

Age-related macular degeneration and quality of life: how to interpret a research paper in health-related quality of life

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Purpose of review

To review how to critically appraise a research article pertaining to changes in health-related quality of life (HRQoL) related to interventions for age-related macular degeneration (AMD).

Recent findings

We searched PubMed using a strategy that combined the text-words, "macular degeneration" and "quality of life" (n = 73; January 17, 2004), while limiting the search to "clinical trials" (n = 6; of which 3 were published within the past year). A randomized clinical trial evaluating the efficacy of self-management as an intervention for AMD has been selected to introduce the reader to the concept of how to critically review a research paper pertaining to HRQoL in AMD. Other pertinent articles used in this review include recent results published from the Age-Related Eye Disease Study and the Submacular Surgery Trial.

Summary

The NEI-VFQ is a reliable, valid, and responsive tool when applied to patients with AMD. Self-management of patients with AMD has been demonstrated to improve their HRQoL by way of an internally valid randomized clinical trial. In this issue of *Current Opinion in Ophthalmology*, we confront the issue of how to assess the validity and importance of a research paper pertaining to the issue of quality of life. To introduce this topic, we will present a real world clinical example to better understand how quality of life may aid in medical decision making.

Keywords

macular degeneration, quality of life, NEI-VFQ, NEI-25, outcomes research, patient-reported outcomes

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Clinical scenario

A 64-year-old man presents with gradual onset of loss of central vision in both eyes. His wife states that she has noticed that over the past few months, he has become somewhat depressed over his visual loss. His visual acuities are 20/200 in both eyes, and clinical examination reveals advanced dry age-related macular degeneration (AMD) in both eyes.

You have a discussion with the patient about the safety and efficacy of high-dose vitamin supplementation [1], because you believe that this may be of benefit in reducing disease progression. In addition, however, he wonders if there is anything that can improve his overall quality of life.

A search of Medline is undertaken to retrieve clinical studies pertaining to AMD and quality of life. To do so, you search both "macular degeneration" and "quality of life" together; this search yields 73 citations (searched January 17, 2004). When the search is limited to only "clinical trials," six citations are noted. One of these studies, a randomized controlled clinical trial, demonstrates the benefits of self-management for patients with AMD in terms of changes in patient-reported outcomes [2••]. This study also analyzes the effects of self-management in a subset of patients with AMD who are clinically depressed.

Even though the article was published in a reputable journal, you retrieve the article and decide to review its merits for yourself, to determine if its conclusions are valid, and if it will help in your decision-making process with your patient.

Introduction

Quality of life (QoL) is a complex and abstract concept that is difficult to define, let alone measure [3]. Consequently, a number of theoretical and operational definitions have been used in QoL studies [4,5]. In its broadest sense, QoL refers to an individual's satisfaction and happiness with life in all the dimensions he or she deems to be important [6]. It is determined by the facets of life that contribute to its fullness, pleasures, and rewards. These aspects are typically grouped into physical, emotional, and social domains. Well-being in any of these

areas is affected by numerous events and experiences in the life of the individual, including those associated with his or her state of health. Thus, health-related quality of life (HRQoL) refers to an individual's happiness and satisfaction with the different domains of life to the extent that they are affected by health.

By analyzing HRQoL, researchers attempt to measure the impact of disease processes and treatments on important aspects of a person's life [7,8]. This is usually accomplished with questionnaires in which patients are asked to report objective amounts or subjective qualities of experiences that are thought to be indicators of the patient's HRQoL [9]. These experiences include signs and symptoms of disease, activities of daily life, emotional stability, social functioning, and sometimes a general assessment of the satisfaction with life [10].

Depending on the patient population, particular experiences might be more relevant than others. If the aim is to assess the impact of distinct conditions, disease-specific instruments are usually needed. Generic questionnaires, however, seek to measure the outcomes of a wide variety of conditions and, albeit less precise, allow comparison across diseases and interventions [11,12]. Certain instruments, labeled patient-specific, use a unique methodology that allows each patient to choose or rank those domains with the most impact on their lives [13,14].

Health-related quality of life questionnaires can be delivered in the form of standardized interviews or surveys and typically limit patients' responses using summative scales with four to seven rating options or yes/no answers. The values assigned to each question and answer can be uniform or weighted to account for differences in the relative importance of the experiences under scrutiny. Individual marks are then combined according to some algorithm to produce an overall questionnaire score [15].

One of the aims of HRQoL measurement is to introduce patient-reported outcomes into the assessment of therapeutic effectiveness, side effects, and monitoring. Indeed, such patient-based appraisals are increasingly found in clinical trials and health care evaluations [16, 17]. This growing importance of patient input in medical care is a result of an increased awareness of the psychosocial determinants of health, the escalating cost of health care, and of society's movement towards greater patient participation in treatment decisions [18].

As a consequence of these changes, clinicians are increasingly faced with treatment recommendations that are based in large part on HRQoL assessments [19]. Often, physicians are not familiar with qualitative methods for measuring well-being and may find it difficult to determine the usefulness of patient-based recommendations [20].

This article is intended as a guide for the critical appraisal and application of the HRQoL literature in ophthalmology. The suggested framework for this is summarized in Table 1 [9].

Is a health-related quality of life measurement necessary?

Interventions that have been shown to significantly prolong or shorten life or to possess a very favorable side-effect profile generally need not be evaluated in terms of their effect on patients' QoL. The issue becomes important when (1) a life-saving or curative treatment elicits moderate or severe adverse reactions; (2) when despite improvements in certain clinical parameters, a treatment has only modest effects on the patient's well-being; (3) when therapy has only a moderate benefit-to-risk ratio; or (4) when the treatment cost effectiveness may be important.

The clinical trial evaluating the efficacy of self-management for patients with AMD meets some of the aforementioned criteria. Given our unfamiliarity with this intervention, when applied to patients with AMD, we can assume *a priori* that the intervention in question will likely be associated with only modest treatment effects, and may be associated with a modest cost-benefit ratio. Given these facts, an assessment of the effects of self-management on patient-reported HRQoL is likely an important undertaking.

Are the results valid?

Perhaps the one of the most fundamental questions to be asked about any HRQoL result is whether the chosen instrument used to quantify HRQoL is actually measuring what it is supposed to. One of the ways an instrument's validity can be determined is by evaluating the degree to which it correlates with other health variables and its reproducibility over time and between people. The validation methodology for objective measurements of subjective variables is derived from the fields of education and psychometrics [21,22].

Table 1. Critical appraisal framework for a health-related quality of life questionnaire (HRQoL) paper

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- I. Is a HRQoL measurement necessary?
 - II. Are the results valid?
 - a. Are all items important to patients?
 - b. Are all relevant aspects being measured?
 - c. Does the instrument appear to measure what is intended?
 - d. Are there logical relationships between questionnaire scores and other measures?
 - e. What kinds of inferences can be made about the HRQoL measurements?
 - III. What are the results?
 - a. Is the observed effect significant?
 - b. Is the observed effect important?
 - IV. How can these results be applied?
 - a. Can these results be generalized to clinical practice?
 - b. Can these results help the patient make a decision?
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Adapted from Guyatt.

Question 1. Are all items important to patients, and are all relevant aspects being measured?

As a first step toward assessing the validity of an instrument, the clinician should ask whether the intended patient population truly values the experiences about which the questionnaire asks. By using focus groups consisting of patients with the condition of interest, items of relevance are generated for inclusion in the instrument. Less sensitive methods include review of the disease-specific literature and discussions with health care professionals with some insight into the patients' illness. In addition, the clinician should question whether the specific concerns of patients are included in the instrument. This, of course, requires a thorough understanding of the patient's experience with disease at the functional, emotional, and social level.

The main instruments used to quantify HRQoL in the study by Brody *et al.* [2••] are the Profile of Mood Scale (POMS) and the National Eye Institute Visual Function Questionnaire (NEI VFQ). The NEI-VFQ is an instrument that was created based on initial interviews conducted with a series of focus groups with various ophthalmic conditions, including subjects with AMD [23].

The POMS questionnaire, an instrument that is frequently used to assess emotional distress, uses items that are relevant to patients who are under psychological stress. In addition, this instrument has been previously used to demonstrate emotional distress in a sample of patients with AMD ($n = 86$); average POMS score = 65.4. These facts lead us to believe that the two instruments used have significant *content* validity with respect to measuring information that is pertinent to depressed patients with AMD.

Question 2. Does the instrument appear to measure what is intended?

Clinicians should use their experience to judge whether plausible links exist between the instrument's items and that which the investigators purport to measure. One way to do this is by asking whether changes in the measured aspects would, on their own, prompt some treatment decision on the part of the patient.

In the case of the randomized clinical trial assessing the efficacy of self-management for AMD, we would likely recommend intervention with self-management to a patient with AMD if the clinical trial demonstrated a change significant change in either the POMS or the NEI-VFQ.

After reviewing the first two questions, the clinician will have an impression of the questionnaire's relevance and comprehensiveness (content validity), as well as the degree to which it seems to measure what is intended (face validity) [21,22].

Question 3. Are there logical relationships between questionnaire scores and other measures?

The investigators should also provide empirical evidence for the validity of their instrument by analyzing how its scores are related to other clinical or psychological variables. Ideally, one of these should be the criterion or gold standard for what is being measured (criterion validity) [21,22]. However, because no such measure typically exists for HRQoL, investigators will often use indicators of disease severity, with the assumption being that more severe disease will be associated with diminished QoL and *vice versa* (convergent construct validity). However, the instrument's scores should not correlate with measures that are thought to be unconnected to HRQoL (divergent construct validity) [21,22].

In the study by Brody *et al.* there was a strong association between the level of self-efficacy (AMD-SEQ) and the extent of emotional distress (POMS) ($r = -0.50$; 95% CI = 0.61–0.38), and the level of functioning (NEI-VFQ) ($r = 0.44$; 95% CI = 0.31–0.55). These results indicate that subjects who reported less distress and better functioning were more likely to report that they had greater self-efficacy. This can be considered to be a form of convergent construct validity.

Question 4. What kinds of inferences can be made about these health-related quality of life measurements?

Health-related quality of life instruments can be classified as discriminative or evaluative, depending on their measurement properties [24]. Discriminative instruments are those that can distinguish between patients with better or worse HRQoL at a given point in time. Evaluative instruments, however, are able to measure changes in HRQoL within the same patient and can therefore aid in the assessment of the treatment's effectiveness.

All measurements are a composite of a true score, commonly referred to as a signal, and random error, otherwise known as noise. The signal is the true difference that is to be detected, and the noise is the background of measurement error over which these differences must be identified [25].

As previously discussed, a useful instrument should measure what is intended, but it should also possess a high signal-to-noise ratio. For discriminative instruments, this ratio is termed reliability and for evaluative ones it is called responsiveness. Thus, reliability refers to the relative sizes of the (true) differences between patients and spurious within-patient differences that result from repeated measurements. In turn, responsiveness compares (true) within-patient change, occurring spontaneously or secondary to an intervention, to within-patient differences from extraneous sources [26].

Investigators will often determine reliability by serially administering a questionnaire to a series of patients whose health is thought to be stable and measuring the correlation between tests. Responsiveness can be established by showing that an instrument can identify patients who have changed, when this is deemed to be the case by other independent criteria. The latter can include physiologic or clinical parameters as well as patients' perceptions of change [27].

The NEI-VFQ has recently been demonstrated to be both reliable (Cronbach's $\alpha = 0.58\text{--}0.91$) and valid (subscale scores strongly correlated to visual acuity in both the better-seeing and worse-seeing eye) in patients with AMD [28••]. In addition, it has recently been demonstrated to be responsive to change [29••]. The construct used to measure change was not a patient-reported perception of change, but rather a three-line change in visual acuity.

What are the results?

Is the observed effect significant? Is it important?

In using HRQoL articles, a crucial task for clinicians is interpreting the results in a clinically meaningful manner. For traditional measures, such as visual acuity, clinicians have an understanding of what constitutes an important difference. In contrast, the meaning of changes in HRQoL scores is less intuitive because clinicians rarely use such measures in clinical practice. To assist in the clinical relevance and widespread adoption of these instruments, authors should always provide some guidance to readers as to what constitute small, medium, or large effects [30].

The magnitude of changes on HRQoL can be understood in a number of ways. It can be related to the statistical distribution of the results or to some type of external anchor. The latter can be a clinical outcome, the likelihood of a subsequent life event, an expression of patient satisfaction, or a rating of patients' perception of change. Using this last approach, it has been established that, for 7-point scales, a 0.5-point change constitutes the minimal difference that patients consider important [31].

Investigators from the Submacular Surgery Trial were able to demonstrate that a change of between 3.6 and 15 points on the NEI-VFQ corresponded to a three-line change in visual acuity [29••]. Brody *et al.* demonstrated that a subgroup of patients with AMD who were depressed had a mean improvement in NEI-VFQ score of 3.58 ($P = 0.03$), which would correlate to a clinically relevant change in overall score. Although we were unable to locate a guide to what constitutes a clinically meaningful change in POMS score in the peer-reviewed literature, the 15.41 absolute score difference in depressed patients with AMD would represent a 19% improvement

from baseline score. This would likely be interpreted as clinically meaningful by most clinicians.

How can these results be applied?

Can these results be generalized to clinical practice?

Can they help the clinician's patient make a decision?

Lastly, the clinician must determine whether a trial's results can be generalized to their clinical practice. Important factors influencing generalizability include the comparability of a given patient's profile to that of the research sample, with respect to demographics, disease duration and severity, associated disability, treatments, and prognosis. In addition, it should also be clear whether the interventions described in the study could actually be replicated, with real-life treatment methods and subjects, in the clinician's practice.

Both the demographic profile of the sample used in the self-management study and the intervention itself seem to be well described by the authors [2••]. We believe that the intervention could be replicated in practice and that the average patient in the study is representative of the patients seen in most clinical retinal practices.

Conclusion

After reviewing the work by Brody *et al.* and the peer-reviewed literature, you are satisfied that the instruments used are relevant and comprehensive, have a high degree of construct validity, and are responsive to meaningful change. Given that the study demonstrates significant change in both instruments in subjects who are similar to the clinical patient, disease self-management is recommended.

References and recommended reading

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