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Review Article

Are opioids indispensable for general anaesthesia?

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Abstract

The drug-induced, reversible coma of anaesthesia requires three clinical outcomes: unconsciousness, immobility, and the control of autonomic nervous system (ANS) responses to surgical stimulation. Producing the anaesthetised state with a single anaesthetic agent, such as an inhaled vapour or propofol, is challenging, primarily because suppressing ANS responses requires very high anaesthetic concentrations, resulting in haemodynamic depression and prolonged recovery. The antinociceptive effects of opioids (i.e. minimum alveolar concentration reduction) are thus central to the well-entrenched 'balanced anaesthesia' concept. In recent years, the notion of 'multimodal general anaesthesia' has extended the concept of balanced anaesthesia to include more drugs that target different neuroanatomical circuits and multiple neurophysiologic mechanisms. The opioid epidemic has provided some of the motivation to move away from opioids toward other adjunct drugs. Persistent opioid use after surgery is a component of the opioid epidemic and is a major concern for perioperative physicians. Potential solutions to the problem of persistent opioid use after surgery have focused on proper 'opioid stewardship' after operation, wherein opioids are used conservatively in combination with other analgesic adjuncts, and excessive opioid prescribing for home use is avoided. But there is a paucity of data on how intraoperative opioid usage patterns may be contributing to persistent opioid use after surgery. There are cogent reasons to moderate perioperative opioid use, including intraoperative opioids, but whether these changes in practice integral to the multimodal general anaesthesia concept will improve anaesthesia outcomes, including persistent opioid use after surgery, is unknown. Studies investigating these issues are an important research priority.

Keywords: opioids; general anesthesia; minimum alveolar concentration; opioid epidemic; persistent pain after surgery

Are opioids indispensable for general anaesthesia? A quick, simple answer is 'of course not.' It is certainly possible to deliver a general anaesthetic without opioids. This was clear from the earliest days of anaesthesia practice. What we now refer to as 'Ether Day', the initial public demonstration of the anaesthetic properties of ether on October 16, 1846 at the Massachusetts General Hospital, proves the point.[1] If opioids had been essential at that landmark event in medical history, the day might have come to be known as 'Ether-Morphine Day'. However, in the modern era, a more reasonable answer to the question of whether opioids are indispensable for general anaesthesia requires a more nuanced response. The question is particularly pertinent in the face of the opioid misuse epidemic, wherein the rationale for the use of opioids in nearly every clinical setting is under intense scrutiny.

This brief review and editorial attempts to provide a more considered answer to the question posed in the title, examining problems associated with producing anaesthesia with a single anaesthetic drug, reasons underpinning the long-standing popularity of opioids for general anaesthesia, and

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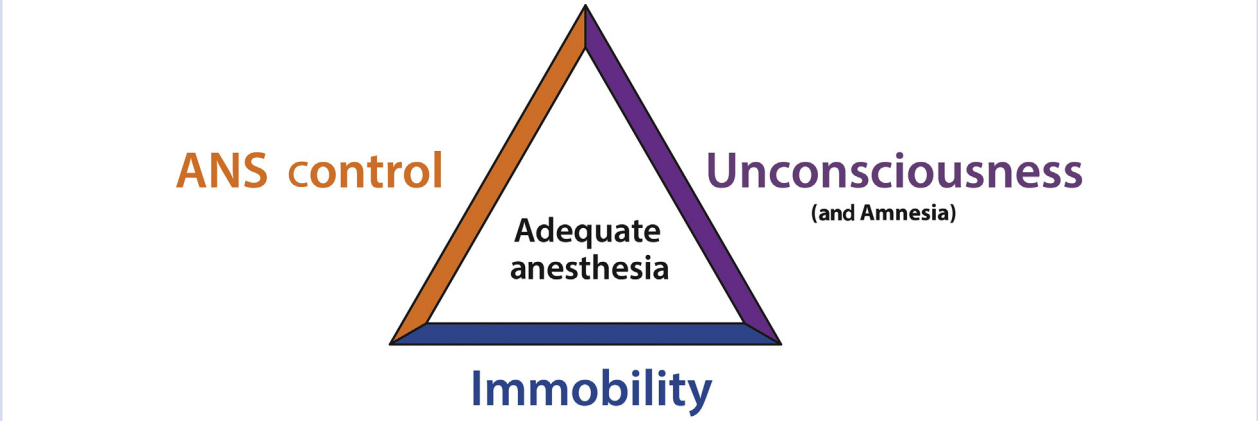

Fig 1. A triangle representing the conventional goals of general anaesthesia. Amnesia is another essential outcome that is presumed to be achieved when a patient is unconscious. ANS, autonomic nervous system. Adapted from Egan and Svensen.[2]

motivations to reduce perioperative opioid use. A particular question of contemporary interest is whether intraoperative opioid usage patterns influence the incidence of persistent postoperative opioid use. This discussion is by no means a comprehensive, exhaustive analysis; it is, rather, presentation of an intellectual framework to think about intraoperative opioid use in contemporary anaesthesia with general recommendations for future practice and research. The overall goal is to stimulate thought about why anaesthesiologists administer opioids for general anaesthesia and why we perhaps should consider using less of them.

Three deliverables of anaesthesia (and amnesia)

The drug-induced, reversible coma of general anaesthesia requires three clinical outcomes that can be imperfectly assessed in real time: unconsciousness, immobility, and the control of autonomic nervous system (ANS) responses to surgical stimulation (Fig. 1).[2] Amnesia, also an essential outcome, is presumed when patients are rendered unconscious, although the achievement of this outcome can only be assessed in retrospect. Current knowledge about memory function under general anaesthesia suggests that when the other three outcomes are apparently achieved, the formation of explicit memories, often referred to as awareness with recall, is rare,[3] even though anaesthetised patients may sometimes exhibit periods of disturbing responsiveness when studied using the isolated forearm technique.[4,5] The frontiers of knowledge about memory function under anaesthesia are rapidly evolving[6]; it is possible that there are altered consciousness states under apparently adequate general anaesthesia that permit some implicit memory function, with the potential to alter postoperative behaviour in the absence of awareness with recall.[7] In any case, we promise our patients 'oblivion', and so we must achieve all three deliverables (unconsciousness, immobility, and control of ANS) to keep our promise. The anesthesiologist's social contract with the patient also includes the support of their vital functions and the defense of their human dignity (e.g., ensuring that the patient is treated with respect while anesthetized), although these elements of anesthesia practice, while critically important, are beyond the scope of this review.

Three corresponding pharmacologic concepts

This triad of clinical deliverables comprising anaesthesia map to three well-developed, widely understood pharmacologic concepts (Fig. 2).[2] Minimum alveolar concentration (MAC),[8] which relates expired anaesthetic concentration to immobility (also referred to as the somatic response to nociception), is perhaps the most unifying idea in anaesthetic pharmacology, and is applied by anaesthesia practitioners on a quotidian basis. MAC-awake is an analogous concept relating to the unconsciousness deliverable[9]; MAC-awake is approximately one-third of MAC. MAC-BAR (block of adrenergic

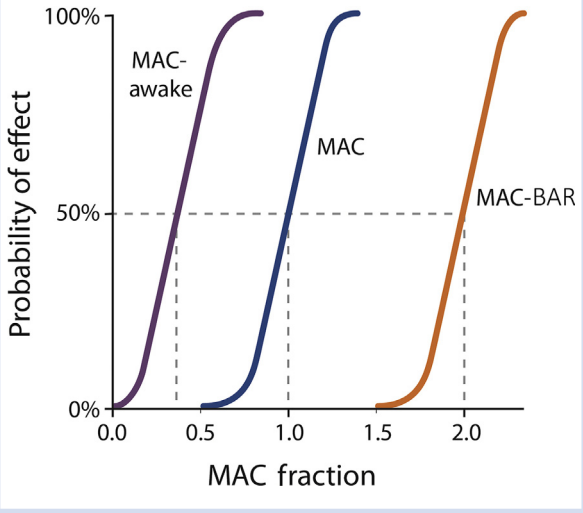

Fig 2. An idealised, graphical representation of the concentration-effect relationships of inhaled anaesthetic agents in terms of MAC, MAC-awake, and MAC-BAR. The trio of anaesthetic outcomes (deliverables) depicted follow the colour scheme introduced in Figure 1. See text for complete explanation. MAC, minimum alveolar concentration. Adapted from Egan and Svensen.[2]

response), which is approximately two times MAC, extends this concept of MAC to the third deliverable, the control of ANS responses to the trauma of surgery.[10]

Although many refer to the control of ANS responses to nociception during general anaesthesia as 'analgesia', one can argue that this is philosophically inelegant because by definition the study of pain in humans requires a conscious patient to report the unpleasant affective experience arising from the noxious stimuli. Thus, in a comatose, anaesthetised patient, we do not have a well-developed theoretical construct to understand or study pain as we currently define it. Nonetheless, we often have clinical evidence that some nociception is occurring during anaesthesia (e.g. HR and BP increases arising from surgical stimuli, elevated biomarkers of the 'fight or flight' response such as epinephrine and cortisol). It is likely that referring to the control of ANS responses to nociception as analgesia simply arose because opioids are commonly used to achieve this deliverable, and opioids belong to a diverse group of drugs known as analgesics.

The relationships among these three variants of the MAC concept have simple and important clinical implications. As anaesthetic concentrations increase, unconsciousness precedes immobility, which precedes control of ANS responses. By definition, at MAC-BAR, only 50% of patients exhibit adequate anaesthesia, and yet the haemodynamic consequences of these doses of volatile anaesthetics (and equivalent concentrations of propofol) are intolerable in many patients.

Neuroanatomical and neurophysiologic targets of anaesthesia

The neuroanatomical targets involved in producing anaesthesia are increasingly well understood (Fig. 3). The particulars of the neuroanatomical circuitry are complex,[11,12] but in simple, schematic terms, unconsciousness and amnesia, produced at the lowest concentrations of volatile agents compared with the other MAC variants, are achieved by targeting mostly higher brain centres in the cortex, limbic system, and thalamus. Immobility, requiring modestly higher concentrations, is achieved primarily by targeting evolutionarily more primitive circuits in the spinal cord. Animal models demonstrating that MAC does not change when the animals are decorticated or decerebrated provide compelling evidence supporting this assertion.[13,14] The control of ANS responses to nociception, requiring considerably higher concentrations than the other two deliverables, also targets more primitive CNS circuits stretching from the spinal cord, to the brainstem and thalamus.

The key point regarding the anatomical targets essential to producing anaesthesia is that the functions of higher brain centres responsible for explicit memory function and consciousness are disrupted at lower anaesthetic concentrations. From an evolutionary biology perspective, the more primitive CNS structures and circuitry involved in producing immobility and control of ANS responses are more difficult to disrupt, presumably because these circuits govern more primitive behaviours such as the withdrawal response and also essential vegetative functions such as control of circulation and breathing.

The neurophysiologic mechanisms (receptor systems) involved in producing anaesthesia are also increasingly well described. Although many other receptor systems can be leveraged to produce anaesthesia, the traditional 'balanced anaesthetic', popular and dominant over the past 50 yr, relies mostly upon the γ-aminobutyric acid type A ($GABA_A$) receptor and the mu-opioid receptor (MOR). Both receptors are widely expressed in the CNS of mammals and both respond to their respective endogenous ligands and pharmacologic agonists (and antagonists). A key point relating to the receptor systems involved in producing the traditional balanced anaesthetic is that two receptor systems are involved (i.e. $GABA_A$ and MOR), not just one.

The problem of one-drug anaesthesia

Anaesthesiologists have long recognised that producing anaesthesia with a single agent is difficult. Although it is

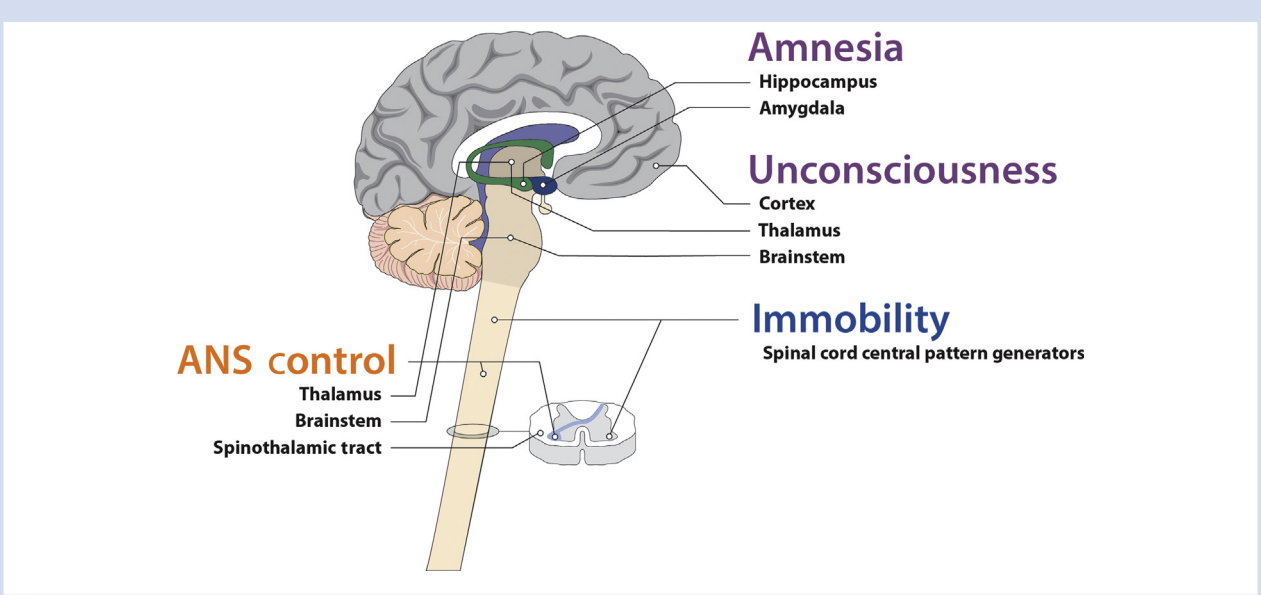

Fig 3. An idealised, highly schematised representation of the neuroanatomical targets of general anaesthesia. The trio of anaesthetic outcomes (deliverables) depicted follow the colour scheme introduced in Figure 1.

possible to produce unconsciousness and immobility with a single anaesthetic drug, such as an inhaled agent or propofol used in isolation, achieving ANS control during surgery with only one drug is more challenging and requires much higher concentrations. Hypnotic agents used in isolation cannot prevent HR and BP increases in response to surgical stimulation without frequent, severe pre-stimulus haemodynamic depression and prolonged recovery.[15–17] Thus, in recent decades anaesthesia practice has utilised two drugs: an inhaled agent or propofol in combination with a second drug to control ANS responses to nociception.[18] Since the advent of the balanced anaesthesia concept,[19,20] opioids have been by far the most commonly used second drug. Opioids are very effective in controlling ANS responses to nociception and have also played an important role in postoperative pain management. Other drugs that modulate ANS activity, such as esmolol or adenosine, have also been used to control ANS responses during surgery, although these techniques never gained traction outside of research settings, perhaps because they were not useful for postoperative pain management and required an additional infusion pump.[21,22]

The utility of two-drug anaesthesia (MAC reduction)

The antinociceptive effects of opioids are central to the traditional balanced anaesthesia concept. Opioids contribute to all three deliverables of general anaesthesia, but are especially useful in controlling ANS responses. In the traditional balanced anaesthesia approach, although both the $GABA_A$ receptor and MOR systems contribute to all three goals of general anaesthesia, the $GABA_A$ system is considered dominant in producing unconsciousness, while the ANS control outcome is principally achieved via the MOR. The two receptor systems together contribute importantly to achieving immobility.

Opioids significantly augment the likelihood of unconsciousness by attenuating nociception-induced arousal.[12] In clinical pharmacology terms, opioids shift the concentration-effect relationships of the primary anaesthetic agents to the left (both volatile agents and propofol).[23,24] This phenomenon is the well-known and often clinically exploited concept of opioid-induced MAC reduction.[25] Inspection of the shape of the MAC reduction curves (Fig. 4) is instructive and reveals several clinically critical concepts. First, opioids synergistically reduce MAC and its variants; this is evident in how the curves 'bow' toward the origin. Second, MAC reduction is substantial (depending on the dose, as much as 75% or more). Third, most of the MAC reduction occurs at moderate opioid concentrations (i.e. even modest opioid doses substantially reduce MAC). Fourth, MAC reduction is not complete (i.e. opioids cannot be relied upon as complete anaesthetics). The addition of the opioid results in MAC curves that asymptotically approach a non-zero minimum; the opioid does not completely eliminate the need for the other anaesthetic. And fifth, there are an infinite number of anaesthetic-opioid combinations that will achieve MAC and its variants (clinicians must choose the optimal combination based on the goals of the anaesthetic and operation). Based on first principles, the synergistic interaction applies to both therapeutic and adverse effects, such as depression of ventilation and haemodynamic variables.[26] Although not expressed in terms of MAC, these synergistic interaction patterns also apply to total i.v. anaesthesia (i.e., TIVA) techniques using propofol and opioids.[27]

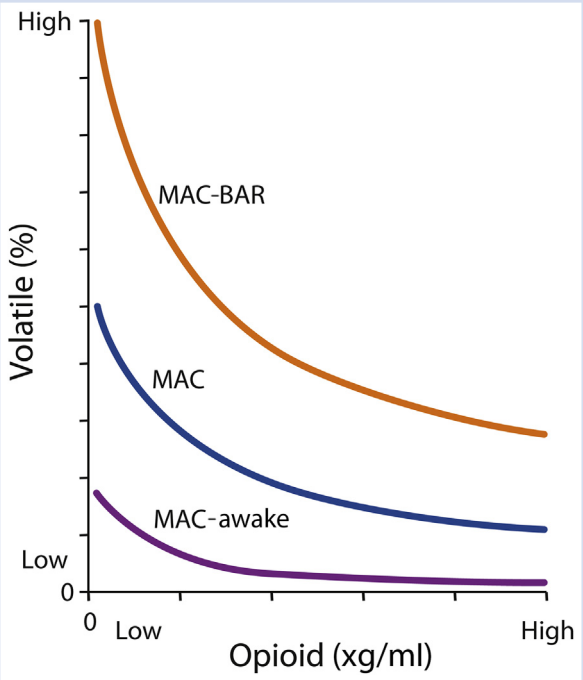

Fig 4. An idealised, graphical representation of the concept of MAC reduction by opioids. The trio of anaesthetic outcomes (deliverables) depicted follow the colour scheme introduced in Figure 1. BAR, block of adrenergic response.

Opioids are especially efficacious in reducing MAC-BAR, presumably because they exert their effects at numerous targets along the neuroanatomic circuits essential to eliciting HR and BP responses to surgical stimulation. The relevant CNS pathway, sometimes referred to as the nociceptive-medullary-autonomic circuit (NMA circuit), is comprised of the dorsal horn of the spinal cord, the spinoreticular tract, the brainstem arousal circuits, and the sympathetic and parasympathetic efferent pathways (Fig. 5).[11] Opioids attenuate nociceptive traffic along this pathway through MOR agonism in the dorsal horn, brainstem, and thalamus, among other sites, modulating both sympathetic and parasympathetic outflow, and thus reducing the likelihood of increases in HR and BP in response to surgery. The NMA circuit is an important neuroanatomical pathway guiding titration of anaesthetics intraoperatively; anaesthetists have relied upon the NMA circuit from the earliest days of the specialty.

The promise of multidrug anaesthesia (multimodal general anaesthesia)

In recent years, the concept of multimodal general anaesthesia has extended the well-entrenched concept of balanced anaesthesia to include more drugs that target different neuroanatomical circuits and multiple neurophysiologic mechanisms,[12] emulating the model of multimodal analgesia in the acute pain management domain. The proposed pharmacopeia for multimodal general anesthesia includes a host of anaesthetic adjuncts including opioids (e.g. remifentanil), alpha-2 agonists (e.g. dexmedetomidine), local anaesthetics

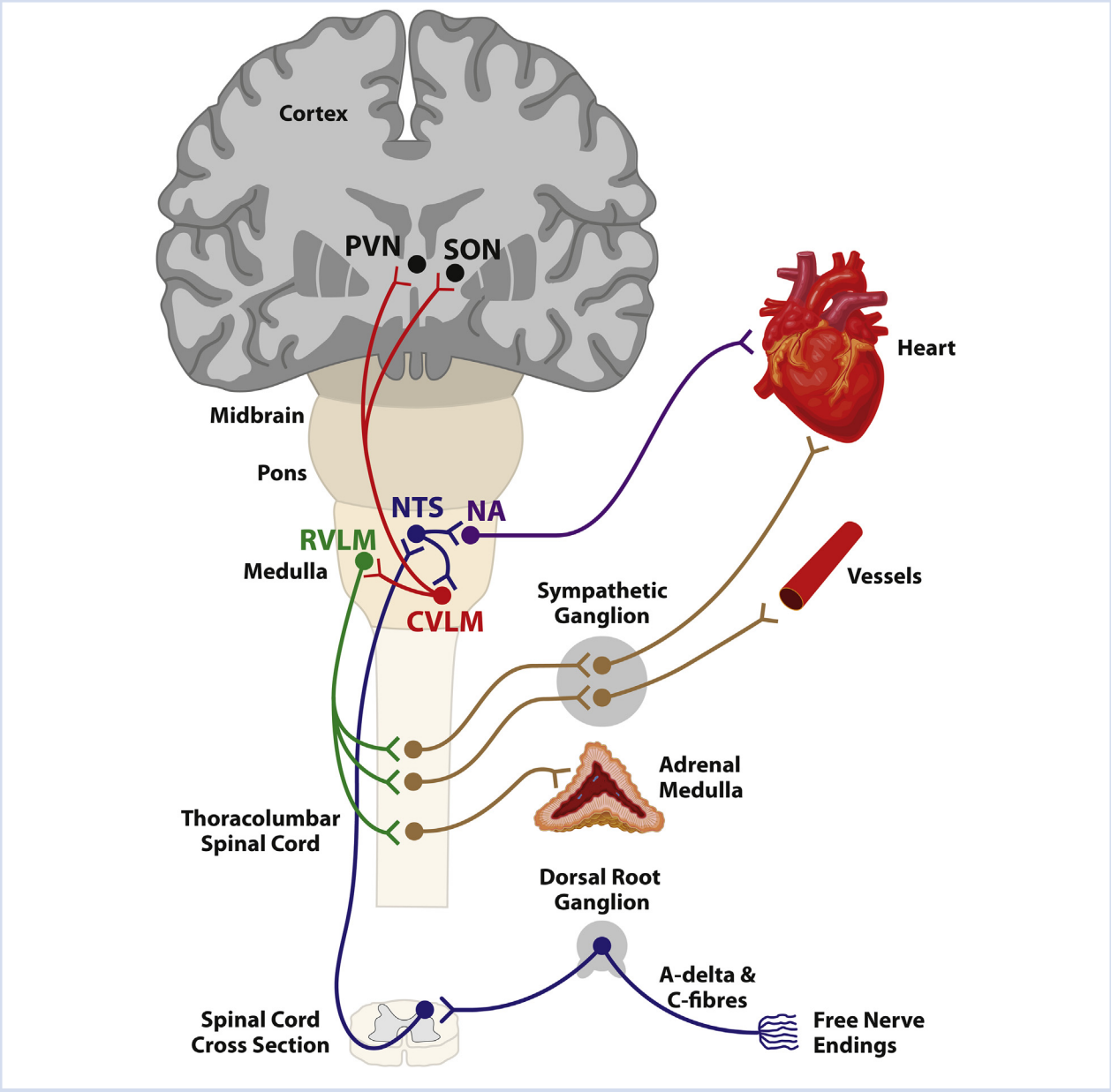

Fig 5. An idealised, highly schematised representation of the nociceptive-medullary-autonomic (NMA) circuit. The ascending nociceptive (pain) pathway begins with A-delta and C peripheral afferent fibres that synapse in the dorsal horn on projection neurones. These projection neurones synapse at multiple sites in the brainstem including the nucleus of the tractus solitarius (NTS) in the medulla. The autonomic response to a nociceptive stimulus is initiated from the NTS which mediates sympathetic output through the rostral ventral lateral medulla (RVLM) and the caudal ventral lateral medulla (CVLM) to the heart and peripheral blood vessels via projections to the thoracolumbar sympathetic ganglia and the adrenal medulla (which is essentially a sympathetic ganglion releasing sympathomimetics to the blood stream). The NTS also projects to the periventricular nucleus (PVN) and supraoptic nucleus (SON) in the hypothalamus. The parasympathetic output is mediated through the nucleus ambiguous (NA) which projects through the vagus nerve to the sino-atrial node of the heart. Adapted from Brown and colleagues.[11]

(e.g. lidocaine), and N-methyl-D-aspartate receptor antagonists (e.g. magnesium, ketamine). The pharmacologic foundation of the multimodal general anaesthesia approach is built on the firmly established observation that when anaesthetic drugs of different mechanisms are combined, they typically interact synergistically, just as with balanced anaesthesia.[28] This synergy affords certain advantages, including faster recovery because the slope of the concentration-effect relationship steepens with synergy, meaning that small decreases in drug concentration lead to larger decreases in drug effect,[27] hastening the passive process of anaesthetic emergence. Because smaller doses of

synergistically interacting drugs can be administered, some adverse effects might be mitigated (e.g. the dose-related nausea associated with opioids, among others). Although multimodal general anaesthesia has considerable theoretical appeal, whether the technique can effect improvements in selected, important anaesthetic outcomes is mostly unproved. In particular, whether the multimodal approach can reduce the incidence of persistent opioid use after surgery is unknown.

Perioperative opioids and opioid misuse

The opioid abuse epidemic has provided some of the motivation to move away from opioids toward other adjunct drugs for provision of general anaesthesia and postoperative pain management. Persistent opioid use after surgery, defined variably in terms of both dosage amount and timing (e.g. daily oral morphine equivalent, frequency of opioid dispensing, duration of opioid dispensing, among others),[29] is a component of the opioid epidemic, and is a major concern for perioperative physicians, pain medicine specialists, and public health officials, although the problem is probably under-recognised.[30,31] Data suggest that perioperative opioid usage patterns may contribute to opioid misuse after operation, although how the administration of intraoperative opioids may influence this problem is unclear.[32,33]

The scope of the problem is immense; persistent opioid use after surgery affects nearly every demographic group and surgical specialty. The problem has been observed in obstetric, paediatric, geriatric, and adult patient populations.[30,34–36] Patient risk factors include lower socioeconomic status, psychiatric co-morbidities, history of substance abuse, preoperative opioid therapy, preoperative use of certain medications (e.g. sedatives, antianxiety medications), and male gender, among others.[30,34,37–40] Certain types of surgery may be associated with higher risk, such as thoracic, major abdominal, bariatric, and joint replacement procedures, although the problem has also been described after minor surgery and dental procedures.[30,38,40–44] Some studies suggest that minimally invasive surgical approaches may have a lower risk.[44] While the risk of persistent opioid use after surgery in opioid naïve patients is low (<1% in some studies), for patients with numerous risk factors, the incidence is considerably higher.[30,44] Preoperative opioid therapy in the chronic pain patient is a notable risk factor. About one in four surgical patients are receiving opioids before operation[45]; these patients have a slower resolution of postoperative pain and are more likely to be on opioids months after surgery.[46] The huge number of patients undergoing surgery annually presumably means that hundreds of thousands of patients or more are at risk for persistent opioid use after surgery internationally.[47]

Most of the conventional wisdom addressing potential solutions to the problem of persistent opioid use after surgery have focused on proper opioid stewardship after operation, wherein opioids are used conservatively in combination with other analgesic adjuncts, and excessive opioid prescribing for home use is avoided.[48] A key observation unpinning this approach is that the quantity of opioid prescribed after operation is associated with higher patient-reported opioid consumption.[49] About one-quarter of patients receiving chronic opioid therapy first received opioids after operation.[50] Each opioid prescription refill after operation greatly increases the risk of persistent opioid use in opioid naïve patients.[51] Evidence-based postoperative opioid prescribing guidelines and electronic medical record-based decision support constraining pill counts appear to have a positive impact in achieving better opioid stewardship.[52,53] Opioid prescribing limits for acute pain are gaining traction as a component of the policy response to the opioid crisis in the USA,[54] although critics of this approach raise concern about inadequate treatment of pain in certain populations.[55]

An innovative risk mitigation strategy is the concept of the transitional pain service, a multidisciplinary team (e.g. physicians, nurses, physical therapists, pharmacists, mental health professionals, among others) that identifies high-risk patients and provides a suite of perioperative supportive services aimed, in part, at preventing development of opioid misuse long-term.[56] Increased communication and collaboration between surgeons and primary care physicians (who are more likely to be the opioid prescriber months after surgery) are likely to be another effective risk mitigation tactic.[57] A Perioperative Quality Initiative (POQI) consensus statement addressing the challenges of perioperative opioid therapy in the face of the opioid epidemic recommends preoperative risk stratification (i.e. using the O-NET+ scale), application of multimodal analgesia techniques, and engagement with appropriate consultants in patients at high risk for postoperative opioid adverse events including persistent opioid use after surgery.[58] In high-risk cases, this collection of POQI recommendations is akin to the transitional pain service approach now gaining popularity.

There is a paucity of data on how intraoperative opioid usage patterns may contribute to persistent opioid use after surgery and the opioid epidemic. Enhanced recovery after surgery (ERAS) protocols implementing multimodal analgesia approaches appear to be associated with lower rates of postoperative opioid use both in-hospital and after discharge.[59] However, perhaps surprisingly, in at least one study, an ERAS protocol aimed at achieving opioid-free anaesthesia intraoperatively did not appear to impact opioid prescribing practices at discharge, perhaps because these prescribing practices are more a function of tradition than evidence.[60] Moreover, applying regional anaesthesia techniques for postoperative pain management (e.g. epidural catheters after major abdominal procedures or nerve blocks for total knee arthroplasty) does not appear to reduce reliably the incidence of persistent opioid use after surgery, at least as analysed using large administrative databases.[61–63]

The concept of multimodal general anaesthesia does not call for the total abandonment of intraoperative opioids, but rather a more eclectic pharmacologic assortment that increases synergy and decreases the total opioid exposure. This approach should reduce dose-related opioid adverse effects perioperatively, and may have some impact on postoperative opioid abuse, although this is speculative. Even if decreasing total intraoperative opioid dosage does not reduce the incidence of persistent opioid use after surgery, it appears to be associated with other important outcomes such as a reduced hospital readmission rate within 30 days.[64]

Conclusions and future directions

Are opioids indispensable for general anaesthesia? The answer is a qualified no. Opioids are definitely not absolutely essential, but they are certainly very useful in producing the drug-induced, reversible coma of anaesthesia. In particular, opioids are extremely efficacious in controlling untoward ANS responses to nociception. The fact that opioids also reduce the

volatile anaesthetic and propofol concentrations necessary to achieve unconsciousness and immobility is another important, clinically useful property.

In the face of the opioid epidemic, there is certainly substantial motivation to decrease perioperative opioid use, although whether intraoperative opioid administration impacts the incidence of persistent opioid use after surgery is still unknown. Similarly, whether multimodal general anaesthesia, wherein traditional opioid doses are reduced, will improve important anaesthetic outcomes is still largely untested. Moreover, whether unanticipated adverse consequences of multimodal general anaesthesia will eventually be described as the technique is more widely and liberally applied, is also unknown.

Based on first principles, decreasing intraoperative opioid administration is likely to reduce dose-related intraoperative and immediate postoperative adverse opioid effects.[65] An additional likely benefit of reducing opioid doses intraoperatively is a reduction in opioid-induced hyperalgesia, a phenomenon that is clearly dose-related.[66] It is also likely that anaesthetic adjuncts (e.g. a local anaesthetic nerve block for an orthopaedic procedure) used efficaciously in place of opioids will reduce challenges presented by opioid-tolerant patients taking substantial doses of opioids before operation and also by patients receiving suboxone therapy for opioid use disorder. More research is necessary to establish that these probable outcomes can be realised; these proposed advantages of lower opioid doses intraoperatively are in great measure still speculative.

More speculative still is whether decreasing intraoperative opioid exposure will reduce opioid prescribing after surgery or reduce the incidence of persistent opioid use after surgery. There are considerable data that characterise the relationship between postoperative opioid prescribing patterns and persistent opioid use after surgery. Unfortunately, very little information is available about how intraoperative opioid administration influences persistent opioid use after operation. The immense human suffering associated with the opioid misuse epidemic make these questions pressing research priorities. Until more information is available for the creation of evidence-based practice guidelines, anaesthesiologists should consider using opioids more conservatively in the perioperative period, including intraoperatively.

Author contribution

TDE wrote the manuscript and supervised the creation of the figures.

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Declaration of interest

The author declares that they have no conflict of interest.

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