Drug policy at the margins: the case of growth hormone replacement for adults with severe growth hormone deficiency

Are current standards of evidence always appropriate when making the decision to subsidise treatment?

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The Pharmaceutical Benefits Scheme (PBS) provides the Australian community with subsidised access to medicines. Decisions about which medicines are listed on the PBS are made by the Minister for Health and Ageing, on the advice of the Pharmaceutical Benefits Advisory Committee (PBAC) — an independent statutory body charged with assessing the clinical benefit and cost-effectiveness of the medicines under consideration.

While Australia is considered to be a world leader in such decision making, interpretations of data surrounding efficacy and cost-effectiveness are often complex and contested. The recent decision by the PBAC not to subsidise recombinant growth hormone (somatropin) for adults with severe growth hormone deficiency (GHD) is a case in point.

Growth hormone (GH) is best known for its role in stimulating growth in children, but it continues to be produced throughout adult life, when it plays a critical role in regulating metabolism and the functional integrity of tissues and organs. Adult growth hormone deficiency (AGHD) — not to be confused with idiopathic growth failure during childhood — can be the result of congenital pituitary abnormalities or acquired loss of pituitary function resulting from tumours, irradiation, intracerebral haemorrhage and head injuries. The clinical picture is characterised by insulin resistance with atherogenic lipid profiles, central adiposity, muscle loss and weakness, osteoporosis, fatigue, demotivation and depression, and a twofold increase in premature cardiovascular mortality.[1]

Over the past 20 years, trials and clinical experience with biosynthetic GH replacement therapy in children and adults have provided substantial evidence that this therapy is safe and well tolerated, and the Therapeutic Goods Administration (TGA) has registered GH for the treatment of adults with severe GHD. GH replacement in adults with GHD has been shown to increase lean body mass and bone mass, reduce fat mass, improve physical function, improve cardiovascular risk profile, improve mood and energy, and reduce the use of health services.[1,2] While, for reasons that will be discussed below, there is limited evidence of the effects of GH replacement on mortality, extrapolation from the improvement in lipid profile alone would suggest that cardiovascular mortality may be reduced as a result of GH replacement.

Consensus guidelines from leading international professional bodies have uniformly endorsed GH replacement therapy for adults with severe GHD caused by organic hypothalamic-pituitary disease, who exhibit characteristics of growth hormone deficiency syndrome, and who fulfil strict diagnostic criteria.[1,3] The National Institute for Clinical Excellence (NICE) in the United Kingdom, for example, recommends GH replacement for those with severe GHD who have significant impairment of quality of life and whose quality of life is demonstrably improved by GH replacement.[4] GH replacement is widely approved for use in the treatment of AGHD, and has been subsidised for adults with severe GHD in several other countries including Spain, Sweden and New Zealand. Despite this, in early 2011, the PBAC decided not to recommend subsidisation of GH for adults with GHD on the basis of "uncertain clinical benefit and highly uncertain cost effectiveness".[5]

There are a number of possible reasons why the PBAC's decision might have differed to those of other agencies: the PBAC could have been presented with different data, the data could have been "packaged" differently, or the PBAC could have different methods and standards for assessing data. Although we do not have the details of the drug company's submission to the PBAC, or of the PBAC's precise decision-making processes, it seems likely that the discrepancy occurs, at least in part, because the PBAC may require higher standards of evidence of clinical benefit and of cost-effectiveness.

Whatever the reason for the discrepancy, on the face of it, the PBAC's decision would seem reasonable, as the data presented to the PBAC demonstrated, at best, minor improvements in quality of life (which was the main variable used to justify the submission) with GH replacement in adults, and limited evidence of cost-effectiveness. There are, however, a number of features of AGHD and GH replacement therapy that might have weighed against a more favourable decision, despite the evidence of benefit described earlier.

First, existing data about the effectiveness of GH replacement do not distinguish consistently between severe AGHD (for which subsidisation was requested) and milder deficiencies. To make matters worse, two of the pivotal studies presented to the PBAC used diagnostic criteria for AGHD that would have led to a number of false-positive diagnoses of GHD, thus skewing the results in the direction of non-efficacy.[6,7]

Second, even if trials are designed appropriately, assessment of the physiological efficacy of GH replacement is made difficult by the rarity of GHD in adults, which curtails the ability to obtain hard therapeutic end points (eg, mortality or fracture reduction). It is also made difficult by the fact that GH acts on several body systems, defying the use of a simple metric to measure efficacy, and by the practical difficulties of conducting

long-term placebo-controlled evaluation of a medication requiring daily injections.[8]

The assessment of quality of life in conditions like GHD is also extremely difficult and highly dependent on the methods used. Thus, while some trials of GH have reported improved quality of life,[1,2] different tools were used to assess quality of life in different life circumstances and in different populations. Matters are complicated further by the fact that quality of life is difficult to assess in young adults with childhood-onset GHD, whose positive experiences of treatment might be masked by negative childhood experiences of daily injections.[9]

This places patients with AGHD and the clinicians who care for them in a difficult situation. For, while there are good reasons on theoretical, physiological and epidemiological grounds for why adults with severe GHD (or at least subsets of such patients) would be likely to benefit from hormone replacement therapy, it is difficult to provide data showing sufficient benefit — let alone cost-effectiveness — to justify its inclusion on the PBS. In this regard, adults with severe GHD are not alone, and such difficulties are likely to increase for patients with other conditions, as diagnoses become increasingly fine-grained, and prognostic markers become more discriminatory, making it increasingly difficult to conduct the research needed to unequivocally demonstrate clinical benefit and cost-effectiveness.

So, what are we to do in such situations, where it seems difficult, if not impossible, to generate the kind of evidence that is required by the PBAC? First, we need to acknowledge that, irrespective of our view of particular decisions, the PBAC makes its decisions on the basis of clearly articulated standards of evidence, as outlined in its *Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee*.[10]

But we do need to question whether or not these standards of evidence are appropriate. If we decide that existing standards are appropriate, and should not be adjusted in situations where perhaps the "best" evidence stems from physiological reasoning, clinical experience or limited epidemiological research, then we need to accept that there will be situations in which access to particular goods and services will be restricted because of our requirements for particular standards of evidence and our concerns about opportunity cost (ie, the money spent on one intervention being therefore not available for another). If, on the other hand, we decide that compromises should be made on moral grounds — because we recognise that the evidence that we usually require is not (and may never be) available, or because treatment of this particular population is justified by reference to an important moral principle such as equity or concern for its vulnerability — then we need clear processes and standards for making such exceptions. With this in mind, we would suggest the following approach to PBAC decision making in situations where standards of evidence have not been met.

First, the sponsoring body (commercial, consumer or professional) needs to do the best possible job of gathering further data, or reanalysing data to identify patients who are most likely to benefit. Where such evidence is not available, the PBAC could either recommend subsidisation, subject to evidence development, or refuse to recommend coverage until evidence has been obtained. If it proves to be impossible to gather this evidence, then the PBAC needs to decide whether it is willing to adjust its usual evidentiary standards with the goal of achieving greater equity, even if this occurs at the expense of (demonstrable) efficacy and/or cost-effectiveness. Whatever it decides, the PBAC then needs to be explicit about how it came to this decision, so that those concerned with the decision are aware of the moral compromises that have been made.

> "Growth hormone acts on several body systems, defying the use of a simple metric to measure efficacy"

Unless sponsors and regulators can agree on how pharmaceutical agents can be assessed where high-quality evidence is lacking, and where characteristics of the disease or patient population make it unlikely that high-quality evidence will ever be attainable, PBAC assessment will remain too blunt an instrument to cope with increasing subcategorisation of disease and with increasing complexity of pharmacotherapies; and unacknowledged, systematic inequities will become an increasingly prominent feature of our pharmaceutical landscape.

Competing interests: Ken Ho has been on an Eli Lilly advisory board and has been a consultant to Pfizer. Richard Day has provided occasional advice to Merck Australia about rofecoxib and etoricoxib.

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