A CRITICAL EXAMINATION OF SEDATION WITHDRAWAL ASSESSMENT IN CHILDREN

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Abstract

Background

Sedation withdrawal is one of the terms used to describe the behavioural response to stopping or reducing sedative drugs in physically dependent patients. Withdrawal behaviours differ according to the drug involved and may be unpleasant and interfere with recovery. Recognition of sedation withdrawal is challenging due to differences in patient presentation and may be further complicated by the patient's condition and concomitant drug therapy.

Overall Aim of the full thesis

To improve the accuracy of sedation withdrawal assessment in critically ill children.

Objectives and Methods

A mixed methods interactive approach comprising six studies.

Study 1 evaluates the psychometric properties of the Sedation Withdrawal Score,

Studies 2 and 3 examine the complexities/challenges of withdrawal assessment by critiquing existing tool validation studies,

A further three studies examine the nurse and parent perspectives of sedation withdrawal assessment in critically ill children.

Study 4 investigates how nurses use a sedation withdrawal tool,

Studies 5 and 6 investigate what behavioural signs parents recognise and ascertain parents' willingness to participate in withdrawal assessments.

Key findings

Nurses found withdrawal behaviours difficult to interpret in critically ill children and there were differences in how these behaviours were construed.

Parents identified a broader range of behaviours than included in existing tools. Most parents were eager to participate in the assessment.

The elusive theoretical basis for the existing approach to withdrawal assessment may account for the lack of a standardisation and poor accuracy of the current tools.

A model of the causal relationship between dependence and withdrawal is proposed.

Recommendations

The model identifies the diagnostic criteria upon which a definition for Pediatric Withdrawal Syndrome may be based. These criteria also provide a novel framework for withdrawal assessment. Focussing on the shared diagnostic criteria and including the parent perspective of the child's behaviours may aid the assessment and support decision-making.

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Table of Contents

List of Tables

List of figures

Appendices

1 The Sedation Withdrawal Score (SWS)

2 The State Behavioural Scale

3 The Withdrawal Assessment Tool - 1

4 The Sophia Observation Score

5 Data extraction sheet for Study 1

6 Study 4 paperwork

7 Published paper

8 Study 5 paperwork

9 Study 6 paperwork

Glossary

SWS Sedation Withdrawal Score

SOS Sophia Observation Scale

WAT-1 Withdrawal Assessment Tool -1

SBOWC Sophia Benzodiazepine and Opioid Withdrawal Score

OBWS Opioid and Benzodiazepine Withdrawal Score

ADR Adverse Drug Reaction

DSM Diagnostic Statistical Manual

HDU High Dependency Unit

PD Pediatric Delirium

PICU Paediatric Intensive Care Unit

CPAP Continuous Positive Airway Pressure

BiPAP Biphasic Positive Airway Pressure

Part 1: Introduction

Part 1 of this thesis presents Chapters 1 to 3.

Chapter 1 introduces the subject of sedation withdrawal and describes the clinical impetus for undertaking the studies in the thesis.

Chapter 2 is the literature review and includes a critical analysis of withdrawal assessment tools. This chapter will provide important background information regarding the key clinical syndromes of withdrawal and pediatric delirium and related pharmacological concepts of physical dependence, adverse drug reactions and opioid conversions. The two validated withdrawal assessment tools, the Withdrawal Assessment Tool -1 (Franck et al 2008) and the Sophia Observation Scale (Ista et al 2009) are presented and critiqued.

Chapter 3 presents the methodology and the conceptual framework. This chapter will provide the rationale for the choice of an interactive multistage mixed methods design, comprising explanatory sequential and convergent components to answer the research questions.

Chapter 1: Introduction

1.1 Introduction

Babies and children admitted to the Paediatric Intensive Care Unit (PICU) will receive sedative and analgesic drugs, to facilitate mechanical ventilation and to relieve pain and suffering. These drugs can cause physical dependence when administered continuously; the rate of dependence depending on duration, dose and patient factors. Patients who are physically dependent may experience withdrawal syndrome if these drugs are stopped abruptly or reduced too quickly. Withdrawal can be ameliorated by weaning or tapering drugs at a rate which can be tailored to the individual depending on their condition, comorbidities and response to recent changes in drug doses. Withdrawal is unpleasant and may slow recovery and delay discharge from the Paediatric Intensive Care Unit (PICU). Prompt detection and treatment of withdrawal can reduce suffering and aid recovery.

1.2 Background to the study

The hospital in which this study took place is a large tertiary children's hospital in the UK with 24 ICU and 30 HDU beds. In this hospital a systematic approach to the assessment and management of withdrawal syndrome has been embedded in practice for 15 years. This approach comprises a withdrawal assessment tool, the Sedation Withdrawal Scale (SWS) with an assessment schedule and treatment cut points, which was created by the pain team in the absence of an existing alternative (Cunliffe et al, 2004) (Appendix 1). The pain team oversee sedation weaning in patients discharged from PICU; a cohort of about 100 patients annually.

Despite clinical utility, there have been recurring issues with the existing approach to withdrawal assessment arising from the diagnostic reliance on non-specific behaviours. The potential for error arises on occasions when the child's typical behaviour or underlying condition imitates withdrawal behaviour. In these instances the child may be diagnosed with withdrawal, but is not withdrawing. In other situations, withdrawing patients may present with only one withdrawal behaviour, which in a score relying on a summing of behaviours, translates to a lower score than is typical in a withdrawing patient.

This thesis owes its inception to a parent story told to me by a mother, whose baby son spent most of his life between PICU and the High Dependency Unit (HDU). This mother described the distress that withdrawal behaviour elicited in both her and her son. She also revealed that despite the existing approach to withdrawal assessments, her son had suffered with withdrawal after every episode of his critical illness. Her son passed away shortly before his first birthday.

This mother's story embodied the shortcomings of the existing approach to withdrawal assessment and prompted the design of a study to investigate whether the parental contribution might be more formally included in and enhance the existing approach to withdrawal assessment. With the overall aim of improving the accuracy of sedation withdrawal assessment in critically ill children, the *a priori* study comprised three phases; to evaluate the current SWS tool, interview parents to explore whether parents recognised withdrawal behaviours and were willing to participate in withdrawal assessments; incorporate a parental component in the assessment and evaluate the new approach. A mixed methods design was considered to best answer the research question; the parent interviews comprised the qualitative inquiry to inform the refinement of the quantitative instrument, the SWS tool. The project evolved to an interactive, emergent design in response to unexpected findings in the planned studies and to changes within the broader theoretical landscape. These changes will be described briefly.

The study evolved initially in response to data analysis in the first study; the SWS tool evaluation study. Unexpected findings prompted an additional study to explore nurse decision-making when using the SWS. Further change was prompted by the interpretation of findings from the parent interviews study. The rich descriptions and diversity of behaviours reported by parents and the insight they demonstrated motivated further exploration of the clinical context at the time of withdrawal and sought to explain the cause of the behaviours described by parents. Five cases demonstrated the unique and complex context and a level of uncertainty, which were poorly reflected and operationalised in the existing approach.

Although the overall aim of the thesis; to improve the accuracy of sedation withdrawal assessment in critically ill children remained the same, the aims and objectives of the component studies altered in response to the change in focus; to examine and illuminate three different perspectives of withdrawal assessment. The first perspective comprised

three studies examining the existing approaches to withdrawal assessment. Study 1 examined the psychometric properties of the Sedation Withdrawal Score (SWS); Study 2 compared two studies which characterised withdrawal signs in critically ill children and Study 3 was a pragmatic critique of the WAT-1 dataset. The following three studies explored the impact of two new perspectives; the nurse's perspective and the parent's perspective, on existing knowledge and understanding of sedation withdrawal assessment.

During the course of this thesis, the entire theoretical landscape surrounding withdrawal has changed fundamentally. Two validated withdrawal assessment tools have been published (Franck et al 2008, Ista et al 2009), the concept of pediatric delirium has been established (Schieveld et al 2007), the focus of withdrawal research has evolved from improving recognition of withdrawal to the identification of risk factors for withdrawal (Best et al, 2016) and most recently, the constructs of withdrawal and delirium appear to be merging (Schieveld et al 2013) and the challenge of differentiating between them has been recognised (Madden et al 2017).

The changes in the component studies of this thesis and the developments in the theoretical landscape have highlighted the complexity of the clinical context within which withdrawal assessments in critically ill children are performed. In turn this has impacted on and broadened the working hypothesis and research questions and provided the theoretical framework of judgement and decision-making.

1.3 Structure of the thesis

This thesis comprises six studies and is presented in twelve chapters, within five parts (See Table 1.1). Part 1 is composed of the first three chapters (Introduction, Literature review and Methodology). Part 2 addresses Chapters 4, 5 and 6 (Studies 1, 2 and 3). Part 3 presents Chapter 7 (Study 4). Part 4 presents Chapters 8 and 9 (Studies 5 and 6). Part 5 presents Chapters 10, 11 and 12 (Integration, synthesis and conclusions). A summary preview of each chapter completes the introduction to this thesis.

Part 1: Introduction. Three chapters are presented in this section.

Chapter 1: Introduction. This chapter introduces the subject of sedation withdrawal and describes the clinical impetus for undertaking the studies in the thesis.

Chapter 2: Literature Review and critical analysis of withdrawal assessment tools. This chapter will provide important background information regarding the key clinical syndromes of withdrawal and pediatric delirium and related pharmacological concepts of physical dependence, adverse drug reactions and opioid conversions. The two validated withdrawal assessment tools, the Withdrawal Assessment Tool -1 (Franck et al 2008) and the Sophia Observation Scale (Ista et al 2009) are presented.

Table 1.1 The presentation of studies in the thesis.

Part	Chapter	Title
Part 1 Introduction	1	Introduction
	2	Literature review and critical analysis of withdrawal assessment tools
	3	Methodology
Part 2 Nurse assessment	4	Study 1 Retrospective evaluation of SWS
	5	Study 2 Comparison of OBWS and SBOWC
	6	Study 3 Pragmatic review of the WAT-1 data set
Part 3 Nurse judgement	7	Study 4 The Nurse Perspective
Part 4 Parent perspective	8	Study 5 Parent recall of SWS signs
	9	Study 6 Parents' experiences
Part 5 Towards a theory of withdrawal in critically ill children.	10	Case studies as test cases
	11	Withdrawal sign synthesis
	12	Conclusions, contributions, implications

This review highlighted the lack of theoretical and operational clarity regarding withdrawal, including an operational definition, risk factors, empirical indicators, assessment approach and treatment. As part of the critical consideration of the literature a propositional model was constructed to make explicit the causal relationships between the factors linking sedation, physical dependence and withdrawal syndrome in the critically ill child.

Chapter 3: Methodology. This chapter will provide the rationale for the choice of an interactive multistage mixed methods design, comprising explanatory sequential and

convergent components to answer the research questions. The additional study investigating the nurses' perspective introduced/ embraced the notion of subjective reality; people perceive things differently. The move away from the deductive truth of rationalism towards the induction and abduction of empiricism, prompted a realigning of the thesis research methodology towards a pragmatic mixed methods approach.

The theories of judgement and decision-making provide the analytical framework for this thesis. Decision-making theory is pertinent to each of the component studies. The studies cover the clinical utility and generalisability of withdrawal assessment tools, nurse judgement and decision-making and parental perception and interpretation of their critically ill child's behaviours. A conceptual model of withdrawal assessment is presented showing how each component study provides a different perspective of withdrawal signs. The conceptual model and provides the structure for the presentation of the thesis which will be presented in sections, according to the model.

A thesis map of the mixed methods studies comprising the qualitative, quantitative and mixed methods components is presented. Integration is a key component of mixed methods research and delineates mixed methods aims from qualitative and quantitative aims.

Part 2: Nurse assessment. This section comprises three chapters, presenting three studies which focus on the existing approach to withdrawal assessment using different withdrawal assessment tools.

Chapter 4: Study 1. The retrospective evaluation of SWS. The aim of this study was to evaluate the psychometric properties of the SWS tool with the purpose of establishing whether improvements were indicated. The highest SWS score was selected and the likelihood of withdrawal at that time point was assigned. In the absence of an existing measure that could be retrospectively applied, criteria were developed drawing on current criteria for diagnosis of withdrawal from opioid and sedative drugs in adult practice and for assessing the probability of adverse drug reactions in adults.

The findings from this study demonstrated a variation in presentation of patients with different levels of likelihood of withdrawal. The accuracy of the operational cut-point for withdrawal was calculated and discussed in light of this heterogeneous presentation. The disparity between a dichotomous cut point and treatment options was highlighted. Analysis of the data highlighted occasions when the motivation for undertaking a

withdrawal assessment was unclear. These findings were unexpected, due to the widely held assumption that nurses consider the clinical context during the assessment and exclude other causes for the behaviours (Ista et al 2013, Harris et al 2016).

Chapter 5: Study 2. Comparison of OBWS and SBOWC. The aim of this study was to compare the characterisation and operationalisation of withdrawal across different sites. The purpose of this study was to identify to what extent there is a shared or generalisable component of the construct of withdrawal and to consider how this comparison might aid understanding about the construct of withdrawal and add to the existing knowledge base of withdrawal. Similarities and differences in the assessment and presentation of babies and children undergoing withdrawal assessments were examined. The data were drawn from the results of two published studies (OBWS (Franck et al 2004) and SBOWC (Ista et al 2008)) and transformed to enable comparison.

Chapter 5: Study 3. A pragmatic review of the WAT-1 study data. The aim of the study was to critically evaluate the operationalisation of withdrawal underpinning the construction and validation studies of WAT-1. This study demonstrates the influence that different perspectives can have on the presentation and meaning of a single dataset. WAT-1 (Franck et al 2012) was developed as part of a large multicentre sedation study (Curley et al 2015). Other studies reporting secondary analysis of this study data, in relation to withdrawal assessment have been included for the additional perspectives they contribute.

WAT-1 was critically reviewed in Chapter 2 using a realist framework reflecting the quantitative nature of the study. A contrasting approach was taken to the evaluation of these studies offering multiple perspectives, reflecting the pragmatic ontology, decision-making perspective and inductive/abductive methods underpinning this thesis. Krathwohl's (2009) standards for credible results provided the pragmatic framework.

Part 3: Nurse Judgement. This section comprises one chapter, presenting a study which focuses on the decision-making stages involved in undertaking a withdrawal assessment.

Chapter 7: Study 4. The Nurse Perspective. The aim of this study was to explore nurses' decision making when using the SWS with the purpose of identifying and understanding variations in use of the tool. Using two developmental vignettes during cognitive interviews, nurses described how they diagnosed withdrawal and how they defined and recognised four of the component items (insomnia, irritability, respiratory distress and

hypertonicity) in the SWS tool. The existing withdrawal assessment presents a significant cognitive burden and does not diminish the potential for cognitive error.

Part 4: The Parent Perspective. This section comprises two chapters, presenting two studies which focus on the parent perspective of withdrawal.

Chapter 8: Study 5. Mixed methods study of parent's recollections off, and distress evoked by, signs of withdrawal, in children less than 5 years of age and
Chapter 9: Study 6. A multiple case study of parents' experiences of their child's withdrawal

Studies 5 and 6 are a nested multiple case study exploring parents recall and impressions of their child's withdrawal using questionnaires and interviews. The aim of study 5 was to examine parents' recall of SWS signs when their child was withdrawing and the distress these signs evoked. The aim of study 6 was to further explore parents' perceptions of their child's withdrawal and ascertain the acceptability of a potential role for parents in withdrawal assessment. Findings revealed that parents recalled both SWS and other behaviours and also described behaviours suggestive of other differential diagnoses in addition to withdrawal. Most parents were receptive to the idea of participating in withdrawal assessments in collaboration with nurses, to share their unique perspective of their child. This was perceived as reducing rather increasing their stress burden.

Part 5: Towards a theory of withdrawal in critically ill children. This section presents the concluding three chapters in the thesis, integrating and synthesising the findings from the studies.

Chapter 10: Case studies as test cases. Theoretical substruction provided the framework linked to the propositional model identified in Chapter 2 to identify the gaps in the existing theoretical basis for withdrawal assessment. Findings from Studies 1-5 sought to illuminate those gaps. The lack of such a framework for withdrawal and the presence of poorly defined construct and concepts have hampered evaluation of findings in the studies in this thesis.

An adverse drug reaction (ADR) causality assessment tool was adapted by the researcher and renamed the Withdrawal Causality Assessment Tool (W-CAT). The W-CAT was applied to five case studies derived from Study 5 to test clinical utility.

Chapter 11: Withdrawal sign synthesis. The integration chapter merges the findings from each of the component quantitative and qualitative studies in relation to the signs of withdrawal in critically ill children. Integrating the findings from the SWS evaluation, nurse perspective and parent perspective in relation to behavioural signs facilitates a more complete understanding of the construct to emerge, compared with either qualitative or quantitative results alone.

Chapter 12: Conclusions, original contribution to knowledge and implications for practice and policy. The final chapter summarises the findings of the thesis introduces a new construct of and diagnostic criteria for Paediatric Withdrawal Syndrome, and proposes a propositional model.

The main contributions of this thesis arise from recognition of the complexity that surrounds the withdrawing child. The theoretical proposition is that withdrawing patients share diagnostic features, rather than a specific presentation in common. This proposition challenges the existing approach to withdrawal assessment, which relies on a shared presentation.

Chapter 2: Literature review and critical analysis of withdrawal assessment tools

2.1 Introduction

In this chapter an integrative review of the literature regarding withdrawal syndrome will be discussed with the aim of determining the evidence base for the existing approach to the assessment and management of withdrawal syndrome. This review has evolved over time, in response to findings from the studies in this thesis. As a consequence a range of competing differential diagnoses for children being assessed for withdrawal syndrome, including Pediatric Delirium (PD), is also presented. The term PD is presented with the US spelling, which reflects the origins of the literature about this syndrome.

The review will consider what is known about withdrawal syndrome in critically ill children and the challenges in identifying withdrawal in light of other differential diagnoses that coexist in the critically ill child. Following this, a critical review the two validated withdrawal assessment tools is presented; the Withdrawal Assessment Tool -1 (WAT-1) (Franck et al 2008) and the Sophia Observation Scale (SOS) (Ista et al 2009).

2.2 Search strategy

All peer-reviewed publications that referred to withdrawal syndrome or delirium in children aged less than 18 years were identified for consideration. Studies were primarily identified through online searches using Medline, EMBASE and CINAHL. The date of the last search attempt was July 2017. No start date was specified for the literature searches and the final articles included in the review dated from 1986 to 2017.

The search terms included the following terms “withdrawal syndrome”, “delirium” “pediatric” and “critical care.” Limits were set to include only human populations from birth to 12 years of age (including preschool and child but not adolescent populations) in English language, peer reviewed articles. The detailed search strategy is shown in Tables 2.1 and 2.2. Reference lists of articles were also examined. Articles describing Neonatal Abstinence Syndrome or Emergence Delirium were excluded manually.

Table 2.1 Search strategy for Withdrawal syndrome

	Search term used for withdrawal syndrome in critically ill children	Medline results	EMBASE results	CINAHL results
1	Exp "Substance withdrawal syndrome" OR ("Substance withdrawal syndrome").ti,ab OR ("withdrawal syndrome").ti,ab	22872	31776	2838
2	Exp "critical illness" OR exp "Intensive care units, pediatric" OR ("critical illness"). ti,ab OR ("paediatric intensive care unit*").ti,ab OR ("pediatric intensive care unit*").ti,ab	43816	36125	17040
3	1 AND 2 (filtered)	73	27	64

Filters: English, human, child (infant and child)

Table 2.2 Search strategy for Pediatric Delirium

	Search terms used for Pediatric delirium	Medline results	EMBASE results	CINAHL results
1	Exp delirium OR (delirium).ti,ab	13060	27007	4704
2	Exp "critical illness" OR exp "Intensive care units, pediatric" OR ("critical illness"). ti,ab OR ("paediatric intensive care unit*").ti,ab OR ("pediatric intensive care unit*").ti,ab	43816	36125	17040
3	1 AND 2 (filtered)	57	79	28

Filters: English, human, child (infant and child)

2.3 Physical dependence and withdrawal

Physical dependence is the physiological adaptation in response to repeated administration, which necessitates the continued presence of the drug(s) to maintain the modified physiological equilibrium (Jenkins 2002). When these drugs are reduced or withdrawn, the adaptive mechanisms take time to readjust and are manifested as the unpleasant behavioural signs of withdrawal syndrome (Jenkins 2002). Withdrawal syndromes are a class of adverse drug reactions (ADR), occurring when drugs capable of causing physical dependence are stopped or reduced after prolonged use. Withdrawal syndrome is classed as a Type E or end-of-use ADR (Edwards and Aronson, 2000). An ADR is a response to a drug which is noxious and unintended (ICH, 1994); a reaction that "warrants prevention, treatment, alteration of the dose regime, or withdrawal of the product" (Edwards and Aronson 2000, p1255). Classes of drugs causing physical dependence in babies and children in critical care include opioids, such as morphine and fentanyl, sedative, hypnotic or anxiolytic drugs, such as benzodiazepines and chloral

hydrate and the inhaled anaesthetic, isoflurane. This review will consider the diagnosis, incidence, risk factors and treatment of withdrawal in critically ill children.

2.3.1 Diagnosing withdrawal

Drugs causing physical dependence are more commonly prescribed to adults rather than children, so the adult literature was also reviewed. The Diagnostic and Statistical Manual of Mental Disorders (DSM) provides diagnostic criteria for withdrawal for opioid and sedative, hypnotic or anxiolytic drug classes (DSM-5, 2013). In addition to a drug-specific criterion, there are three standard criteria for diagnosing substance withdrawal;

- a change in behaviour causing significant distress or impairment,
- a temporal link to the reduction or stopping of a drug,
- the change in behaviour is not due to another medical condition or disorder (Table 2.3).

Table 2.3 Criteria for substance withdrawal (DSM-5 2013)

Criterion A	The development of a substance-specific problematic behavioural change, with physiological and cognitive concomitants, that is due to the cessation of, or reduction in, heavy and prolonged substance use.
Criterion B	Substance specific withdrawal symptoms developing within minutes to several days after Criterion A:
Criterion C	The substance-specific syndrome causes clinically significant distress or impairment [in social, occupational, or other important areas of functioning].
Criterion D	The symptoms are not due to another medical condition and are not better explained by another mental disorder.

The substance specific criteria set for opioid and sedative, hypnotic or anxiolytic withdrawal is shown in Table 2.4. Some symptoms are common to the withdrawal syndromes of both classes of drugs; these symptoms are shown in bold type.

2.3.2 Withdrawal in critically ill children.

Withdrawal in critically ill children differs to adults in three of the DSM-5 diagnostic criteria. In Criterion A, substance use may not be prolonged, as withdrawal has been described after as little as four days continuous treatment of opioids and benzodiazepines (Franck et al 2004). “Heavy” use may not be a relevant concept in this population, but the causal relationship between peak doses, cumulative doses and

withdrawal has been investigated (Da Silva et al 2016, Amigoni et al 2014, Franck et al 2012, Ista et al 2013). Studies draw different conclusions about whether these variables are risk factors for withdrawal or not, as the table drawn up from the literature by the researcher, demonstrate (Table 2.5).

Table 2.4 Examples of drug-specific withdrawal symptoms (DSM-5 2013)

Opioid withdrawal (e.g morphine, fentanyl)	**Sedative, hypnotic or anxiolytic withdrawal** (e.g benzodiazepines)
Dysphoric mood **Nausea or vomiting*** Muscle aches Lacrimation or rhinorrhea Pupillary dilation, piloerection or **sweating*** Diarrhoea Yawning **Fever*** **Insomnia***	Autonomic hyperactivity (e.g. **sweating***, increases in heart rate, respiratory rate, blood pressure or **body temperature***) Hand tremor **Insomnia*** **Nausea or vomiting*** Transient visual, tactile, or auditory hallucinations or illusions Psychomotor agitation Anxiety Grand mal seizures

*Symptoms common to both withdrawal syndromes are shown in **bold**

Table 2.5 Risk factors, incidence and treatment of withdrawal syndrome in critically ill children

Characteristic	Finding	Author
Risk factors	Midazolam peak dose > 0.35 mg/kg/hr	Da Silva 2016
	Midazolam peak dose > 0.42 mg/kg/hr	Amigoni 2014
	Midazolam, cumulative dose (Yes)	Franck et al 2012, Ista et al 2013.
	Midazolam, cumulative dose (No)	Amigoni 2014
	Fentanyl, cumulative dose (Yes)	Franck et al 2012
	Opioid peak dose (No)	Amigoni 2014

In Criterion B more than one drug may be implicated. Opioids and sedative drugs are administered to children in PICU to minimise the child's distress from, and to promote compliance with, mechanical ventilation. The most common opioid/sedative drug combination administered to critically ill children in the UK is morphine and midazolam (Blackwood and Tume 2015) and this was the drug combination that patients were being weaned from in the validation studies of WAT-1 and SOS (Franck et al 2008, Ista et al 2009). However, more than 20 opioid and sedative drugs are administered to patients in PICU (Playfor 2003, Jenkins 2007) and each class of drug will have substance specific

withdrawal symptoms. Withdrawal from Isoflurane, an inhalational anaesthetic agent, has been reported in children (Arnold et al 1993, Hughes et al 1993, Kelsall et al 1994, Sackey et al 2005, Cooper and Bateman 2007). Data from these case reports and short case series was collated by the researcher to characterise isoflurane withdrawal (Table 2.6). In these cases, the substance specific withdrawal symptoms were profound agitation, seizures, motor disturbances, hallucinations and confusion for up to 5 days. In Criterion D numerous other differential diagnoses exist, which share behaviours in common with, and risk factors for withdrawal. These differentials include the patient's primary medical condition (Franck et al 2008), pre-existing behaviours, pediatric delirium and other adverse drug effects including drug-drug interactions and adverse drug reactions such as neuroleptic malignant syndrome, akathisia and non-convulsing status epilepticus (Schieveld et al 2007, Pershad et al 1999, Godinho et al 2002, Mejia and Jankovic 2016, Abend and Duglos 2007). The researcher compared the clinical features and risk factors of these differential diagnoses to demonstrate the similarities in presentation of these conditions (Table 2.7). Whilst there is an assumption that the nurse will exclude other causes for behaviours during a withdrawal assessment (Harris et al 2016), this step is neither an integral component of the tools nor practical given the similarity in presentation of these differentials.

2.3.4 Diagnosing withdrawal in critically ill children

Three published tools have been developed to monitor withdrawal in children; the Sedation Withdrawal Score (SWS) (Cunliffe et al 2004), the Withdrawal Assessment Tool (WAT-1) (Franck et al 2008) and the Sophia Observation Score (SOS) (Ista et al 2009). Each is a checklist of non-specific signs that, in combination, appear to support a diagnosis of withdrawal. The researcher compared the item content of the three tools to identify similarities and differences of item content (Table 2.8). The tools share items in common and have a combined item pool of 22 withdrawal behaviours. Six behaviours (27%) are common to all three tools, a further six (27%) are shared by two tools and the remaining ten (46%) occur in one tool only. The diagnostic principle, upon which these tools are based, is the correlation between an increasing number of non-specific withdrawal behaviours and intensity of withdrawal, as proposed by Finnegan et al (1975) during the development of the Neonatal Abstinence Score (NAS).

Table 2.6 Case reports of withdrawal syndrome after Isoflurane

Author	Pt	Age	Gender	Diagnosis	Duration of Isoflurane	Behaviours after isoflurane stopped	Concurrent sedatives
Arnold et al (1993)	1	9 mo	NR	Bronchiolitis	95 hours	No behavioural complications	Opioid and benzodiazepines
	2	6y	NR	Pulmonary haemorrhage	6 days	No behavioural complications	Opioid and benzodiazepines
	3	4y	Male	Radiation pneumonitis	32 days	Marked hypertension, tachycardia, agitation, diaphoresis, and diarrhoea	Opioid and benzodiazepines
	4	6mo	Female	Bronchiolitis	73 hours	No behavioural complications	Opioid and benzodiazepines
	5	3wk	NR	Congenital diaphragmatic hernia	30 hours	No behavioural complications	Opioid and benzodiazepines
	6	2.5y	NR	Near drowning	10 days	Marked agitation, choreoathetoid movements	Opioid and benzodiazepines
	7	4y	NR	Bacterial pneumonia	7 days	Marked agitation, non purposeful movements	Opioid and benzodiazepines
	8	6mo	NR	Bacterial pneumonia	17 days	Marked agitation, tremulous non purposeful	Opioid and benzodiazepines
	9	19y	NR	Status asthmaticus	29 hours	No behavioural complications	Opioid and benzodiazepines
	10	6mo	NR	Aspiration pneumonia	18 days	Marked agitation, non purposeful movements	Opioid and benzodiazepines
Hughes et al (1993)	11	7y	Male	15% burns	NR	Hallucinations, generalised seizure, disorientation for 5 days	NR
Sackey et al (2005)	12	11/12y	Male	Acute pancreatitis, abdominal sepsis	6 days	Clonus L foot, resolved in 48h. ? but sedatives increased/ commenced <24h after stopping Isoflurane.	Morphine, clonidine

	13	9y	Male	Status epilepticus	2 x 96 hours, with 48 hours between	Two seizures, no other typical withdrawal signs or surgical abnormalities	Midazolam restarted 24h before Isoflurane weaned and stopped.
	14	4y	Male	Hirshsprungs, abdominal sepsis	Almost 8 days	Involuntary movements and ataxia, resolved over 4-5 days	Morphine, midazolam, clonidine.
Cooper and Bateman (2007)	15	4y	Female	Bronchospasm Ex prem, Chronic lung disease	64 days	Profound choreoathetoid movements causing significant bronchospasm, difficulty with secretions, and poor respiratory coordination. Jittery, muscle twitching.	Fentanyl and lorazepam weaned to off.
Kelsall et al (1994)	N= 12	NR	NR	Croup/ epiglottitis	>24 hours	Reversible ataxia, agitation, hallucinations and confusion ≤72 hours	NR
	N= 5	NR	NR	Croup/ epiglottitis	1-15 hours	No neurologic dysfunction	NR

NR = not recorded

Table 2.7 Differential diagnoses for critically ill children treated with opioid and sedative drugs

Author	Differential diagnosis	Clinical features				Risk factors
		Consciousness	Motor disturbance	Autonomic effects	Other	
Schieveld et al (2007)	Pediatric delirium	Reduced awareness	Purposeless actions	Autonomic dysfunction	Inconsolability	High dose and/or prolonged use of opioids and/or benzodiazepines
Pershad et al (1999)	Drug- drug interaction (Chloral and furosemide)		Agitation	Sweating, flushing, tachycardia, alterations in blood pressure		Occurs within 5 mins of dose of furosemide, lasts 15-20 mins, if chloral given within previous 24 hours.
Godinho et al (2002)	Neuroleptic malignant syndrome	Confused, altered consciousness	Rigid muscles	Temperature > 38C, autonomic imbalance		Promethazine, chlorpromazine, rapid withdrawal of benzodiazepines.
Mejia and Jankovic (2016)	Akathisia		Need for constant motion, restless legs		Inner sense of restlessness	Promethazine, chlorpromazine, rapid withdrawal of opioids and/or benzodiazepines.
Abend and Duglos (2007)	Non-convulsing status epilepticus	Fluctuating consciousness	Motor disturbance	Autonomic dysregulation	Complex cortical functions disrupted	Acute withdrawal from sedative-hypnotics

In the UK, just under half of PICUs (10 of 23) use withdrawal assessment tools, with WAT-1 most commonly used (n=5), followed by SWS (n=4) and SOS (n=1) (Blackwood and Tume 2015). The SWS is the withdrawal assessment tool and treatment protocol developed and used in the study hospital since 2002. The SWS has proven clinically useful in identifying withdrawal signs in PICU and ward-based patients, but has not been validated (Macqueen & Bruce 2012). Both WAT-1 (Franck et al 2008) and SOS (Ista et al 2009) have been validated but rigorous psychometric testing was hampered by the lack of a gold standard, and clinical utility is further limited by the lack of treatment protocols linked to identified cut points. A critical review of WAT-1 and SOS will be presented later in the chapter.

Table 2.8 Comparison of withdrawal behaviour content in SWS, SOS and WAT-1.

Withdrawal sign	Agreement	SWS	SOS	WAT-1
Sweating	Item occurs in all 3 tools.	✓	✓	✓
Tremor		✓	✓	✓
Fever		✓	✓	✓
Diarrhoea		✓	✓	Loose, watery stool
Vomiting		✓	✓	and retching, gagging
Hypertonicity		✓	✓	✓
Insomnia	Item occurs in 2 of 3 tools.	*✓	✓	
Irritability		✓	✓	
Respiratory distress		✓	Tachypnoea	
High pitch cry		✓	Inconsolable crying	
Sneezing		✓		✓
Motor disturbance			✓	Uncoordinated, repetitive movement
Agitation	Item occurs in 1 tool only.		✓	
Hallucinations			✓	
Convulsion		✓		
Yawning				✓
Tachycardia			✓	
Grimacing			✓	
Startle to touch				✓
SBS**≥ +1				✓
Time to regain calm state (SBS≤ 0)				✓
Anxiety			✓	
Item total		12	15	12

*originally 'hyperactivity' in Cunliffe (2004)

**SBS State Behavioural Score (Curley et al 2006)

2.3.5 Scale development and item content

Withdrawal cannot be measured directly, so withdrawal assessment scales have been developed to infer the existence of withdrawal from observable behavioural consequences. Measurement theory requires that "items must share one and only one underlying variable if they are to be combined into a scale" (DeVellis, 2012 p.159). This means items in a withdrawal assessment share a single common cause (of withdrawal). In the absence of characteristic signs of withdrawal, signs, either singly or in combination, are indicative of withdrawal only if a temporal relationship exists with a recent reduction or stopping of a drug capable of causing physical dependence; conditions which correspond to Criteria A, B and C (DSM-5 2013). However, even in this context, the same combination of equivocal signs might indicate another differential diagnoses, including those listed in Table 2.7. Madden et al (2017) have demonstrated this challenge recently in their paper describing the overlap in features of withdrawal, delirium and anticholinergic drug toxicity in critically ill children. If there are other coexisting causes for these signs, Criterion D (DSM-5 2013) may not be met. The complexity of the context within which withdrawal assessments occur cannot be underestimated; a level of uncertainty that is not reflected in a dichotomous yes/no diagnosis of withdrawal.

The item pool for SWS, WAT-1 and SOS was derived predominantly from case reports and short case series published over 20 years, from the mid-1980s. The demographic details of the cases reported are shown in Table 2.9 and the withdrawal signs reported are shown in Table 2.10. This literature provides a rich description of the withdrawal behaviours first documented in children and young people after treatment with opioids and benzodiazepines. These behaviours can be broadly delineated as abnormal movements, communication disturbances, neurological instability, autonomic signs, symptoms (relying on patient self-report, rather than observable signs) and other signs. All categories contributed items to one or more of the tools (SWS, WAT-1 and SOS) except for "communication disturbances." Whilst absent from withdrawal assessments, communication disturbances, defined as "inattention" is the most fundamental sign of pediatric delirium (Smith et al 2016). This suggests that the early literature, whilst reporting what the authors considered to be withdrawal syndromes, and in the absence of either withdrawal, or delirium assessment tools, may also have been describing children and young people with delirium.

Table 2.9 Demographics of early sedation and/or opioid withdrawal case reports in children							
Author	No of patients	Age	Gender	Diagnosis	Opioid	Midazolam	Duration of treatment
Miser et al (1986)	N=2	15y	Female	Osteosarcoma	Hydromorphone	No	7 days
		14y	Male	Leukaemia	Hydromorphone	No	7 days
Sury et al (1989)	N=3	4y	Male	Pneumonia	Morphine	Yes	7 days
		11y	Female	Asthma	Morphine	Yes	14 days
		12y	Female	Asthma	Morphine	Yes	17 days
Lane et al (1991)	N=5	1.9y	Male	Closure of abdominal defect	Fentanyl	Yes	7.8 ±4.9 days
		1.9y	Female	Croup	Fentanyl	No	
		0.5y	Male	Subglottic stenosis	Fentanyl	Yes	
		2y	Male	Subglottic stenosis	Fentanyl	Yes	
		3.5y	Female	Subglottic stenosis	Fentanyl	Yes	
Bergman et al (1991)	N=3	5 mo	Female	Bronchiolitis	Fentanyl	Yes	6 days
		15mo	Female	Wheezing	Fentanyl	Yes	10 days
		3mo	Female	Repair left anomalous coronary artery	Fentanyl	Yes	5 days
Van Engelen et al (1993)	N=2	15mo	Male	Septicaemia		Yes	12 days
		14day	Male	Repair of patent ductus arteriosus	Nicomorphine	Yes	29 days
Hughes et al (1994)	N=4	1.3y	unknown	Croup	Morphine	Yes	77h
		1.7y	unknown	Croup	Morphine	Yes	37h
		3y	unknown	Croup	Morphine	Yes	189h
		3y	unknown	Epiglottitis	Morphine	Yes	22h
Hughes (1994)	N=1	18mo	Female	Repair of Fallot's Tetralogy	Diamorphine Fentanyl	No	7 days 14 days
Ducharme et al. (2005)	N=1	40mo	Male	Tracheolaryngoplasty	Fentanyl	Yes	7 days
(Carnevale and Ducharme 1997)	N=5	11mo	Female	Repair of Fallot's Tetralogy	Fentanyl	Yes	3 days

		7mo	Male	Skull fracture	Fentanyl	Yes	8 days (Fent) 9 days (Midaz)
		16mo	Female	30% burn	Morphine	Yes	24 days (Morph) 16 days (Midaz)
		2mo	Male	Bronchiolitis	Fentanyl	Yes	5 days (Fent) 6 days (Midaz)
		5mo	Female	Bronchiolitis	Fentanyl then morphine	Yes	16 days

Y = years; mo = months

Table 2.10 Signs and symptoms of withdrawal identified from early case reports (1986-2005) in children and young people after treatment with opioids and benzodiazepines.

Abnormal movements	Communication disturbance	Neurological instability	Autonomic signs	Symptoms	Other signs
Chorea Myoclonus Ataxia **Constant choreathetotic movements of head, face, tongue, extremities when awake.** Frequent dyskinetic movements Puppet- like movements Non-purposeful movements Moving all 4 limbs vigorously **Small amplitude choreic movements of hands, feet, tongue** **Grimacing** **Odd repetitive facial grimacing** **Rapid repetitive tongue thrusting** **Twitch** **Stiff posture** **Hands fisted**	Uncommunicative Not recognising parents Poor visual following Globally aphasic No social interaction Unaware of parent's presence Unresponsive to mother/ nursing staff Inconsistent/ not fixing/following	**Insomnia** **Convulsions** Jittery **Hyperactive** **Irritability** **Tremor** **Restlessness** Fussy	**Tachypnoea** **Tachycardia** **Pyrexial** Chilling without fever	Abdominal pain **Anxiety** Disorientation **Visual hallucinations** **Auditory hallucinations**	**Inconsolable crying** **Gagging** Poor feeding **Vomiting** Itching Aggressive Inappropriate laughter Aerophagia **Looking at objects in the air** **Reaching out for objects in the air, picking at clothes as if visual hallucinations**

Items in **bold** occur in one or more of SWS, WAT-1 and SOS.

One of these original withdrawal papers (Sury et al 1989) has recently been interpreted by Hatherill et al (2009) as reporting delirium in children undergoing benzodiazepine withdrawal. These observations, along with similarities in both risk factors and presentation point to a possible association, or coexistence between withdrawal and delirium in critically ill children. In light of this, the literature on assessment of pediatric delirium will be reviewed briefly.

2.4 Pediatric delirium

Delirium is an acute brain dysfunction caused by systemic illness or the effects of treatment, which is characterised by acute onset, fluctuating course and disturbance of awareness and cognition (Schieveld et al 2007, Turkel et al 2013, Traube et al 2014). The DSM diagnostic criteria for delirium (Table 2.11) are applicable in children (Turkel et al 2013). The delirium assessment relies on verbal communication and diagnosis is usually undertaken by a psychiatrist.

Table 2.11 DSM-5 criteria for delirium (DSM-5, 2013)

Criterion A	A disturbance of attention (i.e reduced ability to direct, focus, sustain and shift attention) and awareness (reduced orientation to the environment).
Criterion B	The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
Criterion C	An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
Criterion D	The disturbances in Criteria A and C are not better explained by another pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.
Criterion E	There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of another medical condition, substance intoxication or withdrawal, or exposure to a toxin, or is due to multiple aetiologies.

In pre-verbal infants and toddlers, recognition of behaviours synonymous with the disrupted regulation of state and attention are critical to the diagnosis, due to the challenge of assessing perceptual disturbances, such as hallucinations, in children under 3 years of age. (Turkel et al 2013). As the majority of patients in PICU are less than one year of age (Schieveld et al 2013), behaviour-based tools have been developed to allow for assessment of the youngest critically ill patients using DSM diagnostic criteria (Traube et al 2014, Smith et al 2016).

2.4.1 The Cornell Assessment of Pediatric Delirium (CAPD) tool (Traube et al 2014)

The CAPD tool (Traube et al 2014) contains eight behavioural items, which operationalise the diagnostic domains of consciousness (awareness) and cognition (including orientation), and also measures psychomotor activity and affect/distress (See Table 2.12). Each item taps into one or more of these domains and is scored 0-4 depending on the frequency that it is observed. A CAPD score greater than 9 indicates pediatric delirium. The CAPD is validated from birth and anchor points for seven developmental stages between newborns and 2 year olds have been published to aid and standardise assessment (Silver et al 2015).

Table 2.12 The Cornell Assessment of Pediatric Delirium Items and DSM domains (Traube et al 2014)

	Item	DSM Domain
1	Does the child make eye contact with the care giver?	Consciousness
2	Are the child's actions purposeful?	Cognition
3	Is the child aware of his/her surroundings?	Consciousness Orientation
4	Does the child communicate needs and wants?	Consciousness Psychomotor activity
5	Is the child restless?	Cognition Psychomotor activity Affect/distress
6	Is the child consolable?	Orientation Cognition Affect/distress
7	Is the child underactive – very little movement when awake?	Orientation Affect/distress
8	Does it take the child a long time to respond to interactions?	Consciousness Psychomotor activity

2.4.2 The Preschool Confusion Assessment Method for ICU (psCAM-ICU) (Smith et al 2016)

The psCAM-ICU (Smith et al 2016) is valid from 6 months, and categorises the features of pediatric delirium as mental status, inattention, altered level of consciousness and disorganised brain (Table 2.13). The first criterion; an acute change or fluctuating course of mental status performs the function of a starting rule; if this behaviour is absent, the diagnosis of pediatric delirium does not need to be considered and no further assessment is required. This is an elegant feature of this tool.

Table 2.13 Delirium components of the psCAM-ICU (Smith et al 2016)

Delirium feature	Behavioural components
Feature 1: mental status	Acute change in mental status Fluctuation in mental status
Feature 2: inattention	No eye contact No tracking of the cards* No purposeful action Attends to ≤7 cards* Lack of attention between prompts
Feature 3: altered level of consciousness	Alert and calm vs other
Feature 4: disorganised brain	Inconsolability Unawareness of surroundings Sleep-wake cycle disturbance

*Mirror and picture cards are used as a standardised visual stimulus.

However, debate about behavioural components of two of the features has arisen, pointing to the challenges of agreeing behavioural manifestations of the underlying pathophysiology of brain dysfunction. In psCAM-ICU, "no purposeful action" is a feature of inattention and "unawareness of surroundings" is a feature of disorganised brain. Schieveld et al (2016) consider the reverse is more accurate ("unawareness of surroundings" suggests inattention and "no purposeful action" suggests disorganised brain).

Some features of pediatric delirium are similar to features of withdrawal, such as inconsolability, insomnia and restlessness. Strikingly, each of the communication disturbances described in the original withdrawal case reports, which were absent from withdrawal tools (Table 2.10), subsequently feature in one or both of these delirium tools. The overlap of signs between pediatric delirium and withdrawal presents a risk that these conditions may be confused or hard to differentiate. With similar risk factors it is also possible that withdrawal and pediatric delirium may co-exist in critically ill children undergoing weaning of analgesic and sedative drugs. It is also unclear whether inattention is a sign of withdrawal, as the earlier case reports suggest, or is a sign of both withdrawal and pediatric delirium.

2.4.3 Recognising subtle behavioural changes

Assessing inattention and unawareness of surroundings in the youngest patients might be challenging for a clinician who is unfamiliar with the baby and their developmental baseline. This issue has been dealt with in different ways by research teams. Smith et al (2016) report these features and other subtle neuropsychiatric behaviours might be more

difficult for a clinician to recognise, limiting their sensitivity or specificity for delirium. Hatherill et al (2009, p.160) describe the primary caregiver as "a crude yardstick against which apparent deficit can be measured in relation to usual functioning". Despite this ungenerous description, Hatherill (2009, p.163) subsequently appreciated parental input in recognising subtle behavioural changes, preferred their presence at the bedside for all assessments and valued parents as "a cornerstone of the environmental management" of young children with delirium. The participation of the primary caregiver features substantially in the CAPD assessment, incorporated in behavioural anchor points for three of the items, such as "holds gaze, prefers primary parent", "upset when separated from preferred caregivers" and "not soothed by usual comforting actions."

2.5 Distinguishing between differential diagnoses

The possibility of delirium superimposed on withdrawal in critically ill children raises similar diagnostic challenges to the issues that delirium superimposed on dementia (DSD) raises in older adults. When delirium occurs concurrently with a pre-existing dementia, delirium is frequently unrecognised or misattributed to dementia (Inouye et al, 2001). Whilst a relationship exists between delirium and dementia, delirium features including an acute change in mental status, impaired attention, symptom fluctuation and altered level of consciousness are not features of dementia (Steis et al 2012). In a study measuring nursing identification of DSD using standardised case vignettes, 83% (n=25) of nurses correctly identified dementia alone, but the diagnoses of delirium only (hyperactive 52% (15), hypoactive 41% (n=12), and DSD (hyperactive 59% (n=17), hypoactive 21% (n=6)) were more challenging (Fick et al 2007). In the hard-to-assess patients with dual diagnoses, these results highlight that the diagnosis was perceived incorrectly by nursing staff about half of the time. In hard-to-assess patients, validated tools are also prone to the same error rate. The CAPD tool showed a specificity of 51.2 % in children with developmental delay (correctly identifying those children without PD only half of the time, compared with 86.5% in children without developmental delay (Traube et al 2014).

These studies demonstrate the difficulties, with cognitive or behavioural assessments, of ascertaining a difference from baseline in patients whose baseline function is not known to the assessor. Acknowledgement of the unique position that family caregivers are in

has led to the development of a screening tool for delirium which is completed by family caregivers (Steis et al 2012). The Family Confusion Assessment Method (FAM-CAM) (Steis et al 2012) demonstrated a high level of agreement with an interviewer rating using a standard diagnostic assessment and a sensitivity and specificity of 88% and 98% respectively. As care providers with most contact with the older person, family caregivers notice characteristic changes promptly; the study concluded that caregivers provided accurate and timely information to determine whether delirium was present, which could then be brought to the attention of clinicians, prior to a formal diagnostic assessment.

2.5.1 Differential diagnosis of withdrawal in conditions of uncertainty

As previously highlighted, a diagnosis of withdrawal is complicated in the paediatric critical care population due to the non-specific behavioural signs of withdrawal and the number of other possible differential diagnoses with a similar behaviour profile. Given the unstable nature of these patients, and in the absence of a definitive diagnosis, a working diagnosis of withdrawal should be continually reviewed in light of the child's overall condition, to detect and treat any clinical deterioration promptly. Causality may also be complicated in this population by the tapering or stopping of more than one opioid or sedative drug concurrently as effective treatment requires the reintroduction of the causal drug rather than any sedative drug (Edwards and Aronson 2000).

A key concept in adverse drug reactions (ADR) is causality, which describes the strength of the causal and temporal relationship between the drug and the undesired effect (Smyth et al 2014). In the absence of a definitive test, an ADR diagnosis is described in terms of probability (certain, probable, possible, unlikely), depending on four criteria (Table 2.10);

1. Temporal relationship between the drug use and the adverse event.
2. Absence of other competing causes (medications, disease process itself).
3. Response to drug withdrawal or dose reduction (dechallenge).
4. Response to drug re-administration (rechallenge).

As withdrawal is a Type E (end-of-use) ADR (Edwards and Aronson 2000), criteria 3 and 4 would be reversed; the harm arising from stopping the drug (dechallenge), with improvement expected if restarted (rechallenge). Classifying the likelihood of withdrawal in infants and children in critical care as probable, possible or unlikely (WHO-UMC, Gill 1995, Gallagher et al 2011) may be better reflect these uncertain withdrawal circumstances, rather than the dichotomous diagnosis of yes/no or absent/present.

Table 2.14 The WHO–UMC causality assessment criteria (https://www.who-umc.org/media/2768/standardised-case-causality-assessment.pdf)

Categories	Temporal relationship	Absence of differential diagnoses	Dechallenge*	Rechallenge*
Certain	Yes	Yes	Yes	Yes
Probable	Yes	Yes	Yes	No
Possible	Yes	No	No	No
Unlikely	No	No	No	No

*Reversed in withdrawal

2.6 Incidence and treatment of withdrawal syndrome in critically ill children

There is considerable difference in the incidence of withdrawal reported between studies, ranging between 5% - 87% (Best et al 2015). It is not clear what the causes for this variation are, but as withdrawal may take up to 36 hours to manifest (Fernandez-Carrion, 2013), the time frame over which monitoring for behavioural signs of withdrawal occurs, may play a part. Other contributing factors may be the different sedative combinations administered in PICU, or the absence of a consistent approach to the detection of withdrawal syndrome and/or a heterogeneous individual presentation of withdrawal. Withdrawal occurs in response to reducing or stopping sedative drugs in the physically dependent patient (DSM-5 2013). In critically ill children, rapid tapering of sedative drugs may occur in patients being prepared for extubation (to avoid opioid induced respiratory depression and maximise the chance for successful extubation) and subsequent discharge from the critical care environment (Best et al 2015). Abrupt discontinuation of sedative drugs may also occur inadvertently due to unexpected loss of intravenous access or as a consequence of vomiting after an oral drug has been administered. In these circumstances the potential for withdrawal may be overlooked, or the more immediate focus on readiness for extubation may take precedence over the possible consequent development of a drug withdrawal syndrome.

Despite the potentially high incidence of withdrawal, there is a paucity of literature regarding the treatment of withdrawal syndrome in critically ill children (Table 2.15). Treatment strategies, where described, include tapering at 10-50% per day and converting to oral equivalents of the causative drugs, slowing or stopping reductions in response to signs of withdrawal and adding in clonidine.

Table 2.15 Treatment of withdrawal syndrome in critically ill children

Author	Weaning protocol
Cunliffe et al (2004)	Continue reducing; stop reducing; increase to previously tolerated dose; seek advice/ add clonidine.
Amigoni et al (2014) DaSilva et al (2016)	10 -20 % reductions per day, convert benzodiazepines to lorazepam and opioids to methadone.
Neunhoeffer et al (2015)	Decrease sedatives by 50% every 24 hours if duration <5 days, or by 10-20% every 24 hours if duration ≥ 5 days. Suspend reductions for 24 hours if SOS ≥4.

2.7 Validated withdrawal assessment tools

The main focus of the research into withdrawal in critically ill children has been on improving the detection of withdrawal. Two validated tools have been published; the Withdrawal Assessment Tool -1 (Franck et al 2008) and the Sophia Observation Scale (Ista et al 2009). These tools will be critically reviewed in this second half of the chapter.

2.8 The Withdrawal Assessment Tool-1 (WAT-1) (Franck et al 2008)

The Withdrawal Assessment Tool – 1 (WAT-1) was constructed and validated within the context of a multicentre clinical trial testing a sedation management protocol on children intubated and mechanically ventilated for acute lung disease in the United States of America (USA) (Franck et al 2008, 2012). The Randomised Evaluation of Sedation Titration for Respiratory Failure (RESTORE) trial required standardised assessments of adverse events including inadequate sedation management and clinically significant iatrogenic withdrawal across 31 study sites (Curley et al 2015). The State Behavioural Scale (SBS) (Curley et al 2006), the tool adopted in the RESTORE trial to assess inadequate sedation, is a component of the WAT-1 tool. A brief overview of the construction and psychometric testing of SBS will be presented prior to a synopsis of the published WAT-1 studies, an overview of the WAT-1 assessment, a comprehensive review of the reliability and validity components of these studies and identification of any omissions in reporting in light of the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) checklist (STARD 2015).

2.8.1 The State Behavioural Scale (SBS) (Curley et al 2006)

The SBS was designed to describe the sedation/agitation level in intubated patients on PICU (Curley et al 2006) (Appendix 2). The SBS score ranges from -3 to +2 and is based on the child's behaviours before, during and after a standard progressive stimulus is applied to elicit a response (Table 2.16). The nature of the response is not specified. The initial validation study for SBS was undertaken on 91 patients, aged 6 weeks to 6 years, sedated with a combination of opioids and benzodiazepines. Exclusions included patients who were in pain, were physiologically unstable, at risk of opioid withdrawal or were receiving neuromuscular blockade. Five distinct levels along the sedation-agitation continuum were identified from the data. The majority of patients were either calm or sedated, with fewer than 10% (n= 8) of patients presenting in an agitated state (SBS +1). Curley et al (2006) added a further level (SBS +2) to represent extreme agitation, based on their clinical experience, although no patients in their study fitted this profile. Validation of this level and further validation studies of SBS are awaited. Given the low levels of agitated behaviour displayed and the exclusion of children at risk of opioid withdrawal, this study casts serious doubt on the reliability or rationale for including SBS in a withdrawal assessment tool. There also appears to be a blurring of boundaries across the constructs of sedation and pediatric delirium, in light of the recently published delirium tools. Behaviours which are common to both SBS and the delirium tools are inattention, restlessness and inconsolability (Traube et al 2014; Smith et al 2016; Curley et al 2006).

Table 2.16 SBS progressive stimulus (Curley et al 2006)

Sequence	Stimulus	
1	Voice	Nurse says the patient's name in a calm voice.
2	Touch	If no response, nurse says the patient's name and gently touches the patient's body
3	Noxious stimulus	If no response, patient's response to a planned noxious stimulus, such as endotracheal suctioning, or <5 secs nailbed pressure is elicited.

The WAT-1 is a scale consisting of eleven physiological or observational items, which are summed to provide a withdrawal score ranging from 0 to 12 (Franck et al 2008) (Appendix 3). WAT-1 scores ≥ 3 indicate withdrawal. The authors have published two papers containing construction and validity data for WAT-1 (Franck et al 2008, 2012). Both studies took place within the context of a clinical trial testing a sedation management protocol. The inclusion and exclusion criteria WAT-1 are those of the parent RESTORE

trial (Table 2.17). Patients, who were at least two weeks of age and less than 18 years old and who were intubated and mechanically ventilated for acute lung disease, were included in the RESTORE study.

Table 2.17 RESTORE trial inclusion and exclusion criteria

Inclusion criteria	• At least 2 weeks of age (and at least 42 weeks post-menstrual age) and less than 18 years of age • Intubated and mechanically ventilated for acute lung disease
Exclusion criteria	• Cyanotic heart disease with unrepaired or palliated right to left intracardiac shunt • History of single ventricle at any stage of repair • Congenital diaphragmatic hernia or paralysis • Primary pulmonary hypertension • Critical airway or anatomical obstruction of the lower airway • Ventilator dependent upon pediatric ICU admission • Neuromuscular respiratory failure • Spinal cord injury above the lumbar region • Pain managed by patient-controlled analgesia or epidural catheter • Patient transferred from an outside ICU where sedatives had already been administered for more than 24 hours • Family or medical team has decided not to provide full support • Enrolled in any other critical care interventional clinical trial concurrently or in the 30 days before study entry • Known allergy to any of the study medications • Pregnancy

The initial construction study by Franck et al, included 83 children, median age 35 months (IQR 7-121 months) and was conducted in two PICUs between 2004 and 2006 (Franck et al 2008). Exclusion criteria were not reported in this study and no reference was made to the exclusion criteria of the parent RESTORE study. A prior study, the Opioid and Benzodiazepine Withdrawal Score (OBWS) (Franck et al 2004) contributed a pool of withdrawal items for the WAT-1 construction study. The OBWS study will be examined in Chapter 4. Items defined as redundant (assessing sweating, unco-ordinated /repetitive movement, tremor, yawning and behavioural state during both prestimulus and stimulus stages), nonspecific (elevated respiratory rate, suctioning, dilated pupils) or difficult to assess (although no items were defined in this category) were rejected to create WAT-1.

The subsequent validation study by Franck et al (2012) included 126 children, median age 1.6 years (IQR 0.6-7.7 years) and was conducted in children with acute respiratory failure

supported on mechanical ventilation, in a multi-centre trial in 21 PICUs. The authors reported good psychometric performance and generalisability. Exclusions were reported as cyanotic heart disease, immediate post-surgery or neuromuscular respiratory failure, rather than the full list of RESTORE study exclusions.

2.8.2 Performing a WAT-1 assessment

WAT-1 is designed to be used twice a day, alongside the SBS sedation assessment, at 8 am and 8 pm, and at other times if clinically indicated, during weaning of analgesics and sedatives. The format and 12-hourly assessment schedule was copied from a neonatal withdrawal tool (The Neonatal Withdrawal Index, Zahorodny et al 1998); the rationale being to standardise the assessment period to before, during and after routine cares and reducing bias that occurs with frequent, serial measurement (Franck et al 2008). No justification is provided for why the observation of withdrawal behaviours must be time-limited, or the basis for a concern about serial assessments and the nature of the bias.

The WAT-1 assessment schedule involves observing the child before, during and after the progressive stimulus, undertaken as part of the SBS sedation assessment (Curley et al 2006) (Appendix 2). During the 2-minute pre-assessment period the SBS score and five behaviours (tremor, sweating, uncoordinated repetitive movement, yawning or sneezing) are scored; a further two behaviours (startle to touch and muscle tone) are observed in response to the progressive stimulus and after the stimulus, the time taken for the child to calm (SBS score≤ 0) is also scored. Three further items (loose, watery stool, any vomiting, retching or gagging and temperature greater than 37.8C) are identified from the patient's record over the previous 12 hours. The SBS component of the withdrawal assessment can contribute a maximum of 3 points to the WAT-1 score.

2.8.3 Interrater Reliability

In the initial study, Frank et al (2008) reported interrater reliability as good; assessed by correlating WAT-1 scores of two nurses (a clinical nurse specialist and the bedside nurse), who simultaneously applied WAT-1 to 30 children (Cohen's kappa 0.80; intraclass correlation 0.98).

In the subsequent study, Frank et al (2012) assessed interrater reliability across 21 sites in the USA by correlating WAT-1 scores of two bedside nurses. Absolute agreement occurred in 349 of 420 (83%) paired assessments. The reason for variance in the remaining 17% of paired scores was not explored, but it is interesting, from a clinical

perspective, to speculate why these different perceptions of a patient's behaviour may occur. Nurses may have differed in their recognition of four component behaviours requiring a yes/no response (e.g., absent versus present), and/or their rating of behaviour intensity of the six behaviours requiring a severity rating (e.g., normal/mild versus moderate/severe). Whatever the reason, the concordance rate for WAT-1 <3 versus WAT-1 ≥3 was much greater, at 97.4% and the Spearman rank correlation coefficient between paired scores was 0.93. The difference between exact and ranked paired scores, in favour of ranked scores, demonstrates that there was a subjective, but consistent difference in the way individual nurses perceive the WAT-1 behaviours. The concordance figures also show that differences in paired assessments did not result in to a difference in withdrawal diagnosis and so were not clinically meaningful.

2.8.4 The impact of the inclusion of SBS on the internal consistency, content and construct validity of WAT-1: clinical perspective

That WAT-1 measures a single phenomenon is cast into doubt by the inclusion of the State Behavioural Scale (SBS) (Curley et al 2006) impacting on construct validity. No evidence is provided that demonstrates the necessary causal link between state behaviour and withdrawal syndrome which is an essential prerequisite for content validity (DeVellis 2012). The justification for including SBS in the WAT-1 tool was not elucidated, other than the motivation for mirroring the style of the SBS assessment in terms of standardising the time over which the nurse observes for signs of withdrawal. The rationale for this may have been a pragmatic attempt to minimise the assessment burden on the nurses participating in the trial, in order to optimise compliance with the assessment schedule, by combining the sedation and withdrawal assessments. However, it is not known whether the WAT-1 structure of 8am and 8pm is a representative time frame or assessment period. Limiting the withdrawal assessment to a fixed duration at the start of a nursing shift, akin to a behavioural snapshot, risks the assessment being confounded by other aspects of the child's clinical condition or transient causes of distress, rather than a reflection of the child's general state. This structure is entirely different to the SWS approach, where the assessment is based on behaviours noted over the previous 6 hours, which reduces the impact of transient distress (Cunliffe et al 2004).

The cut point of WAT-1 as "a reasonable designation of clinically significant [withdrawal] symptoms" is a WAT-1 score ≥3 (Franck et al 2012, p147). This score can be accrued entirely from the SBS content of the WAT-1 tool, in a child who is distressed at the time of

the withdrawal assessment, regardless of the reason for distress. The opportunity to undertake additional assessments at other times when clinically indicated was not documented and not explained. Given that a child's distress may stimulate the nurse to undertake an additional WAT-1 assessment; this has the potential to be a self-fulfilling prophecy resulting in a specious diagnosis of withdrawal, which further limits construct validity. This possibility appears to be borne out by the number of patients (n= 242, 29%) who were reported as distressed at the start of the withdrawal assessment (SBS≥ 1) (Franck et al 2012). A similar number of patients (n= 268) took more than two minutes to settle after the withdrawal assessment; of these 109 (41%) took more than five minutes to settle (Franck et al 2012).

Sedation is administered to the intubated child in an effort to achieve a calm but responsive state, signifying that the child is tolerating mechanical ventilation. Sedation assessments are performed in the intubated child to monitor and maintain the treatment goal and to identify a child who is under- or over sedated. Sedation and withdrawal assessments assess different aspects of care. Whereas agitation in the intubated child may indicate poorly tolerated mechanical ventilation, this is not the case for the extubated child where agitation may indicate, depending on the context, imminent hypoxia, pain, withdrawal, delirium, distress, fear or an ADR (Van der Zwaan, 2012). Withdrawal assessments are performed on intubated and extubated patients. This aspect of the WAT-1 binds the assessment in the self-ventilating child to their response to being disturbed for cares, which might provoke an unfavourable response from the child, compared with observing behaviours at rest.

It should be noted that peri-extubation agitation may prompt a withdrawal assessment. Whilst the study protocol advised against sedation assessments related to extubation, there was no mention about withdrawal assessments and the potential for Type II error inherent in agitation-based assessments during this time.

2.8.5 The impact of the inclusion of SBS on the internal consistency, content and construct validity of WAT-1: statistical perspective

Internal consistency is about the factor structure of a set of items. Franck et al undertook exploratory factor analysis in 2008, when the relationship between the items was unknown. Subsequently in 2012, confirmatory factor analysis with varimax rotation, was undertaken which is a popular technique where all factors remain uncorrelated with each other and which aims to distribute items uniformly and load factors on one item only

(Streiner and Norman 2003). Four factor solutions were identified in both studies, which accounted for 58% (2008) and 56% (2012) of the variance in analysis of all assessments. Factor structure varied between the 2008 and 2012 studies (Table 2.18 and 2.19). The factor loading in the 2008 study varied for children over 6 years (n=35, 42%) compared with the younger age groups (n=48, 58%). In the older age group, motor-related symptoms and behavioural state loaded on the same factor and yawning and startle did not meet the threshold for inclusion in any factor (Franck et al 2008). The main differences between factor solutions in the two studies include the absence of sneezing from any of the factors in 2008; the combination of yawning and sneezing in 2012 and their subsequent inclusion in two factors, albeit with factor loadings (0.43 and 0.46 respectively) just above the threshold for inclusion in any factor (0.4). The rationale for inclusion of yawning/sneezing was due to the occurrence of significantly higher WAT-1 scores on the few assessments (n=67, 8%) when these behaviours occurred. WAT-1 scores median (IQR) were 4(3-6) when yawning/sneezing occurred and 1(0-3) when absent (Franck et al, 2012). These differences in factors by age and study cast doubt on the identified factors being the high level interrelated solutions, typical of factor analysis.

Table 2.18 Four-factor solution for WAT-1 (2008)

Factor 1	Factor 2	Factor 3	Factor 4
Motor-related symptoms	**Behavioural state**	**Autonomic**	**Gastrointestinal and yawning**
Tremor Startle to touch Uncoordinated/repetitive movements Muscle tone	Prestimulus state and return to calm state	Temperature Sweating	Any vomiting, retching, gagging. Any loose/watery stools. Yawning

Table 2.19 Four -factor solution for WAT-1 (2012)

Factor 1	Factor 2	Factor 3	Factor 4
Motor-related and yawning/sneezing	**Behavioural state**	**Gastrointestinal**	**Temperature and yawning/sneezing**
Tremor Startle to touch Uncoordinated/repetitive movements Muscle tone Yawning or sneezing	Time to gain calm state ≥ 2 mins SBS ≥ +1 or awake, distressed Sweating	Any vomiting, retching, gagging. Any loose/watery stools.	Yawning or sneezing. Temperature > 37.8C

2.8.6 Concurrent validity

The bedside nurse's clinical judgement was the existing standard of care, which Franck et al (2008) described as a 'tin standard,' reflecting the lack of a gold (criterion) standard. Concurrent validity was assessed by Frank et al (2008) by comparing WAT-1 scores with the same nurses' subjective rating of withdrawal intensity on a 0-10 Numeric Rating Scale (NRS). This showed a predictably high degree of convergence, given that the same nurse applied both the index (WAT-1) and criterion (NRS) tests. Concurrent validity requires the independent corroboration that the instrument is measuring what it means to measure against a criterion standard (Bowling 2004). This interdependence demonstrates a further serious limitation in the design of this study.

2.8.7 Construct validity

In both studies (Franck et al 2008, Franck et al 2012) construct validity was demonstrated by children with WAT-1 ≥3 having longer PICU and hospital stays, longer time undergoing mechanical ventilation, receiving greater cumulative opioid doses over a longer duration, prior to weaning, and taking longer to complete weaning compared with those with WAT-1 <3. Construct validity in these terms is called predictive validity, which is demonstrated if WAT-1 scores are higher in patients who have a greater number of risk factors for withdrawal, than WAT-1 scores in patients with fewer risk factors. However, Franck et al (2008) admit that the speed of weaning may also have been influenced by the initial WAT-1 scores, rather than being an indication of the underlying construct of withdrawal.

The relationship between these variables and their role as risk factors for withdrawal was not explicated by Franck et al (2008, 2012). To better understand the cause and effect relationship between these variables, or risk factors, the researcher created a pictorial representation, as shown in Figure 2.1. The concepts of physical dependence and WAT -1 score ≥3 as an indication of withdrawal are represented as ovals. The variables, or risk factors, are represented as rectangles. Arrows show the direction of influence or effect. This model helps to clarify the causal relationships between the variables described by Franck et al (2008, 2012). It shows that duration of mechanical ventilation is a risk factor for three variables; drug duration, cumulative dose and length of PICU stay. Duration of mechanical ventilation is also indirectly linked to length of hospital stay (through length of PICU stay) and indirectly to physical dependence (through drug duration and cumulative dose).

The five risk factors for WAT-1 ≥3 described by Franck et al (2008, 2012) are what might be best described as a 'clinical tautology' linked to the duration of mechanical ventilation. Patients who spend longer undergoing mechanical ventilation will receive sedatives over a longer duration, which will result in greater cumulative doses and are likely to be in PICU longer compared with patients who spend less time undergoing mechanical ventilation.

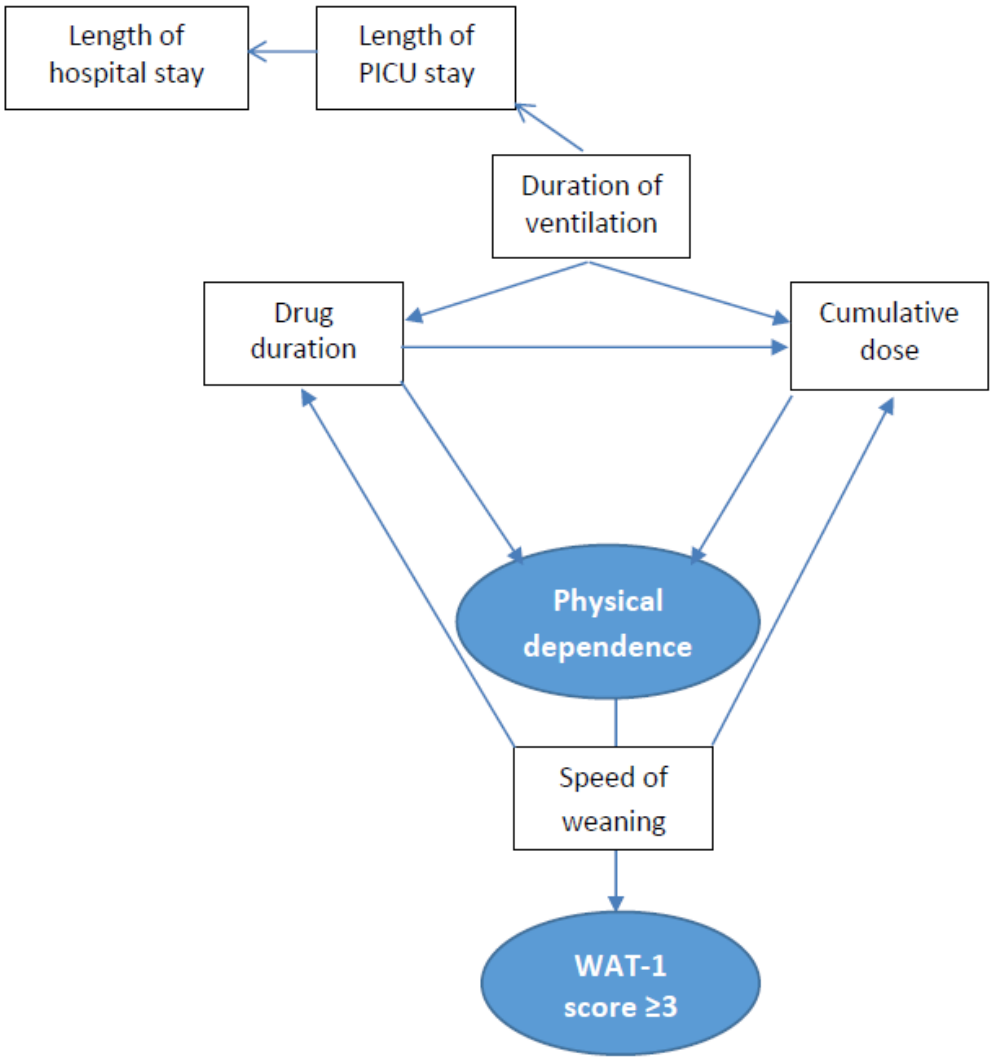

Figure 2.1 A proposition of the causal relationships between the factors supporting construct validity for WAT-1 score ≥3

In terms of risk factors for withdrawal, this model demonstrates that the only causal relationship or risk factor for, withdrawal appears to be the speed of weaning in the context of physical dependence. Franck et al (2008) reported that they were unable to examine the relationship between the weaning rate and the emergence of withdrawal symptoms due to variability of the weaning pattern during the study.

The remaining factors listed in support of construct validity for WAT-1≥3 indicating withdrawal are effects or consequences of the duration of ventilation. In other words, the duration of ventilation and the speed of weaning both have a causal relationship with, or are risk factors for sedative drug duration and the cumulative doses administered. Both of these drug factors, duration and cumulative dose, contribute to the development of physical dependence. Duration of ventilation also has a causal relationship with, or is a risk factor for length of PICU stay and length of hospital stay. As these factors are not risk factors for withdrawal, they do not support predictive validity of WAT-1≥3 indicating withdrawal.

Franck (2008) concluded that WAT-1 showed greater validity than NRS due to better performance in relation to known risk factors such as opioid exposure and length of therapy. This is an illogical proposition, as the validity of the reference test is the basis upon which to demonstrate the criterion validity of the index test; hence questioning the validity of the reference test casts doubt in the validity of the index test. However, evidence of construct validity is considered more important than criterion validity if the index test has been developed to predict the severity of a construct by means of an observable behaviour (Streiner and Norman 2003), as is the case for WAT-1.

2.8.8 Discriminant validity

Discriminant validity, the lack of correlation with unrelated differential diagnoses, was not reported in either study. However, it was highlighted as a limitation on the first study (Franck et al 2008) in relation to the impact on withdrawal symptom intensity of the patient's primary medical condition. It is also not clear that SBS discriminates other causes of agitation including pain, hypoxia and withdrawal, as patients with these conditions were not included in the validation study of SBS (Curley et al 2006).

2.8.9 Measures of diagnostic accuracy

Sensitivity and specificity were presented in the construction study as measures of the diagnostic accuracy of WAT-1 (Franck et al 2008). The Positive Predictive Value (PPV) is a measure of how well WAT-1 discriminates withdrawal from other unrelated differential diagnoses. However, results of the reference standard, prevalence of withdrawal and positive and negative predictive values were not presented. The extent of these omissions can be seen in Figure 2.2; where each of the four boxes in the cross tabulation table should contain accuracy data demonstrating the agreement and disagreement

between the reference standard and the index test. The relationship between sensitivity, specificity, prevalence and positive and negative predictive values is also shown in Figure 2.2 and allows the calculation of the missing figures to be performed. The missing statistics were derived from a key piece of data reported in text in the data analysis section of the paper stating that NRS ≥ 4 represented "top 20th percentile of scores, likely in withdrawal" (Franck et al 2008, p.575).

This statement provided the number of NRS ≥4 scores, from which the number of NRS ≤3 could be determined. The number of NRS ≥4 equates to (TP + FN) and the number of NRS ≤3 equates to (TN + FP). TP was then calculated from sensitivity and FN was calculated from specificity. Calculations performed to identify missing accuracy statistics are shown in Table 2.20. A cross tabulation with these results is shown in Figure 2.3.

As the cross tabulation of index and reference tests was not presented or a rationale for the distribution of alternative diagnoses in the false positive cohort. These omissions limit the validity of this study findings and do not meet the STARD reporting criteria (STARD, 2015), the first version of which was published in 2003, prior to the publication of this study.

		True condition NRS "Tin standard"		
		NRS ≥4 Present	NRS ≤3 Absent	
Predicted condition	WAT-1 ≥ 3	True positive (TP)	False positive (FP) Type I error	Positive predictive value =TP/ (TP+FP)
	WAT-1 ≤ 2	False negative (FN) Type II error	True negative (TN)	Negative predictive value =TN/ (TN+FN)
		Sensitivity =TP/(TP+FN) =**0.872**	**Specificity** =TN/(TN+FP) =**0.880**	Prevalence = (TP+FN)/ (**TP+FP+FN+TN**)

Bold findings were published.

Figure 2.2 Cross tabulation emphasising missing data (2008 study)

Table 2.20 Calculation of diagnostic accuracy for WAT-1

NRS≥4 = top 20th centile = 20% of total (n=816) = 163	
Hence NRS≤3 = total (n=816) - NRS≥4 = 816 – 163 = 653	
NRS≥4 = TP + FN = 163	NRS≤3 = FP + TN = 653
Sensitivity = TP/(TP+FN) =**0.872**	Specificity = =TN/(TN+FP) =**0.880**
TP = 0.872 x 163 = 142	TN = 0.88 x 653 = 575
FN = 163-142 = 21	FP = 653-575 = 78
PPV = 142/(142+78) = 0.65	NPV = 575/(575+21) = 0.96
Prevalence = (142+21) /816 = 20%	

Bold figures were published by Franck et al (2008).

		True condition NRS "Tin standard"		
		NRS ≥4 Present	NRS ≤3 Absent	
Predicted condition	WAT-1 ≥ 3	True positive (TP) 142	False positive (FP) 78	Positive predictive value =TP/ (TP+FP)= 0.65
	WAT-1 ≤ 2	False negative (FN) 21	True negative (TN) 575	Negative predictive value =TN/ (TN+FN)= 0.96
		Sensitivity =TP/(TP+FN) =**0.872**	**Specificity** =TN/(TN+FP) =**0.880**	Prevalence = (TP+FP)/ (**TP+FP+FN+TN**) = 20%

Figure 2.3 Cross tabulation of NRS ≥4 with WAT-1 score ≥3 **Bold** findings were published.

2.9 Sophia Observation Scale (SOS) (Ista et al 2009)

The Sophia Observation Scale (SOS) is a physiological and observational scale consisting of fifteen items that provide a global withdrawal score ranging from 0 to 15 (Appendix 4). The assessment involves observing the patient for three physiological signs (heart rate, respiratory rate and temperature), ten behaviours (sweating, agitation (or irritable or restless or fidgety), anxiety, tremor, motor disturbance (involuntary movements of the limbs, muscle twitching, choreoathetosis of arms, legs and/or head), increased muscle tension, inconsolable crying, grimacing, sleeplessness and hallucinations) and gathering two further items (episodes of vomiting and/or diarrhoea) from the patient's record. SOS is designed to be used every 4 hours, during opioid and benzodiazepine weaning.

The scale components of SOS are derived from a pool of 24 items formulated for the Sophia Benzodiazepine and Opioid Withdrawal Checklist (SBOWC) and published by the same research team (Ista et al 2008). These items were tested on children and refined through a combination of factor analysis and expert opinion. The SBOWC study will be examined in Chapter 4.

The SOS construction study (Ista et al 2009) included 79 children, median age 3.4 months (range 0-15.5 years) and was conducted on a single site. Children in PICU, aged ≤ 16 years, were eligible for inclusion if they received midazolam and/ or opioids by continuous infusion for at least 5 days. Exclusion criteria were status epilepticus treated with midazolam, use of neuromuscular blocking agents and severely disturbed behaviour pattern as a result of underlying neurology. The subsequent validation study (Ista et al 2013) included 154 children, median age 5 months (IQR 0-42 months) and was conducted in the same setting, with the same inclusion and exclusion criteria.

2.9.1 Reliability

2.9.1.1 Interrater reliability

In the SOS construction study (Ista et al 2009), interrater reliability was assessed by correlating scores of two nurses; the bedside nurse, who had received verbal and written instruction on the application of SBOWC, and the principal investigator who simultaneously applied 23 items from SBOWC (ICC 0.97 (95%CI 0.92-0.98). The Cohen's kappa, which tests exact agreement rather than extent of correspondence, for individual items of the SOS ranged from 0.73 to 1.0. Although these kappa scores are satisfactory from a statistical perspective, any kappa less than 1 indicates occasions when two nurses

observing the same child for the same behaviour disagree on the presence or absence of the behaviour. This may be due to the complexity of interpreting behaviour in critically ill children or arise from differences in nurses understanding of the behavioural items. The subsequent study (Ista et al 2013) did not report further reliability testing.

2.9.1.2 Internal consistency

Multidimensional scaling (MDS) was performed and a three dimensional solution was identified, which was described as statistically robust. The purpose of MDS is to simplify a complex matrix to show the relationship between items being analysed. Ista et al (2009) reported that the dimensions did not constitute the homogenous clusters of behaviours, which would be expected when detecting meaningful underlying dimensions. This means that although statistically robust, these dimensions did not translate to a clinically meaningful explanation for the manifestation of withdrawal. This led the team to suggest that withdrawal signs may vary between individuals (Ista et al 2009), an admission which conflicts with the necessary underpinning assumption of homogeneous presentation when constructing an assessment tool with summed behavioural items (Streiner and Norman 2003).

2.9.2 Validity

2.9.2.1 Content validity

Signs of withdrawal were gathered from the literature and refined through a combination of factor analysis and the expert opinion. The expert panel constituted 85 clinicians (22 doctors and 63 nurses) who had worked for a median of 8 years; it was not reported whether this work experience was on PICU.

2.9.2.2 Concurrent validity

Nurses' expert opinion was considered the 'silver standard' by Ista et al (2013), in the absence of a gold standard. The Numeric Rating Scale (NRS) is a 0-10 scale of withdrawal intensity with 0 indicating no withdrawal and 10 indicating the worst possible withdrawal. An NRS score ≥4 was considered to reflect withdrawal syndrome, a claim substantiated by reference to the initial WAT-1 study (Franck et al 2008); where the authors had described the nurses' opinion as a 'tin standard' which infers a second-rate reference test. In common with the WAT-1 studies, the interdependence between index and reference tests demonstrates the same serious limitation in study design. In common with the

WAT-1 study, no details about the validity or inter-rater reliability of the NRS scale, was presented. Concurrent validity was assessed by comparing SOS scores with NRS scores in 3754 paired assessments. Sensitivity and specificity were 0.83 and 0.93 respectively for an SOS ≥4 calculated against an NRS score ≥4.

2.9.2.3 Discriminant validity

The positive predictive value (PPV) was 0.49, which means that among those who had an SOS ≥4, the probability of withdrawal was 49%. Ista et al (2013) reasoned that the low PPV may be due to the overlap of symptoms between pain, distress, delirium and withdrawal. Excluding children whose presentation may make SOS unreliable, limits the clinical utility of the tool. In the conditions within which SOS functions, the item content of the tool covers other differential diagnoses, not just withdrawal. The challenge of interpreting other differential diagnoses and the low PPV suggests that SOS does not make this easier. Similarly to WAT-1, further studies examining whether SOS is more specific for withdrawal than other differential diagnoses, and performance in patients excluded from initial validation studies are awaited.

2.9.3 SOS (Ista et al 2013)

The objectives in the second SOS study were to establish cut-off scores, test sensitivity to change and identify risk factors for withdrawal syndrome (Ista et al 2013). These objectives will be summarised in turn.

The cut-off score of SOS ≥ 4 indicating withdrawal proved controversial, with nursing opinion of withdrawal (NRS ≥ 4) conflicting with this diagnosis in more than half of the assessments where SOS ≥ 4, shown by PPV 0.49. However, no accuracy data for the NRS scale were presented. The measure of diagnostic accuracy will be considered in detail.

2.9.3.1 Measures of diagnostic accuracy

Ista et al (2013) provided most of the diagnostic accuracy data recommended by STARD (2015) for transparency and completeness. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were reported in this study. Sensitivity shows how likely it is that the patient is withdrawing, when they have an SOS score ≥4. Sensitivity of SOS≥4 is 0.83. Interpretation of sensitivity of the new test relies on the reference test being accurate, as this is what the new test is being measured against.

Screening instruments, such as SOS, prioritise high sensitivity to optimise detection of the condition being screened for (Traube et al 2014).

Positive and negative predictive values are the proportions of positive and negative results that are true positive and true negative results, respectively. The PPV of SOS≥4 is 0.49, which means that SOS≥4 accurately reflects withdrawal in less than half of assessments. The low PPV was highlighted as a major flaw by Ista et al (2013), and was explained as the overlap of symptoms with pain, distress and delirium. This justification highlights a fundamental flaw with SOS, as noted earlier "items must share one and only one underlying variable if they are to be combined into a scale" (DeVellis, 2012 p.159). The number of true and false positives and true and false negatives were not reported but these figures were calculated from the data reported in the study. The figures for false positives and negatives reflect the clinical utility of a scale and identify potential strengths and weaknesses. False positives are also described as Type I errors, which indicate a diagnosis of withdrawal when withdrawal is absent. False negative are described as Type II errors, indicating a failure to detect withdrawal.

The relationship between sensitivity, specificity, PPV and NPV can be demonstrated in a cross tabulation table of NRS≥4 with SOS≥4 and also shows how the missing values can be calculated (Figure 2.4). The findings that were published by Ista et al (2013) are identified in bold. Calculations performed to identify missing accuracy statistics are shown in Table 2.21.

These calculations showed that SOS produced 56 false negatives and 258 false positives out of 3754 assessments. These results suggest that nurse opinion (NRS≥4) is more accurate at screening for withdrawal that SOS is.

The prevalence of withdrawal in this sample was 8%. Ista et al (2013) reported the prevalence of withdrawal in the study sample as 48% by describing the population (N) as the number of patients who scored SOS ≥4 (the index test) out of the total of 154 patients in the study. The prevalence of 8% calculated in Table 2.21 reflects the statistical definition of prevalence which is based on the reference test number of true positive and false negative screens (n=303) out of the total number of assessments (n=3754).

		True condition NRS "Silver standard"			
		NRS ≥4 Present	NRS ≤3 Absent		
Predicted condition	SOS ≥ 4 Positive	True positive (TP)	False positive (FP) Type I error	**SOS≥4** (TP+FP) **= 505**	**Positive predictive value** =TP/ (TP+FP) =**0.49**
	SOS ≤ 3 Negative	False negative (FN) Type II error	True negative (TN)	SOS ≤ 3 (FN+TN)	**Negative predictive value** =TN/ (TN+FN) =**0.98**
		NRS≥4 (TP+FN) **= 303**	NRS ≤3 (FP+TN)	Prevalence = (TP+FN)/ (**TP+FP+FN+TN**) **(3754)**	
		Sensitivity =TP/(TP+FN) =**0.83**	**Specificity** =TN/(TN+FP) =**0.93**		

Figure 2.4 Cross tabulation of NRS ≥ 4 with SOS ≥ 4 **Bold** findings were published.

Table 2.21 Calculations of false positives and false negatives for SOS

PPV = TP/(TP+FP) = **0.49**

TP+FP = **505**

Hence TP = 0.49 x 505 = 247 and FP=505-247= 258

TP+FN=**303**

Hence FN= 303-247 =56

TN = 3754 – (TP+FP+FN) = 3754 -561 = 3193

Prevalence = 303/3754 = 8%

2.9.3.2 Sensitivity to change and risk factors

Sensitivity to change was evaluated in 156 paired SOS assessments in 51 patients before and after administration of sedatives or opioids to treat withdrawal symptoms. A mean decrease in SOS scores of 1.47 occurred, which was described as statistically significant. Clinical significance would also require the patient changed to "not withdrawing" (SOS ≤3) in response to the intervention. No further details were provided about this cohort of patients. Sensitivity to change may be more clearly understood if Ista et al (2013) published the range of SOS scores before and after rescue therapy and showed the trend in scores leading up to and after the high score.

Risk factors were analysed by comparing clinical data for those patients who had at least one score of SOS ≥ 4 during the weaning period with the rest of the sample. The basis for comparing these two groups is debatable, given the extent of the disagreement between this cut-off score and nurses' opinion of the diagnosis of withdrawal. No information was presented on what impact a score of SOS≥ 4 had on weaning rates, that is, whether weaning was stopped, slowed or continued as a result. However, duration of weaning was more than twice as long in patients with SOS≥ 4 compared with SOS≤3.

Ista et al (2013) presented risk factors for withdrawal in terms of clinically and statistically significant differences in patients with at least one SOS score ≥4 compared with patients with all SOS scores ≤3. These factors or differences were duration of ventilation, the length of stay on PICU, duration of midazolam infusion, duration of midazolam weaning and cumulative dose of midazolam (Table 2.22). These factors are very similar to those reported by Franck et al (2008) in support of the construct validity for WAT-1. The relationship between these variables and their role as risk factors for withdrawal was not explicated by Ista et al (2013).

Table 2.22 Clinically significant differences between patients with SOS ≥4 and SOS ≤3 (median (Interquartile Range)) (reported by Ista et al 2013)

Characteristic	No withdrawal (n=80) (all SOS scores ≤3)	Withdrawal (n=74) (≥ one SOS score ≥4)	p
Duration of ventilation (days)	10 (6-15)	15 (8-29)	0.001
Length of PICU stay (days)	11 (8-19)	25 (16-44)	<0.0001
Midazolam duration (including taper) (days)	9 (6-14)	17 (9-27)	<0.0001
Midazolam duration of weaning (days)	3 (1-7)	7 (3-15)	<0.0001
Midazolam cumulative dose (mg/kg)	34.8 (16.9-71.8)	77.9 (34.6-169.6)	<0.0001

Referring back to the model of the causal relationship between the variables (Figure 2.1); as these factors do not have a causal relationship with withdrawal, they are not risk factors for withdrawal. These factors are risk factors for physical dependence (ventilation, drug duration, cumulative dose) or the consequence of duration of mechanical ventilation (length of PICU stay). The duration of taper for patients in the SOS ≥4 group was nearly double that of patients in the SOS≤ 3 group. This finding suggests

tapering was slowed or stopped in consequence to the score or patient response, but these interventions were not reported by Ista et al (2013). It may be possible that the speed of weaning may have been influenced by the initial SOS scores, rather than being an indication of the underlying construct of withdrawal, as conceded by Franck et al (2008).

2.10 Discussion (WAT-1 and SOS)

The rigor of both the WAT-1 (Franck et al 2008, 2012) and SOS (Ista et al 2009, 2013) studies suffers from the lack of an independent reference standard, thwarting the prospective design of these validation studies. The observational nature of a withdrawal assessment tool relies on the person applying the tool being familiar with their patient's behaviours, which makes it difficult to undertake the concurrent, independent assessment. The positive predictive value of SOS (0.49) was less than chance. The PPV for WAT-1 was not published, but was calculated by the researcher as 0.65, meaning it correctly identifies withdrawal 2 times out of 3. Content validity of WAT-1 is flawed by the inclusion of a sedation/agitation assessment which has not been validated in patients who are withdrawing or in pain. WAT-1 was only ever tested in a medical population, so it is not clear how the tool would perform in post-operative patients; whether it could discriminate pain behaviour from withdrawal behaviour.

2.10.1 Opioid conversions

One of the steps taken in both validation studies was the conversion of opioids to morphine equivalents to aid analysis and allow for inferences to be made in terms of construct validity of the index test. Construct validity would be demonstrated if the index test performs as predicted in response to a change in a given variable: in this case a positive correlation between withdrawal tool scores and cumulative or peak opioid doses. Franck et al (2012) noted that peak opioid doses may be influenced by opioid conversions used, suggesting a calculation effect, rather than a clinical effect. These studies used the conversion fentanyl 15 micrograms = morphine 1mg (1:66). However, recent commentary on these conversion ratios casts doubt on the assumptions upon which this step was based. The equianalgesic dosing guidance currently used has not been formally validated (Fine et al 2009) and was established on non-opioid tolerant adult patients, with no concurrent illness or comorbidities (Knotkova 2009, Patanwala 2007). These findings

suggest a formulaic conversion between opioids of different potencies is an oversimplification (Patanwala 2007). If, in clinical terms the conversion should be treated with caution, in validity terms, any inferences arising from the conversion should also then be treated with caution.

This validation step also overlooks the inter-individual differences in opioid requirements: essentially a patient effect as well as a drug effect. Katz et al (1994) reported that PICU patients may require a 10-fold variability in fentanyl infusion rates to achieve similar levels of sedation. Anand et al (2010) noted that infants are susceptible to greater tolerance with fentanyl compared with morphine. The impact of both conversion-effect and individual response was demonstrated in a trial of methadone tapering in PICU patients weaning from fentanyl (Bowens, 2011). Patients were randomised to either a standard low dose weight-based methadone dose or a bespoke high dose, which also accounted for their most recent fentanyl dose. Contrary to expectations, both regimes had similar efficacy, even in patients on high dose fentanyl and/or over a longer duration, but over-sedation was a risk in the high dose group. Bowen and colleagues concluded that the methadone dose had to be personalised to each child's response, to minimise the risk of over-sedation or withdrawal, the incidence of which could not be predicted based on the cumulative dose of fentanyl.

Inferences would only be true if there was a clinically accurate conversion and no interpatient variability in dosing.

2.11 Conclusion

This chapter has summarised what is known about the assessment and management of withdrawal in critically ill children. It has also highlighted the contextual complexity within which these assessments are performed; children may be weaning from more than one sedative agent and other differential diagnoses are common and share similarities in their behavioural presentation with withdrawal. WAT-1 and SOS have been developed to standardise the assessment and recognition of withdrawal in PICU patients weaning from opioids and benzodiazepines. However, this is not a homogeneous patient group in clinical practice and evidence from this critical consideration of the tools reveals little support for the diagnostic principle that a single summed score is sensitive enough to differentiate withdrawing and not-withdrawing patients.

Cut points for both tools have been identified but there was little evidence provided in support of these assertions. In addition it is not clear what clinical utility this presents, as children with clinically significant withdrawal presented with a range of scores in both studies. Useful cut points should distinguish between three patient states and treatment options:

- No signs of withdrawal: continuing weaning.
- Signs of withdrawal, some impact on the patient: stop weaning and review.
- Signs of withdrawal, significant impact on the patient: stop weaning, increase / add sedation

This review has also highlighted what is not known about withdrawal. This syndrome lacks a name, a definition and diagnostic criteria. Risk factors for withdrawal are confused with those for physical dependence. This may be because physical dependence and its variable onset in critically ill children are also poorly understood. The next chapter will address how the studies presented in this thesis were designed to increase the evidence base for the assessment and management of withdrawal in critically ill children.

Chapter 3: Methodology and conceptual framework

3.1 Introduction

In this chapter I will present the conceptual framework for this thesis and the methodology and methods employed to answer the research questions. The researcher perspective is also presented to demonstrate reflexivity.
This thesis adds to this body of knowledge about withdrawal syndrome in critically ill children with four studies, each contributing a different perspective of this subject. Two evaluative studies of existing tools will be complemented by exploration of the nurse and parent perspectives of withdrawal assessment. The nurse and parent perspectives will be viewed through the theoretical lens of judgement and decision making; theories which also provide an analytical framework for the clinical impact of the study findings.

The findings from these different perspectives will be merged in a synthesis chapter. Merging these perspectives enhances and enriches the understanding and meaning of the existing single perspective (Creswell and Plano Clark 2011). This process, called integration, is a key feature of mixed methods research (Fetter et al 2013).
The choice of an interactive multiphase mixed methods design is explained and the purpose and design of the component studies articulated. A pragmatic approach is taken, which does not commit to one philosophical view of reality and focuses on solutions to problems, rather than the abstract pursuit of knowledge (Creswell 2013; Morgan 2007).
A thesis map is presented to demonstrate the interactive mixed methods design.

3.2 Conceptual framework

A conceptual framework in a mixed methods study is a framework that provides a general explanation as to what the researcher will find from the results (Greene 1989). This framework can be presented as a model, conceptual framework, theory or philosophy.
To date, published research has focussed on one perspective of withdrawal assessment; the objective stance revealed in efforts to standardise the nurse's assessment using a withdrawal assessment tool. The attempt to standardise represents the positivist view that objectivity is truth (Onwuegbuzie and Leech 2005). The underpinning assumption in this approach is generalisability – which means that all withdrawing patients present in a

similar fashion, or share sufficient signs in common, to be assessed by nurses applying a standardised assessment tool.

3.2.1 *A priori* study conceptual framework

The conceptual framework for withdrawal assessment upon which the *a priori* studies were based is shown in Figure 3.1. These studies were designed to demonstrate how the parental perspective contributed to recognition of withdrawal and could enhance the existing approach based on the assumption that the parent perspective contributed uniquely to the withdrawal assessment. This represents the researcher's view and the study hypothesis that the parental contribution augments an assessment based only on the nurse perspective by providing a more personalised withdrawal assessment, which enhances and enriches the meaning of equivocal behaviours.

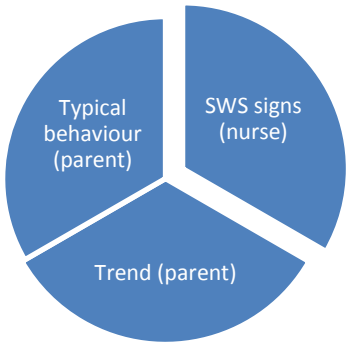

Figure 3.1 Conceptual framework for the *a priori* study

The study design changed in response to analysis of findings from Study 1 (SWS evaluation). This interactive process reflects the models of research design presented by Maxwell and Loomis (2003) and Johnson (2014). Both models place the research questions at the core and describe a non-linear or recursive process between the research questions and stages or steps in the research process. For Maxwell and Loomis (2003) there is a continual interaction of the research questions, purpose, conceptual model, methods and validity the conceptual model, methods and validity. For Johnson (2014) there are eight steps in a continual loop, including choice of and rationale for mixed methods, design, data collection, analysis, validation and interpretation and writing up.

The conceptual framework for withdrawal assessment was modified recursively in response to the continual interaction between findings in the nurse and parent studies to

create a framework which demonstrated why the existing approach was incomplete and prone to error.

3.2.2 Creating the conceptual framework for the studies presented in this thesis

The idea for the structure of the framework was borrowed from the way clinical tools are evaluated by comparing, or cross tabulating results from the index test and the reference test. Cross tabulation by the researcher of the WAT-1 and SOS tools were presented in the literature review chapter (Figures 2.3 and 2.4). Cross tabulation is a tool that allows comparison of the relationship between two variables or factors. The factors underpinning the conceptual framework comprise dualisms of perspective. One perspective encompasses the person-based dualism of nurse and parent. This dualism contrasts the nurses' expertise in assessing children and the parents' expertise about their child; differentiating nurses "*knowing children*" and parents "*knowing their child*." The second perspective encompasses the interpretive dualism of objectivity and subjectivity. This dualism contrasts the objective assessment of withdrawal using a withdrawal assessment tool with the subjective personalised assessment of the patient and their unique context; differentiating the parts of the assessment that are "*agreed upon*" from those that are "*construed*."

When two factors, each containing two levels are cross tabulated, a matrix is created with four cells. The interactive conceptual framework for withdrawal assessment presents these four different combinations as a 2 x 2 factorial matrix with withdrawal signs, at the core (See Figure 3.2). Cross tabulating the person-based dualism and interpretive dualism creates four different combinations;

1. The nurse objective view; "*nurse assessment*"
2. The nurse subjective view; " *nurse judgement*"
3. The parent objective view; "*parent assessment*"
4. The parent subjective view; "*parent judgement*"

The four combinations in the matrix characterise the multiple viewpoints of the pragmatic approach with the different approaches of interpretation or decision-making which frame this thesis. Each combination in the matrix represents a different view of withdrawal behaviour; the nurse's objective view using a withdrawal assessment tool; the nurse's subjective view interpreting the meaning or context of the behaviours; the parent's objective view recognising SWS signs and the parent's subjective view recognising changes in their child's usual behaviour. This framework demonstrates how each study

contributes a novel perspective to understanding this clinical phenomenon. The studies undertaken and presented in the thesis are mapped on the matrix.

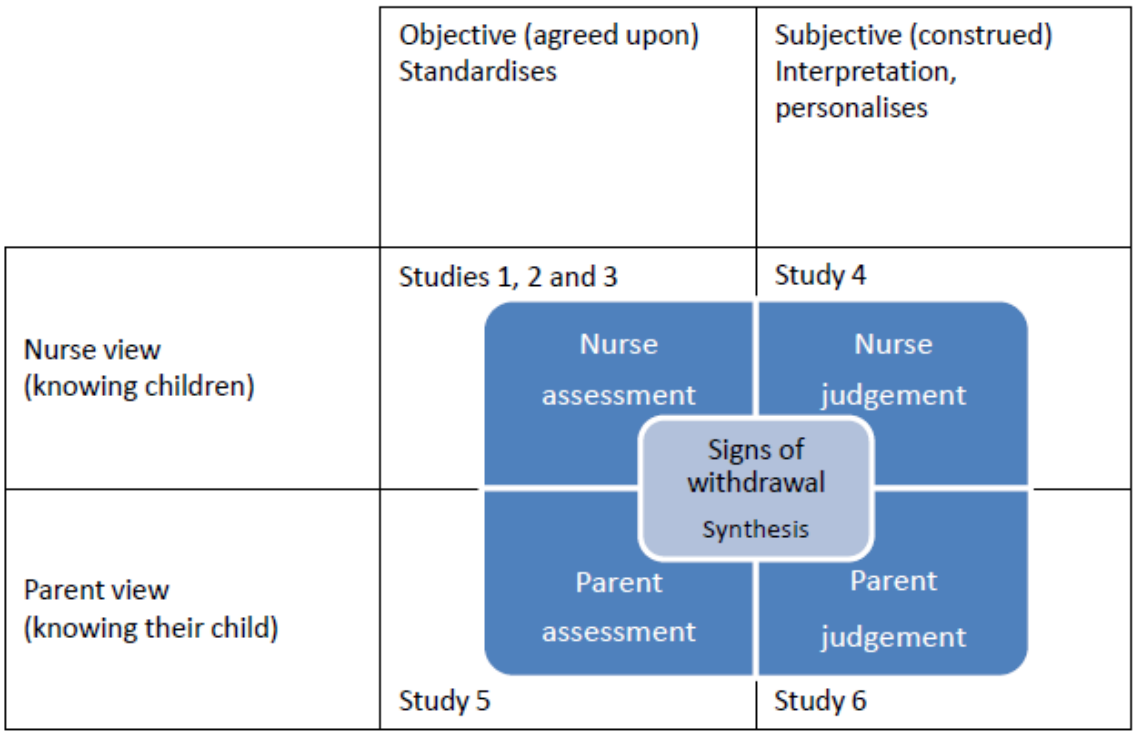

Figure 3.2 The conceptual framework

3.3 The conceptual framework, the pragmatic approach and mixed methods research

Pragmatism is the dominant worldview underpinning mixed methods research.

In harmony with the world view of pragmatism, truth is what works at the time; which contends that whilst the positivist view is one view, other viewpoints exist (Onwuegbuzie and Leech 2005). This contrasts with the positivist view taken by existing withdrawal assessment studies (Franck et al 2008, 2012; Ista et al 2009, 2013). The conceptual framework described above, embraces and transcends opposing philosophical dualisms, placing withdrawal signs at the core to be illuminated by all perspectives. The mixed methods approach allows for problems such as withdrawal assessment to be viewed from multiple perspectives to enhance and enrich the meaning of the existing singular perspective (Bryman 2008).

The existing singular perspective is the nurses' objective view, using withdrawal assessment tools. In terms of the objective/subjective dualism, objective decision-making is seen as standardised and predictable, whereas subjective decision-making is

contextual, personal and unpredictable. In terms of the nurse/parent dualism, this relationship reflects the emic and etic viewpoints of ethnography (Lambert et al 2011). The etic, or nurse perspective is the scientific, outsider or observer view of reality (Spiers 2000). The emic, or parent perspective is the insider view, reflecting multiple realities and is "silent in healthcare literature" (Spiers 2000, p 716).

In terms of ontology, pragmatists consider objective and subjective viewpoints exist on a continuum; the chosen viewpoint depending on the research question being asked (Creswell, 2003). Hypothesising that the nurse and parent may not make the same interpretation of a child's behaviour, challenges the positivist view of truth. Whilst positivists adopt the ontological view of an objective truth or "God's-eye view" (Rorty, 1990 p2), pragmatists accept the notion of practical truths, which describe a contextual, agreed truth (James, 1907). This ontological view corresponds to the different perspectives, contexts and underlying condition which may impact uniquely on how each patient's withdrawal presents and is perceived.

3.4 Research methodology

Pragmatism uses purposeful human inquiry as it focal point (Shields 1998) which emulates the primary focus of this thesis of improving withdrawal assessment. A pragmatic research approach is concerned with finding solution to problems (Patton, 1990) and it is achieved by using research methods that best meet this purpose (Creswell, 2013). A pragmatic epistemology underpinned the mixed methods approach taken, with component studies encompassing both quantitative and qualitative approaches and triangulation of data, research methods and theory. Each study contributed independently to new knowledge, from each of the viewpoints described in the conceptual framework. Each study informed the subsequent studies. Equal contribution from both qualitative and quantitative studies represents an equivalent status design (Tashakkori and Teddlie, 1998). Rorty (1982) supports the view that research should begin with and be guided by previous studies. The qualitative components of this thesis (Part 3 and 4) not only illuminated the nurse and parent perspectives, but also served to aid the interpretation of statistically significant findings from previous quantitative-based research studies.

3.5 Researcher perspective

In mixed methods research, the researcher presents their philosophical beliefs and assumptions about research. This enables the reader to identify the researcher's potential

biases and predispositions and the influence these may have on the research process. Critical self-reflection by the researcher, called reflexivity, describes the process of recognising and minimise these biases (Creswell 2013). The a priori study design reflected the researcher's perspective, which was based on over a decade of clinical experience assessing and managing sedation withdrawal in critically ill babies and children.

The SWS tool is central to the current approach to the assessment and management of sedation withdrawal. The SWS score is assessed by the child's nurse every six hours during weaning of sedative drugs. Whilst clinically useful in identifying behavioural trends in response to sedative weaning rates in stable patients, it is less reliable in unstable patients with a range of differential diagnoses. In these cases, the clinical context must be considered and other causes for behaviours should be excluded.

Anecdotally, the parent perspective contributes a unique interpretation of behaviours to assist the specialist team in differentiating causes which share behavioural signs in common. Parent's knowledge about changes over the previous hours or days arises from their constant presence at the child's bedside; insight which is missing from the formal withdrawal assessment undertaken by nurses. The parent account of the onset and trend of equivocal behaviours also provides contextual insight which assists in identifying or excluding the diagnosis of withdrawal. Alternatively, parents may describe behaviours as being typical of the child prior to critical illness, and which represent "usual behaviour" rather than emerging withdrawal syndrome; an interpretation which relying on familiarity with the child, is not available to nurses. In these circumstances, the parent perspective helps to delineate withdrawal behaviours from other causes and assisted the diagnostic process. As the diagnosis directs the course of action, this assistance expedites the prompt treatment and relief of unpleasant withdrawal behaviours or facilitates optimal reductions of sedative drugs by preventing unnecessary delays or pauses to weaning regimes.

In summary, the researcher believes there is an important role for parents in sedation withdrawal assessment due to their familiarity with their child's usual behaviours and their insight into behavioural trends during critical illness. This theoretical proposition formed the conceptual framework for withdrawal assessment in the a priori study.

3.6 The *a priori* research design

This research project changed from a study to refine and validate a withdrawal assessment tool to the exploration and understanding of withdrawal assessment, in response to the interaction between study findings and the research question.
The phases in the pre-planned study equated to a parallel mixed design; a typology proposed by Tashakkori and Teddlie (2003). The concurrent quantitative (QUAN) and qualitative (QUAL) strands of the study contributed to the mixed methods strand (MM) integrating the findings to design an updated tool (SWS v2), which would encourage parental input (Figure 3.3).

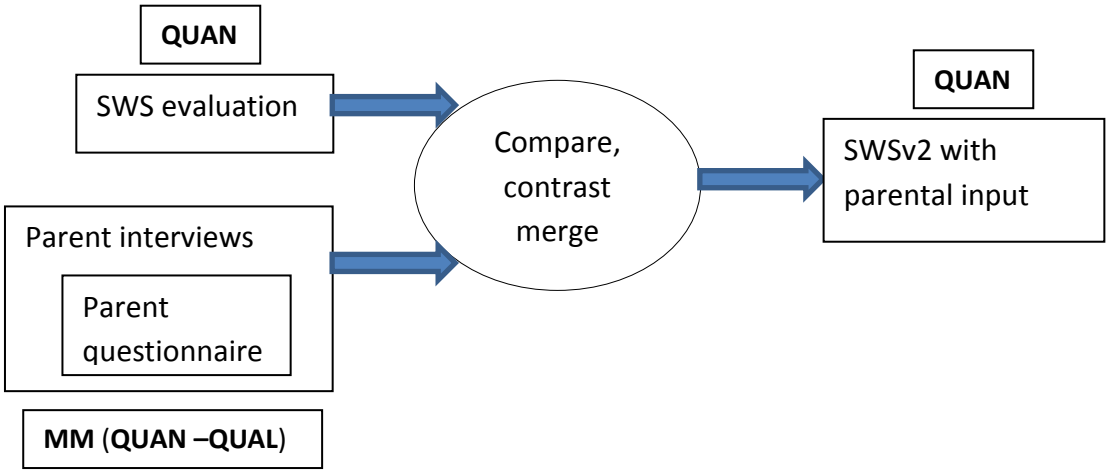

Figure 3.3 The *a priori* study design for SWS tool development with parental input.

3.7 The interactive multilevel mixed methods research design underpinning the studies

The research design changed initially in response to the analysis and interpretation of the data in the first study (the retrospective evaluation of SWS). Unexpected findings prompted the conceptualisation of sequential studies, to expand the breadth of the inquiry into other aspects of the current approach to withdrawal assessment. Further research questions arose in response to the findings of succeeding studies, as new perspectives illuminated further challenges in the process of withdrawal assessment. Each new perspective prompted the recursive analysis and interpretation of existing data, the SOS and WAT-1 validation studies and the literature and extended the scope of the study beyond withdrawal syndrome to co-existing constructs such as PD and ADRs. The interactive process of design describes how the study design is determine by interaction between study findings the research questions and the conceptual framework, an

interaction reflected in the studies in this thesis, compared with a predetermined *a priori* design (Maxwell and Loomis 2003).

The overall study design, having both parallel and sequential strands is defined as a multilevel mixed study (Tashakkori and Teddlie 2003). The thesis map showing the component studies and integration is shown in Figure 3.4. Integration is a key feature of mixed methods research and occurs at the level of the research design, research methods and/or interpretation (Fetter et al 2013). The consequence of integration at the analysis and inference stages is synergy of qualitative and quantitative data (Benz and Newman 2008). This approach was considered best able to illuminate and validate the multiple perspectives of the conceptual framework and synthesise a deeper understanding of sedation withdrawal assessment. The order of the sequential studies (Studies 1→4→2→3) reflects a number of factors. Chronologically, the data collection period of Study 3 spanned the publication of the WAT-1 and SOS validation studies (Franck et al 2012, Ista et al 2013) through to the most recent publication by Best et al (2016); a timeframe that began shortly after the data collection period of Study 1 and finished after Study 4 had been written up and submitted for publication. The order (Study 4 preceding Studies 2 and 3) also reflects the fundamental impact that the findings of Study 4 had on the study design and interpretation of data in Studies 2 and 3.

The conceptual framework also provides the structure for the presentation of the studies in this thesis. Studies 1, 2 and 3 considering the "nurse assessment" are presented in Part 2 of the thesis; Study 3 investigating "nurse judgement" is presented in Part 3. Studies 4 and 5 investigating parents' assessment and judgement are presented in Part 4 and a synthesis of the study findings is presented in Part 5 of the thesis.

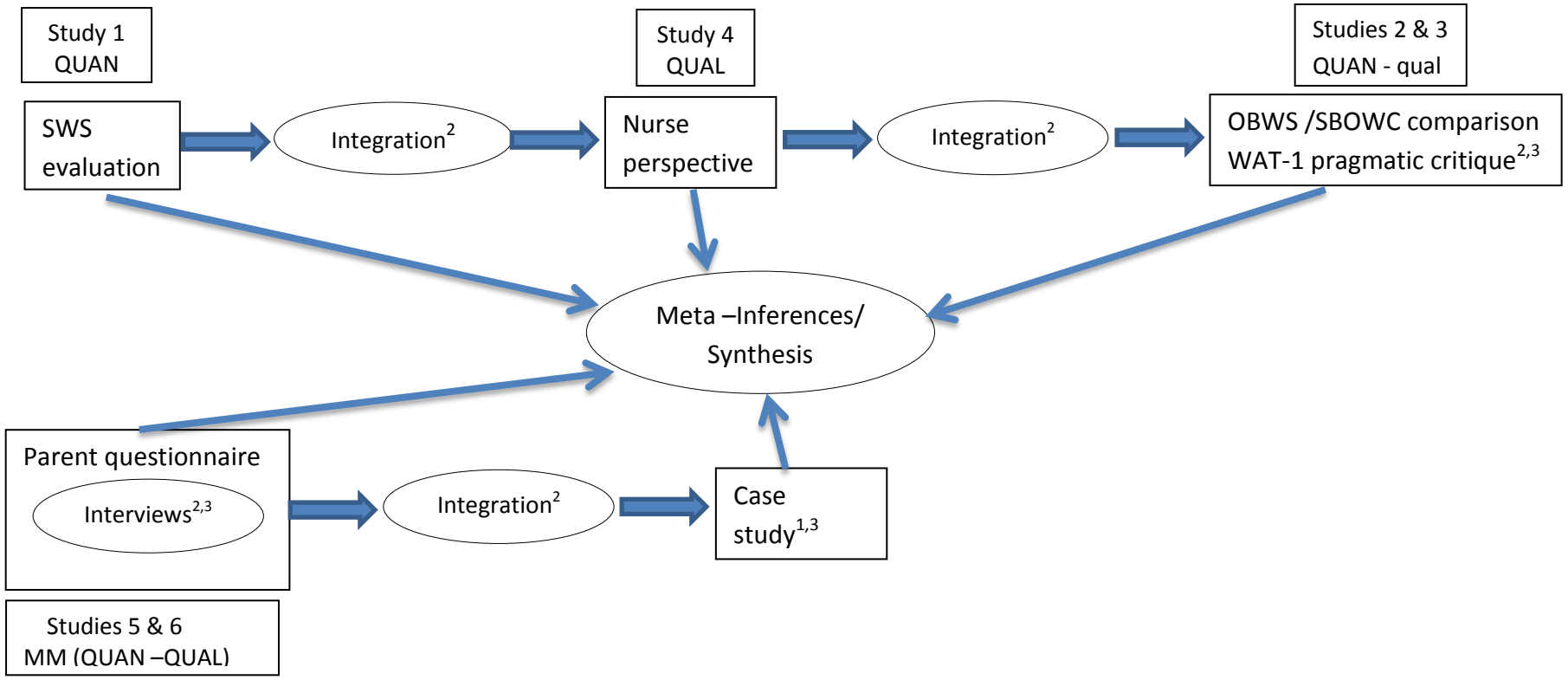

Figure 3.4 Thesis map; ovals show where integration has occurred and arrows show the points of interface in design.

QUAN= quantitative, QUAL= qualitative, MM= mixed methods

[1]Integration at design level case study

[2]Integration at methods level; explaining, understanding connecting building merging embedding

[3]Integration at interpretation level.

Part 2: Nurse Assessment

Part 2 of the thesis presents three studies which build on the existing body of knowledge about the nurses' assessment of withdrawal using withdrawal assessment tools. This aspect of the conceptual framework introduced in Chapter 3, is the dominant perspective upon which the existing withdrawal tools have been developed and validated. In harmony with the mixed methods approach, findings from these studies are integrated in the withdrawal signs synthesis chapter and with the findings of the other studies presented in this thesis, contributing to the meta-inferences about withdrawal signs.

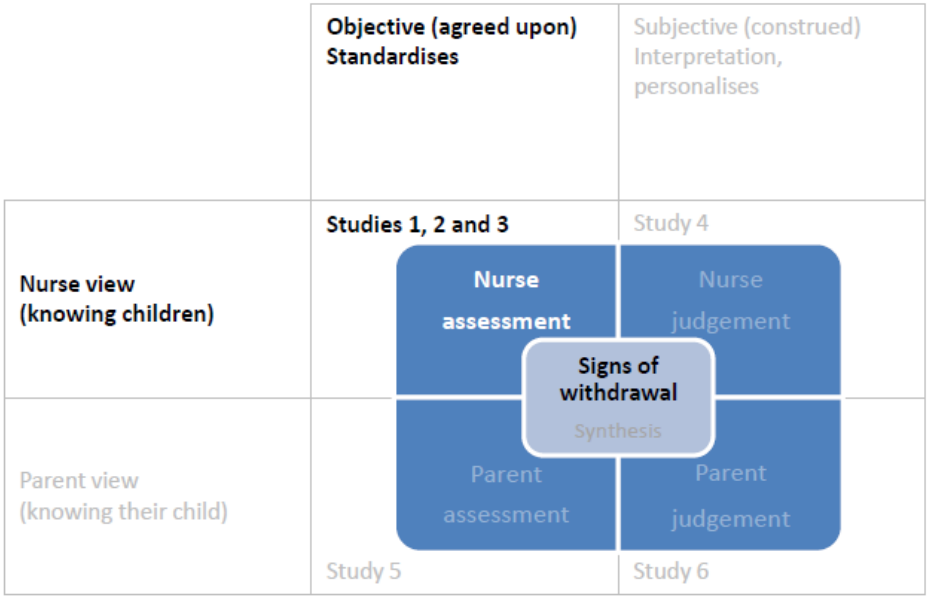

Figure Part 2.1 The conceptual framework showing the contribution of Studies 1, 2 & 3

Chapter 4 (Study 1) is a retrospective evaluation of the Sedation Withdrawal Score (SWS) tool.

Chapter 5 (Study 2) is a comparison of two studies which both characterise withdrawal signs in critically ill children. The datasets were transformed to allow comparison. Comparing and contrasting the results of two studies is an example of integration, which is a key feature of mixed methods research (Fetter et al 2013). Integrating results from two studies allows a comparison to be made and a more complete understanding to emerge, compared with what is provided by either study alone.

Chapter 6 (Study 3) presents a pragmatic critique of the WAT-1 dataset. The WAT -1 study is reviewed using a pragmatic framework proposed by Krathwohl (2009) prior to a review of three papers which each contribute a difference perspective of the same dataset.

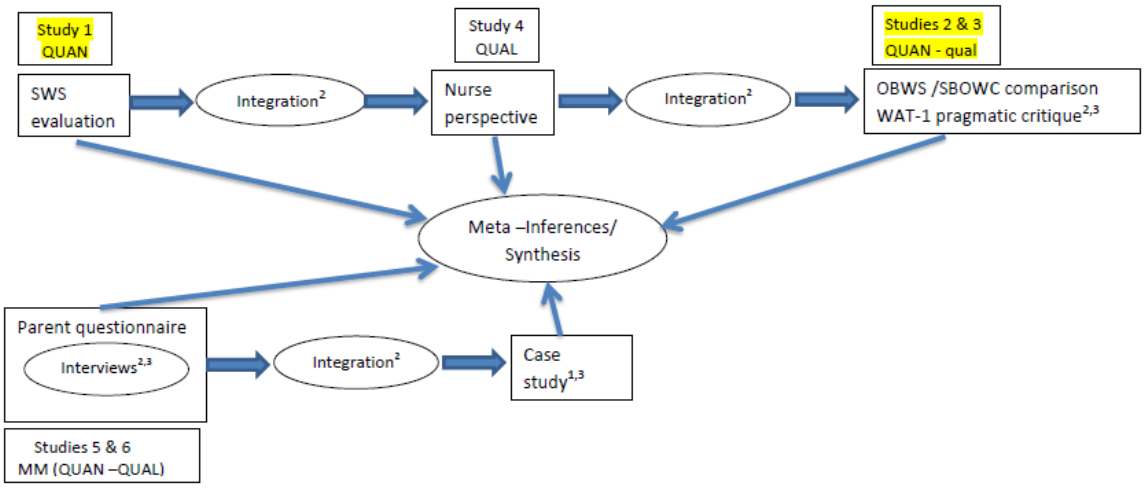

Figure Part 2.2 The thesis map showing Studies 1 and 2 highlighted

Chapter 4: Study 1: Retrospective evaluation of the Sedation Withdrawal Score (SWS); an audit of highest SWS scores in patients undergoing weaning of sedatives and/or opioids

4.1 Introduction

Two validated withdrawal assessment tools exist but neither has been able to identify the treatment cut-points necessary for clinical utility. Exclusion criteria limit generalisability of these tools in a heterogeneous critical care population and flaws in the incomplete independence of the criterion and index tests in both tools, also cast doubt on their concurrent validity. In the absence of a criterion standard, validation studies of both SOS and WAT-1 have relied on the views of the nurse completing the tools as the comparison measure. This is a significant flaw, as the association between criterion and index tests, as the basis for demonstrating concurrent validity, a component of construct validity, relies on the two measures being independent (Bowling 2004). The withdrawal assessment tool used in the study hospital, the Sedation Withdrawal Score (SWS) (Cunliffe et al 2004), has not been formally validated. This study was the preliminary evaluative stage of refining the SWS tool prior to incorporating the parental perspective.

4.2 Background

The Sedation Withdrawal Score (SWS) has been embedded in clinical practice as the existing approach to withdrawal assessment in the study hospital since 2002 (See Appendix 1). The SWS comprises 12 signs of withdrawal, each of which is scored 0, 1 or 2 depending on whether the nurse perceives the behaviour as absent (0), mild (1) or severe (2) in the hours since the preceding assessment. The SWS score is usually assessed every 6 hours and determines subsequent treatment choices, according to the treatment protocol shown in Table 4.1. This protocol delineates four levels of treatment according to withdrawal intensity, which broadly correspond to “no”, “mild”, “moderate” and “severe” withdrawal.

A prospective study entails the independent concurrent comparison of the index test with a criterion standard; a condition which was not met in the validation studies of either WAT-1 (Franck et al 2008) or SOS (Ista et al 2009). As the SWS tool was already

embedded in clinical practice, a retrospective evaluation was performed. This approach permitted an alternative approach to evaluation, exploiting and benefitting from hindsight; the opportunity to reflect on the consequence of the clinical decision in light of "what happened next." This approach provides more evidence to retrospectively support or reject the choice of diagnosis or treatment, compared with the prospective nature of withdrawal assessment decision making in practice. A similar approach has been applied in the evaluation of other clinical criterion standards, such as assessing degree of dehydration (Roland et al 2010).

Table 4.1 SWS treatment protocol

SWS score	Treatment
SWS ≤ 3	Continue with reducing regime
SWS 4-6	Stop reductions
SWS 6-10	Increase (revert to previous regime)
SWS >10	Seek advice

A diagnostic dilemma was revealed during the construction and piloting of the data extraction sheet, in relation to the retrospective allocation of withdrawal status at the time of the highest score. The dilemma arose from assigning a dichotomous withdrawal status (withdrawing vs not withdrawing) in a complex situation where diagnostic uncertainty exists due to the co-occurrence of other causes for behaviours.
With adverse drug reactions (ADRs) causality assessment is classified in terms of probability, rather than a rigid dichotomy, reflecting similar levels of uncertainty to withdrawal. The ADR assessment criteria help to determine the likelihood that the patient's condition is due to the drug implicated rather than the result of other factors. The likelihood rating is assigned according to aggregated evidence of a temporal relationship between the suspected drug and the reaction, the plausibility of the reaction and evidence of de-challenge/ re-challenge (Gallagher et al 2011). Plausibility considers whether the response is a known drug reaction, whether there is a definitive laboratory test and whether there are other possible causes for the reaction. De-challenge means the reaction improves on stopping the medication and re-challenge means the reaction returns when the medication is restarted. The likelihood categories range from certain or definite, through probable and possible to unlikely (Gallagher et al 2011, WHO-UMC, Gill et al, 1995). The ADR causality assessment criteria were considered to reflect the diagnostic uncertainty inherent in this population of critically ill patients. The criteria

were adapted in order to identify predictive validity of SWS by retrospectively assigning a likelihood rating of withdrawal at the time of the highest SWS score in this audit.

4.3 Purpose of Study 1

To evaluate the following psychometric properties of SWS current approach to withdrawal assessment:

1. Construct validity by examining
    a. The range of scores and component items of the highest SWS scores,
    b. The impact of respiratory status and likelihood of withdrawal on the highest SWS score;
2. Content validity by identifying if other behaviours were described at the time of the score
3. Predictive validity of the highest SWS score by cross-tabulating SWS ≥4 and SWS ≤ 3 with the likelihood of withdrawal;
4. Hypothesis testing of SWS≥4 as a cut point for withdrawal unlikely and possible/probable.

4.4 Method

The probability of withdrawal at the time of the highest SWS score was assigned objectively based on ADR causality assessment criteria. This approach provided an independent standard against which the predictive validity of SWS and a cut point of SWS≥4 (Table 4.1) could be assessed. Adaptations to the ADR criteria were made in recognition that withdrawal, as an end-of-use (Type E) ADR, is a consequence of stopping, rather than starting a drug, and only occurs in the context of physical dependence. Plausibility was labelled "*physical dependence possible*." In terms of dechallenge and rechallenge, the actions and consequences of these interventions are reversed in withdrawal compared with other ADRs. Rechallenge (restarting or increasing the drug) is linked to a reduction in withdrawal signs, due to an increase plasma levels and receptor occupancy. Dechallenge is the response manifested as withdrawal, which is provoked by weaning (decreasing plasma levels and reduced receptor occupancy). The terms dechallenge and rechallenge were labelled "*temporal relationship with changes in dose*" to reflect the relationship between changing drug levels and signs of withdrawal.

Of the four main categories of ADR likelihood that exist, “possible”, “probable” and “unlikely” were retained for this study (Table 4.2). The category “definite” was not included due to the lack of a definitive laboratory test and in light of the redundancy of this label, when in contrast with other ADRs, the causal drug may be reintroduced (rechallenge), rather than stopped, in response to the reaction.

Table 4.2 Probability of withdrawal based on WHO–UMC causality assessment criteria (https://www.who-umc.org/media/2768/standardised-case-causality-assessment.pdf)

Withdrawal likelihood	Physical dependence possible	Temporal relationship with change in dose	Absence of differential diagnoses
Probable	Yes	Yes	Yes
Possible	Yes	Yes	No
Unlikely	No	No	No

4.5 Setting

The study was conducted in a large children’s hospital in the Northwest of England. Approximately 1000 patients are admitted to the 21-bedded PICU annually. Sedation cycling is practised, whereby sedation drugs are changed (cycled) every five days, where the patient’s condition allows, in an attempt to minimise the development of physical dependence. The drug combinations cycled are fentanyl and midazolam, clonidine and promethazine and ketamine and diazepam. In addition to these drugs, the use of chloral hydrate is common, with chlorpromazine and isoflurane used occasionally. All patients referred to the pain team, the clinical team who oversee the sedation weaning of patients after discharge from PICU, were included in the audit until data on 100 cases had been collected. Data were collected between January 2010 and June 2012.

4.6 Ethics and governance

This audit was registered with the clinical audit department in the study hospital and approved by the departmental audit lead. Ethical approval was therefore not required.

4.7 Data extraction

A data extraction sheet was created (Appendix 5) to record patient data from a number of different sources; the case notes, electronic nursing records, the SWS assessment

sheet the PICU and ward drug prescription charts and the PICU fluid balance charts. During the timeframe of this audit, the SWS assessment, drug prescriptions and fluid balance charts were paper documents, which after use, were filed in the case notes or scanned onto the electronic patient record. As each source of information was required to contribute the necessary data, patients were excluded from the audit if any of the paper documents was missing from the case notes. All data collection was performed by the researcher.

4.7.1 Patient characteristics

The following data were collected about the patient from the case notes and electronic nursing records; age, gender, underlying condition/s, the reason for PICU admission, and date and time of extubation (for respiratory status).

4.7.2 Sedation Withdrawal Scores

The withdrawal assessment chart is the document where nurses record the presence of the 12 component signs of SWS and assign an intensity score to each item. The highest SWS score was identified from this document and the score, the date and time recorded and the breakdown of the score (the component signs and intensity scores) were collected.

4.7.3 Drug therapy, other signs of withdrawal and differential diagnoses.

Sedative drugs administered routinely in the study setting are opioids, benzodiazepines, chloral hydrate, clonidine and promethazine. Changes in sedative therapy resulting in a reduction in any of these drugs in the 72 hours leading up to the highest score were noted, in order to identify a temporal link between sedation weaning and the highest SWS score. An additional category of “other drug” was included to capture the administration of less commonly used sedatives. In cases where withdrawal was suspected, the suspected causal drug was noted.

Case notes and computerised nursing notes were checked to identify if any other withdrawal symptoms had been documented at the time of the highest SWS score and to ascertain whether other concurrent differential diagnoses may have contributed to the score.

4.7.4 Assigning the likelihood of withdrawal

The diagnosis of withdrawal is based on a context of physical dependence, a temporal relationship to a reduction of sedative medication and exclusion of other possible causes for the behaviours. These three criteria were assessed in order to assign the likelihood of withdrawal for each audit patient. Physical dependence was considered possible if patients had received at least five days drug therapy, either by continuous infusion or regular interval dosing (Franck et al 2004, 2008, Ista et al 2008, 2009) of one of more of the following drugs; opioids, benzodiazepines, chloral hydrate, clonidine, ketamine, promethazine and chlorpromazine.

A temporal relationship with a change in dose was defined as any reduction in the 72 hours prior to the highest score. Changes in sedative drugs and the possibility of other differential diagnoses were assessed from the drug prescription charts and documentation in the case notes and the electronic nursing record.

The operationalisations of the criteria for assigning the likelihood of withdrawal at the time of the highest SWS score are summarised as follows (see Table 4.2);

- *Probable withdrawal* was defined as physical dependence possible, reduction in sedative medication in the previous 72 hours and no other differential diagnoses.
- *Possible withdrawal* was defined as physical dependence possible, reduction in sedative medication in the previous 72 hours, other differential diagnoses.
- *Withdrawal unlikely* was defined as physical dependence unlikely or no reduction in sedative medication in the previous 72 hours, regardless of differential diagnoses.

4.8 Analysis

The audit results were analysed using descriptive and inferential statistics. Descriptive statistics were calculated, including medians and interquartile ranges for the frequency of presentation and number of items in the highest SWS scores.

Construct validity was evaluated by examining the range of scores and component behaviours of highest SWS scores across the entire sample and then by dividing the sample according to level of respiratory support and likelihood of withdrawal (probable, possible, unlikely), in order to identify any patterns or trends in presentation that differentiated levels of withdrawal or condition and to consider alternative diagnoses that might be driving the score (STARD 2015).

Content validity was evaluated by considering the impact of the presence of other behaviours reported in nursing records and case notes at the time of the highest SWS score, which were not part of SWS, but are recognised signs of withdrawal.
Hypothesis testing of SWS ≥4 as a cut point for withdrawal, including identification of Type I and Type II errors, sensitivity, specificity and positive and negative predictive values for the highest SWS score.

4.9 Results

Of 188 patients referred to the pain team for management of sedation weaning during the study period, 97 complete sets of notes were retrieved and included in the study. The remaining 91 case notes were either unavailable or incomplete (one of more of the paper charts missing), so could not be included in the study. The sample of 97 patients comprised 59 males (61%) and 38 females (39%). Sixty six children were aged under 1 year of age (68%) of whom 13 (13%) were neonates. Twenty nine children (30%) were aged 1-5 years and two (2%) children were aged 6 years and over. Forty six patients had an underlying cardiac condition requiring PICU care post-operatively. The remaining 51 patients were admitted to PICU with a range of other medical conditions. One patient was treated for neonatal abstinence and did not require admission to PICU.

4.9.1 Sedative drugs administered

Sedative drugs were usually administered in combinations of two or more sedative drugs. Opioids were administered to 82 patients (85%); fentanyl 73%, morphine 26% and both 1%. Benzodiazepines were administered to 66 patients (69%); midazolam 82%, diazepam 11%, both 7%. In addition, patients received other sedatives including chloral hydrate n=70 (72%), promethazine n=31 (32%), clonidine n=24 (25%), ketamine n=16 (16%) and chlorpromazine n=5 (5%). Two patients had been recruited onto a clinical trial (SLEEPS study) and received a blinded study drug, which was either midazolam or clonidine.

4.9.2 The likelihood of withdrawal

At the time of the highest SWS score, withdrawal was probable in 61 (63%) cases, possible in 18 (18%) cases and unlikely in 16 (16%) cases.
Where withdrawal was probable (n=61), the suspected causal drug was identified in 35 cases (57%). Chloral hydrate was most commonly implicated (n=13), followed by opioids (n=9) (fentanyl n=5, morphine n=4) and benzodiazepines (n=6) (midazolam n=5,

diazepam n=1). In seven cases, withdrawal was precipitated in response to cycling of medication; fentanyl/midazolam to clonidine/promethazine (n=3), fentanyl/midazolam to ketamine/diazepam (n=2), promethazine/clonidine to ketamine/diazepam (n=1) and ketamine/diazepam to clonidine/promethazine (n=1). In these cases, the causal drug could not be identified because two drugs were changed concurrently. Similarly, in the remaining cases (n=26), reductions in more than one drug meant the causal drug could not be identified (n=25) and one patient had neonatal abstinence syndrome.

4.9.3 The range of highest SWS score

The highest SWS scores ranged from 0-18 and were normally distributed (Figure 4.1). The median (IQR) SWS score was 7 (5-9) and the number of items contributing to the score was median (IQR) 5 (4-6). The number of items explains why, despite an SWS score range of 0-24, all but one of the peak scores fell in the lower half of the score range.

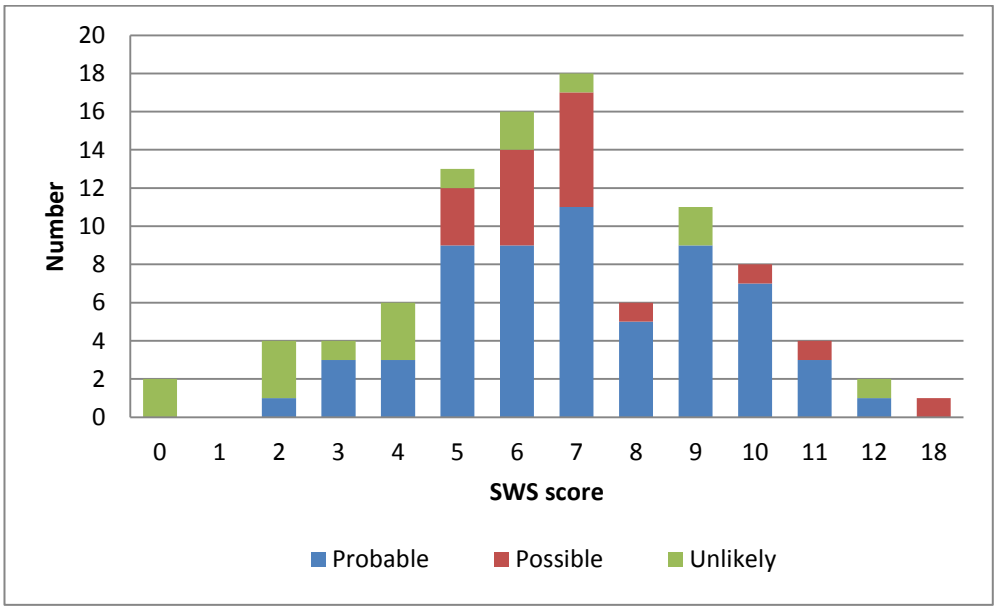

Figure 4.1 Highest SWS scores by likelihood of withdrawal (all cases).

The ranges of SWS scores for "probable" withdrawal was SWS 2-12, for withdrawal "unlikely" the range was SWS 0-12, and for "possible" withdrawal was SWS 5-18. Every SWS score between the range of 2 and 12 was characterised by two or more levels of withdrawal. All three levels of withdrawal were represented in the three modal SWS scores of SWS 5-7 inclusive. The broad range of scores for each category of withdrawal points to the heterogeneous presentation of withdrawal whilst the overlap of scores is evidence of the similarities between withdrawal behaviour and other causes of behaviour in critically ill babies and children.

4.9.4 Symptom content of the highest SWS scores

The twelve items in the SWS tool were analysed for frequency of presentation in the highest scores (see Table 4.3). Three items, irritability, insomnia and diarrhoea, were present in ≥50% cases. A further five symptoms, respiratory distress, sweating, high pitch cry, fever and tremor, were present in 25- 49% cases. The remaining four items occurred in <25% of highest SWS scores.

It is of interest that irritability and insomnia, when documented, were more than twice as likely to be scored as 2 (severe) than 1 (present). The opposite was true with the remaining ten items, which were more frequently scored as 1 (present) than 2 (severe).

Table 4.3 SWS signs represented in highest SWS scores (all cases) according to frequency of item presentation and individual item score.

SWS signs	Frequency of item in sample (%)	Number of patients		
		Score 0	Score 1	Score 2
Irritability	90	10	27	60
Insomnia	86	14	25	58
Diarrhoea	50	48	34	15
Respiratory distress	46	52	28	17
Sweating	45	53	32	12
High pitch cry	38	60	25	12
Fever	30	68	24	5
Tremor	25	73	17	7
Vomiting	20	78	10	9
Sneezing	16	81	15	1
Hypertonicity	12	85	8	4
Convulsions	2	95	2	0

4.9.5 Hypothesis testing of SWS≥4 as a cut point for withdrawal

A contingency table was constructed to cross tabulate the SWS scores, according to the treatment cut points, with the probability of withdrawal. This is shown in Table 4.4. Ticks denote cases where the treatment protocol is consistent with the withdrawal diagnosis. These data were used to calculate the false positive, or Type I errors and the false negative, or Type II errors (Figure 4.1). False positives are those cases where the SWS score ≥ 4 but withdrawal is unlikely (n=10); with a potential for unnecessary slowing of the weaning regimes and possible delay in diagnosing the underlying cause for behaviours. True positives occur where the SWS score ≥ 4 and withdrawal is possible or probable; withdrawal is suspected and treated. False negatives are cases where SWS ≤ 3

but withdrawal is possible or probable (n=4); where the potential is for withdrawal to go untreated. True negatives occur when the SWS score ≤ 3 and withdrawal is unlikely; withdrawal is not diagnosed and weaning continues.

Table 4.4 Contingency table showing SWS treatment cut points and the probability of withdrawal

SWS score	Intervention	Total number	Withdrawal probable	Withdrawal possible	Withdrawal unlikely
≤3	Continue reducing	10	4	0	6✓
4-6	Stop reducing	35	21✓	8✓	6
7-10	Increase sedation	43	32✓	8✓	3
>10	Seek advice	7	4✓	2✓	1
	Total	95	61	18	16

This enables the sensitivity, specificity, positive predictive value and negative predictive value of the highest SWS score to be calculated, as shown in Figure 4.2.

		True condition		
		Withdrawal probable/possible	Withdrawal unlikely	
Predicted condition	SWS ≥ 4	75 True positive (TP)	10 False positive (FP) Type I error	Positive predictive value =TP/ (TP+FP)=0.882
	SWS ≤ 3	4 False negative (FN) Type II error	6 True negative (TN)	Negative predictive value =TN/ (TN+FN)=0.6
		Sensitivity =TP/(TP+FN) =0.95	Specificity =TN/(TN+FP) =0.375	Prevalence = (TP+FP)/ (TP+FP+FN+TN) = 89%

Figure 4.2 SWS cut points and rates of false positives and false negatives (Highest SWS score)

The sensitivity describes the proportion of withdrawing patients (true positives) who are correctly identified as withdrawing by the test: Sensitivity = 0.95

The specificity of describes the proportion of patients not withdrawing (true negatives) who are correctly identified as not withdrawing by the test: Specificity = 0.375

The positive predictive value (PPV) is the probability of withdrawal in those testing positive (scoring SWS≥4): PPV = 0.882

The negative predictive value (NPV) is the probability of the absence of withdrawal in those testing negative (scoring SWS ≤3): NPV =0.6

4.9.6 The impact of respiratory status and likelihood of withdrawal

4.9.6.1 Respiratory status

Forty five patients scored for respiratory distress as a component of their highest SWS score. Four different levels of respiratory support were identified in this cohort; 'intubated and ventilated', 'non-invasive ventilation (CPAP* or BiPAP**)', 'extubated' and 'not ventilated this admission'. Intubated patients were more than twice as likely to score for severe respiratory distress as extubated patients were (Table 4.5). Time since extubation was longer (median 46 hours) for those who scored '1' (mild respiratory distress) compared with those who scored '2' (severe respiratory distress) (median 20 hours).

Table 4.5 Respiratory support in patients scoring for 'respiratory distress' as part of the SWS assessment (n=45).

Respiratory support	Scored for SWS sign 'respiratory distress'		Total
	Score 1	Score 2	
Intubated and ventilated	4	9	13
Non-invasive ventilation	4	0	4
Extubated	19	8	27
Not ventilated	1	0	1
Total	28	17	45

*CPAP= Continuous positive airway pressure **BiPAP = Bilevel positive airway pressure

4.9.6.2 Likelihood of withdrawal

The prevalence of signs was analysed in terms of items occurring in ≥ 50% of all cases and according to the likelihood of withdrawal. Three items were present in ≥50% all cases; irritability (90%), insomnia (86%) and diarrhoea (50%). In the 'withdrawal probable' group (n=61), there were four signs present in ≥50% cases; irritability (92%), insomnia (90%), diarrhoea (59%) and sweating (51%). In the 'withdrawal possible' (n=17), three signs were present in ≥50% cases: irritability (94%), insomnia (94%) and sweating (61%). In the 'withdrawal unlikely' group (n=19), two signs were present in ≥50% cases: irritability (79%) and insomnia (73%) (Table 4.6).

In all groups, irritability and insomnia were ranked first and second by prevalence respectively. With all other SWS signs, differences occurred in item presentation between groups, but not to an extent that could be considered clinically meaningful.

Table 4.6 Top ranking SWS signs present in ≥ 50% by all cases and likelihood of withdrawal

SWS Signs	All cases	Likelihood of withdrawal		
		Probable	Unlikely	Possible
	n=97	n=61	n=19	n=17
Irritability	**90%**	**92%**	**79%**	**94%**
Insomnia	**86%**	**90%**	**73%**	**94%**
Diarrhoea	**50%**	**59%**	(32%)	(41%)
Respiratory distress	(46%)	(47%)	(47%)	(41%)
Sweating	(45%)	**51%**	(32%)	**61%**

(**Bold** shows signs with ≥ 50 % prevalence in one or more groups; bracketed results and respiratory distress (incidence<50%) for comparison).

4.9.7 Other behaviours; additional withdrawal signs reported by clinicians

The following signs were identified from the nursing or clinical notes; jittery n=4, agitated n=3, and single episodes of the following; unsettled, inappropriate movement of arms and legs, lack of eye contact, not responding/interacting with family, doubly incontinent and 'holding medication in mouth'.

4.9.8 Evidence of something else going on

Whilst assigning the likelihood of withdrawal, one of the steps in the causality assessment tool is considering the probability that the event was due to an underlying disease. A number of cases stood out due to the unstable presentation of the child when the withdrawal assessment had been undertaken. This occurred in 11 cases, where there was clearly something other than withdrawal driving the behaviour being assessed. Patients in this cohort varied in terms of age, diagnosis and SWS score, as shown in Table 4.7.

Six patients were ventilated; ventilator issues included the patient not synchronising with the ventilator, being 'over-ventilated' and patients becoming less tolerant of ventilation as sedation reduced in the time leading up to extubation. One patient scored highest at the time of extubation but did not require additional respiratory support. Three patients required additional airway support between one hour and 24 hours after extubation; two

of whom were subsequently reintubated. In two cases the underlying condition (bronchiolitis, meningococcal meningitis) may have driven the score.

4.10 Discussion

This retrospective study is the first to evaluate the SWS tool and the first study to use an objective test to assign probability of withdrawal to SWS scores. The theoretical basis for the development of a generalisable withdrawal scale relies on two key factors. The first is a homogeneous presentation of withdrawal to enable comparison between patients and allow identification of treatment cut points. The second factor is a clear distinction between the presentation of withdrawal and other possible differential diagnoses. A number of findings in this study challenge these essential prerequisites for construct validity and hence the clinical utility of the SWS score as a marker for the diagnosis or treatment of withdrawal. The study findings and these challenges will be considered in light of the existing literature.

4.10.1 Lack of homogeneous presentation

The broad range of scores and indistinct characterisation of the likelihood of withdrawal points to a heterogeneous presentation. The median (IQR) peak SWS score was 7 (5-9) with a wide spread of likelihood of withdrawal. This compares with a peak daily WAT-1 score of 4 (3-6) in 126 patients reported by Franck et al (2012). Ista et al (2013) did not report the SOS score range in their study of 154 patients.

Table 4.7 "Something else going on" (grouped by ventilation status; ventilated, at extubation, extubated)

Audit number	Age	Gender	Diagnosis	SWS score	Withdrawal suspected	Insomnia	Irritability	Sweating	Tremor	Diarrhoea	Vomiting	Fever	High pitch cry	Respiratory distress	Hypertonicity	Convulsion	Respiratory support	Notes
4	2 years	Male	Asthma	5	Probable	2	2					1					Ventilated	Extubated 7h later.
19	4 months	Male	Respiratory failure	6	Possible	2	2							2			Ventilated	Intubated with HFOV
31	3 months	Female	Cardiac surgery	12	Unlikely	2	2	2		2		1		2		1	Ventilated	Not synchronising with the ventilator.
45	6 months	Male	Aspiration pneumonia	7	Possible	1	2	1					2	1			Ventilated	Extubated 14h later.
56	8 months	Male	Bronchiolitis	6	Unlikely		2	2			1	1					Ventilated	Not weaning
86	13 months	Male	Cardiac surgery	7	Possible	2	2		1				2				Ventilated	Difficult to sedate, over-ventilated.
35	1 year	Male	Cardiac surgery	4	Unlikely	1	1			1	1						At extubation	
14	24 days	Female	Closure gastroschisis	9	Unlikely	1	2				2		2	2			Extubated 19h before	Reintubated and diagnosed with diaphragmatic hernia.
24	8 weeks	Male	Bronchiolitis	4	Unlikely	1		1				1		1			Extubated 1h before	Required NPA, then BIPAP then reintubated.
9	18 months	Male	Respiratory failure	5	Probable		1		1	1				1	1		Extubated 24h before	NPA reinserted.
50	6 weeks	Male	Meningococcal meningitis	10	Unlikely	2	2	1	2	1			1		1		Extubated 52h before	

HFOV=high frequency oscillator ventilation NPA=nasopharyngeal airway BiPAP=Bilevel positive airway pressure

Although the range of scores was broad, this encompassed the lower half of the score range. The lack of scores in the top half of the range was a consequence of the number of items contributing to each of these top scores. The median (IQR) number of items was 5 (4-6), a range which demonstrates consistency in the number of items contributing to the top scores. However, this range also highlights that even the "top score" behavioural presentation represented just 33% to 50% of available SWS items. These figures point to a very loose association between the component signs of SWS, rather than the correspondence or convergence between items needed to demonstrate the theoretical relationship underpinning this operationalisation of withdrawal.

4.10.2 No clear cut point for withdrawal

In terms of episodes of withdrawal, Franck et al (2012) described 51 episodes of clinically significant withdrawal in 21 patients, whose median (IQR) WAT-1 scores before and after rescue therapy were 6 (4-8) and 2 (1-3) respectively. Ista et al (2013) reported a mean reduction in SOS score of 1.47 in 51 patients after administration of sedative or opioids to treat withdrawal symptoms. This second result infers, if only by omission, that a range of scores existed, and that decision to treat was based on clinical opinion rather than the score, in common with the reported WAT-1 findings. Despite the lack of transparency about clinically significant withdrawal, SOS and WAT-1 subsequently provided statistical support for cut points of SOS≥4 (Ista et al 2013) and WAT-1≥3 (Franck et al 2012). It is not clear given the broad range of scores and overlap in scores between patients who are withdrawing and not withdrawing whether these cut points have clinical utility.
The ADR causality assessment introduced a novel approach to labelling withdrawal, compared with the existing dichotomous depiction of the diagnosis, as "present" or "absent." These terms portray a certainty that does not reflect the complexities of competing diagnoses and reliance on equivocal clinical signs in clinical practice. Adopting the probability terms of "probable", " possible" and " unlikely" to describe withdrawal may better reflect the level of uncertainty and the impact of withdrawal on co-existing conditions.

4.10.3 Distinct from other differential diagnoses

Other behaviours were noted at the time of the highest score. Two of these signs 'motor disturbance' and 'agitation' appear in the SOS score (Ista et al 2009). Agitation is a component of the SBS sedation assessment for WAT-1 (Franck et al 2008). Two patients had communication disturbances similar to those described in the early literature

describing responses to sedation withdrawal (see Table 2.10 in Chapter 2). Whilst not a feature in WAT-1 or SOS, inattention is a criterion in the pediatric delirium (PD) tools (Traube et al 2014, Smith et al 2016). What is not clear is whether this is an overlapping feature of both PD and withdrawal. Integration of these findings on signs of withdrawal with the findings from subsequent studies will be presented in Part 5.

In addition to the possible overlap of PD and withdrawal, the level of respiratory support in turn appeared to influence the respiratory distress component of the SWS score. This has an impact on construct validity when the outcome is a summed score, as the changes in respiratory support may be driving the score rather than withdrawal (Streiner and Norman 2003). The equivalent signs in SOS and WAT-1 are tachypnoea and respiration rate high for age respectively. These findings demonstrate the challenge of delineating the causal impact of reducing ventilator support and withdrawal on respiratory distress. To be of value as a sign of withdrawal, the behaviour should be uncommon in patients who are not withdrawing. Similarly the high prevalence of both irritability and insomnia in the SWS sample, including those patients classified as unlikely to be withdrawing may indicate that these behaviours are common to PICU patients, rather than specific for withdrawal. Both behaviours feature in SOS but are absent from WAT-1. Irritability and insomnia were the only SWS signs more likely to be interpreted as severe rather than present at the time of the highest score, implying that intensity of behaviour, rather the behaviour itself might indicate withdrawal. This makes sense when considering the additional impact that an unpleasant ADR may have on the critically ill child's underlying physical state.

The positive predictive value is the probability of withdrawal in those testing positive (DeVellis 2012). The low positive predictive value (PPV) of 0.49 for SOS ≥4 indicating withdrawal shows the poor diagnostic value of the SOS tool; at this cut point more patients who test positive are likely to be not withdrawing (51%) than withdrawing (41%). The PPV of WAT≥3 was not reported (Franck et al 2012) but could be calculated from the data presented (See Chapter 2). This gave a PPV value of 0.65; at the designated cut point of WAT-1≥3, the majority of patients are withdrawing (65 %) but this still means that more than a third of patients (35%) are not withdrawing.

The PPV in this study is 0.882, which is higher than both WAT-1 and SOS, but this is a reflection of the higher prevalence of withdrawal in this cohort, where only the highest SWS scores were analysed, compared with the lower prevalence SOS and WAT-1 cohorts,

where all scores were considered (Franck et al 2008, Ista et al 2013). Despite a PPV higher than WAT-1 and SOS, SWS figures still equate to an 11% error rate even in a high prevalence cohort.

4.10.4 "Distribution of alternative diagnoses in those without the target condition"

The distribution of alternative diagnoses is a STARD (2015) requirement when reporting the accuracy of clinical tools. Ista et al (2013) attributed the low positive predictive value of SOS to overlap of withdrawal symptoms with pain, distress and delirium. Franck et al (2008) did not report any consideration of alternative diagnoses. In this study, alternative diagnoses were demonstrated in the cohort of 11 patients. These patients highlight the complexity of the clinical situation with a range of possible differential diagnoses with or without the suspicion of withdrawal. In terms of speculating what had motivated the nurse to undertake a withdrawal assessment at these times, it may be the tool had been used as a "red flag" to highlight the nurse's concerns over the child's clinical condition, which could be described as "intentional false positive" (Van der Zwaan 2012).

Alternatively, this may be due to overinflated confidence in the tool's diagnostic ability (for example, If I get a score for withdrawal, then it is withdrawal). Either way, these findings challenge the common assumption that nurses exclude other possible causes for behaviours prior to the withdrawal diagnosis being confirmed (Harris et al 2016, Ista et al 2013). This also casts doubt on the cogency of using nurses' opinion as a reference standard in tool validation studies (Franck et al 2008, Ista et al 2013).

4.10.5 Criterion validity

When criterion validity is established retrospectively, as in this study, it is termed predictive validity (Streiner and Norman 2003). SOS and WAT-1 established criterion validity by concurrently comparing the index tool to nurse opinion; this is termed concurrent validity (Streiner and Norman 2003). Predictive validity of SWS was established by comparing SWS scores with an objective reference standard, in the form of adapted ADR causality assessment criteria. This approach compares favourably with the "incomplete independence" (Franck et al 2008, p579) between the reference and index tests in the validation studies of both SOS and WAT-1; where the probability of withdrawal was assigned by the bedside nurse who also completed the study test (Ista et al 2009 and Franck et al 2008). The reference (existing) and index (new) tests should be

independent of each other because the accuracy of the new test is based on the correlation with the existing test (nurse opinion). If the nurse's opinion is predicated in part on the results of the new test, or tempered by the process of performing the new assessment, then the reference test is based on the index test and the two measures are artificially correlated (Streiner and Norman 2003). This is called criterion contamination (Streiner and Norman 2003). Given the potential for criterion contamination and an inflated correlation between WAT-1, SOS and their respective reference tests, the PPVs of WAT-1 and SOS are surprisingly modest.
The findings from this study contribute further insights into possible causes for the poor PPV of existing withdrawal assessment tools.

If no clinically useful cut point exists, then consideration might be given to the impact of one diagnostic/statistical error over the other; these are false positive /Type I and false negative/ Type II errors. False negative errors are benign, as the withdrawing child who shows minimal behavioural signs, is at risk of neither delayed diagnosis nor treatment. The negative predictive value (NPV) describes the probability of the absence of withdrawal in those testing negative (DeVellis 2012). The NPV of the withdrawal assessment tools are 0.6 (SWS), 0.96 (WAT-1) (Franck et al 2008) and 0.98 (SOS) (Ista et al 2013). In Type I errors the child's behaviours score for withdrawal but the child is not withdrawing. As shown in the cohort of 11 patients, behaviours might signify the underlying condition, respiratory compromise or clinical deterioration. There are two implications of a false positive diagnosis of withdrawal;

1. delay in appropriate diagnosis and treatment, and
2. unnecessarily prolonging the sedation regime due to slowing or stopping of weaning.

Greater clinical concern arises from overlooking a more serious condition with a false-positive diagnosis of withdrawal, rather than the unnecessary slowing of a weaning regime. However, unnecessary slowing may have a financial consequence by extending the duration of PICU and/or hospital admissions (Traube et al 2016).

4.10.6 Treatment of withdrawal

The treatment protocol linked to SWS describes four treatment levels; continue weaning; stop weaning; increase sedation to previously tolerated level; seek help (Cunliffe et al 2004). This step-wise approach contrasts with WAT-1 and SOS, where treatment of withdrawal relies on administration of rescue boluses of sedation (Franck et al 2008, Ista et al 2013). Franck et al (2008) also used the term "clinically significant withdrawal" to

describe cases where withdrawal signs prompted the administration of rescue doses of sedation. The median WAT-1 score for these cases was higher (SWS 6) than the reported threshold for withdrawal (SWS≥3) (Franck et al 2008). The difference between these scores suggests an overlooked cohort of patients, who may be withdrawing but not to the extent that warrants administration of rescue boluses. As these patients fall below the threshold for rescue boluses of "clinically significant withdrawal", this level of withdrawal might be described as "clinically insignificant withdrawal." This term raises an interesting practice point in terms of management of withdrawal, about what constitutes the threshold for treatment. Clinically insignificant withdrawal suggests withdrawal to an extent that is not hindering the patient's clinical condition / recovery. This might equate to the stage in the SWS treatment protocol, which advises stopping weaning. The four steps in this protocol align to "no", "mild", "moderate" and "severe" withdrawal. This is a similar approach to the management of pain, where the intensity of pain determines a corresponding analgesic intervention (http://www.who.int/cancer/palliative/painladder /en/ accessed July 2017). It is not clear how the cut points for WAT-1 and SOS align to the decision to treat "clinically significant withdrawal."

4.11 Conclusion

The findings from this study cast doubt on the capacity for nurses to exclude other causes of behaviours when undertaking a withdrawal assessment, given the predominance of co-existent causes. Further insight is needed into nurses' decision-making when applying a withdrawal assessment tool in situations when the causes for behaviours may be unclear. This finding prompted the design of a study to investigate nurse decision-making during withdrawal assessments. This study will be presented in Part 3.

This study did not demonstrate the clinical utility of the SWS score as a marker for diagnosis or treatment of withdrawal. The range of scores representing withdrawal seems to be incompatible with the endeavour to identify treatment cut points. The heterogeneous presentations of withdrawal and the impact of underlying conditions contribute to a level of complexity that is not reflected in the current approach to withdrawal assessment. It may be that an individualised assessment of each case is required rather than the application of a standardised tool. The criteria used in this study to assign probability of withdrawal may provide a suitable decision-making framework; the likelihood of withdrawal described as probable, possible or unlikely may also serve to

remind clinical staff of the elusive nature of this clinical construct and the need for ongoing consideration of other causes of behavioural concern. The clinical utility of a decision-making framework will be explored in Part 4 and Part 5.

Chapter 5: Study 2: A characterisation of withdrawal based on OBWS and SBOWC.

5.1 Introduction

The existing body of research about withdrawal diagnosis is based on the association of equivocal behavioural signs and symptoms of withdrawal. Although the WAT-1 (Franck et al 2008), SOS (Ista et al 2009) and SWS (Cunliffe et al 2004) tools share six items in common, these tools draws on a pool of 22 different signs and symptoms.
The aim of Study 2 was to gain further insight into the characterisation and operationalisation of withdrawal in critically ill children, given the lack of agreement about the construct of withdrawal that these differences indicate. Two existing papers provided the data for Study 2; the Opioid and Benzodiazepine Withdrawal Score (OBWS) (Franck et al 2004) and the Sophia Benzodiazepine and Opioid Withdrawal Checklist (SBOWC) (Ista et al 2008).

Study 2 is an illustration of the interactive, emergent design of this thesis, as the impetus for this study emerged from iterative interpretation of the literature and of data and findings from the component studies in this thesis. The lack of agreement about the manifestation of withdrawal, highlighted in the literature review and reinforced by the thesis studies, prompted further consideration of the manifestation of withdrawal. Study 2 is presented in Part 2 of the thesis because it considers the nurses' objective perspective of withdrawal assessment, according to the conceptual framework (Figure 3.2).

5.2 Background

Study 2 is an integrative study that investigated the behavioural signs of withdrawal in critically ill children undergoing tapering or stopping of drugs reported in two papers (Franck et al 2004, Ista et al 2008). Franck's and Ista's studies shared a common purpose of establishing the frequency of withdrawal signs; each study representing the same stage of refining an item pool, in the development of a clinical scale. The authors of these studies subsequently published validated withdrawal assessment tools; the WAT-1 (Franck et al 2008) and the SOS (Ista et al 2009) respectively. Once the definitive tool is published along with evidence of validity and reliability, a rationale for a direct

comparison of these item pool studies may not be indicated from a scale development perspective. However, from a pluralistic perspective, these studies contribute valuable evidence about how the construct of withdrawal has been operationalised. Comparing and contrasting two similar approaches also offers the opportunity to triangulate findings, identify areas of congruence and contention and lead to new insights and understanding of withdrawal. The OBWS (Franck et al 2004) and SBOWC (Ista et al 2008) studies will be presented in brief to demonstrate their comparable design.

5.2.1 The Opioid and Benzodiazepine Withdrawal Score (OBWS) (Franck et al 2004)

Fifteen patients (aged 6 weeks to 28 months of age) with complex congenital heart disease and/or respiratory failure were enrolled on the study. Inclusion criteria were opioid and/or benzodiazepine therapy for more than five days; exclusion criteria were children with significant neurological insult or seizure disorder. Patients were weaned from opioids and benzodiazepines over a median of 11 days at a rate of 10-20% per day (Table 5.1). The OBWS, adapted from the Children's Hospital Oakland Opioid Withdrawal Flowsheet (Franck & Vilardi, 1995), was described as a 21-item checklist of which 17 items were reported in the study. OBWS assessments were performed every four hours until approximately two days after the drugs had been discontinued. In total, 693 assessments were recorded; 151 assessments in 13 children indicated withdrawal, as judged by the nurse caring for the child. Data were presented comparing the occurrence of symptoms in children judged to be experiencing withdrawal (n=151 assessments) and those judged not to be withdrawing (n= 542 assessments). Incidence of withdrawal equated to 22% (n=151) of assessments in 87% (n=13) children (Table 5.1).

5.2.2 Sophia Benzodiazepine and Opioid Withdrawal Checklist (SBOWC) (Ista et al 2008)

Seventy nine patients (aged 0-15 years) with a range of medical and surgical diagnoses were enrolled on this study. Inclusion criteria were opioid and/or benzodiazepine therapy for at least five days: exclusion criteria were status epilepticus treated with midazolam, neuromuscular blocking agents and severely disturbed behaviour due to underlying neurology. The duration of weaning was not reported in this study but weaning rates were described and equated to tapering and discontinuation in 24 - 48 hours for patients receiving median doses (Table 5.1). All patients weaned from midazolam and 92% (n=73) weaned from opioids. The SBOWC contained 27 items derived from the literature,

purporting to include all signs of withdrawal. Assessments were performed at 4am, 2pm and 10 pm, to ensure that the nurse had been caring for the patient in the 4 hours preceding each assessment. Data collection ceased on discharge from PICU. In total, 2616 assessments were recorded, of which 932 (42%) were within 24 hours of tapering or stopping drugs. Ninety three observations in 27 children indicated withdrawal, which was defined as the need for increase in midazolam or opioids to counteract possible withdrawal symptoms. Incidence of withdrawal equated to 0.04% of assessments in 34% (n=27) children (Table 5.1). Data were presented in four groups for comparison, according to the following criteria;

1. The total group: 2161 observations on 79 children,
2. A weaning group: 932 observations in 76 children recorded less than 24 hours after reduction/stopping of sedatives,
3. A high dose group (a subset of the weaning group): 496 observations in 19 children with the highest total doses of midazolam, and
4. An unsuccessful weaning group: 93 observations in 27 children prior to receiving sedatives in response to withdrawal behaviour.

5.3 Purpose of Study 2

The purpose of Study 2 was to explore the characterisation of withdrawal by critically examining the items, or signs included in OBWS (Franck et al 2004) and SBOWC (Ista et al 2008), in order to;

- Consider the construct validity of individual signs by identifying the changes in prevalence of signs between withdrawing and not withdrawing patients
- Consider the generalisability of study findings by comparing and contrasting prevalence of signs across studies, where common items existed.

5.4 Objectives of Study 2

The objectives of Study 2 were to:

1. Transform the data in each study to comparable “withdrawing” and “not withdrawing” groups,

2. Identify the frequency with which signs present in the “withdrawing” and “not withdrawing” groups of OBWS (Franck et al 2004) and SBOWC (Ista et al 2008),

3. Identify the change in prevalence of signs between “not withdrawing” (baseline) and “withdrawing” groups of OBWS (Franck et al 2004) and SBOWC (Ista et al 2008) respectively, and

3. For signs described in both studies, compare the similarities and differences in the frequency, and change in frequency from baseline, in the “withdrawing” and “not withdrawing” groups of OBWS (Franck et al 2004) and SBOWC (Ista et al 2008).

5.5 Method

5.5.1 Sample characteristics

Participants were the patients (n=15) in the OBWS study (Franck et al 2004) and the SBOWC study (n=79) (Ista et al 2008), who were weaning from at least five days opioid and/or benzodiazepine therapy.

OBWS patients were assessed for withdrawal every 4 hours until two days after the drugs had been discontinued (Franck et al, 2004). SBOWC patients were assessed every 8 hours until discharge from PICU (Ista et al 2008).

Patients were weaned according to the respective study protocols, which differed in terms of the rate of weaning. The median tapering period for patients in the OBWS was reported as 11 days (Franck et al 2004). A median tapering period for SBOWC (Ista et al 2008) patients was not reported, but could be calculated from the data provided. The median doses of opioids and benzodiazepines and the taper rates reported in the weaning protocol, suggests the tapering period was 24-36 hours, as shown in Table 5.1.

5.5.2 Ethics and governance

Ethical approval was not required for this study.

5.5.3 Transforming the data

The data from the assessments performed in the OBWS study (693 assessments) was presented as “withdrawing” (151 assessments) and “not withdrawing” (693 assessments) groups (Franck et al 2004). These diagnoses were designated according to the nurse’s clinical judgement of the child at the time of the assessment. The data from the assessments performed in the SBOWC study (2161 assessments) (Ista et al 2008) was

presented differently, so was transformed into two comparable groups to enable comparison of these datasets.

The data from the SBOWC assessments was presented in four groups; the unsuccessful weaning group comprised assessments which were performed before increasing midazolam and/or opioids in response to perceived withdrawal (Ista et al 2008). This group was considered to be comparable with the "withdrawing" group in OBWS. A "not withdrawing" group was created by subtracting the "unsuccessful weaning group" data from the "total group" data. This transformation of the SBOWC data created two groups; a "withdrawing" group comprising 93 assessments and a "not withdrawing" group comprising 2068 assessments.

Table 5.1 Weaning protocols reported in OBWS (Franck et al 2004) and SBOWC (Ista et al 2008) and average duration of weaning.

	Weaning protocol	Sample weaning regime (showing average[1,2] doses and infusion duration)
OBWS	10 or 20% daily taper and slow or stop reductions /reinitiate treatment if needed.	Midazolam 195 microgram/kg/hr[1], tapered over 11 days.
		Morphine 40 micrograms/kg/hr[1] for a median 9 days, tapered over 11 days.
SBOWC	Midazolam reduced by 50 microgram/kg/hr every 8 hours.	Midazolam 176 microgram/kg/hr[2] for a median 10 days. Suggests taper completed over 24 hours.
	Morphine reduced by 10 microgram/kg/hr every 24 hours.	Morphine 14 microgram/kg/hr[2] for a median 8 days. Suggests taper completed over 24-36 hours.

[1] peak median dose [2] median of the mean continuous dose

5.5.4 Identifying the change in the prevalence of signs between the "not withdrawing" and "withdrawing" groups.

A way of categorising the frequency of reported signs was sought in order to demonstrate the change in prevalence of signs between the "not withdrawing" and "withdrawing" groups both within and across studies. The incidence classifications used to describe drug side-effects in pharmacological product literature were selected to categorise any change (BNF 2016) (Table 5.2). These categories provide labels to reflect the differing occurrence of side effects from the "very common" (greater than 1 in 10) to the "very rare" (less than 1 in 10 000). In addition to standardising the incidence, this designation also helped to demonstrate the clinical significance that the change in

prevalence between the two groups might represent to the bedside nurse assessing and interpreting the behaviour.

Table 5.2 The descriptions for incidence of drug side effects in product literature (developed from BNF 2016)

Label	Incidence	Incidence (%)
Very common	greater than 1 in 10	greater than 10%
Common	1 in 100 to 1 in 10	1% to 10%
Uncommon ('less commonly' in BNF)	1 in 1000 to 1 in 100	0.01% to 1%
Rare	1 in 10 000 to 1 in 1000	0.001% to 0.01%
Very rare	less than 1 in 10 000	less than 0.0001%

5.6 Results

In the presentation of these results, the term "withdrawing" will be used to describe the "withdrawal present" and "unsuccessful wean" groups of OBWS (Franck et al 2004) and SBOWC (Ista et al 2008) respectively. The term "not withdrawing" will be used to describe the "withdrawal absent" group in OBWS (Franck et al 2004) and all patients other than the "unsuccessful wean" group in SBOWC (Ista et al 2008).

5.6.1 The frequency with which signs presented in the "withdrawing" and "not withdrawing" groups of OBWS (Franck et al 2004) and SBOWC (Ista et al 2008).

In the OBWS study (Franck et al 2004), all signs were represented in patients in both the "withdrawing" and "not withdrawing" groups. These signs were ranked in order of the frequency they occurred according to the drug side effects taxonomy (BNF, 2016) (Table 5.3). Signs occurred in three frequency categories; "very common", "common" and "uncommon" in both the "withdrawing" and "not withdrawing" groups. The occurrence of 14 signs increased in the "withdrawing" group compared with the "not withdrawing" group. Three signs (frequent suction required, hyperactive Moro reflex and hallucinations) did not change in prevalence. No signs occurred less frequently in the "withdrawing" group compared with the "not withdrawing" group.

Seven signs were very common in both the "withdrawing" and "not withdrawing" groups: temperature > 37.2C (82% vs 68%); sleeping <25% interval (52% vs 11%); diarrhoea (42%

vs 20%); pupils >4mm (36% vs 17%); tremors (36% vs 17%); crying/agitated 25-75% of interval and frequent suction required (27% vs 26%). Most signs were more prevalent in the "withdrawing" group, except for suctioning which stayed the same. Temperature >37.2C was the most common sign in both groups and was also present in most patients in these groups. The other three signs that were very common in the "withdrawing" group were either uncommon or common in the "not withdrawing" group. These signs were crying/agitated >75 % of interval (35% vs 0.2 %), movement disorder (16% vs 0.9 %) and sweating (11% vs 1.8%).

Table 5.3 Comparison of OBWS signs in "withdrawing" and "not withdrawing" patients.

OBWS signs ranked by prevalence	Withdrawing (%, 2 sig fig)		OBWS signs ranked by prevalence	Not with-drawing (%, 2 sig fig)	
Temperature > 37.2C	82	------VERY COMMON------	Temperature > 37.2C	68	--VERY COMMON--
Sleeping < 25% interval	52		Frequent suction required	26	
Diarrhoea	42		Diarrhoea	20	
Pupils >4mm	36		Tremors	17	
Tremors	36		Pupils >4mm	17	
Crying/agitated 25-75% of interval	34		Crying/agitated 25-75% of interval	12	
Frequent suction required	27		Sleeping < 25% interval	11	
Movement disorder	16		Nasal stuffiness	3.7	-COMMON--
Crying/agitated >75% of interval	12		Sweating	1.8	
Sweating	11		Yawning	1.7	
Respiratory rate high for age	7.9	---COMMON---	Hyperactive Moro reflex	1.5	
Nasal stuffiness	7.9		Respiratory rate high for age	1.3	
Yawning	5.3		Movement disorder	0.9	UNCOMMON
Vomiting	3.9		Sneezing	0.7	
Sneezing	2.4		Hallucinations	0.4	
Hyperactive Moro reflex	1.3		Vomiting	0.4	
Hallucinations	0.7	*	Crying/agitated >75% of interval	0.2	

*****= uncommon 2 sig fig = 2 significant figures.

In the SBOWC study (Ista et al 2008) most signs (25 of 27) occurred in both the "withdrawing" and "not withdrawing" groups. Signs are shown ranked in order of the frequency they occurred according to the taxonomy for drug side effects (Table 5.4). Signs occurred in two frequency categories in the "withdrawing" group ("very common" and "common") and in three frequency categories ("very common", "common" and "uncommon" in the "not withdrawing" group. The prevalence of 22 signs increased in the "withdrawing" group, three signs were equally or less prevalent and two signs did not occur compared with the "not withdrawing" group. The three most frequently occurring signs were the same in both groups ("withdrawing" vs "not withdrawing"); these were

sleeps 1-3 hours (60% vs 58%); agitation (46% vs 20%) and tachypnoea (31% vs 28%). The prevalence of two of these behaviours (sleeps 1-3 hours and tachypnoea), however was relatively unchanged, with only agitation showing an increase in prevalence in the "withdrawing" group.

Table 5.4 SBOWC signs ranked by prevalence in the "withdrawing" and "not withdrawing" groups

(Signs in **bold** were considered to "stand out clearly" by Ista et al (2008)).

SBOWC signs ranked by prevalence	With-drawing (%, 2 sig fig))		SBOWC signs ranked by prevalence	Not with-drawing (%, 2 sig fig)	
Sleeps 1-3 h	60	VERY COMMON	Sleeps 1-3 h	58	VERY COMMON
Agitation	**46**		**Tachypnoea**	**28**	
Tachypnoea	**31**		**Agitation**	**19**	
Uncoordinated movements	29		Sweating	19	
Muscle tension	**28**		Fever	18	
Gastric residuals	26		**Anxiety**	**15**	
Anxiety	**25**		**Muscle tension**	**15**	
Fever	25		Diarrhoea	14	
Sweating	23		**Sleeps < 1 h**	**14**	
Sleeps < 1 h	**22**		Uncoordinated movements	13	
Diarrhoea	22		Gastric residuals	12	
Grimace	**19**		**Grimace**	**9.4**	COMMON
Tachycardia	16		Mottling	9.1	
Mottling	15		Hypertension	7.8	
Hypertension	14		Tachycardia	7.4	
Vomiting	12		Muscle jerks	6.9	
Inconsolable crying	11		Inconsolable crying	6.3	
Muscle jerks	8.6	COMMON	Vomiting	4.4	
High pitch crying	4.3		Yawning	2.9	
Yawning	4.3		High pitch crying	2.6	
Tremor, spontaneous	2.2		Tremor, spontaneous	1.9	
Pupils	2.2		**Poor feeding**	**1.6**	
Hallucinations	1.1		Pupils	1.4	
*Tremor, stimulation	1.1		Sneezing	1.3	
Sneezing	1.1		*Tremor, stimulation	1.1	
Poor feeding	**0**	UC	Hallucinations	0.7	UC
Seizures	0		Seizures	0.3	

*Tremor in response to stimulation UC = uncommon

In their analysis, Ista et al (2008) described seven signs as "standing out clearly" in the "withdrawing" group. It is not clear from the paper why these signs were considered to stand out. These stand out signs were agitation, increased muscle tension, anxiety, grimacing, sleeping < 1hour, poor feeding and tachypnoea, which ranked 2nd ,5th ,7th ,11th,

14th and 21st and joint 26th out of 27 signs in order of prevalence in the withdrawing group. Poor feeding was not noted in any patients in the withdrawing group.

5.6.2 The change in prevalence of signs from baseline ("not withdrawing") to "withdrawing"

The change in prevalence of signs between the "not withdrawing" and "withdrawing" groups was calculated for each study in order to consider and explore the differences between withdrawal behaviour and critical illness behaviour (Table 5.5). Signs were ranked in order of the biggest changes in prevalence from baseline, in order to determine those signs, whose change in prevalence might be noticeable to the bedside nurse and therefore clinically significant in terms of withdrawal.

In the OBWS study (Franck et al 2004), ranking the signs by increase in prevalence from baseline produced five "stand out" signs. These signs (crying/agitated >75% of interval, movement disorder, vomiting, sneezing and sweating) showed increases of between 5 and 10 times that of baseline levels, which also prompted a change in their frequency classification. Two behaviours ("crying/agitated >75% of interval" and "movement disorder") showed a more than ten times increase in prevalence in the "withdrawing group" compared with the "not withdrawing" group and changed in classification from uncommon to very common. In this analysis, "crying/agitated >75% of interval" moved from being the least prevalent sign at baseline (0.2%) to being at the top of the table, as the sign with the biggest increase in prevalence in the "withdrawing group" (12%). Movement disorder had the next biggest increase from 0.9% at baseline to 16% in the "withdrawing" group. Two further signs were worthy of comment due to their increase in prevalence, although this was not sufficient to change their classification. Respiratory rate high for age increased by more than five time baseline, but remained common; sleeping < 25 % interval increased by just under five times baseline, but as a very common sign, became prevalent in just over half of all withdrawing patients. No other signs changed their classification due to either no change or modest changes from baseline.

The change in prevalence of signs in the SBOWC study (Ista et al 2004) was less striking, with most behaviours being less than twice as likely in the "withdrawing" group (Table 5.6). The sign with the greatest change was vomiting, which was nearly three times more likely in the "withdrawing" group. Despite the difference in the extent of the change between the two datasets, it is interesting to note that the three signs showing the

biggest increase between “not withdrawing” and withdrawing groups are the same in both studies: these being agitated, movement disorder and vomiting.

Table 5.5 OBWS signs ranked by increase in prevalence from baseline (“not withdrawing”) to “withdrawing”

OBWS signs	Prevalence (Frequency using drug side effect taxonomy)		Increase in prevalence
	Not withdrawing (%)	Withdrawing (%)	
Crying/agitated >75% of interval	0.2 (Uncommon)	12 (Very common)	> 10 times increase
Movement disorder	0.9 (Uncommon)	16 (Very common)	
Vomiting	0.4 (Uncommon)	3.9 (Common)	> 5 times increase but < 10 times
Sneezing	0.7 (Uncommon)	2.4 (Common)	
Sweating	1.8 (Common)	11 (Very common)	
Respiratory rate high for age	1.3	7.9	> 2 times increase but < 5 times
	Common		
Sleeping < 25% interval	11	52	
	Very common		
Yawning	1.7	5.3	
	Common		
Crying/agitated 25-75% of interval	12	34	
	Very common		
Nasal stuffiness	3.7	7.9	
	Common		
Pupils >4mm	17	36	
	Very common		
Diarrhoea	20	42	
	Very common		
Tremor	17	36	
	Very common		
Hallucinations	0.4	0.7	Similar rates (< 2 times increase) or no change
	Uncommon		
Temperature > 37.2C	68	82	
	Very common		
Frequent suction required	26	27	
	Very common		
Hyperactive Moro reflex	1.5	1.3	
	Common		

Table 5.6 SBOWC signs ranked by increase in prevalence from baseline ("not withdrawing" group) (Signs in **bold** were considered to "stand out clearly" by Ista et al (2008)).

SBOWC signs	**Prevalence (Frequency using drug side effect taxonomy)**		**Increase in prevalence**
	Not withdrawing (%)	Withdrawing (%)	
Vomiting	4.4 (Common)	12 (Very common)	> 2 times increase
Tachycardia	7.4 (Common)	16. (Very common)	
Grimace	9.4 (Common)	19 (Very common)	
Agitation	19.2	46	
	Very common		
Uncoordinated movements	13	29	
	Very common		
Gastric residuals	12	26	
	Very common		
Inconsolable crying	6.3	11	Similar rates / no change
	Common	Very common	
Hypertension	7.8	14	
	Common	Very common	
Mottling	9.1	15	
	Common	Very common	
Muscle tension	15	28	
	Very common		
High pitch crying	2.6	4.3	
	Common		
Anxiety	15	25	
	Very common		
Pupils	1.4	2.2	
	Common		
Hallucinations	0.7	1.1	
	Uncommon	Common	
Sleeps < 1 h	14	22	
	Very common		
Diarrhoea	14	22	
	Very common		
Yawning	2.9	4.3	
	Common		
Fever	18	25	
	Very common		
Sweating	19	23	
	Very common		
Tremor, spontaneous	1.9	2.2	
	Common		
Muscle jerks	6.9	8.6	
	Common		
Tachypnoea	28	31	
	Very common		

Sleeps 1-3 hours	58	60	
	Very common		
Tremor, in response to stimulation	1.1	1.1	
	Common		
Sneezing	1.3	1.1	
	Common		
Seizures	0.3	0	
	Uncommon		
Poor feeding	1.6	0	
	Uncommon		

5.6.3 Comparison of prevalence of shared items between the OBWS and SBOWC

Of the 25 and 21 items examined by SBOWC and OBWS respectively, 13 items were investigated by both teams (Table 5.7). Similarities in the prevalence of these behaviours during these studies might be expected. This was not the case. Apart from three low prevalence items; sneezing, yawning and hallucinations, there was incongruence in the prevalence of behaviours between the "withdrawing" groups or "not withdrawing" groups". Sleeping < 25% interval had a similar prevalence in the "not withdrawing" groups (11% OBWS vs 14% SBOWC) but this connection was not maintained in the "withdrawing" group (52% OBWS vs 22% SBOWC).

Table 5.7 Prevalence of items common to OBWS (Franck et al 2004) and SBOWC (Ista et al 2008)

Item	OBWS (%, 2 sig.fig)		SBOWC (%, 2 sig.fig)	
	Withdrawing	Not withdrawing	Withdrawing	Not withdrawing
Crying/agitated	12	0.2	46	19
Movement disorder	16	0.9	29	13
Vomiting	3.9	0.4	12	4.4
Resp rate high for age	7.9	1.3	31	28
Sweating	11	1.8	23	19
Sleeping < 25% interval	52	11	22	14
Sneezing	2.4	0.7	1.1	1.3
Yawning	5.3	1.7	4.3	2.9
Pupils >4mm /dilatation	36	17	2.2	1.4
Diarrhoea	42	20	22	14
Tremor	36	17	3.3	3
Hallucinations	0.7	0.4	1.1	0.7
Temperature (OBWS > 37^{2}C/ SBOWC > 38^{4}C)	82	68	25	18

2 sig. fig = 2 significant figures.

However, there was an unexpected correlation in the prevalence of three behaviours between the "withdrawing group" in OBWS and the "not withdrawing group" in SBOWC. These items were agitation (12% OBWS vs 19% SBOWC), movement disorder (16% OBWS vs 13% SBOWC) and vomiting (3.9% OBWS vs 4.4% SBOWC) (identified in bold in Table 5.7). These were also the three items that had shown the biggest increase in prevalence between the "not withdrawing" and "withdrawing" groups in their respective studies. This finding is unexpected as the size of the change in the prevalence of these items suggests a meaningful difference between the "not withdrawing" and "withdrawing" states in the respective studies: it does not explain why the prevalence of these items in "withdrawing" OBWS subjects then compares with the prevalence of these items in "not withdrawing" SBOWC subjects.

5.7 Discussion

This exploration compared two studies showing how behaviours differed in critically ill children weaning from opioids and benzodiazepines. Data from two studies, Franck et al (2004) and Ista et al (2008), with similar inclusion and exclusion criteria were compared. Critically examining OBWS and SBOWC has delivered new insights into existing data and in so doing has demonstrated the value of triangulation and the mixed methods approach to inquiry. Considering the difference between withdrawing and not withdrawing groups from two perspectives; prevalence and change in prevalence, gave insight into the extent to which each of these equivocal signs may differentiate between withdrawal and critical illness. Compared with more ubiquitous signs, those that increase from uncommon to common/very common may have a discriminant diagnostic value that is clinically meaningful in identifying withdrawal.

These two studies have provided two perspectives of the characterisation of withdrawal. Results showed aspects of both congruence and dissonance, both of which are valued outcomes in a pragmatic approach (Mathison 1988). Triangulation as a mixed methods approach, affords greater confidence in the inferences that can be made in congruent results from more than one perspective. In pragmatic epistemology, divergent results are held in equal regard to congruent results, as consistent with the ideology of difference (Greene 2007), these different outcomes offer a dialectic perspective of withdrawal. The

dissonance invokes further scrutiny and analysis leading to new insights and understanding (Cook, 1985).

The impact of this study in terms of assessing withdrawal will be discussed first in relation to the diagnostic accuracy of WAT-1 and SOS, prior to a consideration of how differences in operationalisation of withdrawal may account for the dissonance in results.

5.7.1 Differentiating between withdrawal and critical illness behaviour

OBWS comprised 17 signs, most of which were very common (n=7) or common (n=5) in the "not withdrawing" group. This finding demonstrated the equivocal nature of these signs by showing that they are already prevalent in critically ill children who are "not withdrawing". Most signs (n=13) showed an increase in prevalence between the "withdrawing" and "not withdrawing groups". Only four signs showed little or no increase in the "withdrawing" group: these signs were temperature >37.2C, hallucinations, frequent suction required and hyperactive moro reflex.

The "stand out" signs in OBWS were four signs that were uncommon in "not withdrawing" patients and became common (sneezing) or very common (movement disorder, vomiting and crying/agitated > 75% of the interval). As these signs are uncommon in critically ill children, their manifestation may act as a red flag to prompt consideration of withdrawal, particularly the two signs (crying/agitated >75% of interval and movement disorder) that increased in prevalence by more than 10 times that of not withdrawing patients. A fifth sign, sweating, although common in the "not withdrawing" group, also stood out, due to a five times increase in prevalence in the "withdrawing" group. It might be that these signs are more discriminant items for withdrawal compared to other more equivocal signs. This is important since a withdrawal assessment tool relies on clinically meaningful differences in the presentation of withdrawal, compared with no withdrawal or other differential diagnoses (DeVellis 2012).

The item content of WAT-1 (Franck et al 2008) was examined in light of these findings. Of the 11 signs in WAT-1, only two signs; startle to touch and muscle tone were not derived from the OBWS checklist. The five "stand out" signs were all included in WAT-1, although "crying/agitation > 75% of interval" was changed to a snapshot assessment of the child's state during each assessment. Of signs that did not change in prevalence, only temperature was retained in the subsequent WAT-1 tool; albeit with an increase in threshold to temperature > 37.8C (Franck et al 2008). The remaining three signs;

loose/watery stools, tremor and yawning, were signs whose prevalence more than doubled in the "withdrawing" group compared with the "not withdrawing group".

SBOWC comprised 27 signs, most of which were very common (n=11) or common (n=14) in the "not withdrawing" group. This finding, similar to the OBWS study also demonstrated the equivocal nature of these signs, given their prevalence in critically ill children who are "not withdrawing". Only six signs showed an increase in prevalence in the "withdrawing" group, but to a much lesser extent than the changes noted in the OBWS study. These signs, which more than doubled their "not withdrawing" prevalence, were vomiting, tachycardia, grimace, agitation, uncoordinated movements and gastric residuals. No signs "stood out" due to their change in prevalence between the groups. The item content of SOS (Ista et al 2009) was examined in light of these findings. All 15 signs in SOS were derived from the SBOWC checklist. This included five of the six signs which had the greatest change in prevalence; gastric residuals was not included. The other ten signs included showed similar rates or no change in prevalence between the withdrawing and "not withdrawing" groups.

These findings point to a possible explanation for the poor positive predictive value of SOS: PPV=0.48 (Ista et al 2013). Ten of the 15 signs in SOS showed similar rates of prevalence in the "not withdrawing" and "withdrawing groups." Put another way, these behaviours are as likely to occur in critically ill children who are not withdrawing, as they are in those who are withdrawing.

5.7.2 The operationalisation of withdrawal

Consistent with the concept of dialectic, the dissonance in findings between the two groups offers the opportunity to reconcile these conflicting perspectives in the pursuit of synergy. Dissonance may be a consequence of the differences of the operationalisation of withdrawal, a consequence of different perceptions of behaviours or a reflection of differences in the severity of withdrawal. Differences between the two datasets included the frequency of assessment, how withdrawal was designated, the incidence of withdrawal and the speed of weaning. These aspects and their possible impact on the differences in presentation will be considered.

5.7.2.1 Frequency of assessment

SBOWC had a less frequent assessment schedule (8-hourly / three times a day) compared with OBWS (4-hourly / 6 times a day). The assessment schedule is a fundamental

operationalisation of the construct of withdrawal. It is not clear which of these schedules best identifies the withdrawing patient.

5.7.2.2 How withdrawal was designated

In OBWS, withdrawal was designated according to the clinical judgement of the bedside nurse. In SBOWC however, withdrawal was designated according to the decision to administer rescue therapy. These may not be comparable delineations for withdrawal and may possibly indicate different levels of withdrawal severity. For example, mild withdrawal signs might be classified as "withdrawing" in the OBWS study, as judged by the nurse. However, the same level may not prompt the administration of rescue therapy in the SBOWC study, so might be classified as "not-withdrawing". There is little evidence for, or agreement regarding the treatment threshold of withdrawal. Without a clear operationalisation, the association between behavioural signs of withdrawal and rescue therapy may reflect individual decision-making rather than the construct of withdrawal. Rather than delineating "withdrawing" and "not withdrawing" patients, these differences suggest a spectrum of withdrawal severity, as implied by the stages in the SWS treatment protocol (Cunliffe et al 2004).

5.7.2.3 The prevalence of withdrawal by observation and by patient

The OBWS cohort had more than twice the incidence of withdrawal by number of children (87% OBWS vs 34% SBOWC) and considerably higher incidence per observation (22% OBWS vs 0.04%). The OBWS incidence equates to 1 in 5 assessments being judged as withdrawal. With an assessment schedule performed every 4 hours (6 times per day) this amounts to a frequency of just under one positive assessment per day.

The SBOWC incidence of withdrawal (0.04%) equates to 1 in 25 assessments being judged as withdrawal. With an assessment performed every 8 hours, or 3 times a day, this amounts to an average of less than one positive assessment per week.

The difference in the rates of diagnosis between the two studies suggests that the OBWS patients were withdrawing throughout the weaning process, compared with the SOS patients who had infrequent and transient episodes of withdrawal.

5.7.2.4 The speed of weaning

When physical dependence is suspected, sedative drugs are weaned, rather than stopped abruptly in an attempt to prevent or minimise withdrawal syndrome. Weaning rates differed considerably between the two studies, with OBWS taking an average of 11 days

and SBOWC appearing to take less than 48 hours, given the doses and reductions reported in the study (Ista et al 2007). The median number of 8-hourly SBOWC assessments was 14 over 6 days. A rapid wean in a physically dependent patient could be expected to cause signs of withdrawal for the duration of the weaning period and for about 72 hours after completion; a timeframe comparable to the SBOWC median assessment period.

If the closest association exists between behaviour rates in the "withdrawing group" in OBWS (Franck et al 2004) and the "not withdrawing group" in SBOWC (Ista et al 2008), then one of the possibilities is that the SBOWC (Ista et al 2008) group were wrongly classified, and were really withdrawing. Whether the patients in the SBOWC "not withdrawing" group were withdrawing or not, there appears little in common in the presentation of patients in different settings. This also implies that the change in behaviour which prompts a diagnosis and/or treatment of possible withdrawal may also differ across settings. Given the difference in weaning rates between the two studies, it might be expected that the incidence of withdrawal was higher in the SBOWC group, who had experienced the more rapid wean. This was not the case, as the reported incidence of withdrawal was much lower in the study with the more rapid wean, a finding that suggests that the interpretation of behaviours varies to such an extent between different settings that comparison is futile and findings cannot be generalised.

5.8 Conclusion

When the difference in presentation between the "withdrawing" and "not withdrawing" groups was determined, the three signs which showed the greatest change were the same in both studies. It might be that these signs -agitation, movement disorder and vomiting- are more discriminant items for withdrawal compared to other more equivocal signs. These findings also conclude that most of the signs examined do not helpfully differentiate the withdrawing and not withdrawing groups. This brings into question the practice of summing behaviours to provide a global score indicative of a diagnosis of withdrawal if these behaviours are also common to those patients without the diagnosis.

Rather than providing evidence in support of the current approach to withdrawal, this study highlighted the dissonance between OBWS and SBOWC and prompts further consideration. Fundamentally, this incongruity points to the differences in the

respective operationalisation of the construct of withdrawal in critically ill children; the speed with which weaning should occur to prevent withdrawal, the frequency with which an assessment of withdrawal should be performed and the delineator for diagnosing withdrawal. It is not known which operationalisation better represents the construct. Further examination of the complexities of withdrawal assessment from different perspectives may offer different insights or possible solutions.

Chapter 6: Study 3: Pragmatic critique of the WAT-1 dataset

6.1 Introduction

Study 3 presents a pragmatic critique the WAT-1 dataset which offers a different perspective to the realist critique of the WAT-1 construction and validation studies (Franck et al 2008, 2012) which was presented in Chapter 2. The evaluative framework of internal integrity will be described first. This will be followed by a pragmatic critique of the WAT-1 construction and validation studies. The WAT-1 data analysis is reviewed in light of three additional studies which present analysis of the same dataset used in the WAT-1 study secondary analysis papers. The chapter concludes with the implications of this critique for the operationalisation of withdrawal.

6.2 Background

The process of critiquing WAT-1 commenced in the development stages of the studies underpinning this thesis. Subsequent insights gained from the findings and analysis of Studies 1 and 2 and a focus on the perception and meaning of withdrawal behaviour for nurses and parents, prompted recursive interpretation of the tool validation studies. Further perspectives came from publications which undertook secondary analysis of the WAT-1 dataset (Grant et al 2012, 2013, Best et al 2016). The different perspectives that the Grant and Best studies bring to the WAT-1 validation study corresponds to the pragmatic philosophical position of this thesis. Triangulation of the findings and analysis of these papers, for the purposes of obtaining corroboration or finding contradictions, is another key feature of mixed methods (Green et al 1989).

The STARD checklist (2015) provided the framework for the critique of WAT-1 in Chapter 2. A different framework was sought to reflect the emergent approach to evaluation of this literature, mirroring the emergent design of the thesis and drawing on the theoretical framework of reasoning. A pragmatic framework which focuses on “internal integrity” was selected and is suitable for evaluating both qualitative and quantitative research, (Krathwohl, 2009).

Internal integrity is a judgement on the decision-making processes which underpins the assurance of a causal relationship being studied (Krathwohl, 2009). In the WAT-1 and SOS validation papers, the use of inferential statistics to demonstrate validity relies on

the correct translation of constructs into operationalisations. The lack of agreement between WAT-1 and SOS about how the construct of withdrawal syndrome is operationalised was another reason why further analysis of the WAT-1 validation study was undertaken and an alternative approach taken to evaluation.

6.3 Aim of Study 3

The aim of Study 3 was to critically evaluate the operationalisation of withdrawal underpinning the construction and validation studies of WAT-1 (Franck et al 2008, 2012).

6.4 Objectives of Study 3

The objectives of Study 3 were to;

1. Apply the pragmatic evaluative approach proposed by Krathwohl (2009) to the WAT-1 validation paper (Franck et al 2012).
2. Evaluate the operationalisation of withdrawal presented in the WAT-1 validation paper in light of findings from publications which undertook secondary analysis of the WAT-1 validation dataset (Grant et al 2012, 2013, Best et al 2016).

6.5 Method

6.5.1 A pragmatic approach to tool evaluation

Internal integrity is defined by five standards which provide both conceptual and empirical support for the conclusions reached in a study (Krathwohl, 2009). According to Krathwohl, conclusions, as new knowledge, equate to a reduction in uncertainty in the topic that has been studied. The extent to which conclusions reduce uncertainty is a product of the internal integrity of the study. Conceptual support for internal integrity is provided by "explanation credibility" and "translation validity." Empirical support is shown by "demonstrated result", "rival explanations eliminated" and "credible result" (Krathwohl, 2009). A brief description of each of these standards is presented followed by the findings of the evaluation of the WAT-1 validation study according to these standards. Ethical approval was not required for this study.

6.5.1.2 Explanation credibility

Described as “plausibility” by Tashakkori and Teddlie (2009), explanation credibility focuses on the relationship between the explanation or rationale for the study and the hypothesis and research questions. This includes defining the constructs involved in the study and describing their interrelation.

6.5.1.3 Translation validity

Described as “quality of implementation” by Tashakkori and Teddlie (2009), translation validity focuses on how the study was carried out (whether the study design and processes are appropriate to answer the research questions).

6.5.1.4 Demonstrated results

Described as “congruence of evidence and explanations” by Tashakkori and Teddlie (2008), a demonstrated result, where the explanation provides an accurate prediction, has the following attributes;

1. Authenticity of evidence. Inferential statistics rely on authenticity of evidence,
2. Precedence (or concomitance) of cause, and
3. Presence of effect. An effect occurred as expected in terms of the relationship described by the hypothesis.

6.5.1.5 Rival explanations eliminated

This is described as “lack of other plausible explanations” by Tashakkori and Teddlie (2008). The researcher should anticipate any rival explanations for the study effect and demonstrate how the causes have been ruled out.

6.5.1.6 Credible results

This is a culmination of the four standards needed to make good inferences in the study. These standards which characterise good inferences in both qualitative and quantitative research were applied critically by the researcher to the construction and validation studies of WAT-1 and SOS.

6.6 Results

6.6.1 Explanation credibility

The aim of the Franck et al (2012) study was to further evaluate the psychometric properties and generalisability of the WAT-1 tool, and to identify cut-points for diagnosing withdrawal. Initial psychometric testing had demonstrated that a WAT-1 score ≥3 predicted a nurse numeric rating (NRS) score >4, with a sensitivity of 0.87 and specificity of 0.88 (Franck et al 2008). This relationship may have been due to these paired assessments (WAT-1 then NRS) being performed by the same nurse. This interrelation limits the extent to which we can be confident that WAT-1 score ≥3 indicates withdrawal syndrome. WAT-1 requires further evaluation to demonstrate that it is a valid and reliable measure of withdrawal syndrome.

6.6.2 Translation validity

This feature considers whether the study has been carried out in a way that will provide evidence in support of WAT-1 as a valid and reliable withdrawal assessment tool. Translation validity considers the following aspects of the study design;

- Focus (what is being studied),
- Study setting (when and where) and participants (who), and
- How is it demonstrated that something of interest occurs.

6.6.2.1 What is being studied

The objectives of the study were to demonstrate three aspects of the construct validity of WAT-1 (as an operationalisation of withdrawal); these were known groups validity, concurrent and predictive validity. These aspects all demonstrate how accurately the WAT-1 tool (including item content, the assessment process and the assessment schedule) measures the construct of withdrawal (Streiner and Norman 2003).
Known groups validity is demonstrated if WAT-1 is sensitive enough to discriminate between groups of patients who are known to be withdrawing and groups who are not withdrawing, or between groups who have differing levels of withdrawal severity.
Concurrent validity is demonstrated if a WAT-1 score provides the same result (withdrawal – yes/no) as other measures of withdrawal when scored at the same time.
Predictive validity is demonstrated if WAT-1 scores in patients who have a greater number of risk factors for withdrawal are higher than WAT-1 scores in patients with fewer risk factors.

6.6.2.2 The study setting and participants

The WAT-1 validation study (Franck et al 2012) was undertaken during the baseline phase of the parent study; the RESTORE study (Curley et al 2015). The RESTORE study was designed to compare a sedation protocol, which directed decisions about sedation, analgesia and withdrawal, to usual care. The aim of the baseline phase was reported as the implementation of valid and reliable instruments to measure the secondary outcomes of the RESTORE study (Curley et al 2015); the incidence of withdrawal was one of the secondary outcomes.

Children (aged 2 weeks to 18 years) with acute respiratory failure supported on mechanical ventilation exposed to at least five days continuous opioids participated in the study. The study schedule planned WAT-1 assessments for patients from the start of opioid tapering until 72 hours after the last opioid dose, at 8am and 8pm daily, and at other times if clinically indicated. Compliance with this schedule could not be assessed in the published results, which reported that WAT-1 was recorded once daily for 23% days, twice daily for 29% of the days and more than twice daily for 48% of the days (Franck et al, 2012). Explanation for non-compliance with the schedule was not reported or discussed.

This was a multisite study in 21 PICUs in the USA. Eligible PICUs did not have a sedation protocol in place and prior to participation in the trial, only 8 of the 22 sites had a standard of care for withdrawal assessment. Aside from the introduction of assessment tools for pain, sedation and withdrawal, all sites continued with usual care during this study. The usual care of participating PICUs was not described. The lack of standardisation in treatment for participants across the sites impacts on inferences that can be gained from the findings. In terms of making the decision to treat withdrawal signs, it is not clear whether the newly introduced WAT-1 tool featured in the decision-making. It is not known if staff were aware of the hypothesised cut-point of WAT -1≥3 for withdrawal or whether there was a temporal link between the WAT-1 score and decision to treatment withdrawal signs. As subjects continued to receive usual care, the range of treatment options for withdrawal was not reported. A causal relationship between WAT-1 scores and treatment decisions cannot be inferred from the data presented.

6.6.2.3 How is it demonstrated that something of interest occurs

Demonstrating that a WAT-1 score ≥3 indicates withdrawal due to a causal relationship, rather than due to chance, entails evaluation of the reliability and validity of findings. To be assured of a causal relationship rather than a chance occurrence, the researcher must demonstrate interrater reliability (IRR), showing that all subjects were assessed in a standardised way. Each site completed three rounds of IRR testing before and during the study. Support for IRR was reported as an overall concordance rate for WAT-1 score <3 and WAT-1 score ≥3 (97.4%); the Spearman rank correlation coefficient between simultaneous WAT-1 scores (0.93) and the frequency with which pairs of nurses recorded identical scores (83.1%). It is not clear from these data that IRR was sufficiently established prior to the start of the study; presenting results for each round of testing rather than the aggregate result may have provided assurance that this was the case.

Subjects in this study were being weaned from ≥5 days opioids, so all were at risk of withdrawal. When demonstrating known groups validity, concurrent and predictive validity the study compared scores across groups expected to differ and examined the association between WAT-1 scores and variables hypothesised to be indicative of withdrawal (amount of drug exposure, length of weaning). The approach to demonstrating each of these aspects of validity will be considered.

6.6.2.3.1 Known groups validity

This study did not compare scores across groups expected to differ, so known groups validity was not demonstrated. Subjects who ever had a WAT-1 score ≥3 were compared with those with lower WAT-1 scores in relation to three factors thought to contribute to the likelihood of withdrawal; analgesia and sedative treatment during weaning, peak and cumulative opioid and benzodiazepine exposure and duration of pre weaning and weaning phases. Splitting the group according to the WAT-1 score does not show the discriminatory power of the score. This is called criterion contamination (Streiner and Norman 2003). To demonstrate discriminatory power, the group should be split according to one of the contributing factors before comparing the WAT-1 scores of patients in these groups.

Given the similar behavioural presentation between pain, under sedation and withdrawing, demonstrating that WAT-1 can discriminate between patients who are

withdrawing and patients who are under-sedated would provide even stronger support for construct validity.

6.6.2.3.2 Concurrent validity

Concurrent validity was not demonstrated in this study as no other measures of withdrawal were applied to assess withdrawal at the same time as the WAT-1 tool.

6.6.2.3.3 Predictive validity

Predictive validity is demonstrated if WAT-1 scores are higher in patients who have a greater number of risk factors for withdrawal than WAT-1 scores in patients with fewer risk factors. This could not be demonstrated by splitting the group according to WAT-1 score, rather than according to a risk factor for withdrawal.
Contrary to the claims of statistical support for construct validity presented by Franck et al (2012), this pragmatic approach does not provide evidence that the stated construct validity aims were achieved in the WAT-1 validation study.

6.6.3 Demonstrated results

Demonstrated results show whether explanations prove to be good predictors of the construct of withdrawal and considers authenticity of evidence, precedence of cause and presence of effect. Each of the aspects of demonstrated results will be considered in turn.

6.6.3.1 Authenticity of evidence

The discrepancy between the number of subjects who ever scored WAT-1≥3 (n=97) and the number reported to have clinically significant withdrawal (n=21) was not explained. Clinically significant withdrawal as a construct was not defined at the start of the study, but first appeared in the results section as “any patient receiving rescue therapy (an opioid or benzodiazepine bolus or an increase in opioid or benzodiazepine infusion) to manage an increase in WAT-1 symptoms after the start of weaning (not for treatment of new pain or new sedation needs).” This definition came from the RESTORE trial protocol (Curley et al 2015), but is not clear whether this protocol directed the management of an increase in WAT-1 symptoms in this study (the baseline phase). Franck et al (2012) reported in the study design that subjects would receive usual care during the baseline phase, at the discretion of the medical team, rather than according to the study protocol.

It is also not clear whether the proposed cut-point of WAT-1≥3 was known to nurses applying the tool in this study. If this was known, then the WAT-1 score, rather than the child's presentation and/or clinical opinion, might have driven the decision to treat. Even if the cut-point was not known, the introduction of a scoring system is a change which may impact on usual care. The rationale underpinning the decision to treat or not treat is not reported or explained, so may not have been consistent across the 21 sites of this study.

Of the 97 subjects who ever had a WAT-1 score ≥3, 21 subjects received rescue medication. It follows therefore, that the majority of patients who ever had a WAT-1 score ≥3 (n=76 patients, 78%) were not treated for withdrawal.
The findings presented do not support the study conclusion that a WAT-1 score ≥3 appears to be a reasonable designation of clinically significant withdrawal symptoms.

6.6.3.2 Precedence of cause

A demonstrated result shows a precedence or concomitance of cause. This would be demonstrated in this study if reductions in sedative dosing preceded an increase in WAT-1 scores. However, this temporal link pertains to all subjects in this study, who were all being weaned from opioids during the study period. The reduction in sedatives does not differentiate patients whose WAT-1 scores increased compared with those whose scores did not increase. A causal relationship could be better established by comparing WAT-1 scores in patients who were weaning sedatives and those who were not weaning sedatives.

6.6.3.3 Presence of effect

Einhorn and Hogarth (1986) described contiguity of cause and effect and congruity of the effect of the cause. The former refers to the proximity of, or association between the reduction in opioid dosing and the WAT-1 score ≥3. This was not presented in the results. Congruity means the size of the cause and effect should correspond; a larger reduction in opioids should manifest as a greater WAT-1 score compared with a smaller reduction in opioids. This was also not presented in the results.

Presence of effect can also be demonstrated if rescue treatment was administered in response to a WAT-1 score ≥3 and the WAT-1 score reduced in response to this treatment. Such an effect was reported in 21 subjects who had 51 episodes of withdrawal and received rescue therapy (a bolus of opioid or benzodiazepine or an

increase in infusion rate) to manage an increase in WAT-1 symptoms. The median (IQR) WAT-1 score of these patients before and after rescue therapy was 6 (4-8) and 2 (1-3) respectively (Franck et al, 2012). The temporal link between rescue therapy and the before and after WAT-1 assessments was not reported, so the strength of the association is not known.

6.6.4 Rival explanations eliminated

This standard considers other possible reasons for the patient to score WAT-1 score ≥3. Exclusion of these possible causes supports the diagnostic capacity of this cut point. The definition of clinically significant withdrawal reported in the previous section was contingent on the administration of rescue therapy to manage an increase in WAT-1 symptoms. However, this rescue therapy may also have been administered to treat unmet sedation or pain needs. The sedation and pain scores of patients who received rescue therapy for an increase in WAT-1 scores were not reported in this study, both of which are plausible explanations for the administration of rescue therapy. Sedation was assessed using the State Behaviour Scale (SBS) (Curley et al 2006) at least every 4 hours (hourly if the patient was agitated), pain was also assessed at least every 4 hours and withdrawal was assessed at least every 12 hours (Curley et al, 2015).

The SBS is a component of WAT-1, contributing 3 points of the 12-point range in a child who is awake/ distressed at the start of the assessment and then takes more than 5 minutes to settle once the assessment was completed. In these circumstances the patient would score for withdrawal (WAT-1 = 3) and under sedation (SBS ≥+1). The pain scale used in non-verbal children under 6 years was the Faces, Legs, Activity, Cry and Consolability Scale (FLACC) (Merkel et al 1997). The behavioural parameters of this tool also overlap with those of SBS: an SBS+1 or +2 could score as FLACC 4 (due to difficulty to console, squirming and restless or kicking legs.

The interdependence of SBS, WAT-1 and FLACC challenges the capacity to differentiate pain, under sedation and withdrawal, any of which might be plausible diagnoses in this cohort. This study did not provide assurance that rival explanations had been eliminated.

6.6.5 Credible results

Franck et al (2012, p 147) concluded “WAT-1 score ≥3 a reasonable designation of clinically significant (withdrawal) symptoms.” The design and presentation of the study did not support this conclusion. The following changes would be required to produce

evidence that links the variables in a causal relationship and reduce the uncertainty inherent in this study. The demonstrated results attributes of "authenticity of evidence" "precedence of cause" and "presence of effect" were not established in this study. Demonstrating these attributes would require;

- Evidence of the causal link between the WAT-1 score and decision to treat withdrawal with a rescue bolus or an increase in withdrawal,
- Evidence of a clear temporal relationship between reduction in sedative and WAT-1, demonstrating congruity where bigger reductions in sedative result in higher WAT-1 scores than smaller reductions do, and
- Evidence of a clear temporal relationship between the administration of the rescue therapy in response to a high WAT-1 score and the lower WAT-1 score on reassessment

"Elimination of rival explanations" was also not established in this study. Demonstrating this attribute would require;

- Elimination of pain and under-sedation as rival explanations for patients with WAT-1 scores ≥3 by undertaking concomitant assessment of pain and sedation.

6.7 Discussion

The findings of the pragmatic evaluation of the WAT-1 validation study (Franck et al 2012) will be discussed in light of the studies which undertook and published secondary analysis of the WAT-1 validation dataset. The different perspectives are provided by Grant et al 2012, Grant et al 2013 and Best et al 2016. The RESTORE trial was a multicentre prospective sedation trial (Curley et al 2015). The same data set of patients enrolled in baseline pre-randomisation phase of this trial was described and analysed in two further studies relating to withdrawal, in addition to the WAT-1 study (Franck et al 2012). Grant et al (2012) prospectively evaluated sedation-related adverse events and subsequently published operational definitions of sedation-related adverse events (Grant et al 2013). Best et al (2016) characterised sedation weaning patterns in patients who received at least five consecutive days of opioids (Table 6.1). These studies were reviewed in order to examine the different perspectives they might afford the WAT-1 validation study.

6.7.1 RESTORE trial (Curley et al 2015)

PICUs without an existing sedation protocol were eligible to participate in RESTORE (Curley et al 2015). All 22 participating units had a standard of care for pain assessment, but fewer had standards for sedation/agitation assessment (55%, n=12) or withdrawal assessment (36%, n=8) (Curley et al 2015). Standardised assessments for pain, sedation and withdrawal were introduced in the baseline phase but study subjects continued to receive usual care. This meant that sedation and pain control were managed at the discretion of the care team; no recommendations were made by the RESTORE team. WAT-1 was used to assess opioid withdrawal in patients receiving at least five days opioids.

Table 6.1 RESTORE studies by author, purpose of study and year of publication

Author and year	Purpose of the study
Franck et al 2012	Further evaluate the psychometric properties and generalisability of WAT-1 in children recovering from acute respiratory failure.
Grant et al 2012	Define and estimate sedation-related adverse events
Grant et al 2013	Test operational definition and estimate the rate and site to site heterogeneity of prospectively collected sedation-related AEs in patients intubated and mechanically ventilated for acute respiratory failure at 22 PICUs.
Best et al 2016	Characterise sedation weaning patterns in patients who received at least 5 consecutive days opioids.

6.7.2 RESTORE trial sedation-related adverse events (Grant et al 2012, 2013)

Grant et al (2012, 2013) published two papers relating to sedation-related adverse events. The first was a prospective evaluation of adverse events in the RESTORE baseline phase, to test operational definitions and estimate the incidence of inadequate pain and sedation management in mechanically ventilated paediatric patients (Grant et al 2012). The second paper published estimates for sedation-related adverse events for the RESTORE trial (Grant et al 2013) (Table 6.2).

Table 6.2 Specified event definitions and estimated rate of events (Grant 2013)

Clinically significant iatrogenic withdrawal is defined in patients weaning from ≥5 days of continuous infusion or round-the clock narcotics as; any patient receiving rescue therapy (defined as an opioid or benzodiazepine bolus or an increase in opioid or benzodiazepine infusion) to manage an increase in WAT-1 symptoms after the start of weaning and not for treatment of new pain or sedation needs. Available evidence identifies iatrogenic withdrawal as a WAT-1 score ≥3. Event rate: < 75% patients. **Inadequate sedation management** is defined as; agitation defined by an SBS>0 (or assumed agitation in patients receiving neuromuscular blockade) for 2 consecutive hours, not related to a planned extubation attempt. Event rate: <10% patients **Inadequate pain management** is defined as; pain score >4 (or assumed pain present) for 2 consecutive hours not related to a planned extubation event. Event rate: < 20% patients.

The rate of two adverse events (withdrawal and sedation) reported in the baseline trial (Grant et al 2012) differed substantially to the event rates published in the subsequent paper (Grant et al 2013). During the baseline phase of the trial, clinically significant iatrogenic withdrawal was reported at 8.7%, which was nearly ten times than the chosen estimated rate for the trial (Table 6.3).

Table 6.3 Actual event rates (Grant 2013)

308 subjects / 594 AEs Withdrawal incidence = 54 events in 24 subjects (8.7 %) subjects. Although reported as 8.7 % in paper, the calculation 24/308 gives the incidence as **7.8%** This is out of 308 subjects/ 594 AEs (not all of whom were > 5 days opioids). In patients≥ 5 days opioids (n=141 or 142); Withdrawal incidence equates to 24/(141 or142) = 17 % subjects. Inadequate sedation management = 242 events in 93 (30 %) subjects Inadequate pain management = 173 events in 83 (27 %) subjects Subjects with inadequate sedation and pain= 56 (18 %) subjects (number of events not provided).

This figure was calculated inaccurately in the published paper, as the denominator used was the number of patients in the trial (n=308) but should have been the number of patients receiving at least 5 consecutive days of opioids, which was reported as 46% participants (n=141 or 142). This gives an incidence of withdrawal of 17%, which is still considerably lower than the estimate for the RESTORE trial (Grant et al 2013). Cases of inadequate sedation were three times more prevalent during the baseline study, than the estimated rate and inadequate pain management which was the same as the estimated rate.

Prior to entering the trial, all PICUs undertook pain assessments, one half (55%, n=12) undertook sedation/agitation assessments and one third (36%, n=8) undertook withdrawal assessments (Curley et al 2015). The differences between estimated prospective rates and actual rates for adverse events in the baseline study appear to be inversely proportional to the presence of existing assessments prior to the study. The biggest difference between actual and expected rates was for withdrawal, which had only been assessed in one third of PICUs prior to this study. This compared with no difference between expected and actual rates for inadequate pain, for which all PICUs had an existing assessment. Despite the intention to continue with usual care, the introduction of a new assessment may have led to an altered interpretation of the patient's behaviour and an inadvertent change in usual care.

Due to the anticipated potential for site to site heterogeneity in the reporting of sedation-related AEs, statistical analysis methods allowed for clustering of observations within a site (Grant et al 2013). The events with the largest intraclass coefficient (ICC) were inadequate sedation management (0.13), clinically significant iatrogenic withdrawal (0.088) and inadequate pain management (0.08). These values represent moderate site-to-site heterogeneity for these adverse events. The ICCs measuring the proportion of variation in outcome attributable to the natural variation between sites rather than between subjects in sites was 7.8% to 13%.

Grant et al (2013) concluded that there was moderate variation in event reporting, despite clear operational definitions, training, monitoring and adjustment for the age of the child, severity of condition and functional health. This conclusion diminishes the reliability of the findings in the WAT-1 study (Franck et al 2012).

Reliability is the ratio of subject variance to subject + error variance (Streiner and Norman, 2004). Reliability appears to improve when the extent of the variance between participants is increased relative to the error variance. Administering the scale in a heterogeneous population artificially inflates variance, giving a flawed impression of the reliability to discriminate patients at risk of withdrawal.

6.7.3 Characterising sedation weaning patterns (Best et al 2016)

The purpose of this study was to characterise sedation weaning patterns in patients who received at least 5 consecutive days of opioids. Two weaning patterns were identified from the data. ***Intermittent wean*** described patients with a 20% or greater increase in daily opioid dose after the start of weaning and ***steady wean*** described all other patients (Table 6.4). In the steady wean group, opioid weaning was completed in median (IQR) 2 (1-5) days. Fifty patients (63%) in this group had WAT-1 scores performed, of whom 23 (46%) scored WAT-1 score ≥3. The same number (n=50, 63%) also had opioid boluses and forty-nine (62%) had benzodiazepine boluses during opioid weaning. Seventy-two patients (91%) required other sedatives during opioid weaning. Fifty-nine patients (75%) received two or more classes of sedatives during this period. In the intermittent weaning group, opioid weaning took longer 10.5 (8-13) days, and a higher proportion of patients had WAT-1 scores performed (94%, n=62), scored WAT-1 score ≥3 (85%, n=53), received opioid (86%, n=57) and benzodiazepine (85%, n=56) boluses and required two or more additional classes of sedatives (94%, n=62) during the weaning period.

The assessment method and frequency of adverse event assessments was dictated by the RESTORE team but all subjects received usual sedation and pain control at the discretion of the care team in the 22 different sites. The study protocol scheduled (at least) 12-hourly WAT-1 scores during opioid weaning, but 23% patients (n=33) did not have any WAT-1 assessments performed during this time (Best et al 2016). Of the remaining patients who had one or more WAT-1 assessments performed (77%, n=112), these patients made up a greater proportion of the intermittent wean group compared with the steady weaning group (94% versus 63%) respectively.

Table 6.4 Patient characteristic by pattern of weaning (Best et al 2016)

Characeteristic	Steady wean n=79 (54%)	Intermittent wean n=66 (46%)
Opioid weaning duration median (IQR) days	2 (1-5)	10.5 (8-13)
Opioid boluses during weaning	n=50, 63%	n=57, 86%
Benzo bolus during op weaning	n=49, 62%	n=56, 85%
≥ 2 additional classes of sedatives*	n=59, 79%	n=62, 94%
WAT-1 assessments performed	n=50, 63%	n=62, 94%
WAT-1 ever ≥3	n=23 patients/50 (46%)	n=53 patients/62 (85%)
Peak WAT-1 score, median (IQR)	2 (1-5) /50 assessments	5 (4-6) /62 assessments

*Required during opioid weaning

6.7.3.1 What predicts administration of boluses or prompts a withdrawal assessment?

The number of patients in each group who required rescue therapy (additional opioid boluses and/or benzodiazepine boluses) is very closely correlated with the number of WAT-1 assessments undertaken, rather than with the number of assessments defined as clinically significant withdrawal (WAT-1 score ≥3) (Table 6.4). This correlation raises the possibility that the patient's state typically prompted both a WAT-1 assessment and treatment with opioids and sedatives, rather than adhering to the assessment schedule in the study screening schedule. It is not clear from the data, however, whether the assessments and interventions related to the same patients. Insufficient information is provided to understand the relationship between assessments, scores and bolus administration.

These findings cast doubt on the assertions of construct validity made in the Franck et al (2012) study as this level of information about interventions and the trend in scores was absent in the analysis of that study (Franck et al 2012). There are also differences in the figures reported. Franck et al (2012) reported 51 episodes in 21 patients, defined as "any patient receiving rescxue therapy defined as an opioid or benzodiazepine bolus or an increase in opioid or benzodiazepine infusion" (p 146). Best et al (2016) reported that 107 patients received opioid and/or benzodiazepine boluses during weaning, but did not report the number of episodes. The figures reported by Best et al (2016) that correspond most closely to those reported by Franck et al (2012) are the cohort of patients (n=50) in

the steady wean group (n=79). This cohort had a WAT-1 assessment performed during weaning, of which 23 had a WAT-1≥3. However 50 patients in this group received opioid and benzodiazepine boluses over a median (IQR) of 1(1-2) and 2 (1-3) days respectively (Best et al 2016).

6.7.3.2 Risk factors of withdrawal

Best et al (2016) described these patients as steady and intermittent wean. Intermittent wean patients had a pattern of weaning including a 20% or greater increase in the total daily opioid dose at any time during the weaning period (Best et al 2016). Graphs of two representative patients were presented by Best et al (2016) (Figure 6.1).
Patient A had lower daily doses of opioid and benzodiaepines than Patient B with a peak opioid dose of 4.5 mg/kg on day 9. The opioid was weaned at consistent rates over 11 days, as shown by the steady slope of the dose graph.

Patient B had higher daily doses of opioids and benzodiazepines than Patient A with a peak opioid dose of 7.5 mg/kg on day 6. The opioid and benzodiazepine was weaned rapidly by at least 30% of the peak dose on day 7 as shown by the steep slope of the dose graph. Opioid weaning then slowed on day 8 and the rate was increased on day 9.

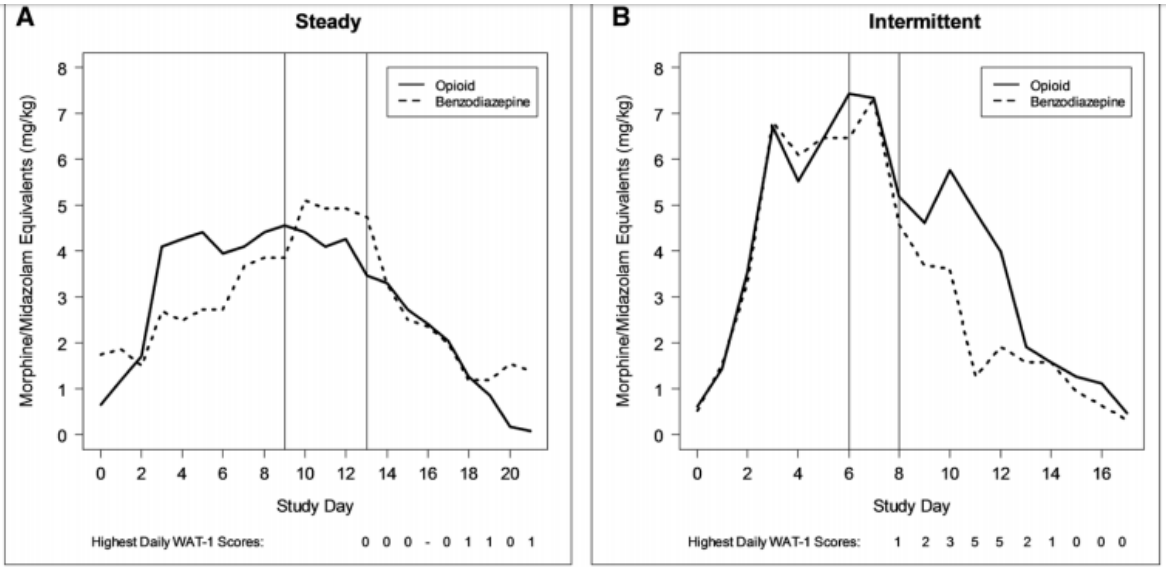

Figure 2. Opioid weaning patterns. Representative graphs of daily opioid and benzodiazepine doses among patients with steady (**A**) and intermittent (**B**) patterns of opioid weaning. Note: The *first vertical line* marks the day of the peak opioid dose, while the *second vertical line* represents the start of the opioid weaning period.

22 www.pccmjournal.org January 2016 • Volume 17 • Number 1

Figure 6.1 Dose curves presented by Best et al (2016)

6.7.3.2.1 Interpretation by Best et al (2016)

Best et al (2016) described tolerance as a doubling of the day 2 opioid dose prior to the start of weaning; according to this definition, both patient A and B are tolerant. All

patients in this study are also at risk of physical dependence as the inclusion criteria required patients to have received at least 5 days continuous opioids (Best et al 2016). Patients with intermittent patterns of weaning were reported to have received significantly more doses of sedatives during the weaning period, had higher total cumulative opioid and benzodiazepine doses and experienced longer durations of mechanical ventilation and PICU and hospital lengths of stay when compared with patients who were weaned steadily (Best et al 2016).

Conversely, steadily weaned patients tolerated rapid decreases in opioid and benzodiazepine doses with a lower incidence of withdrawal (Best et al 2016).
Best et al (2016) concluded that higher cumulative doses, peak doses of opioids and benzodiazepines and longer exposures are associated with withdrawal (Best et al 2016).

6.7.3.2.2 My interpretation (An alternative proposition)

The basis for these assertions can be challenged by the extent to which these variables are causal factors of withdrawal or are the cause or consequence of other related factors. The researcher would argue that the only causal factor for withdrawal is the rate of weaning. From this perpective, the increase in opioid dose used to define the intermittent weaning, is a response to withdrawal signs provoked by too fast a rate of weaning.

According to this model, if patient B was weaned at the rate of patient A, then B may not have withdrawn. If patient A was weaned at the rate of patient B then A might have withdrawn. Changing the rate of weaning changes the risk of withdrawal. By changing rate of weaning; the factors related to the duration of mechanical ventilation are unchanged but the factors related to treating withdrawal – more sedative doses during weaning and a longer wean would be changed.

The propositional model, devised by the researcher as a means of clarfying and illustrating the causal relationship between variables, presented earlier (Chapter 2), is shown in figure 6.2. The model has been adapted slightly to incorporate all variables and consequences described by Best et al (2016) but the cause and effect relationships they represent are unchanged. Additions to the model presented earlier include the role of peak dose, which contributes to cumulative dose and the onset of physical dependence (Ambigoni et al 2014, DaSilva et al 2016). The terms “too fast” and “optimal” delineate the speed of weaning in relation to the patient’s response to the chosen rate.

In patients who are physically dependent, the risk factor for withdrawal is the rate of weaning prescribed by the clinical team. All other factors are a consequence of the length of mechanical ventilation. In support of my proposition, Best et al (2016) reflected that patients with intermittent patterns of weaning experienced greater frequency and severity of WAT-1 scores, concluding;

> *"The question whether intermittent weaning patterns are the outcome of preweaning risk factors or a contributory cause of higher WAT-1 scores and more intense or protracted weaning remains unanswered"* (Best et al 2016, p 10).

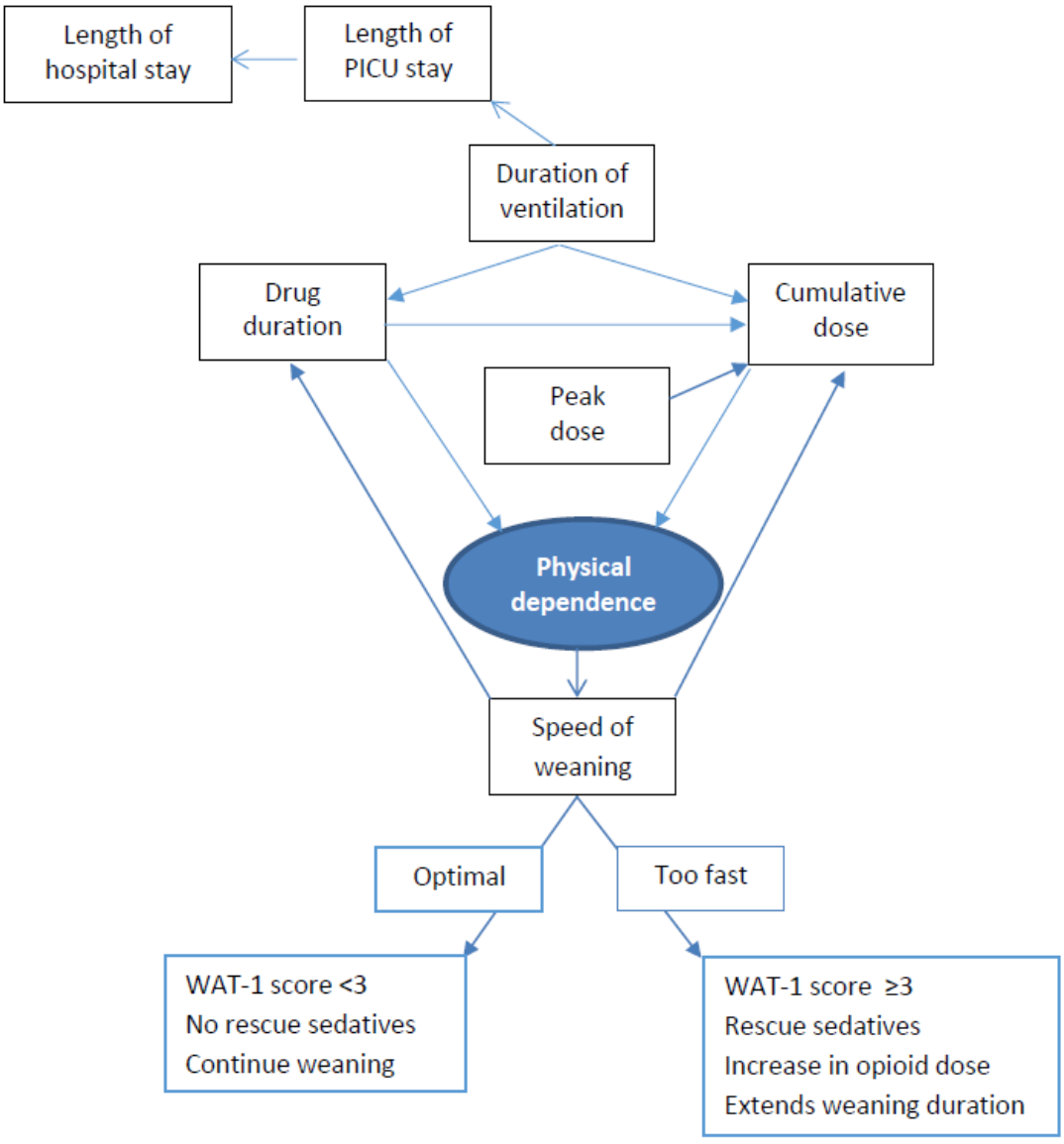

Figure 6.2 A proposition of the causal relationships between factors linked to physical dependence and withdrawal syndrome.

6.7.4 Flow of participants (STARD, 2015)

One of the STARD criteria includes the flow of participants through the study. As each study shared the same patient population, the flow of participants through the three studies (Franck et al 2012, Grant et al 2012, Best et al, 2016) was expected to be the same. Studies reported differences in enrolment, inclusions and exclusions (Table 6.5).

Table 6.5 Flow of participants

		Franck et al 2012	Best et al 2016	Grant et al 2012
Recruited	Approached	348	NR	468
	Refused	11	NR	160
	Enrolled	308	308	308
	Exposed to ≥ 5 days opioids	206*	186*	141/142*
Exclusions	Total excluded	80	41	NR
	Did not start weaning during study period	16	0	NR
	Did not complete weaning in 28-day study period	0	36	NR
	Lost to follow up	0	1	NR
	Died	3	4	NR
	No WAT-1 assessment	61 (excluded)	33 (included)	NR
	Final sample	126*	145*	141/142
	Total WAT-1 score ≥3	97 WAT-1≥3	76 WAT-1≥3	NR
	Total WAT-1 score <3	29 WAT-1<3	36 WAT-1<3	NR
	Episodes of withdrawal (number of patients)	51 (21)	NR	54 (24)

*Differences in flow of participants NR = not reported

The number of patients enrolled in the study was the same across the three studies. However, differences occurred in the number of patients who had at least five consecutive days of opioids, ranging from 206 (Franck et al 2012) to 141/142 (Grant et al 2012). Reasons for exclusion also differed between teams, impacting on differences in the final sample size and the proportion of WAT-1 scores ≥ 3 (Table 6.5)

The study protocol defined clinically significant iatrogenic withdrawal as WAT-1 score ≥3 and requiring rescue therapy (Curley et al 2015). Reporting of this differed between studies. In Franck et al (2012) the median (IQR) WAT-1 score associated with clinically significant withdrawal was 6 (4-8) in 51 scores and 21 patients, compared with WAT-1 score of 6 (4-7) in 54 scores and 24 subjects (Grant et al 2013). Best et al (2016) did not

report episodes of clinically significant withdrawal, but did report the number of patients (n=107) who required opioid and benzodiazepine boluses during weaning.
These differences imply failure in translation validity (Krathwohl, 2009), a standard which underpins the credibility of the inferences made.

6.7.5 Missing data (STARD 2015)

The extent of missing data has implications for validity and reliability and should be presented in the study. The flow of participants' data in Table 6.4 shows that 61 patients who were recruited did not have any WAT-1 scores performed, leaving a sample size of 126 patients (Franck et al 2012); this figure implies compliance with the assessment schedule was poor. The study protocol required WAT-1 assessments to be performed twice daily from the first day of opioid weaning until 72 hours after the last dose of opioid, up to a maximum study period of 28 days.

Franck et al (2012) reported 836 assessments in 126 children; the number of assessments per child was not reported, but these figures equate to a mean of 6.6 assessments per child. WAT-1 was performed once daily for 23% study days and at least twice daily for the remaining 77% study days, proportions which suggests reasonable compliance with the assessment regimen.

As the extent of missing data was not published, an approximation was inferred from data presented about the number of assessments, the length of participation in the study and the assessment schedule (Table 6.6). The median opioid wean was 9 days (Franck et al 2012) and assessments continued until 72 hours after the last opioid dose the median duration of study participation should be 12 days, or 24 WAT-1 assessments per child. In 126 participants this equates to 126 x 24 = 3024 expected assessments. With 836 actual assessments, this equates to a response rate of 28%, which demonstrates poor compliance with the assessment regimen. In the absence of published data, these figures have been calculated using median data points, so whilst not precise, should be representative. On average, WAT-1 assessments were performed for only 50 % of both the expected frequency and duration. The extent of the missing data has implications for validity and reliability and might explain why the prevalence of withdrawal was lower than anticipated.

Table 6.6 Inferred data in the absence of published findings (Bold findings published)

Median opioid wean = 9 days (Franck et al 2012)
Median duration of study participation = 12 days
Number of assessments expected;
Two assessments per day for 126 patients over 12 days = 2 x 126 x 12
= 3024 assessments (expected)
Number of assessments performed = 836 (actual)
Compliance with study schedule = 836/3024 = 28%
Mean number of assessments per child = 836/126 = 6.6 assessments.

6.7.6 Differential diagnoses

Grant et al (2013) acknowledged that differentiating pain and sedation is difficult in this population. The operational definitions of sedation/agitation and withdrawal both comprised an SBS score ≥1 and the lack of validity of SBS in withdrawing patients and patients in pain, has been highlighted earlier in this chapter.

The difference between these WAT-1 scores and the operational definition are not explained, do not equate to the operational definitions of WAT-1 score ≥3 and do not compare to the figures in Best et al 2016 regarding the number of patients requiring opioid or benzodiazepine boluses and are nearly ten times less prevalent than the estimated event rate (8.7% vs 75%).

Patients (n=109) who took more than 5 minutes to settle would score WAT-1 score 2 from this alone and WAT-1 score 3 if they had also been distressed (SBS ≥1) during the pre-stimulus (Franck et al 2012). In these withdrawal assessments, similarities exist with the operational definition of inadequate sedation; SBS ≥ 0 for 2 consecutive hourly assessments. Patients were ventilated for median (IQR) 9.4 (5.9-13.3) days, opioids were administered for 7 (5-11) days and benzodiazepines for 6 (4-9) days. The duration of weaning was a median of 9 days, for both opioid and benzodiazepines. These figures suggest opioid weaning was commenced 2.4 days prior to extubation and weaning was completed about a week after extubation.

WAT-1 assessments were performed for a median of 6 days (Franck et al 2012) which was 50% of the expected study period. These figures differ from those presented in Best et al

(2016). Patient data included in analysis differed due to inclusion of patients without WAT-1 assessments in Best et al (2016). The impact of including the patients without WAT-1 scores is surprising; weaning duration reduced to a median of 2 days for the steady wean half of the group, of whom only 63% had any WAT-1 scores performed during weaning. This implies weaning rates were slowed in patients who had withdrawal assessments. An alternative explanation is that the child's agitated state prompted a withdrawal assessment. The correlation between number of withdrawal assessments and the frequency of administration of opioid or benzodiazepine boluses suggests that the patient's agitation was the motivation for both undertaking a withdrawal assessment and administering boluses. No details were provided about patients who had their opioid or sedative infusion rates increased.

6.7.7 The majority of WAT-1 scores are low

The WAT-1 score range was not comprehensively described. Overall, the median (IQR) for 836 assessments was 2 (0-4) and in the 92% (n=769) patients who did not score for yawning/sneezing the WAT-1 median (IQR) was 1 (0-3). These ranges indicate that 25% scores were WAT-1 score 0, 50% scores were WAT-1 score ≤2 and 69% scores were WAT-1 score ≤3, showing that most of the scores were skewed in the bottom quarter of the possible WAT-1 score range 0-12. Although good from the clinical perspective as there appears to be minimal withdrawal, from a statistical perspective, if the majority of scores are low, approaching the 'floor', it means that many items are being wasted (Streiner and Norman 2003). The solution is to introduce items that will result in scores near the middle of the scale, or alter the threshold at which existing items count. This is a legitimate way of increasing true variance and reliability (Streiner and Norman 2003).

The proportion of missing assessments may be partly explained by the potential for low or no WAT-1 scores. If most assessments are WAT-1 =0, this might have limited nurses motivation for documenting non-scores. Equally, the opposite might be true, whereby nurses had more time to document trial data when the patient was calm. Some acknowledgement and explanation for the high number of missing assessments would contribute to the interpretation of the clinical utility of the WAT-1 scale.

6.8 Conclusion

The pragmatic approach using Krathwohl's Internal integrity framework (2009) to evaluate the WAT-1 validation study (Franck et al 2012) established that conclusions reported in the study were not supported by the data. The components of Internal integrity which afford conceptual and empirical support for the WAT-1 tool demonstrated the lack of both conceptual and empirical evidence. No evidence was provided that a WAT-1 score ≥3 was a reasonable designation of withdrawal; neither was psychometric evaluation of the WAT-1 confirmed or extended.

Different perspectives of the WAT-1 dataset were provided by an additional three papers (Grant et al 2012, Grant et al 2013, Best et al 2016). These studies were reviewed to determine to what extent they supported or refuted the findings of Franck et al (2012). Although different approaches were taken to analysing the data, these approaches only served to undermine the conceptual basis for the WAT-1 tool. Episodes of clinically significant withdrawal were poorly defined and there appeared to be a risk that these might have been interpreted as episodes of under-sedation or pain. That extubation was routinely performed during the weaning period may also have confused the clinical picture regarding the cause of agitation.

Although efforts were made to standardise the assessment performed during data collection, there was no standardisation of the treatment that patients received. Each study attempted to demonstrate associations between scores of the index tool being validated (WAT-1) and clinical factors prescribed by the clinical teams including drug dosing and duration of mechanical ventilation. Although there appeared to be a positive correlation between the WAT-1 assessment and an extended weaning regime, there is no evidence that the care children received across the 22 units was comparable and therefore any associations between clinical factors and WAT-1 scores may be due to chance.

Part 2 Summary and conclusions

This chapter has highlighted the absence of an articulated theory for withdrawal syndrome. The attempts to demonstrate the construct validity of any of the existing scales (SWS, WAT-1 or SOS) has been hampered by the lack of "a formal description of the construct, how it will manifest itself objectively and how it is related to other constructs and behaviours" (Streiner and Norman 2003, p182).

In the exploration of how the nurses' objective assessment of withdrawals syndrome, contributes to the theoretical basis for withdrawal syndrome, Studies 1 and 2 were undertaken. A retrospective review of the SWS tool concluded that the heterogeneous presentation of withdrawal seemed incompatible with the existing approach of assigning a summed score to aid diagnosis of withdrawal. The use of a summed score relies on an homogenous presentation of the underlying construct. This study also revealed the complexity of the clinical conditions in which withdrawal assessment are performed. This finding prompted the design of Study 2 to investigate nurse decision which is presented in Part 3. The level of complexity also prompted the development of three criteria upon which to assign the probability of withdrawal. These criteria are; the likelihood of physical dependence, a temporal association between the reduction or stopping of drug(s) with onset of behavioural signs and an exclusion of other causes for the behaviours. The utility of the criteria will be examined further in Parts 4 and 5.

Study 2 transformed data to enable comparison of the characterisation of withdrawal from two existing studies. Many of the equivocal signs of withdrawal were common or very common in "not withdrawing" patients, so an increase in prevalence in "withdrawing patients" may not be recognised as clinically significant. This study demonstrated differences in the characterisation of withdrawal which may be a consequence of the different rates of weaning, differences in the assessment schedules or differences in the way withdrawal was assigned. Despite all these differences, the data from both studies demonstrated that three signs – agitation, movement disorder and vomiting – showed the greatest change in prevalence between "withdrawing" and "not withdrawing" groups, differences in prevalence that may be recognised as clinically significant.

In Study 3 a pragmatic critique of the WAT-1 validation study (Franck et al 2012) was undertaken. Three peer reviewed papers presenting secondary analysis of the same

dataset from which WAT-1 was validated were also reviewed. The critique could not support the conclusions made by Franck et al (2012) that WAT-1≥3 is a reasonable designation of clinically significant withdrawal. The analysis of these three papers provided further evidence to challenge this assertion and no evidence in support of this construct.

The findings in these chapters are predicated on the lack of theoretical underpinning for the assessment, risk factors and assessment of withdrawal syndrome. Without an articulated theory, the assessment tools cannot be validated. Theory must precede the development of a tool as it underpins the content of the tool and is the basis for determining the performance of the tool (Cronbach and Meehl 1955).

In the absence of existing theoretical concepts for withdrawal, the propositional model presented in Chapter 2 (Figure 2.2) has been further developed (Figure 6.1) to demonstrate the relationship between the constructs of withdrawal and physical dependence and the associated variables of duration of mechanical ventilation and drug dosing and duration (Figure 6.1). This model will be extended in subsequent chapters in this thesis.

Introduction

Part 3 of the thesis presents a study of nursing judgement (Study 4), which was prompted by the findings in Study 1 which highlighted instances when behaviours caused by competing diagnoses drove the withdrawal score. It has been assumed that nurses exclude other causes for equivocal behaviours (Ista et al 2013, Harris et al 2016) but in some instances where differential diagnoses coexist, it may not be possible to exclude other causes.

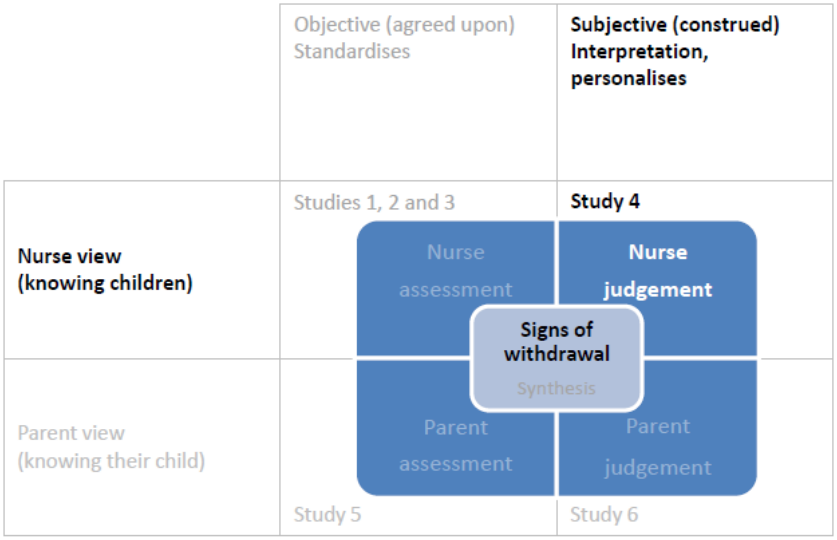

Figure Part 3.1 The conceptual framework highlighting the contribution of Study 4

Study 4 investigates nurse decision-making under experimental conditions, allowing the researcher to control the information received by nurses in a way that would not have been possible in the naturalistic clinical setting.

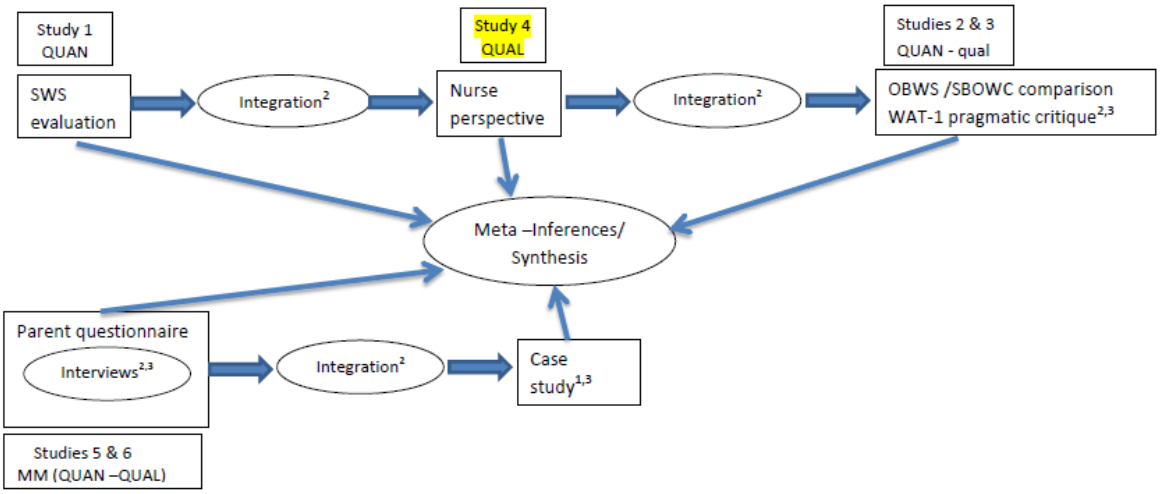

Figure Part 3.2 The thesis map showing Study 4 highlighted.

Chapter 7: Study 3: Cognitive interviews with children's nurses: decision-making during the assessment and management of sedation withdrawal.

7.1 Introduction

A brief review of the literature regarding judgement and decision-making is presented; terms which are used synonymously with the term clinical reasoning in this chapter. In the method section, the rationale for the choice of cognitive interviewing is presented along with other approaches to minimise research participation effects.
Results are presented according the different stages of decision-making and different aspects of the withdrawal assessment. The discussion reviews these results in the context of the literature and the existing knowledge about the subject. Study conclusions are followed by an integration of the findings of this study with the findings of Part 2.

7.2 Background

The assessment of withdrawal syndrome in children is complex. Structured and repeatable assessments are recommended to assist detection, but it is often unclear how these are applied by nurses. Three published tools have been developed to monitor withdrawal in children; the Sedation Withdrawal Score (SWS) (Cunliffe et al 2004), the Withdrawal Assessment Tool (WAT-1) (Franck et al 2008) and the Sophia Observation Score (SOS) (Ista et al 2009). Each is a checklist of non-specific signs that, in combination, appear to support a diagnosis of withdrawal. The SWS is the withdrawal assessment tool and treatment protocol used in our hospital since 2004. The SWS has proven clinically useful in identifying withdrawal signs in PICU and ward-based patients, but has not been validated (Macqueen & Bruce 2012). Both WAT-1 (Franck et al 2008, 2012) and SOS (Ista et al 2009, 2013) have been validated but the studies excluded patients whose existing behaviour might confound the withdrawal assessment and clinical utility is further limited by the lack of linked treatment protocols.

The assessment of sedation withdrawal is complex due to the multiple drug and patient factors to be considered. Drug factors include the likelihood of physical dependence, which varies depending on drug dose and duration of therapy (Amigoni et al 2014; Da Silva et al 2016) but also appears highly individualised (Best et al 2016) and may be

further complicated by concurrent tapering of more than one sedative or analgesic drug (Best et al 2016). Patient factors include the highly individualised effects of withdrawal on the child's recovery (Franck et al 2008) and the confounding effect of the patient's primary medical condition on withdrawal intensity (Franck et al 2008). Findings in Chapter 4 (Study 1) highlighted that assumptions that nurses will modify the assessment to ensure the underlying condition or any external factors do not skew the withdrawal score (Franck & Vilardi 1995, Ista et al 2013, Harris et al 2016) may be flawed. Complex tasks like this demand a degree of cognitive effort and focussed attention on the part of the nurse, to make correct judgments and decisions. Given that the judgement of the bedside nurse has been described as both a 'tin standard' (Franck et al 2008) and a 'silver standard' (Ista et al 2009) in tool validation studies, it is important to understand how nurses think when undertaking withdrawal assessments and making treatment choices (Easley & Nichols 2008).

Two key theoretical approaches to clinical decision-making are reasoning and intuition (Banning 2008). Different academic disciplines including the airline industry, medicine, education and information studies have investigated the analytical, rational approach of reasoning. Models have emerged, which describe similar key stages of the process (Table 7.1). Endsley (1995) and Tanner (2006) each describe a three stage process- situation awareness- that comprises perception, comprehension and projection (Endsley 1995). These stages are described as noticing, interpreting and responding by Tanner (2006). Remaining open minded throughout these stages is vital, as relevant cues can be subtle and may be overlooked, particularly if the situation is changing quickly or there is too much to take in simultaneously (Gaba et al 1995). Knowing how to filter tenuous cues and focus on relevant ones is a feature of expert nursing practice (Harbison 2006).

Intuition is defined as "a way of knowing something immediately as a whole that improves with experience" (Rew & Barrow 2007, p. E25). This enables the clinical expert to process and identify key diagnostic components subconsciously (Lyneham et al 2008). In high-pressure situations, the rational approach is somewhat idealistic as clinical decisions are often required despite incomplete knowledge of the situation (Graber et al 2002). Under these conditions, experienced clinicians rely on intuition to "think fast" (Kahneman 2011, p. 13), using pattern recognition (Berner & Graber 2008; Gobet & Chassy 2008) and heuristics (Elstein 1999; Cranley et al 2009). However, intuitive processing can be flawed (Graber et al 2005), especially in an unpredictable environment

(Kahneman & Klein 2009) such as critical care. The intuitive heuristic describes circumstances where clinicians faced with a complex clinical problem resolve a simpler issue instead, without realising they have done so (Kahneman 2011).

Table 7.1 The key stages of decision-making

Model	Disciplinary background	Stage 1	Stage 2		Stage 3
Situation Awareness (Endsley 1995)	Airline industry Medicine	Perception	Comprehension		Projection
Thinking like a nurse (Tanner 2006)	Nursing	Noticing	Interpreting		Responding
Bruner's phases of interpretation (Kuhlthau 1993)	Learning and education	Perception	Process of recognising patterns	Making inferences	Prediction
Cognitive Model of Response Processes (Tourangeau et al 2000)	Information studies	Comprehension	Retrieval	Judgment	Response

No published papers were identified that considered how nurses make decisions about the assessment and management of withdrawal in children. This study sought to fill this knowledge deficit by attending to the three stages of decision making; noticing, interpreting and responding.

7.3 Aim of Study 4

The aim of the study was to explore registered children's nurses' decision-making during the assessment and management of sedation withdrawal in children by examining the three stages described by Tanner (2006). The stages equated to;

1. Noticing; the nurses' recognition and understanding of four clinical signs from the SWS tool,
2. Interpreting; the meaning of an SWS score, in terms of a diagnosis of withdrawal, presented in two clinical vignettes, and
3. Responding; the treatment choices made in response to the withdrawal diagnosis.

7.4 Method

Recognising the value of the nurse perspective in identifying ways to improve the existing approach to withdrawal assessment fits with a pragmatic approach that focuses on

finding the solutions to problems (Creswell 2013). The nurse using the assessment tool in clinical practice could be viewed as the emic, or insider perspective contrasting with the etic perspective presented by the formal tool validation studies. Cognitive interviews were undertaken using clinical vignettes to explore the study aim.

7.4.1 Validity and reliability

Validity and reliability were considered carefully in design and implementation of the study. A challenge in studying usual behaviour is how to do this without observation bias or research participant effects (McCambridge et al 2014). In decision-making studies, the ideal research method has minimal impact on typical, subconscious reasoning and does not lead to an altered, more conscious level of reasoning. Research participant effects - the change in behaviour as a consequence of being studied (McCarney et al 2007) have been demonstrated in observational studies investigating antibiotic prescribing behaviour in paediatricians (Mangione-Smith et al 2002) and compliance with hand hygiene in clinical settings (Eckmanns et al 2006; Maury et al 2006). In these studies, participants were more likely to demonstrate or take a best practice approach. In studies investigating decision-making, the manner of questioning may also stimulate new thinking (McCambridge et al 2014) or change the effort paid to the cognitive task (Sitterding et al 2012). These effects may limit the generalisability of clinical research to routine practice (McCarney et al 2007). The cognitive interview technique is inherently suited to this study as it is not considered to alter the effort or attention paid to the task and is also widely used in psychometric testing of survey instruments (Sofaer, 2002).

Cognitive interviews are a recognised approach to explore cognitive processing in relation to decision-making (Willis 2005, Ross et al 2012). The fundamental features of cognitive interviews are think aloud and verbal probing; these techniques permit the researcher to listen in to the complex and usually hidden evolution of (clinical) reasoning without interfering with the cognitive processes being uncovered (Fonteyn et al 1993). Verbal probing delivered in a neutral manner enables the interviewer to drill down on the issues under investigation, so clinical expertise in the subject area is necessary to recognise when a response needs further probing (Sofaer 2002). All other interaction between researcher and participant is minimised to reduce biasing participants' responses (Sofaer 2002).

The cognitive interview approach has been employed in other studies investigating nurse decision-making (Cioffi 1998; Simmons et al 2003; Twycross & Powls 2006; Hoffman et al

2009); these are now presented in brief. Cioffi (1998) investigated the effects of experience and uncertainty on triage assessments made by emergency nurses and Simmons et al (2003) described cognitive processes used by experienced nurses during their patient assessments in elderly care. Work by Twycross and Powls (2006) explored how children's nurses made clinical decisions and Hoffman et al (2009) compared clinical cues collected by novice and expert nurses in intensive care. The cognitive interview approach has also been applied to the psychometric testing of self-report clinical assessment tools, to check that terminology is understood and interpreted consistently by patients (Sofaer, 2002; DiBenedetti et al 2013).

7.4.2 Measures

An experimental setting, using vignettes, was chosen over a naturalistic setting in order to control the clinical data provided to participants and allow comparison between them (Willis 2005, Berner and Graber 2008). By standardising the data, the only variable lay in the nurses' decision making processes (Cook and Rumrill 2005), enabling focus on the abstruse stages of 'noticing' and 'interpreting' rather than simply the outcome or response (Veloski et al 2005).

Two clinical vignettes were developed by the researcher (an experienced pain/sedation nurse specialist) to illustrate a typical, complex clinical situation featuring a patient with severe neurological disability (Figure 7.1). The vignettes were based on a real case from clinical practice to enhance believability (Endacott et al 2010). Face and content validity was undertaken to check that the vignettes were comprehensible and contained sufficient detail to prompt participants to think about the scenario. This was assessed by piloting the vignette and the explanation about cognitive interviewing with four senior clinical nurses (members of the pain team and an Advanced Nurse Practitioner in critical care) experienced in withdrawal assessment. This process did not prompt any changes to either the vignettes or the introductory explanation. The sensitivity and specificity of the vignettes was subsequently evident in that they generated data that identified both cognitive errors and correct decisions.

Typical levels of cognitive stimulation were prompted by using developmental vignettes (Barrows & Feltovich 1987, Veloski et al 2005*),* to measure nurses' usual or 'everyday' practice (Peabody et al 2004). Developmental vignettes present a scenario that unfolds in stages (Jenkins et al 2010). The first vignette (V1) supplied minimal information, to reflect initial interpretation at the moment when the SWS score is completed. A diagnosis

at this stage would indicate the inclination to 'make do' with limited information, thus uncovering the usually hidden assumptions which are made to fill in knowledge gaps. The second vignette (V2) provided additional clinical details reflecting the range of information required to underpin a more considered, contextual interpretation of the same assessment.

Vignette 1
18 month old boy admitted to ICU 18 days ago in respiratory failure (Lower respiratory tract infection secondary to tracheomalacia).
His SWS score is 5 (insomnia 1, irritability 1, tremor 1, respiratory distress 1 and hypertonicity 1)

Vignette 2
History of presenting condition 18 month old boy admitted to ICU 18 days ago in respiratory failure (Lower respiratory tract infection secondary to tracheomalacia).
Past Medical History severe hypoxic ischaemic encephalopathy, chronic lung disease, epilepsy.
Past Surgical History Aortopexy 6 days ago.
He was extubated 4 days previously but within 24 hours required insertion of NPA and CPAP. NPA removed 24 hours ago.
Sedation fentanyl and midazolam infusions for 48 hours post op stopped 4 days ago. Regular chloral hydrate and codeine started 3 days ago. Chloral hydrate weaning started yesterday and codeine stopped.
His SWS score is 5 (insomnia 1, irritability 1, tremor 1, respiratory distress 1 and hypertonicity 1)

Intervention(s)
What intervention would you recommend? You can provide one or more answers.

- Give codeine*
- Stop weaning chloral hydrate
- Increase dose of chloral hydrate
- Restart fentanyl
- Restart midazolam
- No intervention
- Other intervention – please state

*Codeine was included in the list of interventions as this study took place prior to restrictions in the use of codeine in children under 18 years of age, were issued by the Medicines & Healthcare products Regulatory Agency (MHRA, 2013).

Figure 7.1 Vignettes and Intervention(s)

7.4.3 Sample/ participants

The study was conducted in a large children's hospital in the Northwest of England. The study participants were registered children's nurses, who undertook withdrawal assessments in their clinical role. Purposive sampling was employed to recruit nurses from the clinical areas where patients experiencing withdrawal were usually nursed (the Paediatric Intensive Care Unit (PICU), the High Dependency Unit (HDU) and the cardiac ward). Nurses were eligible for inclusion if they undertook withdrawal assessments regularly and considered themselves familiar with the SWS tool. Nurses were recruited by poster or by word of mouth by the researcher during clinical rounds and they gave written consent to participate (See Appendix 7 for study information and consent forms). Interviews took place in Autumn 2013 in quiet rooms adjacent to the clinical areas (see also Ethical considerations section).

7.4.4 Data collection

The interviews were conducted by the researcher (who had training in cognitive interviews and clinical expertise in the recognition and management of withdrawal syndrome). The interviews were audio-recorded with the participant's permission. Demographic data included gender and experience, in years, of applying the SWS tool in practice was collected from participants at the start of the interview. No further demographic data were collected, as the relationship between factors such as years since qualification, level of expertise and level of educational attainment on decision-making is unclear (Lauri & Salanterä 1998; Hoffman et al 2004; Fick et al 2007). Consideration was given to the sequence of the interview to minimise the potential impact on typical thought processes by unintentionally problematising aspects of nursing care that may be relatively routine (Jenkins et al 2010).

The first part of the interview: interpreting SWS scores and responding with treatment choices, aimed to replicate routine clinical practice using the SWS tool and reflect the largely subconscious and automatic synthesis of information nurses undertake. V1 was presented followed by V2. After reading each vignette, the participant was asked to 'think aloud' whilst responding to the pre-set questions and scripted probes e.g., "Is this patient withdrawing?" and "How easy or difficult is it to decide whether the patient is withdrawing?" A list of treatment options for the patient in V2 was then presented and the participant was reminded to 'think aloud' whilst they made a decision. Options

included all drugs mentioned in V2 in addition to 'no intervention' and 'another intervention'.

The second part: noticing (recognising and understanding) individual withdrawal signs was anticipated to be more cognitively taxing, possibly causing participants to critically reflect on their current approach to, and alter subsequent, withdrawal assessments. Consequently, participants were asked not to discuss their interview experience with colleagues until the study was completed. In order to encourage deeper reflection on issues raised by the vignette, the participant was then asked to define four pre-selected SWS terms ('insomnia', 'irritability', 'respiratory distress', 'hypertonicity'). These terms were selected due to the equivocal meaning of the behaviours in terms of withdrawal or critical illness. The participants were also asked how easy or difficult it is to decide when a patient displayed one of these four behaviours.

7.4.5 Ethical considerations

The study was approved by the Liverpool East Research Ethics Committee, REC number 12/NW/0681.

Ethical issues pertinent to this study included minimising the risk of coercion, freedom to stop or withdraw from the study, maintaining confidentiality and protecting anonymity. These issues were covered in the participant information leaflet (PIL)(See Appendix 6). The researcher's clinical role as a member of the pain team that oversees sedation weaning meant she was known to nurses prior to their participation in the study. To minimise the risk of coercion, nurses self-selected to participate and contacted the researcher to express their willingness to participate. Information provided to potential participants included verbal information about the purpose of the study, and assurances of confidentiality, that participation was voluntary and that non participation would not affect their working relationship with the researcher. The PIL reinforced the mitigation of these ethical issues in writing, provided assurance that the study posed no risk to them and identified the process for raising any concerns about any aspect of the study. Written consent was gained from nurses who agreed to participate by the researcher.

7.4.6 Data analysis

The interviews were transcribed by a professional transcriber and checked by the researcher for accuracy and completeness. "Informal analysis", the approach proposed by (Willis 2005, p. 156) was used to identify cognitive problems with decision-making.

Subjective interpretation is key to informal analysis, which rather than a formal coding scheme, relies on expert judgement to identify problems (Fonteyn et al 1993). The conceptual framework used with this analysis incorporates the dualisms of objective decision-making and subjective decision-making described in Chapter 3. These opposing perspectives were used as the analytic structure for categorising the decisions made by nurses. Identifying and examining cognitive challenges arising from the existing approach to withdrawal assessment is the basis for considering how to minimise errors and aligns with the overall purpose of the thesis to improve sedation withdrawal assessment. Analysis involved two stages; firstly the identification of the decision-making processes including cognitive errors made when noticing, interpreting and responding within individual interviews and secondly, comparison across interviews to elucidate trends. The term cognitive error is used to describe any flawed judgement or inaccurate decision made by the participants.

For the purpose of this study, the putative diagnosis of withdrawal syndrome was based on two core features drawn from the literature:

1. Physical dependence on a drug therapy administered continuously for at least five days or sooner if administered at high doses (Macqueen & Bruce 2012, Harris et al 2016),
2. Behavioural signs of withdrawal, in response to the drug(s) stopping or reducing that are not better explained by other physical, illness or environmental causes (Macqueen & Bruce 2012, Ista et al 2013, Harris et al 2016).

These features are comparable with the criteria adapted from the ADR causality assessment tool, which was used to assign the probability of withdrawal in Study 1 (Chapter 4). Provision of incomplete, equivocal information in the vignettes was designed to reflect the "fuzziness of unstructured real life situations" (Benner and Tanner 1987, p.24). V1 provided no data on either of the core features of withdrawal. V2 provided data about the likelihood of physical dependence, but in the absence of a baseline SWS score or trend, insufficient information was available to establish the cause of behavioural signs.

7.5 Results

Twelve registered children's nurses participated in the interviews; four from the PICU, four from the Cardiac Ward and four from the HDU. All participants were female. The nurses had been undertaking withdrawal assessments for between 4 and 13 years (median 10 years) so were experienced in this aspect of their clinical role. Interviews lasted between 21 and 47 minutes.

7.5.1 Interpreting the meaning of an SWS score

In both vignettes, nurses drew on all three options: 'withdrawing', 'not withdrawing' and 'unsure' (Table 7.2). In V1, two nurses recognised there was insufficient information upon which to make any judgement. Responses to 'How easy or difficult was it to decide?' ranged from 'easy' to 'very difficult' with one nurse commenting that it "should be easy with more information". All nurses who found the diagnosis 'easy' made a definite diagnosis. In V2, the responses to 'How easy or difficult was it to decide?' ranged from 'quite easy' to 'very difficult'. Some nurses found V2 "easier than previous [vignette]" and one thought it was "harder with more information". Again, those finding the diagnosis 'easy' all made a definite diagnosis. Those who found it "easier than previous" each gave a different diagnosis of withdrawal. The nurse finding V2 "harder with more information" was 'unsure' in both vignettes. In terms of consistency of opinion across the vignettes, three people who made a diagnosis in V1, persisted with their diagnosis in V2 ('yes' n=2, 'no' n=1). Four nurses were 'unsure' in both vignettes. The two nurses who could not comment in V1 were 'unsure' in V2 and found the decision 'difficult'. Diagnosis of withdrawal was commonly based on the SWS score in V1, although the child's underlying condition was recognised as a possible cause for the score (Table 7.3). In V2, more nurses recognised that the SWS score might reflect either the child's underlying conditions or their normal behaviour. Some nurses recognised that the duration of sedation described was too short to cause physical dependence and hence withdrawal symptoms. The three nurses who diagnosed 'not withdrawing' made this observation along with one nurse who still diagnosed the patient as 'withdrawing'. Four nurses made explicit assumptions during their deliberations in V1. Three of these nurses diagnosed withdrawal; one was 'unsure'.

Table 7.2 Participant demographics, results of vignette diagnosis and intervention

Nurse	Ward	Experience (years)	Vignette 1		Vignette 2		Intervention				
			Patient withdrawing?	Ease of decision	Patient withdrawing?	Ease of decision	Give codeine	Stop weaning chloral	Increase chloral	No intervention	Other intervention
N1	PICU	5	Yes	Easy	Yes	Not difficult	Maybe	Yes	Maybe		Distraction
N2	HDU	7	Yes	Not easy	Don't know	Difficult	Yes	Yes			
N3	HDU	5	No	4/10 easy	No	Easier than previous				No intervention	Investigate tremor
N4	HDU	10	Probably	Quite easy	Don't know	Harder with more info		Yes			Paracetamol, speak to mum
N5	PICU	5	Don't know Possible	Difficult (v)	Don't know	Very difficult				No intervention	Monitor
N6	Cardiac ward	13	Yes	Easy	Yes	Quite easy	Yes	Yes	Maybe		
N7	PICU	10	Don't know	Very difficult	Don't know Yes	Easier than previous	Yes	Yes			
N8	Cardiac ward	13	Yes possible	Should be easy with more information	No	Quite easy	Maybe				Paracetamol, oral morphine, pain team, neurology
N9	Cardiac ward	13	Can't comment		Maybe	Difficult	Yes	Yes	Maybe		Paracetamol, physio, neurology
N10	PICU	10	Can't comment		No	Quite difficult	Maybe				Speak to parents
N11	HDU	13	Yes	Quite hard	Don't know No	Not asked	Maybe	Maybe			Paracetamol
N12	Cardiac ward	4	Don't know	DNA	Yes	Easier for this one	Yes	Yes	Maybe		Paracetamol

Table 7.3 What nurses considered when deciding about withdrawal

V1 (Insufficient information provided)

	N1	N2	N3	N4	N5	N6	N7	N8	N9	N 10	N 11	N 12
Diagnosis	W	W	N	?	?	Y	?	?	C	C	W	?
SWS Score	✓	✓		✓		✓		✓	✓			✓
Underlying condition/ pain/environment		✓	✓		✓	✓	✓	✓			✓	✓
Need info about SWS score trend (T)/ drug therapy (D)								D	TD			D
Made assumptions	✓	✓			✓					✓		

W = Withdrawing N = Not withdrawing ?= Unsure C = Can't comment

V2 (Information provided about co-morbidities and potential for physical dependence)

	N1	N2	N3	N4	N5	N6	N7	N8	N9	N 10	N 11	N 12
Diagnosis	W	?	N	?	?	W	?	N	?	N	?	W
Underlying condition/ normal behaviour		✓	✓	✓	✓		✓	✓	✓	✓	✓	
Drug therapy		✓				✓	✓			✓		✓
Not physically dependent			✓	✓	✓			✓	✓	✓		✓
Made assumptions	✓						✓					

Two nurses made assumptions in V2. One nurse made assumptions in both vignettes, and diagnosed 'withdrawal' in both cases. The second nurse was 'unsure' in both vignettes, but found V2 "easier than previous". The common assumption in V1 was based on the length of ICU stay and related to possible sedatives the child might have received. One nurse reflected that '*he's been on ICU eighteen days and I'm assuming he's been receiving some kind of sedation for that long.'* (N5) Another nurse thought '*there's a possibility that he may have failed extubations and been re-ventilated so he's been awake and asleep quite a few times within those eighteen days possibly.'* (N1)

7.5.2 Response to the withdrawal diagnosis

Treatment choices corresponded to the diagnosis when the diagnosis was definite but varied amongst nurses who were "unsure" (Table 7.3 and Figure 7.2). Nurses who diagnosed 'withdrawing' chose to stop weaning chloral hydrate and 'maybe' increase chloral and give codeine ('yes' n=2, 'maybe' n=1). In contrast, nurses who diagnosed 'not withdrawing' chose to continue weaning chloral hydrate. Two nurses considered giving additional analgesia including codeine, paracetamol and oral morphine. Nurses who were 'unsure' chose a range of interventions, including stop weaning chloral hydrate, increase chloral, give codeine and no intervention. Paracetamol was chosen as 'another

intervention' by five nurses who had varied opinions about whether the child was withdrawing. Failed heuristics and biases were identified during protocol analysis and these cognitive errors were categorised according to definitions cited by Croskerry (2003) (Table 7.4). Cognitive errors occurred during the decision-making processes involved in both the interpretation of and response to the SWS score. Every nurse made cognitive errors: the number ranging between 1 and 4 errors per nurse. Not all cognitive errors led to diagnostic errors, as two nurses made assumptions during their deliberations in V1, but these did not translate into an inaccurate diagnosis. No nurse made errors at every stage of the decision-making process.

7.5.3 Noticing (recognising and understanding) SWS behaviours

Nurses shared an accurate understanding of the terms 'insomnia' and 'respiratory distress' and were confident and succinct in their definitions. They found 'irritability' harder to define, but it was usually described as difficulty in consoling the child despite trying the usual comfort measures and parental presence. 'Hypertonicity' was the most problematic term with one nurse unable to offer a definition and another giving an inaccurate definition; *"being unable to relax, quite tense, they often have trouble staying still, their little arms and legs keep going"* (N8). Although the remaining nurses offered a definition of "increased tone", half of them expressed doubt or lacked confidence about their explanation.

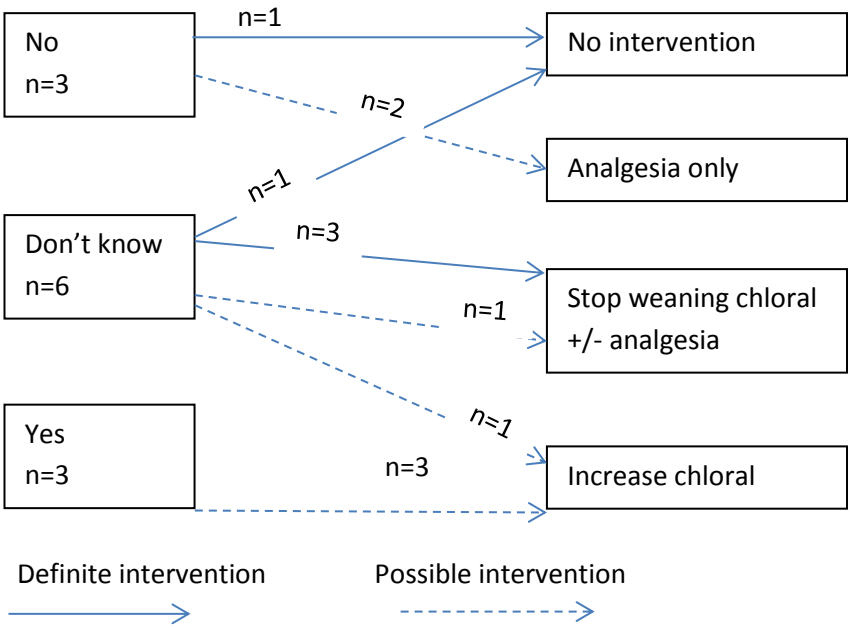

Figure 7.2 Withdrawal diagnosis and Interventions chosen

When talking about the definitions, there was a tendency for nurses to blur the boundaries between signs, describing the co-existence or overlapping of some behaviours. Two nurses described the interdependence of insomnia and irritability. During a definition of 'irritability', one nurse explained *"it's linked a bit to the insomnia where you can see that they are tired and want to sleep"*(N5). Another nurse's definition of 'irritability' appeared to overlap with 'insomnia'; *"you sort of think they are settled, they sort of shut their eyes and they go still and then two minutes later they're awake you know, they're off again"* (N10).

Inaccurate mapping of other behaviours to SWS signs was identified as another perceptual problem. Descriptions of motor disturbance were made by half of the nurses during their definitions of insomnia, irritability or hypertonicity. When defining 'insomnia' one nurse commented that *"They may be active, arms, legs, head, generally moving so they're not peacefully asleep"* (N10). A definition of 'irritability' included *"thrashing their arms and legs around or their head around"* (N9). 'Hypertonicity' was described as:

> *"Just constant moving of arms and legs, inability to stay still really, some of the babies they look like they're riding bikes lying in their cot because their legs just keep going round and their arms keep waving."* (N8)

Table 7.4 Cognitive errors identified during protocol analysis

Cognitive error	Example	Nurse
Commission bias	Stopping chloral hydrate despite being unsure about withdrawal.	2,4,7,9
	Administering analgesia.	4,8,9,12
Confirmation bias	Diagnosing withdrawal despite recognising the duration of sedation was too short.	12
Overconfidence bias	Acting on incomplete information or intuitions. Any definitive diagnosis in V1.	1,2,3,6,11
	Making assumptions.	1,2,5,7,11
Availability heuristic	Accepting a diagnosis that springs easily to mind. Relying on the SWS score alone to make a diagnosis without considering the wider context.	1
Anchoring heuristic	Choosing to stick with one's original diagnosis despite more information becoming available.	1,3,6

'Insomnia' presented challenges for nurses in terms of both recognising and interpreting this behaviour. Lack of familiarity with the patient made it difficult to know if the patient's behaviour was different to normal, as one nurse described *"unless you know*

exactly what they're like without any of the illness, medication and what have you" (N4). Trying to making sense of current behaviour by ascertaining recent trends was also complicated by the perceived subjective nature of the assessment *"if you look at the previous 12 hours, you've only got the chart to go from, so when somebody's marked down awake or asleep, you don't know if they've really been asleep for a whole hour or is it just 10 minutes"* (N7). However, confidence grew throughout the shift *"because you've done a whole day with them…."* (N10) and nursing a child on consecutive days was also viewed positively, because *"then you've got a better comparison as to whether they are more or less alert than they were the previous day"* (N9). Environmental factors were also identified as possible causes of insomnia, as one ICU nurse described, *"ICU is noisy, it's loud, we forget and our colleagues talk and have to be shushed a lot of the time throughout the night, the monitors are always bleeping…"* (N5).

The main challenge with interpreting 'irritability' related to deciding whether this behaviour was a result of withdrawal or other co-morbidities. Nurses talked about undertaking a process of eliminating other possible causes of 'irritability' before attributing it to withdrawal. As one nurse described *"it's never the first thing I think when they're crying, they might be hungry or I'll check their nappy, and when I've covered all the bases then I'll be like actually they're irritable* (N12).

Lack of familiarity with the patient was voiced but some nurses described working with parents to interpret the child's behaviour, because *"they know them better than us"* (N2). In children with neurological impairment, nurses described relying on parents to identify whether behaviours differed from normal, as one nurse explained; "*I walk into the situation and I don't know the child I might think – 'oh my word this baby's really agitated'. But the parent's might go – 'well that's him when he's well'"* (N8). Nurses appeared to be most confident in recognising 'respiratory distress' but found the challenge was judging whether it was a sign of withdrawal or another co-morbidity. One nurse commented *"It's hard with the respiratory distress side of things, because if he's chronic lung disease, it's like Catch 22 isn't it?"* (N6).

7.6 Discussion

No published studies have been identified that describe the use of cognitive interviews and vignettes to examine the stages of decision-making undertaken by nurses in the

assessment and management of withdrawal syndrome. This study showed that nurses used a variety of approaches alone or in combination including intuition, reasoning, biases and heuristics, as reported by Tanner (2006). The use of SWS did not standardise nurses' assessment of withdrawal and cognitive challenges arose in each stage (noticing, interpreting and responding) of decision-making examined. These stages will be discussed in light of the overarching clinical goal of improving the assessment and management of withdrawal syndrome. As SWS shares a similar format and content to SOS and WAT-1, these findings suggest that cognitive challenges may also exist for nurses using SOS and WAT-1. As all nurses in the study made at least one cognitive error, there did not appear to be a relationship between quality of decision-making and either their experience or their clinical specialism. These results support the view that "*simply possessing clinical experience is no predictor of high quality decision-making*" (Thompson et al 2009, p. 610).

The noticing stage - identifying and describing individual withdrawal behaviours - presented the greatest cognitive challenge for nurses and the widest variation in responses. When asked to describe withdrawal signs, nurses could plainly visualise a withdrawing child, demonstrating the "pattern recognition" of expert judgement and decision-making (Berner & Graber 2008, p. S12). Difficulty arose in separating the component behaviours to fit a list of withdrawal signs, leading to a blurring of boundaries between terms and inaccurate mapping of other signs. Although deconstruction of withdrawal syndrome into an item pool of component behaviours may be a necessary stage in scale development (DeVellis 2012), within the experimental conditions of this study, this step appears to add complexity rather than simplifying the assessment.

Nurses recognised that they lacked knowledge needed to interpret some SWS items presented in the vignette, as they were mostly not cognisant of the child's normal behaviour. Knowing the patient and their pattern of responses is considered fundamental to sound clinical judgement (Tanner 2006) promoting a corresponding sense of salience (Benner & Tanner 1987), whilst less knowledge impacts on the capacity to notice subtle cues or changes.

Interpretation of the vignettes differed widely, despite every nurse being presented with the same information and clinical cues. This variation in decision-making in the face of identical information mirrors other studies involving nurses and pain assessment (Hodgins 2002), nurses and critical event risk assessment (Thompson et al 2009) and triage assessments made by emergency nurses (Cioffi 1998). These findings support the

view that clinical judgements are influenced more by what nurses bring to the situation than by the clinical data available to them (Tanner 2006). The effort required to reach a diagnosis also varied widely: nurses who made a definite diagnosis found the decision easier than those who were unsure. For some nurses in V1, the score alone gave a clear diagnosis of withdrawal, abnegating the cognitive burden of interpreting the meaning of ambiguous clinical signs. Indeed Benner & Tanner (1987, p28) warned against the over-reliance on assessment tools, which could encourage a complacent "checklist mentality" rather than the rigour of "active enquiry".

The ability to see some aspects as more important than others has also been described as a sense of salience by Sitterding et al (2012): this sense of salience was lacking amongst the nurses who overlooked the fundamental importance of recent drug history as the context for a withdrawal assessment. In the face of such complexity, and the need to consciously consider the context of drug dependence, the role for the subconscious cognitive processing characteristic of intuitive thinking is unclear. Nurses who were unable to reach a diagnosis found the task harder, reflecting their recognition of the ambiguities, complexity and incompleteness of the available information; this demonstrated what (Brannon & Carson 2003) would consider being superior decision-making. This quality was also suggested by nurses who made probability judgements (possibly, probably or maybe withdrawing), which appeared to acknowledge the contextual challenge and inferred a cognitive flexibility to modify their opinion in light of further information (Szolovits & Pauker 1978). Whether as a result of complacency, overconfidence or a checklist mentality, the findings from this study suggest that some nurses have a misplaced confidence in the diagnostic capacity of SWS, which if they were directed primarily by the score, may consequently limit further enquiry. The potential for cognitive errors during this interpretive phase highlights the importance of learning clinical reasoning skills, ideally during nurse training (Levett-Jones et al 2010, 2015).

The responding stage was the most consistent phase of decision-making with treatment decisions corresponding to nurses' definite diagnoses. Cioffi (1999) describes the relationship between cues and inferences as decision rules or "if…then" rules. For example, "If a patient is withdrawing (cues) then the drug reductions should cease (inference)" or "If a patient is not withdrawing, then drug weaning should continue." However, when nurses were unsure of the diagnosis, an inclination towards 'doing something' meant the most common intervention was to stop weaning chloral hydrate.

This tendency towards action rather than inaction, despite no supporting evidence for the decision, is known as commission bias (Croskerry 2003). However, such bias can result in poorer outcomes as the unnecessary slowing of weaning regimes should be avoided, as prolonging sedative treatment may prolong recovery and hospitalisation. Administration of analgesics was another common treatment choice made by nurses, regardless of withdrawal diagnosis, perhaps reflecting an 'obligation towards beneficence' another example of commission bias (Croskerry 2003) - despite no supporting evidence within the vignette of the need for analgesia.

7.6.1 Content validity

Content validity relies on a common understanding of the terms used in the tool. Results demonstrated inconsistencies in the understanding of some of the items in the score, with nurses describing recognised withdrawal behaviours but attributing them inaccurately to another withdrawal term. This occurred most frequently with 'motor disturbance', a behavioural sign included in the SOS (Ista et al 2009) and WAT-1 (Franck et al 2008) tools but not in SWS. It is to the nurses' credit that they noticed this behaviour in withdrawing patients and recognised it as part of the constellation of withdrawal. In this respect, they were demonstrating "pattern recognition", a feature of expert judgement and decision-making (Berner and Graber, 2008, p. S12). A robust scoring tool for withdrawal syndrome must limit item content otherwise the resulting tool would model many clinical conditions and result in low specificity for withdrawal. The consequence of limiting signs, in a complex condition such as withdrawal, is that nurses can only log those signs included in the tool, and may inadvertently 'fit' other observed behaviours into the available signs. The interdependence of some behavioural signs (e.g., insomnia causing irritability) highlighted another weakness in terms of the content validity of SWS. Ensuring a common understanding requires either a clear definition of each of the items included in the tool or the exclusion of some behavioural signs on pragmatic grounds.

7.6.2 Construct validity

Construct validity of the tool came under scrutiny as a result of the cognitive challenge presented by the interpretation of behavioural signs. Where similar behavioural responses may also be a consequence of the child's underlying medical condition, their current illness or an environmental artefact, this may confound withdrawal assessment. The SWS was based on the Neonatal Abstinence Syndrome (NAS) tool (Finnegan et al

1975). However, the major difference between the two patient cohorts is in the meaning of these non-specific signs, which have much greater sensitivity and specificity for NAS in the newborn population than they do for withdrawal in the critical care population. An additional personalisation of the measure is required for critical care patients who unwittingly "score for withdrawal" by nature of their underlying or pre-existing condition; an outcome described as a false positive or Type 1 error in statistical testing. Patients with severe neurological disability may be excluded from tool validation studies for psychometric convenience (Ista et al 2009). The vignette patient represented such a child and these findings suggest that assuming nurses will modify their assessment in light of underlying behaviours, is wrong. The ipsative nature of withdrawal scores in some critical care patients is a phenomenon also recognised in self-assessment pain scoring in children (Connelly and Neville, 2010). This means changes in scores in the same patient, over time, may provide a more personalised assessment for withdrawal, and minimise unnecessary treatment, rather than attempting to identify standardised cut-points for pharmacological intervention.

Tools are only ever tested under ideal conditions, whereby the tool developer has dictated the way in which the tool is applied through a robust training programme for participants. Once a tool becomes established, it is not unreasonable to imagine it will be applied differently by different users. This is an example of the false consensus effect, whereby tool developers make inaccurate assumptions about the performance of the users applying their tool. They expect the tool to be applied as they have designed it to be applied and this may not be true for the inexperienced or untrained user (Roland et al 2010).

7.7 Limitations

Study 4 has a number of limitations. This was a small sample of nurses from one hospital who volunteered for the study, so may not have been a representative sample. However, whilst the cognitive interview technique is unique in revealing cognitive processes in participants, results are not generalisable to a wider population. The use of a developmental vignette under experimental conditions to reproduce the conditions of clinical practice and illuminate the judgements and decisions nurses make may be flawed. Equally the efforts made to minimise observation bias and prompt typical levels of

reasoning may have been unsuccessful. Nonetheless, the range of diagnoses in the results and the evidence of a range of cognitive errors both suggest that research participant effects were minimised. The interviewer works as a nurse specialist in the hospital where the study took place and was known to the nurses participating in the interviews; this relationship may have been a source of bias

The bedside treatment schedule of withdrawal in the study hospital includes guidance to stop weaning with SWS scores between 3 and 6. The treatment schedule was not presented or discussed but it may be that some nurses recalled that a score of 5 linked to guidance to stop weaning. The number of withdrawal diagnoses in V1 may have been influenced by the fact that the participants were aware that the study was addressing sedation withdrawal; this might have created a diagnostic strategy of 'going for the obvious' that may not reflect typical decision-making.

7.8 Conclusion

This study using cognitive interviews with vignettes has provided insight into nurses' judgement and decision-making in a complex and ambiguous clinical situation. Focussing on the whole decision-making process (noticing, interpreting and responding) identified a significant cognitive burden and the potential for cognitive error at each stage. Nurses perceived and interpreted the scenario differently and gave a range of diagnoses in response to the same clinical information. The conditions necessary for withdrawal to be a possible diagnosis were not considered consistently. Nurses also demonstrated a blurring of boundaries between different behaviours, in an inadvertent effort to fit behaviours to the available signs. These findings do not support the existing approach to withdrawal assessment.

Key areas for improvement are in recognising the clinical context necessary for withdrawal and minimising the use of biases and failed heuristics. A structured approach to withdrawal assessment which focuses on the core features of withdrawal rather than the identification of ambiguous behaviours may reduce the likelihood of cognitive errors.

Conclusions to Part 3: Integration of findings from Study 4 with Parts 1 and 2.

Study 4 showed that the stages of decision-making aligned with different aspects of the withdrawal assessment and illuminated the potential chances for cognitive error. This discourse will consider two ways in which the findings of this study illuminate the existing approach to withdrawal. The first consideration is the extent to which the existing approach to withdrawal assessment is underpinned by the principles of decision-making. The second consideration is the integration of the stages of decision-making into the propositional model of the causal relationship between factors linked to physical dependence and withdrawal.

The existing approach to withdrawal assessment and decision-making

The effort required to interpret the child's behaviours was a salient finding from a decision-making perspective. The SWS tool exists to aid diagnosis, but inadvertently focuses effort on the inconsistent, unique and equivocal presentation of withdrawal rather than the more consistent core features of withdrawal. Cognitive effort was expended in both deconstructing the child's presentation into component behaviours to fit the tool and in interpreting the meaning of these equivocal behaviours. What might have naturally been System 1 intuitive thinking of pattern recognition is changed to effortful System 2 thinking at the detriment of considering whether the conditions for withdrawal had been met. The consequence of focusing the cognitive effort on this one equivocal aspect of withdrawal assessment is to "effectively blind" (Kahneman 2011, p34) nurses to other aspects of the assessment.

Consider the intuitive System 1 observation of "This child is behaving like they might be withdrawing." The next step depends on which decision-making system is engaged. One option is to apply the SWS tool to see if you are right, a biased process which confirms what you already suspect. The alternative option, which is assumed rather than supported by the current approach, is to consider whether the core features of withdrawal exist. This second approach acknowledges the possibility of other causes for the behaviours, which initially prompted the intuitive impression of withdrawal.
The motivation for Study 4 was the finding from Study 1 that highlighted occasions when nurses undertook a withdrawal assessment when something other than withdrawal was driving the patient's behaviour. Decision-making theories explain how intuitive, System 1 thinking offers immediacy, which may be expert intuition or heuristic intuition

(Kahneman 2011). Heuristic intuition may have reflected the decision-making in the complex context of the deteriorating critically ill child, reflected by the eleven cases reported in Study 1 where withdrawal and other causes coexisted. The nurse when faced with the difficult question of 'What is the cause of the child's deterioration?' unintentionally answers an easier question – 'Does the child score for withdrawal?' Encouraging the System 2 thinking of deliberation (Kahneman 2011) supports the nurse to ask the pertinent question; 'Are the conditions right for withdrawal to be a possible cause of behaviours?'

Integrating the stages of decision-making into the propositional model

The conditions for withdrawal have been discussed previously in the literature review (Chapter 2), Study 1 (Chapter 4) and Study 3 (Chapter 6) and a model of the relationship between these variables has been introduced in this thesis. This model was reviewed in light of the stages of decision-making illuminated by Study 4, to examine how these stages might be integrated in the model (Figure Part 3.3).

The first condition is the onset of physical dependence. The risk of physical dependence is 50% after 5 days of continuous sedative drugs, but may occur sooner at higher doses (Ista et al 2007). If physical dependence is suspected, then the next condition is a reduction in the drug or drugs, whether planned or inadvertent, which links to the onset of a behavioural response indicative of withdrawal.

The noticing phase of decision-making involves perception of the risk factors for physical dependence, followed by interpreting the likelihood of dependence. The likelihood of dependence should determine the speed of weaning. The cycle of decision-making then continues recursively, with a response to the speed of weaning being an indicator of how well the child tolerated weaning. No behavioural response supports the chosen rate whereas a behavioural response indicative of withdrawal indicates the speed of weaning is too fast and contributes to the interpretation of the risk of physical dependence and influences the response in terms of modifying the speed of weaning.

This model demonstrates how the desired pattern of reasoning when determining the cause of equivocal signs follows a top-down deductive approach based on the premise or condition of physical dependence. By contrast the abductive bottom-up style of heuristic intuition which seeks to find the simplest explanation for an observation may result in an

erroneous diagnosis. This discourse will be expanded upon in the conclusions section in Part 4.

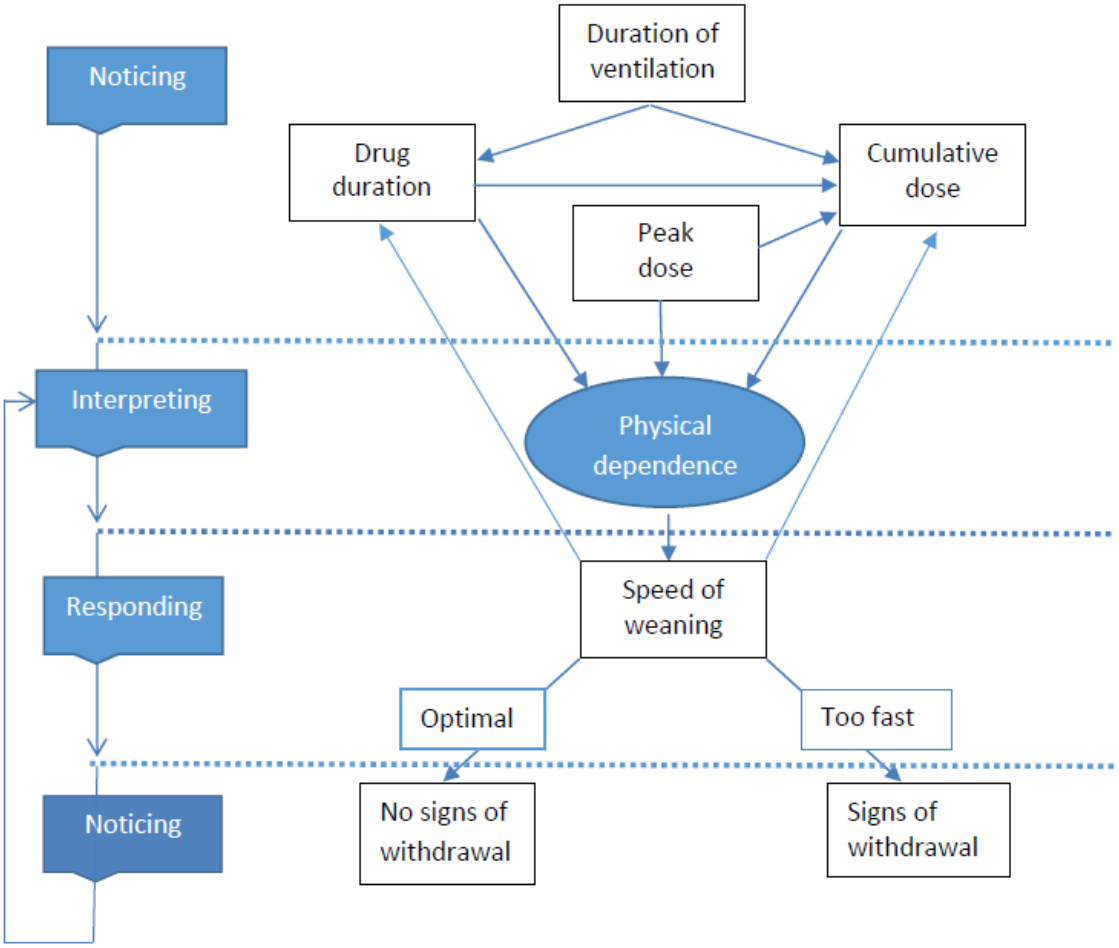

Figure Part 3.3 Propositional model linking the stages of decision making performed during a withdrawal assessment to the proposition of the causal relationships between factors linked to physical dependence and withdrawal syndrome.

Part 4 The parent perspective

This section presents Study 5 (Chapter 8) and Study 6 (Chapter 9) that explore the parent perspective of withdrawal in critically ill children. In the absence of existing evidence, these studies were exploratory in design; evolving abductively in response to the data collected.

The hypothesis that parents contribute a novel and valuable perspective to withdrawal assessment relies on two assumptions;

1. Parents recognise behaviour changes indicative of withdrawal in their critically ill child, and
2. Parents are willing to participate in their critically ill child's withdrawal assessment.

Study 5 was designed to answer the first assumption; to identify parents recall of, and distress evoked by SWS withdrawal signs during their child's sedation weaning.

Study 6 was designed to fulfil two aims;

1. Identifying parental willingness to participate in the withdrawal assessment.
2. Exploring the parents experience of their child' withdrawal.

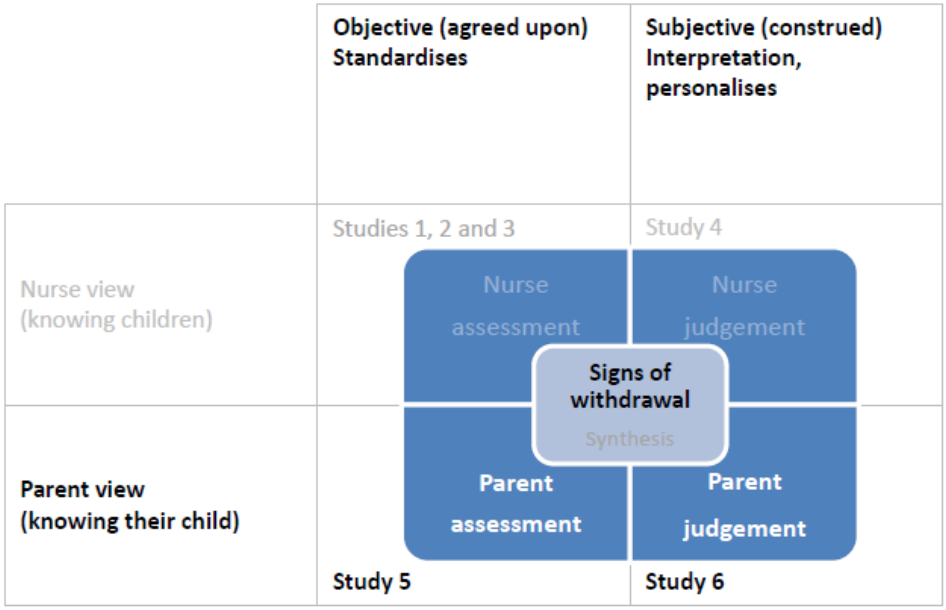

Figure Part 4.1 The conceptual framework showing the contribution of Studies 5 and 6

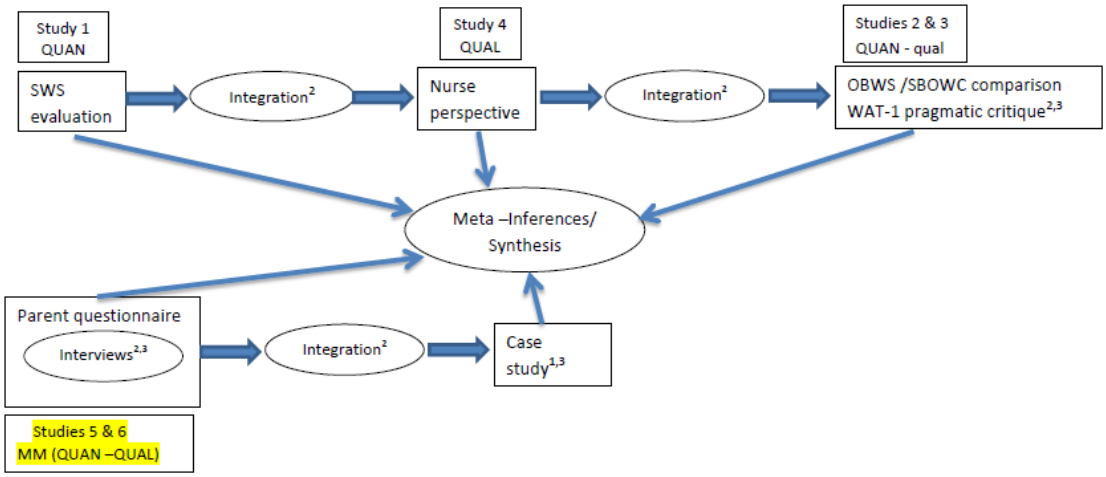

Figure Part 4.2 The thesis map showing Studies 5 and 6 highlighted

Chapter 8: Study 5: Mixed methods study of parent's recollection of, and distress evoked by, signs of withdrawal in children aged less than 5 years.

8.1 Introduction

In the researcher's clinical role overseeing the management of sedation withdrawal in critically ill children, seeking the parent's opinion about trends in their child's behaviours aids clinical decision-making. This anecdotal evidence of the value of the parent perspective underpinned the design of a study to examine parents' recollection of, and distress evoked by signs of withdrawal.

8.2 Background

The theoretical basis for the assessment and management of withdrawal syndrome is sparse. As a consequence, there is little evidence to delineate withdrawing and not-withdrawing patients. Some authors refer to clinically significant withdrawal symptoms, requiring administration of rescue medication, but it is not clear how this is construed (Franck et al 2012, Grant et al 2012, Curley et al 2015). In adults, the diagnostic criteria for drug withdrawal describes a behavioural change that causes clinically significant distress of impairment (DSM, 2013). These terms imply a sub-syndromal category of withdrawal, where withdrawal signs may be present but not to an extent that is deemed to require pharmacological intervention. There is evidence in the tool development studies that such a cohort exists (Franck et al 2012, Ista et al 2013). When undertaking withdrawal assessments in conditions of uncertainty, there is evidence that nurses may stop weaning sedation as a cautionary measure, despite no evidence of a worsening trend (Craske et al 2017). This published paper reports the findings from Study 4 (Appendix 7).

There is an assumption that nurses elicit the view or opinion of parents during the withdrawal assessment on PICU (Harris et al 2016, Ista et al 2013): in pediatric delirium, the opinion of caregivers is sought to assist in evaluation of the child's behaviour (Schieveld et al 2009). Nurses report that they seek the parent's opinion to assist in the interpretation of a child's withdrawal behaviours (Craske et al 2017), but the parents

perspective has not been explored. It is not known whether parents recognise behaviours indicative of withdrawal in their critically ill children and if so, how distressing these behaviours are from the parents' perspective.

8.3 Aims of the study

The *a priori* aims of this study were to

- Examine the parent perspective of withdrawal by examining recall and distress evoked by SWS signs.
- Triangulate SWS data and nursing notes with the parent perspective to determine likelihood of withdrawal at the time of the highest SWS score.

A further aim evolved in response to the findings from Study 1, to

- further evaluate the SWS tool by examining the item content and the influence of differential diagnoses at the time of the highest SWS score for the patients in this study.

8.4 Objectives of the study

The specific objectives were to;

1. Explore parental recall of behavioural signs consistent with withdrawal syndrome in their critically ill child.
2. Explore the parental view of how distressing these behaviours are to observe.
3. Compare parental recollections of items with those recorded prospectively by nursing staff at the time of the highest SWS score.
4. Retrospectively categorise the likelihood of withdrawal at the time of the highest score
5. Identify differential diagnoses in cases where the likelihood of withdrawal was possible or unlikely.

8.5 Method

A convergent mixed methods design (questionnaire and retrospective chart review) was employed to address the aims of the study. A questionnaire was used to elicit parent recall of SWS signs and the distress these signs evoked. The convergent design enabled integration by merging of results from the questionnaire and from a retrospective chart

review, so that a comparison could be made and a more complete understanding of the parental perspective could emerge than what was provided by the questionnaire data alone.

These data sources were triangulated in two ways;

1. Parent recall of SWS signs was compared and contrasted with their child's highest SWS score.
2. The distress evoked by the recalled signs was validated as a reflection of their child's withdrawal, rather than in response to clinical deterioration or other differential diagnoses, by triangulation with clinical records.

8.5.1 Study population

The study was conducted in a large children's hospital in the Northwest of England. Data were collected between December 2012 and December 2014. Parents whose child had completed sedation weaning during their inpatient stay were recruited. A purposive sample frame was used to select parents with two characteristics; the nature of the circumstances of the PICU admission (planned or emergency) and previous experience of PICU. It was anticipated that these two features may impact on parents' recollections and views of how distressing they found their children's behaviours to be. This produced four groups;

- Elective admissions with no previous experience of PICU
- Elective admission with previous experience of PICU
- Emergency admissions with no previous experience of PICU
- Emergency admissions with previous experience of PICU.

Inclusion criteria were parents of children aged birth to five years. This age range encompasses the majority of PICU admissions; the majority of whom are preverbal or non-verbal, so represent a group of patients for whom parental experience is a proxy measure of the child's experience. Exclusion criteria were parents of children aged six years or older and parents where neither parent was sufficiently proficient in English to complete the questionnaire.

8.5.2 Procedure

Parents were invited to participate in the study during their child's hospital admission, after weaning of sedation had been completed and they were no longer under the care of the Pain and Sedation Service overseeing sedation withdrawal. Potential participants,

identified by the Pain and Sedation Service were approached by a member of staff not directly involved in the child's care and provided with verbal and written information about the study. Written consent was gained from parents who agreed to participate by the researcher (See Ethics section later).

A questionnaire was developed to collect data on parents' recall of and distress evoked by the component signs of withdrawal in the Sedation Withdrawal Score (SWS), when their child was withdrawing. The twelve SWS signs were listed and additional descriptors were included for terms which might be perceived as unfamiliar (Appendix 8). Parents identified their recall of the sign by circling one of three responses; yes /no / don't know. For each sign recalled, the parents also rated how distressed they had felt, when seeing their child display that behaviour. This was identified using an 11-point Likert scale of 0-10 (0 = not distressing, 10 = extremely distressing). Face and content validity were checked prior to data collection, by pilot-testing the questionnaire on two parents who met the inclusion criteria, to ensure comprehension of the terms used and acceptability. One questionnaire was completed per child. The questionnaire was labelled with hospital unique study number to allow triangulation with nursing and medical documentation of withdrawal behaviours. Completed questionnaires were sealed in a pre-addressed envelope and returned via hospital mail or collected from the ward.

8.5.3 Measures

8.5.3.1 Parent characteristics

Demographic data were not collected from parents who participated in this study. This was an exploratory study and insufficient is known about the relationship between parental characteristics and parental participation in PICU care to identify sample characteristics, which may impact on the generalisability of findings.

8.5.3.2 Patient characteristics

The following data were collected about the patient from nursing and medical records; age, gender, underlying condition/s, the reason for PICU admission, the date and time of extubation and the duration of PICU admission. The date and time of the highest SWS score was identified and recorded along with the component items and their severity scores. Data were recorded on an Excel spreadsheet.

8.5.3.3 Likelihood of withdrawal

An indication of the likelihood of withdrawal at the time of the highest score (probable, possible, unlikely) was made using the same method described in Study 1; an adaptation of the WHO-UMC causality assessment criteria for adverse drug reactions (WHO-UMC) (Table 8.1).

Table 8.1 Classification of the probability of withdrawal, adapted from ADR causality tool

Probability of withdrawal	Physical dependence possible	Temporal relationship with change in dose	Absence of differential diagnosis
Probable	Yes	Yes	Yes
Possible	Yes	Yes	No
Unlikely	No	No	No

The temporal relationship was defined as any reduction or stopping of sedative or opioid drugs in the 72 hours prior to the highest score. Differential diagnoses were defined as any other concomitant causes for the behaviours documented in the highest withdrawal score. Data regarding drug administration and the child's clinical condition were collected from nursing and medical records.

8.5.4 Analysis

The questionnaire results were analysed using descriptive statistics, including median and interquartile range. The pragmatic approach of triangulation was taken to demonstrate these findings were not due to other underlying causes.

A comparison of the frequency of parent and nurse-reported SWS behaviours was made in an attempt to establish some degree of concordance, and thereby validate the parents reporting of behaviours as signs of withdrawal.

Assigning a retrospective probability of withdrawal in this study legitimised the parents' experience and view of withdrawal, by ascertaining the extent of uncertainty at the time of the highest score, in case the child's clinical instability or deterioration was driving the distress rating, rather than withdrawal.

The further evaluation of the current approach to withdrawal assessment, included analysis of the highest SWS scores in terms of frequency of presentation of component signs and the cumulative contribution of each sign to the highest scores across study patients.

8.5.5 Ethics

The study was approved by the Liverpool East Research Ethics Committee, REC number 12/NW/0681.

Ethical issues pertinent to this study included minimising the risk of coercion, maintaining confidentiality and protecting anonymity. These issues were covered in the participant information leaflet (PIL) (Appendix 8). The researcher's clinical role as a member of the team that oversees sedation weaning meant she may have been known to parents, prior to their participation in the study. To minimise the risk of coercion, parents were not approached until sedation weaning had been completed, so the researcher's possible clinical involvement with the child was complete. The initial approach to the parents was also made by another member of staff; either the nursing shift co-ordinator or another member of the Pain and Sedation Service. Information provided to potential participants included verbal information about the purpose of the study, and assurances of confidentiality, that participation was voluntary and that non –participation would not affect their child's care. The PIL reinforced the mitigation of these ethical issues in writing, provided assurance that the study posed no risk to the child and identified the process for raising any concerns about any aspect of the study. The questionnaire (Appendix 8) was included with the PIL, so that parents could see what their potential participation entailed. Written consent was gained from parents who agreed to participate by the researcher.

8.6 Results

Twenty parents completed the questionnaire (Table 8.2). For ten parents, this was the first time their child had been admitted to PICU; five were planned admissions and five were emergency admissions. Of the ten parents with previous experience of PICU, seven admissions were planned and three were emergency admissions.

Table 8.2 Parent characteristics by nature of PICU admission and previous experience.

	First PICU admission	Previous PICU admission
Elective admission	5	7
Emergency admission	5	3

8.6.1 Patient Characteristics

The children, whose behaviours were ranked by their parents, ranged in age from 27 days to 44 months at the time of their highest SWS score (Table 8.3). Seventeen patients (85%) were aged less than 36 months, 13 patients (65%) were aged less than 12 months. Twelve patients (60%) were male. This sample is representative of the European PICU population (80% < 36 months, 50% <12 months, Schieveld 2013).

All planned admissions (n=12) were post-surgery (cardiac surgery n=11, general surgery n=1). Most emergency admissions (n=8) were due to respiratory infections (n=5), (bronchiolitis n=2, lower respiratory tract infection=2 and adenovirus n=1). Other reasons for admission were diaphragmatic hernia (n=1), undiagnosed cardiac condition (n=1) and sepsis (n=1). The median (IQR) length of stay on PICU was 19.5 (11.5-33) days. The median (IQR) highest SWS score recorded was 9 (8-10).

8.6.2 Recall of SWS signs

Parents recalled a median (IQR) number of 6 (5-7) SWS behaviours during their child's withdrawal (Table 8.4). In their ranking of SWS signs, 'insomnia' and 'irritability' were recognised most frequently (n=18), followed by 'sweating' (n=14), 'diarrhoea' and tremor' (n=12), 'respiratory distress' (n=10), 'sneezing' (n=9), 'vomiting' (n=8), 'fever' and 'high pitch cry' (n=6), 'hypertonicity' (n=5) and 'convulsions' (n=2).

Most parents (n=15) were confident about their recollection of SWS signs, providing definitive responses. Five parents were less sure and responded with "don't know" in relation to two or more of the items listed. These items were sweating (n=1), diarrhoea (n=3), respiratory distress (n=2), sneezing (n=1), vomiting (n=1), fever (n=2), high pitch cry (n=2) and hypertonicity (n=2). Each of the four groups defined by nature of admission and previous experience of PICU were represented in the parents who responded "don't know.

8.6.3 Distress caused to parents

Most items (n=11) were moderately (median scores 5-7) or severely (median scores 8-10) distressing to observe; only sneezing was not distressing (median 0) (Table 8.5). Ranked from most distressing to least distressing were convulsions, respiratory distress, irritability, tremor, high pitch cry, hypertonicity, insomnia, fever, sweating, diarrhoea and vomiting. It is noteworthy that the least prevalent sign was also the most distressing sign.

Nine parents gave one of more SWS items a maximum score of 10. Three parents represented the "planned/previous" group; the remaining six parents were spread evenly across the other three groups. Two parents gave a maximum score of 10 for more than half of the items they recalled; these parents represented the "planned/ previous" and "emergency/ 1st" groups.

8.6.4 Likelihood of withdrawal and differential diagnoses

The likelihood of withdrawal at the time of the highest score was classified according to the adapted ADR causality assessment tool (Table 8.1). Withdrawal was classified as probable in 13 patients, possible in 6 patients and unlikely in 1 patient. In patients who were probably withdrawing (n=13), the median (IQR) highest SWS score was 9 (8-10), which matched the figures for the whole, heterogeneous sample.

In the cases where withdrawal was considered either possible or unlikely, further details regarding weaning regimes and other differential diagnoses demonstrated the complexity in distinguishing withdrawal from other causes of distress (Table 8.6). The only patient who was considered unlikely to be withdrawing had not been weaned in the 96 hours preceding the highest SWS score. Their score of SWS 7 may have been due to the effect of his underlying cardiac condition and/or an adverse drug reaction to prostaglandin. Six patients were categorised as possibly withdrawing; these patients had been weaned within 72 hours of the highest score. The presence of other differential diagnoses however, meant it was not possible to definitely differentiate the cause of behavioural distress. In two cases, where patients were weaning fentanyl (P9, P20), a bolus of fentanyl did not reduce behavioural signs, which would be expected if they were experiencing fentanyl withdrawal. In another two cases patients had tolerated weaning at a consistent rate (P4, P16), which they subsequently did not tolerate; respiratory support was increased in both cases. These four cases demonstrate clinical circumstances where, although weaning was taking place, the underlying condition may have had a greater influence on the SWS score, or on the child's capacity to tolerate the weaning regime.

Table 8.3 Patient demographics including highest SWS score and likelihood of withdrawal

	Planned/ emergency	1st/ previous	Age	M/F	Reason for PICU admission	Co-existing conditions	Number days PICU	Highest SWS score, day (D), location	Withdrawal suspected
1	Planned	1st	3 years	F	Cardiac surgery (Atrial septal defect closure)	None	31	9 D30 PICU	Probable
2	Planned	Previous	1 year	M	Cardiac surgery (RV-PA conduit)	VACTERL Association	19	8 D3 ward	Probable
3	Planned	Previous	9 months	M	Cardiac surgery (Fallots repair)	None	28	10 D5 HDU	Probable
4	Planned	Previous	10 months	F	Cardiac surgery (Cavopulmonary anastamosis)	None	98	10 D60 PICU	Possible
5	Planned	Previous	1 year	M	Cardiac surgery (RV-PA conduit)	None	10	8 D7 PICU	Probable
6	Planned	1st	5 weeks	M	Cardiac surgery (Transposition of the Great Arteries, septostomy)	None	35	8 D30 PICU	Possible
7	Planned	1st	5 months	M	Cardiac surgery (Tetralogy of fallot)	None	7	5 D6 PICU	Possible
8	Planned	Previous	5 months	M	General surgery (Roux en y)	Neurodevelopmental delay	19	10 D16 PICU	Probable
9	Emergency	1st	8 weeks	F	Diaphragmatic hernia	Congenital cardiac anomaly	104	11 D62 PICU	Possible
10	Emergency	1st	6 months	M	Lower respiratory tract infection	None	11	11 D10 PICU	Probable
11	Emergency	1st	5 months	M	Bronchiolitis	Ex 34 week premature birth	6	10 D2 ward	Probable
12	Emergency	Previous	9 weeks	M	Respiratory collapse	Congenital cardiac anomaly	20	9 D20 PICU	Probable

13	Emergency	1st	4 months	F	Bronchiolitis	Trisomy 21, Congenital cardiac anomaly, Tracheobronchomalacia,	12	10 D8 PICU	Probable
14	Planned	Previous	5 months	M	Cardiac surgery (Redo hypoplastic aortic arch)	Williams syndrome	6	8 D0 ward	Probable
15	Planned	1st	3 months	F	Cardiac surgery (Truncus)	None	40	9 D23 PICU	Probable
16	Emergency	1st	2 years	F	Adenovirus	Kabuki syndrome	20	10 D3 HDU	Possible
17	Planned	1st	27 days	M	Cardiac surgery (Transposition of the Great Arteries)	None	38	7 D27 PICU	Unlikely
18	Emergency	Previous	3 years	M	Sepsis	Cerebral Palsy, TPN dependent, Developmental Delay Tracheomalacia	13	8 D11 PICU	Probable
19	Emergency	Previous	10 months	F	Lowe respiratory tract infection	Chronic Lung Disease, Ex 26 week premature birth	29	11 D12 PICU	Probable
20	Planned	Previous	2 years	F	Cardiac surgery (Redo RV-PA conduit)	Bronchomalacia, recurrent LRTIs	19	8 D11 PICU	Possible

M=male

F= female

RV-PA = right ventricle – pulmonary artery conduit surgery

LRTI = lower respiratory tract infection

TPN = total parenteral nutrition

Table 8.4 SWS signs recalled by parents

	Parent																				Y (✓)	No (x)	?
SWS sign	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20			
Insomnia	✓	✓	✓	x	✓	x	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	18	2	0
Irritability	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	18	2	0
Sweating	✓	x	✓	✓	x	✓	✓	✓	✓	✓	x	✓	✓	✓	✓	✓	?	✓	x	x	14	5	1
Diarrhoea	✓	x	✓	✓	✓	✓	✓	?	?	✓	✓	✓	✓	x	x	✓	?	x	✓	✓	13	4	3
Tremor	✓	x	x	✓	✓	✓	✓	✓	✓	✓	x	✓	x	x	x	x	✓	✓	x	✓	12	8	0
Respiratory distress	x	✓	✓	✓	✓	x	x	✓	?	✓	✓	Md	x	x	✓	✓	✓	x	?	x	10	7	2
Sneezing	✓	x	x	x	x	✓	x	✓	✓	x	✓	Md	✓	✓	✓	x	✓	x	?	x	9	9	1
Vomiting	✓	x	✓	✓	✓	✓	x	?	x	x	✓	Md	✓	x	✓	x	✓	x	x	x	9	9	1
Fever	✓	x	✓	x	x	x	Md	✓	?	?	✓	Md	x	x	x	✓	✓	x	x	x	6	10	2
High pitch cry	x	✓	x	x	x	x	✓	?	?	✓	x	✓	x	✓	x	x	x	x	✓	x	6	12	2
Hypertonicity	x	x	✓	x	x	x	x	✓	✓	?	x	Md	x	x	✓	x	?	✓	x	x	5	12	2
Convulsions	x	x	x	x	x	x	x	✓	x	x	x	Md	x	x	x	x	✓	x	x	x	2	17	0
Signs recalled	8	4	8	6	6	5	6	9	6	7	7	6	5	5	7	6	8	5	4	4	? = don't know Md =missing data		
Don't know								3	4	2							2		2				

Table 8.5 SWS signs ranked by distress caused to parents

	Parent																				Distress score
SWS sign	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Median (IQR)
Convulsions								10									10				10
Respiratory distress		5	10	9	2			10		9	8				9	9	8				9 (8-9)
Irritability	6	8	8	7	2		6	10	10	10	7	10		8	9	7	5	7	10	8	8 (7-10)
Tremor	7			7	5	8	8	10	8	10		7					8	9		2	8 (7-8.5)
High pitch cry		6					8			10		8		2					9		8 (6-9)
Hypertonicity			2					9	8						9			4			8 (4-9)
Insomnia	3	9	2		2		10	10	10	10	4	10	4	10	7	7	4	7	7	5	7 (4-10)
Fever	8		3					8			5					3	8				6.5 (3-8)
Sweating	7		6	5		0	5	7	4	5		5	2	0	8	5		7			5 (4-7)
Diarrhoea	6		10	5	5	0	8			5	2	5	4			7			3	4	5 (4-6)
Vomiting	5		10	5	1	3					7		3		7		7				5 (3-7)
Sneezing	0					0		4	3		0		0	0	5		3				0 (0-3)

Table 8.6 Differential diagnoses in cases where withdrawal categorised as possible or unlikely

Patient	Withdrawal likelihood	Sedation, weaning and other possible causes of behaviours
4	Possible	Intubated, long term ketamine and diazepam at consistent doses for the last 3 weeks. Chloral reduced daily for the previous 7 days. No changes for the following 6 days. Weaning ventilation support, previous 12h alternating between BIPAP and CPAP.
6	Possible	Increased work of breathing, ventilation support increased from CPAP to BIPAP, resolving sepsis. Fentanyl weaned and stopped 90h before. Midazolam changed to diazepam 6 days ago, reduced 48h before. Vomited diazepam dose prior to high score, so given IV diazepam, lungs wet, diuresis, settled.
7	Possible	Midazolam stopped 36 h previously after 4 ½ days. Fentanyl stopped a few hours earlier. Insomnia previous night. Possible episode of Junctional Ectopic Tachycardia requiring alteration to pacemaker.
9	Possible	19h post extubation. Fentanyl weaning, bolus of fentanyl administered with no effect. Settled after diazepam (but had not been on midazolam).
16	Possible	Weaning fentanyl and midazolam at rates previously tolerated. Respiratory acidosis, commenced CPAP, pyrexial, blood cultures taken, fluid overloaded.
17	Unlikely	Cycled after 5 days clonidine and promethazine 96h before to oral morphine and diazepam. Dose unchanged. 30h post extubation. Milrinone stopped 7h previously, prostaglandin in progress, respiratory acidosis, flow increased. Clonidine restarted 66h prior due to tachycardia and pyrexia after prostaglandin restarted (possible ADRs to prostaglandin)
20	Possible	Weaning fentanyl for the previous 2 weeks with minimal signs of withdrawal. Opisthotonos, agitated. Clonidine, promethazine and ketamine unchanged. Bolus of fentanyl no effect, bolus of ketamine settled for 3 mins. Diazepam 0.4 mg given, settled quickly and pulse and BP recovered over the next 30 mins. Extubated previous day to non-invasive ventilation.

CPAP/ BiPAP = continuous/ bilevel positive airway pressure non-invasive ventilation.

8.6.5 Component items of highest SWS scores

Nurses documented a median (IQR) number of 5.5 (5-6) behaviours at the time of the highest score. The component items of the highest SWS scores are shown in Table 8.7. Eleven of the 12 behaviours were identified in this sample: convulsions did not feature in any of the highest scores. Insomnia, the most prevalent item, was a component of every

score and scored a maximum intensity of '2' in most (n=16) cases. Irritability (n=18) was also highly prevalent and scored '2' in most (n=15) cases. Of the two patients who did not score for irritability, one was probably withdrawing and one was possibly withdrawing. The remaining SWS signs identified, in order of the frequency they occurred were respiratory distress (n=14), diarrhoea (n=12), sweating (n=11), fever (n=8), vomiting (n=7), tremor (n=7), high pitch cry (n=7), sneezing (n=4) and hypertonicity (n=2).

The frequency at which SWS signs were recalled by parents during the course of their child's withdrawal was compared to the frequency behaviours were documented by nurses in the child's highest recorded SWS score (Table 8.8). Although not directly comparable, it was anticipated that parents would be most likely to recall their child's behaviour when the child had been most agitated or distressed; the time which was likely to also be captured by the highest SWS score. The frequencies at which behaviours were recalled by parents corresponded with nurses' documentation. The similarities between the two columns provide a degree of support for both the capacity for parents to recognise SWS behaviours in their child and the construct validity of the SWS tool.

Table 8.8 Comparison of frequency at which SWS signs were noted by nurses and recalled by parents

Frequency n (% of sample)	**Parents recall** (n=20)	**Nurse documentation** (n=20)
16-20 (76-100%)	Insomnia, irritability	Insomnia, irritability
11-15 (51-75%)	Sweating, diarrhoea, tremor	Sweating, diarrhoea, respiratory distress
6-10 (26-50%)	Sneezing, vomiting, fever, high pitch cry, respiratory distress	Tremor, vomiting, fever, high pitch cry
0-5 (up to 25%)	Hypertonicity, convulsions.	Sneezing, hypertonicity, convulsions.

Table 8.7 Component items of highest SWS scores ranked by frequency documented.

	Patient ID																				Scores		
SWS item	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	2	1	0
Insomnia	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	2	2	16	4	0
Irritability	2	2	2	2	2	1	0	1	2	2	2	2	0	2	2	2	1	2	2	2	15	3	2
Respiratory distress	0	2	2	1	1	0	0	1	2	1	2	1	1	0	0	2	2	0	2	2	8	6	6
Diarrhoea	0	1	1	0	1	1	1	2	0	2	0	1	1	0	0	1	0	0	2	2	4	8	8
Sweating	1	0	2	1	0	1	0	0	0	2	2	1	0	2	2	2	0	0	1	0	6	5	9
Fever	0	1	0	1	2	0	0	2	0	0	0	0	2	0	0	2	1	0	2	0	5	3	12
Vomiting	2	0	2	2	0	2	1	0	0	0	0	0	2	0	2	0	0	0	0	0	6	1	13
Tremor	2	0	0	1	0	0	1	2	2	0	0	0	0	0	1	0	0	2	0	0	4	3	13
High pitch cry	0	0	0	0	0	1	0	0	1	1	2	2	0	1	0	0	0	2	0	0	3	4	13
Sneezing	0	0	0	0	0	0	0	0	0	1	0	0	2	1	0	0	2	0	0	0	2	2	16
Hypertonicity	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	2	0	0	2	0	18
Convulsions	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	20
SWS score	9	8	10	10	8	8	5	10	11	11	10	9	10	8	9	10	7	8	11	8	71	39	110

The cumulative contribution that each of the SWS items made to the highest SWS score was calculated in all 20 patients (Table 8.9 and Figure 8.1). The extent of the impact that individual signs had on the cumulative score varied considerably between the greatest influence (insomnia, 20%) and the least influence (convulsions, 0%). Three signs (insomnia, irritability and respiratory distress) contributed 50 % of value of the highest scores; a further four items (sweating, diarrhoea, vomiting and fever) contributed 33% and five signs contributed the remaining 17% of the score.

Table 8.9 The cumulative contribution of the frequency and intensity rating of SWS items to the highest SWS scores.

	Insomnia	Irritability	Resp. distress	Diarrhoea	Sweating	Fever	Vomiting	Tremor	High pitch cry	Sneezing	Hypertonicity	Convulsions	Total
Score "2" (n)	16	15	8	4	6	5	6	4	3	2	2	0	142
Score "1" (n)	4	3	6	8	5	3	1	3	4	2	0	0	39
Combined score (n)	36	33	22	16	17	13	13	11	10	6	4	0	181
% cumulative contribution	20	18	12	9	10	7	7	6	6	3	2	0	100

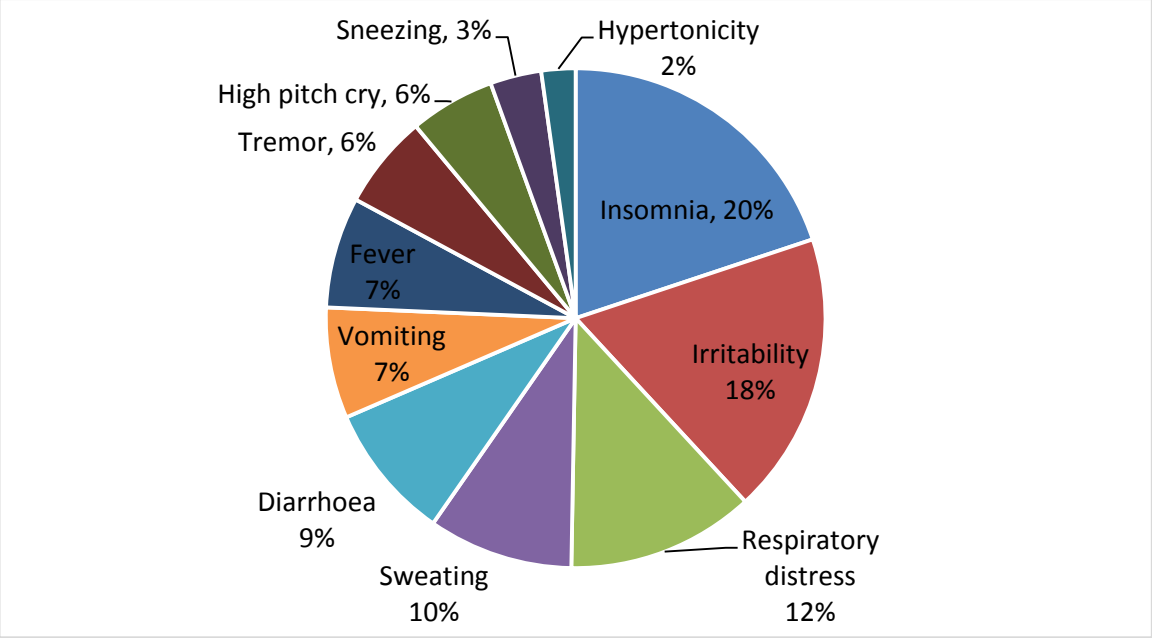

Figure 8.1 The percentage contribution of component items to the highest SWS scores in 20 patients

8.7 Discussion

Study 5 has demonstrated that parents recalled SWS signs during their child's critical illness. This was a main aim of this study, and reflects an important first step in the process of including the parent perspective in the withdrawal assessment. This study has also highlighted the distress evoked by these signs. These findings will be discussed in turn.

8.7.1 Parent recall of SWS behaviours

This is the first study to demonstrate that parents recalled their child displaying SWS signs during weaning from sedation. Most parents were definitive in their recall or otherwise of the twelve SWS signs. However, a minority were not sure about some signs. These items included sneezing, diarrhoea and sweating, these are familiar terms which suggest the lack of confidence may be simply due to recall rather than an unsolicited burden to interpret behaviours.

The similarity in findings between parents' recall of signs and the nurses' prospective withdrawal assessment at the time of the highest score shows *fit of data integration* which by confirming the results of the other, affords the results greater credibility (Fetters et al 2013). Validation of the congruence of parent and nurse assessments supports a role for parents and opposes the assumption that parents are too overwhelmed to participate in their child's care (Campbell-Yeo et al 2008). Even away from the critical care environment there is little evidence of parent participation in clinical assessment, despite parents knowing the child best (Roland 2015).

Although there may be anecdotal evidence to support the inclusion of the parent perspective in clinical assessments, there is a dearth of literature about this topic. Parental concern is a component of a minority of Pediatric Early Warning Scores (PEWS) in recognition that the person who knows the child best may improve recognition of the deteriorating child (Roland 2015). The parent perspective has been described in a primary care setting. A study comparing parental and medical perceptions of the symptoms of childhood asthma, found differences between parental reporting and clinician expectations of the influence of symptoms on perception of severity (Yoos et al 2005). Twenty percent of parents used none of the standard symptoms when describing an exacerbation of their child's asthma and even fewer (16%) reported a symptom considered to be a hallmark by clinicians. Another study about parental assessment of

pain in children with profound special needs found parents relied on knowing their non-pain child, to recognise the unique changes in response, activity and behaviour, which indicated pain (Carter et al 2002).

Distress evoked by SWS signs SWS signs varied in the level of distress they evoked and only one of the signs; sneezing did not evoke some degree of distress. Of the remaining SWS signs, the median distress ratings were in the top half of the 0-10 rating scale. That the majority of withdrawal signs evoke medium to high levels of distress for parents is a finding with clinical relevance. It is known that the child's behaviour is a source of stress for parents in PICU (Board and Ryan-Wenger 2000, Siederman et al 1997) and seeing their child suffer causes suffering in parents (deWeerd 2015). The parents' sense of helplessness can be moderated when clinicians help them to understand their child's behaviours (Ames et al, 2011). However, the provision of parent information is ranked more highly by parents than by PICU nurses (Latour et al 2011). Demonstrating that parents recognised and were distressed by signs of withdrawal, highlights the importance of telling parents when their child is being assessed for withdrawal syndrome.

It was expected that parents who were unfamiliar with the PICU environment or whose child had been admitted as an emergency may have had higher levels of stress, be less likely to recall their child's behavioural signs or more likely to perceive behaviours as distressing. There appeared to be no association or impact between these factors and parental capacity to either recall SWS signs or the distress these signs evoked.

8.7.2 Prevalence of SWS signs

The prevalence with which SWS signs were documented by nurses and recalled by parents was similar. The dominance of insomnia and irritability, which were the highly prevalent signs in Study 1, the SWS evaluation study (Chapter 4), was corroborated by the parental perspective in this study. This finding both supports and challenges the validity and reliability of SWS, depending on the perspective taken. The parental view provides independent, concurrent validity on the one hand, of the behavioural presentation at the time of the highest score. However, internal consistency is unclear given the unequal contribution to the SWS score of the component behaviours (DeVellis, 2012). The three signs with the highest combined prevalence and intensity contributed as much to the cumulative score as the remaining nine signs (insomnia, irritability and respiratory distress). These signs are present in SOS (Ista et al 2009) but not present in WAT-1 (Franck et al 2008). The uneven contribution of the dominant items to the SWS score and

the absence of these items from one of the validated scales challenge the theoretical concept of withdrawal underpinning these scales (Streiner and Norman 2003). Component items are attempting to measure different underlying characteristics or factors of withdrawal; it is not clear how the dominant manifestations in one tool can be absent from another tool.

The purpose of withdrawal assessment tools is to discriminate withdrawal (from non-withdrawal), component items should be answered differently by the withdrawing group (Streiner and Norman 2003). In this small sample the use of the ADR causality assessment tool did, however, provide a measure that discriminated likelihood of withdrawal due to component criteria that were answered differently by these groups (Table 8.1). It may be that this structure provides an alternative approach to withdrawal assessment, compared with the existing approach based on manifestation alone.

8.7.3 Likelihood of withdrawal

Assigning a likelihood of withdrawal was designed to highlight the diagnostic complexities inherent in the diagnosis of withdrawal and in this study to identify the influence of withdrawal as the driver for the parent distress ratings. Three categories of withdrawal likelihood at the time of the highest score were identified retrospectively. In most cases the child was probably withdrawing, but in a third of cases the child's underlying condition may have driven the score. This finding has two implications for this study. From a scale development perspective, it challenges both the specificity and positive predictive value of SWS (DeVellis, 2012). From a parental perspective, the distress evoked by observed behaviours may have represented times when their child was clinically unstable and/or mirrored a sense of clinical uncertainty.
Further study is needed to determine why parents find these signs distressing.

8.8 Limitations

This study has a number of limitations. This was a small sample of parents from one hospital so may not have been a representative sample and results may not be generalisable. This study investigated parents' recall of their child's behaviours during weaning of sedation. However, these behaviours may have been a result of withdrawal, or the child's clinical condition, or a combination of both.

The child's highest SWS score was used to validate both parent recall of signs and to identify withdrawal as the causal diagnosis for the distressing items. It might be a flawed assumption that parent recall is most likely to reflect the time of the highest SWS score. Some parents' recollections may have been influenced by discussions with nursing or medical staff about the likelihood of withdrawal at the time the behaviours occurred. The recall and ranking questionnaire was undertaken at the earliest opportunity, once weaning was complete, to optimise accurate recall. However, there is a possibility of both false positive and negative recall.

8.9 Conclusions

Study 5 has shown that parents recalled signs displayed by their critically ill child, which were synonymous with withdrawal syndrome. Although varying in the levels of distress they evoked, most signs caused high levels of distress. Parents' recall and scoring did not appear to be effected by previous experience of, or the nature of admission to PICU.

Clinical staff may be able to reduce parental anxieties with proactive information about prevention, assessment and treatment of withdrawal behaviours. Study 6 will further explore the causes of distress.

As parents recognised signs of withdrawal, they may be able to contribute to and enhance behavioural assessments during their child's stay on PICU. Study 6 (Chapter 9) also explores parents' views about participating in these assessments.

Chapter 9: Study 6: A multiple case study of parents' experiences of their child's withdrawal syndrome

9.1 Introduction

A role for parents during the assessment of withdrawal has been presented in the literature and/or assumed by healthcare professionals (Chapter 7), but the parent perspective has never been studied.

Using a nested sample of parents from the participants of Study 5, a multiple case study approach sought to explore parents' experiences of withdrawal and acceptability of a potential role for parents in withdrawal assessment. Triangulation of data using nursing and medical record served to explain the parents' perspective and provide an in-depth understanding of the case. Parent interviews were matched to the questionnaires from the previous study, with withdrawal assessments of the child and documentation in the child's medical and nursing records, with the overarching aims of exploring parental recognition of withdrawal signs, their feelings about their child's withdrawal event and their willingness to participate in withdrawal assessments.

9.2 Aim of the study

The study aimed to explore parents' perceptions of their child's withdrawal and the acceptability of a potential role for parents in withdrawal assessment in light of their actual experiences.

9.3 Objectives of the study

The specific objectives of the study were to:

1. Identify what behaviours parents recognised whilst their child was withdrawing and compare with behaviours documented in clinical data.
2. Ascertain whether parents would be willing to participate in withdrawal assessments during their child's critical illness.

3. Explore parent's experiences and perceptions of having a child undergoing withdrawal syndrome.
4. Explore how parents felt about seeing their child suffering withdrawal.

9.4 Method

Case studies can be explanatory, exploratory or descriptive and can be used to capture the complexity, temporal changes and context of a case (Yin 2009). In this study, the a priori rationale for the case study approach was to explain the parent perspective and experiences of withdrawal, using a combination of qualitative and quantitative methods. This approach fits with the pragmatic approach as "… case study is defined by interest in individual cases, not by the methods of inquiry used." Stake (2003, p 134).

A longitudinal approach was taken encompassing the time period of 72 hours before and after the highest SWS score. This timeframe allowed insight into the possible causes for the behaviours; identifying the likelihood of withdrawal or other differential diagnoses, and response to interventions or changes to the weaning regime. Within-case analysis provided validation of the individual parent perspective in each case (Yin 1994). Cross case analysis synthesised the shared components of the parent experience (Yin 1994). During the course of the study, the design evolved iteratively due to integration at the interpretation level (Fetters et al 2013). Integration with the findings of Study 1 and abductive reasoning led to a collective case study approach (Stake 2003). Hammersley defines abduction as "the development of an explanatory or theoretical idea, resulting from close examination of particular cases" (2005, p5). The nascent utility of the adapted ADR causality assessment tool, as a withdrawal causality assessment tool (W-CAT) was demonstrated in Study 1. Using abduction, the emergent theoretical proposition was that the contingency of sedation withdrawal is better described by the probability terms in W-CAT, than the dichotomy of WAT-1 and SOS.

Case studies can be undertaken to test such an explanatory framework, or proposition (Thomas and Myers 2015). The unit of analysis, or subject of the study is the case. The object of the study is the analysis, or theorisation by which the case is explicated.

the theme on which the study intends to shed light, in this case withdrawal assessment,

A multiple case study design was used in recognition of the heterogeneity of the sample, which was highlighted in the findings of the previous study.

This methodology utilises multiple sources of information (Creswell, 2013). In this study, these sources included parent interviews, the questionnaire responses from Study 5 and

nursing and medical observations and documentation. The use of multiple sources increases rigour by contributing to completeness of data and by demonstrating concordance between sources (Knafl and Breitmayer 1991).

9.4.1 The interviews

A pragmatic approach was ideally suited to this study, using a descriptive qualitative approach and thematic analysis. The researcher sets aside, or brackets their own beliefs and perceptions to facilitate an open approach to the parents lived experience of withdrawal and elicit rich and descriptive data. The participants' children may have been patients of the interviewer prior to recruitment to the study, so the interviewer may have been cognisant of the course of the child's weaning and withdrawal. Fundamental to the bracketing of these experiences was the acknowledgement that the parent and clinical perspectives of a shared experience may be fundamentally different; both perspectives are valid and with neither having supremacy over the other. The conceptual framework values the diversity of views. This framework contends that these multiple perspectives and the richness of data they afford enhance the rigour of the study findings.

The etic (outsider) and emic (insider) perspectives are assigned in relation to the expertise and knowledge of the individual child rather than expertise and knowledge of sedation withdrawal. In this respect, the etic view is assigned to the researcher and the emic view to the parent, as the expert of their child. This approach is congruent with pragmatic ontology, which holds that truth and reality are subjective constructs, which vary depending on the perspective through which they are experienced.

9.4.2 Study population

This study followed on from Study 5 (see Chapter 8). Parents who completed the questionnaire were then given the option of a follow-up interview to discuss their experiences further by ticking a box at the bottom of the sheet. Inclusion and exclusion criteria, study setting and period of data collection were the same as described in Study 4. Purposive sampling was used again to select parents for interview with both prior PICU experience and no prior experience, elective and emergency admissions.

9.4.3 Procedure

Interviews took place at the child's bedside or in a quiet room adjacent to the ward, according to the parents' preference after weaning had been completed and prior to their discharge home. This time frame aimed to minimise recall bias by interviewing

parents as soon as weaning was completed. A semi-structured interview protocol was constructed to meet the aims of the study. During the development stage of the study, the researcher presented an overview of the study to a parent support group at the local branch of the Children's Heart Federation. The purpose was to gain feedback regarding the acceptability of the study design and face validity for the proposed interview questions from parents who had experienced PICU care after their child's cardiac surgery. Parents supported all aspects of the study discussed.

Pre-determined interview questions covered aspects of withdrawal assessment, where responses would confirm or refute the proposed participation of parents in future assessments: parents were asked about their recognition of and feelings evoked by behaviours displayed by their withdrawing child and their views on the option of including the parental perspective in future assessments (Table 9.1). Questions exploring the parent perspective were open –ended in order to prompt discussion, to afford the opportunity to explore themes or responses further and to allow participants to discuss and raise issues that had not been considered. The existing approach to withdrawal was evaluated by examining parent's experiences of their child's withdrawal syndrome, ascertaining the relative impact of this aspect of their child's critical illness and the extent to which they were aware of or had been involved in withdrawal assessments.

9.4.4 Ethics

Ethical approval was granted by the Liverpool East NHS Ethics committee (12/NW/0681). Parents volunteered to participate in this part of the study by ticking a box at the end the questionnaire. This method of recruitment allowed parents to self-select as potential participants for the second, more in depth phase of the study after completion of the brief questionnaire. Whilst this approach minimised the risk of coercion, parents were assured they could withdraw from the study at any time. The approach to maintaining confidentiality and protecting anonymity was described in the previous study. In addition, parents were informed that any names mentioned in interviews would be removed during transcription.

Consideration was given to the risk that parents might get upset when recalling their child's critical illness. If this occurred, the interview would be paused and opportunity given to continue after a suitable break or stop the interview. Additional support from their child's clinical team was also offered. Written information about these issues was contained in the participant information leaflet (PIL). Written consent was gained from

parents who agreed to participate by the researcher in audio-recorded interviews (See Appendix 9 for study paperwork including information leaflets and consent forms).

Table 9.1 Interview guide

1. How is [child's name] getting on now?
2. Please tell me about why [child's name] was admitted to Intensive Care.
3. Please tell me about what sedation [child's name] was given. What were you told about the drugs? (and who told you this)?
   If not mentioned in response to this question: Were you told about weaning or withdrawal?
4. Thinking back to when [child's name] was in Intensive Care, please can you tell me about their withdrawal and what symptoms s/he had. Take your time and tell me as much as you can remember. I am interested in the little things you might not think are important. [The researcher will write down the symptoms on small cards]. When did you become concerned? What were the first things you noticed about [child's name]?
   [After the parent has completed their description, the researcher will show them their completed questionnaire].
5. Apart from the symptoms you've already described, did [child's name] have any other symptoms?
6. For any symptoms identified in Q4 or Q5; what is your description of each of these symptom in your own words?
7. How did you feel about seeing [name of child] withdrawing? How did it compare with other stressful aspects of [child's name]'s hospitalisation?
8. Using cards with [child's name] symptoms, could you rate each of these symptoms on a ladder? Put the worst one/s at the top of the ladder and the less distressing ones further down.
9. Your child's nurse would have scored [name of child] four times a day for withdrawal.
   a. Was this score or [name of child]'s symptoms discussed with you?
   b. Was there a discussion about how [name of child]'s symptoms would be managed? Were you involved in this discussion?
   c. Who talked to you about sedation withdrawal while you were on ICU?
   d. How would you feel about participating in the withdrawal assessment in partnership with the nurses caring for your child?
10. Is there anything else you want to tell me about you and your child's experiences, that you feel is important, and that we haven't covered already?

9.4.5 Data analysis

The interviews were professionally transcribed and checked by the researcher for accuracy and completeness. Quantitative data were analysed using descriptive statistics. The median and interquartile ranges were calculated for the frequency of withdrawal sign recall across the sample and the number recalled per participant. In Study 5, concordance between the frequency of signs in the highest SWS score and parent recall had validated parent reporting of SWS signs. In this study, parent recall of non-SWS signs was triangulated with nursing and medical notes, in order to interpret the parents' recollections of their child's behaviours and characterise individual experiences of withdrawal. Recall of withdrawal signs was presented as individual cases. Preference for parent participation in withdrawal assessment was presented as a percentage. Qualitative data were subjected to a thematic analysis and presented as cross-case themes (Yin 1994). Thematic analysis is not tied to a particular theoretical position, so can be applied across the range of theoretical approaches (Braun and Clarke 2006).

The steps taken in analysing the data were modelled on the phases of thematic analysis described by Braun and Clarke (2006). In the first phase; familiarisation with the data, all transcripts were read several times to obtain an overall feeling for them. Preliminary notes were made of initial impressions. Significant statements were identified from each transcript which related to the lived experience of parenting a child who was withdrawing; these statements generated the initial codes for phase two. In the third phase of searching for potential themes across the data set, shared meanings and themes emerged from the significant statements. Emergence of themes was predicated by the underpinning aim to synthesise lessons from all cases, in order to inform advances in withdrawal assessment by optimising parental participation. Validation of the themes was verified by presentation of the thematic map to a team of clinical psychologists who support children and their families in PICU, and who verified them as resonant with the concerns typical of parents with a child in PICU. This process reflecting refinement of the themes was phase four of the analysis. The fifth phase; defining and naming the themes identified one metatheme and three subthemes to the stress and challenge of being a parent of a child with withdrawal syndrome. The process of data analysis was more iterative than these distinct steps suggest, reflecting Krathwohl's (1998) account of three phases; observing [immersive reading of the transcripts], coding and interpreting, which

occur concurrently but with different emphasis throughout the study. The write-up of the study constituted the concluding phase of analysis.
Quotes from individual interview transcripts are identified by the codes P1 through to P11; a following "M" refers to mothers and "F" to fathers.

9.5 Results

Of the 20 parents who participated in Study 5, 13 parents of 11 children participated in interviews. Eleven interviews were held; six with the mother only, three with the father only and two with both parents present. Interviews lasted between 23 and 68 minutes. For five parents this was the first time their child had been admitted to PICU; two were planned admissions and three were emergency admissions. Of the six parents with previous experience of PICU, four admissions were planned and two were emergency admissions (Table 9.2). Suspected withdrawal at the time of the highest scores was "probable" in nine cases, "possible" in one case and "unlikely" in one case.
Results will be presented in three parts, starting with quantitative data, followed by the individual case studies and then the qualitative data.

9.6 Quantitative results

9.6.1 Parental recognition of their child's withdrawal behaviours

During the weaning of sedative and analgesic drugs, parents recalled a median of 10 (IQR 7-11) behaviours per patient, of which 3 (IQR 1-5) were non-SWS behaviours (Table 9.3). Parents were asked if the behaviours noted were improving or had resolved to support their association with withdrawal; the majority (n=10, 91%) did. The non-SWS signs identified by parents fitted most of the categories of signs identified in the early case reports describing withdrawal in the literature review (Chapter 2, Table 2.5); abnormal movements, communication disturbances, neurological instability, symptoms and other signs (Table 9.4). Communication disturbances were recognised by seven parents and described in different ways, but most commonly as "not recognising me" (n=3) "vacant" (n=2) and "not focusing" (n=2). Motor disturbances were recognised by four parents describing 13 behaviours, including most commonly "lip smacking" (n=3) and "moving arms about" (n=3).

Table 9.2 Patient demographics including highest SWS score and likelihood of withdrawal

Case study	Parent interviewed	Child demographics							Study number in previous study 5
		Plan/ Emergency 1st/ previous	Age	Gender	Reason for PICU admission and underlying condition	Number of days on PICU	Highest SWS score, day (D), location	Withdrawal suspected	
1	Mother	Planned 1st	3 years	Female	Cardiac surgery	31	9 D30 PICU	Probable	1
2	Both parents	Planned Previous	1 year	Male	Cardiac surgery VACTERL Association	19	8 D3 ward	Probable	2
3	Mother	Planned Previous	9 months	Male	Cardiac surgery	28	10 D5 HDU	Probable	3
4	Father	Planned Previous	5 months	Male	General surgery Neurodevelopmental delay	19	10 D16 PICU	Probable	8
5	Father	Emergency 1st	5 months	Male	Bronchiolitis Ex premature 34/40	6	10 D2 ward	Probable	11
6	Mother	Emergency Previous	9 weeks	Male	Respiratory collapse Cardiac patient	20	9 D20 PICU	Probable	12
7	Mother	Emergency 1st	4 months	Female	Bronchiolitis, Trisomy 21, AVSD Tracheobronchomalacia,	12	10 D8 PICU	Probable	13
8	Both parents	Planned Previous	5 months	Male	Cardiac surgery Williams syndrome	6	8 D0 ward	Probable	14
9	Father	Emergency 1st	2 years	Female	Adenovirus Kabuki syndrome	20	10 D3 HDU	Possible	16
10	Mother	Planned 1st	27 days	Male	Cardiac surgery	38	7 D27 PICU	Unlikely	17
11	Mother	Emergency Previous	3 years	Male	Sepsis Cerebral Palsy, TPN dependent, Developmental Delay, Tracheomalacia	13	8 D11 PICU	Probable	18

M=male, F= female TPN =Total parenteral nutrition AVSD= atrial ventricular septal defect

Table 9.3 Parent recall of withdrawal behaviours, ranked in order of the distress they evoked. (Bold = non SWS signs)

P1M	P2 (Both)	P3M	P4F	P5F	P6M	P7M	P8 (Both)	P9F	P10M	P11M
Insomnia	**Vacant**	**Uncertainty**	Convulsion	**Eyes**	Insomnia	**Sore**	Insomnia	Respiratory	Convulsions	**Not**
Irritability	**Not**	**of**	Respiratory	**looking**	Irritability	**bottom**	Irritability	distress	Tremor	**recognising**
Sweating	**engaged/**	**neurological**	distress	**down**	Diarrhoea	Insomnia	Sweating	Diarrhoea	Fever	**me**
Diarrhoea	**focussing**	**damage**	Insomnia	Respiratory	Sweating	Diarrhoea	HP cry	**Blank canvas/**	Respiratory	Irritability
Vomiting	Insomnia	**Not**	Tremor	distress	Tremor	Sweating	Sneezing	**not**	distress	Tremor
Tremor	Respiratory	**recognising**	Hypertonicity	Irritability	HP cry	Sneezing	**Stiff arms**	**communicating**	Insomnia	Hypertonicity
Fever	distress	**me**	Irritability	**Agitated**	**Looked**	Vomiting	**and legs**	HP cry	Irritability	Insomnia
Sneezing	Irritability	**Different**	**Rapid eye**	**Looking**	**dazed**		**Tongue**	Irritability	Vomiting	Sweating
Jittery	**Moving**	**baby**	**movement**	**through me**			**protruding**	Insomnia	Sneezing	**Hallucinations**
Jumping	**arms about**	Irritability	**Not**	**(not there)**			**Lip**	**Hallucinations/**	Sweating	
about	**Reaching**	Insomnia	**focussing**	Fever			**smacking**	**throwing arms**		
Distressed	**out to grab**	**Lip smacking**	Fever	Vomiting				**about**		
Hallucinations	**things**	**Jerky**	Sweating	Insomnia				**Swimming**		
Shaky	**Scratching**	**movements**	Sneezing	Diarrhoea				**movements**		
Floating	**and itching**	**Rubbing face**		Sneezing				**with arms**		
hands	HP cry	**and nose**						Fever		
Twitchy head	**Lip**	Hypertonicity						Sweating		
	smacking	Sweating								
	Dilated	Respiratory								
	pupils	distress								
	Restlessness	Fever								

P= parent M= mother F= father

Table 9.4 Non-SWS behaviours recalled by parents

Abnormal movements	Communication disturbance	Neurological instability	Symptoms	Other signs
Floating hands	Vacant	Jittery	Hallucinations	Distressed
Twitchy head	Not engaged or focussing	Jumping about	Reaching out to grab thing	Scratching and itching
Moving arms about	Not recognising me	Shaky		Dilated pupils
Lip smacking	Not focussing	Restlessness		Sore bottom
Jerky movements	Eyes looking down	Agitation		
Rubbing face and nose	Looking through me			
Rapid eye movement	Looked dazed			
Stiff arms and legs	Blank canvas/not			
Tongue protruding	communicating			
Swimming movements with arms				

'Hallucinations' were also reported by four parents. Only one of these children could verbalise and she had described to her parents, how she "was swimming with mermaids" without "mummy and daddy" and that she had been "dropped in the water with no arm-bands and she couldn't float" (P1). In the other cases the presence of hallucinations was based on parents' interpretation of behaviours suggesting visual hallucinations, including "reaching out to grab things" (P2), "sort of treading water, as if she was swimming with her hands, as if she was batting things away" (P9) and "sometimes he'd lie there and have a little giggle" (P11). Parent descriptions of signs are further reported in the case studies section of the results and in the sign synthesis chapter.

9.6.2 Parent participation in withdrawal assessments

The majority (n=10/11, 91%) of parents were receptive to the idea of active participation in the withdrawal assessment. Qualitative findings about this objective are presented in the qualitative section of the results.

9.7 Qualitative results

9.7.1 Stress and challenge of being a parent of a child with withdrawal syndrome

While the primary aim of this study sought to identify a role for parents in sharing their insider knowledge to benefit withdrawal assessments, this contrasted sharply with the dearth of communication that parents received about withdrawal: it was striking how alone and/or vulnerable parents seemed with their concerns at times. The parents described their concerns about the meaning of their child's behaviours and their occasional unsolicited participation in decisions about weaning. Parents revealed that the overall experience of parenting a child with withdrawal syndrome was stressful and challenging, and differed from other challenges presented by their child's critical illness. This sense of "**stress and challenge**" became the overarching metatheme and comprised of three subthemes (Figure 9.1);

1. Withdrawal was an unexpected part of their child's critical illness, which caused distress (***the burden of withdrawal***).
2. Parents noticed changes in their child's behaviours and did not know what these changes signified (***parents' recognition of their child's withdrawal behaviours and parental distress***).

3. ***The parents' sense of powerlessness and their preferred role in the assessment and management of withdrawal***;

Although open visiting for parents on PICU affirms the parent's place at their child's bedside, their role appears to resemble that of "passive bystander" (Glasper 2015, p73) rather than partners in care. This etic role parents experienced in practice contrasted sharply with the emic role they were assigned in the research design. The three subthemes will be presented in turn.

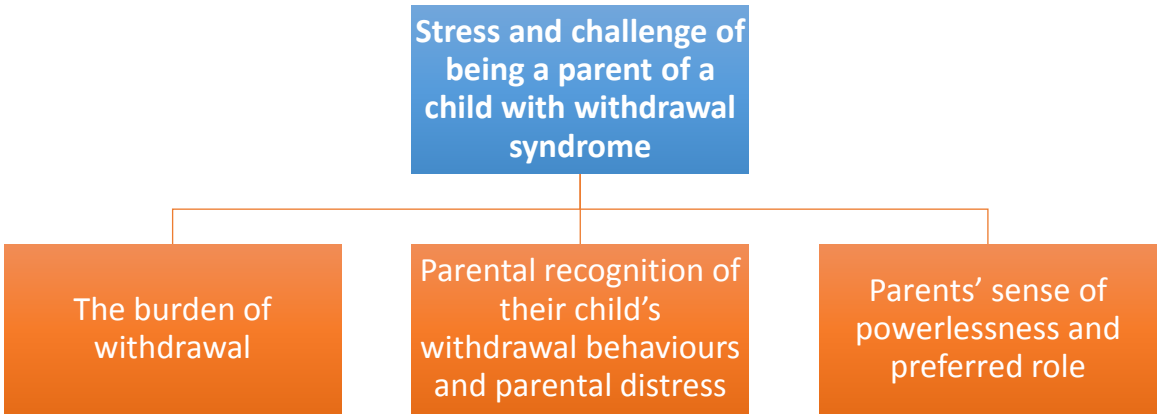

Figure 9.1 Diagram showing the metatheme and subthemes of the stress and challenge of being a parent of a child with withdrawal syndrome.

9.7.1.2 Subtheme 1: The burden of withdrawal

Parents described withdrawal as a distinct part of their child's critical illness "It's like a separate issue, like being sick again" (P5F). Another parent described how "you don't realise it can be quite an ordeal and that it brings a different set of problems" (P9F); another described it as "a horrendous 24 - 48 hours" out of a 20-day PICU admission, (P6M). Comparing withdrawal to all the other stressful aspects of their child's PICU stay, parents expressed a range of views. Although all parents found aspects of withdrawal stressful, one parent summed up the typical feeling that although distressing, it was "not in the same way as the operations and the bad news" and that the most distressing thing was "the fact you might not be taking your child home" (P1M). Other parents expressed other views during their interviews. In one case, a parent explained "I wouldn't say overall it was a mega issue, but the factors in it, like insomnia, I found as stressful as

seeing them do stuff on PICU, it was on a par with that" (P8M). Another parent explained how, in one respect "It's not as distressing as what we went through on PICU because we thought he was going to die……but it was an unexpected part." However, this parent subsequently explained that "This [withdrawal] has probably been one of the most distressing bits – this last two weeks has been a huge thing" (P2M). Similar sentiments were expressed by another parent who declared "compared to being told there was a possibility he might die, the withdrawal was nothing really," then later explained that "In the grand scheme of things, it's nothing, at least he's alive, but on a day to day basis it's everything" (P3M).

One father described how the reality of his child's suffering evoked a different response to the anguish of not knowing if his child would survive, which possibly explains the paradox;

> *"When they're on a ventilator they look very peaceful… if you look deeper they're very poorly. When they wake, you see their distress and they're struggling to breathe, you see withdrawal and pain – it's a different kind of emotion." (P9F)*

In some cases seeing their child undergo withdrawal ranked very highly in terms of stressful events during the child's critical illness. A father whose son had had multiple PICU admissions explained

> *"The thing I dread every time is withdrawal…… I dread it every time……It's just a nightmare as a parent to see your child go through that….. it's heart-breaking, it's absolutely awful" (P4F).*

However, a contrasting view was held by a mother whose son had also had multiple PICU admissions;

> *"I didn't worry about it each time……He was so poorly that everything else sort of takes over, all you want them to do is get better." (P11M)*

9.7.1.3 Subtheme 2: Parental recognition of their child's withdrawal behaviours and parental distress

Parents found some withdrawal behaviours more distressing than others. One parent differentiated between distressing signs where "you can see there is something wrong with him" (P5F) and others that were not distressing, because they were "just side effects" (P5F). Another parent described the basis upon which she perceived each sign as distressing or not, as "I understand why these sort of things happen, so they are less scary" (P2M). In some cases, the child's underlying condition dictated which signs were more distressing because "we knew some were more serious than others" (P9F). Parents expressed concern that some signs might compromise the child's recovery, as one parent explained; "Restlessness and irritability I don't like to watch, especially when you've got a child with a heart problem, you are worrying that they're going to get tired." (P2M).

Other behaviours evoked distress because they were not typical of their child, so parents were concerned about what these might mean, as one parent explained "It's just not his normal behaviour and so it's upsetting, you just don't know what's going on" (P11M). Communication disturbances ranked highly amongst these atypical signs as one mother explained, "Not recognising me was the most upsetting really, because they didn't know if there was something wrong with his brain" (P11M). This was a rational concern, because, as one parent explained, "it could be a sign of neurological problems, which is a part of what we signed on the consent" [form before heart surgery as a risk of the operation] (P2M). Despite attempts by staff to reassure parents about the temporary nature of withdrawal signs, one mother worried that

> *"it could be that it's never going to go away…..that's more distressing than insomnia, because hopefully that can be reversed"(P2M).*

Concerns about neurological injury were also shared by staff, as one parent explained; "the nurse thought there was something wrong with his brain and they took him for a scan at 9 o'clock at night, because they didn't know what was wrong with him" (P11M). The spectre of neurological damage was pervasive; "It's probably more upsetting than anything else really" (P11M). A mother of a 3-year-old daughter explained

> *"You'd speak to her and she'd just look right through you….. It was like there was nothing there; there was no light, there was no sparkle and that upset me" (P1M).*

This caused her to think; “Am I going to get the same child back? Those first few days were really worrying. That was one of my major concerns” (P1M). Another mother described how living with the uncertainty of neurological damage was “like waiting for heart surgery, it’s a massive albatross round your neck” (P3M).

9.7.1.4 Subtheme 3: The parents’ sense of powerlessness and their preferred role in the assessment and management of withdrawal

The immediate impact of altered communication on the parental comforting or nurturing role was described by other parents. One parent described; “You want your child to know who you are, that’s all you want back when they’ve been so poorly, and then you wait ages for them to realise that ‘mummy’s here’” (P11M). Another mother, who was able to lip-read, described how upset she felt when her daughter, who was still intubated and ventilated, kept repeating over again ‘I want my mummy, I want my mummy’ because “I can’t do anything to help you, I can’t pick you up” (P1M).

Subsequently, when she was first allowed to cuddle her daughter, she described how “I sat her on my knee and she just literally kicked off. It was like – I don’t want you” leading this parent to think “she really doesn’t like me” (P1M). The ineffectiveness of parental nurturing was also shared by fathers. One father summed up a sense of helplessness that was common;

> *“You can’t control it, there’s no control over it, all you can do is sit there and be with them, and watch them go through it. But there’s no comforting him, no matter what you do” (P4F).*

In addition to the sense of helplessness, not being able to comfort their child caused frustration, “you can’t do anything for him, can’t understand what he wants” (P5F), and stress; “why can’t he sleep?” “Why can’t I get him to sleep?” (P8M). One mother, whose son had been ventilated from birth, felt it was “reflecting on me, my skills as a mother, that I obviously wasn’t good enough yet at comforting him” (P6M). This made her feel “like I was a bit of a useless mother” (P6M). This sense of despair was also shared by a more experienced mother whose baby was a few months old and had previous PICU experience, who described her inability to comfort her baby as what “upset me the most” (P8M).

Parents were asked whether they were aware of, or had participated in the nurses' clinical withdrawal assessments. Awareness was mainly predicated on parental enquiry rather than nurses volunteering information. One parent explained; "You'd hear the discussions and so naturally ask what's going on" (P5F). When parents were informed about the purpose of the withdrawal assessment they reported feeling "more comfortable" (P10M) and "more relaxed" (P2M) as they were reassured that this was expected behaviour and "what other children do" (P2M). However, some parents were not informed and felt "left in the dark" (P4F) or had to be "nosey" (P8M). This was seen to be detrimental as "it's a scary time for parents" (P4F) and they would have preferred to have known about the "score… or what the next stage is going to be." (P4F)

In terms of parental participation, there appeared to be an inconsistent approach to including or involving parents in the withdrawal assessment. One father explained how although he "didn't participate in scoring," he found "it was interesting as a parent to look down the list and keep an eye out for things." (P9F). Parents acknowledged that their constant presence at the bedside gave them a different insight than the nurses into their child's behaviour. This was manifested by reporting behaviour the nurse might not have seen; "you missed this bit where she was happy and singing" (P1M) or by recognising subtle changes in behaviour because "they've [nurses] got nothing to compare to, there's no consistency, people can't work 24/7" (P9F). One parent noticed how her daughter's behaviour altered during the nursing assessment and this might lead to an inflated score;

> *"They were saying she was really agitated and he [father] disagreed. I think because nurses are in uniform, she thinks "what are they going to do?" She would only really become agitated when they were approaching her" (P1M).*

Conflicting opinions about withdrawal scores were highlighted by some parents who felt the nurse score was higher than their own view. Despite parents feeling the child had had a "really good day" (P8M), lack of familiarity with the patient meant the nurse scored behaviours on face value, despite the mother explaining "He does that anyway, it's just how he is" (P8M). The withdrawal score determines treatment changes and one parent described how they were successful in asserting their opinion; "She's not a '6' and we want that turning down tonight." (P1M)

There was also evidence that parents acted as gatekeepers to stop too many reductions occurring simultaneously. One mother described how; "I started waiting by his bed ready to pounce on anyone if they wanted to change 2 or 3 things" (P10M), after her son experienced a "very bad" withdrawal and was "just in a mess really" after a number of concurrent treatment changes to medication, sedation and respiratory support had made it difficult to determine the cause of his distress. Another mother commented on the frequency that her son's sedative infusion was being reduced at, as "Even I know it takes ages to get out of your system." This was frustratingly described as the staff being "trigger happy" in contradiction to the weaning plan suggested by the pharmacist, resulting in her son being in "a right state" (P11M).

At times, a more collaborative approach was described by parents, with evidence of both staff and parents talking to achieve a consensus about decisions to omit sedative drugs. One mother described how the nurse involved her in the decision-making;

> *"They started telling me what he [child] was scoring. One night they said "We're onto '6' and they said should we ride it out, should we not?" Whether they were really involving me or not, I felt like they were and I felt like I was part of the decision" (P10M).*

In another example, the parent appeared to instigate the discussion and described the exchange using language suggestive of an equal partnership;

> *"Last night we [nurse and mother] managed to hold off. She said "He's doing really well, he's not distressed and he's asleep." So I said "If he's asleep when it's due and not upset, can we skip that dose and see how he goes?" The nurse said "Yes, that's great." And we managed to do it" (P8M).*

One mother explained succinctly why a collaborative approach should be endorsed; "I think if parents want to be involved they should be. I'm not an expert on sedation, but I am on my son and that's the same for every parent, isn't it?" (P11M).

The majority of parents were receptive to the idea of active participation in the withdrawal assessment, but qualified that this might not suit all parents. Only one parent did not like the idea of participating and felt that being asked about the presence or absence of specific behaviours might "cause worry to a parent unnecessarily" (P7M). Other parents felt involvement would help them feel "competent" (P1M) and

"comfortable with what's going on" (P4F) or "reassured" (P6M). They felt it could assist the clinical assessment by establishing "the norm" (P8) and assist nurses if parents "keep an eye out" (P3M) for signs. However, one parent recognised the responsibility involved in participation and expressed concern about the impact of the accuracy of their assessment;

> *"I wouldn't want to score him too high and have someone put something back up that actually we are trying to get him off, or I wouldn't want to miss something that would mean he should actually have it taken back up." (P10M)*

Although one parent felt the nurses' objective view "is probably better" (P5F) and another parent recognised that they may have a "differing opinion" (P9F) to the nurse, overall a collaborative approach was endorsed, as summarised by one father;

> *"Knowledge is power and once you get that little bit of knowledge, once you've learned that little bit you can help a lot more, but you can't learn until somebody tells you what's going on." (P4F)*

9.8 Discussion

This is the first study, to describe parental perceptions of the signs and experiences of their child's withdrawal syndrome. Parents recognised behaviour changes in their children and most felt that a partnership approach to withdrawal assessment would benefit both them and their child. This study has also highlighted the suffering and distress arising from the weaning of sedative and analgesic drugs in PICU. Findings will be discussed in light of the existing literature and then consider ways to ameliorate this experience by changes in the existing approach to withdrawal assessment.

This study demonstrates that parents varied in how distressing they perceived each sign, depending on the meaning or interpretation of the sign for them. In common with the findings of other studies, behavioural signs ranked high for parental distress if they were perceived as potentially exacerbating the child's underlying condition, if they were indicative of neurological damage or if they prevented the parent from being able to comfort their child (Board and Ryan-Wenger 2000, Carter 1985, Siederman et al 1997, de Weerd 2015). These behaviours may matter more to parents than the staff and be quite

divergent from clinical causes for concern. The typical timeline for withdrawal syndrome is during recovery from critical illness, as the child's condition improves, is extubated and then discharged to the ward (Cunliffe et al 2004). This is when the child poses less of a clinical challenge to staff, and more care may be delegated to parents and is known to be an anxious time for parents, despite the obvious improvements in the child's condition that this step represents (Keogh, 2001). This study has emphasised that, even though their child is recovering, this might be a tough time for parents. The parental perspectives of distress, recall of behaviours and participation in the withdrawal assessment will be discussed in light of the broader literature on parental participation in care. Insights that that the parental perspective brings to the current approach to withdrawal assessment will also be discussed.

9.8.1 Parents' distress

Using parents as a surrogate measure highlighted how, whilst the behaviour itself might not cause physical suffering to the child, the meaning a parent attaches to the behaviour might cause existential suffering for the parents (deWeerd et al 2015). Many of the parents did not feel that they had been adequately prepared for the signs of withdrawal their child might develop. Studies have shown that parents on PICU value being kept up to date with their child's condition, having explanations for the behavioural changes they see in their child (Siederman et al 1997), being reassured of the normalcy of their child's behaviour (Ames et al 2011), and being prepared for what to expect as the child's condition progresses (Shudy et 2006). These explanations help to moderate the parents' emotional reactions. A striking finding of this study was the stress parents experienced due to uncertainty much of which, albeit an inherent feature of PICU, could potentially have been allayed by better communication between the staff and parents (Latour et al 2010, 2011). Whilst some parents in this study described instances where the nurse-parent partnership was effective and provided reassurance, this was an inconsistent feature. This may be a consequence of the extent to which individual nurses consider or dismiss a parent's perspective (Callery and Luker, 1996) or the positive or negative impact of communicating uncertainty on parental trust and confidence in the health care team (Latour 2011, Carnevale et al 2016).

The rationale for relieving withdrawal signs matches the rationale for using sedation - to minimise the child's distress and suffering (Cunliffe et al 2004). Behaviours synonymous

with distress are also known to be a major stressor for family members of adult patients, not just parents of children in PICU. In the case of delirium, family members are more distressed about the delirium episodes experienced by their adult loved ones, than the patients themselves (Breitbart et al 2002). From the parents' perspective, the alteration in the parental role (de Weerd 2015, Board and Ryan-Wenger 2000, Siederman et al 1997, Franck 2004, Carter et al 1985) also causes distress. These stressors may be exacerbated when parents are unable to hold or comfort their child in response to their physical distress (de Weerd 2015, Ames et al 2011), or do not know how to help their child (Siederman et al 1997).

9.8.2 Parents' recall of behaviours

Parents' insights and perceptions into the behavioural signs of withdrawal provide an opportunity to reflect on the behaviour content of the SWS tool. Parents recalled a range of behaviours, including all signs contained in the SWS as well as some that are not currently scored for. These additional signs included motor disturbance, which features in both the SOS (Ista et al 2009) and WAT-1 (Franck et al 2008), hallucinations, which features in SOS (Ista et al 2009) alone and one sign, communication disturbances, which does not appear in any of the three tools. The challenge in identifying hallucinations, which is a patient-reported symptom, rather than a sign, relies on interpretation of behaviour in a non-verbal patient, which may be based on the assumption that uncoordinated movements are in response to a visual hallucination, rather than simply being motor disturbance. Only one patient in this study was old enough (aged 3 years) to subsequently describe hallucinatory symptoms. Concurrent self-report is the only reliable way to confirm presence of hallucinations prospectively during a withdrawal assessment, because symptoms are experienced by the individual. This study does not provide any evidence that the parents' perspective offers any benefit over that of the staff.

Parents used a range of words, in addition to 'irritability', to describe an agitated state. These terms included 'restlessness', 'agitated', 'jittery', 'shaky' and 'scratching and itching', sometimes distinguishing between them, by identifying more than one of these behaviours in their child. The subjective nature of these terms may complicate the assessment, which the SOS tool (Ista et al 2009) has simplified by using the global term of 'agitation' to cover the behaviours 'irritable, restless, agitated, fidgety.' Using an

umbrella term that incorporates a range of similar, overlapping and subjective behaviours might enhance interpretability, but only if all terms reflect the same underlying factor of withdrawal (Streiner and Norman 2003).

Communication disturbances, recognised by more than half of parents, do not feature in any of the published withdrawal tools but were described in original case reports describing withdrawal syndrome (Hughes and Choonara 1998, Lane et al 1991, Miser et al 1986). The absence of this sign may reflect the way in which these tools were developed, based either on the Neonatal Abstinence Score (Finnegan et al 1975) where recognition of the caregiver is a redundant behaviour, or on the opinion of an expert panel of clinicians, who may overlook this behaviour compared with parents.

9.8.3 Construct validity and the meaning of behavioural signs

Scoring tools must limit their item content otherwise the resulting tool would model many clinical conditions and result in low specificity for withdrawal. However, the findings of this study suggest that recognition of communication disturbance, and the consequent loss to the patient of reassurance from parental presence, may be important behavioural indicators of withdrawal that the parent can uniquely contribute to a clinical assessment of withdrawal syndrome.

Another possibility for the presence of communication disturbances is that parents have detected signs of pediatric delirium (PD), which is not currently assessed for in the study hospital. The most common signs of PD in children under 3 years of age are impaired attention, sleep disturbance, irritability and agitation (Turkel et al 2013). Delirium may result from infection, drugs and toxins, metabolic dysfunction, malignancy or other serious illness (Turkel and Hanft 2014). Recognition of inattention in a preverbal child is complicated in a person not known to the child, such as a nurse, who would not expect to be acknowledged. A parent would be much better placed to recognise this sign than nurses.

9.8.4 Parents' participation in care

There may be an assumption that parents in PICU are too overwhelmed to participate in their child's care (Campbell-Yeo et al 2008), yet this study demonstrates that, in addition to being willing participants, they offer a unique perspective to complement the clinical assessment of withdrawal. Although parental participation in care is widely advocated,

parents' role is often described in terms of resuming their usual parenting role (Ames et al 2011, Latour et al 2005, Siederman et al 1997). This study suggests that parents may enhance the clinical assessment of withdrawal due to their privileged knowledge of their child's typical behaviour and their constant presence at the bedside, as also seen in other situations such as pain assessment (Carter et al 2002, Hunt et al 2004).

Where parental influence on withdrawal assessment and management was evident, this appeared to be in the direction of lower SWS scores, compared to nurses, and concomitant parental inclination to continue with sedative tapering. The Shared Decision-making Continuum (Koh 2010) describes five points between 100% patient responsibility for decisions and 100% physician responsibility for decisions, in the adult patient – physician relationship. Adapted for the PICU setting, these five points would equate to 100% parent-driven, nurse recommendation (predominantly parent decision), equal partners, informed non-dissent (predominantly nurse-decision) and 100% clinician-driven. These levels of shared decision-making were evident in this study although decisions were predominantly nurse-driven. If partnership in decision-making is beneficial, strategies to increase partnership should be considered. If parent-driven decisions prevent the unnecessary slowing of sedative weaning regimes, this is a demonstrable benefit of parental participation; similar to the benefits demonstrated by parent-driven decisions about the use of antibiotics for otitis media in primary care (Merenstein et al 2005) and family activation of a medical emergency team in tertiary care (Brady et al 2015).

Being present, participating in care and being kept informed of their child's condition have been shown to help parents to cope with the stress of PICU (Carnevale et al 2016, October 2014, Ames et al 2011, Shudy et al 2006, Siederman et al 1997). Evidence about what parental participation means in practice ranges from a passive role (Glasper et al 2015, Franck and Callery 2004, Simons et al 2001) through aspects of their usual caregiving role, such as washing, changing nappies and comforting the child (Latour et el 2005, Siederman et al 1997) to participation in clinical assessments (Carter et al 2002) and decision-making (Lipstein et al 2012).

9.8.5 Reciprocity in sedation withdrawal assessment

It was striking how alone and/or vulnerable parents seemed with their concerns at times.

Vulnerability describes "experiences of being unprotected and open to damage from threatening environments (Stevens et al 1992, p758)." Unmet communication needs for these participants led to parents being unprotected from the threat posed by their child's distress. The unfamiliar behaviours, with their unknown meaning were also threatening due to their possible impact on recovery or an implication of brain damage.

The parents' described their unmet needs to understand the meaning of their child's behaviours and their occasional unsolicited participation in decisions about weaning. These findings contrast with the nurses reports in Study 4 of the challenges they faced when interpreting equivocal behaviours and deciding when to alter weaning regimes in response to the child's state. Both parties had unmet information needs, which could be fulfilled through dialogue with the other party. This exchange of information, being mutually beneficial to both parent and nurse, and moreover to the patient, describes "reciprocity." A reciprocal relationship between nurses and parents focussed on withdrawal syndrome has been diagrammatised (Figure 9.2).

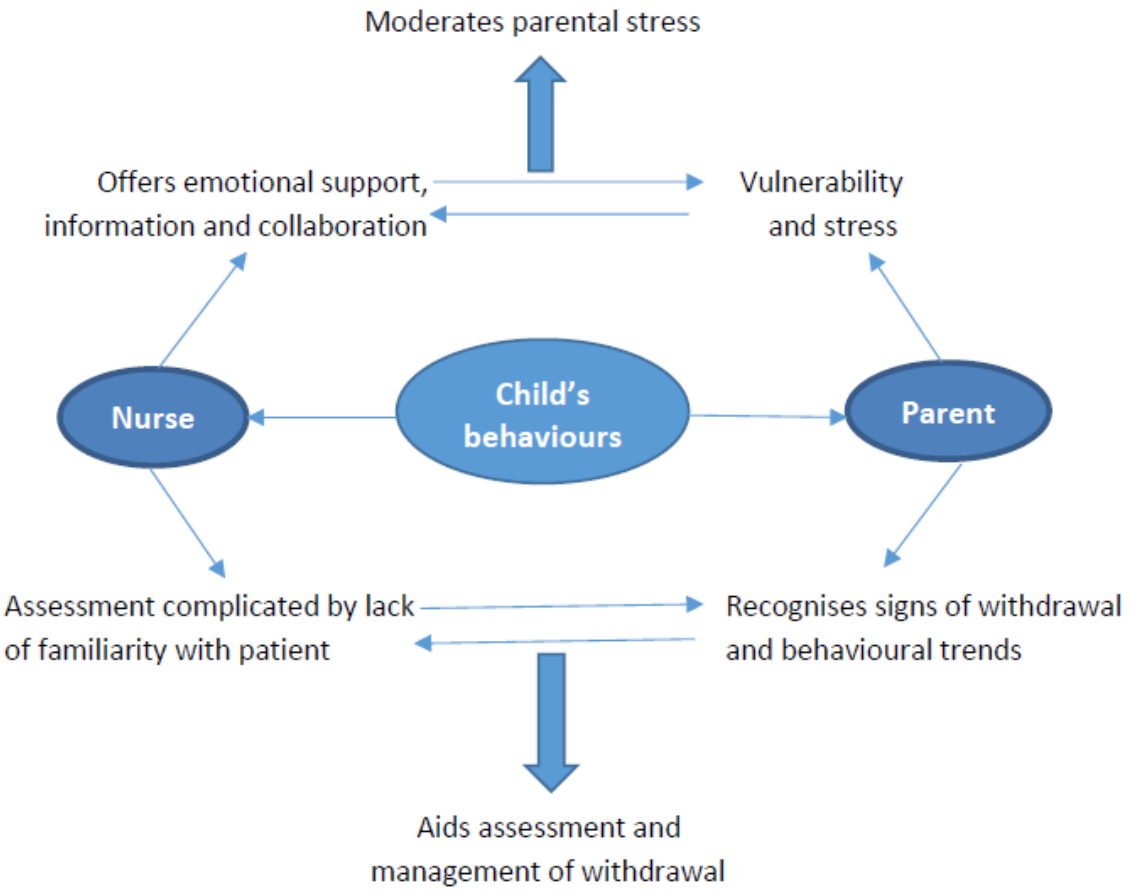

Figure 9.2 Benefits of reciprocity (nurse-parent collaboration) in withdrawal syndrome.

A reciprocal relationship may promote partnership and parental participation, enabling the parent to contribute their unique knowledge of the child in the identification of behavioural signs and the nurse to reciprocate with reassurance, explanation and information about the behaviours. A reciprocal relationship regarding decisions about weaning of sedation may speed the duration of weaning if nursing caution about the meaning of behaviours is balanced by parental assurance that current behaviours represent an improving trend or are normal behaviours.

Partnership may not suit all parents and parents' preferences for participation in care may vary during the course of their child's PICU admission depending on both personal and situational factors. In keeping with the mutual benefits of reciprocity, it is therefore vitally important that nurses establish and review the level of participation that meets the expectations of parents (October 2014). The Shared Decision Making Continuum (Kon 2010) could be adapted to encompass any level of reciprocity and demonstrate different levels of participation according to parent preference.

9.9 Strengths and limitations

There are a number of limitations in this study to acknowledge. The questionnaire listing the SWS signs may have biased parents to 'recognise' these behaviours at interview. There is also a risk of bias as parents self-selected for interviews, which may have resulted in parents who were more distressed with withdrawal and other aspects of the PICU experience, agreeing to take part.
However, a strength of this study is that interviews were undertaken as soon as weaning was completed, to minimise the parents' recall bias.

9.10 Conclusion

Study 6 has shown that withdrawal signs are a source of distress for parents due to uncertainty about the meaning of the signs and their impact on both their child's immediate and long term recovery. Parental awareness of the performance of withdrawal assessments was not consistent; despite this parents recalled a range of withdrawal behaviours, which was broader than represented in the SWS assessment tool. Parental participation in withdrawal assessments was viewed as a positive potential role by most parents. Parents described how being present, participating in care and being

kept informed of their child's condition helped them cope with the stress of their child's critical illness. Enabling parental participation in withdrawal assessments may encourage these aspects of care. A collaborative relationship between nurses and parents with a two-way flow of information may be beneficial to both parties; providing a timely flow of information and reassurance to parents, aiding nurses understanding of the child's behaviours and increasing confidence to continue weaning sedation.

Conclusions to Part 4: Integration of findings from Studies 5 and 6 with Parts 1, 2 and 3.

Studies 5 and 6 showed that parents recalled a broader range of withdrawal signs than is reflected in the item content of the SWS tool. Having sought the parent perspective with the aim of improving withdrawal assessment, instead this insight has cast doubt on the validity of the existing approach. The impact of this finding will be integrated into the discourse regarding withdrawal assessment and decision-making, which was begun in the conclusions to Part 3. This discourse will consider the ways in which the findings of Studies 5 and 6 illuminate the existing approach to withdrawal and how integrating a potential role for parents might expand on the propositional model of withdrawal assessment and decision-making.

The existing approach to withdrawal assessment

The range of behaviours recalled by parents was broader than the item content of the SWS tool, which guides the existing assessment of withdrawal. In a similar way to how the focus of effort on deconstructing and interpreting equivocal behaviours effectively blinds the nurse to other aspects of the assessment, so limiting the "noticing" stage of decision-making to behaviours listed in the SWS tool, also effectively blinds the nurse to other behavioural changes.

In Study 6 parents demonstrated that they intuitively recognised behaviour changes in their critically ill child, typically without either the SWS tool as a prompt or the contextual awareness to understand the meaning of behaviours. The ability to recognise these behaviour changes in the absence of a prompt or contextual understanding supports the idea that the "noticing" stage naturally aligns with System 1 intuitive thinking of pattern recognition (Kahneman 2011). Parents recognised changes because they know their child and are usually a consistent presence at their critically ill child's bedside, so notice behavioural trends. These findings support a collaborative role for parents in the withdrawal assessment, of noticing behaviour changes.

Integrating a potential role for parents into the propositional model

If the 'noticing' stage in the withdrawal assessment is a role that might be performed by parents (Figure Part 4.3), the nurses' role and expertise can focus on the other two decision-making stages;

- ‘interpreting’ the meaning of the behaviour change in light of the likelihood of physical dependence and the temporal relationship with reductions in sedative drugs, and
- ‘responding’ with decisions regarding weaning or the need for medical review.

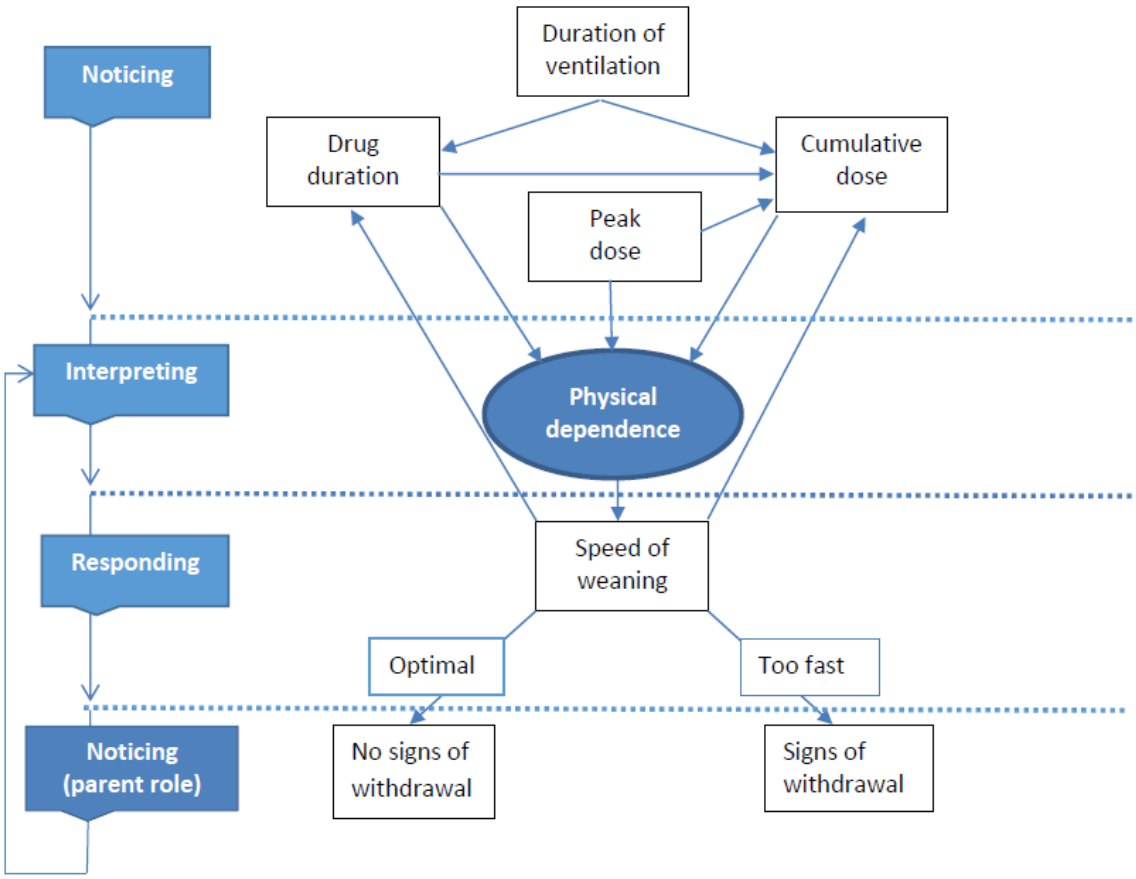

Figure Part 4.3 Propostional model integrating a role for parents in the decision-making stages performed during a withdrawal assessment.

A different approach, which is less prescriptive in terms of identifying specific behaviours and focuses on changes in behaviour may represent a more individualised approach to withdrawal assessment. An approach focussing on the child may be more empowering for parents, as it emphasises the parents’ role in being most able to recognise their child’s behavioural trends. The parents’ contribution to the assessment would support the nurses’ interpretation of the likelihood of physical dependence and underpin changes to the weaning regime.

Parents described behaviours indicative of inattention, which is a clinical features of PD. This finding reflects the clinical context within which the withdrawal assessment takes place; a context which is missing from the propositional model. It is not known whether

the children who were inattentive were also delirious or to what extent the features of withdrawal and delirium overlap. Parents did however highlight the interaction between features of withdrawal and their child's critical illness. The impact of the critical illness and other coexisting conditions on withdrawal assessment will be discussed in the next chapter.

Introduction

The aim of the studies in this thesis was to improve the assessment of withdrawal by including the parent perspective; the studies focussed on operational aspects of withdrawal. The lack of a theoretical basis supporting the existing operationalisations of withdrawal became apparent during the literature review and studies 1-6 when seeking to compare results to previously developed theories or propositions. As a consequence, a propositional model and withdrawal causality assessment tool were developed from the research literature, against which to consider and evaluate the study findings.
This concluding part of the thesis will identify gaps in the existing evidence base and then integrate and synthesise the findings of studies 1-6 in an attempt to fill these gaps. Part 5 of the thesis consists of three chapters.

In Chapter 10, the adapted ADR Causality Assessment Tool is renamed the Withdrawal Causality Assessment Tool (W-CAT). The clinical utility of W-CAT is evaluated using case studies from Study 5 as test cases. An in depth consideration of the substruction of physical dependence in each case will seek to illuminate the relationship between the features of physical dependence and withdrawal.

In Chapter 11 a synthesis of the findings from Studies 1-6 in relation to signs of withdrawal will be undertaken and the epistemic assumptions that link these behavioural variables with withdrawal will be considered.

In Chapter 12, the conclusions, original contributions to knowledge and implications for practice and policy are presented.

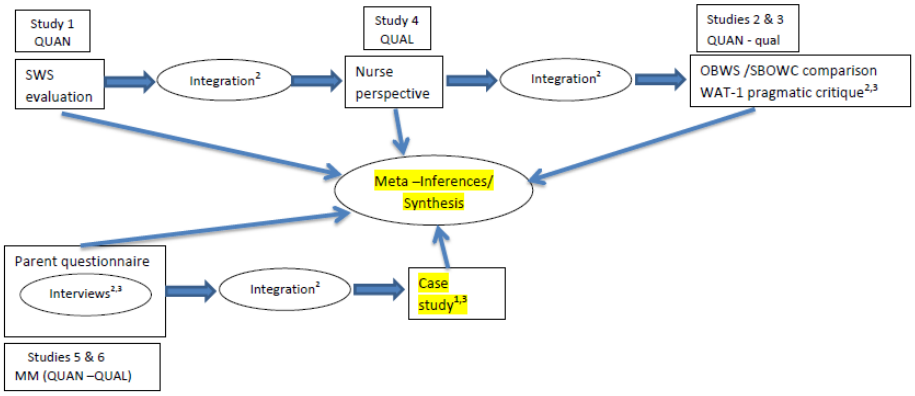

Figure Part 5.1 The thesis map showing Part 5 highlighted.

Background

Theoretical substruction will provide a framework for the integration and synthesis chapters and identify the contributions of these studies towards a theory of withdrawal syndrome in critically ill children. Theoretical substruction is a process that demonstrates the hierarchical relationship between the constituent constructs, concepts, variables and indicators of a theory (Franck and Callery 2004, Hinshaw, 1979). This framework was selected due to the lack of an explicit theoretical basis for withdrawal in critically ill children. Theoretical substruction also demonstrates the link between the theoretical and operational components of a construct (Trego 2009) and the structure of the substruction model can then be used to identify gaps in the evidence base (Dulock and Holzemer 1991).

Theoretical substruction of physical dependence and withdrawal syndrome

The hierarchical relationship between the constructs, concepts, variables and indicators of physical dependence and withdrawal are shown in Figure Part 5.2. Table Part 5.1 provides definitions for the terms used in Figure Part 5.2. The relationship between physical dependence, withdrawal syndrome and signs of withdrawal in critically ill children was first described in case reports more than thirty years ago (Miser et al 1986). Three withdrawal assessment tools have since been published, which operationalise this theoretical relationship (Cunliffe et al 2004, Franck et al 2008, Ista et al 2013). However, these tools, as empirical indicators were constructed and tested based on the statistical association between variables, rather than by examining the theoretical association between variables and the empirical indicator as shown in Figure Part 5.2.

The consequence of a statistical, rather than theoretical basis for the operationalisation of withdrawal is manifest by the differences between the assessment tools. From an item pool of 22 withdrawal signs, the three withdrawal assessment tools share only six items in common. Study 6 (Chapter 9) highlighted behaviours recalled by parents that were over and above this item pool. The statistical basis for the withdrawal tools also did not account for the heterogeneous presentation of withdrawal or the equivocal nature of some of the behaviours which are very common in critically ill children, who are not withdrawing (Franck et al 2004, Ista et al 2008).

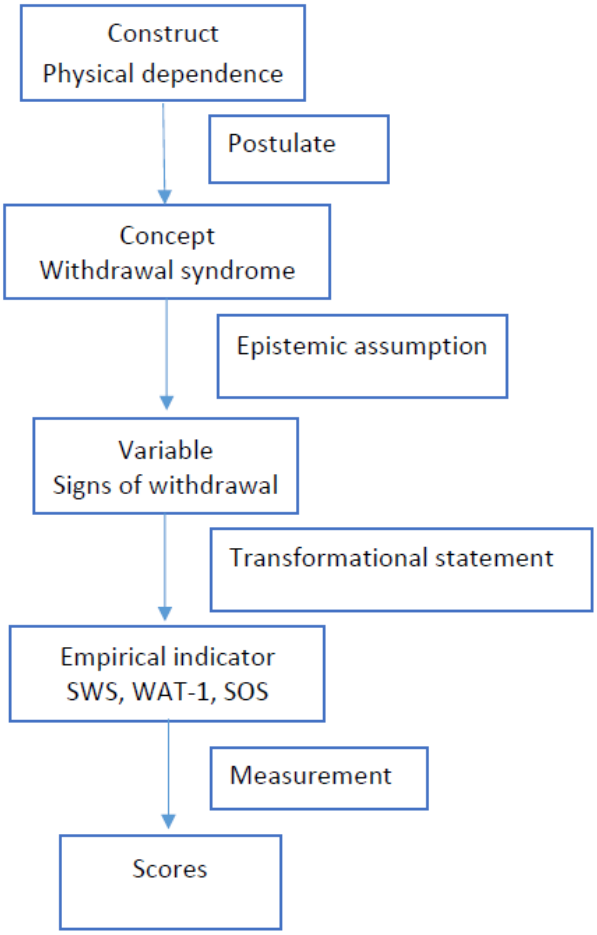

Figure Part 5.2 Theoretical substruction of physical dependence and withdrawal

Table Part 5.1 Definitions of theoretical substruction terms (Franck and Callery 2004, Bekhet and Zauszniewski 2008, Dulock and Holzemer 1991)

Construct is a highly abstract notion that can be partially defined
Concept is a word that expresses a mental image of some phenomenon
Variables are dimensions of the phenomenon
Empirical indicators are instruments or other observable evidence of the phenomena of interest
Postulate is a relational statement between construct and concept
Epistemic assumption is the assumption made to link the concept with the variable.
Transformational statement is the relationship between variables and empirical indicators which are logically derived.

Identifying the gaps

The element of the theoretical substructions; “construct”, “concept” and “variable” were mapped onto the propositional model introduced in Chapter 2, to examine the theoretical basis for withdrawal (Figure Part 5.3).

The theoretical aspects of substruction include the identification of the construct, concept and variables and a description of the relationships between them, according to the theory (Hinshaw 1979). The construct of physical dependence and the concept of withdrawal syndrome in critically ill children are not well defined. The theoretical relationship between physical dependence and withdrawal (the postulate) and between withdrawal and the signs of withdrawal (the epistemic assumption) are also poorly defined. The synthesis studies in Chapters 10 and 11 will seek to fill these gaps by introducing a new definition for withdrawal syndrome in critically ill children; “Paediatric Withdrawal Syndrome” and describing the epistemic assumptions and transformational statements that link the construct, concept and variables.

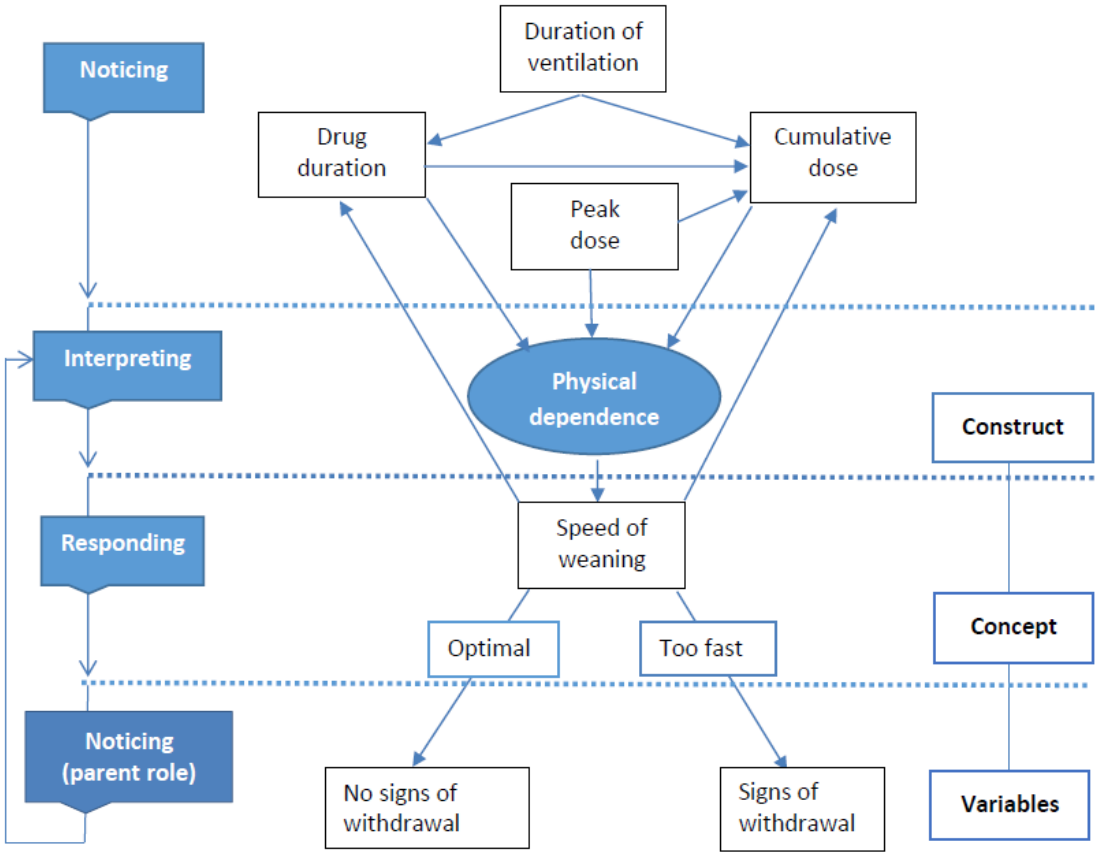

Figure Part 5.3 Mapping of theoretical substruction terms onto the propositional model.

10.1 Introduction

A different approach to withdrawal assessment was devised during Study 1 as a reference standard with which to evaluate the SWS tool and to retrospectively assign the likelihood of withdrawal in an objective manner. The tool was adapted from an ADR causality assessment tool (WHO-UMC) and contained criteria which were similar to the DSM-5 substance withdrawal diagnostic criteria (DSM, 2013). This adapted tool was also used in Studies 5 and 6 in order to ascertain the likelihood that withdrawal rather than another cause was driving the behaviours recalled by parents. This tool differs from existing withdrawal assessment tools by considering contextual features of withdrawal, including the likelihood of physical dependence and a temporal relationship between the onset of signs of withdrawal and reductions of sedative drugs, rather than just the child's behavioural presentation. Another feature was the assigning of probability of withdrawal rather than the dichotomous yes/no of WAT-1 (Franck et al 2008) and SOS (Ista et al 2013). This tool will be called the Withdrawal Causality Assessment Tool (W-CAT).

Table 10.1 The Withdrawal-Causality Assessment Tool (W-CAT) based on WHO–UMC causality assessment criteria (https://www.who-umc.org/media/2768/standardised-case-causality-assessment.pdf)

Withdrawal likelihood	Physical dependence possible	Temporal relationship with change in dose	Absence of differential diagnoses
Probable	Yes	Yes	Yes
Possible	Yes	Yes	No
Unlikely	No	No	No

10.2 Purpose of the chapter

The purpose of this chapter is;

1. To consider the utility of the Withdrawal Causality Assessment Tool (W-CAT) retrospectively in five case studies, and

2. An in depth consideration of the substruction of physical dependence in each case to illuminate the characteristics of, and the theoretical relationship between, physical dependence and withdrawal.

10.3 Method

Three types of instrumental case studies were developed for the purpose of analytic generalisation, which is a measure of generalisability or transferability of findings (Yin 2003). Rather than drawing inferences from data to a population, as in statistical generalisation, analytic generalisation generalises to a previously developed theory or theoretical proposition. The theoretical proposition is the use of the W-CAT to assign clinically meaningful levels of withdrawal probability.

Five individual cases are presented from Study 6 to demonstrate the different levels of withdrawal probability; three cases of probable withdrawal which highlight the impact of patient and contextual factors and one case each of possible withdrawal and withdrawal unlikely. These five cases challenge the clinical utility of the existing, dichotomous approach and provide evidence for analytic generalisation of the W-CAT approach to withdrawal assessment (Yin 2010). Each case is presented as a test case to "confirm, challenge, or extend the theory" (Yin 2003, p40).

Yin (2010) emphasises the following points to increase the analytic generalisation of the cases presented, which have been adhered to in this chapter;

- The theory should be presented at the beginning of the case study, which is the utility of W-CAT as an empirical indicator of withdrawal,
- The theory should be grounded in research literature. W-CAT is adapted from an existing ADR causality assessment tool,
- Findings should show how the results of the case study either support or challenge the theory,
- Examining rival hypotheses will strengthen claims of analytical generalisation, and
- Generalisability increases if similar results are found with other case studies

10.3.1 Subject

Five cases were selected from Study 6 to test the clinical utility of W-CAT; these cases were selected to reflect the complexity and variety of cases in clinical practice. These cases included the one 'withdrawal unlikely' case, the one 'withdrawal probable' case and

three ‘withdrawal possible’ cases. The subject of each study is the clinical case in the 72 hours both leading up to and following the highest SWS score. The object of the study is the W-CAT, which provides the theoretical frame through which each case is viewed and explicated (Thomas and Myers, 2015).

Each subject will be presented as an integration of data and findings from Study 5, presented consecutively. After a brief introduction of the case, the following subheadings will organise the presentation and discussion of the data;

Sedative drug therapy 72 hours before and after the highest SWS score, presented and discussed in terms of interpreting the likelihood of withdrawal and/ or other causes, or rival hypotheses

Highest SWS score, presented as table showing component scores and as a graph showing the trend of scores in the 72 hours leading up to and following the highest score

Probability of withdrawal according to the W-CAT criteria

Identifying a causative agent by considering the drug therapy, weaning rates and any changes in drug therapy in response to the highest SWS score and interpreting the meaning for the likelihood of withdrawal.

Parent perspective presents an excerpt from the transcripts of the interview where this contributes further insight.

Withdrawal signs from nurse documentation and parent interviews, presented as pie chart (Nurse documentation) and a table (parent-reported signs)

Discussion of the utility of W-CAT as an empirical indicator of withdrawal.

10.4 Case study 1 (Withdrawal probable)

A 3 year old girl underwent cardiac surgery (ASD repair) and spent the following 31 days on PICU. During this time she returned to theatre twice, had a cardiac arrest and spent 8 days on ECMO.

10.4.1 Sedative drug therapy

The patient was sedated with fentanyl and midazolam throughout her PICU stay. Peak doses were fentanyl 4.6 micrograms/kg/hr and midazolam 288 micrograms/kg/hr prior to slow weaning of both infusions (10 % wean per day) commencing on day 12. Promethazine (1mg/kg every 6 hours) was commenced to facilitate weaning of fentanyl and midazolam. A ketamine infusion was also commenced to facilitate the weaning of fentanyl and midazolam on day 17: starting at 15 micrograms/kg/minute and increasing to 30 micrograms/kg/min within 24 hours. Promethazine was stopped and chlorpromazine (0.5 mg/kg every 6 hours) commenced on day 22 due to high SWS scores. The patient was extubated on PICU day 27.

Perception and interpretation

This patient required high doses of sedatives for a prolonged period and weaning was very slow despite the addition of other high dose sedatives. This picture describes a "hard to sedate" patient; the causes of which may not be recognised or identified during the critical illness but could include their underlying condition, an ADR or pediatric delirium.

10.4.2 Highest SWS score

The highest withdrawal score, SWS 9, occurred on PICU day 30, three days after extubation (Table 10.2). SWS scores had increased six hours prior to the highest score from a modal score of SWS 3 to SWS 6. The nursing documentation described the patient as agitated, very unsettled, withdrawing severely, large pupils, tremors, constantly rolling in the bed and severe twitching.

Scores remained at a modal score of SWS 6 for a further 57 hours prior to declining.

Interpretation

Schieveld et al (2010) described pediatric delirium (PD) as "refractory agitation." This child was diagnoses with "severe withdrawal" as pediatric delirium was not assessed in this PICU, so was not a diagnostic option.

Table 10.2 Highest SWS score components (Case study 1, SWS score 9)

Insomnia	Irritability	Respiratory distress	Diarrhoea	Sweating	Fever	Vomiting	Tremor	High pitch cry	Sneezing	Hypertonicity	Convulsions
2	2	0	0	1	0	2	2	0	0	0	0

10.4.3 Probability of withdrawal

Likelihood of withdrawal was probable at the time of the highest score (Table 10.3) in the absence of PD as a possible differential diagnosis.

Table 10.3 Likelihood of withdrawal (Case study 1)

Criterion	**Case 1**
Physical dependence possible	Fentanyl and midazolam for > 5 days
Temporal relationship with change in dose	Fentanyl and midazolam weaning by less than 10% per day
Absence of differential diagnosis	Yes

10.4.4 Identifying a causative agent

10.4.4.1 Drug therapy and weaning rates

The patient was sedated with four sedative agents at the time of the highest score; fentanyl, midazolam, chlorpromazine and ketamine. Chlorpromazine continued at the the same dose of 0.5 mg/kg every 6 hours throughout this period. Three drugs had been reduced in the 72 hours prior to the highest score so were possible causes of withdrawal.

Fentanyl

Weaning of the fentanyl infusion had recommenced five days prior to the highest SWS score, after no changes for the preceding 4 days (in response to an SWS score 5). The weaning rate was 0.05 micrograms/kg/hr every 12 hours.

Midazolam

The midazolam infusion had been reducing fairly consistently by 0.05 micrograms/kg/hr every 12 hours for the 10 days preceding the highest score. Reductions had paused for 48 hours a week prior to the highest score (at the same time as fentanyl reductions had paused) and had been increased for 24 hours, 1-2 days prior to the highest score.

Ketamine

Ketamine reductions had been commenced 60 hours prior to the highest score, were recorded as not tolerated (although the SWS score was 3 at each assessment that day) and were increased back to the original rate of 30 micrograms/kg/minute.

10.4.4.2 Changes in drug therapy in response to the highest SWS score

In response to the SWS score, fentanyl was increased from 1.4 to 2 micrograms/kg/hr, an increase equivalent to 3 days' worth of reductions. The midazolam infusion was increased from 54 to 60 micrograms/kg/hr, equivalent to one 12-hourly reduction, a modest reduction considering the dose 72 hours previously had been 102 micrograms/kg/hr. The difference in the extent of these dose increases suggests that fentanyl withdrawal was blamed for the cause of the withdrawal score. Figure 10.1 shows changes in fentanyl and midazolam rates in relation to the SWS scores.

During the 24 hours following the high score, the ketamine infusion (30 microg/kg/min) was stopped (hence no temporal relationship with highest SWS score) and choral hydrate 25 mg/kg every 3-6 hours as required was commenced. Fentanyl and midazolam continued unchanged for the following 72 hours.

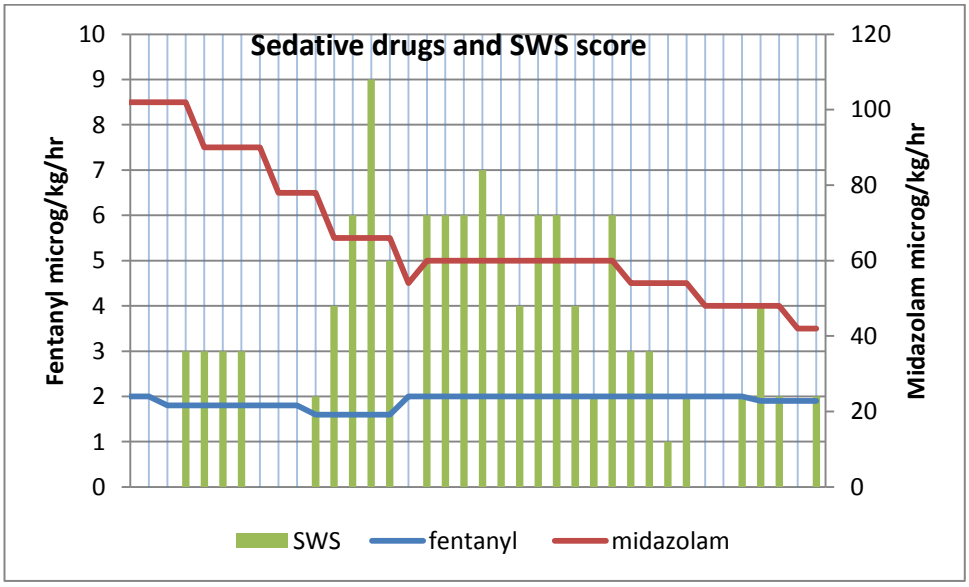

Figure 10.1 Sedative drug weaning and SWS scores (Case study 1)

Interpretation

As SWS scores remained high and the increase in fentanyl failed to relieve the SWS signs, fentanyl withdrawal was unlikely to be driving the SWS score. This implicates either midazolam as the likely cause of withdrawal or another cause, such as PD.

10.4.5 Parent perspective

This excerpt, taken from the interview transcripts in Study 6 gives the mother's perspective on which drugs caused issues for her daughter during the weaning of sedation:

> *"Then they decided to change her over to the Ketamine which it did seem to make quite a big difference if I'm honest because she was more comfortable with that and rather than the absolute jumping about she was just more shaky which we found a bit easier to deal with. I think although the Ketamine wasn't a sedative we did see a difference once that came off. I think that was the right decision because she wasn't handling coming off the sedation at all while she was still on Ketamine because there was vomiting and diarrhoea as well. We found that the worst withdrawal we've seen was coming off Ketamine and then it's been a nice smooth process coming from the Fentanyl and the Midazolam since that's come away. So that's been a big difference for us and I do think that the Chlorpromazine has made things a little bit more comfortable for her as well, because we did find that when she became distressed and they've administered that she was fine within a few minutes and stuff so that has made a difference."* (P1M)

Prior to ketamine stopping, SWS scores had increased and the highest SWS score had occurred, so there was no temporal relationship with the change in ketamine dose and the highest SWS score. Ketamine is not considered to cause physical dependence, although this patient had been on a continuous high dose infusion of ketamine for 13 days. The mother's report suggests another possible cause, as when ketamine was started, there was an improvement in comfort and a reduction in jumpiness. It may be these behaviours re-emerged in response to a diminishing therapeutic response as ketamine was reduced, rather than due to a withdrawal response. The therapeutic response to chlorpromazine also implies an undiagnosed and underlying contributing cause for distress, as this treatment would be unlikely to improve signs of fentanyl or midazolam withdrawal, in the manner that the child's mother describes.

Interpretation

Although midazolam withdrawal is probable, a coexisting undiagnosed cause for behavioural signs is also possible. In the absence of delirium or ADR assessment tools, this interpretation is based on the mother's retrospective description of behaviours.

10.4.6 Withdrawal signs

10.4.6.1 Nurse documentation

All SWS scores over the timeframe were collated and the contribution of component signs was presented in a pie chart (Figure 10.2). This shows that two signs; irritability and tremor contributed over half of the SWS score during this time frame.

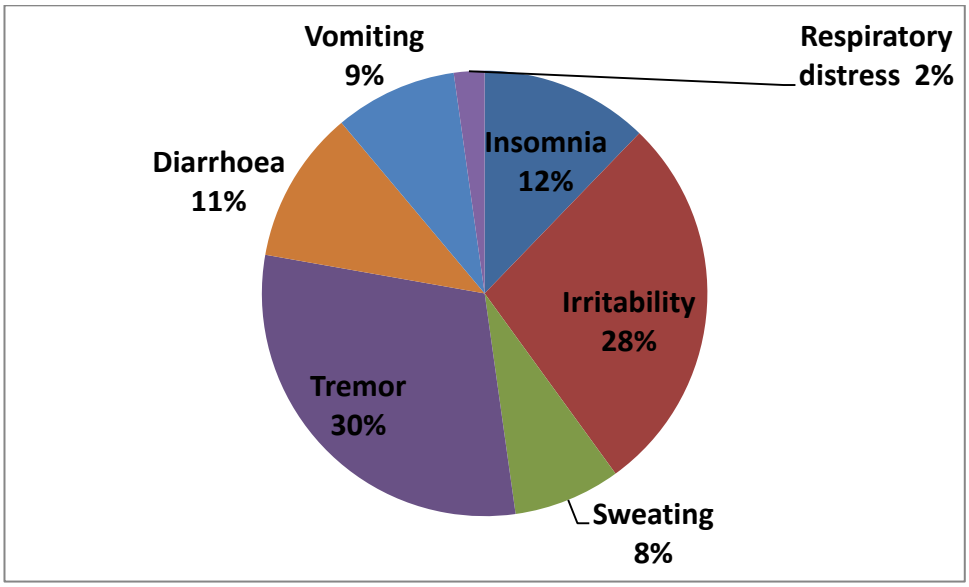

Figure 10.2 Contribution of component SWS signs (Case study 1)

10.4.6.2 Parent interviews

The two dominant SWS behaviours from the nurses' withdrawal assessments encompassed seven distinct behaviours recalled by the patient's mother (Table 10.4). The SWS item "tremor" was matched to "jittery", "jumping", "shaking" and "floating hands." The mother's description of "tremor" referred to parkinsonism-type movement disorder. The SWS item "irritability" was matched to "distressed." The mother's description of "irritability" described severe tantrum-like behaviour.

These behaviours, along with hallucinations and inattention ("not recognising me"), describe features of other differential diagnoses, including PD and ADRs; (extrapyramidal side effects from chlorpromazine, hallucinations from ketamine).

Table 10.4 Parent report of behaviours during weaning (Case study 1)

Jittery	"Her legs were sort of lifting up and her hands were like shaky. When you picked her hand up she was really like 'tremory'."
Jumping	"Like when you jump in your sleep but it was more sort of violent. When you just see someone jump in their sleep it's just a little like 'bounce', she just seemed to lift up that little bit more. It frightened us because it was such a sudden movement. It was like – I think I was more distressed, even though I knew she was sedated, [thinking] what's happening to her? Is she ok? Is she experiencing anything that's upsetting her or can she feel any pain? She just seemed to jump, but obviously there was no sound."
Distressed	"When she had periods of being a little bit more lucid with her eyes open, although we couldn't hear what she was saying I can lip read because I'm deaf and she was just repeating over and over again – "I want my mummy, I want my mummy, I want my mummy". That upset us because I couldn't do anything to help her, because I couldn't pick her up and things like that. You could clearly see sometimes you would be talking to her, and I don't know whether it was just because of her eyes being like closed for so long, but to us when she started having a tear down her face that upset us to think - is she crying because is she aware what's going on? It might just be her eyes were aching but it just seemed like an emotional reach for some comfort and stuff. We felt so helpless with her."
Shaking	"If you tried to pick her up and move her up the bed, her body, it was just that little bit shaky. Her hands it was like, if you put a cup or something in her hand you just knew she wouldn't be able to hold it."
Hallucinating	"Her eyes frightened me sometimes because it was like she was looking at something that we can't see and she was screaming." "She's been telling us that she was swimming with mermaids and that me and daddy weren't there, and she's been dropped in the water with no arm-bands and she couldn't float." "I had red hair when I came in and I did find that when (name of child) was first coming off it I couldn't go near her. I changed my hair colour and she's been absolutely fine so I'm wondering whether it's been 'clowns' or something like that because it's been so red. But she was screaming quite a lot when I was coming near her as well and she wouldn't entertain me. She was fine with dad, I'm just assuming it's because he's always had the same colour and his face looked more familiar."

Irritability	"Tantrums, screaming, she's been a bit violent towards me. She won't entertain you when you try to reason with her, things like that. I know a normal three-year old has tantrums, but these are literally screaming and throwing herself about the bed. She's tried to pull her lines out. She tried to wrench the sides off the bed. Her heart rate would shoot up and we just didn't want her to make herself [ill]."
Tremor	"Like someone with Parkinson's at first because her hands were really shaking. She was struggling to hold things in her hands."
Floating hands	"We called it the floating hand, because she'd just bring her arm up. I used to say to her – "Are you doing the backstroke?" She'd be on her back and just bring this arm up. It was almost like a twitch of the head, but it was like when you start to bring your shoulder up and twitch your head. She does still do that from time to time, but we make a joke of it and she just laughs so it's not a major thing."
Not recognising me	"You'd speak to her and she'd just look right through you. It was like there was nothing there and she just looked like horrible, terrible, like the eyes were out, there was like no light there, no sparkle, and that upset me more because– am I going to get the same child back? Those first few days were really worrying."

10.4.7 Discussion

This patient demonstrates the complexities of a withdrawal assessment, which relies on a fixed number of equivocal behaviours and assumes, rather than encourages the exclusion of other possible causes of these behaviours. The W-CAT provides this structure. Assessing the causal indicators for physical dependence encourages a consideration of previous drug therapy and endorses the option of withdrawal as a possible diagnosis. The temporal relationship between behaviour change and the change in drug dose supports a rational consideration of the conditions. In this case the failure in a recent trial of reducing ketamine may have biased subsequent judgement despite the absence of a temporal relationship.

The absence of a differential diagnosis may not be an accurate reflection of the case, but reflects the diagnostic options available to clinical staff at the time. The similarities in presentation between withdrawal, pediatric delirium and adverse drug reactions (ADRs) has recently been highlighted (Madden et al 2017). Whether in this case, behaviours were driven by withdrawal, delirium or ADRs cannot be determined retrospectively. The W-CAT category "absence of differential diagnoses" does not reflect the possibility of the

co-existence of withdrawal and other causes; the context of critical illness may mean it is not possible to exclude other causes. Rather than assigning probable or possible withdrawal according to the absence or otherwise of other causes, differentiating the main driver for the behaviours, rather than excluding other causes, may better reflect the context of critical illness.

Although the existing (SWS) approach to withdrawal assessment provided a structure for regular assessment of this patient and an opportunity to demonstrate trends in scores, the complexities of this case may have been better supported by the W-CAT criteria and a PD assessment tool.

10.5 Case study 2 (Withdrawal probable)

A 5 month old boy (twin 1) was admitted to PICU with RSV positive bronchiolitis, rhinovirus and parainfluenza virus. He was born at 34 weeks gestation and this was his third episode of lower respiratory tract infection, due to mild tracheomalacia and moderate right bronchomalacia. He was intubated for 5 days and spent 6 days on PICU. Two days later he required increasing ventilatory support, was transferred to HDU for CPAP and was diagnosed with Haemophilus influenza four days later.

10.5.1 Sedative drug therapy

The patient was sedated with morphine and midazolam whilst intubated on PICU. Peak doses were morphine 40 micrograms/kg/hr and midazolam 116 micrograms/kg/hr in the first 24 hours prior to reducing to 20 micrograms/kg/hr and 75 micrograms/kg/hr respectively for the following 4 days. Both infusions were stopped without weaning between 2 hours (morphine) and 7 hours (midazolam) prior to extubation on PICU day 5.

Perception and interpretation

After five days sedation, this patient had a 50% risk of being physically dependent. Peak doses were neither high nor administered for prolonged periods, so weaning was not indicated.

10.5.2 Highest SWS score

The highest withdrawal score, SWS 10, occurred on ward day 2, three days after extubation (Table 10.5). SWS scoring commenced 10 hours after extubation, were SWS 4-7 for the first 48 hours, rising to SWS 7-10 the following day. SWS scores gradually reduced to SWS 4 over the following 3 days, then remained SWS≤4 for the following week. (See Figure 10.3).

Table 10.5 Highest SWS score components (Case study 2, SWS score 10)

Insomnia	Irritability	Respiratory distress	Diarrhoea	Sweating	Fever	Vomiting	Tremor	High pitch cry	Sneezing	Hypertonicity	Convulsions
2	2	2	0	2	0	0	0	2	0	0	0

10.5.3 Probability of withdrawal

Likelihood of withdrawal was probable at the time of the highest score (Table 10.6).

Table 10.6 Likelihood of withdrawal (Case study 2)

Criterion	Case study 2
Physical dependence possible	Morphine and midazolam for 5 days
Temporal relationship with change in dose	Stopped 72 hours previously
Absence of differential diagnosis	Yes

10.5.4 Identifying a causative agent

10.5.4.1 Drug therapy and weaning rates

Morphine and midazolam were administered for 5 days and stopped without weaning within 6 hours of each other. Both drugs are possible causative agents.

10.5.4.2 Changes in drug therapy in response to the highest SWS score

Diazepam was commenced regularly on the day of the highest score having been administered "as required" since the previous day. Chloral hydrate was administered intermittently in the 48 hours prior to the highest score with brief effect.

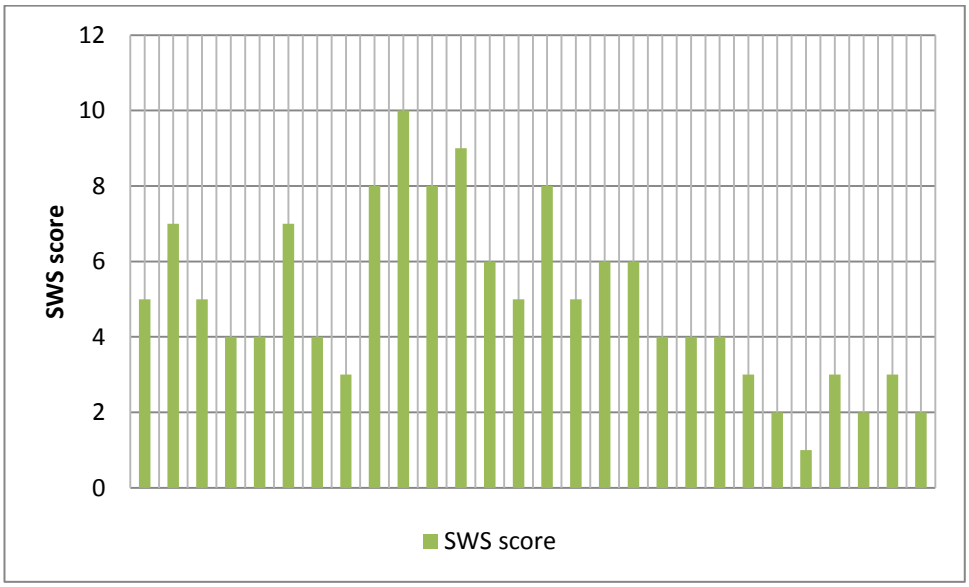

Figure 10.3 SWS scores (Case study 2)

Interpretation

As SWS scores remained high and starting diazepam failed to relieve the SWS signs, midazolam withdrawal was unlikely to be driving the SWS score. This implicates either morphine as the likely cause of withdrawal or another cause.

10.5.5 Parent perspective

This excerpt, taken from the interview transcripts in Study 6 gives the father's perspective on issues for his son during the weaning of sedation:

> *"My feeling was he wasn't well enough yet to start the weaning process. I think maybe he needed, I might have got this wrong, but I think we started getting him off the oxygen and the drugs at the same time and he couldn't handle it. I think maybe we needed to do one and then do the other or leave him in ICU a little bit longer or give him more support with the oxygen a little bit longer before."*(P5F)

10.5.6 Withdrawal signs

10.5.6.1 Nurse documentation

All SWS scores over the timeframe were collated and the contribution of component signs was presented in a pie chart (Figure 10.3). This shows that two signs; irritability and respiratory distress contributed over half of the SWS score during this time frame.

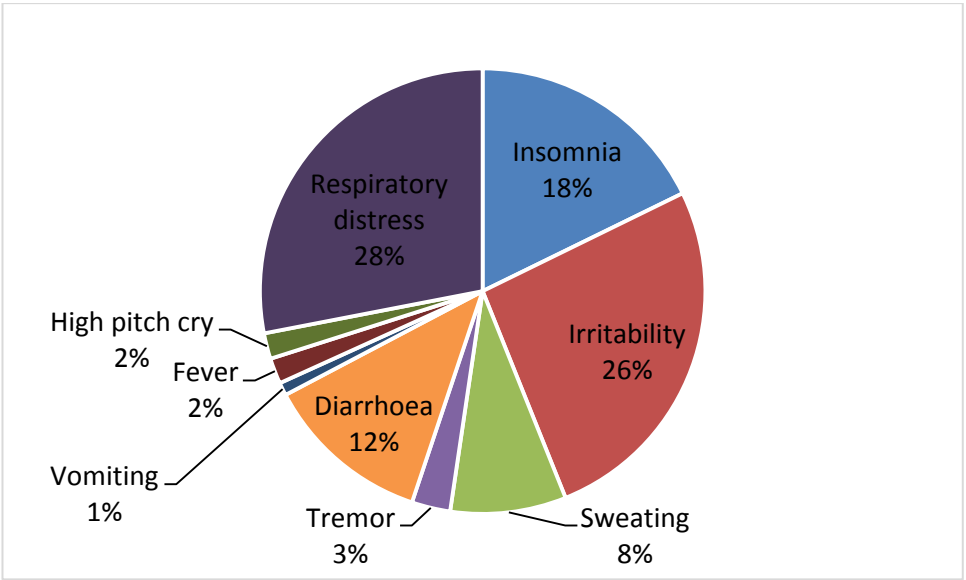

Figure 10.4 Contribution of component SWS signs (Case study 2)

10.5.6.2 Parent interviews

The two dominant SWS behaviours from the nurses' withdrawal assessments were also reported by the father and described as being linked. A further behaviour that was described as "panic attack/agitated" was also linked to irritability (Table 10.7). This parent also described his son "looking through him."

Table 10.7 Parent report of behaviours during weaning (Case study 2)

Looking through you	"Even when he was awake though he's not properly awake for me, he's not really there. For me he obviously wasn't himself, he's not there. I mean if he's looking at you he's looking through you. His eyes weren't focusing, I don't think it mattered if it was me or a nurse or a doctor I don't think he was focusing on anybody or anything, he had his eyes open but looking through you as such." "He had a strange thing where he did this thing where his eyes disappeared, he's looking down and his pupils are like disappearing."
Panic attack / agitated	"He was having a bit of a funny turn where he didn't like being touched. His eyes were kind of like flicking and his eyes were disappearing down, and it's a very bizarre thing. He'd be ok if you kind of left him alone I think but because he needed medication and treatment as soon as you did anything with him, change his bum, he starts getting, he starts like hyperventilating, he's getting more and more agitated and his throat's going and then I think he just winds himself up."
Irritability	"He's very irritable, he didn't want to be touched which – I mean he's a premature baby and I think you know he's not been a big fan of being faffed about with anyway. But in particular when he's kind of like whimpering or whatever and you want to pick him up but every time we did that it made him worse so you leave him alone. So he got very irritable with any kind of intervention at the height of it. He's got better as time's gone on but he's still a little bit moany!"
Respiratory distress	"Linked to the being irritable that's the whole body going, the chest, his whole tummy and the chest going up and down. They were the ones (along with eyes) that were probably the most distressing because you can see there is something wrong with him."

10.5.7 Discussion

This patient demonstrates the complexities of differentiating withdrawal from the child's critical illness. In this case, the child deteriorated and required additional respiratory support. The gradual increase in behavioural distress occurred during the time

withdrawal would be expected, so the patient may have been withdrawing. The highest SWS score was temporally linked to the patient's deterioration. The prevalence of respiratory distress and irritability in his withdrawal assessments point to his underlying condition driving both the scores and his behaviour. The parent perspective was illuminating, identifying the additional burden that even mild withdrawal might have posed for his son. The parent also linked irritability with respiratory distress and agitation, which in combination, would indicate hypoxia and collapse rather than withdrawal. Similarly to the previous case, the W-CAT did not reflect the possibility of this co-existence of withdrawal and other causes. In this case, it appears that the underlying condition was the main driver for the behaviours, possibly exacerbated by the presence of withdrawal.

10.6 Case study 3 (Withdrawal probable)

A 5 month old boy was admitted to PICU following cardiac surgery (hypoplastic aortic arch). He has William's syndrome. He was intubated for 4 days and spent 6 days on PICU.

10.6.1 Sedative drug therapy

The patient was sedated with fentanyl and midazolam whilst intubated on PICU. Peak doses were fentanyl 3 micrograms/kg/hr and midazolam 170 micrograms/kg/hr. Fentanyl continued at this dose for 72 hours and was then weaned and stopped over 48 hours. Midazolam was reduced every 24 hours and stopped after 72 hours. The patient was extubated on the PICU day 4.

Perception and interpretation

After four days sedation, this patient had less than a 50% risk of being physically dependent. Peak doses of fentanyl were high however and administered for 72 hours.

10.6.2 Highest SWS score

The highest withdrawal score, SWS 8, occurred on the day of discharge from PICU, two days after extubation (Table 10.8). SWS scoring was commenced when the patient was transferred to the ward. SWS scores gradually reduced to SWS ≤3 over the following 2-3 days (Figure 10.5).

Table 10.8 Highest SWS score components (Case study 3, SWS score 8)

Insomnia	Irritability	Respiratory distress	Diarrhoea	Sweating	Fever	Vomiting	Tremor	High pitch cry	Sneezing	Hypertonicity	Convulsions
2	2	0	0	2	0	0	0	1	1	0	0

10.6.3 Probability of withdrawal

Likelihood of withdrawal was probable at the time of the highest score (Table 10.9).

Table 10.9 Likelihood of withdrawal (Case study 3)

Criterion	Case study 3
Physical dependence possible	Fentanyl at high dose for 4 days.
Temporal relationship with change in dose	Stopped 48 hours previously
Absence of differential diagnosis	Yes

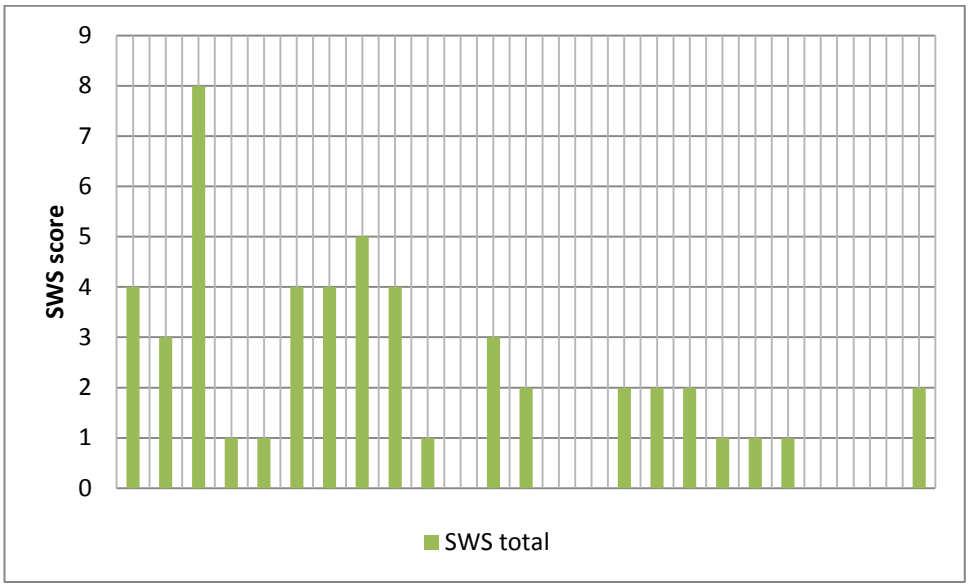

Figure 10.5 SWS scores (case study 3)

Interpretation
Motivation for initiating a withdrawal assessment was possibly perception of behavioural signs indicative of withdrawal.

10.6.4 Identifying a causative agent

10.6.4.1 Drug therapy and weaning rates

Fentanyl was the likely causative agent due to the high doses administered, despite less than 5 days therapy.

10.6.4.2 Changes in drug therapy in response to the highest SWS score

Clonidine 15 micrograms every 6 hours and chloral hydrate 120 mg every 3 hours were commenced after extubation but SWS scores did not cover this time frame.

10.6.5 Withdrawal signs

10.6.5.1 Nurse documentation

All SWS scores over the timeframe were collated and the contribution of component signs was presented in a pie chart (Figure 10.6). This shows that one sign; irritability contributed over one third of the SWS score during this time frame.

10.6.5.1 Parent interviews

The dominant SWS behaviour from the nurses' withdrawal assessments was also reported by the parents. The severe breath-holding attacks described by the parents and the PICU nursing notes covered the time when SWS assessments were not undertaken. (Table 10.10). Additional clinical details from nursing documentation are presented in Table 10.11.

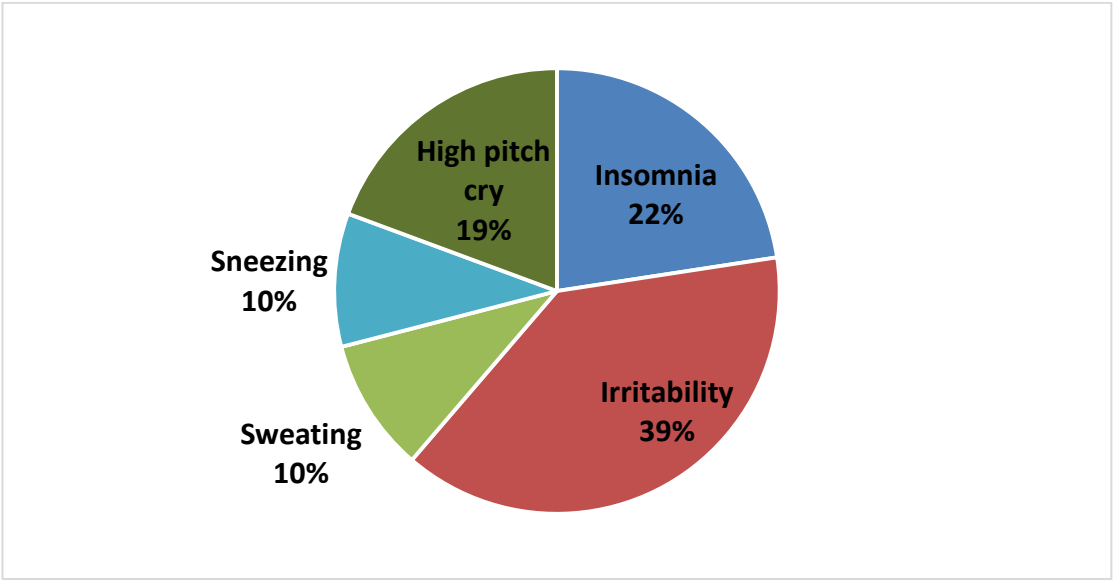

Figure 10.6 Contribution of component SWS signs (Case study 3)

Table 10.10 Parent report of behaviours during weaning (Case study 3)

Insomnia	"I noticed it that last night in Intensive Care because he was just so, so tired you could see he was absolutely shattered, his eyes were rolling round his head and he just couldn't sleep. And every noise that went off, every sound - there was someone coughing over the way - would make him jump and it was just horrendous and I was starting to think – right there's something not quite right. But I'm thinking - oh no maybe he's just coming round and he's feeling more aware and that's why he can't sleep. Then I think he was awake for about six to eight hours and

	then finally, every time he closed his eyes you'd think he was starting to fall asleep and then he'd hear a noise and he would be jumping and waking back up again. His eyes were red raw all along the bottom rim and he had one eye just had loads of bloodshot in it, it was horrible and he just looked wired, he looked strange, he didn't look normal because he was all funny. And I said it's not normal for him to not sleep at all for his age from six o'clock in the morning we are coming onto four o'clock in the afternoon now."
Tongue had a mind of its own	"But when he was having withdrawal, his tongue was wild. Like his tongue had a mind of its own. It was like he didn't actually want to keep his tongue in his mouth. For a baby who normally at home has his dummy 24/7 he couldn't keep it in his mouth. And I was saying – "Why can't he keep his dummy on his tongue?" At first we thought, he's getting teeth at the bottom and we thought maybe it's that because his tongue was just constantly out of his mouth. He was moving it so much." "I was thinking he's not going to be able to catch his sleep if he can't suck properly because it was like he wanted a dummy and then he'd - wah, wah, wah - (*Mother makes a sound to indicate baby not able to hold onto dummy*) and then he'd be looking for it and then you'd put it in and then it would just be over and over again."
Irritability	"And when I was trying to comfort him, to cuddle him in he was pushing me away, but it was like he didn't know what he wanted because when I put him in the pram he didn't want to be there. Pick him up he didn't want to be picked up so it was strange." "There was just nothing you could do to settle him because you have many things you do, she picks him up and has him up on her chest but that wouldn't work, he was just constantly moving about and he wouldn't keep his dummy in. He was just constantly irritable for hours. Even after he started to sleep he was still irritable when he was awake."
Sweating	"All his back, it was all his back and the back of his head and you could feel it on his forehead he had like little beads on his forehead. He doesn't sweat like that normally. It was really, really wet so I changed his babygro a few times. And when I picked him up and put his face close to me his face was wet, it was cold and it was like a clammy sweat."
Sneezing and yawning	"Every day he has some sort of sneezing fit and he yawns all the time. But they were saying they were signs of you know – because he'd had the operation then so I don't know if they thought he was having a bit of withdrawal then but I was like "No, I really know that's nothing to do with that, that's just how he is.""

Breath holding	"When he went through his rough period when we were letting the sedation wear off and try and let him come round. Then he'd have these big paddies and every new nurse was having the full panic and like, you know, "Ring the bell and get the doctors." But we knew what he was doing and we know he would hold his breathe and he would make his heart rate drop to zero but he would eventually stop but obviously the nurses were coming in like "Oh my god this baby is blue. get someone!"" "Yes and that was just his temper so the nurses instantly were bolus this, bolus this, because they like couldn't handle that fact that he was getting so distressed which obviously none of us wanted him to do."
High pitch cry	"It was a bit more prolonged and there was a slight difference to it. It had a different tone to it and it stayed at that tone instead of reaching a high and then a low, it stayed at that same level which was different. So it wasn't like he'd get upset and it would be a wail, wail, wail (*wailing sound from Mother*) and go down it sort of stayed, it was a weird cry."
Hypertonicity	"When I was picking him up, when I was trying to comfort him I suppose he was in a sense doing it but it wasn't just his hands and arms it was his whole body. Like when I'm trying to do something with him he'd sort of do it with everything as if to say – you are not doing anything to me. And that was something he was doing when I was trying to either hold him, or put him back down, he was holding his body in a stiff way which was a bit more unusual because it wasn't a behaviour that he does a lot."

10.6.7 Discussion

This case study demonstrates the potential for withdrawal to be overlooked when the duration of drug treatment falls below the expected threshold for causing withdrawal. PICU did not perform withdrawal assessments. This may be because withdrawal was not expected or that the main cause of behavioural distress was severe breath-holding episodes, which do not appear in the SWS assessment, so may have been overlooked as a sign of withdrawal.

Another key feature of this patient's withdrawal was lip smacking, which the mother described as issues with her baby's tongue. This caused parental distress due to the consequent impact on the baby's ability to suckle on a dummy and settle to sleep.

Physical dependence in this case occurred in less time than the threshold assigned during the adaptation of the ADR causality assessment tool. The W-CAT would need to reflect the possibility of physical dependence occurring in less than five days.

Table 10.11 Additional clinical details from nursing documentation (Case study 3)					
PICU day 4	PICU day 5	PICU day 6/Ward day 1	Ward day 2	Ward day 3	Ward day 4
Extremely agitated at times, wakes angry. Grumpy and agitated. Hypertensive systolic 190 when upset and breath-holding. Esmolol started and increased post extubation. Normal when asleep, high even if awake and settled. Breath-holding, going purple, bradycardic 1st time to 80, 2nd time to 30 requiring bag and mask ventilation. CPR not required. Upset when urine bag removed, HR 80, desaturated to 60%, hand ventilated, but remained very unsettled. Fentanyl bolus no effect. MDZ bolus good effect. Nappy changed, bradycardic to 70, sucrose and fentanyl bolus to settle.	Overnight. 3 episodes of desaturation to 40%, bradycardic to 80, purple, hand-bagged, bolus fentanyl and MDZ. Settled after PRN chloral. Not very happy when awake. Regular chloral given. Fentanyl stopped.	Overnight. Unsettled ? wind, settled with Infacol. Slept for a few minutes and v unsettled again. PRN chloral. Bradycardic to 84, no desaturation, self-correcting. Hypotensive, 5 am clonidine not given. Unsettled at times.	Overnight. V irritable at start of shift. Paracetamol given, feeds increased, only settling with chloral.	Overnight. Irritable at times. Medication good effect.	Overnight. Irritable when chloral due, otherwise settled.
Bowels open loose ++++ mum	Day Quite unsettled throughout the day, no chloral needed. CVL and art line out. Mum able to settle baby down.	Day PICU. Mum trying to soothe baby. Very agitated. Paracetamol as required. Ward. Unsettled and unable to sleep since	Day. More settled but waiting for next dose of chloral.	Day. Much more settled since yesterday. Sleeping for periods. A little unsettled	Day. Much better again since yesterday. Grizzly for ½ h before chloral due, otherwise settled. Smiled at mum. Family feels he's more like himself. Unsettled

says this is normal	One episode of bradycardia at 6pm.	yesterday, lip smacking, irritable, restless. Restarted chloral, much more settled.		at times.	periods but parents advise this is no different from home.
Extubated 11.00 and PD cath removed		To ward 11.40			

10.7 Case study 4 (Withdrawal possible)

A 2 year old girl was admitted to PICU with a chest infection (adenovirus). She has Kabuki syndrome. She was intubated for 17 days and spent 20 days on PICU.

10.7.1 Sedative drug therapy

The patient was sedated with midazolam and ketamine on admission to PICU. On PICU day 4, ketamine was stopped and fentanyl was commenced. In addition, chloral hydrate and promethazine were cycled every five days for the duration of the PICU admission. The peak dose of fentanyl was 3 micrograms/kg/hr and for midazolam was 183 micrograms/kg/hr. Fentanyl was administered for 8 days before reaching peak dose on PICU day 12-15 and was then weaned gradually over 11 days. Midazolam was at peak dose for two 48 hour periods (PICU days 3-4 and 12-13) and was then also weaned over 11 days. Both drugs were converted to oral equivalents due to loss of IV access and weaning continued for a further 5 days to completion. The patient was extubated on the PICU day 17.

Perception and interpretation

The patient will be physically dependent after 20 days continuous administration of fentanyl and midazolam. Tolerance occurred over the first two weeks resulting in increasing doses to maintain optimum sedation. Slow weaning commenced shortly afterwards as the child's condition improved.

10.7.2 Highest SWS score

The highest withdrawal score, SWS 10, occurred on HDU day 3, six days after extubation (Table 10.12). Apart from this episode SWS scores ranged from SWS 1-5 (Figure 10.7).

Table 10.12 Highest SWS score components (Case study 4, SWS score 10)

Insomnia	Irritability	Respiratory distress	Diarrhoea	Sweating	Fever	Vomiting	Tremor	High pitch cry	Sneezing	Hypertonicity	Convulsions
1	2	2	1	2	2	0	0	0	0	0	0

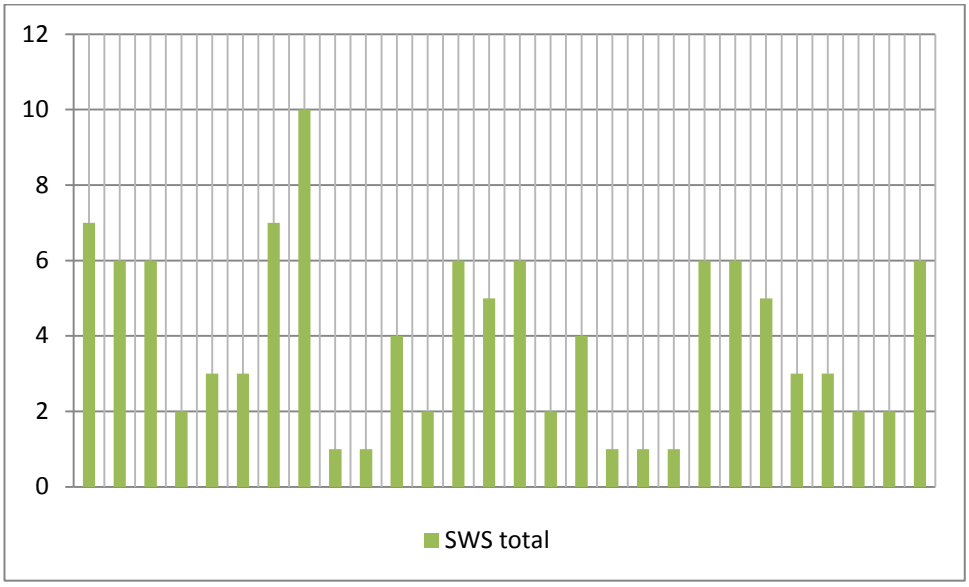

Figure 10.7 SWS scores (Case study 4)

10.7.3 Probability of withdrawal

Likelihood of withdrawal was possible at the time of the highest score (Table 10.13).

Table 10.13 Likelihood of withdrawal (Case study 4)

Criterion	Case study 4
Physical dependence possible	Fentanyl and midazolam for > 5 days.
Temporal relationship with change in dose	Weaning consistently for the previous 9 days.
Absence of differential diagnosis	No

10.7.4 Identifying a causative agent

10.7.4.1 Drug therapy and weaning rates

Fentanyl and midazolam infusions were being weaned slowly every 12 hours at consistent rates; these rate reductions had been tolerated over the previous 9 days with SWS score ranging from SWS 1-5, with a modal score of SWS 2.

10.7.4.2 Changes in drug therapy in response to the highest SWS score

There was no change in drug therapy in response to the high score.

Interpretation

Not tolerating a previously tolerated weaning regime suggests that either the child's condition has changed or that the sedation was having an inadvertent therapeutic effect, which is diminishing as drug levels reduce.

10.7.5 Withdrawal signs

10.7.5.1 Nurse documentation

All SWS scores over the timeframe were collated and the contribution of component signs was presented in a pie chart (Figure 10.8). This shows that four signs; diarrhoea, respiratory distress, irritability and insomnia contributed to most of the SWS score during this time frame.

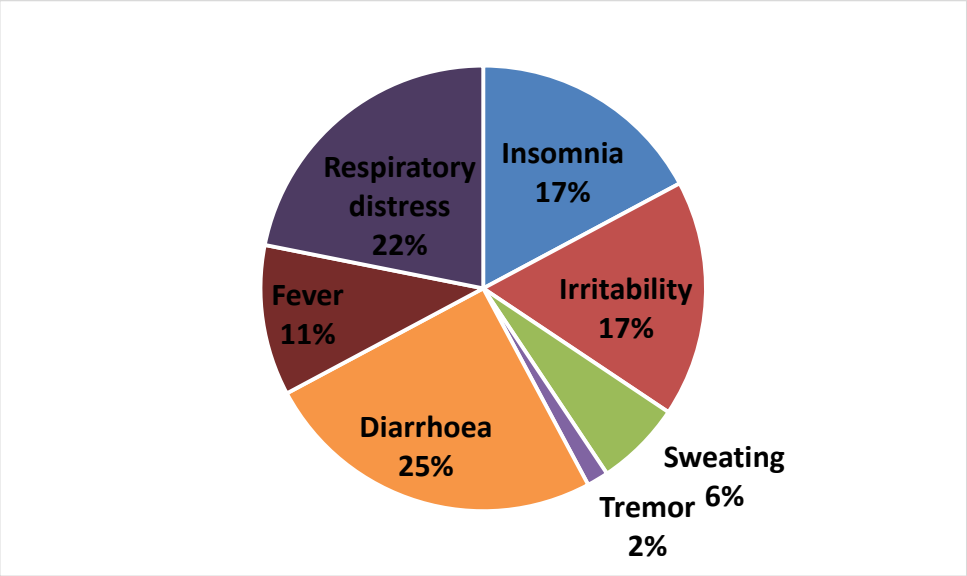

Figure 10.8 Contribution of component SWS signs (Case study 4)

10.7.5.2 Parent interviews

The SWS behaviour from the nurses' withdrawal assessments was also reported by the parent. There was a differentiation between signs which appeared more indicative of being unwell with a chest infection; insomnia, irritability and diarrhoea and signs which were more likely to indicate withdrawal; hallucinations, high-pitch noise and inattention (blank canvas) (Table 10.14). Additional clinical details from nursing documentation are presented in Table 10.15.

Retrospective interpretation

Indications that the SWS score was driven by the child's underlying condition rather than withdrawal are that the SWS score varied despite ongoing slow weaning and other than the peak dose, there was no trend in scores (either increasing or decreasing). The dominant component of the SWS score was diarrhoea, which the father reported was a pre-existing condition.

10.7.6 Parent perspective

This excerpt, taken from the interview transcripts in Study 6 gives the father's perspective on issues for his daughter's during the weaning of sedation:

> *"So I think she did show signs of withdrawal but I also think that the plan in terms of the weaning off was managed effectively to probably reduce those. But again the difficult is knowing she may have had no withdrawal at all and just had those side effects which was just – I'm trying to think what (the child) scored high on which was diarrhoea, irritability, not being able to go to sleep. Well we've spoken about (the child) teething in the last month all of those three things could be the result of teething so there is a possibility that she didn't withdraw at all but from a nurse's point of view when they are scoring they can only score what's in front of them"* (P9F)

Table 10.14 Parent report of behaviours during weaning (Case study 4)

Diarrhoea	"She had chronic diarrhoea for four weeks before she came in here."
Insomnia	"Not being able to get to sleep and when she did finally get to sleep not being able to stay asleep for periods of time. Her sleep pattern was all over the place. I found that when she is sleeping for long periods during the day she will then be awake for three hours during the night, so I just think she was all of a mix up in terms of day and night and trying to deal with that. She was on a pump feed and that was making her poo in the night. As soon as she pooed her bottom was so sore it was waking her up in pain and then she couldn't get back to sleep and we were back in the same situation, so she was never into a deep sleep because she was pooing every half-hour."
Irritability	"She was permanently irritable because she was so poorly and I think in terms of eating she seemed to have, you know lots of things like wind makes her irritable and she was a very windy baby. So yes I would say she was irritable for a couple of weeks but you would expect that given the fact that she was poorly and at times now she still does

	get irritable, you know with her breathing she still gets irritable you can see. But certainly there was a link between the insomnia and the irritability, she became irritable because she couldn't go to sleep, she wasn't irritable at other times of the day."
Hallucinations	"This was at night-time and with a child this age you can't communicate with them to find out what they are experiencing but there were times when she was sort of treading water, as if she was swimming with her hands, as if she was batting things away. I think it looked like something was there and she was sort of batting it away with her hand or it was distressing her in some way. It's a movement which I've never seen her do before."
High-pitched noise	"They were noises that I'd never heard (child's name) make before in terms of pitch, in terms of – this is very early, this is when she first came off her vent. But I think her throat was very sore so I think her normal cry didn't sound like her normal cry. (child's name) wasn't like - I remember I had this conversation - (child's name) wasn't like (child's name) in terms of the noises she made they were completely different but she was sort of throwing her arms and was irritable."
Blank canvas	"There was nothing at first because I was asking the doctor is there something wrong with her, has there been some sort of event that's made her [*like this*]? I was thinking the worst, I was thinking is there something wrong with her brain or something because she was conscious but there was nothing coming back in terms of no smiles. I did think, does she know who I am? She was a blank canvas, there was no personality at all and it was difficult to explain to the doctors because obviously they don't know what her personality was before."

10.7.7 Discussion

This case study presents a patient with possible withdrawal, assigned due to the possibility that the child's underlying condition was driving the behaviour rather than the sedation weaning regime.

The W-CAT provides a diagnostic framework which emulates the uncertainty inherent in some withdrawal assessments. The temporal relationship criterion may not reflect cases such as this one, where a previously tolerated weaning rate is no longer tolerated, indicating a change in the relative impact of the underlying condition, or another cause. Using the weaning regime as a heuristic (the child is weaning, so a behavioural change indicates withdrawal) is prone to error in circumstances such as this case.

Table 10.15 Patient details from electronic nursing records

HDU day 2	HDU day 3	HDU day 4	HDU day 6	HDU day 7
Overnight T 38^{3}, bowels open x4 bottom sore, retching. Slept well	Overnight Agitated 2 x chloral, 1 x promethazine	Overnight settled	Restless Tolerated weaning	Overnight Tachycardic at times, mainly when upset. Agitated, restless.
Awake and looking round, not upset. Agitated around lunchtime. Settled and slept pm.		Increased WOB 6 am. Blood gas OK, lactate raised, Airvo to CPAP. T 38^{8}, rash, blood cultures SWS score 7 and 10 however difficult to assess due to symptoms associated with pyrexia.		Settled pm
Airvo ventilation		Alert and responsive interacting with family in the morning.		
		18.00 Sleeping, once established on CPAP and had chloral.		

No documentation HDU day 5

The withdrawal signs described by the father portray the equivocal nature of these behaviours. At face value this child scores for withdrawal. The father's perspective however views some of these signs (diarrhoea, insomnia and irritability) in the light of his daughter's underlying condition. Other signs (high pitch cry, hallucinations and blank canvas) rely on a level of interpretation based on knowing the child's usual behaviour. This case highlights the value of the parent perspective when interpreting behaviours.

The items in the SWS did not cover all this patients behaviour changes, which impacts on the construct validity of the SWS tool.

Similarly to previous case studies, the likelihood in this case is a co-existence of withdrawal and the underlying condition. Treatment decisions depend on the relative impact of these clinical issues, determining whether increased respiratory support will reduce behaviours and permit the continuation of weaning, or whether stopping weaning will improve the child's respiratory status.

10.8 Case study 5 (Withdrawal unlikely)

A newborn baby boy was admitted to PICU on the first day of life following complications after an emergency atrial septostomy. He had an antenatal diagnosis of a congenital heart defect (Transposition of the Great Arteries). A prostaglandin infusion, to improve blood flow, was stopped on day 16 but recommenced on day 23 due to a drop in oxygen saturations despite an increase in ventilatory support. A scan confirmed narrowing of the ductus arteriosis and prostaglandin was continued (until surgery six weeks later). An infusion of milrinone, an inotrope, was stopped on day 20 and recommenced on day 24 for 48 hours. He was extubated onto Optiflow on PICU day 25. Six days later, a chest X ray revealed an enlarged left ventricle. He was discharged to the ward 2 days later prior to further cardiac surgery. The highest SWS score was on PICU day 26.

10.8.1 Sedative drug therapy

The patient was cycled every 5 days in combinations of fentanyl and midazolam, morphine and chloral and ketamine and midazolam in an attempt to prevent physical dependence. The fourth cycle (clonidine 1 microgram/kg/hr and promethazine 1mg/kg every 6 hours) was stopped on PICU day 21. Enteral sedation was commenced on day 21 with diazepam 0.1 mg/kg every 8 hours; oral morphine 50 micrograms/kg every 6 hours was added on day 23. On day 24, an IV clonidine infusion was recommenced at a rate of 0.1 microg/kg/hr. No changes were made to the enteral sedation regime for the following 8 days. Clonidine rates varied between 0.1 and 0.5 microgram/kg/hr for the first 4 days and were then weaned by 0.1 microgram/kg/day over 5 days until stopped.

10.8.2 Highest SWS score

The highest withdrawal score, SWS 7, occurred on PICU day 26, one day after extubation (Table 10.16). SWS scores varied between SWS 1 and SWS 6 over the following 5 days. (See Figure 10.9)

Table 10.16 Highest SWS score components (Case study 1, SWS score 7)

Insomnia	Irritability	Respiratory distress	Diarrhoea	Sweating	Fever	Vomiting	Tremor	High pitch cry	Sneezing	Hypertonicity	Convulsions
1	1	2	0	0	1	0	0	0	2	0	0

Figure 10.9 SWS scores (Case study 5)

10.8.3 Probability of withdrawal

Physical dependence possible

The patient was at low risk of physical dependence after cycling sedation every 5 days. Enteral sedation doses were within the normal range.

Temporal relationship with change in dose

There was no temporal link to changes in sedation, as the patient appeared very settled after cycling from clonidine and promethazine to a low dose of enteral diazepam.

Absence of differential diagnosis

In the hours prior to the highest SWS score, milrinone was stopped and the baby was described as "working harder, tachypnoea and had respiratory acidosis. The ventilation flow rate was increased in response and an IV fluid bolus administered. The temporal link is to reductions in inotrope support, the patient's clinical deterioration and the adverse effects of prostin (tachycardia, pyrexia, vomiting (BNF 2016)).

The likelihood of withdrawal was categorised as unlikely at the time of the highest score (Table 10.17).

Table 10.17 Likelihood of withdrawal (Case study 5)

Criterion	Case study 5
Physical dependence possible	Unlikely.
Temporal relationship with change in dose	Five days since change in sedation.
Absence of differential diagnosis	No.

10.8.4 Identifying a causative agent

10.8.4.1 Drug therapy and weaning rates

No causative agent for withdrawal was suspected.

10.8.4.2 Changes in drug therapy in response to the highest SWS score

There was no change in sedative drug therapy in response to the high score.

10.8.5 Withdrawal signs

10.8.5.1 Nurse documentation

All SWS scores over the timeframe were collated and the contribution of component signs was presented in a pie chart (Figure 10.10). This shows that two signs; fever and respiratory distress contributed over half of the SWS score during this time frame. These signs are likely to be a consequence of the child's clinical condition and ADR to prostin.

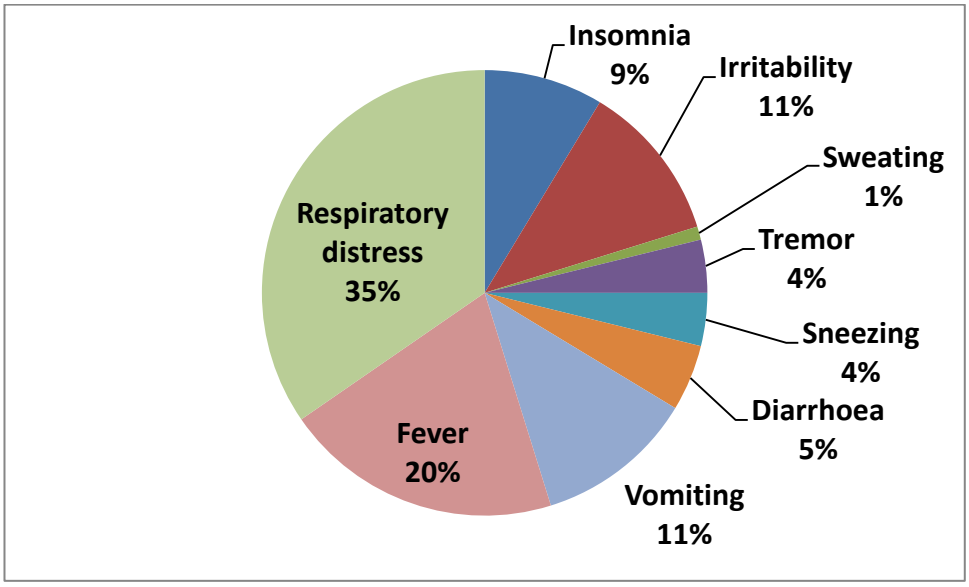

Figure 10.10 Contribution of component SWS signs (Case study 5)

10.8.5.2 Parent interviews

The SWS behaviour from the nurses' withdrawal assessments was also reported by the parent. There was a differentiation between signs which appeared more indicative of being unwell with a chest infection; insomnia, irritability and diarrhoea and signs which were more likely to indicate withdrawal; hallucinations, high-pitch noise and inattention (blank canvas) (Table 10.18).

10.8.6 Parent perspective

This excerpt, taken from the interview transcripts in Study 6, gives the mother's perspective on her son's condition:

> *"One of the sedations he was on he had a very bad sort of like case of withdrawal from that and we had seizure movements, he went grey, he was very sick, the diarrhoea and constant sneezing, and it was all from obviously the product. They checklist then and at that point they said because his heart rate started going nuts and the numbers started beeping and all this, and we were thinking – oh what's this, this time, what's happened now – and then they started ticking off lists and said – "Oh look we've got this green sheet and he's actually scoring quite high on the withdrawal". At that point I think they were trying to wean his midazolam off quite quickly and put him onto clonidine. The midazolam time he was still on the ventilator, nowhere near being extubated and that was the worst one. And his second worst one he'd just been extubated and then they changed so many things at once, including the extubating him within the first twelve hours I think."(P10M)*

10.8.7 Discussion

This case study presents a patient who was unlikely to be withdrawing at the time of the highest score. There was no temporal link to changes in sedation and there was a possibility that the child's underlying condition was driving the behaviour. The mother described two episodes of withdrawal; the second episode relates to the highest score reported here. The earlier episode linked to reducing midazolam, but did not have a corresponding SWS score, so could not be included in the analysis. At that point withdrawal was possible due to a temporal link with changes in midazolam dose. However, other causes could not be excluded as prostin had been stopped and the baby was described as *"grey, clammy, gasping and fighting the ventilator"* in the nursing notes.

Table 10.18 Parent report of behaviours during weaning (Case study 5)

Fever	"He'd had a fairly high temperature throughout the day, despite being barely warm his temperature just sky rocketed. They did all the bloods, he was being sick and a bit restless. His heart rate was like two-hundred-and-five, two-hundred-and-ten because it was racing, manic racing. He was just dripping with sweat and really, really hot." "We had a few nights of restlessness and a high temperature but he wasn't as upset as he had been before and his colour didn't change as much and it was some of the same symptoms but just on a lower grade if you like."
Insomnia	"Going from being quite sleepy to suddenly fighting it and almost not wanting to sleep. He was restless and taking ages to get to sleep - I think it was probably about two or three hours and that was the longest he'd been awake and when he finally did go to sleep then he started doing seizure type tremor movements. But then he just seemed uncomfortable and he still had his tubes in at the time, he was making like flapping movements. Like at the time he still had his tubes, his ventilator through his nose rather than through his mouth so he could move his mouth whilst he was crying but obviously no sound came out so there'd be some lip trembling movement."
Irritability	"The arms flapping and not being able to settle, he was trying to move himself a bit more yet he still didn't have enough – like now he can turn himself from side to side roughly, he couldn't do that because he still didn't have the full use of his limbs but he was trying to move. At that point nothing would settle him, so stroking his face didn't work or touching his bum and stuff. Obviously I couldn't lift him at the time which would be my normal instinct to pick him up."
Tremor	"I think there was the sort of seizure but then I think the next morning they said he'd had a couple of little tremor- like movements, a shiver and a bit of shaking."
Respiratory distress	"He chokes anyway because of his condition but his heart rate would fly up and he was like (*sharp intake of breath by mother to illustrate*) you know. He seemed to be struggling sometimes and gasping in air. They were saying – "He was working very hard" but again sometimes that was tied in with changes to some of his heart medication."
Convulsions	"His right shoulder just started twitching; it was quite a violent sort of movement like that on the right side of his body. It lasted about a minute or two and tied in with that his colour started to change and then his heart rate went up and more sick came out. They gave him anti-seizure medication but then there's not been anything since then. He just had one dose I believe in the early hours of that morning."

Table 10.19 Additional clinical details from nursing documentation									
PICU day 23	PICU day 24	PICU day 25	PICU day 26	PICU day 27	PICU day 28	PICU day 29	PICU day 30	PICU day 31	PICU day 32
Intubated	Intubated	Extubated to Optiflow	Optiflow	Optiflow	Optiflow	Optiflow	Optiflow	Optiflow	Optiflow
Oxygen saturations <50% Ventilation increased.	Tachycardic, Pyrexial, ? due to withdrawal or to prostin Blood gases x 2, indicating over - ventilation	Oxygen saturations > 70%. Plan to extubate, ventilation weaned.	Working harder, tachypnoea pm Respiratory acidosis Flow increased	Frequent episodes of being unsettled and crying, settles with comfort measures. ? withdrawal		Does not like being disturbed, but is easily comforted and settles		Respiratory effort increased tachypnoea, nasal flaring, moderate recession.	Vomiting overnight x 5; medical review – due to withdrawal.
Prostin restarted and increased. Gelofusin bolus	Milrinone restarted. Prostin rate reduced and temperature reduced. Prostin then increased as scan showed narrowing in duct. Gelofusin bolus x 3	Milrinone continues Prostin continues	Milrinone stopped 11h Prostin continues. Fluid bolus (10% dextrose)	Prostin continues	Prostin continues	Prostin continues	Prostin continues	Prostin continues Tachycardia, CXR shows enlarged R ventricle. ? seizures as eyes appear to be rolling back when in/out of sleep.	Prostin continues Eyes rolling back at times.
BO x 10 Vomited x 2	BO x 7 Vomited x 1	BO x 4	BO x 5	BO x 3	BO x 4 Vomited x 1	BO x 5 Vomited x 2	BO x 5	BO x 4 Vomited x 3	BO x 3 Vomited x 5

Chloral 100mg PRN x2	Chloral 100mg PRN x2 Clonidine infusion started .	Clonidine continues	Clonidine reduced but not tolerated.	Clonidine reduced daily	Clonidine reduced daily	Clonidine reduced daily	Clonidine reduced daily	Clonidine stopped.	
Oral morphine 250 microg 6h	Oral morphine 250 microg 6h	Oral morphine 250 microg 6h	Oral morphine 250 microg 6h	Oral morphine 250 microg 6h	Oral morphine 250 microg 6h	Oral morphine 250 microg 6h	Oral morphine 250 microg 6h	Oral morphine 250 microg 6h	Oral morphine 250 microg 6h
Diazepam 0.5 mg 8h	Diazepam 0.5 mg 8h	Diazepam 0.5 mg 8h	Diazepam 0.5 mg 8h	Diazepam 0.5 mg 8h	Diazepam 0.5 mg 8h	Diazepam 0.5 mg 8h	Diazepam 0.5 mg 8h	Diazepam 0.5 mg 8h	Diazepam 0.5 mg 8h

BO= bowels opened.

10.9 Discussion of the utility of W-CAT in light of five case studies

These cases demonstrated the differences in the presentation and likelihood of withdrawal that exists in a small sample of patients. These differences presented challenges for the existing approach to withdrawal assessment and each of these cases was diagnosed as withdrawing, based on behaviours alone. Reflecting on the different presentations of these cases helps to illuminate the relationship between dependence and withdrawal. However, the W-CAT criteria offer a link between the construct of physical dependence and the concept of withdrawal providing the basis of a theoretical relationship, which is missing from the existing approach.

This discussion will address the utility of the W-CAT by considering the component diagnostic criteria and their clarification of the theoretical relationship between physical dependence and withdrawal in critically ill children.

10.9.1 W-CAT diagnostic criteria

10.9.1.1 Physical dependence

The likelihood of physical dependence is generally accepted to be 50% after five days of continuous sedative infusions (Ista et al 2007), occurring sooner at higher doses. One patient in this study was dependent after 4 days of fentanyl and another after 5 days of morphine and midazolam. The speed of onset of physical dependence in critically ill children is in direct contrast with the adult patients for whom the DSM diagnostic criteria were developed. The criterion for likelihood of physical dependence refers to signs of withdrawal after heavy or prolonged use (DSM, 2013). The DSM criteria also refer to a substance-specific syndrome relating to a single pharmacological agent, whereas critically ill children may be at risk of withdrawal from more than one concurrent sedative drug.

10.9.1.2 Temporal relationship

The diagnostic insight gained from considering the temporal relationship between onset of behaviours and sedative weaning may assist in the identification of causal relationships. This relationship is not a feature in the existing approach, which was highlighted in two cases. In case 1, the child's behaviour was linked to ketamine withdrawal despite the highest score occurring before the ketamine was stopped. In case 5, the child's agitation was linked to clonidine withdrawal, despite clonidine being started in response to the child's agitation.

10.9.1.3 Differential diagnoses

Excluding the possibility that other causes might explain the behavioural response is an assumption made in the ADR causality assessment tool (WHO-UMC), the DSM-5 criteria for substance withdrawal in adults (DSM, 2013) and the literature regarding withdrawal in critically ill children (Ista et al 2013, Harris et al 2016). However, this proved a challenge in some of the cases, due to the context of critical illness within which withdrawal occurs. In case 1, weaning stopped due to the SWS score, despite the score remaining high. In case 2, the baby's underlying condition was impacting on the opportunity to wean; if he had not been so unwell he may have weaned sooner. In case 4 the child had tolerated weaning at a consistent rate and then had a high SWS score; in retrospect this responded to changes in medical management including an increase in respiratory support. In case 5, withdrawal was consistently diagnosed, despite no risk of dependence and no temporal link to a change in dose.

A more pertinent consideration, rather than excluding other causes, may be whether withdrawal or critical illness is driving the behaviour; a dichotomy underpinning whether withdrawal or critical illness should be treated. In four cases in this sample, where other possible causes for the behaviours existed, the impact of these behaviours varied. As withdrawal exists in the context of critical illness, then a continuum exists whereby the clinical impact of behaviours is due to the combined effect of withdrawal and the critical illness. At one end of the continuum, behaviours will be 100% driven by withdrawal, with no impact from critical illness. At the other end of the continuum, behaviours will be 100% driven by the critical illness, with no impact from withdrawal. The point where each case lies on the continuum reveals whether clinical intervention should focus on treating withdrawal or treating the critical illness. A proposed withdrawal- critical illness continuum is presented in Figure 10.11.

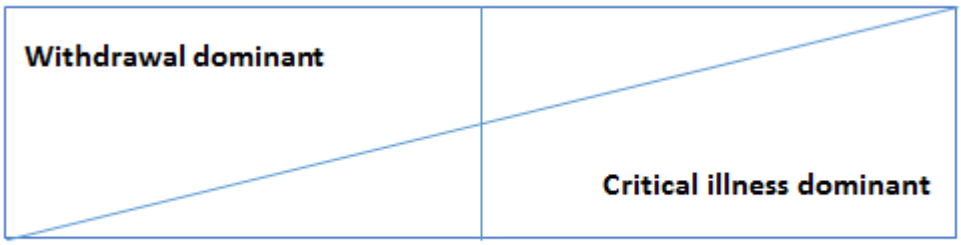

Figure 10.11 Withdrawal – critical illness continuum

This continuum also illustrates the impact that ongoing critical illness may have on withdrawal severity. A dominant influence of critical illness would indicate underlying

illness or deterioration was limiting the capacity to wean, such as case 2; whereas a dominant influence of withdrawal would indicate sedative weaning had been too rapid, such as case 3.

10.9.2 Signs of withdrawal

The contribution of component behaviours in the SWS scores in the 72 hours before and after the highest score demonstrated the dominance of a minority of signs in some patients; signs which may have been driven by the child's underlying condition. This was a retrospective review, so in some cases the patients were being assessed for withdrawal before subsequent diagnoses were known. One child who was diagnosed with influenza after the highest score had the greatest contribution to his cumulative SWS score from the items, respiratory distress and irritability (case 2). Respiratory distress accounted for one third of another child's cumulative SWS score, who was subsequently diagnosed with heart failure (case 5). The child who withdrew after 4 days of fentanyl exhibited irritability predominantly. These cases reflect the broader findings from Study 1 that showed the median number of items contributing to the highest SWS score was 5. Each of these findings supports the heterogeneous presentation of withdrawal, which challenges an implicit assumption scale development, that items contribute equally to the total score (Streiner and Norman 2003).

In addition to these cases where one or two SWS items dominated and possibly drove the withdrawal assessment score, parents described a range of other signs which were not accounted for in the score. The parental perspective suggests that the possible behaviour combinations may far exceed the range that is possible in any single tool. There was no evidence that a summed score aided assessment of withdrawal in this small sample, given the impact of underlying condition and the possibility of overlooking other behaviours that do not feature in the SWS tool.

10.9.3 W-CAT diagnostic features as the structure of a new definition of withdrawal in critically ill children

The complexity of the clinical context may be better interpreted using diagnostic criteria, which focus on the shared diagnostic features of withdrawal rather than focussing on the unique heterogenous aspects of the individual's presentation. The diagnostic criteria in W-CAT focus on the shared diagnostic features of withdrawal and may support decision-making by providing a structure to the assessment. The assigning of a probability term to the withdrawal diagnosis may provide a more accurate reflection of this diagnosis in light

of other possible causes for behaviours, than the existing definitive diagnoses of SWS, WAT-1 and SOS do.

The diagnostic features of W-CAT (Table 10.1) describe the relational statement, or postulate, between the construct of physical dependence and the concept of withdrawal. This postulate is the rate of reductions of sedative drugs in the context of physical dependence. The W-CAT features can also form the basis of the characterisation of withdrawal in critically ill children as a clearly defined syndrome. It is proposed that the newly defined syndrome is termed Paediatric Withdrawal Syndrome (PWS). The diagnostic criteria for Paediatric Withdrawal Syndrome (PWS) are;

Table 10.20 The diagnostic criteria for Paediatric Withdrawal Syndrome

Criterion A	A change in behaviour causing distress or impacting on the child's clinical condition which develop after stopping or reducing one or more sedative or analgesic infusions, or regular medications, which have been administered for at least four days.
Criterion B	Withdrawal signs develop within minutes to two days after Criterion A.
Criterion C	The behavioural signs are not due to the critical illness or deterioration and are not better explained by another medical condition or drug effect e.g pediatric delirium, adverse drug reactions.
Criterion D	Behaviours improve when the drug is restarted or increased to the previously tolerated dose, if clinically indicated.

10.10 Conclusion

The W-CAT demonstrated clinical utility in this retrospective evaluation, using case studies as test cases. The W-CAT criteria, focussing on the shared features of withdrawal syndrome appear to support and reflect the stages of clinical reasoning shown on the propositional model (Figure Part 5.1). Plotting the terms 'construct' and 'concept' on the model identified the relationship between the construct of physical dependence and the concept of withdrawal. This relationship; the rate of reductions of sedative drugs in the context of physical dependence, is a diagnostic criterion in the W-CAT. The discussion of the five case studies supported the relationship, or postulate and provided preliminary evidence of the utility of W-CAT criteria as both the defining, and diagnostic criteria for paediatric withdrawal syndrome (PWS).

Chapter 11 will consider the behavioural signs of withdrawal (Criterion B) and seek to identify a logical relationship between these variables and the concept of withdrawal.

11.1 Introduction

The conceptual framework that guided the studies presented in this thesis featured withdrawal signs at the core. These signs have been studied from a range of perspectives. These perspectives have identified flaws in the current approach to withdrawal assessment. Study 1 demonstrated that the three modal SWS scores of SWS 5, 6 and 7 comprised patients with three different likelihoods of withdrawal, which cast doubt on the diagnostic reliability of a summed score. Study 2 demonstrated that many withdrawal signs were common in children who were not withdrawing, but also revealed three signs which are much more prevalent in withdrawing patients. Study 3 revealed how the lack of a formal definition or description of withdrawal and how it manifests has hampered the validation of withdrawal assessment tools. Study 4 revealed the challenges nurses face distinguishing individual signs in a constellation of behaviours and then interpreting the meaning of these behaviours. Study 5 revealed that parents recalled SWS signs and found them distressing. Study 6 showed that parents recognised other signs of withdrawal that are not included in the SWS tool. The literature review and pointed to a heterogeneous presentation of withdrawal, resulting in a high proportion of false positive diagnoses of withdrawal (33% WAT-1 (Franck et al 2008), 51% SOS (Ista et al 2013)).

11.2 Purpose

The purpose of the interpretive synthesis presented in Chapter 11 is to:

1. Integrate the multiple sources of data presented in Studies 1-5 regarding the manifestation of withdrawal syndrome, to consider the ease of interpretation and clinical utility of signs of withdrawal, and
2. Consider the epistemic assumptions, or underlying physiological mechanisms that link these behavioural variables to withdrawal.

11.3 Method

All SWS signs and those signs identified by at least one parents were included in the synthesis. The following features were collated and considered for each sign;

1. A definition of each sign along with a comparison of similar signs,
2. The pathophysiological mechanism for the behaviour in withdrawal syndrome,
3. The inclusion of the signs in SWS, WAT-1 and SOS,
4. Results from the SWS evaluation (Study 1),
5. Nurses recognition and scoring for the four behaviours: insomnia, irritability, respiratory distress and hypertonicity (Study 4),
6. Parents' descriptions of behaviours and their intensity ratings (Study 5 and 6)
7. Additional description of behaviours from computerised nursing notes.

11.4 Insomnia

Insomnia is not formally defined in the SWS tool (Cunliffe et al 2004) but was defined as "sleeps for no more than 1 hour at a stretch" in SOS (Ista et al 2009) and similarly as "sleeping less than 1 hour in the previous 4 hour period" in the OBWS study (Franck et al, 2004).

Insomnia is a recognised sign of opioid and benzodiazepine withdrawal (Ista et al 2007), features in one of the pediatric delirium (PD) tools as "*sleep-wake cycle disturbance*" and is also a known feature in ICU patients. Recent studies have investigated the impact of the different factors of critical illness, drugs and the ICU environment on sleep. The ICU environment has features which interfere with sleep, such as noise and light, which results in sleep fragmentation, with nearly half of sleep occurring during daytime, even in healthy adult volunteers (Drouot 2008). Sleep and waking is regulated by many neurotransmitters, including noradrenaline, serotonin, acetylcholine, dopamine, histamine, gamma-aminobutyric acid (GABA), the pituitary hormones and melatonin. Any drugs that alter the balance of these neurotransmitters, as opioids and benzodiazepines do, may affect sleep (Benyamin 2008). The pathogenesis of either primary or withdrawal-induced insomnia is not clear. Primary insomnia is thought to be a consequence of hyperarousal, which is exhibited as hypervigilance during the day and difficulty initiating and maintaining sleep at night (Bonnet and Arand 1997).

11.4.1 Presence of insomnia as an item in withdrawal assessment tools

Insomnia is included in SWS (Cunliffe et al 2004) and SOS (Ista et al 2009) and featured in OBWS (Franck et al 2004). Insomnia was highly prevalent in the SWS evaluation (Study 1), occurring in 86% of cases and was the most frequently observed behavioural sign in the OBWS study (Franck et al 2004) occurring in 52% of withdrawing patients. Subsequent refining of OBWS in the WAT-1 study (Franck et al 2008) however, did not include insomnia and gave no rationale for its omission.

11.4.2 Nurse perspective

Nurses found assessment and scoring for 'insomnia' challenging because it was difficult to decide whether the patient had insomnia (N1), whether insomnia was due to withdrawal (N3,5) and the subjective nature of the intensity scoring (N2,4,7,8). Two nurses admitted to always scoring patients '1' (N6,12), whilst another felt limited by the choice of only two intensity options (N4). Nurses' definitions of 'insomnia' sometimes included features of 'irritability' or 'motor disturbance.'

11.4.3 Parent perspective

Eighteen of 20 parents who completed questionnaires identified insomnia in their child, which they gave a median (IQR) rating of 7 (4-10) for distress. Ten of 11 parents who were interviewed, described insomnia. These descriptions covered absence of sleep (n=6), broken sleep (n=4) and delayed onset of sleep (n=1) (Table 11.1).

Table 11.1 Parents' descriptions of their child's insomnia

Parent	Description of insomnia
P1	Broken sleep
P2	Three and a half days without sleep. Sleep disturbance for 3 weeks.
P3	36-48h without sleep. And irregular sleep patterns.
P4	No sleep at all for 3-4 days.
P5	Broken sleep
P6	Slept only about 3h in a 48 hour period
P8	24h with very little sleep; only sleeping for a few minutes at a time
P9	Broken sleep, sleeping during the day.
P10	Taking ages to get to sleep.
P11	Just not being able to sleep ?24h

11.4.4 Summary

It is important to differentiate the sleep disruption typical to most ICU patients and insomnia as a sign of withdrawal, which is the striking absence of sleep described by parents. The high prevalence of insomnia in the SWS audit may represent a blurring of these two states, limiting the diagnostic value of this sign. Blurring of boundaries between SWS signs also occurred in the nurses' definitions.

Lack of sleep, to the extent described by parents, was distressing; not only to see their child going so long without sleep but also their concern that this might have a detrimental impact on their child's recovery. Absence of sleep to this extent did not appear to translate to nursing documentation. This may be a consequence of the nursing shift pattern, which may impose a diurnal interpretation, with sleeplessness at night being more noticeable than that occurring during the day, consequently obscuring the cumulative impact over successive shifts. "Sleeps for no more than 1 hour at a stretch" (SOS, OBWS) is objective and elegantly distinguishes between sleep disruption, insomnia and other SWS behaviours.

11.5 Irritability/irritable (agitation, restless, fidgety) and anxiety (and inconsolable)

Irritability describes a broad concept rather than a specific behaviour and a range of definitions exist; the medical, paediatric and colloquial definitions may each be relevant to withdrawal assessments (Table 11.2). The overlapping definitions and terms are shown in bold in Table 11.2 to demonstrate how these terms intermingle. The clinical impact of interpreting the meaning of irritability as a broad behavioural concept is further demonstrated, by the occurrence of two of the terms in the overlapping definitions; "restlessness" and "inconsolable" featuring in the PD tools. Restlessness and inconsolability encompass four of the five delirium domains; cognition, psychomotor activity, affect/ distress and orientation in the CAPD tool (Traube et al 2014) and disorganised brain in psCAM-ICU (Smith et al 2016).

11.5.1 Presence of irritability as an item in withdrawal assessment tools

Irritability occurs in SWS and in SOS, as "irritable"; which is a component of agitation (with restless and fidgety). Once again, the clinical utility of SOS is enhanced with the inclusion of four similar terms, which captures the broad-spectrum of behaviour that is sought, compared with the more restrictive use of a single term. SOS also includes the

similar term of “anxiety”, which is defined as “unrest or anxious face (eyes wide open, eyebrows tense and raised). Behaviour can vary from panicky to draw back” (Ista et al 2009). Anxiety as a symptom, can only be reported by the patient, so is redundant in the PICU population, where the majority of patients are pre-or non-verbal. With agitation being the manifestation of anxiety, the presence of both terms in SOS presents the opportunity of scoring a single behaviour twice, which implies a flaw in content validity. The rationale for using facial expression as a measure of anxiety in infants is also not provided.

Table 11.2 Definitions of irritability and related terms (bold terms show overlap with other terms

Term	**Definition**
Irritability (medical)	“the state of being abnormally responsive to slight stimuli, or unduly sensitive” (Miller-Keane Encyclopedia and Dictionary of Medicine, Allied Health and Nursing, 7th ed, 2003, Saunders.)
Irritability (paediatrics)	the “over response by an infant to harmless stimuli; fussiness, whining, fretfulness, despite attempts to comfort and console by the caregiver, but not necessarily crying. (Overlaps with **inconsolable**.)
Irritability (colloquial)	“the quality of a tendency to being easily annoyed.”
Agitation (medical)	“the excessive, purposeless cognitive and **motor activity** or **restlessness**, usually associated with a state of tension or **anxiety**; the manifestation of **anxiety**. Also called psychomotor agitation.” (Dorlands Medical Dictionary, 2007 Saunders).
Agitation (colloquial)	“a state of **anxiety** or nervous excitement.”
Anxiety	A symptoms, which may be manifested as agitation.
Anxiety (Colloquial)	“ants in pants, fidgeting, pacing, pulling of clothes” (McGraw-Hill Concise Medical Dictionary, 2002). (Overlaps with **uncoordinated /repetitive movements.)**

11.5.2 Nurse perspective

Nurse definitions of ‘irritability’ sometimes included features of ‘insomnia’ or ‘motor disturbance.’ One nurse used the term ‘irritated’ when defining ‘irritability’ (N1). Nurses found anything less than severe irritability hard to score, due to not knowing the child’s normal behaviour (N9) and differed in their opinion as to whether intensity (N10) or duration of irritability (N4, 11) or consolability (N5,6,7) should guide the score. Differentiating between irritability as a sign of withdrawal or induced by clinical interventions or care was highlighted by two nurses (N2,3). One nurse admitted to always scoring patients ‘1’ (N12), whilst another felt limited by the choice of only two intensity options (N3).

11.5.3 Parent perspective (recognition of irritability and other similar signs)

Eighteen of 20 parents who completed questionnaires identified irritability in their child, which they gave a median (IQR) rating of 8 (7-10) for distress. When interviewed, all but one parent described irritability, which manifested as a range of idiosyncratic behaviours (Table 11.3).

Table 11.3 Parent descriptions of irritability (bold terms show overlap with other terms)

Parent	Irritability	Other related terms
1	Yes	Tantrums, screaming.
2	Yes	moving arms about, reaching out to grab things (**hallucinations**), scratching and itching, **restlessness**. Not keeping still, constantly itching, scratching and **thrashing his arms around**
3	Yes	**Moving head side to side, rubbing face and nose, lip smacking**
4	Yes	Very **jittery**, not settling
5	Yes	**Agitated**, didn't want to be touched
6	Yes	Kicking round a lot, wriggling round a lot
7	No	No
8	Yes	**His tongue was wild, constantly out of his mouth, lip smacking**
9	Yes	**Swimming movements with arms**, throwing arms about (**hallucinations**)
10	Yes	**Restless, flapping movements, arms flapping**, trying to move himself
11	Yes	**Agitation, thrashing round the bed**,

11.5.4 Signs documented in nursing clinical records

Irritability was the only behaviour that prompted nurses to document additional information for every patient in the study. In ten of these patients, nurses described the behaviour as 'agitated' (Table 11.4).

11.5.5 Summary

This is a complicated term due to the range of idiosyncratic behaviours described within one SWS sign. The high prevalence of the behaviour in the SWS audit again suggests that this is a ubiquitous behaviour in critically ill children, rather than having diagnostic value in identifying withdrawal. This inference was reinforced by the challenges nurses described in differentiating irritability due to illness (such as the patient subsequently diagnosed with a large ASD), withdrawal or other co-morbidities (purposeless actions and inconsolability also being features of pediatric delirium (Creten et al 2011). The challenge of interpreting behaviours is also revealed in the patient who was described as "very nosey" (P3), but who may have been more accurately described as 'abnormally

responsive to slight stimuli'. Whether there is any clinically relevant difference between the terms agitation and irritability in terms of withdrawal behaviour, is debatable, but the extensive use of the former term by nurses suggests irritability alone is insufficient to describe the patient's state.

Table 11.4 Nurse documentation of behaviour related to irritability

Patient	Nurse documentation related to irritability
Pt 1	**Jittery**, **restless**, **agitated**, very unsettled.
Pt 2	**agitated**
Pt 3	**agitated**, unsettled very nosey, reacting to all noises on the ward
Pt 4	**agitated**, **restless** but not irritable.
Pt 5	very **agitated** with cares, very unsettled, **hard to console** (abnormal eye movements)
Pt 6	very unsettled, very **agitated**, doesn't like to be handled (then diagnosed with large ASD)
Pt 7	very **agitated**, does not like to be disturbed
Pt 8	extremely **agitated**, unsettled, **restless**, grizzly
Pt 9	Agitated, **restless**.
Pt 10	Does not like to be disturbed.
Pt 11	Very unsettled, very **agitated**.

11.6 Sweating

Sweating, as a sign of withdrawal, occurs as a result of autonomic dysfunction and is one of six signs that occur in all three withdrawal tools. In SOS, sweating is scored "if not caused by room temperature, clothing, swaddling etc."
In WAT-1, any sweating during the two minutes of pre-stimulus observation is scored.

11.6.1 Nurse perspective

Two nurses documented additional information under this sign describing one patient as 'clammy' (Pt 3) and another as 'sweating profusely' (Pt 5).

11.6.2 Parent perspective

Sweating was recognised by 14/20 parents and scored a median (IQR) rating of 5(4-17) for distress. When interviewed, 9/11 parents described sweating (Table 11.5) and also raising the issue about this sign being typical of patients with cardiac conditions.

Table 11.5 Parent descriptions of sweating.

Parent	Description of sweating
P3	Beaded sweat across hairline and forehead
P4	His head and hair get soaked (but sweating is part of underlying condition)
P6	The back of his head was wet, very clammy for 24-48h.
P8	His back and the back of his head, little beads on his forehead, face was wet and clammy.
P10	Dripping with sweat (and tachycardic)

11.6.3 Summary

This sign may indicate withdrawal if sweating is not typical to the child.

11.7 Tremor

Tremor occurs as an item in SWS, SOS and WAT-1. Tremor was one of three signs that showed the greatest difference in prevalence between the withdrawing and not withdrawing groups in the OBWS and SBOWC studies described in Chapter 5.
In SOS, as an indication of central nervous system (CNS) irritability, tremor is defined as "slight, involuntary rhythmic of hands and/or feet, either spontaneously, or in response to environmental stimuli". In WAT-1, moderate or severe tremor is scored, whereas mild or intermittent tremor is not scored.

11.7.1 Parent perspective

Tremor was recognised by 12/20 parents and scored a median (IQR) rating of 8 (7-8.5) for distress. When interviewed, 5/11 parents described tremor; their varied descriptions pointing to a range of disordered movement other than tremor (Table 11.6). This suggests that parents construed 'tremor' in a similar way to 'irritability' as an umbrella term to describe a range of behaviours, the aetiology and meaning of which, in terms of withdrawal, may vary. Movement and muscle tone are regulated by the extrapyramidal system (EPS), of which the basal ganglia are the main nuclei. Damage to the EPS or basal ganglia results in disordered movement known as dyskinesias. Tremor is one example of dyskinesia. It appears that withdrawal may temporarily disrupt the function of the EPS or

basal ganglia, which is manifested as abnormal movement and/or muscle tone. P11 infers an overlap in perception or interpretation of abnormal movement and convulsions; it is not clear which behaviour this represented.

Table 11.6 Parent descriptions of tremor

Parent	Description of tremor
P4	Constantly shaking, arms are never still, like a really bad **twitch**, his legs and arms are going. For a couple of days he's never still.
P6	**Jittery** hands
P10	Tremor-like movements, a shiver and a bit of shaking.
P11	Really big shakes, like **seizures** or rigors.

11.7.2 Summary

SOS and WAT-1 score different intensities of tremor and parents described a range of movement disorders under this term. This sign may be open to interpretation by nurses but was not investigated in this study. A broader umbrella term such as movement disorder, may better or more accurately represent the range of dyskinesias expressed by withdrawing children.

11.8 Sneezing and yawning

Sneezing occurs in two of the three tools: SWS and WAT-1.
In WAT-1, more than one yawn or sneeze during the 2 minutes of pre-stimulus observation is scored, whereas only one sneeze or yawn is not scored.
Yawning is due to hyperstimulation of the parasympathetic system.

11.8.1 Parent sign

Sneezing was recognised by 9/20 parents and had the lowest ranked score median (IQR) of 0 (0-3) for distress. It was also recognised by 6/11 interviewed parents, one of whom expressed frustration that this was typical of her child, but was being interpreted by nurses as a sign of withdrawal:

> *"every day he has some sort of sneezing fit and he yawns all the time. The nurses said it was signs of withdrawal, but that's just how he is. I really know it's nothing to do with that." P8*

11.8.2 Summary

This sign does not cause distress but may indicate withdrawal if it differs from the child's typical or baseline behaviour: this depends on parent input during the assessment.

11.9 Diarrhoea

Diarrhoea, as a sign of withdrawal, occurs as a result of autonomic dysfunction and is one of six signs that occur in all three withdrawal tools.

In SOS, under gastrointestinal dysfunction, diarrhoea is defined as watery stool, not related to feeding changes, or when the result of breastfeeding. In WAT-1, diarrhoea is defined as any loose or watery stool in the previous 12h.

The underlying aetiology of each sign is an important part of better understanding withdrawal; it is not clear whether this is gastrointestinal or autonomic.

11.9.1 Parent signs

Diarrhoea was recognised by 13/20 parents and was scored a median (IQR) 5 (4-6) for distress. During interview, 6/11 parents reported this sign, one of whom explained that the diarrhoea had started before weaning was commenced, which limited the diagnostic potential of the sign; "*She had diarrhoea for 4 weeks before she came in" (P9).* Another parent explained that their child was usually loose and wasn't worse during withdrawal; *"He always had sloppy-ish bowel movements, so I'm not sure if there was additional*" (P10).

11.9.2 Summary

This sign may indicate withdrawal if other causes for diarrhoea can be discounted: this includes typical behaviour, which also depends on parent input during the assessment.

11.10 Vomiting

Vomiting, as a sign of withdrawal, occurs as a result of autonomic dysfunction and is one of six signs that occur in all three withdrawal tools. It was also one of three signs that showed the greatest difference in prevalence between the withdrawing and not withdrawing groups in the OBWS and SBOWC studies described in Study 2 (Chapter 5). In SOS, under gastrointestinal dysfunction, vomiting is scored if occurring at least once in the previous 4 hours, if not related to feeding changes. In WAT-1, any vomiting, spontaneous retching or gagging in the previous 12 hours, is scored. These two criteria, whilst enabling an objective assessment of the behaviour, present operational differences

in terms of frequency and intensity. Consequently the scoring threshold for WAT-1 is one vomit in 12 hours compared with a threshold for SOS of two vomits in 4 hours.

11.10.1 Parent perspective

Vomiting was recalled by 9/20 parents and was scored a median (IQR) 5 (3-7) for distress.

11.10.2 Nurse perspective

Only one additional description was documented in nursing records, which recorded Pt6 as "gagging on the (endotracheal) tube". Gagging on the tube is indicative of under sedation rather than a sign of withdrawal.

11.10.3 Summary

This evidence does not indicate a cohesive presentation or aetiology for vomiting as a sign of withdrawal. Other causes and gagging as a sign of under sedation in the ventilated child, may further confuse the meaning of this behaviour.

11.11 Fever

Fever, as a sign of withdrawal, is one of six signs that occur in all three withdrawal tools. The child's temperature is not specified in SWS. In SOS, fever is scored for any temperature >38.4C in the previous 4 hours. In WAT-1, fever is scored if the most frequent temperature is >37.8C in the previous 12 hours. In the OBWS study, temperature >37.2C was scored, which was very common in both withdrawing (82%) and not-withdrawing (68%) patients respectively (Franck et al 2004). The rationale for the differences in scoring thresholds is not clear.

The rationale for including fever as a sign of withdrawal is also not clear. Temperature dysregulation is a feature of autonomic instability. The autonomic component of thermoregulation mediates responses such as shivering, sweating and vasoconstriction to maintain body temperature. Fever on the other hand, is an immune defence, mediated by endogenous pathogens which increase the usual target body temperature (Sessler et al 2008). Autonomic instability may manifest as regulatory responses such as shivering or sweating being triggered at normal body temperature, or the absence of such responses when hypothermic or hyperthermic respectively.

11.11.1 Parent perspective

Fever was recalled by 6/20 parents and was scored a median (IQR) 6.5 (3-8) for distress.

11.11.2 Summary

Fever lacks a cohesive operational definition and the aetiology as a sign of withdrawal is unclear.

11.12 High pitch cry/distress

All tools score crying or distress, each using slightly different terminology; high pitch cry (SWS), inconsolable crying (SOS), grimacing (SOS) and awake/distressed in WAT-1.
In SWS, high pitch cry is a sign of neurological impairment, which is susceptible to subjective interpretation by the assessing nurse. In SOS, under CNS irritability, inconsolable crying is scored if the child cannot be consoled by parents by offering distraction e.g. pacifier, food, or game playing with older children. Silent crying is scored in intubated children. Grimacing, also under CNS irritability, is scored separately and defined as eyebrows contracted and lowered, nasolabial fold visible. This is another SOS sign which is redundant in part of the PICU population, as this is describing an infant-only parameter. In WAT-1, 'state' is scored if the child is awake/ distressed during the two minute pre-stimulus observation and additionally, if time taken to settle after stimulus is more than two minutes.

Inconsolability is a feature of both PD tools. In CAPD (Traube et al 2014), it is considered to reflect the DSM delirium domains of cognition, psychomotor activity and affect/distress. In psCAM-ICU (Smith et al 2016) it reflects the feature "disorganised brain."

11.12.1 Parent perspective

High pitch cry was recalled by 6/20 parents and was scored a median (IQR) 8 (6-9) for distress. The parent descriptions add a novel perspective in terms of aetiology (Table 11.7). Three parents described a cry that struck them as different from their usual cry, but they were not describing a high pitch cry. Their description of a different cry is supported by research that suggests that neurological deficits alter the baby's control of their vocal cords, which results in changes in the cry acoustics (Reggiannini et al 2013).

Table 11.7 Parent descriptions of high pitch cry

Parent	Description of high pitch cry
P1	Constant cry-ey, moany, making a lot of noise.
P6	Not a cry I've heard before, constant, his eyes looked sad.
P8	Bit more prolonged, slightly different, a different tone and stayed at that tone. It was a weird cry.
P9	Noises I'd never heard before in terms of pitch.
P11	He had that phase when he was crying a lot and really upset.

11.12.2 Nurse perspective

Nurses documented behaviours synonymous with distress on four occasions (Table 11.8)

Table 11.8 Nurse documentation of distress behaviours

Patient	Additional comments in nursing records.
Pt 1	Very distressed, upset.
Pt 2	wimpering
Pt 3	moany
Pt 8	grumpy

11.12.3 Summary

It is not clear that high pitch cry, inconsolable crying, grimacing and distress are linked concepts in terms of withdrawal. The aetiologies for these overlapping signs include neurological, extrapyramidal, pain and emotion, all of which limit its usefulness as an indication of withdrawal assessment.

Parents may be able to recognise neurological dysfunction by subtle changes in their baby's cry, which would not be perceptible to clinicians. This sign may indicate a number of differential diagnoses, including withdrawal and pediatric delirium.

11.13 Respiratory distress

Respiratory function occurs in two of the three tools: SWS and SOS. In SOS, under autonomic dysfunction, tachypnoea is defined as a breathing rate, which exceeds baseline value by ≥15%. A baseline is hard to define in this cohort, who are usually admitted to hospital with breathing difficulties and may be intubated and mechanically ventilated.

11.13.1 Parent perspective

Respiratory distress was recalled by 10/20 parents and was scored a median (IQR) 9 (8-9) for distress, which was the highest score for a withdrawal sign, apart from convulsions.

11.13.2 Nurse perspective

Differentiating between respiratory distress as a sign of withdrawal or the patient's underlying condition was highlighted as a challenge by four nurses (N5,6,7,8). One nurse admitted to always scoring patients '1' (N12), whilst another felt limited by the choice of only two intensity options, particularly when accounting for the patient's baseline (N2,3). Others gave a rationale for their severity scoring based on effort and duration of respiratory distress (N4,9,10,11).

There are many causes for respiratory distress in the critically ill child: their underlying condition, an artefact of mechanical ventilation, failure to tolerate reducing ventilatory support or clinical deterioration (Van der Zwaan, 2012).

11.13.3 Summary

Tachypnoea, as a sign of autonomic dysfunction, is a possible sign of withdrawal syndrome. However, there is no evidence to link the broader construct of respiratory distress with withdrawal. This sign also lacks diagnostic value in this critically ill population for whom respiratory distress is widespread and, unlike a putative diagnosis of withdrawal, requires immediate intervention and treatment.

11.14 Hypertonicity

Hypertonicity, as a sign of withdrawal, is one of six signs that occur in all three withdrawal tools. In SOS, under CNS irritability, increased muscle tension is defined as clenched fists or tense, clenched toes. In WAT-1, muscle tone is scored if tone is increased during the one-minute stimulus observation.

11.14.1 Nurse perspective

Nurses did not feel confident about the scoring of this behaviour, either in terms of identification or severity. In relation to children with behavioural abnormalities, two nurses described seeking the parents' opinion (N1,7). Two nurses were unfamiliar with the term (N9,12).

11.14.2 Parent perspective

The descriptions offered by parents again shed light on the meaning of behaviours (Table 11.9). Some of these descriptions appear to describe other concepts. Two parents (P4

and P8) may be describing behaviour synonymous with 'negativism' (apparently motiveless resistance), which is a sign of catatonia (Esseveld et al 2013). It is concerning that nurses appeared dismissive of one parent's concerns that her son was having a seizure.

Table 11.9 Parent descriptions of hypertonicity

Parent	Description of hypertonicity
P3	…clench fists, bring them up to his face, very stiff joints and limbs and if you tried to relax them, it would be very difficult.
P4	Lock his arms or legs straight or both. There would be no shifting him, you wouldn't be able to move him until he was ready to be moved. Lasting a minute or two a few times a day.
P8	When I was picking him up, trying to comfort him, it was his whole body, as if to say "you're not doing anything to me." He was holding his body in a stiff way.
P11	He would be lying comfortably then you would see him legs extended, arms extended, shaking like children have seizures, like when he's had a seizure before, but they come up and say "No, it's sedation-related." (Copied to convulsions)

11.14.3 Summary

This signs demonstrates the diverse behavioural interpretations that can be made by parents and nurses. A clear definition is required to describe this behavioural manifestation of withdrawal and minimise the blurring of different conditions with similar presentations.

11.15 Convulsions, startle to touch and muscle twitching

This sign only occurs in SWS, although SOS includes muscle twitching and WAT-1 includes 'startle to touch'. Muscle twitching is included within the definition of motor disturbance, as an element of CNS irritability. During the one-minute stimulus observation in WAT-1, moderate or severe 'startle to touch' scores, whereas mild 'startle to touch' does not score.

11.15.1 Parent perspective

Convulsion was the least commonly recalled sign by parents but scored a maximum distress score of 10 on both occasions. During interview, one other parent described similar behaviours (Table 11.10), which was discounted as a convulsion by the nurse.

Table 11.10 Parent descriptions of convulsions

Parent	Description of convulsions
P4	Twitchy, seizures (eyes in the back of his head, shaking, going stiff, respiration rate and pulse up) lasting a few seconds.
P10	Quite jumpy, quite a violent movement on the right side of his body. It lasted a minute or 2 and tied in with his colour started to change, his heart rate went up and he vomited. His right shoulder started twitching.
P11	He would be lying comfortably then you would see him legs extended, arms extended, shaking like children have seizures, like when he's had a seizure before, but they come up and say "No, it's sedation-related."

11.15.2 Nurse perspective

Nurses documented signs on four occasions (Table 11.11)

Table 11.11 Nurse documentation of behaviours synonymous with convulsions/ twitching

Patient	Additional comments from nursing records
Pt 1	Jittery, severe twitching.
Pt 3	Flickering eyes, twitching hand (also referred to jerky hand under movement disorder and fidgety hand), 5 min episode eye tracking, lip smacking. Fidgety movements in hand when unsettled. Groaning on handling, becoming stiff, cries and grimaces,
Pt 5	Abnormal eye movements. Eye rolling.
Pt 10	Eyes rolling back.

11.15.3 Summary

This sign appeared to be open to misinterpretation and it is not clear which of the different operationalisations in the withdrawal assessment tools best reflects withdrawal behaviour.

11.16 Movement disorder

This occurs as motor disturbance in SOS and uncoordinated/repetitive movement in WAT-1. It was also one of three signs that showed the greatest difference in prevalence between the withdrawing and not withdrawing groups in the OBWS and SBOWC studies described in Chapter 5. In SOS, under CNS irritability, motor disturbance, occurring either spontaneously or in response to environmental stimulus, is defined as either slight muscle jerks (involuntary, of forearms/lower legs, muscle twitching) or uncontrolled, robust movements (choreoathetosis of arms, legs and/or head). In WAT-1, moderate or severe

uncoordinated/ repetitive movements are scored if occurring during the 2 minute pre-stimulus observation.

11.16.1 Parent perspective

Movement disorders were recalled by seven parents during interview (Table 11.12).

Table 11.12 Parent description of behaviours synonymous with movement disorder

Parent	Description of movement disorder
P2, P3, P4, P8	Lip smacking is a tic (sign of disruption to extrapyramidal system control).
P1, P9	Swimming movements: Floating hand, bringing her arm up like backstroke. Sort of treading water, as if she was swimming with her hands, as if she was batting things away. It looked like there was something there and she was batting it away with her hand, or it was distressing her in some way.
P1	Head twitch, Shaky (like Parkinson's disease), jumping (sounds like myoclonus from description).
P2	**Restlessness**, he just couldn't rest
P3	Head movements from left to right [**(head shaking no-no)**], rubbing his face, rubbing his nose, twitchy, lip smacking, licking his lips, rubs his eyes, rubs his hands and wrists together, jerked movements of hands and arms.
P4	(describing tremor) Lip smacking and moving his tongue around. Constantly shaking, arms are never still, like a really bad twitch, his legs and arms are going. For a couple of days he's never still.
P8	His tongue was wild, like it had a mind of his own. His tongue was just constantly out of his mouth, he was moving it so much. He couldn't keep his dummy in his mouth (usually has it 24/7). **Neurological symptoms include lingual-oral dyskinesias e.g., protrusion of the tongue.**
P10	Restless, flapping movements, arms flapping, trying to move himself

11.16.2 Nurse perspective

Nurses documented behaviours synonymous with movement disorders in four patients (Table 11.13).

Table 11.13 Nurse documentation of movement disorder

Patient	Additional comments from nursing records
Pt 1	Jittery, constantly rolling in the bed, shaky, jerky movements, arching back, writhing round the bed.
Pt 2	Lip smacking, flaying around.
Pt 3	Lip smacking, jerky movements in hands.
Pt 5	Cycling arms and legs

11.16 3 Summary

A number of the movements described in this section are defined as automatisms, which are non-purposeful, stereotyped and repetitive movements, which occur in complex partial seizures (Alarcon 2012). Oral automatisms include lip smacking and chewing; motor automatisms include cycling movements, swimming movements, right-to-left head rolling, rubbing the nose with fingers and yawning. Some of these automatisms are described as archaic, or ancestral, which were linked to survival reflexes, such as walking or swimming (Alarcon 2012). It is thought that myoclonic jerking as one such reflex to stop us falling out of a tree, or nest at the onset of sleep. This group of behaviours and their range of possible causes highlight the wide ranging disruption to neurotransmission and state regulation of withdrawal syndrome.

11.17 Communication disturbance

None of the withdrawal assessment tools include this sign, but most parents (8 of 11) described this behaviour in their child, half of whom ranked it as the most distressing feature. The absence of this sign from SWS, SOS and WAT-1 is worthy of further consideration. SOS is based on signs and symptoms from the literature, within which communication disorders were described (Hughes 1994, Sury et al 1989) but this did not feature in SBOWC (Ista et al 2008). SWS was based on the Neonatal Abstinence Tool (NAS) (Finnegan et al 1975) and a newborn population, for whom these elements of communication are developmentally inappropriate.

Communication disturbance is one of the diagnostic criteria for delirium (DSM-5 2013) and is a feature in both PD tools. In the CAPD tool (Traube et al 2014), "*Does the child make eye contact with the care giver?*" reflects the DSM domain of consciousness (DSM 2013). In the psCAM-ICU (Smith et al 2016), "*No eye contact*" reflects the delirium feature of 'inattention' and "*Unawareness of surroundings*" reflects 'disorganised brain.' If however, inattention is a fundamental sign of delirium (Smith et al 2016) it is difficult to determine whether the communication disorder described in the literature (Hughes 1994) and by these parents is a sign of withdrawal, a sign of delirium, or both. It is not clear whether evidence exists in terms of onset, duration and treatment of communication disorders to support its place as a sign of withdrawal and/or delirium.

11.17.1 Parent perspective

Seven parents recalled communication disturbances (Table 11.14)

Table 11.14 Parent description of communication disturbances

Parent	Description of communication disturbance
P1	Not recognising me/nothing there
P2	Not engaging, not focussing on anything, looking vacant
P3	No recognition, no communication
P5	Had his eyes open but looking through you
P6	Staring off past me, glazed look.
P9	There was nothing coming back, she didn't know who I was, she was a blank canvas.
P11	Eyes pinned open constantly, but he wasn't there, he didn't respond when I was talking to him.

11.17.2 Nurse perspective

Only one nurse documented signs of communication disturbances, which related to P3 who was noted as "not fixing or following." This patient was subsequently diagnosed with neurological impairment.

11.17 3 Summary

There is insufficient evidence from the sign synthesis or the literature to determine whether communication disturbance is a feature of withdrawal and delirium, or just delirium.

11.18 Hallucinations

Hallucinations are perceptual disturbances (DSM-5 2013). This sign features in one withdrawal assessment tool (SOS) but is also one of the diagnostic criteria for delirium (DSM-5 2013).

11.18.1 Parent perspective

Four parents recalled behaviours that they interpreted as hallucinations (Table 11.16).

Table 11.16 Parent recall of hallucinations

Parent	Description of hallucination
P1	Swimming with mermaids, dropped in the water with no arm bands.
P2	Reaching out, like there was something there that he was trying to grab.
P9	Sort of treading water, as if she was swimming with her hands, as if she was batting things away. It looked like there was something there and she was batting it away with her hand, or it was distressing her in some way. (copied to movement disorder too)
P11	Sometimes he'd lie there and have a little giggle. I don't know what it was.

11.18.2 Summary

Hallucination is another challenging item, because this item relies on patient report and most patients on PICU are non-verbal. Pt 1 was old enough to describe her hallucinations to her mother at a later stage in her recovery. Relying on a behavioural interpretation may be inaccurate. Perceptual disturbances are also a signs of Pediatric delirium (Traube et al 2014). Patient reported symptoms should be avoided given the very young age of the patient population in PICU.

11.19 Summary synthesis

Each of the four perspectives of withdrawal signs presented in this thesis; nurse objective, nurse subjective, parent objective and parent subjective, contributed a different view of these equivocal signs and added a layer of complexity that highlighted the challenge of interpreting these signs and behaviours. In the absence of definitive signs of withdrawal, clinical utility of each sign depends on a shared recognition, understanding and meaning. The data from this synthesis have been drawn together to demonstrate to what extent there is agreement in operational definition between the withdrawal assessment tools and evidence of agreement in observer interpretation, from this synthesis (Table 11.18).

Table 11.18 Agreement in definition and interpretation of signs identified by parents

	Agreement in operational definition SWS/ WAT-1/ SOS	Agreement in observer interpretation	May indicate other differential diagnoses
Insomnia	×	×	✓
Irritability Agitation Anxiety	×	×	✓
Sweating	✓	✓	✓ (P)
Tremor	×	×	✓
Sneezing and yawning	✓	✓	✓ (P)
Diarrhoea	✓	✓	✓
Vomiting	✓	✓	✓
Fever	×	×	✓
High pitch cry Distress	×	×	✓ (P)
Respiratory distress	×	×	✓
Hypertonicity	✓	×	✓ (P)
Convulsion Startle, Twitching	×	×	✓ (P)
Movement disorder	×	×	✓
Communication disturbances	×	×	✓ (P)
Hallucinations	✓	×	✓

✓Yes ×No (P) parent perspective may aid interpretation

Signs which showed both a clear operational definition and agreement in observer interpretation were sweating, sneezing and yawning, diarrhoea and vomiting. Six signs also showed potential to be more easily interpreted by parents than nurses; these were sweating, sneezing and yawning, cry, hypertonicity, convulsion/twitch and communication disturbances. A clearer definition may improve interpretation and

be more indicative of withdrawal in the cases of insomnia (complete absence of sleep rather than sleep disruption) and movement disorder (distinct behaviours).

Signs such as irritability, agitation, fever and respiratory distress are highly prevalent in PICU patients. These signs do not differentiate withdrawal from other differential diagnoses and their presence may indicate deterioration and should prompt a medical review. Two signs; irritability and communication disturbance, overlap with the diagnostic criteria of pediatric delirium (PD). It is not clear whether this overlap is due to the co-existence of withdrawal and PD, or to inaccurate diagnoses of these conditions in the studies in this thesis and in the literature. The inclusion of signs in a withdrawal assessment, which are highly prevalent in PICU patients and/or indicative of deterioration and/or PD may bias decision-making, increasing the likelihood of cognitive error and a false positive diagnosis of withdrawal.

11.19.1 The theoretical link between withdrawal syndrome and signs of withdrawal

There are a wider range of signs of withdrawal than can be contained in one withdrawal assessment tool. This synthesis has shown that different interpretations of behaviours are possible; blurring of boundaries between some signs occurred with parent descriptions and formal definitions, similarly to the nurse interview findings in Study 3.

The W-CAT focuses on the shared diagnostic features of withdrawal, rather than the heterogeneous presentation. Whilst recognition of behavioural signs of withdrawal is a necessary component of a withdrawal assessment, the existing focus on identifying and summing behaviours may be less useful and more burdensome than a consideration of the impact of the behaviours on the child. A focus on the impact of behaviours, rather on the inconsistent, unique and equivocal presentation of withdrawal, may provide a clearer indication of the clinical need to intervene with rescue medication or slowing the weaning rate.

11.20 Conclusion

Integration of the multiple sources of data presented in Studies 1 to 6 regarding the manifestation of withdrawal syndrome demonstrated differences in both the characterisation of withdrawal by the assessment tools and the potential for differences in interpretation of behaviours, which both limit clinical utility.

The sign synthesis did not identify a combination of signs that supports withdrawal assessment. Neither was a logically derived relationship between the concept of withdrawal and the signs of withdrawal identified. No evidence was identified to support the specific combination of signs in any of the three existing withdrawal assessment tools; SWS (Cunliffe et al 2004), WAT-1 (Franck et al 2008) or SOS (Ista et al 2009). The lack of evidence underpinning the existing approach reinforces the consideration of a different approach. The W-CAT, with a focus on shared features of withdrawal may offer an alternative approach, which also acknowledges the possibility of other causes for the behaviours.

Chapter 12: Conclusions, original contribution to knowledge and implications for practice and policy.

12.1 Overview of conclusions

The propositional model presented in Chapter 2 and expanded upon in response to the findings of Studies 1-6 of this thesis provided the framework for exploring the theoretical basis for withdrawal. The development of the model, in response to the literature review and findings from Studies 1-3 in Part 2 of the thesis, highlighted what is not known about withdrawal. Withdrawal syndrome lacked a definitive name, a definition and diagnostic criteria; risk factors for withdrawal were confused with those for physical dependence, possibly because physical dependence and its variable onset in critically ill children are also poorly understood. Studies 1-3 also highlighted the contextual complexity within which withdrawal assessments are performed; children may be weaning from more than one sedative agent and other differential diagnoses are common and share similarities in their behavioural presentation with withdrawal.

Study 4 in this thesis is the first study to consider the nurses' perspective of withdrawal assessment, investigating how the decision-making stages of clinical reasoning aligned with different aspects of the withdrawal assessment. The findings illuminated the potential chances for cognitive error and also revealed the complexity of the context within which withdrawal occurs. The existing approach to withdrawal assessment does not support decision-making, as the focus of cognitive effort is on the identification and interpretation of ambiguous behaviours rather than on the core features of withdrawal.

Studies 5 and 6 in this thesis are the first studies to consider the parents' perspective of withdrawal assessment. The findings revealed that parents recalled a broader range of withdrawal signs than feature in the existing withdrawal assessment tools and that these signs were a cause of distress for parents. Parents' preference for an active role in withdrawal assessment contrasted with their mostly passive role during their child's critical illness. The benefits of a reciprocal parent – nurse relationship for withdrawal assessment were proposed. The nurse would benefit from parents' perception of their child's behaviour changes whilst parents benefit from active participation in care and being kept informed of their child's condition.

The main contributions of the studies in this thesis arise from recognition of the complexity that surrounds the withdrawing child. The context of the child includes the importance of knowing the child's usual behaviour and the recent trend in behaviours to interpret the current behaviours. The theoretical proposition is that withdrawing patients share diagnostic criteria, rather than a specific presentation in common. This proposition challenges the existing approach to withdrawal assessment, which relies on a homogeneous presentation.

The synthesis chapters (Chapters 10 and 11) of the thesis sought to illuminate the theoretical relationship between physical dependence and withdrawal and between withdrawal and the signs of withdrawal; relationships which would underpin the construct validity of the existing withdrawal assessment tools; SWS (Cunliffe et al 2004), WAT-1 (Franck et al 2008) and SOS (Ista et al 2009). Identifying these relational links provides a basis for improving assessment of withdrawal and delineating withdrawal from PD and other competing causes.

The retrospective utility of the Withdrawal Causality Assessment Tool (W-CAT) was identified in Chapter 10. The emerging clinical utility of W-CAT is further strengthened by evidence of the operationalisation of the relational links presented in the propositional model to the diagnostic criteria of W-CAT (Table 12.1 and Figure 12.1). The diagnostic criteria form the new defining criteria for paediatric withdrawal syndrome (PWS); a term which defines the unique features of physical dependence and withdrawal in this group of critically ill patients.

Table 12.1 The Withdrawal-Causality Assessment Tool (W-CAT)

Withdrawal likelihood	Physical dependence possible	Temporal relationship with change in dose	Absence of differential diagnoses
Probable	Yes	Yes	Yes
Possible	Yes	Yes	No
Unlikely	No	No	No

The sign synthesis in Chapter 11 did not identify a combination of signs that supports withdrawal assessment. Neither was a logically derived relationship between the concept of withdrawal and the signs of withdrawal identified. Further research is needed to examine the overlap of behavioural signs of withdrawal and PD and to explore the nature of the relationship between these syndromes. Further research is also needed to identify

how clinical reasoning can be supported to distinguish the different co-existing causes of behavioural distress in critically ill children.

The existing withdrawal assessment tools provide a structured assessment of withdrawal albeit in the absence of a theoretical basis to underpin the superiority of any one approach. Until such theoretical support is established, the propositional model supports the use of any of these tools, in partnership with the W-CAT criteria.

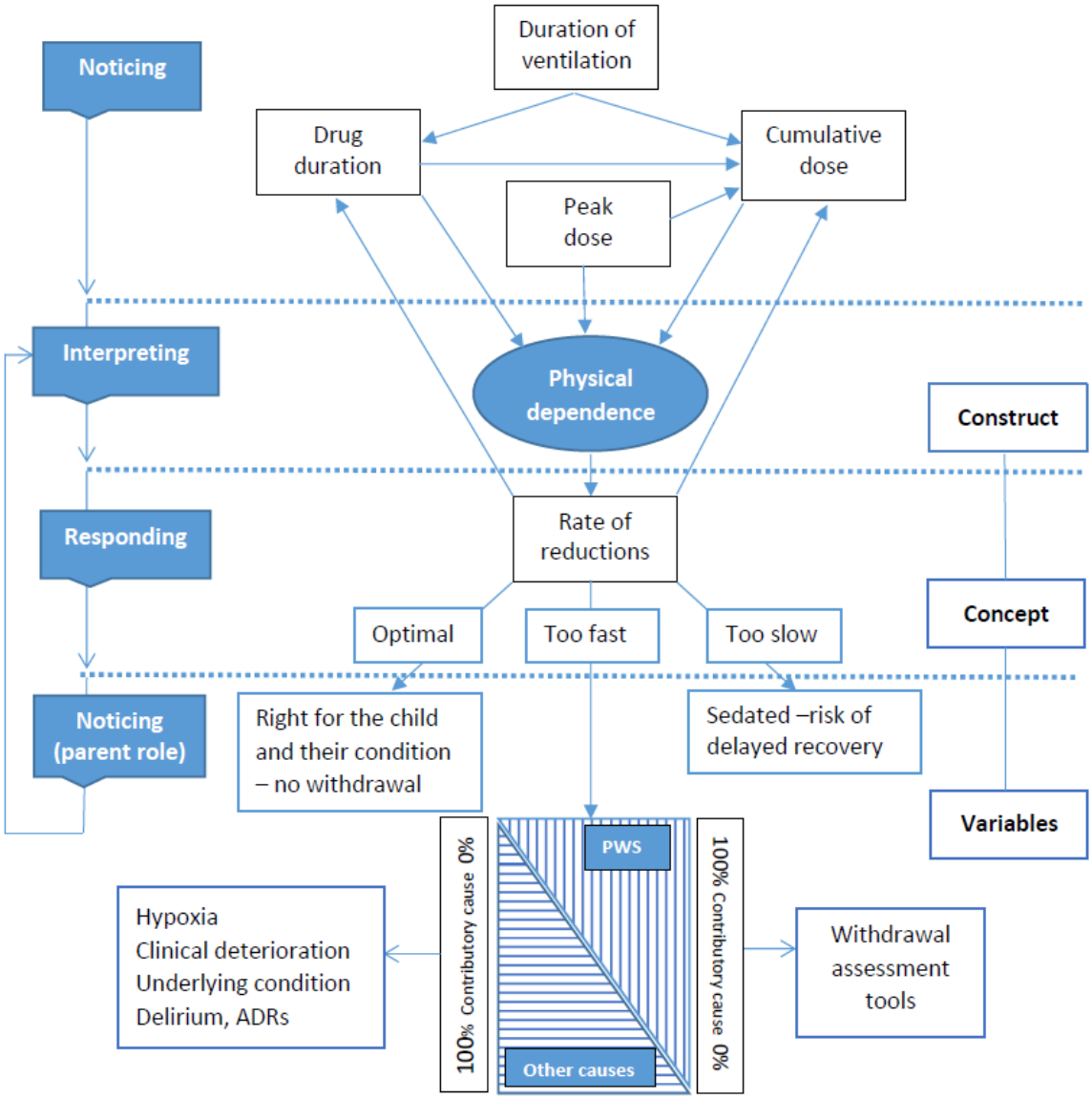

Figure 12.1 Propositional model incorporating co-existence of Paediatric Withdrawal Syndrome (PWS) and other causes

Paediatric withdrawal syndrome (PWS) has been introduced in this thesis as a term to describe withdrawal in critically ill children. Diagnostic criteria for the likelihood of paediatric withdrawal syndrome are shown in Table 12.1.

Table 12.2 Diagnostic criteria of Paediatric Withdrawal Syndrome (PWS)

Criterion A	A change in behaviour causing distress or impacting on the child's clinical condition which develop after stopping or reducing one or more sedative or analgesic infusions, or regular medications, which have been administered for at least four days.
Criterion B	Withdrawal signs develop within minutes to two days after Criterion A.
Criterion C	The behavioural signs are not due to the critical illness or deterioration and are not better explained by another medical condition or drug effect e.g pediatric delirium, adverse drug reactions.
Criterion D	Behaviours improve when the drug is restarted or increased to the previously tolerated dose, if clinically indicated.

12.2 Summary of original contributions to knowledge

- A conceptual framework demonstrating how the nurse and parent perspectives have contributed to a greater understanding of the challenges inherent in a withdrawal assessment in a child recovering from critical illness.
- A propositional model that maps the links between sedation, physical dependence and withdrawal syndrome and provides an evaluative framework for withdrawal studies.
- A formal definition and diagnostic criteria for paediatric withdrawal syndrome (PWS).
- Diagnosis of withdrawal described in terms of probability (unlikely, possible, probable) to reflect the complexity of the context and the potential co-existence with other diagnoses, which may influence treatment decisions.

12.3 Implications for practice and policy

The propositional model identified the current knowledge gaps and provides a framework upon which future research on paediatric withdrawal syndrome can be based.

Adoption of agreed diagnostic criteria for paediatric withdrawal syndrome will increase the generalisability of studies examining sedation weaning and withdrawal assessment.

The W-CAT provides diagnostic criteria which, after formal evaluation, should be implemented into the clinical practice of sedation withdrawal assessment.

The relational link between physical dependence and withdrawal proposes that the incidence and severity of withdrawal may be moderated by considering ways to minimise the risk of physical dependence.

12.4 Dissemination strategy

The following dissemination strategies will be considered regarding the practical implications of the studies in this thesis.

12.4.1 Publication plan

One study (Study 4) has been published in the peer reviewed Journal of Advanced Nursing, which has an impact factor of 1.998. A paper presenting the findings of Study 6 will be submitted to the forthcoming special issue of Intensive and Critical Care Nursing on Family Centred Care in the ICU. Further papers addressing the propositional model and the indistinct characterisation of withdrawal will be submitted to peer reviewed journals within six months of completing the PhD.

12.4.2 Presentation strategy

Implications of the clinical findings from the studies in this thesis will be presented firstly to the pain service (the clinical service that manages withdrawal assessment) at the hospital where this research took place. The multidisciplinary team will debate potential changes to our existing approach to withdrawal assessment. Guidelines will be written or adapted to reflect changes and will be highlighted to clinical teams with a presentation at the hospital's "Grand Round."

Implications of the findings from Study 4 focus on clinical reasoning. Improving awareness of System 1 intuitive thinking and System 2 deliberate thought will be implemented through the use of vignettes in in-house pain training for clinical staff. Discussion with clinical educators will take place to consider how clinical reasoning may be education programmes for nursing students.

Presentation at an international level will be include submitting abstracts to the 7th Congress of the European Academy of Pediatric Societies (EAPS) meeting in October 2018.

12.5 Recommendations for future research

Recommendations for future research include;

I. Devising and prospectively evaluating the safety and efficacy of a paediatric withdrawal syndrome assessment based on W-CAT criteria, considering the clinical utility from the nurse perspective and the efficacy, acceptability and operationalisation of parent participation, from the nurse and parent perspectives.
II. Investigating ways to reduce the incidence of withdrawal by examining the risk factors for physical dependence, including peak doses of sedative drugs and duration of treatment, and the impact of different approaches to weaning sedative drugs.
III. Examining the experiences of withdrawal in critically ill children aged five years and older.
IV. Exploring how nurses and parents differentiate between withdrawal and delirium in critically ill children.

12.6 Conclusion

The mixed methods studies in this thesis permitted the complexity of the child and context to be illuminated rather than concealed. The level of complexity presents challenges for the existing approach. The studies in this thesis present a new approach, which incorporates diagnostic criteria, the likelihood of withdrawal and justification for parents' participation in withdrawal assessment.

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Appendix 1: The Sedation Withdrawal Score (SWS) (Cunliffe et al 2004)

ALDER HEY CHILDREN'S NHS FOUNDATION TRUST - SEDATION WITHDRAWAL

Background

Sedation is an essential part of the management of the critically ill child receiving artificial ventilation. Opioids and benzodiazepines are the most widely used drugs to treat pain and sedate children. Unfortunately tolerance and dependence can develop, usually after 5 -10 days, but more rapidly if maximum doses are used. Tolerance and dependence will lead to the patient experiencing withdrawal reactions if the drugs are reduced or stopped suddenly. Withdrawal reactions normally occur between 12 and 48 hours after reducing/ stopping these drugs. Withdrawal reactions have also been seen following treatment with the oral sedatives chloral hydrate and promethazine, and are similar to that reported with opioids and benzodiazepines.

Symptoms associated with withdrawal of opioids and / or benzodiazepines	
Central Nervous System: Irritability, agitation, dysphoria, anxiety, insomnia, restlessness, high pitched cry, dilated pupils, hallucinations, convulsions **Cardiovascular**: Tachycardia, hypertension **Musculoskeletal**: Tremors, with or without stimulation, myoclonic jerks, hyperreflexia, hypertonicity, choreic movements **Gastrointestinal**: Diarrhoea, nausea, vomiting, feeding intolerance, anorexia, weight loss	**Skin**: Sweating, piloerection, flushing, pruritis, mottling, excoriation due to excess rubbing, skin temperature variation **Respiratory**: Apnoea, tachypnoea, increased respiratory effort, 'fighting' the ventilator **Other**: Fever, yawning, impaired suck reflex, rhinorrhoea, sneezing, lacrimation, salivation ,impaired social interaction, decreased visual attentiveness

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4 Parkinson L et al (1997). A randomised controlled trial of sedation in the critically ill. Paediatric Anaesthesia.: 7: 405-410.

SEDATION WITHDRAWAL SCORE

1. Score the child every 6 hours based on the child's behaviour over the previous 6 hours.
2. Each category is scored 0,1 or 2 depending on whether the symptom is absent (0), mild (1) or severe (2).
3. The total score will range between 0 and 24 and helps to determine subsequent actions.
4. If the child scores for insomnia, irritability, sweating and tremors, suspect withdrawal regardless of the overall score

Please take into account that high scores might indicate a change in the child's condition, rather than withdrawal.

Score < 3 Reducing regime to continue **Score 4-6** Do not reduce regime further **Score 6-10** Revert to previous regime **Score > 10** Seek advice

DATE																												
TIME																												
Insomnia																												
Irritability																												
Sweating																												
Tremor																												
Sneezing																												
Diarrhoea																												
Vomiting																												
Fever																												
High pitch cry																												
Respiratory distress																												
Hypertonicity																												
Convulsions																												
TOTAL																												
Systolic blood pressure																												

Score systolic blood pressure for 24 hours after clonidine has been stopped to monitor for rebound hypertension; if present report to medical team urgently

Revised September 2010

Appendix 2: The State Behavioural Scale (SBS) (Curley et al 2006)

State Behavioral Scale (SBS)[1] **Score as patient's response to voice then touch then noxious stimuli** (Planned ETT suctioning or <5 seconds of nail bed pressure)		
Score	Description	Definition
-3	**Unresponsive**	No spontaneous respiratory effort No cough or coughs only with suctioning No response to noxious stimuli Unable to pay attention to care provider Does not distress with any procedure (including noxious) Does not move
-2	**Responsive to noxious stimuli**	Spontaneous yet supported breathing Coughs with suctioning/repositioning Responds to noxious stimuli Unable to pay attention to care provider Will distress with a noxious procedure Does not move/occasional movement of extremities or shifting of position
-1	**Responsive to gentle touch or voice**	Spontaneous but ineffective non-supported breaths Coughs with suctioning/repositioning Responds to touch/voice Able to pay attention but drifts off after stimulation Distresses with procedures Able to calm with comforting touch or voice when stimulus removed Occasional movement of extremities or shifting of position
0	**Awake and Able to calm**	Spontaneous and effective breathing Coughs when repositioned/Occasional spontaneous cough Responds to voice/No external stimulus is required to elicit response Spontaneously pays attention to care provider Distresses with procedures Able to calm with comforting touch or voice when stimulus removed Occasional movement of extremities or shifting of position/increased movement (restless, squirming)
+1	**Restless and difficult to calm**	Spontaneous effective breathing/Having difficulty breathing with ventilator Occasional spontaneous cough Responds to voice/ No external stimulus is required to elicit response Drifts off/ Spontaneously pays attention to care provider Intermittently unsafe Does not consistently calm despite 5 minute attempt/unable to console Increased movement (restless, squirming)
+2	**Agitated**	May have difficulty breathing with ventilator Coughing spontaneously No external stimulus required to elicit response Spontaneously pays attention to care provider Unsafe (biting ETT, pulling at lines, cannot be left alone) Unable to console Increased movement (restless, squirming or thrashing side-to-side, kicking legs)

Appendix 3: Withdrawal Assessment Tool – 1 (Franck et al 2008)

WITHDRAWAL ASSESSMENT TOOL VERSION 1 (WAT – 1)

Patient Identifier													
	Date:												
	Time:												
Information from patient record, previous 12 hours													
Any loose /watery stools	No = 0 Yes = 1												
Any vomiting/wretching/gagging	No = 0 Yes = 1												
Temperature > 37.8°C	No = 0 Yes = 1												
2 minute pre-stimulus observation													
State	SBS[1] ≤ 0 or asleep/awake/calm = 0 SBS[1] ≥ +1 or awake/distressed = 1												
Tremor	None/mild = 0 Moderate/severe = 1												
Any sweating	No = 0 Yes = 1												
Uncoordinated/repetitive movement	None/mild = 0 Moderate/severe = 1												
Yawning or sneezing	None or 1 = 0 ≥2 = 1												
1 minute stimulus observation													
Startle to touch	None/mild = 0 Moderate/severe = 1												
Muscle tone	Normal = 0 Increased = 1												
Post-stimulus recovery													
Time to gain calm state (SBS[1] ≤ 0)	< 2min = 0 2 - 5min = 1 > 5 min = 2												
Total Score (0-12)													

WITHDRAWAL ASSESSMENT TOOL (WAT – 1) INSTRUCTIONS

- Start WAT-1 scoring from the **first day of weaning** in patients who have received opioids +/or benzodiazepines by infusion or regular dosing for prolonged periods (e.g., > 5 days). Continue twice daily scoring until 72 hours after the last dose.
- The Withdrawal Assessment Tool (WAT-1) should be completed along with the SBS[1] at least once per 12 hour shift (e.g., at 08:00 and 20:00 ± 2 hours). The progressive stimulus used in the SBS[1] assessment provides a standard stimulus for observing signs of withdrawal.

Obtain information from patient record (this can be done before or after the stimulus):

- ✓ **Loose/watery stools**: Score 1 if any loose or watery stools were documented in the past 12 hours; score 0 if none were noted.
- ✓ **Vomiting/wretching/gagging**: Score 1 if any vomiting or spontaneous wretching or gagging were documented in the past 12 hours; score 0 if none were noted
- ✓ **Temperature > 37.8°C**: Score 1 if the modal (most frequently occurring) temperature documented was greater than 37.8 °C in the past 12 hours; score 0 if this was not the case.

2 minute pre-stimulus observation:

- ✓ **State**: Score 1 if awake and distress (SBS[1]: ≥ +1) observed during the 2 minutes prior to the stimulus; score 0 if asleep or awake and calm/cooperative (SBS[1] ≤ 0).
- ✓ **Tremor**: Score 1 if moderate to severe tremor observed during the 2 minutes prior to the stimulus; score 0 if no tremor (or only minor, intermittent tremor).
- ✓ **Sweating**: Score 1 if any sweating during the 2 minutes prior to the stimulus; score 0 if no sweating noted.
- ✓ **Uncoordinated/repetitive movements**: Score 1 if moderate to severe uncoordinated or repetitive movements such as head turning, leg or arm flailing or torso arching observed during the 2 minutes prior to the stimulus; score 0 if no (or only mild) uncoordinated or repetitive movements.
- ✓ **Yawning or sneezing** > 1: Score 1 if more than 1 yawn or sneeze observed during the 2 minutes prior to the stimulus; score 0 if 0 to 1 yawn or sneeze.

1 minute stimulus observation:

- ✓ **Startle to touch**: Score 1 if moderate to severe startle occurs when touched during the stimulus; score 0 if none (or mild).
- ✓ **Muscle tone**: Score 1 if tone increased during the stimulus; score 0 if normal.

Post-stimulus recovery:

- ✓ **Time to gain calm state** (SBS[1] ≤ 0): Score 2 if it takes greater than 5 minutes following stimulus; score 1 if achieved within 2 to 5 minutes; score 0 if achieved in less than 2 minutes.

Sum the 11 numbers in the column for the total WAT-1 score (0-12).

[1]Curley et al. State behavioral scale: A sedation assessment instrument for infants and young children supported on mechanical ventilation. Pediatr Crit Care Med 2006;7(2):107-114.

Figure Legend: Withdrawal Assessment Tool (WAT-1) and instructions. [1]Reprinted with permission **Pediatric Critical Care Medicine** 2008;9(6):577.

Appendix 4: The Sophia Observation Scale (SOS) (Ista et al 2009)

SOS - Sophia Observation withdrawal Symptoms-scale
(Children 0 – 16 years)

Sticker with patient's name

Date _____

Time _____

Observer _____

Step 1		**Explanation**
Heart rate	/min.	*Enter highest rate in past 4 hours if present, otherwise read the monitor first or feel pulse.*
Breathing rate (tachypnoe)	/min.	*Enter highest rate in past 4 hours if present, otherwise read the monitor first or count breathing.*
Baseline value heart rate	/min.	*Please turn over for instruction on determining baseline value.*
Baseline value breathing rate	/min.	*Please turn over for instruction on determining baseline value.*

Step 2	**Tick if yes**	
Autonomic dysfunction		
1 Tachycardia	☐	*Yes if heart rate exceeds baseline value by ≥ 15%.*
2 Tachypnea	☐	*Yes if breathing rate exceeds baseline value by ≥ 15%.*
3 Fever	☐	*Yes if body temperature exceeded 38.4 °C in past 4 hours.*
4 Sweating	☐	*Not caused by room temperature, clothing, swaddling e.g.*
Central nervous system irritability		
5 Agitation	☐	*Yes if child shows at least one of these signs: irritable, restless, agitated, fidgety.*
6 Anxiety	☐	*Unrest or anxious face (eyes wide open, eyebrows tense and raised). Behavior can vary from panicky to draw back.*
7 Tremors: ***(pick one)***		*Slight, involuntary rhythmic movements of hand and/or feet.*
• Spontaneous	☐	*Note: please turn over for instructions.*
• In response to environmental stimuli	☐	
8 Motor disturbance: ***(pick one of four)***		
Slight muscle jerks:		*Involuntary, of forearms/lower legs, muscle twitching.*
• Spontaneous	☐	
• In response to environmental stimuli	☐	
Uncontrolled, robust movements:		*Choreoathetosis of arms, legs and/or head.*
• Spontaneous	☐	
• In response to environmental stimuli	☐	
9 Increased muscle tension	☐	*Clenched fists or tense clenched toes.*
10 Inconsolable crying	☐	*Yes if child cannot be consoled by parents or by offering distraction, e.g. pacifier, food; or game playing for older children. Score silent crying in intubated children.*
11 Grimacing	☐	*Eyebrows contracted and lowered, nasolabial fold visible.*
12 Sleeplessness	☐	*Sleeps not more than 1 hour at a stretch.*
13 Hallucinations	☐	*During the past 4 hours child seems to see, hear or feel things that are not there.*
Gastrointestinal dysfunction		
14 Vomiting	☐	*At least once in past 4 hours, not related to feeding changes.*
15 Diarrhea	☐	*Watery stools, not related to feeding changes (do not score e.g. when the result of breastfeeding).*
Count ticked boxes	☐	***Maximum score is 15***

Please turn over for further instructions

Appendix 5: Data extraction sheet Study 1

Part 1 Demographic data

AH number	DOB	Gender	Ethnicity	Trisomy 21	Underlying condition	Reason for ITU admit	Age
		M/F		**Y/N**			

Part 2 Clinical data regarding withdrawal

Withdrawal suspected	Highest SWS score	Opioid	Benzodiazepine	Chloral	Promethazine/ Chlorpromazine	Other drug	Withdrawal drug/s suspected	**When drug stopped** (days before highest SWS score)	**Extubated** (hours before withdrawal suspected)	**Days on ITU** (days since admission to highest SWS score)
Y/N		F/Mo	MDZ/D	Y/N	P/C					

Opioids ***M****orphine /* ***F****entanyl*
Benzodiazepines *Midazolam (MDZ) /* ***D****iazepam*

Part 3 Breakdown of SWS score

Insomnia	Irritability	Sweating	Tremor	Sneezing	Diarrhoea	Vomiting	Fever	High pitch cry	Respiratory distress	Hyper-tonicity	Convulsions

Notes

Appendix 6: Study 4 documents

Improving the recognition of sedation withdrawal in children under 5 years of age.

You may have already heard about the research that's been going on over the last 6 months looking at improving the sedation withdrawal assessment tool we use at Alder Hey.

What we have done so far.

The first stage looked at how the current sedation withdrawal (SWS) tool was used. We looked at the highest scores of 100 patients with sedation withdrawal to see how frequently each of the 12 symptoms was seen and to look at the circumstances when these high scores occurred. The current stage involves parents who experienced their child undergoing sedation withdrawal; initially finding out what symptoms 50 parents recognise in their children and how distressing they found them, and then interviewing 12 of these parents to find out more about their experiences.

We need your help now.

The next stage involves finding out about nurses' views of the current SWS tool. We need your help to achieve this. If you use the SWS to assess patients we would like to interview you. We hope to interview 12 nurses, so we get a range of nurses from different clinical areas and with varying levels of experience.
We want to find out how you use the SWS and how easy or difficult you find it. This is not a test and there are no right or wrong answers. If there are any questions you do not want to answer just tell the interviewer and she will move on to the next question. You can also stop the interview at any time.
The interview will take about an hour. We would like to audio-record the interview if that's OK with you.
We will make a typed copy of the interview but remove all identifying details. This means some of your comments might end up in the final report but no-one will know they were yours.

The small print.

- You do not have to take part at all. If you agree to and then change your mind that's OK too.
- If you take part we will ask you to sign a consent form.
- We do not anticipate any risks to taking part in this study.
- If there's a problem, speak to Jennie Craske or Lyvonne Tume. If you're still unhappy and wish to complain contact Dot Lambert, Research and Development Manager; dot.lambert@alderhey.nhs.uk
- This study has been given a favourable opinion by Liverpool East Research Ethics Committee.
- Contact Jennie (ext 2003,jennie.craske@alderhey.nhs.uk) or Lyvonne (ext 4588, lyvonne.tume@alderhey.nhs.uk) if you have any questions or want further information.

Thank you very much for taking the time to read this poster. If you are interested in taking part in the study, please contact Jennie Craske (ext 2003, jennie.craske@alderhey.nhs.uk)

Phase 1d 19/07/2013 v1

Nurse recruitment poster

Nurse consent form (Phase 1d)

Improving the recognition of sedation withdrawal in children under 5 years of age

Participant identification number for this study _____

Name of researcher Jennie Craske

		Please initial box
1.	I confirm that I have read and understand the information sheet, dated 19/07/2013 (version 1) for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason.	
3.	I understand that my interview will be audio-recorded and transcribed and that brief quotations from some interviews may be included in study reports.	
4.	I agree to study records (including transcripts of my interview) being accessed by both student's supervisory team and relevant regulatory authorities	
5.	I agree to take part in the above study.	

Name of participant	Date	Signature
Name of person taking consent	Date	Signature

When completed, 1 for participant and 1 for research site file.

Appendix 7: Published paper

Craske J, Carter B, Jarman IH, Tume LN. Nursing judgement and decision-making using the Sedation Withdrawal Score (SWS) in children. J Adv Nurs. 2017;00:1–12. https://doi.org/10.1111/jan.13305

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ORIGINAL RESEARCH:
EMPIRICAL RESEARCH—QUALITATIVE

WILEY JAN

Nursing judgement and decision-making using the Sedation Withdrawal Score (SWS) in children

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Abstract

Aims: The aim of the study was to evaluate registered children's nurses' approaches to the assessment and management of withdrawal syndrome in children.

Background: Assessment of withdrawal syndrome is undertaken following critical illness when the child's condition may be unstable with competing differential diagnoses. Assessment tools aim to standardize and improve recognition of withdrawal syndrome. Making the right decisions in complex clinical situations requires a degree of mental effort and it is not known how nurses make decisions when undertaking withdrawal assessments.

Design: Cognitive interviews with clinical vignettes.

Methods: Interviews were undertaken with 12 nurses to explore the cognitive processes they used when assessing children using the Sedation Withdrawal Score (SWS) tool. Interviews took place in Autumn 2013.

Findings: Each stage of decision-making—noticing, interpreting and responding—presented cognitive challenges for nurses. When defining withdrawal behaviours nurses tended to blur the boundaries between Sedation Withdrawal Score signs. Challenges in interpreting behaviours arose from not knowing if the patient's behaviour was a result of withdrawal or other co-morbidities. Nurses gave a range of diagnoses when interpreting the vignettes, despite being provided with identical information. Treatment responses corresponded to definite withdrawal diagnoses, but varied when nurses were unsure of the diagnosis.

Conclusion: Cognitive interviews with vignettes provided insight into nurses' judgement and decision-making. The SWS does not standardize the assessment of withdrawal due to the complexity of the context where assessments take place and the difficulties of determining the cause of equivocal behaviours in children recovering from critical illness.

KEYWORDS
cognitive errors, cognitive interviewing, critical care, nursing assessment, paediatric

1 | INTRODUCTION

Children admitted to the paediatric intensive care unit (PICU) require adequate sedation and analgesia for the duration of their critical illness (Jenkins, 2002). Many of these drugs cause physical dependence, which means that once the child is recovering the drugs should to be tapered, rather than being stopped abruptly to prevent withdrawal syndrome (Cunliffe, McArthur, & Dooley, 2004; Easley & Nichols, 2008). Although each drug has a distinctive withdrawal syndrome, many of the signs of withdrawal are the same across drug

groups. Individually, however, these equivocal signs are ambiguous in the critically ill child, possibly indicating pain, delirium, the underlying condition, deterioration or withdrawal (Harris et al., 2016).

1.1 | Background

The assessment of withdrawal syndrome in children is complex. Structured and repeatable assessments are recommended to assist detection, but it is often unclear how these are applied by nurses. Three published tools have been developed to monitor withdrawal in children; the sedation withdrawal score (SWS) (Cunliffe et al., 2004), the Withdrawal Assessment Tool (WAT-1) (Franck, Harris, Soetenga, Amling, & Curley, 2008) and the Sophia Observation Score (SOS) (Ista, van Dijk, de Hoog, Tibboel, & Duivenvoorden, 2009). Each is a checklist of non-specific signs that, in combination, appear to support a diagnosis of withdrawal (Table 1). The SWS is the withdrawal assessment tool and treatment protocol used in our hospital since 2004. SWS has proven clinically useful in identifying withdrawal signs in ICU and ward-based patients, but has not been validated (Macqueen & Bruce, 2012). Both WAT-1 (Franck et al., 2008; Franck, Scoppettuolo, Wypij, & Curley, 2012) and SOS (Ista, de Hoog, Tibboel, Duivenvoorden, & van Dijk, 2013; Ista et al., 2009) have been validated but the studies excluded patients whose existing behaviour might confound the withdrawal assessment and clinical utility is further limited by the lack of linked treatment protocols.

The assessment is complex due to the multiple drug and patient factors to be considered. Drug factors include the likelihood of physical dependence, which varies depending on drug dose and duration of therapy (Amigoni, Vettore, Brugnolaro, Brugnaro, Gaffo, Masola, Marzollo, & Pettenazzo, 2014, da Silva, Reis, Fonseca, & Fonseca, 2016), and also appears highly individualized (Best, Asaro, Franck, Wypij, & Curley, 2016) and may be further complicated by concurrent tapering of more than one sedative or analgesic drug. Patient factors include the highly individualized effects of withdrawal on the child's recovery (Franck et al., 2008) and the confounding effect of the patient's primary medical condition on withdrawal intensity (Franck et al., 2008). Assumptions are made that the nurse will modify the assessment to ensure the underlying condition or any external factors do not skew the withdrawal score (Franck & Vilardi, 1995; Harris et al., 2016; Ista et al., 2013). Complex tasks like this demand a degree of cognitive effort and focussed attention on the part of the nurse, to make correct judgements and decisions. Given that the judgement of the bedside nurse has been a "silver standard" in tool validation studies (Franck et al., 2008; Ista et al., 2009), it is important to understand how nurses think when undertaking withdrawal assessments and making treatment choices (Easley & Nichols, 2008).

Two key theoretical approaches to clinical decision-making are reasoning and intuition (Banning, 2008). Different academic disciplines have investigated the analytical, rational approach of reasoning, and similar models have emerged to describe the key stages of the process (Table 2). Remaining open minded throughout these stages is vital, as relevant cues can be subtle and may be overlooked, particularly if the situation is changing quickly or there is too much to take in simultaneously (Gaba, Howard, & Small, 1995). Knowing how to filter tenuous cues and focus on relevant ones is a feature of expert nursing practice (Harbison, 2006).

Intuition is defined as "a way of knowing something immediately as a whole that improves with experience" (Rew & Barrow, 2007; p. E25). This enables the clinical expert to process and identify key diagnostic components subconsciously (Lyneham, Parkinson, & Denholm, 2008). In high-pressure circumstances, the rational approach is somewhat idealistic as clinical decisions are often required despite incomplete knowledge of the situation (Graber, Gordon, & Franklin, 2002). Under these conditions, experienced clinicians rely on intuition to "think fast" (Kahneman, 2011; p. 13), using pattern recognition (Berner & Graber, 2008; Gobet & Chassy, 2008) and heuristics (Cranley, Doran, Tourangeau, Kushniruk, & Nagle, 2009; Elstein, 1999). However, intuitive processing can be flawed (Graber, Franklin, & Gordon, 2005), especially in an unpredictable environment (Kahneman & Klein, 2009) such as critical care.

Why is this research/review needed?

- There is little research that considers how children's nurses make decisions in complex clinical situations with regard to assessment of withdrawal syndrome.
- Assessment of withdrawal syndrome is challenging due to competing differential diagnoses and inaccurate assessment may lead to unnecessary changes to a child's treatment.

What are the key findings?

- Making the right decisions in complex clinical situations is not simple and the Sedation Withdrawal Score tool did not support the depth of thinking necessary to successfully negotiate the confounding factors.
- Once a validated tool is adopted into clinical practice the challenge is that individual practitioners think differently and at different levels to each other and this is rarely accounted for in the development of scoring tools to support clinical decisions.
- Not every practitioner will approach the complexity of the task with the same level of critical thinking.

How should the findings be used to influence policy/practice/research/education?

- Complex clinical situations cannot be made simpler but users of tools can be supported to improve their critical thinking; incorporating metacognition into education is one approach.
- Multiple scoring tools are used in health care, yet the way these are actually used is rarely studied. If tools are to achieve their intended outcomes then more research should be undertaken to explore the way they are used.

No published papers were identified that considered how nurses make decisions about the assessment and management of withdrawal in children. This study sought to fill this knowledge deficit by attending to the three stages of decision-making; noticing, interpreting and response.

2 | AIM

The aim of the study was to explore registered children's nurses' decision-making during the assessment and management of withdrawal in children by examining:

1. Noticing: the nurses' recognition and understanding of four clinical signs from the SWS tool.
2. Interpreting: the meaning of an SWS score, in terms of a diagnosis of withdrawal, presented in two clinical vignettes;
3. Response: the treatment choices made in response to the withdrawal diagnosis.

TABLE 1 Comparison of withdrawal tools.

Symptom	Agreement	SWS	SOS	WAT-1
Sweating	Symptom occurs in all 3 tools.	✓	✓	✓
Tremor		✓	✓	✓
Fever		✓	✓	✓
Diarrhoea		✓	✓	Loose, watery stool
Vomiting		✓	✓	and retching, gagging
Hypertonicity		✓	✓	✓
Insomnia	Symptom occurs in 2 of 3 tools.	✓	✓	
Irritability		✓	✓	
Respiratory distress		✓	Tachypnea	
High pitch cry		✓	Inconsolable crying	
Sneezing		✓		✓
Motor disturbance			✓	Uncoordinated, repetitive movement
Agitation	Symptom occurs in 1 tool only.		✓	
Hallucinations			✓	
Convulsion		✓		
Yawning				✓
Tachycardia			✓	
Grimacing			✓	
Startle to touch				✓
Time to regain calm state				✓
Anxiety			✓	

3 | DESIGN

Cognitive interviews were undertaken using clinical vignettes to explore the study aims. Cognitive interviews are a recognized approach to explore cognitive processing in relation to decision-making (Ross et al., 2012; Willis, 2005). The fundamental features of cognitive interviews are think aloud and verbal probing: techniques which permit the researcher to listen in to the complex and usually hidden evolution of (clinical) reasoning without interfering with the cognitive processes being uncovered (Fonteyn, Kuipers, & Grobe, 1993). Verbal probing delivered in a neutral manner enables the interviewer to drill down on the issues under investigation, so clinical expertise in the subject area is necessary to recognize when a response needs further probing (Sofaer, 2002). All other interaction between researcher and participant is minimized to reduce biasing the participants' responses (Sofaer, 2002).

The cognitive interview approach has been employed in other studies investigating nurse decision-making (Cioffi, 1998; Hoffman, Aitken, & Duffield, 2009; Simmons, Lanuza, Fonteyn, Hicks, & Holm, 2003; Twycross & Powls, 2006); these are now presented in brief. Cioffi (1998) investigated the effects of experience and uncertainty on triage assessments made by emergency nurses, and Simmons et al. (2003) described cognitive processes used by experienced nurses during their patient assessments in elderly care. Work by Twycross and Powls (2006) explored how children's nurses made clinical decisions and Hoffman et al. (2009) compared clinical cues collected by novice and expert nurses in intensive care. The cognitive interview approach has also been applied to the psychometric testing of self-report clinical assessment tools, to check that terminology is understood and interpreted consistently by patients (DiBenedetti, Price, & Andrews, 2013; Sofaer, 2002), so was well suited to the aims of this study.

An experimental setting, using vignettes, was chosen over a naturalistic setting to control the clinical data provided to participants and allow comparison between them (Berner & Graber, 2008; Willis, 2005). By standardizing the data, the only variable lay in the

TABLE 2 Decision-making key stages.

Model	Stage 1	Stage 2		Stage 3
Situation awareness (Endsley, 1995)	Perception	Comprehension		Projection
Thinking like a nurse (Tanner, 2006)	Noticing	Interpreting		Responding
Bruner's phases of interpretation (Kuhlthau, 1993)	Perception	Process of recognizing patterns	Making inferences	Prediction
Cognitive model of response processes (Tourangeau, Rips, & Rasinski, 2000)	Comprehension	Retrieval	Judgment	Response

nurses' decision-making processes (Cook & Rumrill, 2005), enabling focus on the abstruse stages of "noticing" and "interpreting" rather than simply the outcome or response (Veloski, Tai, Evans, & Nash, 2005). Clinical vignettes were developed by JC (an experienced pain/sedation nurse specialist) to illustrate a typical, complex clinical situation featuring a patient with severe neurological disability (Table 3). The vignettes were based on a real case from clinical practice to enhance believability (Endacott, Scholes, Buykx, Cooper, Kinsman, McConnell-Henry, 2010). Face and content validity were assessed by four senior clinical nurses (members of the Pain and Sedation Service and an Advanced Nurse Practitioner in critical care) experienced in withdrawal assessment (Brattebo, 2009).

Typical levels of cognitive stimulation were prompted by using developmental vignettes (Barrows & Feltovich 1987; Veloski et al., 2005), to measure participants' usual or "everyday" practice (Peabody et al., 2004). The first vignette (V1) supplied minimal information to reflect initial interpretation at the moment when the SWS score is completed. A diagnosis at this stage would indicate the inclination to "make do" and uncover the usually hidden assumptions which are made to fill in knowledge gaps. The second vignette (V2) provided additional clinical details reflecting the range of information required to underpin a more considered, contextual interpretation of the same assessment.

TABLE 3 Vignettes and intervention(s).

Vignette 1
18 month old boy admitted to ICU 18 days ago in respiratory failure (Lower respiratory tract infection secondary to tracheomalacia).
SWS score is 5 (insomnia 1, irritability 1, tremor 1, respiratory distress 1 and hypertonicity 1)
Vignette 2
History of presenting condition 18 month old boy admitted to ICU 18 days ago in respiratory failure (Lower respiratory tract infection secondary to tracheomalacia).
Past Medical History severe hypoxic ischaemic encephalopathy, chronic lung disease, epilepsy.
Past Surgical History Aortopexy 6 days ago.
He was extubated 4 days previously but within 24 hours required insertion of NPA and CPAP. NPA removed 24 hours ago.
Sedation fentanyl and midazolam infusions for 48 hours post op stopped 4 days ago. Regular chloral hydrate and codeine started 3 days ago. Chloral hydrate weaning started yesterday and codeine stopped.
His SWS score is 5 (insomnia 1, irritability 1, tremor 1, respiratory distress 1 and hypertonicity 1)
Intervention(s)
What intervention would you recommend? You can provide one or more answers.
Give codeine[a]
Stop weaning chloral hydrate
Increase dose of chloral hydrate
Restart fentanyl
Restart midazolam
No intervention
Other intervention—please state

[a]Codeine was included in the list of interventions as this study took place prior to restrictions in the use of codeine in children under 18 years of age, issued by the Medicines & Healthcare products Regulatory Agency (MHRA, 2013).

For the purpose of this study, diagnosis of withdrawal syndrome is based on two core features:

1. Physical dependence on a drug therapy administered continuously for 5 or more days, or sooner if administered at high doses (Harris et al., 2016; Macqueen & Bruce, 2012)
2. Behavioural signs of withdrawal, in response to the drug(s) stopping or reducing that are not better explained by other physical, illness or environmental causes (Harris et al., 2016; Ista et al., 2013; Macqueen & Bruce, 2012).

Provision of incomplete, equivocal information was designed to reflect the: "fuzziness of unstructured real-life situations" (Benner & Tanner, 1987, p. 24). V1 provided no data on either of the core features of withdrawal. V2 provided data about the likelihood of physical dependence, but in the absence of a baseline SWS score or trend, insufficient information to establish the cause of behavioural signs.

3.1 | Sample/participants

The study was undertaken at a specialist children's hospital in England. The study participants were registered children's nurses, who undertook withdrawal assessments regularly. Purposive sampling was employed to recruit nurses from the clinical areas where withdrawal patients were usually nursed [the paediatric intensive care unit (PICU), the high dependency unit (HDU) and the cardiac ward]. Nurses were eligible for inclusion if they undertook withdrawal assessments regularly and considered themselves familiar with the SWS tool. Nurses were recruited by poster or by word of mouth by the researcher during clinical rounds and gave written consent to participate. Interviews took place in Autumn 2013 in quiet rooms adjacent to the clinical areas.

3.2 | Data collection

Demographic data included gender and experience, in years, of applying the SWS tool in practice. No further demographic data were collected, as the relationship between factors such as years since qualification, level of expertise and level of educational attainment, on decision-making is unclear (Fick, Hodo, Lawrence, & Inouye, 2007; Hoffman, Donoghue, & Duffield, 2004; Lauri & Salanterä, 1998). Consideration was given to the sequence of the interview to minimize the potential impact on typical thought processes by unintentionally problematizing aspects of nursing care that may be relatively routine (Jenkins, Bloor, Fischer, Berney, & Neale, 2010). The first part of the interview: interpreting SWS scores and responding with treatment choices, aimed to replicate routine clinical practice using the SWS tool and reflect the largely subconscious and

automatic synthesis of information nurses undertake. V1 was presented followed by V2. After reading each vignette, participants were asked to "think aloud" while responding to the pre-set questions and scripted probes, e.g. "Is this patient withdrawing?" and "How easy or difficult is it to decide whether the patient is withdrawing?" A list of treatment options for the patient in V2 was then presented and nurses were reminded to "think aloud" while they made a decision. Options included all drugs mentioned in V2 in addition to "no intervention" and "another intervention".

The second part: noticing (defining and interpreting) individual withdrawal signs was anticipated to be more cognitively taxing, possibly causing nurses to critically reflect on their current approach to and alter subsequent, withdrawal assessments. Consequently, nurses were asked not to discuss their interview experience with colleagues until the study was completed. To encourage deeper reflection on issues raised by the vignette, nurses were asked to define four preselected SWS terms ("insomnia", "irritability", "respiratory distress" and "hypertonicity") that preliminary work had identified as being differently understood by nurses at our hospital. The nurses were also asked how easy or difficult it is to decide when a patient displayed one of these four behaviours.

3.3 | Ethical considerations

Research Ethics Committee approval for the study was obtained from an NHS Research Ethics Committee.

3.4 | Data analysis

Interviews were conducted by JC (who had training in cognitive interviews and clinical expertise in the recognition and management of withdrawal syndrome) and were audio-recorded and transcribed by a professional transcriber. "Informal analysis", the approach proposed by (Willis, 2005; p. 156) was used to identify cognitive problems with decision-making. Subjective interpretation is key to informal analysis, which rather than a formal coding scheme, also relies on expert judgement to identify problems (Fonteyn et al., 1993). Analysis involved two stages; firstly the identification of the decision-making processes including cognitive errors made when noticing, interpreting and responding in individual interviews and secondly, comparison across interviews to elucidate trends. The term cognitive error is used to describe any flawed judgement or inaccurate decision made by the participants.

3.5 | Validity and reliability

Validity and reliability were considered carefully in design and implementation of the study. A challenge in studying usual behaviour is how to do this without observation bias or research participant effects (McCambridge, Witton, & Elbourne, 2014). In decision-making studies, the ideal research method has minimal impact on typical, subconscious reasoning and does not lead to an altered, more conscious level of reasoning. Research participant effects—the change in behaviour as a consequence of being studied (McCarney et al., 2007)—have been demonstrated in observational studies investigating antibiotic prescribing behaviour in paediatricians (Mangione-Smith, Elliott, McDonald, & McGlynn, 2002) and compliance with hand hygiene in clinical settings (Eckmanns, Bessert, Behnke, Gastmeier, & Ruden, 2006; Maury, Moussa, Lakermi, Barbut, & Offenstadt, 2006). In these studies, participants were more likely to demonstrate or take a best practice approach. In studies investigating decision-making, the manner of questioning may also stimulate new thinking (McCambridge et al., 2014) or change the effort paid to the cognitive task (Sitterding, Broome, Everett, & Ebright, 2012). These effects may limit the generalizability of clinical research to routine practice (McCarney et al., 2007). The cognitive interview technique is inherently suited to this study as it is not considered to alter the effort or attention paid to the task and is also widely used in psychometric testing of survey instruments (Sofaer, 2002).

The vignettes were based on a real case and therefore reflected real practice and these and the verbal probes were pilot tested prior to use in the study. Their sensitivity and specificity was evident in that they generated data that identified both cognitive errors and correct decisions. The rigour of interpretive thinking and analysis was supported through dialogue and challenge by the supervisory team.

4 | FINDINGS

Twelve registered children's nurses participated in the interviews; four from the PICU, four from the Cardiac Ward and four from the HDU. All participants were female. The nurses had been undertaking withdrawal assessments for between 4-13 years (median 10 years) so were experienced in this aspect of their clinical role. Interviews lasted between 21-47 min.

In both vignettes, nurses' drew on all three options: "withdrawing", "not withdrawing" and "unsure" (Table 4). In V1, two nurses recognized there was insufficient information on which to make any judgement. Responses to "How easy or difficult was it to decide?" ranged from "easy" to "very difficult" with one nurse commenting that it "should be easy with more information". All nurses who found the diagnosis "easy" made a definite diagnosis.

In V2, the responses to "How easy or difficult was it to decide?" ranged from "quite easy" to "very difficult". Some nurses found V2 "easier than previous [vignette]" and one thought it was "harder with more information". Again, those finding the diagnosis "easy" all made a definite diagnosis. Those who found it "easier than previous" each gave a different diagnosis. The nurse finding V2 "harder with more information" was "unsure" in both vignettes. In terms of consistency of opinion across the vignettes, three people who made a diagnosis in V1, persisted with their diagnosis in V2 ("yes" $n = 2$, "no" $n = 1$). Four nurses were "unsure" in both vignettes. The two nurses who could not comment in V1 were "unsure" in V2 and found the decision "difficult".

Diagnosis of withdrawal was commonly based on the SWS score in V1, although the child's underlying condition was recognized as a

possible cause for the score (Table 4). In V2, more nurses recognized that the SWS score might reflect either the child's underlying conditions or their normal behaviour. Some nurses recognized that the duration of sedation described was too short to cause physical dependence and hence withdrawal symptoms. The three nurses who diagnosed "not withdrawing" made this observation along with one nurse who still diagnosed the patient as "withdrawing". Four nurses made explicit assumptions during their deliberations in V1. Three of these nurses diagnosed withdrawal; one was "unsure". Two nurses made assumptions in V2. One nurse made assumptions in both vignettes and diagnosed "withdrawal" in both cases. The second nurse was "unsure" in both vignettes, but found V2 "easier than previous". The common assumption in V1 was based on the length of ICU stay and related to possible sedatives the child might have received and the likelihood of mechanical ventilation.

4.1 | Treatment response

Treatment choices corresponded to the diagnosis when the diagnosis was definite but varied among nurses who were "unsure" (table 5 and figure 1). Nurses who diagnosed "withdrawing" chose to stop weaning chloral hydrate and "maybe" increase chloral and give codeine ("yes" $n = 2$, "maybe" $n = 1$). In contrast, nurses who diagnosed "not withdrawing" chose to continue weaning chloral hydrate. Two nurses considered giving additional analgesia including codeine, paracetamol and oral morphine. Nurses who were "unsure" chose a range of interventions, including stop weaning chloral hydrate, increase chloral, give codeine and no intervention. Paracetamol was chosen as "another intervention" by five nurses who had varied opinions about whether the child was withdrawing.

Failed heuristics and biases were identified during protocol analysis and these cognitive errors were categorized according to definitions cited by Croskerry (2003) (Table 6). Cognitive errors occurred during the decision-making processes involved in both the interpretation of and response to the SWS score. Every nurse made cognitive errors: the number ranging between 1 and 4 errors per nurse. Not all cognitive errors led to diagnostic errors, as two nurses made assumptions during their deliberations in V1, but these did not translate into an inaccurate diagnosis. No nurse made errors at every stage of the decision-making process.

4.2 | Noticing (defining and interpreting) SWS behaviours

Nurses shared an accurate understanding of the terms "insomnia" and "respiratory distress" and were confident and succinct in their definitions. They found "irritability" harder to define, but it was usually described as difficulty in consoling the child despite trying the usual comfort measures and parental presence. "Hypertonicity" was the most problematic term with one nurse unable to offer a definition and another giving an inaccurate definition. Although the remaining nurses offered a definition of "increased tone", half of them expressed doubt or lacked confidence about their explanation.

When talking about the definitions, there was a tendency for nurses to blur the boundaries between signs, describing the co-existence or overlapping of some behaviours. Two nurses described the interdependence of insomnia and irritability. During a definition of "irritability", one nurse explained "it's linked a bit to the insomnia where you can see that they are tired and want to sleep."(N5) In another nurse's definition of "irritability", it appeared to overlap with "insomnia"; "you sort of think they are settled, they sort of shut their eyes and they go still and then two minutes later they're awake you know, they're off again" (N10).

Inaccurate mapping of other behaviours to SWS signs was identified as another perceptual problem. Descriptions of motor disturbance were made by half of the nurses during their definitions of insomnia, irritability or hypertonicity. When defining "insomnia," one

TABLE 4 What nurses considered when deciding about withdrawal.

	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11	N12
V1 (Insufficient information provided)												
Diagnosis	Y	Y	N	?	?	Y	?	?	C	C	Y	?
SWS Score	✓	✓		✓		✓		✓	✓			✓
Underlying condition/pain/environment		✓	✓		✓	✓	✓	✓			✓	✓
Need info about SWS score trend (T)/drug therapy (D)								D	TD			D
Made assumptions	✓	✓			✓					✓		

Diagnosis Y Withdrawing N Not withdrawing ? Unsure C Can't comment

	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11	N12
V2 (Information provided about co-morbidities and potential for physical dependence)												
Diagnosis	Y	?	N	?	?	Y	?	N	?	N	?	Y
Underlying condition/normal behaviour		✓	✓	✓	✓		✓	✓	✓	✓	✓	
Drug therapy		✓				✓	✓			✓		✓
Not physically dependent			✓	✓	✓			✓	✓	✓		✓
Made assumptions	✓						✓					

TABLE 5 Application of the SWS tool.

							Intervention				
Nurse	Ward	Experience	Vignette 1		Vignette 2		Codeine	Stop weaning chloral	Increase chloral	No intervention	Other intervention
N1	PICU	5y	Yes	Easy	Yes	Not difficult	Maybe	Yes	Maybe		Distraction
N2	HDU	7y	Yes	Not easy	Don't know	Difficult	Yes	Yes			
N3	HDU	5y	No	4/10 easy	No	Easier than previous				No intervention	Investigate tremor
N4	HDU	10y	Probably	Quite easy	Don't know	Harder with more info		Yes			Paracetamol, speak to mum
N5	PICU	5y	Don't know Possible	Difficult (y)	Don't know	Very difficult				No intervention	Monitor
N6	Cardiac ward	13y	Yes	Easy	Yes	Quite easy	Yes	Yes	Maybe		
N7	PICU	10y	Don't know	Very difficult	Don't know yes	Easier than previous	Yes	Yes			
N8	Cardiac ward	13y	Yes possible	Should be easy with more information	No	Quite easy	Maybe				Paracetamol, oral morphine, pain team, neurology
N9	Cardiac ward	13y	Can't comment		Maybe	Difficult	Yes	Yes	Maybe		Paracetamol, physio, neurology
N10	PICU	10y	Can't comment		No	Quite difficult	Maybe				Speak to parents
N11	HDU	13y	Yes	Quite hard	Don't know no	Not asked	Maybe	Maybe			Paracetamol
N12	Cardiac ward	4y	Don't know	DNA	Yes	Easier for this one	Yes	Yes	Maybe		Paracetamol

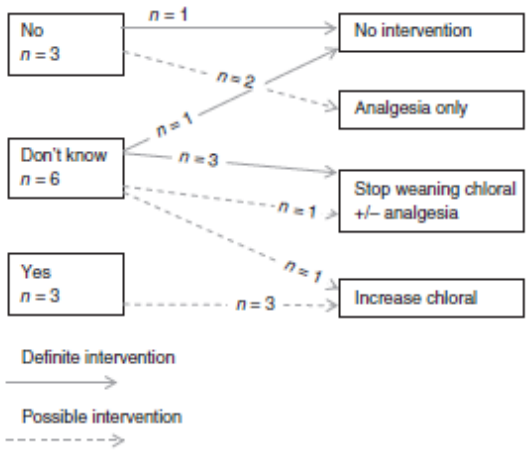

FIGURE 1 Withdrawal diagnosis and interventions chosen.

nurse commented that "They may be active, arms, legs, head, generally moving so they're not peacefully asleep" (N10). A definition of "irritability" included "thrashing their arms and legs around or their head around" (N9). "Hypertonicity" was described as:

> *Just constant moving of arms and legs, inability to stay still really, some of the babies they look like they're riding bikes lying in their cot because their legs just keep going round and their arms keep waving. (N8)*

TABLE 6 Cognitive errors identified during protocol analysis.

Cognitive error	Example	Nurse
Commission bias	Stopping chloral hydrate despite being unsure about withdrawal.	2,4,7,9
	Administering analgesia.	4,8,9,12
Confirmation bias	Diagnosing withdrawal despite recognizing the duration of sedation was too short.	12
Overconfidence bias	Acting on incomplete information or intuitions. Any definitive diagnosis in V1.	1,2,3,6,11
	Making assumptions.	1,2,5,7,11
Availability heuristic	Accepting a diagnosis that springs easily to mind. Relying on the SWS score alone to make a diagnosis without considering the wider context.	1
Anchoring heuristic	Choosing to stick with one's original diagnosis despite more information becoming available.	1,3,6

"Insomnia" presented challenges for nurses in terms of both recognizing and interpreting this behaviour. Lack of familiarity with the

patient made it difficult to know if the patient's behaviour was different to normal, as one nurse described "unless you know exactly what they're like without any of the illness, medication and what have you" (N4). Trying to making sense of current behaviour by ascertaining recent trends was also complicated by the perceived subjective nature of the assessment "if you look at the previous 12 hr, you've only got the chart to go from, so when somebody's marked down awake or asleep, you don't know if they've really been asleep for a whole hour or is it just 10 min" (N7). However, confidence grew throughout the shift "because you've done a whole day with them. …' (N10) and nursing a child on consecutive days was also viewed positively, because "then you've got a better comparison as to whether they are more or less alert than they were the previous day" (N9). Environmental factors were also identified as possible causes of insomnia, as one ICU nurse described, "ICU is noisy, it's loud, we forget and our colleagues talk and have to be shushed a lot of the time throughout the night, the monitors are always bleeping. . ." (N5).

The main challenge with interpreting "irritability" related to deciding whether this behaviour was a result of withdrawal or other co-morbidities. Nurses talked about undertaking a process of eliminating other possible causes of "irritability" before attributing it to withdrawal. As one nurse described "it's never the first thing I think when they're crying, they might be hungry or I'll check their nappy and when I've covered all the bases then I'll be like actually they're irritable" (N12).

Lack of familiarity with the patient was raised again but some nurses described working with parents to interpret the child's behaviour, because "they know them better than us" (N2). In children with neurological impairment, nurses described relying on parents to identify whether behaviours differed from normal, as one nurse explained; "I walk into the situation and I don't know the child I might think—"oh my word this baby's really agitated". But the parent's might go—"well that's him when he's well" (N8). Nurses appeared to be most confident in recognizing "respiratory distress" but found the challenge was judging whether it was a sign of withdrawal or another co-morbidity. One nurse commented "It's hard with the respiratory distress side of things, because if he's chronic lung disease, it's like Catch 22 isn't it?" (N6).

5 | DISCUSSION

This paper is the first to our knowledge describing the use of cognitive interviews and vignettes to examine the stages of decision-making undertaken by nurses in the assessment and management of withdrawal syndrome. Our study showed that nurses used a variety of approaches alone or in combination including intuition, reasoning, biases and heuristics, as reported by Tanner (2006).In The use of SWS did not standardize nurses' assessment of withdrawal and cognitive challenges arose in each stage (noticing, interpreting and responding) of decision-making examined. These stages will be discussed in the light of the overarching clinical goal of improving the assessment and management of withdrawal syndrome. As SWS shares a similar format and content to SOS and WAT-1, these findings suggest that cognitive challenges may also exist for nurses using SOS and WAT-1. As all nurses in the study made at least one cognitive error, there did not appear to be a relationship between quality of decision-making and either experience or their clinical specialism. Our results support the view that "simply possessing clinical experience is no predictor of high quality decision-making" (Thompson et al., 2009, p. 610).

The noticing stage—identifying and describing individual withdrawal behaviours—presented the greatest cognitive challenge for nurses and the widest variation in responses. When asked to describe withdrawal signs, nurses could plainly visualize a withdrawing child, demonstrating the "pattern recognition" of expert judgement and decision-making (Berner & Graber, 2008; p. S12). Difficulty arose in separating the component behaviours to fit a list of withdrawal signs, leading to a blurring of boundaries between terms and inaccurate mapping of other signs. Although deconstruction of withdrawal syndrome into an item pool of component behaviours may be a necessary stage in scale development (DeVellis, 2012), in the experimental conditions of this study, this step appears to add complexity rather than simplifying the assessment.

Nurses recognized that they lacked knowledge needed to interpret some SWS items, as they were mostly not cognizant of the child's normal behaviour. Knowing the patient and their pattern of responses is considered fundamental to sound clinical judgement (Tanner, 2006) promoting a corresponding sense of salience (Benner & Tanner, 1987), while less knowledge has an impact on the capacity to notice subtle cues or changes. Although no reflection on the nurses in this study, this deficit in personal knowledge of the child is a limitation in the application of SWS. Accurate withdrawal assessment relies not only on a shared meaning of clinical terms but also on a shared interpretation of these behaviours in each patient. Despite the close observation possible in critical care, recognizing subtle behavioural changes is more challenging in an unfamiliar patient. Including parents routinely in the assessment may benefit the process in identifying a personalized baseline of behaviours on which to consider new signs or identify trends, an approach endorsed in other complex clinical situations such as delirium (Schieveld et al., 2009) and pain assessment in children with severe neurological disability (Hunt et al., 2004).

Interpretation of the vignettes differed widely, despite every nurse being presented with the same information and clinical cues. This variation in decision-making in the face of identical information mirrors other studies involving nurses and pain assessment (Hodgins, 2002), nurses and critical event risk assessment (Thompson et al., 2009) and triage assessments made by emergency nurses Cioffi (1998). These findings support the view that clinical judgements are influenced more by what nurses bring to the situation than by the clinical data available to them (Tanner, 2006). The effort required to reach a diagnosis also varied widely: nurses who made a definite diagnosis found the decision easier than those who were unsure. For some nurses in V1, the score alone gave a clear diagnosis of withdrawal, abnegating the cognitive burden of interpreting the

meaning of ambiguous clinical signs. Indeed Benner and Tanner (1987) warned against the over-reliance on assessment tools, which could encourage a complacent "checklist mentality" rather than the rigour of "active enquiry".

The ability to see some aspects as more important than others has also been described as a sense of salience by Sitterding et al. (2012): this sense of salience was lacking among nurses who overlooked the fundamental importance of recent drug history as the context for a withdrawal assessment. In the face of such complexity and the need to consciously consider the context of drug dependence, the role for the subconscious cognitive processing characteristic of intuitive thinking is unclear. Nurses who were unable to reach a diagnosis found the task harder, reflecting their recognition of the ambiguities, complexity and incompleteness of the available information, demonstrated superior decision-making (Brannon & Carson 2003). Some nurses made probability judgements (possibly, probably or maybe withdrawing), which also inferred a cognitive flexibility to modify their opinion in the light of further information (Szolovits & Pauker, 1978). Whether as a result of complacency, overconfidence or a checklist mentality, this study suggests that some nurses have a misplaced confidence in the diagnostic capacity of SWS, which would consequently limit further enquiry. The potential for cognitive errors during this interpretive phase highlights the importance of learning clinical reasoning skills, ideally during nurse training (Levett-Jones et al., 2010, 2015).

The responding stage was the most consistent phase of decision-making with treatment decisions corresponding to nurses' definite diagnoses. Cioffi (1999) described the relationship between cues and inferences as decision rules or "if…then" rules. For example, "If a patient is withdrawing (cues) then the drug reductions should cease (inference)" or "If a patient is not withdrawing, then drug weaning should continue." However, when nurses were unsure of the diagnosis, an inclination towards "doing something" meant the most common intervention was to stop weaning chloral hydrate. This tendency towards action rather than inaction, despite no supporting evidence for the decision, is commission bias (Croskerry, 2003). Unnecessary slowing of weaning regimes should be avoided, however, as prolonging sedative treatment may prolong recovery and hospitalization. Administration of analgesics was another common treatment choice made by nurses, regardless of withdrawal diagnosis, perhaps reflecting an "obligation towards beneficence" another example of commission bias (Croskerry, 2003)—despite no supporting evidence of the need for analgesia.

5.1 | Limitations

This study has several limitations. While the cognitive interview technique is unique in revealing cognitive processes in participants, results are not generalizable to a wider population. The interviewer works as a nurse specialist in the hospital where the study took place and was known to the nurses participating in the interviews and they identified themselves as competent in using the SWS: these factors may have affected the nurses' responses.

The bedside treatment schedule of withdrawal in the study hospital includes a guidance to stop weaning with SWS scores between 3 and 6. The treatment schedule was not presented or discussed but it may be that some nurses recalled that a score of 5 linked to guidance to stop weaning. The number of withdrawal diagnoses in V1 may have been influenced by the fact that the participants were aware that the study was addressing sedation withdrawal; this might have created a diagnostic strategy of "going for the obvious" that may not reflect typical decision-making.

6 | CONCLUSION

This study using cognitive interviews with vignettes has provided insight into nurses' judgement and decision-making in a complex and ambiguous clinical situation. Focussing on the whole decision-making process (noticing, interpreting and responding) identified a significant cognitive burden and the potential for cognitive error at each stage. The use of a withdrawal assessment tool did not appear to simplify the process or reduce the burden.

There appears to be an inherent flaw in relying on a behavioural assessment using non-specific signs in a population where knowledge of usual behaviour is an essential prerequisite. Including parents in the assessment may expedite recognition of behavioural changes or trends. Key areas for improvement are in recognizing the clinical context necessary for withdrawal and minimizing the use of biases and failed heuristics. Revealing typical thought processes provides opportunity to reflect on complex cases, which may help to support critical thinking and reduce cognitive errors.

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CONFLICT OF INTEREST

No conflict of interest has been declared by the authors.

AUTHOR CONTRIBUTIONS

All authors have agreed on the final version and meet at least one of the following criteria [recommended by the ICMJE (http://www.icmje.org/recommendations/)]:

- substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
- drafting the article or revising it critically for important intellectual content.

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Parent consent form (Phase 1b symptom sheet)

Improving the recognition of sedation withdrawal in children under 5 years of age

Study number Participant identification number for this study _____

Name of researcher Jennie Craske

Please initial box

1.	I confirm that I have read and understand the information leaflet, dated 14/07/2013 (version 4) for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason.	
3.	I agree to study records being accessed by both student's supervisory team and relevant regulatory authorities	
4.	I agree to take part in the above study.	

Name of patient

Name of parent(s) Date Signature

Name of person taking consent Date Signature

When completed, 1 for participant, 1 for research site file and 1 (original) to be kept in medical notes.

Who is organising and funding the research?

The research is being undertaken by Jennie Craske who is doing a PhD funded by Liverpool John Moore's University.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, welfare and dignity. This study has been given a favourable opinion by Liverpool East Research Ethics Committee.

Who can I contact for further information?

If you have any questions at all, at any time, please contact;
Jennie Craske, Pain Control Service, Department of Anaesthesia, Alder Hey Children's NHS Foundation Trust, Eaton Road, Liverpool L12 2AP.
Tel: 0151 252 5003 Email: jennie.craske@alderhey.nhs.uk

Alternatively, you may prefer to contact the following people who are supervising the study;
Dr Lyvonne Tume Tel: 0151 282 4588
Email: lyvonne.tume@alderhey.nhs.uk
Professor Bernie Carter Tel: 01772 893720 Email: bcarter@uclan.ac.uk

Thank you very much for taking time to read this information leaflet and for considering taking part in the study.

Version 4.0 Phase 1b (Symptom recognition) 14/07/13

Improving the recognition of sedation withdrawal in children under 5 years of age

Parent Information Leaflet

Phase 1b Withdrawal symptoms

You are invited to take part in a research study. Please take time to read the following information carefully and discuss it with others if you wish. If any information is unclear or you would like more information, please feel free to contact Jennie Craske from the research team (details overleaf).

What is the purpose of the study?

In the Intensive Care Unit, babies and children often have drips of sedative and pain-relieving medicines. Sedation withdrawal can occur when these medicines are stopped or reduced suddenly. When withdrawal is identified, treatment can be given to relieve the symptoms. Nurses use an assessment tool to help them decide if a child is withdrawing. We would like to find out what symptoms you noticed in your child when s/he was withdrawing. **The purpose of the study is to improve the assessment of sedation withdrawal in children under 5 years of age.**

Why have I been chosen?

Your child has been treated for sedation withdrawal during this admission.

What will happen if I take part?

We will show you a list of 12 withdrawal symptoms. For each of these symptoms we would like to know if you noticed this symptom in your child. For symptoms you did notice, we would also like to know how distressing or upsetting this symptom was to you as a parent.

If you are also willing to talk to Jennie about your experiences of sedation withdrawal, there is space at the end of the sheet to say this. If you are happy to complete the symptom sheet but don't want to be interviewed that is OK too.

Version 4.0 Phase 1b (Symptom recognition) 14/07/13

Do I have to take part?

No, it is up to you entirely. If you decide to take part, you will be asked to sign two consent forms, one for you to keep and one for the researcher. You are free to stop taking part at any time, without giving a reason. If you decide to stop, this will not affect the care your child receives.

Will my taking part in this study and my child's data be kept confidential?

All information collected during this study will be kept confidential. This means that apart from Jennie, no one will know what you have marked on the sheet. Your completed symptom sheet will be marked with a number only, and with your permission, stored securely until the end of the study. You or your child will not be named or identified in any reports of the study.

What are the possible risks and benefits of taking part?

We do not anticipate any risks to your child in taking part in this study; however it is possible that you might get upset when remembering about the withdrawal symptoms your child experienced. Although this study will not benefit your child, we hope it will help nurses, doctors and parents in the future in caring for children with sedation withdrawal.

What if there is a problem?

If you have a concern about any aspect of this study, you can speak to Jennie or one of the supervisory team, who will do their best to answer your questions (details overleaf). If you remain unhappy and wish to complain formally, then you should contact the Patient Advisory Liaison Service, Alder Hey Children's NHS Foundation Trust, Eaton Road, Liverpool L12 2AP. Tel : 0151 252 5161. Email: PALS@alderhey.nhs.uk

Withdrawal symptom sheet for parents (Phase 1b) AH number _____ v1 20.08.12

When you have completed the sheet, please place it in the envelope provided and hand it to your nurse. Many thanks for taking part in this project.

Withdrawal symptoms	Did you notice this symptom? (please tick)	If yes, please circle a number on the 0 – 10 scale to show how distressing this symptom was to you as a parent. 0 represents 'not distressing' and 10 represents 'extremely distressing'
Insomnia Poor sleep, not sleeping	Yes ☐ No ☐ Don't know ☐	0 1 2 3 4 5 6 7 8 9 10
Irritability Fussy, whiney or fretful. Not easy to comfort.	Yes ☐ No ☐ Don't know ☐	0 1 2 3 4 5 6 7 8 9 10
Sweating	Yes ☐ No ☐ Don't know ☐	0 1 2 3 4 5 6 7 8 9 10
Sneezing	Yes ☐ No ☐ Don't know ☐	0 1 2 3 4 5 6 7 8 9 10
Diarrhoea	Yes ☐ No ☐ Don't know ☐	0 1 2 3 4 5 6 7 8 9 10
Vomiting	Yes ☐ No ☐ Don't know ☐	0 1 2 3 4 5 6 7 8 9 10
Tremor Trembling or shaking movements in hands or feet	Yes ☐ No ☐ Don't know ☐	0 1 2 3 4 5 6 7 8 9 10
Fever High temperature	Yes ☐ No ☐ Don't know ☐	0 1 2 3 4 5 6 7 8 9 10
High pitch cry	Yes ☐ No ☐ Don't know ☐	0 1 2 3 4 5 6 7 8 9 10
Respiratory distress Breathing causing chest or tummy to move more than usual, needing oxygen	Yes ☐ No ☐ Don't know ☐	0 1 2 3 4 5 6 7 8 9 10
Hypertonicity Arms or legs look stiff	Yes ☐ No ☐ Don't know ☐	0 1 2 3 4 5 6 7 8 9 10
Convulsions A seizure or fit	Yes ☐ No ☐ Don't know ☐	0 1 2 3 4 5 6 7 8 9 10

If you might also be willing to be interviewed about your experiences of sedation withdrawal, please tick the box and the researcher will come to discuss this with you in more detail later today. Yes ☐ No ☐

Parent consent form (Phase 1c interviews)

Improving the recognition of sedation withdrawal in children under 5 years of age

Study number Participant identification number for this study _____

Name of researcher Jennie Craske

Please initial box

1.	I confirm that I have read and understand the information leaflet, dated 14/07/2013 (version 4) for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason.	
3.	I understand that my interview will be audio-recorded and transcribed and that brief quotations from some interviews may be included in study reports.	
4.	I agree to study records (including transcripts of my interview) being accessed by both student's supervisory team and relevant regulatory authorities	
5.	I agree to take part in the above study.	

Name of patient

Name of parent(s) Date Signature

Name of person taking consent Date Signature

When completed, 1 for participant, 1 for research site file and 1 (original) to be kept in medical notes.

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Professor Bernie Carter Tel: 01772 893720 Email: bcarter@uclan.ac.uk

Thank you very much for taking time to read this information leaflet and for considering taking part in the study.

Improving the recognition of sedation withdrawal in children under 5 years of age

Parent Information Leaflet

Phase 1c Interviews

Version 4.0 Phase 1c (Interviews) 14/07/13

You are invited to take part in a research study. Please take time to read the following information carefully and discuss it with others if you wish. If any information is unclear or you would like more information, please feel free to contact Jennie Craske from the research team (details overleaf).

What is the purpose of the study?

In the Intensive Care Unit, babies and children often have drips of sedative and pain-relieving medicines. Sedation withdrawal can occur when these medicines are stopped or reduced suddenly. When withdrawal is identified, treatment can be given to relieve the symptoms. Nurses use an assessment tool to help them decide if a child is withdrawing. We would like to interview parents to find out what they noticed about their child when their child was withdrawing. **The purpose of the study is to improve the assessment of sedation withdrawal in children under 5 years of age.**

Why have I been chosen?

Your child has been treated for sedation withdrawal during this admission.

What will happen if I take part?

We would like you to take part in an interview with Jennie Craske who is doing this research study. The questions in the interview will be about what you noticed about your child when they had withdrawal symptoms and about your experiences when they were withdrawing. If there are any questions you do not want to answer just tell the interviewer and she will move on to the next question. You can also stop the interview at any time. The interview will take about 45 minutes.
We would also like to audio-record the interview if that's OK with you. We will make a typed copy of the interview but remove all identifying details. A copy of the interview will be available to you should you wish.

When and where will the interview take place?

This can happen either when your child is still in hospital or at your first clinic appointment, about a week after you have been discharged from hospital. It's up to you. The interview will take place in a private room on the ward or near the clinic.

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Do I have to take part?

No, it is up to you entirely. If you decide to take part, you will be asked to sign two consent forms, one for you to keep and one for the researcher. You are free to stop taking part at any time, without giving a reason. If you decide to stop, this will not affect the care your child receives.

Will my taking part in this study and my child's data be kept confidential?

All information collected during this study will be kept confidential. This means that apart from Jennie, no one will know what you have said. Although names may be mentioned during interviews, these will not be included when the typed copy of the recording is made. The audio-recordings will be destroyed once the typed copy is made. You or your child will not be named or identified in any reports of the study.

What are the possible risks and benefits of taking part?

We do not anticipate any risks to your child in taking part in this study; however it is possible that you might get upset when remembering certain things about when your child was in hospital. Although this study will not benefit your child, we hope it will help nurses, doctors and parents in the future in caring for children with sedation withdrawal.

What if there is a problem?

If you have a concern about any aspect of this study, you can speak to Jennie or one of the supervisory team, who will do their best to answer your questions (details overleaf). If you remain unhappy and wish to complain formally, then you should contact the Patient Advisory Liaison Service, Alder Hey Children's NHS Foundation Trust, Eaton Road, Liverpool L12 2AP. Tel : 0151 252 5161. Email: PALS@alderhey.nhs.uk