Editorial

Comparative effectiveness research and acromegaly

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In the study by Marko et al., a comparative effectiveness review was performed to assess efficacy, cost, and quality of life (QOL) in the treatment of patients with acromegaly caused by a pituitary microadenoma. Treatments reviewed included surgery, radiotherapy, stereotactic radiosurgery (SRS), and pharmacotherapy with a somatostatin analog and/or a growth hormone (GH) receptor antagonist. A management decision tree was used to identify 5 treatment strategies, each with up to 4 potential treatment steps. This comparative effectiveness research (CER) analysis provides a framework to inform clinical decisions among alternate management strategies. The authors concluded that the choice of management strategy must be individualized for each patient with acromegaly. Their CER analysis found that for the typical patient, when integrating efficacy, cost, and QOL, the ranking of best treatment option from highest to lowest was surgery, medical therapy, followed by SRS.

Comparative effectiveness research is the assessment of methods to prevent, diagnose, treat, and monitor health care conditions to help consumers, clinicians, and policy makers improve individual and population-based health care. Researchers have spent years assessing variations in health care across the US, that is, practice pattern variation. Proponents have argued that if unwarranted variation were abolished, health care quality would increase and achieve savings of up to 30%. Fisher and colleagues found that patients in the highest-spending regions of the US receive 60% more health care services than those in the lowest-spending regions, yet this has not been associated with improved outcomes. The rising expense of medical care in the US and these kinds of analyses have helped spark CER.

Federal divisions such as the Healthcare Research and Quality Agency have been implemented in part to incorporate CER to build census guidelines. President Obama’s $1 billion stimulus package was flagged to include CER measures. Although critics argued that CER may be used to limit patient health care options, the bill was eventually approved by the Senate with measures to utilize CER. The greatest difficulty of CER is often comparing different standards of outcomes between various diagnostic tests or treatments. For example, between surgery, medical therapy, and radiation, the outcomes of gross-total resection, time to recurrence, endocrinological remission, patient discomfort, and overall QOL, are not easily comparable. It is also difficult to account for more uncommon side effects, even though these may be appreciable in an additive fashion.

Additionally, standards of outcomes change over time, which may result in outcomes bias. This may alter the utility of older studies in which biochemical criteria for cure or control were less stringent. The latest consensus statement guidelines published in 2010 define acromegaly remission as an insulin-like growth factor–1 (IGF-1) level in the age-adjusted, normal range plus either a random GH of less than 1 μg/L in patients treated medically, or glucose-suppressed GH less than 0.4 μg/L in patients treated with other modalities, except pegvisomant, for which only IGF-1 levels are used. Although these guidelines have also yet to be substantiated in long-term studies, we have recently found significant alterations in endocrine remission rates when adopting the newest consensus guidelines in surgically treated patients with acromegaly.

One general issue in CER and the analysis performed by Marko et al. is that outcomes, such as efficacy, cost, and QOL, are ranked equally. Some critics would argue that various factors should be ranked unequally; the overall outcome of patient morbidity and mortality is more important than cost. Sometimes these outcomes go together and as a result are additive; for example, patients achieving remission from surgery had the highest QOL. Additionally, interaction may result in an exponential equation rather than an additive ranking, for which this CER fails to account. Further studies can quantify interaction and confounding in regression analysis. Prior treatments are often not reported in the literature, which can cause bias. In many instances, a particular treatment was carried out following the failure of a single or multiple treatments. This can cause a bias in the results reported. We have found that, although patients with a history of prior surgery are less likely to achieve a cure after a second surgery, the rates of remission following a failed first surgery are quite high. This is less developed in the literature as it relates to acromegaly, but it is well addressed in other fields such as multiple treatments for patients with Cushing’s disease. The type of surgery is also not accounted for, and there may be differences in both remission rates and QOL according to surgical intervention.

Other factors often confounding CER analysis are differences in length of follow-up, which vary significantly across the different studies assessed and incorporated into analysis. Long-term follow-up is necessary to assess actual remission rates. In this case, analysis with time-dependent covariates and/or survival analysis may be necessary.

In the past, randomized clinical trials have been the gold standard of determination of treatment efficacy, that is, an analysis of whether a treatment option works. Comparative effectiveness research will be a growing element of health care assessment. The authors should be commended for their in-depth review of treatment options for acromegaly. In the future, “pragmatic trials” that measure effectiveness or the benefit of a treatment regimen in clini-
cal practice will likely be an increasing form of health care evaluation.15

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The author reports no conflict of interest.

References


Response

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We wish to thank Dr. Starke for his thoughtful comments in response to our comparative effectiveness analysis of alternate treatment strategies for acromegaly. We are grateful for his mutual interest in calling the attention of the neurosurgical community to the strengths and limitations of this research paradigm, and we commend the effort that he has applied to this task.

In particular, we would like to echo and to emphasize an important concern raised in his commentary. Dr. Starke appropriately notes that assigning equal ranks to the domains of efficacy, cost, and QOL may not be an ideal analytic model. We were confronted by the same issue when conducting this investigation, and we were unpleasantly surprised by the apparent lack of literature discussing potential strategies for confronting this problem.

The ultimate success of a robust CER enterprise in the US mandates that careful thought be given to how efficacy, cost, and QOL will be balanced when attempting to assess the true effectiveness of alternate therapeutic modalities. While discussions regarding the economic value of a quality-adjusted life year or the true balance between effectiveness and cost are uncomfortable, unpopular, and generally avoided, such discussions must take place if meaningful CER is to proceed.

The reason that these discussions must occur is that health care spending in the US continues to increase, both in absolute dollars and as a percentage of the gross domestic product. Financial resources are not unlimited, and, to paraphrase Charles Dickens, “annual income $15 trillion, annual expenditure $14.5 trillion, result happiness. Annual income $15 trillion, annual expenditure $15.5 trillion, result misery.” As health care vies with defense as the largest category of federal budgetary expenditure and with the US continuing to rank highest in the world in health care spending as a percentage of gross domestic product (at ~18%), it is no mystery where the government is likely to turn when real cost cutting becomes inevitable.

As physicians, we currently have the opportunity to shape and leverage the CER paradigm as one strategy for identifying opportunities for economically viable measures to improve QOL and cost savings that do not come at the expense of patient outcomes. However, if we choose not to engage in this process, then we should not be surprised when those assigned to the task approach the problem with a different set of priorities. The situation is perhaps best summarized in the words of a colleague, who notes that, “If you’re not at the table, then you’re on the table.”

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