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GLP-1 receptor agonists – an evolving paradigm in perioperative medication management

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INTRODUCTION

The 20th century saw a profound shift in global health, with a dramatic rise in metabolic diseases. In high-income countries, including Australia, rates of obesity and type 2 diabetes have surged. Current estimates are that 66% of Australians are overweight or obese[1] and 5.3% are living with diabetes.[2] Obesity is a risk factor for type 2 diabetes and both conditions greatly increase the risk of stroke and cardiovascular disease.[3]

Many interventions have been trialled to halt the rise of metabolic disease. These include dietary interventions, physical exercise programs, behavioural interventions, appetite suppressants, absorption inhibitors, bariatric surgery and public health measures aimed at reducing the availability of highly dense caloric ingredients such as high fructose corn syrup.[4] However, most of these interventions have limited efficacy, can cause significant rebound weight gain, or are invasive surgical treatments.

Glucagon like peptide-1 receptor agonists (GLP-1 RA) are a new class of medication that has recently emerged. GLP-1 RA are being prescribed to an increasing number of patients for the treatment of diabetes and/or obesity. The market for GLP-1 RA was estimated to be worth $US10.8 billion in 2023 and is projected to grow at a compound annual growth rate of 7.8% to reach $US21.2 billion by 2032.[5] In Australia, among non-insulin glucose lowering drugs, the proportion of GLP-1 RA being used has increased from 1.7% in 2013 to 11.7% in 2023. In 2023, it was estimated that GLP-1 RA were being used by 192,000 people. GLP-1 RAs were also the most expensive drug class, costing $308 million in 2023, representing 11.7% of utilisation but 35% of overall spending on non-insulin glucose-lowering drugs.[6] Due to the sharp rise in popularity, anaesthetists are increasingly encountering patients taking these drugs perioperatively.

This article explores the history of GLP-1 RA development, current perioperative management guidelines, controversies and future directions. Additionally, it discusses how the medical community recognises and adapts to the evolving landscape of perioperative medication management, and the current status of GLP-1 RA in this journey.

DEVELOPMENT OF GLP-1 RA

During the mid-to-late 20th century, it was observed that intestinal extracts could reduce blood glucose levels. Furthermore, it was discovered that injecting glucose into the intestinal lumen triggered the production of more insulin than injecting it into a vein. These discoveries led to the search for incretin hormones, released from the intestine (predominantly the small bowel) to stimulate pancreatic insulin secretion. In the 1970s the first incretin hormone, known as glucose-dependent insulinotropic polypeptide (GIP) was identified, and later another hormone glucagon-like peptide-1 (GLP-1) was characterised.[7]

GLP-1 is an endogenous incretin hormone released mainly from the ileum that lowers blood glucose levels by promoting insulin release from pancreatic beta cells and decreasing glucagon secretion from alpha cells.[8] Importantly, studies demonstrated that the effect of GLP-1 on insulin secretion was glucose-dependent and, therefore, did not cause hypoglycaemia.[8] By the early 1990s, GLP-1 was identified as a promising diabetes drug.

However, GLP-1 has an ultrashort half-life, being rapidly degraded by dipeptidyl peptidase-4 (DPP-4) and cleared by the kidneys, which created major challenges utilising it as a drug.[9] The key intervention that allowed GLP-1 RA to be viable as medications were various structural modifications which markedly extended the half-life.[10]

In 2005, exenatide (Byetta), was the first injectable GLP-1 RA medication worldwide to receive United States (US) Food and Drug Administration (FDA) approval for the treatment of type 2 diabetes. Exenatide had a modified amino acid sequence making it resistant to dipeptidyl peptidase-4 (DPP-4) degradation,[6] with a half-life of 2-4 hours making it suitable for twice-daily administration subcutaneously.

In 2009, liraglutide (Victoza) from Novo Nordisk was granted approval by the European Medicines Agency (EMA), followed by US FDA approval in January 2010, for managing type 2 diabetes. Liraglutide had an acylated fatty acid which further increased its half-life to 13 hours, allowing once daily injectable dosing and making it more convenient for patients.[7]

Eli Lilly introduced dulaglutide as a further improvement using a fusion protein of GLP-1 bound to an immunoglobulin fragment which increased the half-life to 5 days. The US FDA approved dulaglutide in 2014 for treating type 2 diabetes, and it is administered once a week by injection. Dulaglutide was more appealing to patients due to its once-weekly injection dosing. It was also shown to have better glycaemic control that liraglutide.[11]

In 2017, Novo Nordisk launched semaglutide (Ozempic), which has a half-life of 7 days due to the addition of a fatty acid side-chain which binds to albumin, enabling weekly administration by injection. In addition, when semaglutide (Ozempic) was administered to patients with diabetes, it was discovered that 40% of them lost more than 10% of their body weight. Further clinical trials then investigated semaglutide as a treatment for obesity.[12] In 2019, the US FDA granted approval for a unique formulation of semaglutide (Rybelsus), which was the first oral GLP-1 analogue treatment for adults with type 2 diabetes administered once a day.[7] Rybelsus was preferred by some patients who are averse to self-injections and prefer oral formulations. In 2021, semaglutide (Wegovy) once weekly injection was approved by the FDA for chronic weight management in adults with obesity. The higher doses in Wegovy at 2.4 mg, as compared to Ozempic at 0.5 mg, showed a dose-dependent increase in weight loss.[13]

Eli Lilly unveiled tirzepatide (Mounjaro) in 2022, a new dual GLP-1/GIP receptor agonist. It is administered once a week via subcutaneous injection and activates both GLP-1 and GIP receptors. GIP can reduce body weight by curbing food intake and increasing energy consumption.[10] When combined with a GLP-1 RA, it may have a more significant impact on blood glucose levels and body weight.[7]

Newer generations of GLP-1 RAs were modified to increase their half-life, therefore reducing administration frequency and improving convenience for patients. The development of an oral formulation also benefited patients who are averse to injections. Newer generations of GLP-1 RA and new dual GLP-1/GIP receptor agonist also showed improved efficacy in glycaemic control and weight loss. Table 1 shows the GLP-1 RAs and dual GLP-1 and GIP co-agonists registered for use in Australia.

BENEFITS OF GLP-1 RAS AND GLP/GIP CO-AGONISTS

For patients with type 2 diabetes, GLP-1 RA has been shown to have better glucose-lowering effects than oral medications such as SGLT2 inhibitors, DPP-4 inhibitors, and sulphonylureas.[14] A systematic review

conducted in 2024 showed that GLP-1 RAs and GLP/GIP co-agonists effectively lowered HbA1c and fasting plasma glucose concentrations. Tirzepatide was the most successful medication for glycaemic management, causing the greatest decrease in HbA1c and fasting plasma glucose levels.[11] Additionally, it has been demonstrated that GLP-1 RAs significantly improve the ability of patients with type 2 diabetes to control their weight. In a study of semaglutide vs placebo for weight loss in patients with type 2 diabetes, semaglutide resulted in 6.2% mean weight loss vs placebo.[15] In addition to glycaemic control and weight loss, several trials have also demonstrated that GLP-1 RAs reduce the risk of major adverse cardiovascular events (MACE) compared to placebo in patients with type 2 diabetes.[16-18] The results of the cardiovascular outcome trial for tirzepatide are expected in late 2025.

For patients without diabetes and utilising GLP-1 RA for weight loss, a cohort study observed that semaglutide (-5.1%) was more effective than liraglutide (-2.2%). It also observed that patients utilising GLP-1 RA for obesity as a treatment indication (-5.9%) had more weight loss in one year as compared to patients utilising GLP-1 RA for type 2 diabetes as a treatment indication (-3.2%).[19]

Table 1. GLP-1 RAs and Dual GLP-1 and GIP co-agonists registered for use in Australia

Agent	Receptor agonism	Elimination half-life	Administration schedule and route of administration	Trade name	Status
Exenatide twice daily	GLP-1	3.3-4.0 hours	Twice daily Subcutaneous	Byetta	Withdrawn for commercial reasons, global discontinuation of drug
Liraglutide	GLP-1	12.6-14.3 hours	Once daily Subcutaneous	Victoza (up to 1.8 mg) Saxenda (up to 3.0 mg)	Not PBS listed
Exenatide once weekly	GLP-1	3.3-4.0 hours	Once weekly Subcutaneous	Bydureon	Withdrawn for commercial reasons, global discontinuation of drug
Dulaglutide	GLP-1	4.7-5.5 days	Once weekly Subcutaneous	Trulicity	PBS listed for type 2 diabetes
Semaglutide	GLP-1	5.7-6.7 days	Once weekly Subcutaneous, or once daily oral	Ozempic (up to 1 mg SC) Wegovy (up to 2.4 mg SC) Rybelsus (up to 14 mg daily orally)	Ozempic: PBS listed in 2020 for type 2 diabetes Wegovy: TGA approved but not yet PBS listed (as of 2024) Rybelsus: TGA approved
Tirzepatide	GLP-1 & GIP	4.2-6.1 days	Once weekly Subcutaneous	Mounjaro	Not yet PBS listed (as of 2024) Unavailable until 31 August 2025 due to global demand for GLP-1 RAs

GLP-1 = Glucagon like peptide 1, GIP = Glucose-dependent insulinotropic polypeptide, PBS = Pharmaceutical Benefits Scheme, SC= subcutaneous, TGA = Therapeutic Goods Administration Australia. Table adapted from Clinical Practice Recommendation on Periprocedural Use of GLP-1/GIP Receptor Agonists and reproduced with permission[20]

RISK OF HARM

The gastrointestinal adverse effects of GLP-1 RA include nausea, vomiting, and diarrhoea,[21] attributable to delayed gastric emptying and direct central effects of GLP-1 RA. It has been observed that GLP-1 RA do not significantly prolong gastric emptying further in patients with type 2 diabetes who already have diabetes-related gastroparesis.[12,22] The risk of aspiration linked with delayed gastric emptying is of particular concern to anaesthetists and has been reported recently in a number of case reports involving patients taking GLP-1 RA perioperatively for weight loss or type 2 diabetes indications.[23] More research is needed to delineate the risk period and return of gastric function after cessation of GLP-1 RA.

In early 2022, there was an unexpected increase in demand of semaglutide (Ozempic) due to off-label prescribing for weight loss.[24] In Australia, this was largely fueled by increased reporting and unlawful advertising on digital platforms including social media.[25] The result was a worldwide shortage of semaglutide, which also affected Australia. Certain Australian compounding pharmacies responded to this demand by producing replicas of Ozempic and Mounjaro. This sparked major concerns that the large-scale unregulated manufacture of these compounded products posed risks to human health. A Therapeutic Goods Administration (TGA) investigation into one of these laboratories revealed unsanitary conditions. There were also reports of alarming side effects from the use of these replica drugs.[26] In May 2024, compounding pharmacies in Australia were banned from producing replica versions of Ozempic and Mounjaro.[27]

Both Ozempic and Wegovy are expensive. Ozempic is listed on the PBS for type 2 diabetes only, costing approximately $10 per week. However, patients using Ozempic for weight loss need to pay the full price of approximately $45 per week. Costs are less for the indication if a patient has a concession card. Wegovy is currently not PBS listed and costs approximately $115 per week.[28]

EXISTING GUIDELINES

As of December 2024, there is no consensus among international guidelines regarding perioperative management of patients who take GLP-1 RA. For a drug to be completely cleared from the body, it should be withheld for three to five half-lives. Withholding GLP-1 RA for this period of time results in a washout period of more than four weeks. Withholding GLP-1 RAs in patients with diabetes causes worsening glycemic control. Additionally, patients often attend preoperative clinics only weeks prior to their procedures to receive medication advice. Therefore, withholding GLP-1 RA often results in delaying the procedure to allow washout.[29] In Australia, the Australian and New Zealand College of Anaesthetists (ANZCA) published a consensus clinical practice recommendation in June 2024 endorsed by the Australian Diabetes Society (ADS), National Association of Clinical Obesity Services (NACOS) and Gastroenterological Society of Australia (GESA) (Table 2).

Table 2. Guidelines for the perioperative management of GLP-1 RA

Organisation	Date	Recommendation
Australian and New Zealand College of Anaesthetists, Gastroenterological Society of Australia, National Association of Clinical Obesity Services, Australian Diabetes Society	2025	• Patients should be asked about the use of GLP-1 RAs and GLP-1/GIP RAs prior to anaesthesia or sedation for surgical and endoscopic procedures and be involved in discussion and planning regarding the risk of aspiration. • Elective preprocedural cessation of GLP-1 RAs and GLP-1 RA/GIP RAs is not recommended, and risks hyperglycaemia in people with diabetes and may compromise weight control where patients are taking GLP-1 RAs and GLP-1/GIP RAs for this indication. • Patients should be asked about the use of other medications and medical conditions which may exacerbate gastrointestinal symptoms and delay gastric emptying, such as, but not limited to bowel dysmotility, gastroparesis, and Parkinson's disease. • Preprocedural diet modification with 24-hour fluid diet, and then following recommended 6-hour fasting guidelines, should be recommended for all patients receiving GLP-1 RAs and GLP-1 RA/GIP RAs. • Risk mitigation options should be undertaken for those who have not withheld solids for 24 hours. These include detection of residual gastric contents, prokinetic agents, modification of anaesthesia, or deferral of procedure.[20]
American Society of Anesthesiologists, American Gastroenterological Association, American Society for Metabolic and Bariatric Surgery, International Society of Perioperative Care of Patients with Obesity, Society of American Gastrointestinal and Endoscopic Surgeons	October 2024	• GLP-1 RA therapy may be continued preoperatively in patients without elevated risk of delayed gastric emptying and aspiration. When an elevated risk of delayed gastric emptying and aspiration exist, withholding of GLP-1 RA should be balanced with the surgical and medical risk of inducing the potential for a hazardous, metabolic disease state, like hyperglycaemia. Further, bridging therapy off a GLP-1 RA may be resource-intensive, cost or insurance prohibitive, and risk other adverse side effects like hypoglycaemia. Finally, withholding GLP-1 RA perioperatively only for patients with the diseases of overweight and obesity, could constitute overweight and obesity bias, which should be avoided. • If the decision to hold GLP-1 RAs is indicated given an unacceptable safety profile following shared decision-making in the preoperative period, the duration to hold therapy is unknown. At this time, it is suggested to follow the original guidance of the American Society of Anesthesiologists, holding the day of surgery for daily formulations, and a week prior to surgery for weekly formulations. All patients should still be assessed on the day of procedure for symptoms suggestive of delayed gastric emptying. • Preoperative diet modification (preoperative liquid diet for at least 24 hours, as performed in patients undergoing colonoscopy and bariatric surgery) can be utilised in patients when there is concern for delayed gastric emptying based on clinical symptom review.

American Society of Anesthesiologists, American Gastroenterological Association, American Society for Metabolic and Bariatric Surgery, International Society of Perioperative Care of Patients with Obesity, Society of American Gastrointestinal and Endoscopic Surgeons	October 2024	• When clinical concern for retained gastric contents exists on the day of the procedure, point-of-care gastric ultrasound could be used to assess aspiration risk. This technology may be clinically limited based on institutional resources, inter-user variability, and credentialing requirements. • When clinical concern for retained gastric contents exists or is confirmed on the day of the procedure, providers should engage patients in a shared decision-making model and consider the benefits and risks of rapid sequence induction of general anesthesia for tracheal intubation to minimise aspiration risk versus procedure cancellation.[30]
Centre for Perioperative Care, United Kingdom	October 2023	Do not withhold GLP-1 RA.
Society for Perioperative Assessment and Quality Improvement, United States	March 2021	• Continue GLP-1 RA before the day of surgery unless heightened concern for postoperative nausea, vomiting or gut dysfunction (e.g. GI surgery). In these situations, consider holding 24 hours for once or twice daily preparations, and up to one week before surgery for weekly preparations (including holding dose within seven days before surgery). • Withhold GLP-1 agonists on the morning of surgery. • If a weekly dose is due on morning of surgery, delay taking until later in the day after surgery.[31]

GLP-1 = Glucagon-like peptide 1, GIP = Glucose-dependent insulinotropic polypeptide

Currently, none of the guidelines recommend different perioperative management strategies based on the indication of GLP-1 RA (weight management vs diabetes management). The American multi-society clinical practice guidance states that it could constitute obesity or overweight bias if only patients taking GLP-1 RA for weight management are asked to withhold GLP-1 RA perioperatively.[30] Both the Australian and American multi-society guidelines have suggested the use of point-of-care gastric ultrasound if there is a clinical concern for retained gastric contents.[30,20] It can be an accurate and reliable tool to assess gastric content and aspiration risk. The I-AIM (Indication, Acquisition, Interpretation and Medical Decision Making) framework is recommended as a standardised approach to minimise error.[32] However, this skill may be limited by inter-user variability, institutional resources and training requirements.

SAFETY CYCLE – THE REACTION TO NEW MEDICATION CLASSES

The desire to protect our patients from harm can paradoxically place them at risk when excessive caution is used. The medical profession as a whole, but in particular the field of anaesthesia, is replete with examples of evolving changes to management of new medications. There is a familiar cycle of introduction of a new class of medication, emergence of case reports of isolated harm, response to case reports with conservative guidelines and widespread appropriate caution, followed by large observational and/or randomised controlled trials often demonstrating different findings to the initial case reports, sometimes with evidence of harm from the initial conservative guidance. Sodium-glucose co-transporter-2 (SGLT2) inhibitors and direct oral anticoagulants (DOACs) provide two recent instructive examples.

SGLT-2 inhibitors

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are anti-hyperglycemic agents that promote glucosuria by inhibiting renal glucose reabsorption.[33] As the number of patients taking SLGT2 inhibitors increased, case reports emerged of patients developing severe ketoacidosis with normal blood glucose levels requiring perioperative intensive care or high dependency unit admissions.[34] This resulted in widespread concern, advice to withhold SGLT2 inhibitors for all procedures in some cases up to two weeks prior to surgery,[31] and cancellation of any perioperative patient who had not ceased an SGLT2 inhibitor prior to surgery or even those who had ceased but had ketone levels above 1 mmol/L.[35]

After many studies were undertaken, predisposing factors for diabetic ketoacidosis in patients using SGLT-2 inhibitors were identified and updated evidence emerged with the current ANZCA guidance updated almost 10 years after the initial FDA approval for the first SGLT2 inhibitor.[36]

Direct oral anticoagulants

Direct oral anticoagulants (DOAC) are now commonly used in the treatment and prevention of venous thromboembolism and prevention of stroke in non-valvular atrial fibrillation.[37] When they were first used in 2010, there were no studies available to guide the timing of perioperative interruption and resumption of DOAC therapy. It was also unclear whether heparin bridging should be administered and if preoperative coagulation function testing was necessary. Patients of high thrombotic risk were often required to bridge with heparin when their DOAC was withheld, and patients having surgeries with high bleeding risk often needed APTT or thrombin time monitoring to ensure adequate drug elimination. This resulted in patients having coagulation testing as well as injectable anticoagulants[38] that were later found to be unnecessary.

The Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study published in 2019 found that withholding DOACs perioperatively in patients with atrial fibrillation resulted in low rates of major bleeding and thromboembolic events. The PAUSE study provided a simple and safe perioperative DOAC management strategy that laid the foundation for the publication of future guidelines.[39] "Regional Anaesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy" published by the American Society of Regional Anaesthesia and Pain Medicine (ASRA) in 2018 did not recommend routine bridging therapy for patients on DOAC therapy.[40] This recommendation is similar to the process Drummond suggests, including that clinicians consider the type of DOAC, whether it is a prophylactic or therapeutic dose, the type of procedure and the patient's renal function when deciding the duration for withholding the DOAC before the procedure.[37] With the advent of more evidence, there is now more consensus among various guidelines for the perioperative management of DOACs, including advice that bridging with heparin and coagulation profile testing are not recommended.

Given the history of evolving changes to perioperative medication management, it is incumbent on the profession to view the rise of GLP-1 RA in this context and ensure unrestrained safety advice without randomised controlled trial informed guidance does not result in unintended harms. For example, the current ANZCA guidelines recommend that "risk mitigation options should be undertaken for those who have not withheld solids for 24 hours" which would suggest conducting a rapid sequence intubation. If the procedure or predisposing patient factors does not require a muscle relaxant to be used, this recommendation exposes patients to the additional risk of anaphylaxis to muscle relaxants.

ISSUES TO CONSIDER WHEN MANAGING A PATIENT TAKING GLP-1 RA IN THE PERIOPERATIVE PERIOD

1. Perioperative management of GLP-1 RA should be based on shared decision making of the patient with a multidisciplinary team (anaesthetists, proceduralists and prescribing teams e.g. endocrinologists).[30]
2. Consider the individual patient's metabolic need for GLP-1 RA and risk profile.
    a. Escalation phase (when patients are given increasing doses of GLP-1 RA, typically lasting 4 to 8 weeks) vs maintenance phase is associated with higher risks of delayed gastric emptying.[41]
    b. The higher the dose of GLP-1 RA, the higher the risk of gastrointestinal side effects.[41]
    c. Weekly formulations are associated with increased gastrointestinal side effects compared to daily formulations.[42]
    d. Symptoms such as vomiting, nausea, dyspepsia, abdominal pain and constipation are suggestive of delayed gastric emptying.[43]
    e. Other pre-existing medical conditions that can also delay gastric emptying such as gastroparesis, bowel dysmotility and Parkinson's disease.[30]
3. When an increased risk of delayed gastric emptying and aspiration exist, withholding of GLP-1 RA should be balanced with the surgical and medical risk of inducing the potential for a dangerous metabolic disease state like hyperglycaemia.[30]
4. Consider preoperative diet modification (clear liquid diet for 24 hours) in patients with an increased risk of delayed gastric emptying.[43]
5. Consider point-of-care gastric ultrasound to assess aspiration risk on the day of the procedure if there is clinical concern of retained gastric contents.[44]
6. If clinical concern for retained gastric contents exists or is confirmed on the day of the procedure, multidisciplinary teams should engage in shared decision making with the patient and consider the risks vs benefits of rapid sequence induction to minimise aspiration risk vs cancellation of procedure.[30]

FUTURE DIRECTION OF GLP-1 RA

GLP-1 RA are an evolving class of drugs and continue to increase in public popularity for the treatment of obesity. It is likely that GLP-1 RA will be PBS listed for the treatment of obesity in the future in Australia. Recent advances in drug development have led to the combination of GLP-1 RA with other new bioactive peptides resulting in dual or triple agonists. CagriSema, a dual GLP-1 and amylin agonist, containing semaglutide and cagrinlintide, is in phase 3 trials. Similar to GLP-1, amylin also delays gastric emptying and reduces appetite, leading to glucose-lowering effects and weight loss.[45]

Advances in drug delivery systems can also improve the ease of administering GLP-1 RA. New orally-available preparations of GLP-1 RA are available which further lowers the barrier for patient adoption. Additionally, a recent report showed that incorporating GLP-1 RA in a new hydrogel enables a "sustained-release depot" of the drug that may require dosing only once every four months.[46]

Researchers are also investigating the use of GLP-1 RA beyond the indications of type 2 diabetes and obesity. GLP-1 RA have anti-inflammatory effects.[47] Areas of potential benefit include reduction of major adverse cardiovascular events, kidney disease, metabolic liver disease and even neuroprotection and addiction. We may see broader uses of GLP-1 RA in the future such as for the treatment of Alzheimer's disease and chronic kidney disease.[48]

CONCLUSION

Given the positive effects of GLP-1 RA on glycaemic control, weight loss and cardiovascular risk reduction, use of these medications in the community will rise over time. The perioperative conundrum of whether to withhold GLP-1 RA to reduce aspiration risk, or continue to mitigate hyperglycaemia and potentially cardiovascular disease risk will continue to stir debate until more definitive evidence emerges. As perioperative medicine specialists, we should carefully consider the best way to manage these novel agents during this phase before high-quality evidence emerges and reflect on how we should manage agents with a lack of perioperative evidence.

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