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# Sedation for moderate-to-severe traumatic brain injury in adults (Protocol)

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[Intervention Protocol]

# Sedation for moderate-to-severe traumatic brain injury in adults

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## ABSTRACT

### Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of sedative, analgesic, and anaesthetic drugs on neurological outcomes in adults with moderate-to-severe traumatic brain injury.

# BACKGROUND

## Description of the condition

Traumatic brain injury is defined as a disturbance in brain function, or other evidence of brain pathology, caused by an external force. It is a leading cause of morbidity and mortality worldwide [1]. Severity of traumatic brain injury is commonly classified using the Glasgow Coma Scale (GCS) and the duration of loss of consciousness and post-traumatic amnesia [2, 3]. The GCS assesses eye, motor, and verbal responses. It is a simple standardised measurement which grades traumatic brain injury as mild (GCS 14 or 15), moderate (GCS 9 to 13), and severe (GCS 3 to 8). The duration of loss of consciousness and post-traumatic amnesia can also be used to classify traumatic brain injury severity [2]. Trauma to the brain is classified as primary or secondary, and both types of injury can occur simultaneously as a continuum of overlapping neurological insults [4]. Primary injury occurs with the initial trauma in which the external forces directly damage brain tissue and disrupt brain function [4, 5]. These damages also induce secondary injuries such as cerebral oedema and intracranial haemorrhage, any of which can raise intracranial pressure, reduce cerebral perfusion pressure, or worsen cerebral ischaemia [4, 5]. Secondary intracranial (raised intracranial pressure) and extracranial insults such as hypercapnia, hypoxia, and systemic hypotension can induce additional damage. Both primary and secondary brain injuries are associated with increased mortality, as well as long-term neurological morbidity (e.g. impairments in memory and reasoning, as well as behavioural and mental health disorders) [5, 6].

## Description of the intervention and how it might work

Sedatives and opioids are commonly used in the intensive care unit to facilitate the use of life-supporting technologies (e.g. support ventilator synchrony), mitigate pain, and reduce anxiety and agitation [7, 8, 9]. While these drugs facilitate tolerance of the intensive care unit environment, there are notable complications associated with their use. Careful selection of drug(s) and method of titration are endorsed by the Society of Critical Care Medicine given the accumulating data indicating suboptimal sedation practices may prolong mechanical ventilation, and increase delirium and long-term cognitive impairment [8, 10, 11, 12, 13, 14, 15, 16, 17]. In addition to the traditional application of sedation in the intensive care unit, drugs may be administered in people with traumatic brain injury, especially in the acute phase following the initial injury [18]. Sedatives and opioids, as well as anaesthetics, are often used in the traumatic brain injury population to control intracranial pressure, reduce metabolic rate (e.g. cerebral metabolic rate of oxygen), manage or prevent seizures, and improve mechanical ventilator synchrony to achieve optimal arterial blood gas (partial pressure of carbon dioxide in arterial blood and partial pressure of oxygen in arterial blood) concentrations [19, 20, 21, 22, 23].

Unfortunately, many of these drugs are associated with adverse effects (e.g. haemodynamic instability) that may consequently increase the risk of secondary brain injury [24, 25, 26]. In addition, the long-term effects of these agents on cognitive outcomes are unknown. An ideal sedative for people with acute severe traumatic brain injury would: 1. confer neuroprotection (e.g. intracranial pressure control and reduction in cerebral metabolic rate of oxygen) without compromising systemic haemodynamics or causing adverse effects (e.g. propofol infusion syndrome); 2. permit frequent neurological assessment; 3. address specific symptoms of agitation, anxiety, ventilator dyssynchrony, and pain; and 4. improve clinical outcomes (e.g. neurological function, duration of mechanical ventilation, and survival) [19, 23, 25].

Various sedative, opioid, and anaesthetic agents are used in the acute management of moderate-to-severe traumatic brain injury [18, 27]. These drugs can be used in the traditional context of sedation and analgesia, but can also be employed for their neuroprotective properties (e.g. reduction of cerebral metabolic rate and oxygen consumption). Therefore, sedatives, opioids, and anaesthetics may play a role in the optimisation of patient care, improving both short- and long-term (e.g. neurological function) outcomes. Unfortunately, the majority of these drugs can also cause important adverse effects (e.g. systemic hypotension, bradycardia), especially when administered at higher doses to achieve deep sedation. Propofol, benzodiazepines, and barbiturates are thought to act as neuroprotectants through their modulation of gabaminergic transmission, where they reduce cerebral blood flow, cerebral metabolic rate of oxygen, and intracranial pressure [25, 26]. The alpha$_2$-adrenergic agonist dexmedetomidine reduces cerebral blood flow and intracranial pressure, and ketamine is an antagonist of N-methyl-D-aspartate receptors, where it decreases cerebral glutamate activity [25, 28]. Lastly, opioids modulate the mu receptor where they affect pain, but they can also be used for their sedating properties. Many of the aforementioned drugs confer broad therapeutic effects. For example, ketamine can be used for analgesia, and propofol, benzodiazepines, and barbiturates have anticonvulsant properties.

## Why it is important to do this review

In 2019, 27 million new cases of traumatic brain injury were reported worldwide [29]. The economic burden of traumatic brain injury is considerable: in the US alone, the lifelong cost estimation of the 2,123,120 traumatic brain injuries reported in 2012 was 758 billion US dollars [30]. Although survival following traumatic brain injury has improved over the last decades, as many as 65% of moderate-to-severe traumatic brain injury survivors develop long-term physical, cognitive, and psychological disorders [31, 32].

The Society of Critical Care Medicine 2018 Pain, Agitation and Delirium Guidelines recommend a light level of sedation using either protocolised sedation or daily sedation interruption in adults in the intensive care unit, as this is associated with improved clinical outcomes [8]. However, these guidelines do not provide direction on general sedation practice for people with moderate-to-severe traumatic brain injury. The Brain Trauma Foundation guidelines for the management of severe traumatic brain injury suggest high-dose barbiturates may be necessary to control elevated intracranial pressure refractory to standard drug or surgical interventions while ensuring haemodynamic stability [19]. The guidelines also caution against the use of high-dose propofol for intracranial pressure management given the associated adverse events (e.g. metabolic acidosis, rhabdomyolysis) and morbidity [8]. There is an overall sparsity of resources to guide the clinical management of moderate-to-severe traumatic brain injury and existing reviews are outdated or have only considered comparisons between two types of sedative agents [19, 24, 33, 34]. In addition, there is also a growing use of new sedative agents (e.g. dexmedetomidine, volatile gases, and ketamine) in the traumatic brain injury population [28, 35, 36, 37]. An updated knowledge synthesis in

this area will inform treatment algorithms and provide guidance to clinicians, ultimately guiding future research protocols and knowledge translation opportunities.

## OBJECTIVES

To assess the effects of sedative, analgesic, and anaesthetic drugs on neurological outcomes in adults with moderate-to-severe traumatic brain injury.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include randomised controlled trials, including those of open-label design. We will exclude cross-over studies, quasi-randomised studies, and studies examining the effects of sedatives for procedural purposes specifically (e.g. intubation). We will also exclude studies of prehospital care of people with traumatic brain injury. We will only include trials that were prospectively registered, unless the final report was published before 2010.

#### Types of participants

We will include studies that enrol adults aged over 16 years diagnosed with moderate-to-severe traumatic brain injury. If a study includes only a subset of participants eligible for the review, we will include the study in the descriptive reporting, but will only include the study in meta-analysis if we can extract the outcome of the given subset from the total.

#### Types of interventions

We will include studies comparing any sedative, analgesic, or anaesthetic to an alternative drug of either the same or different class, or to placebo, for the management of moderate-to-severe traumatic brain injury. Interventions will include alpha$_2$-agonists (e.g. dexmedetomidine), anaesthetics (e.g. ketamine, volatile gases), benzodiazepines (e.g. midazolam), non-benzodiazepine sedatives (e.g. propofol), barbiturates (e.g. pentobarbital), and opioids (e.g. fentanyl). For this analysis, there will be no restriction on drug dose, duration of use, and route of administration. We will include all studies regardless of any co-interventions.

### Outcome measures

To reduce selective reporting bias, we will include all studies regardless of the reported outcome data.

#### Critical outcomes

1. **Neurological outcome** (Glasgow Outcome Scale (GOS) or the Glasgow Outcome Scale Extended (GOSe), measured at three and six months). In the event of studies reporting both the GOS and the GOSe, we will report the GOSe.

#### Important outcomes

1. **Cerebral haemodynamic measures** (i.e. intracranial pressure, cerebral perfusion pressure) in the acute phase (i.e. 24 to 72 hours, related to the primary traumatic brain injury and the main reason for administering sedation)
2. **Cerebral oxygenation** (cerebral metabolic rate of oxygen) in the acute phase (i.e. 24 to 72 hours)
3. **Duration of mechanical ventilation** (days)
4. **Intensive care unit and hospital length of stay** (days)
5. **Mortality** (e.g. one, three, six, or 12 months, or as reported by study authors)
6. **Incidence of agitation** (measured with the Richmond Agitation-Sedation Scale (RASS), Riker Sedation-Agitation Scale (SAS) or other validated scale)
7. **Adverse events** (e.g. hypotension, bradycardia)

### Search methods for identification of studies

To reduce publication and retrieval bias, we will not restrict studies based on language, date, or status of publication.

#### Electronic searches

We will search the following databases.

1. Cochrane Central Register of Controlled Trials (CENTRAL; latest issue) in the Cochrane Library
2. Ovid MEDLINE(R) ALL (1946 to present) (Ovid)
3. Embase Classic+Embase (1947 to present) (Ovid)
4. APA PsycInfo (1806 to present) (Ovid)
5. CINAHL (EBSCO)
6. Web of Science (core databases)
7. Clinicaltrials.gov (https://clinicaltrials.gov/)
8. WHO International Clinical Trials Registry Platform (https://trialsearch.who.int/)

The MEDLINE strategy (Supplementary material 1) will be peer reviewed prior to finalisation by an experienced information specialist using the PRESS checklist [38]. We will adapt the search strategy as necessary for other databases.

We will use a modified version of the "Cochrane Highly Sensitive Search Strategies" for identifying randomised controlled trials in MEDLINE, Embase, APA PsycInfo, CINAHL, and Web of Science [39]. We will capture any postpublication amendments published on included or eligible studies.

#### Searching other resources

We will identify important conferences through Embase, for example, Society of Critical Care Medicine, World Congress on Brain Injury, Neurocritical Care Society, and European Society of Intensive Care Medicine. We will search for unpublished and ongoing trials at the World Health Organization International Clinical Trials Registry Platform (https://trialsearch.who.int/) and ClinicalTrials.gov (https://clinicaltrials.gov/) using the term "traumatic brain injury" and applicable synonyms. We will handsearch the reference lists of all screened and included studies, as well as any reviews published in the five years prior to the review's search date focusing on sedation in people with traumatic brain injury for identification of potential additional studies.

### Data collection and analysis

#### Selection of studies

Two review authors (LD, LB) will develop and pilot the study screening form on five studies to ensure its ability to accurately identify studies meeting the inclusion criteria (Supplementary material 2). At least two review authors (LD, LB, DW) will

independently use the study screening form to examine each title and abstract generated through the searches. We will refer any disagreements to a third review author (AT), if needed. This systematic review will adhere to best practice reporting guidelines using the PRISMA criteria [40]. A PRISMA-compliant flow diagram will demonstrate the search and study selection process.

### Data extraction and management

We will perform data extraction using a standardised electronic form developed by at least two review authors (LD, LB, DW) and piloted on three studies to ensure its ability to capture all relevant data. Pairs of review authors (LR and DW; SM and EG; ND and NA) will independently extract the data using the standardised data extraction form.

We will extract data related to the following.

1. Study design
2. Publication year and authors
3. Trial population (e.g. sample size, age, percentages of people with moderate and severe traumatic brain injury in the sample)
4. Interventions (i.e. sedative agent used, dose, duration of use, route of administration)
5. Control or comparators
6. Selected outcomes

We will also extract data on randomisation methods, allocation concealment, blinding, frequency and handling of missing data, adherence to intention-to-treat, and selective reporting of outcomes [41]. Given our familiarity with the literature, we will not blind data extractors to the authors of included studies. All data extraction will be checked for accuracy, and any discrepancies will be resolved by an independent review author (DW, LB).

We are aware that all outcomes may not be reported in each trial. Whenever possible, if outcomes of interest have been omitted, we will attempt to contact the corresponding author(s) of eligible trials to obtain additional information. In the event that abstracts are identified that present relevant data, we will also endeavour to contact study authors directly for additional study details.

### Risk of bias assessment in included studies

Three pairs of review authors (DW, LR, SM, EG, NA, AFT) will independently assess the risk of bias of included studies using the Cochrane RoB 2 tool [41]. Assessment of bias will be compared between review authors, and one review author (LB) will resolve discrepancies, if necessary. We will assess the risk of bias for the primary outcome of neurological outcome (GOS or GOSe) and the secondary outcomes of duration of mechanical ventilation, intensive care unit length of stay, hospital length of stay, and mortality. We will measure the primary outcome and the secondary outcome of mortality up to three months. We will measure the primary outcome as a fixed dichotomy with a favourable outcome defined as a GOS of 4 or 5 or a GOSe of 5 or greater and an unfavourable outcome as a GOS of 1 to 3 or a GOSe less than 5. We will measure duration of mechanical ventilation, intensive care unit, and hospital length of stay as continuous outcomes and mortality as a dichotomous outcome.

These assessments will use a domain-based evaluation embedded in the data extraction form. We will evaluate the following domains.

1. Risk of bias arising from the randomisation process
2. Risk of bias due to deviations from the intended interventions
3. Risk of bias due to missing outcome data
4. Risk of bias in measurement of the outcome
5. Risk of bias in selection of the reported result

For each domain, we will assess the risk of bias as 'low risk of bias,' 'some concerns,' and 'high risk of bias.' Once the risk of bias is agreed upon, each study will be assigned to one of the following categories:

1. low risk of bias: the study is judged at low risk of bias for all domains for this result;
2. some concerns: the study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain;
3. high risk of bias: describes studies where one or more domains are scored as 'no' indicating 'high' risk of bias; or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

For cluster-randomised controlled trials, we will use the dedicated versions of the RoB 2 tool, adjusting the bias assessment based on type of
study. We will illustrate the risk of bias using 'traffic light' plots. We will use an Excel tool provided by Cochrane Assist with RoB 2 assessments (https://www.riskofbias.info/welcome/rob-2-0-tool). Finally, the risk of bias assessment will inform the GRADE assessment and summary of findings table.

### Measures of treatment effect

For cerebral outcomes, we will meta-analyse between-group differences in the acute phase (i.e. 24 to 72 hours) (this acute period finding will be reported in the summary of findings table) if there are sufficient data for pooling. We will analyse functional outcome measures (e.g. GOS and GOSe) in a dichotomous manner. Unfavourable outcome measures will be defined as a GOS of 1 to 3 or a GOSe of 1 to 4, while favourable outcomes will be defined as a GOS of 4 or 5 or a GOSe of 5 to 8 [42]. We will express dichotomous outcomes as risk ratios with 95% confidence intervals.

Risk ratio was selected over risk difference to measure the effects of binary outcomes due to its superior consistency across a range of baseline risks [43]. We will assess continuous variables (e.g. length of intensive care unit stay, duration of mechanical ventilation, intracranial pressure, cerebral perfusion pressure) using a mean difference and 95% confidence intervals. If the data are skewed, these will be log transformed. We will consider two-sided $P \leq 0.05$ to be statistically significant.

### Unit of analysis issues

We will use individual study participants in each trial arm as the unit of analysis. For any included cluster-randomised controlled trials, we will reanalyse the results according to the guidance provided in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* [44].

### Dealing with missing data

We will contact the study authors to request missing or additional data, or for clarification on how missing data were dealt with in a

particular study. If we are unable to obtain the missing data, we will report the data as missing and analyse only the available data.

### Reporting bias assessment

Reporting biases can occur due to an increased likelihood of positive trials (large or small) being published compared to negative trials. To minimise publication bias or determine publication bias, we will search trial registries to identify completed trials that have not been published elsewhere. In comparisons where there are at least 10 studies, we will construct funnel plots to assess for possible publication bias [45].

### Synthesis methods

We will conduct pair-wise meta-analyses with a random-effects model using Review Manager software for analyses for the following outcomes where three or more studies are available [46]: neurological outcome, duration of mechanical ventilation, intensive care unit and hospital length of stay, mortality, and adverse events (e.g. hypotension, bradycardia) [46]. When possible, we will pool the different pharmacological classes separately (benzodiazepines, non-benzodiazepine sedatives such as propofol, barbiturates, opioids, anaesthetics, and alpha$_2$ agonists). For the primary outcome of neurological outcome and the secondary outcome of mortality, we will use the data available closest to the three-month time point when multiple time assessments are reported. A random-effects model employs a more conservative approach than a fixed-effect model, as it considers the variability within a study as well as among studies. In the primary analysis, we will include all eligible studies, irrespective of risk of bias.

If assessed outcomes lack data, or if studies are too clinically or methodologically (or both) heterogeneous to permit pooling of data, we will conduct a narrative synthesis according to Synthesis Without Meta-analysis (SWiM), as described in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* [44].

Where appropriate, we will assess for statistical heterogeneity using the Chi$^2$ and I$^2$ tests. The Chi$^2$ test assesses whether the observed differences in results are compatible with chance alone. A low P value provides evidence of heterogeneity of intervention effects that is beyond chance ($P < 0.10$ will be significant) [47]. Assessment of the I$^2$ statistic describes the percentage of variability in effect estimates that is due to data heterogeneity rather than chance (i.e. sampling error). Studies will also be assessed for types and sources of heterogeneity, either clinical or methodological, when making the decision to pool data. Clinical heterogeneity will be assessed through examination of the type and dose of sedative, and use of rescue sedation. We will also assess for heterogeneity by performing analyses based on potential modifiers of treatment effect, including the severity of traumatic brain injury.

### Investigation of heterogeneity and subgroup analysis

We will perform the following subgroup analyses.

1. Severity of traumatic brain injury: moderate (i.e. GCS 9 to 12) versus severe (i.e. GCS 3 to 8)
2. Indication for sedation (i.e. presence or absence of intracranial pressure monitoring with an elevated intracranial pressure)

We will use interaction tests to determine differences between subgroup results.

#### *Equity-related assessment*

We do not plan an assessment in relation to equity given the interventions evaluated in this review are life-sustaining treatments delivered in an intensive care unit.

### Sensitivity analysis

We will conduct a sensitivity analysis of studies at low risk of bias if enough studies are available.

### Certainty of the evidence assessment

We will present each comparison and selected outcomes of the review using summary of findings tables, including the following outcomes.

1. Neurological outcome as measured by GOS/GOSe (at three months)
2. Duration of mechanical ventilation
3. Intensive care unit and hospital length of stay
4. Mortality
5. Adverse events (hypotension and bradycardia)

We will present these outcomes for the following drug class: benzodiazepines, non-benzodiazepine sedatives (propofol), and opioids.

The summary of findings tables will include an overall grading of the evidence using the principles of the GRADE system [48]. We will grade the certainty of the evidence for our selected outcomes as high, moderate, low, or very low, based on risk of bias, within-study evidence directness, heterogeneity, precision of effect estimates, and publication bias. The overall risk of bias judgment assessed using RoB 2 will inform the GRADE assessment. We will base the control event rates for the calculation of absolute risks on the number of events in the included studies. Two review authors (DW, LD) will independently perform the GRADE assessment, with any disagreements resolved by a third review author (LB).

## Consumer involvement

We will not involve consumers in this review due to limited resources.

## SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD012639.

**Supplementary material 1** Search strategies

**Supplementary material 2** Study screening form

## ADDITIONAL INFORMATION

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### Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article:

1. Sign-off Editor (final editorial decision): Juan Sahuquillo, Department of Neurosurgery, Vall d'Hebron University Hospital, Barcelona, Spain

2. Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Sue Marcus, Central Editorial Service
3. Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Jessenia Hernandez, Central Editorial Service
4. Copy Editor (copy editing and production): Anne Lawson, Cochrane Central Production Service
5. Peer-reviewers (provided comments and recommended an editorial decision): Mayur B Patel, MD, MPH, Division of Acute Care Surgery, Department of Surgery, Section of Surgical Sciences, Critical Illness, Brain dysfunction, and Survivorship (CIBS) Center, Vanderbilt University Medical Center (clinical/content review); Luis Rafael Moscote-Salazar, AV Healthcare Innovators, LLC, Madison, Wisconsin, USA (consumer review); Jo-Ana Chase, Cochrane Evidence Production and Methods Directorate (methods review); Jo Platt, Central Editorial Information Specialist (search review).

## Contributions of authors

DW wrote the protocol; reviewed inclusion of population, outcomes, and study design based on literature review.

LD wrote the protocol; reviewed inclusion of population, outcomes, and study design based on literature review.

WC contributed to protocol manuscript review as a methods expert.

BH contributed to protocol manuscript review as a methods expert.

BS developed the search strategy for the medical literature search.

SM contributed to protocol manuscript review as content and methods expert in the field.

EG contributed to protocol manuscript review as content and methods expert in the field.

AT contributed to protocol manuscript review as content and methods expert in the field.

NA contributed to protocol manuscript review as content and methods expert in the field.

LR reviewed the protocol, reviewed inclusion of population, outcomes, and study design based on literature review.

LB wrote the protocol, reviewed inclusion of population, outcomes, and study design based on literature review.

## Declarations of interest

DW has received funding for the Canadian Institutes of Health Research for a study on dexmedetomidine in traumatic brain injury.

LD: none.

WC: none.

BH: none.

BS: none.

SM: none.

EG: none.

AT: none. AT is a Cochrane Editor but was not involved in the editorial process.

NA: none.

LR: none.

LB: none.

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### Internal sources

- Fonds de recherche en Santé – Québec, Canada

  Clinical Scholar grant for David Williamson

### External sources

- Fondation Neurotrauma Marie Robert, Canada

  Grant

## Registration and protocol

Cochrane approved the proposal for this review in March 2025.

## Data, code and other materials

Data sharing is not applicable to this article as it is a protocol, so no datasets were generated or analysed.

## What's new

| Date | Event | Description |
|---|---|---|
| 6 May 2025 | New citation required and major changes | Revised protocol with updated methods |

## History

Protocol first published: Issue 4, 2017

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