The effectiveness of intraoperative pharmacologic opioid minimization strategies on postoperative patient-centred outcomes

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Preface

I have led all phases of the research projects presented in my thesis including the design of the research question, assembling a multidisciplinary team, organizing and planning meetings, organizing relevant funding applications, and developing the dissemination plan. A detailed description of my contributions and contributions of co-authors for each phase is presented in the preface and contribution section of each manuscript presented in this thesis.

Abstract

For close to a century, opioid administration has been a standard of care to complement anesthesia during surgery. Considering the worldwide opioid epidemic, this practice is now being challenged and opioid alternatives are being used (eg. opioid minimizing strategies). As such, there is a need to generate evidence on the effectiveness and safety of opioid alternatives with a focus on outcomes that are the most meaningful to patients (ie. patient-centred). My proposed research program, called **O**ptimizing **P**atient-centred outcomes **U**sing opioid minimization **S**trategies (**OPUS**), directly addresses this evidence and knowledge gap while focusing on four of the top ten perioperative research priories in Canada (i.e. impact of reducing opioids during anesthesia, pain control after surgery, how can patient-centred outcomes be improved, and long-term side effects of anesthesia). The ultimate objective of OPUS is to assess the effectiveness of promising intraoperative pharmacologic opioid alternative (opioid minimizing) strategies through pragmatic clincal trials. My thesis represents foundational studies needed to meet this objective. I have 1) synthesized evidence from clinical trials assessing the patient-centred effectiveness of pharmacologic intraoperative opioid minimization strategies in adult surgical patients, and assessed the effectiveness of a promising opioid minimization pharmacologic strategy, 2) assessed Canadian anesthesiologists' opinions on intraoperative opioid minimizing practices used in adult surgical patients, and 3) designed a pilot multicentre pragmatic RCT to assess the feasibility of conducting a large trial in Canada to improve patient-centred outcomes among adult surgical patients.

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Céline, merci pour ta détermination, ton temps et ta générosité
Ton courage m'inspire tous les jours

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Chapter 1. Introduction

1.1 General anesthesia

1.1.1 Epidemiology

Each year, 300 million surgical procedures are performed worldwide with half undergoing general anesthesia.[1,2] Perioperative care safety, including general anesthesia, has improved drastically during the last 50 years. At the international level, perioperative mortality has decreased significantly with around 34 deaths per million (95% confidence interval [CI], 29 to 39) in surgical cases between the years 1990 and 2000, compared to 357 per million (95% CI, 324 to 394) in surgical cases before 1970.[3] However, patient expectations in terms of quality of care, quality of recovery experience, and analgesia are increasing while the need for shorter hospital lengths of stay is also a priority. Considering the increasing demand, the aging population,[4] and the limited available resources;[5] the importance of finding innovative solutions in order to provide efficient and high quality of care is critical.

1.1.2 Definition

General anesthesia Based on the American Society of Anesthesiologists, general anesthesia is clinically defined as:

> "A state in which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired."[9]

Physiologically, this state can be identified as a pattern of slower frequency and higher wave amplitude on the electroencephalogram (e.g. a monitor that records brain activity).[8] General anesthesia is also considered a reversible state of drug-induced unconsciousness[6,7] usually

composed of three subsequent clinical phases, namely the induction (i.e. phase during which the patient loses consciousness), maintenance (i.e. stable anesthetic phase during which a procedure, such as a surgery, can be performed), and emergence (i.e. phase when the patient regains consciousness).

1.1.3 Objectives

The ultimate objective of general anaesthesia is to facilitate and allow for the conduct of a procedure (e.g. a surgery) while the patient is unconscious and physiologically stable. Specific objectives of general anesthesia for patients undergoing surgery are to provide akinesia (i.e. absence of movement), amnesia (i.e. absence of memory), unconsciousness, and to maintain physiological stability (cardiovascular, respiratory, and thermoregulatory).[6,7] Pain management is also frequently initiated while the patient is under general anesthesia in order to facilitate postoperative pain management (i.e. preventive analgesia).[10] Analgesia (i.e. providing pain treatment) is, however, not achievable during general anesthesia considering that pain is a subjective experience that cannot be experienced while a patient is unconscious. Based on an established pain definition provided by the International Association for Study of Pain (IASP), pain is:

> " An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." [11]

This is why "nociception (i.e. pain transmission) management" is generally the type of "pain management" provided during general anesthesia.[12]

1.1.4 Pharmacologic component of general anesthesia

To achieve the specific objectives (section 1.c) while minimizing adverse effects associated with the use of a single pharmacologic agent, general anesthesia is usually conducted using multiple pharmacologic agents. This is referred to as "balanced anesthesia".[12] Three types of drugs are commonly used for this purpose, namely: anesthetics/hypnotics (i.e. propofol, anesthetic gas,

etc.), paralytics (depolarizing or non-depolarizing neuromuscular blocking agents), and adjuvants (opioids and opioid alternatives [opioids minimization strategies]). Adjuvants are pharmacologic strategies used as a complement to the other classes of agents to help achieve one or more specific objectives (section 2).[12] Opioids are the most frequently used adjuvants, largely because they offer a simple approach for providing a stable anesthesia and also due to some belief that they potentially improve postoperative recovery and analgesia.[13]

1.2 Opioid use during general anesthesia

1.2.1 Definition and classes of opioids

Opioids are "natural, synthetic or semi-synthetic chemicals that interact with opioid receptors on nerve cells in the body and brain, and reduce the intensity of pain signals as well as the feeling of pain".[14,15] There are three main classes of opioids, namely the naturally occurring (i.e. morphine, codeine, thebaine and papaverine), semi-synthetic (i.e. diamorphine, dihydromorphine, buprenorphine, and oxycodone) and synthetic compounds (i.e. fentanyl, alfentanil, remifentanil, sufentanil, etc). Opioids can also be classified according to the type of opioid receptor they bind with (e.g. mu, delta, and/or kappa), which is linked to their clinical effects (Table 1).[16,17]

Table 1. Classification of opioid receptors and main clinical effects[16,17]

Type of receptor	Mu	Delta	Kappa
Clinical effects	Analgesia Euphoria Physical dependence Miosis Bradycardia Hypothermia Urinary retention	Analgesia Depression of ventilation Physical dependence Constipation Urinary retention	Analgesia Dysphoria Sedation Low abuse potential Miosis Diuresis

Opioid receptors are primarily located in the central nervous system, namely in the brain (periaqueductal gray, locus coeruleus, and rostral ventral medulla) and in the spinal cord (interneurons and neurons in the dorsal horn). Outside the central nervous system, there is also a small quantity of opioid receptors on immune cells, gastrointestinal cells, and sensory neurons explaining their multisystemic effect.

1.2.2 Potential benefits associated with opioid use during general anesthesia

For over fifty years intraoperative opioid administration has been recognized as a standard of care adjunct to general anesthesia for patients undergoing surgery.[18] During general anesthesia, opioids' main mechanism of action is the blockade of pain receptors (nociceptor) through binding of opioid receptors in the brainstem and the spinal cord which reduce sympathetic reaction to stimulus (i.e. surgical incision, endotracheal intubation, etc.).[19,20] Clinically, this can help maintain overall patient stability (heart rate, blood pressure, metabolic). The benetifs of intraoperative opioid use on postoperative pain management are, however, uncertain.[21-23]

During general anaesthesia, in an opioid naïve patient, opioid use reduces the risk of tachycardia (increased heart rate) by enhancing cholinergic input to the sinoatrial node in the heart which slows down heart rate.[12,24] This effect can further facilitate maintaining hemodynamic stability (stable blood pressure and heart rate) during surgery.[12 25] There are also other short-term clinical advantages of using opioids as an adjuvant during general anesthesia, such as blunting gag reflex induced by the endotracheal tube insertion (i.e. intubation during the induction phase) or withdrawal (ie. extubation during the emergence phase),[26,27] reducing the risk of patient movement, and reducing total general anesthetic requirements.[28] Opioids also have an effect on the respiratory system by three main mechanisms, namely a decrease in respiratory rate (effect on the brainstem), sedation (effect on the hypothalamus) and a decrease in upper airway muscle tone leading to upper respiratory tract obsutruction.[29] These mechanisms are important to note since most opioid-related deaths are due to respiratory depression (i.e., opioid-induced ventilatory impairment).[29] Respiratory depression is generally of little importance during general anesthesia as ventilatory parameters can be controlled; however, opioids given while the patients are under general anesthesia can have sustained effects following the emergence phase.

1.2.3 Potential harms associated with intraoperative opioid use during general anesthesia

There are potential impacts from opioid use during surgery on patient outcomes and experience after surgery.[30-32] Opioids that are used during the intraoperative period are extremely potent (e.g. fentanyl is approximately 100 times more potent than morphine), thus leading to an increased risk of opioid tolerance[33 34] and hyperalgesia[33 35 36] (i.e. higher pain intensity for the same stimulus), which in turn, can increase short-term opioid needs after surgery (mean difference [MD] of oral morphine equivalent for complete intropeative opioid avoidance vs intraoperative opioid use: -6.00 mg, 95% CI -8.52 to -3.48).[37,38] Based on a 153 902 participants observational study conducted in the United States, there is also an increased risk of 30-day hospital readmission when higher intraoperative doses of opioids are used compared with lower doses (OR: 1.75, $p< 0.001$).[39] This observed increased risk of hospital readmission is also supported by the fact that opioid-related adverse effects (i.e. vomiting and ileus) are also among the most frequent reasons for unplanned hospital readmission after surgery[40,41] and there is an established dose-response relationship between opioid use and opioid-related adverse effects.[42] As a corollary, complete avoidance of opioids during surgery is associated with a reduction in postoperative nausea and vomiting (odds ratio [OR] 0.32, 95% CI 0.22 to 0.46) as well as a reduction in postoperative short-term opioid use based on a systematic review of 26 randomized controlled trials.[22,38] Despite these insights, the impact of opioid use during surgery on overall health (well-being, functional outcomes, patient satisfaction, impact on ability to perform daily life activities, and quality of life) after surgery and anesthesia remains uncertain and under studied.[30,36,39,43-56]

1.2.4 Context of the worldwide opioid epidemic

In Canada, one million surgical procedures are performed annually and approximately 2% of adult surgical patients (who were not previously using opioids) develop long-term postoperative opioid use. This conservatively translates into 20 000 new patients every year with long-term opioid dependence after surgery.[57-59] Opioids administered during perioperative care have been

identified as an important risk factor for long-term opioid use after surgery.[60] This opioid use creates a supply source in the community that is subject to diversion, increased illicit use,[61,62] overdose and deaths.[63-65] *Notably, perioperative opioid exposure often begins during the intraoperative period.*[13,18]

To date, there are no established effective interventions to prevent postoperative persistent opioid use and dependence in previous opioid-naive surgical patients. Some candidate interventions have been identified as promising, such as the use of mobile interactive applications providing advice on pain medication use,[66] postoperative physiotherapy,[67] and protocol implementation to reduce opioid prescriptions [68] [69,70] following hospital discharge. However, the level of evidence is weak for each of the interventions and the role of pharmacologic interventions during the intraoperative period to reduce long-term opioid use remains unknown.

1.2.5 Clinical Guidelines and Recommendations

For patients under general anesthesia, specific clinical guidelines and recommendations on effective and safe adjuvant *intraoperative* pharmacologic strategies (opioid or non-opioid alternatives) do not currently exist.[71,72] In general, opioids are controlled drugs that should be administered only when necessary, for the shortest amount of time possible, and with the lowest effective dose, based on the 2017 Canadian Guideline for Opioid Therapy[73] as well as the 2022 Centers for Disease Control and Prevention (CDC) Clinical Practice Guideline for prescribing opioids for pain (ambulatory setting).[74] [75] For patients receiving general anesthesia, this recommendation is challenging to apply, as there is no valid monitoring to evaluate nociception (i.e. pain transmission) or reliable clinical signs of nociception to guide opioid administration.[6,71,72] Of note, the level of evidence that supports perioperative recommendations in North America and Europe is generally low.[76,77] The methodological quality underlying the Enhanced Recovery After Surgery Society (ERAS) guidelines, an international and widely approved group in perioperative medicine, is also low.[78] Important methodological weaknesses identified are the frequent absence of a priori analytical plan and the lack of stakeholder involvement, limiting applicability of the findings.

1.2.6 Practices during general anesthesia

Opioids are still the most frequent adjuvant used during surgery. There are however significant changes in practices among anesthesiologists. Based on the results from a 1,104,324 participants multicentre (n=10 institutions) observational cohort study conducted in the United States, there has been a decrease in opioid use during general anesthesia (i.e. approximately 15% decrease in the mean quantity of opioids administered during surgery between 2012 and 2016).[79] There is also a significant variation in practices that remains unexplained. Potential contributors to this heterogeneity in practices were sex (increased opioid administration in women compared with men), procedure types, the use of non-opioid alternatives, and the type of institutions.[79] These findings were also supported by other large observational cohort studies.[80] Similar heterogeneity in practices have been observed for opioid and non-opioid analgesic regimen prescription *after* surgery.[81] There is, however, a lack of data to inform opioid and opioid minimization strategies among Canadian anesthesiologists during general anesthesia.

1.3 Opioid minimization strategies during general anesthesia

1.3.1 Definition and classes of opioid minimization strategies

Over the last two decades, in the context of an increased awareness about opioid-related adverse effects (section 2.c), there has been an emergence of opioid minimization strategies (i.e., non-opioid alternative strategies to complement general anesthesia as adjuvant).[12] Opioid minimization strategies are strategies aimed at reducing or eliminating opioid use during anesthesia and they can be classified into pharmacologic or non-pharmacologic strategies.[51]

1.3.2 Non-pharmacologic strategies

Non-pharmacologic strategies are further divided in two broad categories, namely physical interventions (e.g. acupuncture, physical therapy, therapeutic exercise, yoga, bracing, heat, cold, elevation, compression, chiropractic interventions, massage, manual therapy, transcutaneous

electrical nerve stimulation, and pulsed electromagnetic field therapy) and behavioural or psychological interventions (e.g. positive affirmations, cognitive behavioural therapy, acceptance/commitment therapy, mindfulness, distraction, guided imagery, meditation, biofeedback, relaxation, hypnosis, breathing exercise, and energy healing).[82] The feasibility and level of evidence to support the perioperative use of non-pharmacologic strategies is, however, very low[74,83] and implementation of most of these interventions can be challenging and sometimes impossible for surgical patients under general anesthesia.[84]

1.3.3 Pharmacologic strategies

Pharmacologic strategies are further divided in two broad categories, namely invasive and non invasive interventions. Invasive strategies, such as regional analgesia (peripheral or central nerve blocks), require technical expertise and their effectiveness have been demonstrated in specific surgical context (e.g. labor,[85] and gastro-intestinal surgery[86,87]). In these surgical contexts, the use of invasive opioid minimizing techniques is associated with pain reduction, improved intestinal transit recovery, and hospital length of stay reduction.[88-90] However, this type of opioid minimization strategy is not always feasible (i.e. procedure in anatomical location not accessible with block) or indicated (i.e. bleeding disorder increasing risks associated with the procedure). Thus, there is an obvious need for strategies that can be used routinely.

Non-invasive pharmacologic opioid minimization strategies include a diverse and large number of classes of opioid-minimization interventions. They are defined as alternatives or complements to opioids (e.g. general anesthetic adjuncts), with antinociceptive properties, that can be used to minimize opioid administration.[51] These agents include (but are not limited to): N-Methyl-D-aspartate receptor antagonists (e.g. ketamine, magnesium), anticonvulsants (e.g. gabapentinoids), acetaminophen, corticosteroids, alpha-2 adrenergic agonists (e.g. dexmedetomidine, clonidine), beta-adrenergic antagonists, antidepressants, nonsteroidal anti-inflammatory drugs, cannabinoids, methylxanthine adenosine receptor antagonists, and sodium channel blockers.[91,92] Most of these classes of agents are increasingly used during general anesthesia to reduce opioid use and potentially improve clinical outcomes after surgery.

1.3.4 Potential benefits associated with the use of pharmacologic opioid minimization strategies

Overall, opioid-free anesthesia (complete avoidance of opioids during general anesthesia while using opioid minimizing strategies) is feasible in some surgical contexts and has gained increasing interest over the last decade.[93,94] However, evidence to support clinically meaningful benefits for patients has not been established.[18,38,95,96] Results from a systematic review and meta-analysis of 23 randomized controlled trials (n=1304 patients) comparing opioid-free anesthesia with opioid-inclusive anesthesia showed no difference in postoperative acute pain (mean difference [MD] = -0.2; 95% CI, -0.5 to 0.2) and no clinically significant difference on other secondary outcomes.[22]

To assess the effectiveness of specific opioid minimization strategies, previous reviews and randomized controlled trials (RCTs) have focused primarily on the evaluation of *indirect* patient outcome measures (e.g. short-term quantity of opioids administered) or unidimensional instruments (e.g. pain intensity assessment or hemodynamic stability).[40,41,44-56,71,72,81,97-109] Results have suggested that opioid alternatives can reduce short-term opioid use during and after surgery. However, the impact from opioid alternatives used during or after surgery[110] on long-term opioid use as well as on outcomes that are most meaningful to patients (i.e. patient-centred outomes) are not well known.[90] Results from a systematic review synthesizing published meta-analyses assessing the effectiveness of non-opioid pharmacological perioperative interventions revealed a critical need for high quality meta-analyses in this area.[83] Among the 17 published studies included, most of them were of low (n=9) or critically low (n=6) methodological quality and only one[111] was rated as high quality based on AMSTAR-2 critical appraisal tool and one as moderate quality.[112]

1.3.5 Potential harms associated with the use of pharmacologic opioid minimization strategies

Opioid minimization strategies can also be associated with adverse events especially when they are adopted before there is sufficient evidence about their risks and benefits. For example,

compared with usual care, gabapentinoids were shown to be associated with an increased risk of respiratory depression when co-administered with opioids as well as an increased incidence of dizziness, visual disturbance, and dependence disorder.[113 114-116] This represents an opioid minimization strategy that was routinely used off-label (i.e. use of an approved drug for an unauthorized indication) for perioperative care worldwide and its perioperative use is now being discouraged and de-implemented.[117] This example emphasizes the importance of careful and critical evidence appraisal of opioid minimization strategies before recommending their utilization, and the need to apply rigorous methods to assess possible benefits *and* risks. Other opioid minimization strategies were also shown to be associated with adverse events, such as bradycardia (risk ratio [RR] for bradycardia for alpha-2 agonists compared with placebo: 1.88, 95% CI 1.35 to 2.62),[118] nightmares (4% absolute increase in the risk of nightmares with intraoperative ketamine compared with placebo [p= 0.03]),[119] delayed awakening (time for recovery of orientation after general anesthesia with magnesium compared to placebo: standardize mean difference [SMD] 1.13 min, 95% CI 0.83 to 1.43), and potential increased in postoperative chronic pain (corticosteroid compared with placebo [relative risk: 1.2, 95% CI 1.06 to 1.41]).[120] However, the clinical significance of these potential harmful adverse events remains unclear.

1.4 The Emergence and Importance of Patient-Centred Outcomes in Anesthesiology

1.4.1 "Traditional" clinical outcomes in Anesthesia

In anesthesiology and perioperative research, traditional clinical outcomes have largely been "provider-centric", meaning that they were a priority for the provider, but not necessarily for patients/participants in trials. For example, short-term opioid administration, hospital length of stay, and acute pain intensity using unidimensional pain scales (i.e. visual analogue scale), were among the most frequently assessed outcome measures in previous studies, providing conflicting results that could not be applied to the patient bedside.[40,41,44-56,71,72,81,97-109] Acute pain management after surgery is still a major clinical challenge and is one of the most important perioperative endpoints for surgical patients. However, the reliance on unidimensional pain scales (i.e. visual analogue scale) to assess pain intensity (for research and clinical care) is

neither valid or reliable[121] and not patient-centred.[122,123] Indeed, the use of pain intensity score reduction as a unique goal for postoperative pain management without considering the patients overall recovery (e.g. functional recovery and adverse effects) can paradoxically harm the patient.[121,124-129] This type of pain management frequently results in opioid overuse.[130,131] This is why postoperative pain management should be guided and balanced by the following three main components: pain intensity reduction, functional recovery and minimization of adverse effects.[132] The evaluation of short-term opioid use can also be misleading due to indirectness (i.e., surrogate outcome that is not directly important to the patient).[133] For example, a reduction in opioid administration during the immediate postoperative period can be caused by pain relief, but it can also be caused, for instance, by an increase in opioid-related adverse effects (i.e. dizziness, nausea, respiratory depression, etc.) and the amount of opioid administered being reduced accordingly. Interpretation of "traditional" outcomes can be very challenging and imprecise.

1.4.2 Patient-centred outcome definition and classification

In light of the weaknesses of indirect and unidimensional postoperative outcome measures, patient-centred outcomes are recommended as they provide a holistic portrait of the patient experience. The importance of multidimensional and patient-centred outcome assessment is emphasized by multiple international societies,[134] patients with lived experience identified priorities,[134-136] and guidelines such as the American Society for Enhanced Recovery & Perioperative Quality Initiative Joint Consensus,[44] as well as The International Association for the Study of Pain.[136]

Based on the Patient-Centered Outcomes Research Institute (PCORI), patient-centeredness refers to "the extent to which the preferences, decision-making needs, and characteristics of patients are addressed."[137] In perioperative care, patient-centred outcomes classification and guidance on the most important outcome measures and instruments to be used have been established by the Standardised Endpoints in Perioperative Medicine initiative (StEP-COMPAC group) following the Core Outcome Measures in Effectiveness Trials (COMET) recommendations (Table 1).[138-140] A total of five outcome measure domains were identified: patient satisfaction, patient well-being, health-related quality of life, functional outcome, and life impact.[141,142] These outcome measures

have been deemed essential to capture the patient's global experience following surgery, including pain and pain impact on daily life, and they are also multidimensional, but they remain critically underrepresented in clinical practice guidelines[138,143] and quality and safety indicators in the perioperative field.[144] For each outcome of the five domains, the StEP-COMPAC group also provides recommendations on the specific validated instruments that should be prioritized to capture this component of patient recovery after surgery. The importance of a holistic approach when assessing pain and recovery after surgery has also been highlighted by patients, patient advocates, international expert societies, and other interested parties.[129,134,136,145,146]

Table 1. StEP-COMPAC group recommendations for patient-centred outcome assessments in perioperative clinical trials[141] and our prioritization order tailored to pharmacologic interventions

	Patient-centred outcome domains				
	Patient well-being	Health-related quality of life	Functional outcome	Patient satisfaction	Life impact
Instruments to be prioritized based on StEP-COMPAC recommendations	Quality of recovery-15 [147]	EuroQol 5 Dimension, five-level version with visual analogue scale [148]	WHO Disability Assessment Schedule version 2.0 [149]	Bauer patient-satisfaction measure [150]	Days alive and out of hospital after surgery (at 30 days and one year) and discharge destination

1.4.3 Patient-centred outcome measures recommendations

It is recommended to report at least one patient-centred outcome measure in all perioperative trials based on the StEP-COMPAC group recommendations.[141] These recommendations are also aligned with the findings from the American Society for Enhanced Recovery & Perioperative Quality Initiative Joint Consensus.[44] In addition to accounting for patient perspectives in research, these outcomes further promote shared decision-making and can also be used as metrics for quality of care.[124-126] Understanding which patient-centred outcomes have been and

have not been evaluated is critical to making informed decisions on the effectiveness of opioid-minimization strategies and for informing future research.[127-129] There is also a growing interest for patient-centred outcome measures in perioperative research to improve relevance and applicability of findings.[46,124,127,151,152]

1.4.4 Patient-centred outcomes and opioid minimization strategies

Among the few trials and reviews that have been conducted to assess the impact of intraoperative pharmacologic interventions on patient-centred outcomes,[153] results suggest that some strategies could improve patients overall health after surgery. A meta-analysis of five trials showed that perioperative dexmedetomidine infusion was associated with a clinically significant improvement in the quality of recovery after surgery (mean difference [MD] = 15.71 on a 40-point scale; 95% CI [0.43 to 31], low quality of evidence).[154] Similar findings were also found for intravenous local anesthetics[155] as well as perioperative magnesium administration during mastectomy.[156] However, the level of evidence remains low and understanding which interventions are most effective and in which context of perioperative care remains unclear.[97-103]

1.5 Thesis objectives: proposed methods, approach, and research question

1.5.1 Description of the overall objective and methods

My thesis will adopt a programmatic approach to create a research program called **O**ptimizing **P**atient-centred outcomes **U**sing opioid minimization **S**trategies (**OPUS**). The OPUS program will include the design and execution of a comprehensive scoping review, a national survey, a systematic review, and the development of a "granting agency-ready" protocol for a pilot clinical trial. Main objectives will be to describe evidence, knowledge gaps and determine the patient-centred effectiveness of pharmacologic opioid minimization strategies. My thesis work will also help to evidence-inform the planning of a large pragmatic clinical trial that will focus on the patient-centred effectiveness of a promising opioid-minimizing intervention during surgery in adult patients.

1.5.2 Rationale

In light of the worldwide opioid crisis, and evidence regarding chronic postoperative use, the routine administration of opioids during and after surgery is being challenged and re-evaluated.[157] Multiple identified knowledge users (Health Canada, Choosing Wisely Canada, SolvingPain) [158,159] have advised that opioid minimization strategies be developed and carefully assessed using an approach involving patients and key stakeholders, as well as assessing patient-centred outcomes. The use of opioid minimization strategies must, however, be evidence based. The focus on intraoperative opioid minimization strategies was confirmed as a patient and caregiver priority in Canada as determined by the recent James Lind Alliance led *Canadian Anesthesia Research Priority Setting*.[146] In addition, my program addresses 4 of the top 10 perioperative research priorities in Canada (impact of reducing opioids, pain control after surgery, identification of factors that improve patient-centred outcomes, and long-term side effects of anesthesia).[146]

1.5.3 Specific objectives for each thesis project

Objective 1 - Scoping Review: From published trials, identifying and mapping a) potential pharmacologic intraoperative opioid minimization strategies, and b) outcome measures and tools to assess patient-centred outcomes after surgery (e.g. the postoperative quality of recovery, quality of life, functional recovery, etc.). Through these efforts, I will identify gaps in literature as well as promising opioid minimization strategies.

Objective 2 – Systematic Review: Synthesizing available knowledge by assessing effectiveness of a promising opioid minimization strategy identified in Objective 1. This will synthesize current knowledge, identify knowledge gaps, and inform critical decisions for the first clinical trial (e.g. patient population, dose and timing of intervention, etc.).

Objective 3 - Survey: Assessing Canadian anesthesiologists' opinions on intraoperative opioid minimizing practices used among adult surgical patients. I will describe the knowledge-to-evidence gap (by comparing Objective 3 with Objective 1 and 2).

Objective 4 – Pilot Trial Protocol: Designing a pilot multicentre pragmatic RCT to assess the feasibility of a multicentre randomized clinical trial in Canada. This pilot RCT will assess the feasibility of a large multicentre RCT to assess the effectiveness of the leading opioid minimization strategy/strategies informed by objectives 1-3 for improving patient-centred outcomes (i.e. quality of recovery) compared with usual care in adult surgical patients.

1.5.4 Approach: Integrated knowledge translation

Across all aims and stages of my research program, I will use an integrated knowledge translation (iKT) approach based on the CIHR iKT definition: "The central premise of iKT is that involving knowledge users as equal partners alongside researchers will lead to research that is more relevant and more likely to be useful to the knowledge users." I will be following the principles from the CIHR *Guide to Knowledge Translation Planning*,[160] and will be using a partnership focused approach.[161] I identified key Canadian interested parties (see Figure 1, Chapter 8 for partner organizations) to be part of our initiative through stakeholder analysis, using nominal group discussion and based on the toolkit developed by the World Health Organization (WHO).[162,163] Interested parties were chosen based on their high level of influence and to represent our target audience; anesthesiologists, patient partners, surgeons, nurses, policy makers, patients, pain experts, researchers, and research funders.[164] I will create unique opportunities for interactions between different levels of stakeholders including our patient partners that will be embedded in the design of our research program.[165,166]

Chapter 2. Manuscript 1 - Engaging patients in anesthesiology research: a rewarding frontier

2.1 Preface to manuscript 1

An important component of my integrated knowledge translation approach is patient engagement (i.e., involving patients as partners in research). I am thus collaborating with four patient partners (i.e., patient panel) with lived surgical experience as research team members for co-creating my research program on intraoperative opioid minimization strategies and patient-centred outcomes. Considering the importance of patient-centred outcomes in the research program and the need to involve the community in patient-oriented research, this partnership was instrumental.

In this reflective article, I summarize important principles for patient engagement in anesthesiology research based on our experience of applying the established CIHR Strategy for Patient Oriented Research framework. Specifically, I describe our patient engagement approach for the first phase of our research program; a scoping review aiming to identify potential promising opioid minimization strategies to be used during general anesthesia. I also provide resources and guidance to help other anesthesiologists, patients and researchers to involve patient partners in their research project.

I co-presented this work at the Patient Partner Town Hall of The Ottawa Hospital (TOH) on March 1st 2023 with the patient partner panel (4 patient partners who participated in this collaborative work). I also co-presented with Megan Graham in front of the Quality Improvement Committee of The Ottawa Hospital (TOH) on January 19th 2023.

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2.2 Manuscript 1

Engaging patients in anesthesiology research: a rewarding frontier

Short Title: Patient engagement in anesthesiology research

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Authors Contribution: All authors participated in the conceptualization of the article, reviewed the content, and approved the final version. The lead author (MV) wrote the first draft of the article following extensive discussions with all members of the team (including patient partners). Patient partners (MG, ML, AG, FZ) wrote the first draft of the section *Patient Engagement Benefits: a Patient Partners Perspective*. To write this section, patient partners initially wrote individual statements about their experience and learning during the project and these statements were then merged together through group discussion meetings (two meetings). These meetings involved the lead author (MV), a patient-oriented research facilitator (SN) and the four patient partners (MG, ML, AG, FZ).

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Implication Statement

Our reflective letter presents a Canadian example of patient engagement in anesthesiology research. We hope this example of early engagement promotes this practice among other researchers conducting anesthesia research in Canada and elsewhere and encourages patient partners to accept and advocate for such opportunities.

Patient Oriented Research in Anesthesiology

Patient-oriented research is an emerging approach that engages patients, clinicians and researchers to ensure research studies focus on patient-identified priorities aiming at improving patient care and outcomes.(1) From a clinical perspective, involving patients in medical decisions is required by law and professional code (ie. informed consent). Informed consent requires evidence that is pertinent to the decision at hand, but also information that is deemed relevant by the decision maker (the patient). Despite the importance of research in providing evidence to inform such clinical decisions, engaging patients in clinical research is not frequently done, is often suboptimal, and is certainly not required by regulations and good practice. The failure to engage patients in clinical research has led to large swathes of research that neither addresses patient priorities nor collects data on outcomes that are meaningful to patients and their families.

This paradox is highly relevant to the field of perioperative research. Indeed, the low quantity and quality of the involvement of interested parties in perioperative care guidelines development, including the incorporation of patient preferences, was identified as a methodological weakness in North America and European guidelines for anesthesiologists.(2)

Internationally, patient-oriented anesthesia research is gaining traction with large pragmatic trials such as REGAIN (3) evaluating effectiveness based on patient-centred outcome assessment (in that case assessing the effect of general versus spinal anesthesia on death or inability to walk 10 feet independently following repair of hip fracture). However, documented examples of patient-oriented research in anesthesia remain few and far between. Results from a systematic review showed that the prevalence of patient engagement in interventional research is very low with less than 1% of published trials having meaningfully involved patients.(4) In Canada, priorities in patient-oriented anesthesia research were recently determined with a James Lind Alliance-process by the *Canadian Anesthesia Research Priority Setting Partnership*.(5) The Canadian Anesthesiologists' Society, the Canadian Perioperative Anesthesia Clinical Trials group and others supported a multidisciplinary panel (inclusive of patients and caregivers) to generate a

top-ten list of patient-oriented research priorities. This important initiative is intended to act as a roadmap to guide Canadian patient-oriented research in anesthesia and perioperative medicine.

Our team has taken up this call to action by developing a research program to identify intraoperative pharmacologic opioid minimization strategies that could alter patient-centred outcomes after surgery. In order to identify and assess these strategies we are first conducting a scoping review that will inform planned surveys, systematic reviews, and ultimately a pragmatic randomized controlled trial of an opioid minimizing intervention. Our program addresses three important priorities from the *Canadian Anesthesia Research Priority Setting Partnerhsip*, namely the impact of reducing opioids during anesthesia, pain control after surgery, and long-term side effects of anesthesia after surgery.(5) In order to ensure that our review is relevant to adult patients undergoing general anesthesia and who might be receiving opioids, we made an early decision to partner with patients to collaborate and co-create our scoping review. In an effort to promote this approach and provide a Canadian example of patient engagement in anesthesiology research, we describe our efforts to integrate 'patient engagement' in the research process, that is to meaningfully and actively collaborate with patients as partners.

Patient Engagement in Healthcare Research

Patient engagement is an important component of quality and relevance in healthcare research.(6-8) While we use the term patient engagement here, terms such as patient consultation, patient and public involvement (PPI), or public participation, may be used synonymously. However, the terms used locally may vary depending on jurisdiction and in some cases the same terms may have differing meaning.(1, 9) We chose to define our work based on the Canadian Institutes of Health Research (CIHR) taxonomy as our project was developed in Canada.(10) The CIHR defines patient engagement as "an approach where patient partners can potentially contribute to every stage of the research process, including governance, priority setting, and conduct of research. They can also summarize, distribute, share, and apply its resulting knowledge (i.e. the process known as knowledge translation and exchange)".(10) Importantly, research is conducted with patients as true partners in the process, and the research is not done "to" or "for" them specifically. As such, patient engagement in research ultimately

aims to increase relevance and applicability of the research to patients, caregivers, and families. The growing evidence indicates that patient engagement can help refine research questions and protocols, improve recruitment in clinical trials by making research more patient-centric, and facilitate shared decision-making at the patient's bedside by providing applicable and relevant evidence.(11, 12) Moreover, the ethical and moral imperative for involving patients in research is clear as patients are the ultimate users of healthcare research; they are the beneficiaries of clinical care.(13)

How Can we Apply Patient Engagement in Anesthesiology Research ?

As an exemplar, we engaged with patient partners in the preliminary phase of designing our research program (eg. a scoping review to inform next phases of the program). Based on the World Health Organization toolkit for stakeholder analysis, patients were identified as a key interested party for our initiative (14, 15) thus we sought to form a panel of patient partners to join our investigative team. We, as a group of researchers and patient partners, designed a patient-oriented scoping review to describe the current evidence from randomized controlled trials (RCTs) assessing the effectiveness of intraoperative opioid minimization strategies.

Our approach to identifying patient partners leveraged our institutional infrastructure that facilitates the matching of patient partners with research teams (16) using an advertisement distributed through our hospital's Patient and Family Engagement Program (>200 patients who have volunteered to serve as advisors for clinical processes, policy decisions, and/or research). The advertisement included information regarding the proposed study area, ideal experience (lived experience of surgery and general anesthesia) as well as anticipated commitments. Four patient advisors consequently expressed an interest in partnering on the project and the Patient and Family Engagement Program (PFEP) Lead organised an introductory meeting between the patient advisors and the research team. Following an initial meeting to explain the project and discuss the likely time requirements, we invited all four patients with lived perioperative experience to join us as patient partners and all agreed. Working with the patient partners, we co-developed a formal engagement strategy and a terms of reference document (https://osf.io/afm3z/). This discussion, and the resulting documents, included methods of

compensation, acknowledgement, authorship, training and support for patient partners and researchers, as well as approaches to be taken to evaluate the patient engagement activities.(1, 17) In developing our process, we explicitly considered how we would implement the guiding principles set out by the CIHR Strategy for Patient Oriented Research (SPOR) Framework (18) while also addressing barriers frequently encountered in clinical research. Solutions were developed based on the context of perioperative medicine as well as locally available support and resources.(16) The SPOR principles, identified barriers, and implemented solutions are outlined in Table 1.(19-23)

We chose the SPOR partnership-focused approach,(18) as this "principle-based framework" is designed to optimize collaborative partnerships between researchers and patients or organizations.(24) By focusing on a principle-based approach we were able to adapt our processes to the specific context of our study, as opposed to being tied to specific methods or practical approaches. In keeping with some engagement principles, we have built strong and sustainable relationships (over a 1-year period) through transparency (mutual goals agreed on), commitment, respect, regular communication and feedback (email updates, group discussion), and ongoing evaluation. This type of approach was facilitated by our institution and through the Ontario SPOR Support Unit, of which our organization (Ottawa Hospital Research Institute) is an active member through the Ottawa Methods Centre. Our institutional structure is called the "Ottawa model."(16) This model provides useful guidance on developing infrastructure and facilitating patient engagement in research. This structure also allowed us to have methodological support. For example, each meeting with the patient partners is co-led by a patient-oriented research facilitator who is affiliated with the SPOR Support Unit.(19) Based on the CIHR's Spectrum of Citizen Engagement (eg. five levels of pariticipation, namely: communications, listening, consulting, engaging, and partnering), the levels of patient engagement in our research project met the criteria of consulting, engaging, and partnering depending on the phases of research.(25) Of note, patient engagement is often described as a continuum and labelling and description of each level can vary depending on jurisdiction and country.(26)

Table 1. Strategies to Facilitate Patient Engagement Tailored to Perioperative Research and Adapting the Strategy for Patient Oriented Research (SPOR) Framework (18)

Identified barriers to patient engagement in clinical research	**Guiding principle based on the SPOR framework with definitions**	**Strategies and resources to overcome barriers that are tailored to our local context**	**Desired outcome based on the SPOR framework**
Representativity of patient partners	Inclusiveness: Integrate the diversity of patient perspective	-Use existing local networks (ie. the PFEP*) to identify and recruit a diverse group of patient partners.(19) -Explicitely consider diversity of patients' experiences when selecting patient partners. selecting patient partners. In Canada, the provincial SPOR* SUPPORT Unit can assist reaching this objective. -Develop and distribute a document with all researchers and patient partner team member biographies and personal pictures that emphasized the importance of all team members as equal partners. -Use gender-neutral language in oral and written communication.	Inclusive mechanisms and process are created
Medical jargon and fear of tokenism (20)	Mutual respect: Value each other expertise and experiential knowledge	-Co-develop an evergreen terms of reference document describing objectives, rules of conduct, and expectations (https://osf.io/afm3z/) -Use first names and no titles during meetings -Offer training and leadership support to patient partners through a patient engagement facilitator. In Canada, the provincial SPOR SUPPORT Unit * can assist reaching this objective. -Appoint more than one patient partners to panels/committees to promote diversity of opinions and strengthen the patient voice. It also provide peer support.	Respectful collaboration is established amongst patients and researchers
Organization and time (20)	Support: Provide adequate support and flexibility to ensure	-Seek funding from local institution for patient-oriented research through local SPOR* Unit.	Common goal of timely

	patients can contribute fully to the discussions and decisions	-Use a flexible approach regarding meeting planification (total length of the meetings, timing in the day, etc.) and adapt schedule to patient needs.	implementation of quality research
Power dynamic	Co-build: Patients, researchers and practitioners work together from the beginning to identify problems and set priorities	-Deliver focused presentation to explain core concepts based on identified patient knowledge needs regarding the clinical context. -Empower patients in all phases of the research process, including choice of the research question and outcomes. -Use open access videos to explain the research and publication process.(27) -Allow ample time for questions at every meeting. -Use of a satisfaction survey to evaluate and improve our patient engagement approach.(28) -Use the CEPPP* Engagement Assessment toolkit (or other ones) to ensure your evaluation instrument meets the aims of your evaluation process.(29) -Use accessible language for oral and written communication and use web-based application when in doubt about the level of literacy needed.(30) -Involve patients early and meaningfully. -Provide orientation and ongoing support.	Research is informed and co-directed by patients (ie. there is a shared project decision-making)
Lack of compensation and meeting patient expectations (31)	Support and inclusiveness	-Be available for individual discussion when needed. -Include patient partner compensation in the budget.(22) -Provide regular updates and a newsletter to show progress and impact of patient partners work on the study. -Include patient partners in article and manuscript writing and offer authorship opportunities.	The experiential knowledge of patients is valued as evidence as part of the research process

* PFEP: Patient and Family Engagement Program, SPOR: Strategy for Patient Oriented Research, CEPPP: Centre of Excellence on Partnership with Patient and the Public

The Patient Partners' Perspective on Engagement Benefits

As patient partners, we had either very different or limited experiences with patient engagement in research, and therefore our expectations for the opioid minimization in surgery project, were extremely open. As patient partners, we felt we were an integral part of the team and we brought our lived experiences which informed not only how we saw the research question, but also what information, or data, were most relevant to us. To date, we have provided input into the review through discussions and written comments, including assessment of the relevance of the scope of the review, the outcomes, the plain language abstract, the planned items for extraction, revision of grants application, and helped to plan the dissemination phase. More specifically, we helped shape how and which patient-centred outcomes would be accounted for in the review through group discussions, assessment of certain scales and instruments and revision of the literature. We also assessed the perioperative patient-centred outcomes consensus proposed by the Standardised Endpoints in Perioperative Medicine international initiative (ie. the StEP-COMPAC group) to ensure they were adequately relevant, comprehensive and applicable to our context.(32) Through this process, we challenged some of the measures suggested by the StEP-COMPAC. For example, we decided that the lack of endpoints to assess chronic pain following surgery was an important omission.

We appreciated the openness and inclusion of our views and preferences received from researchers and having ample opportunity for collaborative discussion. We were a diverse team, in terms of age, hospital exposure and treatment and opioid related experiences: we all came from different circumstances, and feel we were listened to from the beginning, with the same respect, regardless of our professional, patient, or ongoing family interaction with hospital services and protocol. We now know what a scoping review is, what stages are involved in such a review and some of the challenges. Hence, we were able to provide relevant insights, ideas, and judgments throughout the process. We also learned about what anaesthetic options are used in general surgery along with their variations in practice. We appreciated being invited to join the project early, as we believe that our various and unique lived experiences helped the research team foster the question to better answer our community needs and be aligned with the end-user priorities. We appreciated the patience and camaraderie of the researchers and clinicians, as this time invested helped us to feel like genuine colleagues and a legitimate part of the team. Perhaps

most importantly, we know that we are helping improve quality of care through patient-oriented research.

The Importance of Evaluating Patient Engagement

Evaluating patient engagement is a necessary step to ensuring the collaboration is meaningful (ie. the collaboration is not tokenistic). Evaluation not only strengthens the patient partnership process, it can also help uncover facilitators and challenges that arise during the execution phase of the research study.

In order to achieve meaningful and active collaboration with patient partners, our team co-developed an improvement-oriented evaluation plan (ie. developmental evaluation aiming at improving the process of engagement within the project) following the CIHR Guide to Evaluation in Health Research.(33) As a part of this approach, we chose to assess patient partners satisfaction. To aid us in identifying the most relevant tool we used the Centre of Excellence on Partnership with Patients and the Public (CEPPP) Engagement Assessment Toolkit. This toolkit is a decision aid informed by a previous systematic review of existing evaluation tools.(34) Using this structured decision-process we decided to use the Public & Patient Engagement Evaluation Tool [PPEET] because of its comprehensiveness, methodological rigour, and the presence of free text sections.(28, 29) This tool can be used in a wide range of settings and is centred on four main principles: integrity of design and process, influence and impact, participatory culture and collaboration.(28) We administered a first PPEET survey shortly after we started and based on feedback from this survey evaluation, the researchers realized a knowledge gap among some patient partners regarding their understanding of general anesthesia. In addition, it was difficult for the patients to grasp their impact of the project early on. In order to address these knowledge gaps, we changed the structure of our meetings (starting with summary of the research projects, focused learning session, and patient partner impact) and also began to provide regular progress newsletters to the project team (patient partners, knowledge user organizations and researchers) and regular oral feedback on how patient partners' input had been incorporated into the project.

Lessons Learned and Suggestions for Other Groups

Based on our collective experiences, we – as patient partners and researchers – have been in a continuous learning cycle. A key lesson has been that patient engagement needs to be tailored to available resources and research context. We have been fortunate to be able to draw on a method centre (The Ottawa Methods Centre) that provides specific support around patient engagement in research, and we are based in a country where the main health research funding body has a dedicated funding stream for patient-oriented research. In Canada, across all provinces and territories, Support for People and Patient-Oriented Research and Trials (SUPPORT) Units provides services for researchers, patients, policy makers, and clinicians for patient-oriented research activities.(35) Regardless of the resources available to a team, we believe clinicians and researchers can and should strive to engage patients and end users in clinical research; either by a call to action within your institution or by engaging with patients in your own research depending on your local context. Lower levels of patient engagement (such as simply informing or consulting) can be impactful for the project and the community as well, but we suggest teams should strive to partner with patients by engaging them in the earliest phases of the research project (ideally with patients and researchers co-creating the research question from the start) as the potential impact is stronger when initiated at the design phase. In our experience, having all interested parties (patients, clinicians, and researchers) involved early in the process was noted to be appreciated from all parties. It increased the efficiency of the process as it ensured common goals were maintained and agreed on through all phases of the project.

The team must work to build trust among all team members by communicating openly and often, developing ways to accommodate all team members, identifying and removing any hierarchical barriers, and encouraging learning and participation by using language patient partners can easily understand. Researchers need to demonstrate humility, and treat patients with respect for the knowledge, experiences and the wisdom of the lived experiences they bring to the team and project. It takes time, energy and patience to engage patient partners, but the investment is worthwhile. Ultimately, the goal of clinical research is to improve clinical care and patient outcomes. Imagine the advances we can make when patient partners and researchers work together to produce and conduct research.

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Chapter 3. Manuscript 2 - Intraoperative pharmacologic opioid minimization strategies and patient-centred outcomes after surgery: a scoping review

3.1 Preface to manuscript 2

In partnership with our patient partners panel and our partner organizations, I developed a scoping review of randomized controlled trials (RCTs). The primary objective of this scoping review was to map and characterize the RCTs assessing the patient-centred effectiveness of pharmacologic intraoperative opioid minimization strategies in adult surgical patients. I included a description of the pharmacologic strategies assessed and identification of promising pharmacologic strategies. Co-authors involved in this project helped for the supervision the project, revision of the manuscript, screening of the studies and extraction of the data. Patient partners and partner organizations contributed to refine the research question, determine outcome prioritization, provided input on the design of the study as well as on the development of the dissemination plan.

I presented the protocol of this scoping review at the SEPH research day in February 2022 (2nd position award in the PhD students category, 10 minutes oral presentation) and I presented the final results of this scoping review at the SEPH research day in January 2024 (1st position award in the PhD students category 10 minutes oral presentation).

This scoping review protocol was published in BMJ Open:
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3.2 Manuscript 2

Intraoperative pharmacologic opioid minimization strategies and patient-centred outcomes after surgery: a scoping review

Short title : Opioid minimization strategies during anesthesia

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Title: Intraoperative pharmacologic opioid minimization strategies evaluating patient-centred outcomes after surgery: a scoping review

Background
Postoperative patient-centred outcome measures are essential to capture the patient's experience following surgery. Although a large number of pharmacologic opioid minimization strategies (i.e. opioid alternatives) are used for patients undergoing surgery, it remains unclear which strategies are most promising in terms of patient-centred outcome improvements. This scoping review had two main objectives: (1) to map and describe evidence from clinical trials assessing the patient-centred effectiveness of pharmacologic intraoperative opioid minimization strategies in adult surgical patients, and (2) to identify promising pharmacologic opioid minimization strategies.

Methods
Searches of MEDLINE, Embase, CENTRAL, Web of Science and CINAHL databases were conducted from their inception to February 2023. We included trials investigating the use of an opioid minimization strategy in adult surgical patients and reporting at least one patient-centred outcome. Study screening and data extraction were conducted independently by at least two reviewers.

Results
A total of 24,842 citations were screened for eligibility. 2803 trials assessed the effectiveness of intraoperative opioid minimization strategies. Of these, 457 trials (16%, 67,060 participants) met eligibility criteria by reporting on at least one patient-centred outcome. Among trials that included a patient-centred primary outcome (n=107 trials), patient well-being was the most frequently used domain (46 %, n=55 trials). Based on aggregate authors' findings, dexmedetomidine, systemic lidocaine, and COX-2 inhibitors were categorized as promising strategies and acetaminophen, ketamine, and gabapentinoids were categorized as less promising. Almost half of the trials (n=253 trials) did not report a protocol or a registration number.

Conclusions
There is a need for trialists to prioritize and include patient-centred outcomes in the assessment of opioid minimization strategies effectiveness. We identified three potentially promising pharmacologic intraoperative opioid minimization strategies that should be further assessed through systematic reviews and multicentre trials. Findings from our scoping review may be influenced by selective outcome reporting bias.

Study registration
https://osf.io/7kea3/?view_only=49946e5dc46c41a59911d247191c9049

Key words
Pain management, Adult anaesthesia, opioid minimization strategies, Clinical pharmacology, patient-centred outcomes

INTRODUCTION

Amid the global opioid crisis, pharmacologic approaches aiming at reducing opioid use, known as opioid minimization strategies, are increasingly gaining traction in perioperative care.(1-6) Such interventions are often started during surgery, specifically in the intraoperative period while the patient is under general anesthesia. While the use of opioid minimization strategies is increasing, there is also unexplained variation in practices, and it is unclear if these practices are supported by patient-centred evidence.(6-15)

There is a growing recognition and demand for patient-centred outcome measures in perioperative research to enhance the relevance and applicability of study findings.(16-20) These outcome measures capture the patient's experience following surgery, including pain levels, analgesic adverse effects (i.e. nausea, vomiting, constipation, dizziness, etc.), and the impact of pain on daily life; which are key components to determine perioperative effectiveness.(21) Opioid minimization strategies are attractive to improve patient-centred outcomes as they can reduce opioid-related adverse effects while still providing analgesia.(6-15, 19, 22-42) Nevertheless, patient-centred outcomes are currently underrepresented in perioperative research and clinical practice guidelines that endorse the perioperative use of opioid minimization strategies, such as the Enhanced Recovery After Surgery Society (ERAS) guidelines.(43-45) The Standardised Endpoints in Perioperative Medicine initiative (StEP-COMPAC group) has established key patient-centred outcome measures and instruments for use in trials of perioperative care.(44, 46, 47) The integration of patient-centred outcomes in practice, research, and guidelines have also been emphasized by perioperative national and international expert consensus statements.(48-53)

Previous systematic reviews have focused primarily on the effect of pharmacologic opioid minimizing strategies on indirect patient outcome measures (i.e., short-term quantity of opioids administered) or unidimensional instruments (i.e., pain intensity assessment or hemodynamic stability).(6-15, 19, 22-41) Results suggest that opioid alternatives can reduce short-term opioid use during and after surgery. However, these systematic reviews were generally, of low methodological quality(54) and often neglected important patient-centred outcomes.(6-15, 19,

21-41) Furthermore, considering the heterogeneous and complex nature of intraoperative opioid minimization strategies,(55, 56)(57) a scoping review serves as a valuable approach for assessing the extent, range and nature of this field and provide insights for future research.(58)

Therefore, we designed a scoping review of randomized controlled trials using a collaborative approach involving multiple interested parties and partner organizations (e.g., patient partners, perioperative clinicians, partner organizations, and methodologists). Our objective was to map and describe evidence from clinical trials assessing the patient-centred effectiveness of pharmacologic intraoperative opioid minimization strategies in adult surgical patients and to identify promising pharmacologic opioid minimization strategies.

METHODS

Our scoping review was conducted in accordance with the recommendations from the Joanna Briggs Institute (JBI)(59) and followed the methodological framework developed by Arksey and O'Malley.(58) We wrote this manuscript in accordance with the reporting guidelines from the Preferred Reporting Items for systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews.(60) Our protocol was published,(61) and any modifications made to the original protocol were documented and posted on the OSF platform (https://osf.io/7kea3/?view_only=).

As detailed in our protocol and in a separate reflective article,(62) we used a collaborative approach involving multiple partner organizations. We defined pharmacologic opioid minimization strategy as any non-opioid drug with antinociceptive properties administered orally, intramuscularly, subcutaneously or intravenously during the intraoperative period. While multiple definitions are available within and across countries to describe patient-centred outcomes, we followed recommendations developed by a rigorous international consensus process specifically tailored to the perioperative care context: the StEP-COMPAC consensus.(63) Accordingly, we included any outcome measures falling within one of the five StEP-COMPAC consensus domains, namely: well-being, functional status, patient satisfaction, health-related quality of life, and life impact. In addition, based on input from our partner organizations, expert clinicians, and patient partners, we also considered two additional patient-centred domains; opioid specific outcomes (long-term opioid use [≥1month] and opioid-related adverse effects [multidimensional assessment]), and pain-related outcomes (acute pain [multi-dimensional assessment <3 months] and postoperative chronic pain [≥3 months]). A summary of important definitions can be found in appendix 1.

Search strategy and eligibility criteria

We developed our search strategy in collaboration with method experts, clinicians, patient partners and two information specialists. Our search strategy was applied to MEDLINE, Embase, CENTRAL, Web of Science, and CINAHL from their inception to February 2023 and the search strategy was validated according to the Peer Review of Electronic Search Strategy (PRESS) recommendations (eFigure 1).(64) We included randomized clinical trials assessing the impact of

systemic intraoperative (i.e. initiated the day of surgery, before anesthesia emergence) pharmacologic opioid minimization strategies. The intervention could include opioid-free anesthesia (i.e., complete avoidance of opioids), but it was not required for eligibility. Trials must have included adult patients undergoing general anesthesia for any surgical procedure. Eligible comparators were opioids, placebo or no intervention. At least one patient-centred outcome must have been reported and only trials written in English or French were included. To be included, the minimal sample size required for an eligible trial was 30 participants. Further details on the eligibility criteria can be found in the protocol.(61)

Study selection

We used Distiller SR, a cloud-based audit-ready software designed for scoping reviews to collect citations, remove duplicates, and facilitate screening of titles and abstracts.(65) Given the anticipated large number of citations, we leveraged the active-machine learning feature of Distiller SR's artificial intelligence to prioritize and enhance title and abstract screening of citations.(66, 67) To pilot test the Level 1 screening form and to train the active-machine learning tool, reviewers independently screened 100 citations and all disagreements were resolved. We performed conflicts resolution every 2-3 days to maintain reliability of the active-machine learning tool. Once we achieved a predicted recall rate of ≥90% (indicating that the active machine leaning had identified approximately ≥90% of trials eligible for inclusion), one reviewer was replaced by the artificial intelligence in the duplicate screening process. For the full text screening phase, we utilized the InsightScope platform (www.insightscope.ca), a web-based application that allowed the creation of a large online team to facilitate the screening of the expected large number of citations to review.(68) In order to be considered eligible as a reviewer for the project, each candidate was required to obtain at least 80% sensitivity in a test set validated by three senior reviewers (eTable 3) and participate in at least two training sessions.

Criteria for identifying promising opioid minimization strategies

Our approach for identifying promising opioid minimization strategies is detailed in our protocol that was published a priori (i.e., strategies that could be effective based on authors' findings, but that requires further systematic research assessment).(61) First, we ranked patient-centred outcome measure domains of interest based on potential impact and plausibility with our patient

partners and partner organizations (Table 1).(62) Patient well-being, assessed with the Quality of Recovery instrument was given the highest score. We also considered within the scope of patient-centred outcomes two additional domains; namely, opioid related (long-term use [≥1month] and adverse effects [multidimensional assessment]), and pain-related (acute pain [multi-dimensional assessment, <3 months] and postoperative chronic pain [≥3 months]). Next, we calculated the relative (i.e. relative to the total number of included trials) and absolute number of clinical trials reporting positive (i.e. benefit associated with the intervention) results for a pharmacologic strategy based on authors' conclusion and interpretation (i.e. aggregating authors' findings). Then, this same assessment was conducted among trials reporting at least one patient-centred outcome measurement (eTable 4) as their primary outcome of interest (well-being, functional outcomes, patient satisfaction, quality of life and life impact, opioid-related adverse effects, or pain-related). Finally, we summarized this evidence and discussed it with patient partners, clinicians and researchers to confirm the potential applicability and relevance of the identified promising strategy(ies). We used no quantitative thresholds to choose promising strategies as each of the chosen promising opioid minimization strategies will require systematic review and meta-analysis to confirm findings. Using the same approach, we also identified less promising pharmacologic strategies based on the relative and absolute number of published articles with null or negative conclusion (i.e. intervention judged as having no effect, being deleterious or of uncertain efficacy based on author's conclusion).

Data abstraction, analysis and presentation of the results

We extracted data from included trials using a standardized data abstraction document (eTable 1). At least two reviewers extracted data independently, in duplicates and conflicts were resolved with a third senior reviewer when necessary.

To describe outcome measures, each instrument reported was categorized based on the classification from the StEP-COMPAC consensus. We also described compliance with the StEP-COMPAC recommendations (Figure 1) for each trial using stacked bar charts.(63) We visualized the number of trials assessing each pharmacologic opioid minimization strategy's effectiveness according to the patient-centred outcome that was reported in the trial with a bubble chart.

Patient and public involvement

We formed a patient panel of four individuals with lived perioperative experience to co-produce this scoping review following the principles laid out in the Canadian Strategy for Patient-Oriented Research (SPOR) Patient Engagement Framework.(69) In line with these principles of inclusiveness, support, mutual respect, and co-building, the patient panel met regualarly with members of the team. The patient partners were involved in all phases of research, namely, designing the research question, determining the outcome choice and prioritization, providing insight on the planned items for extraction, co-developing grants and articles, etc. Details of our patient engagement approach has been described in another publication.(62)

RESULTS

From the 24,842 citations that were screened for eligibility, we included a total of 457 trials representing 67,060 participants. The screening process and reasons for exclusion at full text are summarized in eFigure 2. The artificial machine learning feature report is provided is Appendix 2. We found that 16% (457 of 2803) of published trials assessing pharmacologic opioid minimization strategies effectiveness met our eligibility criteria of reporting at least one patient-centred outcome (eFigure 2). We excluded two articles because they were retracted and recognized as fraudulent reports.(70, 71)

Characterizing the trials evidence assessing patient-centred effectiveness of pharmacologic opioid minimization strategies

Characteristics of the 457 included articles are summarized in Table 2 and eTable 2. The highest proportion of trials was conducted in China (18%, n=83 trials) followed by United States (18%, n=81 trials) and Turkey (9%, n=42 trials). In terms of design and methodology, randomization was at the individual level for 99% of the trials (n=454 trials), and 92% (n=419) of trials were conducted in a single-centre. A total of 56% trials (n=253 trials) reported a protocol or a registration number and 85% of trials (n=389 trials) reported a sample size calculation in their manuscript or their protocol.

Most of the trials (84%, n=382 trials) examined a single active agent. Among these trials, alpha-2 agonists (n=71 trials), gabapentinoids (n=49 trials), corticosteroids (n=49 trials) and NMDA antagonists (n=76 trials) were the pharmacologic strategies that were assessed most frequently (Table 2). Trials that examined a combination of agents primarily studied alpha-2 agonists with lidocaine or NMDA antagonists. 88% of strategies were compared to placebo (n = 401 trials), and 8% (n=38 trials) and 5% (n=25 trials) were compared to opioids or no intervention, respectively. Details of all the included pharmacologic interventions were described in eTable 5.

The median sample size of the included trials was 86 participants (range: 30 to 8880 participants). The median length of participant follow-up was 3 days (range: 1 day to 4 years). Regarding the target population, 3% of the trials (n=14 trials) focused specifically on a geriatric surgical population, and less than 1% either focused specifically on patients with chronic pain

history (n=2 trials)(72-74) or chronic opioid use (n=1 trial).(75) A total of 2% of trials (n=7 trials) included sex and gender considerations as part of their analyses.(76-82) The most frequent types of surgery included were gastro-intestinal (n=107 trials), obstetric/gynaecologic (n=95 trials), and orthopedic (n=87 trials, see eFigure 3).

Knowledge gaps in patient-centred outcomes according to the pharmacologic opioid minimization strategies and compliance with StEP-COMPAC recommendations

The number of published trials assessing at least one patient-centred outcome per year has been increasing over the last two decades (eFigure 4). More than half of the trials reporting at least one patient-centred outcome were published after 2014 (58%, 264 trials) and few before the year 2000 (5%, 21 trials). Among included trials, 24% (n=107 trials) used a patient-centred outcome as their primary outcome of interest. Reported primary patient-centred outcome measures are described in eFigure 7.

The most frequently reported outcome domains were patient satisfaction (46%, n=210), well-being (39%, n=178 trials) and pain-related (acute and chronic pain) (25%, n=112 trials); while less frequently reported domains were the health-related quality of life (7%, n=34 trials), functional outcomes (15%, n=67 trials), life impact (5%, n=25 trials) and opioid-related (adverse effects and long-term opioid use) (5%, n=21 trials) (Figure 1).

A list of instruments that we used to assess each domain is available in eTable 4. The most frequently studied instrument for each domain were: quality of recovery (QoR-40, -15, and -9 score) (49%, n=88 of 178 trials in the well-being domain), daily activity level (15%, n=10 of 67 trials in the functional status domain), satisfaction numerical or categorical rating scale (99%, n=207 of 210 trials in the satisfaction domain), Short Form (SF-36, and -12) (62%, n=21 of 34 trials in the health-related quality of life domain) and time to return to usual activities (40%, n=10 of 25 trials in the life impact domain). Among the trials that assessed postoperative acute pain using a multidimensional instrument, the most frequently used instrument was the Brief Pain Inventory (52%, n=14 of 27 trials). Only six trials reported a multidimensional opioid-

related adverse effects assessment. At least one adverse event was assessed in 93% of the included trials (n=426 trials).

Compliance with the StEP-COMPAC recommendations (i.e. the use of the most recommended instrument to assess a patient-centred outcome domain [Table 1]) was low across all domains (range: between 0% and 49%, Figure 2). The highest compliance rate was observed in the domain of patient well-being; specifically, the use of the Quality of Recovery instrument [9, 15 or 40] in 49% of trials [n=88 trials] assessing the patient well-being). Overall, the compliance rate with the StEP-COMPAC recommendations was 31% from 2019 onwards (i.e. the year the StEP-COMPAC consensus on patient-centred outcome was published) and 14% before 2019 (Figure 1).

Identifying potential promising pharmacologic opioid minimizing strategies

Three pharmacologic strategies were identified as potentially promising (Figure 3): dexmedetomidine (proportion of trials reporting positive results: 85%), COX-2 inhibitors (proportion of trials reporting positive results: 82%), and systemic lidocaine (proportion of trials reporting positive results: 76%). Our results were consistent when restricting for trials that used a patient-centred outcome as a primary outcome measure (eFigure 5, n=107 trials) and when the primary outcome was the patient well-being assessed with a Quality of Recovery instrument (eFigure 6, n=43 trials) which was the most important patient-centred outcome measure as guided by key interested parties (Table 1). There was however no trial evaluating the effectiveness of COX-2 inhibitors using a Quality of Recovery instrument (QoR-9, -15, or -40). The less promising pharmacologic strategies based on the relative and absolute number of published articles with null or negative conclusion overall were acetaminophen (proportion of trials reporting positive results: 35% of trials), ketamine (proportion of trials reporting positive results: 47% of trials), and gabapentinoids (proportion of trials reporting positive results: 49% of the trials) (Figure 3).

DISCUSSION

Our review demonstrates that patient-centred outcomes are rarely used to assess the effectiveness of intraoperative opioid minimization strategies in clinical trials. Among trials that did report a patient-centred-outcome, compliance with well-established recommendations was generally low across all patient-centred outcome domains. Furthermore, while it is recommended that at least one patient-centred outcome be measured and reported in all perioperative trials, the vast majority of trials (84%) did not report any.(63) Our analysis also identified significant knowledge gaps in terms of patient-centred outcome measures and several weaknesses in published clinical trials. As such, few trials reported outcome measures assessing life impact, health-related quality of life, and opioid-related adverse effects. We also noted that few trials were multicentred, duration of follow-up was frequently short and half of the trials did not report a registration or a protocol publication. Additionally, based on the available evidence from published trials, we identified three promising pharmacologic intraoperative opioid minimization strategies (dexmedetomidine, systemic lidocaine, and COX-2 inhibitors) and three strategies that are not supported by patient-oriented evidence (acetaminophen, ketamine and gabapentinoids)

Our findings align with a systematic review that examined the efficacy of perioperative pharmacotherapy in preventing postoperative chronic pain.(83) In that review, systemic lidocaine and NSAIDs were identified as promising strategies for reducing postoperative chronic pain. Our scoping review strengthens the existing body of evidence on these two strategies and further supports the plausible improvement of other patient-centred outcomes following surgery through the use of these strategies. We also provide further description of the patient-centred outcome knowledge gap (i.e. lack of compliance with established recommendations). Our results are consistent with a previous review(55) and cross-sectional(84) analyses of perioperative trials that identified a knowledge gap in perioperative patient-oriented clinical trials. Nevertheless, we further describe areas for methodology improvement as well as interventions and outcomes that needs further assessment. For instance, our findings indicate that less than 10% of the published trials assessing the effectiveness of pharmacologic opioid minimization strategies were multicentre trials. We identified other important methodological weaknesses in a high proportion

of trials (i.e. lack of registration, short follow-up, and the lack of a sample size calculation reported) which aligns with multiple expert consensuses and calls to action, such as the *American Society for Enhanced Recovery & Perioperative Quality Initiative Joint Consensus Statement)* that highlight the importance of rigorous multicentre trials in order to assess perioperative opioid alternatives.(28, 50, 53) We provide clear and practical guidance to inform research agendas and facilitate the planning of subsequent systematic reviews and clinical trials that could impact practices and improve patient-centred perioperative care.

Including patient-centred outcomes in the evaluation of opioid minimization strategies is extremely important in perioperative care. Only relying on short or long term opioid reduction could be misleading.(16, 17, 21, 85-88) Indeed, an increase in opioid exposure does not necessarily translate into worse health outcomes, which is ultimately what matters the most.(89, 90) Assessing health outcomes, through patient-centred outcomes, is also recommended from a public health perspective in order to evidence inform the judicious prescribing of opioids (i.e., avoiding over and under prescription), as highlighted by the "opioid ecosystem."(91)

Our study has strengths that contribute to its overall quality and impact. First, our scoping review was characterized by a collaborative effort involving key stakeholder organizations and content experts that actively engaged patient partners throughout the research process. This inclusive approach ensured diverse perspectives were considered, enhancing the relevance and applicability of our findings. This approach led to the prioritization of the quality of recovery as an outcome measure, which is also supported by two different established and international recommendations for endpoint prioritization in perioperative clinical trials (patient-centred(63) and patient comfort(23)) from the StEP-COMPAC initiative. Secondly, we adopted an innovative approach by developing a patient-oriented scoping review that will guide future more focused systematic reviews and clinical trials. This approach optimizes the use of available resources and strategically targets promising strategies for further investigation. Thirdly, our focus on patient-centred outcomes (i.e. at least one patient-centred outcome measure was needed for an eligible trial), coupled with an in-depth description of domains and instruments reported, will contribute to directly inform future systematic reviews and trials in perioperative research of opioid minimization strategies. Additionally, we carefully adhered to established international

recommendations for evaluating patient-centred outcomes in perioperative research.(63) By following these guidelines and involving knowledge users and patient partners, we helped ensure the scientific rigour and relevance of our study.

Our study has limitations. Firstly, we did not undertake a formal risk of bias assessments given our objective was to map and describe the current evidence. The risk of bias assessment is not generally conducted in scoping reviews for this reason.(59) Furthermore, we relied on the narrative conclusions reported by the authors and there may be discrepancies with the actual quantitative findings. Selective outcome reporting may also be present, especially considering the high proportion of trials that did not report a protocol or a registration number. Our findings need to be confirmed through multicentre trials and systematic reviews. Another limitation of our study is that the primary outcomes assessed in the eligible trials may not necessarily align with patient-centred perspectives as not all trials used a patient-centred outcome as their primary endpoint. Nevertheless, our sensitivity analyses conducted among trials that reported a patient-centred outcome as their primary endpoint, consistently supported the results obtained. Outcomes definitions are also variable and could interfere with interpretation.(92) However, this will be further addressed in future systematic reviews. Lastly, although patient-centred outcomes are recognized as outcomes that should drive clinical practice, additional outcomes that we did not included in our scoping review are also important and needed to complement clinical decision-making. For instance, opioids are useful in controlling the autonomic response to nociception (i.e., pain transmission).(93) This property of opioids helps maintain a stable hemodynamic during general anesthesia and also facilitates rapid emergence (through lower doses of inhalation anesthetics).

Conclusion

Through our scoping review, we found that patient-centred outcomes are assessed in relatively few clinical trials of intraoperative opioid minimization strategies. This demonstrates a clear need for rigorous multicentre trials assessing these important outcomes. We identified promising strategies (dexmedetomidine, systemic lidocaine and COX-2 inhibitors) that warrant further assessment through systematic reviews and large pragmatic clinical trials. We also identified three strategies that were less promising and not supported by patient-oriented evidence

(acetaminophen, ketamine and gabapentinoids). Further implementation initiatives to promote the use of established recommendations (i.e., StEP-COMPAC) for evaluating patient-centred outcomes are needed in perioperative clinical trials to ensure relevancy to the health system.

Details of authors' contributions

Conceptualization and study question: all authors

Design and methodology: MV, DF, ML, AFT, FZ, MG, ML, AG, NHL, PACT

Develop search strategy: MV, DF, ML, AFT, NHL, RS

Outcome prioritization: all authors

Formal analysis: MV, NHL, MH, JBPL, BH

Drafting the manuscript: MV, DF, ML, NHL, MH

Critical revision of the manuscript: all authors

Guide artificial intelligence feature for screening titles and abstracts: BH

Design data extraction form: all authors

Visualization: MV, NHL, ML, MH, JBPL, DF, PACT

Project administration: MV

Led patient engagement activities: MV, SN

Led knowledge user partnership activities: MV, DF, ML

Screening, data abstraction, and data charting: MV, NHL, MH, JBPL, LY, MK, AA, DEA, MT, PT, JA, SS, AAM, NAF,

Funding acquisition: MV, NHL, ML, SN, AFT, DM, MH, JBPL, IG, BH, FZ, MG, ML, AG, MB, PP, RS, HD, GM, JM, HM, DF

All authors reviewed the content of the manuscript and approved the final version.

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Declaration of interests

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Table 1. Standardised Endpoints in Perioperative Medicine (StEP-COMPAC) group recommendations for patient-centred outcome assessments in perioperative clinical trials[38] and our prioritization order tailored to pharmacologic interventions

	Patient-centred outcome domains				
	Patient well-being	Health-related quality of life	Functional outcome	Patient satisfaction	Life impact
Instruments to be prioritized based on StEP-COMPAC recommendations	Quality of recovery-15 (QoR-15)[2]	EuroQol 5 Dimension, five-level[3]	WHO Disability Assessment Schedule version 2.0	Bauer patient-satisfaction measure	Days alive and out of hospital after surgery (at 30 days and one year) and discharge destination
Prioritization by our team (Steering committee)[1]	1	2	3	4	5

[1]Prioritization based on a) Plausibility for effect between intraoperative pharmacologic intervention and outcome b) Patient and knowledge user priority
[2]Quality of Recovery (QoR)-9 and 40 were also accepted for the purpose of our scoping review
[3]EuroQol 3 Dimension (EQ-3D-3L) was also accepted for the purpose of our scoping review

Variable	NMDA receptor antagonists (n=76)	Alpha-2 agonists (n=71)	Systemic lidocaine (n=46)	COX-2 inhibitors (n=22)	Non-selective anti-inflammatories (n=31)	Corticosteroids (n=49)	Gabapentinoids (n=49)	Acetaminophen[a] (n=19)	Combinations (n=21)	Multiple intervention arms[b] (n=53)	Others[c] (n=20)	Overall (n=457)
Single-centre	74	67	43	17	26	40	48	17	18	50	19	419
Multicentre	2	4	3	5	5	9	1	2	3	3	1	38
Study protocol (published or registered)												
• Yes	35	43	36	6	12	32	21	13	15	22	18	253
• No	41	28	10	16	19	17	28	6	6	31	2	204
Sample size randomized:												
• <50	14	10	5	3	7	6	8	1	2	1	1	58
• 50-99	37	34	29	11	14	9	22	7	7	25	18	213
• 100-499	24	25	12	8	9	28	19	10	12	27	1	175
• >=500	1	2	0	0	1	6	0	1	0	0	0	11
Sample size calculation or minimally importance difference defined												
• Yes	64	60	42	19	19	42	45	17	18	45	20	391
• No	12	11	4	3	12	7	4	2	3	8	0	66
Type of surgery:												
• Cardiac	4	5	3	0	0	9	5	2	0	0	1	29
• Non-cardiac	72	66	43	22	31	40	44	17	21	53	19	428
Route of administration:												
• Intravenous	76	62	45	11	27	47	0	19	12	29	13	341
• Oral	0	7	0	11	1	1	49	0	3	14	7	93
• Intramuscular	0	2	0	0	2	0	0	0	0	1	0	5
• Mixed	0	0	1	0	1	1	0	0	6	9	0	18
Timing of administration:												
• Intraoperative only	57	59	30	11	20	31	18	6	12	30	13	287
• Intraoperative, continued to postoperative	19	12	16	8	11	18	30	13	8	21	7	165
• Mixed	0	0	0	1	0	0	1	0	1	2	0	5

[a]This category also include paracetamol.

[b]Multiple intervention arms: trials with 2 or more intervention arms

[c]Others: opioid minimization strategies with less 10 trials each: beta-blockers, antidepressants, cannabinoids, non-opioid central analgesics (nefopam, metamizole), and methylxanthine.

Table 2. General characteristics of included trials

Figure 1. Compliance with Standardised Endpoints in Perioperative Medicine (StEP-COMPAC) recommendations among included trials

In RCTs of perioperative care, the most important outcome measures and instruments to be used have been established by the StEP-COMPAC group initiative and these recommendations were published in 2019. HRQOL = Health-related quality of life

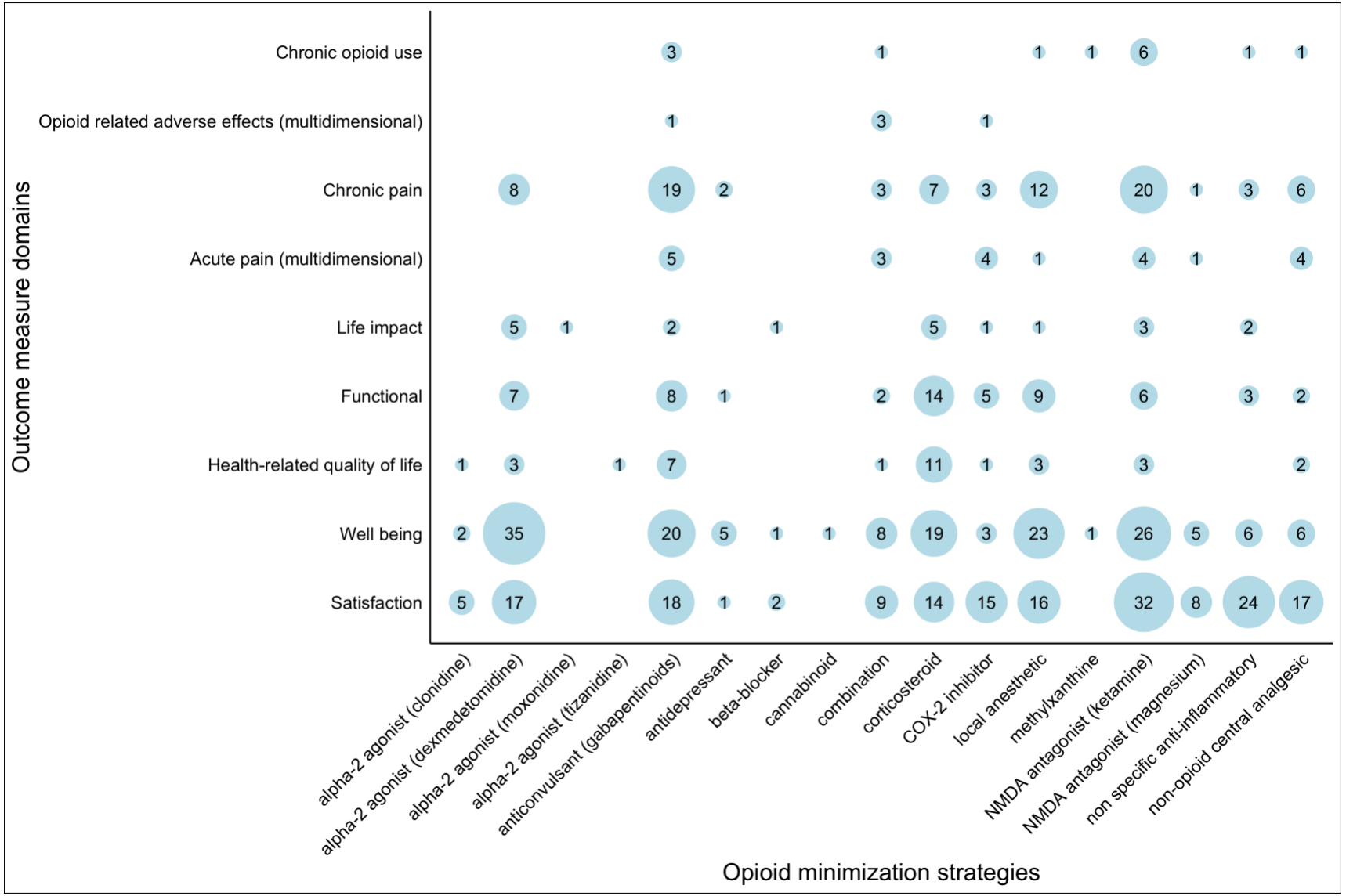


Figure 2. Bubble plot for the number of trials published according to the type of opioid minimization strategy and the patient-centred outcome measure domain reported

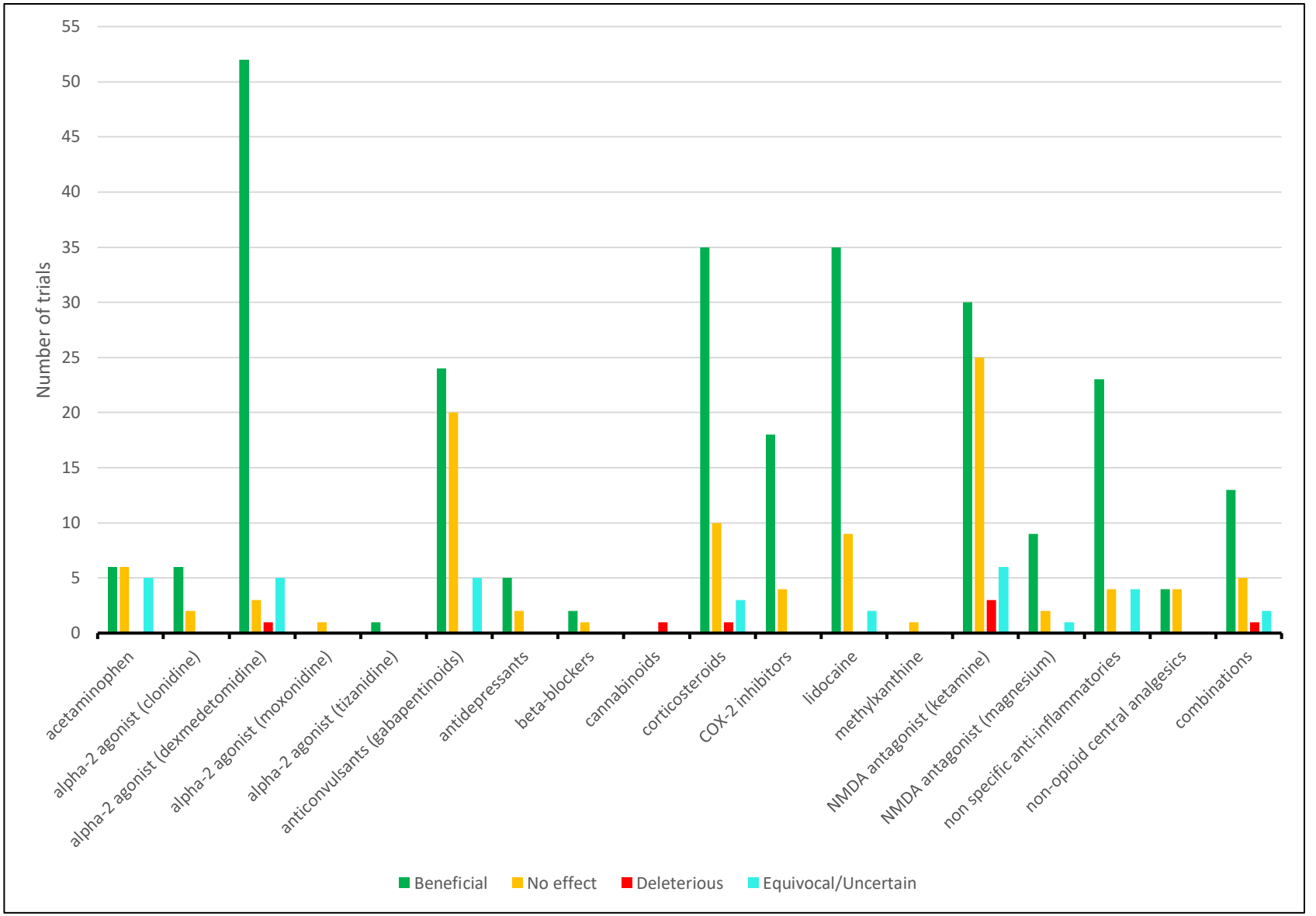


Figure 3. Number of trials showing beneficial, no effect, deleterious or equivocal/uncertain results for each opioid minimization strategies based on reported findings (trials with 2 or more intervention arms are not shown)

eTable 1. Abstraction data items

Information to extract	Definitions and Details	Example extraction or choices
First Author	Last name and First name	
Year of Publication	Numerical value of year of publication	
Multi-centre or single-centre	Indicate whether study was conducted at a single centre or multiple centres	• Multicentre • Single centre
Country for participant recruitment	Country where participants were recruited	• Argentina • Australia • Brazil • Canada • China • France • Germany • India • Japan • South Korea • Spain • Taiwan • Turkey • United States • Other (free text entry)
Study protocol was pre-published or registered	Whether study protocol was published as a journal article or pre-registered in a database	• Yes • No
Randomization unit	Whether participants were randomized as individuals or as clusters (group units)	• Individual level unit • Group unit (cluster)
Number of study arms	Number of study arms, including placebo and/or control groups.	
Were only geriatric patients?	Whether the study only included geriatric patients (based on author's definition)	• Yes • No
Chronic opioid use history in participants	Whether patients with chronic opioid use/opioid addiction were excluded, included, or exclusively included in the study.	• Only patients with chronic opioid use/opioid use disorder are included • Patients with chronic opioid use/opioid disorder are included • Patient with chronic opioid use/opioid disorder are excluded • Not specified
Chronic pain history	Whether patents with chronic pain history were excluded, included, or exclusively included in the study.	• Patients with chronic pain history are included • Only patient with chronic pain history are included • Patients with chronic pain history are excluded • Not specified
Type of patient populations	Whether the study focused on oncologic patients exclusively, non-oncologic patients exclusively, or a mixed patient population	• Not oncologic • Oncologic patients only • Mixed • Not specified
Type of surgery (specialty)	The surgical specialty of the procedures performed on study participants.	• Cardiac • Dermatologic • Endocrine • Gastrointestinal • Mastectomy/lumpectomy • Neurosurgery • Obstetric-gynecologic

		• Ophthalmic • Oral-maxillofacial • Orthopedic • Otorhinolaryngologic • Plastic & reconstructive • Thoracic (non-cardiac) • Urologic • Vascular • Unspecified • Other (free text entry)
Sample size randomized	The number of participants undergoing randomization	
Minimally important difference calculation or rationale	Whether	
Comparator	Whether the control group received placebo (active or inactive), usual care (or standard of care), and/or an opioid comparator	• Placebo (active or inactive) • Usual care or no treatment • Opioid comparator
Intervention: combination or single agent(s)	Whether the intervention group(s) received a combination of pharmacologic agents, a single agent, or a mix of both types of interventions	• Single agent • Combination • Mixed
Opioid minimization strategy	Whether the intervention group received some intraoperative opioid (opioid-reducing) or completely avoided intraopereative opioid (opioid-free)	• Opioid-free • Opioid-reducing
Mechanism of action	The mechanism of action of the pharmacologic agent in the intervention group(s)	• Acetaminophen (also paracetamol) • Alpha-2 adrenergic agonist • Antidepressant • Anticonvulsant (non-gabapentinoid) • Beta-adrenergic antagonist • Cannabinoid • COX-2 inhibitor • Corticosteroid • Gabapentinoid • Magnesium • Methylxanthine adenosine receptor antagonist • NMDA receptor antagonist • Non-opioid central analgesic • Non-specific anti-inflammatory (NSAID) • Systemically administered local anesthetic (lidocaine)
Mode of administration	Route of administration of the intervention pharmacologic agent(s)	• Oral • Intramuscular • Subcutaneous • Intravenous
Timing of the intervention	The perioperative phase of care where the intervention(s) was administered	• Intraoperative only • Intraoperative, then continued to pos-operative • Both (at least one intervention arm per each approach)

Pharmacologic agent(s)	The specific pharmacologic agent(s) administered to the intervention group(s)	For example, Single agent(s): "acetaminophen" A combination: "ketamine + dexmedetomidine" Mixed: "acetaminophen; lidocaine + dexmedetomidine"
Patient-centred outcome; satisfaction	The specific instrument(s) used to assess patient-centred outcome(s) under the satisfaction domain	• Evaluation du vécu de l'anesthésiera générale (EVAN-G) • Heidelberg questionnaire • Heidegger's 29-item • Numerical or categorical rating scales (e.g. NRS,...) • Caljouw's Leiden questionnaire • Bauer score • Other (free text entry)
Patient-centred outcome; well-being	The specific instrument(s) used to assess patient-centred outcome(s) under the well-being domain	• Complete recovery within 30 days (self-assessed) • Beck depression inventory • Zung depression index • State-trait anxiety inventory • Hospital anxiety and depression scale • Psychological general well-being index • Self rating of anxiety level, depression, relaxation and inner peace (VAS, 10 each) • Geriatric depression scale • Quality of recovery 40 (QoR-40) • Quality of recovery 15 (QoR-15) • Quality of recovery 9 (QoR-9) • Sleep quality • Patient health questionnaire (PHQ-8) • Other (free text entry)
Patient-centred outcome; health-related quality of life	The specific instrument(s) used to assess patient-centred outcome(s) under the health-related quality of life domain	• EuroQol-5D-5L • EuroQol-3D-3L • SF-12 • SF-36 • World Health Organization (WHO) Quality of life (brief) • EuroQol-VAS • 15d HRQOL score • SF-6D • Health Utilities Index Mark 3 • VAS (0-100 or 0-10) for general health status • Patient-reported outcomes measurement information system (PROMIS0-10 • PostOp-QRS • RAND-36 • Recovery Index, 49-item

		• Core Outcome Measures Index (COMI) • Other (free text entry)
Patient-centred outcome; functional status	The specific instrument(s) used to assess patient-centred outcome(s) under the functional status domain	• Modified rankin scale • WHO disability assessment schedule 2.0 (DAS) 12-question • WHO disability assessment schedule 2.0 (DAS) 36-question • Timed up and go test • Six minute walk test • ECOG performance status • Karnofsky performance index • Functional assessment of chronic illness therapy-fatigue • Identity-consequence fatigue scale • Roland-morris low back pain and disability questionnaire • Fatigue severity scale • Oswestry low back pain questionnaire/disability index • Berthel index • Other (free text entry)
Patient-centred outcome; life impact	The specific instrument(s) used to assess patient-centred outcome(s) under the life impact domain	• Discharge destination • Number of days alive and out of hospital (1 year time point) • Number of days alive and out of hospital (30 days time point) • Time to return to work • Days off work at particular endpoints postoperative • Restricted activity days/bed rest in previous 14 days • Time to return to usual activities • Other (free text entry)
Patient-centred outcome; pain	Whether chronic pain assessment and/or a multi-dimensional acute pain assessment was performed	• Chronic pain outcome (>= 3 months/90 days) • Acute pain multi-dimensional (<3 months)
Patient-centred outcome; pain	Whether the study assessed persistent opioid use (>= 1 month/30 days), dependence, use disorder, overdose, and/or postoperative opioid-related adverse effects (as a composite multi-dimensional instrument)	• Persistent opioid use (>=1 month/30 days)/use or dependence/use disorder/overdose • postoperative opioid related adverse effects (multidimensional)
Which of the follow outcomes was a primary, or co-primary outcome of the study?	Reviewer was instructed to selected any of the specific instruments selected in the preceding outcome-related questions was primary or a co-primary outcome of the study. If not, reviewer was instructed to indicate what the primary or co-primary outcome(s) of the study was in free text.	• *A selection of all the preceding outcome choices* *<u>With the following additions:</u>* • Hospital length of stay • Post-operative nausea and/or vomiting • Short-term opioid use / administration (<1 month)

		• Other (free text entry) • Not specified
Author's conclusion	Whether the study's author(s) concluded that the study intervention had no effect, a beneficial effect, or a deleterious effect when compared against the control group(s); or whether it was inconclusive (i.e. a combination of harms and benefits).	• No effect • Equivocal/uncertain • Beneficial effect • Deleterious
Adverse events assessed	Whether the study assessed adverse events	• Yes • No
Serious adverse events assessed	Whether the study assessed serious adverse events	• Yes • No
Follow-up period (days)	The reported follow-up period, extracted as a number of day(s).	
Patient engagement in the trial	Whether patient engagement was reported in the study.	• Yes • No
Funding source	The funding source as reported in the study. Reviewer was instructed to clarify between no funding ("None") and not reported by the author(s) ("Not reported").	• Government • Foundation / charity • Industry (including in-kind such as the pharmacologic agent) • Institutional/academic • Not reported • None
Sex and gender consideration	Whether the study considered sex and/or gender of the study participants in the analysis of the study outcome(s) (e.g. subgroup analysis) Demographic report of sex and/or gender is not sufficient to select "Yes".	• Yes • No
Genetic factors account for	Whether the study examined genetic factors (e.g. gene polymorphism in drug metabolization) in study participants	• Yes • No

eTable 2. Detailed characteristics of included trials

Study	Country	Study protocol	Number of patients randomized	Surgery type	Intervention(s)		Patient-centred outcome domains assessed (instruments in parentheses)	Follow-up period (days)	Author's overall conclusion of the intervention(s)[a]	Patient engagement (yes or no)	Funding source
					Intervention group(s)	Timing					
Aantaa et al. (1991)	Finland	No	108	Obstetric-Gynecologic	Dexmedetomidine	Intraoperative only	- Well-being (VAS/NRS Anxiety)	Unspecified	Equivocal/uncertain	No	Industry
Abdelfatah et al. (2021)	Egypt	Yes	60	Gastrointestinal	Esmolol	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Abdelmalak et al. (2019)	United States	Yes	381	Gastrointestinal Urologic Vascular Others	Dexamethasone	Intraoperative, then continued to post-operative	- HRQOL (SF-12) - Function (Fatigue severity scale)	30	No effect	No	Industry Institutional/ Academic
AbdelRady et al. (2021)	Egypt	Yes	60	Gastrointestinal	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	None
Abdelrahman et al. (2021)	Egypt	Yes	30	Gastrointestinal	Dexmedetomidine; Ketamine; Lidocaine	Intraoperative only	- Satisfaction (NRS or categorical)	0	Beneficial effect	No	Unreported
Abdulla et al. (2012)	Germany	No	120	Obstetric-Gynecologic	Parecoxib; Metamizol; Acetaminophen	Intraoperative only	- Satisfaction (NRS or categorical)	1	No effect	No	None
Abdulla et al. (2012)	Germany	No	120	Obstetric-Gynecologic	Parecoxib; Metamizol; Acetaminophen	Intraoperative only	- Satisfaction (NRS or categorical)	1	No effect	No	None
Adam et al. (1999)	France	No	130	Mastectomy/lumpectomy	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	1	No effect	No	None
Ahn et al. (2015)	South Korea	No	50	Gastrointestinal	Lidocaine	Intraoperative only	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	Government
Akca et al. (2004)	Turkey	No	80	Gastrointestinal	Tenoxicam	Intraoperative only	- Satisfaction (NRS or categorical) - Function (Time to ambulation)	Unspecified	Beneficial effect	No	None
Akça et al. (2016)	Turkey	No	75	Urologic	Dexmedetomidine; Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Andjelkovic et al. (2018)	Slovenia	Yes	59	Gastrointestinal	Lidocaine; Dexmedetomidine	Intraoperative only	- Function (Time to return to bowel) - Acute pain multi-dimensional (Other)	60	Beneficial effect	No	Unreported
Antila et al. (2019)	Finland	Yes	40	Gastrointestinal	Hydrocortisone	Intraoperative, then continued to post-operative	- Well-being (Sleep quality) - Life impact (Other - any medication use or sleep disturbance attributable to pain over the previous 7 days at 6 months)	90	Beneficial effect	No	Government Foundation/ Charity
Arain et al. (2004)	United States	No	34	Orthopedic Others	Dexmedetomidine	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Areeruk et al. (2016)	Thailand	Yes	52	Obstetric-Gynecologic	Dexamethasone	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Institutional/ Academic
Argiriadou et al. (2004)	Greece	No	45	Gastrointestinal	Ketamine	Intraoperative only	- Well-being (Self-rating VAS)	1	Beneficial effect	No	Industry

Arikan et al. (2016)	Turkey	No	120	Obstetric-Gynecologic	Ketamine; Magnesium	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	2	Equivocal/uncertain	No	None
Arslan et al. (2013)	Turkey	No	300	Gastrointestinal	Acetaminophen	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Artime et al. (2017)	United States	No	100	Neurosurgery	Acetaminophen	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	Equivocal/uncertain	No	Government Industry
Ates et al. (2020)	Turkey	No	55	Otorhinolaryngologic	Lidocaine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Unreported
Ates et al. (2021)	Turkey	No	48	Otorhinolaryngologic	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Unreported
Attia et al. (2017)	Egypt	Yes	120	Orthopedic	Duloxetine; Etoricoxib; Duloxetine + Etoricoxib	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	Unreported
Aubrun et al. (2000)	France	No	50	Orthopedic	Ketoprofen	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Well-being (Self-rating VAS)	1	Beneficial effect	No	Industry
Aubrun et al. (2007)	France	No	90	Obstetric-Gynecologic	Ketamine	Intraoperative, then continued to post-operative	- Well-being (VAS/NRS Mood)	2	No effect	No	Institutional/ Academic
Aveline et al. (2014)	France	No	75	Orthopedic	Nefopam; Ketamine	Intraoperative, then continued to post-operative	- Function (Other-Knee Injury and Osteoarthritis Outcome Score-Physical function Shortform) - Chronic pain	365	Beneficial effect	No	None
Avidan et al. (2017 & 2018)	Canada, United States, South Korea, India	Yes	672	Cardiac Gastrointestinal Obstetric-Gynecologic Orthopedic Otorhinolaryngologic Thoracic (non-cardiac) Urologic Vascular	Ketamine	Intraoperative only	- Well-being (PHQ-19) - Acute pain multi-dimensional (Other)	30	Deleterious	No	Government Unreported
Awal et al. (2022)	India	Yes	50	Obstetric-Gynecologic	Lidocaine	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (QoR-40)	1	Beneficial effect	No	Unreported
Baloch et al. (2021)	Pakistan	No	84	Orthopedic	Pregabalin	Intraoperative, then continued to post-operative	- Function (Roland-Morris)	Unspecified	Beneficial effect	No	None
Bekawi et al. (2014)	Egypt	No	90	Gastrointestinal	Pregablin; Gabapentin	Intraoperative, then	- Satisfaction (NRS or categorical)	1	Equivocal/uncertain	No	Unreported

						continued to post-operative					
Bekker et al. (2013)	United States	No	66	Orthopedic	Dexmedetomidine	Intraoperative only	- Well-being (QoR-40) - Function (Fatigue severity scale)	30	Beneficial effect	No	Foundation/ Charity Industry Institutional/ Academic
Beloeil et al. (2018)	France	Yes	237	Specialty Unspecified	Nefopam; Ketoprofen; Acetaminophen; Nefopam + Ketoprofen; Nefopam + Acetaminophen; Ketoprofen + Acetaminophen; Nefopam + Ketoprofen+ Acetaminophen	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Chronic pain - Multidimensional opioid adverse effect scale	90	Beneficial effect	No	Government
Benhamou et al. (1994)	France	No	40	Gastrointestinal	Clonidine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	Unspecified	No effect	No	None
Bhatia et al. (2004)	India	No	50	Gastrointestinal	Magnesium Sulfate	Intraoperative only	- Satisfaction (Other - VAS discomfort) - Well-being (Sleep quality)	1	Equivocal/uncertain	No	None
Bielka et al. (2018)	Ukraine	Yes	60	Gastrointestinal	Dexmedetomidine	Intraoperative only	- Chronic pain	180	Beneficial effect	No	None
Bilgen et al. (2012)	Turkey	No	140	Obstetric-Gynecologic	Ketamine	Intraoperative only	- Chronic pain	365	No effect	No	None
Bisgaard et al. (2003)	Denmark	No	88	Gastrointestinal	Dexamethasone	Intraoperative only	- Function (Fatigue severity scale) - Life impact (Time to return to work)	30	Beneficial effect	No	Government Institutional/ Academic
Bisgaard et al. (2007)	Denmark	No	200	Gastrointestinal	Prednisone	Intraoperative only	- Function (Fatigue NRS/VAS)	30	No effect	No	None
Bjerregaard et al. (2017)	Denmark	Yes	120	Thoracic (non-cardiac)	Methylprednisolone	Intraoperative only	- Well-being (Sleep quality)	84	Beneficial effect	No	Foundation/ Charity
Blitz et al. (2012)	United States	No	118	Gastrointestinal Obstetric-Gynecologic	Dexamethasone	Intraoperative only	- Function (Other-Quality of Life–Functional Living Index-Emesis (QOL-FLIE))	4	No effect	No	Industry
Bolliger et al. (2007)	Switzerland	Yes	141	Vascular	Moxonidine	Intraoperative, then continued to post-operative	- Life impact (#day alive and out of hospital at 1yr)	365	No effect	No	None
Bouzia et al. (2017)	Greece	Yes	101	Cardiac	Pregabalin	Intraoperative only	- Well-being (Sleep quality) - Chronic pain - Aberrant opioid use post-op	90	Beneficial effect	No	None
Brinck et al. (2020)	Finland	Yes	198	Orthopedic	Ketamine	Intraoperative only	- Well-being (Beck inventory) - Chronic pain	730	No effect	No	Institutional/ Academic
Brulotte et al. (2015)	Canada	Yes	114	Thoracic (non-cardiac)	Pregabalin	Intraoperative, then continued to post-operative	- Chronic pain	90	No effect	No	Institutional/ Academic

Bryson et al. (2010)	Canada	Yes	93	Obstetric-Gynecologic	Lidocaine	Intraoperative only	- Well-being (QoR-9) - Acute pain multi-dimensional (Brief pain inventory)	7	No effect	No	Institutional/ Academic
Burke et al. (2010)	Ireland	No	40	Orthopedic	Pregabalin	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Well-being (Hospital anxiety & depression scale) - HRQOL (SF-36) - Function (Roland-Morris) - Life impact (Other - Number of patients back at work at 3 months) - Chronic pain - Acute pain multi-dimensional (McGill)	90	Beneficial effect	No	Industry
Burns et al. (2021)	United States	Yes	79	Orthopedic	Celecoxib	Intraoperative, then continued to post-operative	- Function (Orthopedic functional recovery) - Chronic pain	365	No effect	No	Foundation/ Charity Industry Institutional/ Academic
Buvanendran et al. (2010)	United States	No	240	Orthopedic	Pregabalin	Intraoperative, then continued to post-operative	- Well-being (Sleep quality) - Function (Other-Osteoarthritis Outcome Score–Physical function Short-form (KOOS-PS)) - Chronic pain	180	Beneficial effect	No	Industry
Cai et al. (2016)	China	Yes	100	Thoracic (non-cardiac)	Dexmedetomidine	Intraoperative only	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	None
Cakan et al. (2008)	Turkey	No	40	Orthopedic	Acetaminophen	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	Equivocal/uncertain	No	None
Cameron et al. (2019)	Canada	Yes	82	Cardiac	Ketamine	Intraoperative only	- Life impact (Time to return to usual activities) - Chronic pain - Acute pain multi-dimensional (Brief pain inventory)	90	No effect	No	Foundation/ Charity
Canbay et al. (2006)	Turkey	No	43	Obstetric-Gynecologic	Diclofenac	Intraoperative only	- Satisfaction (NRS or categorical)	2	No effect	No	None
Carabine et al. (1991)	Ireland	No	80	Obstetric-Gynecologic	Clonidine	Intraoperative only	- Well-being (VAS/NRS Anxiety)	Unspecified	Beneficial effect	No	None
Chang et al. (2017)	China	No	60	Mastectomy/lumpectomy	Dexmedetomidine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Government Foundation/ Charity
Chau-in et al. (2008)	Thailand	No	49	Obstetric-Gynecologic	Etoricoxib	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Institutional/ Academic

Chen et al. (2015)	China	No	64	Otorhinolaryngologic	Parecoxib	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Chen et al. (2016)	China	Yes	62	Gastrointestinal	Dexmedetomidine	Intraoperative only	- Well-being (Sleep quality)	3	Beneficial effect	No	Government
Chen et al. (2020)	China	Yes	126	Gastrointestinal	Dexamethasone	Intraoperative only	- HRQOL (EuroQol-5D-3L)	3	Beneficial effect	No	Government
Chen et al. (2021)	Taiwan	Yes	160	Neurosurgery	Dexmedetomidine	Intraoperative only	- Function (Modified Rankin)	30	Beneficial effect	No	Government Institutional/ Academic
Chen et al. (2023)	China	Yes	81	Obstetric-Gynecologic	Dexmedetomidine + Esketamine	Intraoperative, then continued to post-operative	- Well-being (Sleep quality)	30	No effect	No	Unreported
Cheng et al. (2022)	China	Yes	80	Thoracic (non-cardiac)	Ketamine	Intraoperative only	- Well-being (Hospital anxiety & depression scale)	2	Beneficial effect	No	None
Cheung et al. (2011)	China	Yes	105	Oral-maxillofacial	Dexmedetomidine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	3	Beneficial effect	No	Institutional/ Academic
Cho et al. (2018)	South Korea	Yes	202	Orthopedic	Dexamethasone	Intraoperative only	- Well-being (QoR-15)	3	Beneficial effect	No	None
Choi et al. (2012)	South Korea	No	60	Plastic & reconstructive	Lidocaine	Intraoperative only	- Satisfaction (NRS or categorical) - Function (Time to return to bowel)	3	No effect	No	None
Choi et al. (2013)	South Korea	Yes	120	Orthopedic	Pregabalin; Pregabalin + Dexamethasone	Intraoperative, then continued to post-operative	- Function (Daily activity level) - Chronic pain	180	Beneficial effect	No	None
Choi et al. (2016)	South Korea	Yes	56	Endocrine	Lidocaine	Intraoperative only	- Satisfaction (NRS or categorical)	3	Beneficial effect	No	Government
Choi et al. (2016)	South Korea	Yes	90	Endocrine	Lidocaine	Intraoperative only	- Well-being (QoR-40) - Chronic pain	90	Equivocal/uncertain	No	Government
CHoi et al. (2019)	South Korea	Yes	44	Thoracic (non-cardiac)	Dexmedetomidine	Intraoperative only	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	None
Choi et al. (2021)	South Korea	Yes	90	Gastrointestinal	Dexmedetomidine	Intraoperative only	- Well-being (QoR-40)	1	Equivocal/uncertain	No	None
Choi et al. (2022)	South Korea	Yes	78	Obstetric-Gynecologic	Dexmedetomidine+Lidocaine	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	Government
Chumbley et al. (2019)	United Kingdom	Yes	77	Thoracic (non-cardiac)	Ketamine	Intraoperative, then continued to post-operative	- Chronic pain - Acute pain multi-dimensional (Brief pain inventory) - Aberrant opioid use post-op	360	No effect	No	Government
Claeys et al. (1992)	Belgium	No	40	Orthopedic	Diclofenac	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Clarke et al. (2015)	Canada	No	184	Orthopedic	Pregabalin	Intraoperative, then continued to post-operative	- Well-being (Hospital anxiety & depression scale) - Function (Timed	90	Equivocal/uncertain	No	Industry Institutional/ Academic

							up and go) - Chronic pain				
Coloma et al. (2001)	United States	No	53	Obstetric-Gynecologic	Esmolol	Intraoperative only	- Satisfaction (NRS or categorical) - Life impact (Time to return to usual activities)	1	Beneficial effect	No	None
Coloma et al. (2002)	United States	No	140	Gastrointestinal	Dexamethasone	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (Other QoR)	1	Beneficial effect	No	Industry
Comez et al. (2015)	Turkey	No	60	Thoracic (non-cardiac)	Dexketoprofen	Intraoperative only	- Satisfaction (NRS or categorical) - Chronic pain	180	Beneficial effect	No	None
Cooke et al. (2018)	United States	Yes	128	Gastrointestinal	Acetaminophen	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Well-being (QoR-15)	2	Beneficial effect	No	Industry Institutional/ Academic
Corcoran et al. (2021)	Australia, China , New Zealand, Hong Kong	Yes	8880	Others	Dexamethasone	Intraoperative only	- Well-being (QoR-15) - Chronic pain	180	Equivocal/uncertain	No	Government Institutional/ Academic
Coşkun et al. (2014)	Turkey	No	120	Specialty Unspecified	Acetaminophen; Lornoxicam; Acetaminophen + Lornoxicam	both (at least one arm intraoperative only and at least one other arm intraoperative and postoperative)	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Crisp et al. (2017)	United States	Yes	90	Obstetric-Gynecologic	Acetominophen	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	14	No effect	No	Institutional/ Academic
Cui et al. (2019)	United States	Yes	74	Orthopedic	Dexamethasone	Intraoperative, then continued to post-operative	- HRQOL (Other QoL measure) - Function (Disability index) - Chronic pain	365	Beneficial effect	No	Foundation/ Charity
Cuvillon et al. (2017)	France	Yes	78	Gastrointestinal	Nefopam	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	2	No effect	No	Institutional/ Academic
Czarnetzki et al. (2020)	Switzerland	Yes	160	Orthopedic	Ketamine	Intraoperative only	- Chronic pain - Aberrant opioid use post-op	365	No effect	No	Institutional/ Academic
Dahl et al. (1997)	Norway	No	66	Obstetric-Gynecologic	Ibuprofen; Acetaminophen	Intraoperative only	- Well-being (Sleep quality)	4	No effect	No	Industry
Dahl et al. (2011)	Norway	Yes	93	Orthopedic	Parecoxib + Valdecoxib; Etoricoxib; Dexamethasone	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	7	Beneficial effect	No	None

Dai et al. (2020)	China	No	120	Gastrointestinal	Lidocaine	Intraoperative only	- Well-being (QoR-15) - Chronic pain	90	Beneficial effect	No	Unreported
De Kock et al. (1992)	Belgium	No	200	Gastrointestinal	Clonidine	Intraoperative only	- Satisfaction (NRS or categorical)	7	Beneficial effect	No	None
De Kock et al. (1994)	Belgium	No	80	Gastrointestinal	Clonidine; Clonidine + lidocaine	both (at least one arm intraoperative only and at least one other arm intraoperative and postoperative)	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	None
De Oliveira et al. (2010)	United States	Yes	120	Obstetric-Gynecologic	Dexamethasone	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	Institutional/ Academic
De Oliveira et al. (2011)	United States	Yes	120	Obstetric-Gynecologic	Dexamethasone	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	Institutional/ Academic
De Oliveira et al. (2012)	United States	Yes	70	Obstetric-Gynecologic	Lidocaine	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	Institutional/ Academic
De Oliveira et al. (2013)	United States	Yes	50	Mastectomy/lumpectomy	Magnesium	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	Institutional/ Academic
De Oliveira et al. (2014)	United States	Yes	51	Gastrointestinal	Lidocaine	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	None
De Oliveira et al. (2018)	United States	Yes	70	Obstetric-Gynecologic	Esmolol	Intraoperative only	- Well-being (QoR-40)	1	No effect	No	Institutional/ Academic
Deng et al. (2009)	China	No	200	Orthopedic	Ketamine		- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Deniz et al. (2012)	Turkey	No	51	Urologic	Gabapentin	Intraoperative only	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	None
Desjardins et al. (2004)	United States	No	203	Orthopedic	Parecoxib	Intraoperative only	- Satisfaction (NRS or categorical)	14	Beneficial effect	No	Industry
Dewinter et al. (2016)	Belgium	Yes	80	Obstetric-Gynecologic	Lidocaine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Dewinter et al. (2017)	Belgium	Yes	70	Orthopedic	Lidocaine	Intraoperative, then continued to post-operative	- HRQOL (SF-12)	30	No effect	No	None
Diaz-Borjon et al. (2017)	Canada, United States, Australia, Argentina, Chile, New Zealand, Bulgaria, Czech Republic, Poland, Romania, Ukraine,	Yes	281	Orthopedic	Parecoxib + Valdecoxib	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Acute pain multi-dimensional (Brief pain inventory) - Multidimensional opioid adverse effect scale	7	0	0	Industry

	Finland, Israel, and South Africa										
Dieleman et al. (2017)	Netherlands	No	4494	Cardiac	Dexamethasone	Intraoperative only	- HRQOL (EuroQol-5D-5L)	365	Beneficial effect	No	Government Foundation/ Charity
Ding et al. (1992)	United States	No	136	Specialty Unspecified	Ketorolac	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (Self-rating VAS)	1	Beneficial effect	No	None
Ding et al. (2023)	China	Yes	70	Orthopedic	Duloxetine	Intraoperative, then continued to post-operative	- Well-being (Hamilton scale) - Function (WOMAC) - Chronic pain	84	Beneficial effect	No	Government Institutional/ Academic
Dissanayake et al. (2018)	Australia	Yes	164	Orthopedic	Dexamethasone	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	42	Beneficial effect	No	Institutional/ Academic
Doksrod et al. (2012)	Norway	Yes	121	Endocrine	Dexamethasone	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (Sleep quality) - Function (Fatigue NRS/VAS)	30	No effect	No	Institutional/ Academic
Du et al. (2018)	China	Yes	84	Obstetric-Gynecologic	Dexmedetomidine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Government
Dualé et al. (2009)	France	Yes	86	Thoracic (non-cardiac)	Ketamine	Intraoperative, then continued to post-operative	- HRQOL (SF-36) - Chronic pain - Aberrant opioid use post-op	120	No effect	No	Government
Dullenkopf et al. (2009)	Switzerland	No	120	OrthopedicSpecialty Unspecified	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical) - Chronic pain	90	No effect	No	None
Edwards et al. (1991)	Wales	No	80	GastrointestinalObstetric-Gynecologic	Diclofenac	Intraoperative only	- Life impact (Time to return to usual activities)	2	No effect	No	None
Ekman et al. (2006)	United States	No	200	Orthopedic	Celecoxib	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Industry
El Chaar et al. (2016)	United States	Yes	100	Gastrointestinal	Acetominophen	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	30	Beneficial effect	No	Industry
Ergenoglu et al. (2012)	Turkey	Yes	64	Urologic	Acetaminophen	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Eskandar et al. (2013)	Egypt	No	80	Orthopedic	Pregabalin	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Farag et al. (2013)	United States	Yes	116	Neurosurgery Orthopedic	Lidocaine	Intraoperative, then	- HRQOL (SF-12)	90	Beneficial effect	No	Institutional/ Academic

						continued to post-operative					
Feng et al. (2008)	China	No	37	Orthopedic	Rofecoxib	Intraoperative only	- Satisfaction (NRS or categorical)	3	Beneficial effect	No	Foundation/ Charity
Fleckenstein et al. (2016)	Germany	Yes	103	Gastrointestinal Obstetric-Gynecologic Thoracic (non-cardiac)	Etoricoxib	both (at least one arm intraoperative only and at least one other arm intraoperative and postoperative)	- Acute pain multi-dimensional (German Society for the Study of Pain)	3	No effect	No	Industry Institutional/ Academic
Forget et al. (2019)	Belgium	Yes	203	Mastectomy/lumpectomy	Ketorolac	Intraoperative only	- Life impact (Other - Disease-Free Survival (DFS) at two years)	780	No effect	No	Foundation/ Charity Institutional/ Academic
Forget et al. (2020)	Belgium	Yes	203	Mastectomy/lumpectomy	Ketorolac	Intraoperative only	- Chronic pain	730	Equivocal/uncertain	No	Foundation/ Charity Institutional/ Academic
Foster et al. (1985)	United Kingdom	No	40	Oral-maxillofacial	Lysine Acetylsalicylate	Intraoperative only	- Satisfaction (NRS or categorical)	1	Equivocal/uncertain	No	Industry
Fujii et al. (2002)	Japan	No	120	Obstetric-Gynecologic	Dexamethasone	Intraoperative only	- Satisfaction (NRS or categorical)	5	Beneficial effect	No	None
Gaber et al. (2019)	Egypt	No	60	Thoracic (non-cardiac)	Pregabalin	Intraoperative, then continued to post-operative	- Chronic pain - Acute pain multi-dimensional (Other)	90	Beneficial effect	No	Unreported
Gan et al. (2004)	United States	No	276	Gastrointestinal	Parecoxib + Valdecoxib	Intraoperative, then continued to post-operative	- Acute pain multi-dimensional (Brief pain inventory) - Multidimensional opioid adverse effect scale	4	Beneficial effect	No	None
Ge et al. (2015)	China	Yes	71	Gastrointestinal	Dexmedetomidine	Intraoperative only	- Well-being (QoR-40) - Function (Fatigue severity scale)	14	Beneficial effect	No	Unreported
Ge et al. (2016)	China	Yes	64	Obstetric-Gynecologic	Dexmedetomidine	Intraoperative only	- Well-being (QoR-40) - Function (Fatigue severity scale)	14	Beneficial effect	No	None
Ge et al. (2021)	China	No	105	Gastrointestinal	Parecoxib	Intraoperative, then continued to post-operative	- Chronic pain	90	Beneficial effect	No	Institutional/ Academic
George et al. (2014)	Canada	Yes	101	Obstetric-Gynecologic	Pregabalin	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - HRQOL (SF-36) - Function (Daily activity level)	180	No effect	No	Foundation/ Charity
Ghimire et al. (2020)	Nepal	Yes	64	Gastrointestinal	Lidocaine	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (QoR-	90	Beneficial effect	No	Unreported

							40) - Chronic pain				
Gianesello et al. (2012)	Italy	No	60	Neurosurgery	Pregabalin	Intraoperative, then continued to post-operative	- HRQOL (EuroQol-5D-5L)	365	Beneficial effect	No	Unreported
Gilron et al. (2005)	Canada	No	110	Obstetric-Gynecologic	Gabapentin; Rofecoxib; Gabapentin + Rofecoxib	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Well-being (Sleep quality)	30	Beneficial effect	No	None
Gilron et al. (2009)	Canada	Yes	89	Gastrointestinal	Gabapentin; Meloxicam; Gabapentin + Meloxicam	Intraoperative only	- Satisfaction (NRS or categorical) - Life impact (Time to return to work)	30	No effect	No	None
Gonano et al. (2011)	Canada	No	40	Orthopedic	Pregabalin	Intraoperative only	- Well-being (VAS/NRS Anxiety)	1	Beneficial effect	No	Unreported
Gopalraju et al. (2013)	India	No	40	Oral-maxillofacial	Ketorolac	Intraoperative only	- Satisfaction (NRS or categorical)	5	Beneficial effect	No	None
Govindarajan et al. (2005)	United States	No	50	Gastrointestinal	Ketorolac	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Grady et al. (2012)	United States	No	50	Obstetric-Gynecologic	Lidocaine	Intraoperative only	- Satisfaction (NRS or categorical)	3	Beneficial effect	No	Government
Grady et al. (2012)	United States	No	64	Obstetric-Gynecologic	Lidocaine, Ketamine	Intraoperative, then continued to post-operative	- Function (6-minute walk)	2	Deleterious	No	Institutional/ Academic
Greenberg et al. (2017)	United States	Yes	140	Neurosurgery	Acetaminophen	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	Equivocal/uncertain	No	Industry
Grigoras et al. (2012)	Ireland	No	36	Mastectomy/lumpectomy	Lidocaine	Intraoperative only	- Well-being (Hospital anxiety & depression scale) - Chronic pain	90	Beneficial effect	No	None
Grosen et al. (2014)	Denmark	Yes	104	Thoracic (non-cardiac)	Gabapentin	Intraoperative, then continued to post-operative	- Well-being (Sleep quality) - Function (6-minute walk) - Chronic pain	180	No effect	No	Government Foundation/ Charity
Gupta et al. (2016)	United States	No	78	Orthopedic	Acetaminophen	Intraoperative, then continued to post-operative	- Well-being (QoR-40)	5	Beneficial effect	No	Unreported
Haddad et al. (2019)	Tunisia	No	62	Urologic	Parecoxib	Intraoperative only	- Satisfaction (NRS or categorical) - Chronic pain	365	Beneficial effect	No	None
Hah et al. (2018)	United States	Yes	422	Mastectomy/lumpectomy Orthopedic Thoracic (non-cardiac)	Gabapentin	Intraoperative, then continued to post-operative	- Chronic pain - Aberrant opioid use post-op	730	No effect	No	Institutional/ Academic
Hah et al. (2020)	United States	Yes	410	Mastectomy/lumpectomy Orthopedic	Gabapentin	Intraoperative, then	- Well-being (Beck inventory) - HRQOL (EuroQol-	730	Equivocal/uncertain	No	Government Institutional/ Academic

				Plastic & reconstructive Thoracic (non-cardiac)		continued to post-operative	VAS) - Chronic pain - Aberrant opioid use post-op				
Hakim et al. (2019)	Egypt	No	80	Obstetric-Gynecologic	Dexmedetomidine	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	Unreported
Halvorsen et al. (2003)	Norway	No	294	Cardiac	Dexamethasone	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	6	Beneficial effect	No	Institutional/ Academic
Han et al. (2019)	China	No	80	Obstetric-Gynecologic	Dexmedetomidine	Intraoperative only	- Chronic pain	365	Beneficial effect	No	Government
Hanna et al. (2003)	United Kingdom	No	172	Orthopedic	Ketoprofen; Dexketoprofen	Intraoperative, then continued to post-operative	- Well-being (Sleep quality)	1	Beneficial effect	No	Industry
Hasegawa et al. (2020)	Japan	Yes	124	Gastrointestinal	Methylprednisolone	Intraoperative only	- Life impact (Other - number of days alive and out of hospital (90 days time point); Comprehensive Complication Index (Clavien-Dindo Classification))	90	Beneficial effect	No	Unreported
Hauer et al. (2012)	Germany	Yes	111	Cardiac	Hydrocortisone	Intraoperative, then continued to post-operative	- Well-being (Hamilton scale)	180	No effect	No	Foundation/ Charity
Hayes et al. (2004)	Australia	No	45	Orthopedic	Ketamine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Chronic pain	180	No effect	No	None
Hegarty et al. (2011)	Ireland	No	32	Orthopedic	Pregabalin	Intraoperative only	- Well-being (Hospital anxiety & depression scale) - Function (Roland-Morris) - Acute pain multi-dimensional (McGill)	1	No effect	No	Institutional/ Academic
Helmond et al. (2016)	Netherlands	Yes	138	Mastectomy/lumpectomy	Parecoxib + Celecoxib	Intraoperative, then continued to post-operative	- HRQOL (Other - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30) - Chronic pain	365	No effect	No	Industry
Hetta et al. (2020)	Egypt	Yes	88	Mastectomy/lumpectomy	Duloxetine	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	Institutional/ Academic
Heydari et al. (2017)	Iran	No	129	Orthopedic	Ketamine; Acetaminophen; Magnesium Sulfate	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Ho et al. (2010)	Singapore	No	50	Orthopedic	Duloxetine	Intraoperative, then continued to post-operative	- Chronic pain	180	Beneficial effect	No	None

Hontoir et al. (2016)	Belgium	Yes	66	Mastectomy/lumpectomy	Clonidine + Ketamine	Intraoperative only	- Well-being (QoR-40)	1	Equivocal/uncertain	No	None
Hu et al. (2014)	China	No	81	Thoracic (non-cardiac)	Ketamine	Intraoperative, then continued to post-operative	- Chronic pain	180	No effect	No	Unreported
Huang et al. (2014)	Taiwan	No	55	Otorhinolaryngologic	Parecoxib	Intraoperative only	- Satisfaction (NRS or categorical)	1	No effect	No	None
Hudetz et al. (2009)	United States	No	52	Cardiac	Ketamine	Intraoperative only	- Well-being (Geriatric depression scale)	7	Beneficial effect	No	Government
Huyan et al. (2019)	China	No	360	Thoracic (non-cardiac)	Dexmedetomidine	Intraoperative only	- Well-being (Sleep quality)	7	Beneficial effect	No	Government Foundation/ Charity Institutional/ Academic
Ibrahim et al. (2018)	Egypt	Yes	40	Orthopedic	Lidocaine	Intraoperative only	- Chronic pain	90	Beneficial effect	No	Unreported
Ibrahim et al. (2022)	Egypt	Yes	103	Gastrointestinal	Dexmedetomidine + Ketamine + Lidocaine	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	Unreported
Issioui et al. (2002)	United States	No	112	Otorhinolaryngologic	Acetaminophen; Celecoxib; Acetaminophen + Celecoxib	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (Other QoR)	1	Beneficial effect	No	Foundation/ Charity
Ithnin et al. (2019)	Singapore	Yes	90	Obstetric-Gynecologic	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (Other -Profile of Mood Scale)	1	No effect	No	Foundation/ Charity
Ittichaikulthol et al. (2009)	Thailand	No	80	Obstetric-Gynecologic	Pregabalin	Intraoperative only	- Satisfaction (NRS or categorical)	0	Beneficial effect	No	None
Ittichaikulthol et al. (2010)	Thailand	No	120	Orthopedic	Celecoxib; Parecoxib	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Jain et al. (2012)	India	No	86	Mastectomy/lumpectomy	Dexmedetomidine	Intraoperative, then continued to post-operative	- HRQOL (Other QoL measure) - Chronic pain	Unspecified	Beneficial effect	No	None
Jakobsson et al. (1996)	Sweden	No	200	Obstetric-Gynecologic	Diclofenac; Ketorolac	Intraoperative only	- Well-being (VAS/NRS Anxiety)	Unspecified	Beneficial effect	No	None
Jaoua et al. (2010)	Tunisia	No	42	Gastrointestinal	Magnesium	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Well-being (Sleep quality)	1	No effect	No	None
Javaherforooshzadeh et al. (2018)	Iran	Yes	90	Orthopedic	Gabapentin	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (Self-rating VAS)	1	Beneficial effect	No	Institutional/ Academic
Jeffs et al. (2002)	United Kingdom	No	60	Gastrointestinal Obstetric-Gynecologic	Clonidine	Intraoperative only	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	None
Jelacic et al. (2015)	United States	Yes	68	Cardiac	Acetaminophen	Intraoperative only	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	Industry
Jena et al. (2023)	India	no	100	Otorhinolaryngologic	Dexmedetomidine	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	None

Jendoubi et al. (2017)	Tunisia	Yes	63	Urologic	Lidocaine; Ketamine	Intraoperative, then continued to post-operative	- Function (6-minute walk) - Chronic pain	90	Beneficial effect	No	Unreported
Jeyamohan et al. (2015)	United States	Yes	112	Neurosurgery	Dexamethasone	Intraoperative, then continued to post-operative	- HRQOL (SF-12) - Function (Disability index) - Chronic pain	720	Equivocal/uncertain	No	Institutional/ Academic
Jiang et al. (2016)	China	Yes	120	Orthopedic	Ketamine	Intraoperative only	- Well-being (PHQ-19)	5	Beneficial effect	No	Government Foundation/ Charity Institutional/ Academic
Jiang et al. (2019)	China	Yes	60	Plastic & reconstructive	Dexmedetomidine	Intraoperative, then continued to post-operative	- Well-being (QoR-40)	1	Beneficial effect	No	Government Foundation/ Charity
Jokela et al. (2008)	Finland	No	91	Obstetric-Gynecologic	Pregabalin	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	5	Equivocal/uncertain	No	Government Foundation/ Charity
Jokela et al. (2009)	Finland	No	129	Obstetric-Gynecologic	Dexamethasone	Intraoperative only	- Satisfaction (NRS or categorical)	5	Beneficial effect	No	Foundation/ Charity
Jones et al. (2009)	Australia	No	82	Neurosurgery	Parecoxib	Intraoperative only	- Satisfaction (NRS or categorical)	1	No effect	No	Institutional/ Academic
Jones et al. (2022)	United States	Yes	82	Orthopedic	Ketorolac	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Chronic pain - Aberrant opioid use post-op	84	Beneficial effect	No	Foundation/ Charity
Joseph et al. (2012)	France	Yes	60	Thoracic (non-cardiac)	Ketamine	Intraoperative, then continued to post-operative	- Chronic pain	90	No effect	No	None
Joshi et al. (2013)	India	No	40	Cardiac	Pregabalin	Intraoperative, then continued to post-operative	- Chronic pain	90	Beneficial effect	No	Unreported
Joung et al. (2018)	South Korea	Yes	40	Thoracic (non-cardiac)	Dexamethasone	Intraoperative only	- Well-being (QoR-40)	3	No effect	No	Unreported
Jouybar et al. (2022)	Iran	Yes	60	Plastic & reconstructive	Dexmedetomidine	Intraoperative only	- Satisfaction (NRS or categorical)	0	Equivocal/uncertain	No	Institutional/ Academic
Jules-Elysee et al. (2012)	United States	Yes	36	Orthopedic	Hydrocortisone	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	180	Beneficial effect	No	Unreported
Kang et al. (2020)	South Korea	Yes	184	Mastectomy/lumpectomy	Ketamine	Intraoperative only	- HRQOL (EuroQol-5D-5L) - Chronic pain	180	Equivocal/uncertain	No	Unreported
Karaman et al. (2008)	Turkey	No	60	Gastrointestinal	Lornoxicam	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Unreported
Kararmaz et al. (2003)	Turkey	No	40	Urologic	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	None

Kasputyte et al. (2020)	Lithuania	No	40	Gastrointestinal	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	Unspecified	Equivocal/uncertain	No	Unreported
Kassim et al. (2018)	Egypt	Yes	75	Obstetric-Gynecologic	Dexamethasone + Duloxetine; Duloxetine	Intraoperative only	- Satisfaction (NRS or categorical)	Unspecified	Beneficial effect	No	Unreported
Katz et al. (1993)	United States	No	48	Dermatologic Endocrine Cardiac Gastrointestinal Mastectomy/lumpectomy Neurosurgery Obstetric-Gynecologic Ophthalmic Oral-maxillofacial Orthopedic Otorhinolaryngologic Plastic & reconstructive Thoracic (non-cardiac) Urologic Vascular	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	Unspecified	Beneficial effect	No	None
Katz et al. (2004)	Canada	No	143	Urologic	Ketamine	Intraoperative only	- Well-being (State-trait inventory) - Chronic pain - Acute pain multi-dimensional (McGill)	180	No effect	No	Government Industry
Kaur et al. (2015)	India	No	80	Gastrointestinal	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Unreported
Kavak Akelma et al. (2014)	Turkey	No	48	Gastrointestinal	Lidocaine, Esmolol	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Kaygusuz et al. (2007)	Turkey	Yes	60	Urologic	Lornoxicam	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Kendall et al. (2018)	United States	Yes	148	Mastectomy/lumpectomy	Lidocaine	Intraoperative only	- Well-being (QoR-40) - Chronic pain	180	Beneficial effect	No	Institutional/ Academic
Khademi et al. (2022)	Iran	Yes	110	Mastectomy/lumpectomy	Dexmedetomidine	Intraoperative only	- Chronic pain	90	Beneficial effect	No	Institutional/ Academic
Khan et al. (2019)	Canada	Yes	100	Mastectomy/lumpectomy	Pregabalin; Lidocaine; Pregabalin + Lidocaine	Intraoperative, then continued to post-operative	- HRQOL (SF-36) - Chronic pain - Acute pain multi-dimensional (McGill) - Aberrant opioid use post-op	90	Equivocal/uncertain	No	Institutional/ Academic
Khanduja et al. (2014)	India	No	60	Gastrointestinal	Dexmedetomidine	Intraoperative only	- Well-being (Other QoR)	Unspecified	Beneficial effect	No	Unreported
Khurana et al. (2014)	India	No	90	Neurosurgery	Gabapentin; Pregabalin	Intraoperative, then continued to post-operative	- Function (Oswestry) - Chronic pain	90	Beneficial effect	No	Unreported
Kim et al. (2010)	South Korea	Yes	99	Endocrine	Pregabalin	both (at least one arm intraoperative only and at least one other arm	- Chronic pain	90	Beneficial effect	No	None

						intraoperative and postoperative)					
Kim et al. (2011)	South Korea	No	84	Orthopedic	Pregabalin	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	Unreported
Kim et al. (2013)	South Korea	Yes	34	Gastrointestinal	Lidocaine	Intraoperative only	- Satisfaction (NRS or categorical) - Function (Other-time to return to regular diet)	2	Beneficial effect	No	Government
Kim et al. (2013)	South Korea	Yes	51	Orthopedic	Lidocaine	Intraoperative only	- Satisfaction (NRS or categorical)	5	Beneficial effect	No	None
Kim et al. (2013)	South Korea	No	60	Neurosurgery	Ketamine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	None
Kim et al. (2013)	South Korea	Yes	92	Mastectomy/lumpectomy	Dexmedetomidine	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	None
Kim et al. (2013)	South Korea	Yes	100	Oral-maxillofacial	Dexmedetomidine	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	None
Kim et al. (2017)	South Korea	Yes	58	Otorhinolaryngologic	Nefopam	Intraoperative only	- Chronic pain	90	Beneficial effect	No	None
Kim et al. (2017)	South Korea	Yes	126	Mastectomy/lumpectomy	Lidocaine; Magnesium	Intraoperative only	- Well-being (QoR-40) - Chronic pain - Acute pain multi-dimensional (McGill)	90	Beneficial effect	No	Unreported
Kim et al. (2018)	South Korea	Yes	135	Endocrine	Lidocaine; Magnesium	Intraoperative only	- Well-being (QoR-40)	2	Beneficial effect	No	Institutional/ Academic
Kim et al. (2019)	South Korea	Yes	169	Endocrine	Dexmedetomidine	Intraoperative only	- Well-being (QoR-40)	1	No effect	No	None
Kim et al. (2020)	South Korea	Yes	132	Urologic	Lidocaine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Unreported
Kim et al. (2021)	South Korea	Yes	100	Orthopedic	Dexamethasone	Intraoperative only	- Satisfaction (NRS or categorical)	28	Beneficial effect	No	Institutional/ Academic
Kim et al. (2022)	South Korea	Yes	98	Orthopedic	Lidocaine	Intraoperative, then continued to post-operative	- Function (Orthopedic functional recovery) - Chronic pain	90	Beneficial effect	No	None
Kinney et al. (2012)	United States	Yes	146	Thoracic (non-cardiac)	Gabapentin	Intraoperative only	- Chronic pain	90	No effect	No	Foundation/ Charity
Kleif et al. (2017)	Denmark	Yes	78	Gastrointestinal	Methylprednisolone	Intraoperative only	- Well-being (QoR-15)	3	No effect	No	Foundation/ Charity Institutional/ Academic
Kleine-Brueggeney et al. (2015)	Switzerland	Yes	40	Mastectomy/lumpectomy Obstetric-Gynecologic	Delta-9-Tetrahydrocannabinol	Intraoperative only	- Well-being (Sleep quality)	1	Deleterious	No	Institutional/ Academic
Klinger et al. (2019)	United States	Yes	478	Cardiac	Lidocaine	Intraoperative, then	- Well-being (State-trait inventory)	365	No effect	No	None

						continued to post-operative	- HRQOL (SF-36) - Function (Daily activity level)				
Kok et al. (2015 & 2018)	Netherlands	No	1244	Cardiac	Dexamethasone	Intraoperative only	- Well-being (Beck inventory) - HRQOL (SF-36)	1460	Equivocal/uncertain	No	Foundation/ Charity
Konstantatos et al. (2016)	Australia	No	100	Thoracic (non-cardiac)	Pregabalin	Intraoperative, then continued to post-operative	- HRQOL (SF-12) - Chronic pain - Acute pain multi-dimensional (McGill)	270	No effect	No	Industry
Koshyari et al. (2019)	India	No	90	Obstetric-Gynecologic	Lidocaine	Intraoperative only	- Well-being (QoR-40) - Function (6-minute walk)	5	Beneficial effect	No	Institutional/ Academic
Kroll et al. (2010)	United States	Yes	319	Obstetric-Gynecologic	Ibuprofen	Intraoperative, then continued to post-operative		5	Beneficial effect	No	Industry
Le et al. (2016)	United States	Yes	55	Gastrointestinal	Ibuprofen	Intraoperative only	- Well-being (Geriatric depression scale) - Function (Fatigue severity scale)	3	Beneficial effect	No	Institutional/ Academic
Lee et al. (2016)	South Korea	Yes	111	Thoracic (non-cardiac)	Dexmedetomidine	Intraoperative only	- Well-being (QoR-40)	2	Beneficial effect	No	Government
Lee et al. (2017)	South Korea	Yes	64	Endocrine	Ketamine	Intraoperative only	- Chronic pain	90	Beneficial effect	No	Institutional/ Academic
Lei et al. (2017)	China	Yes	110	Orthopedic	Dexamethasone	Intraoperative, then continued to post-operative	- Function (Identity-consequence fatigue scale)	5	Beneficial effect	No	Government
Lei et al. (2020)	China	Yes	165	Orthopedic	Dexamethasone	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Chronic pain	90	Beneficial effect	No	Government
Li et al. (2015)	China	No	44	Obstetric-Gynecologic	Dexmedetomidine	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Li et al. (2017)	China	Yes	285	Cardiac	Dexmedetomidine	Intraoperative, then continued to post-operative	- Well-being (Sleep quality)	30	No effect	No	Institutional/ Academic
Li et al. (2018)	Canada	Yes	47	Obstetric-Gynecologic	Gabapentin	Intraoperative only	- Well-being (Self-rating VAS)	1	No effect	No	Unreported
Li et al. (2018)	China	No	112	Orthopedic	Hydrocortisone	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Function (Daily activity level)	30	Beneficial effect	No	None
Li et al. (2020 & 2023)	China	Yes	620	Specialty Unspecified	Dexmedetomidine	Intraoperative only	- HRQOL (WHO brief) - Life impact (#day alive and out of hospital at 30d)	1095	Beneficial effect	No	Government Foundation/ Charity None
Li et al. (2021)	China	No	75	Thoracic (non-cardiac)	Dexmedetomidine	Intraoperative only	- Chronic pain	180	Beneficial effect	No	Government Foundation/ Charity

											Institutional/ Academic
Li et al. (2022)	China	Yes	83	Orthopedic	Esketamine	Intraoperative only	- Well-being (Hospital anxiety & depression scale)	3	Beneficial effect	No	None
Li et al. (2022)	China	Yes	100	Orthopedic	Dexamethasone	Intraoperative, then continued to post-operative		3	Beneficial effect	No	Government
Li et al. (2023)	China	Yes	260	Neurosurgery	Dexmedetomidine	Intraoperative only	- Well-being (QoR-15) - Life impact (#day alive and out of hospital at 30d)	30	Beneficial effect	No	Government
Lierz et al. (2012)	Germany	Yes	66	Orthopedic	Etoricoxib	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Industry
Liu et al. (2022)	China	Yes	120	Oral-maxillofacial	Dexmedetomidine	Intraoperative only	- Well-being (Sleep quality)	1	No effect	No	Government
Lu et al. (2022)	China	Yes	64	Thoracic (non-cardiac)	Lidocaine	Intraoperative only	- Chronic pain	180	Beneficial effect	No	Unreported
Lunn et al. (2015)	Denmark	Yes	120	Orthopedic	Escitalopram	Intraoperative, then continued to post-operative	- Well-being (Hospital anxiety & depression scale)	7	No effect	No	Government Foundation/ Charity
Lunn et al. (2015 & 2018)	Denmark	Yes	300	Orthopedic	Gabapentin	Intraoperative, then continued to post-operative	- Well-being (Hospital anxiety & depression scale) - Chronic pain	1456	Equivocal/uncertain	No	Industry None
Luo et al. (2022)	China	No	128	Neurosurgery	Dexmedetomidine	Intraoperative only	- Well-being (Beck inventory)	3	Beneficial effect	No	None
Luscombe et al. (2010)	Australia	No	90	Obstetric-Gynecologic	Parecoxib	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (QoR-9) - Function (Daily activity level) - Acute pain multi-dimensional (Brief pain inventory)	1	Beneficial effect	No	None
Lv et al. (2021)	China	Yes	138	Gastrointestinal	Lidocaine	Intraoperative only	- Well-being (QoR-40) - Function (Time to return to bowel)	3	Beneficial effect	No	Government Institutional/ Academic
Lysak et al. (1994)	United States	No	90	Gastrointestinal	Ketorolac; Piroxicam	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Ma et al. (2004)	United States	No	60	Gastrointestinal	Rofecoxib	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Well-being (QoR-9) - Life impact (Time to return to usual activities)	14	Beneficial effect	No	Foundation/ Charity Institutional/ Academic
Ma et al. (2021)	Taiwan	Yes	56	Orthopedic	Parecoxib	Intraoperative only	- Satisfaction (NRS or categorical) - Function (Other-Maximum Range of Motion with	14	Beneficial effect	No	Unreported

							Continuous Passive Motion Device tolerance)				
Magill et al. (2017)	United Kingdom	Yes	1350	Gastrointestinal	Dexamethasone	Intraoperative only	- HRQOL (EuroQol-5D-5L) - Function (Chronic illness therapy-fatigue)	30	Beneficial effect	Yes	Government Foundation/ Charity
Maheshwari et al. (2020)	United States	Yes	299	Orthopedic	Gabapentin; Acetaminophen; Lidocaine; Ketamine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Well-being (QoR-15) - Multidimensional opioid adverse effect scale	3	No effect	No	Institutional/ Academic
Manimaran et al. (2018)	India	No	100	Otorhinolaryngologic	Dexmedetomidine	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	None
Mao et al. (2020)	China	Yes	62	Thoracic (non-cardiac)	Dexmedetomidine	Intraoperative, then continued to post-operative	- Well-being (Sleep quality) - HRQOL (Other - Short Form 8 (SF-8) health survey) - Chronic pain	90	Beneficial effect	No	Institutional/ Academic
Mariappan et al. (2021)	India	No	60	Obstetric-Gynecologic	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	1	No effect	No	Institutional/ Academic
Martins et al. (2018)	Brazil	Yes	70	Gastrointestinal	Pregabalin	Intraoperative only	- Well-being (QoR-40)	1	No effect	No	None
Massoth et al. (2021)	Germany	Yes	157	Obstetric-Gynecologic	Dexmedetomidine + Esketamine	Intraoperative only	- Satisfaction (NRS or categorical)	Unspecified	Equivocal/uncertain	No	None
Masud et al. (2017)	Bangladesh	No	60	Gastrointestinal	Clonidine	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Matsota et al. (2020)	Greece	Yes	42	Gastrointestinal	Ketamine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Well-being (Sleep quality)	2	Beneficial effect	No	Unreported
Mayson et al. (2000)	Canada	No	43	Urologic	Clonidine	Intraoperative only	- Satisfaction (NRS or categorical)	2	No effect	No	None
McDonald et al. (2019)	United States	Yes	128	Orthopedic	Ketorolac	Intraoperative, then continued to post-operative	- Well-being (Sleep quality)	84	Beneficial effect	No	None
Mendola et al. (2012)	Italy	No	66	Thoracic (non-cardiac)	Ketamine	Intraoperative, then continued to post-operative	- Chronic pain - Aberrant opioid use post-op	180	No effect	No	None
Menigaux et al. (2001)	France	No	50	Orthopedic	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical) - Function (Time to ambulation)	3	Beneficial effect	No	Government Foundation/ Charity
Mentes et al. (2008)	Turkey	No	83	Gastrointestinal	Magnesium	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Mercanoglu et al. (2022)	Turkey	No	90	Gastrointestinal	Ketamine; Dexmedetomidine	Intraoperative only	- Well-being (QoR-15)	2	Beneficial effect	No	None
Merry et al. (2004)	New Zealand	No	1001	Specialty Unspecified	Tenoxicam	Intraoperative, then	- Well-being (Sleep quality)	14	Equivocal/uncertain	No	None

						continued to post-operative					
Mitchell et al. (1999)	New Zealand	No	65	Cardiac	Lidocaine	Intraoperative, then continued to post-operative	- Well-being (Beck inventory)	180	Equivocal/uncertain	No	Government Foundation/ Charity
Mitchell et al. (2009)	New Zealand	No	158	Cardiac	Lidocaine	Intraoperative, then continued to post-operative		175	No effect	No	None
Mizrak et al. (2012)	Turkey	No	40	Otorhinolaryngologic	Dexmedetomidine	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Unreported
Moeen et al. (2019)	Egypt	Yes	111	Urologic	Lidocaine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	3	Beneficial effect	No	Institutional/ Academic
Mohamad et al. (2014)	Australia	Yes	240	Obstetric-Gynecologic	Acetaminophen; Parecoxib; Acetaminophen + Parecoxib	Intraoperative only	- Satisfaction (Other - Overall Benefit of Analgesia Score) - Well-being (QoR-9) - Acute pain multi-dimensional (Other)	1	No effect	No	Institutional/ Academic
Mohamed et al. (2010)	Egypt	No	150	Mastectomy/lumpectomy	Venlafaxine, Gabapentin	Intraoperative, then continued to post-operative	- Chronic pain	180	Beneficial effect	No	None
Momon et al. (2019)	France	Yes	160	Orthopedic	Dexamethasone; Pregabalin; Dexamethasone + Pregabalin	Intraoperative only	- Chronic pain - Aberrant opioid use post-op	180	No effect	No	None
Moro et al. (2017)	Brazil	Yes	135	Gastrointestinal	Ketamine	Intraoperative only	- Well-being (QoR-40)	1	No effect	No	Unreported
Mostafa et al. (2022)	Egypt	Yes	70	Otorhinolaryngologic	Duloxetine	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Murphy et al. (2011)	United States	No	117	Cardiac	Dexamethasone	Intraoperative only	- Well-being (QoR-40)	Unspecified	Beneficial effect	No	None
Murphy et al. (2021)	United States	Yes	130	Orthopedic	Ketamine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	3	Beneficial effect	No	Institutional/ Academic
Myhre et al. (2017)	Norway	Yes	80	Urologic	Pregabalin	Intraoperative, then continued to post-operative	- Well-being (Sleep quality) - Chronic pain	365	Beneficial effect	No	None
Myles et al. (1999)	Australia	No	156	Cardiac	Clonidine	Intraoperative only	- HRQOL (SF-36)	180	Beneficial effect	No	None
Na et al. (2016)	South Korea	Yes	94	Mastectomy/lumpectomy	Nefopam	Intraoperative only	- Chronic pain	90	Beneficial effect	No	Unreported
Nakhli et al. (2018)	Tunisia	Yes	90	Gastrointestinal	Pregabalin; Gabapentin	Intraoperative only	- Well-being (Sleep quality) - Function (Time to ambulation)	2	Beneficial effect	No	Institutional/ Academic
Nasr et al. (2013)	Egypt	No	40	Obstetric-Gynecologic	Gabapentin	Intraoperative only	- Well-being (State-trait inventory)	1	Beneficial effect	No	None

Nesek-Adam et al. (2012)	Croatia	No	80	Gastrointestinal	Diclofenac; Ketamine; Diclofenac + Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Newman et al. (2019)	United States	No	143	Plastic & reconstructive	Acetaminophen, Gabapentin	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	30	Beneficial effect	No	Unreported
Nielsen et al. (2015 & 2016)	Denmark	Yes	160	Orthopedic	Dexamethasone	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (Sleep quality) - Function (Daily activity level) - Life impact (Days off work) - Chronic pain	365	Deleterious	No	Institutional/ Academic
Nielsen et al. (2017 & 2019)	Denmark	Yes	150	Neurosurgery	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (Hospital anxiety & depression scale) - HRQOL (EuroQol-5D-5L) - Function (Oswestry) - Life impact (Time to return to work) - Chronic pain - Aberrant opioid use post-op	365	Beneficial effect	No	Institutional/ Academic
Nikanne et al. (2005)	Finland	No	120	Otorhinolaryngologic	Celecoxib; Ketoprofen	Intraoperative, then continued to post-operative	- Life impact (Time to return to usual activities) - Acute pain multi-dimensional (Other)	21	Beneficial effect	No	Institutional/ Academic
Ning et al. (2016)	China	No	120	Gastrointestinal	Parecoxib Sodium	Intraoperative, then continued to post-operative	- HRQOL (Other QoL measure)	2	Beneficial effect	No	Unreported
Nistal-Nuno et al. (2014)	Spain	Yes	48	Gastrointestinal	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	1	No effect	No	Unreported
Nistal-Nuno et al. (2017)	Spain	Yes	48	Obstetric-Gynecologic	Ketorolac	Intraoperative only	- Satisfaction (NRS or categorical)	1	No effect	No	Unreported
Nong et al. (2013)	China	Yes	80	Obstetric-Gynecologic	Parecoxib	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	Institutional/ Academic
Ohnesorge et al. (2009)	Germany	No	87	Mastectomy/lumpectomy	Acetaminophen; Metamizol	Intraoperative, then continued to post-operative	- Function (Time to ambulation)	1	Beneficial effect	No	Industry Institutional/ Academic
Olgun et al. (2012)	Turkey	No	60	Gastrointestinal	Magnesium Sulphate	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Ormel et al. (2011)	Norway	No	337	Obstetric-Gynecologic	Dexamethasone + Ondansetron + Droperidol	both (at least one arm intraoperative only and at	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None

						least one other arm intraoperative and postoperative)					
Ozer et al. (2012)	Turkey	No	100	Plastic & reconstructive	Dexketoprofen	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Ozgencil et al. (2011)	Turkey	No	90	Neurosurgery	Pregablin; Gabapentin	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Well-being (Self-rating VAS)	1	Beneficial effect	No	None
Ozhan et al. (2015)	Turkey	No	60	Gastrointestinal	Ketamine	Intraoperative only		Unspecified	Equivocal/uncertain	No	None
Ozmete et al. (2016)	Turkey	Yes	60	Obstetric-Gynecologic	Acetaminophen	Intraoperative only	- Satisfaction (NRS or categorical)	0	Beneficial effect	No	Institutional/ Academic
Pan et al. (2008)	United States	No	64	Obstetric-Gynecologic	Dexamethasone	Intraoperative, then continued to post-operative	- HRQOL (Other - FLIE questionnaire)	5	Beneficial effect	No	None
Paris et al. (2009)	Germany	Yes	60	Otorhinolaryngologic	Clonidine	Intraoperative only	- Well-being (Self-rating VAS)	1	Beneficial effect	No	None
Park et al. (2020)	South Korea	Yes	120	Urologic	Magnesium	Intraoperative only	- Satisfaction (NRS or categorical)	Unspecified	Beneficial effect	No	Institutional/ Academic
Parker et al. (1994)	United States	No	210	Obstetric-Gynecologic	Ketorolac	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Well-being (Self-rating VAS) - Function (Time to return to bowel)	3	Equivocal/uncertain	No	None
Patil et al. (2022)	India	No	60	Orthopedic	Dexmedetomidine	Intraoperative only	- Satisfaction (NRS or categorical)	0	Beneficial effect	No	Unreported
Paul et al. (2015)	Canada	Yes	102	Orthopedic	Gabapentin	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	3	No effect	No	Institutional/ Academic
Paulin et al. (2021)	India	Yes	52	Orthopedic	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical) - Function (Timed up and go)	30	No effect	No	Institutional/ Academic
Pauls et al. (2015)	United States	Yes	74	Obstetric-Gynecologic	Dexamethasone	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	None
Peng et al. (2010)	Canada	Yes	165	Gastrointestinal	Pregabalin	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Well-being (QoR-40)	7	No effect	No	Industry
Peng et al. (2016)	China	Yes	94	Neurosurgery	Lidocaine	Intraoperative only	- Well-being (Hamilton scale)	180	No effect	No	Institutional/ Academic
Pereira et al. (2023)	Portugal	Yes	138	Gastrointestinal Obstetric-Gynecologic	Ketamine	Intraoperative only	- Well-being (QoR-15)	1	No effect	No	None
Pesonen et al. (2011)	Finland	No	70	Cardiac	Pregabalin	Intraoperative, then continued to post-operative	- Chronic pain	90	Beneficial effect	No	Institutional/ Academic

Peyton et al. (2017)	Australia	Yes	80	Gastrointestinal Mastectomy/lumpectomy Thoracic (non-cardiac)	Ketamine	Intraoperative, then continued to post-operative	- Well-being (QoR-15) - Function (WHO DAS 2.0 12-question) - Chronic pain - Acute pain multi-dimensional (Brief pain inventory)	180	No effect	No	Institutional/ Academic
Pinar et al. (2017)	Turkey	Yes	42	Orthopedic	Ibuprofen	Intraoperative only	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	Institutional/ Academic
Pinsornsak et al. (2022)	Thailand	Yes	84	Orthopedic	Nefopam	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Function (Timed up and go)	Unspecified	Beneficial effect	No	Institutional/ Academic
Puura et al. (2006)	Finland	No	75	Gastrointestinal	Acetaminophen + Etoricoxib; Etoricoxib	Intraoperative only	- Satisfaction (NRS or categorical) - Function (Fatigue NRS/VAS)	1	Beneficial effect	No	Institutional/ Academic
Qiu et al. (2018)	China	Yes	48	Endocrine	Dexmedetomidine	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Institutional/ Academic
Qiu et al. (2022)	China	Yes	184	Obstetric-Gynecologic	Ketamine	Intraoperative only	- Well-being (Hospital anxiety & depression scale)	3	Beneficial effect	No	Government
Quail et al. (2017)	United States	Yes	100	Gastrointestinal	Gabapentin	Intraoperative, then continued to post-operative	- HRQOL (SF-12) - Chronic pain	730	No effect	No	None
Ragazzoni et al. (2019)	Uganda	Yes	46	Gastrointestinal Mastectomy/lumpectomy Oral-maxillofacial Orthopedic Otorhinolaryngologic Urologic	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	1	No effect	No	Unreported
Raja et al. (2018)	India	No	100	Neurosurgery Orthopedic	Acetaminophen, Ketorolac And Pregabalin	Intraoperative only	- Satisfaction (Other - North American Spine Society (NASS) satisfaction scale) - Function (Disability index)	90	Beneficial effect	No	Foundation/ Charity
Raksakietisak et al. (2022)	Thailand	Yes	50	Neurosurgery Orthopedic	Nefopam	Intraoperative only	- Acute pain multi-dimensional (Other)	30	No effect	No	Institutional/ Academic
Ran et al. (2021)	China	Yes	126	Thoracic (non-cardiac)	Dexmedetomidine	Intraoperative only	- Function (Daily activity level)	30	Equivocal/uncertain	No	None
Rapchuk et al. (2010)	Australia	No	60	Cardiac	Gabapentin	Intraoperative, then continued to post-operative	- Well-being (QoR-9)	3	No effect	No	None
Reagan et al. (2017)	United States	Yes	138	Obstetric-Gynecologic	Celecoxib+ Gabapentin + Dexamethasone +Acetaminophen	Intraoperative, then continued to post-operative	- Acute pain multi-dimensional (Brief pain inventory)	9	Beneficial effect	No	Institutional/ Academic
Rekatsina et al. (2021)	Greece	Yes	91	Obstetric-Gynecologic	Dexmedetomidine; Lidocaine	Intraoperative only	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	Government

							- Well-being (Sleep quality)				
Rekatsina et al. (2022)	Greece	Yes	81	Obstetric-Gynecologic	Dexmedetomidine; Lidocaine	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (Sleep quality) - Chronic pain	365	Beneficial effect	No	Government
Remérand et al. (2009)	France	No	160	Orthopedic	Ketamine	Intraoperative, then continued to post-operative	- Chronic pain	180	Beneficial effect	No	None
Ren et al. (2022)	China	No	104	Gastrointestinal	Ketamine	Intraoperative only	- Well-being (Hospital anxiety & depression scale)	3	Beneficial effect	No	Government
Richebé et al. (2013)	France	Yes	90	Cardiac	Nefopam	Intraoperative, then continued to post-operative	- Well-being (QoR-40) - Chronic pain	365	No effect	No	Unreported
Rindos et al. (2019)	United States	Yes	183	Obstetric-Gynecologic	Acetaminophen	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Well-being (QoR-40)	28	No effect	No	Institutional/ Academic
Royse et al. (2017)	Canada, United States, Australia	Yes	555	Cardiac	Methylprednisone	Intraoperative only	- HRQOL (PostOp-QRS)	180	No effect	No	Government
Ryu et al. (2008)	South Korea	No	50	Obstetric-Gynecologic	Magnesium	Intraoperative only	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	Government
Sahin et al. (2012)	Turkey	No	60	Obstetric-Gynecologic	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	Unspecified	Deleterious	No	None
Sahmeddini et al. (2018)	Iran	Yes	180	Orthopedic	Lidocaine, Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Unreported
Salman et al. (2009)	Turkey	No	60	Obstetric-Gynecologic	Dexmedetomidine	Intraoperative only	- Satisfaction (NRS or categorical)	Unspecified	Equivocal/uncertain	No	None
Sampson et al. (1996)	United States	No	99	Obstetric-Gynecologic	Ketorolac	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Industry
Sanders et al. (2017)	New Zealand	Yes	73	Otorhinolaryngologic	Gabapentin	Intraoperative only	- Life impact (Time to return to work)	14	No effect	No	Institutional/ Academic
Saravanaperumal et al. (2021)	India	No	66	Obstetric-Gynecologic	Dexmedetomidine	Intraoperative only	- Well-being (QoR-15)	1	Beneficial effect	No	Unreported
Sattari et al. (2020)	Iran	Yes	60	Obstetric-Gynecologic	Duloxetine	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	None
Schelling et al. (2004)	Germany	No	48	Cardiac	Hydrocortisone	Intraoperative, then continued to post-operative	- Well-being (PTSD-10)	180	Beneficial effect	No	Foundation/ Charity
Schietroma et al. (2010)	Italy	No	82	Gastrointestinal	Dexamethasone	Intraoperative only	- Function (Fatigue NRS/VAS)	30	Beneficial effect	No	None
Schlachta et al. (2007)	Canada	No	44	Gastrointestinal	Ketorolac	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	4	Beneficial effect	No	Foundation/ Charity
Schulmeyer et al. (2010)	Chile	No	82	Gastrointestinal	Pregabalin	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Institutional/ Academic

Seman et al. (2021)	United States	No	39	Gastrointestinal	Ketamine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Well-being (Self-rating VAS) - Life impact (Other - Pain interference with daily activities)	2	Beneficial effect	No	Institutional/ Academic
Sen et al. (2009)	Turkey	No	60	Obstetric-Gynecologic	Ketamine; Gabapentin	Intraoperative only	- Satisfaction (NRS or categorical) - Life impact (Time to return to work)	180	Beneficial effect	No	Institutional/ Academic
Shakir et al. (2023)	Pakistan	No	60	Gastrointestinal	Lidocaine	Intraoperative, then continued to post-operative	- Function (Time to ambulation)	1	Beneficial effect	No	Institutional/ Academic
Shan et al. (2022)	China	Yes	114	Urologic	Dexmedetomidine	Intraoperative, then continued to post-operative	- Function (Berthel) - Life impact (#day alive and out of hospital at 1yr)	365	Beneficial effect	No	Government Foundation/ Charity Institutional/ Academic
Shariffuddin et al. (2018)	Malaysia	Yes	60	Urologic	Dexmedetomidine	Intraoperative only	- Life impact (Time to return to usual activities)	5	Beneficial effect	No	Institutional/ Academic
Sharma et al. (2017)	India	No	100	Gastrointestinal	Dexmedetomidine; Acetaminophen	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Sharma et al. (2022)	India	Yes	70	Gastrointestinal	Lidocaine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Sherif et al. (2017)	Egypt	Yes	150	Gastrointestinal	Lidocaine; Dexmedetomidine	Intraoperative only	- Well-being (QoR-40)	3	Beneficial effect	No	Institutional/ Academic
Shi et al. (2017)	China	No	54	Mastectomy/lumpectomy	Dexmedetomidine	Intraoperative only	- Well-being (QoR-40) - Function (Fatigue severity scale)	7	Beneficial effect	No	Government Foundation/ Charity
Shi et al. (2020)	China	Yes	106	Thoracic (non-cardiac)	Dexmedetomidine	Intraoperative only	- Well-being (Self-rating VAS)	7	Beneficial effect	No	Government
Shivaji et al. (2021)	India	Yes	96	Obstetric-Gynecologic	lidocaine; Dexmedetomidine; lidocaine + Dexmedetomidine	Intraoperative only	- Well-being (QoR-15)	Unspecified	Beneficial effect	No	None
Shu et al. (2022)	China	Yes	120	Endocrine	Lidocaine; Dexmedetomidine	Intraoperative only	- Well-being (QoR-15)	1	Beneficial effect	No	Institutional/ Academic
Schurr et al. (2009)	United States	No	55	Gastrointesntinal	Rofecoxib	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Acute pain multi-dimensional (Brief pain inventory)	5	Beneficial effect	No	Industry
Siddiqui et al. (2014)	Canada	No	82	Gastrointestinal	Gabapentin	Intraoperative only	- Multidimensional opioid adverse effect scale	2	No effect	No	Institutional/ Academic
Silinsky et al. (2020)	United States	Yes	57	Gastrointestinal	Meloxicam	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	3	Beneficial effect	No	Industry
Sinatra et al. (2006)	United States	No	164	Obstetric-Gynecologic	Rofecoxib	Intraoperative, then	- Satisfaction (NRS or categorical)	5	Beneficial effect	No	Industry

						continued to post-operative					
Singh et al. (2013)	India	No	100	Obstetric-Gynecologic	Ketamine + Propofol	Intraoperative only	- Satisfaction (NRS or categorical)	0	Deleterious	No	Unreported
Sivakumar et al. (2018)	United States	Yes	212	Neurosurgery	Acetaminophen	Intraoperative, then continued to post-operative		2	Equivocal/uncertain	No	Institutional/ Academic
Smischney et al. (2012)	United States	Yes	85	Specialty Unspecified	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Institutional/ Academic
Sohn et al. (2017)	South Korea	Yes	66	Thoracic (non-cardiac)	Magnesium	Intraoperative only	- Chronic pain	365	Beneficial effect	No	Unreported
Sohn et al. (2022)	South Korea	Yes	80	Orthopedic	Magnesium	Intraoperative only	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	Institutional/ Academic
Spence et al. (2011)	United States	No	70	Orthopedic	Gabapentin	Intraoperative, then continued to post-operative	- Well-being (Sleep quality)	2	Equivocal/uncertain	No	None
Spreng et al. (2010)	Norway	Yes	83	Gastrointestinal	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical) - Chronic pain - Aberrant opioid use post-op	90	Deleterious	No	None
Srivastava et al. (2012)	India	No	44	Orthopedic	Etoricoxib	Intraoperative only	- Well-being (Sleep quality)	1	Beneficial effect	No	None
Subramaniam et al. (2011)	United States	No	38	Neurosurgery	Ketamine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Function (Daily activity level)	2	No effect	No	None
Subramaniam et al. (2022)	United States	Yes	180	Gastrointestinal	Acetaminophen	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - HRQOL (SF-12)	30	No effect	No	Government Industry
Sun et al. (2014)	China	Yes	40	Otorhinolaryngologic	Dexmedetomidine	Intraoperative only	- Well-being (Self-rating VAS)	1	Beneficial effect	No	Government
Taheri et al. (2021)	Iran	No	70	Gastrointestinal	Pregabalin	Intraoperative, then continued to post-operative	- Well-being (Sleep quality) - Acute pain multi-dimensional (Brief pain inventory)	2	Beneficial effect	No	Unreported
Takmaz et al. (2019)	Turkey	Yes	80	Obstetric-Gynecologic	Duloxetine	Intraoperative, then continued to post-operative	- Well-being (QoR-40)	2	No effect	No	Institutional/ Academic
Tavanaei et al. (2022)	Iran	Yes	104	Neurosurgery	Magnesium; Pregabalin; Magnesium + Pregabalin	Intraoperative only	- Function (Oswestry) - Chronic pain	84	Beneficial effect	No	None
Terkawi et al. (2015)	United States	Yes	80	Mastectomy/lumpectomy	Lidocaine	Intraoperative, then continued to post-operative	- Chronic pain	180	Beneficial effect	No	Institutional/ Academic
Thomas et al. (2012)	Jamaica	No	84	Obstetric-Gynecologic	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	1	Equivocal/uncertain	No	None

Tirault et al. (2010)	France	No	210	Gastrointestinal Neurosurgery Obstetric-Gynecologic Orthopedic Otorhinolaryngologic	Gabapentin	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Tochie et al. (2022)	Cameroon	Yes	36	Obstetric-Gynecologic	Lidocaine + Magnesium + Ketamine	Intraoperative only	- Well-being (QoR-40) - Function (Time to return to bowel)	28	Beneficial effect	No	Unreported
Togrul et al. (2011)	Turkey	No	50	Plastic & reconstructive	Acetaminophen	Intraoperative only	- Satisfaction (NRS or categorical)	1	Equivocal/uncertain	No	None
Toner et al. (2021)	Australia	Yes	150	Mastectomy/lumpectomy	Lidocaine	Intraoperative, then continued to post-operative	- Well-being (QoR-15) - Function (WHO DAS 2.0 36-question) - Life impact (#day alive and out of hospital at 30d) - Chronic pain	180	Beneficial effect	No	Foundation/ Charity Industry Institutional/ Academic
Townsend et al. (2018)	United States	Yes	110	Otorhinolaryngologic	Gabapentin	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	3	No effect	No	Foundation/ Charity
Tramer et al. (1996)	Switzerland	No	42	Obstetric-Gynecologic	Magnesium Sulfate	Intraoperative, then continued to post-operative	- Well-being (Sleep quality) - Acute pain multi-dimensional (Other)	30	Beneficial effect	No	None
Tramer et al. (2007)	Switzerland	No	200	Gastrointestinal Vascular	Magnesium	Intraoperative only	- Well-being (Sleep quality)	3	No effect	No	None
Tsai et al. (2010)	Taiwan	Yes	40	Otorhinolaryngologic	Dexmedetomidine	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Tsaousi et al. (2020)	Greece	Yes	74	Neurosurgery	Magnesium Sulfate	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Tseng et al. (2021)	Taiwan	Yes	36	Gastrointestinal	Dexmedetomidine	Intraoperative only	- Satisfaction (NRS or categorical) - Life impact (Restricted activity/bed rest)	2	Beneficial effect	No	None
Tufanogullari et al. (2008)	United States	Yes	80	Gastrointestinal	Dexmedetomidine	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (QoR-9)	7	Beneficial effect	No	Industry Institutional/ Academic
Tuncer et al. (2003)	Turkey	No	50	Obstetric-Gynecologic	Ketoprofen	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Turan et al. (2006)	Turkey	No	40	Orthopedic	Gabapentin	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Well-being (QoR-9)	3	Beneficial effect	No	Institutional/ Academic
Turan et al. (2006)	Turkey	No	100	Obstetric-Gynecologic	Gabapentin; Rofecoxib; Gabapentin + Rofecoxib	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Well-being (QoR-9) - Life impact (Time to return to work) - Chronic pain	90	Beneficial effect	No	Institutional/ Academic

Turan et al. (2015)	Canada, United States, Australia, China	Yes	1043	Cardiac	Methylprednisolone	Intraoperative only	- Chronic pain	180	No effect	No	Institutional/ Academic
Turan et al. (2017)	United States	Yes	150	Cardiac	Acetaminophen	Intraoperative, then continued to post-operative	- Chronic pain - Acute pain multi-dimensional (Brief pain inventory)	90	No effect	No	None
Turan et al. (2020)	United States	Yes	580	Gastrointestinal Obstetric-Gynecologic Urologic	Acetaminophen	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Well-being (QoR-15) - HRQOL (SF-12) - Function (Fatigue NRS/VAS) - Acute pain multi-dimensional (Brief pain inventory)	90	No effect	No	Industry
Turan et al. (2020)	United States	Yes	798	Cardiac	Dexmedetomidine	Intraoperative, then continued to post-operative	- Well-being (Sleep quality) - Chronic pain	90	Deleterious	No	Industry
Turner et al. (2019)	United States	Yes	202	Obstetric-Gynecologic	Acetaminophen	Intraoperative only	- Acute pain multi-dimensional (American Pain Society Outcome)	30	No effect	No	Foundation/ Charity
Ucak et al. (2011)	Turkey	No	40	Cardiac	Gabapentin	Intraoperative, then continued to post-operative	- Chronic pain	90	Beneficial effect	No	None
Unal et al. (2013)	Turkey	No	60	Obstetric-Gynecologic	Acetaminophen; Dexketoprofen	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	Equivocal/uncertain	No	Unreported
Unal et al. (2015)	Turkey	No	60	Urologic	Acetaminophen	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	No effect	No	Unreported
Valentin et al. (2016)	Brazil	Yes	140	Others	Dexamethasone	Intraoperative only	- Well-being (Beck inventory) - HRQOL (SF-36)	180	Beneficial effect	No	Government
Van Elstraete et al. (2004)	France	No	40	Oral-maxillofacial	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	1	No effect	No	None
van Norden et al. (2021)	Germany	Yes	63	Cardiac Gastrointestinal	Dexmedetomidine	Intraoperative only	- Well-being (VAS/NRS Anxiety) - Chronic pain	90	Beneficial effect	No	Industry
Varas et al. (2020)	Chile	Yes	63	Plastic & reconstructive	Ketamine; Magnesium	Intraoperative only	- Chronic pain	90	Beneficial effect	No	Unreported
Varrassi et al. (1994)	Italy	No	95	Gastrointestinal	Ketorolac	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Institutional/ Academic
Vasigh et al. (2016)	Iran	Yes	114	Orthopedic	Gabapentin; Celecoxib	Intraoperative, then	- Satisfaction (NRS or categorical)	1	Beneficial	No	Institutional/ Academic

						continued to post-operative					
Vasigh et al. (2016)	Iran	Yes	114	Neurosurgery	Gabapentin; Gabapentin + Celecoxib	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Institutional/ Academic
Vig et al. (2019)	India	Yes	80	Mastectomy/lumpectomy	Pregabalin	Intraoperative, then continued to post-operative	- Chronic pain	90	No effect	No	Unreported
Viscusi et al. (2012)	United States, Taiwan, Spain. Austria, Estonia, Hungary, Ireland, Sweden, Mexico, Peru, Philippines	Yes	440	Obstetric-Gynecologic	Etoricoxib	Intraoperative, then continued to post-operative	- Function (Time to return to bowel) - Multidimensional opioid adverse effect scale	14	Beneficial effect	No	Industry
Vlisides et al. (2021)	United States	Yes	65	Gastrointestinal	Caffeine Citrate	Intraoperative, then continued to post-operative	- Well-being (Hospital anxiety & depression scale) - Aberrant opioid use post-op	30	No effect	No	Government Institutional/ Academic
von Plato et al. (2019)	Finland	Yes	130	Gastrointestinal	Pregabalin	Intraoperative only	- Satisfaction (NRS or categorical)	30	No effect	No	Government
Wallon et al. (2022)	France	Yes	144	Otorhinolaryngologic	Lidocaine	Intraoperative, then continued to post-operative	- Chronic pain - Aberrant opioid use post-op	180	No effect	No	Foundation/ Charity Institutional/ Academic
Wang et al. (2008)	China	Yes	236	Mastectomy/lumpectomy	Flurbiprofen	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Wang et al. (2015)	China	No	60	Urologic	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	Unspecified	Beneficial effect	No	Institutional/ Academic
Wang et al. (2016)	China	Yes	84	Thoracic (non-cardiac)	Dexmedetomidine	Intraoperative only	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	Foundation/ Charity
Wang et al. (2019)	China	Yes	40	Obstetric-Gynecologic	Lidocaine	Intraoperative only	- Well-being (QoR-40)	5	Beneficial effect	No	Unreported
Wang et al. (2020)	China	Yes	99	Otorhinolaryngologic	Lidocaine	Intraoperative only	- Well-being (QoR-40)	2	Beneficial effect	No	Government
Wang et al. (2020)	China	No	181	Urologic	Gabapentin	Intraoperative only	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	Unreported
Wang et al. (2020)	China	No	417	Obstetric-Gynecologic	Ketamine	Intraoperative only	- Well-being (Hamilton scale)	30	Beneficial effect	No	Government
Wang et al. (2021)	China	Yes	70	Thoracic (non-cardiac)	Lidocaine	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	Unreported
Wang et al. (2022)	China	Yes	125	Urologic	Dexmedetomidine	Intraoperative only	- Well-being (Zung index)	3	Beneficial effect	No	Government
Wang et al. (2022)	China	Yes	200	Gastrointestinal	Lidocaine	Intraoperative only	- Well-being (QoR-40)	7	Beneficial effect	No	Government

Wang et al. (2022)	China	Yes	356	Vascular	Dexmedetomidine	Intraoperative only	- Well-being (Sleep quality)	0	Beneficial effect	No	None
Wang et al. (2023)	China	Yes	80	Thoracic (non-cardiac)	Dexmedetomidine + Lidocaine	Intraoperative only	- Well-being (QoR-40)	2	Beneficial effect	No	Government
Wanna et al. (2004)	Thailand	No	100	Obstetric-Gynecologic	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (Sleep quality)	1	Beneficial effect	No	Industry Institutional/ Academic
Webb et al. (2007)	Australia	No	120	Gastrointestinal	Ketamine	Intraoperative, then continued to post-operative	- Well-being (Sleep quality)	Unspecified	Beneficial effect	No	None
Wei et al. (2022)	China	Yes	62	Mastectomy/lumpectomy	Lidocaine	Intraoperative only	- Well-being (QoR-15)	2	Beneficial effect	No	Unreported
Wei et al. (2022)	China	Yes	62	Mastectomy/lumpectomy	Lidocaine	Intraoperative only	- Well-being (QoR-15)	2	Beneficial effect	No	Unreported
Weis et al. (2006)	Germany	No	36	Cardiac	Hydrocortisone	Intraoperative, then continued to post-operative	- Well-being (PTSD-10) - HRQOL (SF-36)	180	Beneficial effect	No	None
White et al. (2009)	United States	No	108	Gastrointestinal Otorhinolaryngologic Plastic & reconstructive Urologic	Pregabalin	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (QoR-9)	7	No effect	No	Foundation/ Charity Institutional/ Academic
Williams et al. (1999)	United States	No	48	Otorhinolaryngologic	Methylprednisolone; Dexamethasone	Intraoperative only	- Well-being (Sleep quality) - Life impact (Other - Restriction of diet and physical activity for 7 days.)	7	No effect	No	None
Wu et al. (2009)	Taiwan	No	60	Gastrointestinal	Dexamethasone	Intraoperative only	- Satisfaction (NRS or categorical)	7	Beneficial effect	No	None
Wu et al. (2018)	China	Yes	150	Orthopedic	Dexamethasone	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	90	Beneficial effect	No	Government Foundation/ Charity
Xia et al. (2022)	China	Yes	82	Mastectomy/lumpectomy	Lidocaine	Intraoperative only	- Chronic pain	0	Beneficial effect	No	Institutional/ Academic
Xu et al. (2017)	China	No	50	Mastectomy/lumpectomy	Ketamine	Intraoperative only	- Well-being (Hamilton scale)	7	Equivocal/uncertain	No	None
Xu et al. (2018)	China	Yes	108	Orthopedic	Dexamethasone	Intraoperative, then continued to post-operative	- Function (Identity-consequence fatigue scale)	3	Beneficial effect	No	Government
Xu et al. (2018)	China	Yes	182	Orthopedic	Dexamethasone	Intraoperative, then continued to post-operative	- Chronic pain	90	Beneficial effect	No	Government
Xu et al. (2021)	China	Yes	260	Gastrointestinal	Lidocaine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical) - Function (Time to return to bowel)	3	Beneficial effect	No	Government Institutional/ Academic
Yalcin et al. (2012)	Turkey	No	90	Obstetric-Gynecologic	Ketamine; Acetaminophen	Intraoperative only	- Satisfaction (NRS or categorical)	2	Beneficial effect	No	None

Yamauchi et al. (2008)	Japan	No	202	Orthopedic	Ketamine	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	10	Beneficial effect	No	None
Yao et al. (2021)	China	Yes	84	Thoracic (non-cardiac)	Lidocaine	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (QoR-15)	2	No effect	No	Government Foundation/ Charity Institutional/ Academic
Yazicioglu et al. (2015)	Turkey	Yes	60	Gastrointestinal	Tizanidine	Intraoperative, then continued to post-operative	- HRQOL (SF-36)	30	Beneficial effect	No	Unreported
Yeo et al. (2022)	South Korea	Yes	99	Thoracic (non-cardiac)	Nefopam	Intraoperative only	- Chronic pain	90	No effect	No	Unreported
Yik et al. (2019)	Singapore	Yes	87	Orthopedic	Pregabalin	Intraoperative, then continued to post-operative	- HRQOL (SF-36) - Function (WOMAC)	180	No effect	No	Institutional/ Academic
Yon et al. (2014)	South Korea	Yes	36	Gastrointestinal	Lidocaine	Intraoperative only	- Satisfaction (NRS or categorical)	2	No effect	No	Institutional/ Academic
Yoon et al. (2022)	South Korea	Yes	90	Thoracic (non-cardiac)	Nefopam	Intraoperative, then continued to post-operative	- Well-being (QoR-15) - Chronic pain - Aberrant opioid use post-op	90	Beneficial effect	No	Industry
Yu et al. (2022)	China	Yes	96	Otorhinolaryngologic	Dexmedetomidine	Intraoperative only	- Well-being (QoR-40)	2	Beneficial effect	No	None
Yuan et al. (2022)	China	Yes	91	Thoracic (non-cardiac)	Esketamine	Intraoperative only	- Satisfaction (NRS or categorical) - Well-being (Sleep quality) - Chronic pain	180	Beneficial effect	No	Government Foundation/ Charity
Yuce et al. (2013)	Turkey	No	152	Obstetric-Gynecologic	Ketamine	Intraoperative only	- Satisfaction (NRS or categorical)	Unspecified	Beneficial effect	No	None
Yucel et al. (2011)	Turkey	No	90	Obstetric-Gynecologic	Pregabalin	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	Unspecified	Beneficial effect	No	Unreported
Yücel et al. (2016)	Turkey	No	50	Otorhinolaryngologic	Lornoxicam	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	None
Yuvaraj et al. (2023)	India	Yes	60	Mastectomy/lumpectomy	Ketamine+lidocaine +dexmedetomidine	Intraoperative only	- Well-being (QoR-40)	30	No effect	No	Unreported
Zargar-Shoshtari et al. (2009)	New Zealand	Yes	70	Gastrointestinal	Dexamethasone	Intraoperative only	- Function (Identity-consequence fatigue scale)	2	Beneficial effect	No	Foundation/ Charity
Zeeni et al. (2019)	Lebanon	Yes	60	Gastrointestinal	Dexmedetomidine	Intraoperative only	- Well-being (QoR-40)	0	Beneficial effect	No	Institutional/ Academic
Zhang et al. (2012)	China	Yes	126	Obstetric-Gynecologic	Parecoxib	Intraoperative, then continued to post-operative	- Acute pain multi-dimensional (Brief pain inventory, American Pai Society Outcome)	2	Beneficial effect	No	Unreported
Zhang et al. (2016)	China	Yes	120	Obstetric-Gynecologic	Flurbiprofen	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Foundation/ Charity

Zhang et al. (2018)	China	Yes	52	Gastrointestinal	Dexmedetomidine	Intraoperative only	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Foundation/ Charity
Zhang et al. (2019)	China	No	100	Thoracic (non-cardiac)	Dexmedetomidine	Intraoperative only	- Well-being (QoR-15)	2	Beneficial effect	No	None
Zhao et al. (2021)	China	Yes	100	Mastectomy/lumpectomy	Ketamine	Intraoperative only	- Well-being (Hospital anxiety & depression scale) - Function (Identity-consequence fatigue scale) - Chronic pain	Unspecified	No effect	No	Foundation/ Charity
Zhao et al. (2022)	China	Yes	70	Neurosurgery	Lidocaine	Intraoperative only	- Well-being (QoR-40)	Unspecified	Beneficial effect	No	Unreported
Zheng et al. (2020)	China	No	60	Gastrointestinal	Dexmedetomidine	Intraoperative only	- Well-being (QoR-40)	1	Beneficial effect	No	Government Foundation/ Charity
Zhou et al. (2021)	China	Yes	84	Neurosurgery	Ketamine	Intraoperative only	- Well-being (Hospital anxiety & depression scale)	60	Beneficial effect	No	Institutional/ Academic
Zhu et al. (2022)	China	Yes	99	Mastectomy/lumpectomy	Esketamine	Intraoperative only	- Well-being (QoR-15)	90	Equivocal/uncertain	No	Foundation/ Charity
Zi et al. (2020)	China	Yes	139	Cardiac	Dexmedetomidine	Intraoperative only	- Well-being (Zung index)	1	Beneficial effect	No	Government Foundation/ Charity Institutional/ Academic
Waikakul Waraporn et al. (2011)	Thailand	No	99	Orthopedic	Gabapentin; Celecoxib; Gabapentin + Celecoxib	Intraoperative, then continued to post-operative	- Satisfaction (NRS or categorical)	1	Beneficial effect	No	Institutional/ Academic
[a]based on reviewer's interpretation											

eTable 3. Test set of citations for crowdsourced screening

First Author (Year)	Paper title	**Screening decision (based on Titles & Abstracts only)**	**Reason for exclusion**
Jokela (2010)	The influence of ondansetron on the analgesic effect of acetaminophen after laparoscopic hysterectomy	Include	
Zargar-Shoshtari (2009)	Randomized clinical trial of the effect of glucocorticoids on peritoneal inflammation and postoperative recovery after colectomy	Include	
Sen (2009)	A comparison of gabapentin and ketamine in acute and chronic pain after hysterectomy	Include	
Hudetz (2009)	Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery	Include	
Duale (2009)	Perioperative ketamine does not prevent chronic pain after thoracotomy	Include	
Bekker (2013)	The effect of intraoperative infusion of dexmedetomidine on the quality of recovery after major spinal surgery	Include	
Wang (2019)	Efficacy of intravenous lidocaine in improving post-operative nausea, vomiting and early recovery after laparoscopic gynaecological surgery	Include	
De Oliveira (2018)	Esmolol does not improve quality of postsurgical recovery after ambulatory hysteroscopy: A prospective, randomized, double-blinded, placebo-controlled, clinical trial	Include	
Liu (2018)	A prospective, randomized, double-blind, placebo-controlled trial of acute postoperative pain treatment using opioid analgesics with intravenous ibuprofen after radical cervical cancer surgery	Include	
Moon (2018)	Preventative effect of ketamine on post-surgical hyperalgesia induced at a body part remote from the surgical site	Include	
Cameron (2020)	Intraoperative Ketamine for Analgesia Post-Coronary Artery Bypass Surgery: A Randomized, Controlled, Double-Blind Clinical Trial	Include	
Mishina (2018)	Comparison between dexmedetomidine and midazolam as a sedation agent with local anesthesia in inguinal hernia repair: randomized controlled trial	Exclude	Ineligible population
Higgins (2018)	The Effect of Prophylactic Phenylephrine and Ephedrine Infusions on Umbilical Artery Blood pH in Women With Preeclampsia Undergoing Cesarean Delivery With Spinal Anesthesia: A Randomized, Double-Blind Trial	Exclude	No intervention of interest
Diaz (2010)	Therapeutic strategies for severe acute lung injury	Exclude	No intervention of interest
Çöçelli (2010)	Effects of preoperatively or postoperatively initiated thoracic epidural analgesia in patients undergoing elective lung surgery	Exclude	No eligible comparator
Preckel (2010)	Perioperative beta-Rezeptoren-Blockade.	Exclude	Wrong study design
Singla (2010)	Phase II study to evaluate the safety and efficacy of the oral neurokinin-1 receptor antagonist casopitant (GW679769) administered with ondansetron for the prevention of postoperative and postdischarge nausea and vomiting in high-risk patients	Exclude	No intervention of interest
Lugli (2010)	Protein balance in nondiabetic versus diabetic patients undergoing colon surgery: effect of epidural analgesia and amino acids	Exclude	Non-systemic intervention
Zimmer (2010)	Bupivacaine use in the Insuflow device during laparoscopic cholecystectomy: results of a prospective randomized double-blind controlled trial	Exclude	Non-systemic intervention
Essving (2010)	Reduced morphine consumption and pain intensity with local infiltration analgesia (LIA) following total knee arthroplasty: a randomized double-blind study involving 48 patients	Exclude	Non-systemic intervention

Stephens (2010)	State of the science: beta-blockers and reduction of perioperative cardiac events	Exclude	Wrong study design
Neumann (2010)	The surgical treatment of hepatic metastases in colorectal carcinoma	Exclude	No intervention of interest
Paloheimo (2010)	Autonomic nervous system state: the effect of general anaesthesia and bilateral tonsillectomy after unilateral infiltration of lidocaine	Exclude	No intervention of interest
Gutierrez (2010)	Trendelenburg chest optimization prolongs spontaneous breathing trials in ventilator-dependent patients with low cervical spinal cord injury	Exclude	Ineligible population
Hartrick (2010)	Aprepitant vs. multimodal prophylaxis in the prevention of nausea and vomiting following extended-release epidural morphine	Exclude	No eligible comparator
Gunda (2010)	Vasopressor choice for hypotension in elective Cesarean section: ephedrine or phenylephrine?	Exclude	No intervention of interest
Ritzema (2010)	Physician-directed patient self-management of left atrial pressure in advanced chronic heart failure	Exclude	No intervention of interest
Kasaee (2010)	External dacryocystorhinostomy: local versus general anesthesia	Exclude	Ineligible population
Waddell (2010)	The use of hyaluronan after arthroscopic surgery of the knee	Exclude	No intervention of interest
Heidari (2010)	Does intraoperative autologous blood transfusion in coronary artery bypass grafting surgery reduce the incidence of postoperative mediastinal bleeding?	Exclude	No intervention of interest
Gajarski (2010)	Adrenocortical response in infants undergoing cardiac surgery with cardiopulmonary bypass and circulatory arrest	Exclude	Wrong study design
Sia (2010)	Axillary block by "selective" injections at the nerves involved in surgery using a peripheral nerve stimulator: a comparison with a "standard" triple-injection technique	Exclude	Ineligible population
Harousseau (2009)	Achievement of at Least Very Good Partial Response Is a Simple and Robust Prognostic Factor in Patients With Multiple Myeloma Treated With High-Dose Therapy: Long-Term Analysis of the IFM 99-02 and 99-04 Trials	Exclude	No intervention of interest
Poldermans (2009)	Perioperative Strokes and beta-Blockade	Exclude	Wrong study design
Parmenter (2009)	Intravenous lidocaine and its effect on intraoperative and postoperative outcomes...State of the Science General and Oral Poster Sessions, AANA Annual Meeting, San Diego, California	Exclude	Wrong study design
Jagsi (2009)	Postmastectomy radiation therapy for patients with locally advanced breast cancer	Exclude	No intervention of interest
Boutonnet (2009)	Perioperative beta-blockade: how long does the perioperative period last?...Acta Anaesthesiol Scand. 2009 May;53(5):553-5	Exclude	Wrong study design
Inoue (2009)	Safety and efficacy of ketorolac in children after cardiac surgery	Exclude	Ineligible population
Messerli (2009)	Cardioprotection with beta-blockers: myths, facts and Pascal's wager	Exclude	Wrong study design
Pennington (2009)	Patients' assessment of the convenience of fentanyl HCl iontophoretic transdermal system (ITS) versus morphine intravenous patient-controlled analgesia (IV PCA) in the management of postoperative pain after major surgery	Exclude	No intervention of interest
Nilsson (2009)	Soothing music can increase oxytocin levels during bed rest after open-heart surgery: a randomised control trial	Exclude	No eligible comparator
Pandya (2009)	Predictors of hemodynamic compromise with propofol during defibrillator implantation: a single center experience	Exclude	Ineligible population
Jarden (2009)	The effect of a multimodal intervention on treatment-related symptoms in patients undergoing hematopoietic stem cell transplantation: a randomized controlled trial	Exclude	No intervention of interest
Tu (2009)	Phase I study of concurrent weekly docetaxel and repeated samarium-153 lexidronam in patients with castration-resistant metastatic prostate cancer	Exclude	No intervention of interest

Hosey (2009)	The effect of transmucosal 0.2 mg/kg midazolam premedication on dental anxiety, anaesthetic induction and psychological morbidity in children undergoing general anaesthesia for tooth extraction	Exclude	Ineligible population
Nolan (2009)	A pilot study of a nursing intervention protocol to minimize maternal-infant separation after Cesarean birth	Exclude	No intervention of interest
Bax (2009)	Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial	Exclude	No intervention of interest
Karon (2009)	Conservative management of continence in women over the age of 65 years living in the community: a review	Exclude	Wrong study design
El-Dawlatly (2009)	Ultrasound-guided transversus abdominis plane block: description of a new technique and comparison with conventional systemic analgesia during laparoscopic cholecystectomy	Exclude	Non-systemic intervention
Short (1991)	Propofol and midazolam act synergistically in combination	Exclude	No intervention of interest

eTable 4. Number of trials for each patient-centred outcome measure instruments

Domain	Outcome measure/instrument	Number of trials
Satisfaction	Bauer	0
	Evaluation du vécu de l'anesthésie Générale (EVAN-G)	0
	Heidelberg questionnaire	0
	Heidegger's 29-item	0
	Numerical or categorical rating scales (e.g. NRS,…)	206
	Caljouw's Leiden questionnaire	0
	Other	
	North American Spine Society satisfaction scale	1
	Overall Benefit of Analgesia Score	1
	VAS discomfort	1
	Total	**209**
Well-being	Quality of recovery 40 (QoR-40)	58
	Quality of recovery 15 (QoR-15)	21
	Quality of recovery 9 (QoR-9)	9
	Complete recovery within 30 days (self-assessed)	0
	Beck Depression inventory	6
	Zung depression index	2
	State-trait anxiety inventory	6
	Hospital anxiety and depression scale	14
	Psychological general well-being index	0
	Self rating of anxiety level, depression, relaxation	11
	Geriatric depression scale	2
	Sleep quality	51
	Patient health questionnaire (PHQ-9)	2
	Other quality of recovery (QoR) instrument	4
	PTSD-10	2
	VAS/NRS Anxiety	6
	VAS/NRS Mood	3
	Hamilton depression and anxiety scale	5
	Other	
	Karnofsky Performance Status (KPS) for quality of life	1
		1

	Kessler K-10 Psychological Destress Scale and Patient Catastrophizing Scale	1
	Mental Health Inventory	1
	Profile of Mood Scale	1
	Rey Auditory Verbal Learning Test	1
	Self-Rating Inventory for PTSD (SRIP)	1
	Social Support Scale	1
	Veterans Rand 12 Survey; Richards Campbell Sleep Questionnaire (RCSQ); Positive and Negative Affect as evaluated by the Positive and Negative Affect Schedule	**210**
	Total	
Functional	WHO disability assessment schedule 2.0 (DAS) 12-question	1
	WHO disability assessment schedule 2.0 (DAS) 36-question	1
	Modified Rankin scale	1
	Timed up and go test	3
	6 minute walk test	6
	ECOG performance status	0
	Karnofsky Performance Index	0
	Functional assessment of chronic illness therapy-fatigue	1
	Identity-consequence fatigue scale	4
	Roland-morris low back pain and disability questionnaire	3
	Fatigue severity scale	7
	Oswestry low back pain questionnaire/disability index	3
	Berthel index	2
	Time to return to bowel	8
	Time to ambulation	6
	Daily Activity Level	10
	Disability Index	3
	WOMAC	3
	Orthopedic Functional Recovery Scores	6
	VAS/NRS Fatigue	6
	Other	
	Maximum Range of Motion with Continuous Passive Motion Device tolerance	1
	Functional outcome swallowing scale; modified Japanese Japanese Orthopaedic Association myelopathy scores; Neck disability index	1
	Osteoarthritis Outcome Score–Physical function Short-form (KOOS-PS)	1
	Quality of Life–Functional Living Index-Emesis (QOL-FLIE)	1
	Sports activity, walk more than 1000m (Daily Activity Level)	1
	Time to return to regular diet	1
	Total	**80**
Health-related quality of life	EuroQol-5D-3L	1
	EuroQol-5D-5L	5
	EuroQol-3D-3L	0
	SF-12	8
	SF-36	13

	Who Quality of life (brief)	1
	EuroQol-VAS	1
	15d HRQOL score	0
	SF-6D	0
	Health Utilities Index Mark 3	0
	VAS (0-100 or 0-10) for general health status	0
	Patient-reported outcomes measurement information system (PROMIS0-10)	0
	PostOp-QRS	1
	RAND-36	0
	Recovery Index, 49-item	0
	Core Outcome Measures Index (COMI)	0
	Other QoL scales	3
	Other	
	Short Form 8 (SF-8) health survey	1
	FLIE questionnaire	1
	"European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30"	1
	Total	**37**
Life impact	Discharge destination	0
	Number of days alive and out of hospital (1 year time point)	2
	Number of days alive and out of hospital (30 days time point)	4
	Time to return to work	6
	Days off work at particular endpoints postoperative	1
	Restricted activity days/bed rest in previous 14 days	1
	Time to return to usual activities	10
	Other	
	Pain interference with daily activities	1
	Any medication use or sleep disturbance attributable to pain over the previous 7 days at 6 months	1
	Disease-Free Survival (DFS) at two years	1
	Number of days alive and out of hospital (90 days time point); Comprehensive Complication Index (Clavien-Dindo Classification)	1
	Number of patients back at work at 3 months	1
	Post-operative work transfer	1
	Restriction of diet and physical activity for 7 days.	1
	The Dane Spine Questionnaire (also included sports active, walking distance)	1
	Total	**32**
Opioid-related outcomes	Persistent opioid use (>=1 month/30 days)/use or dependence/use disorder/overdose	15
	Postoperative opioid related adverse effects (multidimensional)	6
	Total	**21**
Pain-related outcomes	Chronic pain outcome (>= 3 months/90 days)	95
	Acute pain multi-dimensional (<3 months)	25
	American Pain Society Patient Outcome questionnaire	2
	McGill Pain questionnaire	6
	Brief Pain Inventory	15

	Other	
	Multi-dimensional (unvalidated) questionnaire	1
	Neuropathic Pain Symptom Inventory	1
	DN4 and painDETECT questionnaires	1
	Leeds Assessment of Neuropathic Symptoms and Signs scale	2
	Interference of acute pain with normal activities	1
	Overal Benefit of Analgesia Score	1
	Total	**121**

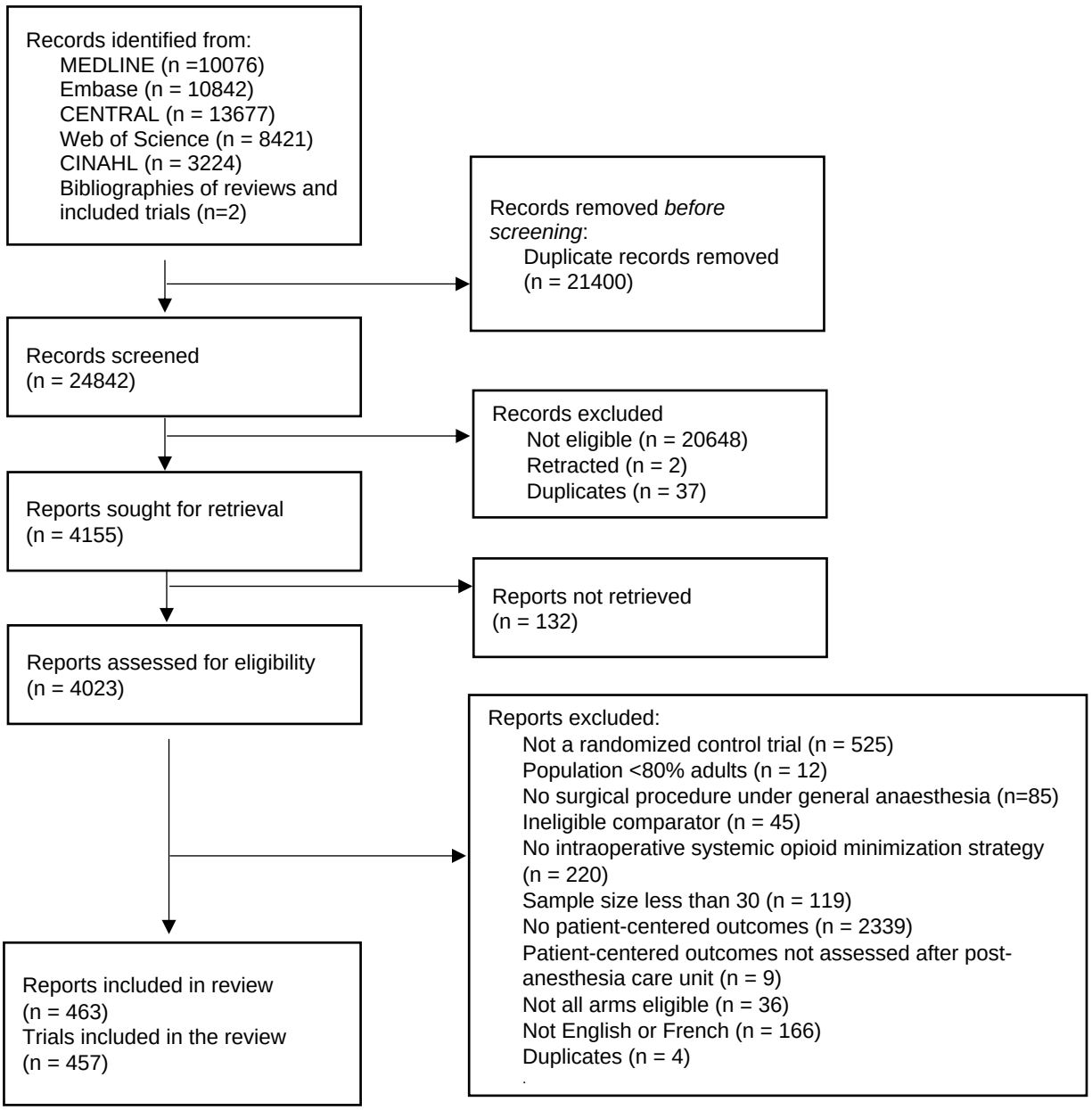
Pharmacologic agent class	Specific agents
Acetaminophen	Acetaminophen Paracetamol
Alpha-2 agonists	Clonidine Dexmedetomidine Moxonidine Tizanidine
Gabapentinoids	Gabapentin Pregabalin
Antidepressants	Duloxetine Escitalopram Venlafaxine
Beta-blockers	Esmolol
Cannabinoids	Delta-9-tetrahydrocannabinol
COX-2 inhibitors	Celecoxib Etoricoxib Parecoxib Rofecoxib Valdecoxib
Systemically administered local anesthestic	Lidocaine
Methylxanthine	Caffeine citrate
NMDA antagonists	Ketamine Magnesium
Non-specific anti-inflammatories	Diclofenac Flurbiprofen Ketorolac Ketoprofen Dexketoprofen Ibuprofen Lornoxciam Lysine acetylsalicylate Meloxicam Piroxicam Tenoxicam
Non-opioid central analgesics	Metamizol Nefopam

eTable 5. List of all included pharmacologic agents and their respective class

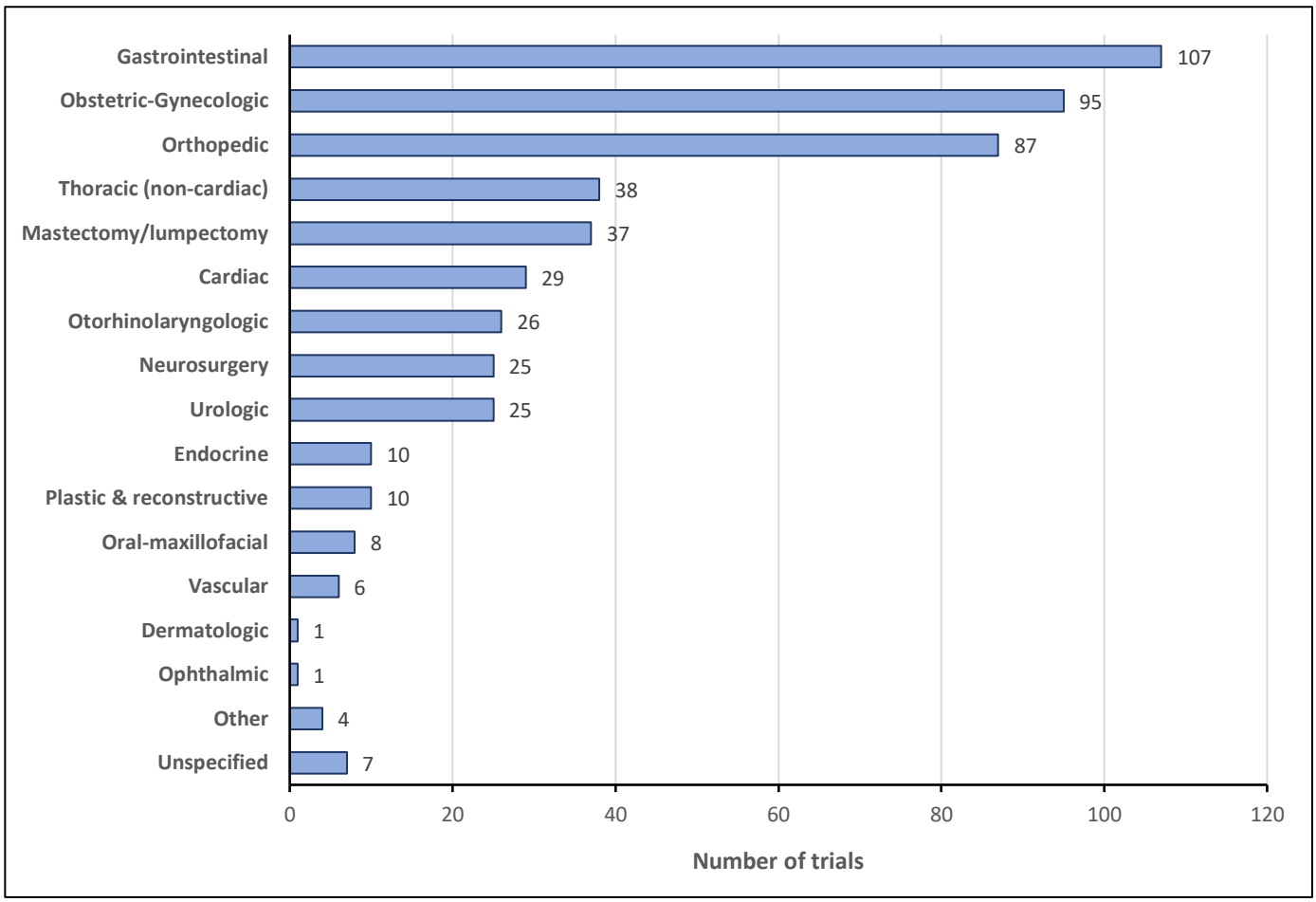
eFigure 1. Search strategy for MEDLINE/Ovid

1 exp Surgical Procedures, Operative/
2 su.fs. or (surger* or surgical*).tw,kf.
3 (curettage or debridement or electrosurger* or fasciotom* or Keratectom* or laparotom* or lymph node excision or mastectom* or metastasectom* or microsurger* or myotom* or neurosurgical procedure* or orthopedic procedure* or amputation or Osteotom* or pelvic exenteration or pneumonectom* or prosthesis implantation or reoperation or splenectom* or symphysiotom* or transplantation).tw,kf.
4 or/1-3
5 ((opioid* or opiate*) adj3 (sparing or minimi?ation or free)).tw,kf.
6 (multimodal adj5 (an?esthes* or analges*)).tw,kf.
7 5 or 6
8 analgesics/ or exp analgesics, non-narcotic/
9 exp Adrenergic alpha-2 Receptor Agonists/
10 Caffeine/
11 exp anti-inflammatory agents/
12 exp Adrenal Cortex Hormones/
13 exp Cyclooxygenase 2 Inhibitors/
14 exp Adrenergic beta-Antagonists/
15 Receptors, N-Methyl-D-Aspartate/ai [Antagonists & Inhibitors]
16 magnesium compounds/ or magnesium sulfate/
17 exp Anticonvulsants/
18 (Lidocaine or Alpha-2 Receptor Agonist* or Caffeine or Corticosteroid* or Beta block* or NMDA receptor antagonist* or Magnesium or Acetaminophen or NSAID* or Anti-convulsant* or anticonvulsant* or Antidepressant* or gabapentinoid* or cox-2 inhibitor*).tw,kf.
19 Dexmedetomidine/ or lidocaine/ or ketamine/ or Propanolamines/ or Clonidine/
20 (Pregabalin or Gabapentin or Carbamazepine or Carbazepin or Esmolol or Propanolamine* or Metoprolol or Labetolol or Clonidine or Dexmedetomidine or Catapressan or Caffeine or Ketamine or Dextromethorphan or Dexamethasone or Methylprednisolone or hydrocortison* or Prednisone or magnesium or Amitriptyline or Duloxetine or Tryptophan or Bicifadine or Desipramine or fluoxetine or Venlafaxine or Citalopram).ti.
21 or/8-20
22 perioperative period/ or intraoperative period/ or exp Administration, Intravenous/ or Combined Modality Therapy/
23 (perioperat* or peri operat* or intra operat* or intraoperat*).tw,kf.
24 (an?esthes* adj2 induction).tw,kf.
25 or/22-24
26 21 and 25
27 7 or 26
28 4 and 27
29 randomized controlled trial.pt.
30 controlled clinical trial.pt.
31 random*.tw.
32 placebo.ab.
33 clinical trials as topic.sh.
34 trial.ti.
35 or/29-34
36 exp animals/ not humans/
37 35 not 36

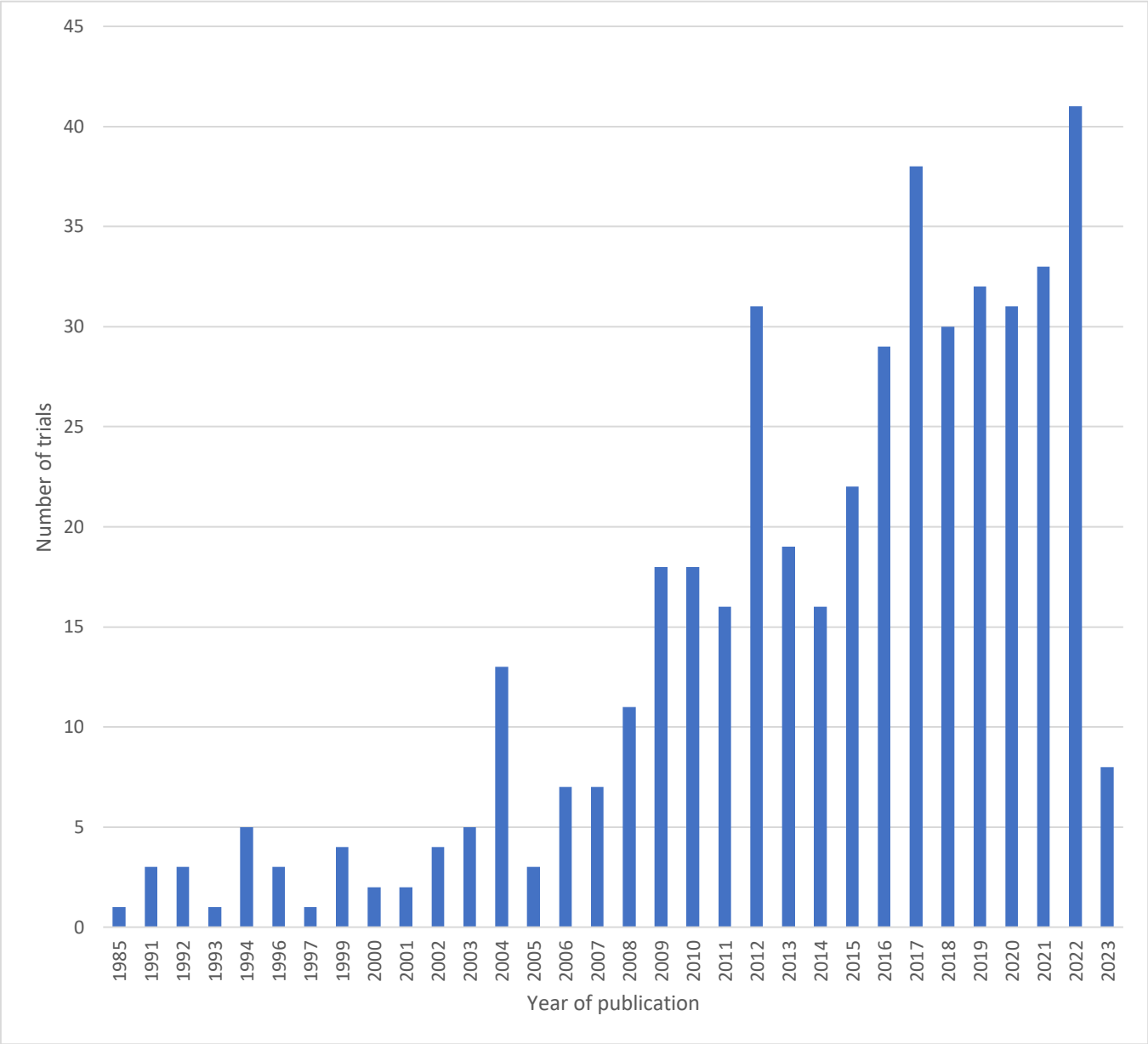
38 28 and 37
39 38 use medall



eFigure 2. Flow diagram

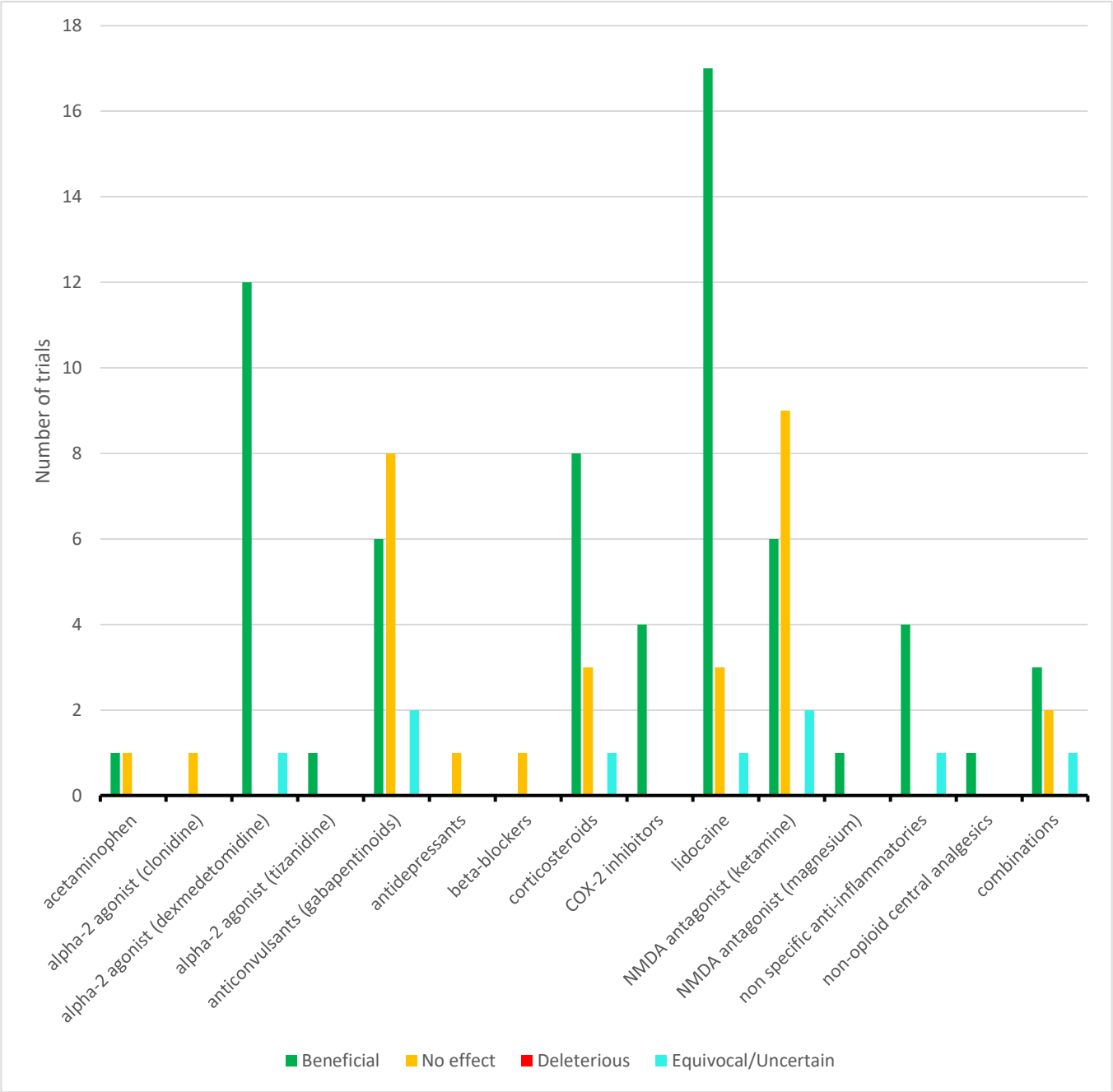


eFigure 3. Types of surgery represented among included trials

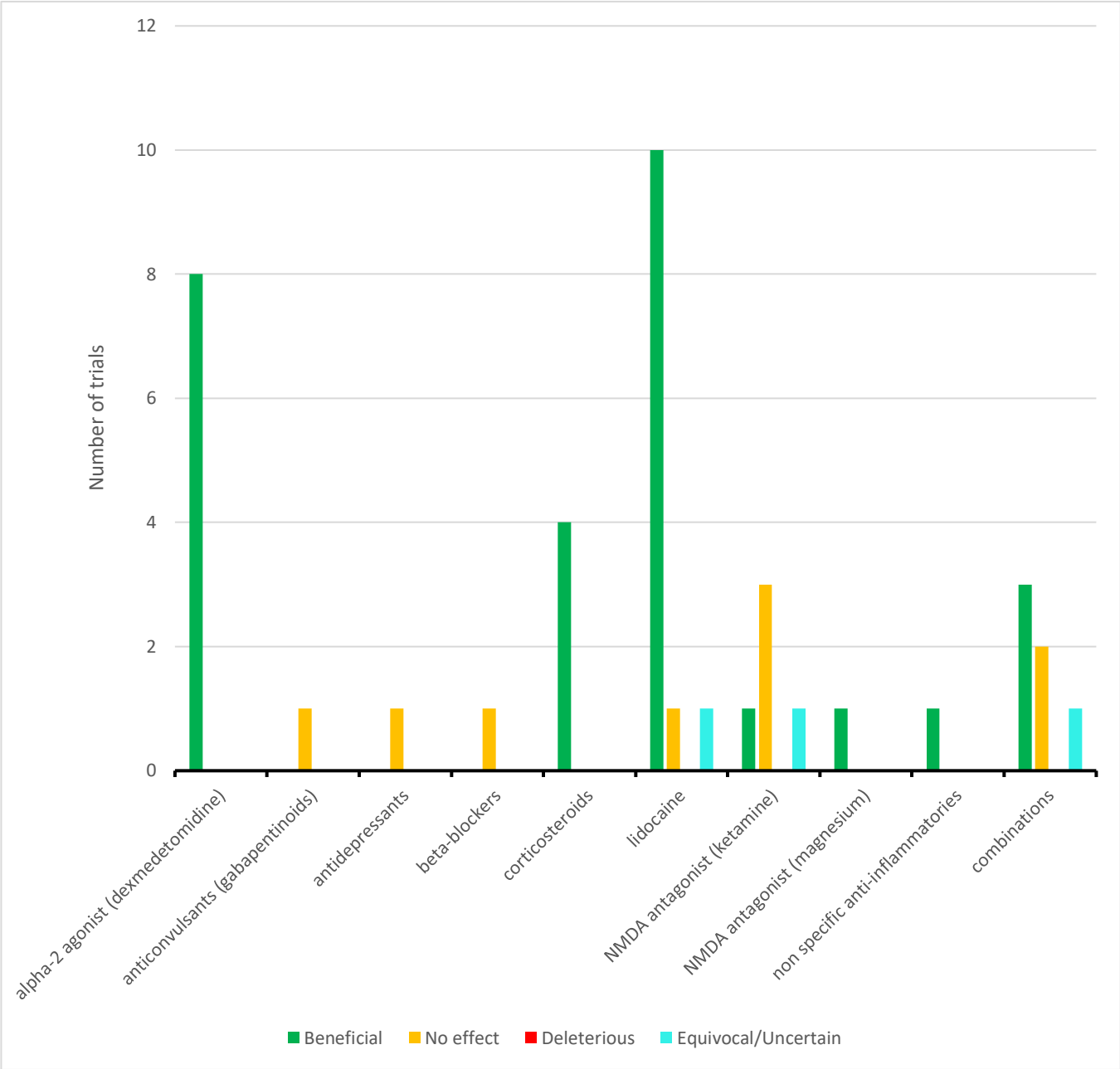


*The year 2023 is incomplete as the search strategy was ran in February 2023.

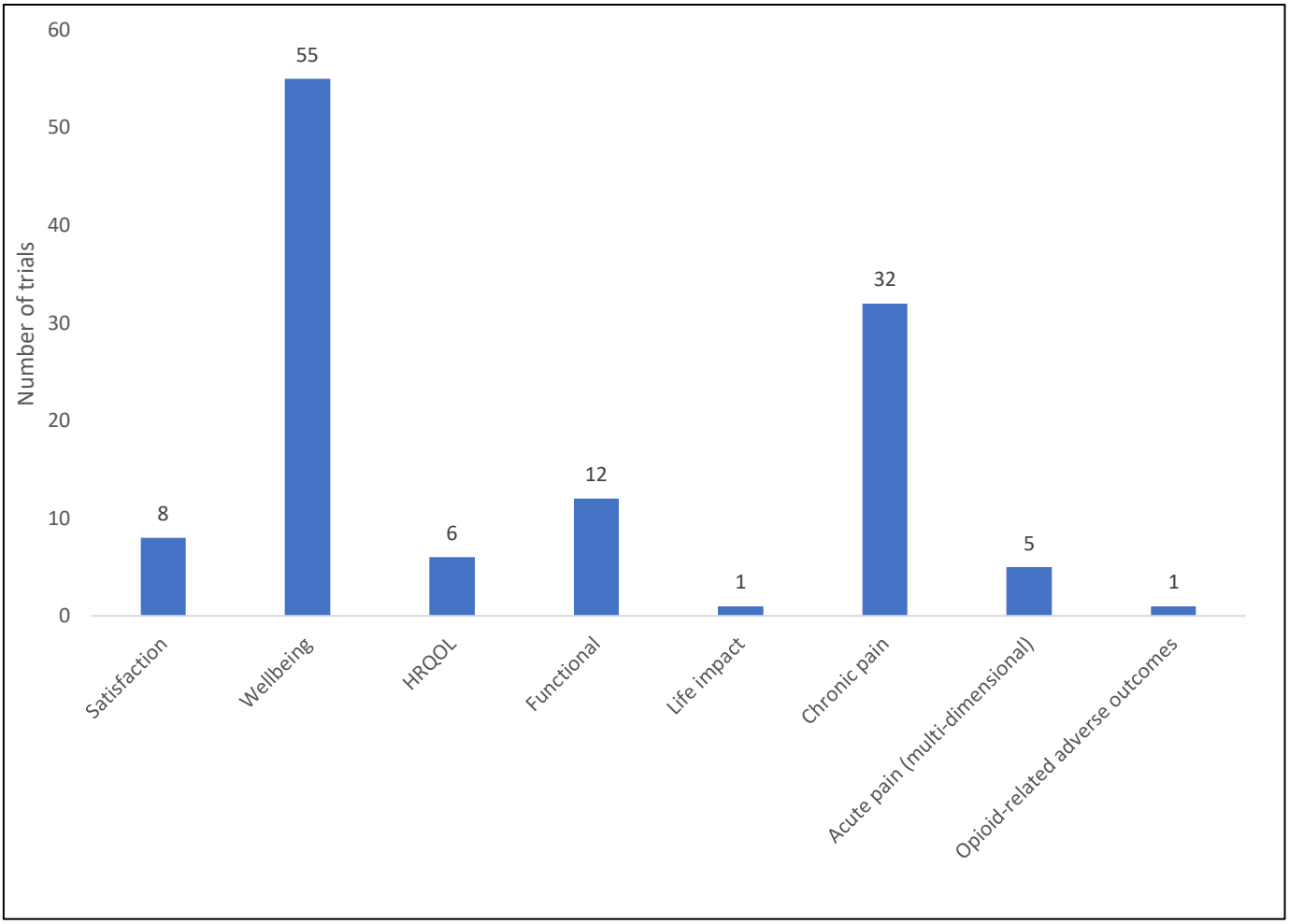
eFigure 4. Randomized control trials on pharmacologic opioid minimization strategies and assessing at least one patient-centred outcome per year of publication



eFigure 5. Number of trials showing beneficial, no effect, deleterious or equivocal/uncertain conclusion for each opioid minimization strategies based on reported findings (restricted to trials assessing patient-centred outcome as a primary outcome, n=107 trials) (trials with 2 or more intervention arms are not shown)



eFigure 6. Number of trials showing beneficial, no effect, deleterious or equivocal/uncertain conclusion for each opioid minimization strategies based on reported findings (restricted to trials assessing patient well-being via Quality of Recovery (QoR) as a primary outcome, n=43) (trials with 2 or more intervention arms are not shown)



HRQOL = Health-related quality of life

eFigure 7. Primary outcome measure among trials with a patient-centred primary outcome

Appendix 1. Definitions

Intraoperative period: For our research program, pharmacologic interventions administered the same day of surgery and before patient's extubation will be considered as intraoperative based on mechanism of action and effect duration properties.

Opioid minimization strategy: Any non-opioid drug with antinociceptive properties.

Multimodal strategies: The use of different classes of drugs, combining different action mechanisms aiming to reduce adverse effects and improve benefits.

Patient-centred outcome domains: well-being, functional outcomes, patient satisfaction, quality of life, life impact, opioid-related, and pain-related.

Systemic administration: Oral, intravenous, intramuscular or subcutaneous administration.

Appendix 2. Distiller SR's artificial intelligence active machine learning report

Distiller SR's artificial intelligence (AI) active machine learning feature was used as a second reviewer for title and abstract screening once a predicted relevant reference rate of 92% (4323 references discovered /4658 references predicted, which was reached after screening by two reviewers of 16,340 citations) was reached (i.e. approximative proportion of included trials that the active machine learning predicts we have identified at a specific time point). The AI reviewer was set to exclude all remaining records while a human reviewer inspected all remaining citations, consulting a second human reviewer anytime there was a decision that conflicted with that if the AI reviewer. We also used the audit tool to ensure no relevant studies were excluded in error.

Appendix 3. Group authorship

Hongda Li, Allison Chhor, Malvika Agarwal, Rahym Belrachid, Katie O'Hearn and Ravichandra Rachamalla.

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Chapter 4. Manuscript 3 - Effectiveness of dexmedetomidine on patient-centred outcomes in surgical patients under general anesthesia: a systematic review and Bayesian meta-analysis

4.1 Preface to manuscript 3

The most promising strategy identified in Chapter 3 (scoping review) was dexmedetomidine. In partnership with our patient partners panel (c.f. approach and development in Chapter 2) and our partner organizations, I led a systematic review and Bayesian meta-analysis of RCTs to evaluate the impact of intraoperative dexmedetomidine on patient-centred outcomes and to assess the certainty of evidence supporting this practice. Co-authors involved in this project helped for the supervision the project and analytical plan, revision of the manuscript, screening of the studies, extraction of the data and to conduct certainty of evidence assessment in duplicates. Patient partners and partner organizations contributed to refine the research question, provided input on the design of the study as well as on the development of the dissemination plan.

This systematic review protocol was published in BMJ Open:
Verret M, Le JBP, Lalu MM, et al. Effectiveness of dexmedetomidine during surgery under general anaesthesia on patient-centred outcomes : a systematic review and Bayesian meta-analysis protocol. BMJ Open. 2024. 14:e080012.

I anticipate submitting the manuscript reporting the final results in March 2024.

4.2 Manuscript 3

Effectiveness of dexmedetomidine on patient-centred outcomes in surgical patients under general anesthesia: a systematic review and Bayesian meta-analysis

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ABSTRACT

Importance: Dexmedetomidine is increasingly used for surgical patients requiring general anesthesia. However, its effectiveness on patient-centred outcomes including quality of recovery remains uncertain.

Objective: Evaluate the patient-centred effectiveness of intraoperative dexmedetomidine for adult patients requiring surgery under general anesthesia.

Data Sources: We conducted a systematic search of MEDLINE, Embase, CENTRAL, Web of Science and CINAHL from inception to October 2023.

Study Selection: Randomized controlled trials (RCTs) comparing the intraoperative use of dexmedetomidine to placebo, opioid, or usual care in adult patients requiring surgery under general anesthesia. At least one patient-centred outcome, as defined by the Standardised Endpoints in Perioperative Medicine (StEP-COMPAC) consensus, was required to be eligible.

Data Extraction and Synthesis: Study selection, data extraction, and risk of bias assessment were performed by two reviewers independently. We synthesized data using a random effects Bayesian regression framework to derive effect estimates and the probability of a clinically important effect. For continuous outcomes, we pooled instruments with similar constructs using standardized mean differences (SMD) and we converted SMD and credible intervals (CrI) to their original scale when appropriate. We assessed statistical heterogeneity using tau-squared and explored sources of heterogeneity with meta-regression. We assessed the risk of bias of included RCTs using the Cochrane's Risk of Bias tool (RoB 2.0) and the certainty of evidence using GRADE methodology.

Main Outcome(s) and Measure(s): Our primary outcome was quality of recovery after surgery. To guide interpretation on the original scale, the Quality of Recovery-15 (QoR-15) instrument was used (range: 0-150 points, minimally important difference [MID] of 6 points).

Results: We identified 49,069 citations, from which 44 RCTs involving 5904 participants were eligible. Intraoperative dexmedetomidine administration was associated with an improvement in postoperative quality of recovery (mean difference in QoR-15 = 9.04; 95% credible interval [CrI]; 3.58 to 14.11, n = 21 RCTs, low certainty of evidence). We found a 99% probability of any benefit and an 88% probability of achieving MID. We estimated a 99% probability of any benefit on chronic pain incidence (OR=0.42, 95%CrI: 0.18 to 0.79, n= 7 RCTs, low certainty of evidence). There was also an increased risk of clinically significant hypotension (OR=1.98, 95%CrI: 0.84 to 3.92, n= 8 RCTs) and clinically significant bradycardia (OR=1.74, 95%CrI: 0.93 to 3.34, n= 10 RCTs), with very low certainty of evidence for both.

Conclusions and Relevance: Dexmedetomidine initiated during general anesthesia may result in clinically important improvement in the quality of recovery and chronic pain after surgery. Pragmatic multicentre RCTs are needed to confirm clinical significance of these findings considering the low certainty of evidence.
PROSPERO registration number: CRD42023439896

KEY POINT

Question: What is the impact of systemic dexmedetomidine initiated (i.e., intraoperative) during general anesthesia on postoperative patient-centred outcomes among adult surgical patients?

Findings: In this systematic review and Bayesian meta-analysis, 44 randomized controlled trials were included. The probability of clinically significant effect (i.e., reaching the minimally important difference) from dexmedetomidine on the quality of recovery after surgery was high and the certainty of evidence was low. There was limited evidence to inform the risk of clinically significant adverse events associated with dexmedetomidine.

Meaning: Intraoperative dexmedetomidine may result in clinically meaningful improvement of postoperative quality of recovery. High quality randomized controlled trials are needed to confirm effectiveness and safety.

INTRODUCTION

Since its approval in 1999 for sedation of critically ill patients in the intensive care unit, dexmedetomidine (i.e. an alpha-2 agonist) has been increasingly used as an off-label opioid minimization strategy during surgery.(1-5) Dexmedetomidine can reduce short-term opioid use(6, 7) and some adverse effects related to opioids (i.e., nausea and vomiting and respiratory depression).(8-11) However, its impact on patient-centred outcomes remains uncertain and as a result, its use during surgery requiring general anesthesia is still debated.(12, 13)

Patient-centred outcomes are those identified as meaningful and important to patients and caregivers.(14) They can provide a holistic perspective on the patient postoperative experience including the quality of recovery and pain impact on function and daily living,(15-21) which are core domains that should drive evidence-based strategies to minimize opioid utilization.(22-28) Prominent perioperative national and international expert consensus statements(22-26, 29-34) such as *American Society for Enhanced Recovery & Perioperative Quality Initiative Joint Consensus Statement* (35, 36) emphasized the importance of patient-centred outcomes in the assessment of opioid minimization strategies.

Previous systematic reviews and randomized controlled trials (RCTs) have evaluated the effectiveness of dexmedetomidine using unidimensional (e.g. visual analogue scale for pain intensity) or indirect (e.g. short-term opioid exposure) endpoints without direct patient-centred outcome assessment, limiting relevance and applicability of the findings.(37-39) However, a recent scoping review of RCTs evaluating potential opioid minimization strategies in which patient-centred outcomes were assessed, indicated that dexmedetomidine was among the most promising pharmacologic strategies for intraoperative use.(40) Our objective was to estimate the magnitude and certainty of intraoperative dexmedetomidine's effect on patient-centred outcomes, such as the quality of recovery and chronic pain after surgery, among adult patients requiring surgery under general anesthesia.

METHODS

We performed a systematic review and Bayesian meta-analysis following the recommendations from the Cochrane Handbook for Systematic Reviews of Interventions.(41) Our review is reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and the WAMBS-checklist for Bayesian analysis.(42-44) We registered our systematic review in PROSPERO (CRD42023439896) and published our protocol prior to data analyses.(45) As detailed in our protocol and in a separate reflective article,(46) we used a collaborative approach involving a multidisciplinary team, patient partners, and multiple partner organizations across all steps of this systematic review (eTable 1). Our patient engagement approach is reported according to the Guidance for Reporting Involvement of Patients and the Public (GRIPP2-2) (eTable 2).(47)

Information sources and search strategy

Our search strategy was used in our scoping review inclusive of all opioid minimization strategies (Appendix 1).(38, 40) We systematically searched MEDLINE, Embase, CENTRAL, Web of Science and CINAHL from inception to October 17th 2023 for relevant key terms with no language or date restrictions. The search strategy was developed following the Peer Review of Electronic Search Strategies (PRESS) recommendations and was peer-reviewed independently by two information specialists.(44)

Study selection

We included peer-reviewed RCTs assessing the effectiveness of systemic dexmedetomidine compared to placebo, opioids, or usual standard of care. To be considered eligible, dexmedetomidine had to be initiated during the intraoperative period (i.e., day of surgery before the patient is in the post anesthesia care unit). RCTs were included if they reported at least one patient-centred outcome after the post-anaesthesia care unit phase of care.(48) We defined and classified patient-centred outcomes based on the Standardised Endpoints in Perioperative Medicine initiative (StEP-COMPAC) recommendations and examples can be found in eTable 3.(48) In addition, we included long-term opioid use (including opioid substance use disorder or overdose), opioid-related adverse effects (multidimensional assessment), acute pain (multidimensional assessment <3 months) and postoperative chronic pain (≥3 months) as patient-

centred outcomes.(46) RCTs published in suspected predatory journals (i.e., not peer-reviewed) were excluded. A predatory journal was defined as an open-access journal that is not registered nor in the Directory of Open Access Journals (DOAJ, https://doaj.org/), nor in Committee on Publication Ethics (COPE, https://publicationethics.org/).(49, 50)

Data extraction

After removing duplicates in Zotero (https://www.zotero.org), we imported the citations into InsightScope (i.e., an online software designed to facilitate large reviews, https://insightscope.tech/).(51) We performed study selection and data abstraction independently and in duplicate and resolved conflicts with a third senior reviewer when needed (M.V, J.B.P.L, R.R, and H.L).(51) We used a standardized data extraction form, informed by our multidisciplinary team, which included: (1) study design characteristics, (2) study methods, (3) patient eligibility criteria, (4) surgery, (5) the type of anaesthesia and analgesia, (6) pain intensity associated with the procedure, and (7) the source of funding.(45)

Outcomes

Our primary outcome was the postoperative quality of recovery, regardless of the measurement instrument used (see eTable 3 for examples).(52) When multiple time points were available, we prioritized the 24-hour time point or the closest time point available. If multiple quality of recovery instruments were reported in an RCT, we prioritized the Quality of Recovery-15 (score between 0 and 150, minimally important difference ≥ 6 points)(53) as this valid and reliable instrument(54) is recommended by the StEP-COMPAC group (patient-centred and patient comfort consensus)(48, 55) and also highly ranked by our multidisciplinary team including patient partners.(45, 46)

We assessed other patient-centred outcomes, such as well-being (i.e. other than quality of recovery), patient function, health-related quality of life, life impact, acute pain (multidimensional assessment), chronic pain, opioid-related adverse events (multidimensional assessments) and chronic opioid use (see eTable 3 for examples).(48)

We assessed non-patient-centred outcomes including hospital and post anaesthesia care unit lengths of stay, adverse events including delirium, non-fatal/fatal cardiac arrest, mortality, and respiratory depression as well as adverse events requiring intervention (i.e. bradycardia, hypotension, tachycardia, hypertension).(56, 57)

Risk of bias

We (M.V, J.B.P.L, R.R, and H.L) assessed the domain-specific and overall risk of bias in duplicate using the Cochrane Collaboration Risk of Bias (RoB 2.0) tool.(58-60) The risk of bias assessment was outcome-oriented using our three outcome categories: quality of recovery, other patient-centred outcomes, and additional outcomes separately.(58)

Data synthesis and analyses

For each outcome measure reported, we conducted a random-effects Bayesian Meta Analysis.(61-63) Bayesian modelling directly estimates the probability of an effect (or a certain effect size) being credible based on a combination of prior knowledge and the observed data, in contrast to a frequentist approach which estimates the probability of the observed data (e.g., p-value based null hypothesis testing). We pooled instruments with similar constructs using standardized mean differences and their 95% credible intervals.(64) For our primary analysis, we assessed the effect of dexmedetomidine on the quality of recovery. We used hierarchical models (i.e., a random effect for each study, and study level estimates as fixed effects) to estimate the standardized mean difference and corresponding 95% credible intervals (CrIs) using linear regression. We also converted standardized mean differences to their original scale (i.e., QoR-15) to facilitate clinical interpretation (i.e. multiplication of the pooled SMD by the QoR-15 mean standard deviation across intervention groups of included RCTs [SD = 10.87]).(65) We calculated the probability of any benefit/harm using the highest density probability interval of the posterior distribution and the probability of achieving a mean difference as large or larger than the minimally important difference (MID) using the empirical cumulative distribution function (ECDF). The same approach was used for pooling secondary outcomes; modelling continuous data with mean differences (or SMD if more than one instrument sharing similar constructs) and standard errors (i.e. linear regression) and binary data with odds ratio (logarithmic scale) and standard errors along with 95% credible intervals. A SMD equal or larger than 0.2 was

considered clinically significant.(41) We used weak informative prior distributions for effect size estimation of continuous outcomes and binary outcomes, and we conducted sensitivity analyses using non-informative priors (see Appendix 2 for priors and model specifications). We estimated the heterogeneity distribution using tau (τ; prior distribution: Half-Cauchy∼0,0.5).(66-68) We interpreted τ as reasonable (between 0.1 and 0.5), fairly high (between 0.5 and 1.0) or fairly extreme (higher than 1.0).(62, 69) We assessed potential publication bias with funnel plots when more than ten trials were included in a meta-analysis.

Subgroup group analyses

For each patient-centred outcome measure that was reported in ten or more RCTs,(41) we performed meta-regressions to explore sources of heterogeneity, namely: type of surgery (high risk of chronic pain vs. not),(70) population (older adults [≥65] vs. younger, chronic pain or opioid use at baseline vs. not vs. mixed), type of dexmedetomidine administration (bolus vs. bolus and infusion vs. infusion vs. target plasma concentration), the dosage of dexmedetomidine (concentration and duration), risk of bias within RCTs with available data (low, high, or some concerns), mean pain intensity in the control group (low vs. moderate or severe pain intensity (≥ 4 on a 10-point scale), and type of funding (academic, industry, academic and industry).(71)

Model diagnostics and code

Bayesian meta-analyses and posterior distribution results were calculated using the brms package in R version 4.3.2.(63) We implemented our sampling procedure using the Markov Chain Monte Carlo-based method, with an iteration phase of 6000, a warm-up phase of 2000 iterations followed by 4 chains as the initial approach.(72) We assessed model convergence and validity with the Rhat values (<1.01 for adequate convergence) and Potential Scale Reduction Factor (PSFR) approach.(73, 74) We also assessed visual mixing of the chains (density plots), marginal posterior distribution of parameters (i.e., similarity between observed and predicated data), and autocorrelation using lag plots.

Certainty assessment

To determine confidence in the estimates, for each outcome, we assessed the certainty of evidence in duplicate using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group methodology.(75)

RESULTS

Study characteristics and study selection

We identified 49,069 citations from our search, of which 46 RCTs involving 6024 participants (range: 39 to 798 participants per RCT) were included in our systematic review. Some results could not be included in meta-analyses (reasons provided in eTable 4), and a total of 44 RCTs involving 5904 participants were included in our meta-analyses (Figure 1).

Most RCTs were conducted in one centre (n=40; 3912 participants) and 13% were multicentre RCTs (n=6; 2112 participants). The mean age of participants was 56 ± 14 years old and 51% were female (eTable 5). The most common types of surgery within RCTs were gastrointestinal surgery (24%, n=11; 742 participants), non-cardiac thoracic surgery (17%, n=8; 726 participants), and obstetrics-gynaecological surgery (13%, n=6; 405 participants). The comparator was placebo in 91% (n=42; 5774 participants), opioids in 7% (n=3; 186 participants), and usual care in 2% of RCTs (n=1; 64 participants). Dexmedetomidine was administered as a bolus (i.e., single dose) in 17% of RCTs (n=8; 712 participants), an infusion in 35% of RCTs (n=16; 1963 participants), and using a combination of a bolus followed by an infusion in 48% of RCTs (n=22; 3349 participants). In 17% of RCTs (n=8; 1884 participants), dexmedetomidine administration continued during the postoperative period. The median duration of infusion was 2.3 h (IQR: 1.7-3.9) and the median dose of the bolus and intraoperative infusion respectively were 0.5 µg/kg (IQR: 0.5-1.0) and 0.5 µg/kg/h (IQR: 0.4-0.5). Analyses accounting for sex (i.e., stratification for sex) were performed in 15% of RCTs (n=7; 1436 participants). A summary of characteristics of included RCTs is provided in eTable 5. Quality of recovery was reported in 25 RCTs (n=2155), other patient-centred outcomes were reported in 23 RCTs (n=4271), and clinically important adverse events or lengths of stay were reported in 37 RCTs (n=5387). Results from RCTs that could not be pooled are summarized in eTable 4. Authors were contacted to provide detail quantitative results of quality of recovery,(76) sleep quality,(77) quality of life,(77) acute pain,(78) and chronic pain,(77) but no responses were obtained.

Risk of bias

For the 25 RCTs in which the primary outcome (quality of recovery) was reported, the overall risk of bias was considered low for 40% (n = 10), unclear (n = 13), and high for 8% (n = 2). The overall risk of bias for other patient-centred outcomes (n=23) was low for 22% (n = 5), unclear

for 65% (n = 15), and high for 13% (n = 3). The overall risk of bias for the clinically important adverse events and lengths of stay was low for 19% (n = 7), unclear for 68% (n = 25), and high for 13% (n = 5) (eTable 6-8 and eFigure 1-3).

Primary outcome

Quality of recovery

Among the 25 RCTs that assessed the quality of recovery, 21 RCTs (n = 1793 participants) were pooled (i.e., outcome measure with same or similar construct). The quality of recovery instruments pooled were the Quality of Recovery-9 (n=1), Quality of Recovery-15 (n=5), and Quality of Recovery-40 (n=15). The timing of evaluation was 24 hours after surgery except for two RCTs that reported a later time-point.(76, 79)

The estimated mean increase in the quality of recovery was 0.83 SMD units (95%CrI: 0.33 to 1.30, Tau = 1.12). Results were similar when using a non-informative prior (SMD=0.86, 95%CrI: 0.34 to 1.38, Tau=1.17) (eTable 9 and Appendix 4). Following conversion to original scale (QoR-15), the mean increase in the Quality of Recovery was 9.04 points (95%CrI: 3.58 to 14.11) (Table 1 and Figure 2).(65) The posterior probability of any benefit (i.e., probability that there is a difference between groups in favour of dexmedetomidine [MD>0]) from dexmedetomidine on the quality of recovery was 99% and the probability of a clinically significant benefit (MD>6.0 units on QoR-15 scale) was 88%.(53) After removing three RCTs with extreme results (i.e., >3 times the pooled SMD), the posterior probability of clinically significant benefit [MD>6.0 units on QoR-15 scale]) was 81%. The certainty of evidence was low (Table 1). Based on forest plot visual inspection and meta-regression coefficients (Figure 3), some factors partly explained heterogeneity, such as the risk of bias (i.e., RCTs at lower risk of bias reported larger effect sizes from dexmedetomidine), dosage regimen (the use of combined bolus and infusion were associated with increased effect size), and type of population (increased effect size when used among the non-geriatric population). The duration of infusion (in hours) had no strong impact on the quality of recovery based on meta-regression (SMD=0.02, 95%CrI: -0.07 to 0.10).

Other patient-centred outcomes

Life impact

There was little evidence that dexmedetomidine improved patient independance after surgery (MD=-5, 95%CI: -5 to 0, n= 1 RCT evaluated with the Barthel score).(80) The certainty of evidence was very low (Table 1, Appendix 3).

Patient health-related quality of life

Pooled estimates suggested no strong benefit from dexmedetomidine on health-related quality of life after surgery (SMD=0.05, 95%CrI: -0.61 to 0.72, Tau = 0.40, n= 2 RCTs). The posterior probability of any benefit was 46% (combining Short Form-8 (SF-8) and SF-12). The certainty of evidence was low (Table 1, Appendix 3).

Multidimensional acute pain

One RCT evaluated the effect of dexmedetomidine on DN4 (i.e., Neuropathic Pain Detection Questionnaire) and found no impact from dexmedetomidine (i.e., absence of neuropathic pain in all intervention and control arms).(78) No RCTs reported multidimensional acute pain assessment.

Well-being (Sleep quality)

The posterior probability of any benefit from dexmedetomidine on sleep quality was 94% (MD=-0.61 [NRS 0 to 10, lower is better], 95%CrI: -1.29 to 0.10, Tau = 0.89, n= 7 RCTs, low certainty of evidence) (Table 1, Appendix 3).

Postoperative function

No RCTs reported data on postoperative function.

Chronic pain

The posterior probability of any benefit (OR<1) was 99% and the posterior probability of clinically significant benefit (OR<0.70) on postoperative chronic pain incidence was 95% (OR=0.42, 95%CrI: 0.18 to 0.79, Tau = 0.77, n= 7 RCTs, low certainty of evidence) (Table 1, Appendix 3).

Other outcomes

The posterior probability of any harm on hypotension requiring an intervention was 94% (OR=1.98, 95%CrI: 0.84 to 3.92, Tau = 0.91, n= 8 RCTs, very low certainty of evidence) and it was 95% for bradycardia requiring an intervention (OR=1.74, 95%CrI: 0.93 to 3.34, Tau = 0.62, n= 10 RCTs, very low certainty of evidence). The posterior probability of any benefit on mortality was 93%, (OR=0.69, 95%CrI: 0.37 to 1.21, Tau = 0.36, n= 10 RCTs, low certainty of evidence). The posterior probability of any benefit on hypertension requiring an intervention was 90% (OR=0.81, 95%CrI: 0.25 to 2.15, Tau = 0.62, n= 2 RCTs, very low certainty of evidence), and 80% for the posterior probability of any benefit on tachycardia requiring an intervention (OR=0.80, 95%CrI: 0.25 to 2.37, Tau = 0.65, n= 2 RCTs, very low certainty of evidence).
The posterior probability of any benefit on postoperative delirium was 99% (OR=0.62, 95%CrI: 0.39 to 0.92, Tau = 0.52, n= 12 RCTs). There was no effect from dexmedetomidine on the odds of respiratory depression (OR=1.14, 95%CrI: 0.42 to 2.48, Tau = 0.51, n= 10 RCTs, posterior probability of any benefit=47%). No RCTs reported results on chronic opioid use, fatal/non-fatal cardiac arrest, and opioid-related adverse effects (multidimensional assessment) outcome. measures.

Lengths of stay

The posterior probability for dexmedetomidine increasing post anesthesia care unit duration was 88% (MD=0.69 minutes, 95%CrI: -0.49 to 1.79, Tau = 1.8, n= 16 RCTs), and the posterior probability of a reduction in hospital length of stay was 92% (MD=-0.18 days, 95%CrI: -0.49 to 0.05, Tau = 0.33, n= 21 RCTs).

Publication biases

For all meta-analyses including more than ten RCTs, we found no evidence of publication bias based on visual assessment of funnel plots (eFigure 4-8).

Model diagnosis

All our models converged adequately with Rhat <1.01 (i.e., representative regions were explored by the chains) and marginal posterior distributions were adequate (i.e., results from statistical models resembled the observed data). We also obtained good mixing of the Markov chains based

on the trace plots and there was no autocorrelation (i.e., dependency among Markov chain samples) except for the primary outcome model (i.e., QoR) as well as for health-related quality of life that was resolved with increased thinning (i.e., subsampling each chain of simulation generated by the model), while providing similar effect estimates (thin=5). Density plots, trace plots, posterior check and autocorrelation figures are provided in Appendix 4. Results were similar whether a weak informative or a non-informative prior was used (eTable 9).

Protocol deviation

All diagnostic tests (convergence, replication, density) were satisfactory (Appendix 4). While we planned to explore the impact of the dose (continuous variable) of dexmedetomidine administration on our primary outcome (i.e., quality of recovery), we decided to categorize this independent variable given the overall limited range of doses utilized (i.e. low: 0 to 0.49 mcg/kg, medium: 0.5 to 0.99 mcg/kg, and high: ≥1 mcg/kg).

DISCUSSION

In this systematic review and meta-analysis of RCTs, we found a high probability that dexmedetomidine improves the quality of recovery after surgery among adult patients undergoing surgery requiring general anesthesia. There was also a high probability that this effect may be clinically significant.(53) The certainty of evidence was, however, low as a result of the risk of bias and the high level of statistical heterogeneity (i.e., inconsistency). We identified factors that partially explained heterogeneity such as risk of bias, dosage regimen, and type of population. While the certainty of evidence was also low, we found a high probability that dexmedetomidine improved postoperative chronic pain. Intraoperative dexmedetomidine was also promising to improve sleep quality, and delirium incidence. Dexmedetomidine may increase the risk of clinically significant (i.e., requiring an intervention) hypotension and bradycardia, but the certainty of evidence was very low. However, mortality and hospital length of stay were reduced with the use of dexmedetomidine, indicating that bradycardia and hypotension episodes had likely minimal impact on patients. There were either few RCTs or none reporting the effect of dexmedetomidine on life impact, health-related quality of life, postoperative acute pain (multidimensional assessment), long-term opioid use, fatal/non-fatal cardiac arrest, clinically significant tachycardia, clinically significant hypertension, and opioid-related adverse effects outcome measures.

Our findings are consistent with a previous systematic review and meta-analysis that included nine RCTs evaluating the effect of dexmedetomidine on the quality of recovery among patients undergoing elective surgery.(37) Results from this previous systematic review have also shown a statistically significant effect from dexmedetomidine on the postoperative quality of recovery (MD: 15.71; 95% CI, 0.43 to 31.00). However, their analysis was restricted to one type of instrument (QoR-40, score range between 40 and 200) and the analyses did not address the clinical (vs. statistical) significance of the findings. Thus, our results strengthen previous findings regarding the effectiveness of dexmedetomidine in improving the quality of recovery and suggests that the effect may be clinically meaningful.

Other systematic reviews have shown a lack of evidence to inform the analgesic effectiveness of dexmedetomidine in perioperative care.(12, 81) While we focused our short-term analgesic

assessment on multidimensional pain assessment or pain interference scores, our findings are congruent with previous reviews; confirming an absence of evidence in the area.(12) Furthermore, our assessment is compliant with an updated international pain definition incorporating the subjective experience and expert consensus recommending multidimensional pain assessment in clinical care and research.(82) As for long-term analgesic effectiveness (i.e., prevention of chronic pain), our findings are incongruent with previous systematic reviews that did not observe evidence of an effect.(81) As a result of our exhaustive search strategy and new evidence that have been published, we observed that intraoperative dexmedetomidine may reduce the incidence of postoperative chronic pain after surgery.

Our review has a number of strengths. We employed a rigorous and contemporary approach for conducting our systematic review. First, emphasizing the importance of patient-centred outcomes in perioperative care and to inform appropriate use of opioid minimization strategy, we conducted a comprehensive patient-centred assessment to determine effectiveness. We thus implemented the StEP-COMPAC consensus recommendations for perioperative patient-centred outcomes which was previously identified as an important knowledge gap.(40) It also represents a pragmatic approach to identify promising alternatives in the context of the worldwide opioid crisis.(28) Second, to enhance the clinical relevance and applicability of our findings, we evaluated the clinical significance of our findings using established minimally important difference thresholds (e.g., QoR-15 MID = 6.0) and following guidelines for patient-reported outcome measures evaluation.(65) Third, we used the most recent version of the risk-of-bias assessment tool (RoB 2.0) and adhered to Cochrane group guidance for systematic review. Fourth, we implemented a Bayesian framework to allow modelling of heterogeneity, enable efficient utilization of available data, and to enhance the interpretability of our results.(66) Finally, we used an innovative co-creation approach, actively involving partner organizations and patient partners throughout the research process, thereby fostering a collaborative and multidisciplinary perspective.

Our review also had limitations. First, while patient-centred outcomes are extremely important to guide clinical decision-making during general anesthesia, other important outcomes may be relevant to clinicians. Our systematic review doesn’t include RCTs that did not assess at least

one patient-centred outcome, thus our assessment of harms is not exhaustive. Second, our systematic review does not compare dexmedetomidine with other opioid minimization strategies (i.e., comparative effectiveness research).

CONCLUSION

Our pooled analyses suggest that intraoperative systemic dexmedetomidine may be a promising pharmacologic strategy to improve the quality of recovery after surgery and potentially reduce postoperative chronic pain incidence among adult patients. However, the certainty of evidence was low. Thus, there is a need for further high-quality RCTs evaluating the patient-centred effectiveness and safety of dexmedetomidine initiated during the intraoperative period.

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Conceptualization and study question: MV, JBPL, MML, DM, SN, AFT, BH, FZ, MG, ML, AG, MB, IG, PP, HD, GM, JM, HM, DF

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Development of search strategy: MV, DF, MML, AFT, RS

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Drafting the manuscript: MV, JBPL, DF, MML, MSJ

Critical revision of the manuscript: MV, JBPL, MML, DM, SN, AFT, BH, FZ, MG, ML, AG, MB, IG, PP, HD, GM, JM, HM, DF, KOH, MSJ

Design data extraction form: MV, JBPL, MML, DM, SN, AFT, BH, FZ, MG, ML, AG, MB, IG, PP, HD, GM, JM, HM, DF

Develop statistical analytical plan: MV, DF, DM, BH, MSJ

Conduct statistical analyses: MV, MSJ

Visualization: MV, JBPL, ML, DM, DF, MSJ

Project administration: MV

Lead patient engagement activities: MV, SN

Lead knowledge user partnership activities: MV, DF, MML

MV, JBPL, MML, MSJ, DM, SN, AFT, BH, FZ, MG, ML, AG, MB, IG, PP, HD, GM, JM, HM, DF reviewed the content of the manuscript and approved the final version.

Additional contributions:

Our partner organizations were SolvingPain (https://www.solvingpain.ca), Pain BC (https://painbc.ca), Health Canada (https://www.canada.ca/en/health-canada.html), Réseau Québécois de Recherche sur la Douleur (https://qprn.ca/fr/), Choosing Wisely (https://choosingwiselycanada.org), the Ontario SPOR SUPPORT unit (https://ossu.ca), the Canadian Anaesthesia Society (https://www.cas.ca/en/home), the Canadian Chronic Pain Network (https://cpn.mcmaster.ca), and the Canadian Perioperative Anaesthesia Clinical Trials (PACT) group (https://canadianpact.ca). They helped refine the research question, provide input on the design of the study as well as in the development of the dissemination plan.

Data statement:

The list of included trials is included in eTable 4. Additional meta-data can be provided upon request to the corresponding author.

Conflict of Interest Disclosures:

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Table 1. Summary estimates from Bayesian meta-analyses with the assessment of the certainty of the evidence

Outcome	Relative effect (95%CrI or CI)[e]	Posterior Probability of any benefit[h]	Number of RCTs	Number of participants		Heterogeneity using Tau (95% CrI)	Certainty of the evidence (GRADE)
				Dexmede-tomidine	Comparator		
Primary							
Quality of Recovery[f]	MD=9.04 (95%CrI: 3.58 to 14.11)	99%	21	908	885	1.12 (0.81 to 1.56)	Low[a]
Secondary							
Health-related quality of life (Short-Form score)	SMD=0.05 (95%CrI: -0.61 to 0.72)	46%	2	209	219	0.40 (0.01 to 1.36)	Low[c]
Life impact (Barthel Index)[g]	MD=-5 (95%CI: -5 to 0)	NA	1	55	55	NA	Very low[b]
Sleep Quality (Numerical Rating Scale)	MD=-0.61 (95%CrI: -1.29 to 0.10)	94%	7	858	854	0.89 (0.47 to 1.60)	Very low[b]
Chronic Pain Incidences	OR=0.42 (95%CrI: 0.18 to 0.79)	99%	7	692	683	0.77 (0.23 to 1.60)	Low[a]
Mortality	OR=0.70 (95%CrI: 0.37 to 1.21)	93%	10	1254	1261	0.36 (0.01 to 1.12)	Low[c]
Delirium	OR=0.62 (95%CrI: 0.39 to 0.92)	99%	12	1457	1459	0.52	Very low[b]
Bradycardia requiring an intervention	OR=1.74 (95%CrI: 0.93 to 3.34)	5%	10	1106	888	0.62 (0.08 to 1.49)	Very low[b]
Hypotension requiring an intervention	OR=1.98 (95%CrI: 0.84 to 3.92)	6%	8	1026	808	0.91 (0.40 to 1.72)	Very low[b]
Tachycardia requiring an intervention	OR=0.8 (95%CrI: 0.25 to 2.37)	80%	2	195	196	0.65 (0.03 to 1.91)	Very low[b]
Hypertension requiring an intervention	OR=0.81 (95%CrI: 0.25 to 2.15)	80%	2	180	180	0.62 (0.02 to 1.90)	Very low[b]

OR, odds ratio; MD, mean differences; SMD, standardized mean difference

[a]Due to risk of bias and inconsistency
[b]Due to risk of bias, inconsistency, and imprecision
[c]Due to risk of bias and imprecision
[e]95%CrI: 95% credible interval and 95%CI: 95% confidence interval
[f]Conversion of pooled Quality of Recovery results in Quality of Recovery-15 unit by multiplying the pooled SMD by the QoR-15 mean standard deviation across intervention groups of included RCTs. Score range between 0 (very poor recovery) and 150 (excellent recovery).
[g]Score range between 0 and 100 with lower score indicating increased disability.
[h]Calculated with Empirical Cumulative Distribution Function

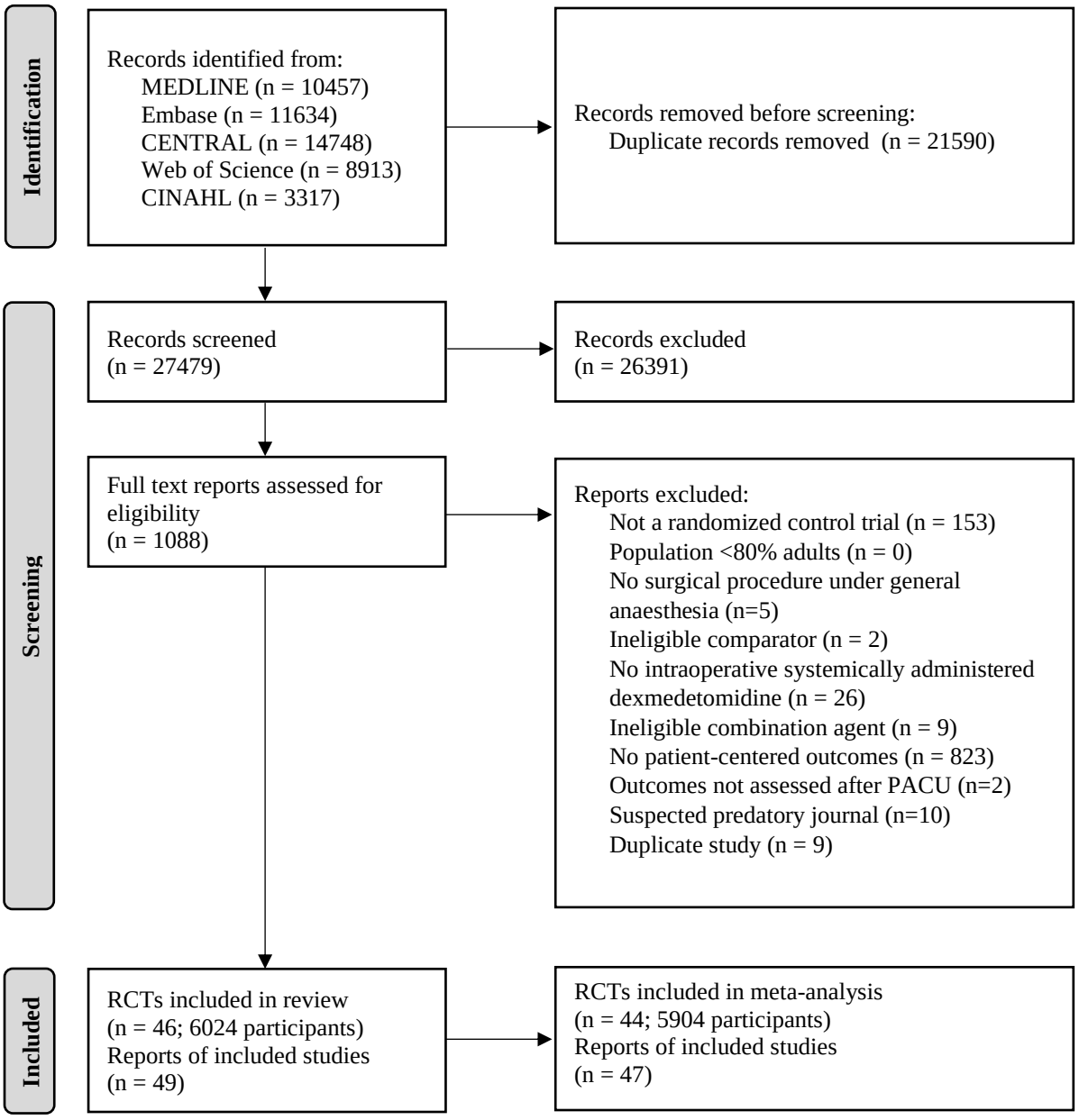


Figure 1. Flow diagram

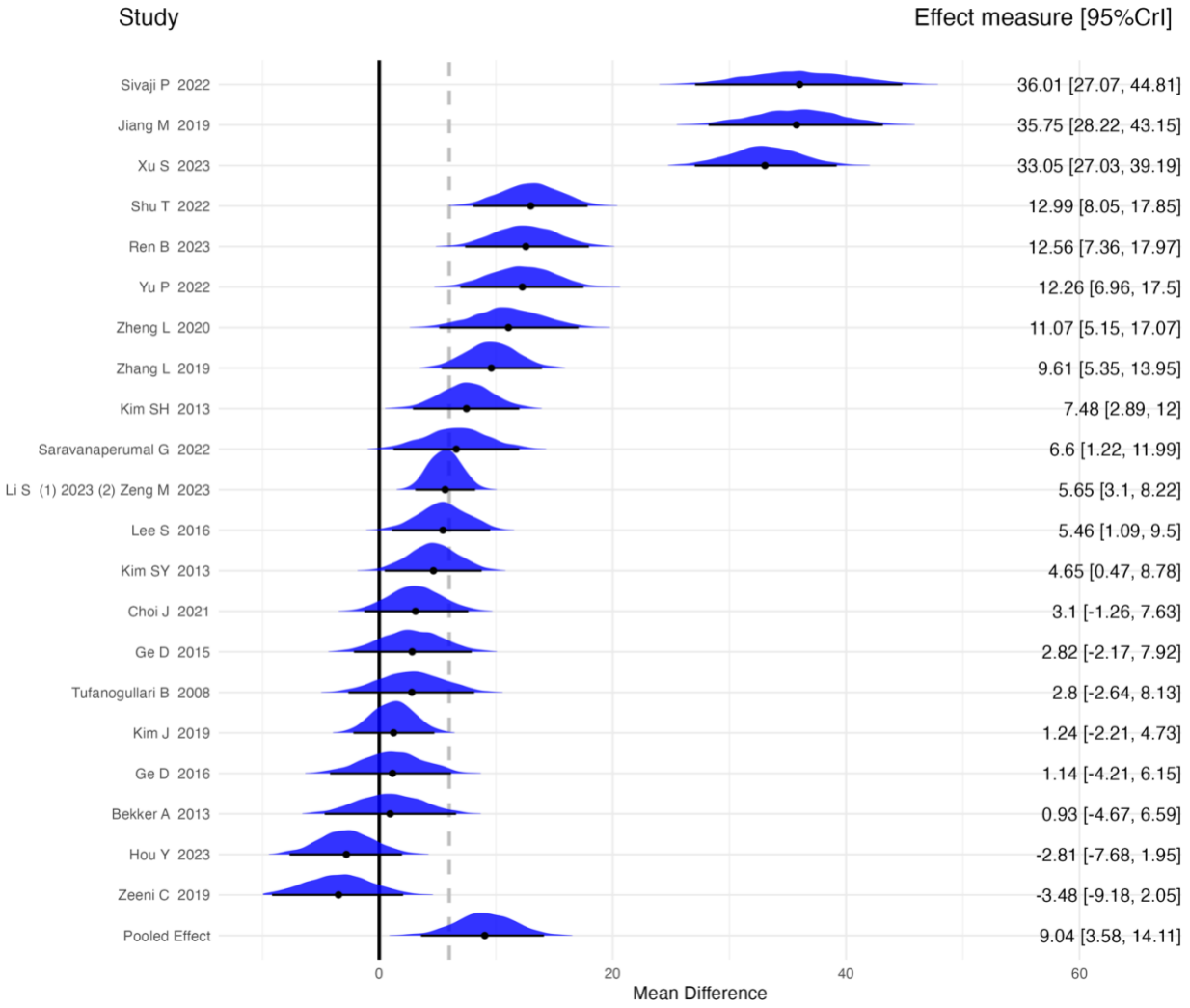


Figure 2. Forest plot for Quality of Recovery outcome measure (mean difference)
Black vertical line indicates null value (mean difference = 0), grey dashed vertical line indicates the threshold for minimally important difference. A value above zero (right direction) favors dexmedetomidine. A value below zero (left direction) favors control.

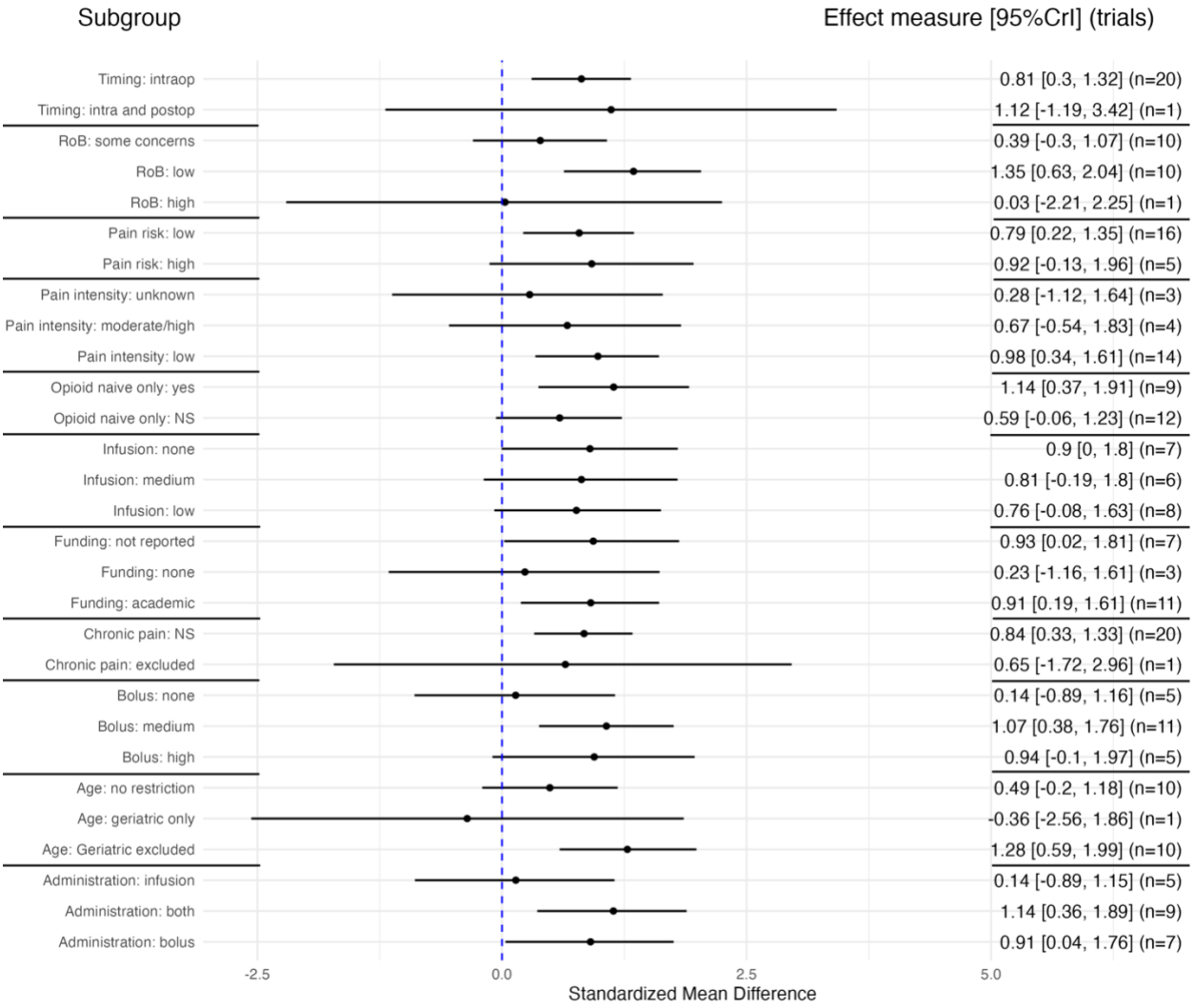


Figure 3. Forest plot showing meta-regression results
Blue dashed vertical line indicates nul value (standardized mean difference = 0). Values above zero (right direction) favours dexmedetomidine.

eTable 1. Partner organizations

Type of knowledge users	Interested parties identified
Practitioners and researchers Anesthesiologists	Anesthesiologists Surgeons Nurses Pain expert Psychologist Researcher Trainee
Patients	Patient panel
Patient organization	Strategy for Patient-Oriented Research (SPOR)
Policy makers	Health Canada Choosing Wisely
Institutions	Department of Anesthesia and Pain Medicine (University of Ottawa)
Interdisciplinary organization	Pain BC Solving Pain Réseau Québécois de Recherche sur la Douleur Chronic Pain Network
Researcher and practitioner organization	Perioperative Anesthesia Clinical Trials group Canadian Anesthesia Society

eTable 2. GRIPP2 short form

Section and topic	Item	Reported on page No
1: Aim	Report the aim of PPI in the study	4
2: Methods	Provide a clear description of the methods used for PPI in the study	4
3: Study results	Outcomes—Report the results of PPI in the study, including both positive and negative outcomes	5
4: Discussion and conclusions	Outcomes—Comment on the extent to which PPI influenced the study overall. Describe positive and negative effects	5 (additional information provided in our reflective article [Verret et al. CJA. 2023])
5: Reflections/critical perspective	Comment critically on the study, reflecting on the things that went well and those that did not, so others can learn from this experience	N/A (additional information provided in our reflective article [Verret et al. CJA. 2023])

PPI=patient and public involvement

eTable 3. Patient-centred outcome measure domains and instruments

Outcome measure domain	**Instruments**[1,2]
Well-being (quality of recovery)	*Quality of Recovery (QoR) – 9, 15, 40
	Functional Ability Questionnaire (FAQ)
	Post Discharge surgical recovery (PDSR)
	General Symptom Distress Scale (GSDS)
	Functional Status Questionnaire (FSQ)
	Post Anesthesia Short-term Quality of Life (PASQOL)
	Surgical Recovery Index (SRI)
	Functional Recovery Index (FRI)
	Postoperative Quality of Recovery Score (PQRS)
	Surgical Recovery Scale (SRS)
Function (≤ 1 month)	*WHO disability assessment
	Six-minute walk test (6MWT)
	ECOG performance status
Health-related quality of life	*EuroQuol 5D-5L
	EuroQuol 3D-3L
	*SF-36
	SF-12
	SF-8
Life Impact	30 days alive and out of hospital
	1 year alive and out of hospital
	Time to return to work
	Time to return to usual activity
	Barthel index
Acute pain multidimensional assessment[3]	*Brief Pain Inventory
	McGill Pain Questionnaire
	Activity-based checks of pain (ABCs)
	American Pain Society Patient Outcome questionnaire
Opioid-related adverse events multidimensional assessments	*Opioid-Related Symptom Distress Scale (ORSDS)
	Numerical Opioid Side Effect (NOSE) scale
	Opioid Side Effect Scale (OSES)
	Side Effect/Symptom Distress Score(s)
Chronic pain[3]	Chronic pain incidence[4]

Chronic opioid use, disorder, or overdose	Any tool assessing opioid use/disorder/overdose[4]

[1]Non exhaustive list of instruments that should be assessed once the patient has left the recovery room to be eligible
[2]24 hours after surgery of closest time point available will be extracted except for intermediate or long-term instruments (i.e. time to return to work, chronic pain and chronic opioid use)
[3]Pain at surgery site will be prioritized
[4]Latest time point available after 3 months will be extracted
*Instruments that will be prioritized if more than one is reported for the same domain in the same trial

eTable 4. Summary of randomized controlled trials that could not be included in meta-analyses with reasons that preclude quantitative pooling

Study	Instruments	Binary or Continuous	Intervention sample size (analyzed)	Intervention effect ± SD (or number of events) [2]	Control sample size (analyzed)	Control effect ± SD (or number of events) [2]	Findings[1]	Reason for exclusion from meta-analysis
Well-being (quality of recovery)								
Efe Mercanoglu 2022	Quality of Recovery - 15	Continuous	30	Not specified	30	Not specified	No effect	No quantitative results
Sherif 2017	Quality of Recovery – 40	Continuous	49	182.0	49	140.0	Benefit	Uncertainty regarding effect size and variance of mean.
Khanduja 2014	Clinical recovery score	Continuous	30	10.2 ± 0.61	30	9.67 ± 0.661	Benefit	No other RCT reporting this instrument
Mao 2020	Surgical Recovery Scale	Continuous	29	32.97 ± 9.59	29	32.86 ± 13.41	No effect	No other RCT reporting this instrument
Well-being (other outcome measures)								
van Norden 2021	Sleep Quality	Continuous	Not specified	Not Specified	Not specified	Not specified	Not specified	No quantitative results
Wang 2022	Sleep Quality NRS (1-6)	Continuous	283	3.34 ± 1.61	68	3 ± 1.48	No effect	No other RCT reporting this instrument
Mao 2020	St. Mary's Hospital Sleep Questionnaire	Continuous	29	4.5 ± 7.4	29	4.0 ± 0.0	Benefit	No other RCT reporting this instrument

Study	Instruments	Binary or Continuous	Intervention sample size (analyzed)	Intervention effect ± SD (or number of events) [2]	Control sample size (analyzed)	Control effect ± SD (or number of events) [2]	Findings[1]	Reason for exclusion from meta-analysis
Well-being (other outcome measures)								
Zi 2020	Zung's Self-Rating Anxiety Scale	Continuous	62	47.5 ± 9.2	61	51.2 ± 9.1	No effect	No other RCT reporting this instrument
Wang 2022	Zung's Depression Scale Score	Continuous	60	40.8 ± 2.8	60	40.7 ± 2.5	Benefit	No other RCT reporting this instrument
	State-Trait Anxiety Inventory	Continuous	60	42.9 ± 2	60	43.6 ± 1.6	No effect	No other RCT reporting this instrument
Yu 2023	Beck Anxiety Inventory	Continuous	156	12.6 ± 7.2	154	14.0 ± 5.9	Benefit	No other RCT reporting this instrument
Life impact								
Ran 2021	Activity of Daily Living 14 items score	Continuous	52	21.6 ± 3.6	50	26.1 ± 3.6	No effect	No other RCT reporting this instrument
Chen 2022	Barthel Index	Continuous	80	-3.33 ± 7.4	80	-6.67 ± 11.11	No effect	Reported reduction from baseline
Shan 2022	Barthel Index	Continuous	56	26.67 ± 3.7	55	28.33 ± 3.7	No effect	No other RCT reporting this instrument with adequate data
Shariffuddin 2018	Ability to return to daily activities	Binary	35	24	35	19	Benefit	No other RCT reporting this instrument
Health-related Quality of Life								
Jain 2012	Quality of Life Score	Continuous	34	80.5 ± 8.2	35	68.0 ± 9.6	Benefit	No other RCT reporting this instrument

Study	Instruments	Binary or Continuous	Intervention sample size (analyzed)	Intervention effect ± SD (or number of events) [2]	Control sample size (analyzed)	Control effect ± SD (or number of events) [2]	Findings[1]	Reason for exclusion from meta-analysis
Health-related Quality of Life								
van Norden 2021	EuroQol-5D	Continuous	Not specified	Not Specified	Not specified	Not specified	No effect	No quantitative results
(1) Li 2020 (2) Xing 2023	World Health Organization Quality of Life-brief version	Continuous	243	Values provided in multiple domains	234	Values provided in multiple domains	No effect	No other RCT reporting this instrument
Acute pain Multidimensional								
Andjelkovic 2018	DN4 and Pain Detection Questionnaire	Continuous	20	Not specified	19	Not specified	No effect	No quantitative results
Chronic Pain								
van Norden 2021	Chronic Pain Intensity (VRS/NRS)	Continuous	Not specified	Not Specified	Not specified	Not specified	Not specified	No quantitative results
(1) Li 2022 (2) Zeng 2023	SF-MPQ-2	Continuous	128	1.0 ± 2.2	124	1.7 ± 2.2	Benefit	No other RCT reporting this instrument

[1] Whether the effect was a statistically significant reduction or increase
[2] Intervention ± SD for continuous outcomes. Number of events for binary outcomes

eTable 5. Characteristics of included randomized controlled trials

Study	Year	Country	Number of patients		Surgical characteristics		Anaesthaesia and Analgesia		Age		Sex (%female)	Comparator	Intervention			Patient-centred outcome	Other outcomes
			Control	Dex[1]	Surgery type	Mean Pain Intensity in Control[2]	Type of General Anaesthesia	Regional analgesia	Control	Dex[1]			Bolus dose (ug/kg)	Intra-operative Infusion dose (ug/kg/h)	Duration of Infusion (mins)[3]		
Shu, T	2022	China	40	40	Endocrine	Low (<4)	Intravenous anaesthetics	No	46.2 ± 11.5	45.6 ± 11.9	76	Placebo	0.5	0.5	84	- Quality of Recovery 15	- Post anaesthesia care unit or PACU Length of Stay (in mins) - Bradycardia requiring an intervention - Hypotension requiring an intervention - Respiratory failure
Sivaji, P	2022	India	24	24	Obstetric-gynecologic	Low (<4)	Anaesthetic gases	No	46.6 ± 5.2	45.8 ± 5.5	100	Placebo	1	0.6	Duration not specified	- Quality of Recovery 15	- None
Ge, D	2015	China	35	36	Gastro-intestinal	Moderate / High (≥4)	Intravenous anaesthetics	No	53.2 ± 1.3	52.8 ± 1.9	49	Placebo	NA	0.4	134	- Quality of Recovery - 40	- Post anaesthesia care unit or PACU Length of Stay (in mins) - Respiratory failure
Wang, W	2022	China	69	287 (4 arms)	Vascular	Not specified	Anaesthetic gases	No	57.0 ± 8.9	60.3 ± 10.8	47	Placebo	NA	0.45[b]	94	- Sleep Quality	- Hospital Length of Stay (in days) - Post anaesthesia care unit or PACU Length of Stay (in mins) - Bradycardia requiring an intervention - Hypotension

																requiring an intervention
Efe Mercanoglu, E	2022	Turkey	30	30	Gastro-intestinal	Low (<4)	Intravenous anaesthetics	No	36.4 ± 8.1	36.4 ± 7.8	55	Placebo	1	0.5	90	- Quality of Recovery 15	- None
Shan, X	2022	China	57	57	Transplant	Low (<4)	Anaesthetic gases	No	43.3 ± 10.9	43.5 ± 10.7	42	Placebo	NA	0.4	180[d]	- Barthel Index	- Hospital Length of Stay (in days) - Mortality
Li, H	2021	China	37	38	Thoracic (non-cardiac)	Low (<4)	Intravenous anaesthetics	Yes	59.8 ± 8.1	58.2 ± 7.3	33	Placebo	0.5	0.5	181	- Chronic Pain Incidences	- None
Bekker, A	2013	United States	33	33	Spinal	Not specified	Intravenous anaesthetics	No	57 ± 11.1	55.3 ± 12.3	33	Placebo	NA	0.5	211	- Quality of Recovery - 40	- None
Chen, C	2016	China	31	31	Gastro-intestinal	Low (<4)	Anaesthetic gases	No	60.2 ± 1.6	56.7 ± 2.7	52	Placebo	1	0.3	178	- Sleep Quality	- None
Zhang, L	2019	China	50	50	Thoracic (non-cardiac)	Not specified	Intravenous anaesthetics	No	58.0 ± 12	56.0 ± 11	47	Placebo	1	0.4	113	- Quality of Recovery 15	- None
Andjelkovic, L	2018	Slovenia	20	19	Gastro-intestinal	Low (<4)	Intravenous anaesthetics	No	58.0 ± 14.8	68.0 ± 18.5	51	Placebo	NA	0.5	115	- DN4 and Pain Detection Questionnaire	- Hospital Length of Stay (in days) - Delirium

Zheng, L	2020	China	40 (2 arms)	20	Gastro-intestinal	Moderate / High (≥4)	Anaesthetic gases	No	53.9 ± 8.3	57.3 ± 9.0	36	Opioid	0.8	0.45[a]	148	- Quality of Recovery - 40	- None
Bielka, K	2018	Ukraine	30	30	Gastro-intestinal	Low (<4)	Anaesthetic gases	No	56.0 ± 12.6	55.0 ± 8.9	89	Placebo	NA	0.5	Duration not specified	- Chronic Pain Incidences	- None
Kim, SY	2013	South Korea	50	50	Otorhino-laryngologic	Low (<4)	Anaesthetic gases	No	33 ± N/A	32 ± N/A	28	Placebo	NA	0.4	77	- Quality of Recovery - 40	- Post anaesthesia care unit or PACU Length of Stay (in mins) - Bradycardia requiring an intervention
Kim, SH	2013	South Korea	46	46	Mastectomy/ lumpectomy	Low (<4)	Anaesthetic gases	No	52.0 ± 9.0	53.0 ± 8.0	100	Placebo	0.5	NA	No infusion	- Quality of Recovery - 40	- Hospital Length of Stay (in days) - Post anaesthesia care unit or PACU Length of Stay (in mins) - Bradycardia requiring an intervention - Hypotension requiring an intervention
Zeeni, C	2019	Lebanon	30	30	Gastro-intestinal	Low (<4)	Anaesthetic gases	No	38.0 ± 10.4	38.0 ± 12.4	Not Specified	Opioid	1	0.5	100	- Quality of Recovery - 40	- None
Han, C	2019	China	40	40	Obstetric-gynecologic	Not specified	Intravenous anaesthetics	No	50.9 ± 7.0	52.7 ± 8.4	100	Placebo	NA	0.5	85	- Chronic Pain Incidences	- None

Khanduja, S	2014	India	30	30	Gastro-intestinal	Not specified	Anaesthetic gases	No	40.4 ± 11.1	42.2 ± 12.1	80	Placebo	0.25	0.6	Duration not specified	- Quality of Recovery: Clinical Recovery Sore	- None
Kim, J	2019	South Korea	85	84	Endocrine	Not specified	Anaesthetic gases	No	42.0 ± 9.0	43.0 ± 11.0	74	Placebo	0.5	NA	No infusion	- Quality of Recovery - 40	- Post anaesthesia care unit or PACU Length of Stay (in mins) - Bradycardia requiring an intervention - Hypotension requiring an intervention
Jain, G	2012	India	43	43	Mastectomy/ lumpectomy	Low (<4)	Anaesthetic gases	No	52.1 ± 14.0	50.8 ± 16.4	100	Placebo	1	0.5	142[d]	- Quality of Life Scale - Chronic Pain Incidences	- None
Turan, A	2020	United States	398	400	Cardiac	Not specified	Anaesthetic gases	No	62.0 ± 12.0	63.0 ± 11.0	30	Placebo	NA	0.2[a]	Duration not specified[d]	- SF-12 - Chronic Pain Incidences	- Hospital Length of Stay (in days) - Mortality - Bradycardia requiring an intervention - Hypotension requiring an intervention - Non-fatal/fatal cardiac arrest - Delirium

Sherif, A	2017	Egypt	50	50	Gastro-intestinal	Moderate / High (≥4)	Anaesthetic gases	No	39.0 ± 8	39.0 ± 9.0	81	Placebo	1	0.4	Duration not specified	- Quality of Recovery - 40	- None
Mao, Y	2020	China	31	31	Thoracic (non-cardiac)	Moderate / High (≥4)	Intravenous anaesthetics	No	63.5 ± 8.4	65.2 ± 7.3	19	Placebo	0.5	0.3[a]	168[d]	- Quality of Recovery: Surgical Recovery Score - Sleep Quality - SF-8 - Chronic Pain Incidences	- Hospital Length of Stay (in days) - Post anaesthesia care unit or PACU Length of Stay (in mins) - Time to discharge (Days) - Mortality - Delirium
Lee, S	2016	South Korea	57	54	Thoracic (non-cardiac)	Low (<4)	Anaesthetic gases	No	62 ± 11.5	62 ± 10.5	51	Placebo	1	NA	No infusion	- Quality of Recovery - 40	- None
Ge, D	2016	China	35	35	Obstetric-gynecologic	Low (<4)	Intravenous anaesthetics	No	52.6 ± 11.9	53 ± 11.2	100	Placebo	NA	0.4	115	- Quality of Recovery - 40	- Post anaesthesia care unit or PACU Length of Stay (in mins) - Respiratory failure
Jiang, M	2019	China	30	30	Plastic & reconstructive	Low (<4)	Anaesthetic gases	No	37.6 ± 11.1	37.1 ± 12.2	32	Placebo	0.5	NA	No infusion	- Quality of Recovery - 40	- Post anaesthesia care unit or PACU Length of Stay (in mins) - Respiratory failure
van Nordon, J	2021	Germany	33	30	Multiple	Not specified	Both	No	70.5 ± 6.2	70.4 ± 7.1	30	Placebo	NA	0.7[a]	409	- Sleep Quality - EuroQoL-5D - Chronic Pain - VAS/NRS (0-100)	- Hospital Length of Stay (in days) - Mortality - Delirium

Shi, H	2020	China	53	53	Thoracic (non-cardiac)	Low (<4)	Intravenous anaesthetics	Yes	68.7 ± 3.4	68.7 ± 4.6	0	Placebo	NA	0.5	180	- Sleep Quality	- None
Tufanogullari, B	2008	United States	20	60 (3 arms)	Gastro-intestinal	Low (<4)	Anaesthetic gases	No	43.0 ± 16	45.0 ± 10.2	76	Placebo	NA	0.47[b]	126	- Quality of Recovery - 9	- None
(1) Li, C (2) Xing, M	(1) 2020 (2) 2023	China	310	310	Multiple	Low (<4)	Both	No	69.0 ± 6.4	69.0 ± 6.6	60	Placebo	0.6	0.5	156	- Sleep Quality - World Health Organization Quality of Life brief	- Hospital Length of Stay (in days) - Mortality - Delirium
Shariffuddin, I	2018	Malaysia	30	30	Urologic	Moderate / High (≥4)	Anaesthetic gases	No	46.3 ± 13.1	39.2 ± 11.2	27	Placebo	0.5	NA	No infusion	- Ability to return to usual activity	- None
Li, X	2017	China	143	142	Cardiac	Moderate / High (≥4)	Both	No	67.5 ± 5.3	66.4 ± 5.4	31	Placebo	0.6	0.4	170[d]	- Sleep Quality	- Hospital Length of Stay (in days) - Mortality - Bradycardia requiring an intervention - Hypotension requiring an intervention - Tachycardia requiring an intervention - Hypertension requiring an intervention - Non-fatal/fatal cardiac arrest - Delirium

Zi, J	2020	China	61	62	Cardiac	Not specified	Intravenous anaesthetics	No	66.2 ± 6.3	64.6 ± 8.2	33	Placebo	NA	0.65[c]	Duration not specified[d]	- Zung's Self Rated Anxiety Scale	- None
Liu, T	2022	China	60	60	Oral-maxillofacial	Low (<4)	Intravenous anaesthetics	No	72.1 ± 5.9	71.3 ± 6.7	50	Placebo	0.5	0.4	160	- Sleep Quality	- Hospital Length of Stay (in days) - Respiratory failure - Delirium
Yu, P	2022	China	32	32	Otorhino-laryngologic	Low (<4)	Intravenous anaesthetics	No	39.7 ± 2.2	40.3 ± 1.9	50	Usual Care	0.5	NA	No infusion	- Quality of Recovery - 40	- None
Wang, F	2022	China	63	62	Urologic	Not specified	Intravenous anaesthetics	No	66.7 ± 4.1	65.6 ± 3.4	43	Placebo	NA	0.4	64	- Zung's Self-Rated Depression Scale - State-Trait Anxiety Inventory	- None
(1) Rekatsina, M (2) Rekatsina, M	(1) 2021 (2) 2022	Greece	30	31	Obstetric-gynecologic	Moderate / High (≥4)	Anaesthetic gases	No	49.8 ± 10.1	45.2 ± 7.2	100	Placebo	0.6	0.6	112	- Sleep Quality NRS (0-10) - Chronic Pain - VAS/NRS (0-100)	- Time to discharge (Days) - Bradycardia requiring an intervention - Hypotension requiring an intervention
Ran, J	2021	China	63	63	Thoracic (non-cardiac)	Moderate / High (≥4)	Anaesthetic gases	No	62.1 ± 7.5	59.0 ± 7.7	41	Placebo	0.5	0.5	107	- Activity of Daily Living Score	- Hospital Length of Stay (in days) - Mortality
(1) Li, S (2) Zeng, M	(1) 2022 (2) 2023	China	130	130	Neurosurgery	Moderate / High (≥4)	Both	Yes	44.0 ± 14.1	45.0 ± 12.6	48	Placebo	0.6	0.4	240	- Quality of Recovery 15 - Sleep Quality - SF-MPQ2 - Chronic	- Hospital Length of Stay (in days) - Post anaesthesia care unit or PACU

																Pain Intensity - Chronic Pain Incidences	Length of Stay (in mins) - Mortality - Delirium
Saravanaperumal, G	2022	India	33	33	Obstetric-gynecologic	Low (<4)	Intravenous anaesthetics	No	29.7 ± 2.8	30.6 ± 2.8	100	Opioid	1	NA	No infusion	- Quality of Recovery 15	- None
Ren, B	2023	China	33	33	Thoracic (non-cardiac)	Moderate / High (≥4)	Intravenous anaesthetics	No	60.7 ± 7.9	57.2 ± 10.2	50	Placebo	0.5	0.5	175[d]	- Quality of Recovery - 40	- Hospital Length of Stay (in days) - Mortality
Xu, S	2023	China	40	40	Obstetric-gynecologic	Low (<4)	Intravenous anaesthetics	No	49.6 ± 4.4	50.9 ± 5.1	100	Placebo	0.5	0.4	75	- Quality of Recovery - 40 - Sleep Quality	- None
Choi, J	2021	South Korea	45	45	Gastro-intestinal	Low (<4)	Anaesthetic gases	No	46.3 ± 11.0	41.7 ± 11.0	50	Placebo	0.5	NA	No infusion	- Quality of Recovery - 40	- None
Chen, P	2021	Taiwan	80	80	Neuro-surgery	Not specified	Intravenous anaesthetics	Yes	54.7 ± 16.3	57.3 ± 14.1	61	Placebo	NA	0.5	234	- Barthel Index	- Hospital Length of Stay (in days) - Mortality - Delirium
Hou, Y	2023	China	38	42	Thoracic (non-cardiac)	Low (<4)	Both	No	69.6 ± 5.0	70.0 ± 5.4	51	Placebo	0.5	0.5	101	- Quality of Recovery - 40	- Hospital Length of Stay (in days) - Post anaesthesia care unit or PACU Length of Stay (in mins) - Bradycardia requiring an

																	intervention - Hypotension requiring an intervention - Hypertension requiring an intervention - Respiratory failure
Yu, Y	2023	China	175	175	Trauma	Low (<4)	Intravenous anaesthetics	No	39.2 ± 10.4	41.2 ± 10.0	42	Placebo	NA	0.1	95[d]	- Sleep Quality - Beck Anxiety Inventory	- None

[1] Dex = Dexmedetomidine
[2] Pain recorded at 24 hours was prioritized
[3] When duration of infusion was not specified, mean duration of surgery was substituted as appropriate
[a] Dose of dexmedetomidine administered could be adjusted by the physician or was variable according to surgery duration (within same arm), so average doses were calculated
[b] Dose of dexmedetomidine administered varied across different arms, so average doses were calculated
[c] Dose of dexmedetomidine administered was reported as a median and IQR
[d] The infusion was continued after surgery (duration reported exclude postoperative duration)

eTable 6. Risk of bias evaluation for quality of recovery assessment

Study ID	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Shu 2022	Low	Low	Low	Low	Low	Low
Sivaji 2022	Low	Low	Low	Low	Low	Low
Ge 2015	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Efe Mercanoglu 2022	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Bekker 2013	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Zhang 2019	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Zheng 2020	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Kim 2013	Low	Low	Low	Low	Some concerns	Some concerns
Kim 2013	Low	Low	Low	Low	Low	Low
Zeeni 2019	Low	Low	Low	Low	Low	Low
Khanduja 2014	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Kim 2019	Low	Some concerns	Some concerns	Low	Low	Some concerns
Sherif 2017	Low	Low	Low	Low	High	High
Mao 2020	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Lee 2016	Low	Low	Low	Low	Low	Low
Ge 2016	Low	Low	High	Low	Some concerns	High
Jiang 2019	Low	Low	Low	Low	Low	Low
Tufanogullari 2008	Low	Low	Low	Low	Some concerns	Some concerns
Yu 2022	Low	Low	Low	Low	Some concerns	Some concerns
(1) Li 2022 (2) Zeng 2023	Low	Low	Low	Low	Low	Low
Saravanaperumal 2022	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Ren 2023	Low	Low	Low	Low	Low	Low
Xu 2023	Low	Low	Low	Low	Low	Low
Choi 2021	Low	Low	Low	Low	Low	Low
Hou 2023	Low	Some concerns	Low	Low	Some concerns	Some concerns

eTable 7. Risk of bias evaluation for other patient-centred outcomes assessment

Study ID	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Wang 2022	Low	Low	Low	Low	Some concerns	Some concerns
Shan 2022	Low	Low	Low	Low	Some concerns	Some concerns
Li 2021	Some concerns	Low	Low	Low	Some concerns	Some concerns
Chen 2016	High	Low	Low	Some concerns	Low	High
Andjelkovic 2018	Low	Low	Low	Low	Low	Low
Bielka 2018	Low	Low	Low	Low	Low	Low
Han 2019	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns
Jain 2012	Low	Low	Some concerns	Low	Some concerns	Some concerns
Turan 2020	Low	Low	High	Low	Some concerns	High
Mao 2020	Low	Some concerns	Some concerns	Low	Low	Some concerns
Shi 2020	Low	Low	Low	Low	Some concerns	Some concerns
(1) Li 2020 (2) Xing 2023	Low	Low	Low	Low	Low	Low
Shariffuddin 2018	Low	Low	Low	Low	Some concerns	Some concerns
Li 2017	Low	Low	Some concerns	Low	Low	Some concerns
Zi 2020	Low	Low	Low	Low	Low	Low
Liu 2022	Low	Low	Low	Low	Some concerns	Some concerns
Wang 2022	Low	Low	Low	Low	Low	Low
(1) Rekatsina 2021 (2) Rekatsina 2022	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Ran 2021	Some concerns	Some concerns	High	Low	Some concerns	High
(1) Li 2022 (2) Zeng 2023	Low	Low	Low	Low	Some concerns	Some concerns
Xu 2023	Low	Low	Low	Low	Some concerns	Some concerns
Chen 2021	Low	Low	Low	Low	Some concerns	Some concerns
Yu 2023	Low	Low	Some concerns	Low	Some concerns	Some concerns

eTable 8. Risk of bias evaluation for adverse events and lengths of stay assessment

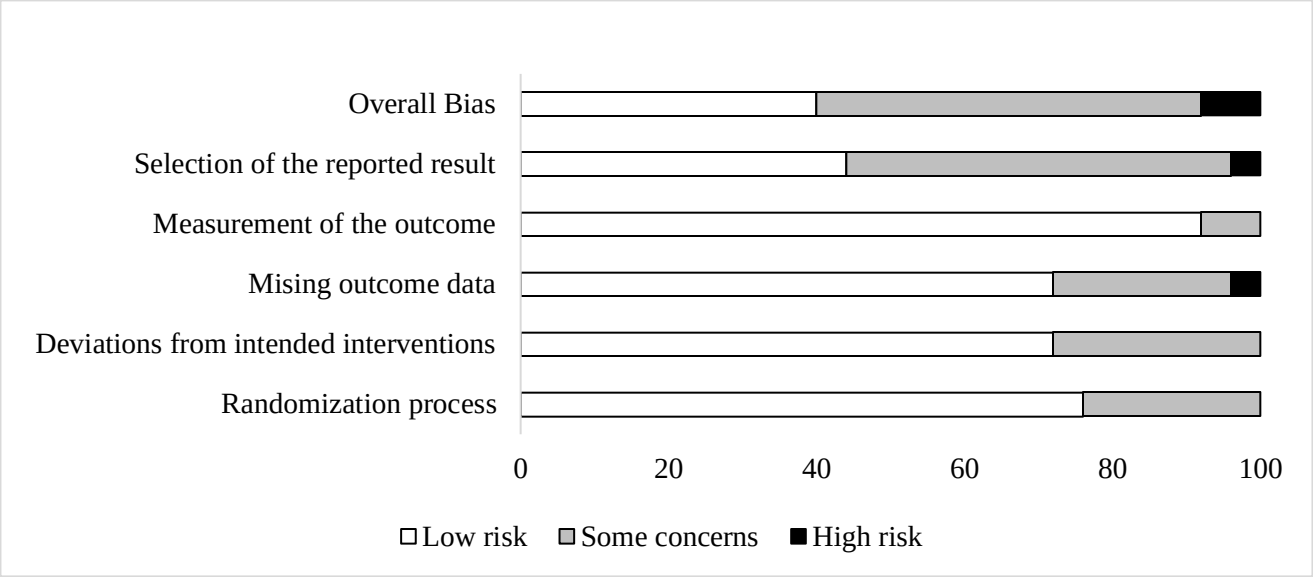
Study ID	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Shu 2022	Low	Low	Low	Low	Some concerns	Some concerns
Sivaji 2022	Low	Low	Low	Low	Some concerns	Some concerns
Ge 2015	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns
Wang 2022	Low	Low	Low	Low	Some concerns	Some concerns
Efe Mercanoglu 2022	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Shan 2022	Low	Low	Low	Low	Low	Low
Bekker 2013	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Chen 2016	High	Low	Low	Low	Low	High
Zhang 2019	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Andjelkovic 2018	Low	Low	Low	Low	Low	Low
Bielka 2018	Low	Low	Low	Low	Some concerns	Some concerns
Kim 2013	Low	Low	Low	Low	Some concerns	Some concerns
Kim 2013	Low	Low	Low	Low	Some concerns	Some concerns
Kim 2019	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Turan 2020	Low	Low	Low	Low	Some concerns	Some concerns
Sherif 2017	Low	Low	Low	Low	Some concerns	Some concerns
Mao 2020	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Lee 2016	Low	Low	Low	Low	Some concerns	Some concerns
Ge 2016	Low	Low	High	Low	Some concerns	High
Jiang 2019	Low	Low	Low	Low	Some concerns	Some concerns
van Norden 2021	Low	Low	Low	Low	Some concerns	Some concerns
Shi 2020	Low	Low	Low	Low	Some concerns	Some concerns
Tufanogullari 2008	Low	Low	Low	Low	Some concerns	Some concerns
(1) Li 2020 (2) Xing 2023	Low	Low	Low	Low	Low	Low
Li 2017	Low	Low	Some concerns	Low	Low	Some concerns
Zi 2020	Low	Low	Low	Low	Some concerns	Some concerns
Liu 2022	Low	Low	Low	Low	Low	Low
Yu 2022	Low	Low	Low	Low	Some concerns	Some concerns

Study ID	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Wang 2022	Low	Low	Low	Low	Some concerns	Some concerns
(1) Rekatsina 2021 (2) Rekatsina 2022	Low	High	Low	Low	Some concerns	High
Ran 2021	Some concerns	Some concerns	High	Low	Some concerns	High
Li 2022 Zeng 2023	Low	Low	Low	Low	Low	Low
Ren 2023	Low	Low	Low	Low	Low	Low
Xu 2023	Low	Low	Low	Low	Low	Low
Chen 2021	Low	Low	Low	Low	Some concerns	Some concerns
Hou 2023	Low	Some concerns	Low	Low	Some concerns	Some concerns
Yu 2023	Low	Low	Some concerns	Low	High	High

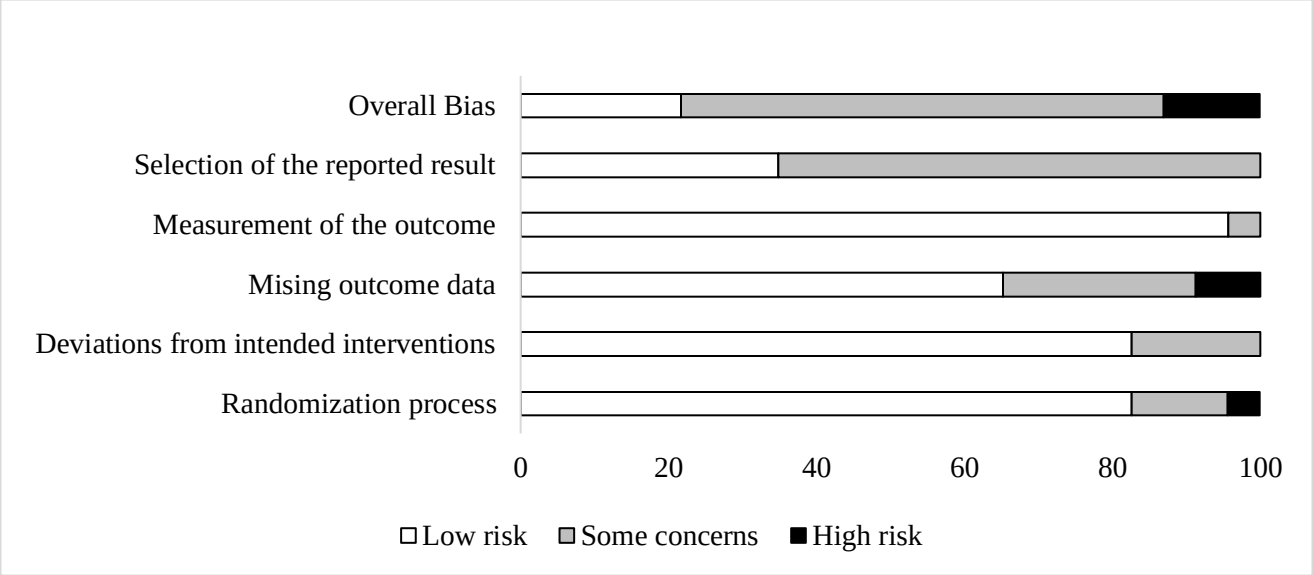
eTable 9. Sensitivity analyses to compare the impact of priors on effect estimate

Outcome measure	**Effect estimate**	
	Weak prior	**Non-informative_prior**
Quality of recovery	0.83	0.86
Health related quality of life	0.05	0.07
Chronic pain	0.42	0.34
Mortality	0.70	0.65
Delirium	0.62	0.59
Respiratory failure	1.14	1.02
Hypotension	1.98	1.99
Bradycardia	1.74	1.81
Hypertension	0.81	0.65
Tachycardia	0.80	0.71
Sleep NRS	-0.61	-0.66
PACU length of stay	0.69	0.81
Hospital length of stay	-0.18	-0.18

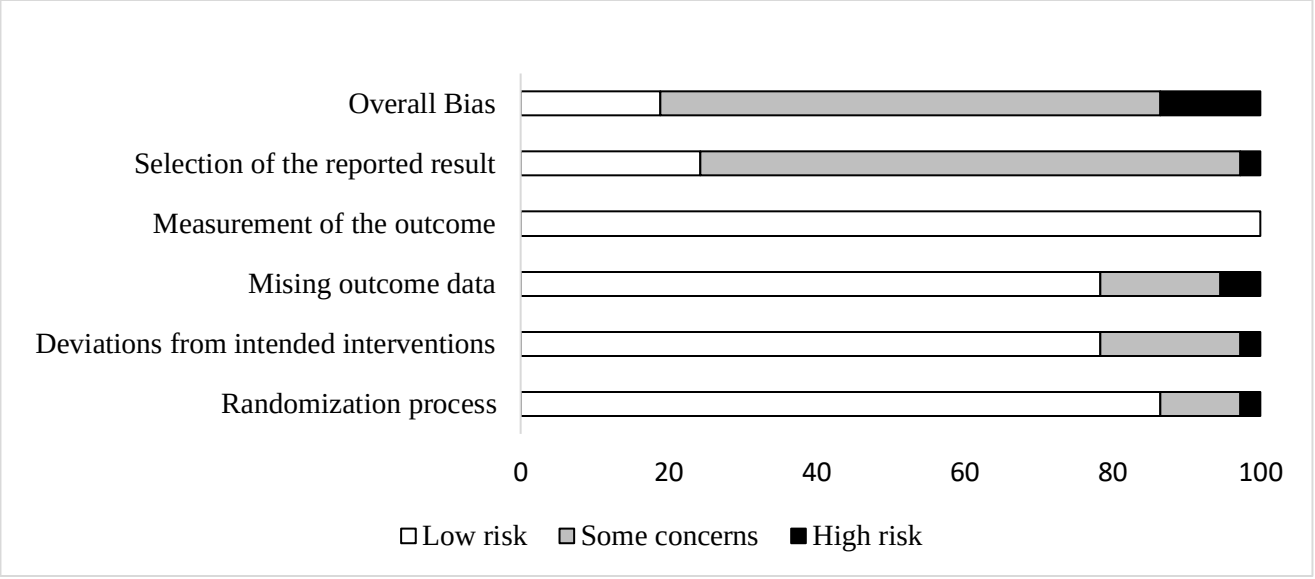
eFigure 1. Summary of the risk of bias assessments of included randomized controlled trials for quality of recovery assessment



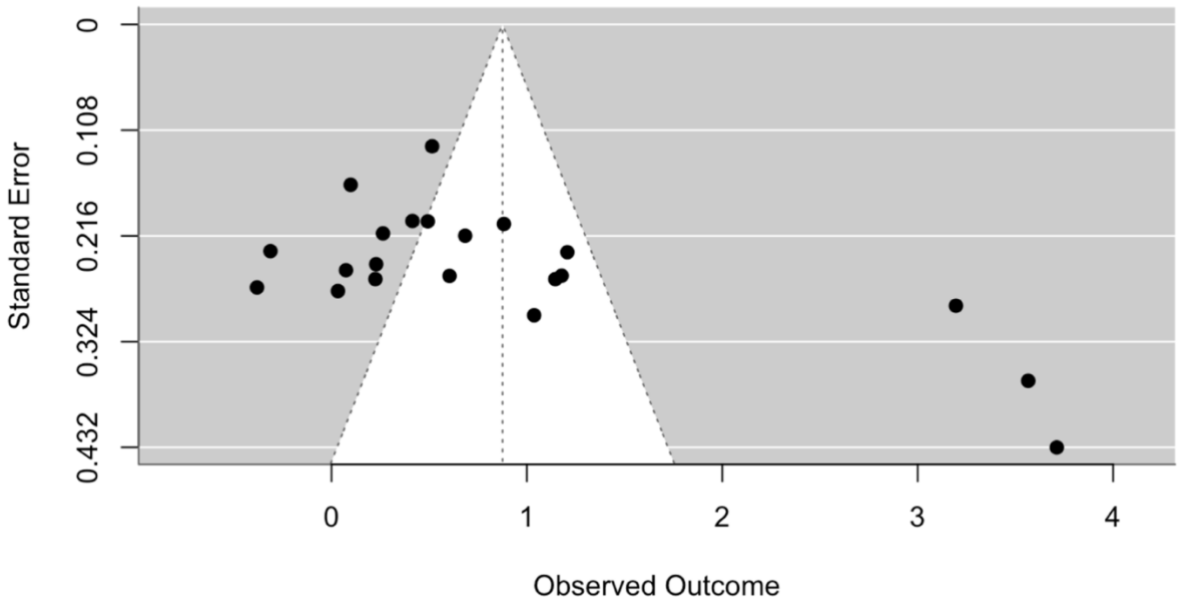
eFigure 2. Summary of the risk of bias assessments of included randomized controlled trials for other patient-centred outcomes assessment



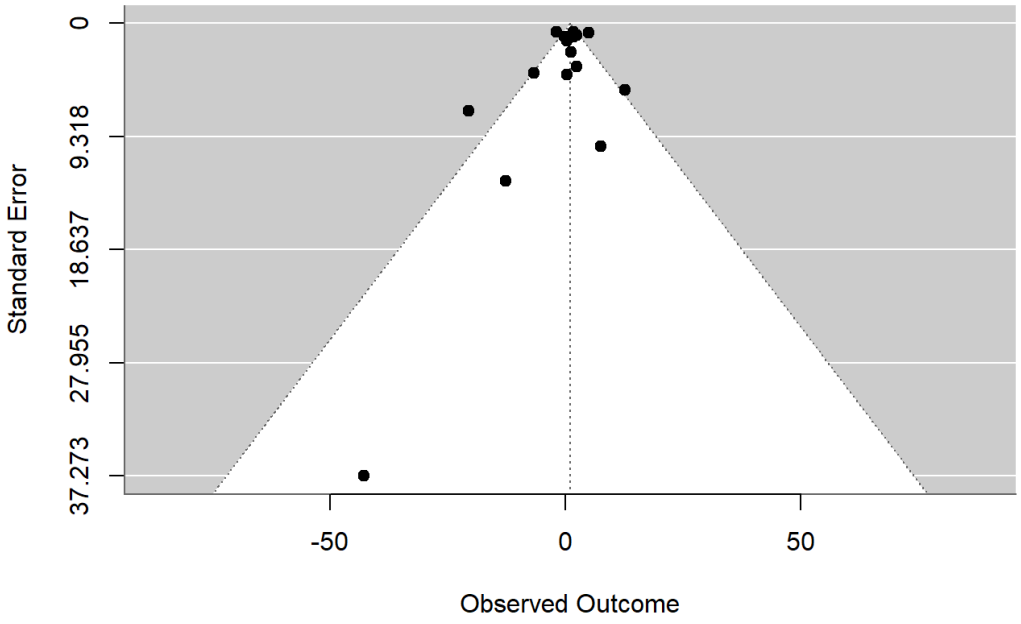
eFigure 3. Summary of the risk of bias assessments of included randomized controlled trials for other outcomes (adverse events and lengths of stay)


Overall Bias
Selection of the reported result
Measurement of the outcome
Mising outcome data
Deviations from intended interventions
Randomization process
0
20
40
60
80
100
Low risk
Some concerns
High risk

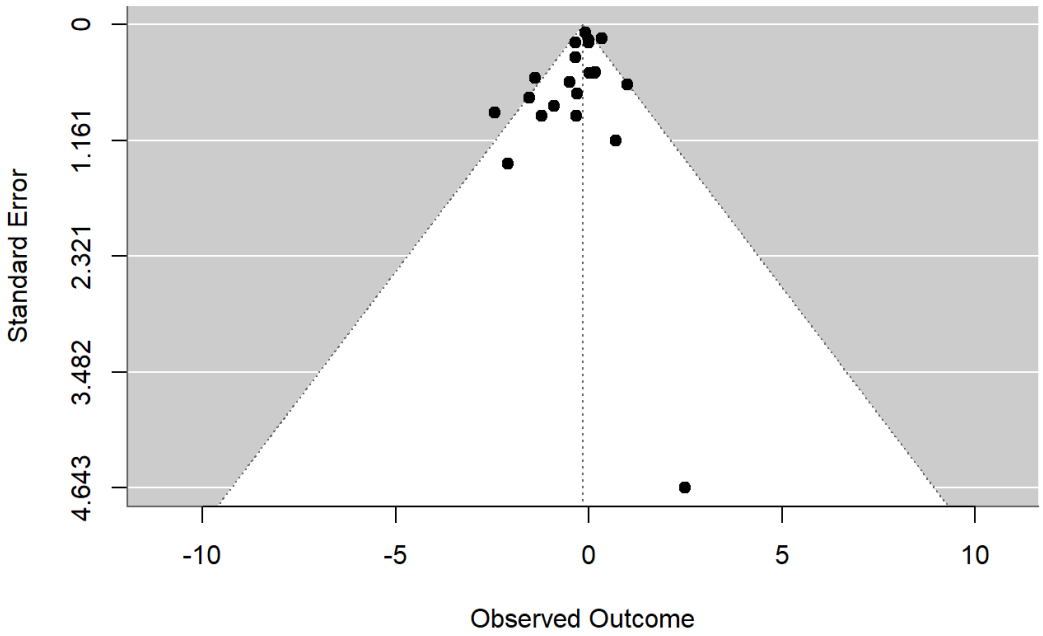
eFigure 4. Funnel plot for Quality of Recovery



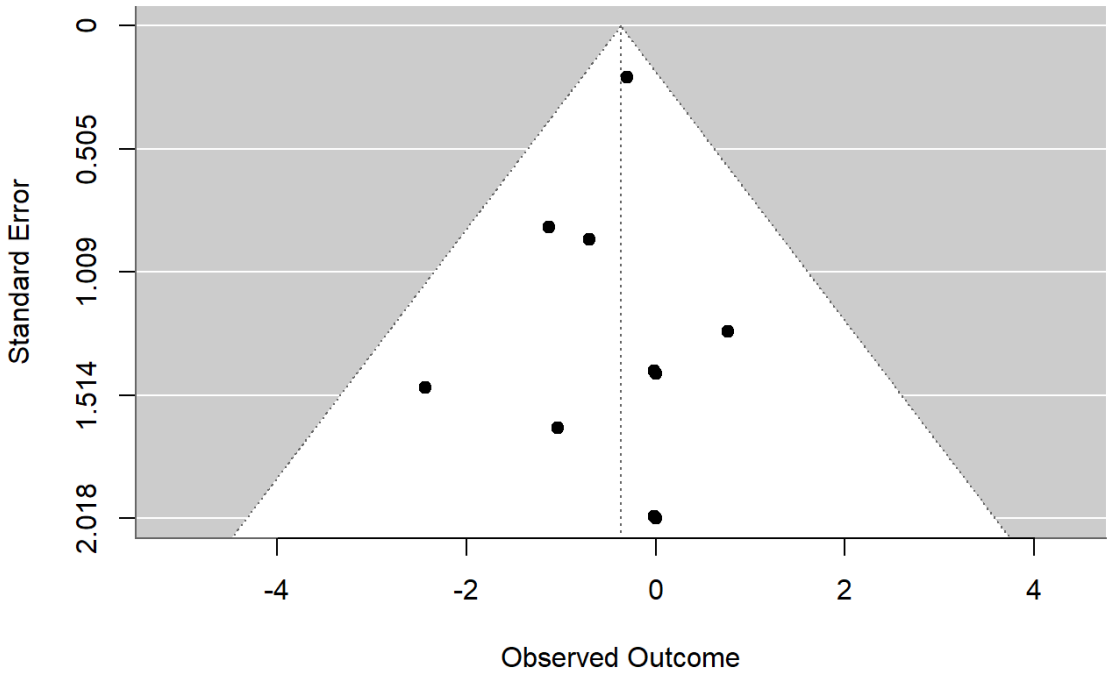
eFigure 5. Funnel plot for post anesthesia care unit length of stay



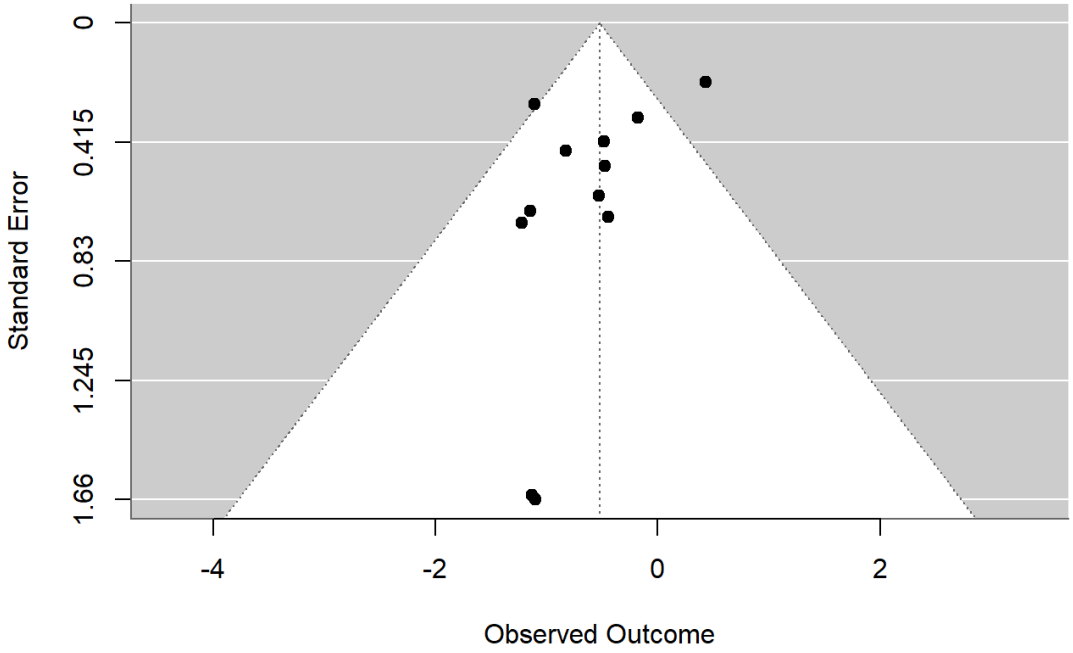
eFigure 6. Funnel plot for hospital length of stay



eFigure 7. Funnel plot for mortality



eFigure 8. Funnel plot for delirium



Appendix 1. Search strategy

MEDLINE/Ovid

1	exp Surgical Procedures, Operative/
2	su.fs. or (surger* or surgical*).tw,kf.
3	(curettage or debridement or electrosurger* or fasciotom* or Keratectom* or laparotom* or lymph node excision or mastectom* or metastasectom* or microsurger* or myotom* or neurosurgical procedure* or orthopedic procedure* or amputation or Osteotom* or pelvic exenteration or pneumonectom* or prosthesis implantation or reoperation or splenectom* or symphysiotom* or transplantation).tw,kf.
4	or/1-3
5	((opioid* or opiate*) adj3 (sparing or minimi?ation or free)).tw,kf.
6	(multimodal adj5 (an?esthes* or analges*)).tw,kf.
7	5 or 6
8	analgesics/ or exp analgesics, non-narcotic/
9	exp Adrenergic alpha-2 Receptor Agonists/
10	Caffeine/
11	exp anti-inflammatory agents/
12	exp Adrenal Cortex Hormones/
13	exp Cyclooxygenase 2 Inhibitors/
14	exp Adrenergic beta-Antagonists/
15	Receptors, N-Methyl-D-Aspartate/ai [Antagonists & Inhibitors]
16	magnesium compounds/ or magnesium sulfate/
17	exp Anticonvulsants/
18	(Lidocaine or Alpha-2 Receptor Agonist* or Caffeine or Corticosteroid* or Beta block* or NMDA receptor antagonist* or Magnesium or Acetaminophen or NSAID* or Anti-convulsant* or anticonvulsant* or Antidepressant* or gabapentinoid* or cox-2 inhibitor*).tw,kf.
19	Dexmedetomidine/ or lidocaine/ or ketamine/ or Propanolamines/ or Clonidine/
20	(Pregabalin or Gabapentin or Carbamazepine or Carbazepin or Esmolol or Propanolamine* or Metoprolol or Labetolol or Clonidine or Dexmedetomidine or Catapressan or Caffeine or Ketamine or Dextromethorphan or Dexamethasone or Methylprednisolone or hydrocortison* or Prednisone or magnesium or Amitriptyline or Duloxetine or Tryptophan or Bicifadine or Desipramine or fluoxetine or Venlafaxine or Citalopram).ti.
21	or/8-20
22	perioperative period/ or intraoperative period/ or exp Administration, Intravenous/ or Combined Modality Therapy/
23	(perioperat* or peri operat* or intra operat* or intraoperat*).tw,kf.
24	(an?esthes* adj2 induction).tw,kf.
25	or/22-24
26	21 and 25
27	7 or 26
28	4 and 27
29	randomized controlled trial.pt.

30 controlled clinical trial.pt.
31 random*.tw.
32 placebo.ab.
33 clinical trials as topic.sh.
34 trial.ti.
35 or/29-34
36 exp animals/ not humans/
37 35 not 36
38 28 and 37
39 38 use medall

Search strategy for Embase

40 exp *surgery/
41 (surg* or surgical*).tw.
42 (curettage or debridement or electrosurger* or fasciotom* or Keratectom* or laparotom* or lymph node excision or mastectom* or metastasectom* or microsurger* or myotom* or neurosurgical procedure* or orthopedic procedure* or amputation or Osteotom* or pelvic exenteration or pneumonectom* or prosthesis implantation or reoperation or splenectom* or symphysiotom* or transplantation).tw.
43 40 or 41 or 42
44 ((opioid* or opiate*) adj3 (sparing or minimi?ation or free)).tw.
45 (multimodal adj5 (an?esthes* or analges*)).tw.
46 44 or 45
47 exp *analgesic agent/
48 exp *alpha 2 adrenergic receptor stimulating agent/
49 *caffeine/
50 exp *antiinflammatory agent/
51 exp *corticosteroid/
52 exp *cyclooxygenase 2 inhibitor/
53 exp *beta adrenergic receptor blocking agent/
54 exp *n methyl dextro aspartic acid receptor stimulating agent/
55 *magnesium/
56 *magnesium sulfate/
57 exp *anticonvulsive agent/
58 (Lidocaine or Alpha-2 Receptor Agonist* or Caffeine or Corticosteroid* or Beta block* or NMDA receptor antagonist* or Magnesium or Acetaminophen or NSAID* or Anti-convulsant* or anticonvulsant* or Antidepressant* or gabapentinoid* or cox-2 inhibitor*).tw.
59 *dexmedetomidine/
60 *lidocaine/
61 *ketamine/
62 *propanolamine derivative/
63 *clonidine/
64 (Pregabalin or Gabapentin or Carbamazepine or Carbazepin or Esmolol or Propanolamine* or Metoprolol or Labetolol or Clonidine or Dexmedetomidine or Catapressan or Caffeine or Ketamine or Dextromethorphan or Dexamethasone or Methylprednisolone or hydrocortison* or Prednisone or magnesium or Amitriptyline or Duloxetine or Tryptophan or Bicifadine or Desipramine or fluoxetine or Venlafaxine or Citalopram).ti.
65 or/47-64
66 *perioperative period/
67 intraoperative period/
68 (perioperat* or peri operat* or intra operat* or intraoperat*).tw.
69 anesthesia induction/
70 *intravenous drug administration/
71 (an?esthes* adj1 induction).tw.

72 or/66-71
73 65 and 72
74 46 or 73
75 43 and 74
76 random*.tw. or placebo*.mp. or double-blind*.tw. or trial.ti.
77 75 and 76
78 (exp animal/ or nonhuman/) not exp human/
79 77 not 78
80 79 use emczd

Search strategy for CENTRAL

81 exp Surgical Procedures, Operative/
82 su.fs. or (surger* or surgical*).tw,kw.
83 (curettage or debridement or electrosurger* or fasciotom* or Keratectom* or laparotom* or lymph node excision or mastectom* or metastasectom* or microsurger* or myotom* or neurosurgical procedure* or orthopedic procedure* or amputation or Osteotom* or pelvic exenteration or pneumonectom* or prosthesis implantation or reoperation or splenectom* or symphysiotom* or transplantation).tw,kw.
84 or/81-83
85 ((opioid* or opiate*) adj3 (sparing or minimi?ation or free)).tw,kw.
86 (multimodal adj5 (an?esthes* or analges*)).tw,kw.
87 85 or 86
88 analgesics/ or exp analgesics, non-narcotic/
89 exp Adrenergic alpha-2 Receptor Agonists/
90 Caffeine/
91 exp anti-inflammatory agents/
92 exp Adrenal Cortex Hormones/
93 exp Cyclooxygenase 2 Inhibitors/
94 exp Adrenergic beta-Antagonists/
95 Receptors, N-Methyl-D-Aspartate/ai [Antagonists & Inhibitors]
96 magnesium compounds/ or magnesium sulfate/
97 exp Anticonvulsants/
98 (Lidocaine or Alpha-2 Receptor Agonist* or Caffeine or Corticosteroid* or Beta block* or NMDA receptor antagonist* or Magnesium or Acetaminophen or NSAID* or Anti-convulsant* or anticonvulsant* or Antidepressant* or gabapentinoid* or cox-2 inhibitor*).tw,kw.
99 Dexmedetomidine/ or lidocaine/ or ketamine/ or Propanolamines/ or Clonidine/
100 (Pregabalin or Gabapentin or Carbamazepine or Carbazepin or Esmolol or Propanolamine* or Metoprolol or Labetolol or Clonidine or Dexmedetomidine or Catapressan or Caffeine or Ketamine or Dextromethorphan or Dexamethasone or Methylprednisolone or hydrocortison* or Prednisone or magnesium or Amitriptyline or Duloxetine or Tryptophan or Bicifadine or Desipramine or fluoxetine or Venlafaxine or Citalopram).ti.
101 or/88-100
102 perioperative period/ or intraoperative period/ or exp Administration, Intravenous/ or Combined Modality Therapy/
103 (perioperat* or peri operat* or intra operat* or intraoperat*).tw,kw.
104 (an?esthes* adj2 induction).tw,kw.
105 or/102-104
106 101 and 105
107 87 or 106
108 84 and 107
109 108 use cctr
110 39 or 80 or 109

Search strategy for Web of science

1. (TS=(surg*)) OR TS=((curettage or debridement or electrosurger* or fasciotom* or Keratectom* or laparotom* or lymph node excision or mastectom* or metastasectom* or microsurger* or myotom* or neurosurgical procedure* or orthopedic procedure* or amputation or Osteotom* or pelvic exenteration or pneumonectom* or prosthesis implantation or reoperation or splenectom* or symphysiotom* or transplantation))
2. TS=(((opioid* or opiate*) NEAR/3 (sparing or minimi?ation or free)))
3. (TS=(multimodal NEAR/5 (an$esthes* or analges*)))
4. (#2) OR #3
5. (TS=(nonnarcotic analges*)) OR TS=(non narcotic analges*)
6. TS=((Pregabalin or Gabapentin or Carbamazepine or Carbazepin or Esmolol or Propanolamine* or Metoprolol or Labetolol or Clonidine or Dexmedetomidine or Catapressan or Caffeine or Ketamine or Dextromethorphan or Dexamethasone or Methylprednisolone or hydrocortison* or Prednisone or magnesium or Amitriptyline or Duloxetine or Tryptophan or Bicifadine or Desipramine or fluoxetine or Venlafaxine or Citalopram))
7. (TS=(Nonsteroid* anti-inflammatory)) OR TS=(Nonsteroid* antiinflammatory)
8. TS=((Lidocaine or Alpha-2 Receptor Agonist* or Caffeine or Corticosteroid* or Beta block* or NMDA receptor antagonist* or Magnesium or Acetaminophen or NSAID* or Anti-convulsant* or anticonvulsant* or Antidepressant* or gabapentinoid* or cox-2 inhibitor*))
9. (((#5) OR #6) OR #7) OR #8
10. TS=(intravenous) OR TS=(an$esthes* NEAR/2 induction)
11. ALL=(perioperat* or peri operat* or intra operat* or intraoperat*)
12. (#10) OR #11
13. (#9) AND #12
14. (#13) OR #4
15. (#1) AND #14
16. TS=((randomised OR randomized OR randomisation OR randomisation OR placebo* OR (random* AND (allocat* OR assign*)) OR (blind* AND (single OR double OR treble OR triple))))
17. TS=((animal or animals or pisces or fish or fishes or catfish or catfishes or sheatfish or silurus or arius or heteropneustes or clarias or gariepinus or fathead minnow or fathead minnows or pimephales or promelas or cichlidae or trout or trouts or char or chars or salvelinus or salmo or oncorhynchus or guppy or guppies or millionfish or poecilia or goldfish or goldfishes or carassius or auratus or mullet or mullets or mugil or curema or shark or sharks or cod or cods or gadus or morhua or carp or carps or cyprinus or carpio or killifish or eel or eels or anguilla or zander or sander or lucioperca or stizostedion or turbot or turbots or psetta or flatfish or flatfishes or plaice or pleuronectes or platessa or tilapia or tilapias or oreochromis or sarotherodon or common sole or dover sole or solea or zebrafish or zebrafishes or danio or rerio or seabass or dicentrarchus or labrax or morone or lamprey or lampreys or petromyzon or pumpkinseed or pumpkinseeds or lepomis or gibbosus or herring or clupea or harengus or amphibia or amphibian or amphibians or anura or salientia or frog or frogs or rana or toad or toads or bufo or xenopus or laevis or bombina or epidalea or calamita or salamander or salamanders or newt or newts or triturus or reptilia or reptile or reptiles or bearded dragon or pogona or vitticeps or iguana or iguanas or lizard or lizards or anguis fragilis or turtle or turtles or snakes or snake or aves or bird or birds or quail or quails or coturnix or bobwhite or colinus or virginianus or poultry or poultries

or fowl or fowls or chicken or chickens or gallus or zebra finch or taeniopygia or guttata or canary or canaries or serinus or canaria or parakeet or parakeets or grasskeet or parrot or parrots or psittacine or psittacines or shelduck or tadorna or goose or geese or branta or leucopsis or woodlark or lullula or flycatcher or ficedula or hypoleuca or dove or doves or geopelia or cuneata or duck or ducks or greylag or graylag or anser or harrier or circus pygargus or red knot or great knot or calidris or canutus or godwit or limosa or lapponica or meleagris or gallopavo or jackdaw or corvus or monedula or ruff or philomachus or pugnax or lapwing or peewit or plover or vanellus or swan or cygnus or columbianus or bewickii or gull or chroicocephalus or ridibundus or albifrons or great tit or parus or aythya or fuligula or streptopelia or risoria or spoonbill or platalea or leucorodia or blackbird or turdus or merula or blue tit or cyanistes or pigeon or pigeons or columba or pintail or anas or starling or sturnus or owl or athene noctua or pochard or ferina or cockatiel or nymphicus or hollandicus or skylark or alauda or tern or sterna or teal or crecca or oystercatcher or haematopus or ostralegus or shrew or shrews or sorex or araneus or crocidura or russula or european mole or talpa or chiroptera or bat or bats or eptesicus or serotinus or myotis or dasycneme or daubentonii or pipistrelle or pipistrellus or cat or cats or felis or catus or feline or dog or dogs or canis or canine or canines or otter or otters or lutra or badger or badgers or meles or fitchew or fitch or foumart or foulmart or ferrets or ferret or polecat or polecats or mustela or putorius or weasel or weasels or fox or foxes or vulpes or common seal or phoca or vitulina or grey seal or halichoerus or horse or horses or equus or equine or equidae or donkey or donkeys or mule or mules or pig or pigs or swine or swines or hog or hogs or boar or boars or porcine or piglet or piglets or sus or scrofa or llama or llamas or lama or glama or deer or deers or cervus or elaphus or cow or cows or bos taurus or bos indicus or bovine or bull or bulls or cattle or bison or bisons or sheep or sheeps or ovis aries or ovine or lamb or lambs or mouflon or mouflons or goat or goats or capra or caprine or chamois or rupicapra or leporidae or lagomorpha or lagomorph or rabbit or rabbits or oryctolagus or cuniculus or laprine or hares or lepus or rodentia or rodent or rodents or murinae or mouse or mice or mus or musculus or murine or woodmouse or apodemus or rat or rats or rattus or norvegicus or guinea pig or guinea pigs or cavia or porcellus or hamster or hamsters or mesocricetus or cricetulus or cricetus or gerbil or gerbils or jird or jirds or meriones or unguiculatus or jerboa or jerboas or jaculus or chinchilla or chinchillas or beaver or beavers or castor fiber or castor canadensis or sciuridae or squirrel or squirrels or sciurus or chipmunk or chipmunks or marmot or marmots or marmota or suslik or susliks or spermophilus or cynomys or cottonrat or cottonrats or sigmodon or vole or voles or microtus or myodes or glareolus or primate or primates or prosimian or prosimians or lemur or lemurs or lemuridae or loris or bush baby or bush babies or bushbaby or bushbabies or galago or galagos or anthropoidea or anthropoids or simian or simians or monkey or monkeys or marmoset or marmosets or callithrix or cebuella or tamarin or tamarins or saguinus or leontopithecus or squirrel monkey or squirrel monkeys or saimiri or night monkey or night monkeys or owl monkey or owl monkeys or douroucoulis or aotus or spider monkey or spider monkeys or ateles or baboon or baboons or papio or rhesus monkey or macaque or macaca or mulatta or cynomolgus or fascicularis or green monkey or green monkeys or chlorocebus or vervet or vervets or pygerythrus or hominoidea or ape or apes or hylobatidae or gibbon or gibbons or siamang or siamangs or nomascus or symphalangus or hominidae or orangutan or orangutans or pongo or chimpanzee or chimpanzees or pan troglodytes or bonobo or bonobos or pan paniscus or gorilla or gorillas or troglodytes))
18. (#16) NOT #17
19. (#15) AND #18

Search strategy for CINAHL

S1	(MH "Surgical Patients")
S2	(MH "Surgery, Operative+")
S3	TI ((curettage or debridement or electrosurger* or fasciotom* or Keratectom* or laparotom* or lymph node excision or mastectom* or metastasectom* or microsurger* or myotom* or neurosurgical procedure* or orthopedic procedure* or amputation or Osteotom* or pelvic exenteration or pneumonectom* or prosthesis implantation or reoperation or splenectom* or symphysiotom* or transplantation)) OR AB ((curettage or debridement or electrosurger* or fasciotom* or Keratectom* or laparotom* or lymph node excision or mastectom* or metastasectom* or microsurger* or myotom* or neurosurgical procedure* or orthopedic procedure* or amputation or Osteotom* or pelvic exenteration or pneumonectom* or prosthesis implantation or reoperation or splenectom* or symphysiotom* or transplantation))
S4	TI surger* OR AB surger* OR TI surgical* OR AB surgical*
S5	S1 OR S2 OR S3 OR S4
S6	opioid* N3 sparing OR opioid* N3 minimi* OR opioid* N3 free
S7	opiate* N3 sparing OR opiate* N3 minimi* OR opiate* N3 free
S8	multimodal N5 an*esthes OR multimodal N5 analges*
S9	S6 OR S7 OR S8
S10	(MH "Analgesics") OR (MH "Analgesics, Nonnarcotic+") OR (MH "Anesthesia Adjuvants+")
S11	(MH "Adrenergic Beta-Agonists+")
S12	(MH "Caffeine")
S13	(MH "Antiinflammatory Agents+")
S14	(MH "Adrenal Cortex Hormones+")
S15	(MH "Adrenergic Beta-Antagonists+")
S16	(MH "Magnesium Compounds+")
S17	(MH "Anticonvulsants+")
S18	(MH "Lidocaine")
S19	(MH "Ketamine")
S20	"Dexmedetomidine"

S21 (MH "Propanolamines")

S22 (MH "Clonidine")

S23 TI ((Lidocaine or Alpha-2 Receptor Agonist* or Caffeine or Corticosteroid* or Beta block* or NMDA receptor antagonist* or N-Methyl-D-aspartate receptor antagonist* or Magnesium or Acetaminophen or NSAID* or Anti-convulsant* or anticonvulsant* or Antidepressant* or gabapentinoid* or cox-2 inhibitor* or Nonsteroidal anti-inflammator*)) OR AB ((Lidocaine or Alpha-2 Receptor Agonist* or Caffeine or Corticosteroid* or Beta block* or NMDA receptor antagonist* or N-Methyl-D-aspartate receptor antagonist* or Magnesium or Acetaminophen or NSAID* or Anti-convulsant* or anticonvulsant* or Antidepressant* or gabapentinoid* or cox-2 inhibitor* or Nonsteroidal anti-inflammator*))

S24 TI (Pregabalin or Gabapentin or Carbamazepine or Carbazepin or Esmolol or Propanolamine* or Metoprolol or Labetolol or Clonidine or Dexmedetomidine or Catapressan or Caffeine or Ketamine or Dextromethorphan or Dexamethasone or Methylprednisolone or hydrocortison* or Prednisone or magnesium or Amitriptyline or Duloxetine or Tryptophan or Bicifadine or Desipramine or fluoxetine or Venlafaxine or Citalopram)

S25 S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24

S26 (MH "Intraoperative Period")

S27 (MH "Administration, Intravenous")

S28 (MH "Combined Modality Therapy")

S29 TI ((perioperat* or peri operat* or intra operat* or intraoperat*)) OR AB ((perioperat* or peri operat* or intra operat* or intraoperat*))

S30 TI an*esthes* N2 induction OR AB an?esthes* N2 induction

S31 (MH "Anesthesia Induction")

S32 S26 OR S27 OR S28 OR S29 OR S30 OR S31

S33 S25 AND S32

S34 S9 OR S33

S35 S5 AND S34

S36 (MH "Randomized Controlled Trials+") OR (MH "Double-Blind Studies") OR (MH "Triple-Blind Studies") OR (MH "Clinical Trials")

S37 TI random* OR AB random* OR TI placebo OR AB placebo OR TI trial

S38 (control W5 group)

S39 (MH "Random Assignment")

S40 S36 OR S37 OR S38 OR S39

S41 S35 AND S40

S42 (MH "Animals+")

S43 (MH "Animal Studies")

S44 TI animal model*

S45 S42 OR S43 OR S44

S46 (MH "Human")

S47 S45 NOT S46

S48 S41 NOT S47

S49 S41 NOT S47

Appendix 2. Model specifications

$$y_i \sim Normal(\theta_i, \sigma_i^2) \quad \text{(Likelihood)}$$
$$\theta_i \sim Normal(\mu, \tau^2)$$
$$\mu = \beta_0 + \beta_{subgroup[k]} \quad \text{(for subgroup analysis)}$$

$$\mu \sim \text{Normal}(0, 1) \quad \text{(Weakly informative prior)}$$
$$\tau \sim \text{Half-Cauchy}(0, 0.5)$$

$$\mu \sim \text{Students t}(3, 0, 2.5) \quad \text{(Non-informative prior)}$$
$$\tau \sim \text{Half-t}(3, 0, 2.5)$$

$$\beta \sim \text{Flat Prior} \quad \text{(Subgroup prior)}$$

Formula for continuous outcomes: SMDcohen | se(seSMD) ~ 1 + (1 | Study)

Formula for dichotomous outcomes: = LnES| se(seTE) ~ 1 + (1 | Study)

Formula for outcomes on their original scale: Effect_size| se(seES) ~ 1 + (1 | Study)

Formulas for univariable meta-regression:
Risk of bias = SMDcohen | se(seSMD) ~ 1 + RoB + (1 | Study)

Type of surgery (at risk high risk of pain vs. not) = SMDcohen | se(seSMD) ~ 1 + high_risk + (1 | Study)

Type of administration (bolus vs. bolus and infusion) = SMDcohen | se(seSMD) ~ 1 + administration + (1 | Study)

Pain intensity in control group = SMDcohen | se(seSMD) ~ 1 + Apain_control + (1 | Study)
Type of population (geriatric population vs. not) = SMDcohen | se(seSMD) ~ 1 + only_geriatric+ (1 | Study)

Type of funding= SMDcohen | se(seSMD) ~ 1 + funding + (1 | Study)

Timing of administration = SMDcohen | se(seSMD) ~ 1 + timing_intervention + (1 | Study)

Bolus dose = SMDcohen | se(seSMD) ~ 1 + bolus_dose_c_numeric + (1 | Study)

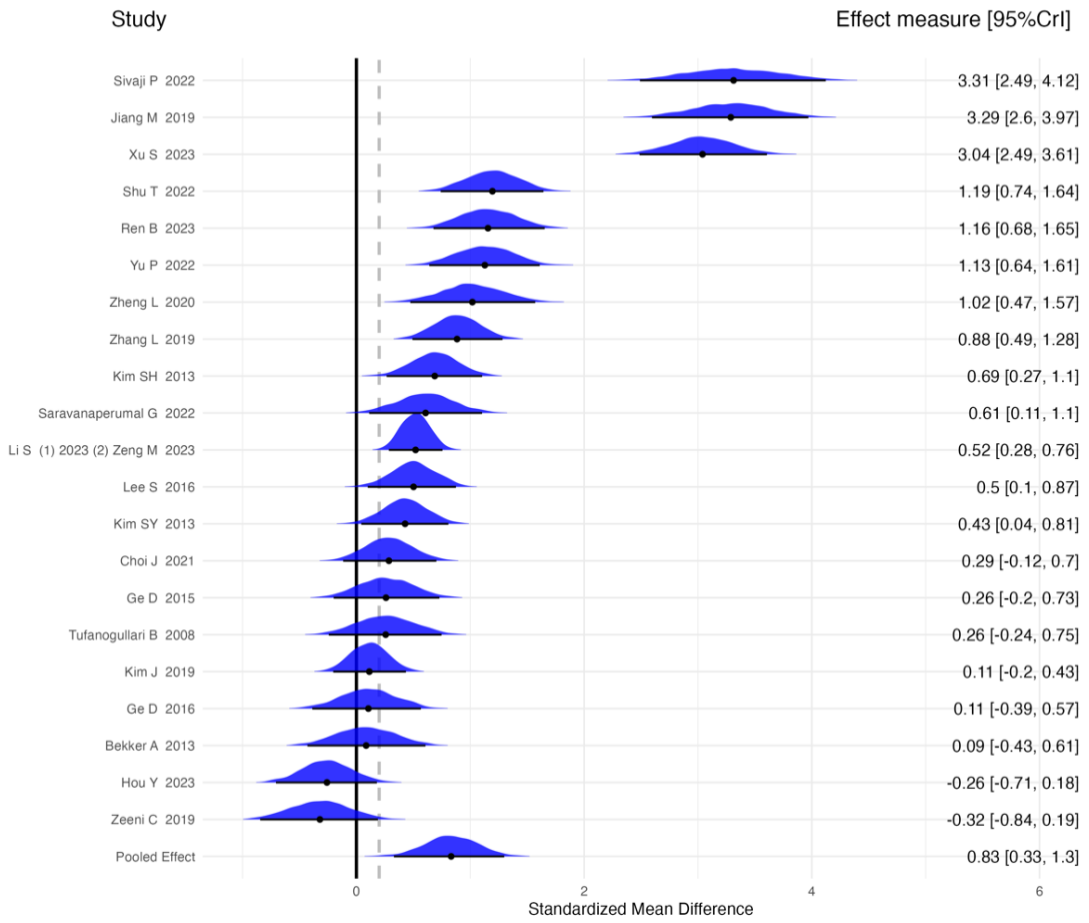
Infusion dose = SMDcohen | se(seSMD) ~ 1 + infusion_dose_c_numeric + (1 | Study)

Duration of infusion = SMDcohen | se(seSMD) ~ 1 + total_duration + (1 | Study)

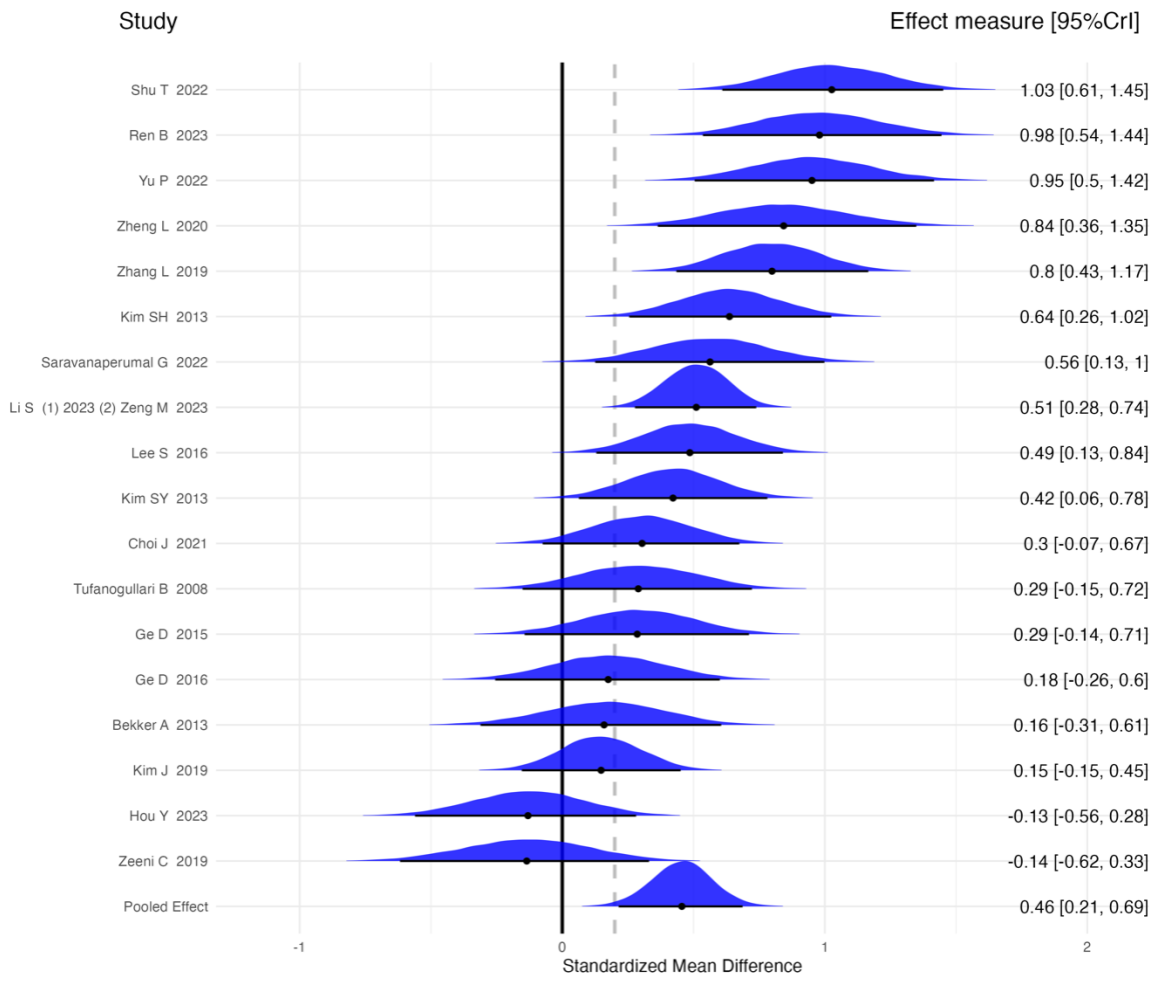
Patient with chronic opioid use = SMDcohen | se(seSMD) ~ 1 + chronic_opioid_use + (1 | Study)

Patient with baseline chronic pain = SMDcohen | se(seSMD) ~ 1 + chronic_pain + (1 | Study)

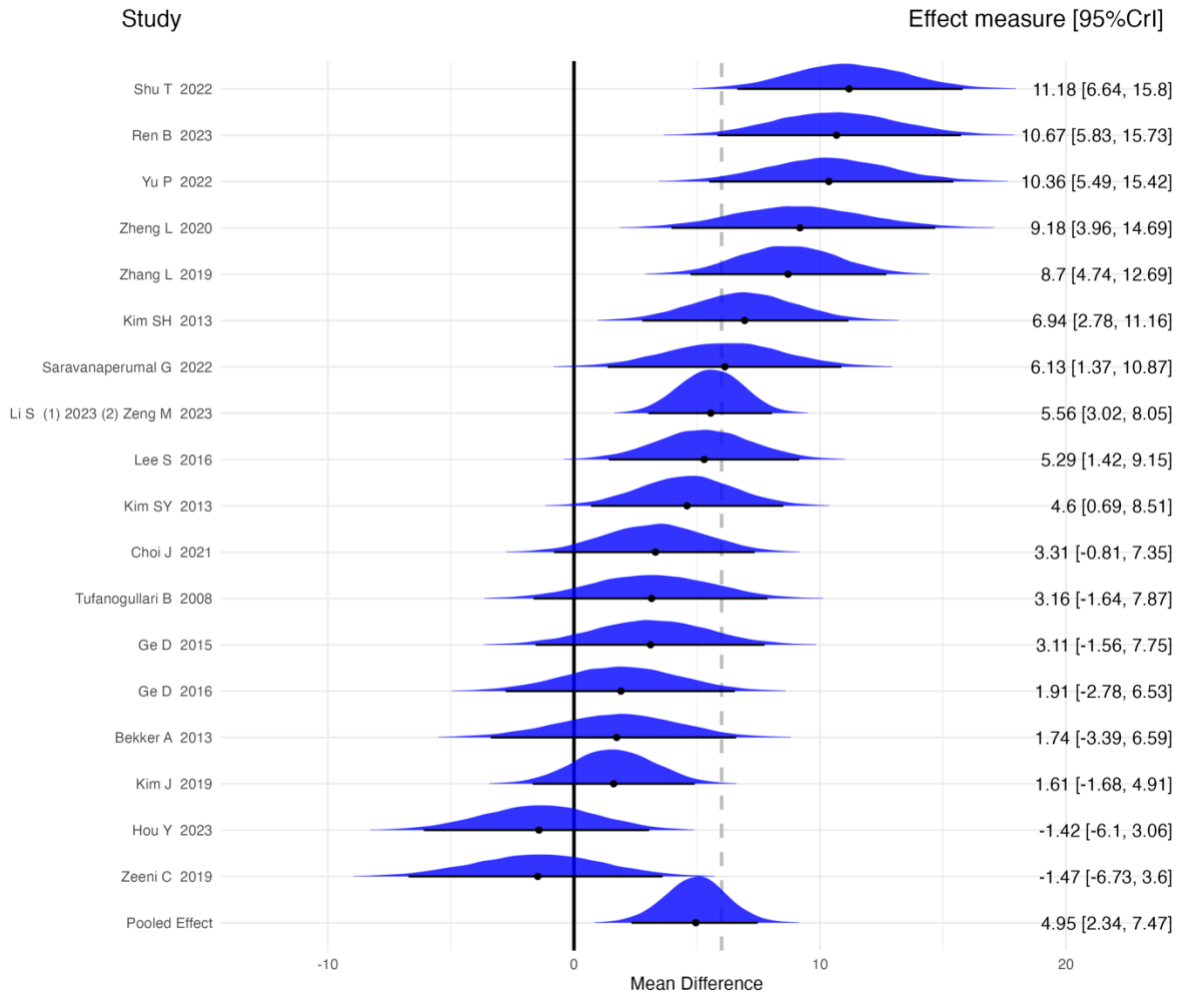
Appendix 3. Forest plots for all outcome measures



Forest plot for Quality of Recovery outcome measure (Standardized mean difference)
Black vertical line indicates null value (standardized mean difference = 0), grey dashed vertical line indicates the threshold for minimally important difference. A value above zero (right direction) favors dexmedetomidine. A value below zero (left direction) favors control.

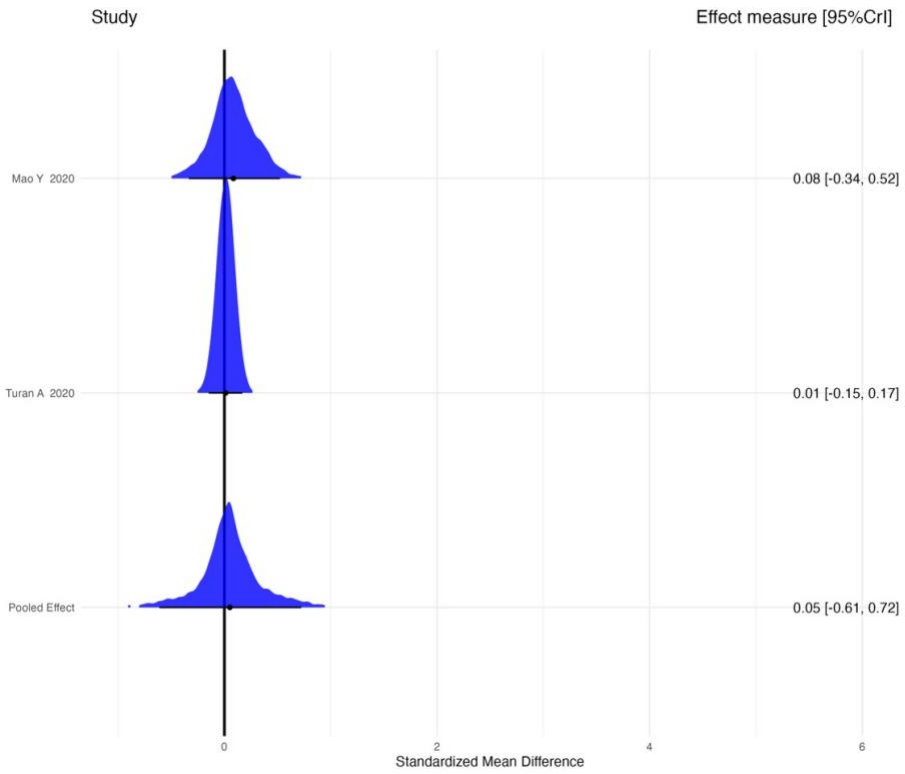


Sensitivity analysis (exclusion of extreme values): Forest plot for Quality of Recovery outcome measure (Standardized mean difference)
Black vertical line indicates null value (standardized mean difference = 0), grey dashed vertical line indicates the threshold for minimally important difference. A value above zero (right direction) favors dexmedetomidine. A value below zero (left direction) favors control.

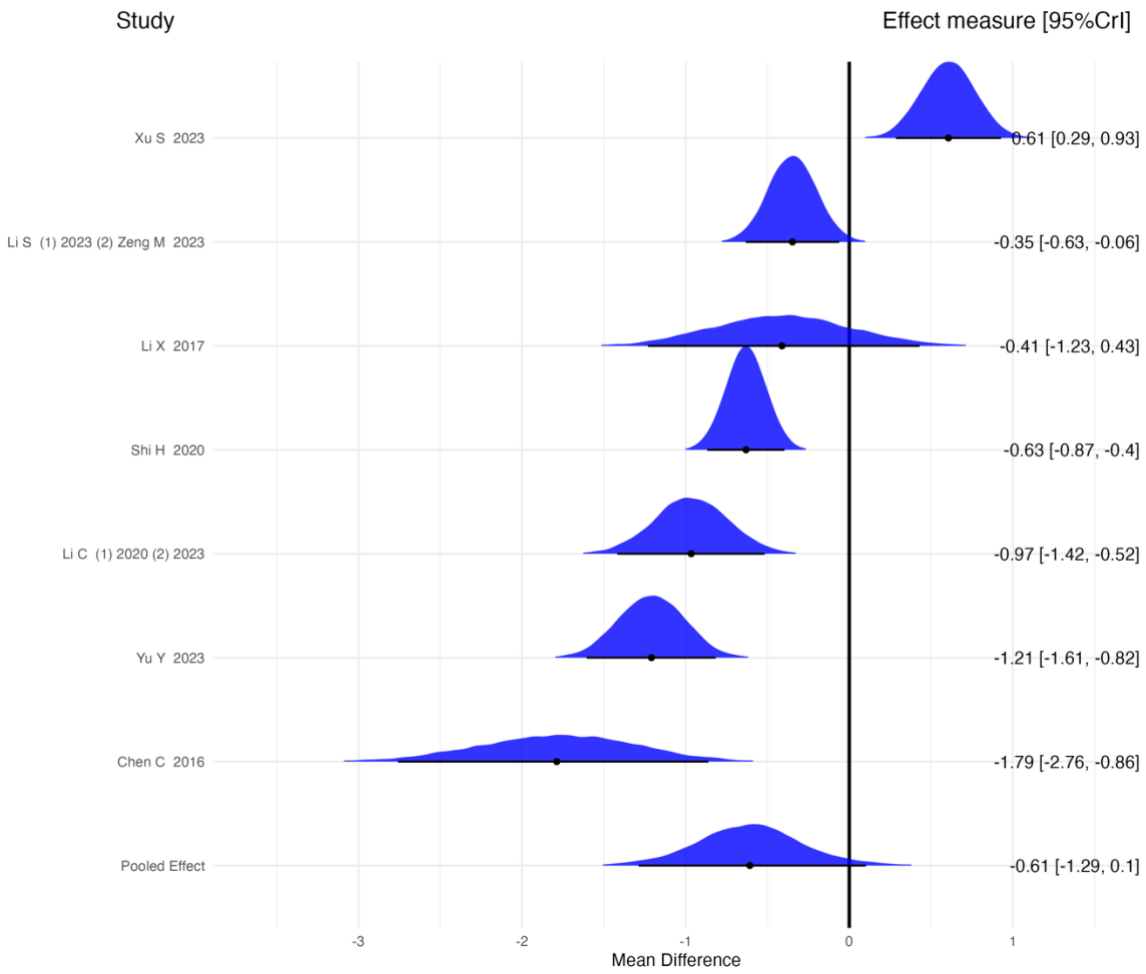


Sensitivity analysis (exclusion of extreme values): Forest plot for Quality of Recovery outcome measure (original scale)

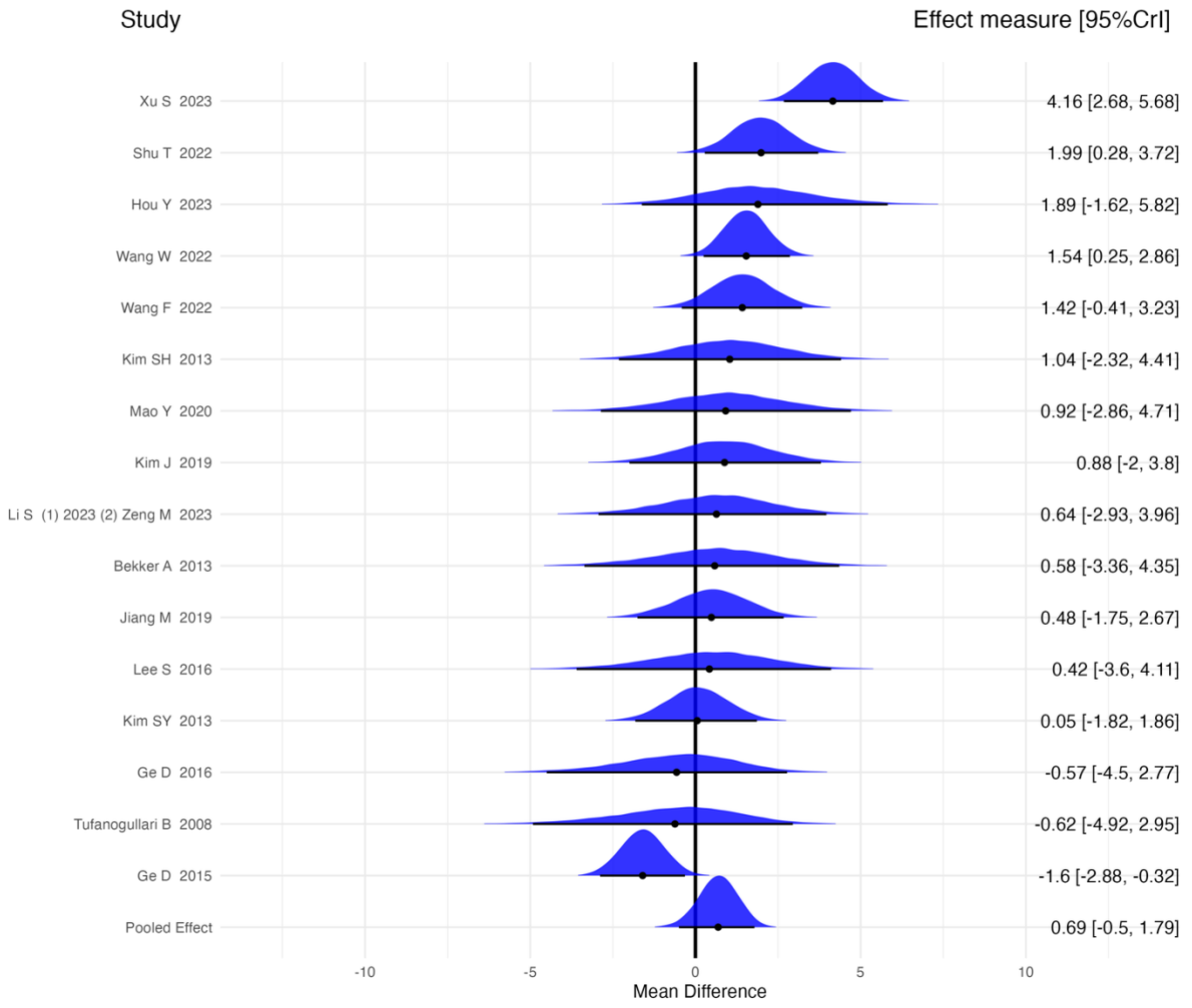
Black vertical line indicates null value (mean difference = 0), grey dashed vertical line indicates the threshold for minimally important difference. A value above zero (right direction) favors dexmedetomidine. A value below zero (left direction) favors control.



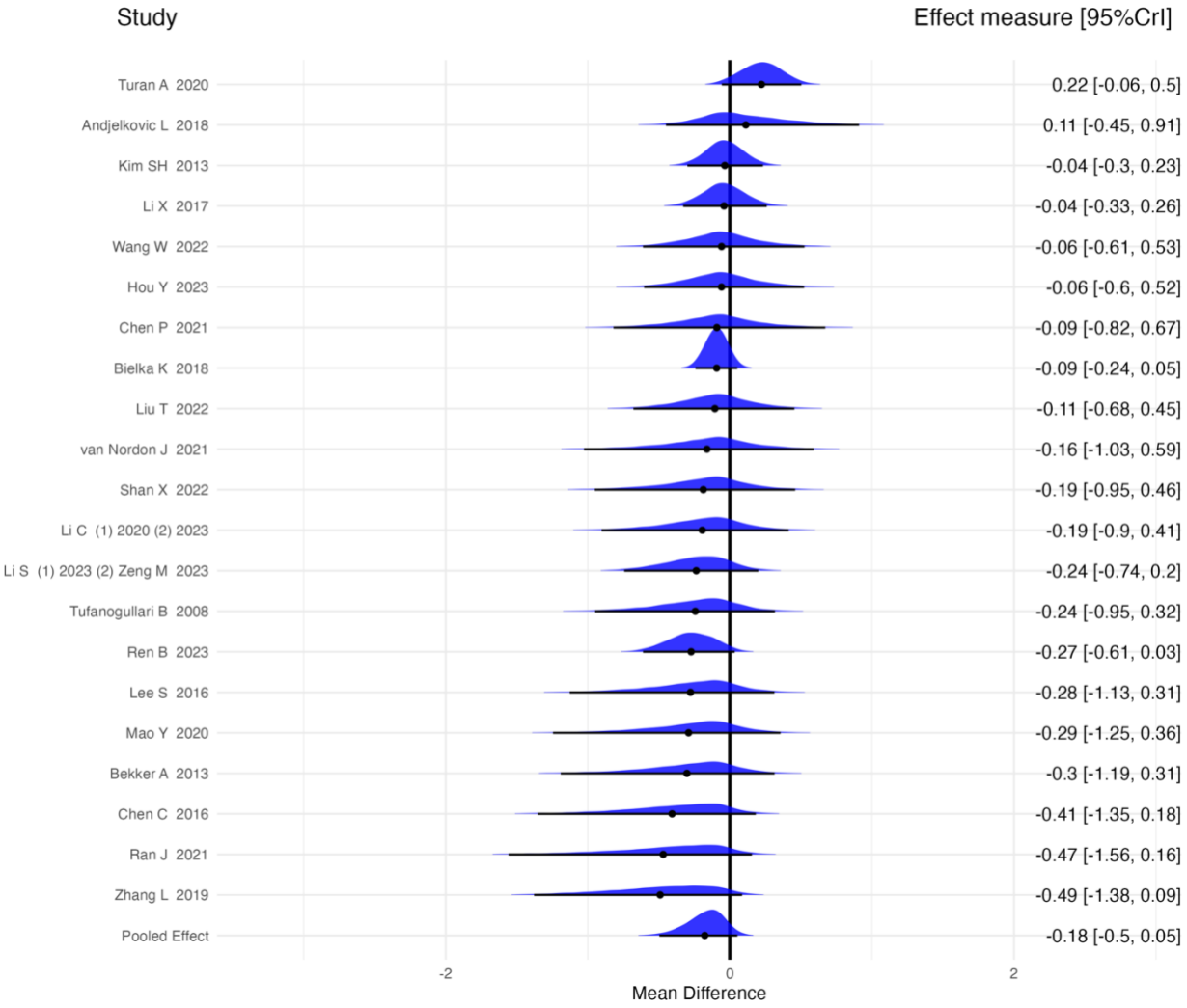
Forest plot for health-related quality of life assessed with Short Form-8 (SF-8) and SF-12
Black vertical line indicates null value (standardized mean difference = 0). A value above zero (right direction) favors dexmedetomidine. A value below zero (left direction) favors control.



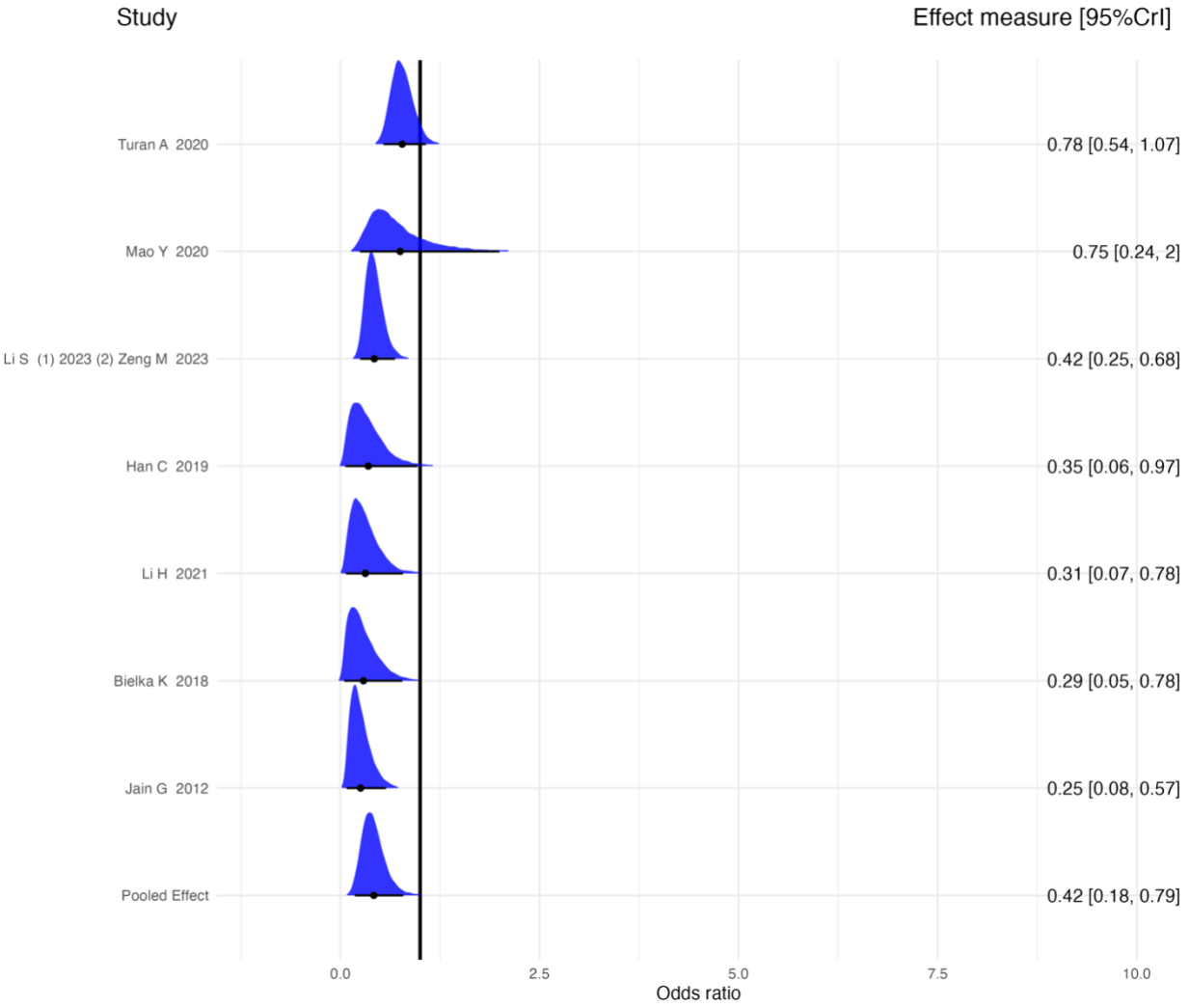
Forest plot for sleep quality (NRS) assessment
Black vertical line indicates null value (mean difference = 0). A value above zero (right direction) favors dexmedetomidine. A value below zero (left direction) favors control.



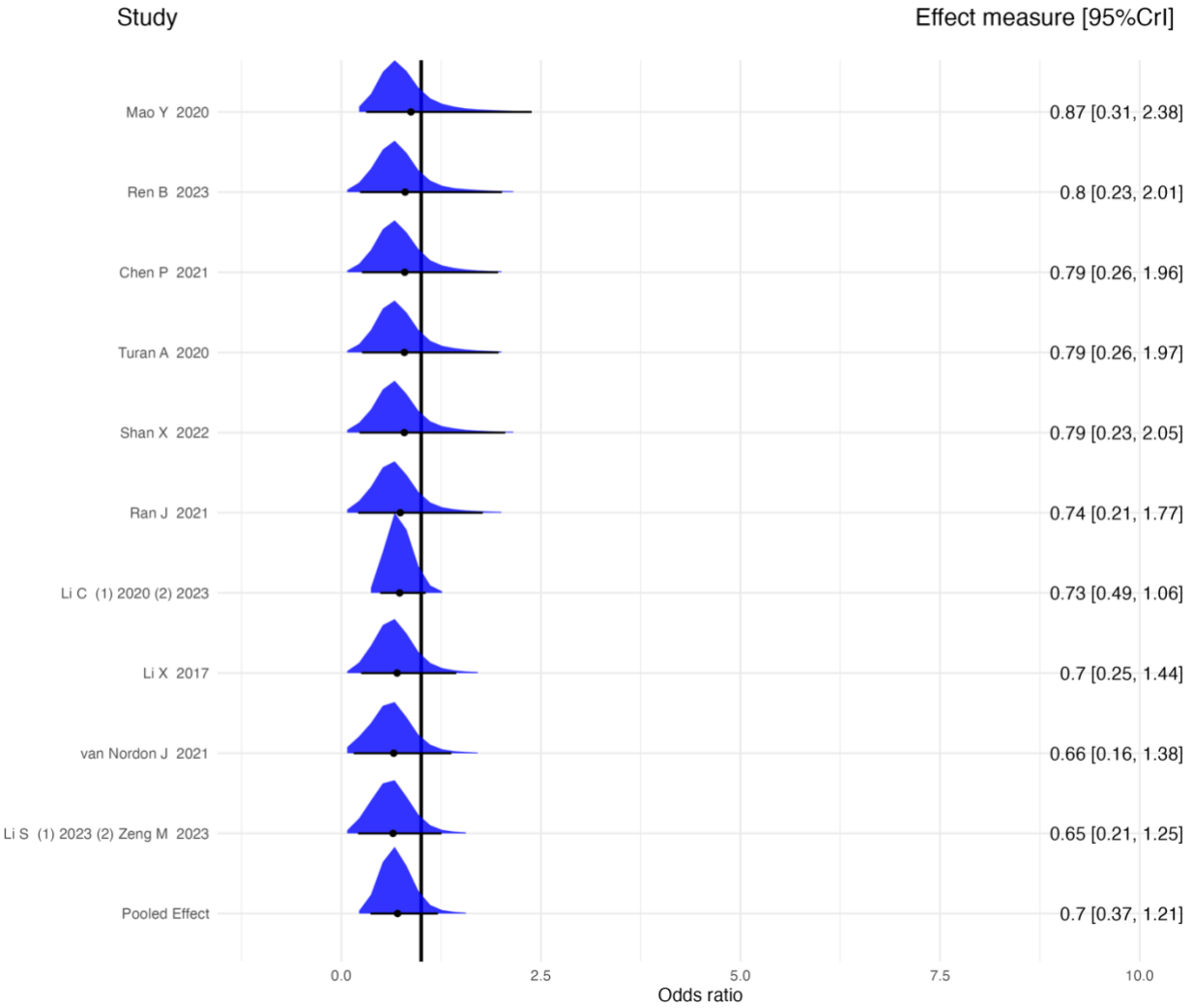
Forest plot for post anesthesia care unit (PACU) length of stay duration (minutes) assessment Black vertical line indicates null value (mean difference = 0). A value above zero (right direction) favors dexmedetomidine. A value below zero (left direction) favors control.



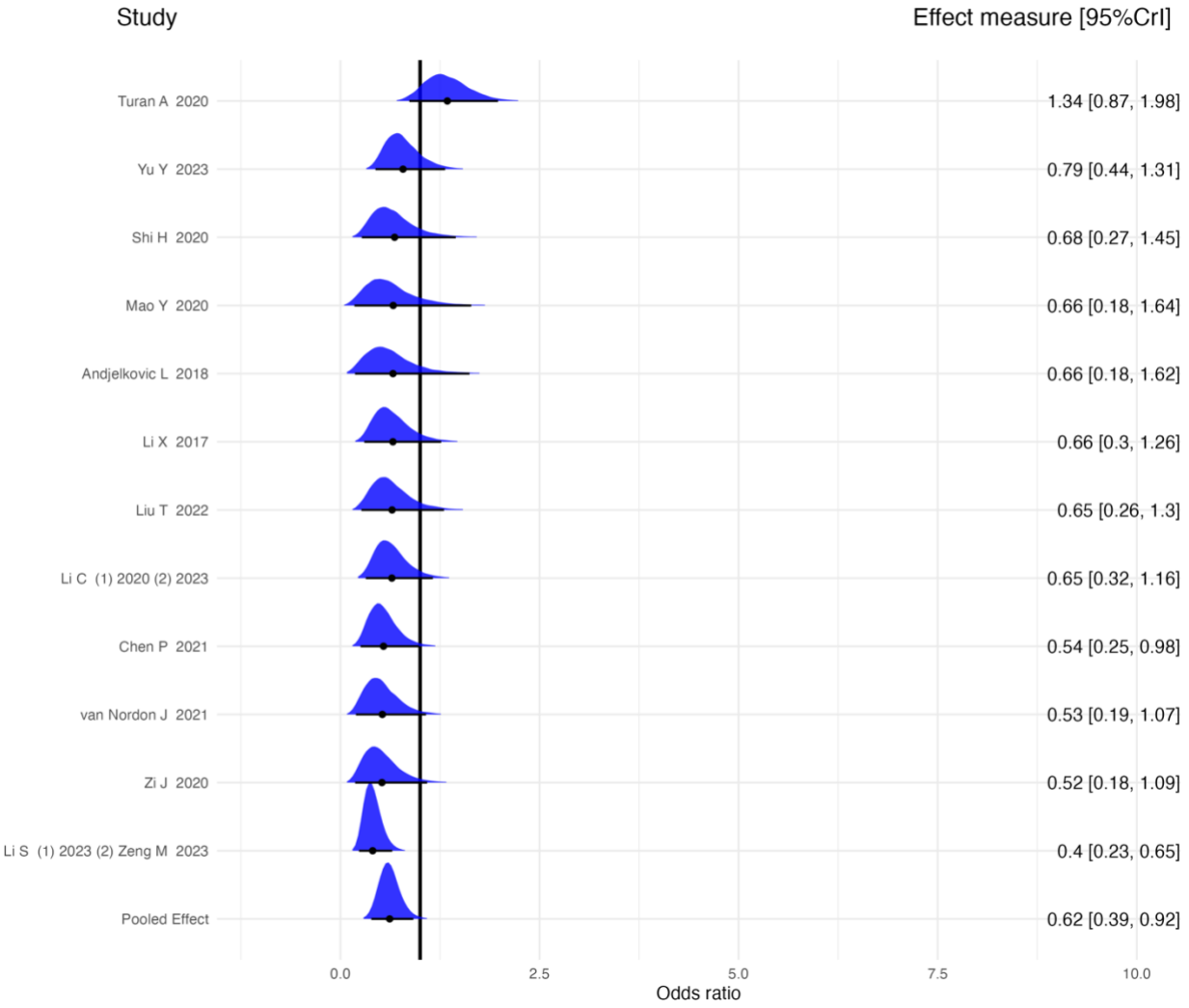
Forest plot for hospital length of stay duration (days) assessment
Black vertical line indicates null value (mean difference = 0). A value above zero (right direction) favors dexmedetomidine. A value below zero (left direction) favors control.



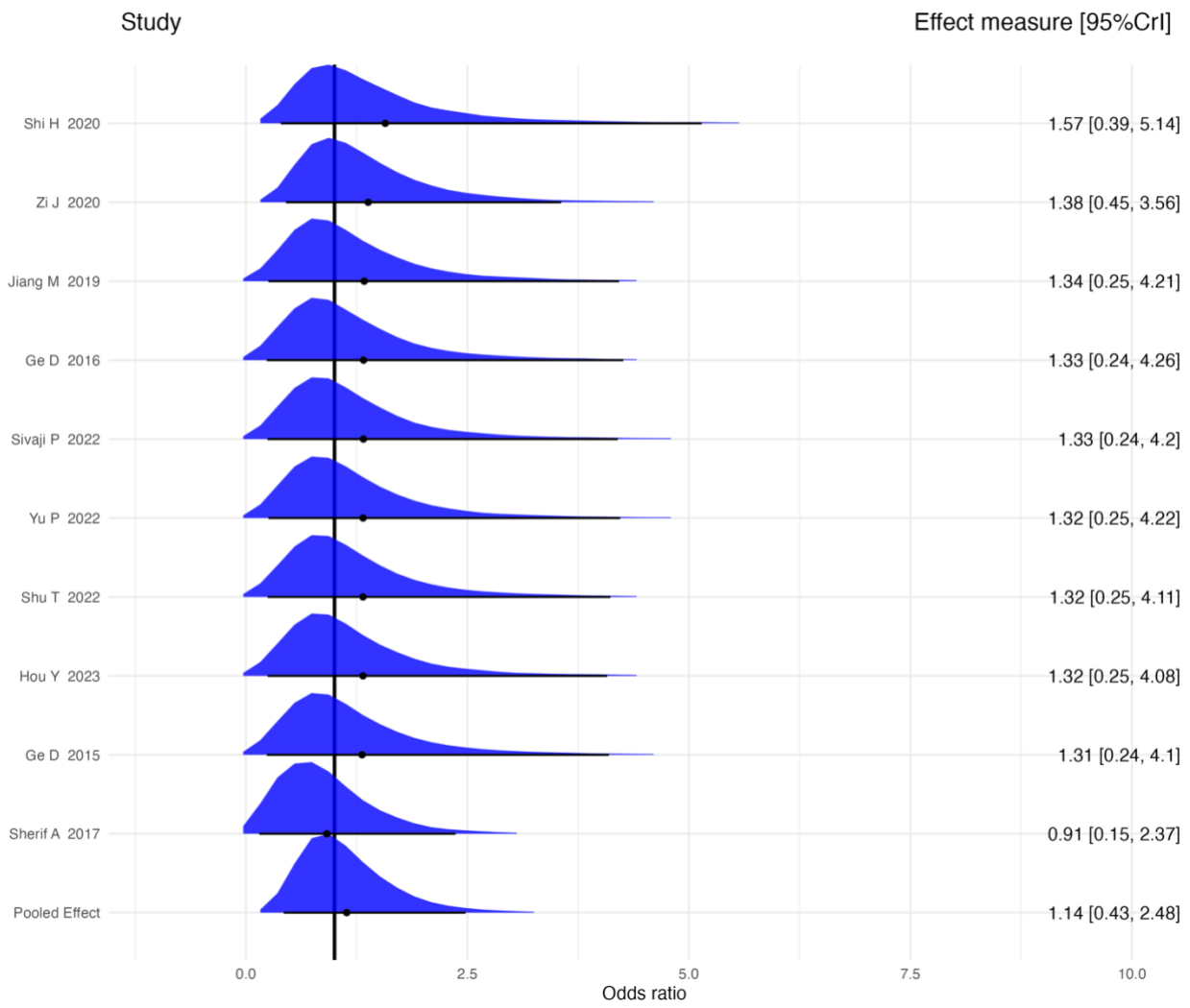
Forest plot for chronic pain incidence assessment
Black vertical line indicates null value (odds ratio = 1). A value above one (right direction) favors dexmedetomidine. A value below one (left direction) favors control.



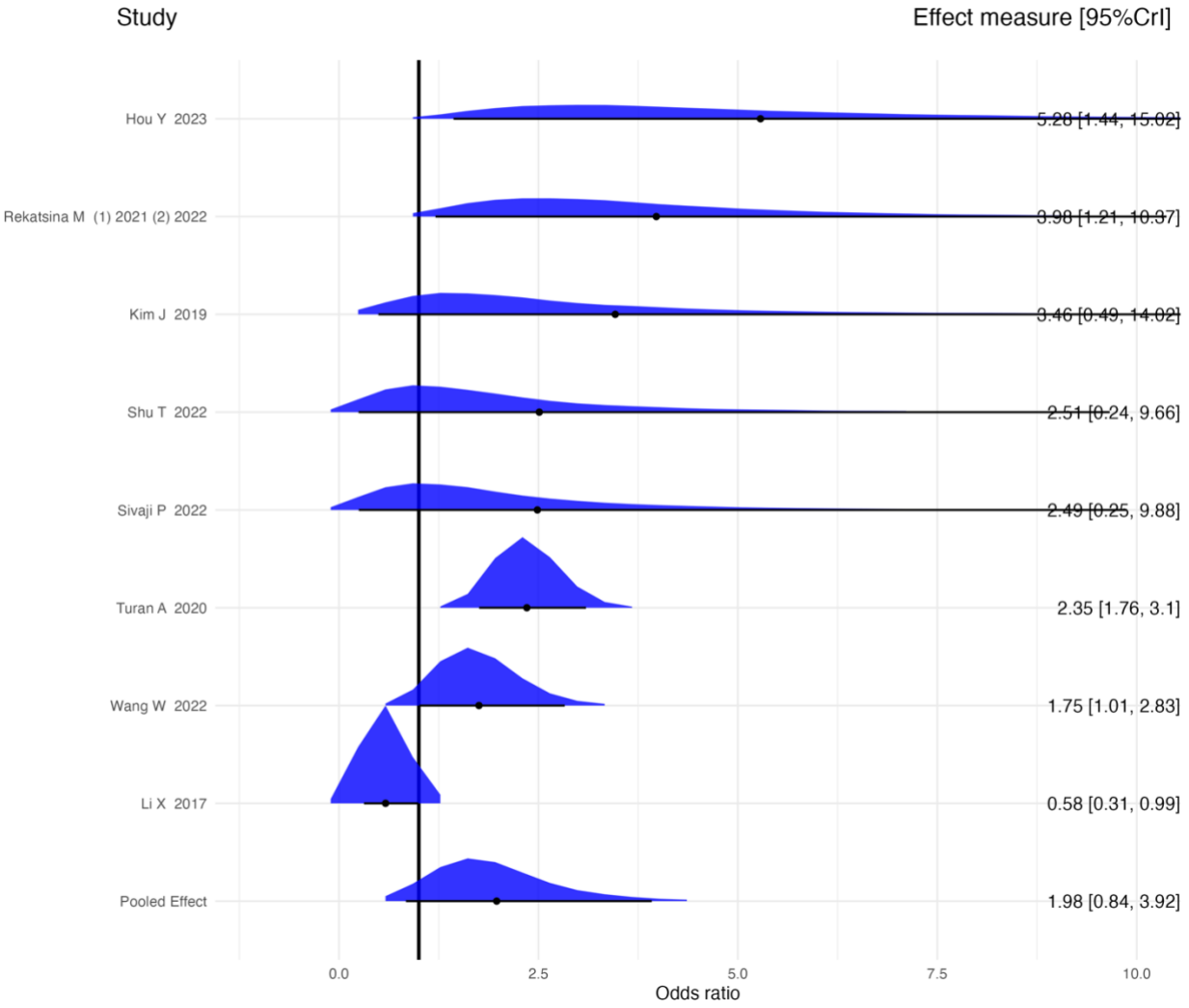
Forest plot for mortality assessment
Black vertical line indicates null value (odds ratio = 1). A value above one (right direction) favors dexmedetomidine. A value below one (left direction) favors control.



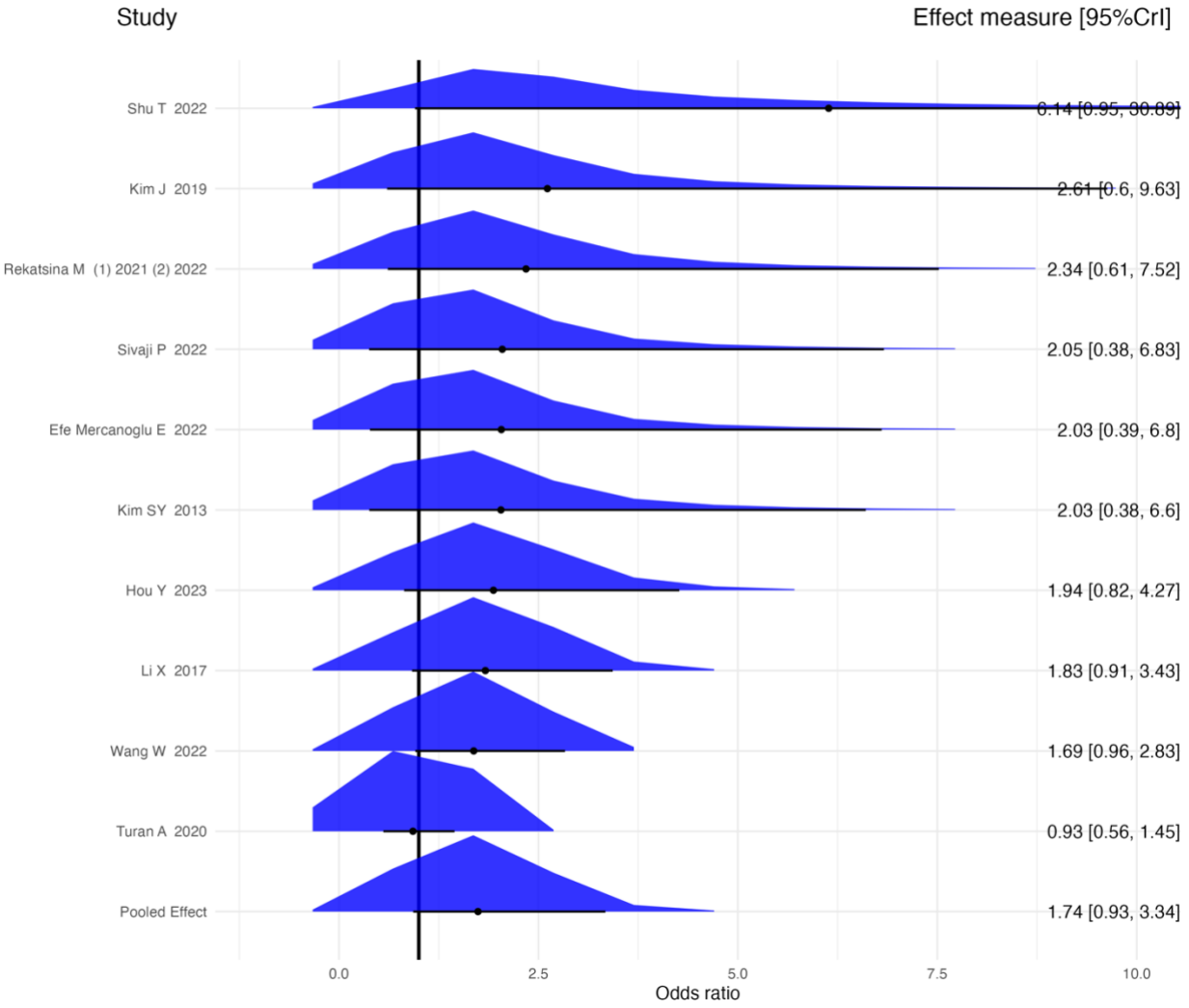
Forest plot for delirium assessment
Black vertical line indicates null value (odds ratio = 1). A value above one (right direction) favors dexmedetomidine. A value below one (left direction) favors control.



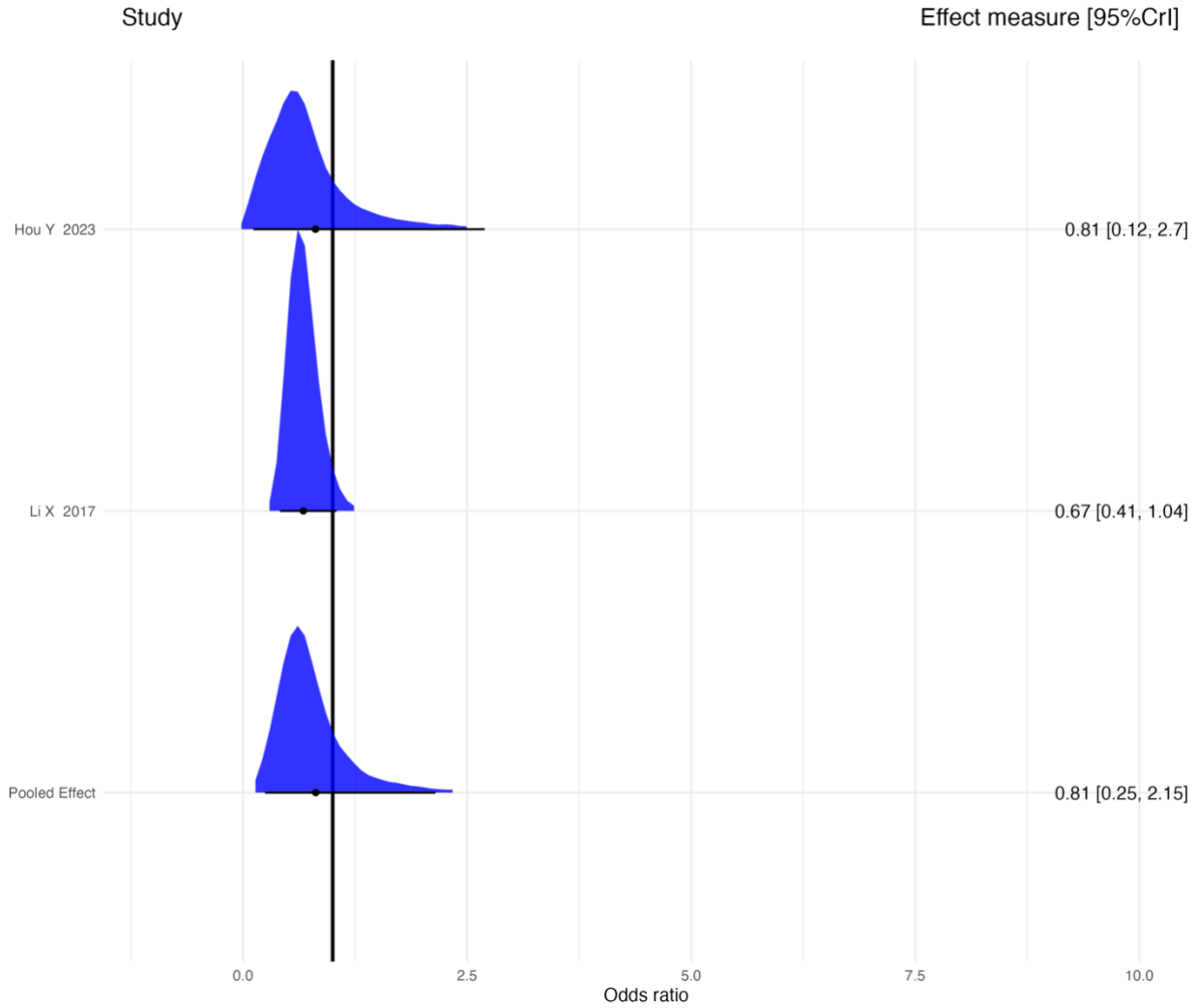
Forest plot for respiratory failure assessment
Black vertical line indicates null value (odds ratio = 1). A value above one (right direction) favors dexmedetomidine. A value below one (left direction) favors control.



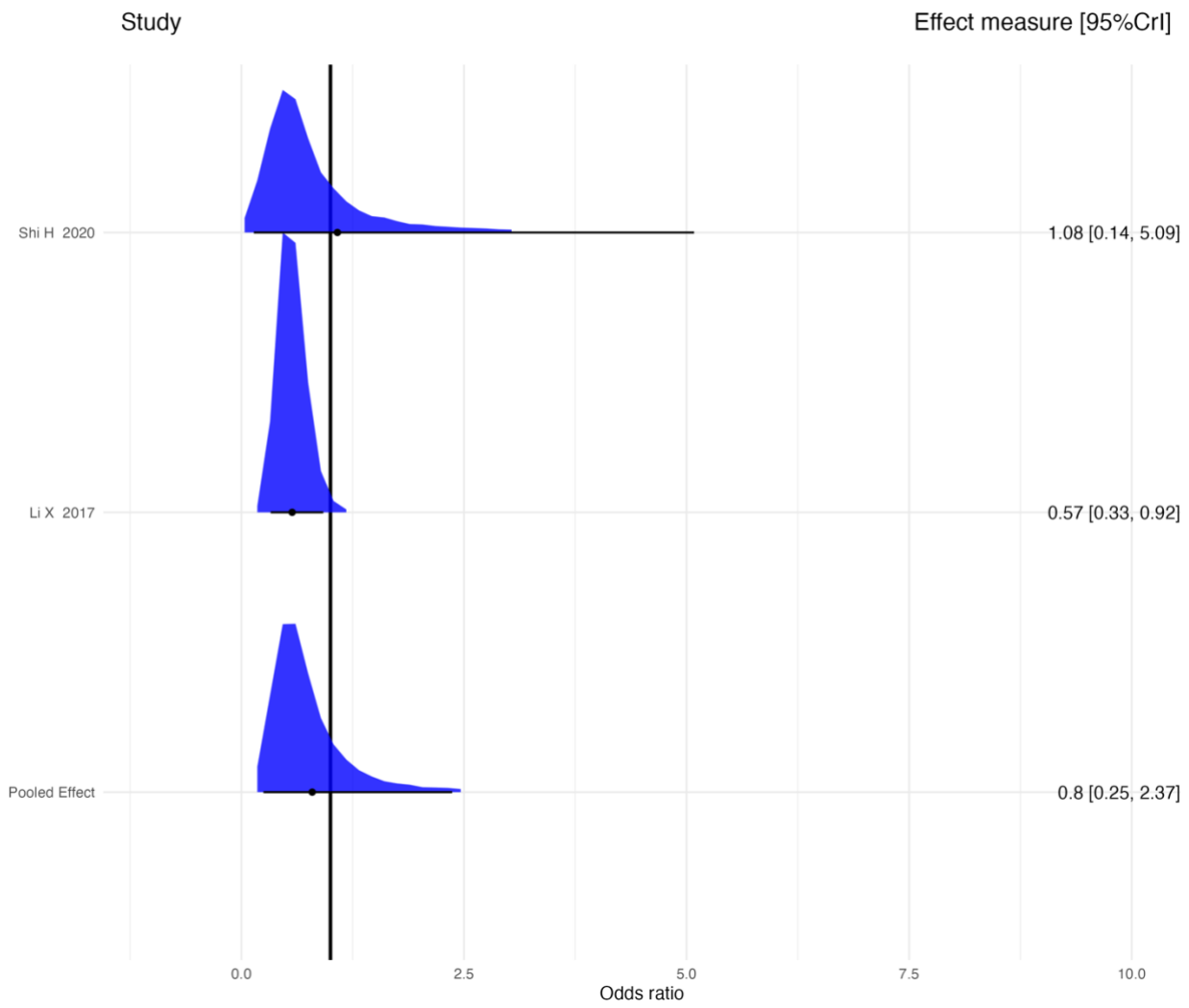
Forest plot for hypotension assessment
Black vertical line indicates null value (odds ratio = 1). A value above one (right direction) favors dexmedetomidine. A value below one (left direction) favors control.



Forest plot for bradycardia assessment
Black vertical line indicates null value (odds ratio = 1). A value above one (right direction) favors dexmedetomidine. A value below one (left direction) favors control.

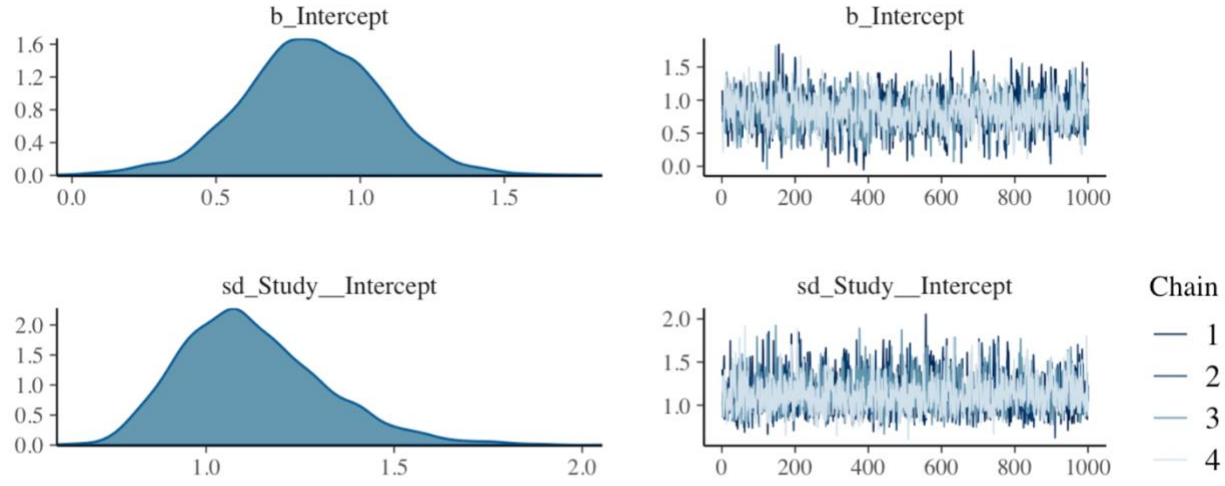


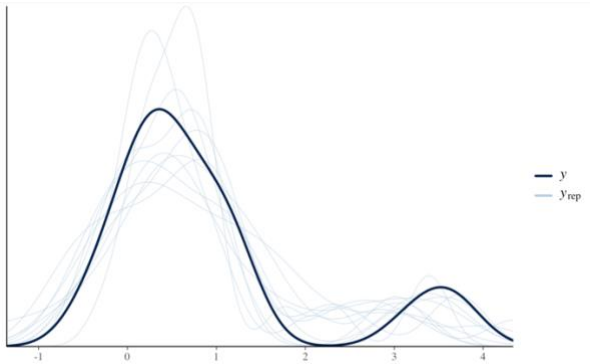
Forest plot for hypertension assessment
Black vertical line indicates null value (odds ratio = 1). A value above one (right direction) favors dexmedetomidine. A value below one (left direction) favors control.

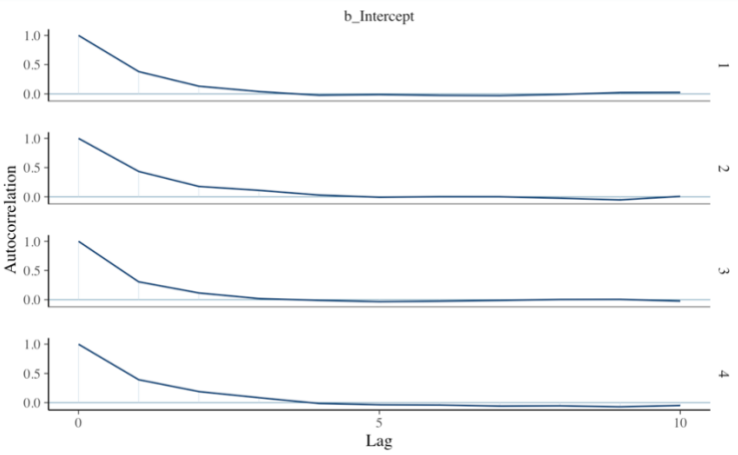


Forest plot for tachycardia assessment
Black vertical line indicates null value (odds ratio = 1). A value above one (right direction) favors dexmedetomidine. A value below one (left direction) favors control.

Appendix 4. Model diagnostics
Diagnostics for the assessment of the quality of recovery (weak prior, thin = 5)







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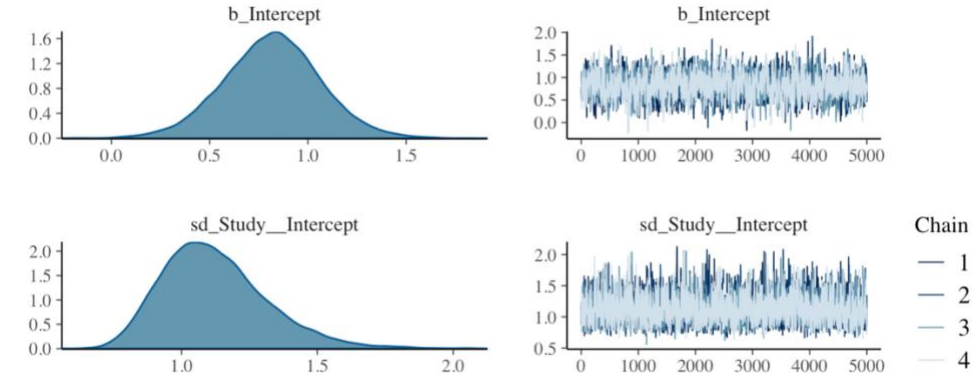
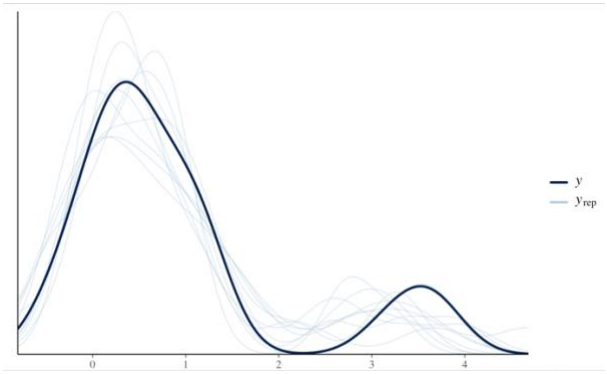
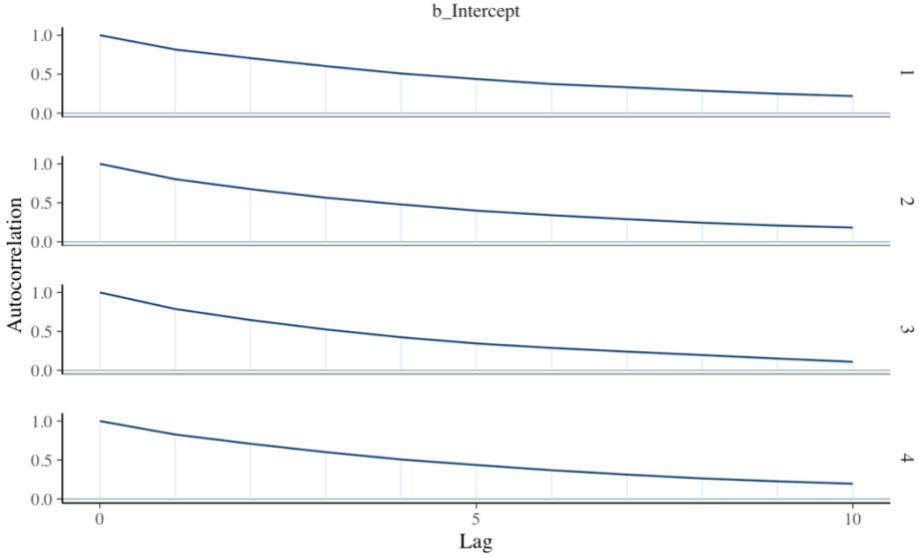
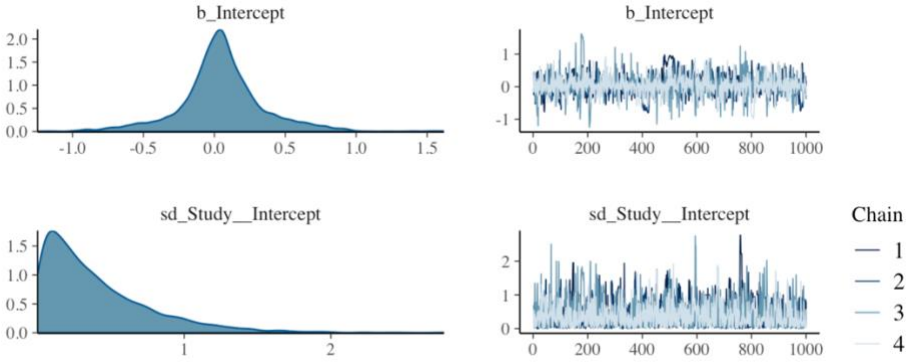
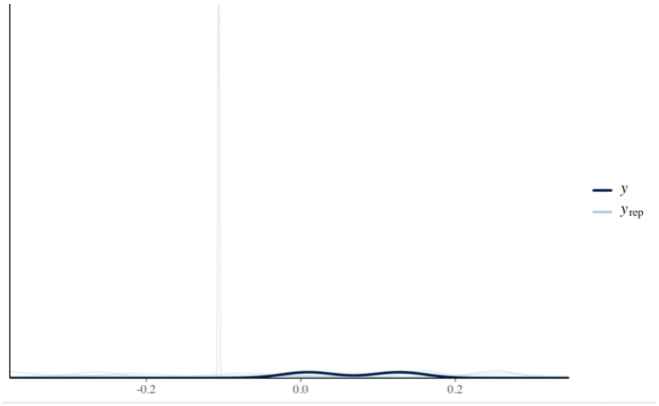


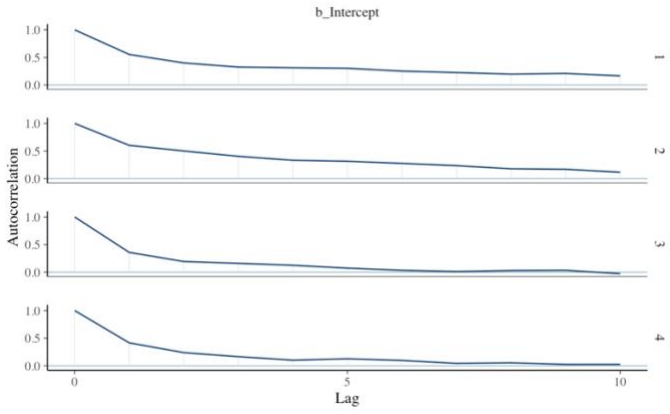




Diagnostics for the assessment of health-related quality of life (SF) (weak prior, thin = 5)







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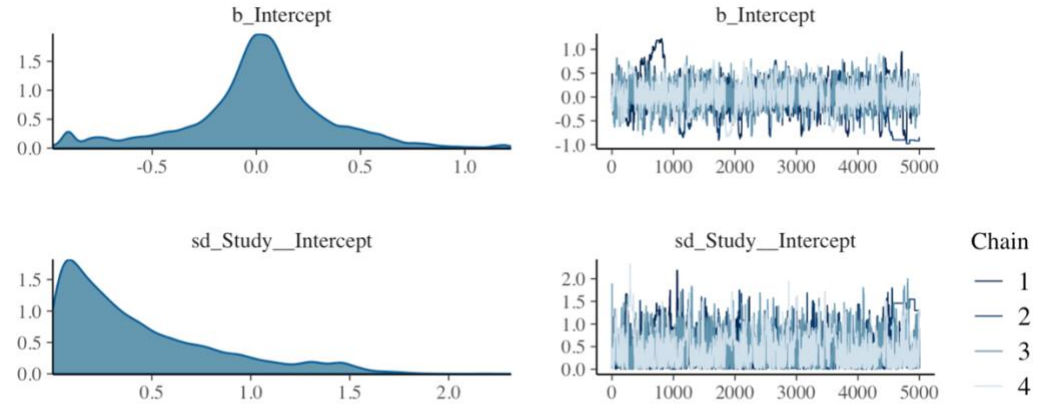
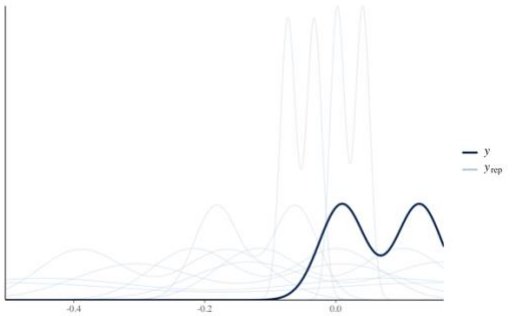
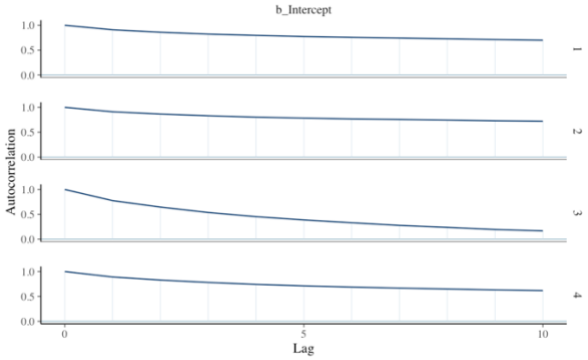
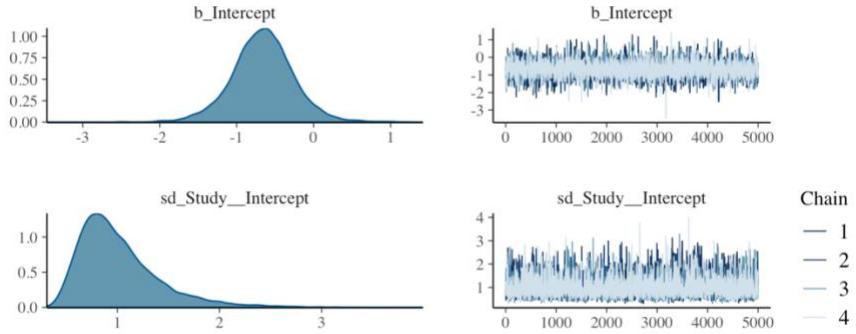
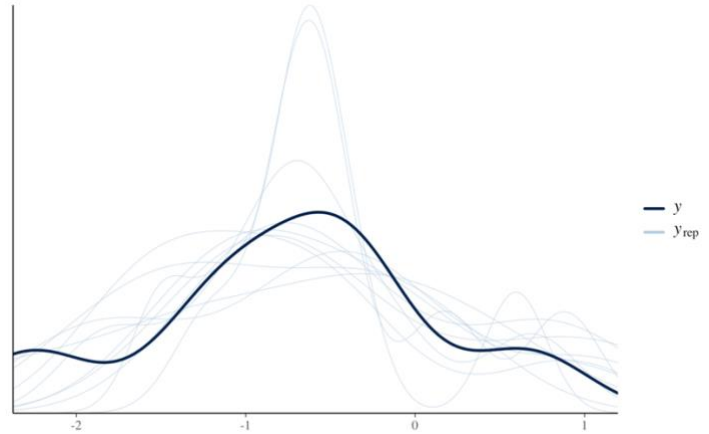


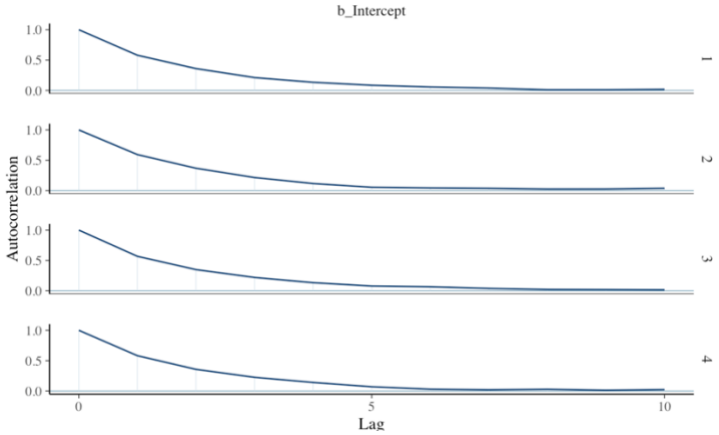




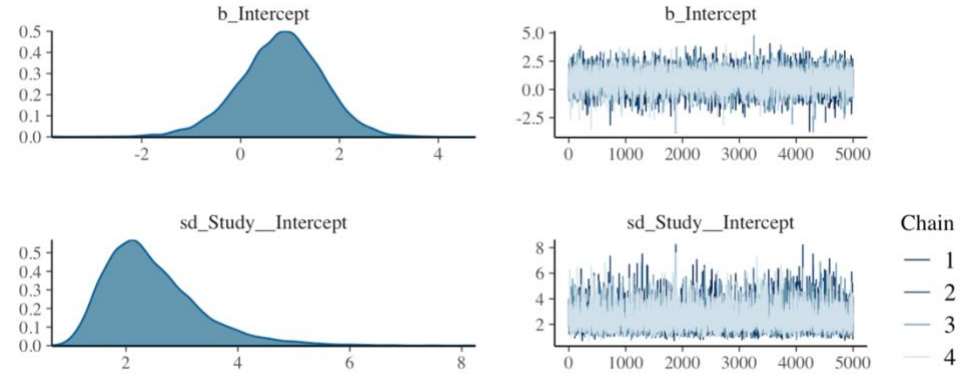
Diagnostics for the assessment of the postoperative sleep (NRS) (weak prior, thin = 1)

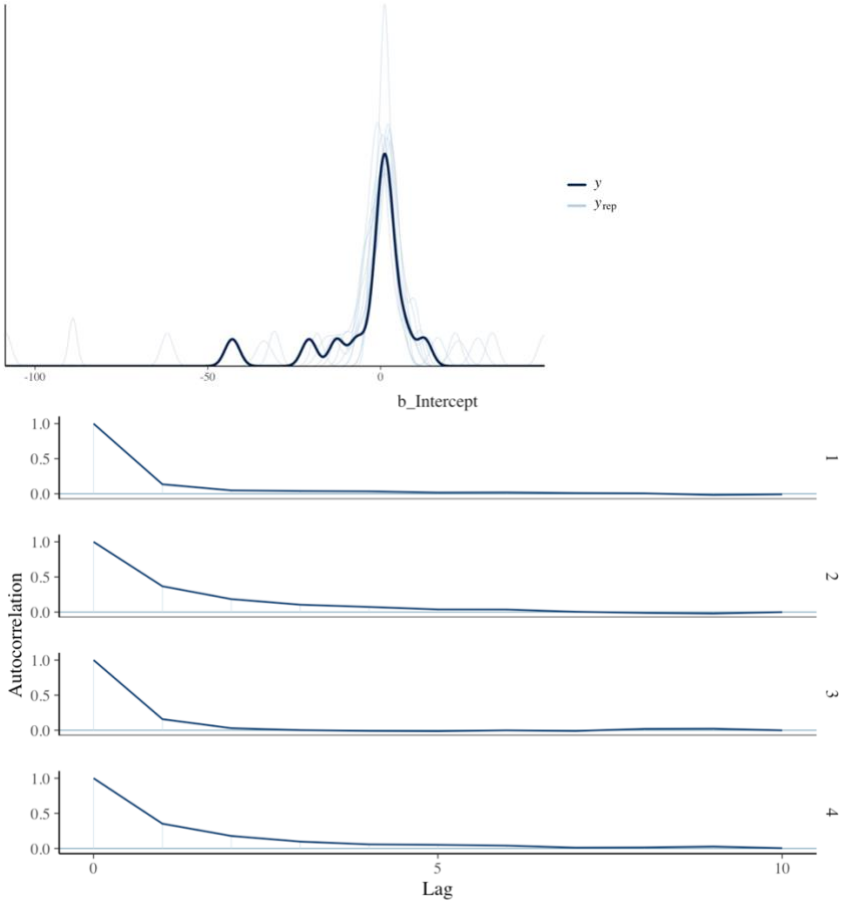




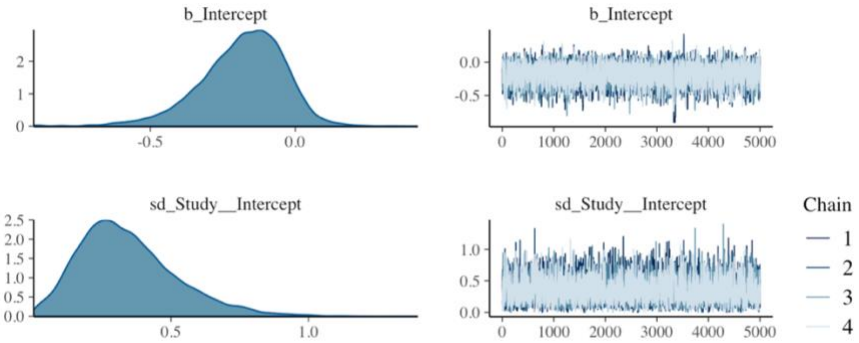


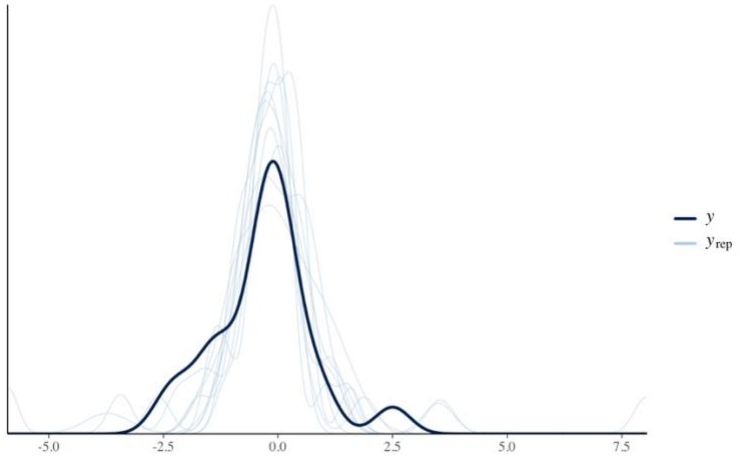
Diagnostics for the assessment of PACU (weak prior, thin = 1)

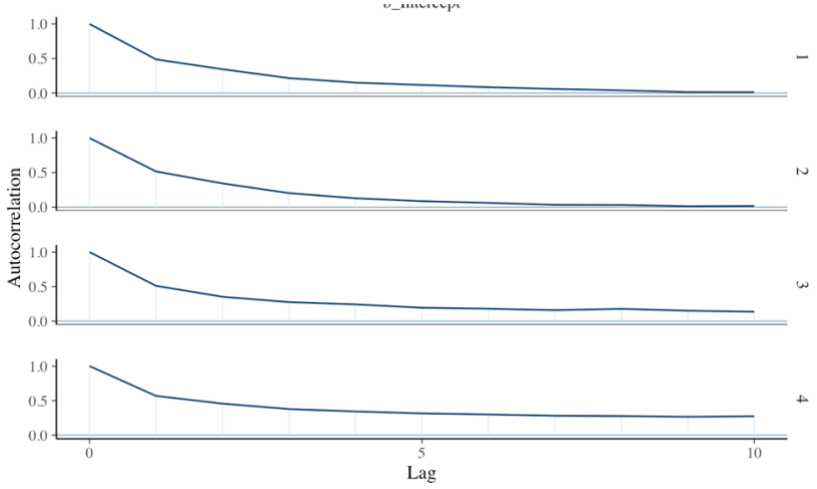




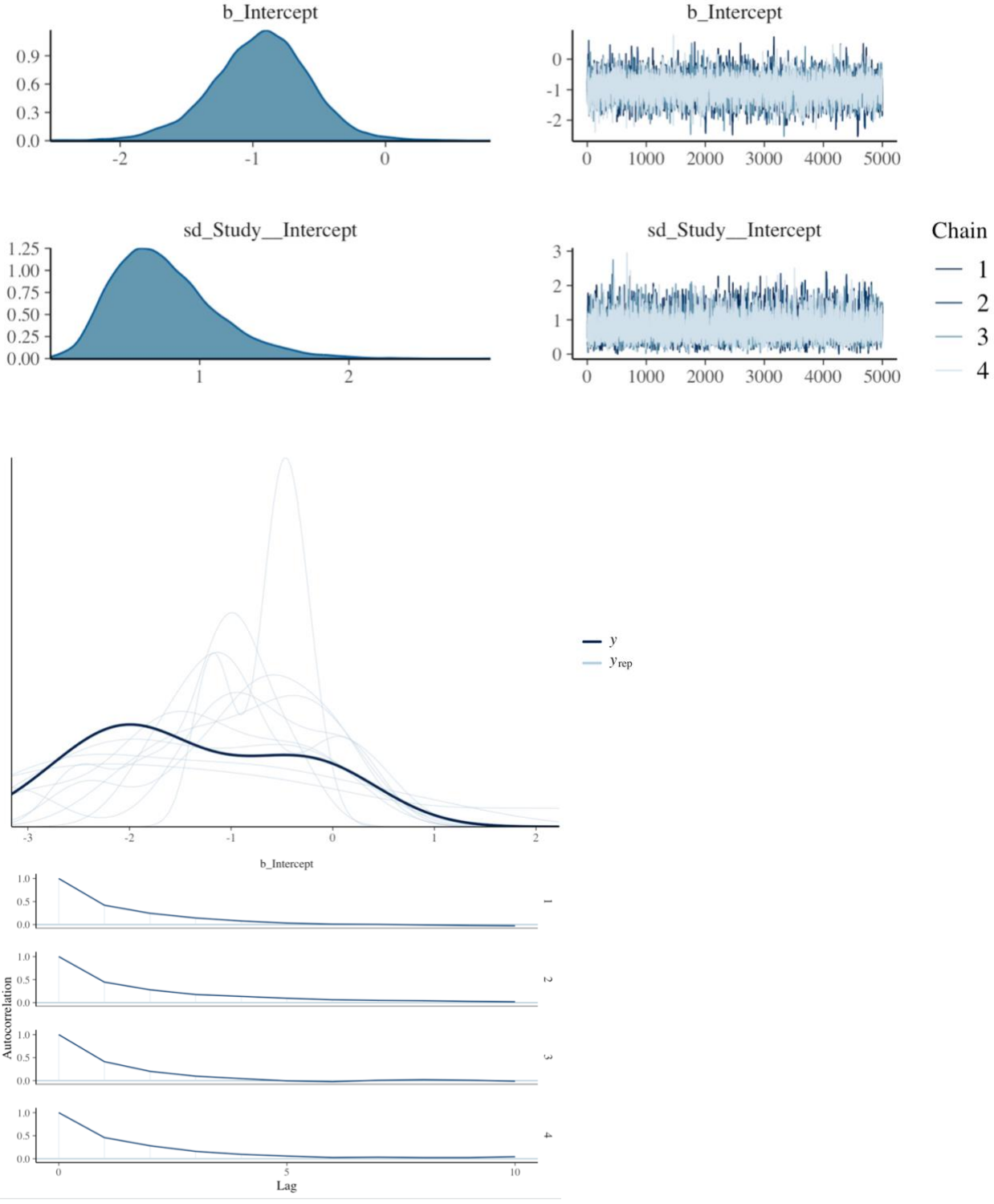
Diagnostics for the assessment of hospital length of stay (weak prior, thin = 1)



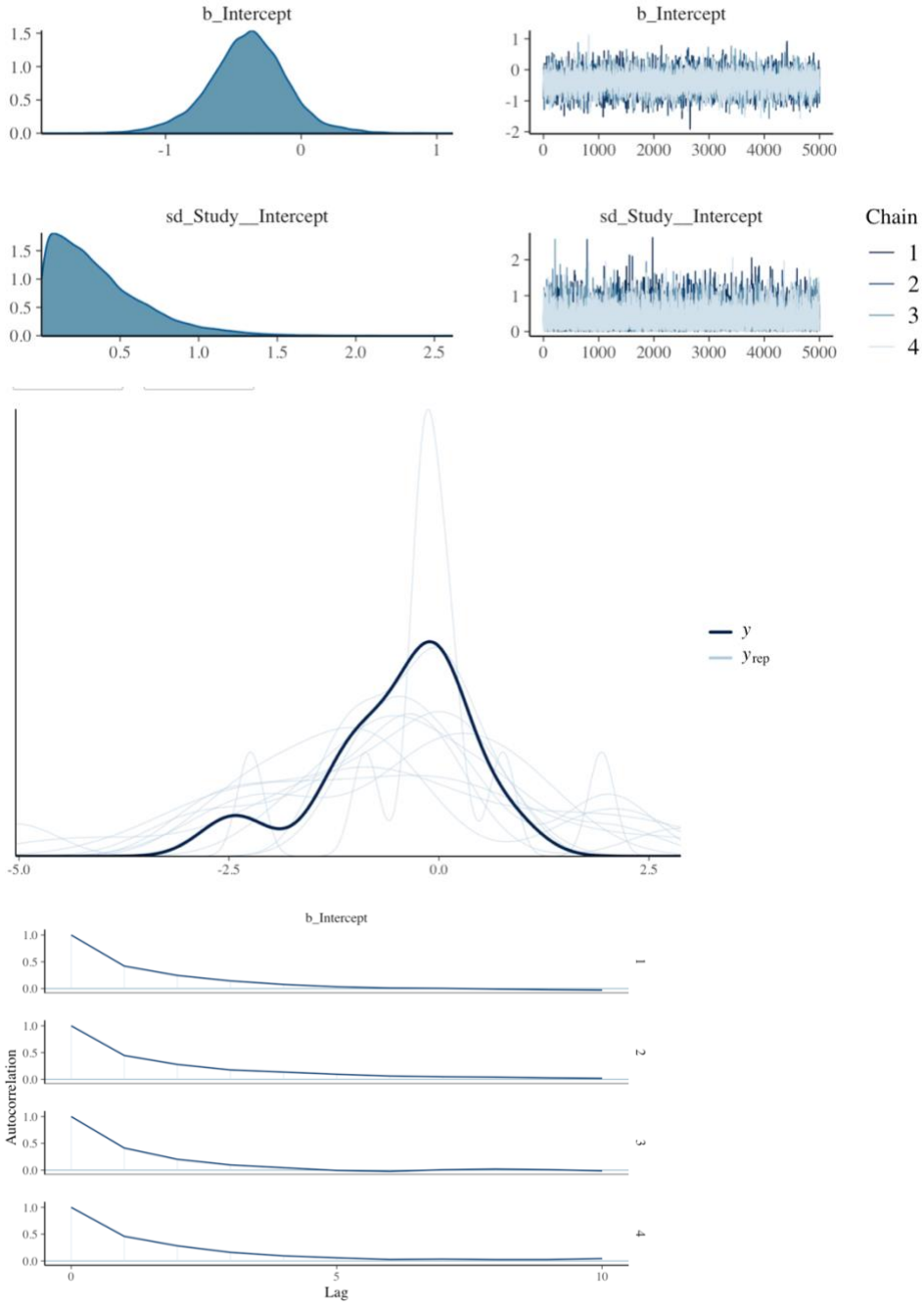




Diagnostics for the assessment of postoperative chronic pain incidence (weak prior, thin = 1)



Diagnostics for the assessment of mortality (weak prior, thin = 1)



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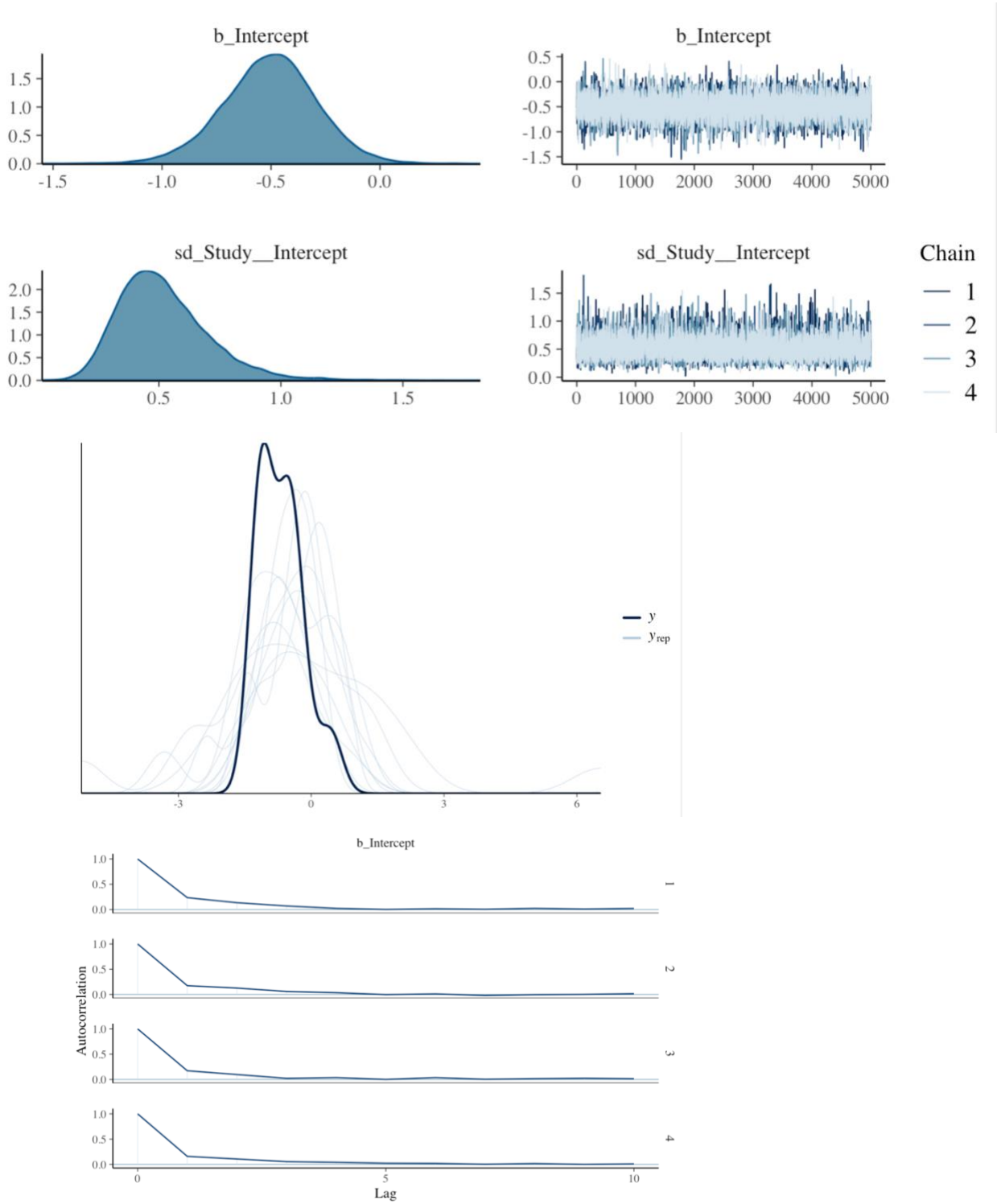

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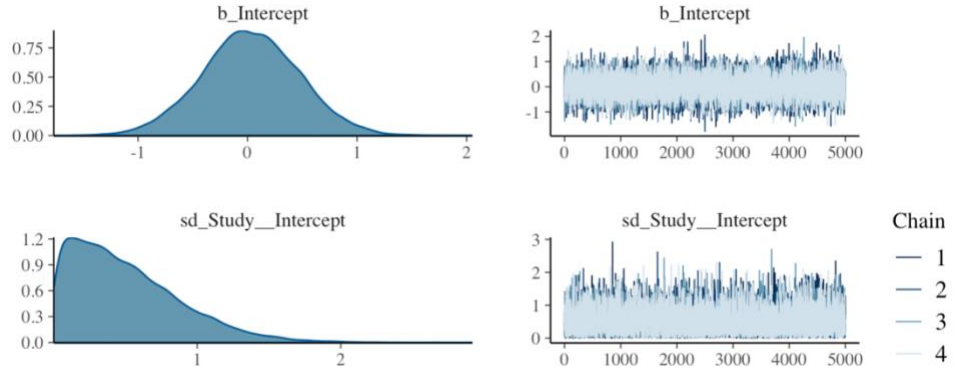

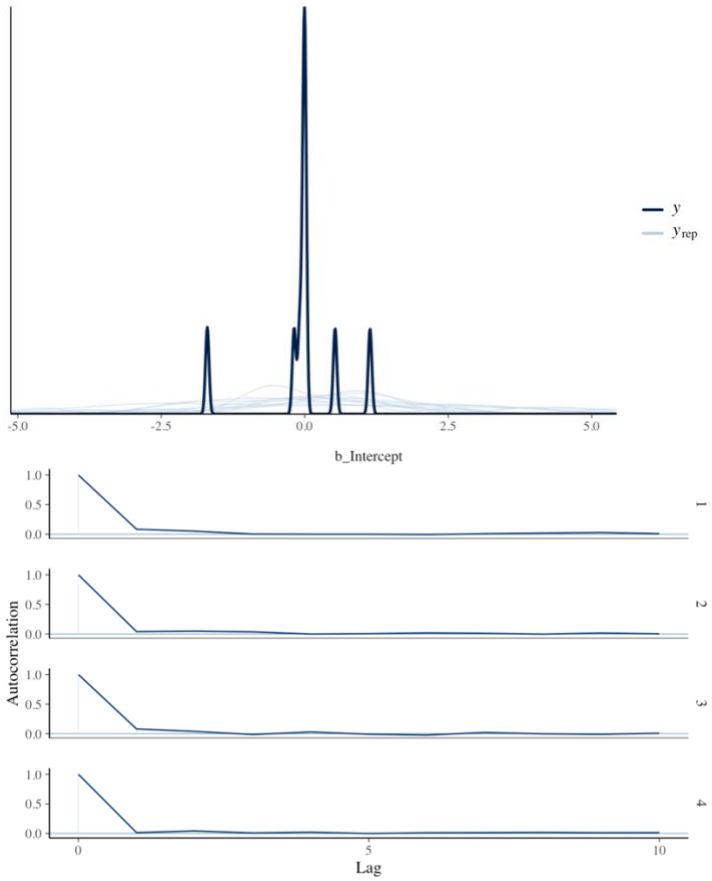

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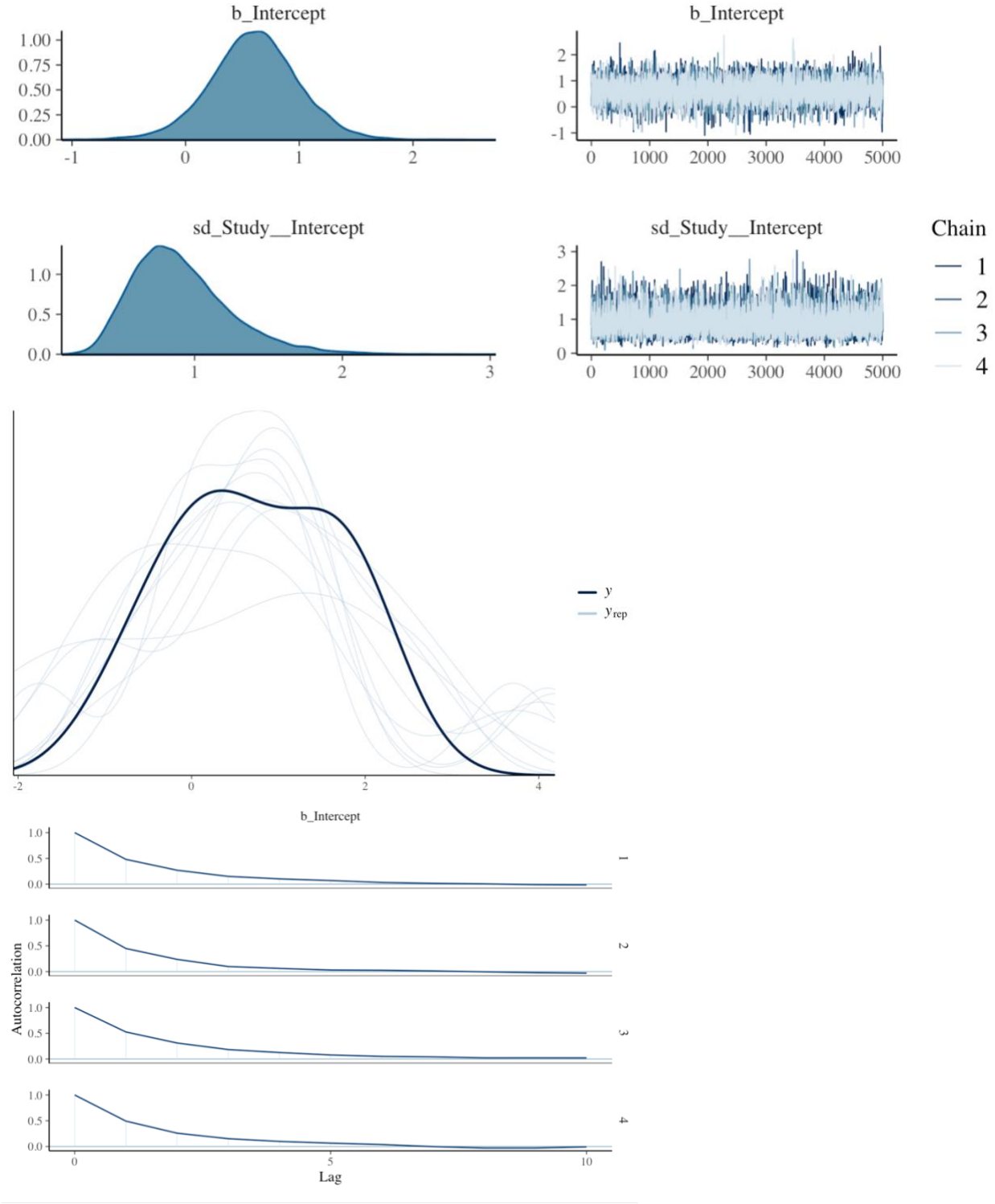

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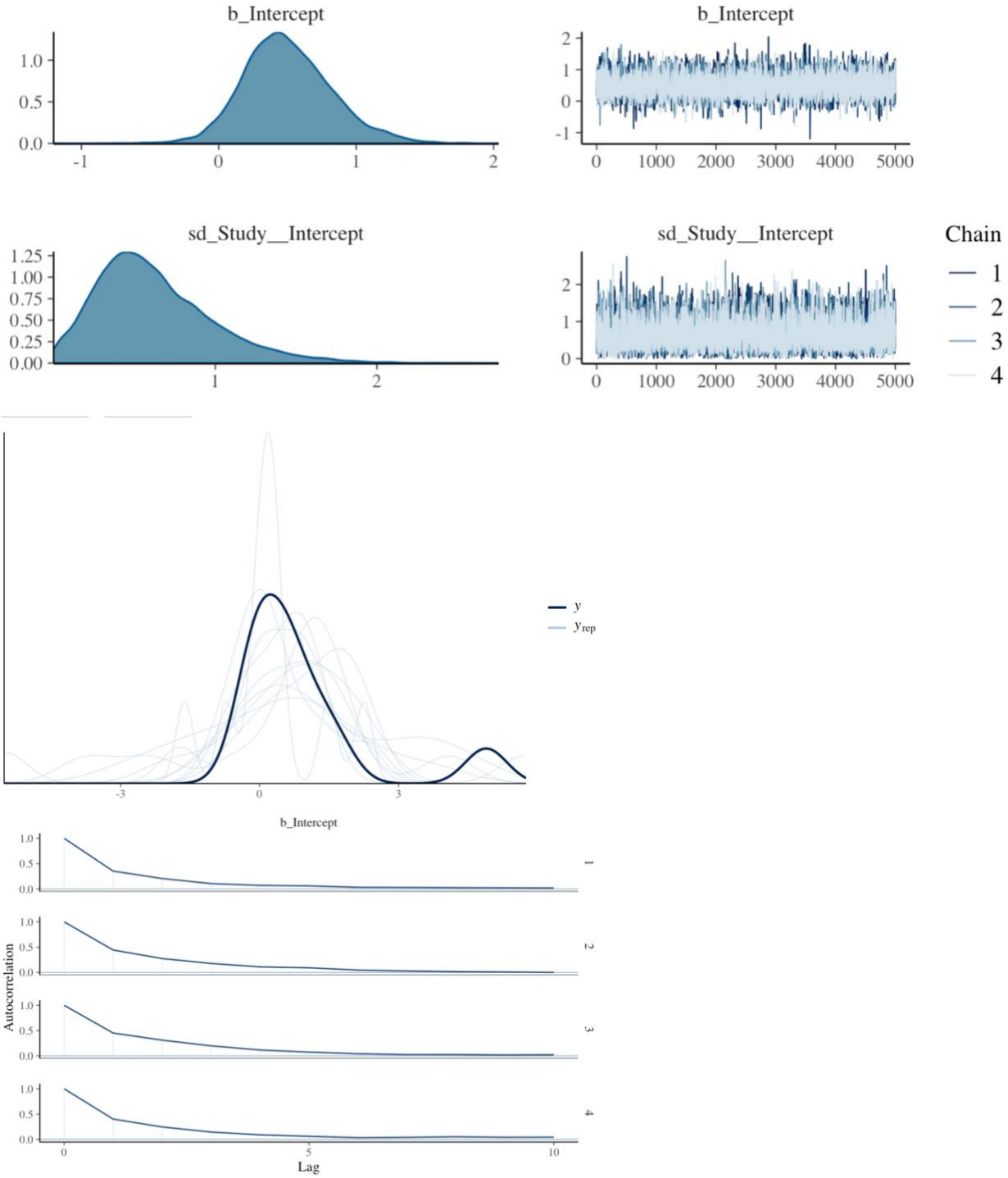
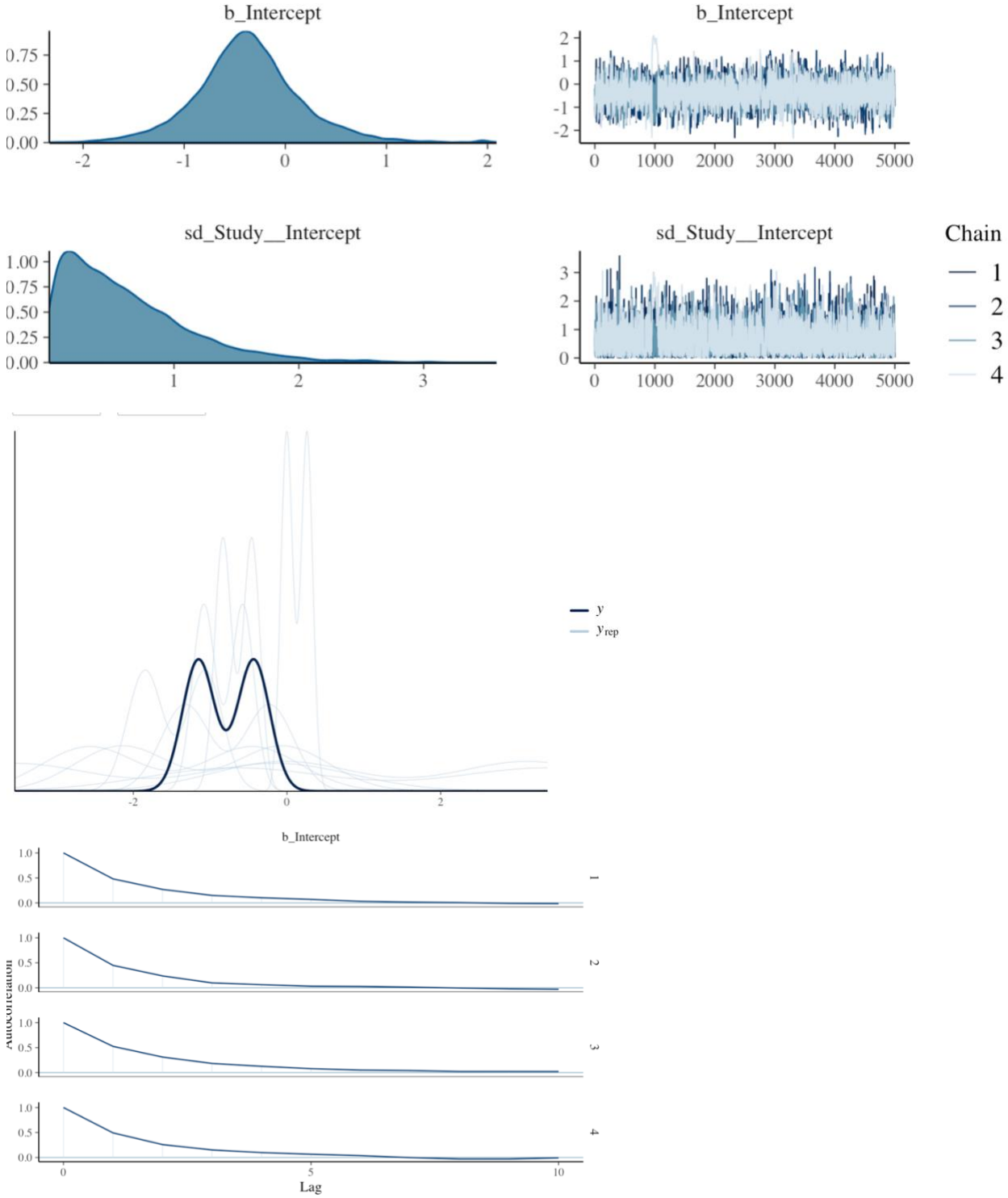


Diagnostics for the assessment of hypertension (weak prior, thin = 1)



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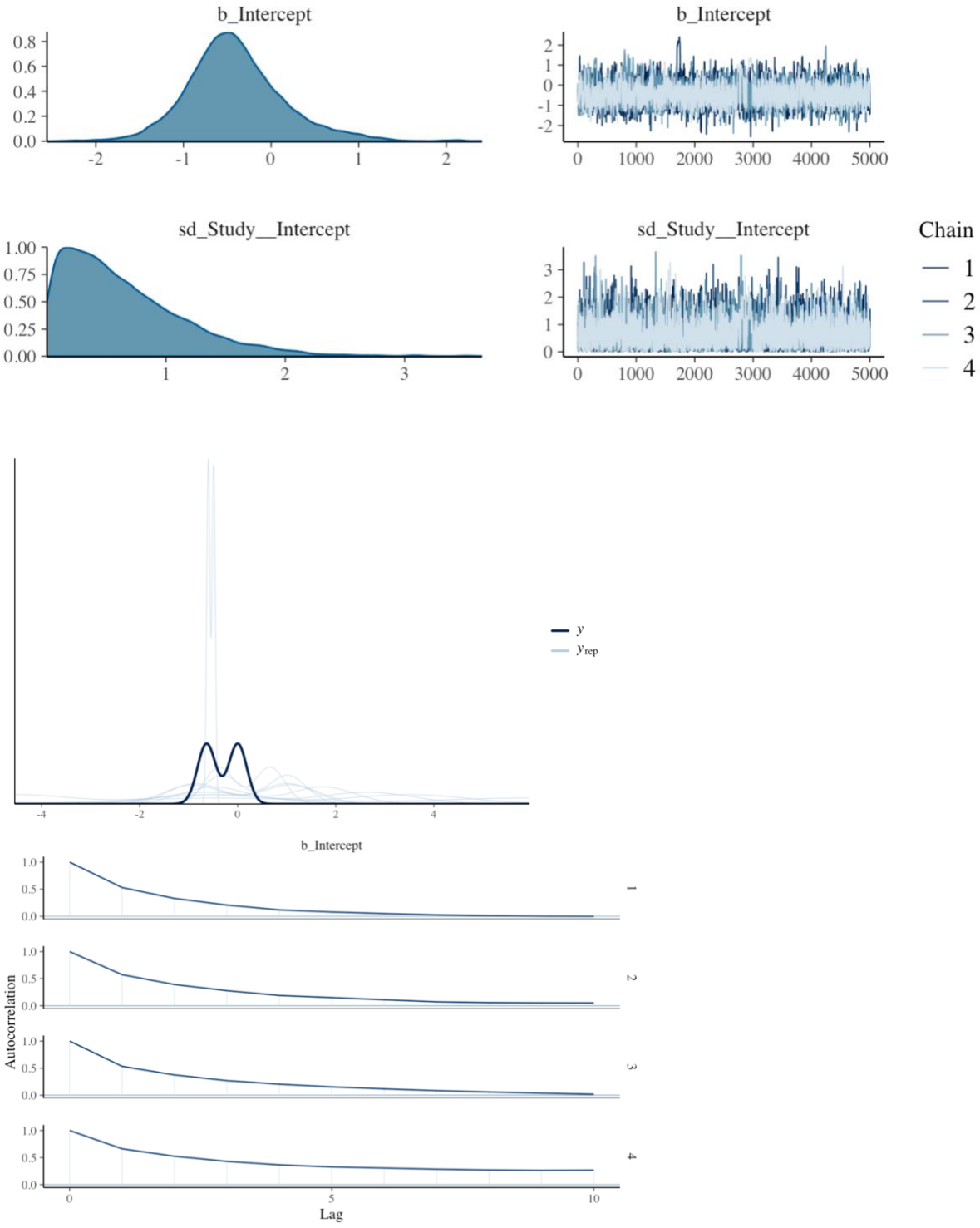

Chapter 5. Manuscript 4 - Use of opioids and opioid alternatives during general anesthesia: a pan-Canadian survey among anesthesiologists

5.1 Preface to manuscript 4

In order to supplement evidence from RCTs described in the scoping review and the systematic review with clinicians' opinions and reported practices, I completed a pan-Canadian survey among anesthesiologists. I obtained REB approval for this project on September 8th 2023 (20230359-01H) as well as for an amendment on October 19th 2023 (20230359-01H). Co-authors involved in this project helped for the supervision of the project, revision of the manuscript, for the development, testing and piloting the questionnaire. Patient partners and partner organizations contributed to refine the research question, provided input on the design of the study as well as on the development of the dissemination plan and distribution of the questionnaire.

This survey manuscript has not been submitted for publication and only responses collected up to January 5th 2024 are included in the results of this manuscript. I anticipate submitting the manuscript in April 2024.

5.2 Manuscript 4

Use of Opioids and Opioid Alternatives During General Anesthesia: A Pan-Canadian Survey Among Anesthesiologists

Michael Verret[1,2,3,4], Manoj Lalu[2,5,10], Alexandre Assi[11], Stuart G. Nicholls[2], Alexis F. Turgeon[1,3], Francois Martin Carrier[12,13], Daniel McIsaac[2,6,10], Ian Gilron[6], Fiona Zikovic[7], Megan Graham[7], Maxime Le[7], Allison Geist[7], Guillaume Martel[2,8], Jason McVicar[2,5] Husein Moloo[2,8], and Dean Fergusson[2,4,8,9,10] on behalf of the Perioperative Anesthesia Clinical Trials (PACT) group

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Registration: none

Author contributions:
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Methodology: Michael Verret, Dean Fergusson, Manoj Lalu, Alexis Turgeon, François M. Carrier, Stuart Nicholls

Writing – original draft: Michael Verret
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Translation of the questionnaire in French: Michael Verret, Alexandre Assi, François M. Carrier

Title: Use of Opioids and Opioid Alternatives During General Anesthesia: A Pan-Canadian Survey Among Anesthesiologists

Background

There is a growing interest in the use of pharmacologic opioid minimization strategies (i.e., opioid alternatives) for adult surgical patients requiring general anesthesia. Despite the importance of the topic, the opinion of Canadian anesthesiologists regarding the use of opioids and opioid minimization strategies to complement general anesthesia is unknown.

Methods

We conducted a pan-Canadian web-based survey of anesthesiologists that was distributed using a modified Dillman technique. Our multidisciplinary team, including a patient panel, participated in the process of domains and items generation, items reduction, formatting and composition. Our sampling frames were the members of the Canadian Anesthesiologists' Society and the members of the Association des Anesthésiologistes du Québec. We used the newsletters of each organization to distribute our survey, which was available in English and French and housed in the Lime Survey platform.

Findings

From our eligible sampling frame, 15% of the anesthesiologists completed our survey questionnaire (n=297 respondents out of 2,008 eligible participants). Most respondents were male (58%, n=172) with a full-time clinical practice (79%, n=235). Most of the respondents believed that using opioid minimization strategies during general anesthesia could improve postoperative clinical outcomes, including pain control (84.0% agree or strongly agree, n=288). Reported use of pharmacologic opioid minimization strategies was variable, however, most respondents believed that NSAIDs, acetaminophen, NMDA antagonists, alpha-2 receptor agonists [i.e., dexmedetomidine], corticosteroids, and intravenous lidocaine improve postoperative clinical outcomes. Most important outcomes that could alter practice were postoperative acute pain intensity, the impact of acute pain on functioning, patient well-being (i.e., Quality of Recovery) and patient satisfaction with care. A lack of evidence was the most important barrier limiting the use of opioid minimization strategies.

Conclusion

In our survey of Canadian anesthesiologists, several opioid minimization strategies were believed to be effective complements to general anesthesia, although there was substantial variation in their reported use. Respondents identified a lack of evidence as a barrier to the use of opioid minimization strategies and felt that patient-reported outcome measures should be prioritized in future research.

Background

Over the last two decades, the use of opioid minimization strategies (i.e., opioid alternatives) has gained interest (e.g., systemic lidocaine, ketamine, dexmedetomidine, magnesium, etc.) to complement general anesthesia. Results from observational studies have confirmed that intraoperative opioid use is decreasing while opioid minimization strategies are increasingly being used.[1] However reasons and preferences explaining those changes are unclear.

Several perioperative guidelines promote the reduction of opioid use during and after surgery.[2 3] Despite these guidelines' recommendations, significant variation in clinical practice, not explained by patient characteristics, has been observed in the United States and in Europe.[1 4] By improving our understanding of practice variation and clinicians beliefs, we may be able to inform study design and behavioural interventions that will help support meaningful change in practice for the use of opioids and opioid minimization strategies.

As such, a contemporary overview of Canadian anesthesiologists beliefs on intraoperative opioid use and opioid minimization strategy practices for adult patients undergoing non-cardiac surgery is required.[5] Our survey objectives were to: 1) identify intraoperative opioid minimizing strategies believed to improve clinical outcomes including pain after surgery, 2) describe reported use and beliefs on the effectiveness of opioid minimization strategies, and 3) identify reasons for using or avoiding opioid minimization strategies.

Methods

We designed a pan-Canadian self-administered anonymous web-based survey with our team of clinicians, four patient partners, and researchers using a modified Dillman technique.[6] The team that developed the survey included participants with expertise in anesthesia, surgery, pain, clinical trials, survey methodology, and lived experience with surgery. This survey was approved by the Ottawa Health Science Network Research Ethics Board (20230359-01H).

Population and sampling frame

Our target population was anesthesiologists registered to practice in Canada. Our sampling frames were the members of the Canadian Anesthesiologists' Society [CAS] (for anesthesiologists registered to practice in Canadian provinces except the province of Québec) as well as the members of the Association des Anesthésiologistes du Québec [AAQ] (for anesthesiologists registered to practice in the province of Québec). In November 2023, our sampling frame included a total of 2008 anesthesiologists (CAS: 1225 anesthesiologist members and AAQ: 783 anesthesiologist members). We excluded anesthesiologists exclusively practicing pediatric or cardiac anesthesia, as outcome measures and recommendations are different in these populations.[7-9]

Survey questions generation and formatting

Our team participated in the process of domain and item generation, item reduction, formatting and composition.[10] Important opioid minimization strategies addressed in the survey were identified through a scoping review,[11] review of the available guidelines,[3 12-15] systematic reviews and expert input. We organized two group discussions with anesthesiologists, methodologists, and patient partners for the process of domain generation and then one group meeting with the same people for the process of items reduction. Each meeting summary report was sent by email to all main investigators using a summary table including the list of all retained domains and items. Written comments and suggestions were provided between meetings. A summary of the final domains and items is provided in Table 1. For the composition and formatting of the questionnaire, we used a five-page questionnaire (i.e., one for each domain) consisting of

closed-ended questions with scalar categories for each item identified. To develop questions related to decision-making factors (c.f. Table 1, section D) we used the Theoretical Domains Framework to ensure the comprehensiveness and relevance of the questions.[16] Exclusion criteria were self-identified in the first question and socio-demographic questions were added at the end of the questionnaire. The questionnaire was developed in English and French and housed in the Lime Survey platform.[17] Participants were allowed to modify responses and return to previous pages, and a progress bar was displayed throughout the completion of the survey.

Pilot procedure and testing

The survey was piloted by eleven members of our research team (including seven anesthesiologists, two surgeons, and two methodologists) to assess the flow and clarity of the questionnaire. The survey questionnaire was also reviewed by four patient partners to ensure their perspectives and priorities were accounted for in the survey (through meetings and written feedback). The overall flow of the questionnaire was then assessed by an external group of 20 senior residents in anesthesiology who completed the questionnaire twice, 2-weeks apart. The comparability of French and English questionnaires were ensured through revision of the questionnaire by six bilingual anesthesiologists. After final refining of the questionnaire (i.e., to ensure consistency of the terms used across the questionnaire and ensure coherence of likert scale items) the content and face validity were assessed by five anesthesiologists with expertise in the field of pain medicine. At each step, modifications of the questionnaire were made though feedback received. Through piloting, our survey was estimated to take approximately 10 minutes to complete (Appendix 1 and 2).

Survey procedure

All eligible participants were contacted by email on November 22nd 2023 and were asked to complete the survey. The survey was distributed using a general link through the newsletter of the Canadian Anesthesiologists' Society [CAS] as well as the Association des Anesthésiologistes du Québec [AAQ]. The same approach was used to send reminders. The AAQ sent three email reminders; at 1, 3, and 7 weeks following the initial

invitation. The CAS sent two reminders; at 1 and 8 weeks following the initial invitation based on their respective communication policies. Responses were collected up until February 15th 2024. To avoid double invitation, anesthesiologists registered to practice in the province of Québec were removed from the distribution list of the CAS.

Analyses

The response rate was calculated using the American Association for Public Opinion Research (AAPOR) guidelines.[18] The questionnaire was considered completed when at least 80% of the questions were answered. We included incomplete questionnaires and we used descriptive statistics to report our results. We also conducted sensitivity analyses as per pre-planned characteristics (e.g. CAS vs. AAQ members) for the first section of the survey (i.e., beliefs about opioid use and opioid minimization strategies). We assessed the association between perceived usage (questions 3) and perceived usefulness (questions 7) using Spearman-rho correlation coefficients. We performed analyses using R (Version 4.3.2) and RStudio.

Patient engagement

For our collaborative work with patient partners, we followed the principles described in the Strategy for Patient-Oriented Research (SPOR) Patient Engagement Framework.[19] In line with the principles of inclusiveness, support, mutual respect, and co-building, the patient panel met numerous times with the team, and was supported by a patient-engagement facilitator. To support participants we created a welcoming environment, and provided both practical support (information, staff support) and compensation. Our overall patient engagement approach has been described in detail in another publication.[20]

Results

From the 367 respondents, 12 were excluded given their practice was exclusively in either cardiac or pediatric anesthesia. Among the 355 eligible respondents, 297 completed the questionnaire entirely (i.e., provided an answer to at least 80% of the questions). Thus, our overall response rate was 15 % (297 eligible participants who completed the questionnaire out of 2,008 eligible participants).

Characteristics of the respondents

The majority of respondents self-identified as men (58%, n=172) practicing anesthesiology for over 20 years (72% with over 20 years of practice, n=214). Most of the respondents had a full-time clinical practice (79%, n=235) in a centre with an acute pain service (60%, n=179). Most respondents were from Québec or Ontario (74%, n=221). There were no respondents from the three territories or from Nova Scotia. A full description of the respondents' characteristics is provided in Table 2.

Beliefs about opioid use and opioid minimization strategies

Most of the participants believed that limiting opioid exposure during general anesthesia was important (68% agree or strongly agree, n=232) (eFigure 1) for adult patients undergoing non-cardiac surgery. Most of the respondents believed that using an opioid minimization strategy during general anesthesia could improve postoperative clinical outcomes, including pain control (84% agree or strongly agree, n=288) (eFigure 2). Responses were similar, regardless of the mode of distribution (i.e., distribution through AAQ vs. CAS) (eFigure 3).

Reported usage of opioids and opioid minimization strategies

The most frequently used intraoperative pharmacologic opioid minimization strategies reported were nonsteroidal anti-inflammatory drugs (NSAIDS) (91% often or always), acetaminophen (90% often or always) and corticosteroids (85% often or always), while calcitonin (97% never) and naloxone (82% never) were reported to be rarely or never used. Reported use of alpha-2 receptor agonists (e.g. dexmedetomidine), benzodiazepine, beta blockers, NMDA antagonists (ketamine), magnesium, and intravenous lidocaine,

was variable (eFigure 4). Opioids were reported to be used more frequently during the induction period (96% often or always) while the use of opioid minimization strategies was variable across all phases of perioperative care (induction, maintenance and postoperative care) (eFigure 5 and 6). Anesthesiologists believed that some clinical factors were very important to consider when using or not using opioid minimization strategies; such as, chronic opioid use (82% very important), chronic pain condition (77% very important), surgery associated with high pain intensity (73% very important), and history of opioid-related adverse events (63% very important) (eTable 1).

Perceived usefulness of opioids and opioid minimization strategies

Opioid minimization strategies believed to be the most useful were NSAIDS (98% probably or clearly useful), and acetaminophen (99% probably or clearly useful). NMDA antagonists (91% probably or clearly useful), alpha-2 receptor agonists (i.e., dexmedetomidine) (88% probably or clearly useful), corticosteroids (88% probably or clearly useful) and intravenous lidocaine (86% probably or clearly useful) were also believed to be useful by most responders (eFigure 7). There was variability in the reported utility of beta-blockers. Opioids were believed to be most useful (probably or clearly) during the induction, the maintenance and the postoperative period (eFigure 8). Opioid minimization strategies were believed to be most useful (probably or clearly) during the maintenance and the postoperative period (eFigure 9).

Decision-making factors

To guide decision-making about the use of pharmacologic opioid minimization strategies, participants reported that the four most important outcomes that could alter their practice were postoperative acute pain intensity (97% somewhat important or very important), the impact of acute pain on functioning (95% somewhat important or very important), patient well-being after surgery (i.e., Quality of Recovery) (94% somewhat important or very important), opioid-related adverse events after surgery (95% somewhat important or very important), patient satisfaction with care (92% somewhat important or very important), and delirium (92% somewhat important or very important) (eTable 2). The most frequently reported barriers to the use of opioid minimization strategies were the lack of

evidence (50%) and pharmacokinetic profile of some agents (44%) (eFigure 10). The most frequently reported facilitators were the evidence available (73%), personal clinical experiences (73%), the desire to minimize the risk of opioid dependence (64%), and the improvement in patient safety (62%)(eFigure 11).

Comparison between reported usage and perceived usefulness

For most opioid minimization strategies, we found a moderate association between their perceived usage and their perceived usefulness. For most strategies, the reported use was lower than the perceived usefulness. The association between usage and usefulness was stronger for alpha-2 agonists (Correlation: 0.62) and magnesium (Correlation: 0.64), and weaker for acetaminophen (Correlation: 0.22) and negligible for naloxone (Correlation: 0.11) and calcitonin (Correlation: -0.07) (eTable 3).

Discussion

In this pan-Canadian survey, we observed that limiting opioid exposure during the intraoperative period for adult patients undergoing general anesthesia for non-cardiac surgery is important for the majority of Canadian anesthesiologists. Most respondents also believed that opioid minimization strategies can improve postoperative clinical outcomes, including pain control. We identified several pharmacologic opioid minimization strategies believed to be useful (e.g., NSAIDS, acetaminophen, NMDA antagonists, alpha-2 receptor agonists, corticosteroids and intravenous lidocaine). We also noted that the reported usage of most opioid minimization strategies was variable, and the reported usage were generally lower than perceived utility for most strategies. Indeed, the lack of evidence and the pharmacokinetic profile of some agents were identified as barriers to implementation.

Our findings are consistent with observational studies and surveys conducted in other countries that observed an increase in the use of pharmacologic opioid minimization strategies with substantial variation in practices.[1 4] Importantly, we provide potential explanation for the observed variation in practices as we identified clinical factors that were important for anesthesiologists in their choice of intraoperative pharmacological agents, namely: the patient baseline chronic opioid use or pain condition, the type of surgery (i.e., surgery associated with high pain intensity), and a history of opioid-related adverse events. In contrast, results from a large scoping review have shown that few randomized controlled trials (RCTs) assessing the effectiveness of opioid minimization strategies focused on population of patients with either chronic opioid use (n=1 RCTs out of 457) or pain condition (n=2 RCTs out of 457),[21] which underscores the need for further research in this area. In addition, in our survey, the desire to minimize postoperative opioid dependence was found to be one of the most important facilitators to justify the use of intraoperative opioid minimization strategies while there is limited evidence supporting an impact from any pharmacologic strategies on long-term opioid dependence after surgery.[22 23]

Our survey has strengths. First, we describe the clinician's opinions and beliefs regarding an area where research is critically needed and it will thus help inform further research work (i.e., knowledge gap, important outcome measures, identification of factors that might influence practices, etc.). Second, we leveraged our partnership with well-established and recognized societies (i.e., CAS and AAQ) to distribute the survey efficiently and reach our target population (i.e., Canadian anesthesiologists). Third, we developed this survey using a rigorous process and a multidisciplinary approach involving patient partners, clinicians and partner organizations.

Our study also has limitations. Although we implemented techniques to increase response rate (short survey, closed-ended questions, progress bar indicators, distribution of the questionnaire by recognized societies, etc.), our response rate was low. This might reduce external validity as responders might have different opinions compared with non-responders. However, demographic characteristics of the respondents were comparable with national demographic data on Canadian anesthesiologists collected by the Canadian Medical Association in 2019 (i.e., 67% male and 33% female, mostly full-time clinical practice).[24] Of note, our response rate could be underestimated given that there is likely a significant number of anesthesiologists exclusively practicing in pediatric anesthesia or cardiac anesthesia that we could not subtract from the non-responders category (i.e., exact number unknown). We also obtained large differences in the response rate across provinces that could be caused by the use of two different modes of questionnaire distribution (AAQ vs. CAS). However, stratifying our results as per the mode of distribution of the survey showed no meaningful difference between responders from the province of Québec, compared with responders from other Canadian provinces.

Our survey results identified outcome measures that were prioritized by anesthesiologists for their practice-changing importance (i.e., pain, patient well-being, impact of pain on functioning, patient satisfaction). However, most of these outcomes (i.e., patient-centred outcomes) are critically underrepresented in perioperative original studies[21] and clinical practice guidelines,[14 25] highlighting an important priority for perioperative research. The patient well-being, assessed with instruments such as the Quality of Recovery tools was

also determined to be one of the most important patient-centred outcomes aligned with patient partners priorities previously identified.[20]

Conclusion

Several opioid minimization strategies are believed to improve postoperative clinical outcomes, including pain control although their reported use is variable. The lack of evidence supporting perioperative opioid minimization was identified as a barrier to its implementation. Research is required to inform the use of opioid minimization during general anesthesia.

Acknowledgment

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Table 1. Domains and items assessed in the survey questionnaire

Domains	Items
Section A: Beliefs about opioid use and opioid minimization strategies	Need / importance to reduce intropeative opioids vs. not Context of intervention Definition of intraoperative opioid minimization strategy
Section B: Reported usage (current practices)	Perceived use of opioids and opioid minimization strategies Strategies that are believed to be used Context of use (type of population, surgery, anesthesia)
Section C: Perceived usefulness	Perceived utility of opioids and opioid minimization strategies Strategies that are believed to be useful Described utility (type of population, surgery, anesthesia)
Section D: Decision-making factors	Patient factors (used and believed to be useful) Surgical factors (used and believed to be useful) Pharmacological interaction Triggers for administration Endpoints
Section E: Respondent demographics	Gender Experience Geographic localization

Table 2. Respondents' characteristics

		Number of respondents	%
Gender	Woman	113	38
	Man	172	58
	Prefer not to disclose	11	4
Experience	<1 year	5	2
	1 - 5 years	45	15
	6 – 10 years	33	11
	11 – 20 years	109	37
	> 20 years	105	35
Clinical duty	15 weeks or less	7	2
	Between 16 and 25 weeks	19	6
	Between 26 and 35 weeks	36	12
	36 weeks or more	235	79
Acute Pain Service available	Yes	179	60
	No	113	38
	Uncertain	4	1
Province of practice	British Columbia	27	9
	Alberta	15	5
	Saskatchewan	7	2
	Manitoba	10	3
	Ontario	48	16
	Québec	173	58
	New Brunswick	5	2
	Nova Scotia	0	0
	Prince Edward Island	9	2
	Newfoundland and Labrador	4	1
	Northwest Territories	0	0
	Yukon	0	0
	Nunavut	0	0

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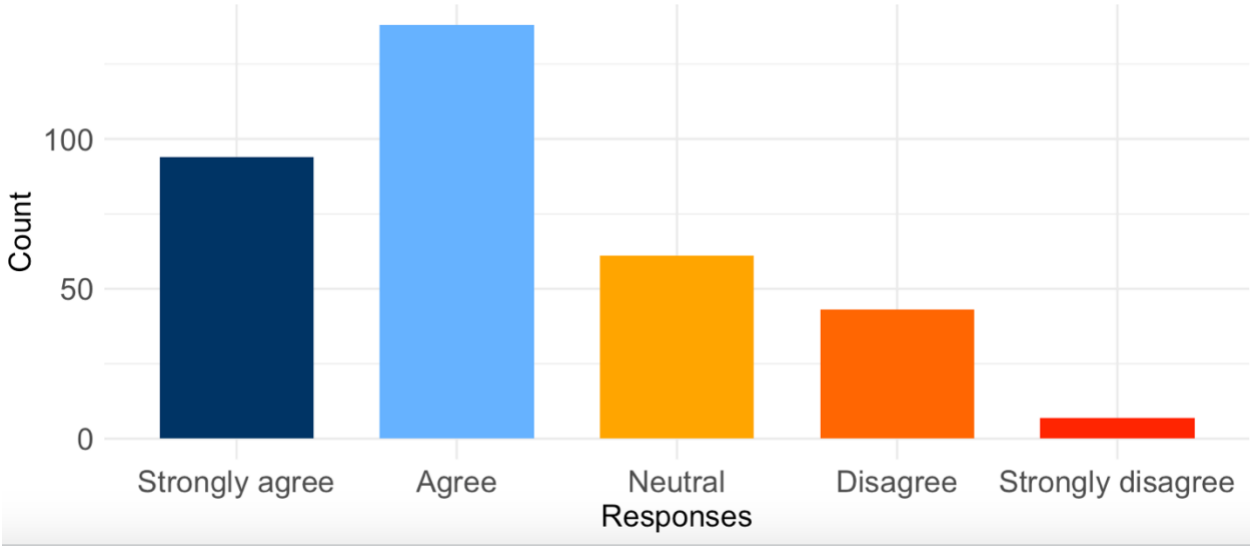
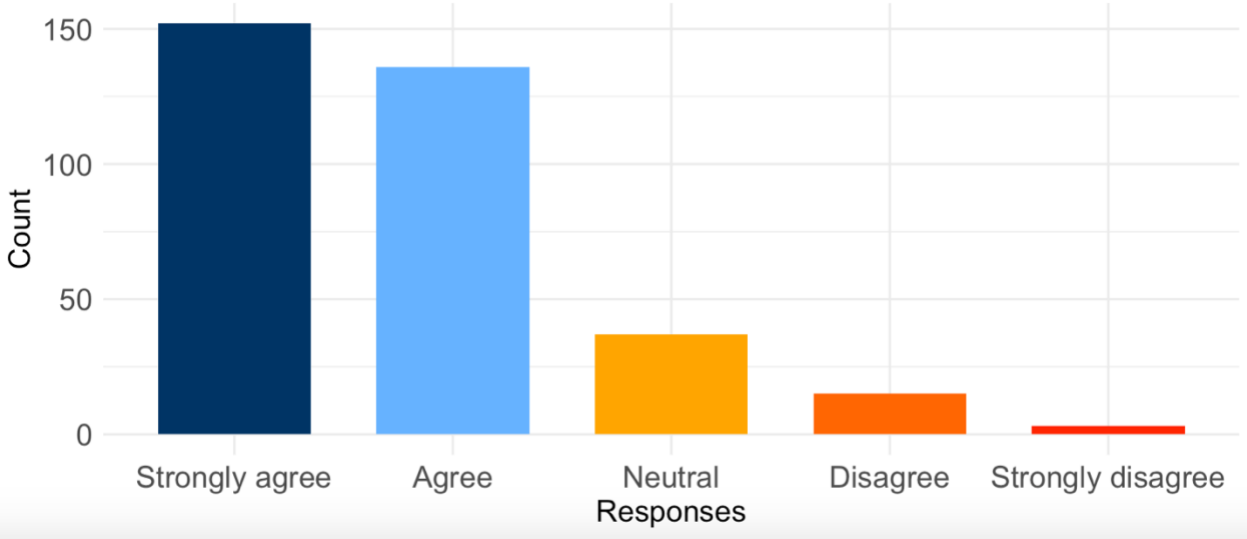
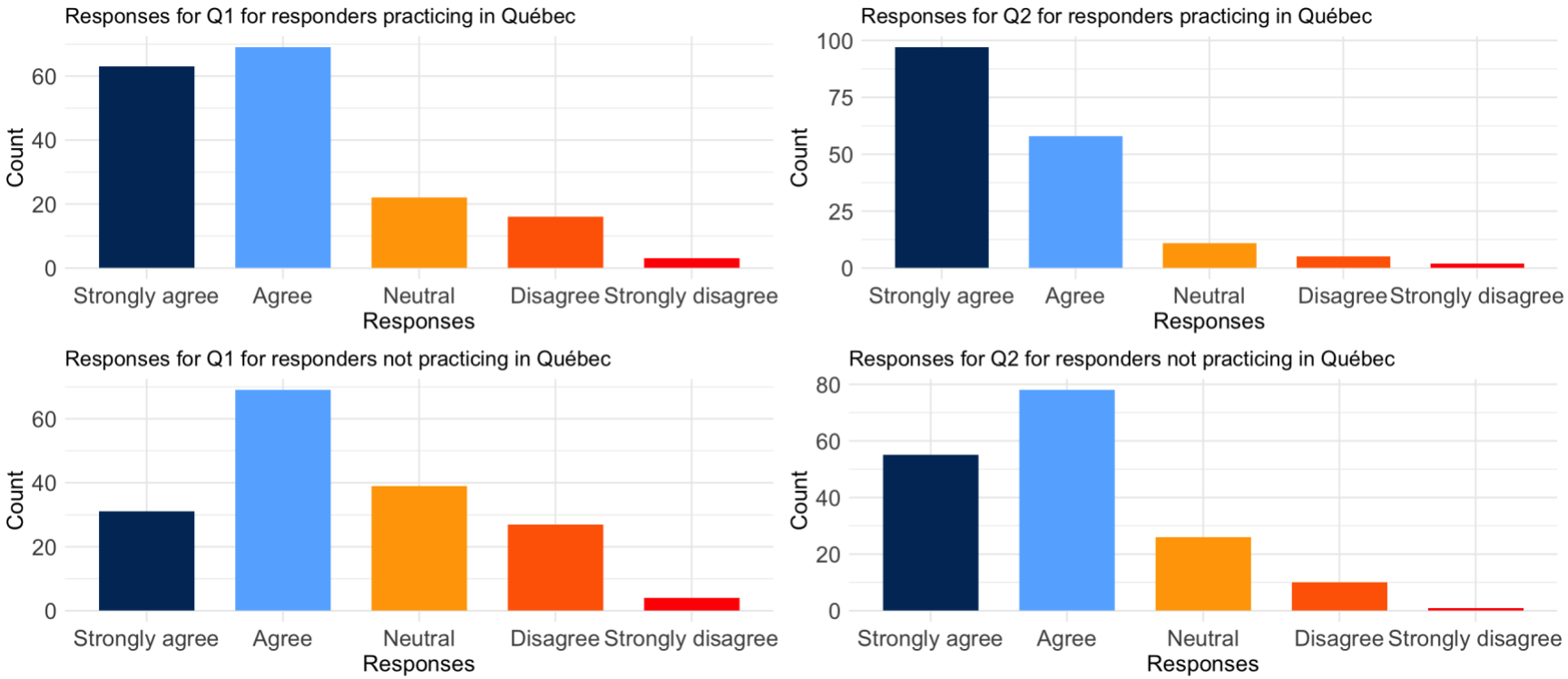


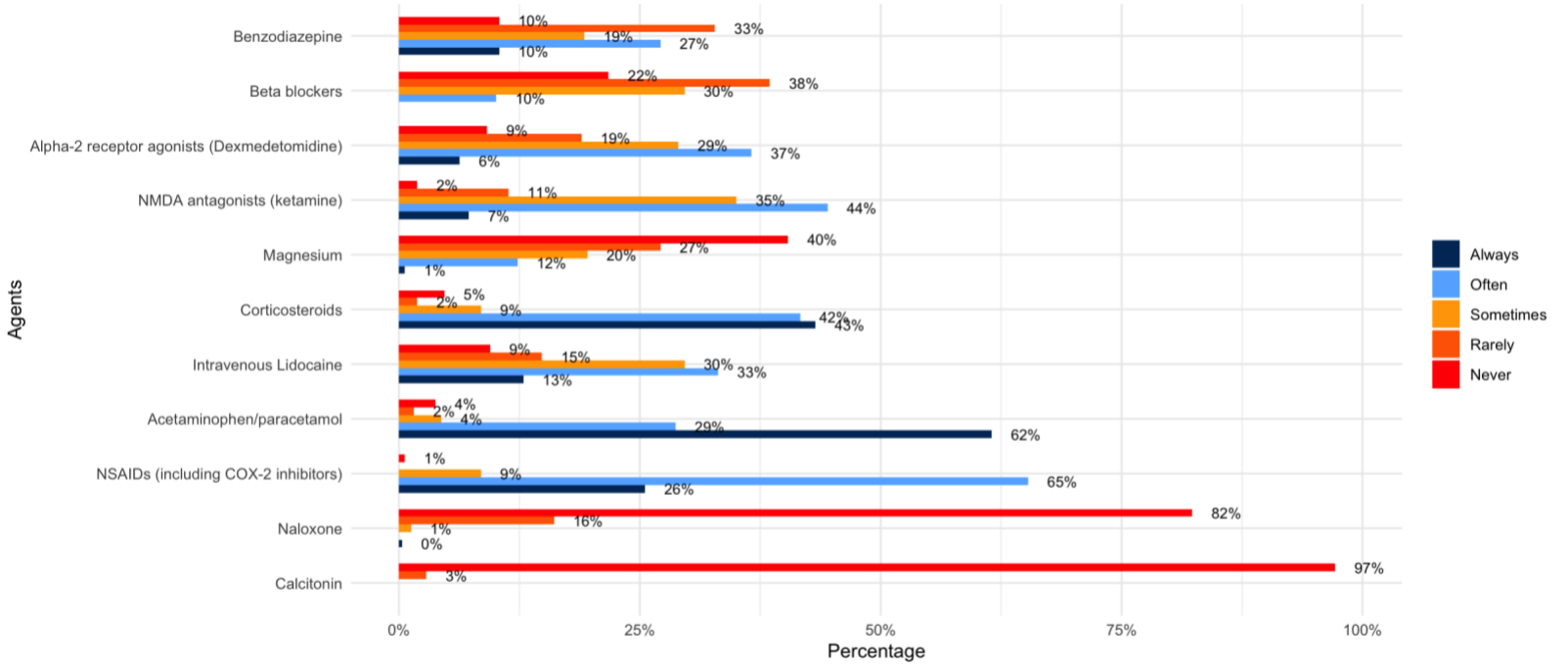
eFigure 1. Distribution of responses for question 1 (How strongly do you agree or disagree that, in general, limiting opioid exposure during the intraoperative period for adult patients undergoing general anesthesia for non-cardiac surgery is important?)



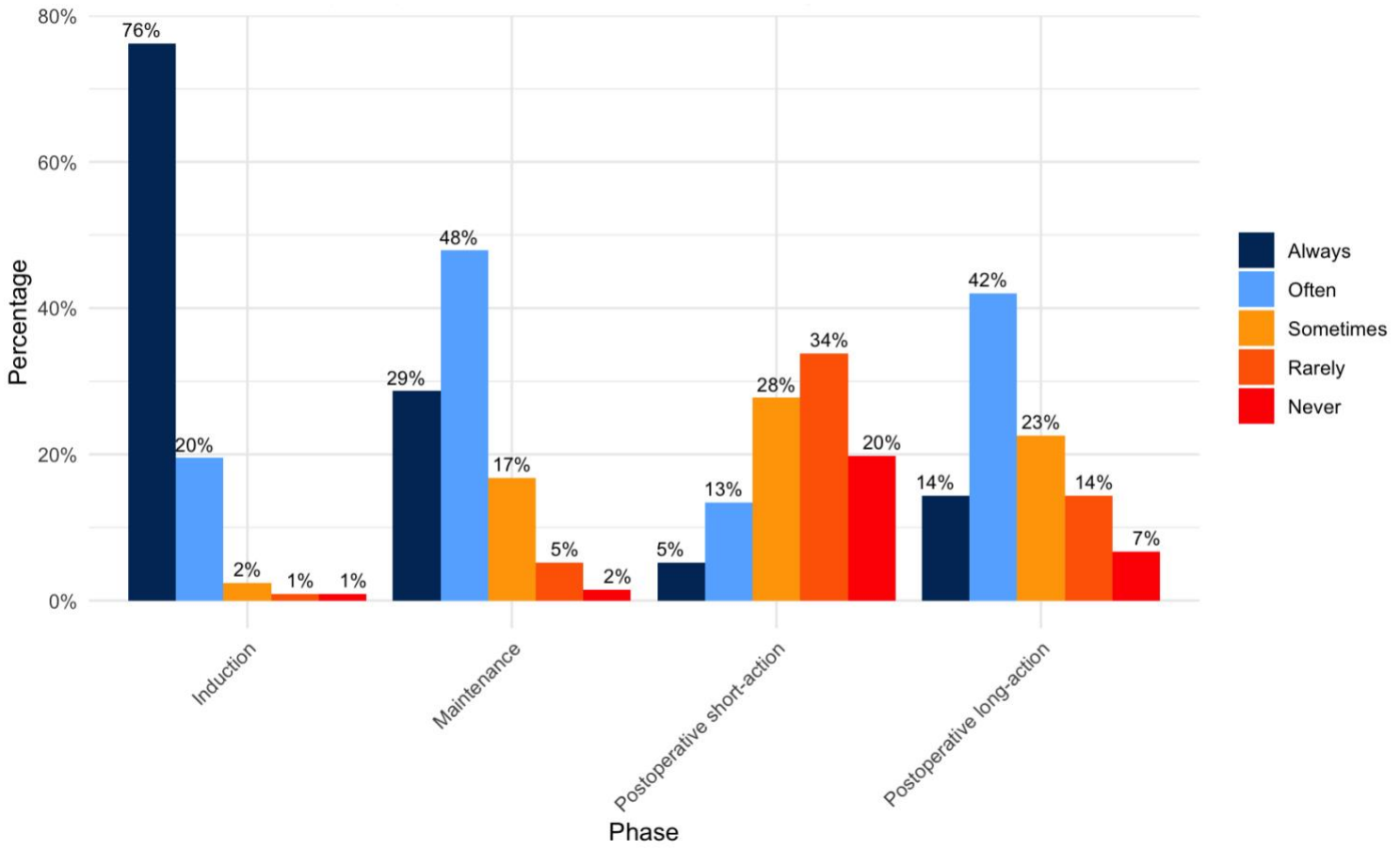
eFigure 2. Distribution of responses for question 2 (How strongly do you agree or disagree that, in general, the use of an intraoperative pharmacologic opioid minimization strategy (i.e. alternatives to opioids that can be used to minimize opioid administration during general anesthesia) can improve postoperative clinical outcomes (including pain control) for adult patients undergoing non-cardiac surgery?)



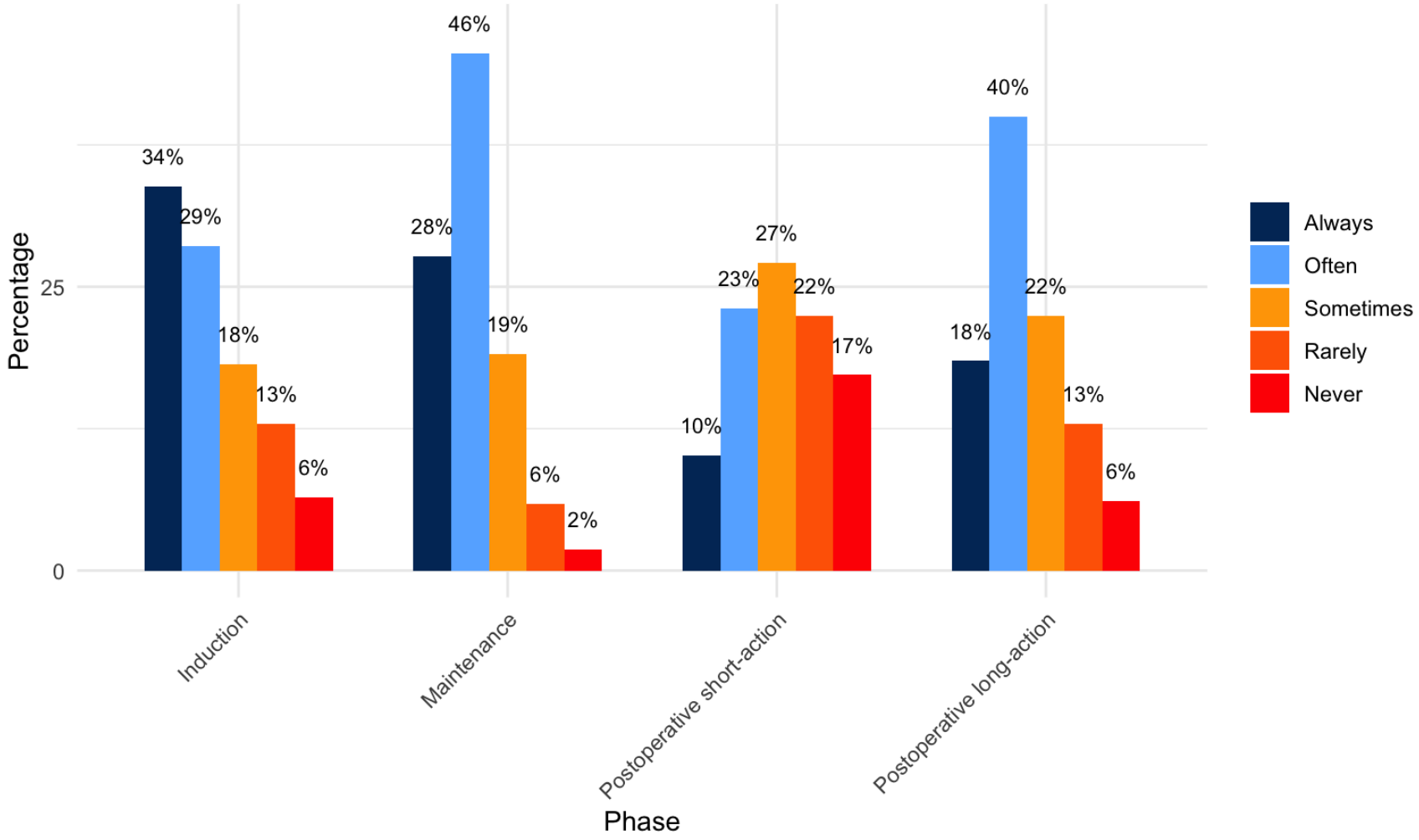
eFigure 3. Distribution of responses for questions 2 and 3 stratified for responders practicing in the province of Québec vs. outside the province of Québec (How strongly do you agree or disagree that, in general, the use of an intraoperative pharmacologic opioid minimization strategy (i.e. alternatives to opioids that can be used to minimize opioid administration during general anesthesia) can improve postoperative clinical outcomes (including pain control) for adult patients undergoing non-cardiac surgery?)



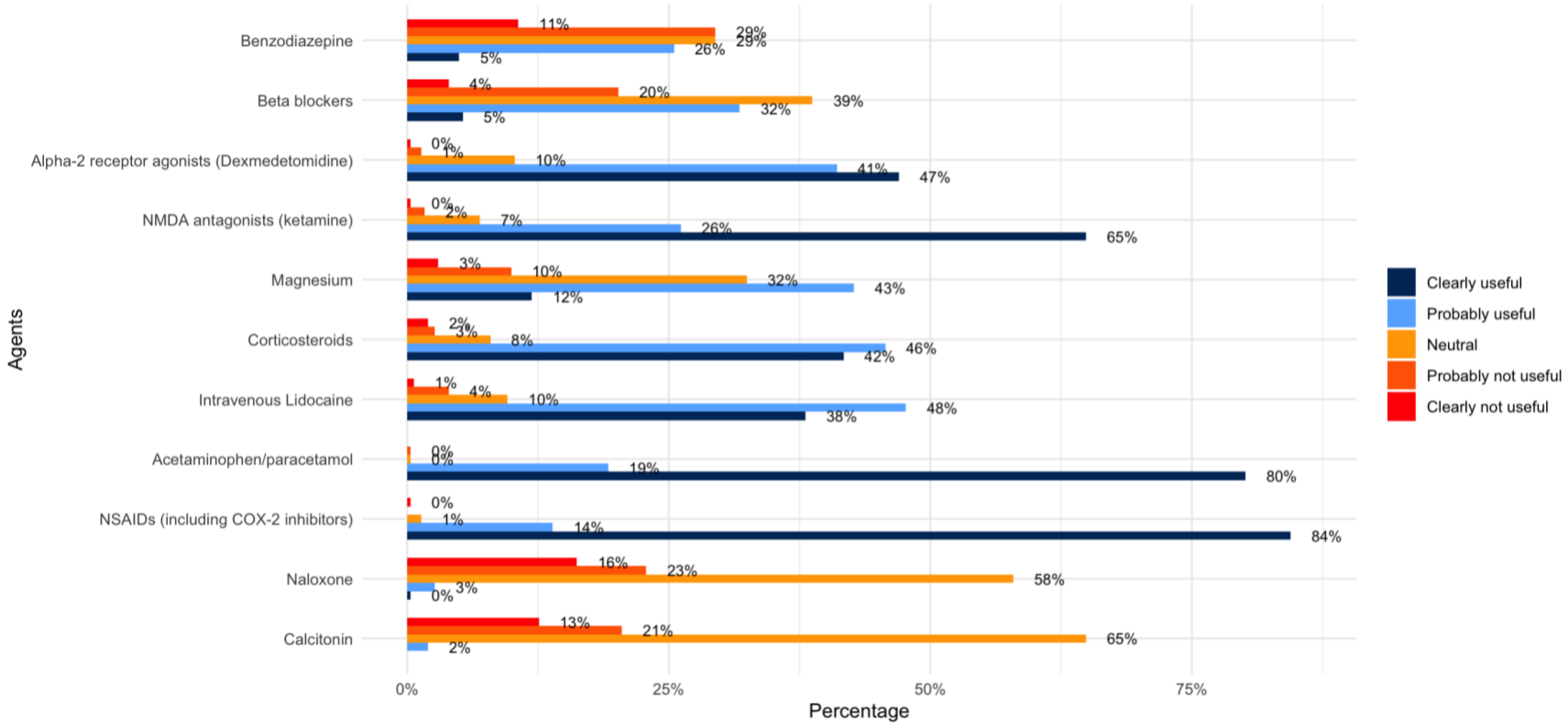
eFigure 4. Distribution of responses for question 3 (In your current clinical practice, how frequently do you use these intraoperative pharmacologic opioid minimization strategies (i.e. alternatives to opioids that can be used to minimize opioid administration during general anesthesia) for adult patients undergoing non-cardiac surgery?)



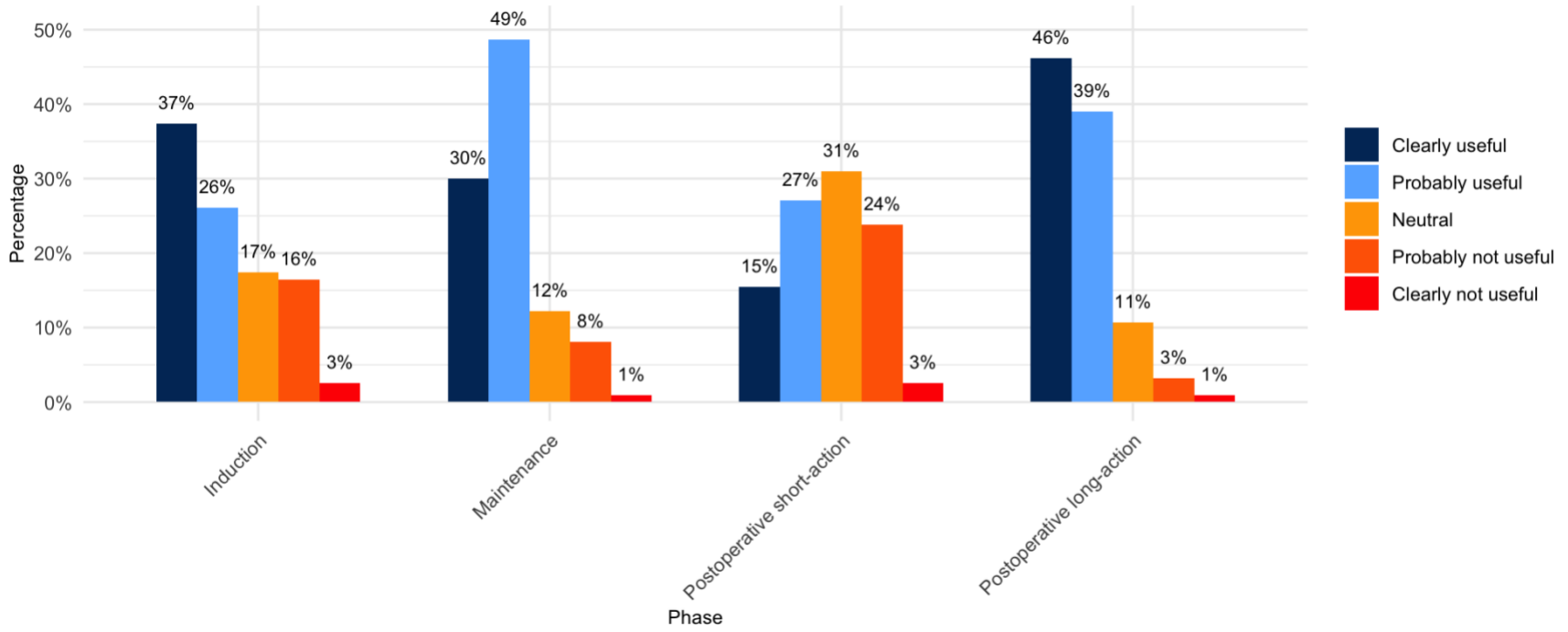
eFigure 5. Distribution of responses for question 4 (In your current clinical practice, in general, when providing general anesthesia for adult surgical patients undergoing non-cardiac surgery, how frequently do you use opioids for the following phases of care?)



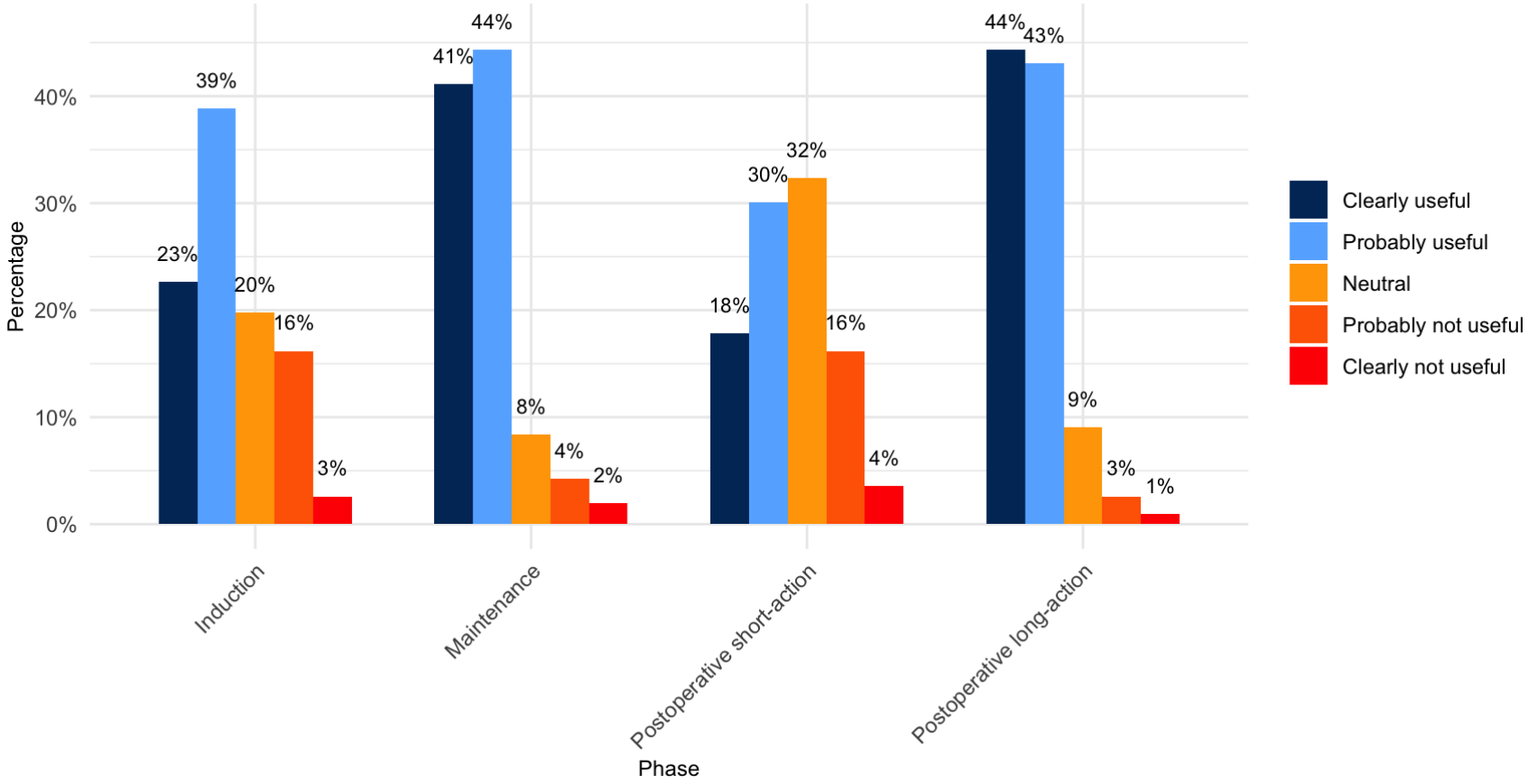
eFigure 6. Distribution of responses for question 5 (In your current clinical practice, in general, when providing general anesthesia for adult surgical patients undergoing non-cardiac surgery, how frequently do you use opioid minimization strategies for the following phases of care?)



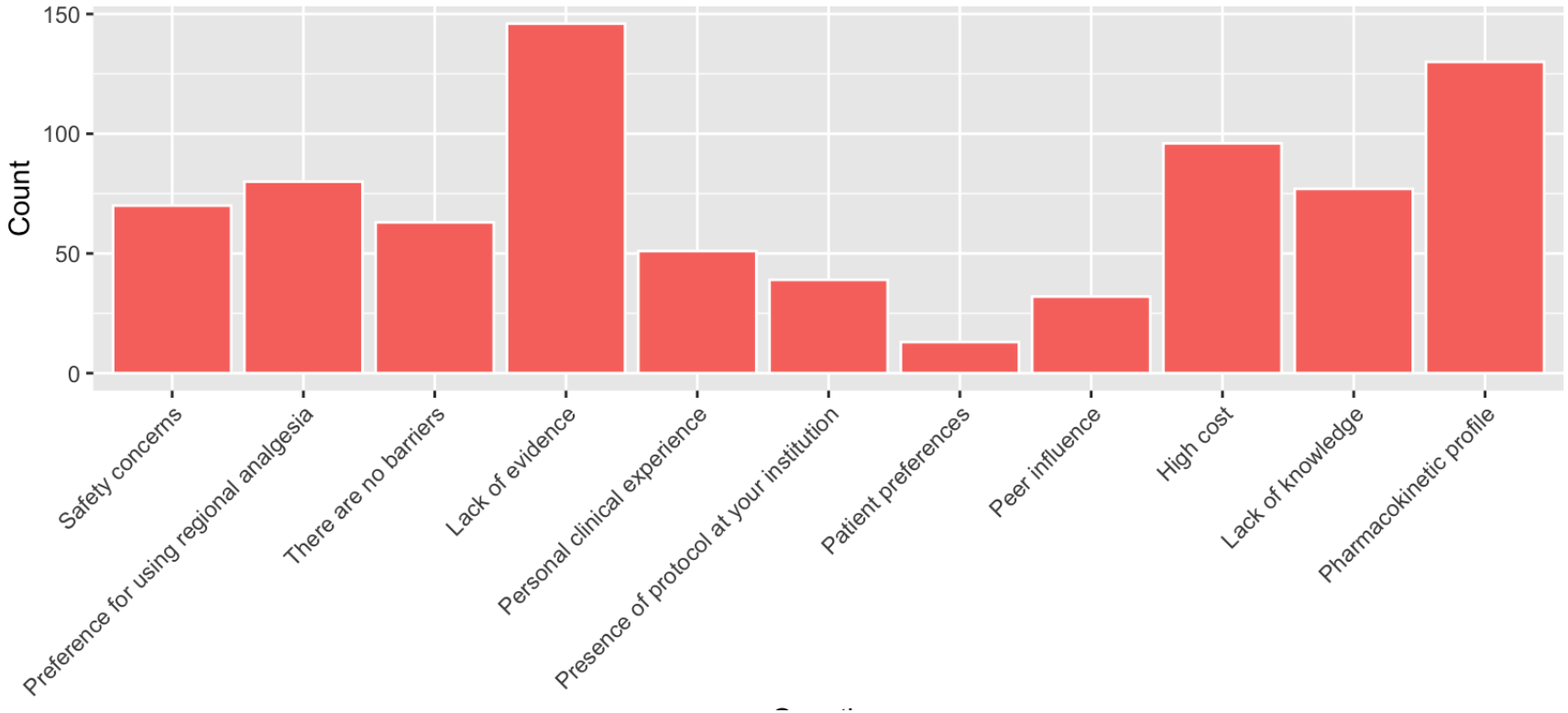
eFigure 7. Distribution of responses for question 7 (In general, when providing general anesthesia for adults undergoing non-cardiac surgery, according to you, how useful are the following pharmacologic opioid minimization strategies (i.e. alternatives to opioids that can be used to minimize opioid administration during general anesthesia) to improve postoperative clinical outcomes, including pain control?)



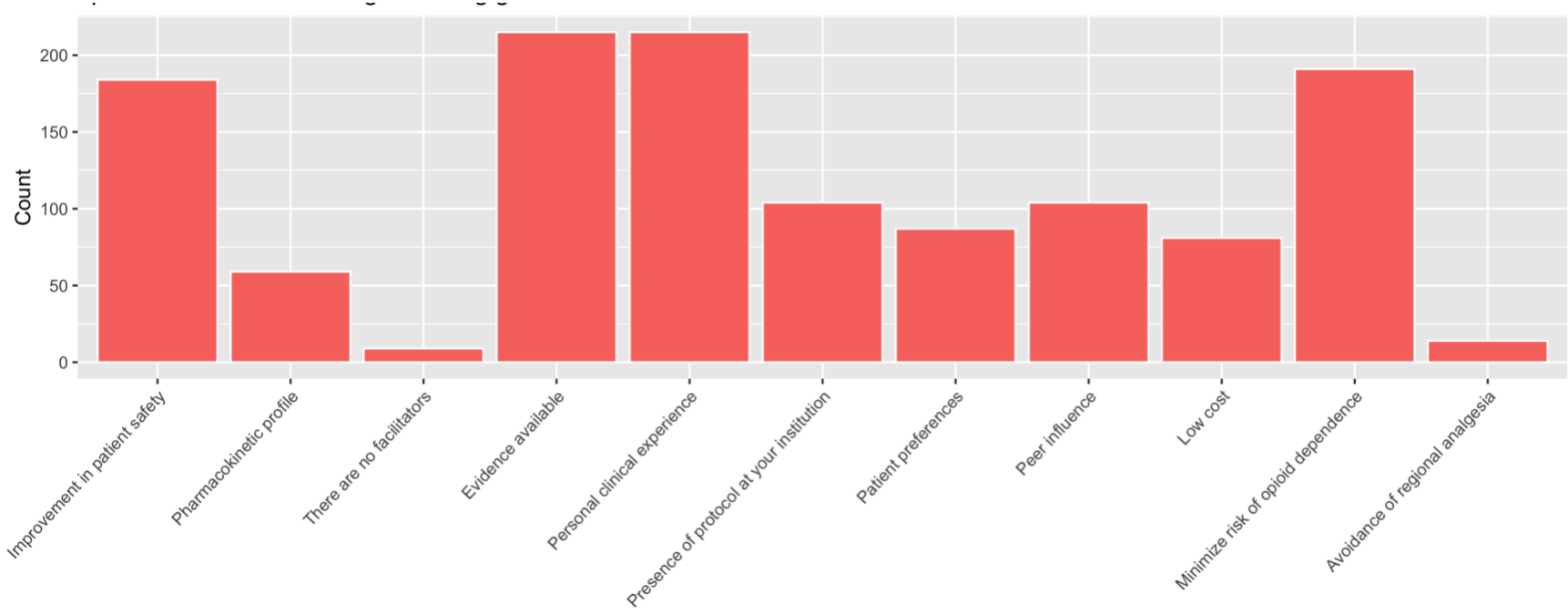
eFigure 8. Distribution of responses for question 8 (In general, when providing general anesthesia for adults undergoing non-cardiac surgery, according to you, how useful are opioids to improve postoperative clinical outcomes, including pain control)



eFigure 9. Distribution of responses for question 9 (In general, when providing general anesthesia for adults undergoing non-cardiac surgery, according to you, how useful are pharmacologic opioid minimization strategies (i.e. alternatives to opioids that can be used to minimize opioid administration during general anesthesia) to improve postoperative clinical outcomes, including pain control)



eFigure 10. Barriers for the use of opioid minimization strategies



eFigure 11. Facilitators for the use of opioid minimization strategies

eTable 1. Importance of clinical context factors to decide on the use or the non-use of pharmacologic opioid minimization strategies (Question 6)

Clinical context factors	Level of importance (%)					
	Very important	Somewhat important	Neutral	Somewhat unimportant	Very unimportant	Uncertain
Age	29	50	12	4	5	0
Patient sex	2	5	43	13	35	2
Patient with coronary artery disease	10	39	33	12	6	1
Chronic pain condition	77	17	4	0	2	0
Chronic opioid use	82	14	2	0	1	0
Cancer history	6	28	44	10	10	2
History of opioid-related adverse events (ie. nausea vomiting hallucination)	63	32	3	0	1	0
Patient with sleep apnea disorder	53	41	4	1	2	0
Patient preferences for avoiding opioids	57	34	5	1	2	1
Patient undergoing a surgery associated with high pain intensity	73	20	4	1	2	0
Patient undergoing outpatient surgery	33	48	14	3	3	0
Patient experiencing tachycardia	10	24	40	10	12	4
Patient experiencing hypertension	9	27	39	10	12	3
Patient with high nociceptive index on nociceptive monitoring (i.e.	13	17	13	1	11	45

NOL index or other)						

eTable 2. Importance of postoperative outcomes for influencing the choice of using or not using pharmacologic opioid minimization strategies (question 10)

Outcomes	**Level of importance (%)**				
	Very important	**Somewhat important**	**Neutral**	**Somewhat unimportant**	**Very unimportant**
Postoperative acute pain intensity	81	16	2	0	0
The impact of acute pain on functioning	69	26	4	1	0
Postoperative chronic pain incidence	62	27	8	2	1
Short-term opioid use (<3 months)	32	44	16	5	3
persistent postoperative opioid use	50	29	13	5	3
Patient well-being (Quality of Recovery scale)	65	29	5	1	0
Patient satisfaction with care	60	32	6	1	0
Opioid-related adverse events after surgery	66	29	4	1	0
Hospital length of stay	37	38	19	6	0
Cardiopulmonary complications	46	34	15	4	2
Mortality	49	22	20	5	3
Delirium	59	33	6	1	1

eTable 3. associations between perceived usage (Q3) and perceived usefulness (Q7) using Spearman rho correlation coefficients.

Opioid minimization strategy	**Spearman rho correlation coefficients**
Benzodiazepine	0.51
Beta blockers	0.55
Alpha-2 receptor agonists (Dexmedetomidine)	0.62
NMDA antagonists (ketamine)	0.50
Magnesium	0.64
Corticosteroids	0.48
Intravenous Lidocaine	0.56
Acetaminophen/paracetamol	0.22
NSAIDs (including COX-2 inhibitors)	0.36
Naloxone	0.11
Calcitonin	-0.07

Appendix 1. Survey questionnaire (English version)

Use of Opioids and Opioid Alternatives During General Anesthesia: A Pan-Canadian Survey Among Anesthesiologists

We developed this short survey to assess Canadian anesthesiologists' opinions on the use of intraoperative opioids and pharmacologic strategies aimed at minimizing or complement opioid use in adult patients during general anesthesia for non-cardiac surgery. The beliefs and attitudes underlying the use of these different strategies are uncertain. This survey will be used to inform the design of a systematic review and a clinical trial on the use of opioids and opioid alternatives during general anesthesia.

Eligibility

In your current clinical practice, do you manage **adult patients undergoing non-cardiac surgery?**

a. Yes
b. No

Section A: Problem identification

In this section we would like to better understand your perspectives on the intraoperative use of opioids and pharmacologic **opioid minimization strategies**. Opioid minimization strategies are alternatives or complements to opioids that can be used to minimize opioid administration such as, but not limited to, ketamine, lidocaine, beta-blockers, magnesium, anti-inflammatory, and alpha-2-agonists.

Specifically, we are interested in the application of systemic (intravenous, subcutaneous, intramuscular or enteral administration) opioid minimization strategies during the **intraoperative** period of care for patients undergoing **general anesthesia**. For the purposes of this survey, the intraoperative period is defined as the phase of care from induction of general anesthesia to the emergence from general anesthesia.

1. How strongly do you agree or disagree that, in general, limiting opioid exposure during the intraoperative period for adult patients undergoing general anesthesia for non-cardiac surgery is important?
    a. Strongly agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly disagree

2. How strongly do you agree or disagree that, in general, the use of an intraoperative **pharmacologic opioid minimization strategy (i.e. alternatives to opioids that can be used to minimize opioid administration during general anesthesia)** can improve postoperative clinical outcomes (including pain control) for adult patients undergoing non-cardiac surgery?
    a. Strongly agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly disagree

Section B: Current practices
In this section we would like to better understand your clinical practices regarding the use of opioids, and their alternatives, during the intraoperative period of care.

3. In your current clinical practice, how frequently do you use these **intraoperative pharmacologic opioid minimization strategies** (i.e. alternatives to opioids that can be used to minimize opioid administration during general anesthesia) for adult patients undergoing non-cardiac surgery?

	Always	**Often**	**Sometimes**	**Rarely**	**Never**
Benzodiazepine	□	□	□	□	□
Beta blockers	□	□	□	□	□
Alpha-2 receptor agonists (Dexmedetomidine)	□	□	□	□	□
NMDA antagonists (ketamine)	□	□	□	□	□
Magnesium	□	□	□	□	□
Corticosteroids	□	□	□	□	□
Intravenous Lidocaine	□	□	□	□	□
Acetaminophen/paracetamol	□	□	□	□	□
NSAIDs (including COX-2 inhibitors)	□	□	□	□	□
Naloxone	□	□	□	□	□
Calcitonin	□	□	□	□	□
Other	□	□	□	□	□

Please name.

4. In your current clinical practice, in general, when providing general anesthesia for adult surgical patients undergoing non-cardiac surgery, **how frequently** do you use **opioids** for the following phases of care?

	Always	**Often**	**Sometimes**	**Rarely**	**Never**
Induction	□	□	□	□	□
Maintenance	□	□	□	□	□

Emergence (short-acting for the extubation phase)	□	□	□	□	□
Emergence (long-acting for reducing pain in the recovery room)	□	□	□	□	□

5. In your current clinical practice, in general, when providing general anesthesia for adult surgical patients undergoing non-cardiac surgery, **how frequently** do you use **pharmacologic opioid minimization strategies** (i.e. alternatives to opioids that can be used to minimize opioid administration during general anesthesia) for the following phases of care?

	Always	**Often**	**Sometimes**	**Rarely**	**Never**
Induction	□	□	□	□	□
Maintenance	□	□	□	□	□
Emergence (short-acting for the extubation phase)	□	□	□	□	□
Emergence (long-acting for reducing pain in the recovery room)	□	□	□	□	□

6. In your current clinical practice, in general, when providing general anesthesia for adult patients undergoing non-cardiac surgery, **how important are the following clinical context factors to decide the use or the non-use of pharmacologic opioid minimization strategies** (i.e. alternatives to opioids that can be used to minimize opioid administration during general anesthesia)?

	Very important	**Somewhat important**	**Neutral**	**Somewhat unimportant**	**Very unimportant**	**Not sure**
Age	□	□	□	□	□	□
Patient sex	□	□	□	□	□	□
Patient with coronary artery disease	□	□	□	□	□	□

Chronic pain condition	□	□	□	□	□	□
Chronic opioid use	□	□	□	□	□	□
Cancer history	□	□	□	□	□	□
History of opioid-related adverse events (ie. nausea, vomiting, hallucination)	□	□	□	□	□	□
Patient with sleep apnea disorder	□	□	□	□	□	□
Patient preferences for avoiding opioids	□	□	□	□	□	□
Patient undergoing a surgery associated with high pain intensity	□	□	□	□	□	□
Patient undergoing outpatient surgery	□	□	□	□	□	□
Patient experiencing tachycardia	□	□	□	□	□	□
Patient experiencing hypertension	□	□	□	□	□	□
Patient with high nociceptive index on nociceptive monitoring (i.e. NOL index or other)	□	□	□	□	□	□
Other	□	□	□	□	□	□

Please name.

Section C: Perceived usefulness
In this section we would like to better understand your perspectives regarding the utility of opioids, and their alternatives, during the intraoperative period of care.

7. In general, when providing general anesthesia for adults undergoing non-cardiac surgery, according to you, how **useful are the following pharmacologic opioid minimization strategies** (i.e. alternatives to opioids that can be used to minimize opioid administration during general anesthesia) **to improve postoperative clinical outcomes, including pain control?**

	Clearly useful	**Probably useful**	**Neutral**	**Probably not useful**	**Clearly not useful**
Benzodiazepine	□	□	□	□	□
Beta blockers	□	□	□	□	□
Alpha-2 receptor agonists (dexmedetomidine)	□	□	□	□	□
NMDA antagonists (ketamine)	□	□	□	□	□
Magnesium	□	□	□	□	□
Corticosteroids	□	□	□	□	□
Lidocaine	□	□	□	□	□
Acetaminophen/paracetamol	□	□	□	□	□
NSAIDs (including COX-2 inhibitors)	□	□	□	□	□
Naloxone	□	□	□	□	□
Calcitonin	□	□	□	□	□
Other	□	□	□	□	□

Please name.

8. In general, when providing general anesthesia for adults undergoing non-cardiac surgery, according to you, how useful are **opioids to improve postoperative clinical outcomes, including pain control** when used during:

	Clearly useful	**Probably useful**	**Neutral**	**Probably not useful**	**Clearly not useful**

Induction	□	□	□	□	□
Maintenance	□	□	□	□	□
Emergence (short-acting for the extubation phase)	□	□	□	□	□
Emergence (long-acting for reducing pain in the recovery room)	□	□	□	□	□

9. In general, when providing general anesthesia for adults undergoing non-cardiac surgery, according to you, how **useful** are pharmacologic **opioid minimization strategies** (i.e. alternatives to opioids that can be used to minimize opioid administration during general anesthesia) **to improve postoperative clinical outcomes, including pain control** when used during:

	Clearly useful	**Probably useful**	**Neutral**	**Probably not useful**	**Clearly not useful**
Induction	□	□	□	□	□
Maintenance	□	□	□	□	□
Emergence (short-acting for the extubation phase)	□	□	□	□	□
Emergence (long-acting for reducing pain in the recovery room)	□	□	□	□	□

Section D: Decision-making factors

10. How **important are the following postoperative outcomes** in influencing your choice of using or not using pharmacologic opioid minimization strategies in your intraoperative practice when providing care for adult patients undergoing non-cardiac surgery requiring general anesthesia?

	Very important	**Somewhat important**	**Neutral**	**Somewhat unimportant**	**Very unimportant**
Postoperative acute pain intensity	□	□	□	□	□
The impact of acute pain on functioning	□	□	□	□	□
Postoperative chronic pain incidence	□	□	□	□	□
Short-term (<3 months) postoperative opioid use	□	□	□	□	□
Persistent (>3 months) postoperative opioid use	□	□	□	□	□
Patient well-being (e.g., Quality of Recovery scale)	□	□	□	□	□
Patient satisfaction with care	□	□	□	□	□
Opioid-related adverse events after surgery	□	□	□	□	□
Hospital length of stay	□	□	□	□	□
Cardiopulmonary complications	□	□	□	□	□
Mortality	□	□	□	□	□
Delirium	□	□	□	□	□
Other outcome that you believe is either very important or absolutely essential	□	□	□	□	□

Please name.

11. What are the barriers limiting the use of **pharmacologic opioid minimization strategies** during general anesthesia? (check all that apply)
    a. Safety concerns with pharmacologic opioid minimization strategies
    b. Lack of evidence of improvement in clinical outcomes
    c. Personal clinical experience that it was not beneficial
    d. Presence of protocol at your institution that is not promoting opioid minimization strategies
    e. Patient preferences for using opioid based anesthesia
    f. Peer influence
    g. High cost of some of the pharmacologic agents
    h. Lack of knowledge about the different pharmacologic agents
    i. Preference for using regional analgesia technique
    j. Pharmacokinetic profile of some pharmacologic agents
    k. There are no barriers
    l. Other

        Please name.

12. What are the facilitators that promote the use of **pharmacologic opioid minimization strategies** during general anesthesia? (check all that apply)
    a. Evidence of improvement in patient safety
    b. Evidence of improvement in clinical outcomes
    c. Personal clinical experience that is was beneficial
    d. Presence of protocol at your institution that is promoting the use of opioid minimization strategies
    e. Patient preferences for using this type of strategy
    f. Peer influence
    g. Low cost
    h. Desire to minimize the risk of opioid dependence
    i. Preference for not using regional analgesia technique
    j. Pharmacokinetic profile of some pharmacologic agents
    k. There are no facilitators
    l. Other

        Please name.

Section E: Respondent demographics

13. For how long have you been practicing anesthesia since completion of training (end of residency)?
    a. <1 year
    b. 1-5 years
    c. 6-10 years
    d. 11-20 years
    e. Over 20 years

14. How many weeks have your practiced anesthesia over the last year (consider five days/week as a full time equivalent)
    a. 15 weeks or less (approximately 0.25 full time equivalent)
    b. Between 16 and 25 weeks (approximately 0.50 full time equivalent)
    c. Between 26 and 35 weeks (approximately 0.75 full time equivalent)
    d. 36 weeks or more (approximately 1 full time equivalent)

15. Is there an Acute Pain Service available at the main hospital where you practice anesthesiology?
    a. Yes
    b. No
    c. Not applicable (no main centre of practice)

16. In which province do you currently work (check all that apply)?
    a. British Columbia
    b. Alberta
    c. Saskatchewan
    d. Manitoba
    e. Ontario
    f. Québec
    g. New Brunswick
    h. Prince Edward Island
    i. Nova-Scotia
    j. Newfoundland and Labrador
    k. Northwest Territories
    l. Yukon
    m. Nunavut

17. Which best describes your current gender
    a. Woman
    b. Man
    c. Transgender man
    d. Transgender woman
    e. Non-binary person
    f. Prefer not to disclose

g. Prefer to self-identify:
I self-identify as:

18. Do you have further thoughts or perspectives?

Appendix 2. Survey questionnaire (French version)

Utilisation d'opioïdes et d'alternatives aux opioïdes pendant l'anesthésie générale : une enquête de pratique pancanadienne auprès des anesthésiologistes

Nous avons développé ce sondage pour mieux comprendre l'opinion des anesthésiologistes canadiens quant à leur utilisation peropératoire d'opioïdes et de diverses stratégies pharmacologiques d'épargne des opioïdes (aussi appelées compléments ou alternatives aux opioïdes) chez les patients adultes pendant l'anesthésie générale pour une chirurgie non cardiaque. Les croyances et les attitudes qui sous-tendent l'utilisation de ces différentes stratégies pharmacologiques sont incertaines. Cette enquête de pratiques servira à guider la conception d'une revue systématique ainsi qu'un essai clinique sur l'utilisation d'opioïdes et des alternatives aux opioïdes pendant une anesthésie générale.

Dans le contexte de votre pratique clinique actuelle, est-ce que votre clientèle inclut des **patients adultes nécessitant une chirurgie non cardiaque**?

a. Oui
b. Non

Section A: Identification du problème

Dans cette section, nous aimerions mieux comprendre vos points de vue sur l'utilisation peropératoire des opioïdes et des stratégies pharmacologiques d'épargne **des opioïdes**. Ces stratégies sont des alternatives ou des compléments aux opioïdes qui peuvent être utilisés pour réduire l'administration d'opioïdes (exemple : la kétamine, la lidocaïne intraveineuse, les bêta-bloqueurs, le magnésium, les anti-inflammatoires et les agonistes alpha-2).

Plus précisément, nous nous intéressons à l'administration systémique (intraveineuse, sous-cutanée, intramusculaire ou entérale) de stratégies d'épargne des opioïdes pendant la période de soins **peropératoires** pour les patients subissant une **anesthésie générale**. Aux fins de cette enquête, la période peropératoire est définie comme la phase de soins débutant lors de l'induction de l'anesthésie générale et se terminant lors de l'émergence de l'anesthésie générale.

1. En général, dans quelle mesure êtes-vous d'accord ou en désaccord avec l'importance de limiter l'exposition aux opioïdes pendant la période peropératoire pour les patients adultes subissant une anesthésie générale en contexte d'une chirurgie non cardiaque?
    a. Tout à fait d'accord
    b. D'accord
    c. Neutre
    d. Pas d'accord
    e. Pas du tout d'accord

2. En général, dans quelle mesure êtes-vous d'accord ou en désaccord pour dire que l'utilisation d'une **stratégie pharmacologique peropératoire d'épargne des opioïdes (c.-à-d. des alternatives ou compléments à l'administration d'opioïdes qui peuvent être utilisés pour minimiser l'administration d'opioïdes pendant l'anesthésie générale)** peut améliorer les issues cliniques postopératoires (y compris le contrôle de la douleur) pour les patients adultes subissant une chirurgie non cardiaque ?

a. Tout à fait d'accord
b. D'accord
c. Neutre
d. Pas d'accord
e. Pas du tout d'accord

Section B : Pratiques cliniques
Dans cette section, nous aimerions mieux comprendre vos pratiques cliniques concernant l'utilisation des opioïdes, et leurs alternatives, pendant la période de soins peropératoires.

3. Dans votre pratique clinique actuelle, à quelle fréquence utilisez-vous **ces stratégies pharmacologiques d'épargne aux opioïdes** (c.-à-d. des alternatives ou compléments à l'administration d'opioïdes qui peuvent être utilisés pour minimiser l'administration d'opioïdes pendant l'anesthésie générale) chez les patients adultes subissant une chirurgie non cardiaque?

	Toujours	Souvent	Parfois	Rarement	Jamais
Benzodiazépine	□	□	□	□	□
Bêta-bloqueurs	□	□	□	□	□
Agonistes du récepteur Alpha-2 (Dexmédétomidine)	□	□	□	□	□
Antagonistes NMDA (kétamine)	□	□	□	□	□
Magnésium	□	□	□	□	□
Corticostéroïdes	□	□	□	□	□
Lidocaïne intraveineuse	□	□	□	□	□
Acétaminophène/para cétamol	□	□	□	□	□
AINS (incluant les inhibiteurs de la COX-2)	□	□	□	□	□
Naloxone	□	□	□	□	□
Calcitonine	□	□	□	□	□
Autre	□	□	□	□	□

Nommez s'il vous plaît.

4. Dans votre pratique clinique actuelle, en général, lorsque vous procédez à une anesthésie générale à des patients chirurgicaux adultes subissant une chirurgie non cardiaque, **à quelle fréquence** utilisez-vous des **opioïdes** pour les phases de soins suivantes ?

	Toujours	**Souvent**	**Parfois**	**Rarement**	**Jamais**
Induction	□	□	□	□	□

Maintien	□	□	□	□	□
Émergence (courte durée d'action pour la phase d'extubation)	□	□	□	□	□
Émergence (action prolongée pour réduire la douleur dans la salle de réveil)	□	□	□	□	□

5. Dans votre pratique actuelle, en général, lorsque vous procédez à une anesthésie générale pour des patients chirurgicaux adultes subissant une chirurgie non cardiaque, **à quelle fréquence** utilisez-vous des **stratégies pharmacologiques d'épargne des opioïdes** (c.-à-d. des alternatives ou compléments à l'administration d'opioïdes qui peuvent être utilisés pour minimiser l'administration d'opioïdes pendant l'anesthésie générale) pour les phases de soins suivantes ?

	Toujours	**Souvent**	**Parfois**	**Rarement**	**Jamais**
Induction	□	□	□	□	□
Maintien	□	□	□	□	□
Émergence (courte durée d'action pour la phase d'extubation)	□	□	□	□	□
Émergence (action prolongée pour réduire la douleur à la salle de réveil)	□	□	□	□	□

6. En général, dans votre pratique clinique actuelle, lorsque vous procédez à une anesthésie générale pour des patients adultes subissant une chirurgie non cardiaque, quelle est l'importance des facteurs de contexte clinique ci-dessous pour orienter le choix d'utiliser ou de ne pas utiliser des **stratégies pharmacologiques d'épargne des opioïdes** (c.-à-d. des alternatives ou compléments à l'administration d'opioïdes qui peuvent être utilisés pour minimiser l'administration d'opioïdes pendant l'anesthésie générale)?

	Très important	**Assez important**	**Neutre**	**Peu important**	**Très peu important**	**Incertain**
Âge	□	□	□	□	□	□
Sexe du patient	□	□	□	□	□	□
Patient atteint d'une maladie coronarienne	□	□	□	□	□	□
Problème de douleur chronique	□	□	□	□	□	□
Consommation d'opioïdes chronique	□	□	□	□	□	□
Antécédents de cancer	□	□	□	□	□	□
Antécédents d'événements indésirables liés aux opioïdes (c.-à-d. nausées, vomissements, hallucinations)	□	□	□	□	□	□
Patient atteint d'un trouble de l'apnée du sommeil	□	□	□	□	□	□
Préférence du patient d'éviter les opioïdes	□	□	□	□	□	□
Patient subissant une chirurgie associée à une intensité élevée de la douleur	□	□	□	□	□	□
Patient subissant une chirurgie ambulatoire	□	□	□	□	□	□
Patient souffrant de tachycardie	□	□	□	□	□	□

Patient souffrant d'hypertension	□	□	□	□	□	□
Patient présentant un indice nociceptif élevé détecté à l'aide d'un outil de surveillance de la nociception (c.-à-d. indice NOL ou autre)	□	□	□	□	□	□
Autre	□	□	□	□	□	□

Nommez s'il vous plaît.

Section C : Utilité perçue
Dans cette section, nous aimerions mieux comprendre votre point de vue concernant l'utilité des opioïdes et leurs alternatives pendant la période de soins peropératoires.

7. En général, lorsque vous procédez à une anesthésie générale pour des patients adultes subissant une chirurgie non cardiaque, selon vous, quelle est **l'utilité** des **stratégies pharmacologiques d'épargnes des opioïdes** suivantes (c.-à-d. des alternatives ou compléments à l'administration d'opioïdes qui peuvent être utilisés pour minimiser l'administration d'opioïdes pendant l'anesthésie générale) en administration systémique **pour améliorer les issues cliniques postopératoires, y compris le contrôle de la douleur**?

	Clairement utile	**Probablement utile**	**Neutre**	**Probablement pas utile**	**Clairement pas utile**
Benzodiazépine	□	□	□	□	□
Bêta-bloqueurs	□	□	□	□	□
Agonistes du récepteur Alpha-2 (dexmédétomidine)	□	□	□	□	□
Antagonistes NMDA (kétamine)	□	□	□	□	□
Magnésium	□	□	□	□	□
Corticostéroïdes	□	□	□	□	□
Lidocaïne	□	□	□	□	□
Acétaminophène/ paracétamol	□	□	□	□	□
AINS (incluant les inhibiteurs de la COX-2)	□	□	□	□	□
Naloxone	□	□	□	□	□
Calcitonine	□	□	□	□	□
Autre	□	□	□	□	□

Nommez s'il vous plaît

8. En général, lorsque vous procédez à une anesthésie générale pour les adultes subissant une chirurgie non cardiaque, selon vous, dans quelle mesure les **opioïdes** sont-ils utiles **pour améliorer les issues cliniques postopératoires, y compris le contrôle de la douleur** lorsqu'ils sont utilisés pendant :

	Clairement utile	Probablement utile	Neutre	Probablement pas utile	Clairement pas utile
Induction	□	□	□	□	□
Maintien	□	□	□	□	□
Émergence (courte durée d'action pour la phase d'extubation)	□	□	□	□	□
Émergence (action prolongée pour réduire la douleur à la salle de réveil)	□	□	□	□	□

9. En général, lorsque vous procédez à une anesthésie générale pour les adultes subissant une chirurgie non cardiaque, selon vous, dans quelle mesure les **stratégies pharmacologiques d'épargne des opioïdes** sont-elles **utiles** (c.-à-d. des alternatives ou compléments à l'administration d'opioïdes qui peuvent être utilisés pour minimiser l'administration d'opioïdes pendant l'anesthésie générale) **pour améliorer les issues cliniques postopératoires, y compris le contrôle de la douleur** lorsqu'elles sont utilisées pendant :

	Clairement utile	Probablement utile	Neutre	Probablement pas utile	Clairement pas utile
Induction	□	□	□	□	□
Maintien	□	□	□	□	□
Émergence (courte durée d'action pour la phase d'extubation)	□	□	□	□	□
Émergence (action prolongée pour réduire la douleur à la salle de réveil)	□	□	□	□	□

Section D : Facteurs décisionnels

10. Quelle est **l'importance des issues cliniques postopératoires suivantes** pour guider votre décision d'utiliser ou de ne pas utiliser de stratégies pharmacologiques d'épargne des opioïdes dans votre pratique peropératoire lors de la prestation de soins à des patients adultes subissant une chirurgie non cardiaque et nécessitant une anesthésie générale?

	Très important	**Assez important**	**Neutre**	**Pas important**	**Très peu important**
Intensité de la douleur aiguë postopératoire	□	□	□	□	□
L'impact de la douleur aiguë sur le rétablissement fonctionnel	□	□	□	□	□
Incidence de la douleur chronique postopératoire	□	□	□	□	□
Utilisation postopératoire d'opioïdes à court terme (<3 mois)	□	□	□	□	□
Utilisation postopératoire persistante d'opioides (>3 mois)	□	□	□	□	□
Bien-être des patients (p. ex. échelle de la qualité du rétablissement)	□	□	□	□	□
Satisfaction des patients à l'égard des soins	□	□	□	□	□
Effets indésirables liés aux opioïdes après la chirurgie	□	□	□	□	□
Durée du séjour à l'hôpital	□	□	□	□	□
Complications cardio-	□	□	□	□	□

pulmonaires					
Mortalité	□	□	□	□	□
Délirium	□	□	□	□	□
Autres issues que vous croyez être très importantes ou absolument essentielles	□	□	□	□	□

11. Quelles sont les barrières à l'utilisation de **stratégies pharmacologiques d'épargne des opioïdes** pendant l'anesthésie générale? (cochez toutes les cases qui s'appliquent)
    a. Préoccupations à l'égard du profil de sécurité de ces stratégies pharmacologiques
    b. Manque de preuves concernant les bénéfices sur des issues cliniques
    c. Expérience clinique personnelle que ces stratégies pharmacologiques n'étaient pas bénéfiques
    d. Présence d'un protocole dans votre établissement qui ne fait pas la promotion de stratégies d'épargne des opioïdes
    e. Préférence des patients pour l'utilisation d'une anesthésie à base d'opioïdes
    f. Influence des pairs
    g. Coût élevé de certains des agents pharmacologiques
    h. Manque de connaissances sur les différents agents pharmacologiques
    i. Préférence pour l'utilisation de techniques d'analgésie régionale
    j. Propriétés pharmacocinétiques de certains agents pharmacologiques
    k. Il n'y a pas de barrière
    l. Autre
        Nommez s'il vous plaît

12. Quels sont les facilitateurs à l'utilisation de **stratégies pharmacologiques d'épargne des opioïdes** pendant l'anesthésie générale? (cochez toutes les cases qui s'appliquent)
    a. Preuves existantes de l'amélioration de la sécurité des patients
    b. Preuves existantes de l'amélioration des issues cliniques
    c. Expérience clinique personnelle que ces stratégies pharmacologiques étaient bénéfiques
    d. Présence d'un protocole dans votre établissement qui favorise l'utilisation de stratégies d'épargne des opioïdes
    e. Préférence des patients pour l'utilisation de ce type de stratégies
    f. Influence des pairs
    g. Faible coût de certaines stratégies d'épargne des opioïdes
    h. Désir de minimiser le risque de dépendance aux opioïdes
    i. Préférence d'éviter les techniques d'analgésie régionale
    j. Propriétés pharmacocinétiques de certains agents pharmacologiques
    k. Il n'y a pas de facilitateurs
    l. Autre
        Nommez s'il vous plaît.

Section E : Données démographiques

13. Depuis combien de temps pratiquez-vous l'anesthésie à partir de la fin de votre formation (la fin de la résidence) ?
    a. <1 an
    b. 1-5 ans
    c. 6-10 ans
    d. 11-20 ans
    e. Plus de 20 ans

14. Combien de semaines avez-vous pratiqué l'anesthésie au cours de la dernière année (considérez cinq jours / semaine comme un équivalent temps plein)
    a. 1 à 5 semaines ou moins (environ 0,25 équivalent temps plein)
    b. Entre 16 et 25 semaines (environ 0,50 équivalent temps plein)
    c. Entre 26 et 35 semaines (environ 0,75 équivalent temps plein)
    d. 36 semaines ou plus (environ 1 équivalent temps plein)

15. Y a-t-il un service de traitement de la douleur aiguë (*Acute Pain Service*) disponible à l'hôpital principal où vous pratiquez l'anesthésiologie ?
    a. Oui
    b. Non
    c. Non applicable (pas de centre de pratique principal)

16. Dans quelle province travaillez-vous actuellement (cochez toutes les cases qui s'appliquent)?
    a. Colombie-Britannique
    b. Alberta
    c. Saskatchewan
    d. Manitoba
    e. Ontario
    f. Québec
    g. Nouveau-Brunswick
    h. Île-du-Prince-Édouard
    i. Nouvelle-Écosse
    j. Terre-Neuve-et-Labrador
    k. Territoires du Nord-Ouest
    l. Yukon
    m. Nunavut

17. Lequel décrit le mieux votre genre actuel
    a. Femme
    b. Homme
    c. Homme transgenre
    d. Femme transgenre
    e. Personne non binaire

f. Préfère de ne pas divulguer
g. Préfère l'auto-identification :
Je m'identifie comme:

18. Avez-vous d'autres pensées ou perspectives?

Chapter 6. Manuscript 5 - Pilot clinical trial protocol

6.1 Preface to manuscript 5

While dexmedetomidine was identified as the most promising opioid minimization strategy (Chapter 3), the systematic review demonstrated that the certainty of evidence supporting its patient-centred effectiveness was low (Chapter 4). We also identified high variation for the reported use of intraoperative dexmedetomidine (Chapter 5). Given the evidence, I developed a multicentre pilot RCT to assess the feasibility of a pan-Canadian multicentre pragmatic RCT to address this knowledge-to-evidence gap. Ultimately, this pan-Canadian multicentre pragmatic RCT will evaluate the patient-centred effectiveness of intraoperative dexmedetomidine for adult patient undergoing non-cardiac surgery. Co-authors involved in this project helped supervise the project, revised the manuscript, and developed the analytical plan. Patient partners and partner organizations contributed to refining the research question, provided input on the design of the study as well as on the development of the dissemination and recruitment plan (participants and centres).

This project has not been submitted for funding, publication, and research ethics approval.

6.2 Manuscript 5

1. The need for a trial

1.1.1 What is the problem to be addressed?

Over 40 million people worldwide are opioid dependent with opioid consumption, overdose, and death increasing steadily over the last two decades particularly in North America.[1] In Canada, we are experiencing an opioid public health emergency (aptly called the opioid crisis), with an average of 20 opioid-related deaths occurring every day.[2,3] Recognizing and responding to the opioid crisis is a major public health priority for the Canadian Government as well as provincial governments with the Government of Canada "*taking action through a comprehensive, collaborative, compassionate and evidence-based approach to drug policy".*[4] Given the urgency of the opioid crisis, identifying effective strategies to confront and address the issue is needed on several fronts involving numerous disciplines and communities.[5]

With this aim in mind, attention needs to be given to the **widespread routine use of opioids in patients undergoing surgery**, including the intraoperative period.[6,7] Intraoperative opioid administration has been recognized as a standard of care for over fifty years to complement general anesthesia for patients undergoing surgery in order to maintain overall stability (heart rate, blood pressure, metabolic) and reduce postoperative pain.[7] However, intraoperative opioids may paradoxically **contribute to increased pain after surgery as well as poor patient-centred outcomes** (i.e., outcomes that are meaningful to the patients) including well-being, functional outcomes, patient satisfaction, impact on ability to perform daily life activities, and quality of life.[8-24] Pain after surgery is still a major challenge affecting patient recovery and the current use of opioids is associated with mixed results at best.[25,26] The impact from adverse effects associated with opioid use on patients experience after surgery (nausea, pruritus, constipation, confusion, respiratory depression, and tolerance) must also be considered.[8,27,28]

1.1.2 What is a possible solution?

Given that patient opioid exposure often begins during the intraoperative period,[29-31] multiple identified knowledge users (Health Canada, Choosing Wisely Canada, SolvingPain)[32,33] have advised pharmacologic opioid-minimization strategies be developed and carefully assessed. Moreover, they advise using an integrated knowledge translation approach involving patient partners and other key stakeholders, as well as focussing on patient-centred outcomes. The emphasis on *intraoperative* opioid minimization strategies was confirmed as a patient and caregiver priority in Canada through the recent James Lind Alliance led *Canadian Anesthesia Research Priority Setting*.[34]

Across all pharmacologic opioid minimization strategies currently used in surgical patients requiring general anesthesia, dexmedetomidine (an alpha-2 agonist) is one of the most promising agents to improve patient-centred outcomes.[35] It is frequently used during surgery in order to reduce the surgical stress response (i.e., metabolic and physiological response to the surgical trauma)[36-39] and it was shown to be associated with a significant reduction in postoperative opioid use.[40,41] In our foundational work for this RCT, we confirmed that dexmedetomidine was a promising opioid minimization strategy that may improve important patient-centred outcomes after surgery (section 1.3.6).[35] Dexmedetomidine thus offers an opportunity not only for reducing opioid exposure, but also improving outcomes that are meaningful to patients. However, the certainty of evidence (i.e., how confident we are that an effect measure is correct and that it can support a recommendation)[42] to inform practice remains low[43] and, thus, there is a need for a large pragmatic, multicentre RCT to help define practice.

1.2 What are the principal research questions to be addressed in the dexOPUS trial?

Our main objective is to determine the feasibility of conducting a large pan-Canadian multicentre pragmatic RCT to evaluate the patient-centred effectiveness of dexmedetomidine administered during surgery. The dexOPUS pilot feasibility RCT (Vanguard phase) will focus on the assessment of three outcome measures:

Primary feasibility outcome: Patient recruitment rate (i.e., proportion of eligible patients that are enrolled).

Secondary feasibility outcomes: Protocol adherence and retention, and compliance with the primary outcome assessment (QoR-15 questionnaire).

Our future large RCT will assess the patient-centred effectiveness of dexmedetomidine compared with usual care among adult surgical patients undergoing non-cardiac surgery. Patient-centred effectiveness will be defined as :

Primary outcome: Quality of recovery after surgery (QoR-15) at 24h

Secondary outcomes: Acute (24h and 7 days) and long-term postoperative pain interference (Brief Pain Inventory score), health-related quality of life, functional recovery, persistent postoperative opioid use, and adverse events (bradycardia, hypotension, and tachycardia requiring intervention).

1.3 Why is an intervention study needed now?

1.3.1 Intraoperative practices

Safety of general anesthesia has drastically improved over the last 50 years.[44] However, patient expectations are increasing and the need for a minimal hospital length of stay while still offering a high

quality of recovery to patients has never been more critical, considering the rapidly increasing demand and limited resources.[45] Still, few trials have evaluated interventions to improve the quality of recovery (i.e., a patient-centred outcome) after surgery even if it is one of the most important goals for patients, physicians and administrators.[35,46,47] In the era of the worldwide opioid crisis, alternatives to opioids (i.e., opioid minimization strategies) are frequently used for off-label indications, especially during the intraoperative period while patients are under general anesthesia. As such, these alternative pharmacologic strategies must be carefully evaluated in order to protect patient safety and provide care according to the highest level of evidence possible. Through our scoping review,[35] systematic review,[43] and survey of Canadian anesthesiologists,[39] dexmedetomidine has been identified as a promising opioid minimization strategy that could improve patient-centred outcomes, such as the quality of recovery after surgery.

1.3.2 Dexmedetomidine as a promising opioid minimization strategy

Dexmedetomidine is an alpha-2 agonist frequently used during surgery in order to reduce surgical stress response, reduce opioid exposure, and potentially improve postoperative outcomes.[36-38] Its impact on short-term postoperative opioid use has been demonstrated (sufentanil reduction during the first 24h after surgery; MD:-13.77µg, 95%CI[-18.56 to -8.97]).[40,41] While it shares some of the short-term benefits associated with opioids (reduction in the surgical stress response and pain), it is not associated with opioid-related adverse effects such as respiratory depression and nausea or vomiting.[48,49] Mechanisms of action implicated are the enhancement of the descending inhibitory nociceptive pathway, and decrease norepinephrine secretion in the central nervous system due to pre-synaptic stimulation of alpha-2 receptors.[50] Perioperative dexmedetomidine also exerts anti-inflammatory properties as shown by a reduction of pro-inflammatory markers (Interleukin-6 mean reduction on the first postoperative day: − 41.55, 95% CI[− 57.41 to − 25.70 pg/ml]) when used during and after general anesthesia based on the results from a meta-analysis of 15 RCTs (n=641 participants).[51] Furthermore, it is associated with a reduction in postoperative delirium, a reduction in postoperative pain, and a reduction in shivering, which could potentially improve patient experience and comfort (i.e., the quality of recovery after surgery).[52-55]

1.3.2 The need to integrate patient-centred outcomes in perioperative research

In previous studies evaluating dexmedetomidine[56-59] and other opioid minimization strategies, the most frequently assessed outcomes were administrative (e.g. length of stay), unidimensional pain measures (e.g. visual analogue score), and indirect (e.g. short-term opioid use), limiting applicability of the

findings.[60-67] **Importantly, these outcome measures are poor surrogates of patient well-being, and are often misleading.[60,66]** Rather, patient-centred outcome measures are essential to capture the patient's global experience following surgery, including pain and pain impact on daily life.[68-70] They are defined as the "evaluation of questions and outcomes meaningful and important to patients and caregivers".[63] In RCTs of perioperative care, the most important outcome measures and instruments to be used have been established by the Standardised Endpoints in Perioperative Medicine initiative (StEP-COMPAC group [Table 3]).[71] These were developed following the Core Outcome Measures in Effectiveness Trials (COMET) recommendations.[69,72,73] Accordingly, patient-centred outcomes are classified in five domains, namely: well-being (including the quality of recovery), functional status, patient satisfaction, health-related quality of life and life impact.[71] With our multidisciplinary team of partner organizations, expert clinicians, and patient partners, we decided to also include multidimensional pain-specific measurement (acute and long-term) as well as persistent postoperative opioid use. Multidimensional postoperative acute pain instruments are defined as any instrument assessing two or more pain-related domains [e.g., physiologic, sensory, affective, cognitive, behavioural, and sociocultural])[74] and they are more relevant and applicable for patients and caregivers than unidimensional scores.[66,75,76] **Perioperative expert consensus emphasizes the urgent need for trials on perioperative opioid minimization strategies, such as dexmedetomidine,** [19,29] and **the importance of multidisciplinary, patient-centred, global health outcomes such as postoperative quality of recovery**.[6,12-24,29,77]

1.3.3 Dexmedetomodine and opioid exposure during surgery

In Canada, one million surgical procedures are performed annually and approximately 2% of adult surgical patients develop long-term postoperative opioid use. This conservatively translates into 20 000 new patients every year with long-term opioid use or dependence.[78-80] Opioids administered during perioperative care have been identified as an important modifiable risk factor for long-term opioid use after surgery,[81] which creates a supply source in the community that is subject to diversion, increased illicit use,[82,83] overdose and deaths.[84,85] Notably, perioperative opioid exposure **often begins during surgery (intraoperative period) as, almost every patient undergoing general anesthesia receive opioids during surgery**.[6,7] Importantly, **opioids used during surgery are extremely potent** (e.g., fentanyl is approximately 100 times more potent than morphine). This leads to an increased risk of opioid tolerance [86,87] and hyperalgesia [86,88] (i.e., higher pain intensity for the same stimulus) potentially reducing the quality of recovery after surgery (i.e. a patient-centred outcome).[89] Given its opioid-

reducing effect (section 1.3.2), dexmedetomidine offers an opportunity to not only minimize opioid exposure, but also to potentially improve patient-centred outcomes such as the quality of recovery.

1.3.4 Pain management during surgery represents a unique challenge

In general, opioids are controlled drugs that should be administered only when necessary, for the shortest amount of time possible, and with the lowest effective dose, based on the 2017 Canadian Guideline for Opioid Therapy [90] and Centers for Disease Control and Prevention (CDC) Clinical Practice Guideline for prescribing opioids.[91] *For patients receiving general anesthesia, this recommendation is challenging to apply, as there is no valid monitoring to evaluate nociception (i.e. pain transmission)* or reliable clinical signs of nociception to guide opioid administration.[92-94] Opioid minimization strategies such as dexmedetomidine are thus recommended, but there is very limited guidance on which agent should be prioritized and how they should be used. Of note, the level of evidence that supports perioperative recommendations in North America and Europe is generally low (1160 of 2280 recommendations [51%]), meaning that further RCTs are very likely to have an important impact on the recommendations.[95-97] Overall, a **lack of knowledge user involvement and patient-centred outcome assessment was identified as a key weakness in perioperative original studies,** resulting in limited applicability of the findings and recommendations.

1.3.5 Unexplained variation in the intraoperative use of dexmedetomidine and opioids

Over the last two decades, more than 20 pharmacologic opioid minimization strategies (i.e., non-opioid alternative strategies that can be used during and after surgery to reduce opioid exposure) have emerged.[50] Notably, many of these **perioperative pharmacologic opioid minimization strategies are being** used "off-label" and **adopted despite limited evidence to inform best practice.**[50,98,99] Opioids are still the most frequent analgesics used during and after surgery, but changes in individual practices have been observed at a global level. Based on the results from a very large multicentre observational cohort study (10 institutions, 1,104,324 participants) conducted in the United States, there has been a decrease in opioid use during surgery, while patients are under general anesthesia (i.e., approximately 15% decrease in the mean quantity of opioids administered during surgery between 2012 and 2016).[100] Importantly, a *12-fold variation in the range of opioid doses administered has been observed*.[100-102] While there are no observational studies describing specific practices for intraoperative dexmedetomidine use, there is an increased utilization of opioid minimization strategies during and after surgery and significant heterogeneity in practices that remains unexplained (i.e., including for dexmedetomidine).[101,103] This variation in practices was also reflected in the results from our pan-

Canadian survey among anesthesiologists.[39] This knowledge gap is important given that some opioid minimization strategies could be associated with meaningful adverse effects as we have shown in a previous systematic review (i.e., gabapentinoids).[99,104]

1.3.6 Summary of preliminary work to support current pilot trial

The Optimizing Patient-centred outcomes Using opioid minimization Strategies (OPUS) research program has incorporated foundational work to support a pragmatic trial evaluating dexmedetomidine (Figure 1). We completed a scoping review of RCTs to map RCTs of pharmacological opioid minimization strategies and we identified promising opioid minimization strategies that could improve patient-centred outcomes.[35] From this scoping review, we found that dexmedetomidine was a promising pharmacologic opioid minimization strategy warranting a more focused systematic review to determine the effectiveness and certainty of evidence. We thus completed a systematic review and Bayesian meta-analysis of RCTs on the patient-centred effectiveness of intraoperative dexmedetomidine.[43] Results from our systematic review and other reviews[105] have shown that dexmedetomidine has a high probability (i.e., posterior probability of 92%) of clinically meaningful effect (reaching the minimally important difference) on the quality of recovery after surgery (one of the most important patient-centred outcomes). Evidence also suggests dexmedetomine is safe.[43] We also observed from the results of our pan-Canadian survey that intraoperative dexmedetomidine is perceived as one of the most useful opioid minimization strategies to improve postoperative outcomes, while there was a significant variation in its reported use.[39]

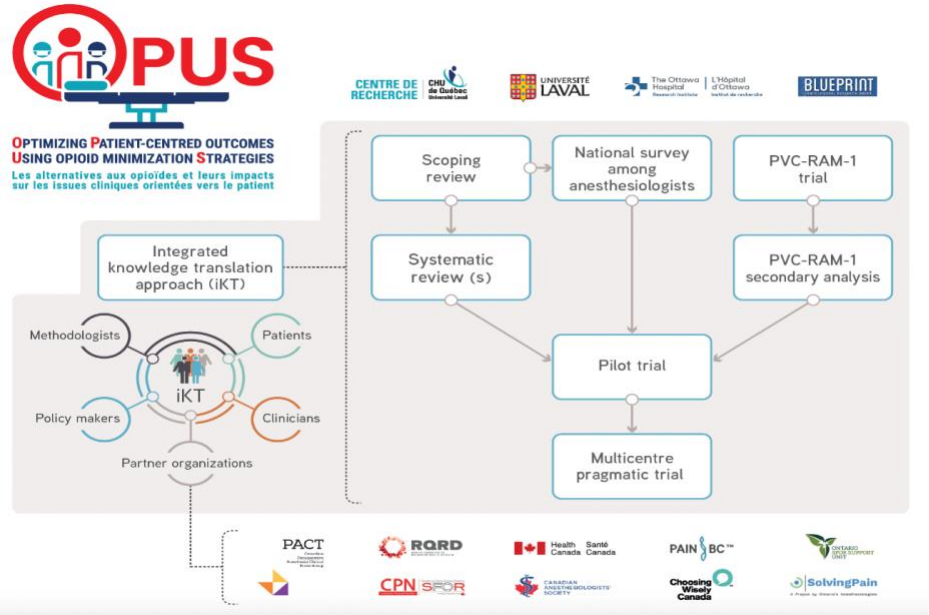


Figure 1. OPUS Research Program

1.4 How will the results of this trial be used?

Our planned large-scale multicentre RCT will have an important impact on perioperative practices regardless of the findings. If we observe a benefit from dexmedetomidine, our findings will improve patient-oriented care while reducing exposure to opioids for millions of patients. If we observe an absence of effect or meaningful adverse effects, this opioid minimization strategy (i.e., dexmedetomidine) will be discouraged. To ensure meaningful impact from our results, we have followed an integrated knowledge translation approach (iKT; Figure 1) by partnering with patient partners, partner organizations and clinicians to help ensure knowledge produced is relevant to end users (health care providers and patients).[106] Using an iKT approach, we co-created this pilot feasibility RCT (Vanguard phase) that will inform our planned large-scale RCT, more specifically 1) recruitment rate of eligible patients 2) compliance to the intervention ≥ 80%, and 3) outcome assessment (completion of the QoR-15 questionnaire).

If feasibility is demonstrated, we will conduct our planned pragmatic multicentre larger RCT and all participants recruited for this pilot RCT will be included in the larger RCT. If there are no major changes to the RCT protocol, all the data from the participants from the pilot RCT (including outcome data) will be transferred to the full trial unanalyzed. Over the course of the pilot RCT, we will collect information on barriers and facilitators to the conduct of the RCT among the three recruiting centres through online surveys and virtual meetings.

1.5 What are the risks to the safety of participants involved in the trial?

Dexmedetomidine is currently used by anesthesiologists across the world, including in Canada for patients requiring general anesthesia or sedation.[39,107] Dexmedetomidine is also routinely used for sedation in the ICU among fragile and critically ill patients; a population in which its safety has been established.[108]

Dexmedetomidine can be associated with adverse effects such as bradycardia and hypotension because of their action on alpha-2 receptors. Results from our systematic review and meta-analysis evaluating the intraoperative effectiveness of dexmedetomidine, have shown that these adverse effects can be clinically significant (i.e., requiring an intervention).[43] The management of bradycardia and hypotension is however simple, and it does not result in increased incidence of mortality or hospital length of stay. It can be effectively treated with medications that are routinely used by anesthesiologists (e.g., glycopyrrolate or atropine). We will implement strategies to mitigate the risk of significant bradycardia and hypotension in our pilot RCT. First, based on our systematic review subgroup analyses

and exhaustive review of the literature, we will use the minimally clinically effective dose of dexmedetomidine as the adverse effects (section 2.2.1)[109] of bradycardia and hypotension are dose-related (i.e., intrinsic). Second, bradycardia associated with the use of dexmedetomidine can be exacerbated in certain populations (e.g. critically ill patients[110]) or with the use of other medications.[111-113] These factors will be exclusion criteria in our RCT (Table 1). Third, the intervention will be stopped when there is a heart rate reduction of more than 30% compared with the patient baseline heart rate to ensure safety in case unanticipated severe bradycardia would occur.[114]

2. The Design Features of the Proposed Trial

2.1 What is the trial design?

We will conduct a multicentre pilot RCT (Vanguard phase) to assess the feasibility of recruitment, screening plan, and data management based on the recommendations and guidance for conducting pilot studies.[115-117] **Our pilot trial design is a parallel group randomized controlled trial comparing dexmedetomidine to usual care in adult patients undergoing elective major noncardiac surgery.** Major surgery will be defined as a surgery requiring at least one night hospital admission.[118] In our systematic review to evaluate dexmedetomidine effectiveness, the type of surgery was not identified as an important factor to explain heterogeneity, which is why we are not restricting for any type of surgery.[43] While we identified other promising opioid minimization strategies in our scoping review, we chose to focus on dexmedetomidine (i.e., 2-arm design) as it was the most promising strategy and there was a large variation in the reported use of this agent based on the results of our pan-Canadian survey.[39] We anticipate that all participants recruited for this pilot RCT will be included in the planned larger pragmatic (Appendix 1 for PRECIS-2 wheel) multicentre RCT.[119] Our protocol was prepared according to the recommendations of the SPIRIT 2013 statement and the manuscript reporting the results will be written following the CONSORT recommendations.[119-121]

2.2 What are the planned trial interventions?

2.2.1 Intervention: Intravenous dexmedetomidine, administered during general anesthesia using a bolus (over 10 minutes) and an infusion (up to 30 minutes before the end of surgery). Given that older age is associated with an increased incidence of bradycardia,[122] patients under 50 years old will be administered a bolus dose of 0.5 mcg/kg (over 10 minutes) followed by an infusion of 0.5 mcg/kg/h, while patients over 50 years old will be administered a bolus dose of 0.3 mcg/kg (over 10 minutes) followed by an infusion of 0.3 mcg/kg/h. Age adjusted doses will be prepared centrally by the pharmacy and the clinicians will need to determine the patient ideal body weight (height[cm]-100)

before administering the medication. While the initial dose of the medication will be determined and prepared centrally by the pharmacy, that anesthesiologist may alter the dose of the infusion up to 0.7 mcg/kg/h. Higher doses are not associated with increased benefits.[123,124]

2.2.2 Comparator: Our comparator will be usual care (the use of dexmedetomidine will not be permitted and access will be restricted centrally by the pharmacy). There will be a notice on top of each medical record not to use dexmedetomidine for study participants except if part of the intervention.

2.2.3 Other study maneuvers: All participants will receive general anesthesia with any general anesthetic (intravenous or gas) as per usual practice.

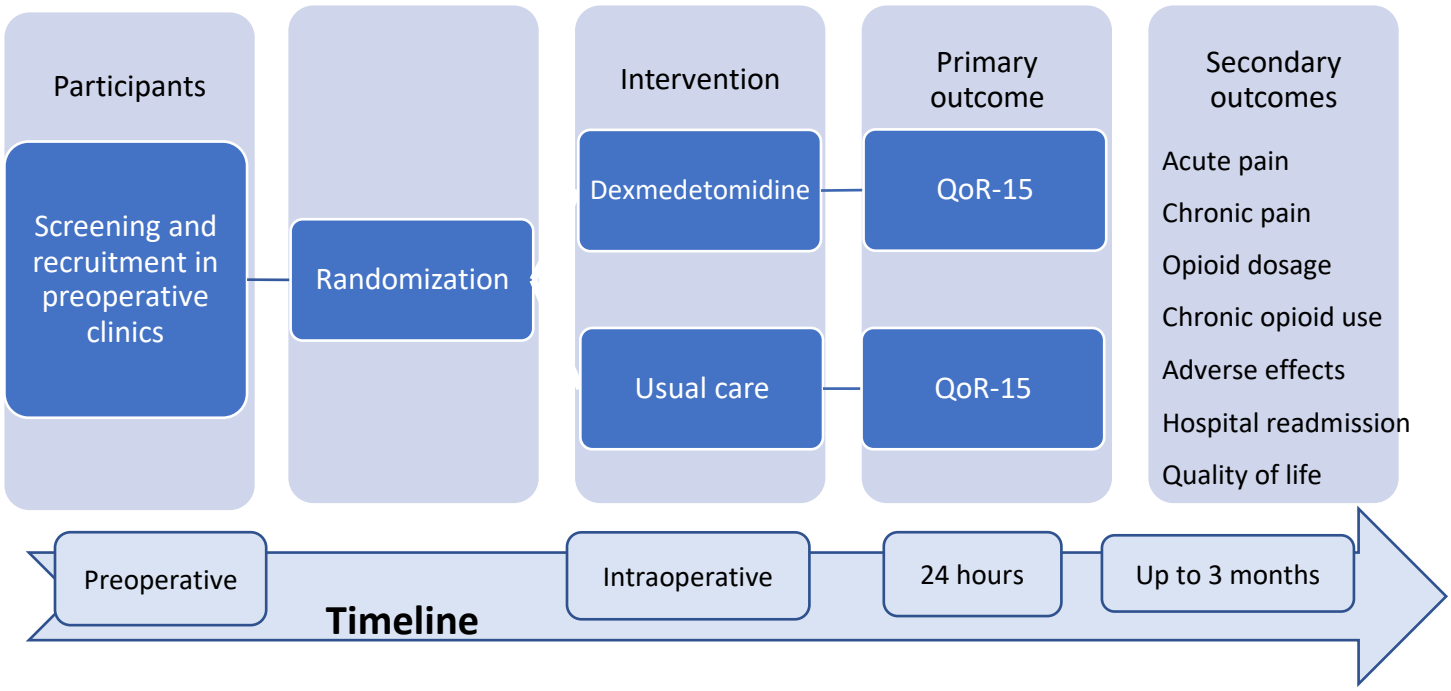


Figure 2. Overview of the design of the RCT

2.3 What are the proposed practical arrangements for allocating participants to trial groups?

We will use a web-based randomization process with computer-generated random listing of the treatment allocations stratified by centre in variable permuted blocks. Access to medical records and study data will be limited to authorized personnel listed on the study delegation log. Data will be collected using a standardized electronic case report form and the data centre will be the Clinical Trial Unit of the CRCHU. The central web-based randomization system is a voice-activated automated program that will ask questions to confirm eligibility, the enrolling centre and patient characteristics.

The system will have backup in the form of a statistician and designate at the coordinating centre, CRCHU. Only the study statistician and designate at the coordinating centre will have knowledge of the randomization codes. At the preoperative clinics of each participating site, trained research nurses will screen patients for eligibility (Table 1) and obtain informed consent. Each morning, a research assistant at the local hospital pharmacy will review the daily operative schedule to identify study participants and confirm eligibility on the day of surgery. The trained technician will then log in the centralized randomization system, enter participant information (participant identification number), and will be provided a randomization allocation. Using the participant identification number, the hospital pharmacy will then prepare the dexmedetomidine medication along with the pump device appropriate concentration (according to age, see section 2.2.1). Bags containing the medication with the pump device will be transported and placed in the anesthesia cabinet around the time the participant enters the operating room.

2.4 What are the proposed methods for protecting against sources of bias?

The study investigators, clinicians, statisticians, and patients will be blinded to treatment allocation. Research nurses collecting data and assessing outcomes will be blinded to participant assignment. They will have no contact with the participants while the intervention is ongoing (i.e., intraoperative period). The anesthesiologist administering the intervention will not be blinded to the treatment allocation due to the nature of the comparator (usual care), but they will not be involved in any other steps of the trial (e.g., outcome assessment, statistical analyses, and interpretation). To limit performance bias, we will use a standardized case report form, and we will provide training to staff (i.e., Good Clinical Practice and practice recruitment sessions in collaboration with patient partners). We have designed a relatively simple protocol and intervention to ensure wide buy-in from anesthesiologists, which should reduce the risk of attrition. Finally, we have chosen objective and semi-objective outcomes which further reduce the risk of information bias.

2.5 What are the planned inclusion/exclusion criteria?

2.5.1 Participant criteria

We will enroll adult patients undergoing non-cardiac surgery from academic (pilot RCT) and non-academic hospitals (pilot and main RCT) and we will use the following pragmatic eligibility criteria:

Table 1. Eligibility criteria

Inclusion criteria[1]	Exclusion criteria[2]
Adult (≥18yrs) patients undergoing an elective major (anticipated to require at least one night hospital stay) non-cardiac surgery requiring general anesthesia Heart rate ≥ 55 Systolic Blood pressure ≥ 100 mmHg Patients must be able to provide responses to the preoperative quality of recovery-15 (QoR-15) questionnaire in French or English	Known allergy to alpha-2 agonists Regular use of alpha-2 agonists drugs, beta-blockers, calcium channel blocker, or digoxin [111,112,125] ASA 4 or 5 [126] Obstetrical procedures or breastfeeding Anticipated bleeding > 1L Regional analgesia or anesthesia

[1] Patients must provide consent and all inclusion criteria must be satisfied to be enrolled.

[2] Only one exclusion criteria needed to exclude a participant.

2.6 What is the proposed duration of treatment period

The duration of the treatment depends on the duration of the surgery (infusion will be stopped 30 minutes before the end of surgery). The choice of 30 minutes prior to end of surgery, is based on the results of our systematic review and meta-analysis which showed no additional benefit when dexmedetomidine was continued during the postoperative period.[43]

2.7 What is the proposed frequency and duration of follow-up?

Screening, run-in, and baseline evaluation (age, sex, presence of pulmonary disease, presence of cardiac disease, mood disorder, substance use disorder, preoperative pain, preoperative QoR-15, American Society of Anesthesiology classification (ASA), Acute Pain Service consultation, and type of surgery) will be assessed and collected by trained research nurses with a standardized data collection form at the preoperative clinic in each hospital. The same standardized data collection form will be used for outcome measures and baseline assessment. Administration of the intervention will be confirmed in each hospital pharmacy using the returned intervention bag (intervention bag returned to the pharmacy at the end of the surgery). Outcome measures collected while the participant is hospitalized will be assessed by a trained research nurse at the bedside and those collected while the participant is out of the hospital will be assessed by phone interviews by a trained research nurse. Intraoperative opioid dosage, bradycardia and hypotension episodes will be collected by a trained nurse

immediately after surgery at the post anesthesia recovery unit (PACU), in order to review the anesthesia chart and to facilitate communication with the treating anesthesiologists if clarification is needed. If a participant is unable to answer the QoR-15 questionnaire after the surgery, and it is anticipated that the participant will not be able to complete the questionnaire during the first month after surgery (according to the treating physician), it will be answered by either a close relative or a trained research nurse. Evaluation of the QoR-15 in similar context has been validated and showed good intraclass correlation coefficient (ICC) between self-administered and investigators administered (ICC = 0.86 [95% CI, 0.77 to 0.92]).[127] For participants who are sedated or intubated during the postoperative period, the QoR-15 questionnaire will be administered when the participant is extubated and awake (Richmond scale score between zero and one).[128] A trained research nurse will visit intubated participants daily to reduce risk of loss to follow up. To calculate cumulative intraoperative and postoperative opioid dose, opioids administration will be converted (mg of intravenous morphine equivalent) according to an international conversion review chart.[129] When the 3-month period follow-up of a participant is completed, a blinded statistician will convert the collected data on the research form into an excel file that will be used for analysis purposes and by the DSMB.

Table 2. Schedule assessment: outcome measurement

	Baseline (preoperative clinic)	**During surgery**	**24h after surgery**	**One week**	**One month**	**Three months**
a. Patient-reported outcome measures collected by nurse						
QoR-15	x		x			
Multidimensional pain assessment (Brief Pain Inventory Short-Form)	x		x	x	x	x
Persistent opioid use				x	x	x
Quality of life (EQ-5D-5L)	x			x	x	x
Functional recovery (WHO Disability Assessment 2.0)[130]				x		
Opioid-related adverse effects (OR-SDS scale)[131]			x	x		
Nausea or vomiting			x			
b. Outcomes measures collected using routinely collected data						
Opioid use	x	x	x			

Adverse event (bradycardia, hypotension or tachycardia requiring intervention)		x	x			
Delirium (Confusion Assessment Method)				x		
Hospital Readmission					x	
Death			x	x	x	x
Hospital length of stay				x		

2.8 What are the proposed primary and secondary outcome measures

Our feasibility outcomes of the proposed pilot RCT have been chosen in consultation and collaboration with the Perioperative Anesthesia Clinical Trials (PACT, a pan-Canadian network of perioperative clinician-researchers) group and they have been determined to reflect important barriers in the conduct of RCTs in perioperative medicine [132-135] and specifically in Canada. The primary effectiveness outcome (Quality of recovery-15) is a validated patient-reported outcome measure that reflects the priorities of patients and clinicians and was also prioritized by our team of patient partners and partner organizations.[106,136]

2.8.1 Feasibility outcomes (pilot RCT, current proposal)

Primary feasibility outcome: recruitment rate (i.e., proportion of eligible patients that are enrolled)

Secondary feasibility outcomes: Protocol adherence (i.e., administration of the intervention), compliance with outcome assessment (i.e., completion of the QoR-15 questionnaire at 24h)

Decision to proceed to full (main) trial: We used the traffic light system developed by the Medical Research Council (MRC) Hubs for Trials Methodology Research to determine our criteria for the progression from pilot to main RCT (Table 3).[137] Satisfaction of feasibility criteria for initiating the main trial (after 6 months) will be assessed with our steering committee (section 3.3).[138] Recruitment challenges will be assessed with focus group discussions, including all sites PI and two patient partners, on a monthly basis and these discussions will be co-lead by a patient engagement facilitator (Québec SPOR Support Unit-SSA affiliated with Université Laval).

Table 3. Criteria to decide on the progression from pilot RCT to main RCT

	Feasibility outcome measures		
Lights	**Recruitment**	**Protocol adherence**	**Outcome assessment**
Green (go)	≥75 %	≥80%	≥90
Yellow (amend)	50 to 75%	70-80%	80-90%
Red (stop)	<50%	<70%	<80%

*At least a yellow light for all feasibility outcomes is required for progression from pilot to main RCT

2.8.2 Effectiveness outcomes (large-scale RCT)

Primary outcome: For the larger trial, the primary outcome will be the validated quality of recovery score (QoR-15) at 24 hours after surgery. It is *the* recommended instrument to assess well-being and comfort after surgery as determined by the Standardised Endpoints in Perioperative Medicine (StEP-COMPAC)[13,71] initiative and by the *American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Patient-Reported* Outcomes.[12] The QoR-15 instrument was evaluated as per the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) checklist, and it is a recommended patient-centred recovery outcome measure.[139,140] Each item is scored from 0 (worst score) to 10 (best score), giving a total score between 0 and 150. It is a 1 single-page, 15-item questionnaire (appendix 2). This questionnaire has been validated in English, Danish, Chinese, Portuguese, French [141,142], and Persian.[143] The minimally clinically important difference (MCID) is 6.[144] This score is correlated with the duration of hospital stay (r=-0.53), postoperative complications, patient satisfaction,[145] resumption of recreational and occupational activities,[142] and patient comfort.[13] The quality of recovery after surgery is also associated with long-term quality of life after surgery,[146] analgesia, and complications.[147-149] Results from a previous cohort of 127 postoperative adult patients showed that the mean time to complete the QoR-15 was 2.4 ± 0.8 min.[150] The QoR-15 is reliable (Cronbach: 0.83)[151] and sensitive to change in quality of recovery.[150]

Secondary outcomes: Persistent postoperative opioid use (defined as at least one opioid prescription filled between 90 and 180 days after surgery[152]), short-term opioid use, acute (24h and 7 days) and long-term (3 months) postoperative pain interference assessed with the Brief Pain Inventory score, health-related quality of life (EQ-5D-5L), and functional recovery (WHO Disability Assessment 2.0).

Adverse events: Bradycardia requiring an intervention, hypotension requiring an intervention, postoperative nausea or vomiting assessed, opioid-related adverse effects, incidence of delirium during

the postoperative hospitalization period,[153-155] measured with the Confusion Assessment Method (CAM) [155,156] and mortality.

2.9 How will the outcome measures be measured at follow-up?

Outcome measures will be assessed using routinely collected data (Table 2, section a), standardized case report form completed by a trained research nurse either by in-person visit to the patient bed side (while patients are hospitalized) or by phone (after hospital discharge) up to 3 months after surgery (Table 2 , section a).

2.10 What is the proposed sample size and what is the justification for the assumptions underlying power calculation?

Pilot RCT*:* We will aim for a minimal sample size of 60 participants (around 20 patients per site), using the 95% upper confidence limit method.[157] Based on a conservative recruitment rate of 50% and the number of eligible patients per day (approximately 1 eligible patient per site per day) across our recruiting sites (Table 3), a completion of the pilot trial recruitment in 2 months is feasible.

Planned large-scale RCT*:* Considering a two-group parallel RCT with individual-level randomization and our primary outcome (QoR-15 with an MICD of 6 points),[140,144] we calculated our sample size using a two-tailed T-test with a superiority hypothesis, a 0.05 level of significance, and 90% power. Considering a standard deviation of 18 points and a MCID of 6 points (QoR-15 score) in patients after major surgery, our estimated sample size is 420 participants.[158,159] This sample size will allow for a 10% non-compliance rate. This is reasonable considering expected loss to follow-up and the short duration of intervention.[160]

2.11 Are health service research issues being addressed?

We will be collecting quality of life measures (i.e., EQ-5D-5L), to be used for a health economic evaluation in the planned large-scale RCT. There will be no economic evaluation performed as part of the feasibility RCT.

2.12 What is the planned recruitment rate and process?

For the pilot trial, we will enroll patients at The Ottawa Hospital (Ottawa), the CHU de Québec-Université Laval (Québec City), and the Centre Hospitalier Universitaire de Montréal (Montréal) following research ethics board approval. Planned recruiting centres for the large-scale RCT are described in Appendix 3.

Table 4. Recruiting centres and sites for the feasibility pilot trial

Centre (city)	**Sites**	**Sites Principal Investigator**	**Yearly major[a] non cardiac surgery among adult patients (based on year 2020-2021)**	**Estimation of yearly eligible patients for DexOPUS**	**Recruitment period**	**Expected number of participants recruited**
CHU de Québec-Université Laval (Québec)	Hôpital Enfant-Jésus Hôtel-Dieu de Québec Hôpital Saint-François d'Assise	Michael Verret Alexis Turgeon	4 195 [1]	1048	20 eligible patients per week (recruitment achieved in 2 weeks for a 50% recruitment rate)	20
The Ottawa Hospital (Ottawa)	Civic Campus General Campus Riverside Campus	Manoj Lalu Daniel McIsaac	3 483 [2]	870	17 eligible patients per week (recruitment achieved in 3 weeks for a 50% recruitment rate)	20
Centre hospitalier Universitaire de Montréal (Montréal)	Hôtel-Dieu de Montréal Centre hospitalier Universitaire de Montréal	François Carrier Martin Girard	2 253 [3]	563	11 eligible patients per week (recruitment achieved in 4 weeks for a 50% recruitment rate)	20

[a]Major surgery defined as a surgery requiring at least one night hospital length of stay
[1]Based on Centre de la valorisation et d'exploitation de la donnée du CHU de Québec-Université Laval (SCIENTA)
[2]Based on Ottawa Hospital Data Warehouse
[3]Based on Centre d'intégration et d'analyse des données médicales (CITADEL) of CHUM

Recruitment of patients will be initiated by anesthesiologists, nurses, surgeons and medical residents at the preoperative clinic. Interested patients will then be referred to a trained site research nurse where the eligibility will be confirmed, and consent form will be signed and explained. Consent documents will be kept in a locked folder for privacy purposes. Potential eligible participants will be identified at the beginning of each day at local preoperative clinics by a trained research nurse looking at the scheduled planned patient visits at the preoperative clinic. On the day of surgery, these participants will be identified and randomized as per section 2.3. The research coordinator from the central coordinating centre will train two research nurses per centre who will be responsible for screening, enrollment and consent form administration at their own centre.

2.13 Are there likely to be any problems with compliance?

As the intervention is of short duration, frequently administered by anesthesiologists, and simple, we do not anticipate significant problems with intervention compliance. We further simplified the delivery process for the clinicians as the appropriate dose will be determined by the pharmacy and the clinician will need to only determine the body weight of the patient to inform intervention dosing. To increase compliance, a reminder note with the study name and study contact phone numbers will be placed by a trained research nurse on the top of each participant's personal medical file before arriving at the operating room. Identification of non-compliance will be made at each hospital pharmacy while assessing the content of the returned intervention bags and will be defined as a participant who received less than 30 mcg of dexmedetomidine (approximately the equivalent of a bolus administration for a 60 kg participant).

2.14 What is the likely rate of loss to follow up?

We expect no significant loss to follow up on our primary outcome (<2%) considering it is a relatively short-term assessment (24 hours). Participants maintained intubated during the postoperative period will represent a more challenging situation since their follow-up will be longer and will require mental state evaluation before administering the questionnaire. Those patients will be visited daily by a trained research nurse until the primary outcome can be assessed. However, they should represent less than 1% of our participants considering that patients intubated before surgery are not eligible (i.e., cannot complete the Quality of Recovery questionnaire). To improve participants' compliance with long-term follow-up (3-month phone interview), participants will be asked before enrollment when is the best time in the day for a 5-minute phone interview. Participants will also be encouraged to give a second

phone number (i.e., close relative) in case the patient is hard to join or unable to answer the phone. We expect no differential rate of loss to the follow-up between groups.

2.15 How many centres will be involved?

We will enroll patients at three centres,The Ottawa Hospital (Ottawa), the CHU de Québec-Université Laval (Québec City), and the Centre Hospitalier Universitaire de Montréal (Montréal) representing eight sites (Table 3).

2.16 What is the proposed type of analysis

Clinical outcome data will not be analyzed as we anticipate patients will be rolled forward into the large-scale multicentre pragmatic RCT (if there are no substantial changes to the protocol).

2.16.1 Primary feasibility outcomes

Primary and secondary outcomes will be analyzed using Wilson's method to generate proportion of patients recruited, clinician compliance with the intervention, and retention with 95% confidence intervals.[161]

2.17 What is the proposed frequency of analyses?

As this is a pilot RCT we will not conduct any interim analyses. Our independent DSMB will, however, monitor adverse events.

2.18 Are there any planned subgroup analyses?

We will not conduct subgroup analyses for the pilot RCT. For the large-scale RCT, we will perform subgroup analyses for the type of population (age, sex, chronic pain at baseline, chronic opioid use), the type of surgery (high postoperative pain intensity), and the preoperative functional status (preoperative QoR-15) which are potential effect modifiers based on our pan-Canadian survey results.[39,162,163]

2.19 Has any pilot study been carried out using this design?

The current proposal is the pilot RCT that will be used to support a large-scale RCT.

2.20 Sex and gender

Sex (as a biological variable) and gender (as a socio-cultural variable) both impact postoperative experience, especially pain and recovery experience.[164-168] For pharmacodynamic and pharmacokinetic

reasons, females generally require higher opioid and opioid alternative dosage during and after surgery and they usually demonstrate increased pain sensitivity after surgery.[164] Females are also at increased risk of opioid dependence.[169] Gender variables are also relevant.[170,171] For example, women tend to visit health care professionals more frequently than men, which increases their risk of receiving a drug prescription, such as opioids. We will collect data on gender adapted from the GOING-FWD framework and will conduct a sex and gender-based analysis following the CIHR GBA+ framework.[172]

3. Trial management

3.1 What are the arrangements for day-to-day management of the study?

The trial will be coordinated by a research coordinator at each site. Each of the participating sites has an experienced research team with research coordinators and research nurses. Coordination of the trial will be conducted by the Clinical Trial Unit of the CRCHU (Director A Turgeon) who has experience in coordinating large scale multicenter RCTs (HEMOTION - NCT03260478). A Project manager (MP Patton) will coordinate the trial assisted by a research coordinator (D Bellemare) and a data monitor (E Cloutier). All research personnel is trained with the Good Clinical Practice (GCP).

3.2 Role of investigators

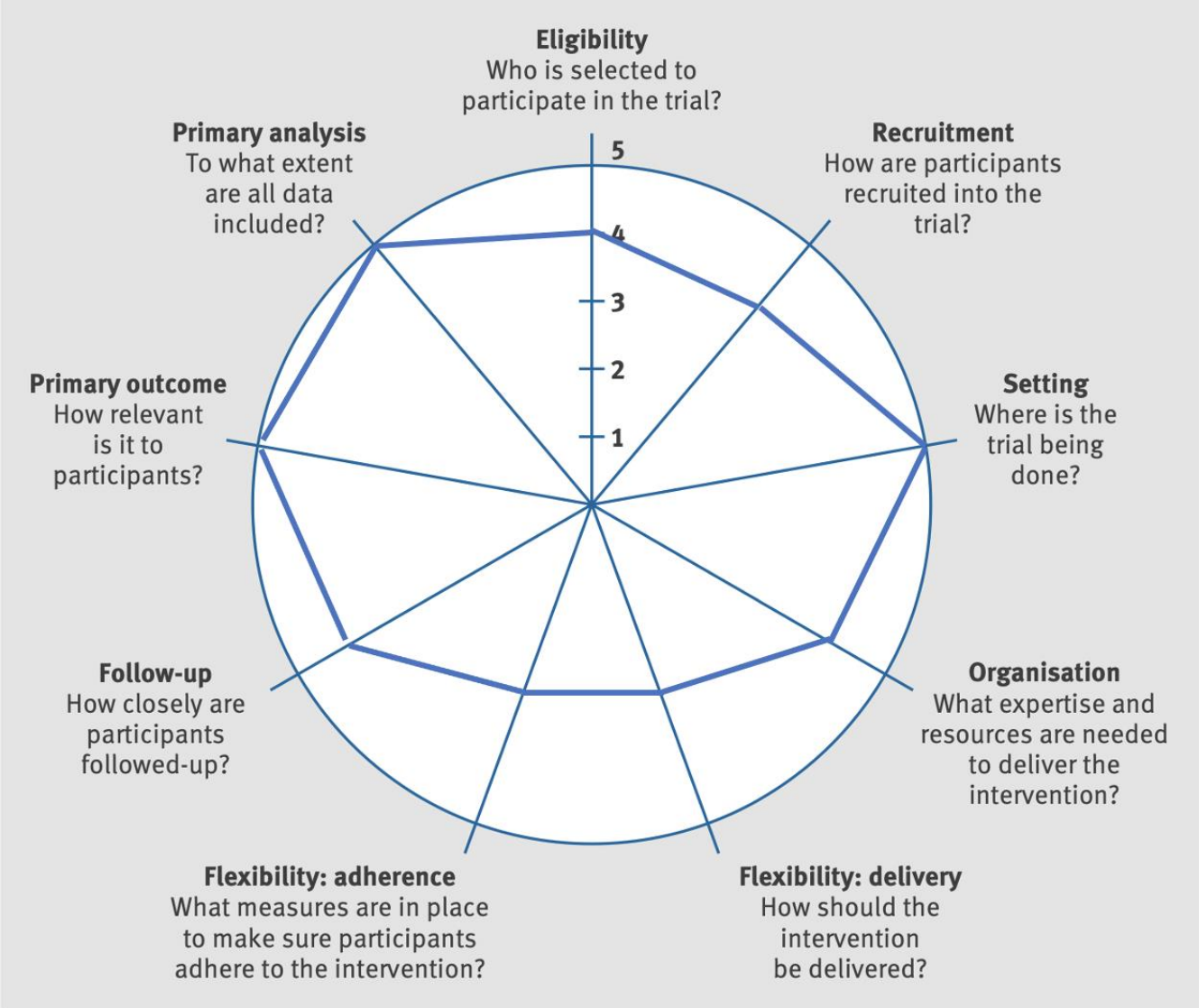
To conduct our pilot RCT, local and national multidisciplinary (surgeons, anesthesiologists, nurses, residents, and patient partners) collaborations are in place, and will be strengthened through the PACT and the Clinical Trial Unit of the CRCHU (ACT consortium; a Pan-Canadian CIHR funded initiative to guide and help strengthen impactful RCTs). We have a team of experienced researchers and clinicians that have conducted multiple perioperative trials in Canada and among the recruited sites (M. Girard and F Carrier [CHUM], D Fergusson, M Lalu and D McIsaac [TOH] and M Verret and A Turgeon [CHUdeQc-UL]). As part of our executive committee, we have the support from experienced trialists (A Turgeon, D Fergusson, F Lauzier, PJ Devereaux) and content experts (M Bérubé, AM Pinard, P Poulin, I Gilron). The project manager (MP Patton) has already led the coordination of several large-scale multicentre trials (HEMOTION, NeurO$_2$). Our team also includes a panel of four patient partners that are trained (CIHR training for patient engagement) and that have been involved in the OPUS program since its early development.

3.3 Trial committees and data safety and monitoring committee

The executive committee will take real-time decisions regarding study management and the steering committee will take decisions regarding the strategies for planning, improvement, anticipation and

dissemination of the study results. The steering committee will include all members of the executive committee (section 3.2), one methodologist (D. Fergusson), four patient partners (partnership already established)[106] and all principal investigators from recruiting sites (Table 3). The steering committee will meet once before initiation of the study and every four weeks once the recruitment has started. An independent DSMB will be constituted before the start of the pilot trial and will include two anesthesiologists, one surgeon, and one trial methodologist.

Appendix 1. PRECIS-2 Wheel



Appendix 2. Quality of recovery-15 questionnaire[150]

QoR-15 Patient Survey

Date: _ _ / _ _ / _ _ Study #: _____

Preoperative ☐ Postoperative ☐

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1.	Able to breathe easily	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
2.	Been able to enjoy food	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
3.	Feeling rested	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
4.	Have had a good sleep	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
5.	Able to look after personal toilet and hygiene unaided	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
6.	Able to communicate with family or friends	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
7.	Getting support from hospital doctors and nurses	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
8.	Able to return to work or usual home activities	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
9.	Feeling comfortable and in control	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time
10.	Having a feeling of general well-being	None of the time	0	1	2	3	4	5	6	7	8	9	10	All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11.	Moderate pain	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
12.	Severe pain	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
13.	Nausea or vomiting	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
14.	Feeling worried or anxious	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time
15.	Feeling sad or depressed	None of the time	10	9	8	7	6	5	4	3	2	1	0	All of the time

Appendix 3. Study centre for the large-scale RCT

Province	**Hospital**
Alberta	Foothills Health Sciences Centre (Alberta), Capital Health - Royal Alexandra Hospital (Edmonton), Capital Health – University of Alberta Hospital (Edmonton).
British Columbia	Royal Columbian Hospital (New Westminster), Vancouver General Hospital (Vancouver), Royal Jubilee Hospital (Victoria).
Manitoba	Winnipeg Health Sciences Centre (Winnipeg).
Ontario	Hamilton Health Sciences Centre (Hamilton), London Health Sciences Centre (London), The Ottawa Hospital (Ottawa), St-Michael's Hospital (Toronto), Sunnybrook Health Sciences Centre (Toronto), Trillium health Hospital (Mississauga), Lakeridge Health Oshawa (Oshawa), Hôpital Monfort (Ottawa).
Québec	Montreal General Hospital (Montréal), Hôpital Sacré-Cœur de Montréal (Montréal), CHU de Québec – Université Laval (Hôpital de l'Enfant-Jésus), CHU Sherbrooke - Hôpital Fleurimont (Sherbrooke).
Nova-scotia	Victoria General Hospital (Halifax).
Back-up centres	Hôpital Hôtel-Dieu de Lévis (Québec), Hôtel-Dieu de Québec (Québec).

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Chapter 7. Next steps

a. Dissemination of thesis work and other projects

In March 2024, I will update the analyses of the survey in order to include the responses for the last reminder from CAS. I will then submit the manuscript reporting the final results for publication in open access peer-reviewed journals for the systematic review on dexmedetomidine and survey research projects. Results will be presented at the Réseau Québécois de Recherche sur la Douleur (FRQS network) meeting as well as the PACT meeting during the Summer of 2024.

The pilot feasibility RCT will be submitted to the CIHR research competition in Spring 2024 and the manuscript reporting the final results will be submitted for publication in open access peer-reviewed journals (i.e., only the feasibility results will be submitted as the participants will also be included in the larger multicentre RCT). I will also submit the pilot feasibility RCT for other national and provincial grant competitions over 2024, in order to launch the pilot feasibility RCT in March 2025. As part of my OPUS research program, I am completing a systematic review and meta-analysis on the perioperative effectiveness of COX-2 inhibitors and a multicentre cohort study to describe perioperative practices during and after general anesthesia.

Chapter 8. Integrated Discussion

1. Introductory section

For my thesis, I developed a research program called **O**ptimizing **P**atient-centred outcomes **U**sing opioid minimization **S**trategies (**OPUS**). OPUS aims to reduce the debilitating burden of the opioid crisis across Canada by finding effective opioid minimization strategies that can reduce opioid use and improve patient-centred outcomes. This main objective has been identified as a key research area in Canada.[167] Multiple knowledge user organizations (SolvingPain, Pain BC, RQRD, Choosing Wisely, and the Canadian Anesthesiologists' Society) have also identified a critical need for the evidence and insights my program will generate (Figure 1).

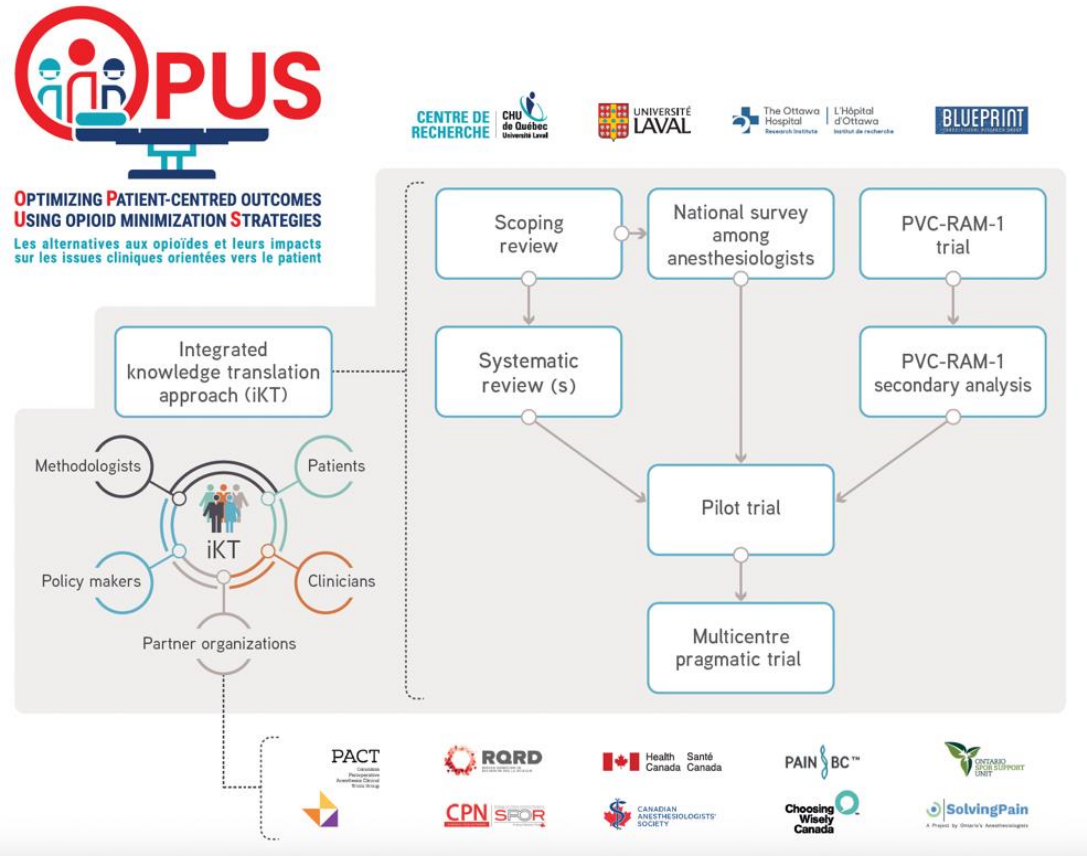

Figure 1. Schematic of the **O**ptimizing **P**atient-centred outcomes **U**sing opioid minimization **S**trategies (**OPUS**) research program

2. Overall summary and individual summary of each individual article

During my PhD, I completed key phases of the OPUS research program including assembling a multidisciplinary team, mapping the evidence, evaluating the certainty of evidence supporting the use of a promising opioid minimization strategy, providing insights of anesthesiologists' opinions and beliefs, and developing a protocol for a feasibility multicentre randomized controlled trial (RCT). These projects will ultimately help inform a pragmatic multicentre RCT in Canada assessing the patient-centred effectiveness of a promising opioid minimization strategy.

First, I assembled a team of partner organizations and patient partners (i.e., group of patients who are collaborating as partners in OPUS), and defined their roles (Table 1). I applied the CIHR Strategy for Patient Oriented Research patient engagement framework to perioperative research and developed solutions to address commonly encountered barriers in the context of patient engagement. Working with patient partners, I reviewed the recommendations for patient-centred outcome assessment in perioperative research (i.e., StEP-COMPAC)[141] and prioritized them in the context of evaluating effectiveness of intraoperative opioid minimization strategies (Table 2).[168] The order of prioritization for patient-centred outcome measures was endorsed by partner organizations and was used for all subsequent research phases of the OPUS program (i.e., guide interpretation of the results of scoping review and determine the primary outcome for systematic review and RCT).

Table 1. Type of partner organizations and roles in OPUS

Type of partner organization	**Interested parties identified**	**Role in our scoping review**
Practitioners and researchers	Anesthesiologists Surgeons Nurses Pain experts Psychologists Researchers Trainees	Steering committee and stakeholder group
Patients	Patient panel	Steering committee and stakeholder group

Patient organizations	Strategy for Patient-Oriented Research (SPOR) Unité de Soutien-SSA	Stakeholder group
Policy makers	Health Canada Choosing Wisely	Stakeholder group
Institutions	Department of Anesthesia and Pain Medicine (University of Ottawa and Université Laval)	Stakeholder group
Interdisciplinary organizations	Pain BC Solving Pain Réseau Québécois de Recherche sur la Douleur Chronic Pain Network	Stakeholder group
Researcher and practitioner organizations	Perioperative Anesthesia Clinical Trials group Canadian Anesthesia Society	Steering committee and stakeholder group

Table 2. StEP-COMPAC group recommendations for patient-centred outcome assessments in clinical trials[141] and our prioritization order tailored to pharmacologic interventions

	Patient-centred outcomes				
Domains	Patient well-being	Health-related quality of life	Functional outcome	Patient satisfaction	Life impact
Instruments to be prioritized based on StEP-COMPAC recommendations	Quality of recovery-15	EuroQol 5 Dimension, five-level	WHO Disability Assessment Schedule version 2.0	Bauer patient-satisfaction measure	Days alive and out of hospital at 30 days after surgery
Prioritization by our team (Steering committee)[1]	1	2	3	4	5

[1]Prioritization based on a) Plausibility for or of effect between intraoperative pharmacologic intervention and outcome b) Patient and partner organizations priority

Second, through a scoping review of RCTs (Objective 1),[169] I described evidence and knowledge gaps in patient-centred outcomes and identified and characterized promising pharmacological opioid minimization strategies evaluated in RCTs. I identified a need for the assessment of patient-centred outcomes in RCTs evaluating the effectiveness of intraoperative opioid minimization strategies as only 16% of RCTs (457 / 2803) evaluating the effectiveness of

intraoperative opioid minimization strategies included at least one patient-centred outcome in the manuscript reporting the results. Based on authors' conclusions, I also identified three promising opioid minimization strategies deserving further formal assessment through systematic reviews and meta-analyses: dexmedetomidine, systemic lidocaine, and COX-2 inhibitors. Of the three, dexmedetomidine, an alpha-2 agonist, was the most promising as based on aggregate authors' findings , the proportion of RCTs reporting positive results was the highest (i.e., 85%). We also identified three strategies that were less promising, namely: acetaminophen, ketamine, and gabapentinoids.

Third, I evaluated the effectiveness of the most promising opioid minimization strategy identified in the scoping review (i.e., dexmedetomidine) through a systematic review and Bayesian meta-analysis of RCTs (Objective 2).[170,171] The findings from my systematic review confirmed findings from the scoping review that dexmedetomidine is a promising strategy (i.e., may result in a clinically significant effect on the Quality of Recovery). However, we also assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and we found a low certainty of evidence due to the risk of bias of included RCTs and a high heterogeneity across included RCTs (i.e. inconsistency). A low certainty of evidence means that "our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect".[172] Thus, while intraoperative dexmedetomidine may be useful to improve the Quality of Recovery after surgery, there is a need for further high-quality RCTs evidence to confirm this hypothesis and inform practice.

Fourth, in order to supplement evidence from RCTs (Objective 1 and 2) with clinicians' opinions and reported practices, I completed a pan-Canadian survey among anesthesiologists (Objective 3).[173] The results demonstrated significant practice variation in opinions regarding best practices for intraoperative opioid minimization strategies, and a need for further evidence to guide practice. I also found that the vast majority of anesthesiologists believe dexmedetomidine to be useful during general anesthesia (88% of respondents believed it was probably useful or clearly useful). On the other hand, while our scoping review and systematic review showed that dexmedetomidine is a promising opioid minimization strategy, it also showed the need for

further high-quality RCTs before confirming its usefulness to improve patient-centred outcomes considering the low certainty of evidence. There is thus a knowledge-to-practice gap between what is believed to be useful among clinicians and what has been confirmed to be useful with strong evidence. Our survey also confirmed the importance of patient-centred outcomes for Canadian anesthesiologists with 94% stating that the postoperative quality of recovery (i.e., a patient-centred outcome measure to evaluate the patient well-being) was considered very important or somewhat important as an endpoint for influencing intraoperative practices.

Fifth, given the knowledge-to-evidence gap identified (Objective 1 and 2 versus Objective 3) and the potentially meaningful benefit of intraoperative dexmdetomidine, I developed a protocol for a multicentre pilot RCT to assess the feasibility of a pan-Canadian multicentre pragmatic RCT.

3. Main points of integrated discussion

Need for patient-centred outcomes to evaluate the effectiveness of opioid minimization strategies

International organizations such as the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) advocate for the use of multidimensional, patient-centred outcome measures (i.e. including functional recovery and adverse effects) that better capture the patient experience in perioperative research compared to traditional indirect (e.g., short term opioid use or length of stay) or unidimensional outcome measures (e.g., unidimensional pain intensity score).[129] Across all research aims, I confirmed the need for patient-centred evidence in perioperative research when evaluating the effectiveness of intraoperative opioid minimization strategies. Patient-centred outcomes were deemed important by patient partners, partner organizations (SolvingPain, Pain BC, Health Canada, Réseau Québécois de Recherche sur la Douleur, Choosing Wisely, Strategy for Patient-Oriented Research, the Canadian Anesthesiologists' Society, the Canadian Chronic Pain Network, and the Canadian Perioperative Anaesthesia Clinical Trials), Canadian anesthesiologists (patient-centred outcomes were ranked among the most important endpoints that could alter practices, based on our pan-Canadian survey), and researchers (patient-centred outcomes are increasingly reported in RCTs according to the scoping review results). I also identified both quantitative and qualitative

knowledge gaps concerning the use of patient-centred outcomes. Quantitatively, from our scoping review, only 16% of RCTs evaluating the patient-centred effectiveness of opioid minimization strategies reported at least one patient-centred outcome.[169] Qualitatively, from our scoping review, I found that the instruments used in RCTs to assess patient-centred outcomes were rarely those recommended by established recommendations (20% of included trials were compliant with StEP-COMPAC recommendations for the assessment of patient-centred outcomes in perioperative research).[141]

Implementation of patient engagement in research

To evaluate, prioritize, and guide interpretation of patient-centred outcomes, patient partners are essential. As a team, we demonstrated that patient engagement was feasible and meaningful across all aims of the OPUS research program.[168] We also demonstrated the value of having a patient partner panel (i.e., four patient partners in our initiative) as opposed to having only one or two patient partners engaged. It helped ensure a fairer representation of experiences and opinions, diversity in cultural backgrounds, and better addressed a potential power imbalance across the team. The quality of our collaboration is also supported by the ongoing feedback and formative evaluation (i.e., patient satisfaction survey) results provided by the patient partners (Megan Graham, Maxime Lê, Allison Geist, and Fiona Zivkovic). The patient partners also provided the following testimonial:

> *"As members of the patient partner panel, Megan Graham, Maxime Lê, Allison Geist, and Fiona Zivkovic, we are delighted to continue working alongside Dr. Verret as well as their team, to guide them in developing and conducting the OPUS program. As members of the team since October 2021, we have attended meetings to discuss the proposed work, provided perspectives on instruments used and the outcome measures for the data which will be collected for analysis, as well as providing input on a grant proposal and dissemination of our patient engagement approach through publications and presentations. We are eager to continue working on this project (i.e., the scoping review) as it will identify future research needs, namely in terms of patient-centred outcomes, which will greatly contribute to identifying opioid minimization strategies that improve the quality of life and recovery for future patients. This*

has been an excellent and rewarding experience to date, and we appreciate the attentive leadership from the main investigator: Michael Verret"

It is estimated that less than 0.1 % of published trials between 2011 and 2016 (n=23/371,159) reported a patient engagement process for any research phase (i.e., design, execution and/or dissemination).[174] In addition, patient engagement initiatives are frequently focused on the early phase of research (i.e., research question and protocol development) and not sustained through the execution and dissemination phases.[175] In this context, there is a need for patient engagement initiatives in research as well as tailored guidance that can be applied to specific research areas. Multiple funding agencies across the world (CIHR, NIH, PCORI, etc.) are also promoting the importance of patient engagement to increase relevance and applicability of research through targeted funding opportunities.[176-178] I hope the description of our sustained patient engagement experience throughout the OPUS program will motivate other groups to engage patient partners in their research programs and projects.[168] Patient-oriented research in anesthesiology is critically needed in Canada as highlighted by the *Canadian Anesthesia Research Priority Setting Partnership*.[167] As patient engagement is an important component of patient-oriented research, it is important for Canadian anesthesiologists to understand patient engagement, its value, best practices, and ways to evaluate it.

Development of applicable evidence (Approach for practice changing research)

In perioperative research, there is a need to generate evidence that is more applicable and relevant to the patient bedside. This has been shown as an important knowledge gap in perioperative research recommendations[78,83,179] and original studies, and the results of my scoping review (lack of patient-centred evidence and lack of patient engagement) also confirmed this important knowledge gap.[169] In order to generate applicable knowledge that can generate practice-changing findings,[180] the OPUS program focuses on the three established domains of applicability; namely the importance, accessibility and suitability.[181] Importance was emphasized by determining and prioritizing patient-centred outcomes, accessibility was promoted by implementing open science best practices (e.g., open access publishing, registered protocols, patient engagement, use of reporting guidelines, etc.), and suitability was ensured through meaningful partnership with stakeholders (i.e., integrated knowledge translation approach).[182]

Accessibility and suitability were further emphasized in my statistical method as I used innovative statistical approaches that facilitate the implementation of the findings by the end users (i.e., anesthesiologists). More specifically, in my systematic review and meta-analyses, instead of using the traditional Frequentist framework, I applied a Bayesian framework.[170] While both methodological approaches are not mutually exclusive, they have significant differences, especially in terms of interpretation and applicability.[183] In the Frequentist approach, a 95% confidence interval is interpreted as : "how often 95 % confidence intervals computed from many studies would contain the true size *if all the assumptions used to compute the intervals were correct*."[184] On the other hand, the 95% credible intervals obtained with the Bayesian statistical approach can be directly interpreted as the 95% probability that the true estimate lies within the credible interval given the observed data. The latter (i.e., Bayesian interpretation of credible intervals) can improve applicability of the findings given that a probability is simpler and more intuitive for end users (clinicians) who are usually not experienced statisticians; it is thus more accessible and suitable.[185-187] In summary, across all the research phases of OPUS, generating applicable findings was prioritized in order to produce relevant, practice changing research.

4. Strengths and limitations

My thesis has strengths. First, I used a robust programmatic approach to help inform a planned large-scale multicentre RCT. My structured and evidence-based approach (i.e., team development, scoping review process, systematic review, survey and feasibility RCT) is extremely important given that approximately half of the RCTs published in impactful medical journals do not report adequate justification (i.e., systematic review evidence) to support their research.[188-191] The prevalence of systematic review evidence to justify RCTs in anesthesiology is even lower than what is reported for medicine in general (i.e., approximately 20%).[192] Second, I have established strong and sustainable relationships with our partners (Figure 1) that will help ensure that the knowledge generated by my research program is relevant and efficiently implemented. For instance, dissemination and implementation will be strengthened by partners and co-investigators network platforms (Chair in Leadership and Teaching on Chronic Pain [Dr. A.M. Pinard] and the Poweroverpain platform [https://portal.poweroverpain.ca, Dr. P Poulin],

Solving Pain [https://www.solvingpain.ca], and Choosing Wisely [https://choosingwiselycanada.org]).

In terms of limitations, first, my thesis work does not include non-pharmacologic strategies which may offer benefits as well. However, with our partners, we determined that the knowledge gap regarding pharmacologic opioid minimization strategies was more important and urgent than non-pharmacologic strategies. Second, there might be new opioid minimization strategies available at the time we launch our large-scale multicentre RCT. Although this is possible, this would be unlikely given the time required to develop new analgesics as well as the probability of successful development program (4.7% success rate for medications with low potential for substance use disorder).[193] We will continue to monitor literature in this area, including pre-clinical research on a monthly basis. If a new promising opioid minimization strategy would arise, I would compare its potential effectiveness with the promising strategies already identified through the scoping review and I would integrate this strategy to OPUS.[169] Third, while my survey was sent to 2008 anesthesiologists, I obtained a participation rate of only 15% potentially limiting generalizability of the findings. This is, however, a common limitation encountered with online survey and multiple techniques were implemented to increase response rates (e.g., reminders, short survey length, progress bar, etc.).[194] Fourth, my systematic review and planned RCT focus on only one opioid minimization strategy (i.e., dexmedetomidine) which will not include the assessment of combinations of pharmacologic opioid minimization strategies nor comparison between two different agents.

5. Implications

Practice implications

While patients are unconscious during general anesthesia and cannot provide real time approval and consent of the treatments administered, intraoperative patient management should still be patient-oriented. Given the short preoperative patient-anesthesiologist interaction and the lack of patient-centred evidence in current guidelines and original studies, it can be challenging for anesthesiologists to provide patient-oriented care.[195]

The findings from my OPUS program confirmed the need for patient-centred evidence to guide practice regarding the use of intraoperative opioid minimization strategies. My program also questions the current off-label use of certain pharmacological opioid minimization strategies such as dexmedetomidine given the low level of patient-centred outcome evidence and potential adverse effects that require further RCTs. Clinicians should carefully assess the evidence before using opioid minimization strategies for patient requiring general anesthesia. As an example, it was recently shown that the use of gabapentinoids (a class of drugs including pregabalin and gabapentin used to minimize opioid exposure) in the perioperative period is associated with important safety concerns (i.e. risk of respiratory depression, mortality, abuse and increase risk of opioid overdose)[115,196-200] without clinically significant patient benefit.[111,201] As a result of these findings, the perioperative use of gabapentinoids is now being discouraged.[117] This example emphasizes the importance of careful and critical appraisal of opioid minimization strategies, and the need to apply rigorous methods to present an accurate picture of possible benefits *and* risks. Patient-centred outcome assessment can help provide this picture given its multidimensional components. I also explained this concept in an editorial that I published in *Anesthesia & Analgesia* during my PhD.[113]

Policy implications in Canada

Given the urgency of the opioid crisis, identifying effective strategies to confront and address the crisis is needed on several fronts involving numerous disciplines and communities.[202] Recognizing and responding to the opioid crisis is also a major public health priority for the Government of Canada as well as provincial governments "*taking action through a comprehensive, collaborative, compassionate and evidence-based approach to drug policy".*[203]

At Health Canada, the Opioid Respond Team recently completed an initiative under The Canadian Pain Task Force 5-year mandate. They completed literature reviews, multidisciplinary expert consultations and developed implementation recommendations for pain management in Canada. Results of this work can be consulted in The Canadian Pain Task Force's final report, entitled *An action plan for pain in Canada* (https://www.canada.ca/en/health-canada/corporate/about-health-canada/public-engagement/external-advisory-bodies/canadian-pain-task-force/report-2021.html). The OPUS program is in line with this recently developed

action plan. More specifically, our research program will help to address goal #2 (providing equitable and consistent access to evidence-informed and patient centred pain care) and goal #4 (promote pain research and the translation of knowledge into real-world impact) of the Pain Task Forces's mandate. Our collaboration with Health Canada will help ensure that the specificity of the intraoperative period of care is accounted for in policy development. Furthermore, the OPUS program will help to develop and inform policy in the long-term through the conduct of RCTs and further systematic reviews.

6. Conclusion from dissertation overall

There is a need for patient-oriented evidence in perioperative care and especially in the field of intraoperative opioid minimization strategies that should be used during general anesthesia. My thesis addresses this knowledge gap and informs a planned large-scale multicentre RCT to assess the patient-centred effectiveness of an opioid minimization strategy (i.e., intraoperative dexmedetomidine). If feasibility is demonstrated, our planned large-scale multicentre RCT will have an important impact on perioperative practices. If we demonstrate the intervention is beneficial, our findings will improve patient-oriented care while reducing exposure to opioids for millions of patients. If we observe an absence of effect or meaningful adverse effects, the opioid minimization strategy will be discouraged in practice.

Chapter 9. References

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