Journal Club: GLP-1 Receptor Agonists in Idiopathic Intracranial Hypertension

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When we sat down with this paper by Sioutas et al [1], what struck us immediately was how much uncertainty still surrounds idiopathic intracranial hypertension (IIH). Elevated body mass index (BMI) probably remains the most important risk factor and therefore target for disease modification.[2], yet the treatments that are currently available are far from perfect. In the absence of impending sight loss, consensus guidelines recommend weight loss and medical therapy with carbonic anhydrase inhibitors.[3] Surgical intervention, including cerebrospinal fluid (CSF) shunting, optic nerve sheath fenestration, and venous sinus stenting are only indicated if there is an imminent risk to vision. Maintained weight loss is often difficult to achieve however, and although bariatric surgery provides a potential alternative in some patients, it is not always readily available.[4] There also remains a lack of efficacious and tolerable medications to lower intracranial pressure (ICP) while weight loss is attempted. Acetazolamide, the mainstay treatment, is frequently stopped due to side effects.[5] Topiramate offers only modest benefit [6] and also carries a substantial side effect burden. We found ourselves asking: what else is out there, and could new therapies change the trajectory for these patients?

One of our group uncovered the rather deadly origins of glucagon-like peptide 1 (GLP-1) receptor agonists (RAs). Originally discovered through researching molecules from the venom of a Gila monster – a venomous lizard native to the US and Mexico which eats 5-10 times per year [Image 1] – Exendin-4 showed significant homology to human GLP-1, forming the basis for the development of synthetic GLP-1RAs.[7] These agents have been used to successfully treat type 2 diabetes, and more recently obesity, with the US seeing a 700% increase in non-diabetic use from 2019-2023.[8] We agreed that the application of these agents to an obesity-associated condition such as IIH seemed like a natural next step.

We all felt that the recent retrospective cohort study by Sioutas et al. leveraged the observation of its anti-obesity effect in the context of IIH with encouraging preliminary findings.[1] Using a large US electronic health records repository, the authors compared outcomes of IIH patients who commenced GLP-1 RAs with propensity-matched controls treated conventionally. We agreed that the top-line summary of the article is that GLP-1 RA cohort showed statistically significant improvements in symptoms including headaches, papilloedema, and visual disturbance, as well as decreased use of acetazolamide and topiramate and fewer surgical interventions. Interestingly, these improvements were associated with only modest reductions in BMI; we wondered if the benefits of GLP-1 RA therapy in IIH extended beyond weight loss, and may influence CSF biomechanics or ICP regulation.

We recognised that the idea of GLP-1 RAs as a disease-modifying therapy in IIH is not a new concept, however. The Birmingham group's IIH Pressure trial provided initial proof-of-concept evidence, indicating decreased ICP and decreased headache frequency with exenatide.[9] Preclinical work in animal models suggested that GLP-1 receptors in the choroid plexus regulate CSF secretion.[10] We felt that this study provides real-world evidence to support the mechanistic rationale.

While we agreed that the study by Sioutas et al. had many strengths, our discussion uncovered important methodological limitations. There was a well-defined and clinically relevant question being posed with pre-defined exposure and outcome definitions. The propensity score matching allowed treatment/control groups to have backgrounds that were closer in nature, but notable differences remained, as GLP-1 patients were heavier, had more

metabolic comorbidity, and had worse symptomatology at the outset than matched control patients. We also noted that the study was reliant upon diagnostic codes, which had a risk of misclassification based on other studies that reported a positive predictive value of just over 63% for IIH coding in US electronic healthcare records using the International Classification of Diseases version 10 (ICD-10).[11]

We felt that several baseline characteristics were not fully aligned. Fewer patients than expected had obesity or papilloedema, raising the possibility of atypical IIH or incomplete coding capture. In addition, there was a discrepancy between the proportion of patients coded as overweight or obese in Table 1, and the distribution of BMIs in Table 2, which raised concerns about the reliability of this key demographic variable. The study used prescriptions to identify treatment exposures, but we did not know if patients were adherent. Additionally, we discussed that the outcome measure "visual disturbance/blindness" was ambiguously coded and mixed mild/moderate and severe visual impairment. We noted the absence of data on adverse events, tolerability or treatment discontinuation, which are important for risk-benefit assessments in real-world clinical practice. We also agreed that one-year follow-up is too brief to determine the durability of GLP-1 RA effects in a chronic relapsing disease. Furthermore, we considered if findings from a US-insured cohort may not capture the socioeconomic diversity seen globally, as IIH patients in many regions often come from disproportionately deprived backgrounds.[12, 13]

Nevertheless, these caveats did not detract us from appreciating some promising clinical findings. We all agreed that the headache absolute risk reduction (15.1%, number needed to treat [NNT] of 7) and papilloedema absolute risk reduction (9.3%, NNT of 11) suggested potential clinical benefit. However, we did feel that the absolute risk reductions were small

for visual disturbance/blindness, surgical interventions, and mortality, suggesting that these outcomes may not be clinically significant. Importantly, we were concerned that the change in BMI between groups was equivalent, suggesting that any sustained benefit after drug withdrawal was questionable if the obesity underlying IIH is not addressed.

During our discussion, we considered the current prescribing landscape globally for GLP-1 RAs. The World Health Organisation (WHO) recently added GLP-1 RAs to its list of essential medications, which highlighted their increasing importance in obesity and diabetes management worldwide [14]. Currently in the UK, the National Institute for Health and Care Excellence (NICE) has licensed semaglutide (Wegovy) and tirzepatide (TZP, i.e. Mounjaro) for obesity, but the eligibility threshold is BMI ≥35 kg/m² with obesity related co-morbidities, and. IIH is not explicitly listed as a qualifying comorbidity [15, 16].Continued prescribing is limited to two years and prescribing of these agents varies widely across the country. A phased rollout of TZP was commenced in June 2025 across specialist weight management services and selected general practices [17]. Moreover, GLP-1 receptor agonists have become widely available through the private sector.

In the United States, GLP-1 RAs are widely prescribed for both diabetes and obesity, though we note that insurance coverage and cost remain significant barriers to access [18]. In Europe, the European Medicines Agency (EMA) has approved several GLP-1 agents for obesity [19-21], but national health systems differ in how tightly they regulate access. Meanwhile, in lower-income countries, affordability and infrastructure pose significant challenges, meaning patients may have little chance of accessing these therapies at all [22, 23]. Thinking globally, we realised that while the science is advancing quickly, the pathways to accessing treatment remain uneven — and that raises important questions about equity,

sustainability, and how health systems worldwide might adapt if GLP-1 RAs prove to be genuinely disease-modifying in IIH.

Collectively, we felt that Sioutas et al. are cautiously optimistic. We appreciate that their study provides real-world evidence suggesting GLP-1 RAs may improve outcomes in IIH. However, we felt that with the methodological limitations, short follow-up, and uncertain generalisability of the results, they do not change practice paradigms at this point.

We all agreed that future research must include prospective adequately powered trials with longer follow-up, and careful economic modelling for both private and public healthcare systems, across high-, middle- and low-income countries. From our discussion, we felt that important questions for these trials to address include comparative efficacy, safety, adherence, and relapse rates. There are now two new randomized controlled trials of TZP in IIH on the horizon: a US hospital-based phase IV trial (TZP in IIH Trial) [24] and a UK community-based trial (IIH-Advance Study) [25]. We felt collectively hopeful that these studies have the potential to determine whether GLP-1 RA therapy can progress from opportunistic use within obesity pathways to a robust, disease-modifying treatment strategy for IIH.

Finally, we agreed that neurologists should engage with commissioners and the wider multidisciplinary team, including colleagues in endocrinology and weight management, to establish IIH as a high-burden condition deserving access priority. The opportunity is tangible, but adoption of GLP-1 RA therapy in IIH will depend on trial-based evidence and creation of clinical infrastructure to monitor patients safely and effectively.

Disclosures

JC, LW and EO'C are Practical Neurology Editorial Fellows.

Competing interests

BRW is the founder of Ceftronics limited and the CEFREF migraine mobile application. He has done consultancy for Invex Therapeutics and received honoraria from AbbVie.

JC, LW and EO'C have no competing interests.

Contributorship

J.C. was responsible for the initial conceptualization of this book club review. E.C prepared the original draft of the manuscript. All authors contributed to the review and editing of the article. All authors have read and approved the final manuscript for publication.

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Figure legends

Figure 1 The Gila monster and effects of GLP-1 RA

"Gila monster (Heloderma suspectum)" by Blueag9, licensed under CC BY-SA 3.0 (https://creativecommons.org/licenses/by-sa/3.0/). GLP-1 RA effects created via www.biorender.com

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