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REVIEW

Advances in the Clinical Application of MAC: A Review of Drug Selection, Combination Therapy, and Administration Methods

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Video abstract

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Abstract: Monitored anesthesia care (MAC) is a widely used anesthetic technique designed to provide titratable sedation and effective analgesia during a variety of medical procedures, ensuring patient comfort and safety. MAC is not only applied in surgical interventions but is also extensively used in diagnostic examinations such as sedation gastrointestinal endoscopy and pediatric magnetic resonance imaging (MRI) scans. With ongoing advances in medical technology, the selection of drugs, optimization of combination strategies, and refinement of administration methods for MAC continue to evolve. This narrative review, based on a structured literature search, summarizes recent developments in MAC drug selection, combination therapy, and administration methods. We highlight the quality and limitations of the current evidence, provide scenario-based practical recommendations, and outline emerging agents and delivery technologies, alongside unresolved questions that warrant further investigation.Overall, the existing evidence indicates that refined drug combinations (eg, propofol or dexmedetomidine in combination with opioids) tailored to specific procedural contexts and individual patient needs, alongside target-controlled infusion technology, are significantly enhancing the safety, comfort, and efficiency of MAC. However, the optimal drug combinations and standardized administration pathways still require further high-quality research.

Keywords: monitored anesthesia care, opioids, sedative agents, combination therapy, procedural sedation

Introduction

MAC delivers titratable sedation and analgesia while maintaining the patient's spontaneous ventilation and protective airway reflexes.[1] According to the American Society of Anesthesiologists (ASA), sedation depth is categorized into minimal, moderate, and deep sedation, whereas general anesthesia is characterized by a complete loss of consciousness. Under minimal sedation, patients remain awake, cooperative, and relaxed; moderate sedation leads to a drowsy state with preserved purposeful response to verbal or tactile stimuli; deep sedation results in patients who are difficult to arouse and who respond only to repeated or painful stimulation. In contrast, general anesthesia causes complete unconsciousness and typically requires endotracheal intubation to ensure adequate ventilation and airway protection. MAC typically encompasses levels ranging from minimal to deep sedation.

Owing to lower drug doses, rapid recovery, and minimal reliance on specialized equipment, MAC demonstrates substantial cost-effectiveness and is often covered by health insurance reimbursement systems, facilitating its broad adoption in outpatient settings. Despite growing demand—driven by an aging population, an increased prevalence of comorbidities, and a rising preference for day-case or ambulatory surgeries—the clinical implementation of MAC varies considerably according to procedural type, operator preference, and individual patient factors. Particular attention must therefore be paid to safety concerns such as oversedation, hypoventilation, and delayed emergence, especially among high-risk populations.

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Accordingly, this narrative review synthesizes current evidence regarding drug selection in MAC-particularly novel agents such as ciprofol and remimazolam—combination therapies with an emphasis on synergy and safety, and advanced drug delivery methods including target-controlled infusion and innovative administration routes. The review focuses on adult patients receiving MAC or procedural sedation for gastrointestinal (GI) endoscopy, bronchoscopy, hysteroscopy, interventional cardiology procedures, and other minor ambulatory or in-hospital interventions. We conducted a structured literature search as detailed under "Search strategy and study selection." Furthermore, this review explores emerging and future drug delivery technologies that may transform the practice of procedural sedation. The ultimate goal is to provide clinicians with evidence-based guidance for optimizing MAC and to identify promising research directions aimed at enhancing both safety and efficacy.

Literature Search and Review Scope

Search Strategy and Study Selection

We performed a structured literature search in PubMed, Web of Science, and Google Scholar for studies published from January 2006 to April 2025. Core keywords included "monitored anesthesia care," "opioids," "sedative agents," "combination therapy,"and "procedural sedation,"used alone or in combination. Inclusion criteria were human studies, adults (≥18 years), English or Chinese language, and relevance to MAC in GI endoscopy, bronchoscopy, interventional cardiology, or minor ambulatory or in-hospital procedures. Reference lists of key studies were also screened. Because this is a narrative review, findings were summarized qualitatively without formal meta-analysis or structured risk-of-bias assessment. The comprehensive workflow of literature screening is detailed in Figure 1.

Scope of This Review

This review focuses on adults (≥18 years) undergoing MAC or procedural sedation for GI endoscopy, bronchoscopy, interventional cardiology, or minor ambulatory or in-hospital procedures. Pediatric data are cited only to illustrate alternative routes and are not the primary focus. Unless specified, all statements refer to adult patients in ambulatory or in-hospital settings.

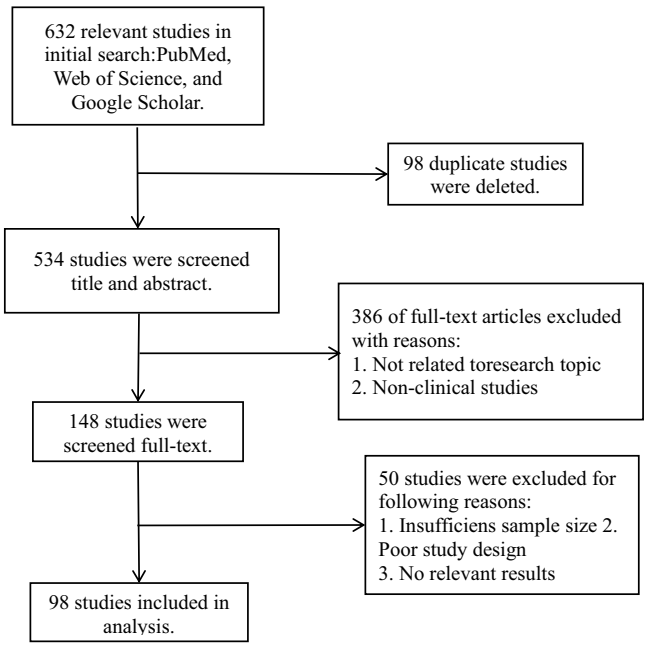

Figure 1 Literature search and screening process.

Commonly Used Sedatives in MAC

Propofol

Propofol serves as a primary sedative agent in MAC and is administered exclusively via intravenous injection. It exhibits high plasma protein binding, rapid blood-brain barrier[2] penetration, and predominantly hepatic metabolism through sulfate and glucuronide conjugation.Propofol potentiates γ-aminobutyric acid (GABA) activity at GABAA receptors, producing rapid onset and smooth emergence. Despite these advantages, attention is required regarding injection pain and dose-dependent hypotension, bradycardia, and respiratory depression.[3] Recent pharmacokinetic advancements are reflected in Eleveld et al ‘s development of a universal pharmacokinetic (PK) model for propofol.[4] These developments have expanded propofol administration beyond conventional bolus or infusion techniques, with Target-controlled infusion(TCI) increasingly adopted in MAC.

Evidence snapshot:Numerous Randomized Controlled Trials (RCTs) and observational studies across endoscopy, bronchoscopy, and minor procedures consistently support propofol’s rapid onset and ease of titration. Evidence quality is high, although most studies involve low-risk adults and short procedures. Adverse events—particularly hypoxemia and hypotension—remain the primary limitations and are dose-dependent. Variability in sedation depth and the need for skilled airway management constrain its use in high-risk populations.

Etomidate

Etomidate produces sedation primarily through GABAA receptor modulation[5] and is characterized by minimal respiratory depression,[6] exhibits minimal cardiovascular impact[7] and relatively stable hemodynamics.[8] These properties make it appealing for MAC in patients with cardiovascular or respiratory comorbidities. However, myoclonus, adrenal suppression, and postoperative nausea limit its widespread use,[9] and careful titration is required.

Evidence snapshot:Evidence consists mainly of small-to-moderate RCTs comparing etomidate with propofol in endoscopy and minor procedures. Results consistently show reduced hypotension and respiratory compromise compared with propofol, although myoclonus rates remain high. Study quality is moderate, with limited multicenter data. Uncertainty persists regarding its routine use outside high-risk populations.

Ciprofol

Ciprofol, a novel short-acting intravenous sedative structurally related to propofol,[10,11] demonstrates similar receptor mechanisms and metabolic pathways but with reduced injection-site discomfort.[12] Early clinical data suggest favorable hemodynamic stability and sedation quality, especially in short procedures.Established findings:Recent RCTs in colonoscopy and short procedures report non-inferior sedation efficacy compared with propofol, with lower injection pain and fewer hemodynamic fluctuations.Uncertain aspects:Ciprofo’s recent market introduction limits long-term pharmacovigilance and high-risk population data, and evidence across diverse procedural settings remains insufficient.

Evidence snapshot:Current evidence consists of small-to-moderate RCTs and emerging real-world reports. Consistency is moderate, but limited sample sizes and short follow-up constrain definitive conclusions.[13]

Dexmedetomidine

Dexmedetomidine is a highly selective α2-adrenergic agonist that produces dose-dependent sedation with minimal respiratory depression while supporting opioid-mediated analgesia.[14] Its characteristic “arousable sedation” enables patient cooperation during procedures.[15] This cooperative sedation mechanism has gained significant traction in MAC applications, though dose-dependent cardiovascular effects (notably bradycardia and hypotension) require vigilant monitoring at elevated doses, particularly during monotherapy.[16] However, bradycardia and hypotension may occur, particularly with higher doses or rapid loading.Established findings:Evidence consistently supports lower respiratory risk compared with propofol or benzodiazepines, and improved patient cooperation in longer or stimulation-requiring procedures.Uncertain aspects:Optimal dosing strategies remain variable, and hemodynamic adverse events limit use in elderly or hypovolemic patients. Non-intravenous routes show promise but lack large-scale validation.

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Evidence snapshot:Multiple RCTs and meta-analyses show moderate-to-high evidence for respiratory preservation and cooperative sedation. Study consistency is good, though heterogeneity in dosing regimens and monitoring limits standardization.

Midazolam

Midazolam is a benzodiazepine widely used for anxiolysis and amnesia during procedural sedation.[17] Its active metabolite, 1-hydroxymidazolam, contributes to prolonged sedative effects in some patients.[18] The primary mechanism involves potentiation of GABA neurotransmission within the central nervous system.[19] Multiple administration routes exist due to its lipophilicity,[20] including intranasal forms useful for patients with difficult venous access.Notably, midazolam nasal spray demonstrates rapid and consistent systemic absorption in both healthy individuals and epileptic patients, achieving detectable plasma concentrations within 5 minutes and observable sedation within 10 minutes post-administration.[21]

Evidence snapshot:Evidence shows predictable anxiolysis and amnesia, although prolonged recovery is common, particularly in elderly or hepatic impairment. Intranasal formulations demonstrate rapid onset in small studies, but variability in absorption and mucosal irritation remain limitations. Overall evidence quality is moderate, with limited large-scale trials.

Remimazolam

Remimazolam is a short-acting benzodiazepine metabolized by tissue esterases into an inactive metabolite, offering rapid onset with minimal accumulation. Compared with midazolam, it demonstrates faster recovery and fewer hemodynamic disturbances.[22] Established findings:RCTs in colonoscopy, endoscopy, and minor procedures demonstrate lower rates of hypotension and respiratory depression compared with propofol.Uncertain aspects:Sedation failure rates vary across studies, and data in complex or high-risk procedures remain limited. Long-term safety and real-world effectiveness require further study.[23]

Evidence snapshot:Evidence is moderate, based on multicenter RCTs and early meta-analyses. Consistency varies due to heterogeneity in dosing and procedural settings. Emerging but promising agent with a growing evidence base.The advantages, limitations, metabolites, and their clinical implications of these drugs are summarized in Table 1.

Commonly Used Analgesics in MAC

Fentanyl

Fentanyl is widely used in MAC due to its rapid onset, predictable analgesic effect, and cost-effectiveness. It acts primarily through μ-opioid receptor activation and undergoes hepatic metabolism to inactive metabolites such as norfentanyl. Intravenous administration remains standard, although alternative routes including intranasal and nebulized formulations have been explored.[24] Intranasal fentanyl demonstrates high bioavailability (≈89%), achieving clinically comparable analgesia to intravenous delivery with a slightly delayed onset of action.[25] Nebulized preparations have shown similar pharmacodynamic profiles in pharmacokinetic studies, though their use in MAC remains limited. Established findings:Fentanyl is well-supported by numerous RCTs and observational studies in endoscopy, bronchoscopy, and minor procedural sedation, consistently demonstrating effective analgesia and predictable dose-response.[26] Uncertain aspects:Evidence supporting intranasal or nebulized fentanyl in MAC is limited to small studies, with heterogeneous dosing and monitoring strategies.

Evidence snapshot:High-quality evidence supports intravenous fentanyl as a standard adjunct in MAC. Alternative delivery routes show promising but low-to-moderate evidence, with small sample sizes and inconsistent methodology. Respiratory depression remains the principal limitation.

Remifentanil

Remifentanil is an ultra-short-acting synthetic opioid rapidly metabolized by nonspecific blood and tissue esterases to inactive carboxylic acid derivatives. These properties make it highly suitable for continuous infusion and TCI-based administration.[27] Multiple pharmacokinetic models—including those developed for obese or pediatric cohorts—have

Table 1 Common Sedatives in MAC

Drug Class	Representative Agent	Advantages	Limitations	Metabolites and Their Clinical Implications
Benzodiazepines	Midazolam	Versatile administration routes;[20] Anxiolytic, muscle relaxant, and anterograde amnesic effects[18]	High risk of oversedation[18]	1-Hydroxymidazolam, 4-hydroxymidazolam, and 1,4-dihydroxymidazolam;1-hydroxymidazolam exhibits sedative effects similar to those of midazolam[17]
Alkylphenols	Propofol	Smooth induction characteristics, Rapid onset/offset[3]	Injection pain,Hypotension, Respiratory depression[3]	Inactive sulfate and glucuronide conjugates, etc[3]
Imidazole derivatives	Etomidate	Minimal respiratory depression;[6] Hemodynamic stability,Neuroprotection[9]	Myoclonus, Adrenocortical suppression,Postoperative nausea[9]	Inactive carboxylic acids, etc[5]
α_2-Adrenoceptor Agonists	Dexmedetomidine	Cooperative sedation ("arousable sedation");[15] Respiratory-sparing,Cerebral perfusion preservation[14]	Dose-dependent bradycardia, Hypotension[16]	Inactive N-glucuronide conjugates and hydroxylated derivatives, etc[14]
New imidazole sedatives	Remimazolam	Reduced injection pain,Improved cardiopulmonary stability vs propofol[22]	Limited clinical data, Insufficient long-term safety evidence[23]	Inactive zolpidem acetate[22]
Novel alkylphenols	Ciprofol	Based on the structural improvement of propofol, the injection pain is less and there is less respiratory and circulatory inhibition[12]	The clinical data is limited and the long-term medication experience is insufficient[13]	Glucuronic acid, etc[12]

been applied to remifentanil, although model performance varies across clinical settings. Dose-dependent respiratory depression remains a major safety concern, particularly at effect-site concentrations ≥2 ng/mL.[28] Established findings: Remifentanil provides highly titratable analgesia with rapid recovery, especially useful for dynamic or stimulation-dependent procedures (eg, endoscopy with intervention).Uncertain aspects:Optimal TCI targets for different procedural types remain inconsistent, and high-risk populations are underrepresented in existing trials.

Evidence snapshot:Evidence quality is moderate-to-high, with consistent findings on rapid onset and precision titratability across MAC studies. Limitations include variability in pharmacokinetic modeling, narrow therapeutic margins, and a high incidence of respiratory adverse events at modest dose increases.

Sufentanil

Sufentanil is a potent μ-opioid agonist with approximately 5–10 times the analgesic potency of fentanyl. It undergoes hepatic and intestinal metabolism to metabolites such as norsufentanil, including N-oxidation productsl,[29,30] which retains reduced activity. Intravenous administration predominates in MAC; however, transmucosal routes—particularly intranasal administration—exhibit variable bioavailability and may cause mucosal irritation. Concerns regarding chest wall rigidity have been reported in pediatric settings. Sublingual sufentanil formulations have recently shown potential in acute pain management, although their role in MAC remains investigational.[31] Established findings:Intravenous sufentanil provides effective analgesia with lower injection volume requirements relative to fentanyl.Uncertain aspects:Non-intravenous routes lack consistency in absorption and safety data, and evidence in MAC populations is sparse.

Evidence snapshot:Current evidence is moderate and largely based on small RCTs or pharmacokinetic studies. Findings support efficacy for intravenous use, while evidence for intranasal or sublingual routes in MAC is low and requires larger clinical evaluation.

Alfentanil

Alfentanil is a short-acting opioid characterized by rapid onset and short elimination half-life owing to hepatic metabolism to inactive metabolites such as noralfentanil.[32] Intravenous administration remains standard, with dosing commonly delivered as intermittent boluses or continuous infusion. Compared with remifentanil or sufentanil, alfentanil may be associated with less respiratory depression and a lower incidence of postoperative nausea and vomiting,[33,34] making it a practical option for certain MAC procedures.Established findings:Alfentanil has demonstrated effective analgesia in short procedures, with rapid recovery relative to longer-acting opioids.Uncertain aspects:Data comparing alfentanil with remifentanil or newer agents in complex or prolonged procedures are limited, and dosing variability remains a concern.

Evidence snapshot:Evidence quality is moderate, with consistent findings from small-to-medium RCTs supporting rapid onset and favorable recovery profiles. Limitations include heterogeneous procedural indications and underreporting of rare adverse events.[35] With careful dosing and vigilant monitoring, opioids continue to serve as a fundamental component of analgesic management in MAC protocols.Both the metabolites along with their clinical implications and the pharmacological characteristics of these drugs are summarized in Table 2.

Other Adjuvant Medications in MAC

Esketamine

Esketamine, the S-enantiomer of ketamine, is a dissociative anesthetic with sedative and analgesic properties mediated primarily through NMDA receptor antagonism. Compared with racemic ketamine, esketamine demonstrates higher NMDA receptor affinity, which has been associated with reduced psychotomimetic effects in some studies.[36,37] Interest in its use as an adjunct in MAC has increased due to its ability to provide analgesia with minimal respiratory depression.Established findings: Small trials in endoscopy and minor procedures suggest that low-dose esketamine may reduce opioid requirements and maintain stable ventilation.[38] Uncertain aspects:Evidence remains limited regarding optimal dosing, impact on recovery profiles, and safety in elderly or cardiovascular-compromised patients. Psychotomimetic symptoms, although reportedly less common than with ketamine, remain a concern. Comparative data against standard regimens are insufficient.

Table 2 Common Analgesic Agents in MAC

	Drug Class	Function Characteristics	Metabolites and Their Clinical Implications
	Opioids	Superior analgesia, rapid onset; adverse effects: respiratory depression, gastrointestinal discomfort, urinary retention, pruritus, rash[35]	
Representative drug	Fentanyl	IV injection is the most common route, suitable for single doses.High bioavailability via intranasal/nebulized administration[25,26]	Largely inactive norfentanyl, etc[24]
	Remifentanil	Rapid metabolism, suitable for TCI; dose-dependent respiratory depression requiring precise rate control[28]	Inactive carboxylic acid metabolites[27]
	Sufentanil	5-10×entanyl potency;[29] debated intranasal use; pediatric caution (chest wall rigidity);[30] sublingual delivery under investigation[31]	Norsufentanil (≈10% potency), N-oxidation products, etc[29,30]
	Alfentanil	Milder respiratory/cardiovascular effects; reduces postoperative nausea/vomiting incidence[33,34]	Inactive noralfentanil, etc[32]

Evidence snapshot:Current evidence is low-to-moderate in quality, consisting mainly of small RCTs and pilot studies. Results are heterogeneous, with inconsistent conclusions regarding analgesic advantage and recovery time. Larger, procedure-specific trials are needed to clarify esketamine's role as an adjunct in MAC.

Lidocaine

Lidocaine, an amide-type local anesthetic, has been used intravenously as an adjunct analgesic in some procedural sedation settings.[39] In MAC, intravenous bolus or low-dose continuous infusion and topical mucosal application are the most common modalities. Lidocaine may contribute to analgesia and opioid-sparing effects; however, its use requires careful monitoring due to potential systemic toxicity, especially with prolonged infusion or cumulative high dosing.[40] Topical formulations may cause mucosal irritation or systemic absorption depending on applied dose and surface area. Established findings:Small clinical studies have reported modest reductions in propofol and opioid requirements with intravenous lidocaine infusion during short procedures.Uncertain aspects:The therapeutic window for intravenous lidocaine in MAC is narrow, with risks including CNS symptoms, arrhythmias, and hepatotoxicity at high doses. Evidence regarding its routine use as an adjunct in MAC is inconsistent, and optimal dosing remains unclear.

Evidence snapshot:Evidence quality is low-to-moderate, largely from small RCTs with variable dosing protocols and limited safety reporting. Current findings suggest possible analgesic and opioid-sparing benefits, but concerns regarding toxicity and lack of standardized protocols limit broader adoption in MAC practice.

Scenario-Based Clinical Practice of Monotherapy in MAC

The following sections integrate evidence across commonly encountered clinical scenarios, which encompass short, low-pain procedures such as esophagogastroduodenoscopy (EGD) and colonoscopy, as well as longer or more painful procedures like endoscopic retrograde cholangiopancreatography (ERCP), endoscopic submucosal dissection (ESD), and bronchoscopy, high-risk or elderly patients, and both ambulatory and in-hospital settings.Monotherapy with sedatives is used in selected MAC settings, particularly those involving brief procedures or limited procedural stimulation.[41,42] Its main advantages include rapid onset, short recovery time, and procedural efficiency.[43] However, monotherapy may be insufficient for painful or prolonged interventions and carries risks of respiratory depression and hemodynamic instability when high doses or rapid boluses are required.[44] The following subsections summarize the evidence for monotherapy across different clinical scenarios.

Short, Low-Pain Procedures

Short procedures such as routine gastroscopy, screening colonoscopy, or minor diagnostic interventions commonly employ sedative monotherapy due to their limited procedural stimulation. Propofol remains the most frequently used

agent, supported by multiple trials demonstrating rapid onset and fast recovery. Evidence suggests that ciprofol may offer comparable sedation with reduced injection pain and modestly improved hemodynamic stability, although data remain limited to small studies.[45] Remimazolam has been associated with fewer cardiopulmonary adverse events but carries a higher risk of sedation failure compared with propofol.[46]

Evidence summary:Overall evidence quality is moderate to high for propofol and moderate for remimazolam and ciprofol. Most studies involve low-risk adult patients undergoing brief endoscopic procedures. Limitations include inconsistent dosing strategies and insufficient high-quality data for newer agents.

Longer or More Painful Procedures

Procedures such as ERCP, ESD and bronchoscopy often require deeper or sustained sedation.[47] In such settings, sedative monotherapy may not provide adequate procedural conditions, leading many clinicians to prefer combination regimens. Nevertheless, propofol monotherapy is still used in some centers, with studies demonstrating acceptable sedation but increased risk of hypotension and hypoxemia. Remimazolam monotherapy has shown favorable safety but higher sedation failure, making it less suitable as a sole agent in longer or more stimulating procedures.[44,47]

Evidence summary:Evidence is moderate for propofol and low to moderate for remimazolam in complex procedures. Heterogeneity in procedural duration, operator experience, and monitoring practices limits generalizability. Current data suggest that monotherapy should be used cautiously for painful or prolonged interventions.

High-Risk or Elderly Patients

In elderly or medically complex patients, sedative monotherapy requires cautious titration due to increased susceptibility to hypotension, hypoventilation, and delayed recovery.[3,16,48] Propofol monotherapy may be associated with exaggerated hemodynamic responses in frail patients. Etomidate offers more stable hemodynamics, although its evidence base in MAC remains limited and concerns regarding myoclonus persist.[48] Remimazolam has demonstrated favorable cardiopulmonary stability, making it a possible option for high-risk patients, though sedation failure remains a barrier to routine monotherapy use.

Evidence summary:Evidence is moderate for propofol and remimazolam and low for etomidate in high-risk populations. Few large-scale trials exist, and optimal titration strategies remain uncertain.

Ambulatory Vs in-Hospital Settings

In ambulatory settings, rapid recovery and minimal postoperative monitoring requirements often favor propofol or remimazolam monotherapy.[46] Ciprofol may also be considered when minimizing injection discomfort is desired. In in-hospital or monitored environments, TCI-based delivery of propofol or remifentanil allows more precise titration but requires infrastructure availability and trained personnel. Monotherapy should be individualized based on patient comorbidity, procedure type, and institutional workflow.

Evidence summary:Evidence is moderate for propofol and remimazolam in ambulatory settings and limited for ciprofol. Studies examining monotherapy in inpatient settings are heterogeneous, and outcomes depend heavily on monitoring and staffing.

Combination Medication Strategies in MAC

Combination regimens are widely used in MAC to improve sedation quality, reduce individual drug doses, and balance the advantages and limitations of different agents. Professional guidelines, including those from the European Society of Anaesthesiology (ESA), highlight their usefulness particularly in complex procedures, high-risk patients, and individualized anesthesia strategies.[49] Combination therapy may enhance synergistic sedative and analgesic effects,[50] but it also increases pharmacokinetic complexity, monitoring demands, and healthcare costs.[51] Therefore, drug selection must consider patient comorbidities, procedural stimulation, and safety requirements, with close intraoperative monitoring to maintain procedural safety.[42]

Common Combination Therapy Among Sedative Drugs

Propofol Combined with Midazolam

Propofol combined with midazolam has been investigated as a strategy to reduce propofol consumption through synergistic effects. Midazolam can increase plasma propofol concentrations by inhibiting propofol clearance.[52] Clinical studies show that the combination may reduce propofol dose requirements without improving sedation quality or physiological parameters, while potentially prolonging recovery time.[53] Established findings:Consistent reductions in propofol dosage across small interventional endoscopy studies.Sedation quality comparable to propofol alone.Uncertain aspects:Evidence limited to single-center trials.Optimal dosing ratios unclear.

Evidence snapshot:Evidence quality is low to moderate, based on small RCTs with consistent dose-sparing effects but slower recovery.

Propofol Combined with Remimazolam

Early pharmacodynamic studies suggest a dose-dependent synergistic interaction between remimazolam and propofol, with one model proposing maximal synergy near a 1:7 ratio (mg/kg).[54] Clinical trials report reduced hypotension and fewer body movements compared with monotherapy, while maintaining adequate sedation depth.[55–57] A multicenter study further found lower hypotension than propofol alone and lower movement incidence than remimazolam alone when the two were combined.[58] Established findings:Improved hemodynamic stability relative to propofol alone.Faster attainment of target sedation than remimazolam alone.Uncertain aspects:Risk of sedation failure still depends on remimazolam dosage.Evidence limited outside GI endoscopy settings.

Evidence snapshot:Evidence quality is moderate, supported by multiple early-phase trials but with heterogeneous dosing strategies.

Propofol Combined with Etomidate

Combining propofol with etomidate may mitigate propofol-related hypotension while maintaining appropriate sedation depth. Clinical studies show reduced hypotension, bradycardia, and hypoxemia compared with propofol alone.[59] Meanwhile, etomidate-related myoclonus may be reduced when combined with propofol rather than used alone.[60] Established findings:Improved hemodynamic stability compared with propofol alone.Lower myoclonus incidence compared with etomidate alone.Uncertain aspects:Unknown efficacy in longer or more painful procedures.Etomidat's endocrine effects remain a concern.

Evidence snapshot:Evidence quality is low to moderate, based on small trials and meta-analyses with consistent hemodynamic trends but limited generalizability.

Propofol Combined with Dexmedetomidine

Dexmedetomidine may reduce propofol requirements while improving procedural tolerance.[61,62] In endoscopic submucosal dissection, this combination lowered propofol infusion needs, decreased restlessness, and improved provider satisfaction, though bradycardia occurred more frequently.[63] Established findings:Reduced propofol dose and improved patient cooperation.Lower incidence of restlessness during long endoscopic procedures.Uncertain aspects:Bradycardia and delayed recovery require careful monitoring.Evidence limited for shorter procedures.

Evidence snapshot:Evidence quality is moderate, drawn from randomized trials in advanced endoscopy with consistent procedural improvements.

The Common Combination of Sedative and Analgesic Drugs

Propofol Combined with Opioid Drugs

Propofol–opioid combinations are widely employed in MAC. Meta-analyses show improved procedure conditions and fewer adverse events with propofol–alfentanil compared with propofol alone in GI endoscopy.[64] Opioids mitigate injection pain, with sufentanil showing lower injection pain incidence than fentanyl or remifentanil when combined with propofol.[29] Comparative data show differing performance among opioid agents, with fentanyl sometimes providing stronger sedative-analgesic synergy,[65] while remifentanil may be more effective during more stimulating procedures such as ERCP.[66] Established findings:Improved analgesia and better procedural tolerance,Reduced injection pain with

sufentanil.Uncertain aspects:Balancing effective analgesia with respiratory depression remains challenging.Optimal opioid choice varies by procedure type.Evidence snapshot:Evidence is moderate to high, supported by large observational studies and multiple meta-analyses, but respiratory safety varies across opioids.

Benzodiazepines Combined with Opioids

Midazolam–opioid combinations typically yield moderate sedation but have slower recovery than propofol-based regimens,[67] and patient preference often favors propofol.[68] Remimazolam combined with sufentanil has shown comparable sedation to propofol–sufentanil but with improved safety in colonoscopy.[69] In elderly patients, remimazolam–fentanyl produced similar recovery times but fewer complications compared with propofol–fentanyl.[70]

Evidence snapshot:Evidence is moderate, with consistent findings of improved safety for remimazolam–opioid combinations in older or high-risk adults.

Dexmedetomidine Combined with Opioid Drugs

Dexmedetomidine–opioid combinations provide moderate sedation with preserved respiratory drive. Systematic reviews in interventional cardiology report benefits of MAC over general anesthesia during transcatheter aortic valve replacement (TAVR), including shorter procedure duration and hospital stay.[71] In bronchoscopy, dexmedetomidine–remifentanil achieved similar procedural quality to propofol–remifentanil but with fewer respiratory adverse events.[72]

Evidence snapshot:Evidence is low to moderate, with potential safety advantages particularly in cardiopulmonary-compromised patients.

Propofol Combined with Opioids Versus Dexmedetomidine Combined with Opioids

Systematic reviews show dexmedetomidine may provide more stable hemodynamics and fewer respiratory complications during procedural sedation.[73,74] However, propofol often delivers deeper and more predictable sedation with higher patient satisfaction in GI endoscopy.[75] Large ICU sedation trials also support dexmedetomidine's advantages in terms of arousability and ventilator weaning.[76,77]

Evidence snapshot:Evidence is moderate, with selection dependent on prioritizing hemodynamic stability (favoring dexmedetomidine) versus depth of sedation (favoring propofol).

Common Combination Therapy Between Sedative Drugs and Other Adjuvant Drugs

Propofol Combined with Esketamine

Esketamine may help counteract propofol-related hypotension and reduce propofol dosing. It can also attenuate opioid-induced respiratory depression via enhanced CO_2 chemosensitivity.[78] Some studies report improved cardiovascular stability compared with opioid–propofol combinations.[79,80]

Evidence snapshot:Evidence remains low, based on small studies with inconsistent outcome measures. Psychotomimetic effects remain a concern.

Dexmedetomidine Combined with Esketamine

Esketamine's sympathomimetic effects may offset dexmedetomidine-induced bradycardia and hypotension,[81] while both agents exert limited respiratory depression.[78,82] Evidence from transforaminal endoscopic surgery shows mixed results: improved analgesia but increased dizziness and neuropsychiatric symptoms.[83]

Evidence snapshot:Evidence is low, with heterogeneous results and limited MAC-specific studies.

Propofol Combined with Lidocaine

Intravenous lidocaine may reduce PONV, lower propofol and opioid requirements, and attenuate injection pain.[84–86] Some evidence supports its role in ERCP and other endoscopic procedures.[84]

Evidence snapshot:Evidence is low to moderate, with significant variation in infusion protocols and limited MAC-specific trials.The following elements of evidence-based combination drug strategies—recommended dosage ranges, common adverse reactions, key supporting evidence, and categorization by clinical setting—are concisely summarized in Table 3.

A consolidated summary of the evidence base supporting each regimen is presented in Table 4.

Table 3 Clinical Practices of MAC Drug Combination Use in Different Clinical Settings

Clinical Setting	The Best Combination of Supportive Medications	Optimal Dosage Range	Common Adverse Effects	Key Supporting Trials/Guidelines
Endoscopy	Propofol + Opioid drugs	Propofol 1–2 mg/kg, Fentanyl 0.5–1μg/kg or Remifentanil 0.05–0.08μg/kg/min	Respiratory depression, hypotension	Yoon et al;[41] Endoscopic Sedation Guidelines;[43] Dossa et al[68]
Cath lab	Dexmedetomidine + Opioid drugs	Dexmedetomidine: initial dose 0.5 μg/kg (10 minutes) + maintenance dose 0.2–0.7μg/kg/h, Fentanyl 0.5–1μg/kg or Remifentanil 0.05–0.08μg/kg/min.	Hypotension, bradycardia	ASA Sedation Guidelines;[42] Barends et al;[61] Fröhlich et al[71]
Minor surgery	Dexmedetomidine/ Propofol + Opioid Drugs	Dexmedetomidine: Initial dose 0.5 μg/kg (10 minutes) + 0.2–0.7 μg/kg/h, (or Propofol 1–1.5 mg/kg), Fentanyl 1–2μg/kg or Remifentanil 0.05–0.08μg/kg/min (TCI:0.8–1.2 ng/mL)	Respiratory depression, bradycardia, hypotension	ASA Sedation Guidelines;[42] ESAIC Guidelines[49]

The Administration Method in MAC

Advances in anesthetic delivery systems have expanded MAC beyond traditional intravenous bolus or continuous infusion techniques. Newer administration modalities aim to improve patient comfort, minimize adverse events, and enhance titration precision across varied procedural settings. The following sections summarize established and emerging approaches with attention to current evidence quality, limitations, and clinical applicability.

Special Administration Methods of Sedative Drugs in MAC Anesthesia

TCI systems were developed to address the limitations of manual propofol infusion, particularly regarding dose predictability and hemodynamic fluctuations. Studies comparing propofol TCI with manual infusion during endoscopic procedures report more stable hemodynamics and faster recovery, with reduced hypotension and hypoxemia.[87] TCI may be particularly useful for longer or more stimulating procedures requiring steady-state sedation.Alternative administration routes for sedatives—particularly intranasal midazolam and dexmedetomidine—have been explored mainly in pediatric or special populations. Intranasal midazolam has demonstrated adequate sedation with high procedural satisfaction in children.[88] Meta-analyses further suggest that intranasal dexmedetomidine may provide equal or greater efficacy than intranasal midazolam for pediatric preoperative sedation,[89] although data in adults remain limited.Established findings: Propofol TCI offers more predictable pharmacokinetics and may reduce adverse events compared with manual infusion, Intranasal midazolam and dexmedetomidine provide feasible alternatives in children.Uncertain aspects:Optimal TCI target concentrations vary across procedures,Limited evidence exists for intranasal sedatives in adults,Device- and model-dependent variability may influence performance.

Evidence snapshot:Evidence is moderate for propofol TCI and low to moderate for intranasal sedatives, with heterogeneity in dosing protocols and limited adult data.

The Special Administration Mode of Analgesic Drugs in MAC

Although fentanyl supports multiple administration routes, intravenous delivery remains the predominant modality in MAC. Data on alternative routes are mixed: sublingual fentanyl tablets permitted successful colonoscopy completion but offered no clear analgesic advantage.[89] Intranasal sufentanil, with significantly higher potency than fentanyl, has shown comparable performance to intravenous midazolam during colonoscopy.[90] For remifentanil, bolus administration has demonstrated favorable outcomes in EGD compared with fentanyl,[91] while TCI-based remifentanil delivery during endobronchial ultrasound-guided transbronchial needle aspiration may improve patient comfort and reduce oversedation.[92] Established findings:Sublingual fentanyl provides workable, though not necessarily superior, analgesia for minor

Table 4 Summary Strength of Evidence

Drug/Regimen	Main Clinical Setting	Evidence Base	Main Outcomes	Limitations	Overall Evidence Strength
Propofol (IV bolus/ infusion)	EGD, Colonoscopy, ERCP, Bronchoscopy, ESD	Numerous RCTs & observational studies	Rapid onset; deep sedation	Respiratory depression; hypotension	High
Propofol TCI	GI endoscopy, Bronchoscopy	Several RCTs	Stable sedation; reduced events	Model variability	Moderate
Midazolam	Minor procedures	Moderate RCTs	Anxiolysis; amnesia	Prolonged sedation	Moderate
Dexmedetomidine	Bronchoscopy, ESD	Multiple RCTs	Arousable sedation	Bradycardia	Moderate
Ciprofol	GI endoscopy	Early RCTs	Less injection pain	Limited long-term data	Low-Moderate
Remimazolam	GI endoscopy, elderly	Multiple RCTs	Less hypotension	Higher sedation failure	Moderate
Propofol+ Opioids	Colonoscopy, ERCP	Multiple RCTs	Strong analgesia; dose sparing	Respiratory depression	High
Propofol+ Remimazolam	GI endoscopy	Early RCTs	Improved hemodynamics	Limited dosage standards	Low-Moderate
Propofol+ Etomidate	GI endoscopy	RCTs+ meta-analyses	Stable hemodynamics	Myoclonus	Moderate
Propofol+ Dexmedetomidine	Long procedures	RCTs	Lower propofol dose	Bradycardia	Moderate
Dexmedetomidine+ Opioids	Bronchoscopy, TAVR	Small RCTs	Better safety	May need rescue sedation	Low-Moderate
Propofol+ Esketamine	Painful procedures	Small RCTs	Improved hemodynamics	Psychomimetic effects	Low
Propofol+ Lidocaine	Endoscopy, ERCP	Small RCTs	Less injection pain	Optimal dosing unclear	Low-Moderate

procedures,Intranasal sufentanil offers rapid onset and adequate procedural sedationRemifentanil bolus and TCI strategies may enhance responsiveness and safety during specific procedures.Uncertain aspects:Optimal dosing for intranasal or sublingual opioid formulations is not standardized,Limited data exist in high-risk adult populations,Device variability affects remifentanil TCI precision.

Evidence snapshot:Evidence is low to moderate, with procedure-specific studies suggesting potential benefits but inconsistent analgesic superiority compared with conventional intravenous(IV) methods.

Special Administration Methods of Other Adjuvant Drugs in MAC

Lidocaine can be administered via several routes depending on procedural needs. In upper GI endoscopy, topical spray improves patient satisfaction compared with viscous solutions, despite similar pain control.[93] During bronchoscopy, topical lidocaine spray may reduce coughing and decrease systemic lidocaine exposure relative to intravenous administration.[94] In large-volume liposuction, segmental infiltration with dilute lidocaine provides prolonged analgesia and suppresses intraoperative discomfort, although extended operative times and large fluid shifts increase risks such as pulmonary edema and thromboembolic events.[95] Established findings:Topical lidocaine is effective for mucosal anesthesia with reduced systemic exposure,Dilute infiltration techniques may support analgesia during prolonged procedures.Uncertain aspects:Wide variability in spray techniques and dosing limits generalizability,Safety concerns persist with high-volume infiltration during long operations,Limited data address lidocaine's role as a systemic adjuvant in standard MAC.

Evidence snapshot:Evidence is low to moderate, reflecting heterogeneous methodologies and limited MAC-specific trials.The characteristics and clinical significance of different administration methods in MAC are summarized in Table 5.

A scenario-based quick-reference guide summarizing practical regimen selection is provided in Table 6.

Table 5 The Drug Administration Methods in MAC

Administration Method	Characteristics	Applicable Drugs	Clinical Significance
Single IV Bolus	Rapid onset; suitable for brief procedures (e.g, colonoscopy)	eg, Propofol, Etomidate	Simplified workflow; requires vigilance for drug accumulation risks
Continuous IV Infusion	Maintains stable plasma concentrations; ideal for prolonged sedation requirements	eg,Propofol, Dexmedetomidine, Remifentanil	Minimizes concentration fluctuations; reduces adverse event incidence
Target-Controlled Infusion	Pharmacokinetic model-driven precision in sedation/analgesia depth modulation.	eg, Propofol (Eleveld universal model), Remifentanil (Kim-Obara-Egan model)	Enhances controllability; accelerates postoperative recovery; optimal for obese/geriatric populations.
Specialized Administration Routes			
Intranasal	Non-invasive;rapid absorption (5–10 min onset); high patient compliance	eg, Dexmedetomidine (pediatric sedation), Fentanyl/Sufentanil (controversial)	Eliminates venipuncture; ideal for children or patients with poor vascular access.
Sublingual	Mucosal absorption bypasses first-pass metabolism; moderate onset speed	eg, Fentanyl/Sufentanil (acute pain management; exploratory use in MAC)	Alternative for non-oral candidates or urgent analgesia needs
Nebulized Inhalation	Direct respiratory tract action; localized analgesia reduces systemic sedative load	eg, Fentanyl, Lidocaine (cough suppression in bronchoscopy)	Mitigates systemic side effects; suppresses airway reflexes; enhances procedural safety
Segmental Local Infiltration	Site-specific pharmacological action	eg, Lidocaine	Alleviates intraoperative discomfort, pain, and anxiety during prolonged surgeries

Table 6 Practical Quick-Reference by Clinical Scenario

Clinical Scenario	Recommended Regimens	Typical Dosing/Mode	Advantages	Drawbacks	Safety Considerations
Short, low-pain procedures (EGD, Colonoscopy)	Propofol; Propofol+ low-dose opioid; Remimazolam	IV Propofol 0.5–1mg/kg; infusion 2–4mg/kg/h; IVRemimazolam 0.1–0.2 mg/kg	Rapid onset; good tolerance	Hypoxemia	Careful titration; HFNO if needed
Longer or painful procedures (ERCP, ESD)	Propofol+ opioid; Propofol +dexmedetomidine;Propofol	Remifentanil TCI 1–3 ng/mL;infusion Dexmedetomidine0.5–1ug/kg/h; Propofol TCI 2.5–4 ug/mL	Stable deep sedation	Cardiovascular depression	Continuous monitoring; prefer TCI
High-risk/ elderly patients	Dexmedetomidine;Remimazolam; Etomidate	Infusion Dexmedetomidine0.2–0.7ug/kg/h; IV Remimazolam 0.05–0.15mg/kg; IV Etomidate 0.05–0.1 mg/kg	Minimal respiratory depression	Bradycardia	Dose reduction; avoid bolus
Ambulatory/ day-case procedures	Low-dose propofol; Remimazolam;	Infusion Propofol 1–3mg/kg/h;IV midazolam 0.2 mg/kg;IV dexmedetomidine 1–2 ug/kg	Fast recovery	Variable absorption	Use short-acting agents

Clinical Efficacy and Safety Evaluation

The clinical effectiveness and safety of MAC depend on continuous evaluation using validated sedation and physiologic metrics. Commonly employed tools include the Bispectral Index (BIS), the Observer's Assessment of Alertness/Sedation (OAA/S) scale, and the Modified OAA/S (MOAA/S). Propofol administered via TCI has been reported to maintain BIS values within a clinically acceptable range (typically 50–70), potentially reducing intraoperative movement during endoscopic procedures.[3] Dexmedetomidine, in contrast, produces "cooperative sedation," often corresponding to OAA/S scores of 4–5, allowing patient responsiveness while preserving overall safety.[83] Patient satisfaction generally favors regimens combining propofol with short-acting opioids over traditional benzodiazepine-based protocols, although safety considerations remain paramount.[83]

Sedation Efficacy and Patient Experience

Clinical studies consistently show that both propofol- and dexmedetomidine-based regimens provide reliable sedation for MAC across diverse procedures. Propofol typically yields faster onset and deeper sedation, whereas dexmedetomidine supports more stable respiratory patterns with preserved arousability. Opioid–propofol combinations may enhance patient comfort, though at the cost of increased risk of respiratory suppression.[83] Overall, sedation efficacy varies by procedure type, patient comorbidities, and the delivery method employed.

Respiratory Safety Considerations

Respiratory depression remains a major concern in MAC. Propofol exerts dose-dependent suppression of ventilatory drive by reducing chemoreceptor responsiveness to CO_2.[3] Remifentanil demonstrates a steep dose–response relationship, with TCI effect-site concentrations ≥2 ng/mL associated with high rates of apnea or desaturation.[28] Adjuncts such as esketamine may mitigate opioid-induced respiratory depression by enhancing CO_2 chemoreflex sensitivity,[78] though this effect requires further validation.Key uncertainties:Optimal dosing thresholds for minimizing respiratory compromise are not standardized,Predictive markers of respiratory suppression remain poorly defined across agents,Data on high-risk populations (eg, obesity, obstructive sleep apnea, frailty) remain limited.

Hemodynamic Safety Considerations

Hemodynamic instability is frequently encountered during MAC. Propofol-induced vasodilation may precipitate clinically significant hypotension, particularly in elderly patients or those with limited physiological reserve.[3] Etomidate offers relative hemodynamic stability and is often considered in patients with cardiovascular compromise,[7] whereas dexmedetomidine carries an increased risk of bradycardia due to α_2-adrenergic agonism, especially in patients receiving β-blockers.[16] Combination strategies—such as propofol–esketamine—may improve hemodynamic balance by counteracting propofol-mediated vasodilation, though evidence remains limited.Key uncertainties:Comparative hemodynamic profiles among emerging agents (eg, ciprofol, remimazolam) require further study.Long-term cardiovascular safety of multi-agent regimens is not well established.

Emerging Agents and Advanced Delivery Systems

Newer sedatives such as remimazolam and ciprofol offer promising pharmacokinetic features, including rapid metabolism and decreased accumulation, which may reduce risks of prolonged sedation or delayed recovery.[12,96] Nonetheless, long-term safety data and real-world evidence across varied procedural settings remain limited. Similarly, advancements such as Eleveld model–based TCI may enhance dosing precision for propofol or remifentanil, but predictive accuracy varies across age groups, comorbidities, and procedural intensity.[28] Uncertain aspects:Limited high-quality head-to-head comparisons with established regimens,Model performance for TCI varies with patient factors (age, obesity, hepatic function),Few large-scale trials examine outcomes such as hypoxemia, hypotension, and recovery time across heterogenous populations.

Evidence Summary

Evidence strength across domains: (1) Sedation efficacy: Moderate (supported by multiple RCTs, consistent across propofol-based MAC). (2) Respiratory safety: Moderate (clear dose–response data for propofol and remifentanil; limited

evidence for esketamine mitigation).(3) Hemodynamic safety: Low to moderate (evidence for etomidate and dexmedetomidine consistent but population-specific). (4) Emerging agents/technologies: Low (early-phase studies; limited long-term data; heterogeneity significant).

Overall, MAC safety relies heavily on agent selection, dose titration strategy, patient comorbidities, and monitoring capability. Continued research is necessary to optimize precision dosing models, identify high-risk phenotypes, and clarify the role of emerging agents in improving safety and recovery outcomes.

Limitations and Future Prospects of MAC Anesthesia

Current Limitations

Despite the widespread use of combination regimens in MAC, the mechanisms contributing to adverse reactions—such as respiratory depression, hemodynamic instability, and drug–drug interactions—remain incompletely understood. Existing research primarily quantifies sedation and analgesia, while mechanistic insights into these adverse events are comparatively limited. This knowledge gap is especially relevant in elderly individuals and patients with significant comorbidities, who may be more vulnerable to polypharmacy-related complications.Current anesthetic delivery predominantly relies on intravenous bolus administration and continuous infusion. Although effective, these approaches offer limited adaptability and imprecise individualized regulation. Bolus dosing lacks real-time adjustability, while continuous infusion may result in drug accumulation and delayed recovery, increasing monitoring burden and workflow complexity.

Research Gaps and Future Directions

Key challenges that remain insufficiently addressed include:The pharmacokinetic and pharmacodynamic interactions among sedative, analgesic, and adjuvant agents in diverse populations;Evidence-based dosing algorithms for multimodal MAC regimens;Standardized predictors of respiratory or cardiovascular compromise during sedation;Limited high-quality data on newer agents such as ciprofol and remimazolam;Insufficient validation of predictive models across age groups and comorbidity profiles.

Future work should prioritize:Mechanistic studies examining how sedatives and analgesics interact at the respiratory and cardiovascular levels;Development of evidence-based, procedure-specific dosing protocols for combination therapies;Advancement of closed-loop anesthesia systems that integrate physiologic monitoring with intelligent feedback algorithms to support individualized titration;Optimizing sedative–adjunct combinations to maximize synergistic effects while minimizing adverse outcomes.These initiatives may help shift MAC practice toward safer, more precise, and patient-centered care.

Emerging and Speculative Technologies

Beyond refinements in infusion systems, several early-stage biomedical strategies are being explored outside the MAC domain and may, in concept, hold future relevance. For example, macrophage-based drug delivery systems—studied primarily in oncology—have been investigated as cellular "carrier" platforms capable of migrating toward inflammatory or surgical sites.[97,98] Preliminary evidence suggests that such approaches could potentially allow more site-specific drug delivery, thereby reducing systemic exposure and theoretically mitigating adverse effects such as respiratory or circulatory depression.[97,98] However, these concepts remain entirely preclinical and face substantial translational challenges, including payload stability, targeting accuracy, immunologic safety, and feasibility in perioperative settings. At present, their applicability to MAC anesthesia is speculative and supported only by early mechanistic studies in other therapeutic fields.

Conclusion

This narrative review summarizes current developments in sedative and analgesic selection, combination strategies, and administration methods in MAC. The available evidence indicates that multimodal regimens and individualized dose titration may enhance sedation quality while reducing the incidence of adverse events. Short-acting intravenous agents and infusion-based techniques—such as propofol, remifentanil, continuous infusion, and TCI—continue to be widely utilized, whereas alternative routes such as intranasal dexmedetomidine have shown potential utility in selected settings.

However, these conclusions remain based on heterogeneous studies with generally small sample sizes, short follow-up, and variable methodological quality.

Although several emerging agents and techniques appear promising, including ciprofol, remimazolam, and advanced infusion systems, current data remain insufficient to fully clarify their long-term safety, pharmacologic interactions, or applicability across diverse procedural contexts. Larger, multicenter studies with standardized outcome measures are needed to strengthen the evidence base.

Arousable sedation strategies may offer particular advantages for procedures requiring patient cooperation or prone positioning, such as percutaneous transforaminal endoscopic surgery or ERCP, especially when implemented with agents like dexmedetomidine or precision titration via TCI. Similarly, high-flow nasal oxygen (HFNO) has been associated with improved respiratory safety in some studies, though the magnitude and consistency of benefit require further confirmation. Ultimately, future research should aim to refine dosing algorithms, characterize mechanistic interactions, evaluate new sedative agents, and validate these approaches across broader patient populations and procedural types,advancing MAC toward more precise, safer, and individualized practice.

Disclosure

The authors report no conflicts of interest in this work.

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