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Short-Acting Agents for Procedural Sedation and Analgesia in Canadian Emergency Departments: A Review of Clinical Outcomes and Economic Evaluation

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Canadian Agency for Drugs and Technologies in Health

Short-Acting Agents for Procedural Sedation and Analgesia in Canadian Emergency Departments: A Review of Clinical Outcomes and Economic Evaluation

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March 2008

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The following manufacturers were provided with an opportunity to comment on an earlier version of this report: Hospira Healthcare Corporation (propofol, propofol injection and etomidate, amidate), Novopharm Limited (propofol, propofol injection), AstraZeneca Canada Inc. (propofol, diprivan), Sandoz Canada Inc (ketamine HCI, ketamine hydrochloride injection USP) and ERFA Canada Inc. (ketamine HCI, Ketalar™). Comments were received from AstraZeneca Canada Inc. and these were considered when preparing the final report.

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Kenneth Bond co-ordinated the project; selected trials, extracted data, performed quality assessment; summarized and interpreted data; and contributed to writing all sections of the report.

Konrad Fassbender acted as the lead for the economic analysis; developed the methodology for the economic analysis; selected studies; extracted, tabulated, and analyzed data; and wrote the economic sections of the report.

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Marco L. A. Sivilotti provided guidance on the development of the clinical review methodology and acted as a content expert in clinical medicine and toxicology.

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Conflicts of Interest

The authors declared no conflicts of interest.

REPORT *IN BRIEF*

March 2008

Short-Acting Agents for Procedural Sedation and Analgesia in Canadian Emergency Departments: A Review of Clinical Outcomes and Economic Evaluation

Technology

Short-acting agents for procedural sedation and analgesia (PSAs) propofol, ketamine HCl, etomidate, and ketamine combined with low-dose propofol (ketofol).

Condition

Adults who present to emergency departments (EDs) for painful procedures (i.e., treatment for bone fractures, major joint dislocations, cardioversion, and other procedures).

Issue

Short-acting agents have been perceived as superior to traditional agents, but uncertainty still remains regarding the optimal use of these agents, partly due to the lack of a comprehensive technology assessment in a Canadian context.

Methods and Results

A systematic review and survey of Canadian practice patterns was conducted. A systematic review of studies that compared short-acting procedural sedation drugs with one another or with conventional opioid and benzodiazepine agents for adult ED PSA was also conducted. Forty-four studies (nine randomized clinical trials, one prospective cohort, and 34 case series studies) were included: 32 evaluated propofol, 13 etomidate, 12 midazolam, eight ketamine, and two ketofol. A cost-minimization analysis was conducted. Propofol, etomidate, ketamine, and ketofol yield cost savings per procedure of $335.70, $301.76, $244.41, and $243.47 respectively, compared with standard therapy.

Implications for Decision Making

- **Clear differences exist between short-acting and traditional agents.** Short-acting agents are at least as effective as other regimens in terms of procedural success and clearly more effective in terms of reduced procedure time. With the exception of etomidate, short-acting agents were associated with no additional risk of minor adverse events (AEs) (and some may argue fewer risks of AEs).
- **Short-acting agents are associated with reduced costs.** Propofol, etomidate, ketamine, and ketofol yield cost savings per procedure of $335.70, $301.76, $244.41, and $243.47 respectively, compared with standard therapy. Etomidate generates the greatest savings from a time and labour costing perspective, but savings associated with propofol are greater because the differences in costs from hospitalization and AE rates more than offset the differences in labour costs.
- **Opportunities for optimal usage exist.** A survey of Canadian EDs revealed traditional agents are still in common usage. Opportunities may exist for the use of these agents by clinicians with less experience (e.g., rural physicians and nonphysician extenders, such as nurse practitioners and paramedics), given enough guidance or training.

This summary is based on a comprehensive health technology assessment available from CADTH's web site (www.cadth.ca): Bond K, Fassbender K, Karkhaneh M, Spooner C, Horton J, Sivilotti MLA, Campbell SG, Vandermeer B, Tjosvold L, Seal R, Rowe BH. *Short-Acting Agents for Procedural Sedation and Analgesia in Canadian Emergency Departments: A Review of Clinical Outcomes and Economic Evaluation.*

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EXECUTIVE SUMMARY

Issue

Despite the perceived superiority of newer short-acting agents compared with conventional opioid and benzodiazepine agents for procedural sedation and analgesia (PSA), evidence of the relative use, efficacy, and safety of these short-acting agents for common painful procedures in Canadian emergency departments (EDs) is limited. As a result, there is uncertainty regarding the cost-effectiveness of these agents in comparison with each other and well-established sedatives. To develop clinical guidelines and effectively allocate resources, decision makers need to know if newer, short-acting agents used in the ED are more effective and cost-effective than conventional agents, and how effective and cost-effective these newer agents are relative to one another.

Objectives

The aim was to evaluate the clinical efficacy, safety, and cost-effectiveness of etomidate, ketamine, "ketofol," (i.e., ketamine with low-dose propofol) and propofol used in Canadian ED PSA for common painful procedures (e.g., treatment for fractures, dislocations, and electrical cardioversion) in adults.

To achieve these objectives, the following research questions were proposed:

- How are these common painful procedures managed for adult patients who present to Canadian EDs?
- What techniques and pharmacological agents are currently utilized for adult patients who present to Canadian EDs?
- What is the comparative efficacy (in terms of procedural success, procedure time, pain, recall, and satisfaction) and safety of the short-acting and dissociative agents when compared with each other and with opioid and benzodiazepine agents for adults who present to the ED requiring brief painful procedures?
- What are the known barriers to the use of short-acting and dissociative agents for adult patients who present to EDs requiring brief painful procedures?
- What is the cost-effectiveness of using short-acting and dissociative agents compared with using opioid agents alone or in combination with benzodiazepine agents in adults presenting to the ED who qualify for procedural sedation?

Clinical Review

Methods: A rigorous systematic review was conducted to identify all randomized controlled trials (RCTs) and prospective observational studies that compared short-acting procedural sedation drugs with one another, or with conventional opioid and benzodiazepine agents for adult ED PSA. The outcomes analyzed were procedural success, procedure time, pain, recall, patient and physician satisfaction, total adverse events (AEs), hospitalization, airway issues, and any other individually reported AEs. Meta-analyses and simple pooling were performed when appropriate.

Results: Few Canadian EDs routinely collect data regarding PSA practice. Orthopedic reductions were the most common procedures for which PSA was employed, followed by abscess drainage and cardioversion. Propofol was the agent most often employed. The use of ketamine, either alone or combined with low-dose propofol, and etomidate remain uncommon. A comprehensive survey of EDs in Alberta showed that urban EDs appear to use PSA more often for cardioversion and other

painful procedures than do rural sites, yet both deal with fractures and dislocations in similar ways. Urban EDs tend to use propofol as their primary agent, whereas rural EDs employ opioids and benzodiazepines. Differences in staffing between the two locations, and thus the ability to follow staffing guidelines for the use of PSA agents, may play an important role in explaining these practice variations. For example, rural sites are smaller, provide single 24-hour coverage by local physicians, infrequently have learners (medical students, interns, and/or residents), and quite often have non-specialized support staff. It is likely that this practice variation exists in other provinces in Canada.

Forty-four studies reporting on 12,404 PSA episodes (nine randomized clinical trials, one prospective cohort, and 34 case series studies) were included: 32 evaluated propofol, 13 etomidate, 12 midazolam, eight ketamine, and two ketofol (clinical trials and some observational studies evaluated more than one drug). Overall, the RCTs were of moderate methodological quality (median Jadad score=3; range=2 to 4), and the observational studies were also of moderate methodological quality (80% of studies fulfilled at least half of the quality criteria). The number of patients ranged from 11 to 4,500. PSA was used mainly for orthopedic reductions, cardioversion, laceration repair, and abscess drainage.

Though there are relatively few direct comparisons of short-acting agents, the available evidence suggests that etomidate, ketofol, and propofol are at least as effective as other regimens in terms of procedural success and are clearly more effective in terms of reduced procedure time. Pooled estimates of pain ratings, patient recall, and patient and physician satisfaction could not be calculated due to the use of incomparable measures and drug comparisons for these outcomes. Estimates from individual studies suggest that differences between drugs for these measures are negligible and often not statistically significant.

Propofol had the lowest probability of AEs (10.0%; 95% CI: 9.4 to 10.7), followed by ketamine (12.2%; 95% CI: 7.8 to 18.4), ketofol (15.4%; 95% CI: 10.6 to 21.9), conventional agents (17.3%; 95% CI: 12.4 to 23.7), and etomidate (27.2%, 95% CI: 23.4 to 31.3). Ketamine and ketofol had the lowest rates of hypotension (0%; 95% CI: 0 to 1.7 and 0%; 95% CI: 0 to 2.7, respectively) followed by conventional agents (2.3%; 95% CI: 0.8 to 6.4), propofol (3.1%; 95% CI: 2.8 to 3.6), and etomidate (3.2%, 95% CI: 2.01 to 5.2). The sensitivity of monitoring in the RCTs resulted in higher AE rates than those reported in larger observational studies for all PSA agents; however, all AEs, except one, were transient, easily managed with routine procedures, and had no long-term effects.

Economic Analysis

Methods: A cost-minimization analysis and multi-way sensitivity analysis were employed to evaluate the cost-effectiveness of short-acting procedural sedation drugs compared with one another, and with conventional opioid and benzodiazepine agents for adult ED PSA.

Results: Propofol, etomidate, ketamine, and ketofol yield cost savings per procedure of $335.70, $301.76, $244.41 and $243.47 respectively, compared with standard therapy. Although propofol generates the greatest overall savings due to its low hospitalization and AE rates, etomidate generates the greatest savings from a time and labour costing perspective. Savings associated with propofol are greater than etomidate because the differences in hospitalization and AE rate costs more than offset the differences in labour costs.

Health Services Impact

Assuming the base case model where propofol is the preferred agent, and recognizing that PSA is performed between seven and 13 out of every 1,000 ED visits, the Canadian health care system could realize a savings of between $33.8 and $59.7 million dollars compared to standard care with benzodiazepines and opioids. Because many large urban EDs already report using short-acting PSA agents, these values represent only an upper estimate because the incremental savings of switching to propofol will be lower if ketamine, etomidate, or ketofol are currently being used in any significant quantities.

Conclusion

This review strengthens the view of emergency medicine researchers that short-acting sedatives induce deep sedation easily and reliably, and to a degree unattainable by midazolam and fentanyl. Moreover, they do so with associated AEs that are almost entirely predictable, not serious, transient, respond to simple measures in the ED, and do not have long-term consequences. These PSA agents are efficacious and safe when employed by emergency physicians. Low event rates and incomplete reporting of side effects prevents a comment about extremely rare complications associated with procedural sedation agents.

Overall, the cost-effectiveness results suggest that propofol is the dominant strategy compared with all other short-acting agents and this dominance occurs under a variety of scenarios and assumptions. While etomidate requires less time, and is perhaps more desirable for clinicians, the overall effectiveness and popularity of propofol suggests that it should be considered for use on a regular basis for PSA in Canadian EDs.

ABBREVIATIONS

AE	adverse event
ASA	American Society of Anesthesiologists
BIS	bispectral
CAEP	Canadian Association of Emergency Physicians
CAEP RC	Canadian Association of Emergency Physicians Research Consortium
CI	confidence interval
ED	emergency department
$EtCO_2$	end tidal carbon dioxide
HTA	health technology assessment
IQR	interquartile range
IV	intravenous
Ketofol	the administration of two separate PSA agents, ketamine and propofol, and not a single drug or mixture of the two above agents
MD	mean difference
NA	not applicable
NOS	Newcastle-Ottawa Scale
OR	operating room
PAR	post-anesthetic recovery
PADSS	post-anesthesia discharge scoring system
PSA	procedural sedation and analgesia
RCT	randomized controlled trial
RR	relative risk
SAM	supportive airway measures
SaO_2	arterial oxygen
SD	standard deviation
SMD	standardized mean difference
TEP	technical expert panel
VAS	visual analogue scale
WMD	weighted mean difference

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1 INTRODUCTION

1.1 Background/Setting in Canada

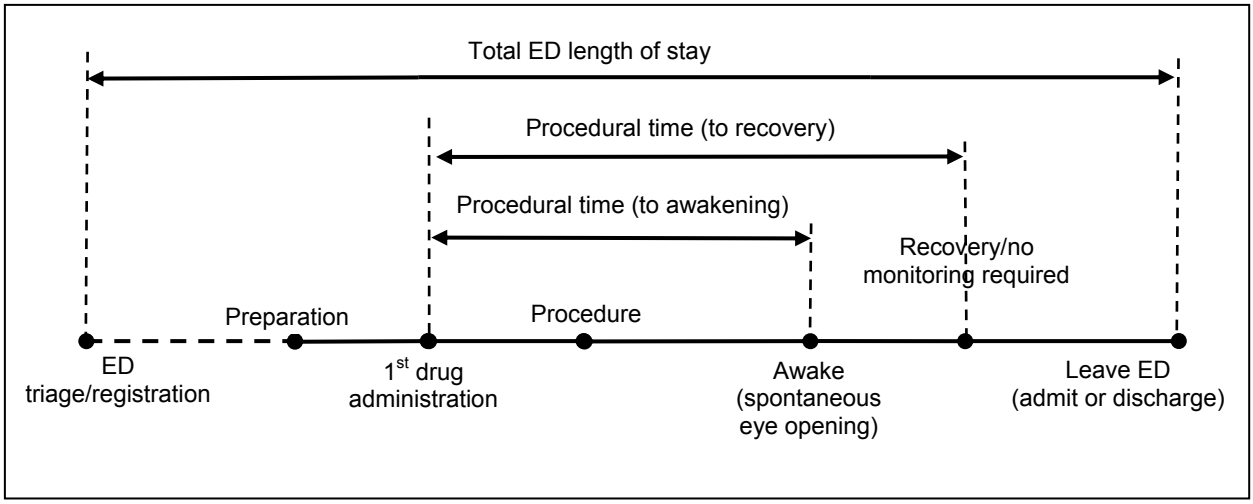
Canadians make more than 14 million Emergency Department (ED) visits annually,[1] and about a quarter of Canadians visit an ED each year either for their own injury or illness or for that of a close family member.[2] In many communities, shortages of primary care physicians mean that the local ED acts as a safety net, providing last-resort care for low acuity and chronic conditions as well as urgent ones. Other than for same-day procedures, most patients admitted to hospital are first seen in an ED, though the vast majority of ED visits do not result in admission. Hence, the ED visit represents an important window through which Canadians view and experience their health care system.[1]

Patients presenting to the ED are often suffering from conditions causing pain and anxiety and requiring procedures that are themselves brief but painful. For these procedures, patients may be sedated using short-acting sedatives, analgesics (drugs that reduce pain), and dissociative agents (drugs that inhibit perception of sight and sound and produce feelings of detachment), alone or in combination, to allow them to more easily tolerate the discomfort of treatment. This process is referred to as "procedural sedation and analgesia" (PSA) and is most often used for fracture or dislocation reduction, abscess drainage, chest tube insertion, burn debridement and electrical cardioversion.[3,4] This shift in practice reflects improvements in patient care and in efficiencies related to bringing the procedure to the patient, the evolution and maturation of the discipline of emergency medicine, and restricted access to in-hospital services.

The PSA process can be conceptualized as an event divided into six stages (Figure 1). The process begins once the patient has moved through triage and ED registration and preparation for the procedure requiring PSA has begun. Because the PSA process has several stages, the end point of the process is viewed variously depending on the aspect of the process that is under investigation. The end is sometimes considered to be the end of the procedure itself (e.g., reduction of the fracture or establishing normal sinus rhythm in atrial fibrillation), sometimes the end of sedation or "awakening" of the patient, sometimes the end of the need for monitoring after meeting some specified "recovery criteria" (e.g., modified-Aldrete score, Glasgow Coma Scale score, post-anesthesia discharge scoring system [PADSS] score), and sometimes the point at which the patient is admitted to the hospital for more treatment or is discharged.

The variety of procedures that are performed and the variation in guidance regarding staffing requirements also mean that staffing is not standardized. Despite this variation, there are some general patterns of practice. A nurse or advanced care paramedic is usually present from preparation to the end of monitoring and a physician will be present from the administration of the drug to the end of monitoring. In larger centres, there is often a sedating physician and a procedure physician, and a respiratory technician for most procedures; in addition, in larger centres an orthopedic technician would assist the procedural physician for orthopedic procedures.

Figure 1: Conceptualization of Emergency Department procedural sedation and analgesia



A variety of relatively simple procedures are encountered by emergency patients on a relatively regular basis. For example, laceration repair is a common procedure in the ED and one that rarely requires hospitalization. Moreover, most ED physicians have expertise in the local anesthetic required to successfully perform this procedure. Other procedures such as the treatment of fractures, cardioversion of cardiac arrhythmias, and reduction of large joint dislocations can be treated relatively quickly, but involve significant pain or discomfort for the patient. In the past, these painful procedures were treated with analgesia and attempts to perform these relatively simple procedures in the ED were often unsuccessful. Regional anesthetic techniques were developed; however, they can be technically difficult, time consuming to administer, and often ineffective.[5] Prior to the development of PSA in the ED, many patients were admitted to hospital for these relatively simple, yet painful, procedures. By employing PSA, ED physicians can successfully complete many procedures without the need for hospitalization. Combinations of opioids and benzodiazepines were the first agents used for PSA, but the newer short-acting agents are now being adopted to address perceived limitations of the former PSA strategy. Nonetheless, inadequate pain relief, recollection of the procedure, and anxiety associated with the procedure may occur,[4] and there are complications associated both with these events and with the PSA drugs employed. Rare adverse events (AEs) have been reported for all agents, and achieving the balance of optimal sedation and analgesia to successfully complete the procedure is a delicate task.

1.2 Current Clinical Practice

ED PSA is unique for several reasons:

- Many painful, non-elective procedures are performed in the ED.
- The procedures are brief and the need for strictly sterile conditions is low, so, as a result, would needlessly consume busy and often scarce operating room (OR) resources.
- The procedures can be stopped immediately if the patient deteriorates.
- Medical staff skilled in airway support and resuscitation are already present in the ED environment.[4]

As a result of its uniqueness and the trend in increasing use of ED PSA, professional medical associations in Canada, the United States, Britain, Australia, and New Zealand have developed various levels of guidance on how PSA should be managed and what agents can be used effectively and safely.[3,4,6-8] The Canadian Association of Emergency Physicians (CAEP) guidelines provide detailed information on the required pre-sedation preparation and assessment steps, physician skills, equipment, patient monitoring, and post-sedation care.[4] While certainly an important tool in the development of PSA protocols for EDs, the guidelines do not provide assistance in the appropriate choice of therapeutic agents, recovery parameters and discharge criteria. Reviews of the literature on PSA conclude that many questions remain regarding ED PSA and note the many challenges that research in this area faces. Such questions and challenges include finding consensus definitions for complications, the clinical significance of respiratory depression criteria and the associated "true rate" of significant respiratory events, optimal dosing strategies, and the association between the complexity of the procedure and procedural success.[9,10]

The resultant uncertainty about PSA is reflected in the substantial practice variability across EDs in North America. For example, sites differ with respect to their approach to patient selection, monitoring and personnel requirements, medications, and criteria for safe discharge. Some centres prefer regional methods,[11] many restrict their practice to propofol (SCG, unpublished observations, 2007), and some are employing combination agents e.g., "ketofol".[5] (In this report, "ketofol" refers to the administration of two separate PSA agents, ketamine and propofol, and not to a single drug or mixture of these two agents.) The use of etomidate in Canada is limited to Health Canada's "Special Access" Program; however, its use appears popular in the USA.[9] This wide variation in implementation is not perceived to be the result of uncertainty regarding the clinical effectiveness or cost-effectiveness of PSA; rather, it is thought to be due to referral patterns, the experience and training of emergency physicians, and differences in how anesthetic agents are currently regulated within institutions in Canada.

Few sites routinely collect the data necessary to determine practice patterns and to accurately ascertain regional variation in practice, so little is known about the variation in practice patterns of ED PSA in Canada (Appendix 5). From the small sample of hospitals with PSA data, however, some patterns were clear. Orthopedic reductions (of dislocations or fractures) are the most common procedures for which PSA is employed. PSA is also often employed for abscess incision and drainage and cardioversion. A variety of other painful procedures (e.g., foreign body removal, hernia reduction, wound debridement, chest tube placement) performed less often in the ED also employ PSA approaches. The proportions appear to vary among sites for reasons that are unclear; however, the location and acuity of the ED clearly influence this. For example, from the Canadian data, abscess incision and drainage is highest in an inner city ED and lowest in a non-urban community ED. In addition, practice variation within and among EDs may also influence the use of PSA for some procedures where evidence provides less guidance to practising clinicians (e.g., cardioversion for arrhythmias such as atrial fibrillation).

In terms of PSA agents, propofol is generally the main PSA agent employed in Canada. Etomidate, though available only under Health Canada's Special Access Program, was used in a relatively large number of cases by one of the responding institutions (St. Paul's Hospital). The use of ketamine for adults, either alone or combined with low-dose propofol (as "ketofol"), remains uncommon in Canada, except in some regional areas (e.g., Kingston General Hospital and North Vancouver's Lion's Gate Hospital). Finally, midazolam and fentanyl also make up a large percentage of the agents used, but likely because they are not only often used together as the main PSA agents, but also used additionally with one of the other agents (e.g., with propofol).

With respect to comparisons between rural and urban centres, the role of location is a clear contributor to PSA use — urban EDs deal with some procedures in a dramatically different way than do their rural counterparts (Appendix 5). For example, urban hospitals tend to use PSA more often for cardioversion and other painful procedures than do EDs in rural hospitals, yet hospitals in both locations deal with fractures and dislocation in similar ways. In addition, urban hospital EDs tend to use PSA agents such as propofol as their primary treatment options, whereas rural ED sites prefer opioid and benzodiazepine combination treatment. In terms of staffing, the use of two ED physicians is rarely seen in rural areas; however, even in urban hospitals a second physician is routine only a third of the time. Some of these differences can be explained by differences in staffing. For example, rural sites are smaller, provide single 24-hour coverage by local physicians, infrequently have learners (medical students, interns and/or residents) and quite often have non-specialized support staff. Conversely, urban and regional EDs have overlap coverage (median 40 hours of coverage per day), availability of consultants and other support staff (e.g., paramedics, respiratory and orthopedic technicians).

Given the recent increased interest in this subject and the publication of new research[5,12-15] (SGC, unpublished observations, 2007), there is a high probability that new evidence is available to add clarity to this topic. With emergency services across the country being strained by bed shortages, overcrowding, increasing acuity, and funding issues, it is critically important to evaluate whether short-acting dissociative and analgesic agents can provide more efficacious and cost-effective management of PSA than the conventional opioid and benzodiazepine agents or more resource-intensive options (i.e. hospitalization).

This report aims to conduct a comprehensive review of the evidence for the effectiveness and safety of ketamine, propofol, and etomidate compared with conventional opioid and benzodiazepine agents for ED PSA for fractures, dislocations, and cardioversion. While current practice in the ED is largely extrapolated from the experience and knowledge gained in the operating room, it is clear that important differences exist between these two environments, including differences in patients, providers, and therapeutic processes and procedures.

1.3 Technology Overview

1.3.1 Interventions

A variety of new and old drugs are used in procedural sedation; most are delivered intravenously. The drugs included in the review are restricted to the short-acting (sometimes referred to as "ultra-short-acting"[16]) dissociative and sedative-hypnotic agents described in Table 1. In addition to providing relaxation, analgesia, amnesia and anxiety reduction (though propofol lacks analgesic effect and is often combined with fentanyl for this reason), these agents have a rapid onset and short duration of action,[10] properties that make them ideal for use in busy EDs.

a) Patient Group

Patients who qualify for PSA include those requiring orthopedic manipulations (e.g., bone fractures and major joint dislocations), cardioversion, and some other procedures (e.g., chest tube placement, foreign body removal, abscess incision and drainage).

b) Current Standard of Care

As noted in Section 1.2, though collection of data on standards of care is limited, the available

evidence suggest that practices vary across Canada: small-volume, single-coverage EDs generally use conventional approaches, whereas large-volume, urban, multiple-coverage EDs use either the newer dissociative agents alone, or in combination with an opioid or benzodiazepine (e.g., ketamine and midazolam, or propofol and fentanyl) (Appendix 5).

Table 1: Short-acting dissociative agents used in Emergency Department PSA

Drug	Supplied	Trade Name	Manufacturer
Propofol	IV 10 mg/mL emulsion (20, 50, 100 mL)	Diprivan	AstraZeneca
	IV 10 mg/mL (20,50,100 mL)	Propofol Injection	Hospira Healthcare Corporation
	IV 10 mg/mL emulsion (20, 50, 100 mL)	Propofol Injection	Mayne Pharma
	IV 10 mg/mL emulsion (20, 50, 100 mL)	Propofol Injection	Novopharm
	IV 10 mg/mL emulsion (50 mL)	PMS Propofol	Pharmascience
Ketamine HCl	IV10 mg/mL (20 mL) IV/i.m. 50 mg/mL (10 mL)	Ketamine Hydrochloride	Sandoz
	IV 10 mg /mL (20 mL) IV/i.m. 50 mg/mL (10 mL)	Ketalar	ERFA Canada
Etomidate	IV 20 mg/mL (10 mL)	Amidate	Hospira Healthcare Corporation (available through Health Canada's Special Access Program)

IV=intravenous

2 THE ISSUE

Despite the perceived superiority of newer short-acting agents compared with conventional opioid and benzodiazepine agents for procedural sedation and analgesia (PSA), evidence of the relative use, efficacy, and safety of these short-acting agents for common painful procedures in Canadian emergency departments (EDs) is limited. As a result, there is uncertainty regarding the cost-effectiveness of these agents in comparison with each other and well-established sedatives. To develop clinical guidelines and effectively allocate resources, decision makers need to know if newer, short-acting agents used in the ED are more effective and cost-effective than conventional agents, and how effective and cost-effective these newer agents are relative to one another.

3 OBJECTIVES

The objectives of this report were to conduct a systematic review and primary economic analysis to evaluate the clinical efficacy, safety and cost-effectiveness of short-acting and dissociative agents (i.e., propofol, ketamine, ketofol, etomidate) for procedural sedation for adults who present to EDs for painful procedures (e.g., treatment for bone fractures and major joint dislocations, and for cardioversion and other procedures).

To achieve these objectives, the following research questions were proposed:

- How are these brief painful procedures managed for adult patients who present to Canadian EDs?
- What techniques and pharmacological agents are currently utilized for adult patients who present to Canadian EDs?
- What is the comparative efficacy (in terms of procedural success, procedure time, pain, recall, and satisfaction) and safety of short-acting and dissociative agents when compared with each other and with opioid and benzodiazepine agents for adults who present to the ED requiring brief painful procedures?
- What are the barriers to the use of short-acting and dissociative agents for adult patients who present to EDs requiring brief painful procedures?
- What is the cost-effectiveness of using short-acting and dissociative agents compared with using opioid agents alone or in combination with benzodiazepine agents in adults presenting to the ED qualifying for procedural sedation?

4 CLINICAL REVIEW

4.1 Methods

The methods for this systematic review and primary economic analysis were developed and described in a protocol developed a priori.

4.1.1 Literature search strategy

Comprehensive searches of electronic databases were performed. Academic Search Premier, BIOSIS Previews, CINAHL, Cochrane Anaesthesia Review Group Register, Cochrane Central Register of Controlled Trials, Dissertation Abstracts, EMBASE, Health Source: Nursing/Academic Edition, International Pharmaceutical Abstracts, MEDLINE, OCLC Papers First, Pascal, Scopus, and Web of Science databases were searched, without language restrictions, for all relevant citations using pre-defined search terms (Appendix 1.1).

The original searches were performed in May 2007. Grey literature searches were conducted by checking reference lists of included studies, hand-searching scientific meeting abstracts for the last five years in *Annals of Emergency Medicine, Canadian Journal of Emergency Medicine*, and *Academic Emergency Medicine* and searching for documents from government and professional associations, theses and dissertations, and a Google™ search (Appendix A). In November 2007, the searches were updated using the original search strategies in MEDLINE, EMBASE, and Web of Science. The citations in the literature selection were managed using Reference Manager, Version 11 bibliographic software (Thomson ISI ResearchSoft, Carlsbad, CA).

Pharmaceutical manufacturers were also contacted by CADTH for information regarding unpublished completed or on-going studies that examined the efficacy and/or safety of propofol, the prevalence of the use of these agents for procedural sedation in Canadian EDs, and any information regarding the cost-effectiveness of these agents.

4.1.2 Selection criteria and method

a) Selection criteria

Broad screening criteria

A study was considered *not* relevant if it met one of the following criteria:

- letter, editorial or lay press article
- majority (>50%) of study participants clearly <18 years old
- clearly not on PSA
- clearly not in an ED setting
- clearly does not include bone fractures, major joint dislocations or cardioversion.

Inclusion/exclusion criteria

To be included a study must have met all of the following criteria:

- publication type: report of primary research (experimental and observational studies)
- study design: clinical trial, controlled before-and-after study, or prospective observational study (cohort, interrupted time series, case series)
- population: >50% adult patients (>17 yrs) and requiring brief painful procedures (treatment for bone fractures or major joint dislocations, or non-elective cardioversion)
- setting: procedure or study takes place in hospital ED
- intervention: etomidate, ketamine, propofol, or combination drug (e.g., "ketofol")
- comparator: opioid agents in combination with sedative-hypnotic benzodiazepine, or regional anesthesia
- outcome: numeric data on at least one outcome of interest (i.e., procedural success, procedure time, pain, recall, satisfaction).

b) Selection method

The literature selection was completed in two stages. Broad screening based on the titles and abstracts of each study was conducted by two reviewers (KB, JH). The screening criteria were applied as broadly as possible to the retrieved titles, subtitles, abstracts, and keywords to ensure that only clearly irrelevant studies were excluded at this stage. The full texts of all potentially relevant articles and of articles designated as "unclear" were retrieved. The level of agreement between the two reviewers was evaluated using the Kappa (κ) statistic. A κ score in the range from 0.0 to 0.40 was considered poor agreement; 0.41 to 0.61 moderate agreement and 0.61 to 0.80 substantial agreement.[17] This agreement phase of the screening was repeated on 10% samples until moderate agreement was reached.

Two reviewers (KB, JH) independently appraised the full text of all the studies classified as "potentially relevant" and "unclear" using a standard form that contained the inclusion and exclusion criteria for studies. In addition, studies that were solely or predominantly procedures that were elective and took place in the ED (e.g., elective cardioversion) were excluded because at least some important patient characteristics (severity of condition, use of medication, and fasting time) varied from characteristics of patients who had non-elective procedures. The decision to isolate PSA for treatment of fractures and dislocations, and for cardioversion was made in consultation with the Peer Review Group and CADTH during the protocol development phase. Disagreements about inclusion or exclusion of studies were initially resolved by consensus between two reviewers, and, when this was not possible, a third reviewer arbitrated (BHR). The decision to exclude each study was documented and reasons for exclusion are provided in Appendix 2.

4.1.3 Data extraction strategy

A detailed data extraction form was developed in collaboration with the Technical Expert Panel (TEP) and was abstracted by one of three TEP members. The form was pre-tested on a sample of five studies and revised accordingly. One reviewer (CS, KB, or MK) extracted the data and a second reviewer verified the data before its entry into an MS Excel™ (2003) spreadsheet (Microsoft Corporation, Redmond, WA). Details extracted were: study design; population characteristics; PSA practice pattern including therapeutic agent used, dosage, time of procedure, and setting of the study; indications; measures of procedural efficacy and definitions; and all AEs and their definitions.

Measures of procedural success, pain, recall, and patient and physician satisfaction were all taken as defined by the authors. For procedural time, putative time differences between actions of the various PSA agents occur in time from administration to sedation and in time to recovery. For this reason, the primary time extracted from each study was time from administration of PSA drug to recovery; however, that may have been defined by the study author (e.g., returned to baseline vitals or achievement of a "recovery score"). If this time was not reported, then other reported times were combined or subtracted to derive this time for comparison. When this time could not be generated from study data, the second time period taken as a measure of effectiveness was time from administration of PSA agent to awake time; however, this was defined by the study authors (e.g., spontaneous eye opening).

In addition, evidence tables were developed to summarize the characteristics of the included studies. The conceptual framework that forms the basis of the qualitative synthesis focused on:

- the drug used (e.g., propofol, ketamine, etomidate or a combination of any of these with another drug) and method of administration (bolus or titration)
- the control group used
- the type of outcome measures that are reported.

The tables include information on the source of the article, study design, setting, treatment groups, inclusion/exclusion criteria, sample size, study quality, and outcomes with effect sizes.

4.1.4 Quality assessment

The methodological quality of each study depends on internal and external validity. Internal validity, which is considered to be the most important element of study quality, is defined as the confidence that the design, conduct and report of a trial prevent or reduce bias in the outcomes.[18]

Four tools were used to assess the randomized controlled trials (RCTs), cohort studies, and case series studies. The methodological quality of RCTs was assessed using the Jadad scale[19] and the Schulz criteria for allocation concealment.[18] The former is a validated five-point scale[19] including three items that require a yes/no answer and that are directly related to internal validity: randomization, double-blinding, and a description of withdrawals and dropouts. The Schulz tool is based on empirical evidence of a strong relationship between concealment of allocation and biased estimates of effect.[18]

Prospective observational studies were assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies.[21] The scale assesses the methodological quality of studies across three domains: sample selection, comparability of the study groups, and the ascertainment of the outcome of interest. Though the NOS identifies eight key components in prospective observational designs and the

face/content validity and inter-rater reliability have been established, studies on criterion and construct validity are still in progress. For this reason, the individual components of the scale were reported for each study, and no overall indicator of quality was calculated.

For the assessment of the case series, we developed a 15-item tool focusing on different aspects of the risk of bias, including selection bias (six questions), attrition bias (one question), detection bias (four questions), and assessment bias (four questions). The reliability and validity of this tool (Appendix 4) have not been formally tested; however, preliminary evaluation demonstrates that it successfully captures information regarding the important features of a well-conducted case series study.

Two reviewers independently evaluated the methodological quality of each of the included studies. Disagreements were resolved by consensus between the two reviewers or adjudicated by a third party (BHR), when necessary. The results of quality assessment for included studies were synthesized and are presented in Appendix 6. As CADTH is not mandated to make recommendations, the overall results were not assessed according to quality rating scales (e.g., Grading of Recommendations Assessment, Development and Evaluation[22]) developed for this purpose.

4.1.5 Data analysis methods

a) Efficacy

When clinical homogeneity among studies existed with respect to design, population, intervention and outcomes, efficacy data was pooled using Review Manager software (Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2007). Risk ratios (RRs) or odds ratios and corresponding 95% confidence intervals (CIs) were used to summarize dichotomous outcomes and weighted mean differences (WMDs) and standardized mean differences (SMDs) with 95% CI to summarize continuous outcomes. Because we were interested in the average treatment effect across studies, random effects models were used in all instances.[23] Heterogeneity between studies was estimated using the I^2 statistic.[24] When there was evidence of substantial statistical heterogeneity among studies (I^2>50%),[24] summary estimates with corresponding 95% CIs were presented separately for each study and potential reasons for the heterogeneity were explored in a subgroup analysis. As most studies report combined results for many procedures, no distinction was made initially to group studies by procedure (fracture, dislocation, cardioversion, etc.). However, if heterogeneity existed in pooled results, the impact of different procedures on treatment efficacy was explored whenever possible by subgroup analysis. When enough studies were available (N≥10), the potential for publication bias was assessed visually using a funnel plot and the trim and fill method.[25]

Because some common outcomes were reported for many interventions, when more than four interventions could be compared, a mixed-treatment comparison was conducted.[26] Indirect comparisons are a valid approach to meta-analysis when there is insufficient direct evidence from randomized trials reporting head-to-head comparisons between interventions.[26,27]

For procedure times, when times were reported variously (e.g., one study reported the time from administration of the drug to the end of the procedure and from the end of the procedure to recovery, while another study of the same drug reported the time from administration to recovery), the individual times were combined to form a total time to allow for pooling of the individual study results. In combining the separate times, conservative estimates of the variance of the multiple time periods were used by using a coefficient of one.

When a sufficient number of studies reported the same outcome and made appropriate comparisons, a mixed-treatment analysis was performed. In this method, a Bayesian formulation of the data is employed. The differences between each intervention and a baseline intervention (in this case, "standard care" was chosen as the baseline) are modelled by choosing a prior distribution for the effect and combining this prior value with the data from the studies to arrive at a posterior estimate and 95% CI. Such an estimate was obtained for all pairwise comparisons of interventions and the comparisons with the baseline intervention. Because the resulting posterior distributions are too complex for direct computation, a Markov Chain Monte Carlo simulation[28] was used to obtain the posterior estimates. This procedure involved simulating the unconditional, unknown posterior distribution by sampling many times from the conditional distribution and averaging the results. We used a sample of 20,000 burn-in iterations followed by 200,000 samples and non-informative normal (point estimate) and uniform (variance estimate) priors to obtain the distributions. We also computed a statistic to estimate the probability that each intervention was the "best" (e.g., had the shortest procedure time) by recording the best intervention at each iteration. This simulation was performed using the WinBUGS software, version 1.4 (MRC Biostatistics Unit, Cambridge, United Kingdom).

b) Safety

When pooling data, studies that did not report data for a particular adverse event (AE) were excluded; no assumption was made that if an event was not reported it did not occur. Also, studies that reported that no clinically significant AEs occurred were excluded from the pooled risk estimate as it was not clear what parameters were measured. To accommodate studies that reported more procedures than patients (as some required additional PSA treatment at a later date), the probability of AEs was calculated by dividing the total number of major AEs by the total number of patients exposed to the drug.

4.2 Results

4.2.1 Quantity of research available

Searches of electronic databases resulted in the identification of 1,794 records. Of these, 1,546 were considered clearly not relevant and excluded. The level of agreement between reviewers for the broad screening phase was moderate to substantial (κ=0.46, 0.55, 0.67, 0.62, 0.62). Because the screening phase was overly inclusive, the principal investigator (BR) reviewed the screening results and identified 32 additional studies considered not relevant based on clinical knowledge. The full texts of the remaining 248 potentially relevant citations were retrieved and assessed using a more detailed set of inclusion criteria (Table 3). Eight additional studies were identified through the grey literature searches (four scientific meeting abstracts, three unpublished manuscripts, and one Canadian regional anaesthetic practice pattern), bringing the total of potentially relevant studies to 256. The updated search identified an additional 127 citations from which broad screening identified 12 potentially relevant citations. The level of agreement between reviewers for this multiple topic inclusion/exclusion phase was also moderate (κ=0.52).

Of the 268 potentially relevant reports, 68 studies were considered relevant to address the four research questions: five (two included solely for this topic) to address Question 1, 47 to address Question 2 (three multiple publications), 19 (18 included solely for this topic) to address Question 3, and seven (one included solely for this topic) to address Question 4 (and were not identified by the literature search for the cost-utility/cost-effectiveness analysis). Figure 1 shows the process of study selection.

The remaining 200 reports were excluded for the following reasons:

- not primary research or no report of barriers (100 studies)
- ineligible study design (20 studies)
- not in ED (six studies)
- not the correct population (34 studies)
- no PSA drugs of interest (i.e., propofol, ketamine, etomidate, or midazolam) (eight studies)
- no outcomes of interest (five studies)
- unavailable (15 studies)
- abstract of included full manuscript (six studies)
- pending translation (six studies).

a) Study characteristics

There were 47 studies included in this clinical review. Three articles[29-31] were considered multiple publications of other published studies,[32-34] yielding 44 unique studies. Of the 44 studies, 9 (20.5%) were randomized controlled trials (RCT), [5,15,35-41] 1 (2.3%) was a prospective cohort study,[42] and 34 (77.3%) were case series with no controls[12,29,33,34,43-71], (SGC, unpublished observations, 2007) (Appendix H). The studies were published between 1974 and 2007 (median year of publication=2005). Most of the studies (27; 61.4%) took place in the United States, with others being conducted in Canada (9; 20.5%), United Kingdom (3; 6.8%), Australia (3; 6.8%), Spain (1; 2.3%), and Korea (1; 2.3%). The number of study participants ranged from 11 to 4,500 [median=74.5; interquartile range (IQR): 43.2 to 134.5] (Appendix 7).

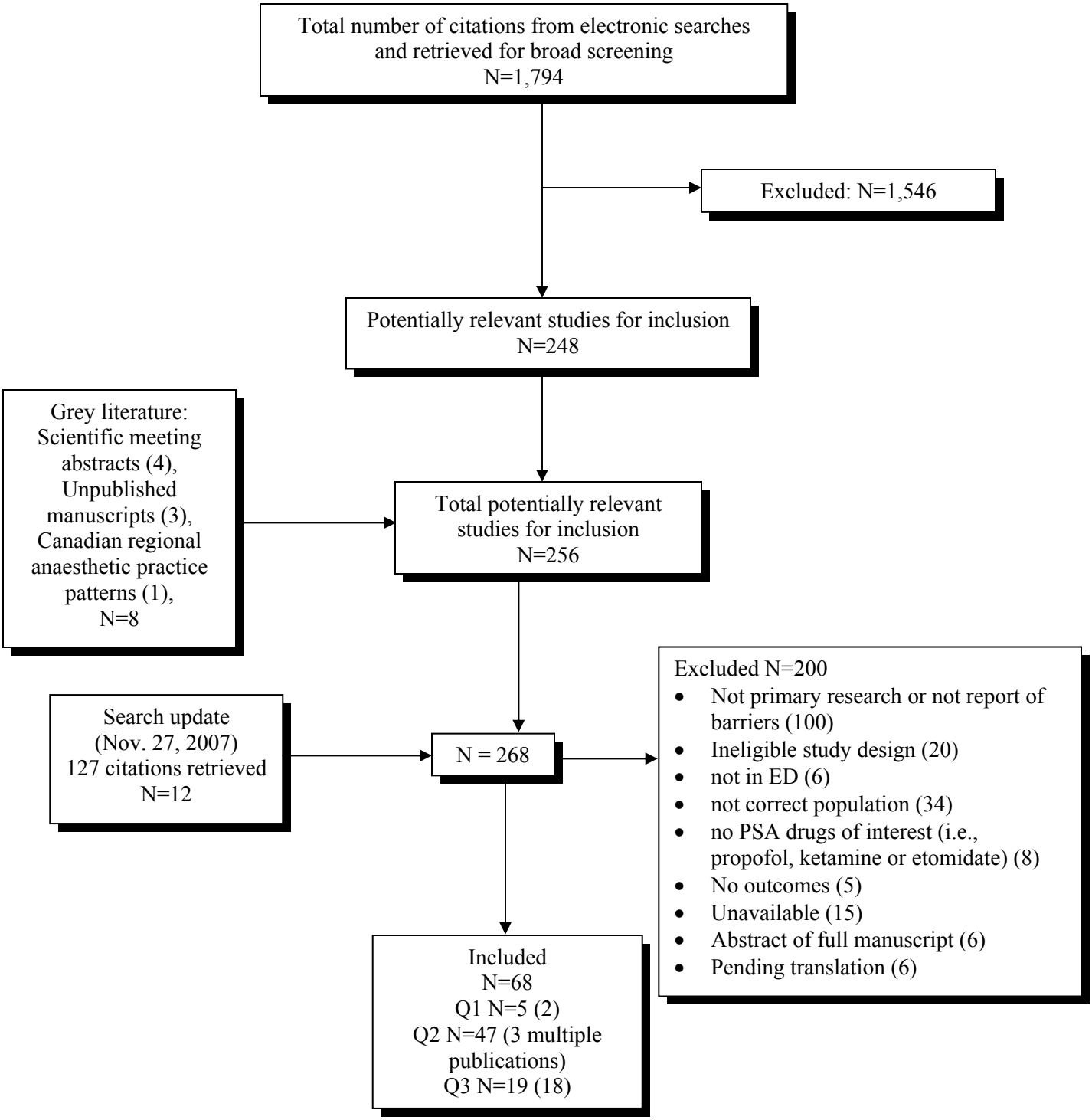
b) Study funding

Most studies (36; 81.8%) did not report funding source (eight RCTs, one prospective, 29 case series); however, eight studies (18.2 %) reported their sources of funding as "foundation/charity" (two RCTs), "internal funds" (one RCT, three case series), "pharmaceutical companies" (one RCT) and "professional organization (one case series). While 38 studies (86.4%) were conducted in a single centre, six (13.6%) were multi-centre. Twenty-three studies (52.3%) were performed in the university/teaching hospitals, 15 (34.1%) in urban hospitals, four (9.1%) in rural hospital/clinics and two (4.5%) in county or community hospitals. The annual number of ED visits was reported in 28 (63.6%) studies and ranged from 30,000 to 209,000 visits (median=60,000).

c) PSA agents

Though the primary focus of this study was the use of etomidate, ketamine, and propofol, researchers have used a number of PSA drugs both individually and in combination for intervention and control groups, so more than one drug was often examined in a single study. Propofol was the drug most commonly used either as intervention or control for ED PSA (32 studies), (SGC, unpublished observations, 2007),[5,12,15,29,33,34,36,37,39-42,45,47,48,50-54,58-64,66,67,69,71] followed by fentanyl (15), (SGC, unpublished observations, 2007),[34,35,37,38,50,53,54,56,59,62,63,65-67] etomidate (13),[15,34-36,38,44,56-58,62,65,66,68] midazolam (12), (SGC, unpublished observations, 2007),[35,37,38,41,42,44,51,56,58,59,63] ketamine (eight), (SGC, unpublished observations, 2007),[12,34,46,49,55,58,59,72], morphine (seven),[15,35,38,39,41,60,69] ketofol (three),[5,43,70] and methohexitol (two).[39,58] A variety of other conventional PSA agents were reported being used in individual studies including hydromorphone, lorazepam, meperidine, and pentobarbital.

Figure 2: Clinical literature search results



d) Populations

Participant age ranged from one month to 92 years old. Twelve studies reported mean and standard deviation of their patients' age while seven reported mean and range of age. Other studies reported age in different ways including;: five median and range, three only range, two only mean, two mean/range/median, two distributions of age, one only median, and in 14 studies age was not reported. The median of the reported mean of ages among the 21 studies was 38.45 years (IQR: 34.4 to 43.9). There were 26 (57%) studies that reported the distribution of patients by sex. The number of male patients ranged from six to 645 and female patients from three to 680. The median of number of male participants was 35 (IQR, 18.5 to 83.7), and that for female participants was 24 (IQR, 9.2 to 60.2).

e) Procedures

Among included studies ED PSA has been used for different emergency procedures including: undifferentiated orthopedic reduction (median=50.4%), joint dislocation (32.8%), bone fracture (10.7%), abscess drainage (9.4%), laceration (4.5%), and cardioversion (3.3%). There were 25 other procedures reported in the studies including: lumbar puncture (1033, 47.2%), unclassified (737, 33.7%), chest tube placement (307, 14.0%), CT scan (43, 2.0%), foreign body removal (37, 1.7%), wound care (4, 0.2%), and hernia reduction (4, 0.2%) (Table 2 and Appendix 7).

Table 2: Procedures performed in PSA studies

	Bone fracture	Joint dislocation	Orthopedic reduction	Cardio-version	Laceration	Abscess drainage	Other
Total number	1,066	1,907	4,001	500	803	1,631	2,355
Range	4 to 277	4 to 632	8 to 1800	1 to 88	1 to 630	1 to 765	Different procedure
Median %	10.7%	32.8%	50.4%	3.3%	4.5%	9.4%	Different procedure
RCT, n (%)	4 (9.1)	6 (13.6)	1 (2.3)	3 (6.8)	0 (0.0)	3 (6.8)	2 (4.5)
Observational	11 (25.0)	15 (34.1)	17 (38.6)	15 (34.1)	7 (15.9)	24 (54.5)	26 (59.1)
Total	15 (34.1)	21 (47.7)	18 (40.9)	18 (40.9)	7 (15.9)	27 (61.4)	28 (63.6)

f) Resources

As personnel involved in ED PSA, ED physicians participated in 31 (70.5%) studies, with 20 (45.5%) studies involving one physician and 11 (25.0%) studies involving two physicians. Other personnel involved included nursing staff in 20 studies (45.5%), medical students and respiratory therapists in four (9.1%) studies each, and research assistants in two (4.5%) studies. The methods of monitoring and recording during the procedures also varied: 30 studies (68.2%) recorded data using a standard PSA form. Oxygen saturation was monitored in 34 studies (77.3%), blood pressure in 33 (75.0%), end tidal CO_2 in 13 (29.5%), and bispecteral electroencephalogram (EEG) in four (9.1%). Additional monitoring was reported in 32 (72.7%) studies, including pulse rate (26, 59.1%), electrocardiogram (ECG) (5, 11.4%), and pulse rate plus Glasgow Coma Score (1, 2.3%). Supplemental oxygen was used in 28 (63.6%) of the studies (Table 3).

Post-procedural assessments were conducted in six (13.6%) studies: level of consciousness was assessed in six (13.6%), return to pre-sedation mental status in five (11.4%), discharge assessment using visual analogue scale in four (9.1%), and post-assessment recovery score in two (4.5%) study. Participant follow-up was conducted in six (13.6%) of the studies using telephone (4, 9.1%), questionnaire (1, 2.3%), and interview (1, 2.3%).

4.2.2 Industry contact

Of six pharmaceutical manufacturers (Hospira, Novopharm, AstraZeneca, Sandoz Canada, ERFA Canada, and Abbott Laboratories) to which a formal letter was sent from CADTH requesting previous and/or ongoing research on PSA drugs and cost-effectiveness data, four did not respond and two indicated that they did not have new reports or unpublished studies. One manufacturer (AstraZeneca) provided the full text of 17 published studies on Diprivan™ (propofol), all of which had been retrieved through our electronic searches and evaluated.

Table 3: Personnel involved, PSA monitoring, supplemental O_2, discharge assessment, and follow-up in the ED PSA

Variable	No. reported (%)	
	Yes	No/NR
Personnel		
ED physician involved	31 (70.5)	13 (29.5)
One physician=20		
Two physicians=11		
Medical student/intern (includes one resident)	4 (9.1)	40 (90.9)
Nursing staff	20 (45.5)	24 (54.5)
Respiratory therapist	4 (9.1)	40 (90.9)
Other (research assistant)	2 (4.5)	42 (95.5)
Monitoring		
PSA monitoring, standard PSA form	30 (68.2)	14 (31.8)
Bispecteral EEG	4 (9.1)	40 (90.9)
O_2 desaturation (pulse oximetry)	34 (77.3)	10 (22.7)
End tidal CO_2	13 (29.5)	31 (70.5)
Blood pressure	33 (75.0)	11 (25.0)
Respiratory rate	26 (59.1)	18 (40.9)
Other	27 (61.4)	12 (27.3)
Pulse rate (PR)=26		
ECG=5		
PR + Glasgow Coma Score=1		
Supplemental O_2 (any use of supplementary O_2)	28 (63.6)	16 (36.4)
Post-procedural assessment		
Discharge assessment, visual analogue scale	4 (9.1)	40 (90.9)
Post-anesthetic recovery (PAR) score	2 (4.5)	42 (95.5)
Level of consciousness (Aldrete PAR)	6 (13.6)	38 (86.4)
Return to pre-sedation mental status	5 (11.4)	39 (88.6)
Follow-up	6 (13.6)	38 (86.4)
Telephone=4		
Questionnaire=1		
Interview=1		

EEG= electroencephalogram; NR=not reported; PR=pulse rate.

Table 4: Methodological quality of RCTs	
Quality components	**No. Yes (%)**
Randomization	9 (100.0)
Description of withdrawals/dropouts	9 (100.0)
Adequate concealment of allocation	6 (67.0)
Appropriate randomization	5 (55.6)
Appropriate method of double-blinding	3 (33.3)
Double-blinding	3 (33.3)
Inappropriate method of randomization	0 (0.0)
Inappropriate method of double-blinding	0 (0.0)

4.2.3 Quality of included studies

a) Randomized controlled trials

Overall, the methodological quality of the nine RCTs was moderate, with overall Jadad scores ranging from 2 to 5 and a median score of 3 (IQR, 2 to 4). Six (66.7%) of the trials had a Jadad score of 3 or higher, indicating high methodological quality. Concealment of allocation was considered adequate in six (66.7%) of the trials and unclear in the other three (Table 4 and Appendix 6).

Individual quality components

We found that all of the trials reported their study as RCTs but only five (55.6%) studies described how the randomization was conducted and were judged to have employed appropriate randomization procedures. Double-blinding was reported in three trials (33.3%) and all explicitly described the methods by which participants and investigators were blinded to the intervention. All of the trials reported withdrawals or dropouts if any occurred or otherwise accounted for all participants.

b) Prospective cohort studies

There was one prospective cohort study in this review.[42] The quality of this study was considered good (7/12 on the NOS) (Appendix 6).

Individual quality components

The participants were considered somewhat representative of the ED patients who needed PSA and selection bias was prevented by choosing a comparison group from the same population as the exposed group. Ascertainment of exposure for both groups was secured using medical records in the ED and the study reported all patients free of the outcome of interest at the start of investigation. In terms of comparability, the groups were matched on age and sex. The study failed to show any method for blinding the assessment of outcomes from investigators. The follow-up period was considered long enough for the outcomes of interest to occur; however, there was no report of follow-up.

c) Case series studies

Quality assessment of case series research was assessed using risk of bias criteria. The median number of items positively identified (meaning a lower risk of bias) was 10/15 (IQR; 8 to 11.7). More than 80% of the studies (29/34) fulfilled at least half of the bias criteria and nine (26.5%) satisfied 12 or more (Table 5 and Appendix 6).

Individual quality components
Six questions about selection bias were applied to the studies. Only 19 (55.9%) of the reports failed to obtain informed consent from the patients under investigation; however, this was sometimes the result of the procedure being considered standard care by the Research Ethics Board and the requirement of consent being waived. The source of the case series was indicated in 33 (97.1%) studies and 21 (61.8%) reported that the study population consisted of a consecutive series of patients. The assessment and categorization of study participants based on the American Society of Anesthesiologists (ASA) physical status classification system (http://www.asahq.org/clinical/physicalstatus.htm) was reported in 14 (41.2%) of the studies. Eleven (32.4%) failed to report the age characteristics of their study population. All studies reported the procedures performed.

The risk of attrition bias was based on reporting losses to follow-up and dropouts. Thirty-three (97.1%) studies reported losses to follow-up of less than 10%. In terms of detection bias, 28 (82.4%) of the case series were clearly conducted prospectively and 30 (88.2%) used predefined criteria for their outcome of interests. Most of the studies (32, 94.1%) reported AEs, but only 14 (41.2%) had collected data prospectively by interviewing patients. Regarding assessment bias, two-thirds (23, 67.6%) of the studies described the treatment protocol for the PSA drug but only 15 (44.1%) explained adjunctive therapy. Only three studies (8.8%) reported using independent observers to record the outcomes; however, 19 (55.9%) reported attending staff as the outcome assessors and data recorders in their ED PSA.

Table 5: Methodological quality of observational studies

Quality components	Yes (%)	No (%)	Unclear (%)
Indications/procedures identified	34 (100.0)	0 (0.0)	0 (0.0)
Source of case series reported	33 (97.1)	1 (2.9)	0 (0.0)
Losses to follow-up <10%	33 (97.1)	0 (0.0)	1 (2.9)
AEs of treatment were recorded	32 (94.1)	2 (5.9)	0 (0.0)
Outcomes of interest were measured using predefined criteria	30 (88.2)	4 (11.8)	0 (0.00)
Study was clearly conducted prospectively	28 (82.4)	5 (14.7)	1 (2.9)
Indication of age (mean, SD or category)	23 (67.6)	9 (26.5)	2 (5.9)
Treatment protocol clearly described	23 (67.6)	11 (32.4)	0 (0.0)
Results from consecutive series of patients	21 (61.8)	6 (17.6)	6 (17.6)
Assessment of outcomes by attending staff	19 (55.9)	1 (2.9)	14 (41.2)
Informed consent	15 (44.1)	5 (14.7)	14 (41.2)
Adjunctive therapies were clearly described	15 (44.1)	17 (50.0)	2 (5.9)
Indication of ASA scoring	14 (41.2)	18 (52.9)	2 (5.9)
Prospective data collection through patient interview in ED	14 (41.2)	17 (50.0)	3 (8.8)
Assessment of outcomes undertaken by independent observers	3 (8.8)	12 (35.3)	19 (55.9)

ASA=American Society of Anesthesiologists; ED=emergency department; SD=standard deviation.

4.2.4 Data analysis and synthesis

a) Efficacy analysis
Nine RCTs [5,15,35-41]were identified as relevant to this review. However, one trial[40] was a comparison of two doses of propofol and thus provided no comparison for use in a meta-analysis. Efficacy measures were procedural success (as defined by individual study authors), procedure time (the time from administration of the drug to recovery or no monitoring), pain (both patient- and physician-

observed), and satisfaction (by both patient and physician). These outcomes were provided for studies of etomidate, ketamine, ketofol, or propofol versus midazolam or another standard sedating agent (e.g., methohexital). Publication bias could not be assessed for any outcome as too few studies were available.

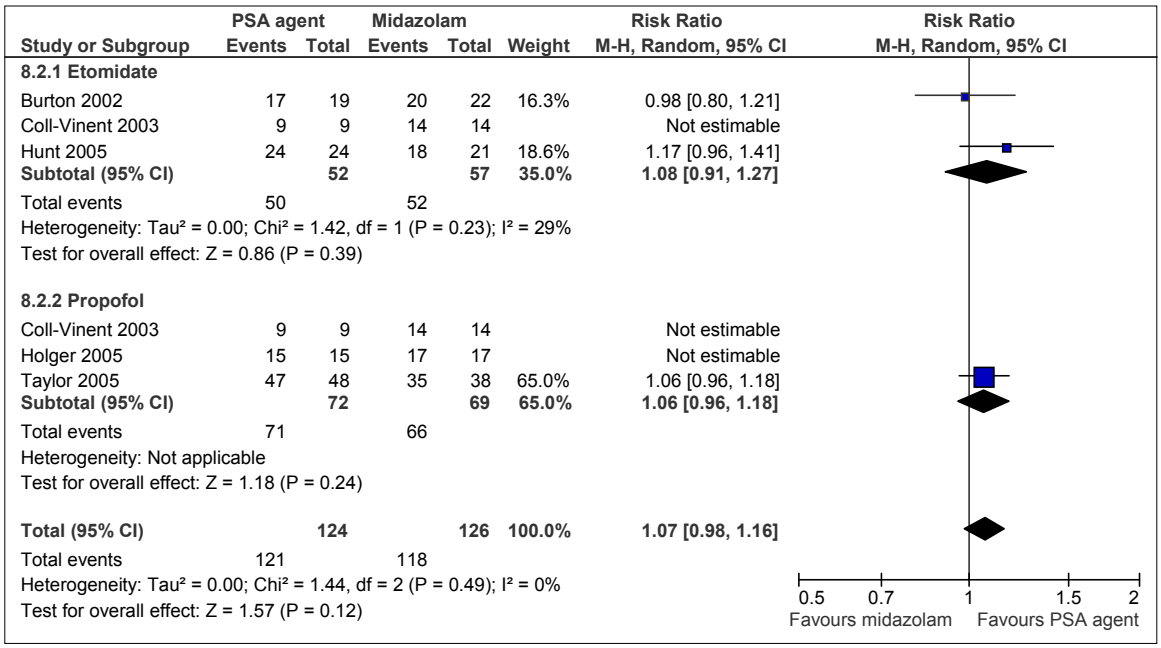
Procedural success

Eight RCTs[5,15,35-39,41] provided data for a meta-analysis on the effects of PSA agents (e.g., etomidate, propofol, ketofol, methohexital and midazolam) on the success of ED procedural sedation.

Etomidate versus midazolam: Three trials[35,36,38] involving 109 participants (etomidate=52, midazolam=57) provided data for a meta-analysis on the effects of etomidate compared with midazolam on procedural success (Figure 3). One study[36] reported 100% success for both the treatment and comparison and no relative risk to the overall estimate of success could be calculated. The combined success rates indicated that etomidate had greater procedural success compared with midazolam, but the difference was not statistically significant (RR=1.08; 95% CI: 0.91 to 1.28). There was low heterogeneity between the three trials (I^2=29%).

Propofol versus midazolam: Three trials[36,37,41] involving 152 participants (propofol=73, midazolam=76) provided data for a meta-analysis of the effects of propofol compared with midazolam on procedural success (Figure 3). Two studies[36,37] reported 100% success and so could not contribute to the overall estimate of success. The remaining trial[41] failed to demonstrate a difference in the procedural success of propofol compared with midazolam (RR=1.06; 95% CI: 0.96 to 1.18).

Figure 3: The effect of etomidate and propofol versus midazolam on procedural success



Etomidate versus propofol: Two trials[15,36] involving 231 participants (etomidate=113, propofol=118) provided data comparing the efficacy of propofol compared with etomidate on procedural success. One study[36] reported 100% success and so could not contribute to the overall estimate of success. The remaining single study[15] showed propofol to have greater success than etomidate (RR=1.09; 95% CI: 1.01 to 1.17). This difference was statistically significant.

Ketofol versus propofol: One trial[5] involving 63 participants (ketofol=32, propofol=31) provided data comparing the effect of low-dose ketamine and propofol ("ketofol") versus fentanyl and propofol on procedural success. The study failed to demonstrate a difference in the procedural success of propofol compared with ketofol (RR=0.97; 95% CI: 0.89 to 1.06).

Propofol versus methohexital: One trial[39] involving 103 participants (propofol=51, methohexital=52) provided data comparing the effect of propofol versus methohexital on procedural success. The study failed to demonstrate a difference in the procedural success of propofol compared with methohexital (RR=1.04; 95% CI, 0.96 to 1.12).

A scatter plot of the results of all studies (RCTs and observational studies) that provided data on success by drug suggests that success rates for all PSA agents are high, with short-acting agents resulting in generally better success than midazolam (Appendix 10, Figure 1).

Procedure time – direct comparisons

Another important factor in evaluating the efficacy of PSA drugs was procedure time. We pooled mean and standard deviation (SD) for the six RCTs[5,15,35-38] that provided data on the time from administration of the PSA drug to the time of recovery or no monitoring. The remaining three trials [39-41] did not provide times for the secondary time measure (time from administration of PSA drug to time to awake) or discrete times that could be combined to produce this measure.

Etomidate versus midazolam: Three studies[35,36,38] involving 102 participants (etomidate=51, midazolam=51) provided data comparing the effect of etomidate versus midazolam on the time from administration of the PSA agent to the time of recovery or no monitoring (Figure 5). The combined procedure times showed that etomidate had a statistically significant reduction in time (SMD=-1.69; 95% CI, -2.82 to -0.57). For the most recent trial[38] this represented approximately 19 fewer minutes compared with the midazolam group. However, there was significant heterogeneity among the study results (I^2=79%).

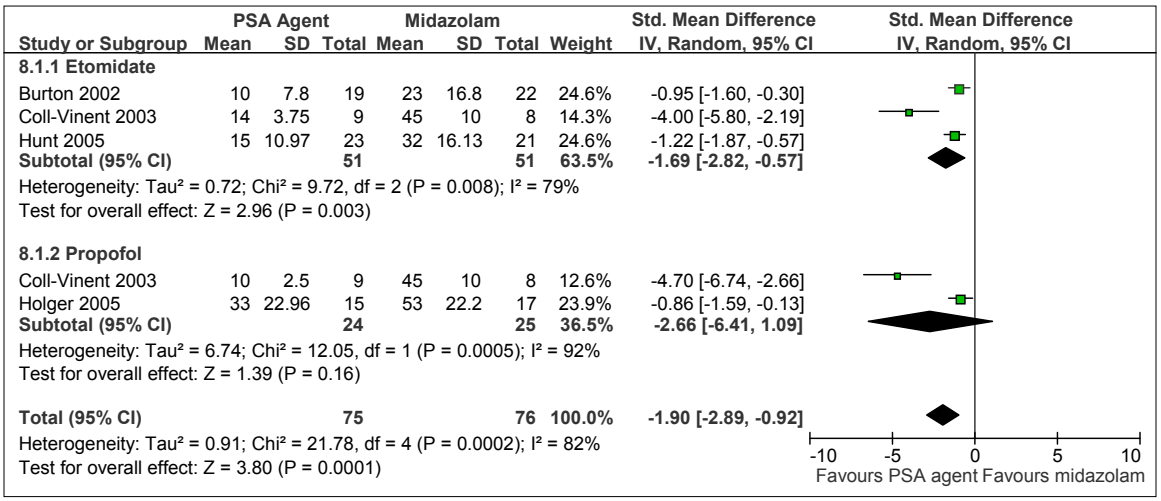
Two studies[35,38] included only PSA for orthopedic procedures, while the third trial[36] included only PSA for cardioversion. A subgroup analysis based on condition demonstrates that the two orthopedic procedures combined are homogeneous in their results (I^2=0%) and showed a statistically significant reduction in time (SMD=-1.09; 95% CI: -1.55 to -0.63) for the etomidate group. The single study[36] evaluating the procedure time for etomidate for cardioversion also showed a statistically significantly reduction in time for the etomidate group; however, the effect size was larger (SMD=-4.00; 95% CI: -5.80 to -2.19) with 31 minutes (95% CI: -38.35 to -23.65) less time required using etomidate.

Propofol versus midazolam*:* Two studies[36,37] involving 49 participants (propofol=24, midazolam=25) provided data comparing the effect of propofol versus midazolam on the time from administration of the PSA agent to the time of recovery or no monitoring (Figure 4). The pooled procedure times failed to demonstrate a statistically significant reduction in time for propofol (SMD=-2.66; 95% CI, -6.41 to 1.09). There was substantial heterogeneity between the study results (I^2=92%).

Both studies took place in similar settings (university teaching hospitals) and neither of the studies employed adjunct agents with the comparators; however, the two studies varied by recovery criteria and by condition treated. One study[36] defined "recovery" as the return to baseline scores on four separate tests: comprehension-collaboration (ability to carry out a set of orders), time-space orientation, hypnosedation (modified Ramsey scale), and memory (recall of attending physician's name). This study enrolled only patients eligible for cardioversion. The other study[37] defined "recovery" as the patients meeting a set of four criteria: normal vital signs, time-space orientation without slurred speech, ability to sit on bedside unassisted, and ability to walk from bed five steps and return unassisted, and enrolled a "convenience sample of patients undergoing painful procedures that required sedation" and did not specify patients' conditions. However, the individual results of both studies identified a statistically significant shorter procedure time for propofol (SMD=-4.70; 95% CI: -6.74 to -2.66 and SMD=-0.86; 95% CI: -1.59 to -0.13, respectively).

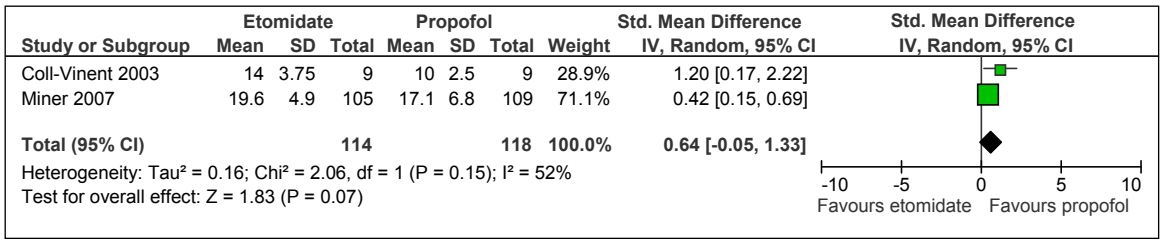
When the studies from both comparisons were combined, the result showed that the fast-acting PSA agents had a significantly shorter procedure time than midazolam (SMD=-1.90; 95% CI: -2.89 to -0.92). There was substantial heterogeneity among the study results (I^2=82%); however, all of the individual MDs demonstrated the effectiveness of the fast-acting PSA agents.

Figure 4: The effect of etomidate and propofol versus midazolam on procedure time



Etomidate versus propofol: Two studies[15,36] involving 232 participants (etomidate=114, propofol=118) provided data comparing the effect of etomidate versus propofol on the time from administration of the PSA agent to the time of recovery or no monitoring (Figure 5). The combined results failed to demonstrate a clear statistically significant difference between the two groups (SMD=0.64; 95% CI: -0.05 to 1.33). There was substantial heterogeneity between the study results (I^2=52%).

Figure 5: The effect of etomidate versus propofol on procedure time



Ketofol versus propofol: One study[5] involving 63 participants (ketofol=32, propofol=31) provided data comparing the effect of ketofol versus propofol on the time from administration of the PSA agent to the time of recovery or no monitoring. Recovery was assessed based on a modified PADSS, a standardized, objective scoring tool.[73] The ketofol group required a mean time of 42.6 minutes (SD=35.5) for recovery and the propofol group required a mean time of 48.3 minutes (SD=21.5). The result failed to identify statistically significant procedure differences between the two agents (SMD=-0.19; 95% CI: -0.69 to 0.30).

Procedure time – mixed treatment comparison

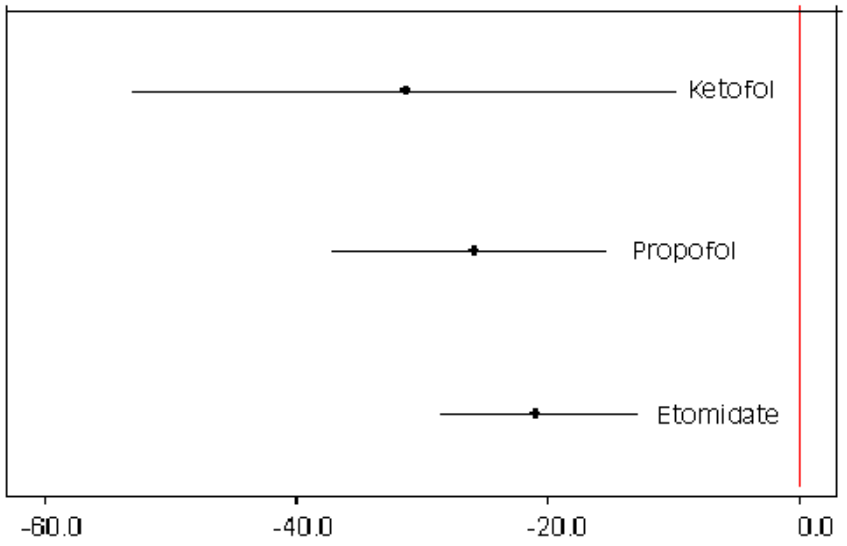
Six trials reported times from direct comparisons that could also be used to estimate the differences in the time from administration to the time to recovery/no monitoring in a mixed treatment comparison.[5,15,35-38] Table 6 and Figure 6 show the results of this analysis ordered by the point estimate of difference in procedure time from that of midazolam. The interventions ranged from reducing procedure time by an average of 31 to 21 minutes. Though the differences from midazolam for the three drugs were all statistically significant, the amount of uncertainty around the point estimates varies greatly depending on the number of studies available for comparison and the type of comparisons that can be made. Though "ketofol" shows the highest probability of being best (73%), there is also much greater uncertainty with respect to the point estimate because only one study was available and this estimate is the result of relatively more indirect comparisons than the estimates for propofol and etomidate. Similarly, the point estimate for etomidate, though the lowest probability of being "best" (3%), is also the most precise estimate of the three because it was based on the greatest number of direct comparisons with midazolam. As a result of this uncertainty, these results should be interpreted cautiously.

In terms of the differences in procedure time between the short-acting agents themselves, a similar analysis showed that there is no evidence of a significant difference between them (ketofol versus propofol: -5.5; 95% CI: -24.1 to 13.7; ketofol versus etomidate: -10.2; 95% CI: -31.4 to 10.3; propofol versus etomidate: -4.4; 95% CI: -14.8 to 3.7).

Table 6: Mixed-treatment comparison of reduction in procedure time by PSA agent

Intervention	Point estimate (min)	95% credible interval	Probability of "best"
Ketofol	-31.4	-52.9, -9.8	73%
Propofol	-25.7	-36.9, -15.5	24%
Etomidate	-21.2	-28.6, -12.8	3%

Figure 6: Procedure time (administration of drug to recovery/no monitoring) of short-acting PSA agents compared with midazolam (minutes)



A scatter plot of the results of all studies (RCTs and observational studies) that provided data on procedure time (the time from administration of the drug to recovery/no monitoring) suggests that times vary anywhere from approximately 10 minutes to 50 minutes with little difference between trials and observational studies (Appendix 10, Figure 2). This variability is not surprising given the different recovery criteria employed and the variety of conditions and populations treated.

Pain

Of the nine RCTs, six[5,15,35,39-41] reported pain assessment in their study. Two trials[5,15,35] collected pain outcomes for patients during the PSA using the visual analogue scale (VAS) of 0 mm to 100 mm and one using a 10-point scale. Two studies[39,40] simply reported frequency of pain perceived by patients and one study[41] only reported the frequency of pain at the intravenous (IV) site. The pooled estimates of pain ratings among clinical trials could not be calculated because of variation in pain measures and drug comparisons.

Etomidate versus midazolam: One study[35] compared pain perceived by patients receiving etomidate or midazolam and also physician-observed pain among patients using a VAS (0 mm to100 mm). Mean measure of pain reported by patients was 11 mm for the etomidate group and 16 mm for the midazolam group. The difference between the groups was considered statistically non-significant [mean difference (MD)=5 mm; 95% CI: -9 to 19]. Physician-observed pain was significantly lower for the etomidate group (16 mm) than for the midazolam group (31 mm; MD=15 mm; 95% CI, 2 to 28).

Propofol versus midazolam: One trial[41] compared the effect of propofol and midazolam on the reported pain at IV sites. Three of 48 patients (6.3%) receiving propofol and one of 38 patients (2.6%) receiving midazolam reported having pain at the IV site. The difference was not statistically significant (p=0.627).

Etomidate versus propofol: One study[15] examined the effect of etomidate versus propofol on patient perception of pain using a VAS (0 mm to 100 mm). The results showed that the mean rating was

higher for etomidate (18.3 mm; 95% CI: 12.8 to 23.8) than for propofol (16.2 mm; 95% CI: 11.2 to 21.3); however, the difference between the two treatments was not statistically significant (MD=2.1; 95% CI: -5.3 to 9.6).

Propofol versus fentanyl, alfentanyl, ketofol, and methohexital: Of nine RCTs, two [5,40] compared propofol with and without alfentanyl, and ketamine. One trial,[40] which compared propofol with and without fentanyl, reported the frequency of patient-perceived pain after the procedure. Among the propofol plus alfentanyl group, four out of 41 patients (10%) reported pain, while in the propofol alone group, eight out of 39 patients (20%) reported pain during the procedure. Another trial[5] comparing propofol plus fentanyl with ketofol reported a mean difference in pain ratings favouring ketofol (MD=-0.20; 95% CI: -1.24 to 0.84). One trial examining propofol and methohexital reported that six out of 52 patients (11.5%) in the methohexital group had pain during the procedure, similar to the four out of 51 patients (8%) reported in the propofol group.

A scatter plot of the results of all studies (RCTs and observational studies) that provided data on dichotomous ratings of pain (etomidate and propofol only) suggests that ratings are variable, with higher quality studies reporting in general more patients experiencing pain (Appendix 10, Figure 3).

Recall

Of nine RCTs, six[5,15,37-39,41] reported data on patient recall of the procedure. Two trials[15,37] used a VAS (0 mm to 100 mm), three [38,39,41] reported the frequency of recall and one[5] used a 10-point scale. In general, "no recall" of procedure would be considered the ideal outcome for PSA.

Etomidate versus midazolam: One trial[38] reported that four out of 24 patients (16.7%) had recall of procedure in etomidate group but none of the patients in midazolam had recall (p-value=0.04).

Propofol versus midazolam: Two studies[37,41] reported recall of the procedure. In one study,[37]a questionnaire that asked patients to rate their recall of the procedure (none, some, most or all) was given to each patient to be returned after a minimum of 24 hours. The difference in recall between the two groups was not significant. In the other study,[41] memory of the procedure favoured propofol (MD=3.7%; 95% CI: -7.7 to 14.6); however, this was not statistically significant (p=0.309).

Etomidate versus propofol: One trial[15] comparing etomidate with propofol reported a non-significant difference (MD=7.8 mm; 95% CI: -0.9 to 16.5) between mean ratings of procedural recall in the etomidate group (23.9 mm, 95% CI: 17.0 to 13.6) and the propofol group (16.1 mm; 95% CI: 10.5 to 21.6).

Propofol versus alfentanyl, ketofol and methohexital: One study[5] comparing propofol plus fentanyl with ketofol reported a mean recall (1-10 scale) of 4.1 (SD=3.7) for patients who received propofol plus fentanyl and 3.2 (SD=3.0) for patients who received ketofol; however, the difference was not statistically significant (p=0.31). The trial that compared propofol with methohexital[39] reported recall of the procedure in four out of 51 patients(12%) who received propofol compared with nine out of 52 patients (17%) who had received methohexital. The difference between the two groups was not statistically significant (p=0.59).

A scatter plot of the results of all studies (RCTs and observational studies) that provided dichotomous data on recall suggests that recall of the procedure is variable for all PSA agents (Appendix 10, Figure 4). However, higher quality studies in general reported lower rates of recall.

Patient and physician satisfaction

Seven[5,15,35-39] of the nine RCTs reported measures of patient satisfaction for use of etomidate, ketofol, and propofol for ED PSA. Three of the nine RCTs[5,37,38] reported measures of physician satisfaction. Four studies[15,35,37,39] reported satisfaction using a VAS (0 mm to 100 mm), two[5,38] used a 10-point scale, and one trial[36] recorded satisfaction using a 5-point Likert scale.

Etomidate versus midazolam: Of the two studies[35,38] that compared the effect of etomidate versus midazolam on satisfaction levels, one study[35] reported a non-significant difference in patient satisfaction between etomidate and midazolam groups (8 mm; 95% CI: -8 to 24). The same study reported a significant difference in physician satisfaction favouring etomidate (35 mm; 95% CI: 21 to 50). The other study[38] reported a non-significant difference (p=0.57) in the quality of sedation between etomidate and midazolam based on ratings on a 10-point scale.

Propofol versus midazolam: One study[37] comparing propofol with midazolam reported a mean overall patient satisfaction measure (VAS) of 94 mm for propofol and 89 mm for midazolam. Physician and nurse satisfaction was rated for three periods: titration, sedation, and recovery. The physician ratings for these periods for propofol were 95 mm, 92 mm, and 93 mm, and the ratings for the same periods for midazolam were 66 mm, 73 mm, and 75 mm. Only the difference between the propofol and midazolam group for the titration period was considered statistically significant (p=0.02). Nurse satisfaction ratings for the three periods for propofol were 85 mm, 90 mm, and 90 mm, and ratings for midazolam were 75 mm, 85 mm, and 89 mm. No differences were considered statistically significant. The differences are for various measures (patient, physician, and nurse satisfaction), so pooling is inappropriate here.

Etomidate versus propofol: Two trials[15,36] compared the effect of etomidate versus propofol on patient satisfaction. One[15] reported a mean patient satisfaction score of 9.8 (95% CI: 6.1 to 13.6) for etomidate and 10.3 (95% CI: 7.0 to 13.6) for propofol. The second trial[36] reported that for both etomidate and propofol seven out of nine patients (78%) reported being "very satisfied" and two reported being "satisfied" on a 5-point Likert scale.

Propofol versus fentanyl, ketofol, and methohexital: One trial[5] comparing ketofol with propofol plus fentanyl reported a mean patient satisfaction score of 9.4 (SD=1.4) on a 10-point scale for both the ketofol and propofol plus fentanyl groups. The mean difference in physician satisfaction scores favoured ketofol (MD=-0.60; 95% CI: -1.64 to 0.44). One trial[39] compared the effects of propofol with methohexital and reported a frequency of patient satisfaction of 45 of 51 (88%) for propofol and 45 of 52 (86%) for methohexital, a difference not considered statistically significant (p=0.77).

A scatter plot of the results of all studies (RCTs and observational studies) that provided data from dichotomous outcomes on satisfaction suggests that patient satisfaction is consistently high for all drugs (Appendix 10, Figure 5 and 6). A large RCT of propofol provided an estimate that differed from the other observational studies; however, the overall results indicate that all short-acting agents achieve satisfactory sedation.

b) Safety analysis

Forty-four studies reporting on 12,404 PSA episodes provided data that permitted examination of the safety of PSA agents in general and also by specific drug. Etomidate (n=489), propofol (n=7388), ketofol (n=156) and standard care (midazolam with or without fentanyl; n=173) were studied using both RCT and observational study designs; ketamine (n=148) and "all PSA" (n=4,050) data were

derived from observational studies alone. Seven studies provided data on the safety of "all PSA" episodes. All of the above agents were used, but the proportion of patients given in each one is not known (Appendix 11, Tables 1 to 6). We report AE risks and 95 % CI from individual studies, a subtotal comparing RCT data with observational study data, and a pooled estimate by drug agent studied.

Fifteen studies indicated that the AEs observed were clinically insignificant, transient, only required supportive interventions and caused no follow-up sequelae.[5,12,15,36,40-42,45,50,56,58-61,71] The data on agents that were studied in both RCTs and observational studies indicate that the proportion of patients with any AE were consistently and statistically significantly higher in RCTs (range 23.2% for standard care to 52.9% with etomidate) than in prospective case series studies (range 6.0% for all PSA to 15.1% for etomidate). This may be a reflection of the rigor with which AE data are collected in RCTs. Table 7 summarizes the pooled risk of AEs from RCT data, Table 8 summarizes the pooled risk of AEs from observational data, and Table 9 summarizes the combined data.

Total adverse events

The pooled risk of any AE occurring is the best estimate that could be calculated based on the available data. It was not always clear if a study was reporting the number of patients with an event or the total number of events with perhaps more than one occurring in the same patient. In these cases, we were sometimes able to contact authors to clarify the reported AEs based on the contact information provided in their report. We report the proportion of patients with an event wherever possible. The studies varied in what parameters the researchers considered an AE and also the definition of that parameter.

In the entire population, 1191 AEs were reported in the 12,404 episodes of PSA (9.6 %).The RCT/observational study combined pooled risk of any AE occurring was highest in the etomidate group (27.2%; 95% CI: 23.4 to 31.3) and lowest in the "all PSA" group (6.0%; 95% CI: 5.3 to 6.8).

Hospitalization or transfer to the operating room

In studies that reported hospitalization or transfer to the operating room for definitive care, seven went to the operating room and 10 were admitted (17/10,833; 0.16%). The reason for admission was stated in only one study; Campbell *et al.* (SGC, unpublished observations) reported that a patient who was given propofol to reduce a fractured ankle aspirated, required intubation, and was transferred to intensive care for treatment of aspiration pneumonitis. At a 3-month follow-up there were no pulmonary concerns.[74]

Twenty-seven trials had no unplanned admissions or admissions due to PSA complications. (If all procedures were successful and there were no significant AEs the assumption of no admissions was made.) Those receiving standard care had the highest pooled hospitalization/transfer risk (2.7; 95% CI: 1.1 to 6.8). There were no admissions in the ketamine and ketofol groups.

Hypotension

Hypotension was most often (N=22) defined as a decrease in systolic blood pressure to 90 mmHg to 100 mmHg or a drop of greater than 20% from baseline. No data were available for the ketamine or all PSA groups with respect to hypotension. In all other groups, 2.42% (269/11,111) reported an episode of hypotension. The simple pooled risk of hypotension was highest in the etomidate (3.2; 95% CI: 2.0 to 5.2) and propofol (3.1; 95% CI: 2.8 to 3.6) groups compared with none for ketamine and ketofol. Most episodes were brief and required no treatment; some reported giving a bolus of fluids.

Airway issues

The types of airway issues recorded in the studies varied both in the types of issues reported and in the severity of the issues reported. Apnea, decreased oxygen saturation (SaO_2), increased end tidal carbon dioxide ($EtCO_2$), bronchospasm, laryngospasm, cough, and obstruction were the most common issues reported. Apnea was reported in 2.99% (79/2,646) of patients. The combined pooled risk was highest in the standard care group (6.6; 95% CI: 3.2 to 13.0), and lowest with the ketofol group (1.8; 95% CI: 0.5 to 6.2). A decrease in SaO_2 to less than 90% to 95% occurred in 3.69% of patients (422/11,448). The risk was greatest with standard care (9.6; 95% CI: 5.9 to 15.3) and least in the "all PSA" group (1.9; 95% CI: 1.5 to 2.4). A change in $EtCO_2$ greater than 10 occurred in 17.55% of patients in all groups; however, ketamine, standard care and all PSA groups did not report this adverse outcome. The risk was highest in patients receiving etomidate (33.8; 95% CI: 26.4 to 42.1) and lowest with ketofol use (9.4%; 95% CI: 3.2 to 24.2). A form of airway spasm, cough or any airway obstruction occurred in 1.0% of patients overall. Etomidate posed the greatest risk (33.3%; 95% CI: 12.1 to 64.6) of a short-lived episode of bronchospasm and patients receiving standard care most commonly experienced a partial airway obstruction (13.2; 95% CI: 5.8 to 27.3). Supportive airway measures that could have included any one or a combination of repositioning, stimulation, supplemental oxygen or bag-valve mask were required in 4.44% of all patients (470/10,575). The risk ranged from 1.9% (95% CI: 1.4 to 2.5) in the "all PSA" group to 12.4% (95% CI: 7.7 to 19.4) in standard care.

Other adverse events observed

There was a low incidence of bradycardia (19/1,953; 0.97%) and emesis (21/2,811; 0.75%). One patient with emesis experienced aspiration, was intubated briefly but recovered and was discharged home from the ED without further sequalae.[54] Myoclonus was observed in 48/579 patients, with the highest risk being in etomidate patients: 45/308 (14.6; 95% CI: 11.1 to 19.0). Two patients receiving propofol and one with ketamine were also reported to experience myoclonus; however, no patients required an intervention. There were a few observations of an unpleasant recovery that involved restlessness, agitation, bad dreams, or delusions. This emergence phenomenon (visual, auditory or proprioceptive illusions) was experienced by 24/1,631 patients (1.47%) and was most commonly reported with ketamine use (7.4%; 95% CI: 4.2, 12.8).

Summary of adverse event profiles

Etomidate: The side effects profile for all agents included in the safety analysis suggested a higher risk of total AEs for etomidate (27.2%; 95% CI: 23.4 to 31.3) than other rapid acting agents (10% to 15%) and higher than standard care comparators (17.3%; 95% CI: 12.4 to 23.7). The AEs did not lead to hospitalization and were predominantly self-limiting, that is, resolved without treatment. The main AEs identified for this agent were airway issues (e.g., composite measure of respiratory events/depression=29.2%; 95% CI: 23.3 to 36.0) and myoclonus (14.6%; 95% CI: 11.1 to 19); however, emesis (1.1%; 95% CI: 0.5 to 2.5) and hypotension (3.2%; 95% CI: 2.0 to 5.2) were uncommon.

Propofol: The side effects profile for all agents suggested lower rates of total AEs for propofol (10%; 95% CI: 9.4 to 10.7) than other rapid acting agents (12% to 27%) and lower than standard care comparators (17.3%; 95% CI: 12.4 to 23.7). The main AEs identified for this agent were airway issues (e.g., composite measure of respiratory events/depression=29.7%; 95% CI: 26.6 to 33). Hypotension (3.1%; 95% CI: 2.8 to 3.6) and emesis (0.4%; 95% CI: 0.2 to 0.9) were uncommon. There was one reported case of aspiration pneumonitis and hospitalization after use of propofol; one other case report involved intubation but the patient recovered and was discharged home without sequelae.

Ketamine: The side effects profile for all agents suggested lower rates of total AEs for ketamine (12.2%; 95% CI: 7.8 to 18.4) than other rapid acting agents (10% to 27%) and lower than standard care comparators (17.3%; 95% CI: 12.4 to 23.7). The main side effects identified for this agent were emergence phenomena (7.4%; 95% CI: 4.2 to 12.8) and emesis (5.2%; 95% CI: 2.2 to 11.6); however, airway issues (e.g., composite measure of respiratory events/depression=4.2%; 95% CI: 1.6 to 10.2) and hypotension (0%; 95% CI: 0.0 to 2.7) were uncommon.

Ketofol: The side effects profile for all agents suggested a moderate rate of total AEs for ketofol (15.4%; 95% CI: 10.6 to 21.9) compared with other rapid acting agents (10% to 27%) and lower than standard care comparators (17.3%; 95% CI: 12.4 to 23.7). The main AEs identified were a drop in SaO_2 (one trial[5] on room air) (9.6%; 95% CI: 5.9 to 15.3) and emergence phenomena (2.6%; 95% CI: 1.0 to 6.4); emesis did not occur.

Standard care comparators: The side effects profile for all agents suggested a moderate rate of total AEs for standard care using midazolam with or without fentanyl (17.3%; 95% CI: 12.4, 23.7) compared with the newer rapid acting agents (10% to 27%). Standard comparators had a higher risk than propofol, ketamine, and ketofol but lower than etomidate (27.2%; 95% CI: 23.4 to 31.3). Standard care had a higher risk of hospitalization (2.7; 95% CI: 1.1 to 6.8) and use of supportive airway measures (12.4%; 95% CI: 7.7 to 19.4) than other agents but emesis was relatively uncommon (2.7%; 0.9 to 7.7) and no bradycardia, myoclonus or emergence phenomena occurred.

5 ECONOMIC ANALYSIS

The economic analysis involved both a review of existing economic literature and an original Canadian economic evaluation. The methods were developed and described in an a priori protocol that was followed throughout the economic evaluation.

5.1 Review of Economic Evaluations: Methods

5.1.1 Literature search strategy

Comprehensive searches were conducted in the following electronic databases, without any language restriction, for all relevant citations using pre-defined search terms (Appendix 1.2): Academic Search Premier (1975 to present), BIOSIS Previews (1969 to present), CINAHL (1937 to present), Cochrane Central Register of Controlled Trials (1900 to present), Cochrane Database of Systematic Reviews (Issue 2 2007), Database of Abstracts of Reviews of Effects (1994 to present), Dissertation Abstracts (1861 to present), EMBASE (1988 to present), Health Source: Nursing/Academic Edition (1975 to present), Health Technology Assessment Database (1995 to present), International Pharmaceutical Abstracts (1970 to present), MEDLINE (1950 to present), NHS Economic Evaluation Database (1995 to present), Ref-PRO© (1990 to present), and Web of Science (1900 to present).

The following sources were hand-searched for relevant references: reviews and guidelines; the American College of Emergency Physicians (ACEP), Canadian Association of Emergency Physicians (CAEP), and Society of Academic Emergency Medicine(SAEM) scientific meeting abstracts (published in *Annals of Emergency Medicine, Canadian Journal of Emergency Medicine*, and *Academic Emergency Medicine*, respectively); theses and dissertations, unpublished studies, and studies in progress. Reference tracking and a Science Citation Index® forward search were also used

to identify relevant studies. The results from the literature searches were entered into a Reference Manager for Windows bibliographic database version 11.0 (ISI ResearchSoft, 2005) for management.

5.1.2 Selection criteria and method

a) Broad screening criteria

- setting: hospital ED

And at least one of:

- intervention: PSA
- population: fracture, joint dislocation or cardioversion
- side effects: hypotension, apnea, emesis, pain, rash, phlebitis, or hospitalization.

b) Inclusion/exclusion criteria

- setting: procedure or study takes place in hospital ED
- population: adult patients (>17 years) requiring brief painful procedure (treatment for bone fracture, major joint dislocation, or cardioversion)
- intervention: etomidate, ketamine, propofol, or combination drug (e.g., "ketofol")
- comparator: opioid in combination with sedative-hypnotic or benzodiazepine, or regional anesthesia
- outcome: event probability, resource use, or costs.

c) Selection method

Two reviewers (JB, GF) independently screened the results of the literature search using the predetermined broad screening criteria. Screened references will be grouped into the following three categories: "potentially relevant," "clearly irrelevant," and "unclear." A report was categorized as "unclear" when insufficient information was available in the abstract, where the abstract was unavailable, or where it was not sufficiently clear that the report satisfied the inclusion criteria.

Two reviewers (JB, GF) independently appraised the full text of all the retrieved studies using a standard form containing the inclusion and exclusion criteria for studies on the economic analysis of PSA. Disagreements about inclusion or exclusion of studies were initially resolved by consensus among reviewers. The decisions to exclude studies were documented and the list of excluded studies and reasons for exclusion is provided in Appendix 3. The citations in the literature selection were managed using Reference Manager version 11 bibliographic software (Thomson ISI ResearchSoft, Carlsbad, CA). Discrepancies in inclusion and exclusion were resolved by consensus between the reviewers or by third-party adjudication (BHR or KF).

Table 7: Summary of pooled risks of adverse outcomes: RCTs [mean % risk (95% CI)]						
Adverse events	**Etomidate n/N**	**Propofol n/N**	**Ketamine n/N**	**Ketofol n/N**	**Standard care n/N**	**All PSA n/N**
Total AEs	52.9 (45.1, 60.5) 83/157	36.4 (31.5, 41.7) 125/343	No Data	46.9 (30.9, 63.6) 15/32	23.2 (16.4, 31.8) 26/112	No data
Hospitalization	0.6 (0.1, 3.5) 1/157	0.0 (0.0, 0.8) 0/343	No data	0.0 (0.0, 7.8) 0/32	2.7 (0.9, 7.6) 3/112	No data
Hypotension	0.7 (0.1, 3.7) 1/148	2.8 (1.3, 5.6) 7/254	No data	0.0 (0.0, 7.8) 0/32	2.0 (0.6, 7.1) 2/98	No data
Observed airway issues						
Apnea	5.8 (2.0, 15.6) 3/52	22.2 (6.3, 54.7) 2/9	No data	No data	10.5 (4.9, 21.1) 6/57	No data
SaO_2 <90% to 95%	10.2 (6.4, 15.9) 16/157	18.2 (14.2, 23.0) 53/292	No data	37.5 (22.9, 54.7) 12/32	10.7 (6.2, 17.8) 12/112	No data
Change $EtCO_2 \geq 10$	26.7 (19.1, 35.8) 28/105	36.1 (29.6, 43.1) 69/191	No data	9.4 (3.2, 24.2) 3/32	No data	No data
Bronchospasm/laryngospasm/cough	33.3 (12.1, 64.6) 3/9	11.1 (2.0, 43.5) 1/9	No data	No data	0.0 (0.0, 16.2) 0/14	No data
Airway obstruction	No data	12.5 (5.9, 24.7) 6/48	No data	No data	13.2 (5.8, 27.3) 5/38	No data
SAM required	22.3 (16.5, 29.4) 35/157	36.6 (31.6, 41.9) 120/328	No data	25.0 (13.3, 42.1) 8/32	14.7 (9.0, 23.2) 14/95	No data
Composite measure of respiratory events/depression	31.5 (23.9, 40.1) 39/124	39.4 (33.0, 46.2) 82/208	No data	No data	15.0 (8.1, 26.1) 9/60	No data
Other adverse events observed						
Bradycardia	0.0 (0.0, 12.5) 0/19	0.0 (0.0, 15.3) 0/15	No data	No data	0.0 (0.0, 6.5) 0/39	No data
Emesis	0.8 (0.1, 4.4) 1/124	1.4 (0.4, 4.9) 2/145	No data	0.0 (0.0, 7.8) 0/32	1.3 (0.2, 7.0) 1/77	No data
Myoclonus	21.0 (15.4, 28.0) 33/157	1.7 (0.5, 6.0) 2/118	No data	No data	0.0 (0.0, 4.5) 0/57	No data
Emergence phenomenon	4.2 (0.7, 20.2) 1/24	0.0 (0.0, 8.0) 0/31	No data	0.0 (0.0, 7.8) 0/32	0.0 (0.0, 11.4) 0/21	No data

Emergence phenomenon=any unpleasant recovery reaction (e.g., agitation, restlessness, anxiety, delusion, bad dream); SAM=supportive airway measures (e.g., any one or a combination of supplemental oxygen, repositioning, stimulation, bag-valve mask); respiratory depression=any one of or a combination of decreased SaO_2, increased $EtCO_2$, airway obstruction, apnea, decreased rate. Note: If an outcome was not specifically mentioned it is not included in the pooled estimates of risk even if they stated no AEs occurred. If a study reported no instances of a specific event then it is included.

Table 8: Summary of pooled risks of adverse outcomes: observational studies [mean % risk (95% CI)]						
Adverse events	**Etomidate n/N**	**Propofol n/N**	**Ketamine n/N**	**Ketofol n/N**	**Standard care n/N**	**All PSA n/N**
Total AEs	15.1 (11.6, 19.3) 50/332	8.7 (8.1, 9.4) 616/7,041	12.2 (7.8, 18.4) 18/148	7.3 (3.9, 13.2) 9/124	6.6 (2.6, 15.7) 4/61	6.0 (5.3, 6.8) 245/4,050
Hospitalization	1.7 (0.7, 4.0) 5/289	0.1 (0.0, 0.2) 6/6,929	0.0 (0.0, 1.8) 0/148	0.0 (0.0, 2.1) 0/114	2.9 (0.5, 14.5) 1/35	0.0 (0.0, 0.2) 1/3,077
Hypotension	4.4 (2.6, 7.2) 14/320	3.2 (2.8, 3.6) 208/6,594	0.0 (0.0, 2.7) 0/96	0.0(0.0, 2.1) 0/124	2.9 (0.5, 14.5) 1/35	1.1 (0.8, 1.5) 36/3,410
Observed airway issues						
Apnea	1.8 (0.5, 6.3) 2/111	3.4 (2.58, 4.7) 34/996	4.3 (1.5, 11.9) 3/70	1.8 (0.5, 6.2) 2/114	2.0 (0.4, 10.7) 1/49	2.3 (1.6, 3.3) 27/1,188
SaO_2 <90% to 95%	4.3 (2.5, 7.3) 12/280	3.6 (3.2, 4.0) 247/6,924	No data	2.4 (0.8, 6.9) 3/124	0.0 (0.0, 14.5) 0/16	1.9 (1.5, 2.4) 67/3,511
Changed $EtCO_2 \geq 10$	58.1 (40.8, 73.6) 18/31	9.84 (7.9, 12.2) 70/712	No data	No data	No data	No data
Bronchospasm/laryngospasm/cough	No data	0.3 (0.0, 1.4) 1/400	1.4 (0.3, 7.7) 1/70	No data	No data	No data
Airway obstruction	No data	0.2 (0.1, 0.3) 7/4,582	No data	2.6 (0.9, 7.5) 3/114	No data	2.3 (1.6, 3.3) 27/1,188
SAM required	5.8 (3.7, 9.1) 17/292	3.2 (2.8, 3.6) 215/6,804	5.7 (2.2, 13.8) 4/70	4.8 (2.24, 10.2) 6/124	3.8 (0.7, 18.9) 1/26	1.98 (1.4, 2.5) 50/2,647
*Composite measure of respiratory events/depression	25.4 (16.7, 36.6) 18/71	26.3 (22.8, 30.0) 152/579	4.2 (1.6, 10.2) 4/96	No data	0.0 (0.0, 18.4) 0/12	No data
Other AEs observed						
Bradycardia	2.0 (0.3, 10.3) 1/51	0.4 (0.1, 1.1) 3/792		0.0 (0.0, 2.3) 0/114	No data	1.6 (1.0, 2.7) 15/923
Emesis	1.2 (0.5, 3.1) 4/332	0.4 (0.2, 0.8) 6/1,688	5.2 (2.2, 11.6) 5/96	0.0 (0.0, 2.1) 0/124	6.1 (1.7, 19.6) 2/33	0.0 (0.0, 1.0) 0/160
Myoclonus	7.9 (4.6, 13.4) 12/151	No data	1.4 (0.3, 7.7) 1/70	No data	0.0 (0.0, 9.4) 0/26	No data
Emergence phenomenon	4.2 (1.2, 14.0) 2/48	8.0 (3.2, 18.8) 4/50	7.4 (4.2, 12.8) 11/148	3.2 (1.3, 8.0) 4/124	No data	0.2 (0.0, 0.6) 2/1,153

Emergence phenomenon=any unpleasant recovery reaction (e.g., agitation, restlessness, anxiety, delusion, bad dream); SAM=supportive airway measures (e.g., any one or a combination of supplemental oxygen, repositioning, stimulation, bag-valve mask); respiratory depression=any one of or a combination of decreased SaO_2, increased $EtCO_2$, airway obstruction, apnea, decreased rate. Note: If an outcome was not specifically mentioned it is not included in the pooled estimates of risk even if they stated no AEs occurred. If a study reported no instances of a specific event then it is included.

Table 9: Summary of pooled risks of adverse outcomes: RCTs + observational studies (mean % risk [95% CI])						
Adverse events	**Etomidate n/N**	**Propofol n/N**	**Ketamine n/N**	**Ketofol n/N**	**Standard care n/N**	**All PSA n/N**
Total AEs	27.2 (23.4, 31.3) 133/489	10.0 (9.4, 10.7) 741/7,384	12.2 (7.8, 18.4) 18/148	15.4 (10.6, 21.9) 24/156	17.3 (12.4, 23.7) 30/173	6.0 (5.3, 6.8) 245/4,050
Hospitalization	1.3 (0.6, 2.9) 6/446	0.1 (0.0, 0.2) 6/6,929	0.0 (0.0, 1.8) 0/148	0.0 (0.0, 1.7) 0/156	2.7 (1.1, 6.8) 4/147	0.0 (0.0, 0.2) 1/3,077
Hypotension	3.2 (2.01, 5.2) 15/468	3.1 (2.8, 3.6) 215/6,848	0.0 (0.0, 2.7) 0/96	0.0 (0.0, 1.7) 0/156	2.3 (0.8, 6.4) 3/133	1.1 (0.8, 1.5) 36/3,410
Observed airway issues						
Apnea	3.1 (1.3, 7.0) 5/163	3.6 (2.6, 4.9) 36/1,005	4.3 (1.5, 11.9) 3/70	1.8 (0.5, 6.2) 2/114	6.6 (3.2, 13.0) 7/106	2.3 (1.6, 3.3) 27/1,188
SaO_2 <90% to 95%	6.4 (4.5, 9.1) 28/437	4.2 (3.7, 4.6) 300/7,216	No data	9.6 (5.9, 15.3) 15/156	9.4 (5.4, 15.7) 12/128	1.9 (1.5, 2.4) 67/3,511
Change $EtCO_2 \geq 10$	33.8 (26.4, 42.1) 46/136	15.4 (13.2, 17.9) 139/903	No data	9.4 (3.2, 24.2) 3/32	No data	No data
Bronchospasm/laryngospasm/cough	33.3 (12.1, 64.6) 3/9	0.5 (0.1, 1.8) 1/409	1.4 (0.3, 7.7) 1/70	No data	0.0 (0.0, 16.2) 0/14	No data
Airway obstruction/malalignment	No data	0.3 (0.2, 0.5) 13/4,630	No data	2.6 (0.9, 7.5) 3/114	13.2 (5.8, 27.3) 5/38	2.3 (1.6, 3.3) 27/1,188
SAM required	11.6 (8.9, 14.9) 52/449	4.7 (4.2, 5.2) 335/7,132	5.7 (2.2, 13.8) 4/70	9.0 (5.4, 14.5) 14/156	12.4 (7.7, 19.4) 15/121	1.9 (1.4, 2.5) 50/2,647
Composite measure of respiratory events/depression	29.2 (23.3, 36.0) 57/195	29.7 (26.6, 33.0) 234/787	4.2 (1.6, 10.2) 4/96	No data	12.5 (6.7, 22.1) 9/72	No data
Other AEs observed						
Bradycardia	1.4 (0.3, 7.7) 1/70	0.4 (0.1, 1.1) 3/807	No data	0.0 (0.0, 2.3) 0/114	0.0 (0.0, 6.5) 0/39	1.6 (1.0, 2.7) 15/923
Emesis	1.1 (0.5, 2.5) 5/456	0.4 (0.2, 0.9) 8/1,833	5.2 (2.2, 11.6) 5/96	0.0 (0.0, 1.7) 0/156	2.7 (0.9, 7.7) 3/110	0.0 (0.0, 1.0) 0/160
Myoclonus	14.6 (11.1, 19.0) 45/308	1.7 (0.5, 6.0) 2/118	1.4 (0.3, 7.7) 1/70	No data	0.0 (0.0, 3.2) 0/83	No data
Emergence phenomenon	4.2 (1.4, 11.5) 3/72	5.0 (1.9, 12.0) 4/81	7.4 (4.2, 12.8) 11/148	2.6 (1.0, 6.4) 4/156	0.0 (0.0, 11.4) 0/21	0.2 (0.0, 0.6) 2/1,153

Emergence phenomenon=any unpleasant recovery reaction (e.g., agitation, restlessness, anxiety, delusion, bad dream); SAM=supportive airway measures (e.g., any one or a combination of supplemental oxygen, repositioning, stimulation, bag-valve mask); respiratory depression=any one of or a combination of decreased SaO_2, increased $EtCO_2$, airway obstruction, apnea, decreased rate. Note: If an outcome was not specifically mentioned it is not included in the pooled estimates of risk even if they stated no AEs occurred. If a study reported no instances of a specific event then it is included.

5.1.3 Data abstraction method

A detailed data abstraction form was developed with the assistance of the TEP members, pre-tested, and revised. Data was abstracted by one reviewer (GF) and entered into a Microsoft Excel™ (2003) spreadsheet (Microsoft Corporation, Redmond, WA) and cross-checked for accuracy and completeness by a second reviewer (JB). Details of study design, population characteristics, treatment outcomes (success, procedure time, AE rates and their definitions), and resource use and costs (e.g., complication rates, manipulation times, recovery times, staffing, and drug costs) were extracted.

5.2 Review of Economic Evaluations: Results

5.2.1 Literature search

The electronic search resulted in 2,501 citations. Of these, 2,300 were considered "obviously irrelevant" and excluded. The assessment of the full text of the remaining 201 potentially relevant studies resulted in 26 studies being identified as relevant to a cost-effectiveness evaluation of ED PSA agents. An additional 15 studies were identified through the grey literature search [reference tracking (n=6), science citation search (n=1), and clinical search (n=8)] (Figure 7). The level of agreement between reviewers for inclusion/exclusion was substantial (κ=0.92).

5.2.2 Study characteristics

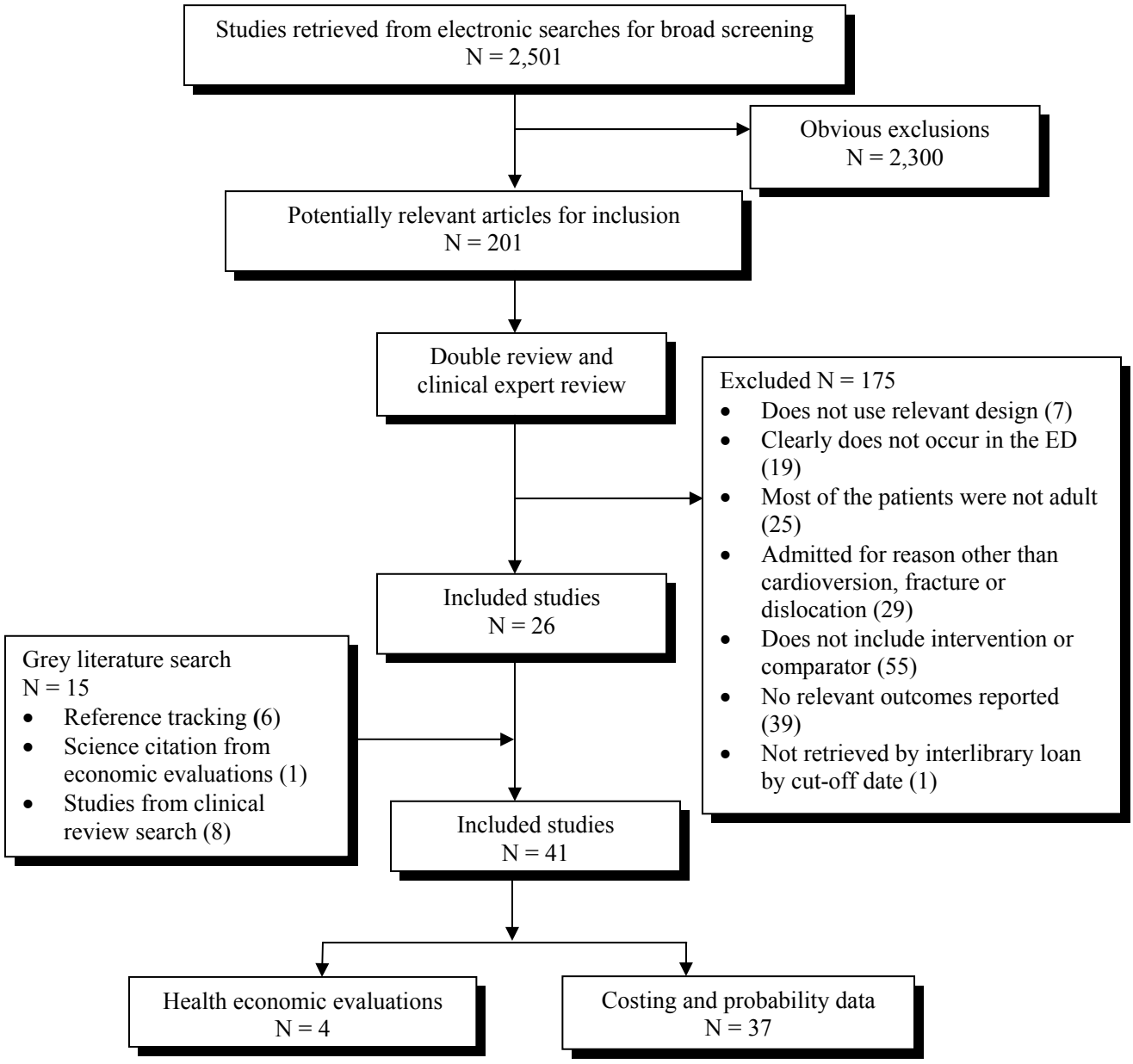
a) General characteristics

The 41 studies that contained relevant economic data on the use of sedatives and analgesics for brief painful procedures in the ED used a variety of designs (Table 10): 17 studies examined health consequences and alternatives (efficacy analysis), 14 provided outcome descriptions of a single agent (outcome description), four compared the costs and health consequences of two PSA agents (economic evaluations), three described the costs and outcomes for a single agent (cost-outcome description), two compared costs of at least two agents (cost-analysis), and one provided cost data on one agent only (cost-description). Of the four economic evaluations, [37,40,75,76] only one[37] examined the use of short-acting agents. The remaining three[40,75,76] examined regional anesthetics or analgesics compared with conventional opioids and benzodiazepines and were not relevant to the decision-making framework assumed by this report because the short-acting agents have been established as superior to hematoma blocks with morphine and lidocaine. Funk *et al.*[75] evaluated a hematoma block in conjunction with midazolam; Rainer *et al.*[76] examined keterolac versus morphine; Miller et *al.*[36] evaluated fentanyl/versed versus lidocaine. A fifth economic evaluation[37] (not identified by the formal systematic search) that examined the use of propofol versus midazolam in a Canadian ED was identified by the authors in January 2008 and was included. The characteristics of the two studies are summarized in Table 11.

b) Patient groups, agents, and procedures

Hohl *et al.*[14] looked at propofol and fentanyl versus midazolam for adults presenting to a Canadian urban tertiary hospital ED in 2006 with indications for routine PSA (e.g., orthopedic reduction or cardioversion). Holger *et al.*[37] compared propofol and fentanyl versus midazolam for adult ED PSA in a US urban teaching hospital ED from November 1999 to May 2000 for a variety of painful procedures including orthopedic reductions and incision and drainage.

Figure 7: Economic literature search results



c) Methods used

Hohl *et al.*[14] conducted a cost-effectiveness analysis with base case unit costs of $2.95/mg for propofol and $1.68/mg for midazolam. Procedure times and probabilities for success and AEs were based on a systematic review[13] of four RCTs that compared propofol with midazolam for adult PSA. The authors assumed a cost estimate for AEs of $199.53. The cost of an ED visit excluding nursing labour and pharmacy costs was based on recovery times reported in a single study. Visits were valued at $154.52 for propofol and $138.71 for midazolam. A difference in nursing times was considered to be the primary variable influencing cost differences between the two sedation strategies.

Table 10: Study designs identified through economic search (including additions from clinical search)			
	Outcomes considered		
	Costs only	**Consequences only**	**Costs and consequences**
Alternatives not considered	Cost description=1	Outcome description=14	Cost-outcome description=3
Alternatives considered	Cost analysis=2	Efficacy analysis=17	Economic evaluations=4
Total Studies: 41			

Table 11: Characteristics of economic evaluations of ED PSA			
Source		**Hohl *et al.* 2008**[14]	**Holger *et al.* 2005**[37]
Study objective		The study evaluated the incremental cost-effectiveness of using propofol versus midazolam for adult ED PSA for painful procedures.	The study evaluated the cost-effectiveness of propofol versus midazolam for adult ED PSA for painful procedures.
Alternatives compared		a) propofol b) midazolam	a) propofol b) midazolam
Location/setting		Canadian urban tertiary hospital ED	US urban teaching hospital ED
Type of economic evaluation		Cost-effectiveness of propofol for adult ED PSA for brief painful procedures.	Cost-effectiveness of propofol for adult ED PSA for brief painful procedures.
Methods	Source of effectiveness data	Success and AE rates were drawn from a meta-analysis of RCTs that compared propofol with midazolam for ED PSA. Recovery times and drug doses were drawn from patient level data from one large RCT.	Monitoring times and satisfaction ratings were drawn from an RCT of 40 patients that compared propofol with midazolam
	Primary outcomes	The primary outcome was the incremental cost-effectiveness of the propofol sedation strategy.	The primary outcome was the cost difference per patient using propofol versus midazolam.
	Cost analysis	The categories of costs and unit costs were reported. Unit cost data were derived from the hospital cost model, drug formulary, finance department and nurse's union. The price year was 2006.	Cost comparison using nursing time and drug costs. The categories of costs and unit costs were reported. The source of unit cost data was not reported. The price year was 2000.
	Analysis of uncertainty	One-way sensitivity analysis and a probabilistic sensitivity analysis were performed.	No description of the analysis of uncertainty.
Results		Propofol costs less (-$17.33; 95% CI: 10.44 to 24.13) per patient than midazolam and has an incremental cost-effectiveness ratio of $597.03 based on its higher rate of procedural success.	Propofol required less nurse monitoring time (52 minutes versus 36 minutes; $p<0.01$) and had lower costs than midazolam (-$11.99 per patient).
Study authors' conclusions		The use of propofol limits resource utilization and is cost-saving compared with midazolam. This result was robust under all scenarios examined, so routine use of midazolam should be discouraged.	Propofol for ED PSA required less nurse monitoring and resulted in lower costs. Less time commitment by physicians for sedation was required and physician satisfaction was higher when propofol was used.

ED=emergency department; PSA=procedural sedation and analgesia.

Holger *et al.*[37] conducted a cost-effectiveness analys.is with base case values for the cost of drugs of $7.98 per vial for propofol with fentanyl and $10.91 per vial for midazolam. The primary outcome measure used was nurse monitoring time with secondary outcomes of procedural times, proportion of complications, and patient, physician, and nurse satisfaction. Procedure times and satisfaction ratings were drawn from an RCT conducted by the authors that used a convenience sample of 40 patients undergoing ED PSA.

d) Results of studies identified

The base case analysis by Hohl *et al.*[14] reported a difference of $17.33 (95% CI: 10.44 to 24.13) per sedation favouring propofol. The authors also reported an incremental cost-effectiveness ratio of $597.03 based on the greater cost-effectiveness and higher success rate of propofol.

Holger *et al.*[37] found a difference of $11.99 per patient favouring propofol driven by significantly longer nurse monitoring times for patients in the midazolam group (52 minutes versus 36 minutes; $p<0.01$). The authors reported no significant difference between the two sedation strategies regarding patient satisfaction. Few AEs were noted in either group.

5.2.3 Summary and discussion

Two reviews[14,37] examining the use of short-acting agents for ED PSA were identified; both examined propofol versus midazolam. While one evaluation[37] conducted its own trial to determine procedure times and satisfaction ratings, the other[14] employed meta-analyses of existing studies to determine procedure times, and success and AE rates. This second study incorporated the results of the first in its determination of recovery times. Though both studies found significant cost differences between the two sedation strategies ($17.33 and 11.99, respectively), both assumed that differences in nursing monitoring times were the only staffing differences relevant to evaluating the cost-effectiveness of the sedation strategies. In addition, neither of the evaluations included hospitalization or resource use after discharge from the ED.

Our review of the 37 additional studies (Figure 7) was intended to provide insight into the resource use profile associated with PSA. Substantial methodological variation prevented reporting of average actual resource use. Synthesis of these papers, however, allowed us to construct a comprehensive model of resource use, including the appropriate personnel in the ED, identification of costs associated with complications, lack of procedural success, and hospitalization. Standard costing methods were then applied to each of the identified resource categories.

5.3 Canadian Economic Evaluation

5.3.1 Type of economic evaluation

Both cost-effectiveness and cost-utility analyses were initially contemplated to address this topic. A review of the literature to date suggests that clinical outcome measures include procedural success and complication rates.[21] As death and disability are exceedingly uncommon, a cost-effectiveness analysis could only be contemplated using these composite measures. A consensus definition of procedural success and complication rates, however, has not emerged. As a result, it is unlikely that such measures would be useful to clinicians. Finally, these denominators are scarcely used in the economic literature.

Based on the above considerations, the evaluation of the cost-effectiveness of propofol, ketamine, and etomidate (or any of these drugs in combination, e.g., "ketofol") versus conventional analgesic and amnestic agents for adult patients with fractures, dislocations or non-elective cardioversion who receive procedural sedation in the ED was addressed through a cost-minimization analysis (CMA). The primary variable examined was procedure cost. Effectiveness, based on rates of admission to, or re-admission to hospital or higher overall use of health care resources for the main subgroups (adults with fracture, dislocation, or elective cardioversion), was also examined. Health service events captured included direct medical costs in the ED. Health service events after discharge from the ED included hospitalization, physician visits, subsequent admissions to emergency and outpatient medications for a maximum 8-week time horizon. Health service events beyond eight weeks could not be attributed to initial procedural sedative agents.

Cost-utility analysis was also considered due to hypothesized variations in the health-related quality of life (HRQoL) profile, both in terms of duration of sedation and the recovery period. The variations, however, are not impressive and would likely not persist beyond discharge from the ED. Finally, the paucity of data arises from the fact that there is neither agreement nor use of standardized HRQoL measures applied to patients in the ED for brief events such as orthopedic reductions, cardioversions and other painful procedures.

5.3.2 Resource use and costs

Resource use associated with the health services events was based on actual, as opposed to ideal practices. Information on event probabilities and resource use and costs was drawn from the literature identified by a systematic and comprehensive economic literature search, from a systematic review of the clinical literature (Section 4), from a prior national survey of ED departments (Appendix 5), from data collected from specific Canadian sites (Appendix 5), from a time-in-motion study of procedural sedation at the University of Alberta Hospital ED (Appendix 14), from Canadian health authorities (Capital Health), from unpublished studies and reports, and from expert opinion.

5.3.3 Modelling

A costing model is described, which combines all resources used from the time of admission to the ED until discharge, either from the ED or the associated hospitalization. The costing perspective is the Ministry of Health, and as such does not include any direct non-medical, indirect or intangible costs.

Costs, probabilities and outcomes are combined to estimate cost differences between various sedation strategies. These strategies are best illustrated using a decision analytic framework as depicted in Figure 8. The diagram is composed of two panels. The first depicts the trunk, or the comparison of short-acting agents as compared with standard opioid therapy. Short-acting agents are further limited to ketamine, propofol and etomidate. Ketofol was the only drug combination noted in the systematic review and was also included. The second panel depicts the subtrees and allows the capture of procedural success, AEs and hospitalization.

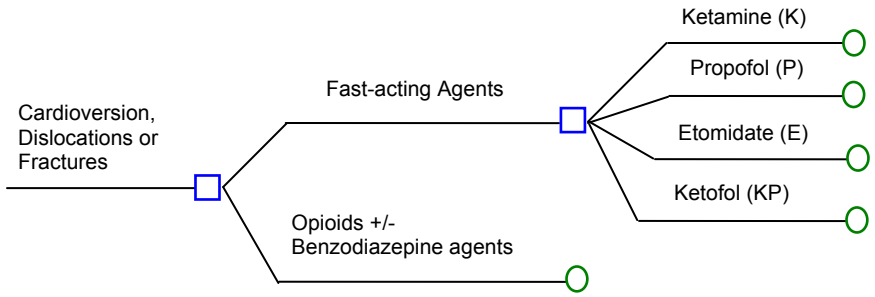
5.3.4 Time-in-motion study

A study was also conducted in the University of Alberta Hospital ED to collect more detailed data on the resources used in the treatment of fractures, dislocations, and cardioversion. The purpose of this study was to determine the time and costs associated with the administration of fast-acting PSA to

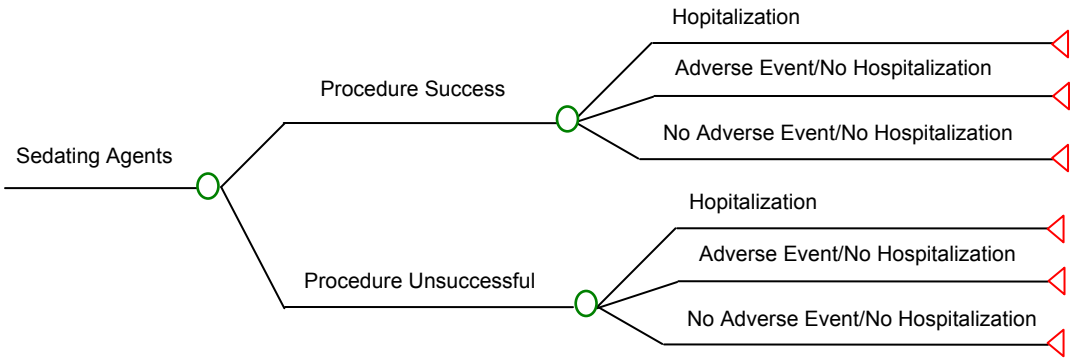
patients in the ED. Data collected included the time of each ED staff member spent with the patient during the administration of PSA, the occurrence of AEs, and the length of the patient's ED stay. The typical staff involvement and time investment was determined and the average time for the PSA calculated to allow for cost determination. The study was approved by the University of Alberta Health Research Ethics Board (Appendix 14).

Figure 8: Decision analytical model

a) Short-acting agent versus standard therapy



b) Sedating agent subtree



Note: A decision tree consists of branches and nodes. Nodes represent decisions (square), probabilities (circle) or outcomes (triangle).

5.3.5 Modelling assumptions

A costing model was developed to account for differences in treatment attributable to the sedation strategy: sedative medications, personnel, procedural success, AEs and hospitalization. Based on the systematic review of the literature, hospitalization comprised the sole attributable health event identified after discharge from the ED.

Resource use, which does not vary by sedation strategy, was omitted from our cost-minimization analysis. For example, capital, overhead and other non-drug and non-labour costs were assumed to be equivalent for all strategies and EDs and were therefore excluded from the model. With the exception of the sedating agent, all other medications and supplies were assumed to be equivalent between strategies.

Sedating strategies, however, were assumed to differ significantly in their impact on time during the patient trajectory. While recovery time constitutes a particular focus, it is not known whether the choice of sedation strategy alters time spent during other periods during the ED visit. Staffing variations are therefore also uncertain and were evaluated. Further, staffing of EDs was observed to differ, especially between urban and rural departments (Appendix 5).

By relying on data from the Alberta ED Director survey and only two urban EDs, we recognize that centre selection bias is a potential problem. This bias was mitigated by performing a sensitivity analysis and supplementing the data with information drawn from the systematic review of efficacy and safety.

Valuation of resources in the base case are reported for the province of Alberta and denominated in 2007 Canadian dollars. Unit costs for the sedating agents, personnel, hospitalization and AEs are summarized in Tables 11 to 16. For all items Canadian Price Index (CPI) indices[77] were used to inflate unit costs to 2007 levels when necessary (unit costs were not always observable in 2007).

a) Sedating agents

Table 12 provides a standard and unit cost for the sedating agents. As these drugs are manufactured and marketed directly to regional health authorities and hospitals, prices are not observable. Further, manufacturers provide "price lists" to which distributor, pharmacy mark-ups and dispensing fees are provided in the case of prescribed medications. For directly marketed products, regional health authorities and hospitals negotiate individual prices, which cannot be disclosed according to purchase agreements. In the case of multiple manufacturers, the least cost alternative list price was selected.

These medications are administered by injection and are typically available in a variety of sizes. In the ED we assume that the physician chooses vial sizes based on convenience; drug costs are infrequently known by physicians and therefore price is not a major consideration. Because these medications cannot be safely shared between patients, wastage is assumed. Our review of the literature revealed a high variation in the actual quantities of drugs administered. Little literature, however, explicitly referred to wastage. It is therefore difficult to express wastage in percentage terms.

Table 12: Sedating agent unit costs

Sedation agent(s)	Drug	Strength	Vial size	Quantity (mg)	Price ($)
Propofol	Propofol	10 mg/mL	20 mL	200	3.20
Etomidate	Etomidate	2 mg/mL	10 mL	20	17.00
Ketamine	Ketamine	10 mg/mL	2x2 mL	40	4.50
Ketofol	Propofol	10 mg/mL	20 mL	200	3.20
	Ketamine	10 mg/mL	20 mL	200	19.20
Total					**22.40**
Standard care	Fentanyl	50 µg/mL	5 mL	0.25	1.10
	Midazolam	5 mg/mL	1 mL	10	2.08
		1 mg/mL	10 mL	10	3.18

b) Personnel

Unit personnel costs are based on average income data and reported in Table 13. A Ministry of Health perspective requires that unit costs include non-wage benefits, which must be added to the

nursing and technician salaries but are included in the physician income. Statistics Canada's labour force survey[78] provides the information used to calculate nursing and technician wages. Personnel costs include non-wage benefits and were estimated at an average rate of 20%. Emergency physician income is assumed to be exempt from overhead expenses that are experienced by their colleagues in private practice. In Alberta, physicians report an average 54-hour work week. In Alberta in 2007, a specific fee is associated with each procedure and is associated with relative value fee for procedures performed on weekends and evenings ($23.70) and overnight ($56.91). For example, the following fees were used to calculate the wage for a procedural physician: dislocation reduction (shoulder) $80; fracture reduction (wrist) $128.83; and cardioversion for atrial fibrillation $91.46. For physicians providing sedation, a sedation fee is payable ($100.00) and is associated with the same relative value fees for procedures. These charges, however, are invariant to the time spent actually performing the procedure. As a result, we use estimates of full-time equivalent income for ED physicians as reported by Alberta Health and Wellness.[79] Industry-standard ED physician rotation schedules allow for the calculation of an average hourly wage. As these fees are paid directly to the physician, overhead expenses are negligible and it is assumed that physicians are responsible for their own benefits. All costs are adjusted to 2007 dollars using the CPI for all items.

Table 13: Personnel unit costs

Category	Calculations	Hourly Cost
Registered nurse	Average annual wages for registered nurses (Stats Can NOC D112), divided by 52 times the average weekly hours plus 20% non-wage benefits, inflated to 2007 dollars.	42.94
Respiratory technician	Average annual wages for registered nurses (Stats Can NOC D214), divided by 52 times the average weekly hours plus 20% non-wage benefits, inflated to 2007 dollars.	49.69
Orthopedic technician	Average annual wages for registered nurses (Stats Can NOC D219), divided by 52 times the average weekly hours plus 20% non-wage benefits, inflated to 2007 dollars.	44.64
ED physician	Average annual income of full-time equivalent emergency room physician (AHW) divided by 46 times an average of 32 clinical hours per week (CMA), inflated to 2007 dollars. It is assumed that emergency physicians do not incur overhead costs and that this rate includes equivalent non-wage benefits.	158.11

Stats Can=Statistics Canada; NOC=notice of compliance; AHW=Alberta Health and Wellness; CMA=Canadian Medical Association.

c) Hospitalization

Not all procedures are successful and even when successful, co-morbidities and illness severity may necessitate hospitalization. Because hospitalization after procedural sedation can occur for a variety of reasons, it is not surprising that it may result in varying lengths of stay. Table 14 includes the costs of representative case mix groups (CMGs) along with the number of costed cases, average length of stay and standard deviation. As can be seen, the codes do not allow for the differentiation between fractures and dislocation. Though the costs for cardioversion were lower, an overall average was assumed to simplify the analysis. Although an average cost for the hospital episode was used in the analysis, the inclusion of average length of stay allows comparison of average daily costs with other EDs. The standard deviations were used to calculate confidence intervals required by the sensitivity analysis.

d) Adverse events

Based on the systematic review of the literature, resource use associated with AEs depends on the definition of an AE, with or without hospitalization. AEs that are treated wholly within the ED are, for the most part, assumed to be minor. Repositioning and the use of bag valve masks are typical for

the treatment of breathing complications. We also did not note utilization of additional materials. Finally, we observed that treatment times were for the most part unaffected. That is to say, the total time in the ED was unaffected by these minor AEs. In the base case, it was assumed that AEs were not associated with the use of additional resources. This assumption was tested in a sensitivity analysis based on an extra 15 minutes of physician time. In any case, the cost of AEs is insignificant when compared with the cost of hospitalization and is ignored in the case of patients experiencing both AEs and hospitalization.

Table 14: Hospital costing assumptions

Description	CMG code	Costed cases	Average LOS	Average cost	95% CI
Cardioversion					
Arrhythmia	237	1,945	4.7	4,749	4,594 to 4,904
Fracture and dislocations					
Femur or pelvic fractures and dislocations	680	677	10.7	8,455	7,901 to 9,009
Fracture of humerus	684	184	8.5	6,367	5,423 to 7,311
Minor lower extremity fractures	691	42	2.4	2,620	2,205 to 3,035
Upper extremity fractures	696	497	1.6	2,271	2,258 to 2,284
Average	NA	3345	5.6	5,193	5,027 to 5,359

e) Treatment time

Hospital costs in general and ED visit costs specifically vary significantly with amount of labour inputs. Figure 9 illustrates a conceptual model for the trajectory of care faced by a typical PSA patient. Estimates of treatment time (Table 15) were derived from a formal meta-analysis of literature, data obtained from selected sites, and primary data collection at the University of Alberta Hospital. Of the average 8.3 hours spent in the ED for a typical PSA, the "procedure" itself takes only 15.5 minutes (3.1% of length of ED stay).

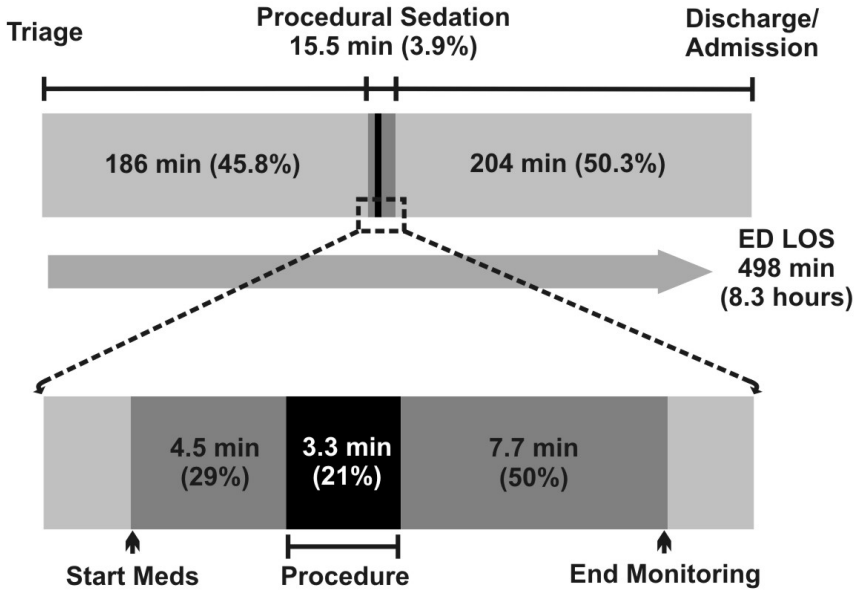
f) Emergency room staffing assumptions

Table 16 summarizes the staffing assumptions required during an ED visit. In this table, a check mark "✓" denotes the presence of the respective staff members. These assumptions are expected to hold true for all conditions requiring procedural sedation. We also acknowledge that the staffing pattern is typical for an urban hospital and not practical for a rural hospital. A "+/-" denotes substantial variation in practice. The base case will assume the presence of the respective staff member. A sensitivity analysis was used to test these assumptions.

g) Probability of procedural success, adverse events, and hospitalization

The probabilities for procedural success, AEs, and hospitalization were obtained through a systematic review and meta-analysis of evidence found in the literature and observed in selected administrative datasets. Table 17 includes the event rates expressed in percentage terms along with the 95% CIs. Procedural success is assumed to be independent of hospitalization and AEs. As a result, it is modelled separately in the decision tree. However, AEs and hospitalization are combined in the decision tree yet reported separately in the literature. Several assumptions are therefore required to address this issue.

Figure 9: Conceptual model of staffing time



Observed variation of treatment times by sedation strategy is provided in the following table.

Table 15: Treatment times by sedation strategy

Event or Drug	Treatment times [minutes (95% CI)]		
	Administration of drug (29%)*	Procedure (21%)	End of monitoring (50%)
Propofol	6.70 (6.26, 7.07)	4.85 (4.54, 5.12)	11.50 (10.80, 12.20)
Etomidate	4.52 (4.23, 4.81)	3.28 (3.07, 3.49)	7.80 (7.30, 8.30)
Ketofol	10.70 (8.44, 13.0)	7.75 (6.11, 9.41)	18.45 (14.55, 22.40)
Ketamine	11.57 (8.73, 14.44)	8.38 (6.32, 10.46)	19.95 (15.05, 24.9)
Standard care	10.32 (8.96, 11.86)	7.48 (6.49, 8.59)	17.80 (15.45, 20.45)

* Proportion of total PSA time spent in each treatment time's stage (heterogeneous population).

Table 16: Staffing needs for ED procedural sedation and analgesia

Event or Staff	Administration of drug	Procedure	Recovery/no monitoring
Nurse	✓	+/-	✓
Procedural physician	+/-	✓	
Sedation physician	✓	✓	✓
Respiratory tech	✓	✓	✓
Orthopedic tech*		✓	

NA=not applicable, +/-=staff may be present or absent during the specified time. *For orthopedic procedures only.

First, the hospitalization branch includes both AEs and patients admitted to hospital after an AE in the ED. This assumption follows from the assumption that hospitalization costs are much larger than costs associated with AEs. Second, hospitalization rates are independent of AE rates. To illustrate, let the probability of hospitalization be denoted by y and AE probabilities be denoted by x. The

probability of an AE rate not requiring hospitalization is therefore calculated as *(1-y)x*. Conversely, the probability of a patient not experiencing hospitalization or an AE is equal to *(1-y)(1-x)*. The first three rows of the table therefore contain observed values obtained from the systematic review, while the last six rows are calculated based on an assumption of independence.

The final assumption is with respect to the probability of hospitalization after an unsuccessful procedure. In the case of simple fractures and dislocations, the probability of hospitalization is very low. That is to say, patients with simple fractures and dislocations can generally be reduced perhaps during a second PSA and sent home for outpatient follow-up. Patients with complex fractures (e.g., compound, comminuted, long-bone, etc.) can be reduced in the ED using PSA; however, they need definite care in the hospital and have a hospitalization rate approaching 100% even if the initial reduction was successful. In the case of cardioversion, the probability of hospitalization is also reasonably independent of procedural success.

5.3.6 Valuing outcomes

a) Expected costs and cost-minimization calculations

Costs associated with individual events were calculated by multiplying the unit costs by the quantity of resources consumed. All unit prices were obtained from the Alberta market. In the context of a decision analytic model, expected costs were then obtained by multiplying "Canadian" quantities by "Alberta" prices. Variations in practice are based on observed differences in the quantities used by individuals. The variation in observed quantities used by individuals was greater in magnitude than the variations in prices between provinces. In the base case, an expected cost was obtained for each of the five drug strategies and for the three conditions. Cost-minimization analysis requires that the costs of the standard therapy be subtracted from the expected costs of the short-acting sedation strategies. A total of four cost-minimization calculations are reported for cardioversion with another four reported for fractures and dislocations.

5.3.7 Handling variability and uncertainty

One-way and multi-way sensitivity analyses were conducted to test the underlying assumptions arising from the cost and probability calculations. Wherever possible, the one-way sensitivity analysis used the 95% CIs. A multi-way sensitivity analysis was performed employing all CIs simultaneously.

5.4 Results

5.4.1 Base case

Expected costs by sedation strategy are provided in Table 18. These costs do not include non-drug or labour costs; only costs that are attributable to variations in sedation strategy are included here. Standard therapy is the most expensive with approximately 57% of the attributable costs due to hospitalization and AEs. Due to the higher costs of the newer PSA agents compared with older alternatives, the cost of the drug itself varies from less than 1% in the case of standard therapy to almost 10% in the case of etomidate.

Table 17: Adverse event rates by sedation strategy					
Event	**Etomidate** n/N (95% CI)	**Propofol** n/N (95% CI)	**Ketamine** n/N (95% CI)	**Ketofol** n/N (95% CI)	**Standard Care** n/N (95% CI)
Procedural success	0.94 (0.89 to 0.98)	0.99 (0.98 to 0.99)	0.94 (0.89 to 0.98)*	0.98 (0.96 to 1.0)	0.93 (0.89 to 0.98)
Total AEs	0.272 (0.234, 0.313)	0.100 (0.094, 0.107)	0.122 (0.078, 0.184)	0.154 (0.106, 0.219)	0.173 (0.124, 0.237)
Hospitalization	0.013 (0.006, 0.029)	0.001 (0, 0.002)	0 (0, 0.018)	0 (0, 0.017)	0.027 (0.011, 0.068)
Procedural success – hospitalization	0.012 (0, 0.027)	0.001 (0, 0.002)	0 (0, 0.173)	0 (0, 0.017)	0.025 (0, 0.063)
Procedural success – AE and no hospitalization	0.252 (0.228, 0.309)	0.099 (0.092, 0.106)	0.115 (0.056, 0.173)	0.151 (0.087, 0.215)	0.156 (0.097, 0.215)
Procedural success – no AE and no hospitalization	0.676 (0.415, 0.937)	0.89 (0.884, 0.896)	0.825 (0.765, 0.886)	0.829 (0.779, 0.879)	0.749 (0.688, 0.809)
No procedural success – hospitalization	0.001 (0, 0.002)	0 (0, 0)	0 (0, 0.001)	0 (0, 0)	0.027 (0, 0.068)
No procedural success – AE and no hospitalization	0.016 (0.002, 0.03)	0.001 (0, 0.002)	0.007 (0, 0.015)	0.033 (0, 0.006)	0.012 (0.004, 0.02)
No procedural success – no AE and no hospitalization	0.043 (0.003, 0.083)	0.009 (0, 0.018)	0.053 (0.009, 0.097)	0.017 (0, 0.034)	0.056 (0.024, 0.089)

*Success rate based on etomidate as no clinical trial evidence was available for ketamine use in adult ED PSA.

Table 18: Total costs by sedation strategy					
	Ketamine	**Propofol**	**Etomidate**	**Ketofol**	**Standard**
Drug	4.50	3.20	17.00	22.40	3.18
Labour	225.55	130.37	88.19	208.59	201.24
Hospitalization + AEs	0.00	5.19	67.51	0.00	270.04
Total	**230.05**	**138.76**	**172.70**	**230.99**	**474.46**

Table 19 summarizes the calculations for the four sedating agents. Propofol yields the greatest cost savings of $335.70 followed by etomidate ($301.76). Ketamine and ketofol, each approximately half the cost of standard therapy, yield the least savings ($244.41 and $243.47, respectively).

While propofol yields the greatest savings overall, etomidate generates the greatest savings from the perspective of labour costs. The implications of this result for physician behaviour are discussed in Section 7.4.

Table 19: Cost savings by sedation strategy

	Ketamine	Propofol	Etomidate	Ketofol
Drug	1.32	0.02	13.82	19.22
Labour	24.30	-70.87	-113.06	7.35
Hospitalization + AEs	-270.04	-264.84	-202.53	-270.04
Total	**-244.41**	**-335.70**	**-301.76**	**-243.47**

5.4.2 Sensitivity analysis

a) Drug costs

Table 20 examines the implications of uncertainty in drug costs. Assuming, for example, that hospitals and health regions obtain a 50% discount on the price of drugs, the differences in total cost would be equal to the cost of the discounted drug itself, varying from $1.59 in the case of standard therapy to $11.20 for ketofol. Expected costs would change 4.9% at most as in the case of etomidate; however, even given these uncertainties, propofol continues to dominate standard therapy and results in a cost savings of $335.71.

Table 20: Sensitivity analyses for variable drug costs assumptions

	Ketamine	Propofol	Etomidate	Ketofol	Standard
Drug – base case	4.50	3.20	17.00	22.40	3.18
Drug – discount	2.25	1.60	8.50	11.20	1.59
%	1.0	1.2	4.9	4.8	0.3
Cost difference	-245.07	-335.71	-308.67	-253.08	0

b) Labour costs

Expected labour and total costs vary primarily as a function of time savings in the ED and are summarized in Table 21. Using 95% CIs, a high and low labour cost was estimated for the full staffing model (L+). In addition, our staffing model allowed for procedure physicians to be absent during the administration of the drug and for nurses to be absent during the procedure (L-). A high and low labour cost is provided for this staffing model as well. Differences in labour costs contribute to the differences in cost savings that are realizable under the different labour assumptions. Three observations are important. First, the "high" and "low" estimates associated with the 95% CIs for procedure time do not alter the results greatly. Second, a more conservative labour model (L-) yields significant savings that do not differ greatly from the base case. Third, propofol yields the greatest estimate of savings in all labour costing scenarios (from $308.88 to $358.17).

Table 21: Sensitivity analyses for various labour cost assumptions						
	Assumption	**Ketamine**	**Propofol**	**Etomidate**	**Ketofol**	**Standard**
Expected labour costs	L+Base	225.55	130.37	88.19	208.59	201.24
	L+Low	170.15	122.10	82.53	164.50	174.67
	L+High	281.51	137.86	93.84	253.32	231.20
	L-Base	189.06	109.24	73.93	174.85	168.70
	L-Low	142.62	102.36	69.19	137.88	146.42
	L-High	235.97	115.56	78.67	212.32	193.80
Total costs	L+Base	230.05	138.76	172.70	230.99	474.46
	L+Low	174.65	130.50	167.04	186.90	447.89
	L+High	286.01	146.25	178.35	275.72	504.42
	L-Base	193.56	117.64	158.44	197.25	441.91
	L-Low	147.12	110.75	153.70	160.28	419.63
	L-High	240.47	123.96	163.18	234.72	467.02
Difference in labour cost	L+Base	0.00	0.00	0.00	0.00	0.00
	L+Low	-55.40	-8.27	-5.65	-44.09	-26.57
	L+High	55.96	7.49	5.65	44.73	29.96
	L-Base	-36.49	-21.13	-14.26	-33.74	-32.55
	L-Low	-82.93	-28.01	-19.00	-70.71	-54.83
	L-High	10.43	-14.81	-9.52	3.73	-7.44
Difference in total cost	L+Base	-244.41	-335.70	-301.76	-243.47	0
	L+Low	-273.24	-317.39	-280.85	-260.99	0
	L+High	-218.41	-358.17	-326.07	-228.70	0
	L-Base	-248.35	-324.27	-283.47	-244.66	0
	L-Low	-272.51	-308.88	-265.93	-259.35	0
	L-High	-226.54	-343.06	-303.84	-232.29	0

L+=full staffing; L-=physicians absent during administration of drug and nurses absent during procedure.

c) Hospitalization

Hospitalization and AE costs are also variable. To simplify this analysis, high (H+) and low (H-) costs from both hospitalization and AEs are combined. We also consider the extreme case where patients are always hospitalized when procedural success is not obtained (PS-). Table 22 summarizes the consequences associated with variation in hospital expenditures. Again, these variations yield some differences in expected costs but these are not large enough to alter the conclusions. Cost-minimization indicators again support propofol as the dominant strategy in all cases, yielding savings varying from $308.88 to $335.70.

Table 22: Sensitivity analyses for hospitalization assumptions						
	Assumption	**Ketamine**	**Propofol**	**Etomidate**	**Ketofol**	**Standard**
Expected labour costs	H+Base	225.55	130.37	88.19	208.59	201.24
	H+Low	170.15	122.10	82.53	164.50	174.67
	H+High	142.62	102.36	69.19	137.88	146.42
	H+PS-	235.97	115.56	78.67	212.32	193.80
Total costs	H+Base	230.05	138.76	172.70	230.99	474.46
	H+Low	174.65	130.50	167.04	186.90	447.89
	H+High	147.12	110.75	153.70	160.28	419.63
	H+PS-	240.47	123.96	163.18	234.72	467.02
Difference in labour cost	H+Base	0.00	0.00	0.00	0.00	0.00
	H+Low	-55.40	-8.27	-5.65	-44.09	-26.57
	H+High	-82.93	-28.01	-19.00	-70.71	-54.83
	H+PS-	10.43	-14.81	-9.52	3.73	-7.44
Difference in total cost	H+Base	-244.41	-335.70	-301.76	-243.47	0
	H+Low	-273.24	-317.39	-280.85	-260.99	0
	H+High	-272.51	-308.88	-265.93	-259.35	0
	H+PS-	-226.54	-343.06	-303.84	-232.29	0

H+=high costs; H-=low costs; PS-=patients always hospitalized when procedure not successful.

6 HEALTH SERVICES IMPACT

6.1 Population Impact

As ED PSA is employed more widely, many more Canadians will be exposed to the benefits and risks of these agents. While some uncertainty exists regarding the relative efficacy among the newer agents, no such uncertainty exists regarding their comparison to older agents. Clearly, any one of these agents would be superior to combinations of opioids and benzodiazepines. Moreover, in the current climate of ED overcrowding, the impact of PSA in the ED performed by emergency physicians is potentially huge. Reducing the time to treatment (compared with waiting for the operating room), improving pain control and reducing hospitalization are all positive patient and societal impacts. As more non-urban physicians become comfortable with these techniques it is likely that rural patients will less commonly require transfer to a tertiary care setting for failed procedural attempts.

6.2 Budget Impact

The total number of ED visits in Canada are not closely monitored and there is no national database of ED visits currently in existence[80]; however, the National Ambulatory Care Records System (NACRS; mainly an Ontario ED database) and the Ambulatory Care Classification System (ACCS; an Alberta ED database) provide some data for estimation. Based on these sources, the Canadian Institute for Health Information estimates the annual number of ED visits to be approximately 14 million.[1]

Moreover, there is no database collecting information regarding PSA delivery in Canada, so the number of cases is largely unknown. It is likely that PSA strategies are employed in virtually all EDs in Canada to some degree and there is variability among hospitals, especially when rural EDs are compared with urban EDs. The search for PSA data across Canada for this CADTH report identified PSA rates as low as 7.2/1,000 ED visits in Kingston, ON to as high as 12.7/1,000 ED visits in Halifax, NS (Appendix 5). The other estimate obtained was from St. Paul's Hospital, which reports a PSA frequency of 10.4/1,000 ED visits (Appendix 5). Using these figures, we assume national estimates for PSA use range from as low as 63,300 PSA cases to as high as 177,800 PSA cases annually.

Consequently, using the assumptions in the base case model where propofol is the preferred agent, the Canadian health care system could realize a savings of between $33.8 and $59.7 million Canadian dollars (approximately $335.78/case) compared with standard care with benzodiazepines and opioids. As large urban EDs report using many of the short-acting PSA agents already, however, these values represent only an upper estimate because the incremental savings of switching to propofol will be lower if ketamine, etomidate or ketofol are currently being used in any significant quantities. Data from specific Canadian centres shows that some sites (St. Paul's) use a short-acting agent other than propofol (ketamine), while others (Queen Elizabeth II) often use conventional agents (fentanyl). However, the fact that fentanyl is often used in combination with other agents means that this high rate of use does not of itself reflect the general use of conventional agents as a sedation strategy. Further, data collected on ED PSA in Alberta showed that a high percentage of large urban areas use propofol for reducing fractures and dislocations (94%) and cardioversion (82%), while rural EDs use predominantly conventional agents for these same procedures (82% for fractures and dislocation and 61% for cardioversion). Though the above percentages do not reflect the actual numbers of cases treated with the various PSA agents, they do suggest that cost savings are likely to vary by location and that the realizable cost savings may be lower than that estimated here.

6.3 Ethical/Equity and Psychosocial Issues

Two cornerstones of ethical practice, beneficence and non-malficence, imply that any PSA agent that is employed ought to be efficacious and carry no incremental risk of minor AEs.[81] The benefits of the short-acting PSA agents include faster treatment and recovery with no additional risk of minor AEs (and some may argue fewer risks of AEs). Although their use is widespread in urban EDs and their efficacy and safety well accepted, the safety profile of these drugs in the variety of ED settings encountered in Canada has not been well evaluated.

7 DISCUSSION

7.1 Summary of Results

Using a comprehensive search strategy, we identified 44 unique studies (9 RCTs and 44 observational studies) published between 1974 and 2007 that reported on the safety and efficacy of PSA in the emergency department. This is surprising given the frequency of the use of PSA in many EDs in Canada and elsewhere. Moreover, the frequency of reported PSA experience from Canadian EDs is also surprisingly low.

PSA is used in Canadian EDs for a variety of procedures. Orthopedic reductions of fractures and/or dislocation were the most frequent procedures performed, followed by abscess drainage, laceration repair, and cardioversion (mostly for atrial fibrillation) and this is also reflected in the studies included in the safety and efficacy review. A miscellaneous group of other procedures was also reported; however, most often studies focused their evaluation of PSA efficacy and safety on a specific procedure (e.g., cardioversion for atrial fibrillation) or a set of procedures for a specific agent.

Etomidate, ketamine, and propofol were used both individually and in combination for intervention and control groups. Propofol was the drug most commonly used, followed by etomidate and ketamine. This is perhaps not surprising because propofol is one of the most popular and longest available short-acting agents and restrictions on its use are less frequent than for etomidate. Moreover, the use of the combination of propofol and ketamine has only been described relatively recently. A variety of other agents were used as comparators in these trials including midazolam, fentanyl, methohexital, and morphine. The most common comparator was midazolam.

Overall, the methodological quality of the trials was moderate. For example, while most reported in detail many of the characteristics thought important to reduce bias, only three trials were double-blinded and few of the RCTs adequately described the method of randomization. All studies but one reported the indications for PSA. Observational studies were also of moderate quality with most studies reporting implementing at least half of the six bias criteria. Over half of the studies used consecutive series of patients considered representative of the study population. Fewer than half of the studies employed some objective criteria to assess the physical status of participants prior to PSA, and almost of the studies reported the indications for PSA. Clearly, this body of work could be improved with greater attention to the methodological quality and standardization of the reporting of outcomes.

In terms of cost-effectiveness, propofol is dominant under a variety of resource and outcome scenarios and generates an expected savings of $335.70. The second most cost-effective drug, etomidate, generates a savings of $301.76. Propofol dominates the evaluation because the costs associated with differences in hospitalization and AE savings are greater than the labour savings from etomidate.

7.2 Efficacy

The efficacy of short-acting PSA agents for painful procedures in the ED have been evaluated in RCTs based on procedural success, time of the procedure, pain, recall, and patient/physician satisfaction. Most of the studies involve a newer PSA agent(s) compared with midazolam with or without a parenteral analgesic. Overall, there were relatively few direct comparisons between newer short-acting PSA agents and no more than three studies could be combined to provide an efficacy estimate for any of the reported outcomes. However, the available evidence suggests that etomidate, ketofol, and propofol are at least as effective as other regimens in terms of procedural success and more effective in terms of reduced procedure time.

With respect to procedural success, the results of a pharmacology review reported that there is no evidence that ketofol is more efficacious than propofol alone for PSA.[82] The comparative success of propofol is based on only two trials[37,41]; however, the comparison failed to identify clear differences between propofol and midazolam. This result is consistent with a Canadian review of the effectiveness of propofol[13] that reported pooled mean difference in the probability of success

favouring propofol (2.9%; 95% CI: -6.5 to 15.2) that was not statistically significant.
The pattern of significantly shorter procedure times found here is consistent with that reported in another review on etomidate.[83] In contrast ketofol did not seem to reduce time to discharge and it may even prolong the duration of action compared with propofol alone.[82,84] Though the pooled result of the two studies comparing procedure times for propofol was not statistically significant, the individual results of both studies identified a statistically significant shorter procedure time for propofol. This is in contrast to the results of a systematic review[13] and cost-effectiveness evaluation[14] that pooled the results of the same two studies and found a statistically significant mean difference of -21.3 minutes (95% CI: 15.5 to 27.1) with little heterogeneity between study results. The review, however, included one trial[41] that reported time from successful reduction to recovery rather than from time of drug administration to recovery. Further, the results of this review include the time from a study[36] that did not employ the recovery criteria set by the other authors. The evaluation of relative procedure times is not only hampered by the variety of times reported across studies, but also by the variation in the use of recovery criteria (Aldrete Score,[85]Glasgow Coma Scale,[86] PADSS,[73] Ramsay Sedation Scale,[87] and study-specific scales employed in the nine efficacy studies). Thus, standardization in the recovery criteria would aid in the evaluation of the relative efficacy of the different PSA agents.

This review found that the definitions for other measures of effectiveness (i.e., pain, recall, and patient and physician satisfaction) were reported inconsistently and often without the use of comparable measurement scales. A descriptive summary of the individual study results suggests that there is likely no significant difference between etomidate, ketofol and midazolam with respect to these outcomes.

7.3 Safety

The combination of observational and clinical trial evidence demonstrates that these agents have AE rates at least as low and often lower than the standard care comparators (commonly midazolam with or without fentanyl). One-third of the studies indicated that the AEs observed were clinically insignificant, transient, only required supportive interventions, and caused no long-term consequences.

The results of 10 studies that reported AEs for etomidate use showed airway issues and myoclonus to be the most common concerns, a finding consistent with other non-ED studies on etomidate that have reported even higher rates of myoclonus.[83,88,89] Apnea, emesis, and hypotension were rare among these patients (overall 3.1%).

Regarding other minor AEs that are inconsistently reported (e.g., nausea, vomiting, visual disturbances, and hallucinations or dreams), the dosage of propofol and/or ketamine is considered to be an important factor in producing these AEs.[82,84]

The results of the 32 studies that reported propofol-related AEs, the lowest rate of total AEs among the three agents reviewed and often the lowest when compared with conventional agents, suggest that propofol is safe and is responsible for only few minor AEs. The results of this review are consistent with other opinions[16,90] on the use of propofol for PSA that the frequency of airway-related, cardiovascular, and gastrointestinal AEs occur less often than with other drugs. Further, when such AEs do occur they are readily addressed with brief interventions and rarely have long-term consequences. Concerns about propofol-related myoclonus[91-93] are not substantiated by this review.

There was great variation in the number and definitions of AEs reported in the studies. For example, hypotension was defined as both a relative and absolute decrease in blood pressure, and the cut-point for both of these varied among studies. Furthermore, saturation cut-points (< 95%, < 92%, < 90%, and so forth) varied among the studies. Finally, variable details and reports of side effects across studies were provided. These observations are likely the result of a lack of consensus regarding the importance of side-effect measures in PSA. Furthermore, RCTs show much greater sensitivity to AEs: RCTs reported AE rates three-and-a-half to six times higher than those reported in observational studies. However, the clinical significance of many of the defined AEs is questionable given the sensitivity and variability in the cut-off points chosen (e.g., for reduction in systolic blood pressure or reduction in SaO_2) and the transient nature of many of the AEs that resolve easily without serious long-term effects.

Given the points just discussed, it was not surprising that every drug demonstrated AEs in almost every category. No single drug can be considered superior in terms of AEs as no single agent is lowest across all of the AE categories. Conversely, no drug can be considered to be the worst as none is highest across all of the AE categories. Hence, all PSA agents appear safe so long as the patient does not have serious co-morbidities, the dose of the drug is appropriate, and the patient is closely monitored by qualified staff.

Though midazolam was the most common comparator (both alone and in combination) in the studies identified, studies on procedures not examined here (e.g., elective cardioversion and intensive care services[94]) often compare propofol with thiopentone, and there is at least one study[95] that compared an inhalation agent (sevoflurane) with propofol IV for this same procedure. The fact that the most evidence exists for propofol is unsurprising given that this is the drug most often used in urban EDs for the three procedures. The frequent use of midazolam as a comparator should provide convincing evidence to those centres where this agent is employed that the shorter acting agents are more effective. However, overcoming differences between rural and urban practice patterns to make more widespread use of these short-acting sedation agents will require individual doctors, departments, institutions, and professional associations to address issues of training and lack of guidance in PSA. Integration of PSA in rural EDs may be problematic as they rarely have the staffing support required to adhere to traditional urban protocols using the newer short-acting agents that require more than one physician or two attending staff to perform ED PSA.

It is important to note that the outcome of procedural success may not measure the success of the PSA agents. Rather, it may indicate the relative success of the procedure when a particular PSA agent is used. As one might expect, the use of an anesthetic allows for greater procedural success over less desirable alternatives because the patient is more relaxed, more compliant, etc. With widespread use of anesthetics, the difference in procedural success may be less dramatic. However, the body may react subtly differently to the action of different anesthetics and differences in the depth of sedation achieved for PSA suggest there may be potential differences in procedural success. Hence, the measurement of success is complicated by the influence of several variables. Success depends on the skill of the physician in terms the administration of the drug and of the physician or technician in the performance of the relevant procedure (fracture or dislocation reduction or cardioversion, for example). The severity of the presenting condition itself also affects the ability to perform the procedure successfully (e.g., the existence of co-morbidities with atrial fibrillation).

More than a decade ago, the problems with the seeming plethora of PSA research were highlighted[96]. A few small sample studies on a given sedative regimen (usually involving a sedation agent with well-established sedative or dissociate properties) are used to support a finding of high success and

low AEs (many of which represent the drug's main pharmacological actions) to support the assertion that the PSA regimen is "promising" or an additional tool for the emergency physician. As the authors point out, in an area in which familiarity and regular experience may result in more skillful use, emergency physicians have need of only those one or two agents that have been shown to have the highest efficacy and best safety profile. Further, given the similarity in procedural success among agents, timing and safety become major deciding factors. However, the studies that provide evidence of safety are typically performed by physicians who already have considerable experience with the sedation regimens, so caution should be exercised in concluding that clinicians and nurses unfamiliar with the same regimen will have similarly good outcomes.[96] Indeed, the evidence from one of the largest studies of adult ED PSA that focused on the role of advanced care paramedics (SGC, unpublished observations, 2007) sheds no light on this aspect of practice. Nevertheless, the combination of high rates of success and low rates of serious adverse events in a variety of settings and by physicians with varying experience suggests that, given sufficient guidance or training, these PSA agents are likely also safe in the hands of clinicians with less experience with the agents (e.g., rural physicians and non-physician extenders such as nurse practitioners and paramedics).

7.4 Economic Analysis

To date, five formal economic evaluations have been completed examining the use of sedative agents in the context of providing ED PSA.[14,37,40,75,76] Only two papers examined the use of fast-acting sedative agents.[14,37] Funk *et al.*[75] evaluated a hematoma block in conjunction with midazolam; Rainer *et al.*[76] examined keterolac versus morphine; Miller *et al.*[36] evaluated fentanyl/versed versus lidocaine; both Holger *et al.*[37] and Hohl *et al.*[14] looked at propofol/fentanyl versus midazolam. In this cost-effectiveness analysis, resources were primarily identified in the ED, whereas Hohl *et al.*[14] considered moderate AE costs on the basis of a single case in their review. No study looked at resource use after discharge from the ED. In the last two studies propofol was found to provide moderate cost savings over standard therapy.

The earlier studies are not relevant in our decision-making framework because the short-acting agents have been established as superior to hematoma blocks with morphine and lidocaine. While these techniques and drugs have limited use in certain situations,[11] they are considered inferior to the fast-acting agents. More importantly, we were interested in establishing which of the short-acting agents compares most favourably with standard therapy, which is most often midazolam with or without fentanyl.

The cost savings identified here are significant and higher than those obtained in other studies,[14] primarily because of the greater labour savings and positive cost consequences associated with hospitalization and AEs. In fact, savings associated with our model on the basis of drug and nursing time alone were similar in magnitude to those estimated in Holger *et al.*[37] and Hohl *et al.*[14] This finding has important implications in that a failure to take into account all attributable costs has resulted in an underestimation of the benefits. Finally, the economic analysis employed data from a variety of sources (e.g., clinical reviews, surveys, and expert opinions) and thus reflects more closely the actual practice in Canadian EDs.

Non-nursing personnel costs are important Because they were found to differ by sedation strategy, a finding that directly contradicts an assumption made in Hohl *et al.*[14] This makes sense because physicians who are completing the procedure (e.g., cardioversion) may be required only for only a portion of the PSA duration. Conversely, while the physician providing sedation may remain with the

patient for longer, the nurse and respiratory technician are often the ED staff members who spend the longest time observing the patient prior to complete recovery. In addition, in busy EDs, physicians may be called to other critically ill patients prior to the patient's full recovery to pre-sedation alertness. In orthopedic manipulations, orthopedic technicians may stay shorter periods of time than the physicians providing sedation, yet longer than the physician performing the actual procedure.

Although Hohl *et al.*[14] include a cost estimate for AE rates ($199.53), their event rates were extremely low. Furthermore, no economic evaluations included hospitalization. In fact, we demonstrate small but important differences in the hospitalization rate among the different PSA agents. Even though the percentages are small, the costs are large and cannot be ignored. While some may argue that patient selection influenced the estimates of the success rate (i.e., perhaps etomidate was employed for more difficult PSA cases), these are the best estimates currently available. Moreover, most physicians have experienced failures in PSA attempts resulting in the need for operative treatments (fractures and dislocations) and/or admission to hospital (all procedures).

Even when sensitivity assumptions are modeled, the cost savings associated with propofol use always dominate the analyses. These result are therefore robust and unlikely to change for EDs across the country. While the use of PSA and various agents varies within and among EDs, PSA is performed in virtually every ED in Canada. Assuming 14 million ED visits per year[1] and a PSA rate that varies from as high as 1.3% in high volume, tertiary care EDs to as low as 0.3% in community or rural sites, these results suggest approximately 51,000 to 177,000 patients per year may be exposed to this physician and institutional decision-making.

Although propofol dominates the overall costs, etomidate dominates the labour cost. What this means is that under fixed reimbursement schemes for physicians, doctors have an incentive to use etomidate because it saves them time. Savings to the system, however, include the cost of AEs and hospitalization. Provincial, regional and hospital formulary managers will need to take this into account if they continue policies to restrict etomidate use for procedural sedation. For most patients requiring PSA, there are few circumstances where etomidate is preferable to other agents, especially when one considers that propofol contraindications are rare in patients who are at low risk for complications (e.g., ASA Class I or II).

Propofol dominates other strategies not only in terms of costs but also in other aspects of PSA. First, it is the most popular agent available on the market based on the survey data and publication of scientific results. Second, it was the most successful agent with respect to procedural success. Third, other evidence from the clinician and patient perspective, albeit rather scarce, did not suggest better performance from the other PSA agents. When a drug is cheaper and has improved benefits it is said to be a "dominant strategy."

7.5 Study Limitations

Some limitations of this review should be acknowledged. First, there was an insufficient number of trials to assess the potential for publication bias in the reporting of efficacy outcomes. Recent evidence suggests that publication bias is less pervasive in the ED literature[97]; however, negative trials are less likely to be published and more likely to be excluded from a review of this nature, potentially biasing the study conclusions. The comprehensive search strategy, which included a hand-search of recent conference proceedings to identify unpublished trials, has likely minimized any such bias. More importantly, we are aware of many North American centres where PSA use with

these agents is routine, yet publication of the safety and efficacy data has not been forthcoming. It is unclear how publication bias influenced the conclusions.

Second, selection bias is always possible; however, all abstracts and primary manuscripts were screened by two independent reviewers using standardized eligibility criteria, decreasing the likelihood of this bias. Third, few comparative trials were found, so the evidence on which these conclusions are based is sparse. Fourth, RCTs and observational studies were used for the AEs and this may have biased the results. Fifth, these agents are relatively new to the ED setting and market, and their use may become more commonly reported in the near future. For example, abstracts for ketofol trials were identified; however, they are pending publication. Finally, although various combinations of the PSA drugs exist, specific attention has been paid in this report to "ketofol" (the combination of two short-acting agents, ketamine and propofol). Though the rates of AEs observed with short-acting agents and conventional opioids (e.g., propofol in combination with fentanyl) or benzodiazepines (e.g., etomidate in combination with midazolam) may be higher than with use of the short-acting agent alone, particularly with respiratory AEs, the evidence collected in this report failed to identify differences in the number of significant or long-lasting AEs between the short-acting agents and these agents in combination with opioids and benzodiazepines. Further, the data on AEs arises mainly from observational studies and is often reported in aggregate, precluding the evaluation of these groups separately.

There was considerable variability in the actual dosage of drugs and the use of supplemental drugs used in the 44 studies included in this review. A potential for bias in the drug costs therefore exists when standard dosages are assumed. Compounding this issue is the fact that PSA prices were not observable and that wastage could not be quantified. The potential bias is limited due to the fact that savings arising from the drug costs were comparatively small.

The cost differences for the PSA drugs were calculated using the combined procedure times for each drug as reported in individual studies and the "not reported differences" between times for drugs. Therefore, the combined time estimates vary based on the procedures included in the studies. As a result, we acknowledge that there is uncertainty in the comparison of labour costs between the short-acting agents. For example, in the case of etomidate, the cost difference is based on limited studies and one estimate from a short duration procedure (e.g., electrical cardioversions) and this may overestimate the cost differences among treatments.

Resource use described in clinical guidelines (staffing, drug doses, length of monitoring, etc.) describes ideal practice. In addition, this study used a base case that employed staffing levels (e.g., two physicians, a nurse, a respiratory therapist +/- an orthopedic technician, depending on the condition) found in busy, tertiary care EDs, which see many PSA cases a year. In centres where PSA is less common, the patient acuity is less severe and/or where staff shortages exist, staffing levels may be less intense. For example, from the ED Director's survey, we were able to determine that rural sites less often use the newer short-acting PSA agents than the tertiary care EDs. In addition, single coverage emergency physician staffing may preclude the two-physician model. Finally, at times in all centres and often in non-tertiary care EDs, dedicated orthopedic and respiratory staff may not always (or ever) be available. We recognize that this fact may influence the magnitude of the results described here; however, they would apply to all estimates and would not change the overall results.

7.6 Generalizability of Findings

The results of this economic evaluation hold across EDs that satisfy the cost assumptions for labour associated with the procedure, hospitalization, and AEs**.** The potential cost savings at the institutional, health authority, and national scale, represent only upper estimates, because the incremental savings of switching to propofol will be lower if ketamine, etomidate or ketofol are currently being used in any significant quantities.

7.7 Knowledge Gaps

Using the results of this technology assessment to guide decision making regarding the availability and use of the various PSA agents will require knowledge about the settings within which they might be used and how currently available PSA agents are being used. The survey of CAEP researchers (Appendix 5) found that there is little information regarding these patterns. In addition, the Alberta ED Director survey highlighted several differences between urban and rural EDs that have a significant impact on what drugs ED physicians may select when performing PSA and even whether or not to perform PSA rather than use a regional anesthetic. As the only study to evaluate the effect of different doses of an agent (high- versus low-dose propofol)[61] was a case series study, future studies should continue to assess optimal dosing strategies for ED propofol, including potential differences based on age, underlying illness, and specific procedures.[90] Further and higher-quality comparative research is needed, especially the evaluation of the use of PSA outside traditional clinical domains (e.g., paramedics, nurse practitioners) appears warranted.

8 CONCLUSIONS

This review strengthens the view of emergency medicine researchers that short-acting sedatives induce deep sedation easily and reliably and to a degree unattainable by midazolam and fentanyl. Moreover, they do so with associated AEs that are almost entirely predictable, not serious, transient, and respond to simple measures in the ED. While a variety of agents can be used alone or in combination (e.g., ketofol) for PSA, no clear efficacy superiority emerged. Conversely, etomidate appears to produce the most side effects, and there is promising evidence that side effects may be less pronounced with the combination of ketamine and propofol; however, evidence still remains sparse and the exact position of this combination of agents in the setting of PSA remains unclear. Given that emergency physicians possess the qualifications for administering deep sedation and dealing with the generally transient complications, such sedation appears safe when administered by these individuals. Low event rates and incomplete reporting of side effects prevents a comment about extremely rare complications associated with procedural sedation agents.

Previous health economic evaluations of PSA have been limited in number and scope. This economic evaluation used data from a variety of sources (e.g., clinical reviews, surveys, and expert opinions) to more closely reflect the actual practice in Canadian EDs. Overall, the results suggest that propofol is the dominant strategy compared with all other short-acting agents and this dominance occurs under a variety of scenarios and assumptions. We suggest that this conclusion is therefore unlikely to vary significantly across Canadian EDs.

9 REFERENCES

1. *Understanding emergency department wait times*. Ottawa: Canadian Institute for Health Information; 2005. Available: http://secure.cihi.ca/cihiweb/dispPage.jsp?cw_page=PG_451_E&cw_topic=451&cw_rel=AR_1266_E.
2. Chan B, Schull MJ, Schultz S, editors. Atlas of emergency department services in Ontario 1992/1993 to 1999/2000. 2001. Toronto; Institute for Clinical and Evaluative Sciences.
3. Godwin SA, Caro DA, Wolf SJ, Jagoda AS, Charles R, Marett BE, et al. Clinical policy: procedural sedation and analgesia in the emergency department. *Ann Emerg Med* 2005;45(2):177-95.
4. Innes G, Murphy M, Nijssen-Jordan C, Ducharme J, Drummond A. Procedural sedation and analgesia in the emergency department. Canadian Consensus Guidelines. *J Emerg Med* 1999;17(1):145-56.
5. Messenger D, Murray H, Dungey P, VanVlymen J, Sivilotti M. Low-dose ketamine versus fentanyl during procedural sedation with propofol: A randomized, clinical trial. *Acad Emerg Med* (under review) 2007;in press.
6. American Society of Anethesiologists. Practice guidelines by the American Society of Anesthesiologists Task Force on sedation and analgesia by non-anesthesiologists: An updated report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Anesthesiology 2002; 96, 1004-17.
7. Australasian College for Emergency Medicine AaNZCoA, Faculty of Pain Medicine and Joint Faculty of Intensive Care Medicine. Statement on clinical principles for procedural sedation. *Emerg Med* 2003;15(2):205-6. Available: http://search.ebscohost.com/login.aspx?direct=true&db=hch&AN=9472936&site=ehost-live
8. Clinical Effectiveness Committee. *Guideline for ketamine sedation in emergency departments*. London: British Association for Emergency Medicine; 2004. Available: www.emergencymed.org.uk
9. Miner JR, Krauss B. Procedural sedation and analgesia research: state of the art. *Acad Emerg Med* 2007;14(2):170-8.
10. Bahn EL, Holt KR. Procedural sedation and analgesia: A review and new concepts. *Emerg Med Clin North Am* 2005;23(2):503-217.
11. Mohr B. Safety and effectiveness of intravenous regional anesthesia (Bier block) for outpatient management of forearm trauma. *CJEM* 2006;8(4):247-50.
12. Mensour M, Pineau R, Sahai V, Michaud J. Emergency department procedural sedation and analgesia: A Canadian Community Effectiveness and Safety Study (ACCESS). *CJEM* 2006;8(2):94-9.
13. Hohl CM, Sadatsafavi M, Nosyk B, Anis A H. Safety and clinical effectiveness of midazolam versus propofol for procedural sedation in the emergency department: a systematic review. *Acad Emerg Med* 2008;15(1):1-8.
14. Hohl CM, Nosyk B, Sadatsafavi M, Anis AH. A cost-effectiveness analysis of propofol versus midazolam for procedural sedation in the emergency department. *Acad Emerg Med* 2008;15(1):32-9.
15. Miner JR, Danahy M, Moch A, Biros M. Randomized clinical trial of etomidate versus propofol for procedural sedation in the emergency department. *Ann Emerg Med* 2007;49(1):15-22.
16. Green SM. Research Advances in Procedural Sedation and Analgesia. *Ann Emerg Med* 2007;49(1):31-6.
17. Seigel DG, Podgor MJ, Remaley NA. Acceptable values of kappa for comparison of two groups. *Am J Epidemiol* 1992;135(571-8):1992.
18. Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet* 2002;359(9306):614-8.

19. Jadad AR, Moore A, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17(1):1-12.

20. Falk J, Zed PJ. Etomidate for procedural sedation in the emergency department. *Ann Pharmacother* 2002;38, 1272-7.

21. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 3rd Symposium on Systematic Reviews: Beyond the Basics. In. Oxford, UK; 2000. Available: Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm (Accessed 23 May 2007).

22. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328(7454):1490-7.

23. Bailey KR. Inter-study differences: How should they influence the interpretation and analysis of results? *Stats Med* 1987;6:351-8.

24. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21(11):1539-58.

25. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56(2):455-63.

26. Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparisons for estimating efficacy of competing interventions: empirical evidence from published meta-analysis. *BMJ* 2003;326(7387):472-6.

27. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stats Med* 2004;23(2020):3105-24.

28. Gilks WR, Richardson S, Spiegelhalter DJ. *Markov chain Monte Carlo in practice*. London: Chapman & Hall; 1996.

29. Bell A, Treston G, Cardwell R, Schabort WJ, Chand D. Optimization of propofol dose shortens procedural sedation time, prevents resedation and removes the requirement for post-procedure physiologic monitoring. *Emerg Med Australas* 2007;(5):411-7.

30. Charles M, McGinnis HD, Wehner P. Propofol for procedural sedation: One versus two physicians. *Ann Emerg Med* 2005;46(3):S73-S74.

31. Sacchetti A, Senula G, Strickland J, Dubin R. Procedural sedation in the community emergency department: initial results of the ProSCED registry. *Acad Emerg Med* 2007;14(1):41-6.

32. Bell A, Treston G, McNabb C, Monypenny K, Cardwell R. Profiling adverse respiratory events and vomiting when using propofol for emergency department procedural sedation. *Emerg Med Australas* 2007;19(5):405-10.

33. Charles M, McGinnis HD, Wehner P. Propofol for procedural sedation in a community emergency department. *Ann Emerg Med* 2005;46(3):S64.

34. Hogan K, Sacchetti A, Aman L, Opiela D. The safety of single-physician procedural sedation in the emergency department. *Emerg Med J* 2006;23(12):922-3.

35. Burton JH, Bock AJ, Strout TD, Marcolini EG. Etomidate and midazolam for reduction of anterior shoulder dislocation: a randomized, controlled trial. *Ann Emerg Med* 2002;40(5):496-504.

36. Coll-Vincent B, Sala X, Fernandez C, Bragulat E, Espinosa G, Miro O, et al. Sedation for cardioversion in the emergency department: analysis of effectiveness in four protocols. *Ann Emerg Med* 2003;42(6):767-72.

37. Holger JS, Satterlee PA, Haugen S. Nursing use between 2 methods of procedural sedation: midazolam versus propofol. *Am J Emerg* 2005;23(3):248-52.

38. Hunt GS, Spencer MT, Hays DP. Etomidate and midazolam for procedural sedation: prospective, randomized trial. *Am J Emerg* 2005;23(3):299-303.

39. Miner JR, Biros M, Krieg S, Johnson C, Heegaard W, Plummer D. Randomized clinical trial of propofol versus methohexital for procedural sedation during fracture and dislocation reduction in the emergency department. *Acad Emerg Med*2003;10(9):931-7.

40. Miner JR, Stephens D, Plummer D, Gray R. Randomized Clinical Trial of Procedural Sedation Using Propofol with and without the Ultra-short Acting Opioid Alfentanil *Acad Emerg Med* 2007;14;S58a.

41. Taylor DM, O'Brien D, Ritchie P, Pasco J, Cameron PA. Propofol versus midazolam/fentanyl for reduction of anterior shoulder dislocation. *Acad Emerg Med* 2005;12(1):13-9.

42. Bigelow S, Strote J, Hauff S, Fay K, Frank L. Case-control comparison of propofol and fentanyl/midazolam for procedural sedation. *Ann Emerg Med* 2005;46(3):S106.

43. Arora SMCFMWJH. Combining ketamine and Propofol ("Ketofol") for procedural sedation in the emergency department. *Ann Emerg Med* 2007;50(3):S121.

44. Burton JH. Comparison of Intravenous Etomidate and Intravenous Midazolam for Procedural Sedation During Reduction of Acute Prosthetic Hip Dislocation. American College of Emergency Physicians. In. Chicago, IL: Pfizer; 2001; 2001. p. 343.

45. Burton JH, Miner JR, Shipley ER, Strout TD, Becker C, Thode HC, Jr. Propofol for emergency department procedural sedation and analgesia: a tale of three centers. *Acad Emerg Med* 2006;13(1):24-30.

46. Caro DB. Trial of ketamine in an accident and emergency department. *Anaesthesia* 1974;29(2):227-9.

47. Charles M, Coyner J, Beckett M, Wehner P. Propofol for deep procedural sedation in the emergency department: Is there a learning curve? *Ann Emerg Med* 2003;42(4):S66-S67.

48. Cheng L, Edwards A. A retrospective review of a propofol procedural sedation protocol in a community hospital. *Ann Emerg Med* 2004;44(4):S59.

49. Chudnofsky CR, Weber JE, Stoyanoff PJ, Colone PD, Wilkerson MD, Hallinen DL, et al. A combination of midazolam and ketamine for procedural sedation and analgesia in adult emergency department patients. *Acad Emerg Med* 2000;7(3):228-35.

50. Dunn MJ, Mitchell R, Souza CD, Drummond G. Evaluation of propofol and remifentanil for intravenous sedation for reducing shoulder dislocations in the emergency department. *Emerg Med J* 2006;23(1):57-8.

51. Dunn T, Mossop D, Newton A, Gammon A. Propofol for procedural sedation in the emergency department. *Emerg Med J* 2007;24:459-61.

52. Engel JC. Propofol for procedural sedation in a rural emergency department. *Ann Emerg Med* 2007;50(3):S122-S123.

53. Frank LR, Strote J, Hauff SR, Bigelow SK, Fay K. Propofol by infusion protocol for ED procedural sedation. *Am J Emerg* 2006;24(5):599-602.

54. Frazee BW, Park RS, Lowery D, Baire M. Propofol for deep procedural sedation in the ED. *Am J Emerg* 2005;23(2):190-5.

55. Green SM, Sherwin TS. Incidence and severity of recovery agitation after ketamine sedation in young adults. *Am J Emerg* 2005;23(2):142-4.

56. Keim SM, Erstad BL, Sakles JC, Davis V. Etomidate for procedural sedation in the emergency department. *Pharmacotherapy* 2002;22(5):586-92.

57. Lee CC. Administration of Etomidate as a Single Agent for Conscious Sedation in the Emergency Department. American College of Emergency Physicians. In. Chicago, IL: Pfizer; 2001; 2001. p. 334.

58. Mace SE. Adverse events of emergency department procedural sedation. *Ann Emerg Med* 2006;48(4):S59.

59. Manoocha A, Innes G, Grafstein E. Are Injection Drug Users at Higher Risk of Adverse Outcomes During Procedural Sedation? *CJEM* 2003;5(3);176.

60. Miner JR, Bachman A, Kosman L, Teng B, Heegaard W, Biros MH. Assessment of the onset and persistence of amnesia during procedural sedation with propofol. *Acad Emerg Med* 2005;12(6):491-6.

61. Miner JR, Huber D, Nichols S, Biros M. The effect of the assignment of a pre-sedation target level on procedural sedation using propofol. *J Emerg Med* 2007;32(3):249-55.

62. Miner JR, Martel ML, Meyer M, Reardon R, Biros MH. Procedural sedation of critically ill patients in the emergency department. *Acad Emerg Med* 2005;12(2):124-8.

63. Peddle M, Lehnhardt K, McLeod S, Mosdossy G. A prospective analysis of procedural sedation practices among academic emergency physicians. *CJEM* 2007;9(3).

64. Reid DK, Mensour M. The use of propofol for procedural sedation in a rural community hospital. *CJEM* 2004;6(3);189.

65. Ruth WJ, Burton JH, Bock AJ. Intravenous etomidate for procedural sedation in emergency department patients. *Acad Emerg Med* 2001;8(1):13-8.

66. Swann A, Williams J, Fatovich DM. Recall after procedural sedation in the emergency department. *Emerg Med J* 2007;24(5):322-4.

67. Swanson ER, Seaberg DC, Mathias S. The use of propofol for sedation in the emergency department. *Acad Emerg Med* 1996;3(3):234-8.

68. Vinson DR, Bradbury DR. Etomidate for procedural sedation in emergency medicine. *Ann Emerg Med* 2002;39(6):592-8.

69. Weaver CS, Hauter WE, Brizendine EJ, Cordell WH. Emergency department procedural sedation with propofol: is it safe? *J Emerg Med* 2007;33(4):355-61.

70. Willman EV, Andolfatto G. A prospective evaluation of "ketofol" (ketamine/propofol combination) for procedural sedation and analgesia in the emergency department. *Ann Emerg Med* 2007;49(1):23-30.

71. Zed PJ, Abu-Laban RB, Chan WWY, Harrison DW. Efficacy, safety and patient satisfaction of propofol for procedural sedation and analgesia in the emergency department: a prospective study. *CJEM* 2007;9(6):421-7.

72. Campbell SG, Petrie DA, MacKinley RP, Froese P, Etsell G, Warren D. Procedural Sedation and Analgesia Facilitator -Expanded scope role for paramedics in the Emergency Department[unpublished]. 2007.

73. Marshall S, Chung F. Assessement of "home readiness": discharge criteria and postdischarge complications. *Curr Opin Anaesthesiol* 1997;10:445-50.

74. Cheung K, Watston M, Field S CS. Aspiration pneumonitis requiring intubation after procedural sedation and analgesia: a case report. *Ann Emerg Med* 2007;49(4):465-7.

75. Funk L. A prospective trial to compare three anaesthetic techniques used for the reduction of fractures of the distal radius. *Injury* 1997;28(3):209-12.

76. Rainer TH, Jacobs P, Ng YC, Cheung NK, Tam M, Lam PK, et al. Cost effectiveness analysis of intravenous ketorolac and morphine for treating pain after limb injury: double blind randomised controlled trial. *BMJ* 2000;321(7271):1247-51.

77. Statistics Canada. *Consumer price index (CPI), 2005 basket, annual (2002=100 unless otherwise noted)*. Ottawa: CANSIM; 2008. [Table 326-002].

78. Statistics Canada. *Labour force survey estimates (LFS), wages of employees by type of work, National Occupational Classification for Statistics (NOC-S), sex and age group, unadjusted for seasonality, monthly (dollars unless otherwise noted)*. Ottawa: CANSIM: CANSIM; 2007. [Table 282-0069].

79. Alberta Health and Wellness. *Health Costing in Alberta: 2006 Annual Report*. Edmonton, AB: Alberta Health and Wellness; 2006.

80. Rowe BH. Data collection on patients in emergency departments in Canada. *CJEM* 2008;8(417):424.

81. Beauchamp TL, Childress JF. *Principles of biomedical ethics*. 5th. New York: Oxford University Press; 2001.

82. Slavik VZ. Combination ketamine and propofol for procedural sedation and analgesia. *Pharmacotherapy* 2007;27(11):1588-98.

83. Canessa R, Lema G, Urzua J, Dagnino J, Concha M. Anesthesia for elective cardioversion: A comparison of four anesthetic agents. *J Cardiothorac Vasc Anesth* 1991;(6):566-8.

84. Loh G, Dalen D. Low-dose ketamine in addition to propokil for procedural sedation and analgesia in the emergency department. *Ann Pharmacother* 2007;41(3):485-92.

85. Aldrete JA, Kroulik D. A postanesthetic recovery score. *Anesth Analg* 1970;49:429-34.

86. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974;2:81-4.

87. Ramsay MAE, Savege TM, Simpson BRJ, Goodwin R. Controlled sedation with alpaxalone-alphadolone. *BMJ* 1974;2(5920):656-9.

88. Ford SR, Maze M, Gaba DM. A comparison of etomidate and thiopental anesthesia for cardioversion. *J Cardiothorac Vasc Anesth* 1991;(6):563-5.

89. Hullander RM, Leivers D, Wingler K. A comparison of propofol and etomidate for cardioversion. *Anesthesia Analg* 1993;(4):690-4.

90. Miner JR, Burton JH. Clinical practice advisory: emergency department procedural sedation with propofol. *Ann Emerg Med* 2007;50:182-7.

91. Thong CL, Wang CY. Propofol-related myoclonic seizures. *Ambulatory Surg* 2004;10(4):207.

92. Walder B, Tramer MR, Seeck M. Seizure-like phenomena and propofol: a systematic review. *Neurology* 2002;58(9):1327-32.

93. Hickey KS, Martin DF, Chuidian FX. Propofol-induced seizure-like phenomena. *J Emerg Med* 2005;29(4):447-9.

94. Wilbur K, Zed PJ. Is propofol an optimal agent for procedural sedation and rapid sequence intubation in the emergency department? *CJEM* 2001;3(4):302-10.

95. Karthikeyan S, Balachandran S, Cort J, Cross MH, Parsloe M. Anaesthesia for cardioversion: A comparison of sevoflurane and propofol. *Anaesthesia* 2002;(11):1114-9.

96. Heller MB, Melanson SW. Conscious sedation: We are getting sleepy, very sleepy. *Am J Emerg* 1996;14(4):440.

97. Ospina MB. Publication bias of randomized controlled trials in emergency medicine. *Acad Emerg Med* 2006;13(1):102-8.

APPENDICES

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