Supplementary File

Appendix 1. Search Strategies

Searches performed on 26th July 2014. *MeSH (Medical Subject Headings)*

Searched MEDLINE AND Embase using OVID:

("Deep Sedation"[MeSH] OR "Conscious Sedation"[MeSH] OR "analgesia"[MeSH] OR "Anaesthetics"[MeSH] OR procedural sedation.mp) AND (("Capnography"[MeSH] OR "Carbon Dioxide"[MeSH]) OR ("end AND tidal AND CO2.mp")) AND (("Emergency Medical Services"[MeSH] OR "Emergency Service, Hospital"[MeSH] OR "Trauma Centres"[MeSH] or "Triage"[MeSH]) OR ((Emerg$))

Scopus

"sedation" AND "capnography" AND "emergency"

CINAHL

("Hypnotics and Sedatives" OR "Sedation" OR "Analgesia" OR "Anaesthesia" OR "Conscious Sedation") AND ("Capnography") OR "Carbon Dioxide" OR ("end AND tidal AND CO2.mp") AND "Emergency Medical Services+") OR (MM "Emergency Service+") OR (MM "Physicians, Emergency") OR (MM "Emergencies+") OR "Emergency Patients" OR ((Emerg$))

Google Scholar

"procedural sedation" AND "capnography" AND "emergency department" AND "clinical trial"

Summary of Search Results

Database	Articles found from search	Articles remaining after title and abstract review
MEDLINE via OVID	105	21
Embase via OVID	190	18
Scopus	83	17
CINAHL	15	6
Google Scholar	282	31

Appendix 2. Risk of Bias Assessment Tools

Criteria for judging risk of bias in the 'Risk of bias' assessment tool for RCTs[13]

Potential source of bias	Assessment criteria
Random sequence generation (selection bias)	Criteria for a judgement of 'low risk' of bias: Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random)
	Criteria for the judgement of 'high risk' of bias: Sequence generated by odd or even date of birth; sequence generated by some rule based on

	date (or day) of admission; sequence generated by some rule based on hospital or clinic record number; allocation by judgement of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; allocation by availability of the intervention.
	Criteria for the judgement of 'Unclear risk' of bias: Insufficient information about the sequence generation process to permit judgement of 'Low risk" or 'High risk'.
Allocation concealment (selection bias)	Criteria for a judgement of 'Low risk' of bias: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
	Criteria for the judgement of 'High risk' of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Criteria for the judgement of 'Unclear risk' of bias: Insufficient information to permit judgement of 'Low risk" or 'High risk'.
Blinding of participants and personnel (performance bias due to knowledge of the allocated interventions by participants and personnel)	Criteria for a judgement of 'Low risk' of bias: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	Criteria for the judgement of 'High risk' of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Criteria for the judgement of 'Unclear risk' of bias: Insufficient information to permit judgement of 'Low risk' or 'High risk'; the study did not address this outcome.
Blinding of outcome data (detection bias due to knowledge of the allocated interventions by outcome assessors)	Criteria for a judgement of 'Low risk' of bias: No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	Criteria for the judgement of 'High risk' of bias. No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Criteria for the judgement of 'Unclear risk' of bias: Insufficient information to permit judgement of 'Low risk' or 'High risk'; the study did not address this outcome.
Incomplete outcome data (attrition bias)	Criteria for a judgement of 'Low risk' of bias: No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention

	groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	Criteria for the judgement of 'High risk' of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; potentially inappropriate application of simple imputation.
	Criteria for the judgement of 'Unclear risk' of bias: Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomised not stated, no reasons for missing data provided); the study did not address this outcome.
Selective Reporting	Criteria for a judgement of 'Low risk' of bias: The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	Criteria for the judgement of 'High risk' of bias: Not all of the study's pre-specified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Criteria for the judgement of 'Unclear risk' of bias: Insufficient information to permit judgement of 'Low risk' or 'High risk'.
Other bias	Criteria for a judgement of 'Low risk' of bias: The study appears to be free of other sources of bias.
	Criteria for the judgement of 'High risk' of bias: For example, the study: Had a potential source of bias related to the specific study design used; or Has been claimed to have been fraudulent; or Had some other problem.
	Criteria for the judgement of 'Unclear risk' of bias: Insufficient information to assess whether an important risk of bias exists; or Insufficient rationale or evidence that an identified problem will introduce bias.

Criteria for judging risk of bias in the 'Risk of bias' assessment tool for non-randomised studies[14]

Potential source of bias	Assessment criteria
Bias due to confounding	Screening question: Is confounding potentially controllable in the context of this study? 1.1. Did the authors conduct an appropriate analysis that controlled for all the critically important confounding domains? 1.2. If yes to 1.1: Were all of the confounding domains measured validly and reliably by the variables adjusted for in this study? 1.3. Did the authors avoid adjusting for post-intervention variables?
Bias in selection of participants into the study	2.1. Do start of follow-up and start of intervention coincide? 2.2. If no to 2.1: Were adjustment techniques used that are likely to correct for the presence of selection biases?
Bias due to departures from intended interventions	*Screening question: Were the intended interventions sufficiently clearly defined and implemented such that a reasonable comparison of them can be made?* 3.1. Were the critical co-interventions balanced across intervention groups? 3.2. Were numbers of treatment switches low enough that they do not threaten the validity of the estimated effect of intervention? 3.3. Was implementation failure minor and unlikely to threaten the validity of the outcome estimate? 3.4. If no to 3.1, 3.2 or 3.3: Were adjustment techniques used that were likely to correct for switches, unbalanced co-intervention and implementation failure?
Bias due to missing data	*Screening question: Are the intervention groups free of critical differences in participants with missing data?* 4.1. Are outcome data reasonably complete? 4.2. Was intervention status reasonably complete for those in whom it was sought? 4.3. Are data reasonably complete for other variables in the analysis? 4.4. If no to 4.1, 4.2 or 4.3: Are the proportion of participants and reasons for missing data similar across interventions? 4.5. If no to 4.1, 4.2 or 4.3: Were appropriate statistical methods used to account for missing data?
Bias in measurement of outcomes or interventions	5.1. Were outcome assessors unaware of the intervention received by study participants? 5.2. Was the outcome measure objective? 5.3. Were the methods of outcome assessment comparable across intervention groups?
Bias in selection of the reported result	6.1. Is it unlikely that the reported effect estimate is available primarily because it was a notable finding among numerous exploratory analyses? 6.2. Is the reported effect estimate unlikely to be prone to selective reporting (on the basis of the results) from among multiple outcome measurements within the outcome domain? 6.3. Is the reported effect estimate unlikely to be prone to selective reporting (on the basis of the results) from among multiple analyses of the outcome measurements? 6.4. Is the reported effect estimate unlikely to be prone to selective reporting (on the basis of the results) from among different subgroups?
Overall bias	Risk of bias judgement

Appendix 3. Excluded & Included Studies

Characteristics of Excluded Studies

Study	Reason for Exclusion
Bassett (2003)[40]	$ETCO_2$ not recorded
Burton (2006)[41]	Review
Capín (2014)[42]	<50 patients; patients <18yo
Cheuk (2005)[43]	$ETCO_2$ not recorded
Deitch (2007)[8]	Did not separate adults and children (potentially relevant)

Green (2002)[44]	Review
Hart (1997)[45]	<50 patients; patients <18yo
Kim (2003)[46]	<50 patients; patients <18yo
Karapinar (2006)[47]	$ETCO_2$ not recorded
Mandt (2012)[48]	$ETCO_2$ not considered separately
McQuillen (2000)[49]	No outcome measure related to $ETCO_2$
Miner (2003)[50]	No outcome measure related to $ETCO_2$
Miner (2005)[51]	No outcome measure related to $ETCO_2$
Miner (2005)[52]	No outcome measure related to $ETCO_2$
Miner (2007)[53]	No outcome measure related to $ETCO_2$
Miner (2007)[54]	No outcome measure related to $ETCO_2$
Miner (2009)[55]	No outcome measure related to $ETCO_2$
Miner (2010)[56]	No outcome measure related to $ETCO_2$
Miner (2013)[57]	$ETCO_2$ not considered separately
Newstead (2013)[38]	Review
Rahman (2010)[58]	<50 patients; did not specify an abnormal ETCO2 threshold in relation to adverse event detection
Rahman (2011)[59]	<50 patients
Padmanabhan (2009)[60]	<50 patients (only 6 patients within the ED)
Soleimanpour (2013)[61]	No outcome measure related to $ETCO_2$
Soto (2004)[62]	<50 patients; outside the ED
van Loon (2014)[63]	Outside the ED
Waugh (2011)[3]	Review
Weaver (2007)[64]	$ETCO_2$ not considered separately
Wright (1992)[65]	<50 patients; no ETCO2 threshold specified
Willman (2007)[66]	$ETCO_2$ not recorded
Yldzdas (2004)[67]	Outside the ED

Characteristics of Included Studies

Burton et al. (2006)[27]

Methods	• Study Design: Prospective Observational • Aim: to determine the ability of $ETCO_2$ monitoring during PSA to detect acute respiratory events before detection by current monitoring methods. • Duration: May 2004 – October 2004
Participants	• Population: 59 adults and children (≥17y/o, median age 38y/o) undergoing procedural sedation in an ED (60 PSAs); adverse event data was separated according to age • Any Subgroups: none • Location: Maine Medical Center • Inclusion criteria: undergoing propofol sedation in the ED, ≥17y/o • Exclusion criteria: unable to give informed consent • Method of recruitment/any blinding: the treatment team was kept blinded to $ETCO_2$ levels • Informed consent obtained: prospective informed consent from each patient
Interventions	• Procedure(s) performed: dislocation/fracture reduction, cardioversion, wound closure, transoesophageal echocardiography, tube thoracostomy, disimpaction, foreign body removal • Analgesic/sedative used: propofol, etomidate, midazolam, ketamine (doses not given) • Supplementary oxygen: 2L/minute by cannula • Standard monitoring used: Monitoring continuous oxygen saturation (SpO_2), heart rate, cardiac rhythm, respiratory rate and interval blood pressure • Equipment used to measure $ETCO_2$: LIFEPAK 12 defibrillator/monitor series (Medtronic Emergency Response Systems, Redmond, WA). $ETCO_2$ monitoring every 30 seconds via a combined oral/nasal cannula for $ETCO_2$
Outcomes	• Definition of an adverse event: acute respiratory event: SpO_2 ≤92%; increase in supplemental oxygen provided in response to observed apnoea, hypoventilation, or desaturation; use of bag-valve mask or oral/nasal airway for

	ventilatory assistance or apnoea; repositioning or airway alignment manoeuvres for ventilation or apnoea; physical or verbal stimulation for depressed ventilation or apnoea; and reversal agent administration; investigational acute respiratory event (abnormal $ETCO_2$: change of ≥10mmHg from presedation baseline, $ETCO_2$ ≤30mmHg, $ETCO_2$ ≥50mmHg) • Reported outcomes: acute respiratory events • Time points reported: time of acute respiratory event, time of clinical recognition
Summary	• Key Conclusions: End-tidal carbon dioxide monitoring of patients undergoing PSA detected many clinically significant acute respiratory events before standard ED monitoring practice did so. • Strengths: Clinicians blinded to capnography. • Weaknesses: not continuous monitoring therefore recording the onset of capnographic and standard monitoring changes was imprecise, study terminated early ($ETCO_2$ monitoring proceeded in an unblinded fashion, but timing of this is not stated); varying $ETCO_2$ changes provides a potential for misinterpretation (32/60 had abnormally low $ETCO_2$, 5/60 had abnormally high $ETCO_2$)

Risk of Bias

	Judgement	Support for Judgement
Confounding	Low risk	Negligible exclusion criteria, supplementary oxygen given to all patients
Participant selection	Low risk	Study size (including power calculation) included, taken from a convenience sample in the ED
Departures from intended interventions	High risk	High risk of attrition bias as the study terminated early, quote: "After review of two 30-patient enrolment blocks, it was determined that further use of $ETCO_2$ monitoring should proceed in an unblinded fashion and the study was terminated".
Missing Data	Low risk	All participants accounted for with clear exclusion criteria
Measurement of Outcome	Unclear risk	Low risk of performance and detection bias quote: "The clinical team was blinded to study monitoring data, including $ETCO_2$ findings, throughout the PSA period". But no blinding of outcome assessment: clinicians were aware of the purpose of the study
Selection of the Reported Result	Low risk	All of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
Notes	Study was approved by the institutional review board for research on human subjects, but no information regarding funding/conflict of interest	

Downs and Black Study Quality Score

Reporting	External Validity	Interval Validity – Bias	Internal Validity – Confounding	Power	Total
8/11	2/3	6/7	2/6	0/5	18/32

Deitch et al. (2008)[28]

Methods	• Study Design: RCT • Aim: to determine whether physicians blinded to capnographic data are able to recognise respiratory depression during procedural sedation • Duration: November 2005 - October 2006
Participants	• Population: 110 adults (>18y/o; median age: 37y/o) • Any Subgroups: patients receiving supplementary oxygen vs. compressed air • Location: Albert Einstein Medical Center, Philadelphia • Inclusion criteria: undergoing propofol sedation in the ED, >18y/o • Exclusion criteria: severe chronic obstructive pulmonary disease; chronic oxygen requirements; haemodynamic instability; respiratory distress; pregnancy; inability to provide informed consent; allergy to study drugs • Method of recruitment/any blinding: the treatment team was kept blinded to $ETCO_2$ levels • Informed consent obtained: written informed consent from each patient

Interventions	• Procedure(s) performed: abscess drainage or fracture/joint reduction • Analgesic/sedative used: 1-1.5mg/kg IV propofol with additional 0.5mg/kg boluses until the desired level of sedation was achieved • Supplementary oxygen: 3/L minute by cannula (56/110 patients) • Standard Monitoring used: pulse oximetry, pulse rate, blood pressure • Equipment used to measure $ETCO_2$: NPB-Microstream 75 $ETCO_2$ monitor (Nellcor Puritan Bennett Inc., Pleasanton, CA) connected to a nasal cannula (continuous sampling)
Outcomes	• Definition of an adverse event: Hypoxia (SpO_2 <93% for >15 seconds); Respiratory depression ($ETCO_2$ ≥50mmHg, ≥10% increase or decrease from baseline, loss of waveform); Hypotension; Bradycardia; Vomiting; Prolonged ED stay (>2 hours after the procedure); Admission • Reported outcomes: hypoxia, respiratory depression • Time points reported: time from first dose of medication to return to baseline alertness
Summary	• Key Conclusions: Blinded capnography frequently identified respiratory depression undetected by the treating physicians • Strengths: Clinicians blinded to capnography, eligible patients were entered into trial consecutively 24 hours per day; continuous sampling • Weaknesses: Investigation of the use of capnography was not the primary aim, the capnography monitor did not provide exact intervals between $ETCO_2$ changes and the onset of hypoxia

Risk of Bias

	Judgement	**Support for Judgement**
Confounding	Low risk	Supplementary oxygen was given to 56/110 patients but these patients were analysed separately
Participant selection	Low risk	All patients undergoing propofol sedation in the ED (aged >18y/o) could be included
Departures from intended interventions	Low risk	None
Missing Data	Low risk	All participants accounted for with clear exclusion criteria
Measurement of Outcome	Low risk	Low risk of performance and detection bias: blinding of personnel - quote: "the treatment team was kept blinded to $ETCO_2$ levels" blinding of the outcome assessment: "The treatment team was unaware that the research associates were evaluating their (i.e., the treatment team's) ability to recognise respiratory depression with standard PSA monitoring."
Selection of the Reported Result	Low risk	All of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way, detailed statistical tests listed.
Notes	Study was approved by the institutional review board, but no information regarding funding/conflict of interest	

Downs and Black Study Quality Score

Reporting	**External Validity**	**Interval Validity – Bias**	**Internal Validity – Confounding**	**Power**	**Total**
10/11	2/3	6/7	3/6	5/5	25/32

Deitch et al. (2010)[26]

Methods	• Study Design: RCT • Aim: to determine whether the use of real-time capnography is associated with a 15% decrease in the incidence of hypoxia compared with standard monitoring alone during ED procedural sedation with propofol • Duration: November 2006 – February 2008
Participants	• Population: 132 adults (>18y/o; median age: 34y/o) • Any Subgroups: none • Location: Albert Einstein Medical Center, Philadelphia • Inclusion criteria: undergoing propofol sedation in the ED • Exclusion criteria: severe chronic obstructive pulmonary disease; chronic oxygen requirements; haemodynamic instability; respiratory distress; pregnancy; inability to provide informed consent; allergy to propofol, morphine

	or fentanyl • Method of recruitment/any blinding: computer-generated randomisation list, blinded capnography • Informed consent obtained: yes (inability to consent was an exclusion criteria)
Interventions	• Procedure(s) performed: abscess incision and drainage; fracture/joint reduction • Analgesic/sedative used: 0.05mg/kg morphine or 0.5μg/kg fentanyl IV for analgesia for at least 30 minutes then 1mg/kg propofol with additional 0.5mg/kg boluses until the desired level of sedation was achieved • Supplementary oxygen: 3/L minute by cannula • Standard Monitoring used: pulse oximetry, pulse rate, blood pressure • Equipment used to measure $ETCO_2$: Capnostream 20 monitor (Oridion Medical, Needham, MA) using a nasal-oral CO2 cannula (data recorded every 5 seconds)
Outcomes	• Definition of an adverse event: Hypoxia (SpO_2 <93% for >15 seconds); Respiratory depression ($ETCO_2$ ≥50mmHg, ≥10% increase or decrease from baseline, loss of waveform ≥15 sec); Hypotension; Bradycardia; Arrhythmia; Vomiting; Prolonged ED stay; Admission • Reported outcomes: hypoxia, respiratory depression • Time points reported: time from capnographic evidence of respiratory depression to hypoxia
Summary	• Key Conclusions: Capnography can provide early warning of ventilatory abnormalities, alerting physicians to respiratory depression before the onset of a hypoxic event. • Strengths: Only RCT to include a control (i.e. patients randomised to capnography or blinded capnography) • Weaknesses: Underpowered: required 72 pts in each arm for 80% power; High rate of hypoxia → a smaller rate (consistent with other studies) may explain why difference between groups was not statistically significant; Capnostream 20 records every 5 seconds (standard monitoring e.g. blood pressure occurred at unspecified spaced intervals; the frequency of monitoring is a confounding factor); clinicians aware of which group they were allocated to; stringent set of criteria for respiratory depression meant higher rate of physician intervention for respiratory depression (in the unblinded group). Fewer physician interventions in this group may have decreased the recorded difference in the rate of hypoxia between the two groups.

Risk of Bias

	Judgement	**Support for Judgement**
Random sequence generation *(Selection bias)*	Low risk	Quote: "Patients were randomly assigned… by research associates using a computer-generated randomisation list"
Allocation concealment *(Selection bias)*	Low risk	Quote: "Research associates and treating physicians were blinded to the randomisation choice until after enrolment"
Blinding of participants and personnel *(Performance and detection bias)*	High risk	Clinicians were aware of which group they were allocated to
Blinding of outcome assessment *(Detection bias)*	Moderate risk	No blinding of outcome assessment
Incomplete outcome data *(Attrition bias)*	Low risk	No missing outcome data
Selective outcome reporting *(Reporting bias)*	Low risk	All of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Other bias	Low risk	The study appears to be free of other sources of bias.

Downs and Black Study Quality Score

Reporting	External Validity	Interval Validity – Bias	Internal Validity – Confounding	Power	Total
10/11	2/3	6/7	6/6	5/5	28/32

Deitch et al. (2011)[29]

Methods	• Study Design: RCT • Aim: to compare the frequencies of subclinical respiratory depression and other adverse events. • Duration: January 2009 – November 2010
Participants	• Population: 117 adults (>18y/o; mean age: 34.5y/o) • Any Subgroups: high-flow oxygen or room air (both 15L/min) • Location: Albert Einstein Medical Center, Philadelphia • Inclusion criteria: undergoing propofol sedation in the ED • Exclusion criteria: severe chronic obstructive pulmonary disease; chronic oxygen requirements; haemodynamic instability; respiratory distress; pregnancy; inability to provide informed consent; allergy to propofol, morphine or fentanyl • Method of recruitment/any blinding: all subjects received capnography, no blinding of capnography • Informed consent obtained: yes (inability to consent was an exclusion criteria)
Interventions	• Procedure(s) performed: abscess incision and drainage; fracture/joint reduction • Analgesic/sedative used: 1mg/kg propofol with additional 0.5mg/kg boluses until the desired level of sedation was achieved • Supplementary oxygen: 15L/min (59/117) • Standard Monitoring used: pulse oximetry, pulse rate, blood pressure • Equipment used to measure $ETCO_2$: Capnostream 20 monitor (Oridion Medical, Needham, MA) using a nasal-oral CO2 cannula (data recorded every 5 seconds)
Outcomes	• Definition of an adverse event: Hypoxia (SpO_2 <93% for ≥15 seconds); Respiratory depression ($ETCO_2$ ≥50mmHg, ≥10% increase or decrease from baseline, loss of waveform ≥15 sec); Hypotension; Bradycardia; Arrhythmia; Vomiting; Prolonged ED stay; Admission • Reported outcomes: hypoxia, respiratory depression • Time points reported: time from initial propofol administration until the patient returned to baseline alertness, time of intervention
Summary	• Key Conclusions: Capnography can provide early warning of ventilatory abnormalities, alerting physicians to respiratory depression before the onset of a hypoxic event. • Strengths: comprehensive exclusion criteria, patients randomised to high-flow oxygen or room air and statistical analyses between the two groups were performed • Weaknesses: Underpowered: defined hypoxia as SpO_2 <93% whereas we believe using the common threshold of 90% would have decreased the incidence of hypoxia; Capnostream 20 records every 5 seconds (standard monitoring e.g. blood pressure occurred at unspecified spaced intervals; the frequency of monitoring is a confounding factor); clinicians aware of which group they were allocated to

Risk of Bias

	Judgement	Support for Judgement
Confounding	Low risk	Comprehensive exclusion criteria, patients randomised to high-flow oxygen or room air and statistical analyses between the two groups were performed
Participant selection	Low risk	Undergoing propofol sedation in the ED
Departures from intended interventions	Low risk	None
Missing Data	Low risk	All participants accounted for
Measurement of Outcome	High risk	Performance and detection bias: blinding of personnel - quote: "We believe that the improved safety real-time capnography provides should

		be part of routine practice, and thus it would not be ethical to blind our clinicians" blinding of the outcome assessment: clinicians were aware that capnography was included as an outcome assessment
Selection of the Reported Result	Low risk	Key results with reference to study objectives summarised. All of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Notes	Study was approved by the institutional review board, but no information regarding funding/conflict of interest	

Downs and Black Study Quality Score

Reporting	External Validity	Interval Validity – Bias	Internal Validity – Confounding	Power	Total
10/11	2/3	4/7	3/6	5/5	24/32

Miner et al. (2002)[30]

Methods	• Study Design: Prospective Observational • Aim: to evaluate the utility of $ETCO_2$ monitors to detect RD in patients undergoing procedural sedation • Duration: December 2000 – April 2001
Participants	• Population: 74 adults (mean age: 37.6 y/o) • Any Subgroups: none • Location: an urban county medical centre • Inclusion criteria: adult ED patients who were monitored during procedural sedation as per ED standard guidelines • Exclusion criteria: inability to give consent • Method of recruitment/any blinding: no blinding • Informed consent obtained: given (method not stated)
Interventions	• Procedure(s) performed: fracture reduction, dislocation reduction, incision and drainage of abscess, thoracostomy tube placement, hernia reduction, cardioversion, complex laceration repair • Analgesic/sedative used: methohexital/propofol/etomidate or fentanyl and midazolam. • Supplementary oxygen: 47/74 (dose not stated) • Standard monitoring used: Pulse oximetry, heart rate, blood pressure, respiratory rate, $ETCO_2$ every 2 minutes + modified version of the *Observer's Assessment of Alertness/Sedation Scale (OAA/S) • Equipment used to measure $ETCO_2$: nasal cannula with portable Capnocheck II (BCI, Waukesha, WI)
Outcomes	• Definition of an adverse event: Respiratory depression (oxygen saturation of <90% for ≥1 minute; $ETCO_2$ >50 mm Hg; absent $ETCO_2$ waveform; $ETCO_2$ change from baseline >10 mm Hg). • Reported outcomes: Respiratory depression • Time points reported: duration of assisted ventilation
Summary	• Key Conclusions: The $ETCO_2$ monitor detected patients who met our criteria for RD who were not detected by pulse oximetry. • Strengths: detailed statistics • Weaknesses: no blinding, the rates of RD between different drugs was significantly different but the number of patients meeting criteria for respiratory depression was not separated according to sedation used, $ETCO_2$ monitoring every 2 minutes, unclear exclusion criteria

Risk of Bias

	Judgement	Support for Judgement
Confounding	High risk	Liberal exclusion criteria, duration of sedation & monitoring not given, 47 patients received supplementary oxygen as part of airway management but they were not considered separately
Participant selection	Low risk	Adult ED patients who were monitored during procedural sedation as per ED standard guidelines
Departures from intended interventions	Low risk	None
Missing Data	Unclear risk	All participants accounted for but reasons for the 2 unsuccessful

		procedures were not given
Measurement of Outcome	Low risk	No blinding
Selection of the Reported Result	Low risk	Key results with reference to study objectives summarised. All of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Notes	Study was approved by The Institutional Review Board (IRB) of Hennepin County Medical Center review board but no information regarding funding	

Downs and Black Study Quality Score

Reporting	External Validity	Interval Validity – Bias	Internal Validity – Confounding	Power	Total
9/11	2/3	3/7	3/6	5/5	24/32

Miner (2003)[31]

Methods	• Study Design: Prospective Observational • Aim: to determine whether there is a correlation between the achieved levels of sedation by the BIS score with the rate of RD as measured by $ETCO_2$ and pulse oximetry • Duration: April 2001 – June 2001
Participants	• Population: 108 adults (>18y/o, mean age: 40.9y/o) • Any Subgroups: none • Location: an urban county medical centre ED • Inclusion criteria: not stated • Exclusion criteria: inability to give consent • Method of recruitment/any blinding: blinded to the BIS monitor only • Informed consent obtained: given (method not stated)
Interventions	• Procedure(s) performed: fracture reduction, dislocation reduction, incision and drainage of abscess, thoracostomy tube placement, complex laceration repair • Analgesic/sedative used: methohexital/propofol/etomidate or fentanyl and midazolam. • Supplementary oxygen: 87/108 (dose not stated) • Standard monitoring used: Pulse oximetry, heart rate, blood pressure, $ETCO_2$ continuously. Bispectral electroencephalographic (EEG) – BIS monitor • Equipment used to measure $ETCO_2$: nasal-sample, equipment not stated
Outcomes	• Definition of an adverse event: Respiratory depression (oxygen saturation of <90%; $ETCO_2$ change from baseline >10 mm Hg; absent $ETCO_2$ waveform); vomiting; aspiration; intubation; transfer to higher level of care after the procedure; assisted ventilation; pain • Reported outcomes: Respiratory depression • Time points reported: duration of assisted ventilation
Summary	• Key Conclusions: The $ETCO_2$ monitor detected patients who met our criteria for RD who were not detected by pulse oximetry. • Strengths: detailed statistics including power analysis • Weaknesses: no blinding, small patient numbers (convenience sample), study finished early, did not include the patient's state of health (such as ASA scores) or a pre- procedure airway assessment in analysis; change in baseline of >10mmHg $ETCO_2$ is not very strict criteria

Risk of Bias

	Judgement	Support for Judgement
Confounding	Low risk	Compared rates of RD between different sedating agents; duration of sedation & monitoring not given
Participant selection	Unclear risk	Inclusion criteria not strictly specified
Departures from intended interventions	Low risk	None
Missing Data	Unclear risk	All participants accounted for but reasons for the 3 unsuccessful procedures were not given
Measurement of Outcome	High risk	No blinding of capnography

Selection of the Reported Result	Low risk	Key results with reference to study objectives summarised. All of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way
Notes	Study was approved by The Institutional Review Board (IRB) of Hennepin County Medical Center review board but no information regarding funding	

Downs and Black Study Quality Score

Reporting	External Validity	Interval Validity – Bias	Internal Validity – Confounding	Power	Total
10/11	2/3	5/7	4/6	5/5	26/32

Sivilotti (2010)[6]

Methods	• Study Design: RCT • Aim: to determine which monitor would first detect a respiratory event: the pulse oximeter or the capnometer • Duration: December 2004 – February 2006
Participants	• Population: 63 adults (21-57y/o, mean age: 39y/o) • Any Subgroups: random assignment to groups receiving ketamine or fentanyl • Location: a university-affiliated tertiary care hospital • Inclusion criteria: Class I or II patients (ASA) • Exclusion criteria: Significant active cardiac, pulmonary, hepatic or renal disease, recent substance abuse, prior/current opioid dependence, OSA, prior psychosis, allergy to ketamine, fentanyl or propofol, weighed >130kg, acutely intoxicated • Method of recruitment/any blinding: none mentioned • Informed consent obtained: written informed consent
Interventions	• Procedure(s) performed: fracture reduction or incision and drainage of abscess • Analgesic/sedative used: 0.3mg/kg ketamine or 1.5µg/kg fentanyl IV then 0.4mg/kg propofol IV 2 minutes later then 0.1mg/kg boluses every 30 seconds • Supplementary oxygen: administered if patients developed oxygen desaturation (number of patients & dose not stated) • Standard monitoring used: Continuous pulse oximetry, ECG and blood pressure • Equipment used to measure $ETCO_2$: Nellcor Smart CapnoLine O2/CO2 Oral Nasal Cannula (Tyco Healthcare), continuous sampling
Outcomes	• Definition of an adverse event: Hypoventilation ($ETCO_2$ > 50mmHg or a rise or fall of >10mmHg from presedation baseline or loss of waveform for >30 seconds or recurrent losses of waveform); Oxygen desaturation (pulse oximetry <92%) • Reported outcomes: hypoventilation, oxygen desaturation • Time points reported: time of an adverse event
Summary	• Key Conclusions: During PSA in adults breathing room air, desaturation detectable by pulse oximeter usually occurs before overt changes in capnometry are identified • Strengths: formed part of a prospective clinical trial thus there was consistent drug titration with only a small number of trained study physicians performing sedations and collecting data, and independent validation of clinician observations with the monitor's automatic data recording; included the patient's state of health (ASA score) • Weaknesses: No a priori null hypothesis tested, substantial variability among and within participants in capnometry at baseline, physicians failed to recognise a 10mmHg rise in $ETCO_2$, capnometric abnormalities were poorly sensitive/late findings in patients with hypoxia on room air; considerable breath to breath variability, use of capnography was not the primary research question; study terminated early (safety in favour of ketamine); not blinded to capnography; did not specify the level of sedation achieved

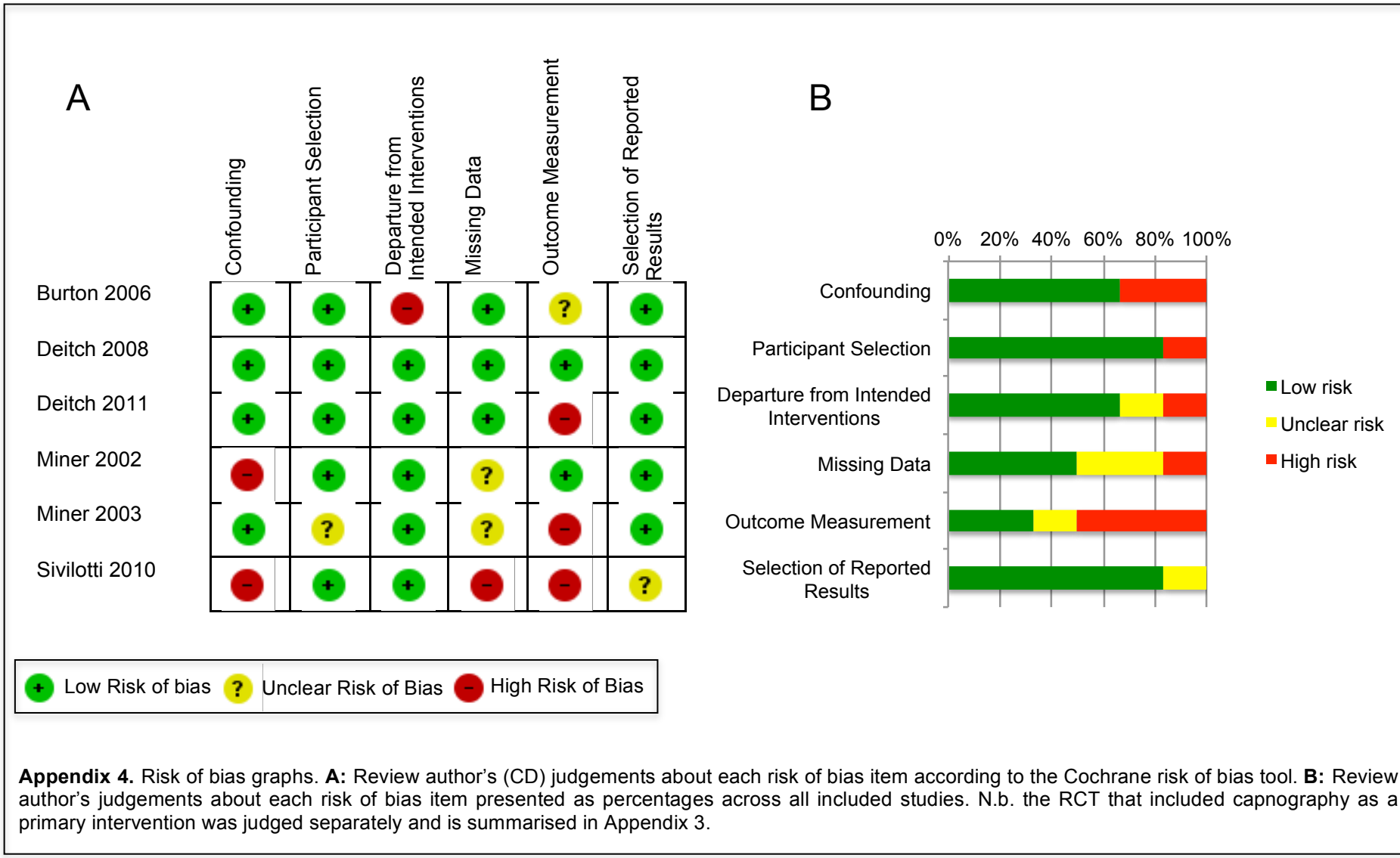
Risk of Bias

	Judgement	Support for Judgement
Confounding	High risk	Consistent drug titration, trained personnel; liberal exclusion criteria; depth of sedation, duration of sedation and duration of monitoring not given. Supplementary oxygen: administered if patients developed oxygen desaturation (number of patients & dose not stated and not included in analysis)
Participant	Low risk	Class I or II patients (ASA)

selection		
Departures from intended interventions	Low risk	None
Missing Data	High risk	Incomplete outcome data “The primary trial was stopped by the data monitoring committee following a planned interim analysis at 50% enrolment when an important difference in safety emerged in favour of ketamine.”
Measurement of Outcome	High risk	No blinding of outcome assessment *(Detection bias),* clinicians were aware that capnography was included as an outcome assessment, quote: “no a priori null hypothesis [related to capnography] tested”, bias against the use of capnography
Selection of the Reported Result	Unclear risk	Reported in the pre-specified way but difficult to analyse given the early termination of the trial
Notes	Study was approved by The Institutional Review Board (IRB) of Hennepin County Medical Center review board but no information regarding funding	

Downs and Black Study Quality Score

Reporting	**External Validity**	**Interval Validity – Bias**	**Internal Validity – Confounding**	**Power**	**Total**
9/11	2/3	4/7	3/6	0/5	18/32



Appendix 4. Risk of bias graphs. **A:** Review author's (CD) judgements about each risk of bias item according to the Cochrane risk of bias tool. **B:** Review author's judgements about each risk of bias item presented as percentages across all included studies. N.b. the RCT that included capnography as a primary intervention was judged separately and is summarised in Appendix 3.

Appendix 5. Summary of Findings Table

Outcomes	Illustrative Comparative Risk*		Relative Effect (Random-effects model, 95% CI)	Heterogeneity: I^2 (95% CI; p-value)	No. of Participants (studies)	Quality of the Evidence (GRADE)	Comments
Diagnostic Accuracy of Capnography	TP x TN (173 x 417)	FP x FN (218 x 65)	Odds Ratio: 5.87 (2.41-14.3)	66.88% (26.18-85.14; 0.006)	662 (7)	⊕⊕⊕◯ Moderate[1]	Low false negative rate, Large OR, Moderate heterogeneity; Average Downs and Black score: 23.29 (moderate quality)
Detection of Adverse Events before Standard Monitoring	154/318 (Adverse events detected solely by $ETCO_2$/Total Adverse Events)		48.82% (32.85-64.92)	52.14% (78.73-93.78; 0.0491)	662 (7)	⊕⊕◯◯ Low[1,2]	High risk of bias; lack of blinding; Average Downs and Black score: 23.29 (moderate quality)

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
*__Illustrative comparative risks__ are typical risks of the outcome occurring without the intervention (assumed risks) and the corresponding risks of the outcome occurring with the intervention. TP (True Positive); TN (True Negative); FP (False Positive); FN (False Negative)
1. Less than ten studies, so creating a funnel plot was not applicable
2. Confidence interval includes zero (no difference)

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Outcomes	Illustrative Comparative Risk*		Relative Effect (Random-effects model, 95% CI)	Heterogeneity: I^2 (95% CI; p-value)	No. of Participants (studies)	Quality of the Evidence (GRADE)	Comments
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