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SUMMARY WITH CRITICAL APPRAISAL

General Anesthesia and Deep Sedation for Dental Treatments in Children: A Review of Clinical Effectiveness and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Context and Policy Issues

Guidelines from the American Academy of Pediatrics and the American Academy of Pediatric Dentistry described the following five goals for the use of sedation in pediatric patients who are undergoing diagnostic or therapeutic procedures:

1. guard the patient's safety and welfare
2. minimize physical discomfort and pain
3. control anxiety, minimize psychological trauma, and maximize the potential for amnesia
4. modify behavior and/or movement so as to allow the safe completion of the procedure
5. return the patient to a state in which discharge from medical/dental supervision is safe, as determined by recognized criteria.[1]

There are four levels of sedation that are used in clinical practice: minimal sedation, moderate sedation, deep sedation, and general anesthesia (GA). The characteristics of each level are summarized in Table 1.

Table 1: Characteristics Levels of Sedation

Characteristics	Minimal sedation	Moderate sedation	Deep sedation	General anesthesia
Consciousness	Maintained	Maintained	Obtunded	Unconscious
Responsiveness	To either verbal command or tactile stimulation	May require either one of or both verbal command and tactile stimulation	Response to repeated or painful stimuli	Unarousable, even to pain
Airway	Maintained	No intervention required	Intervention may be required	Intervention usually required
Protective reflexes	Intact	Intact	Partial loss	Assume absent
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired
Required monitoring	Basic	Increased	Advanced	Advanced

Source: The Royal College of Dental Surgeons of Ontario, 2012[2]

In Canada, treatment of early childhood caries (ECC) was cited as the most common procedure performed under GA in children (31% of all day surgery for children between 1 and 5 years of age).[3] An analysis of day surgeries that were performed under GA for ECC over a four year period (from 2010 to 2014) reported an overall rate of 12.1 per 1000 children in Canada.[3] However, the proportion of surgeries for ECC was much greater for regions with a higher proportion of Indigenous children (i.e., First Nations, Metis, and Inuit) (84.5 per 1000) compared with regions having a lower proportion of Aboriginal children (10.9 per 1000).[3] The authors estimated that the average financial impact of dental surgeries under GA for children with ECC was

over $21 million per year.[3] Similar findings were reported by the Canadian Institute for Health Information (CIHI) in a two-year analysis (2010 to 2012).[4]

To support the development of policies related to the use of GA and deep sedation in Canadian pediatric patients, this report will review the comparative clinical effectiveness and safety of dental treatment under deep sedation or GA compared with lower levels of sedation (i.e., moderate or minimal sedation). Evidence-based guidelines regarding the use of GA or deep sedation will also be reviewed and appraised to identify the dental treatments where the use of GA or deep sedation is appropriate in pediatric patients and the volume of procedures that can be performed under a single deep sedation or GA.

Research Questions

1. What is the clinical effectiveness of dental treatment under deep sedation or general anesthesia compared with moderate sedation or minimal sedation in children?

2. What are the evidence-based guidelines regarding the appropriate dental treatments that can be performed under general anesthesia or deep sedation in children?

3. What are the evidence-based guidelines regarding the volume of procedures that can be performed under a single general anesthesia or deep sedation in children?

Key Findings

One systematic review investigated the use of general anesthesia (GA) in pediatric patients compared with lower levels of sedation; however, there were no randomized controlled trials (RCTs) that met the inclusion criteria for their review. Similarly, there were no RCTs identified that met the inclusion of CADTH's review. One large prospective cohort study reported that there was no statistically significant difference in the frequency of complications for deep sedation/GA compared with moderate sedation for patients undergoing third-molar extraction. One small prospective study, reported that conscious sedation (CS) was associated with statistically significantly lower oxygen saturation compared with GA and a statistically significantly shorter duration for the procedure. One small retrospective cohort study reported that patients who were treated for early childhood caries (ECC) under GA were statistically significantly more likely to exhibit positive behavior during follow-up dental examinations at six months compared with those who received CS; however, there were no statistically significant differences at 12 or 18 months. Indigenous populations were a subgroup of interest for this review; however, there were no studies identified that specifically addressed this population.

There were no Canadian clinical practice guidelines that addressed the question of what dental treatments are appropriate to be performed under GA or deep sedation. One clinical practice guideline from the United Kingdom recommended the following clinical circumstances as situations where the use of GA may be suitable: severe pulpitis requiring immediate relief; acute soft tissue swelling requiring removal of the infected tooth/teeth; surgical drainage of an acute infected swelling; single or multiple extractions in a young child unsuitable for conscious sedation; symptomatic teeth ≥1

quadrant; moderately traumatic or complex extractions; teeth requiring surgical removal or exposure; biopsy of a hard or soft tissue lesion; debridement and suturing of orofacial wounds; established allergy to local anesthesia; and post-operative hemorrhage requiring packing and suturing. There were no evidenced-based guidelines identified in the literature search that specifically addressed the volume of dental procedures that could be carried out under a single GA.

Methods

Literature Search Methods

Rapid Response reports are organized so that the evidence for each research question is presented separately.

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2006 and February 3, 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 2.

Table 2: Selection Criteria

Population	Children (< 18 years) undergoing dental treatment (e.g., extractions, restorations, endodontic services, crowns) • Subgroups of interest: children aged 0 to 3 years, 4 to 7 years, 8 to 11 years, 12 to 18 years; Indigenous populations
Intervention	• Dental treatment under deep sedation or general anesthesia
Comparator	• Dental treatment under moderate sedation (e.g., parenteral conscious sedation) • Dental treatment under minimal sedation (e.g., oral sedation, nitrous oxide)
Outcomes	**Question 1:** • Clinical benefits (e.g., adequate sedation during the procedure) • Harms (e.g., side effects, complications) **Question 2:** Evidence-based guidelines for appropriate dental treatments performed under general anesthesia and deep sedation **Question 3:** Evidence-based guidelines for the volume of procedures performed under general anesthesia and deep sedation

Study Designs	**Question 1:** • Health technology assessments • Systematic reviews • Meta-analyses • Randomized controlled trials • Non-randomized studies **Questions 2 and 3:** • Evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2006.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR instrument,[5] non-randomized studies were critically appraised using the Downs and Black checklist,[6] and guidelines were assessed with the AGREE II instrument.[7] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 665 citations were identified in the literature search. Following screening of titles and abstracts, 643 citations were excluded and 22 potentially relevant reports from the electronic search were retrieved for full-text review. Thirteen potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 26 publications were excluded for various reasons (9 for question 1 and 17 for question 2), while 9 publications met the inclusion criteria and were included in this report (7 for question 1 and 2 for question 2). Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in appendix 4. These include clinical practice guidelines that address issues other than those identified in research question 2.

Summary of Study Characteristics

Systematic Reviews

Ashley et al conducted a systematic review of RCTs to investigate the comparative efficacy and safety of sedation compared with general anesthesia in children who were undergoing dental treatment. The review was initially published in 2009[8] and was subsequently updated in 2012[9] and 2015.[10] The eligibility criteria for the systematic review are summarized in Table 3.

Table 3: Eligibility Criteria for the Ashley et al (2015) Systematic Review

Criteria	Description
Population	• Children and adolescents up to 18 years of age who require dental treatment (i.e., fillings, removal of the nerve from a tooth, and tooth extraction). ▪ Studies involving children or adolescents undergoing complex surgical procedures (i.e., those involving removal of bone) were excluded.
Intervention	• Sedative agents (any route of administration) provided in any setting by one of the following: anaesthetist, dentist, or other healthcare professional
Comparator	• General anaesthesia (any route of administration) provided in any setting by one of the following: anaesthetist, dentist, other healthcare professional
Outcomes	• Primary outcomes: mortality; completion of treatment; postoperative morbidity. • Secondary outcomes: cost to the participant; procedure cost; patient satisfaction; parental satisfaction; intraoperative morbidity; length of stay; length of procedure; facilities, materials, equipment, and staff required for the procedure.
Study designs	• Randomized controlled trials • Cluster randomized controlled trials ▪ Pseudo-randomized trials were excluded

Non-Randomized Studies

There were four non-randomized studies that met the inclusion for this review.[11-14] A summary of key study characteristics are reported below and additional details are provided in Appendix 2.

Inverso et al, 2016[12] conducted a prospective cohort study to evaluate the rate of complications in adolescent patients under 21 years of age who underwent third molar (i.e., wisdom teeth) extraction under moderate sedation compared with deep sedation/general anesthesia. Data were available for a total of 29,548 patients, including 3,109 who received moderate sedation and 26,439 who received deep sedation. The study participants underwent procedures between January 2001 and December 2010. The extraction procedures were performed by 79 surgeons at 58 different sites in the United States. The specific complications of interest included: vomiting (during induction, maintenance, or recovery), laryngospasm, bronchospasm, respiratory arrest and/or hypoventilation that required intervention, new cardiac dysrhythmia that required intervention, syncope, seizure, neurologic impairment, prolonged emergence from anesthesia, and peripheral vascular injury.

Silay et al, 2013[13] conducted a prospective cohort study to compare conscious sedation (CS) with intravenous midazolam (n = 47) against GA (n = 58) in 105 pediatric patients (2 to 12 years of age) undergoing dental procedures or minor oral surgical procedures. The procedures performed in the study were reported as follows (CS and GA, respectively): tooth extraction (75 and 86); restorative treatment (21 and 105); wisdom teeth extraction (14 and 16); root treatment (0 and 23); and phrenilectomy (8 and 5). The CS treatment group received an average dose of 1.5 mg of midazolam with 32 patients receiving a repeated dose due to the length of the procedure being performed. The pharmacological approach that was used in the GA treatment group was not reported in the publication. The outcomes of interest for the study included oxygen saturation, pulse rate, the duration of the procedure, the behaviour of the patient during the procedure, and the comfort of the physician during the procedure. The study appears to have been conducted exclusively in Turkey and the number of surgeons and clinical sites were not reported.

Fuhrer et al, 2009[14] conducted a retrospective cohort study to evaluate the duration of time that was required for eighty pediatric patients (< 36 months of age) to exhibit positive behaviour after receiving treatment for early childhood caries (ECC) under CS (n = 41) or GA (n = 39). The study participants received treatment between 1999 and 2003 at a single site in the United States and were followed-up at 6 months, 12 months, and 18 months to evaluate their behaviour using the Frankl behavioral scale (e.g., definitely negative, negative, positive, or definitely positive).[15] Patients in the CS group were administered choral hydrate (50 mg/kg to a maximum of 1000 mg), hydroxyzine (1 mg/lb to a maximum of 25 mg), nitrous oxide (50%), and protective stabilization. The pharmacological approach that was used in the GA treatment group was not reported in the publication.

Antunes et al, 2016[11] conducted a prospective follow-up study comparing the efficacy of no sedation (n = 17), moderate sedation with midazolam (n = 16), moderate sedation with midazolam and ketamine (n = 13), or GA (n = 4) for the treatment of ECC. The study reports that the patients enrolled in this prospective study had completed an RCT where they were randomized to receive oral sedation with midazolam, oral sedation with midazolam/ketamine, general anesthesia, or no sedation. However, the protocol for the RCT that was cited by the authors states that it was a three-arm RCT that did not include randomization to general anesthesia as an option.[16] Furthermore, the total randomized sample size of the RCT was reported to be 44 patients;[16] whereas, the study by Antunes reports that 56 patients completed the RCT (50 of whom were subsequently enrolled in the prospective follow-up study). Overall, it is uncertain how the treatments were allocated in the Antunes study. The study was conducted in Brazil and the participants were all less than four years of age at the time the procedure for ECC was completed. All of the participants were considered to be ASA-1.

The outcome of interest was time to co-operative behavior assessed using the Ohio State University Behavioral Rating Scale (OBUBRS). The OSUBRS scale consists of the following: 1 point - behavior without crying and without movements (i.e., quiet behavior); 2 points - behavior with crying and no movements; 3 points - behavior with movements without crying; and 4 points - behavior with crying and movements (i.e., resistance behavior). The OBUBRS was applied at the following five time points for each study: entering the dental office, prophylaxis, examination, fluoride application, and the end of the consultation. The co-operative behavior endpoint required an OBUBRS score of 1 at each of the five evaluation time points (i.e., the sum of OBUBRS scores = 5). The children who were enrolled in the study were followed-up for a mean of 25.3 months (standard deviation [SD] 2.5) and none required additional operative care during the study period.

Clinical Practice Guidelines

There were two clinical practice guidelines identified in the literature search.[17,18] The Royal College of Surgeons (RCS) in the United Kingdom published a guideline for the use of general anesthesia in pediatric dentistry in 2008.[18] The guideline makes recommendations for clinical circumstances that are considered suitable for GA and those that would rarely justify the use of GA. The Association of Paediatric Anaesthetists of Great Britain and Ireland (APAGBI) published guidelines for the management of children referred for dental extractions under GA.[17] As indicated in the title of the document, the scope of the guideline is limited to patients undergoing

tooth extractions and, therefore, it does not address a broad range of procedures where GA could be considered an appropriate approach.

Summary of Critical Appraisal

Systematic Reviews

Both the updated and original systematic reviews by Ashley et al were conducted using rigorous well-reported methodology that included: a protocol specified in advance, a comprehensive literature search, and duplicate study selection.

Non-Randomized Studies

The objective and the methods of the studies included in this review were generally well reported in the publications. None of the studies involved random allocation for the assignment of treatment groups; therefore, the patients underlying condition may have influenced the choice of procedure. In the largest study (Inverso et al, 2016), there were numerous statistically significant differences in the baseline characteristics of the two groups. This limits the ability to draw conclusions regarding the comparative safety and efficacy of the different approaches. The study by Inverso et al (2016) included a large number of patients for both the moderate sedation (N = 29,548). The other three studies were limited to small numbers of patients (range: 50 to 105), with as few as four patients in a single treatment group. The characteristics of the study participants were reported in three studies,[11,12,14] but not in one of the studies.[13]

The studies conducted by Inverso et al (2016)[12] and Antunes et al (2016)[11] included a summary of the pharmacological interventions that were provided for different treatment groups. The analyses reported in Inverso et al (2016)[12] were conducted using an aggregate population of either 'moderate sedation' or 'deep sedation/GA'; however, the patients enrolled in both groups had received a wide variety of different pharmacological agents for the purposes of anesthesia. It is possible that there are differences in the safety profile of different approaches for achieving sedation. Similarly, the analysis was conducted using aggregate measures of adverse events (i.e., complications) which may not reflect the unique safety profile that could be associated with different individual approaches for anesthesia.

The studies by Silay et al (2013)[13] and Fuhrer et al (2009)[14] provided details of the pharmacological agents and the dosage regimens that were used for the moderate sedation and CS groups, respectively. However, the pharmacological approach that was used in the GA treatment groups was not reported in either publication. In the Silay et al (2013)[13] study, it was reported that 32 of the 47 (68.1%) patients enrolled in the CS group received repeated dosing of midazolam; however, there were no sensitivity analysis conducted to investigate if there are potential differences in patients who received only a single administration of midazolam.

It is unclear if the included studies had sufficient statistical power to observe meaningful differences between the treatment groups, particularly for the three studies with small sample sizes.[11,13,14] However, even in the larger study, the event rates were low (i.e., less than 1% in each group) and it is unclear if the study had sufficient statistical power to observe differences between the two groups.[12] All of

studies reported numerous statistical analyses without any adjustments for multiplicity, increasing the risk of type 1 error. The results were generally well presented with appropriate use of confidence intervals and p values. The survival curve that is presented in the Antunes et al (2016)[11] publication lacks any reference to sample sizes and does not provide an indication of where data were censored, making the results uninterpretable.

All of the dental procedures were conducted in an unblinded manner. Given that the facilities, personnel, and equipment that are required for GA differ from those needed for moderate sedation, blinding of patients, caregivers, and clinicians would likely be impractical for the studies that investigate parameters that occurred during the dental procedure. The studies that investigated patient outcomes after the procedure had been completed (i.e., OSUBRS in Antunes et al, 2016[11] and Frankl scores in Fuhrer et al, 2009)[14] could potentially have been conducted using blinded evaluators; however, the evaluators were not blinded to the treatment that the patient had received.

Two of the prospective studies had a large proportion of patients who were withdrawn from the studies and the proportion of patients who were lost to follow-up was disproportionate across the groups. In addition, patient disposition was poorly reported with no reasons for early discontinuation provided and no description or discussion of the patient characteristics for those were lost to follow-up. The potential impact of this missing data on the results of the study is uncertain.

Two of the studies were conducted outside of North American (i.e., Brazil[11] and Turkey[13]), which may limit the generalizability of the study to the Canadian setting. The other two studies were conducted exclusively in the United States, one of which only enrolled patients who had received treatment with the assistance of Medicaid. The authors noted that this population is considered to be at a greater risk of developing ECC.

Clinical Practice Guidelines

The guidelines were published in 2008 and 2011 for RCS and APAGBI, respectively, and it is possible that clinical practice has evolved since that time.[17,18] The APAGBI guideline states that an update was planned for 2016;[17] therefore, updated recommendations may be forth coming, but were not available at the time of this review. A detailed critical appraisal of the two included guidelines is provided in Table 9; some of the key strengths and limitations for each guideline are noted below.

The primarily limitation of the guideline was the absence of a description of the methods that used by the guideline development group to formulate the recommendations (i.e., there was no information provided regarding the deliberative process). The guideline included clear statements regarding the objective, scope, questions, target patient population, and intended users of the guidelines. The guideline reported the electronic databases that were included in the literature search and the time periods; however, the key search terms were not reported and the full search strategy was not reported (although it indicates the strategy is available upon request). The criteria that were used to select evidence for the guideline were described in the publication. The strength and limitations of the evidence were assessed using SIGN methodology and the overall quality of evidence was stated in

the report. The evidence that was used to inform each of the recommendations was cited in the report. The methods section states that the guideline was prepared with the assistance of a patient representative; however, there were no statements regarding which preferences and views were sought from the patient representative not how the information was used to inform the guideline development process and/or formation of the recommendations. The details of the external review process were well reported in the document and a summary of the information gathered was provided. Overall, the guideline from APAGBI was conducted using relatively rigorous methodology and was generally well reported.

The RCS guideline has numerous limitations with the reporting of the methodology used by the guideline development group. The electronic database that was used to search for literature and the key search terms were reported in the guideline; however, there were no details provided regarding any of the time periods that were covered in the literature search and the full search strategy was not provided. There was no eligibility criteria reported for selecting evidence that would be considered in formulating the guidelines. There are no statements in the guidelines regarding a process to capture the views and preferences of patients and/or caregivers. The methods that were used to formulate the recommendations were not reported in the guideline document. There were no supporting data included in the guideline document regarding the benefits and harms of GA compared with alternative approaches and there was no explicit links between the recommendations and the evidence on which they are based (particularly for recommendations of interest for this review). The guideline listed the external organizations that reviewed the document and recommendations; however, there were no details reported regarding the outcome of the external review process and no statements regarding how the feedback was considered in the guideline development process.

Summary of Findings

What is the clinical effectiveness of dental treatment under deep sedation or general anesthesia in children?

Systematic Reviews

There were no studies that met the inclusion criteria for either the original or updated systematic reviews conducted by Ashley et al.[8-10]

Non-Randomized Studies

In the study by Inverso et al, baseline characteristics were reported for age, sex, ASA classification, and pre-operative anxiety. The average age of study participants was 17.3 years, with the mean age being slightly greater in the moderate sedation group compared with the GA group (17.5 [SD 1.7] versus 17.3 [SD 1.7] years; *P* <0.001). There was greater proportion of males than females in both the moderate sedation (54.9%) and GA groups 53.8% (*P* = 0.001). The majority of participants in both groups were classified as being ASA-I (87.4% with moderate sedation and 89.4% with GA). The proportion of patients who were ASA-II was 12.2% in the moderate sedation group and 10.4% in the GA group. Less than 1% of patients were classified as ASA-III, ASA-IV, or ASA-V. The proportion of patients in each category of preoperative anxiety score were as follows (moderate sedation and GA, respectively): not anxious (16.2% and 14.6%), somewhat anxious (50.2% and 45.6%), moderately anxious

(22.3% and 24.8%), extremely anxious (6.4% and 9.0%); or panic stricken (0.9% and 1.1%)

Inverso et al reported that adolescent patients who received moderate sedation during the procedure were statistically significantly more likely to have not experienced an adverse complication from anesthesia than those who underwent deep sedation/GA when analyzed using a chi-squared test (99.5% versus 99.2%, respectively; P = 0.032). However, when the analysis was conducted using a multivariable logistic regression approach, the authors reported that there was no statistically significant difference for deep sedation/GA compared with moderate sedation (adjusted odds ratio: 1.63 [95% CI, 0.95 to 2.81]). Table 2 provides a summary of the different categories of adverse events experienced by the patients in each treatment group. There were no seizures or events categorized as new neurologic impairments.

There were no baseline characteristics reported for the study by Silay et al. The authors reported that there were no complications experienced by patients in either the CS or GA treatment groups. The CS treatment group demonstrated statistically significantly lower oxygen saturation compared with the GA group (98.4% versus 99.0%; *P* < 0.001) and a statistically significantly shorter median duration for the procedure (30 minutes versus 60 minutes; *P* < 0.001). The authors reported that the physicians who participated in the trial were able to practice more comfortably for longer periods of time in cases using GA; however, there were no methods or statistics reported regarding how this was evaluated in the study.

In the study by Fuhrer et al, baseline characteristics were reported for age, sex, race, and co-morbidities. The mean age of participants was similar in both groups (2.43 and 2.48 years in the GA and CS groups, respectively). The proportion of males was greater in the GA group compared with the CS group (56% versus 49%; *P* = 0.50). The majority of participants in both the GA and CS groups were African American (67% and 78%, respectively), with Caucasian patients representing the remaining patients in the study (33% and 20%, respectively), with the exception of one Asian patient in the CS group. With respect to co-morbidities, there was a greater proportion of patients with asthma (28% versus 17%; *P* = 0.23) and sensory disabilities (10% versus 0%) in the GA compared with CS group. The proportion of patients with sickle cell anemia was similar in the two groups (5% versus 7% with GA and CS, respectively). The Frankl score prior to the administration of treatment was similar in the GA and CS groups (1.6 and 1.5, respectively; *P* = 0.62).

Fuhrer et al reported that the patients who were treated under GA were statistically significantly more likely to exhibit positive behavior at six months compared with those who received CS (72% versus 40%; odds ratio [OR] 3.9 [95% confidence interval [CI], 1.5 to 10.2]; *P* < 0.01). There was no statistically significant difference between the groups at the 12-month and 18-month follow-up evaluations (GA versus CS): 21 (72%) versus 18 (58%); OR 1.9 (95% CI, 0.6 to 5.6); *P* = 0.25 at 12 months and 18 (82%) versus 16 (67%); OR 2.3 (95% CI, 0.6 to 8.9); *P* = 0.25 at 18 months. There was a statistically significant difference in the number of teeth treated for those receiving GA (mean 11.0 [SD 2.4]) compared with CS (9.0 [SD 3.1]) (*P* = 0.002).

In the study by Antunes et al, baseline characteristics were reported for age, sex, dental exam length, decayed/missing/filled teeth, and baseline OSUBRS. The average age of participants was 27.5 months, ranging from a low of 25.4 (SD 5.7) months in midazolam group to 29.3 (SD 9.7) months in the GA group. The proportion of male patients was 58.8% in the no sedative group, 68.8% in the midazolam group, 53.8% in the midazolam/ketamine group, and 25% in the GA group. The mean number of decayed, missing, and filled teeth was considerable greater in the GA group (16.3; SD 6.8) compared with the other treatment groups (range: 5.6 [SD 3.6] to 6.8 [5.2]). Mean OSUBRS scores were lower in the GA group (9.5 [4.1]) compared with the no sedative group (12.5 [SD 5.3]), midazolam group (10.6 [SD 1.7]), and midazolam/ketamine group (11.3 [SD 2.5]).Dental exam lengths were similar across the groups, ranging from 10.6 (SD 1.7) minutes in midazolam group to 12.9 (SD 4.0) minutes in the no sedative group.

There were no analyses comparing either of the moderate sedation groups against the GA group (i.e., the comparison of interest for this review); however, comparisons were presented for the active treatments against the no sedation group. The authors reported that patients who received midazolam or midazolam and ketamine were statistically significantly more likely to demonstrate quiet behavior compared with those who had received no sedation (OR 2.9 [95% CI, 1.2 to 6.9], P = 0.017 and 4.3 [95% CI, 1.6 to 11.4], P = 0.004). There was no significant difference between the general anesthesia group and the no sedation group (1.8 [95% CI, 0.4 to 7.0], P = 0.427).

Table 4: Studies Comparing Moderate Sedation with Deep Sedation/General Anesthesia

Complication	Overall (n = 29,548)	Moderate Sedation (n = 3,109)	Deep Sedation/General Anesthesia (n = 26,439)	*P* Value
None	29,309 (99.2)	3,094 (99.5)	26,215 (99.2)	.032
Vomiting without aspiration				
Induction/maintenance	21 (<0.1)	1 (<0.1)	20 (0.1)	.39
Recovery	56 (0.2)	7 (0.2)	49 (0.2)	.63
Laryngospasm	29 (<0.1)	0 (0)	29 (0.1)	.07
Bronchospasm	1 (<0.1)	0 (0)	1 (<0.1)	.73
Respiratory arrest or hypoventilation requiring intervention	9 (<0.1)	0 (0)	9 (<0.1)	.30
New cardiac dysrhythmia intervention	7 (<0.1)	2 (0.1)	5 (<0.1)	.12
Syncope	32 (0.1)	1 (<0.1)	31 (0.1)	.17
Seizure	0 (0)	0 (0)	0 (0)	NA
New neurologic impairment	0 (0)	0 (0)	0 (0)	NA
Prolonged emergence from anesthesia	42 (0.2)	4 (0.1)	38 (0.1)	.83
Peripheral vascular injury	38 (0.1)	0 (0)	38 (0.1)	.034
Other	15 (<0.1)	0 (0)	15 (0.1)	.18
Total	250 (0.8)	15 (0.5)	235 (0.9)	NA

Reprinted from the Journal of Oral and Maxillofacial Surgery, 74(3), Inverso G, Dodson TB, Gonzalez ML, Chuang S-K, Complications of moderate sedation versus deep sedation/general anesthesia for adolescent patients undergoing third molar extraction, 474-479, 2016, with permission from Elsevier.[12]

Table 5: Studies Comparing General Anesthesia with Conscious Sedation

Study	Endpoint	Sedation Level		Comparison GA versus CS
		GA	CS	
Silay et al, 2013[13]	Total N	58	47	NA
	Oxygen saturation (%)	99.0 (0.30)	98.4 (1.02)	*P* < 0.001
	Duration of treatment (min)	60 (15)	30 (10)	*P* < 0.001
	Pulse rate	110 (18)	115 (10)	*P* = 0.344
Fuhrer et al, 2009[14]	Total N	39	41	NA
	Positive at 6 months, n (%)	26 (72%)	16 (40%)	OR: 3.9 (95% CI, 1.5, 10.2); *P* < 0.01
	Positive at 12 months, n (%)	21 (72%)	18 (58%)	OR: 1.9 (95% CI, 0.6 to 5.6); *P* = 0.25
	Positive at 18 months, n (%)	18 (82%)	16 (67%)	OR: 2.3 (95% CI, 0.6 to 8.9); *P* = 0.25
	Number of teeth, mean (SD)	11.0 (2.4)	9.0 (3.1)	*P* = 0.002

CI = confidence interval; CS = conscious sedation; GA = general anesthesia; n = number of patients with events; NA = not applicable; OR = odds ratio; SD = standard deviation

What are the evidence-based guidelines regarding the appropriate dental treatments that can be performed under general anesthesia or deep sedation in children?

The guideline from the RCS (2008) provides recommendations for clinical circumstances that are considered suitable for GA and those that would rarely justify the use of GA (summarized in Table 6).[18] The guideline document notes that severe pulpitis and acute infection are the most common pediatric dental conditions that are treated under GA.[18] In the guidelines from the APAGBI (2011), the sole recommendation that is relevant to the research question for this review is one which states that dental extractions should only be performed under GA when it is considered to be the most clinically appropriate method of management.

Table 6: Guidelines for appropriate treatments performed under GA and deep sedation

Organization	Recommendation
Association of Paediatric Anaesthetists of Great Britain and Ireland[17]	Dental extractions should only be performed under general anaesthesia when this is considered to be the most clinically appropriate method of management. (MANDATORY) Evidence Level: 4
UK National Clinical Guidelines in Paediatric Dentistry[18]	Circumstances and conditions suitable for GA: • Severe pulpitis requiring immediate relief. • Acute soft tissue swelling requiring removal of the infected tooth/teeth. • Surgical drainage of an acute infected swelling. • Single or multiple extractions in a young child unsuitable for conscious sedation. • Symptomatic teeth in more than one quadrant. • Moderately traumatic or complex extractions e.g. ankylosed or infra-occluded primary molars, extraction of broken-down permanent molars. • Teeth requiring surgical removal or exposure. • Biopsy of a hard or soft tissue lesion. • Debridement and suturing of orofacial wounds. • Established allergy to local anaesthesia. • Post-operative haemorrhage requiring packing and suturing. • Examination under GA, including radiographs, for a special needs child where clinical evidence exists that there is a dental problem which warrants treatment under GA. Evidence level: Not reported

Organization	Recommendation
UK National Clinical Guidelines in Paediatric Dentistry[18]	Circumstances and conditions which rarely justify GA: • Carious, asymptomatic teeth with no clinical or radiographic signs of sepsis. • Orthodontic extraction of sound permanent premolar teeth in a healthy child. • Patient/carer preference, except where other techniques have already been tried. Extenuating circumstances that override the above limitations are: • Physical, emotional, learning impairment or a combination of two or more of these. • Children who have attempted treatment using local anesthetic alone or local anesthetic combined with conscious sedation and been unable to co-operate. • Medical problems which are better controlled with the use of GA. Evidence level: Not reported

GA = general anesthesia; NR = not reported; UK = United Kingdom

What are the evidence-based guidelines regarding the volume of procedures that can be performed under a single general anesthesia or deep sedation in children?

There were no evidenced-based guidelines identified that addressed the question of what volume of dental procedures could be carried out under a single GA. The guideline from the RCS in the UK recommends comprehensive planning for the procedure should with the aim of ensuring that all of the required treatment required is completed under a single GA. The guideline also notes that repeat GA is undesirable in terms of morbidity, risk of mortality, potential behavioral or emotional effects on the child, and cost.

Limitations

Research Question 1

The CADTH literature review identified only a single systematic review investigating the use of GA in pediatric patients compared with lower levels of sedation.[8-10] Despite the rigorous methodology used by the authors of the review, they identified no RCTs that met the inclusion criteria for their review. Similarly, there were no RCTs identified that met the inclusion of CADTH's review. A 2009 expert commentary on the findings of the review by Ashley et al (2008) noted that the absence of RCT evidence comparing GA with lower levels of sedation is not surprising and that such trials may be impracticable due to the needs for individualized patient care.[19]

There were four non-randomized studies which met the inclusion criteria for CADTH's review (three prospective cohort studies and one retrospective cohort study).[11-14] In the absence of random allocation for the assignment of treatment groups in the cohort studies, it is uncertain if the patients underlying condition influenced the choice of procedure. This selection bias is supported by the fact that there were statistically significant differences in the baseline characteristics of the two groups in the largest study (Inverso et al, 2016); although, it is unclear if the differences are clinically relevant. In addition, three of the studies involved small sample sizes and is unclear if the studies were adequately powered to detect meaningful differences between the groups. The subgroups of interest for this review were ages 0 to 3 years, 4 to 7 years, 8 to 11 years, and 12 to 18 years and indigenous populations. There were insufficient

data in the included studies to comment on the comparative efficacy and safety of GA/deep sedation versus lower levels of sedation in these patient populations. Generalizability may be limited for the two of the studies which were conducted outside of North American.[11,13]

Research Question 2

The CADTH literature search found no Canadian clinical practice guidelines that addressed the question of what dental treatments are appropriate to be performed under GA or deep sedation. The two guidelines identified in the literature search were from the United Kingdom and it is unclear if clinical practice and coverage are similar in Canada. In addition, the guidelines were published in 2008 (RCS) and 2011 (APAGBI) and it is possible that clinical practice has evolved since that time. Only the RCS guideline provided an extensive list of treatments where GA could be considered appropriate; however, the evidence used to support this recommendation was not reported in the guideline document.

Research Question 3

There were no evidenced-based guidelines identified in the literature search that specifically addressed the question of what volume of dental procedures could be carried out under a single GA.

Conclusions and Implications for Decision or Policy Making

One large prospective cohort study reported that there was no statistically significant difference in the frequency of complications for deep sedation/GA compared with moderate sedation for patients undergoing third-molar extraction (adjusted odds ratio: 1.63 [95% CI, 0.95 to 2.81]). One small prospective study conducted in Turkey, demonstrated that CS was associated with statistically significantly lower oxygen saturation compared with GA (98.4% versus 99.0%; $P < 0.001$) and a statistically significantly shorter duration for the procedure (30 minutes versus 60 minutes; $P < 0.001$). One small retrospective cohort study reported that patients who were treated for ECC under GA were statistically significantly more likely to exhibit positive behavior during follow-up dental examinations at six months compared with those who received CS (OR 3.9 [95% CI, 1.5 to 10.2]); however, there were no statistically significant differences at 12 or 18 months. Indigenous populations were a subgroup of interest for this review; however, there were no studies identified that specifically addressed this population.

One clinical practice guideline from the United Kingdom recommended the following clinical circumstances as situations where the use of GA may be suitable: severe pulpitis requiring immediate relief; acute soft tissue swelling requiring removal of the infected tooth/teeth; surgical drainage of an acute infected swelling; single or multiple extractions in a young child unsuitable for conscious sedation; symptomatic teeth ≥1 quadrant; moderately traumatic or complex extractions; teeth requiring surgical removal or exposure; biopsy of a hard or soft tissue lesion; debridement and suturing of orofacial wounds; established allergy to local anesthesia; and post-operative hemorrhage requiring packing and suturing. There were no evidenced-based guidelines identified in the literature search that specifically addressed the volume of dental procedures that could be carried out under a single deep sedation or GA.

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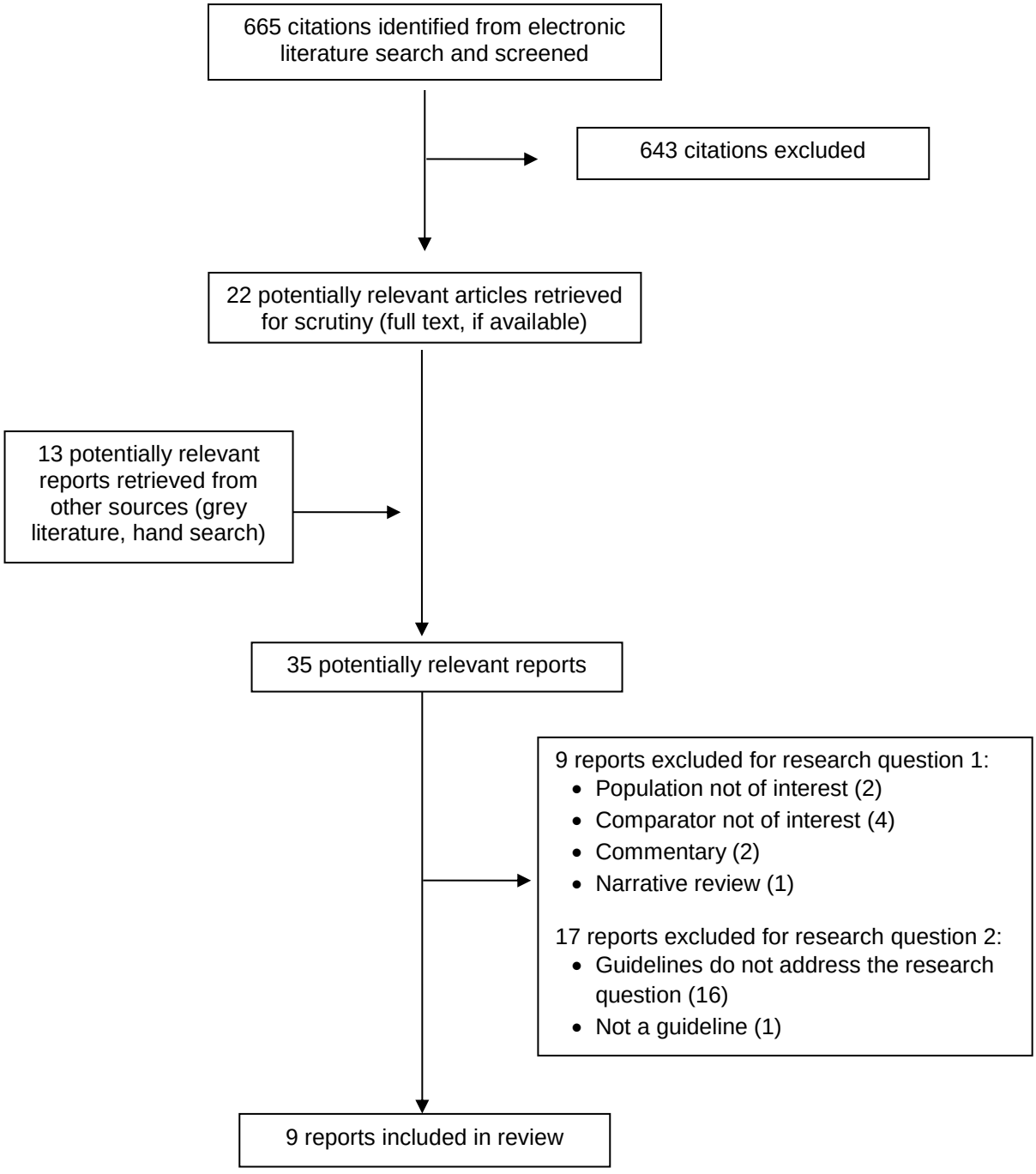
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Author	Design	Population	Interventions	Outcomes
Antunes et al, 2016[11]	Prospective cohort Clinicians: 4 Sites: NR Location: Brazil	• <4 years • Underwent ECC treatment • ASA‑1 • N = 50	• No sedative (n = 17) • Moderate sedation with midazolam (n = 16) • Moderate sedation with midazolam and ketamine (n = 13) • GA (n = 4)	• Ohio State University Behavioral Rating Scale • To time to co-operative behavior (sum of OSUBRS scores = 5)
Inverso et al, 2016[12]	Prospective cohort • Clinicians: 79 • Sites: 58 • Location: US	• <21 years • Undergoing third molar extraction • ASA-I (89.2%) • ASA-II (10.6%) • ASA-III (0.2%) • ASA-IV (<0.1%) • ASA-V (<0.1%) • N = 29,548	• Moderate sedation (n = 3,109) • Deep sedation/GA (n = 26,439)	• Vomiting (with or without aspiration): ▪ during induction and/or maintenance ▪ during recovery • Laryngospasm • Bronchospasm • Respiratory arrest and/or hypoventilation requiring intervention • New cardiac dysrhythmia requiring intervention • Syncope • Seizure • Neurologic impairment • Prolonged emergence from anesthesia • Peripheral vascular injury
Silay et al, 2013[13]	Prospective cohort • Clinicians: NR • Sites: NR • Location: Turkey	• 2 to 12 years • Dental procedures or minor oral surgeries • ASA‑1 • N = 105	• Conscious sedation with IV midazolam (n = 47) • GA (n = 58)	• Initial and repeated doses of anesthetic and sedative agents administered • Oxygen saturation • Pulse rate • Procedures performed • Duration of the procedures • Patients' behaviour patterns • Procedural comfort for the physicians.
Fuhrer et al, 2009[14]	Retrospective cohort • Clinicians: 3 • Sites: 1 • Location: US	• <36 months • Undergoing ECC treatment • N = 80	• Conscious sedation with choral hydrate, hydroxyzine, nitrous oxide, and protective stabilization (n = 39). • GA (n = 41)	• Frankl behavioral scale • Number of teeth involved in procedure

ASA = American Society of Anesthesiologists; ECC = early childhood caries; GA = general anesthesia; IV = intravenous; n = number of patients in the treatment group; N = total number of patients; NR = not reported; OSUBRS = Ohio State University Behavioral Rating Scale; US = United States

Table 7: Characteristics of Included Guidelines

Objectives		Methodology			
Intended users/ Target population	**Intervention and Practice Considered**	**Evidence collection**	**Evidence Quality and Strength**	**Recommendations development**	**Guideline Validation**
Association of Paediatric Anaesthetists of Great Britain and Ireland[17]					
• Intended users: dentists, anesthetists, registered nurses, dental nurses and operating department assistants / practitioners, parents/care givers • Targeted population: children and young people who are referred for dental extractions under GA	• General anesthesia for dental procedures	• Search of electronic databases • Manual searches of guidelines • Studies: meta-analyses, systemic reviews, RCTs, clinical trials, cohort studies, case series • Population: aged 0 to 18 years • Intervention: general anesthesia	• SIGN methodology	• Not reported	• Stakeholder consultation
UK National Clinical Guidelines in Paediatric Dentistry[18]					
• Intended users: not reported • Targeted population: Pediatric dental patients requiring tooth extraction	• General anesthesia for dental procedures	• Search of one electronic database	• Not reported	• Not reported	• Stakeholder consultation

GA = general anesthesia; RCT = randomized controlled trials; SIGN = Scottish Intercollegiate Guidelines Network

Appendix 3: Critical Appraisal of Included Publications

Table 8: Strengths and Limitations of Systematic Reviews using AMSTAR5

Strengths	Limitations
Ashley et al, 2015[8-10]	
• The systematic review was conducted using a protocol that was developed in advance, including the research questions and eligibility criteria. • The literature search was comprehensive and conducted using multiple databases, without language restrictions, and was supplemented with hand searching. A grey literature search was also undertaken. • The complete search strategies were included as appendices in the published report. • Study selection and data extraction were performed in duplicated with a consensus procedure for disagreements. • There were no included studies; however, the detailed study selection results were documented in the report. • A list of excluded studies with reasons for exclusion was included as an appendix in the published report. • There were no included studies; however, the authors reported that methods for critically appraising any included studies were established in advance (i.e., Cochrane risk of bias criteria). • Conflict of interest declarations were provided for each of the authors who contributed to the review (none were declared). • The source of funding for the review was provided in the published report.	• No important limitations were noted.

Table 9: Strengths and Limitations of Guidelines using AGREE II7

Strengths	Limitations
Association of Paediatric Anaesthetists of Great Britain and Ireland[17]	
• The publication includes clear statements regarding the objective and scope of the guidelines. • The health questions addressed by the guideline are clearly reported in the document (section 7). • The target users of the guideline is clearly reported (i.e., dentists, anesthetists, registered nurses, dental nurses and operating department assistants / practitioners, parents/care givers). • The target population of the recommendations is adequately described (i.e., children and young people who are referred for dental extractions under GA). • The names, expertise, and affiliations of each member of the guideline development group were included in the publication document. • The methods section states that the guideline was prepared with the assistance of a patient representative. • The electronic databases that were included in the literature search were reported (e.g., Medline, Embase, CINAHL and **PubMed) and the time periods (i.e., initial search from 1955 to 2010; updated search in 2011).**	• Barriers to implementation and health economics were explicitly excluded from the remit of these guidelines. • There were no statements regarding which preferences and views were sought from the patient representative not how the information was used to inform the guideline development process and/or formation of the recommendations. • The guideline did not report the key terms that were used in the literature search. The guideline did not include a copy of the full search strategy; however, it indicates the strategy is available upon request) • The methods used to formulate the recommendations were poorly reported.

Strengths	Limitations
• The criteria that were used to select evidence for the guideline were described in the publication (i.e., meta-analyses, systematic reviews, RCTs, clinical trials, cohort studies, case series and studies in pediatric patients [0 to 18 years of age]). • The strength and limitations of the evidence were assessed using SIGN methodology and the details were reported in the appendix of the guideline). • The methods and details of the external review process were well reported in the document. A description of those who provided feedback (11 organizations are named) was reported in the appendix and a summary of the information gathered was reported. • The evidence used to inform recommendations is clearly reported in the guideline (briefly in the main document and in detail within the appendices). • The recommendations in the guideline are easy to identify (i.e., summarized in a box). • The guideline indicates that it will be updated in five years. • Details regarding the funding for the development and publication of the guideline were reported in the document. There is a statement indicating that the guideline development group was editorially independent from the funding source. • The publication included competing interest declarations for the authors of the guideline (i.e., none).	
UK National Clinical Guidelines in Paediatric Dentistry[18]	
• The names and expertise of the authors are reported in the guideline document. • The electronic database that was used to search for literature was stated in the guideline (i.e., Entrez PubMed portal to the National Library of Medicine) and key search terms were reported (i.e., general anesthesia, dentistry, teeth, children, pediatric, rehabilitation, and morbidity). • Comparisons made in the guideline are clear (i.e., GA versus lower levels of sedation). • Recommendations appear to reflect considerations of both the benefits and harms of GA (although specific references to data were not provided). In particular, the recommendation related to the use of repeated GA addresses the potential harms associated with this approach. • The guideline listed the external organizations that reviewed the document and recommendations (i.e., Paediatric Dentistry, the Consultants in Paediatric Dentistry Group, and the Specialists in Paediatric Dentistry Group) • The recommendation concerning circumstances and conditions which would rarely justify the use GA includes a description of the patients for whom the recommendation would not apply.	• The guideline was published in 2008 and it is possible that clinical practice has evolved since that time. • The publication lacks clear statements regarding the objective and scope of the guidelines. • The patient population (i.e., pediatric) and intervention (i.e., GA) are clear; however, it is not stated if the intended audience are those who would perform the procedures under GA, those who refer a patient for treatment under GA, or both. • There were no details regarding the institutional affiliations of the authors. • There was no description of the each author's role in the guideline development process. • There are no statements in the guidelines regarding a process to capture the views and preferences of patients and/or caregivers. • There were no details provided regarding any of the time periods that were covered in the literature search. A full search strategy was not included in the guideline document. • There was no eligibility criteria reported for selecting evidence that would be considered in formulating the guidelines (i.e., there were no PICOS statements reported in the document). • There is no description or discussion of the strengths and limitations of the evidence that was considered in formulating

Strengths	Limitations
• The key recommendations of the guideline (from the perspective of this review) were easy to identify within the document (i.e., distinct subheadings with bulleted lists).	the recommendations. • The methods that were used to formulate the recommendations were not reported in the guideline document. • There were no supporting data included in the guideline document regarding the benefits and harms of GA compared with alternative approaches. • The guideline does not include explicit links between the recommendations and the evidence on which they are based. References are occasionally provided within recommendation statements; however, this is inconsistent across the guideline. • There were no details reported regarding the outcome of the external review process and no statements regarding how the feedback was considered in the guideline development process. • The publication does not include a statement regarding if/how the guideline will be updated. • The guideline does not contain any information regarding the potential facilitators and barriers that could influence implementation of the recommendations. • The guideline does not provide advice and/or tools regarding how the recommendations can be applied in clinical practice. • The guideline does not describe the potential resource implications of applying the recommendations. • There were no details provided regarding the funding for the development and publication of the guideline. • There were no declarations of competing interests details provided for any of the authors contributing to the guideline.

Table 10: Strengths and Limitations of Non-Randomized Studies using Downs and Black6

Strengths	Limitations
Inverso et al, 2016[12]	
• The objective of the study is clearly described in the publication. • The main outcomes that were measured in the study were clearly described in the methods section of the publication. • The analysis included a large number of patients for both the moderate sedation (n = 3,109) and deep sedation/GA treatment groups (n = 26,439). • The characteristics of the study participants in both groups were well reported in the publication and differences were appropriately noted by the authors. • The study was conducted in patients who were receiving treatment for the same condition (i.e., wisdom tooth removal). • Although the study did not include any Canadian sites, it was conducted exclusively in the United States; therefore, the findings are likely generalizability to the Canadian setting. • The pharmacological interventions that were provided for both the moderate sedation and deep sedation/GA groups were reported in the publication. • The main findings of the study are clearly described in the	• The primary analysis was conducted using aggregate measures of adverse events (i.e., complications) which may not reflect the unique safety profile that could be associated with different individual approaches for anesthesia. • Numerous statistical analyses were conducted without any adjustments for multiplicity, increasing the risk of type 1 error. • The analyses were conducted using an aggregate population of either 'moderate sedation' or 'deep sedation/GA'; however, the patients enrolled in both groups had received a wide variety of different pharmacological agents for the purposes of anesthesia. It is possible that there are differences in the safety profile of different approaches for achieving sedation. • It is possible that the between group comparisons are confounded by the differences in patient characteristics between the two groups. These may include documented differences or by other undocumented confounding factors. • Event rates were low and it is unclear if the study had sufficient statistical power to observe meaningful differences between the two groups.

Strengths	Limitations
results; however, multiple statistical approaches were used for the same endpoint with differing results. • The estimates of effect for the main outcomes included confidence intervals. • The actual probability values were reported in the results section. • The list of adverse events included in the study was pre-specified and appears to be comprehensive. • There were numerous statistically significant differences in the baseline characteristics of the two groups. In addition, patients were not randomly allocated to the interventions that they received; therefore, the patients underlying condition may have influenced the choice of procedure.	
Silay et al, 2013[13]	
• The objective of the study is clearly described in the publication. • The main outcomes that were measured in the study were clearly described in the methods section of the publication. • The pharmacological agent and the dosage regimen that was used for the moderate sedation group (IV midazolam) were well reported. The number of patients who received repeat dosing was reported. • The same pharmacological agent was used for the moderate sedation group (IV midazolam). • The main findings of the study are clearly described in the results. • The estimates of effect for the main outcomes included a measure of statistical dispersion. • The actual probability values were reported in the results section of the publication, with the exception of those with a value less than 0.001. • Given that the facilities, personnel, and equipment that are required for GA differ from those needed for moderate sedation, blinding would likely be impractical for the comparison being evaluated in this study. • Patients were not randomly allocated to the interventions that they received; therefore, the patients underlying condition may have influenced the choice of procedure.	• The sample sizes were small in both the GA (n = 58) and CS treatment groups (n = 47). • There were no baseline characteristics presented in the report; therefore, it is unclear if the groups should be considered comparable. • 32 of the 47 patients enrolled in the CS group received repeated dosing of midazolam; however, there is no sensitivity analysis conducted to investigate if there are potential differences in patients who received only a single administration of midazolam. • The pharmacological approach that was used in the GA treatment group was not reported in the publication. • It is unclear if the authors collected data on all adverse potential adverse events as the description in the results section simply indicates that “No complications were encountered in the patients under GA or CS.” • Numerous statistical analyses were conducted without any adjustments for multiplicity, increasing the risk of type 1 error. • Although not explicitly stated in the publication, the study appears to have been conducted exclusively in Turkey, which may limit the generalizability of the study to the Canadian setting. • It is unclear if the study had sufficient statistical power to observe meaningful differences between the two groups.
Antunes et al, 2016[11]	
• The objective of the study is clearly described in the publication. • The main outcomes that were measured in the study were clearly described in the methods section of the publication. • The baseline characteristics of the study participants were reported in the publication. • The pharmacological agents and the dosage regimens were reported for all three active treatment groups were well reported. • The estimates of effect for the main outcomes included confidence intervals. • The actual probability values were reported in the results section of the publication.	• The sample sizes were small and the number of participants was imbalanced across the groups (range: 4 with GA to 17 with no sedation). • A large proportion of patients were withdrawn from the study (overall, 22/50 [44%]) and the proportion of patients who were lost to follow-up prior to the sixth evaluation was disproportionate across the groups (i.e., 100% in the GA group, 70% in the midazolam/ketamine group; 29% in the no sedation group; and 25% in the midazolam group). • Reasons for early discontinuation were not reported. • Characteristics of those lost to follow-up were not reported. • The publication reported that the study evaluator (i.e., the person administering the OSUBRS assessment) was

Strengths	Limitations
• The study reports that the patients enrolled in this prospective study had completed an RCT where they were randomized to receive oral sedation with midazolam, oral sedation with midazolam/ketamine, general anesthesia, or no sedation. However, the protocol for the RCT that was cited by the authors states that it was a three-arm RCT that did not include randomization to general anesthesia as an option.[16] • The total randomized sample size of the RCT was reported to be 44 patients;[16] whereas, the prospective study reports that 56 patients completed the RCT (50 of whom were subsequently enrolled in the prospective follow-up study).	unmasked at the time of the follow-up evaluations. • Numerous statistical analyses were conducted without any adjustments for multiplicity, increasing the risk of type 1 error. • The survival curve is presented without sample sizes or an indication of where data were censored, making the results uninterpretable. • The study was conducted exclusively in Brazil, which may limit the generalizability of the study to the Canadian setting. • It is unclear if the study had sufficient statistical power to observe meaningful differences between the two groups.
Fuhrer et al, 2009[14]	
• The objective of the study is clearly described in the publication. • The main outcome that was measured in the study (i.e., Frankl scores) was clearly described in the methods section of the publication. However, the number of teeth included in the procedure was not reported in the methods section and a statistical analysis was provided in the results section. • The baseline characteristics of the study participants were reported in the publication. • The pharmacological agent and the dosage regimen that was used for the conscious sedation group were well reported. • The main findings of the study are clearly described in the results. • The estimates of effect for the main outcomes included confidence intervals. • The actual probability values were reported in the publication, with the exception of those with a value less than 0.001. • Patients were not randomly allocated to the interventions that they received; therefore, the patients underlying condition may have influenced the choice of procedure.	• The pharmacological approach that was used in the GA treatment group was not reported in the publication. • Characteristics of those lost to follow-up were not reported. • A large proportion of patients withdrew from the study and patient disposition was poorly reported in the publication. • Reasons for early discontinuation were not reported. • Characteristics of those lost to follow-up were not reported. • Numerous statistical analyses were conducted without any adjustments for multiplicity, increasing the risk of type 1 error. • The publication did not report if any of the evaluators of the Frankl scores were blinded to the treatment that had been administered during the ECC procedure. • All of the patients enrolled in the study received treatment with the assistance of Medicaid in the United States. The authors note that this population is considered to be a greater risk of developing ECC. It is unclear if this population differs from the typical Canadian patient who requires treatment for ECC. • The study had a small sample size and a high proportion of early withdrawals. It is unclear if the study had sufficient statistical power to observe meaningful differences between the two groups at all of the time points that were evaluated.

Appendix 4: Additional References of Potential Interest

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