Health-Related Quality of Life: Current Status and Future Prospects

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INTRODUCTION

Pharmaceutical outcomes and their associated impact on patients' health-related quality of life (HRQOL) have become major issues in the assessment of pharmaceutical technology. Clearly, prescription drugs have an impact on patients that extends beyond traditional indicators of clinical efficacy and safety, and HRQOL assessment has evolved as a measurement and research paradigm to quantify these benefits or utilities.

HRQOL assessment is occurring worldwide. There is a general consensus that HRQOL assessments of prescription drug therapy are desirable and necessary. A trend is evident to support the recognition of HRQOL outcomes as a valid criterion in the drug approval process and in the context of rational drug prescribing. There remain, however, significant issues to be resolved before HRQOL assessments become universally accepted. As a caveat, much of the literature on HRQOL is concerned with measurement issues: the validity and reliability of general or disease-specific HRQOL instruments. This paper does not focus on opinions of the appropriateness of specific instruments. It focuses instead on general issues, with a concluding note on their implications for pharmacy education.

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HEALTH-RELATED QUALITY OF LIFE DEFINED

HRQOL is a subset of a broader concept known as quality of life (QOL). Briefly, QOL is a global concept that is a function of a variety of factors and their interrelationships: income, health, education, environment, culture, and others. An individual's QOL is a multidimensional concept that transcends explanation by the presence of any one variable and, in a measurement context, is not explained adequately by changes in the value of any particular variable.

As a subset of QOL, HRQOL is defined as the relationship among a patient's health status, socioeconomic background, the specific disease, existing therapeutic interventions and their associated outcomes, and the patient's and physician's perceptions and values. HRQOL is complex and difficult to operationalize and measure.

Due to the intricacy of the theoretical framework, many issues remain unresolved, preventing consensus on a general definition for HRQOL, its operationalization, and its uniform measurement. Recently, Pathak responded to the lack of movement toward a universally accepted definition by offering the following:

> . . . health-related quality of life (HRQOL) can be defined as a comparative judgment based on a point-in-time assessment of an individual's present health state relative to that individual's reference health state(s). (1)

Moreover, he recommends that, at minimum, physical functional status and physiological status should be included in each HRQOL study. He also notes that HRQOL is intertemporal and comparative. Implicit in the latter is the assumption that HRQOL research is conducted in either randomized clinical trials or, at least, in quasi-experimental, prospective clinical studies.

Both patients and physicians have legitimate roles in defining and quantifying changes in HRQOL associated with drug therapy. Smith has commented that each party's value system leads to different interpretations of HRQOL outcomes. Patients' perceptions are largely emotional and highly personalized, whereas physicians' are more empirically-based, employing objective responses and expectations (2). Regardless, the primary determinant is that patients must perceive value or utility in a specific prescription drug

therapy to receive functional benefit. Hence, there is a hypothetical link between patients' perceptions of their HRQOL status and compliance with prescribed regimens.

Patients' and physicians' assessments are influenced by the characteristics of the specific morbidity, including expectations regarding the disease's progression and the projected outcomes of alternative therapies (including nondrug therapies). Some diseases will not have meaningful HRQOL outcomes because the clinical outcome of the disorder is self-limiting and nonepisodic. Conversely, acute disorders (e.g., migraine), which are debilitating to the patient and episodic, will have meaningful HRQOL effects associated with their treatment.

Chronic diseases for which only palliative therapies are available are generally thought to be more relevant than acute conditions for assessing HRQOL outcomes. Regarding prescription drug therapy and chronic diseases, the physician's intentions are to manage symptoms; to prevent or lessen the occurrence of complications; and/or to enable the patient to resume activities of daily living related to work, social life, and leisure. In the cases of terminal and life-threatening illnesses, the expressed intent is often to lift the burden of the patient's primary care giver.

Smith has provided a cogent summary of pharmaceutical outcomes for which HRQOL assessment would be appropriate and useful (2). Paraphrasing Smith, most instances involve situations where the traditional measures of therapeutic outcomes are inadequate or inappropriate indicators of clinical efficacy. In effect, HRQOL instruments and scales are an epexegesis to physiological and terminal end-point measures. A more cynical viewpoint would argue that HRQOL is a gimmick used by pharmaceutical marketers to differentiate marginal products. As noted, there are disease-specific situations (e.g., cancer, AIDS) where the prognosis is poor and the patient's comfort is as important as survival.

THE USES OF HEALTH-RELATED QUALITY OF LIFE RESEARCH

Pharmaceutical manufacturers sponsor extramurally conducted HRQOL assessments of prescription drug products for at least some, if not all, of the following applications:

Pharmaceutical Marketing

- Product differentiation and positioning
- Price justification
- Formulary decision-making support
- Product planning

Regulatory and Public Policy Issues Management

- Price/reimbursement negotiations
- Marketing approval for new indications
- Product line extensions (reimbursement/coverage) (3).

Szeinbach and colleagues studied the use of HRQOL and cost-effectiveness themes in pharmaceutical advertising in clinical and professional journals (4). They noted an increasing frequency of such themes in the years 1980, 1984, and 1988. Moreover, they reported a particularly strong trend in the frequency that HRQOL was used as a theme in journal advertising to physicians, although frequency also increased in journals directed primarily to pharmacists.

From a marketing perspective, the use of HRQOL is relatively straightforward: a product with a promotional claim for improving a patient's HRQOL has a clear positioning advantage over products without this claim. In effect, this information can be used to differentiate a product in the prescriber's mind from other products that are essentially equal in the traditional measures of safety and efficacy. It should be pointed out, however, that a general HRQOL indication in the approved product labeling is not likely to be attained from the Food and Drug Administration (FDA), either now or in the near future. Hence, the FDA's regulatory control over HRQOL is vested in the agency's mandate to monitor and ensure fairness and truth in advertising in promotional claims. Standards for conducting or evaluating HRQOL studies have not been issued; rather, the FDA currently relies on the sponsor's compliance with the state of the art in HRQOL research.

There exists a widely accepted hypothesis (untested) that essentially states that HRQOL may be of more importance to physicians

than to administrators of public and private prescription drug payment programs. Flowing from the acceptance of this hypothesis is the belief that unless HRQOL can be linked to cost-effectiveness comparisons, it will be of finite value in reimbursement, pricing, and coverage (formulary) decisions. Some researchers have proposed that this linkage occur through utility cost analysis (UCA). Briefly, UCA measures the patient's incremental gain in HRQOL via construction of a utility function (the numerator) compared to incremental costs associated with the drug's utilization (the denominator). Work in this area is preliminary but encouraging.

Conventional wisdom also suggests that HRQOL research can be used to obtain additional indications and reimbursement for those indications, notably in selected European countries. Since this strategy is a company's competitive practice, it is difficult to obtain verification, although anecdotal evidence suggests this is the case. It has also been reported that HRQOL has served as the basis for securing reimbursement for certain product line extensions. I believe there is a trend supporting the use of HRQOL in regulatory decision making, although codification of the standards by which the research is conducted is lacking and, hence, not transparent. I also believe sufficient information exists, albeit anecdotal, that European regulators are somewhat more receptive than U.S. regulators to considering HRQOL information in reimbursement and pricing decisions.

MEASUREMENT ISSUES

Instruments or scales measure HRQOL by asking a series of questions related to its conceptual framework: general perceptions of health status, general well-being, functional status, social interactions, and mental status. As expected, HRQOL instruments and scales may be either self-administered or conducted via a personal interview. Frequently, the clinician's or primary care giver's perceptions of the patient's HRQOL are measured.

HRQOL instruments and scales can be developed for general (i.e., healthy) populations or for patient populations with a specific disease. There is a cultural bias associated with instruments, and

cross-cultural validation studies are becoming commonplace. Regardless, the instruments and scales must be subjected to established analytic procedures for scientific validity and reliability. The literature is replete with studies reporting the developmental process of a number of instruments and scales for general and disease-specific populations.

One consensus emerging among HRQOL researchers is that both disease-specific and general instruments and scales should comprise a HRQOL assessment. There is somewhat of a countertrend in the regulatory community, notably Ontario, Canada, which specifically excludes the use of disease-specific instruments under the draft guidelines for the economic evaluation of pharmaceuticals. This position was based on the decision that drug products were to be ranked, and rankings based on disease-specific HRQOL instruments and scales were not warranted. Australia's guidelines essentially discourage the provision of HRQOL information unless the data are linked to economic outcomes. Obviously, some resolution of this discrepancy must occur.

A BRIEF SUMMARY OF MAJOR INSTRUMENTS AND SCALES

An exhaustive presentation and discussion of HRQOL instruments and scales is far beyond the scope of this paper. Instead, the following list is provided to mention a few major HRQOL instruments used worldwide in the assessment of pharmaceuticals. In general, they are well-validated and have been replicated in a number of major languages, disease states, and comparative drug trials and studies (although none was developed for drug trials per se).

- *SF-36*–Measures ability to function in several areas (physical, social, and role), assesses well-being (pain, mental health, etc.) and general health.
- *Quality of Well-Being (QWB)*–Measures life years gained from therapy adjusted for quality gained/lost, physical and social functioning, and symptoms/problems.

- *Sickness Impact Profile (SIP)*–Measures activities of daily living: housekeeping, bathing, rest and sleep, eating, and social interaction.
- *Nottingham Health Profile*–Measures physical activities, social interaction, sleep, amount of energy, and emotional status.

These scales have been continuously refined by the originators and their colleagues as new findings of replication in different populations and subgroups modify original conclusions.

FUTURE PROSPECTS

HRQOL assessments of pharmaceutical alternatives should continue to proliferate during this decade. The incorporation of HRQOL research within Phase II and III development is becoming routine. Moreover, as standards evolve, HRQOL information will likely become increasingly acceptable to regulators as a criterion for marketing approval. As HRQOL data are linked to economic indicators, regulators may well allow HRQOL's role in reimbursement and coverage decisions to grow.

Each of these potential scenarios should be tempered by the abundance of noise in the literature and the number of serious methodological issues that await resolution. Moreover, the degree to which HRQOL information should be considered in relation to clinical efficacy and safety is a research question that is still unexplored. Finally, substantive research should be conducted on the believability/credibility of HRQOL information by clinicians and other decision makers. These are by no means trivial issues, and an ambitious research agenda for both methodological development and policy research will be necessary.

IMPLICATIONS FOR PHARMACY EDUCATION

To a great extent, the theoretical framework for HRQOL has evolved from the academic psychology and sociology communities.

Methodology development has, in turn, emanated from these communities and the applied health services research community, involving collegial links between clinicians and theorists and applied behavioral scientists. Given the attractiveness of the randomized clinical trial design for comparative drug evaluations and HRQOL assessments, this partnership of clinicians and applied researchers has been a natural evolution.

I am personally concerned that the field of HRQOL, with the notable exception of a small number of academic and industry-based researchers, is evolving without major contributions from the pharmacy community. The general observation about the lack of basic or applied research from pharmacy researchers is perhaps premature, but it is of significance in the long term for both education and practice.

If pharmacists are to assume responsibility for ensuring rational drug use, it follows that they must understand HRQOL concepts and applications. Juergens and colleagues have made observations about the lack of curriculum time devoted to providing training in economic analyses of pharmaceuticals. If their conclusions are correct and generalizable to HRQOL, then our present cohort of pharmacy students is not receiving sufficient training to be either end users or producers of this information (5). Competence in HRQOL theory and methods cannot be obtained experientially during residency/clerkship experiences. Competency is probably attainable only during graduate education, which would necessitate the formal pursuit of a minor field in sociology or psychology. Given the dearth of undergraduate pharmacy students in M.S./Ph.D. programs, I am not optimistic about remedying the shortage of pharmacy researchers involved in HRQOL research.

Regardless of the lack of input from pharmacy, research in HRQOL outcomes of prescription drugs will continue. Moreover, research into the utility of HRQOL information will be needed to determine its credibility and proper perspective in rational decision making. These are relatively unexplored areas of inquiry that can be and, in my opinion, should be explored by the academic pharmacy community.

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