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REVIEW

Perioperative Management of GLP-1 Receptor Agonists: Balancing Aspiration Risk with Therapeutic Benefit

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Abstract

The prescribing of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has surged for the treatment of diabetes and obesity, with more than 15 million users worldwide. These medications also delay gastric emptying through neural mechanisms, increasing the risk for perioperative aspiration during anaesthesia and sedation. This narrative review aims to bridge the gap between evidence and clinical practice regarding the use of GLP-1 RAs in the perioperative period by critically evaluating changing clinical recommendations to inform a balance between the risks of aspiration and the potential surgical benefits. Important conclusions drawn from recent meta-analyses involving over 300,000 patients report that while the retained gastric contents are significantly increased (fivefold to tenfold increase; odds ratio 3.35–36.97), rates of pulmonary aspiration (0.1% to 0.2%) remain quite low, with no significant increase in comparison to control groups. Guidelines have evolved considerably from routine medication cessation in 2023 to GLP-1 RA continuation with individualised risk assessment in 2024–2025, illustrating increasing acknowledgment that certain theoretical risks may be underestimated. The evidence supports shared decision-making frameworks, where patient needs, procedure timeframes, and other management approaches, such as liquid diets, ultrasound evaluation of the stomach preoperatively, or anaesthetic modification tailored techniques, are considered primary drivers for care rather than rigid guidelines. The principle under which GLP-1 RAs should be managed has shifted to strategy layering—restoring calculator systems tailored to patients, rather than blanket medication cessation triggers that dominated prior models' suspension approach.

Keywords GLP-1 receptor agonists · Perioperative management · Aspiration · Anaesthesia

Introduction

The use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has expanded rapidly, with more than 15 million people prescribed worldwide and projected market growth to USD 268 billion by 2034 [1]. Initially developed for type 2 diabetes, these drugs are now widely used for obesity and cardiovascular risk reduction, with emerging applications in neurological disease [2, 3]. Their broad uptake has raised perioperative concerns, particularly delayed gastric emptying and aspiration risk during anaesthesia [4, 5]. GLP-1 RAs slow gastric emptying through vagal and central nervous system pathways, leading to retained stomach contents despite standard fasting [6–8]. Early reports of aspiration in fasting patients prompted changes to clinical guidance [4, 5].

Recommendations have shifted from routine medication cessation to continuation with individualised risk assessment [9, 10]. This reflects a more balanced view of potential aspiration risks against proven therapeutic benefits, especially for diabetes and cardiovascular care [11, 12]. As a result, anaesthetists increasingly encounter GLP-1 RAs in daily practice, where decisions affect both surgical safety and long-term outcomes. The aim of this review is to synthesise current evidence, highlight guideline evolution, and outline practical strategies for risk assessment and management. It seeks to guide clinicians in balancing aspiration risk with the therapeutic benefits of continuing GLP-1 RAs perioperatively.

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Methodology

A comprehensive literature review was conducted to examine the perioperative management of GLP-1 receptor agonists and their associated risk of aspiration. Multiple electronic databases were systematically searched, including PubMed/MEDLINE, Embase, Cochrane Library, and Google Scholar, covering publications from January 2020 to April 2025. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords including: "glucagon-like peptide-1 receptor agonist", "GLP-1", "semaglutide", "liraglutide", "dulaglutide", "tirzepatide", "perioperative", "preoperative", "anaesthesia", "anesthesia", "gastric emptying", "aspiration", "regurgitation", "delayed gastric emptying", and "pulmonary aspiration". Boolean operators (AND, OR) were used to combine search terms effectively. Additional sources were identified through manual searching of reference lists from included studies, professional society guidelines, and grey literature, including conference abstracts and institutional reports. Professional guidelines from major organisations, including the American Society of Anesthesiologists, the American Gastroenterological Association, the Australian and New Zealand College of Anaesthetists, the Association of Anaesthetists (UK), and regulatory guidance from health authorities, were specifically reviewed. Case reports, observational studies, randomised controlled trials, systematic reviews, meta-analyses, and expert consensus statements were included without language restrictions. Priority was given to recent publications and high-quality evidence, with emphasis on studies published after 2022 reflecting the evolving understanding of perioperative risks.

Pharmacology and Pathophysiology

Mechanism of Action and Gastric Effects

GLP-1 receptor agonists exert their gastric effects through complex neurally-mediated mechanisms rather than direct gastric smooth muscle actions [13]. The primary pathway involves activation of GLP-1 receptors located in the myenteric plexus of the enteric nervous system, coupled to Gαs protein subunits that activate adenylyl cyclase and increase cyclic adenosine monophosphate (cAMP) levels [14]. This cascade ultimately inhibits vagal motor activity, leading to delayed gastric emptying and increased pyloric tone [15].

Central nervous system mediation occurs through GLP-1 receptors in the hypothalamus and brainstem, particularly the area postrema and nucleus tractus solitarius [8]. These central effects complement peripheral mechanisms and contribute to the overall gastric motility changes observed with GLP-1 RA therapy [16]. The clinical result is a coordinated reduction in antral contractility and increased pyloric resistance, leading to prolonged gastric residence times for both liquids and solids [17]. In this context, "residence time" refers to the duration that ingested food or liquid remains within the stomach before passing into the duodenum. GLP-1 RAs slow both liquid and solid transit, meaning material stays in the stomach longer than expected under normal fasting physiology.

Tachyphylaxis and Duration of Effects

A key feature of gastric effects associated with GLP-1 RA is the phenomenon of tachyphylaxis, where the gastric emptying effects diminish over time with continuous exposure lasting 8 to 24 h [18]. This rapid adaptation focuses on the level of vagal nerves, which is why there is a marked gastric response to insulin in the early phase after a meal, rather than during steady state [19]. Recent studies using scintigraphy suggest that long-acting GLP-1 RAs may have fewer gastric effects than short-acting formulations due to the phenomenon of tachyphylaxis [20]. The attenuation of effect with tachyphylaxis primarily reduces the delay in gastric emptying, with long-acting formulations showing less consistent slowing of emptying compared to short-acting agents.

The effect of tachyphylaxis has considerable clinical significance in the context of perioperative care. Adherence to long-term stable GLP-1 RA therapy appears to result in less delay in gastric emptying compared to patients who have recently started the therapy [21]. Moreover, the duration of impact on gastrin secretion after stopping medication is markedly different due to differences in pharmacokinetic profiles; for example, weekly injections may continue to have an effect for 1–2 weeks after cessation, while daily injections stop having an effect within 24–48 h after stopping [22].

Pharmacokinetic Profiles of Available Agents

The pharmacokinetic diversity amongst GLP-1 RAs has important implications for perioperative decision-making (Table 1). Semaglutide, with its 7-day half-life and once-weekly dosing, represents the longest-acting formulation currently available [23]. Its C18 di-acid side-chain attachment provides enhanced albumin binding and 89% subcutaneous bioavailability, resulting in sustained therapeutic levels for approximately 14 days following discontinuation [24].

Liraglutide, with a 13-h half-life and once-daily dosing, offers more predictable cessation kinetics for perioperative

Table 1 GLP-1 receptor agonists—pharmacokinetic properties and clinical characteristics

Agent	Half-life	Dosing schedule	Peak concentration	Bioavailability	Duration of gastric effects
Semaglutide	7 days (165–184 h)	Once weekly	1–3 days	89%	May persist 1–2 weeks
Liraglutide	13 h	Once daily	8–12 h	55%	24–48 h
Exenatide IR	2.4 h	Twice daily	2.1 h	Variable	24–48 h
Exenatide ER	~2 weeks	Once weekly	Multiphasic	Variable	1–2 weeks
Dulaglutide	5 days	Once weekly	2–4 weeks	Variable	1–2 weeks
Tirzepatide	5 days	Once weekly	4–5 weeks	Variable	Potentially reduced

management [23]. Its C16 fatty acid attachment mechanism provides 55% bioavailability with extensive albumin binding exceeding 98% [25]. The shorter half-life allows for more precise timing of medication cessation when clinically indicated [26].

Exenatide is available in both immediate-release (2.4-h half-life, twice-daily dosing) and extended-release formulations (approximately 2-week half-life with multiphasic profile) [27]. The extended-release formulation maintains therapeutic levels exceeding 50 pg/mL from approximately 2 weeks post-injection, complicating perioperative timing decisions [28].

Dulaglutide utilises a large recombinant fusion protein with Fc fragment for prolonged action, achieving a 5-day half-life with once-weekly dosing [29]. Tirzepatide, the newest dual GLP-1/GIP receptor agonist, has a similar 5-day half-life, but limited data suggest potentially less gastric emptying delay compared to pure GLP-1 agonists due to dual receptor activation [30].

Clinical Evidence

Aspiration Risk Evidence

The clinical evidence regarding GLP-1 RA-associated aspiration risk has evolved from alarming case reports to more nuanced observational data. The landmark Klein and Hobai case report documented the first objectively verified pulmonary aspiration in a 42-year-old patient on semaglutide who underwent upper gastrointestinal endoscopy [4]. Despite 18-h fasting, the patient had substantial gastric contents requiring bronchoscopic removal of food remains from the trachea and bronchi, providing concrete evidence of the potential perioperative risks [4].

Subsequent case reports have documented similar concerning events, including the Gulak and Murphy series describing a 70-year-old male who regurgitated large-volume particulate contents during laryngoscopy two days after semaglutide cessation [5]. This patient developed aspiration pneumonia requiring intensive care unit ventilation, highlighting that effects may persist beyond expected pharmacological half-lives [5].

However, large-scale observational studies have provided more reassuring data regarding actual aspiration rates. The Silveira et al. retrospective analysis of 886 patients found retained gastric contents in 24.2% of semaglutide patients versus 5.1% of controls (adjusted odds ratio 5.15, 95% confidence interval 1.92–12.92), yet actual aspiration occurred in only 1 of 404 patients (0.24%) [31].

Retained Gastric Contents Studies

Multiple studies have consistently demonstrated increased rates of retained gastric contents in patients taking GLP-1 RAs, though with variable magnitude depending on study design and patient populations [32]. The Sen et al. JAMA Surgery study of 1,046 patients identified independent risk factors for food retention with GLP-1 RA use (odds ratio 9.19, 95% confidence interval 2.73–30.8), with tirzepatide demonstrating the strongest association amongst available agents [33].

The prospective Nersessian et al. gastric ultrasound study provides the most robust evidence to date, examining 220 patients and finding retained gastric contents in 40% of semaglutide patients versus 3% of controls (adjusted odds ratio 36.97, 95% confidence interval 16.54–99.32) [34]. This study's strength lies in its prospective design and objective gastric ultrasound assessment, reducing potential bias inherent in retrospective reviews [34].

Importantly, these studies demonstrate a consistent pattern: whilst retained gastric contents are significantly more common in GLP-1 RA users, the absolute rates vary considerably depending on patient factors, medication duration, and assessment methods [35]. Rates of retained gastric contents range from 24 to 40% in GLP-1 RA groups compared to 1.3–5.1% in control groups across major studies [36].

Meta-Analysis Outcomes

Recent meta-analyses have provided crucial insights into the relationship between retained gastric contents and actual aspiration events. The Tarar et al. systematic review of 13

studies encompassing 84,065 patients demonstrated significantly higher retained gastric contents rates (odds ratio 5.56, 95% confidence interval 3.35–9.23) but found no significant difference in actual aspiration rates (odds ratio 1.75, 95% confidence interval 0.64–4.77) [37].

Another meta-analysis by Elkin et al. of 28 studies involving 304,060 individuals with 481 documented aspiration cases found that GLP-1 RA exposure was not associated with increased pulmonary aspiration (odds ratio 1.04, 95% confidence interval 0.87–1.25) despite a significant association with retained gastric contents (odds ratio 5.96, 95% confidence interval 3.96–8.98) [38]. This large-scale analysis provides the most robust evidence to date that increased gastric residual contents do not necessarily translate to clinically significant aspiration risk [38].

These meta-analyses highlight a critical distinction between theoretical risk (retained gastric contents) and clinical outcomes (actual aspiration events). The dissociation between these measures suggests that current risk assessment models may overestimate the clinical significance of delayed gastric emptying in the perioperative setting [39].

Evolving Guidelines and Recommendations

Timeline of Guidance Evolution

The evolution of professional guidance regarding perioperative GLP-1 RA management reflects rapidly accumulating evidence and changing risk-benefit assessments. The American Society of Anesthesiologists (ASA) released initial consensus-based guidance in June 2023, recommending medication cessation: daily dosing held on the day of procedure and weekly dosing held one week prior [9]. This guidance reflected the limited evidence available at the time, consisting primarily of case reports and small case series [40].

The paradigm shifted dramatically with the release of multi-society guidance in October 2024, endorsed by the ASA, American Gastroenterological Association, American Society for Metabolic and Bariatric Surgery, International Society of Perioperative Care of Patients with Obesity, and Society of American Gastrointestinal and Endoscopic Surgeons [10]. This updated guidance states that "most patients should continue taking their glucagon-like peptide-1 receptor agonists before elective surgery" with emphasis on individualised risk assessment and shared decision-making [41]. Given the rapid pace of new clinical data, it is likely that guidelines will continue to evolve. Further prospective studies, particularly on long-term users and high-risk surgical populations, may refine recommendations on fasting duration, imaging use, and anaesthetic modifications. Clinicians should therefore remain alert to emerging updates and apply flexible, evidence-based approaches.

International Consensus Development

International guidelines have shown similar evolution toward continuation with risk mitigation (Table 2). The UK Association of Anaesthetists published comprehensive multidisciplinary consensus in January 2025, recommending that GLP-1 receptor agonists be continued before surgery with individualised risk assessment [42]. The guidance explicitly acknowledges "insufficient evidence to put forward definitive guidance regarding the ideal cessation period" [42].

Australian guidelines from ANZCA and multiple endorsing societies emphasise not withholding medications prior to procedures, recommending that patients who have taken medication in the last four weeks should be considered unfasted [43]. The Australian approach incorporates consideration of 24-h clear fluid diets and prokinetic agent administration as risk mitigation strategies [44].

The UK Medicines and Healthcare products Regulatory Agency issued safety guidance in 2024 requiring healthcare professionals to be aware of aspiration risk whilst emphasising individualised assessment [45]. This guidance specifically notes that patients may not readily disclose off-label aesthetic use of these medications, highlighting the importance of comprehensive medication histories [45].

Key Differences and Commonalities

Despite geographical and organisational differences, several common themes emerge across guidelines. All acknowledge the limited quality of available evidence and rely on consensus-based recommendations rather than high-level evidence [46]. The evolution from 2023 to 2024–2025 represents a

Table 2 Comparison of major professional guidelines

Organisation	Year	Medication management	Risk assessment	Alternative strategies	Evidence grade
ASA USA	2023	Cessation (1 day daily, 1 week weekly)	GI symptom-based	Gastric ultrasound	Consensus
Multi-Society USA	2024	Continue for most patients	Individualised risk assessment	24-h liquid diet	Guidance
UK Association	2025	Continue as normal	Comprehensive assessment	Point-of-care tools	Consensus
ANZCA Australia	2024	Do not withhold	Consider unfasted if used < 4 weeks	Prokinetic agents	Consensus

movement from precautionary cessation to continuation with risk mitigation, reflecting a more sophisticated understanding of risk-benefit profiles [47].

Critical commonalities include emphasis on shared decision-making between patients, surgeons, and anaesthetists; recognition that emergency procedures should proceed with "full stomach" precautions regardless of medication status; and acknowledgement that patient equity considerations must be balanced against theoretical safety concerns [48]. Guidelines consistently recommend enhanced fasting protocols, gastric ultrasound assessment, and modified anaesthetic techniques as alternatives to medication cessation [49].

Clinical Decision-Making Framework

Risk Stratification Approaches

Effective perioperative management of GLP-1 RA therapy requires systematic risk stratification incorporating patient factors, medication characteristics, and procedural considerations [22] (Table 3). High-risk patient factors include active gastrointestinal symptoms (odds ratio 7.66, 95% confidence interval 3.42–17.17), early treatment phase (less than 4 weeks), higher medication doses, pre-existing diabetic gastroparesis, obesity (BMI greater than 30), and gastroesophageal reflux disease [31].

Conversely, protective factors include long-term stable therapy (greater than 3 months) due to tachyphylaxis effects, asymptomatic patients without gastrointestinal complaints, properly timed medication cessation when indicated, and absence of additional gastroparesis risk factors [13]. Procedural factors influencing risk include procedure urgency (emergency versus elective), duration and complexity, requirement for general anaesthesia versus regional techniques, and institutional experience with alternative management strategies [50].

Medication-specific factors require consideration of pharmacokinetic properties, with weekly formulations potentially having more prolonged effects than daily preparations [51]. Tirzepatide, as a dual GLP-1/GIP agonist, may have different gastric effects compared to pure GLP-1 agonists, though evidence remains limited [52].

Preoperative Assessment Algorithm

Systematic preoperative assessment begins with comprehensive medication history, including specific inquiry about weight loss indications that patients may not readily volunteer [53]. Assessment of gastrointestinal symptoms focuses on nausea, vomiting, early satiety, bloating, and abdominal pain, which correlate with increased gastric retention risk [32].

Multi-factorial risk scoring incorporates patient factors, medication characteristics, and procedural requirements to stratify patients into low, moderate, and high-risk categories [54]. Figure 1 illustrates the perioperative management considerations for individuals using GLP-1 RA. Low-risk patients (asymptomatic, long-term stable therapy, properly held medications) may proceed with standard fasting protocols [55]. Moderate-risk patients benefit from enhanced fasting protocols and consideration of gastric ultrasound assessment [56]. High-risk patients require comprehensive evaluation including liquid diet protocols, prokinetic agent consideration, and potential procedure delay [57].

Alternative Management Strategies

When medication cessation is not optimal, several alternative strategies can mitigate aspiration risk whilst preserving therapeutic benefits. Twenty-four-hour clear liquid diets represent the primary alternative for high-risk patients, permitting clear broths, clear juices, gelatin, and tea or coffee without milk whilst avoiding solids, dairy products, and thick liquids [53]. Evidence demonstrates reduced gastric residual volumes with this approach compared to standard fasting alone [58].

Another important factor is the cost of case cancellation. When surgery is delayed or cancelled due to concerns about gastric emptying, hospitals incur financial loss through wasted operating time and resource reallocation. Patients also face indirect costs, including additional leave from work, extended waiting periods, and potential

Table 3 Risk stratification for GLP-1 RA perioperative management

Risk category	Patient factors	Medication factors	Management approach
Low risk	Asymptomatic, long-term stable therapy, no gastroparesis	Properly timed cessation, daily formulations	Standard fasting protocols
Moderate risk	Mild GI symptoms, intermediate therapy duration	Weekly formulations, missed cessation	Enhanced fasting, consider gastric ultrasound
High risk	Active GI symptoms, early therapy, gastroparesis	Recent initiation, high doses	Liquid diet protocol, prokinetic agents, consider delay

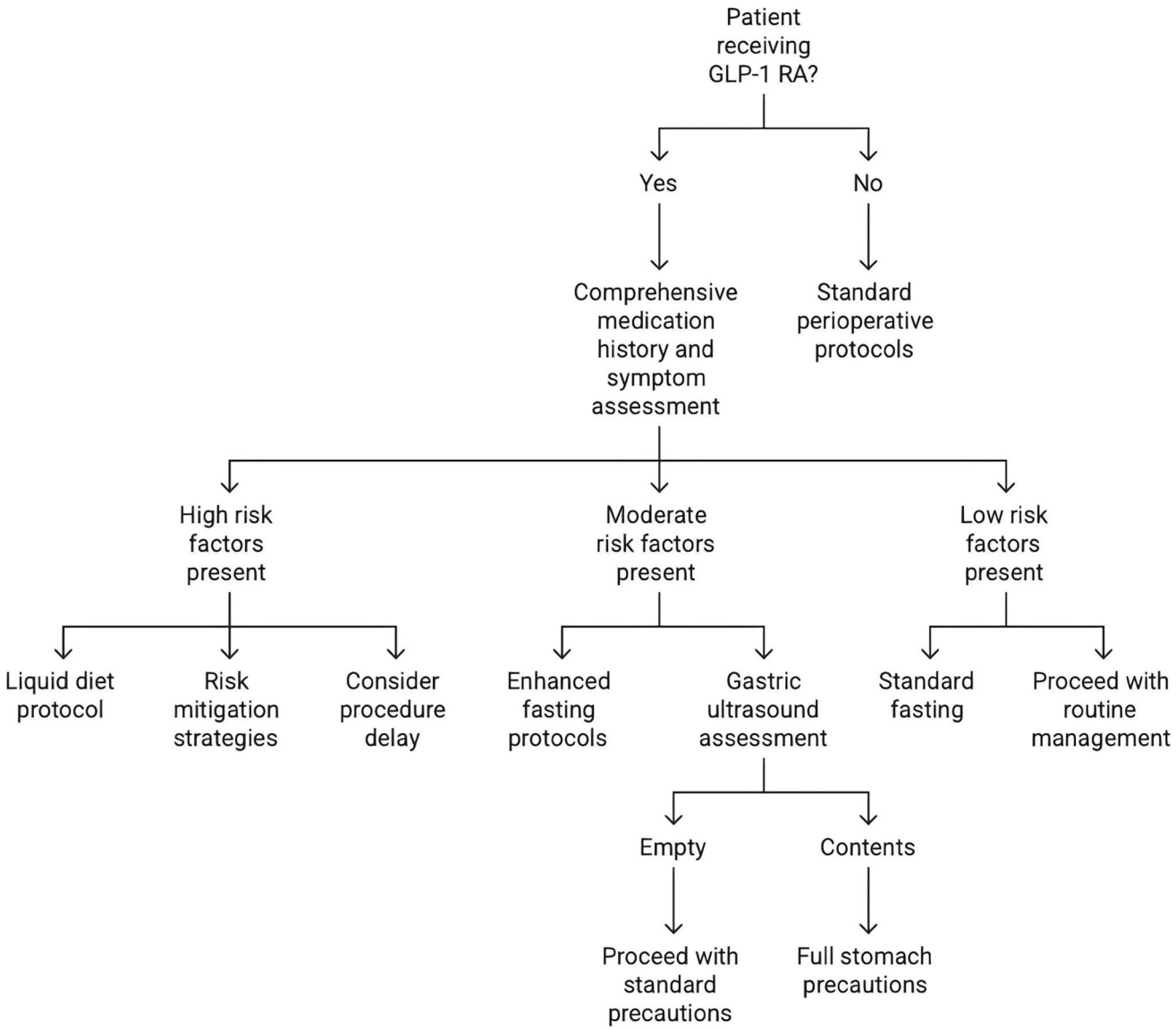

Fig. 1 Clinical decision algorithm for GLP-1 RA perioperative management

deterioration in their health condition. Balancing these tangible costs against theoretical aspiration risks reinforces the need for pragmatic, patient-centered management rather than blanket cancellation policies.

Point-of-care gastric ultrasound provides real-time decision-making capability through qualitative and quantitative gastric content evaluation [59]. Technical considerations include proper patient positioning in right lateral decubitus, antral cross-sectional area measurement, and qualitative assessment categorising gastric contents as empty, clear fluid, or thick fluid/solids [60]. Limitations include user dependence requiring training and experience, potential for false positives and negatives, and inability to completely eliminate aspiration risk [61].

Prokinetic agents offer pharmacological enhancement of gastric emptying, though efficacy in GLP-1 RA patients varies by agent [62]. Erythromycin as a motilin receptor agonist shows promise but faces limitations from tachyphylaxis and drug interactions [63]. Metoclopramide demonstrates mixed results due to central nervous system side effects and limited upper gastrointestinal effectiveness [64]. Domperidone shows effectiveness as a selective dopamine D2 antagonist that does not cross the blood–brain barrier [65].

Regional anaesthesia techniques offer preserved airway reflexes and reduced aspiration risk when appropriate for the surgical procedure [66]. Preferred techniques include spinal anaesthesia for orthopaedic procedures, interscalene blocks for upper extremity surgery, and femoral/sciatic blocks for

lower extremity procedures [67]. Technical contraindications and patient factors may limit applicability, requiring individualised assessment [68].

Take-Home Messages

The routine practice of stopping GLP-1 receptor agonists before surgery has shifted to individualised risk assessment. Current evidence suggests that, although gastric volumes are often higher, aspiration rates remain low.

Perioperative management should focus on patient-centred care, including full medication review, risk profiling, and shared decision-making. The therapeutic benefits of these agents—glycaemic control, cardiovascular protection, and weight management—must be balanced against largely theoretical aspiration risks.

Clinicians should remain vigilant, especially for bariatric and aesthetic procedures. Practical strategies include liquid diets, gastric ultrasound, and regional anaesthesia where appropriate. Future work should develop validated risk tools and standardised protocols to guide safe, evidence-based practice.

Conclusion

GLP-1 receptor agonists illustrate how emerging evidence reshapes clinical practice and refines evidence-based medicine. Current guidance supports stratified risk assessment based on individual patient factors rather than routine medication cessation. Studies show that retained gastric contents do not correlate with increased aspiration risk, challenging earlier conservative approaches. The move from blanket cessation to risk-adjusted continuation reflects improved understanding of therapeutic value, promoting shared decision-making and equity in care. Widespread use of these agents requires systematic perioperative strategies by anaesthetists to balance safety with therapeutic benefit. Most elective surgery patients can safely continue treatment with safeguards. High-risk patients need tailored precautions. The goal remains evidence-informed care that prioritises patient safety and optimises outcomes.

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Declarations

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