Centre universitaire de santé McGill | McGill University Health Centre

Université de Montréal

SOWA-ICU

Signs and symptoms of opioid-associated iatrogenic withdrawal in critically ill adults

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Table of Contents

Abbreviation list

ICU	**Intensive care unit**
IWS	**Iatrogenic withdrawal syndrome**
MGH	**Montreal General Hospital**
MUHC	**McGill University Health Centre**
OIWS	**Opioid-associated iatrogenic withdrawal syndrome**
PICU	**Pediatric intensive care unit**
RVH	**Royal Victoria Hospital**

1. Introduction

Adult medical, surgical and trauma intensive care unit (ICU) patients routinely experience pain, agitation, delirium and anxiety (1). Opioids and benzodiazepines are the primary medications to relieve pain, facilitate mechanical ventilation and decrease physiological and psychological stress in the critically ill (1). In a prospective, observational study in 51 Canadian ICUs, 92% of patients received opioids and sedatives at least once during mechanical ventilation (2). Upon repeated and prolonged administration, opioid tolerance may develop as a result of receptor desensitization and upregulation of excitatory intracellular pathways (2, 3). When these drugs are abruptly discontinued or rapidly tapered, patients may develop a cluster of signs and symptoms known as the acute iatrogenic withdrawal syndrome (IWS). While this phenomenon is well described in the pediatric critical care population, there is a paucity of data in critically ill adults (4-7). IWS has been associated with negative clinical outcomes such as increased length of hospital stays, prolonged duration of mechanical ventilation and higher cost of hospitalization (4-7).

In one prospective, observational study, the reported incidence of IWS in the adult ICU population was 16.7% (8). In prospective studies done in the pediatric ICU (PICU), observed incidence was 7.5 to 100% (9). Two assessment tools have been validated in children: The Withdrawal Assessment Tool-Version 1 (WAT-1) and the Sophia Observation Withdrawal Symptoms-scale (SOS) (10). No such tool currently exists in the adult ICU (9).

Identifying IWS can be challenging in the critically ill. Several confounding factors (delirium, worsening of critical illness, presence of multiple agents with potential to cause withdrawal, comorbidities) may mimic symptoms similar to opioid or benzodiazepine withdrawal (6, 11). To our knowledge, no study on the symptomatology of IWS has been conducted to describe opioid or benzodiazepine withdrawal exclusively. This is most likely due to the presentation similarities of both syndromes and frequent concomitant use of these drugs in the ICU setting (4, 9).

No physiological markers have been identified to correlate with IWS. In outpatients with chronic opioid addiction, several studies have shown a significant association between increased cortisol and catecholamine levels and acute withdrawal following naloxone reversal. Cortisol and catecholamines are two stress markers that reflect the state of distress and adrenergic hyperstimulation characteristic of opioid withdrawal (12).

To date, the clinical presentation of opioid withdrawal in the adult ICU has not been characterized in a prospective setting. The present study thus aims to describe the symptomatology of opioid-associated iatrogenic withdrawal in two adult tertiary care centers in Montréal, Québec, Canada and explore the potential of using serum cortisol as a biomarker (4, 9).

2. Literature review

Research strategy can be found in Appendix I.

Epidemiology

A systematic review on the epidemiology, risk factors and symptomatology of IWS was recently conducted and identified only one prospective study on IWS in the adult ICU population, which reported an incidence of 16.7% (8, 9). In retrospective trials, incidence ranged from 19.7 to 100% (9). These heterogeneous results are likely attributed to the lack of standardized definition and evaluation of IWS (9).

Risk factors

There is significant overlap in the IWS risk factors identified in pediatric and adult populations such as younger age (3, 4, 7, 9) duration of continuous opioid therapy (i.e. more than three to five days) and prolonged benzodiazepine exposure (4, 5, 7, 9, 13-17). Additional risk factors identified specifically in the adult ICU include higher daily doses of opioids and benzodiazepines, as well as the presence of acute respiratory distress syndrome (ARDS) (7, 9). In the PICU, prolonged exposure prior to weaning

and total cumulative opioid and benzodiazepine doses have been associated with an increased risk of IWS (4, 5, 14, 15). The onset of withdrawal symptoms can occur within 12 hours following opioid discontinuation and may be precipitated by an abrupt taper or the administration of opioid antagonists (1, 18).

Clinical presentation

Most literature is extracted from PICU studies designed with the objective of developing or validating IWS assessment tools (16). Ista et al. compiled a list of 26 symptoms of mixed withdrawal as reported in the literature and evaluated the co-occurrence of IWS symptoms in low and high risk patients (19). An expert panel identified 15 symptoms encompassing the central nervous system (anxiety, agitation, inconsolable crying, grimacing, sleep disturbance, hallucinations), autonomic dysfunction (increased muscle tension, muscle twitching, tremors, tachycardia, tachypnea, fever, sweating) and gastrointestinal problems (vomiting, diarrhea) (19, 20). However, the investigators did not control for potential confounders of IWS diagnosis such as inadequate pain management or delirium. A review by Chiu et al. identified symptoms of opioid withdrawal specific to the neonatal and PICU populations such as inconsolable crying, irritability, grimacing, tremors, increased muscle tone, poor feeding, vomiting, diarrhea, sleep disturbance, hyperactive Moro reflex, fever, nasal stuffiness, sweating and yawning (4). However, evaluation of symptoms and outcomes were done by the same practitioner in select studies, which may have confounded the results (4, 21).

Opioid withdrawal appears to present differently in adults (4). In a prospective study evaluating the validity of the WAT-1 in the adult ICU, commonly observed symptoms in the PICU such as diarrhea, vomiting and fever did not correlate with a diagnosis of IWS (8, 22). Chiu et al. reports that withdrawal symptoms in adults tend to begin with anxiety, irritability, agitation and dysphoria, followed by sweating, rhinorrhea, tachypnea, insomnia and yawning in the acute phase. Symptoms such as mydriasis, tachycardia, hypertension, nausea, vomiting, piloerection and fever manifest during subsequent phases of withdrawal (4). In the retrospective study by Cammarano et al., IWS was diagnosed using a modified Himmelsbach scale, which assesses the severity of opioid withdrawal in chronic users only (7, 23). Thus, the symptoms identified in this study may not be applicable to opioid-naive patients. It is currently unclear whether all these symptoms can be identified in opioid-naive critically ill patients

The distinction between opioid and benzodiazepine withdrawal remains unclear because both drugs are often used simultaneously in the ICU setting. Duceppe et al. reports that there are currently no adult or pediatric ICU studies that evaluated the incidence of isolated opioid or benzodiazepine withdrawal symptoms (9). The 2002 adult critical care guidelines, updated in 2013, identifies nausea, vomiting, sweating, agitation, restlessness, irritability, anxiety and muscle cramps as common symptoms to both acute opioid and benzodiazepine withdrawal (1, 18). Benzodiazepine and opioid withdrawal symptoms largely overlap, which contributes to the difficulty in describing both syndromes adequately (20, 24).

Assessment tools

As stated previously, in the PICU, two validated tools are commonly used to assess IWS: the WAT-1 and the SOS. Both are included in the 2016 European clinical guidelines for pain, sedation, withdrawal and delirium assessment in critically ill infants and children (10). However, they were validated in a manner that could potentially affect the results' reliability – in the psychometric evaluation studies, the same nurse scored both the tool and withdrawal severity. The lack of blinding to the presence of IWS and the lack of independent evaluation thus-make those studies susceptible to observer bias. The WAT-1 performed poorly in the adult ICU, suggesting that the presentation of IWS is different in adults as compared to children (4).

Biomarkers

The literature on opioid dependence has consistently demonstrated elevated levels of cortisol (12, 25-38) and catecholamines (12, 39-43) during the acute withdrawal phase. Human and animal

models postulate that long-term use of opioids induces hypoadrenalism through impairment of the hypothalamic-pituitary-adrenal (HPA) axis. Opioid withdrawal leads to marked elevations of cortisol as a result of excess ACTH secretion (26, 32, 35). This HPA activation persists following normalization of the adrenergic system, which led some authors to conclude that cortisol is a more sensitive indicator of opioid withdrawal than catecholamines (30, 32). A small study by Higgins et al. on 5 non-dependent subjects assessed acute opioid withdrawal after a single dose of morphine and observed a dose-dependent increase in cortisol levels when subjects were subsequently injected with naloxone (28). Despite the clinical relevance, several limitations reduce the applicability of those results to our study population, mainly the selection of opioid-dependent subjects and rapid induction of withdrawal – through injection of naloxone or abrupt cessation of opioid with support medications such as alpha$_2$-agonists. Since our subjects are mostly opioid-naive prior to hospitalization and will be gradually weaned off their opioids, the magnitude of increase in cortisol levels will likely be lower.

As for catecholamines, serum epinephrine and norepinephrine appear to increase rapidly following opioid withdrawal in numerous animal and human studies (12, 39-43). However, in contrast with cortisol, catecholamine levels decrease shortly following acute withdrawal. In a study of subjects undergoing rapid opioid detoxification, catecholamine levels peaked two hours following naloxone administration (12). A gradual opioid weaning as often seen in clinical practice is unlikely to be recognized through measurement of serum catecholamines.

3. Research objectives

Research question

What are the signs and symptoms of opioid-associated iatrogenic withdrawal syndrome (OIWS) in the adult ICU population?

Primary objective

To identify specific signs and symptoms of OIWS in mechanically ventilated adult ICU patients receiving at least 72 hours of regular opioids at the Montreal General Hospital (MGH) and the Royal Victoria Hospital (RVH) from February to October 2018

Secondary objective

To determine if the presence of OIWS is associated with an increase in serum cortisol.

4. Methods

4.1 Study design

Multicenter Prospective Observational Open Cohort Study

The clinical presentation of OIWS is poorly described in the adult ICU population. The descriptive study design aims to identify signs and symptoms of OIWS in the prospect of developing a validated bedside screening tool. The prospective approach will enable collection of all relevant information while limiting missing data and assessing for potential confounding variables.

Throughout the study, investigators will be blinded to the diagnosis of OIWS to reduce evaluation bias and increase internal validity. Additionally, on one occasion for each patient, OIWS evaluation will be performed by two physicians, allowing for inter-rater reliability. This will ensure accurate OIWS diagnosis and reduce information bias. Following transfer to the ward, one additional data collection will be performed to optimize OIWS detection.

The study will be conducted in two hospitals of the McGill University Health Centre (MUHC) with different ICU populations, hereby increasing the external validity of the results. The MGH is a Level I trauma center, whereas the RVH treats surgical and medical patients. Furthermore, a multicentric approach will increase the sample size and the likelihood of describing the syndrome adequately.

4.2 Populations

Target population

Mechanically ventilated adult ICU patients receiving continuous or regular intermittent opioids for more than 72 hours

Source population

Mechanically ventilated adult ICU patients admitted to the MGH and the RVH from February to October 2018 receiving continuous or regular intermittent opioids for more than 72 hours and meeting the inclusion and none of the exclusion criteria of the study

Study population

Mechanically ventilated adult ICU patients admitted to the MGH and the RVH from February to October 2018 receiving at least 72 hours of continuous or intermittent opioids, meeting the inclusion and none of the exclusion criteria and consenting to participate in the study

4.3 Subject selection mode

4.3.1 Inclusion criteria

- Patients 18 years of age or older
- Admitted to the RVH and MGH intensive care units from February to October 2018
- Patients requiring mechanical ventilation and receiving continuous or regular intermittent opioids for at least 72 hours (calculated from the hour of administration of the first opioid dose)
    - Recent prospective observational studies in the PICU and adult ICU populations have demonstrated that iatrogenic withdrawal symptoms may develop following 3-5 days of continuous opioid therapy (5, 8)
    - Patient will be considered as receiving regular intermittent opioids if more than half of the scheduled "as-needed" doses within 24 hours were administered.
        - In the event that only prn narcotics are prescribed on a q1h prn or q2h prn basis, patients will be eligible if ≥ 4 prn doses are required per day.
- Weaning of at least 10% from previous stable opioid dose
    - A weaning episode is defined as a ≥ 10% decrease in the total stable opioid dose received over 4 hours for opioid infusions and over 12 hours for intermittent opioid administration (22)
    - According to our previous experience (i.e. WAAICUP-1), the weaning definition of ≥ 10% was chosen for practical reasons (8)

4.3.2 Exclusion criteria

- Patient for whom consent cannot be obtained
- Patient and/or family unable to communicate in French or English
    - May interfere with obtaining informed consent and OIWS assessment
- Patient who is deaf without appropriate hearing aid
    - Hearing impairment may interfere with patient communication and assessment of signs and symptoms
- Imminent and predictable death (< 72 hours) according to medical team
- Patients receiving opioids for the purposes of palliative care or prescribed by the palliative care team.
- Severe brain injury, defined as Glasgow Coma Scale (GCS) score of 8 or less at ICU admission
- Moderate brain injury, defined as GCS between 9 and 12, with elevated intracranial pressure (ICP > 20 mmHg) which requires ICP monitoring and osmotherapy
    - Major confounding factors for withdrawal syndrome by causing shivering, sympathetic drive and autonomic disorders
- Acute neurological condition (e.g. status epilepticus, encephalopathy, stroke)
    - Potential confounders of OIWS assessment

    - If the acute neurological condition resolves within 72 hours, the patient may be included in the study
- Substance abuse prior to ICU admission
    - Chronic alcohol use defined as alcohol consumption of more than 2 drinks/day and/or more than 14 drinks/week for men and 9 drinks/week for women (44)
    - Chronic use of illicit drugs and amphetamines (except amphetamines taken for therapeutic purposes) defined as a consumption of at least 3 times per week
    - Chronic use of opioids (e.g. transdermal fentanyl, methadone, hydromorphone, etc.) defined as a consumption of at least 3 times per week
    - May induce withdrawal and confound OIWS assessment (45)
    - Chronic consumption of these substances will be confirmed by the patient, family, or medical chart
- Admission to the ICU with substance overdose or alcohol withdrawal syndrome.
- Readmission to the MGH or RVH ICU during the recruitment period (limit of one study entry per patient)
- Spinal cord injury above the lumbar region
    - Sympathetic response to withdrawal absent depending on site/level of injury
    - Assessment tools not validated in these patients (DSM-5, RASS, CAM-ICU, CPOT)
- Opioid tolerance prior to ICU admission, defined as regular daily use of opioids for a chronic medical condition or continuous opioid administration for > 7 days prior to ICU admission (46) Does not include patients who take opioids infrequently.
    - The FDA defines opioid tolerance as patients receiving at least 60 mg/day of oral morphine equivalents (600 mcg IV fentanyl IV equivalents/day) for ≥ 1 week (46)

4.4 Definition of variables

4.4.1 Primary outcome variables

Dependent variables

- Presence of signs and symptoms of OIWS
    - According to daily evaluation by investigator after an episode of opioid weaning has begun (See Appendix III)

Independent variables

- **Presence of OIWS** (qualitative nominal - dichotomous)
    - According to DSM-5 evaluation completed daily by physician after an episode of opioid weaning has begun
- **Demographic and clinical variables**
    - **Age** (quantitative continuous): Age in years at ICU admission
    - **Sex** (qualitative nominal - dichotomous)
    - **Weight** (quantitative continuous): Weight in kg at ICU admission
    - **Height** (quantitative continuous): Height in cm at ICU admission
    - **Body mass index** (BMI) (quantitative continuous): In kg/m^2 at ICU admission
    - **Ethnicity** (qualitative nominal)
    - **Site of ICU admission** (qualitative nominal - dichotomous)
    - **Smoking status** (qualitative nominal - dichotomous)
        - Number of cigarettes per day according to medical chart, patient or family at ICU admission (quantitative discrete)
        - Number of pack-years according to medical chart, patient or family at ICU admission (quantitative continuous)
    - **Principal diagnosis at ICU admission** (qualitative nominal)
        - Definite diagnosis according to medical chart at ICU admission using ICD-10 classification
    - **Length of stay in the ICU** (quantitative continuous)
        - Time in hours from ICU admission to ICU discharge, transfer to ward or patient death, according to medical chart
        - Opioid withdrawal has been associated with longer ICU stays (4-6)
    - **Duration of mechanical ventilation** (quantitative continuous)

    - Time in hours according to medical chart
    - Longer duration of mechanical ventilation has been associated with increased risk of IWS in ICU patients (7)
- **Acute Physiology and Chronic Health Evaluation II Score** (APACHE II) (qualitative ordinal)
    - To assess severity of disease and ICU mortality on a scale of 0 to 71 (47)
    - As reported by an archivist based on data from the first 24 hours of ICU admission
- **Glasgow Coma Scale** (GCS) (qualitative ordinal)
    - To assess mental status and severity of brain injury on a scale of 3 to 15 (48)
    - As reported by nurse on patient flow sheet at ICU admission
- **Renal function**
    - Daily serum creatinine in µmol/L according to medical chart (quantitative continuous)
    - Presence of renal replacement therapy according to medical chart (qualitative nominal - dichotomous)
    - Drug accumulation may occur when renal excretion is decreased, minimizing OIWS
- **Level of hepatic dysfunction upon ICU admission**
    - Severity of hepatic dysfunction as calculated by the Child-Turcotte-Pugh score at ICU admission (qualitative ordinal)
    - Drug accumulation may occur when hepatic metabolism is decreased
- **Presence of ECMO** (qualitative nominal - dichotomous)
    - Collected daily according to medical chart
    - Patients on ECMO may require higher fentanyl doses due to sequestration of lipophilic drugs and increased volume of distribution (49)
- **Cumulative opioid dose preweaning** (quantitative continuous)
    - Cumulative opioid dose in fentanyl equivalents (µg/kg) according to medication administration record (MAR) from time of start of opioids during ICU admission
    - Higher cumulative opioid doses have been associated with increased risk of IWS in ICU patients (8)
- **Duration of continuous opioid administration preweaning** (quantitative continuous)
    - Time in hours according to MAR or patient flow sheet
    - Prolonged opioid exposure has been associated with an increased risk of IWS in ICU patients (4, 8, 13-15)
- **Rate of opioid weaning > 10% from previous stable dose** (quantitative continuous)
    - Calculated in % according to MAR or patient flow sheet
        - Continuous infusion: perfusion rate over previous 4h
        - Continuous intermittent administration: total dose over previous 12h
    - Rapid tapering or abrupt discontinuation of opioids has been associated with increased risk of IWS in ICU patients (7, 20)
- **Presence of clonidine, beta-blockers or antidepressants prior to ICU admission** (qualitative nominal - dichotomous)
    - The agent and whether it was represcribed in ICU will be noted according to the medication reconciliation chart at admission
    - These medications may cause withdrawal when discontinued
- **Occasional use of prescribed opioids prior to ICU admission** (qualitative nominal - dichotomous)
    - Agent (qualitative nominal) and daily doses in fentanyl equivalents (µg/kg/day) (quantitative continuous) will be noted according to medication reconciliation chart at admission
    - Chronic opioid users are excluded from the present study (as indicated in exclusion criteria)

- **Prior history of substance abuse** (qualitative nominal - dichotomous)
    - Agent (qualitative nominal) will be noted according to patient, family or medical chart
    - A prior history of substance abuse may render those patients more susceptible to CNS depressants (e.g. opioids and benzodiazepines)

Confounding variables

- **Chronic or occasional use of benzodiazepines prior to ICU admission** (qualitative nominal - dichotomous)
    - Agent (qualitative nominal) and total daily doses in lorazepam equivalents (mg/kg/day) (quantitative continuous) will be noted according to medication reconciliation chart at admission
    - Withdrawal due to benzodiazepines may overlap with OIWS assessment (6, 24)
- **Concomitant administration of benzodiazepines during ICU stay** (qualitative nominal - dichotomous)
    - Agent and total daily dose (mg/kg) will be noted daily (qualitative nominal and quantitative continuous, respectively), as well as total cumulative benzodiazepine dose received since ICU admission in lorazepam equivalents (mg/kg) (quantitative continuous), according to MAR.
    - Higher mean daily doses of benzodiazepines have been associated with an increased risk of IWS in ICU patients (7)
    - Withdrawal due to benzodiazepines may overlap with OIWS assessment (6, 24)
- **Administration of medication that may influence severity of OIWS** (e.g. clonidine, dexmedetomidine, methadone, buprenorphine, propofol, beta-blockers and antipsychotics) (qualitative nominal - dichotomous)
    - Agent, total daily dose will be noted daily according to MAR (qualitative nominal)
    - Clonidine, dexmedetomidine, methadone, buprenorphine and antipsychotics can be used to treat or attenuate symptoms of opioid withdrawal and therefore may confound OIWS assessment (4, 50)
- **Presence of chronic neurological conditions** (e.g. dementia, Parkinson's disease, essential tremor) (qualitative nominal - dichotomous)
    - According to past medical history in medical chart
    - Symptoms of dementia and Parkinson's disease may confound OIWS assessment
- **Presence of delirium** (qualitative nominal - dichotomous)
    - During ICU stay: according to the Confusion Assessment Method for the ICU (CAM-ICU) as measured by investigators during evaluation and/or nursing staff, collected daily once opioid weaning is initiated and until transfer
    - After transfer to ward: according to the Confusion Assessment Method (CAM) measured once by investigators within 24-96 hours of transfer
    - Symptoms of delirium may overlap with OIWS assessment (10, 20, 51)
- **Presence of agitation due to a condition other than OIWS** (qualitative nominal - dichotomous) (10)
    - During ICU stay: according to the Richmond Agitation-Sedation Scale (RASS) as measured by investigators and/or nursing staff, collected daily once opioid weaning is initiated (qualitative ordinal) and until transfer
    - After transfer to ward: according to the Agitated Behavior Scale (ABS), measured once by investigators within 24-96 hours of transfer (qualitative ordinal)
- **Presence of pain** (qualitative nominal - dichotomous)
    - In patients unable to self-report: Critical-Care Pain Observation Tool (CPOT) score > 2, as measured by investigator or medical staff, collected daily once opioid weaning is initiated
    - In patients able to self-report: Numeric Rating Scale (NRS) ≥ 4, collected daily once opioid weaning is initiated
    - The symptoms of uncontrolled pain may confound OIWS assessment (20)

- **Administration of co-analgesia during ICU hospitalization** (e.g. acetaminophen, non-steroidal anti-inflammatory drugs, anticonvulsants, antidepressants, corticosteroids) (qualitative nominal)
    - Agent and total daily dose will be noted daily according to MAR
    - Co-analgesia is used to treat or attenuate pain, which may confound OIWS assessment
    - Anti-inflammatory drugs also act as antipyretics, which may confound OIWS assessment
- **Presence of nicotine replacement therapy during ICU admission** (qualitative nominal - dichotomous)
    - Nicotine consumption in mg (qualitative continuous) prior to ICU admission (e.g. cigarettes, nicotine replacement therapy) and whether nicotine replacement therapy was prescribed in ICU will be noted according to medication reconciliation chart at admission (qualitative nominal)
    - Nicotine withdrawal or nicotine-induced delirium may confound OIWS assessment (45)
- **Factors which may confound specific signs and symptoms of OIWS** (qualitative nominal - dichotomous)
    - Fever secondary to documented or suspected infection
        - According to diagnosis documented in medical chart
    - Diarrhea due to *Clostridium difficile* infection or enteral feeds
        - According to positive *C. difficile* antigen detection test in medical chart or presence of enteral feeds in patient flow sheet
- **Use of physical restraints** (qualitative nominal - dichotomous) (52)
    - Collected daily according to medical chart
    - Patients with restraints are more likely to be given supplemental sedative and analgesic agents which may confound OIWS assessment

4.4.2 Secondary outcome variables

Both serum cortisol levels will only be measured in patients not receiving exogenous corticosteroids.

Independent variables

- **Basal serum cortisol level** (quantitative continuous)
    - Measured ± 2 hours from the start of opioid weaning
- **Weaning serum cortisol level** (quantitative continuous)
    - Measured on the day of transfer to ward or after a maximum of 72 hours after start of weaning, at the same time of day as the first measure, whichever occurs first.
- **Change in serum cortisol levels** (quantitative continuous)
    - Difference between weaning and basal serum cortisol levels

Confounding variables

- **Timing of sample in hh:mm** (quantitative continuous)
    - Cortisol is secreted in a diurnal pattern (53)
    - Serum cortisol samples will be taken at the same time of day
- **Presence of primary adrenal insufficiency** (qualitative nominal - dichotomous)
    - According to past medical history in medical chart
    - Patients with this condition may present with hypocortisolemia and receive exogenous corticosteroids, which may confound serum cortisol assays
- **Presence of acute illness** (infection, trauma, surgery, illness) (qualitative nominal)
    - According to APACHE II score at ICU admission
    - Cortisol has been studied as a marker of severity of disease, with higher levels associated with worse prognosis. This association appears to be stronger during the first two days of admission (54)
    - May thus increase cortisol levels depending on severity of disease (53)

    - May also provoke transient adrenal insufficiency (53)
- **Presence of septicemia or septic shock** (qualitative nominal - dichotomous)
    - Diagnosis of sepsis will be noted according to medical chart
    - Sepsis causes relative adrenal insufficiency in up to 30 to 70% of patients, which may confound results (55-57)
- **Medications (ketoconazole, spironolactone, dopamine agonists, etc.)** (qualitative nominal)
    - May reduce cortisol production (53)

4.5 Data collection and study procedure (Appendix II)

From February to October 2018, patients from the MGH and RVH critical care units will be screened daily from unit patient lists generated through Oasis for eligibility. The investigators will be transiting daily between both centers. Once a patient is approaching 72 hours of mechanical ventilation and regular opioid administration, subjects will be evaluated for inclusion and exclusion criteria according to medical chart, and data will be recorded in the "Patient Screen Log". Once a patient fits our entry criteria, here are the steps for obtaining consent:

1- A member of the treating team (ICU physician or patient nurse) will inform the patient about this research project. If the patient is deemed unfit to provide informed consent, the patient's decision maker will be approached.
2- If patient/decision maker shows interest, a member of the research team, independent of the clinical care of the patient will meet with the patient/decision maker and explain the research and seek informed consent.
3- If the intubated patient verbally agrees but is unable to sign the consent, then a witness will sign the consent and the discussion will be documented on the consent form.
4- If the consent is obtained from a decision maker, then we will further seek direct patient consent as soon as patient is deemed apt to consent.
In this case, we would ask the patient to sign a new consent form and a copy will be provided to the patient and the newly signed consent will be kept in our files.

Once recruitment is completed, the patient will be given a subject number and placed on the "Enrollment List", which includes medical record numbers, admission dates, screen dates and enrollment dates.

After enrollment, demographic, reason for admission, lifestyle and medical data will be collected retrospectively from the medical chart, the patient's family and the medical team, and will be noted in the "Enrollment and Outcomes Form". The reasons for exclusion and the number of patients who refused consent will be collected. Temporarily excluded patients will be re-evaluated daily for possible inclusion into the study.

Once the patient begins the targeted opioid weaning of ≥ 10%, investigators will perform evaluations daily between 10am and 2pm. These evaluations will consist of using pre-tested data collection sheets to record signs and symptoms of possible OIWS, opioid doses, administered medications, laboratory values and other clinical data such as the RASS, CPOT and CAM-ICU scores. Data collection will be based on subject observation and interview when possible, nurse assessments, medical charts and laboratory results. Serum cortisol levels will be measured on the first day of opioid weaning (± 2 hours from dose decrease) and on the day patient is transferred to the ward or 72 hours from start of weaning whichever occurs first.

Once a weaning episode is identified, the physician collaborator will be contacted to perform daily DSM-5 evaluations. DSM-5 evaluations will be placed in opaque envelopes and investigators will be blinded to the results throughout the study. Additionally, for each patient, at least one inter-rater DSM-5 evaluation between 2 physician collaborators will be performed in order to assess interrater reliability. The two evaluations will be done within 2 hours of each other to minimize time-related discrepancies.

If opioid weaning is unsuccessful and opioid dose is re-increased, the subject will continue to be observed, however daily evaluations will only resume at the next weaning episode. Daily follow-up ends on day of transfer to the ward. One additional data collection and DSM-5 evaluation will be performed on the same day within 24 to 96 hours following transfer. Follow up ends 14 days after initial opioid weaning if patient remains in the ICU or if patient dies.

4.6 Measurement tools

DSM-5 (Appendix IV)	- No validated diagnostic tools for OIWS currently exist in the adult ICU - DSM-5 is the gold standard for diagnosing opioid withdrawal in numerous settings - Although not validated in the ICU population, it remains the most appropriate OIWS diagnostic tool for the study (9, 58)
APACHE II score (Appendix V)	- Validated tool to predict the risk of mortality in ICU patients (47, 59) - Calculated by an archivist using data collected in the first 24h of ICU admission - In this study: to assess patient disease severity at enrollment
Glasgow Coma Scale (GCS) (Appendix VI)	- Validated in ICU and trauma patients to assess the severity of head trauma based on ocular, verbal and motor criteria (48) - GCS score ≤ 8: comatose patient with no evidence of eye or verbal response - GCS score 9-15: presence of eye and verbal response (60) - In this study: to assess the level of consciousness of trauma patients and to verify exclusion criteria at ICU admission
Child-Turcotte-Pugh score (Appendix VII)	- Extensively studied in critically ill patients to assess liver function (61) - In the ICU, CTP scores at admission correlate with 12-month mortality (62) - In this study: to assess severity of hepatic dysfunction at ICU admission
Confusion Assessment Method (CAM) (Appendix IX)	- Validated tool to identify delirium in patients on general medicine hospital wards - Enables non-psychiatrist clinicians to quickly determine if delirium is present (63) - In this study: performed by the investigator within 24-96 hours of ICU transfer to ward
CAM-ICU (Appendix VIII)	- Validated tool to identify presence of delirium in a dichotomous manner in the ICU (64) - In this study: collected daily by investigators or according to nurse assessment
Richmond Agitation Assessment Scale (RASS) (Appendix X)	- To assess level of agitation and sedation, and to prevent under or over sedation in ICU - Scale ranges from -5 (unarousable sedation) to +4 (combative) - RASS score ≤ -3 indicates a deeply sedated state (65) - In this study: collected daily by investigator and according to nurse assessment - RASS + 1 defines restlessness and RASS ≥ 2 defines agitation
Agitated Behaviour Scale (ABS) (Appendix XI)	- Originally designed to assess agitation in patients with traumatic brain injury (66) - Validated in numerous settings, including long-term care facility (67) - ABS score ≥ 22: Agitation, ≤ 21: No agitation (68) - In this study: performed once by the investigator within 24-96h of ICU transfer
Critical-Care Pain Observation Tool (CPOT) (Appendix XII)	- To assess pain in critically ill mechanically ventilated patients based on facial expressions, body movements and muscle tension during nociceptive procedures - To qualify pain in patients unable to verbalize; in patients able to communicate, self-reporting of pain remains the gold standard - CPOT > 2: unacceptably high level of pain, ≤ 2: minimal to no pain (68) - In this study: measured daily by investigators and according to nurse assessment
Numeric Rating	- To assess pain intensity on a numerical scale, most commonly ranging from 0 to 10

Scale (NRS) (Appendix XIII)	(NRS-11); only the scale extremities are detailed (69) - In this study: to assess pain during daily evaluations once patients can self-report. Investigators will ask patients to rate their pain on a scale from 0 (absence of pain) to 10 (worst pain imaginable). An NRS ≥ 4 represents an unacceptable level of pain.

5. Data analysis

5.1 Statistical analysis

5.1.1 Descriptive statistics

Demographic and clinical characteristics of patients who developed OIWS will be compared to those who did not. Categorical variables will be presented as proportions. For continuous variables, means and standard deviations will be computed for normal distributions whereas medians (interquartile range) will be used for non-normal distributions.

For the primary outcome, episodes will be compared between the withdrawal positive (W+) group and the withdrawal negative (W–) group. Every day on which the DSM-5 is positive is equivalent to an episode of withdrawal, whereas a negative DSM-5 counts as an episode in which no withdrawal was observed. Patients who are positive for at least one episode of withdrawal make up the W+ group, whereas those who did not have a single episode of withdrawal make up the W– group, thus eliminating crossover. If a single patient experiences multiple days of withdrawal, s/he will account for multiple episodes in the study. Signs and symptoms will be tallied per episode and compared between the two groups. The results will be presented as proportions (i.e. incidence of symptom per total episodes). In the event of a discordant inter-rater evaluation, only the positive result will be taken into account.

For the secondary outcome, serum cortisol levels and changes in serum cortisol levels are continuous variables and therefore descriptive statistics will be used as stated above, depending on the distribution.

5.1.2 Statistical inference

To gauge for presence of evaluation bias, inter-rater agreement will be determined using Cohen's kappa. This test measures the extent to which physicians concur when assessing for presence of OIWS using the DSM-5 criteria. A kappa of ≥ 0.61 is indicative of good inter-rater agreement (70).

For secondary outcomes, baseline, weaning and change in cortisol levels will be compared between patients positive and negative for OIWS. A Student's t-test or a Wilcoxon signed rank test will be used. The test will be determined based on distribution and sample size.

5.2 Sample size

Based on our experience with the WAAICUP studies, 88 patients were eligible to participate in the study in an 8-month period, of which around 50 consented (22). We thus aim to recruit 50 patients based on the feasibility of these previous studies.

6. Advantages and limitations

6.1 Advantages

As stated previously, a prospective approach will limit missing data and enable assessment of potential confounders. The multicentric design enables study of different ICU populations, thereby increasing external validity and sample size.

There is currently no validated tool for OIWS diagnosis in the adult ICU population. Use of the DSM-5 is adequate in this study since it standardizes physician evaluation and is considered a gold standard in numerous settings. Multiple other ICU-validated tools will be used throughout the study such as the RASS, CAM-ICU and CPOT. Validated tools will also be used after transfer to the ward.

Training will be provided to investigators in order to standardize assessment and reduce observer bias. Observer bias will also be minimized by the blinding of investigators to DSM-5 results. Additionally, DSM-5 inter-rater agreement will be assessed on one occasion for each patient. A notable advantage is the supplemental follow-up after transfer to ward, which increases internal validity by limiting loss of patients who might develop OIWS later once transferred out of the ICU.

To our knowledge, no previous study has explored potential biomarkers that correlate with symptoms of OIWS. The exploratory use of serum cortisol in this study is thus a novel research avenue and will enable further characterization of OIWS.

6.2 Limitations

The study is susceptible to several limitations, most of them due to study design Due to lack of randomization, the study is subject to confounding. A notable covariate is the concomitant administration of benzodiazepines, which is difficult to control for since ICU patients frequently receive both opioids and benzodiazepines, and there is significant overlap in their respective withdrawal symptoms. However, administration of benzodiazepines will be noted during daily evaluations. The study is also susceptible to the "clinical trial effect" bias, since the attending physicians are not blinded to patient enrollment in the study and may modify their management consequently. To control for observer bias, pre-tested standardized data collection forms will be used, but it does not eliminate it completely, as evaluations will be performed by different investigators.

Since the sample size was determined on the basis of feasibility rather than statistical power, no statistically significant associations can be made. Statistical analyses will thus be predominantly descriptive in nature.

The exclusion of patients with severe or moderate traumatic brain injury requiring ICP monitoring and osmotherapy reduces external validity. These patients are important consumers of opioids and are therefore at risk of developing OIWS. However, their clinical condition would make the adequate assessment of OIWS impossible.

7. Relevance of study

To our knowledge, this is the first prospective study that aims to describe the clinical presentation of OIWS in the adult ICU setting with a standardized approach, fulfilling an identified research gap (71). As mentioned, OIWS is a clinical entity associated with negative outcomes that is poorly understood in critically ill adults because of diagnostic challenges. With a more accurate description of the clinical presentation, it would be possible to develop reliable screening tools to identify patients most at risk of OIWS and to sensitize the clinician to adopt appropriate measures in their management. An accurate description of the clinical presentation of OIWS is the first step in a series of research advances aimed at correctly recognizing and managing OIWS in adult ICU patients.

8. Ethical considerations and patient consent

The study protocol will be approved by the MUHC Research Ethics Board prior to enrollment. The study procedure does not require direct medical intervention as it is observational in design. The evaluation of signs and symptoms will mostly be done using ICU standard of care assessment tools (e.g. CAM-ICU, CPOT, RASS). Assessments that are not part of routine ICU care include collection of two blood samples per patient for serum cortisol measurement and DSM-5. Investigators will not interfere with usual care, which prevents patient exposure to additional risk

Written and informed consent will be obtained prior to enrollment and a copy will be given to the patient. Consent forms will be available in English and French with detailed descriptions of the study procedure and interventions. If the patient is inapt, consent will be obtained from a legal representative (e.g. family member). Once the patient is apt, direct consent will be sought. If the

patient refuses consent, previously collected data will be destroyed. Patients or their legal representative may decide to withdraw from the study at any moment.

Patient confidentiality will be maintained throughout the study by various means. All data will be de-identified and coded. The code will be maintained by the principle investigator. Computers and files will be password protected. Paper data will be kept in opaque envelopes in a locked cabinet to which only the investigators will have access. Study data will be kept for 7 years and the study itself will be registered on clinicaltrials.gov.

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10. Time frame and budget

Table 1. Time frame

Month	Activities
October 2017	- First draft of protocol
November 3, 2017	- Protocol presentation to the Faculty
November 2017	- Creation of data collection sheets - Final version of research protocol
December 1, 2017	- Research protocol submission to the Faculty
January 2018	- Research protocol submission to the MUHC Research Ethics Board - Pre-evaluation of the data collection sheets - SPSS database creation
January 23, 2018	- MUHC Research Ethics Board approval
February to October 2018	- Data collection - Data entry - Statistical analysis - First draft of manuscript
October 2018	- Manuscript review
November 2018	- Manuscript submission
December 7, 2018	- Poster presentation at the Faculty (*Rendez-vous de la recherche pharmaceutique*)

Table 2. Budget

Description	Type	Total cost
Biomarker measure	Material	$900.00
Statistician ($75.00/h)	Human resources	$0.00 to $200.00
SPSS software	Equipment	$0.00
Paper/Poster	Material	$200.00
Total		**$1,300.00**

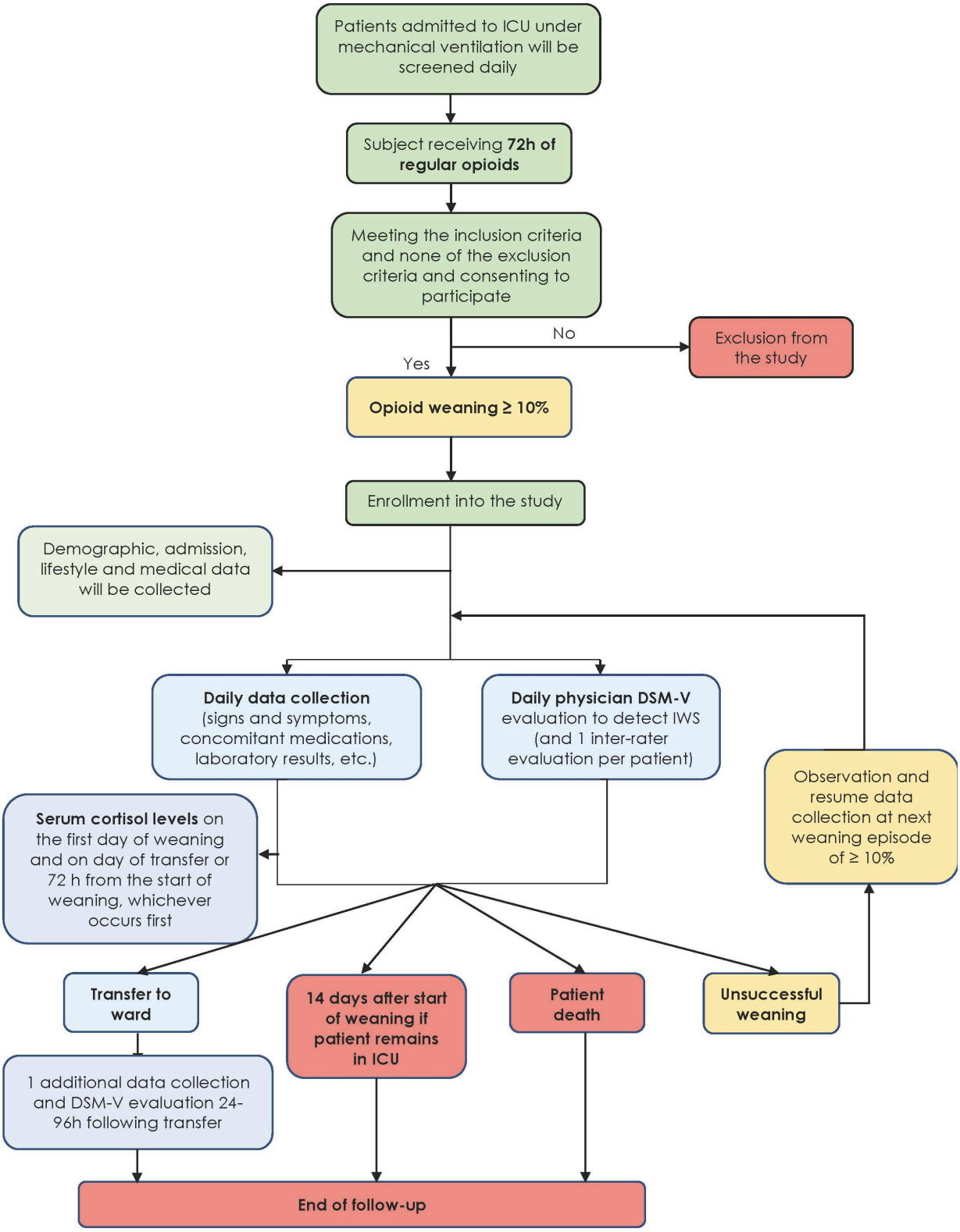
11. Appendices

Appendix I. Research strategy in Medline

Search	Terms
A1: Opioids	exp Narcotics/ or Narcotics, Pharmacological Action/ or exp Opiate Alkaloids/ or exp Fentanyl/ or exp Meperidine/ or exp Morphine Derivatives/ or exp Methadone/ or narcoti*.mp. or opioid.mp. or opium.mp. or opiate.mp. or remifentanil.mp. or fentanyl.mp. or sufentanil.mp. or alfentanil.mp. or codeine.mp. or morphine.mp. or oxycodone.mp. or hydrocodone.mp. or hydromorphone.mp. or methadone.mp. or meperidine.mp.
A2: Sedatives or analgesics	"Hypnotics and Sedatives"/ OR "Hypnotics and Sedatives, Pharmacological Action"/ OR Narcotics, Pharmacological Action/ OR Conscious Sedation/ OR Deep Sedation/ OR exp Narcotics/ OR exp Opiate Alkaloids/ OR exp Fentanyl/ OR exp Meperidine/ OR exp Benzodiazepines/ OR exp Morphine Derivatives/ OR exp Methadone/ OR Clonazepam/ OR Bromazepam/ OR hypnotic.mp. OR sedative.mp. OR sedation.mp. OR narcoti*.mp. OR opioid.mp. OR opium.mp. OR opiate.mp. OR remifentanil.mp. OR fentanyl.mp. OR sufentanil.mp. OR alfentanil.mp. OR codeine.mp. OR morphine.mp. OR oxycodone.mp. OR hydrocodone.mp. OR hydromorphone.mp. OR methadone.mp. OR meperidine.mp. OR benzodiazepine.mp. OR diazepam.mp. OR lorazepam.mp. OR midazolam.mp. OR clonazepam.mp. OR alprazolam.mp. OR oxazepam.mp. OR temazepam.mp. OR bromazepam.mp. OR flurazepam.mp. OR chlordiazepoxide.mp. OR clobazam.mp. OR clorazepate.mp. OR nitrazepam.mp. OR triazolam.mp.
B: Iatrogenic withdrawal	Substance Withdrawal Syndrome/ OR Iatrogenic Disease/ OR Withholding treatment/ OR substance withdrawal.mp. OR drug withdrawal.mp. OR taper.mp. OR tapered.mp. OR tapering.mp. OR wean.mp. OR weaned.mp. OR weaning.mp. OR abstinence.mp. OR iatrogenic disease.mp. OR "withholding treatment".mp. OR "withholding treatment".mp.
C: ICU	exp Critical Care/ OR Subacute Care/ OR Postoperative Care/ OR exp Intensive Care Units/ OR Critical Illness/ OR intensive care.mp. OR critical care.mp. OR ICU.mp. OR PICU.mp. OR subacute.mp. OR postoperative.mp. OR post-operative.mp. OR burn unit.mp. OR burn centre.mp. OR burn center.mp. OR coronary care.mp. OR respiratory care.mp. OR critical illness.mp. OR critically ill.mp.
D: Tools	Decision Trees/ OR algorithms/ OR Checklist/ OR Questionnaires/ OR scale.mp. OR scaling.mp. OR score.mp. OR scoring.mp. OR tool.mp. OR checklist.mp. OR check-list.mp. OR questionnaire.mp. OR instrument.mp. OR WAT.mp. OR WAT-1.mp. OR withdrawal assessment tool.mp. OR decision tree.mp. OR algorithm.mp. OR sedation withdrawal score.mp. OR "opioid and benzodiazepine withdrawal score".mp. OR OBWS.mp. OR Sophia Observation Withdrawal.mp.
E1: Signs and symptoms	exp "Signs and Symptoms"/ OR exp Neurological Examination/ OR Symptom Assessment/ OR exp Vital Signs/ OR Facial Expression/ OR (symptom* OR anamne* OR dysphor* OR nause* OR vomit* OR muscle ach* OR lacrim* OR rhinorrhea OR pupil* dilat* OR piloerection OR sweat* OR diarrhea OR yawn* OR fever OR temperature OR insomnia OR shiver* OR sleep disturbance OR tremor OR anxiety OR agitat* OR suction* OR irritab* OR grimac* OR startl* OR muscle tone OR

	((uncoordinat* OR repetitive) AND movement) OR sneez* OR tachypnea OR mydriasis OR deliri* OR seiz* OR convuls*).mp.
E2: Biomarkers	exp Biomarkers/ OR "Biomarkers, Pharmacological"/ OR Monitoring, Physiologic/ OR Drug Monitoring/ OR Neuromuscular Monitoring/ OR Neurophysiological Monitoring/ OR (stress hormone OR cortisol OR cortisone OR catecholamines OR ((bio OR biological OR lab OR laboratory OR serum OR plasma OR endpoint? OR end-point?) ADJ (marker? OR surrogate?))).mp.
Run #1 (F)	A1 AND B AND C AND D AND E1
Run #2 (G)	(A1 AND B AND C AND D AND E2) NOT F
Run #3 (H)	(A2 AND B AND C AND D AND E1) NOT (F OR G)
Run #4 (I)	(A2 AND B AND C AND D AND E2) NOT (F OR G OR H)
Run #5 (J)	A1 AND B AND E2 (NOT F OR G OR H OR I)
Run #6 (K)	A2 AND B AND E2 (NOT F OR G OR H OR I OR J)

Appendix II. Study procedure



Appendix III. Dependent variables: signs and symptoms of OIWS (4, 15, 19, 20, 24)

Category	Signs and symptoms	Definition	Type of variable
Central nervous system symptoms	Agitation	**During ICU hospitalization:** Highest RASS score recorded in the previous 24h[a] according to nurse assessment [b, c]	Qualitative ordinal
		RASS -5 to 0, 1 (restlessness) or ≥ 2 (agitation)	Qualitative ordinal
		After ICU transfer to another ward: Agitated Behavior Scale (ABS) score during evaluation ≤ 21: No agitation; ≥ 22: agitation	Qualitative ordinal
	Anxiety	According to patient or nurse assessment in the previous 24h	Qualitative nominal (dichotomous)
	Dysphoria	According to physician DSM-5 evaluation	Qualitative nominal (dichotomous)
	Fever	Highest temperature value (°C) according to nurse assessment in the previous 24h	Quantitative continuous
		Temperature ≥ 38.3 degrees in the previous 24h	Qualitative nominal (dichotomous)
	Hallucinations	Patient seems to see, hear or feel things that are not there in the previous 24h, according to patient or nurse assessment	Qualitative nominal (dichotomous)
	Insomnia/sleep disturbance	Number of hours of sleep/night between 10PM and 6AM the night before evaluation according to nurse assessment	Quantitative discrete
		Lack of sleep defined as less than 4 hours of continuous sleep between 10PM and 6AM	Qualitative nominal (dichotomous)
	Startle to stimulus	Startle occurs when patient is stimulated verbally or by light touch during evaluation	Qualitative nominal (dichotomous)
	Time to regain calm post-stimulus	Time (minutes) needed to regain calm post-stimulus	Quantitative continuous
		Normal: < 2 min; Increased: 2 to 5 min; High: > 5 min	Qualitative ordinal
	Seizure	Presence not explained by metabolic disturbances or history of seizures in the previous 24h according to medical chart	Qualitative nominal (dichotomous)
	Tremor	Presence of trembling, involuntary sustained rhythmic movements of hands and/or	Qualitative nominal (dichotomous)

		feet during evaluation or according to nurse assessment in the previous 24h	
	Pupil size	Size (mm) according to nurse assessment in the previous 24h	Quantitative continuous
		≤ 2 mm, > 2 mm	Quantitative discrete (dichotomous)
	Yawning	Number of yawns in the previous 24h according to nurse assessment	Quantitative continuous
		If ≥ 2 yawns observed during evaluation or in the previous 24h according to nurse assessment	Quantitative discrete (dichotomous)
Cardiac symptoms	Hypertension	Highest Systolic blood pressure (mmHg) according to nurse assessment in the previous 24h	Quantitative continuous
		Highest MAP (mmHg) according to nurse assessment in the previous 24h	Quantitative continuous
	Tachycardia	Highest HR in the previous 24h	Quantitative continuous
		Lowest heart rate in previous 24h	Quantitative continuous
		Is patient on a beta-blocker ; Yes or No	Qualitative nominal (dichotomous)
Respiratory symptoms	Frequent suction	Number of times patient required endotracheal suctioning in the previous 24h according to nurse assessment	Quantitative continuous
	Lacrimation	Presence during evaluation or according to nurse assessment in the previous 24h	Qualitative nominal
	Rhinorrhea	Presence during evaluation or according to nurse assessment in the previous 24h	Qualitative nominal (dichotomous)
	Sneezing	Number of sneeze observed during evaluation or according to nurse assessment in the previous 24h	Quantitative continuous
		If more than 1 sneeze observed during evaluation or according to nurse assessment in the previous 24h	Qualitative nominal (dichotomous)
	Significant dyspnea	Highest respiratory rate (RR) recorded in the previous 24h according to nurse assessment	Quantitative continuous
		Lowest respiratory rate (RR) recorded in the previous 24h	Quantitative continuous

		according to nurse assessment	
Gastrointestinal symptoms	Diarrhea	Presence of ≥ 3 BMs (loose/watery stools), in past 24 hours according to nurse assessment	Qualitative nominal (dichotomous)
		Number of BM in the previous 24h according to nurse assessment	Quantitative continuous
		Rectal tube required (yes or no)	Qualitative nominal (dichotomous)
	Feeding intolerance (gastric residuals)	Present if nurse discontinued or decreased enteral feeding during previous 24h due to gastric residuals of more than 500 mL according to nurse assessment	Qualitative nominal (dichotomous)
	Nausea	Presence during previous 24h according to patient, nurse assessment or use of antiemetic medications such as dimenhydrinate and ondansetron (indication to validate with nurse when necessary)	Qualitative nominal (dichotomous)
	Vomiting	Presence or absence of vomiting episode(s) or retching or gagging in the previous 24h according to nurse assessment	Qualitative nominal (dichotomous)
Dermatologic symptoms	Mottling	Presence of violaceous marbled discoloration of the skin during evaluation or according to nurse assessment in the previous 24h	Qualitative nominal (dichotomous)
	Piloerection	Presence during evaluation or according to nurse assessment in the previous 24h	Qualitative nominal (dichotomous)
	Sweating	Presence without apparent reason (not caused by room temperature) during evaluation or according to nurse assessment in the previous 24h	Qualitative nominal (dichotomous)
Musculoskeletal symptoms	Bone, joint or muscle aches	Presence during evaluation or according to nurse assessment in the previous 24h	Qualitative nominal (dichotomous)
	Muscle cramps	Presence during evaluation or according to nurse assessment in the previous 24h	Qualitative nominal (dichotomous)
	Muscle tone	Presence during evaluation or according to nurse assessment in the previous 24h	Qualitative nominal (dichotomous)

		(e.g. clenching wrists and toes, hunched shoulders, abnormal tense position of head, arm or legs)	
	Uncoordinated/ repetitive movement	Presence of involuntary movements of arm and/or legs, muscle twitches, during evaluation or according to nurse assessment in the previous 24h	Qualitative nominal (dichotomous)

[a] Previous 24h designate the interval between midnight of the previous day and midnight of the day on which evaluation of the signs and symptoms occurs. A fixed time frame was chosen to standardize collection of signs and symptoms.

[b] Nurse assessment comprises written (i.e. notes in medical chart or patient flow sheet) and/or verbal communication.

[c] On the day of transfer, patients will be evaluated from midnight of the previous day until time of evaluation. Following transfer to ward, patients will be evaluated from midnight of the current day to time of evaluation.

Appendix IV. Diagnostic and Statistical Manual of Mental Diagnosis-V (DSM-5): "Opioid Withdrawal" criteria.

Diagnostic criteria:
A. Presence of either of the following;

1. Cessation of (or reduction in) opioid use that has been heavy and prolonged (i.e., several weeks or longer).
2. Administration of an opioid antagonist after a period of opioid use.

B. Three (or more) of the following developing within minutes to several days after

1. Dysphoric mood.
2. Nausea or vomiting.
3. Muscle aches.
4. Lacrimation or rhinorrhea.
5. Pupillary dilation, piloerection, or sweating.
6. Yawning.
7. Fever.
8. Insomnia.

C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The signs or symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.

Reference: Association AP. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. Washington, DC: American Psychiatric Publishing; 2013.

Appendix V. Acute Physiology and Chronic Health Evaluation II (APACHE II) developed by Knaus et al.

PHYSIOLOGIC VARIABLE	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
	+4	+3	+2	+1	0	+1	+2	+3	+4
TEMPERATURE — rectal (°C)	≥41°	39°-40.9°		38.5°-38.9°	36°-38.4°	34°-35.9°	32°-33.9°	30°-31.9°	≤29.9°
MEAN ARTERIAL PRESSURE — mm Hg	≥160	130-159	110-129		70-109		50-69		≤49
HEART RATE (ventricular response)	≥180	140-179	110-139		70-109		55-69	40-54	≤39
RESPIRATORY RATE — (non-ventilated or ventilated)	≥50	35-49		25-34	12-24	10-11	6-9		≤5
OXYGENATION: A-aDO_2 or PaO_2 (mm Hg) a. FIO_2 ≥ 0.5 record A-aDO_2	≥500	350-499	200-349		<200				
b. FIO_2 < 0.5 record only PaO_2					PO_2 > 70	PO_2 61-70		PO_2 55-60	PO_2 < 55
ARTERIAL pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	< 7.15
SERUM SODIUM (mMol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
SERUM POTASSIUM (mMol/L)	≥7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		< 2.5
SERUM CREATININE (mg/100 ml) (Double point score for **acute** renal failure)	≥3.5	2-3.4	1.5-1.9		0.6-1.4		< 0.6		
HEMATOCRIT (%)	≥60		50-59.9	46-49.9	30-45.9		20-29.9		< 20
WHITE BLOOD COUNT (total/mm3) (in 1,000s)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		< 1
GLASGOW COMA SCORE (GCS): Score = 15 minus actual GCS									
A Total ACUTE PHYSIOLOGY SCORE (APS): Sum of the 12 individual variable points									
Serum HCO_3 (venous-mMol/L) (Not preferred, use if no ABGs)	≥52	41-51.9		32-40.9	22-31.9		18-21.9	15-17.9	< 15

B AGE POINTS:
Assign points to age as follows:

AGE(yrs)	Points
≤44	0
45-54	2
55-64	3
65-74	5
≥75	6

C CHRONIC HEALTH POINTS
If the patient has a history of severe organ system insufficiency or is immuno-compromised assign points as follows:
a. for nonoperative or emergency postoperative patients — 5 points
or
b. for elective postoperative patients — 2 points

DEFINITIONS
Organ insufficiency or immuno-compromised state must have been evident **prior** to this hospital admission and conform to the following criteria:

LIVER: Biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.

CARDIOVASCULAR: New York Heart Association Class IV.

RESPIRATORY: Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40mmHg), or respirator dependency.

RENAL: Receiving chronic dialysis.

IMMUNO-COMPROMISED: The patient has received therapy that suppresses resistance to infection, e.g., immuno-suppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS.

APACHE II SCORE
Sum of A + B + C :

A APS points _____

B Age points _____

C Chronic Health points _____

Total APACHE II _____

Reference: Knaus W, Draper E, Wagner D, Zimmerman J. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-29.

Appendix VI. Glasgow Coma Scale (GCS) developed by Jennett et al.

test	score	condition
Eye Opening	4	the patient can open his eyes spontaneously
	3	the patient can open his eyes on verbal command
	2	the patient opens his eyes only in response to painful stimuli
	1	the patient does not open his eyes in response to any stimulus
Best Verbal Response	5	the patient is oriented and can speak coherently
	4	the patient is disoriented but can speak coherently
	3	the patient uses inappropriate words or incoherent language
	2	the patient makes incomprehensible sounds
	1	the patient gives no verbal response at all
Best Motor Response	6	the patient can move his arms and legs in response to verbal commands
	2-5	the patient shows movement in response to a variety of stimuli, including pain
	1	the patient shows no movement in response to stimuli

The results of the three tests are added up to determine the patient's overall condition

Total score	scale
13-15	mild head injury
9-12	moderate head injury
3-8	severe head injury

Source: U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Neurological Disorders and Stroke. www.ninds.nih.gov

Reference: Jennett B. The Glasgow Coma Scale: History and current practice. Trauma. 2002;4(2):91-103

Appendix VII. Child-Turcotte-Pugh score developed by Pugh et al.

Table I.—GRADING OF SEVERITY OF LIVER DISEASE

CLINICAL AND BIOCHEMICAL MEASUREMENTS	POINTS SCORED FOR INCREASING ABNORMALITY		
	1	2	3
Encephalopathy (grade)*	None	1 and 2	3 and 4
Ascites	Absent	Slight	Moderate
Bilirubin (mg. per 100 ml.)	1–2	2–3	>3
Albumin (g. per 100 ml.)	3·5	2·8–3·5	<2·8
Prothrombin time (sec. prolonged)	1–4	4–6	>6
For primary biliary cirrhosis:— Bilirubin (mg. per 100 ml.)	1–4	4–10	>10

* According to grading of Trey, Burns, and Saunders (1966).

Reference: Pugh R, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. British Journal of Surgery. 1973 Aug 1;60(8):646-9.

Appendix VIII. Confusion Assessment Method in the Intensive Care Unit (CAM-ICU) developed by Ely et al.

Features and Descriptions	Absent	Present
I. Acute onset or fluctuating course*		
A. Is there evidence of an acute change in mental status from the baseline? B. Or, did the (abnormal) behavior fluctuate during the past 24 hours, that is, tend to come and go or increase and decrease in severity as evidenced by fluctuations on the Richmond Agitation Sedation Scale (RASS) or the Glasgow Coma Scale?		
II. Inattention†		
Did the patient have difficulty focusing attention as evidenced by a score of less than 8 correct answers on either the visual or auditory components of the Attention Screening Examination (ASE)?		
III. Disorganized thinking		
Is there evidence of disorganized or incoherent thinking as evidenced by incorrect answers to 3 or more of the 4 questions and inability to follow the commands? Questions 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does 1 pound weigh more than 2 pounds? 4. Can you use a hammer to pound a nail? Commands 1. Are you having unclear thinking? 2. Hold up this many fingers. (Examiner holds 2 fingers in front of the patient.) 3. Now do the same thing with the other hand (without holding the 2 fingers in front of the patient). (If the patient is already extubated from the ventilator, determine whether the patient's thinking is disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject.)		
IV. Altered level of consciousness		
Is the patient's level of consciousness anything other than alert, such as being vigilant or lethargic or in a stupor, or coma? Alert: spontaneously fully aware of environment and interacts appropriately Vigilant: hyperalert Lethargic: drowsy but easily aroused, unaware of some elements in the environment or not spontaneously interacting with the interviewer; becomes fully aware and appropriately interactive when prodded minimally Stupor: difficult to arouse, unaware of some or all elements in the environment or not spontaneously interacting with the interviewer; becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as the stimulus ceases, stuporous subject lapses back into unresponsive state Coma: unarousable, unaware of all elements in the environment with no spontaneous interaction or awareness of the interviewer so that the interview is impossible even with maximal prodding		
Overall CAM-ICU Assessment (Features 1 and 2 and either Feature 3 or 4): Yes___ No___		

*The scores included in the 10-point RASS range from a high of 4 (combative) to a low of −5 (deeply comatose and unresponsive). Under the RASS system, patients who were spontaneously alert, calm, and not agitated were scored at 0 (neutral zone). Anxious or agitated patients received a range of scores depending on their level of anxiety: 1 for anxious, 2 for agitated (fighting ventilator), 3 for very agitated (pulling on or removing catheters), or 4 for combative (violent and a danger to staff). The scores −1 to −5 were assigned for patients with varying degrees of sedation based on their ability to maintain eye contact: −1 for more than 10 seconds, −2 for less than 10 seconds, and −3 for eye opening but no eye contact. If physical stimulation was required, then the patients were scored as either −4 for eye opening or movement with physical or painful stimulation or −5 for no response to physical or painful stimulation. The RASS has excellent interrater reliability and intraclass correlation coefficients of 0.95 and 0.97, respectively, and has been validated against visual analog scale and geropsychiatric diagnoses in 2 ICU studies.[37,38]

†In completing the visual ASE, the patients were shown 5 simple pictures (previously published[39]) at 3-second intervals and asked to remember them. They were then immediately shown 10 subsequent pictures and asked to nod "yes" or "no" to indicate whether they had or had not just seen each of the pictures. Since 5 pictures had been shown to them already, for which the correct response was to nod "yes," and 5 others were new, for which the correct response was to shake their heads "no," patients scored perfectly if they achieved 10 correct responses. Scoring accounted for either errors of omission (indicating "no" for a previously shown picture) or for errors of commission (indicating "yes" for a picture not previously shown). In completing the auditory ASE, patients were asked to squeeze the rater's hand whenever they heard the letter *A* during the recitation of a series of 10 letters. The rater then read 10 letters from the following list in a normal tone at a rate of 1 letter per second: *S, A, H, E, V, A, A, R, A, T*. A scoring method similar to that of the visual ASE was used for the auditory ASE testing.

This table may be reproduced without permission for clinical use only (Ely EW et al. *JAMA*. 2001;286:2707-2710).

Reference: Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). Jama. 2001;286(21):2703-10.

Appendix IX. Confusion Assessment Method (CAM) developed by Inouye et al.

Appendix Table 1. *The Confusion Assessment Method Instrument*

Acute onset

1. Is there evidence of an acute change in mental status from the patient's baseline?

Inattention*

2. A. Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?

   Not present at any time during interview.
   Present at some time during interview, but in mild form.
   Present at some time during interview, in marked form.
   Uncertain.

   B. (If present or abnormal) Did this behavior fluctuate during the interview, that is, tend to come and go or increase and decrease in severity?

   Yes.
   No.
   Uncertain
   Not applicable.

   C. (If present or abnormal) Please describe this behavior:

Disorganized thinking

3. Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

Altered level of consciousness

4. Overall, how would you rate this patient's level of consciousness?

   Alert (normal).
   Vigilant (hyperalert, overly sensitive to environmental stimuli, startled very easily).
   Lethargic (drowsy, easily aroused).
   Stupor (difficult to arouse).
   Coma (unarousable).
   Uncertain.

Disorientation

5. Was the patient disoriented at any time during the interview, such as thinking that he or she was somewhere other than the hospital, using the wrong bed, or misjudging the time of day?

Memory impairment

6. Did the patient demonstrate any memory problems during the interview, such as inability to remember events in the hospital or difficulty remembering instructions?

Perceptual disturbances

7. Did the patient have any evidence of perceptual disturbances, for example, hallucinations, illusions, or misinterpretations (such as thinking something was moving when it was not)?

Psychomotor agitation

8. Part 1.

   At any time during the interview, did the patient have an unusually increased level of motor activity, such as restlessness, picking at bedclothes, tapping fingers, or making frequent sudden changes of position?

Psychomotor retardation

8. Part 2.

   At any time during the interview, did the patient have an unusually decreased level of motor activity, such as sluggishness, staring into space, staying in one position for a long time, or moving very slowly?

Altered sleep-wake cycle

9. Did the patient have evidence of disturbance of the sleep-wake cycle, such as excessive daytime sleepiness with insomnia at night?

* The questions listed under this topic were repeated for each topic where applicable.

Appendix Table 2. *The Confusion Assessment Method (CAM) Diagnostic Algorithm**

Feature 1. Acute Onset and Fluctuating Course

This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behavior fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?

Feature 2. Inattention

This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?

Feature 3. Disorganized Thinking

This feature is shown by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

Feature 4. Altered Level of Consciousness

This feature is shown by any answer other than "alert" to the following question: Overall, how would you rate this patient's level of consciousness? (alert [normal], vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])

* The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4.

Reference: Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: The confusion assessment methoda new method for detection of delirium. Annals of internal medicine. 1990 Dec 15;113(12):941-8

Appendix X. Richmond Agitation-Sedation Scale (RASS) developed by Sessler et al.

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitation	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
−2	Light sedation	Briefly (less than 10 seconds) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Procedure

1. Observe patient. Is patient alert and calm (score 0)?
   Does patient have behavior that is consistent with restlessness or agitation (score +1 to +4 using the criteria listed above, under DESCRIPTION)?
2. If patient is not alert, in a loud speaking voice state patient's name and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker.
   Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score −1).
   Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score −2).
   Patient has any movement in response to voice, excluding eye contact (score −3).
3. If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response to shaking shoulder.
   Patient has any movement to physical stimulation (score −4).
   Patient has no response to voice or physical stimulation (score −5).

Reference: Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166(10):1338-44.

Appendix XI. Agitated Behavior Scale (ABS) developed by Carrigan et al.

AGITATED BEHAVIOR SCALE

Patient _____ **Period of Observation:**

Observ. Environ._____ **From:**_____ **a.m.** **p.m.**_____/_____/_____

Rater/Disc._____ **To:**_____ **a.m.** **p.m.**_____/_____/_____

At the end of the observation period indicate whether the behavior described in each item was present and, if so, to what degree: slight, moderate or extreme. Use the following numerical values and criteria for your ratings.

1 = absent: the behavior is not present.
2 = present to a slight degree: the behavior is present but does not prevent the conduct of other, contextually appropriate behavior. (The individual may redirect spontaneously, or the continuation of the agitated behavior does not disrupt appropriate behavior.)
3 = present to a moderate degree: the individual needs to be redirected from an agitated to an appropriate behavior, but benefits from such cueing.
4 = present to an extreme degree: the individual is not able to engage in appropriate behavior due to the interference of the agitated behavior, even when external cueing or redirection is provided.

DO NOT LEAVE BLANKS.

_____ 1. Short attention span, easy distractibility, inability to concentrate.
_____ 2. Impulsive, impatient, low tolerance for pain or frustration.
_____ 3. Uncooperative, resistant to care, demanding.
_____ 4. Violent and or threatening violence toward people or property.
_____ 5. Explosive and/or unpredictable anger.
_____ 6. Rocking, rubbing, moaning or other self-stimulating behavior.
_____ 7. Pulling at tubes, restraints, etc.
_____ 8. Wandering from treatment areas.
_____ 9. Restlessness, pacing, excessive movement.
_____ 10. Repetitive behaviors, motor and/or verbal.
_____ 11. Rapid, loud or excessive talking.
_____ 12. Sudden changes of mood.
_____ 13. Easily initiated or excessive crying and/or laughter.
_____ 14. Self-abusiveness, physical and/or verbal.

_____ **Total Score**

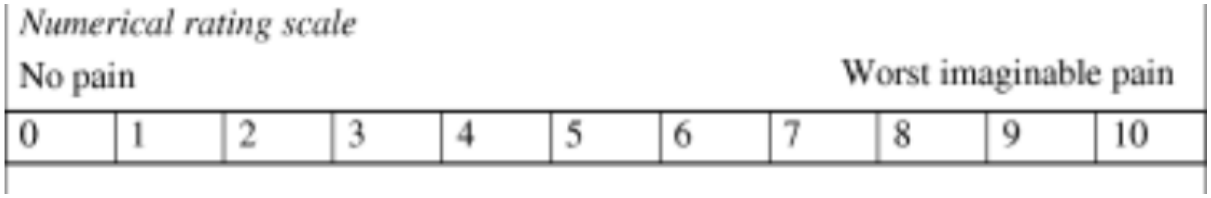
Reference: Corrigan JD. Development of a scale for assessment of agitation following traumatic brain injury. Journal of Clinical and Experimental Neuropsychology. 1989 Mar 1;11(2):261-77.

Appendix XII. Critical-Care Pain Observation Tool (CPOT) developed by Gelinas et al.

Indicator	Score		Checklist
Facial expression	Relaxed, neutral	**0**	No muscle tension observable □ Eyes closed □
	Tense	**1**	Frowning/Brow lowering □ Orbit tightening/Wincing □ Levator contraction □ Mouth opening □ Eye opening □ Eye weeping/tears □ Eyebrow raising □ Blinking □
	Grimacing	**2**	Frowning/Brow lowering □ Eyes tightly closed □ Levator contraction □ Mouth opening □ Biting endotracheal tube/Clenched teeth □ Flushing □
Body movements	Absence of movements or normal position	**0**	Does not move at all □ Normal position □
	Protection	**1**	Slow, cautious movements □ Limb flexion □ Trying to reach pain site/tubes □ Touching pain site/Guarding □ Seeking attention □ Rubbing/Massaging pain site □ Shaking □ Withdrawing □ Decortication □ Decerebration □
	Restlessness/Agitation	**2**	Touching/Pulling tubes □ Fidgeting/Restlessness □ Arching □ Pushing □ Striking at staff/Defensive grabbing □ Attempting to sit up □ Trying to climb out of bed □
Compliance with the ventilator (intubated patients)	Tolerating ventilator or movement	**0**	Alarms not activated, easy ventilation □
	Coughing but tolerating	**1**	Alarms activated, stop spontaneously □ Coughing □ Gag reflex □
OR	Fighting ventilator	**2**	Asynchrony □ Blocking ventilation □
Vocalization (extubated patients)	Talking in normal tone or no sound	**0**	No sound □ Normal tone □
	Sighing, moaning	**1**	Sighing □ Moaning □ Verbal complaints of pain □
	Crying out, sobbing	**2**	Crying out □ Sobbing □
Muscle tension Evaluation by passive flexion and extension of upper limbs when patient is at rest or evaluation when patient is being turned	Relaxed	**0**	No resistance to passive movements □
	Tense, rigid	**1**	Resistance to passive movements □
	Very tense or rigid	**2**	Strong resistance to passive movements □ Clenching fists □
TOTAL	___ / **8**		

Reference: Gelinas C, Fillion L, Puntillo K, Viens C, Fortier M. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care. 2006;15(4):420-7.

Appendix XIII. Numeric Rating Scale (NRS)



Reference: Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. Journal of clinical nursing. 2005 Aug 1;14(7):798-804.