Characterising evidentiary critiques in HTA decision-making for treatments indicated for overweight and obesity

HTA50

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Background

- With many new therapies for overweight and obesity undergoing HTA evaluations in recent years, several therapies continue to experience negative or restricted reimbursement recommendations. This study aims to characterize the most common clinical and economic evidentiary critiques, to enable evidence optimisation early in the product life cycle.

Methods and limitations

- NICE (UK), CADTH (Canada), HAS (France), and PBAC (Australia) HTA websites were searched for obesity HTA reports published up to 31 May 2024
- Key evidentiary critiques were extracted and mapped, with a focus on the criticism received from each agency on the clinical evidence and economic models. Final HTA reports and ongoing assessments were reviewed; HAS reports were translated using the Google Translate tool
- Critiques and limitations noted by the HTAs have been generalized for the purpose of this study; however, each HTA agency has its own criteria for assessment and recommendation

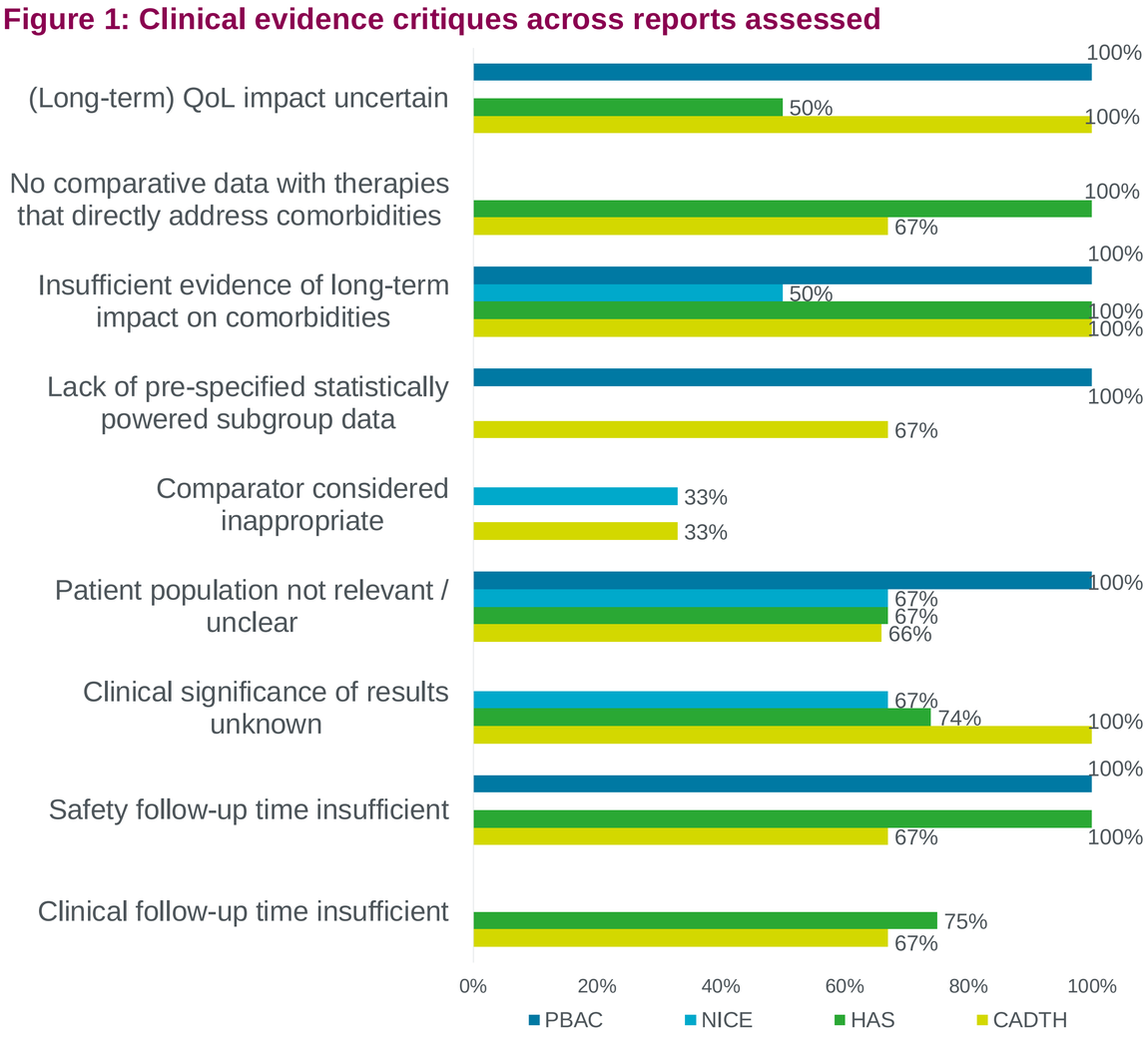
Results

- A total of 13 HTA reports were identified and extracted across seven approved drugs (Table 1)
- As of May 2024, only two drugs have been recommended for the management of overweight and obesity. Semaglutide (SC) has been recommended in the UK and France; liraglutide has only been recommended in the UK
- Semaglutide (SC) and liraglutide are recommended as an option alongside a reduced-calorie diet and increased physical activity. However, there are differences in the recommended populations between France and the UK:
  - In the UK semaglutide (SC) and liraglutide are recommended in adults with BMI ≥ 35 kg/m^2 (or lower in minority ethnic groups). In France semaglutide (SC) is recommended in adults with BMI ≥ 30 kg/m^2

Table 1: Heatmap displaying outcomes of the 13 HTA assessments reviewed

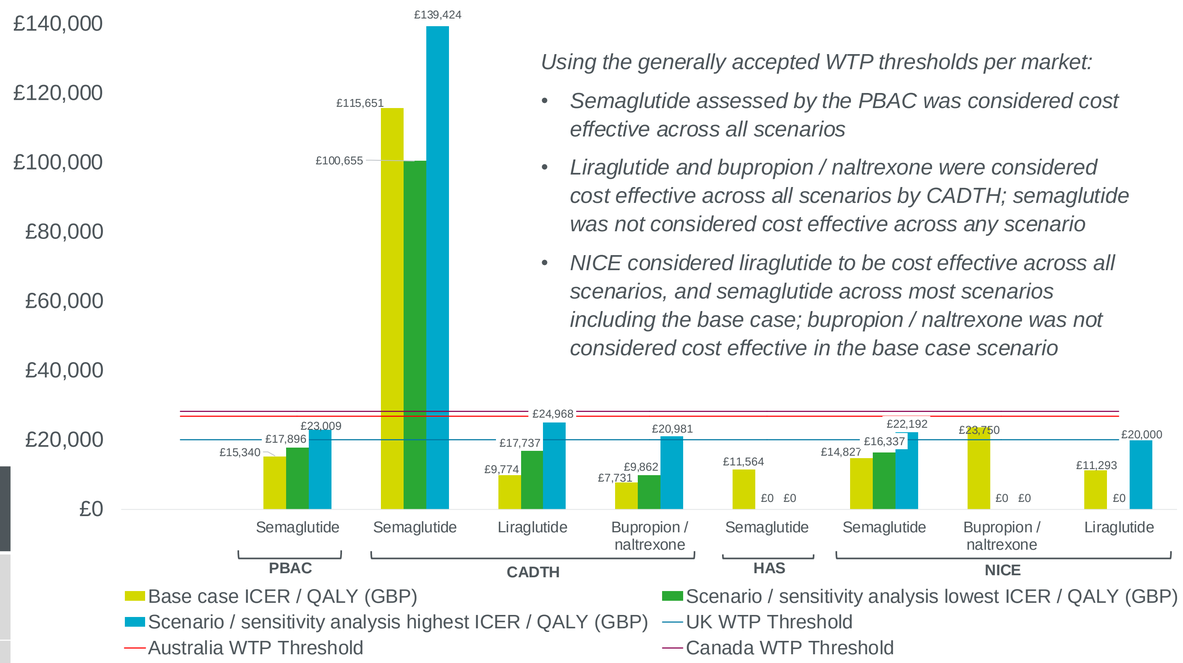
HTA body (market)	Semaglutide (SC)	Semaglutide (PO)	Tirzepatide	Naltrexone-bupropion	Liraglutide	Orlistat	Rimonabant
CADTH (Canada) *Cost effectiveness*	Not recommended	N/A	N/A	Not recommended	Not recommended	N/A	N/A
NICE (England) *Cost effectiveness*	Recommended	Awaiting assessment	Under assessment	Not recommended	Recommended	N/A	N/A
PBAC (Australia) *Cost effectiveness*	Not recommended	N/A	N/A	N/A	N/A	N/A	N/A
HAS (France) *Clinical effectiveness*	Recommended	Not recommended	N/A	N/A	N/A	Not recommended	Not recommended

Figure 1: Clinical evidence critiques across reports assessed



Percentages correspond to the proportion of reports per HTA agency that mentioned the clinical critique in question.

Figure 2: Base case and scenario analyses ICERs across reports assessed

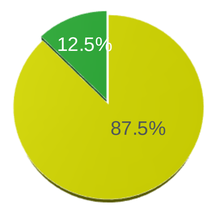


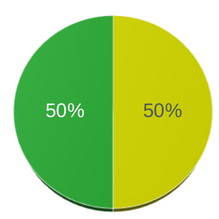
Using the generally accepted WTP thresholds per market:

- *Semaglutide assessed by the PBAC was considered cost effective across all scenarios*
- *Liraglutide and bupropion / naltrexone were considered cost effective across all scenarios by CADTH; semaglutide was not considered cost effective across any scenario*
- *NICE considered liraglutide to be cost effective across all scenarios, and semaglutide across most scenarios including the base case; bupropion / naltrexone was not considered cost effective in the base case scenario*

Of the 13 HTA reports assessed, 8 submitted economic assessments. All costs were converted to GBP using the conversion rate as per 12 September 2024. WTP thresholds were calculated as an average of generally accepted ranges and converted to GBP; $45,000 to $60,000 AUD / QALY (PBAC), $50,000 CAD / QALY (CADTH) and £20,000-£30,000 (NICE). No WTP threshold was available for HAS.

Figure 3: Model structure and type of analysis used across reports assessed





Of the 13 HTA reports assessed, 8 submitted economic assessments and 5 did not present economic analysis.

Markov model ■ Discrete event simulation model ■ Cost utility ■ Cost effectiveness

Key critiques highlighted in the economic models of reports assessed:

Model Structure

- Inaccurately reflected treatment goals and pathways of patients
- Assumed benefits beyond the 1-year treatment period, but did not allow for extension of the treatment period beyond this
- Focused on preventing future comorbidities, not alleviating existing ones
- Assumed long-term benefits on comorbidities without supportive trial data

Model Inputs

- Assumed non-responders to have the same outcomes as patients on standard care
- Assumed full weight regain by 3 years post-treatment, whilst data demonstrated much more rapid weight re-gain

Risk Equations

- Used relative effectiveness of surrogate endpoints for long-term health outcomes, introducing uncertainty
- Assumed instantaneous impact of weight loss on comorbidities and / or mortality reduction without supportive evidence

Comorbidities

- Included too many comorbidities for eligible patients, without focusing on those with higher risk and disease burden
- Assumed a large impact of unsustained weight loss on comorbidities
- Lacked clinical rationale for prerequisite co-morbidities chosen for sub-group analyses

Discussion and conclusions

- Currently, semaglutide (SC) has been recommended in the UK and France after being considered cost-effective by NICE and HAS, respectively, and demonstrating considerably higher efficacy than current therapies. Despite not being mandatory, the semaglutide submission to HAS included an economic model, which may have contributed to favourable access. Liraglutide has only been recommended in the UK and was also considered cost-effective
- Inclusion of long-term follow-up, ensuring endpoints adequately capture impact on comorbidities, ensuring the included patient population accurately reflects clinical practice and ensuring the trial results correlate to real-world outcomes important to patients are vital for acceptance of clinical data packages in this indication. Future trials may be required to provide comparative evidence versus semaglutide and demonstrate similarly high efficacy
- In order to increase certainty in modelled benefits and demonstrate favourable economic outcomes, economic submissions should focus on ensuring models accurately reflect the full treatment pathway, including realistic assumptions about treatment duration, weight regain, and the impact on comorbidities. Risk equations and comorbidity modeling should be refined by relying on direct clinical evidence where possible and focusing on key, high-impact comorbidities, while clearly stating and justifying all assumptions
- Overweight and obesity continues to be one of the most prevalent diseases with a substantial unmet need for effective therapies. Ensuring clinical and economic data packages reflect the highlighted needs will enable access to therapies that deliver safe, sustained weight loss and a positive impact on comorbidities

Abbreviations: BMI: Body mass index; CADTH: Canadian Agency for Drugs and Technologies in Health; GBP: Pound sterling ; HAS: Haute Autorité de Santé; HTA: Health technology assessment; ICER: Incremental cost effectiveness ratio; NICE: National Institute for Health and Care Excellence; PBAC: Pharmaceutical Benefits Advisory Committee; PO: Oral; QoL: Quality-of-life; SC: Subcutaneous; UK: United Kingdom; WTP: Willingness-to-pay

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