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An ethical conundrum: off-label prescribing of diabetes medications

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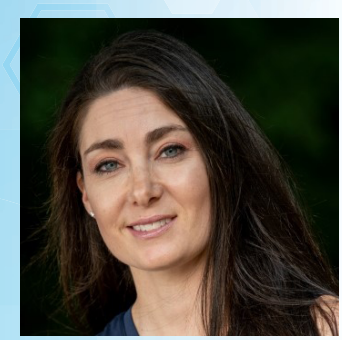

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Learning objectives

You will learn:

- To gain insight into the ethical considerations of off-label prescribing and allocation of scarce resources
- To consider the ethical dilemma presented by patients who desire weight loss with off-label use of low-dose semaglutide (0.25mg, 0.5mg and 1mg), not registered for weight loss
- To understand the ADA/EASD consensus recommendations for a holistic, individualised approach to the management of type 2 diabetes and the ethical role of the physician in not diverting GLP-1 RA therapy away from high-risk patients
- An awareness of registered indications for the use of these dosages of semaglutide, and an understanding of the potential maleficence of off-label prescribing of semaglutide
- An ethical approach to the treatment of obesity for the patient who is not diabetic.

Introduction

The recent indiscriminate off-label use of an effective therapy for the treatment of type 2 diabetes mellitus (T2DM), semaglutide, by patients who do not have diabetes and want to achieve weight loss has given rise to ethical implications. In discussing ethical prescribing habits when contemplating off-label use of medications, Doctors Sundeep Ruder and Martine Joffe considered the principles of how to provide best care for high-risk patients living with diabetes and for those non-diabetic patients who are struggling with obesity.

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Principles of decision-making in medical ethics

The duty of care of the healthcare practitioner is to act in the patient's best interests; this entails not only curing or treating the disease, but also considering the patient's choices. Four principles that are common to both the utilitarian and deontological schools of ethical philosophy provide a framework that enables the doctor to explore a problem from all ethical angles (Table 1).

Table 1. Principles of medical ethics

- Autonomy
  - Respect patient's choices → consent
- Beneficence
  - Act in patient's best interests → duty of care
- Non-maleficence
  - Do no harm → duty of care
  - Interventions should have more benefit than risk
- Justice
  - Treat patients similarly
  - Distribute care evenly/fairly.

However, these four ethical principles apply not only to the individual patient but must also be considered in the context of the 'greater good' and the interests of the population. Dr Ruder explains that the concept of autonomy is frequently misunderstood in the practitioner-patient dynamic, being interpreted as: "Whatever the patient wants, we must give it to them." This is not the case because there are certain prerequisites to autonomy: the patient must choose a treatment based on an understanding of the risks and benefits of that intervention, and they have to grant informed consent, which requires the ability to think critically around the subject. Furthermore, the patient should also have the ability to consider delaying instant gratification because, in medicine, it can take time to attain the desired benefit of an intervention: "Sometimes, a quick fix does more harm over the long term."

When considering off-label drug use, ...the prescribing physician must seek a balance between beneficence and non-maleficence

Off-label prescribing – what are the ethical considerations?

The ethical issues that arise from off-label prescribing will differ depending on particular circumstances and include considerations of whether the off-label use is new or previously established, the urgency of the patient's situation and, importantly, the availability of alternative treatment approaches. When considering off-label drug use, the primary ethical principle from the view of the patient is often self-determination (autonomy), whereas the prescribing physician must seek a balance between beneficence and non-maleficence.[1,2]

Navigating the potential benefits and harms of off-label therapies

The contemporary practice of medicine sees many patients receiving benefit from drugs or devices under circumstances that are not approved and registered for its use by the relevant health authority. For certain patient populations of medical disciplines such as oncology, geriatrics, paediatrics and obstetrics, care for a particular health problem cannot proceed without off-label prescribing. In such cases, when justified by scientific and medical evidence, the ethical justification for off-label prescribing is that it can provide the best available therapy for a particular patient.[1]

Off-label prescribing can also harm patients. This is most often the case when an off-label application lacks a substantial evidentiary basis for its safety and efficacy in that specific population of patients. In such cases, off-label prescribing can lead to malpractice liability if it fails to conform to accepted standards of care.[1] Furthermore, the potential for harm extends beyond that of the patient using off-label treatment; worldwide, medication shortages have become an increasingly frequent problem.[2]

Justice in scarce resource allocation

The practice of indiscriminate off-label prescribing may compromise the fiduciary responsibility of the physician to promote the welfare and best interests of other patients who are using the drug for the treatment of a registered indication and who, possibly, may need it most

Allocation of a scarce medication or medical resource should be made based on evidence-based criteria, transparency and consistency. Observing justice in resource allocation necessitates considering not only whether off-label medication use may cause financial loss and a high burden on the health system; importantly, the practice of indiscriminate off-label prescribing may compromise the fiduciary responsibility of the physician to promote the welfare and best interests of other patients who are using the drug for the treatment of a registered indication and who, possibly, may need it most. Often, no equivalent alternative agent exists for these patients and so the primary criterion for allocating a scarce drug to one patient over another should be evidence of a superior therapeutic effect in that particular patient.[2]

Studies suggest that many physicians rely on experience, anecdotal reports and opinion leaders to guide their treatment decisions. This approach to clinical knowledge can encourage inappropriate off-label prescribing, even in the absence of industry encouragement for that particular use. Physicians have an ethical duty to obtain as much information as feasible about off-label use before obtaining informed consent from the patient to prescribe the drug.[1,3] Requirements of responsible off-label prescribing are to:

1. Evaluate whether there is sufficient credible evidence to justify off-label use.
2. Press for additional information and research when adequate evidence is lacking.
3. Inform patients about the uncertainties and potential costs associated with off-label prescribing.

Principles of ethical allocation of scarce health resources

General allocation principles for scarce health care resources, grounded in distributive justice and utility, can be applied to the circumstances of medication shortages. While it is incontrovertible that all patients should be treated equally, the benefits of a scarce health resource should be maximised towards saving the most lives/life-years and giving priority to the worst off (the sickest and the youngest). In light of such a public health emergency, patient autonomy is diminished as priority shifts to populations rather than individuals.[4]

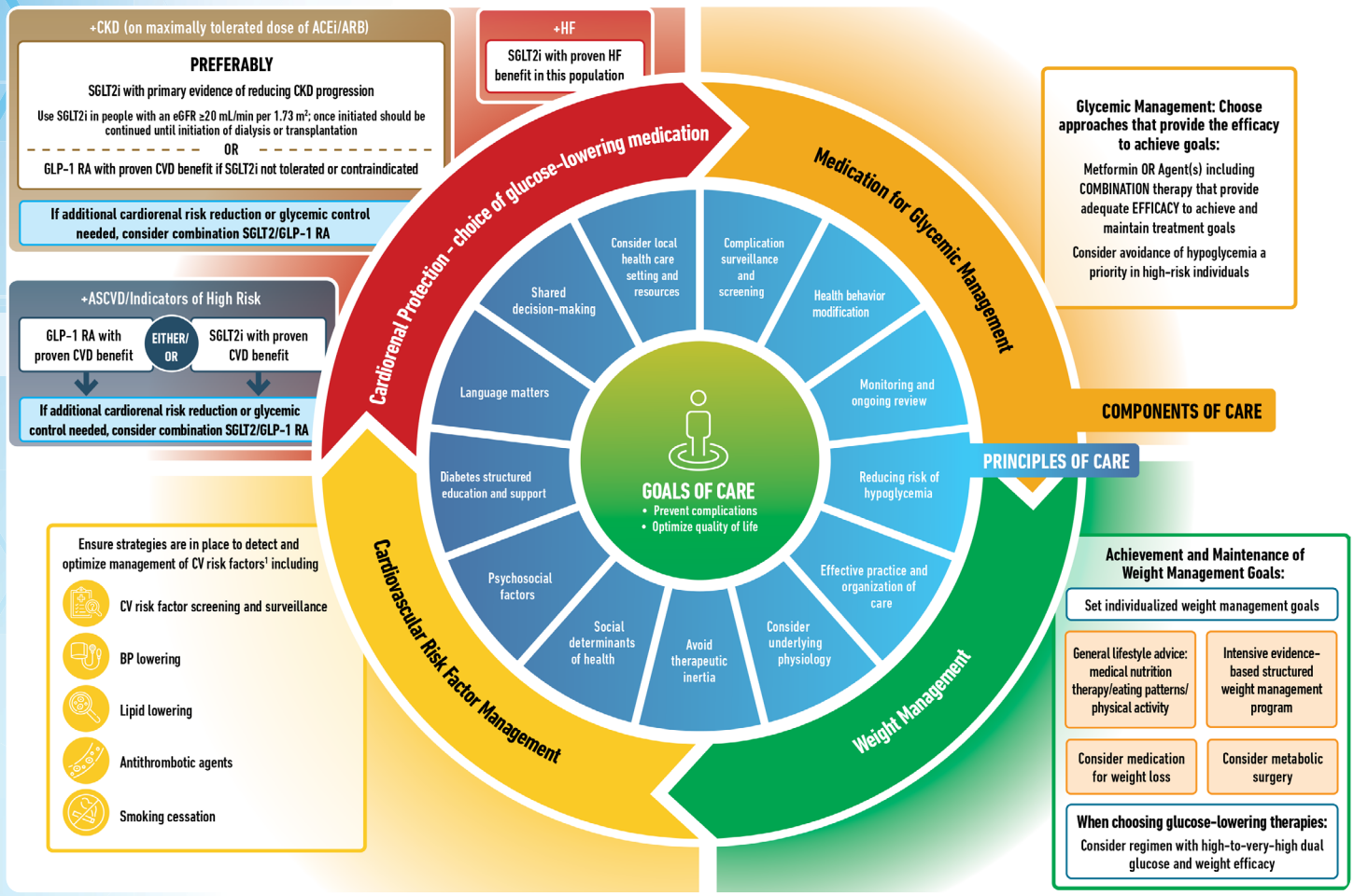
One study[5] has identified five key elements as core drivers behind the impact of a medicine shortage on patients that can be used to mitigate the impact:

- Alternative product
- Disease
- Susceptibility
- Costs
- Number of patients affected.

A holistic approach to the management of T2DM

The most recent consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) emphasises the importance of a holistic, person-centred approach to the management of T2DM (Figure 1).[6] Goals of person-centred T2DM care include:[7]

- Address fear of injectables
- Early achievement and maintenance of glycaemic goals
- Support of weight management goals
- Cardiovascular safety and prevention.



ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blockers; ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; GLP-1 RA: glucagon-like peptide 1 receptor agonist; HF: heart failure; SGLT-2i: sodium-glucose cotransporter 2 inhibitor; T2DM: type 2 diabetes

Figure 1. Holistic person-centred approach to the management of T2DM – ADA/EASD consensus[6]

What is the role of semaglutide in T2DM?

In a manner, semaglutide is a lifesaving drug for diabetes patients with a high cardiovascular risk

In South Africa, indications for the use of the glucagon-like peptide 1 receptor agonist (GLP-1 RA), semaglutide 0.25mg, 0.5mg and 1.0mg, are:

- For the treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise
- As monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- As combination therapy with oral antidiabetic medicines (metformin, thiazolidinediones, sulphonylureas) and basal insulin, with or without metformin and pre-mixed insulin
- To reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with T2DM.

Cardiovascular effects of GLP-1 RAs

Cardiovascular effects of GLP-1 RAs include the prevention of atherogenesis, cardiovascular benefits secondary to weight loss, improved cardiac function, a small increase in heart rate and beneficial effects on blood vessels.[8]

The United States' Food and Drug Administration has published draft guidance on assessing the safety of new T2DM therapies, stating that '…it is important to evaluate the safety of new drugs to improve glycaemic control in the population of patients who will

be using the drugs, including a meaningful number of patients with underlying cardiovascular disease, chronic kidney disease and older patients'.[9]

Cardiovascular outcomes trials (CVOTs) of GLP-1 RAs have demonstrated differing results.[10-15] A semaglutide CVOT has demonstrated non-inferiority to previous diabetes treatments in terms of glycaemic control and, importantly, has shown significant benefit for cardiovascular outcomes. Dr Ruder is of the view: "In a manner, semaglutide is a life-saving drug for diabetes patients with a high cardiovascular risk." The ADA/EASD recommend the use of a GLP-1 RA with proven benefits as an option for the management of the high-risk T2DM patient, such as those with atherosclerotic cardiovascular disease and indicators of high risk, as well as chronic kidney disease.[6]

The ethics of prescribing semaglutide off-label

Prescribing products off-label to improve patients' appearance or lifestyle is ethically justifiable only when very strong evidence demonstrates product safety. In the face of media attention directed at the weight-loss benefit of semaglutide, doctors are increasingly under pressure from patients who are not diabetic to indiscriminately prescribe this agent. There are many reasons, some with good intentions, that a clinician may prescribe semaglutide off-label. They may not want to upset or disappoint a patient with whom they have previously established a good relationship and time constraints may make it easier to prescribe than to seek a holistic intervention for weight loss.

South African law mandates that medication should be prescribed for the given indication based on scientific trials and approvals. Off-label prescribing is considered reasonable in certain circumstances, although this legally requires informed consent on the part of the patient.

What is the impact of using semaglutide off-label?

Worldwide, off-label prescribing of semaglutide for the treatment of obesity has given rise to a situation that compromises quality diabetes care

Worldwide, off-label prescribing of semaglutide for the treatment of obesity has given rise to a situation that compromises quality diabetes care; this medication is now not available to those who need it most. T2DM patients affected include those already using semaglutide in their established treatment regimen, who now have to use a different medication, as well as those at high cardiovascular risk who ideally should be initiated on semaglutide therapy to improve long-term outcomes.

Patients using an established semaglutide regimen may have to switch to a medication that is perhaps inferior in terms of efficacy or does not provide an equivalent cardiovascular benefit over the long term. It is well established that even short periods of hyperglycaemia and greater variability of glycaemic control are associated with poorer outcomes; the temporary lack of adherence can compromise the health of the patient.

The psychosocial impact of constrained semaglutide availability should not be underestimated. The patient is likely to experience anxiety and worry about their short- and long-term health outcomes if their medicine is unavailable and, depending on the alternative agent that is used, the patient may need to adjust their lives around a different dosing schedule. There is also a potential administrative burden, where it may be necessary to apply for funder approval to switch to a different molecule of the same class. A greater numbers of diabetic patients now are using an alternative drug.

In the context of the quagmire of challenges that the diabetic patient experiences due to indiscriminate off-label prescribing of semaglutide, the clinician needs to consider the potential for harm and whether the ethical principle of non-maleficence is therefore compromised.

An ethical approach to obesity treatment for the non-diabetic patient

Obesity, a chronic disease, is defined as a body mass index (BMI) >30kg/m^2 or a BMI >27kg/m^2 plus a weight-related complication such as dyslipidaemia. There are four registered weight loss medications that can be used in conjunction with holistic care for the treatment of patients who do not fulfil the criteria of clinical obesity (Table 2).[16] Affiliated obesity care support programmes are available to the patients using some of these pharmacotherapies. The appropriate treatment can be selected once there is an understanding of the individual metabolic parameters underlying the excess weight, such as hypertension or dyslipidaemia, and of the psychological or neuropsychiatric challenges the patient may face.

Table 2. Obesity pharmacotherapies currently registered in South Africa[16]

Liraglutide 3.0mg	GLP-1 RA with all the class benefits in terms of: • Appetite regulation (improved satiety, reduced hunger) • Some metabolic effects on cholesterol levels and blood pressure, among other cardiovascular parameters. Favourable side effect profile: transient gastrointestinal intolerability; gallstones and pancreatitis over the long term have very occasionally been reported; there is a label warning of thyroid cancer, although this has not been observed in real-world evidence.
Bupropion/ naltrexone combination	These centrally acting drugs can reduce cravings. Caution is advised for use in patients with neuropsychiatric concerns because of the combination's side effect profile.
Orlistat	Reduces fat absorption. Side effects include flatulence, fatty stools, stool urgency and bowel incontinence. Not commonly used, although it may be of benefit for the morbidly obese patient pre-bariatric surgery.
Phentermine	Centrally acting to reduce cravings. Not as effective as the other listed molecules. Caution is advised for use in patients with neuropsychiatric considerations or at high cardiovascular risk.

With regard to patient autonomy, the clinician should have the confidence and the ability to discuss with the patient that it is in their best interests to delay instant gratification in favour of a more sustainable holistic weight loss approach

Appropriately, Dr Joffe emphasises that there are no short cuts when it comes to treating obesity and that the use of medication only is not a sustainable approach to weight loss and weight management. Holistic care entails formulating an individualised weight loss approach based on evaluation of the patient's psychological and behavioural patterns, their diet and levels of physical activity, their cultural context, their work and family circumstances, and their ability to manage stress, among other considerations. Holistic care needs to be supported by a multidisciplinary team, as the patient may require referral for the support of different practitioners, including biokineticists, physiotherapists, exercise trainers, nutritionists or dieticians and, common in the patient with obesity, psychologists and psychiatrists.

An ethical approach to the care of patients with obesity requires a long-term commitment from them. With regard to patient autonomy, the clinician should have the confidence and the ability to discuss with the patient that it is in their best interests to delay instant gratification in favour of a more sustainable holistic weight loss approach. It is important that the patient understands the multifactorial aetiology of obesity and that simply taking a drug is unlikely to solve their problem.

What are the implications for clinical practice?

In essence, doctors are service providers who help people heal from disease. An ethical approach to the treatment of obesity in the patient without diabetes includes numerous considerations:

- Establish if the patient is suffering from a disease.
- Use therapies that are registered for the treatment of the disease; if a molecule has not been tested in a population with a specific disease, off-label prescription of that molecule is potentially harmful.
- If the patient is receptive, encourage conversation about what it is that is bothering them. If their only concern is their weight and underlying pathologies such as hyperthyroidism, hypertension and dyslipidaemia have been excluded or treated, an individualised holistic approach to treatment of their obesity is considered ethical best practice.
- After having considered the circumstances of a specific patient within basic ethical parameters, the decision about off-label prescribing and the responsibility associated with that ultimately rests with the clinician.

The decision about off-label prescribing and the responsibility associated with that ultimately rests with the clinician

Conclusions

T2DM remains a very high-risk disease and, in the opinion of Dr Ruder, the cardiovascular risk is probably underestimated. While long-term glycaemic control is still an important goal of diabetes care, there is the additional need for treatment of comorbidities and other risk factors. In order to avoid disturbed continuity of care for patients already using semaglutide and to ensure availability for those diabetic patients who would benefit from starting semaglutide therapy, ethical vigilance is essential when making the decision to prescribe off-label.

Further reading

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Key learnings

- The ethical issues that arise from off-label prescribing will differ depending on particular circumstances
- Allocation of a scarce medication or medical resource should be made with evidence-based criteria, transparency and consistency; the benefits of a scarce health resource should be maximised towards saving the most lives/life-years and giving priority to the worst off
- A holistic person-centred approach is fundamental to the management of T2DM
- In South Africa, semaglutide 0.25mg, 0.5mg and 1mg is registered only for use in T2DM
- The four principles of ethical decision-making that are common to utilitarianism and deontology should be used when considering off-label prescribing of any medication, which may be considered reasonable in certain circumstances
- Off-label prescribing of semaglutide for the treatment of obesity has given rise to a situation that compromises quality diabetes care
- An ethical approach to obesity treatment for patients who are not diabetic requires holistic multidisciplinary care; four obesity pharmacotherapies are currently registered in South Africa.

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