those persons must execute a WCHN Confidentiality Agreement. This requirement applies to all non-WCHN staff and students involved in the audit at any time in the future.

If the students and non-WCHN staff on this project are subsequently involved on other projects approved by the Committee, a copy of the DCSI Record Check will need to be re-sent to the Committee and a Confidentiality Agreement signed for each specific project.

Yours sincerely,

TAMARA ZUTLEVICS (DR)
CHAIR
WCHN HUMAN RESEARCH ETHICS COMMITTEE

Government of South Australia
SA Health

ResearchMaster

32991 : New Application The SEESAW study. A retrospective cohort Study Exploring Existing Sedation, Anal...
Application Status: **Accepted**
Workflow State: **Finalised**
Other Forms: Human Research Ethics Approval Notification v1

Review Outcome

This page provides the outcome of the reviews by the Human Research Ethics Secretariat and Insurance Office.

Outcome of Review of Notification Form:

Accepted: The University of Adelaide has accepted this notification of Human Research Ethics Committee approval(s).
The University of Adelaide's involvement will be indemnified by The University of Adelaide's insurance(s).

Table 16: 2 x 2 Cross-tabulation to determine the relative risk of withdrawal between patients that received fentanyl or morphine (but not both).

	SOS ≥4 Withdrawal present	SOS ≥4 Withdrawal absent	Total	RR (CI)
Fentanyl	39	20	59	1.5 (0.96 – 2.20)
Morphine	15	18	33	
Total	54	38		p = 0.07

Table 17: 2 x 2 Cross-tabulation to determine the relative risk of withdrawal between patients that received (1) midazolam or dexmedetomidine, (2) midazolam or Propofol, and (3) dexmedetomidine or propofol.

	Withdrawal present	Withdrawal absent	Total	RR (CI)
Midazolam	58	26	84	0.94 (0.76-1.32)
Dexmedetomidine	11	4	15	
Total	69	30		p = 0.73

	Withdrawal present	Withdrawal absent	Total	RR (CI)
Midazolam	58	26	84	1.2 (0.78-1.93)
Propofol	9	7	16	
Total	67	33		p = 0.38

	Withdrawal present	Withdrawal absent	Total	RR (CI)
Dexmedetomidine	11	4	15	1.3 (0.77-2.21)
Propofol	9	7	16	
Total	20	11		p = 0.32

Table 18: Opioid doses and duration comparison for patients with withdrawal present and withdrawal absent.

Primary opioid		withdrawal	no withdrawal
morphine			
average dose (mcg/kg/hr)	Mean (± SD) Median (IQR)	47.5 (± 33.9) 40.9 (24.9-72.2)	27.8 (± 16.7) 22.0 (16.8-30.3)
highest dose (mcg/kg/hr)	Mean (± SD) Median (IQR)	95.9 (± 77.7) 78.0 (40-129)	40.7 (± 26.9) 32.3 (19-60)
cumulative dose (mg/kg)	Mean (± SD) Median (IQR)	16.4 (± 34.0) 6.8 (3.3-13.6)	4.0 (± 9.9) 1.7 (0.7-2.4)
DURATION (days)	Mean (± SD) Median (IQR)	11.6 (± 12.1) 6.7 (4.0-10.3)	5.1 (± 9.0) 3.3 (2.1-3.8)
fentanyl			
average dose (mcg/kg/hr)	Mean (± SD) Median (IQR)	2.3 (± 1.3) 2.0 (1.4-2.9)	1.5 (±1.0) 1.0 (0.8-2.1)
highest dose (mcg/kg/hr)	Mean (± SD) Median (IQR)	4.6 (± 2.6) 4.0 (2.6-5.3)	2.4 (±1.7) 2.0 (1.1-2.7)
cumulative dose (mg/kg)	Mean (± SD) Median (IQR)	0.5 (± 0.4) 0.3 (0.2-0.6)	0.1 (±0.1) 0.1 (0.06-0.2)
DURATION (days)	Mean (± SD) Median (IQR)	10.6 (± 10.8) 5.9 (3.7-12.3)	5.0 (±5.9) 2.7 (2.0-5.6)
Single opioid			
morphine			
average dose (mcg/kg/hr)	Mean (± SD) Median (IQR)	37.0 (± 20.9) 32.5 (19.5-44.8	26.6 (± 16.8) 21.8 (16.0-30.3)
highest dose (mcg/kg/hr)	Mean (± SD) Median (IQR)	67.4 (± 46.6) 50.9 (31.5-96.9)	36.0 (± 22.0) 30.0 (18.7-42.6)
cumulative dose (mg/kg)	Mean (± SD) Median (IQR)	8.6 (± 11.2) 6.0 (2.6-8.2)	3.9 (± 10.4) 1.3 (0.6-2.3)
DURATION (days)	Mean (± SD) Median (IQR)	10.0 (± 11.0) 4.9 (3.9-9.1)	5.1 (± 9.5) 3.3 (1.7-3.7)
fentanyl			
average dose (mcg/kg/hr)	Mean (± SD) Median (IQR)	2.4 (± 1.4) 2.1 (1.5-3.0)	1.6 (± 1.0) 1.4 (0.8-2.1)
highest dose (mcg/kg/hr)	Mean (± SD) Median (IQR)	4.2 (± 2.3) 3.7 (2.6-4.8)	2.5 (± 1.8) 1.9 (1.1-2.8)
cumulative dose (mg/kg)	Mean (± SD) Median (IQR)	0.4 (± 0.5) 0.3 (0.1-0.5)	0.1 (± 0.1) 0.1 (0.05-0.1)
DURATION (days)	Mean (± SD) Median (IQR)	9.4 (± 10.4) 5.4 (3.3-9.6)	3.1 (± 1.8) 2.4 (2.0-4.7)
Both opioids - morphine + fentanyl			
average dose (mcg/kg/hr)	Mean (± SD) Median (IQR)	1.5 (± 0.9) 1.1 (0.8-2.1)	0.7 (± 0.3) 0.7 (0.4-0.9)
highest dose (mcg/kg/hr)	Mean (± SD) Median (IQR)	4.1 (± 3.1) 3.5 (2.0-5.1)	1.6 (± 0.5) 1.7 (1.4-2.1)
cumulative dose (mg/kg)	Mean (± SD) Median (IQR)	0.5 (± 0.6) 0.3 (0.2-0.6)	0.2 (± 0.2) 0.2 (0.1-0.2)
DURATION (days)	Mean (± SD) Median (IQR)	15.0 (± 12.4) 10.6 (6.8-16.7)	12.7 (± 9.6) 7.6 (7.5-21.9)
Combined data			
DURATION OPIOIDS (days)	Mean (± SD) Median (IQR)	11.0 (± 11.2) 6.2 (3.8-11.9)	4.9 (±7.4) 2.9 (2.0-4.7)

Table 19: Dose Tapering

Opioid / Sedative type		Withdrawal present	Withdrawal absent	Difference
morphine				
Pre-weaning infusion rate (mcg/kg/hr)	Median (IQR)	48.5 (30-80)	27.9 (20-41.3)	
Infusion rate prior to cessation (mcg/kg/hr)		13.0 (9.6-46.2)	14.8 (10-21.2)	
fentanyl				
Pre-weaning infusion rate (mcg/kg/hr)		3.3 (2.3-4.6)	1.4 (0.9-2.6)	
Infusion rate prior to cessation (mcg/kg/hr)		1.5 (0.6-3.3)	0.7 (0.3-1.0)	
DURATION OPIOIDS				
Duration – prior to first tapering		3.5 (2.4-5)	2.0 (1.5-3)	
Duration of first tapering		1.0 (0-4)	1.0 (0-2)	
Total duration		6.2 (3.8-11.9)	2.9 (2.0-4.7)	
Tapering opioids as per protocol?	**yes** **no**	**21** **52**	**32** **14**	
midazolam				
Pre-weaning infusion rate (mcg/kg/hr)		48.6 (28.7-78.0)	21.5 (17.5-47)	
Infusion rate prior to cessation (mcg/kg/hr)		28.0 (12.8-49.1)	20.0 (10.6-37)	
DURATION midazolam				
Duration – pre tapering		3 (2-4.7)	2 (1-2.7)	
Duration of tapering		1.0 (0.0-2.0)	0.0 (0-1)	
Total duration		3.7 (2.2-6.3)	2.0 (1.0-3.1)	

Appendix G: Multivariate analysis

The SEESAW study

Logistic regression

Analyses factors in the sedation and analgesic management within PICU that is associated with increased incidence of withdrawal

The logistic regression analyses the following four variables and their association with the incidence of withdrawal:

1. Mean infusion rate
2. Infusion duration
3. Type of Opioid (Fentanyl or Morphine)
4. Peak infusion rate

The Mean infusion rate and Peak infusion rate were adjusted by the type of Opioid (Fentanyl dose x 66 = Morphine dose).
The Mean infusion rate for the two Opioid types once the dose adjustment has been made is as follows:

```
Opioid = Fentanyl

    Variable     |        Obs       Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
Meaninfusionrate |         73    135.1322    85.27887   22.17877   494.7775

Opioid = Morphine

    Variable     |        Obs       Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
Meaninfusionrate |         46    38.52463    28.91004   7.593031   172.7553
```

This indicates the Mean infusion rate mcg/kg/hr was significantly higher for Fentanyl than Morphine, once dosage has been adjusted.

The results for this first run of the logistic regression are as follows:
Note: Peak infusion rate was found to be not statistically significant once adjusted for other variables in the model and hence was dropped from the model.

```
Logistic regression                                     Number of obs     =        119
                                                        LR chi2(3)        =      26.75
                                                        Prob > chi2       =     0.0000
Log likelihood = -66.021407                             Pseudo R2         =     0.1684

------------------------------------------------------------------------------
             Withdrawal | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------------+-----------------------------------------------------------------
       Meaninfusionrate |   1.015061   .0047123     3.22   0.001     1.005867    1.02434
       Infusion duration |   1.089856   .0338147     2.77   0.006     1.025555   1.158188
       Morphine(Baseline)
                Fentanyl |   .4986443   .2793203    -1.24   0.214      .1663344   1.494856
                   _cons |   .3388527   .1393264    -2.63   0.008      .1513636   .7585782
------------------------------------------------------------------------------
```

In the table we see the variable labels, their Odds ratio, standard errors, the z-statistic, associated p-values, and the 95% confidence interval of the variables.
The results indicate the following:

3. For every 1unit increase in the mean infusion rate, the odds of a withdrawal incidence increased by 1.02.
4. For every 1day increase in the infusion duration, the odds of a withdrawal incidence increased by 1.09.

Both these results are statistically significant.
The type of Opioid (Fentanyl or Morphine) is not statistically significant when adjusted for the other variables. This is likely due to the fact, a patient on Fentanyl is likely to have a high Mean infusion rate compared to a patient on Morphine. Any effects on the Withdrawal by Opioid type are accounted for by the Mean infusion rate.
In conclusion Mean infusion rate and Infusion duration are all associated with an increased incidence of withdrawal to varying degrees.

Results split by Opioid Type

The logistic regression will now analyse the "Mean infusion rate" and "Infusion duration" for their association with the incidence of withdrawal by each of the two Opioid Types.

For this analysis the Mean infusion rate is not adjusted for Fentanyl as we are analysing each Opioid separately.

Fentanyl

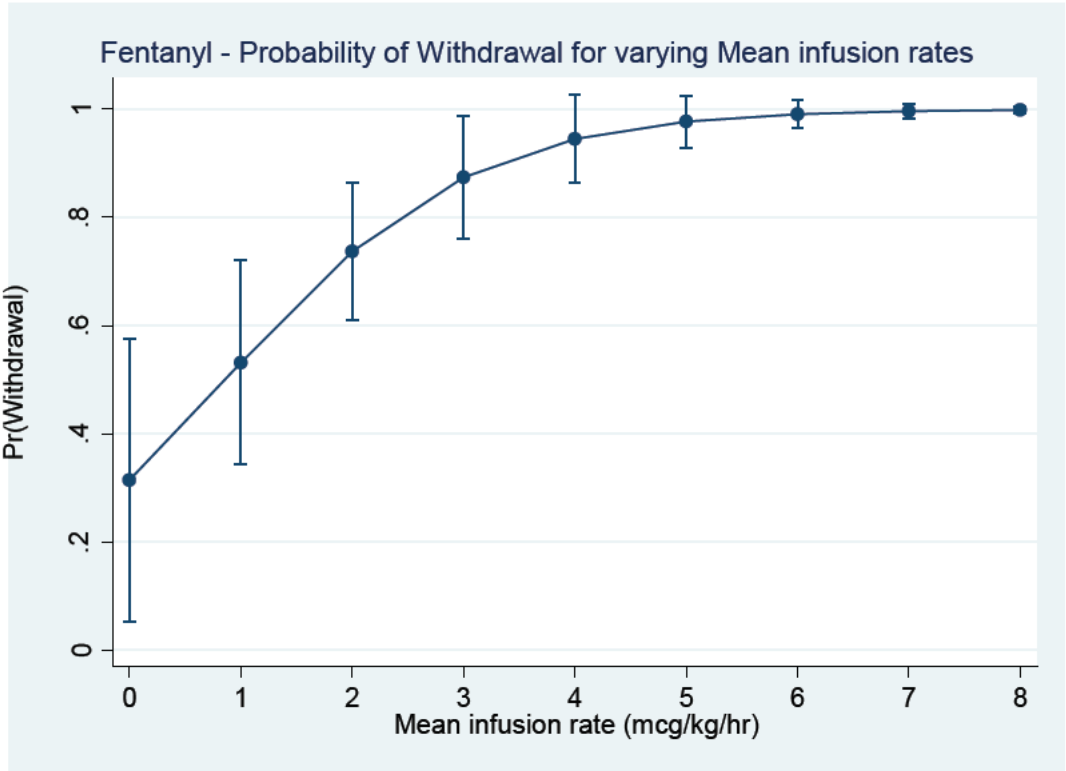
```
Logistic regression                                 Number of obs     =         73
                                                    LR chi2(2)        =      19.11
                                                    Prob > chi2       =     0.0001
Log likelihood = -36.675714                         Pseudo R2         =     0.2067

------------------------------------------------------------------------------
       Withdrawal| Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-----------------+------------------------------------------------------------
Meaninfusionrate |    2.47294   .7757526     2.89   0.004     1.337195     4.57333
Infusion duration |   1.139196   .0597445     2.48   0.013     1.027917    1.262523
           _cons |   .1463518   .1094425    -2.57   0.010      .033796    .6337679
------------------------------------------------------------------------------
```

The results indicate the following:

1. For every 1unit increase in the mean infusion rate, the odds of a withdrawal incidence increased by 2.47.
2. For every 1day increase in the infusion duration, the odds of a withdrawal incidence increased by 1.13.

Figure 7: Probability of withdrawal for varying Mean infusion rates - fentanyl

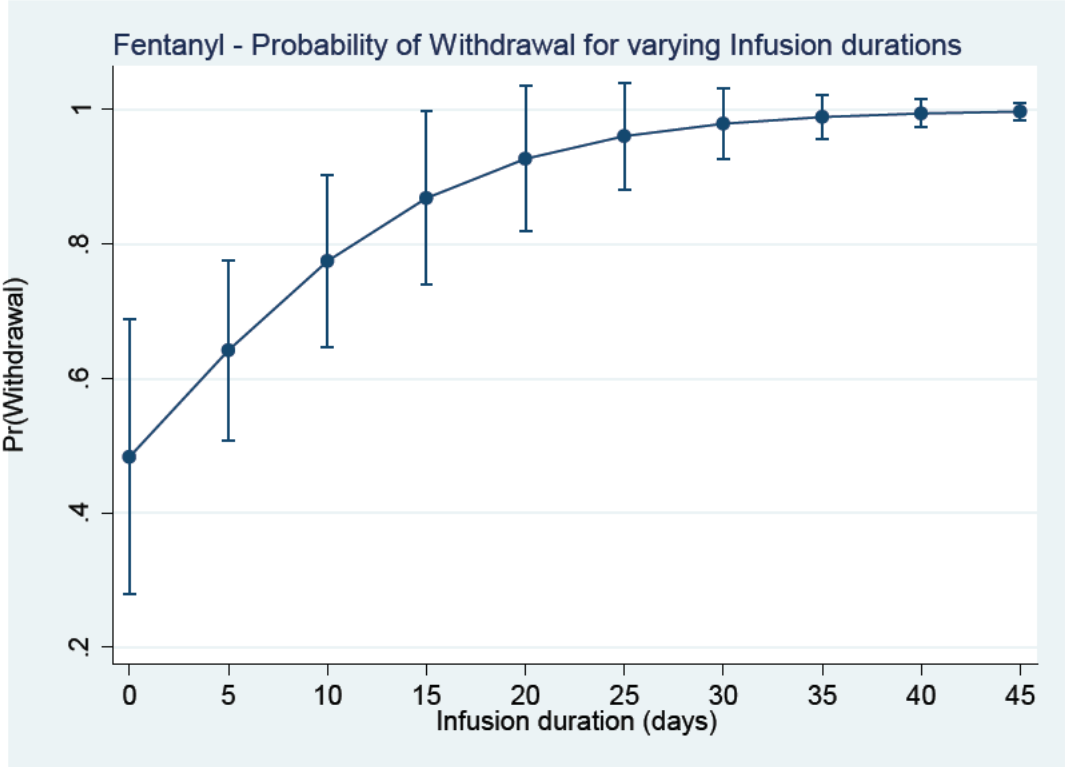
The probability of Withdrawal for varying Mean infusion rates is shown below. This graph assumes the Infusion duration is held constant at its mean of 8.75 days.



The graph illustrates that as the mean infusion rate increases, the probability of withdrawal increases. At a mean infusion rate of 3 mcg/kg/hr, the probability of withdrawal is greater than 80%.

Figure 8: Probability of withdrawal for varying infusion durations - fentanyl

The probability of Withdrawal for varying Infusion durations is shown below. This graph assumes the Mean infusion rate is held constant at its mean of 2.04 mcg/kg/hr.



The graph illustrates that as the Infusion duration increases, the probability of withdrawal increases. At an Infusion duration of 15 days, the probability of withdrawal is greater than 80%. **Morphine**

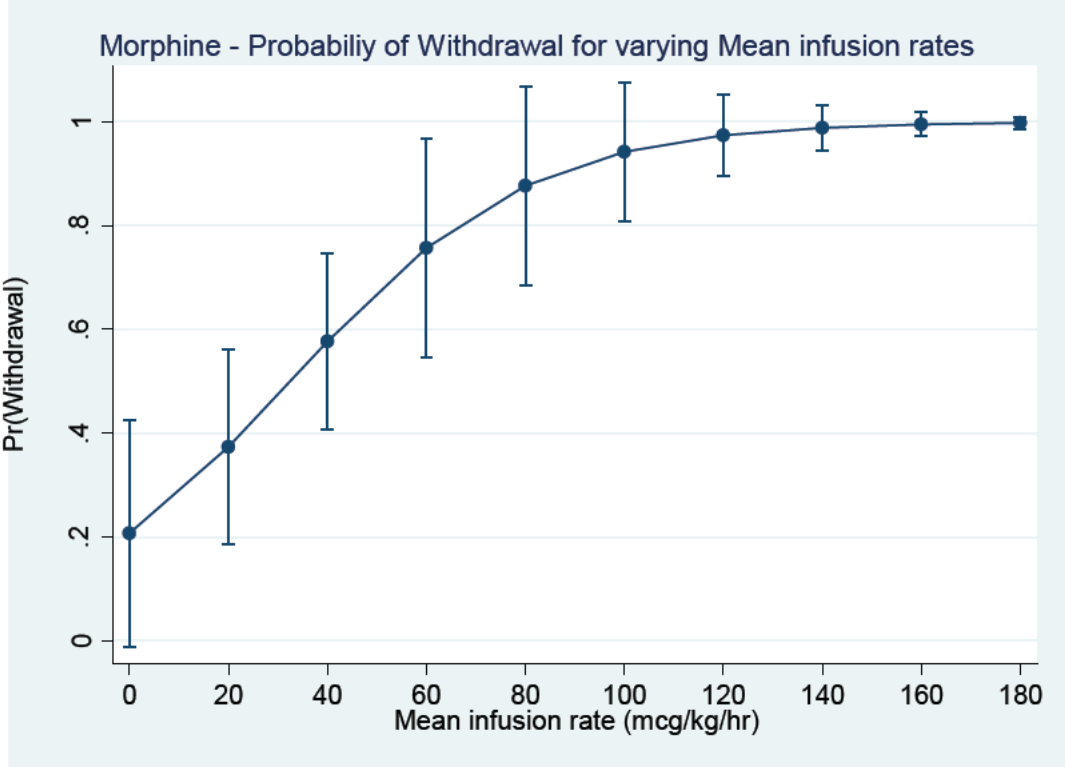
```
Logistic regression                                     Number of obs     =         46
                                                        LR chi2 (2)       =       9.75
                                                        Probee > chi2     =     0.0076
Log likelihood = -26.968214                             Pseudo R2         =     0.1530

------------------------------------------------------------------------------
       Withdrawal | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------+-----------------------------------------------------------
Meaninfusionrate |   1.042165   .0186342     2.31   0.021     1.006275    1.079335
Infusion duration |     1.0407   .0388614     1.07   0.285     .9672534    1.119723
           _cons |   .1848337   .1324364    -2.36   0.018     .0453818    .7528022
------------------------------------------------------------------------------
```

The results indicate the following:

1. For every 1unit increase in the mean infusion rate, the odds of a withdrawal incidence increased by 1.04.
2. For every 1day increase in the infusion duration, the odds of a withdrawal incidence increased by 1.04.

Figure 9: Probability of withdrawal for varying Mean infusion rates - morphine

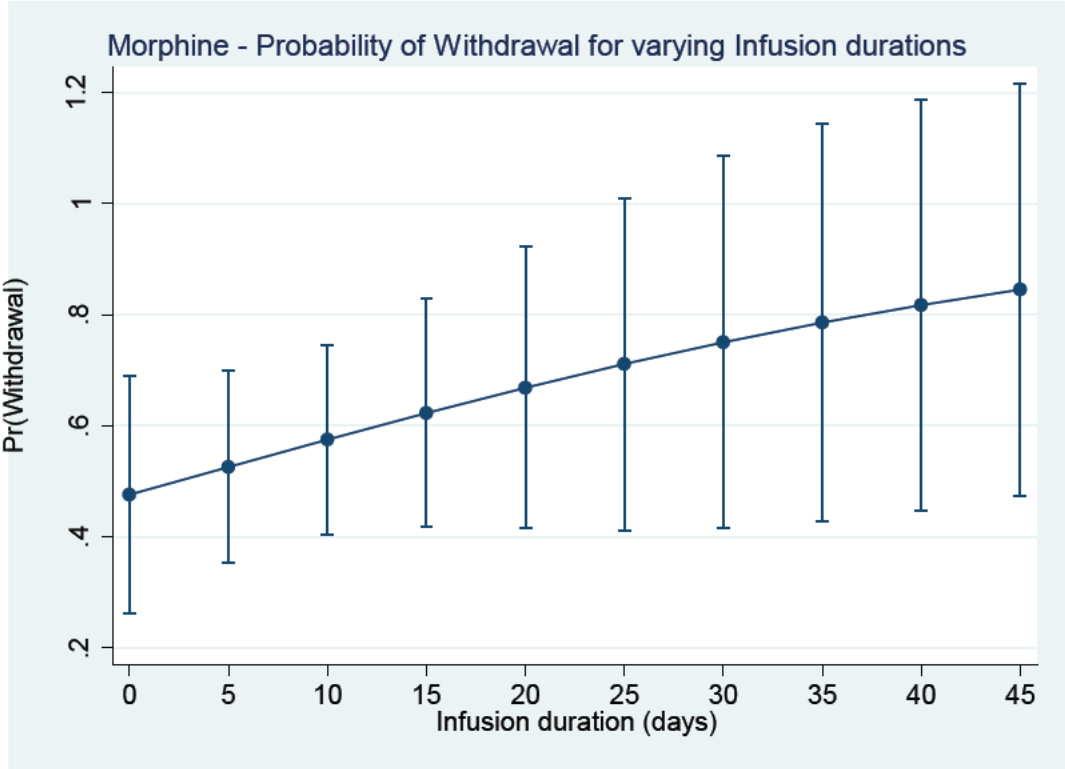
The probability of Withdrawal for varying Mean infusion rates is shown below. This graph assumes the Infusion duration is held constant at its mean of 8.7 days.



The graph illustrates that as the mean infusion rate increases, the probability of withdrawal increases. At a mean infusion rate of 80 mcg/kg/hr, the probability of withdrawal is greater than 80%.

Figure 10: Probability of withdrawal for varying infusion durations - morphine

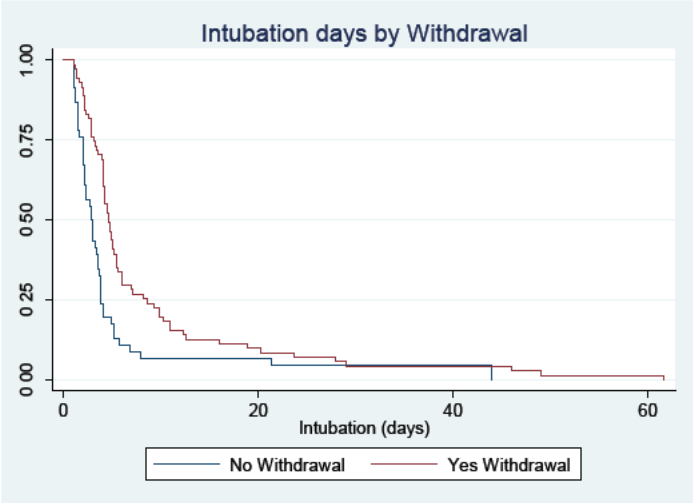
The probability of Withdrawal for varying Infusion durations is shown below. This graph assumes the Mean infusion rate is held constant at its mean of 38.5 mcg/kg/hr.

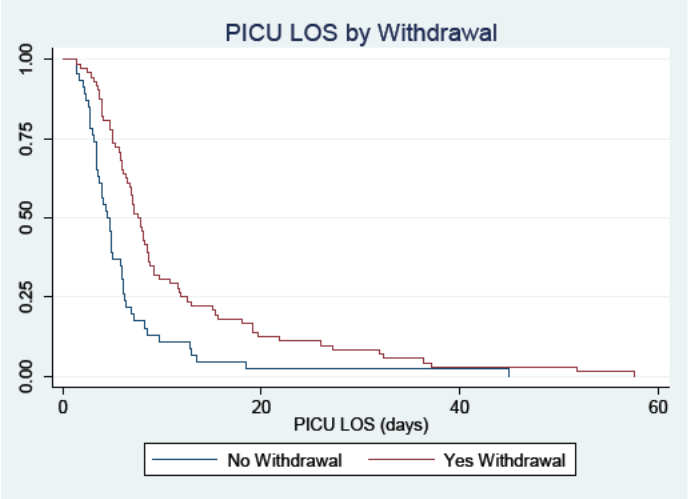


The graph illustrates that as the Infusion duration increases, the probability of withdrawal increases. But at a much lower rate than for Fentanyl. At an Infusion duration of 40 days, the probability of withdrawal is greater than 80%.

Figure 11: Kappler Meier analysis of outcomes

Kappler Meier analysis





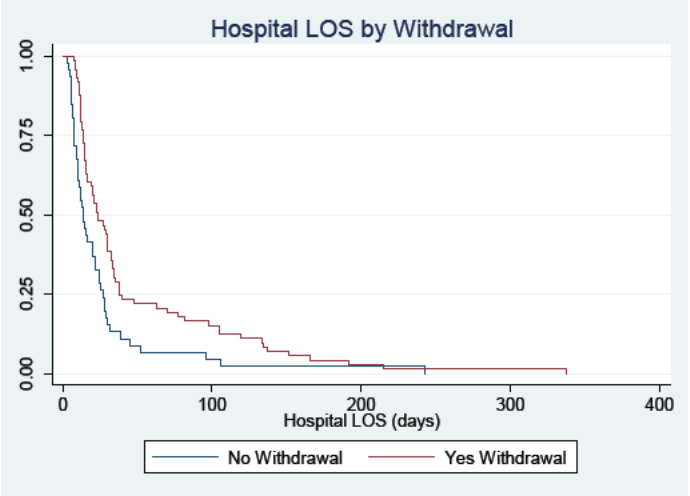


Table 20: Logistic regression analysis of the association between withdrawal and moderate - severe clinical deterioration.

```
Logistic regression                             Number of obs     =        119
                                                LR chi2(2)        =      11.72
                                                Prob > chi2       =     0.0028
Log likelihood = -73.533407                     Pseudo R2         =     0.0738

------------------------------------------------------------------------------
           Withdrawal | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf.
Interval]
----------------------+-------------------------------------------------------
Mild/no _deterioration |
             Moderate  |   1.945946    1.07434     1.21   0.228      .659462
5.742113
               Severe  |   5.837838   3.436258     3.00   0.003     1.841702
18.50482
                       |
                 _cons |   1.027778   .2406072     0.12   0.907      .649575
1.626182
------------------------------------------------------------------------------
```

The results indicate the following:

1. *The odds of withdrawal for a patient with Moderate clinical deterioration are 1.95 times greater than for a patient with Mild/No clinical deterioration. However, this difference is not statistically significant (p = 0.228)*
2. *The odds of withdrawal for a patient with severe clinical deterioration are 5.83 times greater than for a patient with Mild/No clinical deterioration. This difference is statistically significant (p=0.003)*