Evidence Brief: Capnography for Moderate Sedation in Non-Anesthesia Settings

Supplementary Materials

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Prepared for:
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Health Services Research & Development Service

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SEARCH STRATEGIES

1. Search for current systematic reviews (limited to last 7 years) Date Searched: 11-13-2019			
A. Bibliographic Databases:	**#**	**Search Statement**	**Results**
MEDLINE: Systematic Reviews Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to January 06, 2020	1	Capnography/	1323
	2	capnograph*.ti,ab.	1933
	3	1 or 2	2492
	4	Conscious Sedation/	8705
	5	((moderate or conscious) adj sedation).ti,ab.	3302
	6	4 or 5	10377
	7	3 and 6	158
	8	(systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/) or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or citation.tw. or citations.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment outcome/ or treatment outcome.tw. or pmcbook.mp.))) not (letter or newspaper article).pt.	379136
	9	7 and 8	10
	10	limit 9 to english language	10
CDSR: Protocols and Reviews	1	MeSH descriptor: [Capnography] explode all trees	1
	2	(capnograph*):ti,ab,kw	2
	3	#1 or #2	2
	4	MeSH descriptor: [Conscious Sedation] this term only	6
	5	((moderate sedation) or (conscious sedation)):ti,ab,kw	55
	6	#4 or #5	55
	10	#3 and #6	2

1. Search for current systematic reviews (limited to last 7 years) Date Searched: 01-07-2020		
B. Non-bibliographic databases	**Evidence**	**Results**
AHRQ: evidence reports, technology assessments, U.S Preventative Services Task Force Evidence Synthesis	http://www.ahrq.gov/research/findings/evidence-based-reports/search.html Search: capnography; moderate sedation	0
CADTH	https://www.cadth.ca Search: capnography; moderate sedation	4
ECRI Institute	https://www.ecri.org/Pages/default.aspx Search: capnography; moderate sedation	1
HTA: Health Technology Assessments	http://www.ohsu.edu/xd/education/library/ Search: capnography; moderate sedation	0
NHS Evidence	http://www.evidence.nhs.uk/default.aspx Search: capnography; moderate sedation	2
NLM	http://www.ncbi.nlm.nih.gov/books Search: capnography; moderate sedation	1
VA Products - VATAP, PBM and HSR&D publications	A. http://www.hsrd.research.va.gov/research/default.cfm B. http://www.research.va.gov/research_topics/	0

2. Search for systematic reviews currently under development (includes forthcoming reviews & protocols) Date Searched: 11-13-2019		
A. Under development :	**Evidence**	**Results**
PROSPERO (SR registry)	http://www.crd.york.ac.uk/PROSPERO/ Search: capnography; moderate sedation	4
DoPHER (SR Protocols)	http://eppi.ioe.ac.uk/webdatabases4/Intro.aspx?ID=9 Search: capnography; moderate sedation	0
Cochrane Database of	http://www.ohsu.edu/xd/education/library/	0

Systematic Reviews: Protocols	Search: capnography; moderate sedation	

3. Search for primary literature Date searched: 01-07-2020		
MEDLINE [Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to January 06, 2019]		
#	**Search Statement**	**Results**
1	Capnography/	1324
2	capnograph*.ti,ab.	1933
3	1 or 2	2492
4	Conscious Sedation/	8705
5	((moderate or conscious) adj sedation).ti,ab.	3302
6	4 or 5	10377
7	3 and 6	158
8	limit 7 to english language	153
CINAHL [EBSCO]		
#	**Search Statement**	**Results**
1	(MH “Capnography”)	1195
2	TI capnograph* OR AB capnograph*	819
3	S1 or S2	1465
4	(MH "Conscious Sedation")	2923
5	TI ((moderate sedation) or (conscious sedation)) OR AU ((moderate sedation) or (conscious sedation))	583
6	S4 or S5	3041
7	S3 and S6	81
8	limit 7 to english language	81
CENTRAL [EBM Reviews - Cochrane Central Register of Controlled Trials November 2019]		
#	**Search Statement**	**Results**
1	Capnography/	90
2	capnograph*.ti,ab.	494
3	1 or 2	524
4	Conscious Sedation/	1379
5	((moderate or conscious) adj sedation).ti,ab.	1177
6	4 or 5	2260
7	3 and 6	40
8	limit 7 to english language	35

LIST OF EXCLUDED STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Ineligible outcome, 5=Ineligible timing, 6=Ineligible study design, 7=Ineligible publication type 8=Outdated or ineligible systematic review

#	Citation	Exclude reason
1	Cacho G, Pérez-Calle JL, Barbado A, Lledó JL, Ojea R, Fernández-Rodríguez CM. Capnography is superior to pulse oximetry for the detection of respiratory depression during colonoscopy. *Rev Esp Enferm Dig*. 2010;102(2):86–89. doi:10.4321/s1130-01082010000200003	4
2	Bitar G, Mullis W, Jacobs W, et al. Safety and efficacy of office-based surgery with monitored anesthesia care/sedation in 4778 consecutive plastic surgery procedures. *Plast Reconstr Surg*. 2003;111(1):150–158. doi:10.1097/01.PRS.0000037756.88297.BC	2
3	Burton JH, Harrah JD, Germann CA, Dillon DC. Does end-tidal carbon dioxide monitoring detect respiratory events prior to current sedation monitoring practices?. *Acad Emerg Med*. 2006;13(5):500–504. doi:10.1197/j.aem.2005.12.017	2
4	Campbell SG, Magee KD, Zed PJ, et al. End-tidal capnometry during emergency department procedural sedation and analgesia: a randomized, controlled study. *World J Emerg Med*. 2016;7(1):13–18. doi:10.5847/wjem.j.1920-8642.2016.01.002	2
5	Sivilotti ML, Messenger DW, van Vlymen J, Dungey PE, Murray HE. A comparative evaluation of capnometry versus pulse oximetry during procedural sedation and analgesia on room air. *CJEM*. 2010;12(5):397–404. doi:10.1017/s1481803500012549	2
6	Soto RG, Fu ES, Vila H Jr, Miguel RV. Capnography accurately detects apnea during monitored anesthesia care. *Anesth Analg*. 2004;99(2):. doi:10.1213/01.ANE.0000131964.67524.E7	2
7	Miner JR, Heegaard W, Plummer D. End-tidal carbon dioxide monitoring during procedural sedation. *Acad Emerg Med*. 2002;9(4):275–280. doi:10.1111/j.1553-2712.2002.tb01318.x	4

EVIDENCE TABLES

DATA ABSTRACTION OF INCLUDED PRIMARY STUDIES

Author Year N	Setting	Patients (age, gender, comorbidities)	Procedures (type of procedure, medications used, procedure length)	Intervention (capnography)/ Comparator (routine monitoring)	Outcome results 1) Hypoxemia 2) Adverse events 3) Cost 4) Access 5) Subgroup differences
Adams 2015[1] Prospective observational n=200	TEE laboratory within hospital	**Age:** 62.2 years **Gender (% male):** 59% **Comorbidities:** - Currently smoking: 15% - CHF: 18.5% - OSA: 15% - Asthma: 14.5% - COPD: 9% - CPAP/BiPAP use: 7.5% - Opioid use: 9% - Benzodiazepine: 2.5% - Recreational drug use: 0.5%	**Procedure:** Transesophageal Echocardiography (TEE) **Medication:** Midazolam and meperidine (most common), hydromorphone, fentanyl, promethazine (rare - 1 patient) **Procedure length:** NR	**Intervention**: Capnography plus usual monitoring **Comparator:** Usual monitoring (SpO2 and electrocardiogram)	1) Respiratory depression developed in 90 (45%) (using capnography definition). Of these, 28 (31%) received an intervention (based on routine monitoring). Most common intervention was supplemental O2. 2) NR 3) NR 4) NR 5) NR
Barnett 2016[2] Prospective case control n=966	Outpatient endoscopy unit	All comparisons are for cap (n=501) vs pre-cap (n=465) groups **Age (mean):** 58.1 vs 56.6 **Gender (% male):** 46.5% vs 53.1% **Comorbidities:** -10.9% vs 9.2% were current smokers -15.8% vs 26% CVD -1.4 vs 15.5% pulmonary disease	**Procedure:** Colonoscopy (note EGD were excluded because nasal cannula for capnography interfered with EGD scope) **Medication:** Midazolam and fentanyl **Procedure length:** NR	**Intervention:** Capnography plus usual monitoring (after capnography was added with institution) **Comparator:** Usual monitoring (before capnography was used at institution)	1) Overall sedation events were similar in both cohorts (8.2% pre-EtCO2 vs 11.2% EtCO2, P =0.115); no reversal agents needed and no hospitalizations. 2) Cap was associated with greater procedural discomfort rated by patient (1.71 vs 1.00, P <0.001) and nurse (1.82 vs 1.33, P <0.001) on PROSAS survey, which was remained significant even after controlling for age, BMI,

		-0% vs 4.5% neurologic illness -11.2% vs 11.4% kidney/liver disease -17.3% vs 15.7% cancer -1.8% vs 3.2% psych medications 0% vs 0.9% chronic narcotics 12% vs 9% diabetes			gender ethnicity, and ASA score. Nurse assessment of cap utility was neutral/unsure. No other patient harms reported. Cap costs additional $40,169.95 to upgrade procedure rooms and $11.68 3) Cap costs additional $40,169.95 to upgrade procedure rooms and $11.68 increased cost per patient (for cap cannula) 4) NR 5) NR
Brady 2017[3] RCT N=190	Dental clinic (Cork University Dental School and Hospital)	Blinded Capnography control (n=97) vs Capnography intervention (n=93) **Age (mean):** 31.5 (control) vs 31.2 (cap) **Gender (% male):** 26% (capnography) vs 36% (control) **Comorbidities:** -63% (cap) vs 54% (control) were alcohol drinkers -26% (cap) vs 27% (control) were smokers	**Procedure:** Minor oral surgery procedure (*ie*, single tooth removal to surgical removal of impacted wisdom teeth) **Medication used:** Midazolam **Procedure length:** NR	**Intervention:** Capnography **Comparator:** Routine monitoring	1) No difference in the proportion of patients who experienced hypoxemia (SpO2⩽94%) between the capnography and the control group 34.4 vs 39.2% (P = 0.4962, OR = 0.81, 95% CI: 0.45–1.47). The number of patients receiving verbal stimulation to take breaths was higher in the capnography group than in the control group: 54 vs 38. 3 patients in each group required supplemental O2. 2) NR 3) NR 4) NR 5) NR
Ishiwata 2018[4] RCT n=185	Bronchoscopy unit within academic medical center (Japan)	Capnography group (n=94) vs control group (n=91) **Age (mean ± SD)**: 67.1±11(capnography) vs 66.2±13.4 (control) **Gender (% male):** 61%	**Procedure:** Sedated Flexible Bronchoscopy (FB) **Medication used:** Pethidine and midazolam **Procedure length:** NR	**Intervention:** Capnography **Comparator:** Routine monitoring	1) Hypoxemia, defined as at least 1 episode of SpO2 <90%, was observed in 27 (29%) and 42 (46%) patients in the capnography and control groups (p = 0.014), respectively, resulting in an absolute risk difference [ARD]

	vs 63% **Comorbidities:** - Smoking: 60% vs 64% - Regular narcotics: 16% vs 20% - Alcohol abuse: 11% vs 7% - Liver disease: 9% vs 9% - Renal disease: 27% vs 21% - COPD: 17% vs 16% - ILD: 10% vs 9% - SAS: 0% vs 1%		of −17.4% (95% confidence interval [CI], −31.1 to −3.7). After exclusion of 3 patients with missing time course data during FB, the Gehan-Breslow-Wilcoxon test showed a hazard ratio of 0.56 (95% CI, 0.35–0.91; p = 0.034). ARD= −14.8%; 95% CI, −27.1 to −2.6). Mean lowest SpO2 value was significantly higher in the capnography group (90.5 vs 87.6%; p = 0.002; mean difference, 2.9%; 95% CI, 1.0–4.7). Minimum and interquartile ranges of lowest SpO2 were 76% (88–94%) and 62% (83–93%) in the capnography and control groups, respectively. Apnea: 44 (47%) in cap vs and 40 (44%) in control (p = 0.479). 2) Hypotension and bradycardia: 2 in cap vs 1 in control. No patient harms reported; The most frequent intervention against apnea or hypoxemia episodes was increased O2 flow (45 [48%] and 42 [46%] patients in the capnography and control groups, respectively), followed by the chin-lift/jaw-thrust maneuver (14 [15%] and 8 [9%] patients in the capnography and control groups, respectively). There were no patients requiring intubation, anesthesiology assistance, or termination of FB in the study

					population. 83 false alarms detected in 185 patients by capnography, main reason for false apnea alarms by capnography was continuous suction in mouth or trachea with a bronchoscope. 3) NR 4) NR 5) NR
Koniaris 2003[5] Retrospective n=5,446	Adult endoscopy suite at University of Rochester hospital	n=5,446 adult patients **Age**: NR **Gender:** NR **Comorbidities**: NR	**Procedure**: Endoscopic procedures (colonoscopy, gastrostomy, upper endoscopy, polypectomy, ERCP, stone extraction, etc.) **Medication used:** NR although opioid and benzodiazepine use implied **Procedure length**: NR	**Intervention:** Capnography via nasal prong catheter or facemask **Comparator:** Routine monitoring	1) NR 2) Sedation related complications resulting in ventilatory failure that required either assisted bag-mask ventilation or reversal agents identified in 14 (out of 4,846) procedures without capnography and 0 (out of 600) procedures with capnography. 3) Capnographic machine (cost/unit): $2000 – 12,000 - Maintenance contract: $100 - 960 - Capnograph line: $2.02 - Regular cannula: $0.51 - Dual capnograph and oxygen cannula: $2.56 Pulse Oximetry (cost/unit): - Pulse oximeter: $700-3,000 - Oximetry probe: $25-75 4) NR 5) NR
Mehta 2016[6] RCT n=452	Outpatient EGD/colonoscopy unit at Cleveland Clinic	Esophagogastroduodenoscopy (EGD) group (n=209) vs colonoscopy group (n=234) EGD: Cap blinded (n=108) vs Cap open	**Procedure:** Esophagogastroduodenoscopy (EGD) and colonoscopy	**Intervention:** Capnography **Comparator:** Standard monitoring on all patients: Pulse	1) No significant difference in rates of hypoxemia between the blinded and open capnography arms for EGD (54.1% vs 49.5; P =0.5) or colonoscopy (53.8 vs 52.1%; P =0.79)The absolute

	(n=101) **Age: 49.8** vs 51.8 **Gender (% male):** 36.1% vs 35.6% **Comorbidities (n):** - Use of narcotics: 9.3% vs 3% - Use of benzodiazepines: 15.7% vs 10.9% - Liver disease: 4.6% vs 9.9% - Cardiac disease: 38.9% vs 43.6% - Pulmonary disease: 0% vs 4% - Renal disease: 9.3% vs 12.9% - Current smoker: 19.4% vs 15.8% Colonoscopy: Cap blinded (n=114) vs Cap open (n=117) **Age:** 56.6 vs 54.1 **Gender (% male):** 48.2% vs 50.4% **Comorbidities (n):** - Use of narcotics: 1.8% vs 5.1% - Use of benzodiazepines: 4.4% vs 6.8% - Liver disease: 0.88% vs 1.7% - Cardiac disease: 52.6% vs 45.3% - Pulmonary disease: 0.88% vs 1.7% - Renal disease: 2.6% vs 7.7%	**Medication used:** Fentanyl or meperidine, and midazolam **Procedure length:** EGD: **5**.6±2.6 in cap blinded vs 5.6±2.6 cap open, p= 0.99 Colonoscopy: 17.5±7.8 in cap blinded vs 17.3±7.3 cap open, p= 0.83	oximetry, blood pressure monitoring, and visual assessment by experienced registered nurses	hypoxemia risk reduction associated with the use of capnography alarming in EGD is 4.6% (95% confidence interval (CI): −8.7 to 17.8%) and in colonoscopy (open capnography group) is 1.7% (95% CI: −11.1 to 14.5). NNT 22 (one patient in every 22 would benefit from open capnography alarming) in EGD and NNT 59 in colonoscopy (one patient in every 59 would benefit from open capnography alarming). 2) One subject in the EGD open capnography alarm required administration of naloxone-reversal agent post-procedurally (with full completion of the procedure) due to persistent hypoxemia. 3) NR 4) NR 5) NR

		- Current smoker: 7.9% vs 17.1%			
Qadeer 2009[7] RCT n=263	Outpatient endoscopy unit (>90% outpatient), single center	Capnography blinded arm group (n=123) vs capnography open arm group (n=124) **Age:** 60.6 vs 60.8 **Gender (% male):** 50.4% vs 49.2% **Comorbidities (n):** - Current smoker: 19.3% vs 17.9% - Regular narcotic/sedative use: 24.4% vs 29% - Regular benzodiazepine use: 20.3% vs 16.9% - Heart disease: 22% vs 23.4% - Lung disease: 10.6% vs 6.5% - Renal disease: 13% vs 11.3% - Liver disease: 22% vs 23.4% - Sleep apnea: 13% vs 11.3%	**Procedure:** Endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS) **Medication used:** Sedated with midazolam and meperidine or fentanyl; diazepan added when patients difficult to sedate **Procedure length:** >30 minutes	**Intervention:** OPEN arm: Routine monitoring (Continuous display of HR and pulse ox, BP every 5 minutes) with Microstream capnography-based ventilation monitoring system with signaling of resp abnormalities ("not breathing properly") by independent observer within 5-10 seconds of onset **Comparator:** BLINDED arm - same as open arm except that endoscopy was not notified of capnography results unless apnea >30 seconds	1) 85 (69%) from blinded arm and 57 (46%) from open arm developed at least 1 episode of hypoxemia (p<.001). Severe hypoxemia (31% vs 15%); apnea (63% vs 41%), O2 supplementation (67% vs 52%). 2) False alarms: 35 (13%) capnography erroneously displayed flat line for >50 seconds 3) NR 4) NR 5) Capnography was more beneficial during ERCP compared with EUS and in obese patients compared with nonobese patients
Vargo 2002[8] Prospective observational n=49	Hospital (hospitalized patients), single center	Apnea/disordered respiration present group (n=28) vs Apnea/disordered respiration absent group (n=21)	**Procedure:** Elective complex upper endoscopic procedures (ERCP) with expandable metal stent placement, photodynamic therapy, EUS, and	**Intervention:** Sidestream CO2 detector attached to a nasal cannula sampling device provided	1) Episodes of apnea and disordered respiration (ADR) detected by capnography = 54; ADR detected by pulse ox (50%), hypercapnea (5.5%), visual assessment (0%).

	Age (mean): 59 vs 54 **Gender (male/female):** 18/10 vs 10/11 **Comorbidities (n):** - Smoking: 15 vs 10 - Alcohol use: 1 vs 2 - COPD: 5 vs 3 - Ischemic heart disease: 7 vs 0 - Liver disease: 6 vs 6 - Narcotic use: 8 vs 8 - Benzodiazepine use: 3 vs 3 - Other sedatives/psychotropic drugs: 4 vs 4	therapeutic push enteroscopy **Medication used:** Meperidine and midazolam; patients with hx of chronic opioid or EtOH use also received droperidol pre-medication **Procedure length:** >50 minutes	graphic assessment of respiratory activity; monitored by independent physician observer **Comparator:** Pulse oximeter, automated blood pressure cuff, and an electrocardiograph, dedicated RN monitoring in room	*Results were obtained by retrospective review of data captured during procedure 2) NR 3) Costs associated with use of a monitor specifically for graphic assessment of respiratory activity by means of capnography include a one-time software activation fee ($150.00), the cost of an in-line dehumidifying module ($23.00) that is changed weekly, and the cost of disposable nasal cannula ($4.00 per patient). 4) NR 5) NR

CHF=Chronic heart failure; COPD= Chronic obstructive pulmonary disease; cap= capnography; BMI=body mass index; OR=odds ratio; ARD=absolute risk difference; CI=confidence interval; NNT= number needed to treat; TEE=Transesophageal echocardiogram; OSA=Obstructive sleep apnea; CPAP=Continuous Positive Airway Pressure; BiPAP=Bilevel Positive Airway Pressure; SpO2= peripheral capillary oxygen saturation; CVD=Cardiovascular Disease; EGD= Esophagogastroduodenoscopy; EtCO2=End-tidal carbon dioxide; PROSAS= PROcedural Sedation Assessment Survey; ASA= American Society of Anesthesiologists; psych=Psychiatric; RCT= Randomized controlled trial; ILD= Interstitial lung disease; SAS=Sleep apnea syndrome

QUALITY ASSESSMENT OF INCLUDED PRIMARY STUDIES

Quality Assessment of RCTs

Author Year Country	Risk of bias from randomization process	Risk of bias from deviation from intended interventions (assignment)	Risk of bias from missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall Rating (Good, Fair, Poor) / Main limitations of the study
Brady 2017[3]	Low risk Randomized with permuted block randomization by SAS version 9.3, participants and clinicians were aware of treatment allocation by the time sedation administered; similar group characteristics	Some concerns Patients and clinicians aware of assignment by time of sedation; underwent same sedation procedure with variable endpoints	Some concerns 8 pts were removed because more than 20% of their pulse oximetry or capnography data was missing, more of these were from capnography group (6 vs 2).	Some concerns Measurement is appropriate based on body of literature; data collectors were aware of assignment	Low risk Analysis appropriate and all outcomes from Clinicaltrials.gov reported.	**Overall Rating:** Fair **Limitations:** Patients, providers, and observers were aware of treatment arm. Also more patients' data were deemed invalid due to technical difficulties in the capnography arm.
Ishiwata 2018[4]	Low risk Randomized with permuted block randomization; Bronchoscopy team members not informed of assignment until day of procedure; no significant differences between groups at baseline.	Some concerns Not explicitly stated if participants were aware of assignment; bronchoscopy team members were aware of the assignment on the day of the procedure.	Some concerns Similar numbers of pts in each group had incomplete procedural data; post-procedure survey taken by approx. half of patients in each group.	Some concerns Measurement is appropriate based on body of literature; data collectors were aware of assignment	Low risk Analysis appropriate and all outcomes from trial registration reported.	**Overall Rating:** Fair **Limitations:** Providers and observers aware of treatment arm.

Author Year Country	Risk of bias from randomization process	Risk of bias from deviation from intended interventions (assignment)	Risk of bias from missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall Rating (Good, Fair, Poor) / Main limitations of the study
Mehta 2016[6]	Some concerns Randomized using REDCap software but more specifics on methods not provided. Endoscopy team blinded to randomized groups; significantly lower baseline systolic blood pressure in EGD capnography blinded group	Low risk Patients likely not aware of assigned intervention, although not explicitly stated; endoscopy team members blinded to assignment	Some concerns 1 pt excluded from capnography blinded group vs 8 pts from capnography open group.	Some concerns Measurement is appropriate based on body of literature; data collectors were aware of assignment	Low risk ITT analysis appropriate and all outcomes from trial registration reported.	**Overall Rating:** Fair **Limitations:** Lack of information on how randomization was conducted, more pts excluded from capnography open vs blinded group.
Qadeer 2009[7]	Low risk Randomized by separate Biostatistics group with permuted block randomization; patient and endoscopy team blinded to assignment; independent observer not blinded; baseline characteristics similar except for "participation of trainee in procedure" higher in blinded arm	Low risk Patients not aware of assignment; endoscopy team not aware of assignment, but independent observer was aware; initial sedation similar, but variations depending on patient and reaction.	Low risk 4 excluded from analysis in open arm, 1 excluded in blinded arm due to protocol deviation (difference is that 3 in open arm were already oxygen).	Some concerns Measurement is appropriate based on body of literature; data collectors were aware of assignment	Low risk Analysis appropriate; collected outcomes from trial, plus abnormal ventilation	**Overall Rating:** Good **Limitations:** Data collectors aware of assignment

Quality Assessment of Observational Studies

Author, Year	Selection bias	Bias in classification of intervention	Bias due to departures from intended interventions	Bias due to measurement of outcomes	Bias due to confounding	Bias due to missing data	Bias in the selection of reported results	Overall Rating
Adams 2015[1]	Some concerns Doesn't report number of patients approached for study but explicit inclusion/exclusion criteria are given; all participants received capnography and regular monitoring.	Low All participants received capnography and regular monitoring; clinical staff could not see capnography monitor during procedure	Low All pts received both capnography & regular monitoring. Sedation/procedures reflect usual clinical practice.	Some concerns Observer not blinded to capnographic readings, outcomes were objectively measured	Low No significant confounders	Low No missing data or exclusions	Low Analyses included all participants	**Overall Rating**: Fair **Limitations:** Observers not blinded to intervention status, but outcomes related to respiratory depression were objectively measured, unclear how many ppts were approached for study.
Barnett 2016[2]	Some concerns Does not report # of pts who were approached for study. Differences between groups include age,	Low Intervention groups clearly defined at the start of the intervention.	Some concerns Differences in dosage of sedation used between groups.	High Outcome assessors (patients, nurses) aware of intervention, and it could have influenced outcomes related to patient discomfort, level of sedation, and	High Interventions delivered at different time points, so potential for secular trends to influence results.	Some concerns Authors don't report numbers of patients or nurses who rated each survey, adverse	Low Unlikely to be based on multiple analyses, outcome measurements, or subgroups.	**Overall Rating**: Fair **Limitations:** Data collected at different time periods for EtCO2 vs Pre-EtCO2 arm, there were differences in comorbidities

Author, Year	Selection bias	Bias in classification of intervention	Bias due to departures from intended interventions	Bias due to measurement of outcomes	Bias due to confounding	Bias due to missing data	Bias in the selection of reported results	Overall Rating
	comorbiditie s, gender, and only age and gender controlled for in multi-variable analysis.			usefulness of capnography.		sedation events not reported in table so unclear if any data was missing.		at baseline that were not controlled for and outcome assessors were aware of which intervention arm they were in.
Koniaris 2003[5]	High Follow-up and start probably didn't coincide; no information about participant characteristi cs beyond those with adverse effects	Some concerns Retrospectiv e study, so authors aware of intervention; no capnography group n=4,846 cases, while capnography group n=>600; groups were defined prior to study	High No information about procedures; appears to be a variety of endoscopic procedures; limited information about sedation	High Because this was a retrospective study, outcome assessors were likely aware of intervention status.	High Interventions delivered at different times; limited information on comorbidities	High Outcome data only available on patients with adverse effects, 14/5,446 patients	Some concerns Limited analysis, not likely to be subgroup analysis or multiple measureme nts	**Overall Rating**: Poor **Limitations:** Retrospective study that provides very limited data on included patients or on the procedures or sedation, so can't draw conclusions about adverse events
Vargo 2002[8]	Some concerns Doesn't state how many patients were	Low Interventions defined at start of study; all participants received	Low All pts received both capnography & regular monitoring. Sedation/proce	Some concerns Outcome observers not blinded to capnographic readings but outcomes were	Some concerns Heart disease and mean pack-year smoking history	Low No missing data	Low Unlikely to be based on subgroup analysis or multiple	**Overall Rating:** Fair **Limitations:** Different procedures were included, not sure how

Author, Year	Selection bias	Bias in classification of intervention	Bias due to departures from intended interventions	Bias due to measurement of outcomes	Bias due to confounding	Bias due to missing data	Bias in the selection of reported results	Overall Rating
	approached for study but explicit inclusion/exclusion criteria given. All pts received capnography and regular monitoring.	capnography and regular monitoring; clinical staff could not see capnography monitor during procedure.	dures reflect usual clinical practice.	objectively measured.	significantly associated with development of apnea and disordered respiration		measurements	many patients approached for study, significant comorbidities

PEER REVIEW COMMENT TABLE

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	2	Yes	None
2	3	Yes	None
3	4	Yes	None
4	5	Yes	None
5	6	Yes	None
6	7	Yes	None
7	8	Yes	None
Is there any indication of bias in our synthesis of the evidence?			
8	2	No	None
9	3	No	None
10	4	No	None
11	5	No	None
12	6	No	None
13	7	No	None
14	8	No	None
Are there any published or unpublished studies that we may have overlooked?			
15	2	No	None
16	3	No	None
17	4	No	None
18	5	1. Beitz A, Riphaus A, Meining A, Kronshage T, Geist C, Wagenpfeil S, Weber A, Jung A, Bajbouj M, Pox C, Schneider G, Schmid RM, Wehrmann T, von Delius S: Capnographic monitoring reduces the incidence of arterial oxygen desaturation and hypoxemia during propofol sedation for colonoscopy: a randomized, controlled study (ColoCap Study). Am J Gastroenterol 2012; 107:1205-12	We excluded studies where moderate sedation was induced through propofol because we were only interested in studies of moderate sedation in non-anesthesia settings (at the VHA, propofol and other anesthetic drugs can only be administered by an anesthesiologist, nurse anesthetist or other LIP with training to rescue a patient from general anesthesia according to VHA Directive 1073). We have added a few sentences to the *Methods* > *Searches and Study Selection* section to describe this rationale more clearly.
19	5	2. Langhan ML, Shabanova V, Li FY, Bernstein SL, Shapiro ED: A randomized controlled trial of	We excluded studies of children.

Comment #	Reviewer #	Comment	Author Response
		capnography during sedation in a pediatric emergency setting. Am J Emerg Med 2015; 33:25-30	
20	5	3. Slagelse C, Vilmann P, Hornslet P, Jørgensen HL, Horsted TI: The role of capnography in endoscopy patients undergoing nurse-administered propofol sedation: a randomized study. Scand J Gastroenterol 2013; 48: 1222-30	We excluded studies of propofol- see comment #18 above.
21	6	No	None
22	7	No	None
23	8	No	None
Additional suggestions or comments can be provided below.			
24	2	This is a well written report with a thorough review of a very important and controversial topic. I want to thank the authors for their excellent work on this report.	Thank you.
25	2	I have a few minor comments: 1) Page 3, Line 18 (and elsewhere in the document, such as page 5, line 43): It may not be obvious to some readers how use of capnography could lead to access challenges. It may help for the authors to expand on this concept. For example, do they mean that VA facilities may not have capnography equipment available, and would not be able to do moderate sedation procedures until capnography equipment is obtained? This also raises the question of whether or not capnography (should it become mandator in the VA) would be required for non-VA care providers who administer moderate sedation to Veterans while performing services at the request of the VA (and at VA expense).	Added language indicating that wait times could be affected by added procedural time or need for additional staffing or equipment that could reduce the number of procedures that can be completed each day. While it is an interesting question whether capnography would be required for non-VA care providers providing care at the request of the VA (such as in community care settings), this is more of a compliance question than a research one, and is beyond the scope of this review.
26	2	2) Page 5, line 24: "EGD" is misspelled.	Fixed this.
27	2	3) Page 11, line 12: Is this line meant to be a heading? Consider changing the font (e.g. bold or italics)	Fixed this.

Comment #	Reviewer #	Comment	Author Response
28	2	4) Page 11, Cost Section: It may help the audience if the authors could expand the discussion of costs a bit. Perhaps clarify the fixed and variable costs: a) Fixed costs: Each procedure room that uses moderate sedation (e.g. GI, Cardiology, Radiology, Pulmonary) would need to purchase hardware and software b) Variable costs: Each procedure would need a special cannula for measuring exhaled CO2 and the dehumidifying modules that need to be changed weekly	We revised this section to indicate that authors reported both fixed costs (e.g., costs of procuring and maintaining hardware and software for procedure rooms) as well as variable costs (e.g., costs of single-use capnograph lines and cannulas).
29	2	5) Page 12, line 15: Consider use of a heading font?	Fixed this.
30	2	6) Page 15, line 17: Do you mean "suction"?	Changed to “suction.”
31	2	7) Page 19, line 9: Is "ED" defined previously?	Changed to “emergency department.”
32	2	8) Finally, do the authors think that the discussion of the impact of false alarms could or should be expanded? What is known about false alarms in this or comparable settings? Do false alarms distract the proceduralist from performing their procedure? Could it lead to unintended consequences, such as missed pathology, complications or aborted procedures? Or might it lead to "alarm fatigue" whereby the provider learns to ignore the alarms?	We added additional language to the discussion to elaborate on the idea that false alarms could be potentially distracting to clinicians. In this section, we now cite 3 articles. 2 of these articles provide anecdotal accounts of some of the potential drawbacks of capnography monitoring such as “needless disruption, prolongation, or abandonment of procedures that the sedation was intended to facilitate” (Terp 2013 & Green 2010). The third citation is a book chapter that commented that in 2005 the ASA changed their guidelines to indicate that clinicians should not turn off capnography and pulse oximetry alarms, which suggests that some clinicians find them to be more harmful than helpful.
33	3	I feel that the study was well done, particularly to the extent afforded by the available literature. One strong conclusion is that more study really needs to be performed (optimally in the suggested format within this ESP report) before drawing any confident conclusions for the majority of conscious sedation procedures. Even in those GI procedures and bronchoscopy where there was some element of benefit derived with capnography measurements, it's not convincing that the benefits are clinically relevant outcomes.	None.

Comment #	Reviewer #	Comment	Author Response
34	4	No recommended changes.	None.
35	5	The authors are to be congratulated on a well written manuscript. I have concerns related to process which may have led to an inadequate meta-analysis, thereby resulting in faulty summary conclusions. Specifically, the rapid review methodology appears to have excluded at least three RCTs which may have altered the results of the meta-analysis. 1. Beitz A, Riphaus A, Meining A, Kronshage T, Geist C, Wagenpfeil S, Weber A, Jung A, Bajbouj M, Pox C, Schneider G, Schmid RM, Wehrmann T, von Delius S: Capnographic monitoring reduces the incidence of arterial oxygen desaturation and hypoxemia during propofol sedation for colonoscopy: a randomized, controlled study (ColoCap Study). Am J Gastroenterol 2012; 107:1205-12 2. Langhan ML, Shabanova V, Li FY, Bernstein SL, Shapiro ED: A randomized controlled trial of capnography during sedation in a pediatric emergency setting. Am J Emerg Med 2015; 33:25-30 3. Slagelse C, Vilmann P, Hornslet P, Jørgensen HL, Horsted TI: The role of capnography in endoscopy patients undergoing nurse-administered propofol sedation: a randomized study. Scand J Gastroenterol 2013; 48: 1222-30). Additionally, it appears that the authors utilized a random-effects model; accordingly, a minimum of 5 independent RCTs would be required for meta-analysis (Jackson D, Turner R: Power analysis for random-effects meta-analysis. Res Synth Methods 2017; 8:290–302).	See comments #18, 19, & 20 above. We would exclude these 3 studies as 2 administered propofol and 1 was conducted in children.
36	5	Additional concerns related to a lack of clear definitions of "adverse events" with both intermediate and long term patient follow up to better assure safety. Consider adding "lower risk patients" to the title.	In our eligibility criteria, we specify that adverse events include “morbidity and mortality, unplanned interventions or post-procedure ICU or hospital admission, false alarms and other unintended consequences.”

Comment #	Reviewer #	Comment	Author Response
			While it is true that our findings were limited to studies in lower risk patients (ie, those at ASA level I-III), we did not specifically design our protocol to only look for lower risk patients- so adding this to the title could potentially be misleading. Instead, we have revised the title of the report to be "Capnography for Moderate Sedation in Non-Anesthesia Settings."
37	7	Overall valuable contribution to the field. The removal of general anesthesia from the literature synthesis helps understand the relative impact of capnography. Given the motivation is to help VA understand the value of capngraphy, as argued by Porter et al (NEJM 2010) outcomes should be grounded in clinical meaning.	Thank you.
38	7	line 55-57 "Overall, we have low confidence in these findings due to similar study limitations as were seen in the GI studies, as well as an inconsistent effect of capnography across studies." It is not entirely clear what the overall low confidence applies to.	Revised to say that "we have low confidence in these studies' findings."
39	7	I think the manuscript would benefit from a discussion between the measurement of process outcomes vs clinical outcomes. Process outcomes often times have no clinical meaning in contrast to clinical outcomes - such as MI, mortality, need admission, etc. Transient hypoxemia would be considered process as it is meant to serve as a process that could portend, but not actually lead to poor outcome. These trials/studies would suggest that proceduralists, regardless of the use of capnography, can avoid serious (clinically meaningful) outcomes for patients undergoing moderate sedation.	We agree it's important to distinguish between types of outcomes and that serious adverse events are more clinically meaningful than transient hypoxemia. The third paragraph of the background section discusses the role of hypoxemia measurement as an intermediate (or process) outcome on the pathway between use of capnography and improved clinical outcomes.
40	7	Definitions - would be useful to provide a table with outcome definitions. Severe hypoxemia sounds bad - but the definition lacks context. For example, patients who have OSA regularly desaturate below levels of 85% for significant duration of the night. Treatment with PAP does not reduce adverse	We agree it is important to clarify how authors defined their hypoxemia measurements. Because Brady used a different definition of hypoxemia than the other studies, we decided to define each hypoxemia outcome the first time it's discussed in the text, for each study, rather than provide a table of definitions. The definitions used in each study are also

Comment #	Reviewer #	Comment	Author Response
		events (CVA, MI, other CVD outcomes) , but does improve desaturation events and sleep related quality of life. In the LOTT, severe hypoxemia was defined on exercise oximetry of saturations of LT 80% for more than 1 minute. Levels above that would be considered moderate. In that study - tailored oxygen delivery did not produce benefit among patients who had more greater extent of hypoxemia than that under consideration. It is not clear in the manuscript that the definition of severe hypoxemia varied by study. E.g. the Brady article defined severe as LT 90% while others were LT 85%. Some did not use SpO2 (Vargo, Koniaris. Adams). 37.5% of reported studies did not use SpO2 measurement suggesting that this is not a universally important outcome. Hence, it would benefit the use of this manuscript to put the significance of hypoxemia in context of clinical outcomes.	available in tables 1 and 2, the first time each outcome is mentioned.
41	7	No effect was noted on the capnography on clinical outcomes. Capnography was noted to have less transient hypoxemia and severe hypoxemia for selected procedures. It was unclear if these were singular events or repetitive events.	Definitions of each hypoxemia outcome are now provided in the text (see comment #40). In general, authors reported on the percent of participants who had at least 1 hypoxemia event, although Qadeer 2009 also reported recurrent hypoxemia.
42	7	None of the studies provided sufficient evidence to accurately identify patients who may benefit from capnography.	In one RCT, capnography monitoring was more beneficial at reducing hypoxemia during ERCP versus EUS procedures, and for obese patients versus non-obese patients (see *GI procedures > Differences by subgroup*) Otherwise, yes, studies did not conduct the subgroup analyses that would help in understanding which patients benefit the most from capnography.
43	7	Only in the bronchscopy study was the duration of hypoxemia noted. The text may also benefit from including that bronchoscopy is often performed through the nose, along with O2 nasal canula administration and where the locale for capnography measurement. There was a very high rate of false alarms likely related to the location of	We added language indicating that bronchoscopy can be performed through the nose and that this may have interfered with capnography readings (and caused high rates of false alarms) in the bronchoscopy study.

Comment #	Reviewer #	Comment	Author Response
		the sensors and the effect of the procedure itself (suctioning) on measurement.	
44	7	Given the heterogenity across procedures and the limited number of studies within procedure, seems like the conclusion is too strong. For select procedures, single small studies provide incomplete information about the benefits of capnography and collectively with larger GI studies do not suggest clinical benefit. The message "Our findings are consistent with a 2017 Cochrane review28 which found “a lack of convincing evidence that the addition of capnography to standard monitoring in ED PSA [procedural sedation and anesthesia] reduces the rate of clinically significant adverse events.” line 29-31 of discussion seems to be buried. Given the context of the motivation behind this review - this message seems like it should be in the conclusions.	We believe our conclusion is appropriate but have reversed the order so that the conclusion on clinical outcomes comes first. The conclusion now states: “Overall, the evidence does not support an effect of capnography on clinical outcomes compared to routine monitoring, for any procedure type. However, capnography may improve intermediate outcomes such as risk of hypoxemia and severe hypoxemia during ERCP, EUS, bronchoscopy, and severe hypoxemia for colonoscopy compared to routine monitoring.”
45	7	In the conclusion - there is a mention about wait-times. I think that this deserves some further discussion. VA does ~ 1/2 million procedures that use moderate sedation. The requirement of having capnography's effect on productivity - in the event of inability to have it consistently throughout the country is an important concept.	We added language to indicate the VA conducts a large number of procedures under moderate sedation each year (for ex, 300,000 colonoscopies are performed under VA care every year) and given this, even a small increase in wait times could have a large impact on the number of Veterans who receive these procedures in a timely way. We also note that wait times is an especially important outcome for colonoscopy, given the importance of early screening and detection of colorectal cancer on patient outcomes.
46	8	This is an excellent review of the available evidence for capnography in the setting of moderate sedation and the conclusions drawn are evidence based.	Thank you.
47	8	My understanding is that propofol use during GI procedures aims to achieve moderate to deep sedation, thus capnography studies in this setting may still provide additional insights. As sedation is a continuum, studies that specify moderate sedation will include patients who for periods qualify as deep sedation and those studies that allow for deep sedation will include periods of	See comment #18 for explanation for why we excluded studies of propofol.

Comment #	Reviewer #	Comment	Author Response
		moderate sedation as well. These studies may still help answer the question if there were differences in response to hypoxemia between groups (see Slagelse, et al., The role of capnography in endoscopy patients undergoing nurse administered proporol sedation: a randomized study. Scand J Gastroenterol 2013).	
48	8	Is there any data to suggest how often severe hypoxemia or hypoxemia occurs in routine moderate sedation/MAC care by anesthesiologists with or without capnography as well? This comparison likely would be beyond the scope of this rapid review, but could provide additional context as there may be additional data, more robust studies, or could suggest a clinical impact of hypoxemia.	As the reviewer states, evaluating rates of hypoxemia in moderate sedation administered by anesthesiologists was not within the scope of this review. To provide context, we highlighted the success of capnography in the general anesthesia setting in the first paragraph of the background, where we state "Capnography enables earlier detection of hypoventilation than other signs such as low oxygen levels and has been credited with reducing the overall mortality rate associated with general anesthesia, in which capnography monitoring is currently considered the standard of care." With this statement, we also make it clear why hypoventilation is considered to be an important intermediate outcome. In this sentence, we cited the study: *Koniaris LG, Wilson S, Drugas G, Simmons W. Capnographic monitoring of ventilatory status during moderate (conscious) sedation. Surg Endosc. 2003;17(8):1261-1265.*
49	8	I suspect undiagnosed obstructive sleep apnea is likely one of the main culprits of transient hypoxemia during sedation, did studies report OSA incidence and if CPAP was used which may limit capnography monitoring?	We added a paragraph that describes prevalence of OSA as well as CPAP/BiPAP use under *Hypoxemia outcomes* in both the *GI procedures* section and *Non-GI procedures* section. Overall, sleep apnea was mentioned in 5/8 studies. Of these 5 studies, 2 studies reported that they excluded pts with sleep apnea and 1 did not report prevalence (only that sleep apnea was associated with desaturation). In the remaining 2 studies, sleep apnea prevalence was fairly low (11% to 15%).
50	8	P6 line 31: May be helpful to include definition of severe hypoxemia (<85%)	Added definition.
51	8	P6 line 47: Can an estimate of average cost increase be given here? Perhaps the median cost increase in the studies evaluated?	While we could estimate the average or median cost of adding capnography to procedures, ultimately, we don't think it would be a meaningful number, given the variability in procedures, settings, and types of costs that authors reported. However, we did add language to this section to

Comment #	Reviewer #	Comment	Author Response
			indicate that costs were variable depending on setting and procedure type.
52	8	P7 line 22: Would define severe hypoxemia here. On first reading, not clear if severe hypoxemia was limited to one of the 5 studies.	Added definition of severe hypoxemia and clarified that result was only seen in 1 study.
53	8	P7 line 39: Missing a period at end of sentence.	Fixed this.
54	8	P17 line 15: “Differences by subgroups” may need to be bold and separated from prior paragraph	Fixed this.
55	8	P17 line 18: Did any studies report presence of OSA or CPAP use which would contribute to apneic events?	Yes, this was reported in 5/8 studies- see comment #49 for a description of the changes we made.
56	8	P21 line 17: “continuous suction” rather than section?	Yes, fixed this

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