Diuretic induced changes in symptoms and quality of life

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Quality of life merits increasing attention as a means of evaluating the impact of drug treatment on patients during long-term treatment for a variety of clinical conditions. Quality of life is an abstract concept and as such no single variable is adequate to fully describe it. Quality of life may be considered a variable of multiple dimensions encompassing a range of human experiences. It describes important aspects of physical, social, and emotional health that are important to patients. As no single variable can fully evaluate quality of life, it is usually assessed in terms of individual components that may include symptomatic and psychological well being, general level of activity, aspects of intellectual and cognitive function, and general satisfaction with life. These individual components that contribute to quality of life can be individually assessed and from them a composite score may be derived that allows an overall assessment of the impact of treatment on quality of life to be computed. In many cases this will yield numerical data that may be tested statistically; the relevance of such measures to the clinical condition and the clinical importance of the findings may be difficult to interpret.

In general questionnaires are used to collect information for quality of life analyses and these are often termed “instruments”. These instruments have to be validated, that is to say they must be shown to provide reliable answers to the questions asked. In general the questionnaires should be clearly written and simple to administer and interpret. They should also be sensitive to small changes in the patient’s condition and be capable of detecting subtle influences of drug treatment.

A number of problems can be anticipated with the information gathering process for quality of life questionnaires. It is uncertain whether it is best to use a self administered questionnaire or trained interviewers. The training for interviewers, if these are used, must be detailed and specific. Also the interviewers should have specific expertise in the particular questionnaire used. It is recognised that the use of an interviewer may indeed produce misleading results. In one study with mainly female interviewers, impotence was reported far less commonly with the direct interviewer rated method than with the patient self assessment questionnaire.

It is recognised that bias may be introduced by the perspective of the interviewer. For example, the study by Jachuck et al used a quality of life impairment scale to assess the impact of hypotensive drugs in essential hypertension. The quality of life issue, during the chronic treatment of 75 controlled hypertensive patients, was assessed by a scale with excellent validity and high internal reliability. Compared with the physicians’ view of 100% improvement, patients or their close companions showed a considerable discrepancy from this view of the impact of treatment on quality of life variables (fig 1). Thus unlike the physicians’ view of universal benefit, only 48% of the patients considered themselves improved by treatment and 8% were worse. The questionnaires returned by relatives suggested that 25% had had mild adverse effects, 45% moderate, and 30% severe. These deteriorations were attributed to undue preoccupation with sickness, decline in energy, general, and sexual activity, and irritability. Thus the deterioration in quality of life found was not evident to the doctor; however the data suggested that from a patient’s or relatives’ viewpoint, the negative impact of treatment on quality of life created problems in social, marital, and occupational readjustment.

The use of self rated assessments may exclude those with poor literacy. The questionnaires may be given in a clinic or laboratory situation under time constraints that may adversely affect their completion; if the patient is allowed to take the questionnaire home then other family members may influence the responses.

A well designed quality of life instrument should look at the acute and long-term

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**Figure 1** Effect of antihypertensive treatment on quality of life; difference in perceived outcome between physician, patient, and relative. Graph plotted with data from reference 4.
influence of treatments in a large number of patients who have received treatment for a reasonable period of time. It is important to emphasise that a questionnaire that is appropriate for one clinical situation may fail or be inappropriate in a different condition. Thus a valid and specific instrument in essential hypertension may be not translatable to another clinical situation such as angina pectoris or chest pain and its impact on activity level may not be assessed. The conclusions about the impact of a particular drug on quality of life may also be specific to a particular clinical situation and not be universal for that treatment. Thus for example, if one looks at the effects of diuretics in an asymptomatic condition such as essential hypertension then adverse effects such as gout and impotence may rate highly in terms of negative impact on quality of life. In chronic heart failure, however, a dramatic improvement in dyspnoea, reduced frequency of admissions to hospital, and improved exercise capacity may lead to a contrary conclusion, a positive outcome of diuretic actions on quality of life. One can also envisage that use of a β blocker drug for essential hypertension may result in side effects being frequently reported, such as cold peripheries and tiredness (perhaps resulting in a reduced exercise capacity or cold intolerance) and therefore have a negative impact on quality of life. In patients whose ischemic heart disease results in angina, the drug induced reduction in frequency of angina and increased exercise capacity may result in a much higher threshold for reporting these symptoms, due to the perceived improvements in symptoms. Therefore valid instruments may not be readily translatable from one clinical condition to another, and the conclusions from one clinical area may be irrelevant to a different therapeutic area.

In conclusion, study design suggests that a large sample size should be interrogated over a reasonable period with a validated questionnaire or instrument that is appropriate for that specific condition. Caution should be the watchword when extrapolating from one clinical condition to another even within the same drug category.

**Overview of impact of diuretics on quality of life in hypertensive patients**

After the paper by Croog et al there has been a gradual increase in the development of instruments to assess the impact of drugs on quality of life to allow the risk benefit ratio to be more fully assessed during chronic treatment. The impact of drug treatment in a variety of anti-hypertensive trials was analysed by van Hoof et al. Quality of life data from six studies with indapamide was reviewed. These were open studies without a control group; the quality of life data were based on self administered questionnaires with modifications of the techniques of Croog et al or Bulpitt and Dollery. Perceptual measurements were also made with a visual analogue scale.

The lack of control groups in these studies means that the improvement in most of the variables assessed might well have been due to withdrawal of previous treatments, the non-specific effect of inclusion in a clinical trial, or to the hypotensive effect of indapamide. The sensitivity of the studies to detect particular effects was not described and a large number of commonly anticipated side effects of diuretics such as gout, lethargy, muscle cramps, constipation, and impotence were absent from these studies. Thus although there was a reasonable database on quality of life for indapamide, the lack of a control group minimised the value of these data.

The Medical Research Council mild hypertension study did not provide specific data on quality of life although it reported the presence of subjective and metabolic side effects. The cumulative withdrawal of adverse reactions in men was highest in the diuretic group and lower in the β blocker and placebo groups (fig 2). In women the picture was slightly different. Compared with placebo there was a significant increase in impaired glucose tolerance, constipation, lethargy, nausea, dizziness, headaches, and gout. The cumulative withdrawal rate for adverse reactions in women was highest in the β blocker group.

The European Working Party study on high blood pressure in the elderly reported questionnaire data. There was little evidence of the impact of diuretic treatment on quality of life. The Australian trial on mild hypertension reported use of a questionnaire modified from Bulpitt and Dollery. Sleepiness and self assessed depression were found to be more common in the actively treated group after age and sex adjustment of the data. Active treatment could have consisted of either chlorothiazide (up to 1 g daily), propranolol (up to 320 mg), methyldopa (up to 2 g), or a combination.

The hypertension detection and follow up programme looked at two methods of treatment, regular care where the patients were mainly followed up in their routine care systems, or stepped care where the patients were

![Figure 2](http://heart.bmj.com/content/72/suppl/S57/images/figure2)

**Figure 2** Reported adverse reaction rate in men and women in MRC trial of mild hypertension. Graph plotted with data from reference 8.
more closely followed up in specialist clinics. Long-term surveillance data indicated that chlorthalidone caused treatment to end due to side effects less commonly than did other drugs (diuretics chlorthalidone 5%, reserpine 9-9%, methyldopa 9%, hydralazine 7%, and guanethidine 7%).

Van Hoof et al concluded that although indapamide improved quality of life in most variables measured, in five studies this was in sharp contrast with the results obtained with other diuretics in the main studies reported subsequently. The limited controlled data on quality of life with diuretics would lead one to question whether, on the available evidence, a reliable conclusion about the impact of diuretics on the quality of life could be drawn.

The treatment of mild hypertension study (TOMHS) looked at optimal treatment of patients with mild hypertension comparing six first line treatments including placebo, diuretic (chlorthalidone), β blocker (acebutolol), α1 antagonist (doxazosin), calcium antagonist (amlodipine), or angiotensin converting enzyme (ACE) inhibitor (enalapril). Blood pressure control with any of the active treatment regimens was better than with nutritional hygienic advice alone. Data on seven indices of quality of life were reported with higher levels corresponding to improved quality of life. At entry the average levels for most of the scales were close to the upper limit of the scale. Most indices of quality of life after 12 months of follow up were improved but the energy fatigue and general functioning indices showed smaller average increases for participants given doxazosin than for those given acebutolol or chlorthalidone. General functioning indices of participants given acebutolol and chlorthalidone also showed significantly greater improvement than those given doxazosin or placebo. The overall tests that combined the seven quality of life indices showed greater improvement in quality of life for participants given a β blocker (acebutolol) or diuretic (chlorthalidone) than for those given placebo.

A meta-analysis of the impact of quality of life in hypertension studies was attempted by Beto and Bansal. All studies that fulfilled certain criteria such as patients who acted as their own control and that used blind and randomised trials were included. Change in the study was measured by self or interviewer assisted evaluation, standardised psychomotor or cognitive tests, or sleep laboratory observations. Between 1970 and 1990 nine published trials of 27 population groups (n = 1620) identified six pharmacological groups that met the criteria. These were analysed for five quality of life variables: sexual function, sleep, psychomotor function, general well being, and mood. With the meta-analysis technique of Hedges and Olkin a size of effect was computed for each study (by dividing the mean change between baseline and treatment by the standard deviation). The standard deviation adjustment in the denominator of the size of effect formula allowed studies with different measurement scales to be compared and combined. Sizes of effect and 95% confidence intervals (95% CIs) for each construct group were computed. When the CI excludes zero, improvement (<0) or deterioration (>0) with treatment can be concluded. With Cohen's definition a small effect in mathematical terms is <0-2, a medium effect 0-2-0-5, and a large effect size ≥0-8. Overall there were small positive effects seen for sleep, psychomotor function, general wellbeing, and mood, but no effect on average was found for sexual function. None of the drug groups had a clearly superior effect but a more frequent positive effect was seen with ACE inhibitors and β blockers (fig 3). The narrower demographics and small sample size for diuretics and calcium channel blockers may have biased the outcome; however, diuretics were accompanied by an appreciable positive effect for psychomotor function and mood (fig 4). Diuretics had no overall action on sexual function, sleep, or general level of well being.

The use of a mathematical method of combining the studies is useful and allows an estimate of effect to be computed. This does not, however, give information on the likely clinical relevance of the statistical finding. The use of only published studies may further bias outcome by underestimating the contribution.

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**Figure 3** Impact of six different drug groups on quality of life variables in essential hypertension. Graph plotted with data from reference 13.

**Figure 4** Impact of diuretic treatment on quality of life variables in essential hypertension. Graph plotted with data from reference 13.
from negative studies. The limited controlled data on diuretics in particular mean that one cannot have great confidence in the reliability of the effects described.

**Actions of diuretics in heart failure**

Although there are no data on the use of diuretics on quality of life variables in heart failure it seems not unreasonable to use symptoms as a surrogate for quality of life. Several studies have shown the overall improvement in symptoms after diuretic treatment (from one to three months) in patients with New York Heart Association (NYHA) class II to III heart failure.

Data on torasemide (fig 5) seem to suggest a direct relation between the severity of symptoms (judged by NYHA class) and response to diuretic treatment.3 This would suggest that the symptomatically worse patients are likely to gain the greatest improvement in quality of life from diuretic treatment. These findings are supported by those of Oversohl et al.17 Muzolimine treatment, in 36 patients with heart failure, gradually (three to four weeks) reduced systolic blood pressure and body weight. Concomitant with the average 2 kg reduction in body weight and the 11 mm Hg fall in systolic blood pressure, there were overall improvements in symptom scores. With a Framingham heart failure rating method, which summates symptoms (maximum severity score = 10) including oedema, paroxysmal nocturnal dyspnoea, neck vein distension, rales, cardiomegaly, hepatomegaly, and dyspnoea on exertion, the extent of the improvement is clearly documented (fig 6).

A controlled, double blind, clinical trial of the efficacy and tolerance of torasemide in contrast with frusemide in patients with congestive heart failure indicated that symptoms of peripheral oedema, dyspnoea, and central congestion shown by raised jugular venous pressure were dramatically reduced after torasemide (fig 7).16 Objective findings such as hepatomegaly and cardiomegaly were less amenable to treatment after four weeks with torasemide (either 5 or 10 mg daily). A similar symptomatic improvement was noted after frusemide treatment (40 mg). Dusing and Piesche who used torasemide for second line treatment of congestive heart failure found similar symptomatic and objective evidence of improvement after four weeks of treatment with 5 or 10 mg of torasemide daily in contrast with frusemide (40 mg daily).16 Thus symptomatic improvement after four weeks of sustained treatment with loop diuretics may possibly act as a surrogate of quality of life. These findings both for the conventional and newer loop diuretics support dramatic improvement in symptoms and quality of life variables.

One would anticipate that improvement in symptoms of such magnitude might be accompanied by objective evidence of improved exercise capacity during chronic treatment. It is well known that loop diuretics, particularly frusemide in acute coronary care situations are associated with an average fall in resting pulmonary wedge pressure from 20-7 to 15-7 mm Hg (-24%) and usually with an associated fall in cardiac output from 2-77 to 2-46 l/min/′ (-11%). These effects are usually maintained during chronic treatment.19 Several haemodynamic studies evaluated the immediate or sustained actions of torasemide on cardiac performance in severe heart failure. Fiehring and Achhammer compared intravenous torasemide (10 mg) with frusemide (20 mg) at rest and during bicycle ergometry in a controlled double blind and randomised trial of chronic heart failure.20 Eight patients received torasemide and seven frusemide. All pulmonary pressures were reduced on exercise and the pulmonary diastolic pressure was lower at the two highest levels of exercise with a concomitant fall in rate pressure product. Isbary et al compared 20 mg of intravenous torasemide with frusemide (20 mg) in a randomised double blind study of 21 patients with NYHA class III or IV acute heart failure.21 Onset of diuresis averaged eight minutes and there was a gradual, equivalent, and progressive fall in pulmonary wedge pressure over 24 hours (torasemide, 23-6 to 18-1 mm Hg (-23%); frusemide, 23-6 to 16-3 mm Hg (-31%). Cardiac index was unaltered on either treatment.

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Removed (20 mg) heart disease. Within ischaemic was severely impaired sure was pulmonary wedge failure. torasemide (20 mg) were namics 9 by one systemic the Hg: a with lower cardiac diuretics. Several studies have examined this symptom is that the relief of central pressures, and cardiac index was assessed after acute treatment. The pulmonary wedge pressure on chronic treatment was lower during exercise (20-3 to 14-6 mm Hg: 28%) and cardiac index was higher (5-9 to 6-7 l/min/m²: +14%). Interestingly the systemic arterial pressure during exercise was 9 mm Hg lower at the same workload after treatment. This indicates perhaps a decrease in systemic vasoconstriction. Eight of the 12 patients improved their symptom score by one NYHA class.

Thus there seems to be little doubt that at rest and during exercise acute doses of diuretics lower cardiac filling pressures, which may contribute to the relief of central congestion and relief of symptoms of dyspnoea. Undoubtedly of greater interest is the longer term actions of these drugs, their impact of symptoms, exercise capacity, and quality of life. Several studies have examined this question. The longer term (three weeks) actions of piretanide were investigated by Haerer et al. In 46 patients with NYHA class II or III heart failure 3 mg of piretanide produced an average weight loss of 1-6 kg (baseline 77 kg) body weight by three weeks. Echocardiographically there was an associated improvement in fractional shortening (+5.6%: baseline 25.9%) with a fall in cardiac volumes. The 26 patients studied at baseline after 6 mg of intravenous piretanide showed a fall in pulmonary wedge pressure from 20-2 to 11-9 mm Hg with a small concomitant reduction in cardiac index (3-2 to 3-0 l/min/m²). After three weeks treatment there was no attenuation of the haemodynamic actions of piretanide; exercise tolerance increased from 135 to 249 W (+84%). In contrast a control group showed no change in pulmonary wedge pressure (20-0 to 22-8 mm Hg). Radiographic heart volume decreased from 1012 ml to 936 ml (−7.5%). This well conducted study concluded that the acute actions of piretanide were similar to the described actions of frusemide; the improved echocardiographic measures of cardiac performance were probably secondary to altered loading conditions (preload). The actions were well maintained over at least one month of treatment; increased exercise capacity continued.

The haemodynamic actions of the potassium sparing agent amiloride were determined in a double blind placebo controlled crossover study of 11 patients with stable chronic heart failure. The actions of placebo or amiloride (5 or 10 mg) were compared over seven days when added to background treatment of digitalis and hydrochlorothiazide. Haemodynamic variables were measured at rest and at three levels of supine bicycle exercise. The main findings were noted for exercise haemodynamics; amiloride significantly reduced exercise pulmonary wedge pressure (28.6 to 22.1 mm Hg: −22.7%) with an augmented cardiac stroke index (+3%) and stroke work index (+12%). The improved cardiac function was most evident from the change in haemodynamic variables from rest to peak exercise; the increase in pulmonary wedge pressure (placebo/amiloride; +18.7/+13.7 mm Hg: P < 0.001) and left ventricular stroke work index (+15.0/+27.4 gm.m⁻²: P < 0.005) suggesting a much improved cardiac performance.

It would therefore be reasonable to conclude that the initial haemodynamic activity of diuretic treatment that favourably reduced central haemodynamic filling pressures is maintained during long-term treatment and that overall exercise cardiac output is usually augmented at a lower left ventricular filling pressure. This improved cardiac performance is usually accompanied by increased exercise capacity or duration. If symptoms may be used as a surrogate for quality of life, there seems to be a substantial short and medium term improvement; it would seem reasonable to conclude that the balance of probability suggests that long term diuretic treatment improves quality of life dramatically for patients with chronic heart failure.

7 Medical Research Council Working Party. MRC trial of...