Effects of anti-obesity medications in the retina: a gathering storm or sunshine ahead?

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The study by Lakhani *et al*[1] scrutinises data from the US Food and Drug Administration (FDA) Adverse Event Reporting System, revealing formulation and sex-specific associations of the anti-obesity medication (AOM) with ischaemic optic neuropathy (ION). Interestingly, higher odds were associated with males (reporting odds ratio (ROR) 116.37), with greater risks from Wegovy which is used for obesity treatment (ROR 74.89), compared with Ozempic which is used for diabetes (ROR 18.81). These findings add to an emerging body of growing literature reporting ocular complications with AOMs[2] which warrants further scrutiny and urgent clarification for ophthalmologists.

The global prevalence of obesity has tripled since the mid-1970s, presenting one of the greatest healthcare challenges of our time. Obesity is associated with diminished life expectancies of ~5–20 years and the development of comorbidities including endocrinological, musculoskeletal, neurological, oncological as well as gastrointestinal diseases.[3] Compared with conventional bariatric surgery, recent advances in the field of AOMs offer more appealing methods of intervention for effective weight management. Patients safely achieve maximal weight reduction following sustained AOM therapy accompanied by lifestyle changes.[4 5] However, AOMs are also being exponentially used as a lifestyle choice, competing with their medically prescribed use for conditions such as type 2 diabetes. Users would take AOMs indefinitely to maintain their reduced body weight, just as medications to control diabetes and hypertension are also taken chronically.[6] Importantly, different AOMs function via different routes to bring about weight loss. For example, orlistat acts as a lipase inhibitor to reduce the uptake of dietary fat from the gastrointestinal tract.[7] An alternative route is via insulinotropic effects of the glucagon-like peptide-1 (GLP-1), mediated in peripheral tissues to induce satiety and weight loss by regulating activities of neuronal subpopulations in the central nervous system. The newer GLP-1 receptor agonists (GLP-1RA) are more widely used,[8] exemplified by semaglutide and the glucose-dependent insulinotropic polypeptide (GIP)/GLP-1R dual agonist tirzepatide that effectively lowers body weight.[9 10]

The UK has the highest level of obesity in Western Europe (29% of adults are obese, and 64% are overweight or obese: https://www.gov.uk/government/statistics/obesity-profile-may-2025-update/obesity-profile-short-statistical-commentary-may-2025). Given the extent of this obesity crisis, the National Institute for Health and Care Excellance (NICE) recently approved tirzepatide (orlistat is already approved in the UK) for managing excessive weight and obesity, with an estimated 3.4 million people eligible for treatment. Based on these guidelines which were finalised in December 2024, NHS England estimated 2.8 million patients would become eligible within 90 days for treatment (https://commonslibrary.parliament.uk/research-briefings/cbp-10171/). Studies show that AOMs are also beneficial for cardiovascular diseases such as stroke as well as dementia, which has led to AOMs being considered first-line options for some of these conditions,[11] further increasing their potential use. GLP-1RAs also demonstrated beneficial effects for patients with idiopathic intracranial hypertension.[12] Recently, the FDA approved semaglutide for adults with a form of fatty liver disease. An unhealthy diet promoting obesity also acts as lifestyle risk factors for a variety of ocular disorders such as age-related macular degeneration (AMD). By contrast, adherence to a nutritionally balanced Mediterranean diet offsets risks, even in the presence of AMD-linked genes.[13–16] Of known AMD risk genes, *APOE*, *ABCA1*, *LIPC* and *CFH* are linked with poor nutrition and obesity,[17 18] though future studies could reveal the involvement of additional genes.

Although the relationship between diet and AMD requires further unravelling, the possibility of decreasing odds of developing retinopathies such as AMD via dietary improvement offers an appealing incentive for at-risk patients. With the objective of raising public awareness of this link between diet and AMD in mind, we created a high-content three-dimensional animation video summarising the published literature in the field, showcasing how an unhealthy 'Western-style' diet can contribute to AMD, and how adherence to Mediterranean or oriental-style diets could offset risks (https://www.youtube.com/watch?v=Wy_lvfkJVEk&t=6s). This was featured on websites of organisations working in the sight-loss sector and presented at the 2024 Southampton Science and Engineering Festival which included a survey to assess impact. Participants (n=53) overwhelmingly reported an improved appreciation of dietary influences on AMD (93%), indicating a 'very likely' possibility of improving their diet to offset risks (71%).

Ironically, the widespread unregulated use of AOMs as a lifestyle choice has resulted in unforeseen consequences for the retina.[19] Current clinical evidence indicates conflicting effects in patients prescribed AOMs. For example, GLP-1RAs appear to offer some protection against AMD, but AOMs also seem to increase AMD risks with evidence of further complications. Protective effects reported thus far include a retrospective large-scale cohort study where GLP1-RA was associated with reduced risk of non-exudative AMD in an at-risk population with chronic ocular diseases, compared with several diabetes and lipid-lowering medications. GLP-1RA also significantly reduced the risk of exudative AMD compared with patients given insulin after 3 years.[20] Of note, ~84% of these patients had a type 2 diabetes diagnosis with an average high body mass index. This study showed GLP-1RAs outperforming other medications previously associated with reducing non-exudative AMD, advocating

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their possible use for future clinical trials to explore their impact on different AMD stages. By contrast, damaging AOM effects in the retina include evidence from a 3-year follow-up study of 46 334 patients with diabetes, which reported a twofold increase in developing neovascular AMD in those prescribed GLP-1RA, compared with 92 668 unexposed matched patients.[21] Moreover, the incidence of wet AMD increased further with longer GLP-1RA intake (risks increased by three times) alongside advanced age. Individuals transitioning to a pre-diabetic or type 2 diabetic phenotype taking GLP-1 RA, which, given increasing obesity rates, include AMD patients, may be at particular risk, though evidence here also reveals a mixed picture. Some studies indicated higher risks of developing diabetic macular oedema, while others showed protective effects.[22] GLP-1/GLP-1R is expressed in multiple layers of the human retina, but GLP-1 is downregulated in retinas from donors with diabetes.[23] The conflicting effects of AOMs are also reported in the optic nerve as demonstrated by Lakhani and colleagues, and in ocular inflammation.

Non-arteritic ION (NAION), the most common type of ION, is typified by ischaemic infarction of the optic nerve head presenting as unilateral optic disc oedema with abrupt and painless sight loss. Though rare, other studies have also shown patients receiving GLP-1RA to have an increased risk of developing NAION.[22] A recent study recommends screening patients with diabetes for diabetic retinopathy before commencing GLP-1RAs, particularly in high-risk populations. The authors suggest that the risk of ocular complications should be discussed when prescribing GLP-1RA to patients with sight loss in one eye and/or with a prior history of NAION.[24] Given these complications, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee recently concluded NAION to be a very rare side effect of semaglutide which may affect 1 in 10 000 individuals. By contrast, recent findings using health records of 258 026 patients each in GLP-1RA and control groups showed a near halving of risks in developing non-infectious uveitis in those prescribed GLP-1RA.[25]

To complicate matters further, the growing use of AOMs in children typically over the age of 12[26] has caused considerable debate, likely increasing the risks of ocular complications in later life. The full picture of AOM effects in the eye is still unclear, as most studies have only been reported in the past few years. Understanding the consequences of AOM use in children is still further in its infancy. In summary, the data emerging from clinical studies related to AOMs appear to offer new hope for some conditions such as AMD and uveitis, but with potential risks of severe though rare ocular complications such as ION for others. Studies such as those by Lakhani *et al*, which provide insights into AOM formulation and sex-specific effects, enable better stratification of risks. Further studies providing nuanced information of this kind are therefore warranted for better understanding of AOM effects in the eye, especially given their increasing usage. Clinicians should be aware of potential AOM side effects such as documented here and report them via the yellow card route (https://yellowcard.mhra.gov.uk/) so an accurate assessment of their risks can be made.

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