Great Ormond Street Hospital for Children NHS Foundation Trust

Nursing and Allied Health Guideline

Key Points

- Withdrawal symptoms can be prevented by the slow tapering of the drugs.
- The symptoms of withdrawal may also be managed by non-pharmacological treatments used in a complimentary manner

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Drug (opioid or benzodiazepine) withdrawal syndrome – prevention and management

Introduction

Sedation and analgesia are well-established practices for children requiring mechanical ventilation reducing biochemical and physiological stress responses, which can directly affect patient outcome (Ista et al 2007) Opioids and benzodiazepines are the most commonly used agents to treat pain and sedate children in intensive care (Subramaniam & Playfor 2010), however their use is not risk free and children may experience withdrawal symptoms when these are discontinued (Playfor et al 2006).

Withdrawal symptoms can be prevented by the slow tapering of the drugs (Birchley 2009). The symptoms of withdrawal may also be managed by non-pharmacological treatments used in a complimentary manner (Anand et al 2010).

Careful drug tapering will also limit gastrointestinal complications, promote normal sleep-wake cycle, avoid excessive sedation and reduce unnecessary hospitalization (Osborn et al 2003). In infants, slow tapering of these drugs reduces the risks of associated complications such as feeding difficulties, weight loss and the prevention of seizures (American Academy of Pediatrics, Committee on Drugs 1998).

The primary goals of treatment are to provide comfort to the child and reassurance to the family by relieving withdrawal symptoms to a clinically acceptable degree, reducing agitation and distress, promoting normal sleep wake cycle, and avoiding over sedation.

Definitions

Health professionals should have a working knowledge of the definitions for these terms:

Tolerance: The decrease in a drug's effect over time, requiring an increase of the dose to achieve the same effect (Jage 2005, Anand et al 2010).

Physical Dependence: A physical adaptation in neurones, such that abrupt discontinuation of an analgesic or sedative agent will result in withdrawal symptoms and the requirement for continued administration of an agent to prevent the onset of withdrawal symptoms (Jage 2005, Anand et al 2010).

Cross Tolerance: Tolerance to one drug as a result of exposure to another drug; e.g. patients tolerant to morphine often display a degree of tolerance to other opioids (Jage 2005).

Withdrawal: A complication of prolonged therapy whereby sudden discontinuation or reversal of an analgesic or sedative agent that the patient has been exposed to over a prolonged period of time, causes a clinical syndrome. This may be iatrogenic (hospital acquired) (Birchley 2009; Anand et al 2010). Withdrawal syndrome is characterized by a group of physical signs and symptoms, which can complicate the medical course of the critically ill child and potentially prolong hospitalisation (Cunliffe et al 2004).

Addiction: Complex psychological and physical behaviours that may occur as a result of habitual non-medicinal administration of analgesic or sedative agents (Anand et al 2010). This term is not helpful in describing hospital acquired physical dependence and withdrawal and should not be used in this context.

Identifying the child or young person at risk of tolerance and physical dependence

The onset of withdrawal symptoms may vary from patient to patient and can be influenced by several factors. Withdrawal symptoms usually occur after one to two weeks of continuous or regular opioid or benzodiazepine administration, but in some cases, may occur after a few days of therapy (Rationale 1). The use of drugs such as paralyzing agents alongside opioid or benzodiazepine indicates a greater risk of developing tolerance and physical dependence (Rationale 2).

Every child or young person receiving an opioid or benzodiazepine infusion should have regular withdrawal, as well as pain and sedation assessment (Rationale 3) and a weaning plan should be initiated when a reduction in these agents is anticipated (Rationale 4).

Rule out conditions with similar symptoms
Withdrawal symptom is a diagnosis of exclusion (Rationale 5). On-going or associated conditions that have similar symptoms should be investigated and ruled out before a diagnosis of withdrawal is made (Rationale 6). Such conditions include:

- cerebral hypo-perfusion from alterations in cardiac output,
- central nervous system infections,
- cerebrovascular disease
- sepsis
- hypoglycemia
- metabolic abnormalities
- intensive care unit psychosis or syndrome

(Tobias 2000, Schecter et al 2003).

Assessing the Drug History

Prior to weaning, a history of the child or young person's opioid and/or benzodiazepine usage should be taken including:

- Baseline drug dose or infusion rate prior to the commencement of weaning (Rationale 7)
- Number of days drug infusions or doses have been administered (Rationale 8 & 9)
- Any drug reduction already undertaken (as a percentage of the highest constant dose, prior to weaning) (Rationale 10)
- Any additional drugs added to assist in the weaning process that may also need reducing (e.g. chloral hydrate, clonidine etc.) (Rationale 11 & 12)

From this information children and or young people categorized as "at risk" of withdrawal syndrome may be identified.

Categorising the risk of Withdrawal Syndrome
Identifying the risk of the child or young person developing withdrawal syndrome is based on the number of days of continuous infusion of opioids or benzodiazepines (Rationale 13). This can be categorised as:

Category 1: (Minimal Risk)
Continuous opioids or benzodiazepine therapy for < 5 days.

Category 2: (Moderate Risk)
Continuous opioids or benzodiazepine therapy for 5 to 14 days.

C**ategory 3: (Highest Risk)**
Continuous opioids or benzodiazepine therapy for > 14 days.

See the section entitled "Managing Weaning" for recommended weaning protocols.

Withdrawal Assessment Tools

When the decision is made to start weaning the opioid or benzodiazepine the effectiveness of the weaning process should be monitored every 4 hours and more frequently if indicated (Rationale 14) using a clinically tested scoring tool (Rationale 3). A number of validated withdrawal assessment tools are available (Rationale 15). There are two withdrawal assessment tools currently used in the trust:

ITU Withdrawal Assessment Tool

The assessment tool "Withdrawal ITU Observation Chart" should be used for assessing children and young people in intensive care areas (Rationale 78).

The child or young person should be assessed:

- every 4 hours if the score is less than 8 (Rationale 19)
- every 2 hours if the score is 8 or more (Rationale 19)

A score greater than 8 - 12 may indicate withdrawal syndrome (Rationale 19)

This tool is available on the electronic medical record system (CareVue®) or may be downloaded from the Pain Control Service website labelled "Withdrawal ITU Observation Chart" at: http://www.gosh.nhs.uk/health-professionals/clinical-specialties/pain-co...

Non- ITU Observation Withdrawal Assessment Chart

This assessment tool should be used for assessing **children and young people on non-ITU wards** (Rationale 80).

For scores ≥ 3 consider:

- slowing down rate of reduction of opioid or benzodiazepine
- recommencing an opioid or benzodiazepine (whichever was stopped most recently)
- increasing the dose of opioid or benzodiazepine.

For scores ≤ 2:

- continue to reduce opioid or benzodiazepine as per regime.

For scores < 2 for more than 48 hours:

- consider increasing the speed of opioid or benzodiazepine reduction

This tool is available to download from the Pain Control Service website labelled "Withdrawal Non-ITU Observation Chart" (page 1 & 2) at:
http://www.gosh.nhs.uk/health-professionals/clinical-specialties/pain-co...
Modification of assessment tools
Both opioid and benzodiazepine withdrawal assessment tools may be modified, on an individual basis, to exclude symptoms of underlying conditions that may influence the withdrawal score and result in unnecessary treatment (Rationale 16).

Each assessment tool incorporates a final score of "Yes" or "No". This assessment is based on the practitioner's clinical judgment of whether the overall score is indicative of withdrawal and this should be taken into account when interpreting the withdrawal assessment score (Rationale 17).

Managing Weaning

Non-Pharmacological Strategies

Comfort Measures

In addition to drug therapy it is important that the nurse is aware of the non-pharmacological methods that can be utilised (Rationale 36) for all categories of weaning.

Reduce environmental stimulation (Rationale 37) by:

- Nursing the child or young person in a quiet area of ward if possible and safe to do so
- Sequencing nursing procedures to promote minimal disturbance to child or young person.
- Liaising with the family to limit visitors.
- Removing mobiles, balloons, and noisy toys.
- Turning off televisions and radios.
- Dimming lights.
- Ensuring that plain bed sheets and bedside curtains are provided.

For babies and small children, comfort measures can be helpful such as (Rationale 38):

- Swaddling babies
- Holding or rocking
- Increased frequency of feeding
- Bathing and massage
- Non-nutritive sucking, e.g. dummies.

For older children comfort measures may include (Rationale 39):

- Massage
- Relaxation.

Tissue Integrity

Close attention should be paid to the skin integrity of the heels, toes and nappy area (Rationale 40).

Consult the Tissue Viability Nurse for advice regarding pressure-relieving mattresses if necessary.

Nutritional Concerns

Liaise with the dietician for advice regarding appropriate dietary regimes (Rationale 41).

Pharmacological Strategies

The following protocols may form the basis of a weaning strategy (Rationale 18):

Category 1 (Minimal Risk)

Continuous opioids or benzodiazepine therapy for **fewer than 5 days**

1. Assess the child or young person every 4 hours using a withdrawal observation chart (Rationale 19).
2. Taper sedation and analgesic drugs as clinically indicated e.g. prior to extubation (Rationale 9).
3. If withdrawal symptoms are observed, cease weaning and initiate treatment if indicated by scores (Rationale 20). The administration of additional rescue medication should be considered (e.g. a planned dose of opioid) (Galinkin & Koh 2014).
4. Consider consultation from Pain Control Service at any point.

Category 2 (Moderate Risk)
Continuous opioids or benzodiazepine therapy for 5 to 14 days

1. Reduce opioid and/or benzodiazepine infusion rate by 20% of the BASELINE DOSE (Rationale 21) every 24 hours (Rationale 22).
2. Assess the child or young person every 4 hours using a withdrawal observation chart (Rationale 19) and initiate treatment if indicated by scores.
3. Monitor for signs of withdrawal for at least 48 hours post cessation of weaning (Rationale 28).
4. If withdrawal symptoms develop reduce weaning rate to 10% per day, or consider not weaning for a 24 hour period, then reassess and resume weaning if indicated (Rationale 21).
5. If scores indicate moderate to severe withdrawal, consider the following options:
• Re-introduce or add benzodiazepine therapy if symptoms indicate (Rationale 23).
• Increase opioid to previous dose (especially if gastrointestinal symptoms noted) (Rationale 24).
• When symptoms resolve, consider weaning more slowly to prevent symptom recurrence (Rationale 21).
• If symptoms do not resolve, consider initiating clonidine medication (Rationale 25).
• Consider consultation from Pain Control Service at any point.

Initially, only one medication should be weaned at a time. (Rationale 26).

Category 3 (Highest Risk)
Continuous opioids or benzodiazepine therapy for more than 14 days

1. Reduce opioid and benzodiazepine infusions more slowly e.g. by 5 - 10% of the BASELINE DOSE, (Rationale 27) every 24 hours (Rationale 22).
2. Assess the child or young person every 4 hours using a withdrawal observation chart (Rationale 19) and initiate treatment if indicated by scores.
3. Monitor for signs of withdrawal for at least 48 hours post cessation of weaning (Rationale 28).
4. If withdrawal symptoms develop reduce weaning rate to 5% per day, or consider holding weaning for a 24 hour period, then reassess and resume weaning at a slower rate if indicated (Rationale 27).

5. If scores indicate moderate to severe withdrawal, consider the following options:
• re-initiate or add benzodiazepine therapy of symptoms indicate (Rationale 23),
• increase opioid to previous dose (especially if Gastro-Intestinal symptoms noted) (Rationale 24),
• when symptoms resolve, consider weaning more slowly to prevent symptom recurrence (Rationale 27),
• if symptoms do not resolve, consider initiating clonidine medication (Rationale 25),
• consider consultation from Pain Control Service at any point.

Initially, only one medication should be weaned at a time. (Rationale 26).

Documenting the Weaning Plan
The plan should include all drugs that require weaning.

Document the plan for weaning in the:
• child or young persons' medical notes or electronic record (e.g. CareVue)
• Weaning Care Plan & Guideline which should remain at the bedside
• Pain Management Chart (if the child or young person is receiving PCA or NCA therapy)

Documentation should include the:
• Date and time of dose reduction (or increase)
• Route of administration of the drug to be tapered
• Initials of person completing the daily plan
• Clear indication of the day that the drug should be discontinued (e.g. "STOP")

The Weaning Care Plan & Guideline is available to download from the Pain Control Service website at: http://www.gosh.nhs.uk/health-professionals/clinical-specialties/pain-co...

Transfer from intensive care to the general ward setting
Extubation, discharge from ITU, facilitation of early enteral feeding and bed management pressures are not indications for a rapid wean of opioids or benzodiazepines; often children and young people can be returned to the general ward while the weaning process is underway, even if relatively high doses of opioids are being administered (Rationale 29) and the child or young person is not opioid naive.

Lockout settings on Patient Controlled Analgesia (PCA) and Nurse Controlled Analgesia (NCA) infusions should be carefully checked to ensure that they comply with the standard protocol for non-ITU settings or have been documented as "Out of protocol".

Individual PCA/NCA prescriptions and protocols may be downloaded from the Pain Control Service website at: http://www.gosh.nhs.uk/health-professionals/clinical-specialties/pain-co....

The Pain Control Service should be contacted on: Bleep 0577 and informed when the child or young person is being transferred and if necessary, will reassess the weaning plan on a daily basis.

Converting from Intravenous to Oral Drugs

The intravenous opioid or benzodiazepine can be converted to an equivalent oral dose (Rationale 30). However, this is dependent on several factors:

1. The child or young person must be tolerating enteral feeds.
2. The total daily intravenous drug dose (including bolus doses) when converted to oral should not exceed the total daily oral dose as recommended in the BNFC and/or local guidance
3. Withdrawal scores should be stable

If these factors are not met, weaning management should continue on intravenous therapy.

Extreme caution should be taken when converting to oral doses (Rationale 31) Anecdotally, the Pain Control Service has found these **approximate** conversion factors can form the basis of a weaning strategy. Any changes made must be verified by either:

- On call anaesthetist
- Intensivist
- Ward pharmacist

Table 1. Morphine: Suggested Conversion Factors

(Rationale 83, 84)

Route / drug		Conversion factor	Example
from	to		
IV Morphine	Oral Morphine	x 3	**Child's weight**: 4 kg **IV morphine dose**: 10 microgram/kg/hr **Conversion to oral dose**: 10 microgram X 4 kg X 24 hours X 3 (conversion factor) = 2.88 mg/day = 0.72 mg FOUR times a day Round the dose to **0.6 mg or 0.8 mg FOUR times a day** for accuracy

Important Note: Conversion should only take place once the morphine infusion is ≤10 microgram/kg/hour (unless otherwise advised by the pain control service)

Table 2. Benzodiazepine: Suggested Starting Dose

Route / drug			Example
from	to		
IV Midazolam	Oral Diazepam	+3	**Child's weight**: 4 kg **IV midazolam dose**: 1.2 microgram/kg/min **Oral conversion**: 1.2 microgram x 4 kg x 24 hour x 60 mins + 3 (conversion factor) = 2.3 mg/day = 1.15 mg TWICE a day Suggest rounding dose to either **1 mg TWICE a day or 2 mg at NIGHT**
Important Note: Conversion should only take place once the IV midazolam dose is ≤1 5microgrammes/kg/min			
Alternative Option is to use a starting oral Diazepam dose of: 0.1 – 0.2 mg/kg/dose (**maximum of 2 mg**) THREE or FOUR times a day (depending on the child's condition)			

(Rationale 85, 86, 87, 88)

Intensive care areas may also (Rationale 87)

- reduce IV midazolam infusion by 50% and introduce the first dose of enteral diazepam at the same time,
- discontinue IV midazolam infusion with the second dose of enteral diazepam.

Practical considerations when converting from Intravenous to Oral Drugs

The following physiological signs should be observed, alongside regular withdrawal assessment for at least 24 hours (Rationale 32)

- pulse rate
- respiratory rate (respiratory depression)
- sedation score
- blood pressure (hypotension)
- pain assessment

For oral doses:

- No dose reduction should take place on the day of conversion to the oral route,
- Round doses up or down to ensure accuracy of administration (e.g. 1.95 ml rounded to 2 ml),
- Once withdrawal scores are stable, start weaning by reducing frequency of administration e.g. four to three times daily (QDS to TDS),
- When omitting doses, ensure the remaining doses are evenly spaced,
- Eventually a minimum volume for safe administration will be reached. For example, if the dose of oral morphine reaches 0.2 mg (i.e. 0.1ml dose of oral morphine: 10mg in 5mls), do not reduce the dose any further, but begin omitting doses, to wean the drug.

Clonidine

Clonidine administration may be considered for children and young people who are having difficulty weaning from opioids or benzodiazepines. However it should be used with caution (Rationale 33) and after discussion with either the:

- On call anaesthetist
- Intensivist
- Ward pharmacist

If clonidine has been administered for more than 2 weeks (Rationale 85), it should be weaned over 1 to 2 week period, as stopping it abruptly may cause severe symptoms (such as rebound hypertension) (Rationale 35).

Regular vital signs monitoring including heart-rate and blood pressure monitoring should be undertaken throughout its use (Rationale 35).

An initial dose of 0.5 micrograms/kg may be given to determine the effect of the drug on the child or young person's blood pressure.

Clonidine may be chosen as the final drug to be weaned, however due to the need to ensure regular BP checks while weaning clonidine, and due to the difficulty in undertaking this outside the hospital environment, it is sometimes preferable to wean clonidine before other drugs.

Chloral Hydrate

Chloral hydrate is an enteral hypnotic agent (Rationale 43) used as a sedative in ICU patients (Rationale 44) and for non-painful diagnostic procedures (Rationale 45). Its use as an adjunct in children with abstinence syndrome has been documented (Rationale 46).

Prolonged treatment with chloral hydrate (>7 days) may cause withdrawal symptoms if the administration of drug is stopped abruptly (Rationale 69).

Chloral hydrate is well absorbed orally & rectally (Rationale 47) with an onset time of 15- 60 minutes (Rationale 48). It has duration of action of 1-2 hours, which may extend to 8 hours (Rationale 50) particularly in children with moderate or severe renal failure (Rationale 50) or hepatic impairment (Rationale 51). The elimination half-life of chloral hydrate is dependent on the child's age, and may vary from 4 to 12 hours in children, up to 28 -37 hours in neonates (Rationale 52), with adverse events occurring more commonly in children under two years of age (Rationale 53, 54, 55). Oxygen desaturation is one of the most frequently reported adverse events in children receiving chloral hydrate (Rationale 56, 57), with incidences of respiratory depression (Rationale 58, 71) and airway obstruction (Rationale 59) also recorded.

Chloral hydrate administration also has the potential to cause sedation (Rationale 60, 71) and associated complications (Rationale 60, 61) which may be exacerbated by the concomitant use of other sedative agents (Rationale 62).

Hypotension has also been recognised as a potential side effect of prolonged chloral hydrate administration (6 days) (Rationale 68) as has cardiac dysrhythmias (rare) (Rationale 73, 74).

With these side effects in mind, all children and young people receiving chloral hydrate should have vital signs monitoring and pulse oximetry (Rationale 76).

Children and young people receiving chloral hydrate therapy should be nursed with access to oxygen and emergency airway equipment (Rationale 77, 78) and be cared for by appropriately trained staff (Rationale 79).

Gastrointestinal irritation is also commonly reported as adverse effect of chloral hydrate administration (Rationale 64). Observe the child / young person for vomiting and/or diarrhoea (Rationale 65, 66) and avoid use of chloral in those with a history of gastritis (Rationale 67).

Paradoxical hyperactivity (Rationale 72, 73) is also a documented complication of chloral hydrate administration.

In practice, introduction of chloral hydrate does not reduce withdrawal symptoms from opioids or benzodiazepines.

Discharge from hospital while weaning

If the child or young person is being discharged from hospital during the weaning process, the following factors must be considered:

- Ensure that they have been symptom free for 24-48 hours (particularly important in infants)
- The child or young person's medical status is stable
- Conversion of drugs to oral preparations has been completed
- Clear plan written for the remaining weaning process to be followed after discharge
- Education of parent/s or carer in the administration of medications and the symptoms of withdrawal
- Instructions in the event of a withdrawal episode
- If clonidine weaning is continuing following hospital discharge: consider daily blood pressure monitoring by community paediatric team
- Contact details if parent/s or carer has a query (Rationale 42)

Rationale

Rationale 1: Signs of withdrawal may be apparent after 1 hour and anytime up to 24 hours following the reduction of a drug dose (Ducharme et al 2005).

Rationale 2: Those receiving neuro-muscular blocking agents have generally received higher doses of sedative and analgesic agents; also, cues used to titrate such agents are not evident (Tobias 2000).
Rationale 3: To document any withdrawal symptoms observed. A number of scientifically tested withdrawal assessment tools exist (Anand et al 2010).
Rationale 4: Weaning should only be undertaken if the child or young person has no on-going pain requiring increase or continuation of an opioid (Galinkin & Koh 2014).
Rationale 5: Clinical diagnosis of withdrawal may be confounded by pain, ventilator distress, delirium and noise induced stress (Ista et al 2013).
Rationale 6: Interpretation of the assessment tool being employed should be made in light of the child's clinical condition including other differential diagnoses that may be linked to the characteristics observed (Galinkin & Koh 2014).
Rationale 7: Withdrawal symptoms are thought to be related to the total drug doses received (Playfor et al 2006) and the length of time a drug has been continuously infused.(Ducharme et al 2005).
Rationale 8: To establish a threshold (in days) above which children are anticipated to develop physical dependence on opioids or benzodiazepines and therefore the introduction of a weaning policy (Hudak and Tan 2012).
Rationale 9: In general children receiving opioids for less than 7 days may discontinue this agent without weaning. However there is significant individual variation in response to this agent and opioid withdrawal has been identified in children receiving the agent after 5 days of therapy (Galinkin & Koh 2014).
Rationale 10: Daily tapering regimes of 5-10% of the starting dose is standard practice in adult setting and is described by the United Kingdom Paediatric Intensive Care Society Sedation, Analgesia and Neuromuscular Blockade Working Group (Playfor et al 2006).
Rationale 11: Abrupt discontinuation of clonidine has been associated with withdrawal syndrome (Playfor et al 2006).
Rationale 12: Although clonidine has been recommended for the treatment of abstinence syndrome in neonates (American Academy of Pediatrics, Committee on Drugs 1998); due to the risk of over sedation it is not recommended for the treatment of opioid withdrawal in neonates (D'Apolito 2009). The use of clonidine in the paediatric critical care setting has not been studied (Anand et al 2010).
Rationale 13: Children in intensive care settings are more likely to develop dependence and be at risk of withdrawal symptoms due to their longer exposure to continuous opioid and benzodiazepine infusions (Galinkin & Koh 2014). The weaning regime should be tailored to the length of time a drug has been continuously infused and dose reductions should be based on the duration (in days) of the continuous infusions (Ducharme et al 2005).
Rationale 14: Regular assessment is required as breakthrough withdrawal symptoms are frequently observed. Nurses are the primary observer of clinical symptoms in the intensive care setting and therefore should be aware of the signs and symptoms of withdrawal (Birchley 2009). Children and young people should be assessed for signs of withdrawal prior to any change in therapy (Anand et al 2010).
Rationale 15: Each clinical unit should choose a single appropriate assessment tool to limit variability in scoring (Hudak and Tan 2012). More recently validated tools for measuring withdrawal syndrome in critically ill children include:

- Sophia Observation withdrawal Symptoms Scale (Ista et al 2013)
- Withdrawal Assessment Tool-1 (Franck et al 2012).

Rationale 16: The occurrence of loose stools in a child or young person with an ileostomy should be discounted as a symptom of withdrawal, as this is a normal event for this group (Franck & Vilardi 1995).
Rationale 17: Significant symptoms may occur even with the use of a standard withdrawal assessment tool and weaning protocols (Frank et al 2004); strong correlation has been found between nurses' clinical judgement and the occurrence of withdrawal (Frank et al 2012).
Rationale 18: No one standardised withdrawal protocol is observed in UK paediatric intensive care settings (Birchley 2009, Hudak and Tan 2012).
Rationale 19: A score greater than 8 - 12 may indicate withdrawal and children should be assessed:

- every 4 hours if the score is less than 8
- every 2 hours if the score is 8 or more (Franck & Vilardi 1995).

Rationale 20: To ameliorate withdrawal symptoms.
Rationale 21: Administration of opioids and benzodiazepines for more than 5 days are described as risk factors for the onset of withdrawal symptoms (Ista et al 2013). Daily tapering regimes of 5-10% of the starting dose is standard practice in adult setting and is described by the United Kingdom Paediatric Intensive Care Society Sedation, Analgesia and Neuromuscular Blockade Working Group (Playfor et al 2006). Weaning rates of 13-20% are recommended for critically ill children who have received continuous infusions of opioids and benzodiazepines for 4-7 days and 8% for children who have received continuous infusions of opioids and benzodiazepines for 8 – 14 days (Ducharme et al 2005).
Rationale 22: Weaning is usually accomplished by decreasing the dose every 24 to 48 hours (Galinkin & Koh 2014).
Rationale 23: Movement disorders, grimacing, inconsolable crying, and hallucinations result from withdrawal of benzodiazepines (Ista et al 2013).
Rationale 24: Gastrointestinal symptoms associated with opioid withdrawal include vomiting, diarrhoea and poor appetite (Anand et al 2010).
Rationale 25: Clonidine has been included as part of opioid reduction programmes and as an adjunct for children with withdrawal symptoms (Galinkin & Koh 2014). The use of low dose clonidine has been recommended to prevent withdrawal symptoms in children in the intensive care setting who are weaning from infusions of opioids and benzodiazepines of more than 5 days duration (Playfor et al 2006; Larson et al 2013). However the use of clonidine has not been studied in the paediatric critical care setting (Anand et al 2010).
Rationale 26: Further studies are required to identify weaning criteria for tapering both opioids and benzodiazepine infusions at the same time (Ducharme et al 2005) reduction of one medication at a time may be beneficial so that any signs of withdrawal may be more clearly attributed to a single medication (Galinkin & Koh 2014).
Rationale 27: Daily tapering regimes of 5-10% of the starting dose is described by the United Kingdom Paediatric Intensive Care Society Sedation, Analgesia and Neuromuscular Blockade Working Group (Playfor et al 2006). Weaning of opioids must be done more slowly for those receiving opioids of longer than 14 days (Galinkin & Lee Koh 2014), with those having very long exposure to opioids and benzodiazepines requiring a wean of less than 8% (Ducharme et al 2005).

Rationale 28: Symptoms of withdrawal may be observed for up to 48 hours after stopping opioids (Hudak and Tan 2012).
Rationale 29: Children and young people receiving high dose opioids or other agents, mechanical ventilation can be weaned and spontaneous ventilation resumed before the agent is discontinued (Tobias 2003). Children develop tolerance to the respiratory depressive effects of opioids rapidly and there is little evidence to support the rapid weaning or discontinuation of analgesia and sedation to enable extubation (Frank et al 2004).
Rationale 30: Converting from an intravenous to an oral drug simplifies the weaning process and may allow earlier discharge form hospital (Schecter et al 2003) Conversion from intravenous to oral medications removes the requirement for intravenous access (Birchley 2009).
Rationale 31: Cross tolerance of opioids is not necessarily 100%, so that switching from one opioid to another may result in a change in the total dose required not necessarily predictable when calculated on a standard potency ratio (Schecter et al 2003).
Rationale 32: Because experience of switching from intravenous to oral medication is so limited, careful monitoring of cardiorespiratory status is mandatory (Tobias 2000).
Rationale 33: The addition of a sedative such as clonidine may reduce the severity of opioid withdrawal; however there is limited information to support the use of clonidine as a withdrawal agent in the paediatric population (Osborn et al 2003). If clonidine is introduced as an adjunct to the tapering process the heath-professional should be aware of its potential adverse effects, which include hypotension and bradycardia (Playfor et al 2006).
Rationale 34: Clonidine should be weaned gradually in neonates over a 1-2 week period (D'Apolito 2009).
Rationale 35: Abrupt discontinuation of clonidine after extended administration may result in hypertension or seizures (Playfor et al 2006).
Rationale 36: Supportive nursing interventions should be used when managing the child with opioid withdrawal (Osborn et al 2003, Anand et al 2010).
Rationale 37: Care should be used when using non-pharmacological interventions to avoid inducing hallucinations and therefore increasing distress (Birchley 2009). A normal sleep pattern should be maintained where possible. Strategies for light and noise reduction and promotion of night and day orientation should be included in patient care as natural sleep may ameliorate mild withdrawal (Playfor et al 2006; Birchley 2009).
Rationale 38: Supportive treatments for newborn infants used to ameliorate opioid withdrawal symptoms include: swaddling, settling, massage, relaxation baths, pacifiers or waterbeds (Osborn et al 2003).
Rationale 39: Music massage and complementary therapies may ameliorate mild withdrawal (Birchley 2009).
Rationale 40: Skin can become red and broken as a result of abrasion caused by repetitive movement in the irritable withdrawing child. Skin breakdown may also be the consequence of opioid-withdrawal-induced diarrhoea.
Rationale 41: Gastro-intestinal effects of opioid withdrawal include: feeding intolerance, vomiting, diaorrhoea, uncoordinated suck / swallow reflex and persistent residuals with tube feeding (Tobias 2000). Infants may also experience weight loss and calorie depletion as a result of increased activity due to: irritability, crying, tremors, and decreased sleep. Frequent small feeds may be considered for the

withdrawing child. Neonates should have sufficient calorific intake to ensure appropriate weight gain. Calories and electrolytes may also be lost through vomiting, drooling and diarrhoea (American Academy of Pediatrics, Committee on Drugs [AAPCD] 1998; Hudak & Tan 2012).
Rationale 42: Hospital discharge should be delayed in infants and neonates until they are symptom free for 24 to 48 hours after stopping opioids; early discharge should only be considered after assessing the child's overall medical status, the home environment and the families access to prompt medical assistance (Hudak and Tan 2012).
Rationale 43: Chloral hydrate is an enteral hypnotic (sedative) agent (Playfor et al 2006).
Rationale 44: Chloral hydrate use as an enteral sedative agent in critically ill children has grade-B recommendation by the United Kingdom Paediatric Intensive Care Society's Sedation, Analgesia and Neuromuscular Blockade Working Group in (Playfor et al 2006).
Rationale 45: Widely used to induce immobility in infants and young children undergoing non-painful diagnostic procedures including: echocardiogram, radiological procedures and electroencephalogram (Ratnapalan 2014).
Rationale 46: Chloral hydrate has been used in combination with clonidine to treat neonatal abstinence syndrome and has been demonstrated to reduce withdrawal symptoms, duration of treatment and period of hospitalisation, when compared to a combination of morphine and phenobarbital (Esmaeili et al 2010).
Rationale 47: Chloral hydrate is well absorbed orally & rectally (Ratnapalan 2014)
Rationale 48: Chloral hydrate is absorbed rapidly from the gastrointestinal tract with an onset of 15- 60 minutes (Playfor et al 2006) and has an onset of action of 30 to 60 minutes via the oral or rectal routes (Ratnapalan 2014).
Rationale 49: The duration of action is 60-120 minutes (Playfor et al 2006). Chloral hydrate's duration of action can extend from 2 to 8 hours (Ratnapalan 2014).
Rationale 50: While no dosage adjustment is required for children and young people with mild renal failure, chloral hydrate should be avoided in children with severe or moderate renal failure (creatinine clearance <0.8 mL/s) (Ratnapalan 2014). The duration of action is 60-120 minutes but may be longer in children with renal impairment (Playfor et al 2006).
Rationale 51: The duration of action is 60-120 minutes but may be longer in children with hepatic impairment (Playfor et al 2006). Chloral hydrate should be avoided in children with severe hepatic dysfunction (Ratnapalan 2014).
Rationale 52: The elimination half-life of chloral hydrate is dependent on age and may vary from 4 to 12 hours in older children, 28 hours in full-term infants and 37 hours in preterm neonates (Ratnapalan 2014).
Rationale 53: Chloral hydrate should be used with caution in preterm and term infants due to the accumulation of active metabolites, the potential to develop metabolic acidosis, and the possibility of predisposing newborns to conjugated and unconjugated hyperbilirubinemia (Ratnapalan 2014).
Rationale 54: Adverse effects of chloral hydrate are most common in infants younger than 6 months, including apnoea, desaturation, hypotension, vomiting, and prolonged sedation (Ratnapalan 2014).
Rationale 55: Hypoxia is more common in children under two years receiving chloral hydrate for non-painful procedures (Alotaibi et al 2014).

Rationale 56: Oxygen desaturation was the most frequent adverse event in children between the ages of 0-18 years receiving chloral hydrate for a median time of 6 days in the PICU setting (Martinbiancho et al 2009).
Rationale 57: The most commonly reported adverse effect in children and young people receiving chloral hydrate for non-painful procedures people is hypoxia, with an incidence of 5.1%; varying from mild 3.5%, to moderate hypoxia 1.6% (Alotaibi et al 2014).
Rationale 58: There have been reports of respiratory failure following chloral hydrate administration in infants (Ratnapalan 2014).
Rationale 59: The sedative effects of chloral hydrate may induce airway obstruction, therefore monitoring is necessary (Ratnapalan 2014).
Rationale 60 : Adverse drug events in children between the ages of 0-18 years receiving chloral hydrate for a median time of 6 days in the PICU setting include excessive sedation (Martinbiancho et al 2009).
Rationale 61: Chloral hydrate has the potential for re-sedation after recovery from the initial sedation effect which may occur up to 24 hours after administration (Ratnapalan 2014).
Rationale 62: Residual sedation (“hangover”) may occur with chloral hydrate, as with any sedative agent (Ratnapalan 2014).
Rationale 63: The addition of other sedative agents may exacerbate sedation in children taking chloral hydrate (Ratnapalan 2014).
Rationale 64: Gastrointestinal irritation is the most commonly reported adverse side effect (Playfor et al 2006).
Rationale 65: The second most frequently reported adverse event in children and young people receiving chloral hydrate for non-painful procedures people is vomiting (risk of 2.9%) (Alotaibi et al 2014).
Rationale 66: Other adverse drug events in children between the ages of 0-18 years receiving chloral hydrate for a median time of 6 days in the PICU setting included: gastrointestinal bleeding, diarrhoea (Martinbiancho et al 2009).
Rationale 67: Chloral hydrate should be avoided in children with gastritis, esophagitis, or peptic ulcer disease (Ratnapalan 2014).
Rationale 68: Chloral hydrate withdrawal symptoms have been observed in young children (33-months) receiving an average dose of 186 mg/kg/day for a period of 40 days, as part of an analgesia & sedation regime in PICU; and may potentially occur in children after >7 days treatment when used concurrently with other analgesic/sedative agents (da Silva et al 2011).
Rationale 69: Hypotension was the second most frequent adverse event in children between the ages of 0-18 years receiving chloral hydrate for a median time of 6 days in the PICU setting (Martinbiancho et al 2009).
Rationale 70: Other adverse drug events in children between the ages of 0-18 years receiving chloral hydrate for a median time of 6 days in the PICU setting included: apnoea (Martinbiancho et al 2009).
Rationale 71: Other adverse drug events in children between the ages of 0-18 years receiving chloral hydrate for a median time of 6 days in the PICU setting included: excessive sedation (Martinbiancho et al 2009).
Rationale 72: Higher doses of chloral hydrate (100 mg/kg) may be associated with paradoxical hyperactivity (Ratnapalan 2014).
Rationale 73: Other adverse drug events in children between the ages of 0-18 years receiving chloral hydrate for a median time of 6 days in the PICU setting included: agitation (Martinbiancho et al 2009).

Rationale 74: Cardiac dysrhythmias have been reported in children receiving chloral hydrate but are extremely rare (Ratnapalan 2014).
Rationale 75: Other adverse drug events in children between the ages of 0-18 years receiving chloral hydrate for a median time of 6 days in the PICU setting included: bradycardia (Martinbiancho et al 2009).
Rationale 76: All children receiving chloral hydrate should have vital signs monitoring and pulse oximetry (Ratnapalan 2014).
Rationale 77: Hypoxia following chloral hydrate administration for non-painful procedures is reversible using simple interventions including supplemental oxygen therapy (Alotaibi et al 2014).
Rationale 78: Apnoea and desaturations may be managed with oxygen administration and airway repositioning, however 1% to 2% of children and young people may require bag-valve-mask ventilation or assisted ventilation (Ratnapalan 2014).
Rationale 79: Potential adverse events such as respiratory depression and hypoxia following chloral sedations should be managed by appropriately trained staff (Ratnapalan 2014).
Rationale 80: To identify withdrawal using a validated tool. This assessment tool is taken from the Opioid Weaning Flowsheet: Children's Hospital Oakland (Franck & Vilardi 1995).
Rationale 81: This assessment tool is taken from the "Preliminary validity and reliability of the Opioid Weaning Flowsheet" (Franck 1998).
Rationale 82: Equianalgesic doses: Morphine 10 (Parenteral); 30 (PO) (Gammaitoni et al 2003).
Rationale 83: Equianalgesic dose: Morphine; oral 30 mg = Morphine; i.v. 10 mg (Geary et al 2012).
Rationale 84: Clonidine may be stopped immediately if used for <2 weeks (Evelina Formulary online 2016).
Rationale 85: Midazolam shares the actions of other benzodiazepines. Although initial data indicated that the sedative potency of midazolam was about 1.5–2.5 times that of diazepam, cllinical experience with the drug suggests that potency may be 3–4 times that of diazepam (American Society of Health-System Pharmacists [AHFS] 2015).
Rationale 86: Benzodiazepine Equivalents: a) Midazolam is 3 to 4 times as potent per milligram as diazepam based on clinical experience (Micromedex 2016).
Rationale 87: Midazolam Infusions can be converted to oral Diazepam once the Midazolam rate is reduced to 60-120micrograms/kg/hour (Bennett et al 2013) [ie. 1–2 micrograms/kg/minute].
Rationale 88: Conversion of IV Midazolam to IV or PO Diazepam:
1) Calculate the total daily dose of IV midazolam in milligrams
2) Divide total daily dose by 3 to give total daily dose of enteral diazepam in milligrams
3) Divide total daily dose of diazepam by 4 to ensure 6 hourly dosing
4) Start diazepam and decrease IV midazolam infusion by 50% with 1st dose of IV or enteral diazepam.
5) Cease IV midazolam infusion with 2nd dose IV or enteral diazepam
(Hospital for Sick Children [SickKids] 2014).

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