

APPLICATIONS OF HRQOL ASSESSMENT FOR NEUROLOGIC CONDITIONS

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OVERVIEW

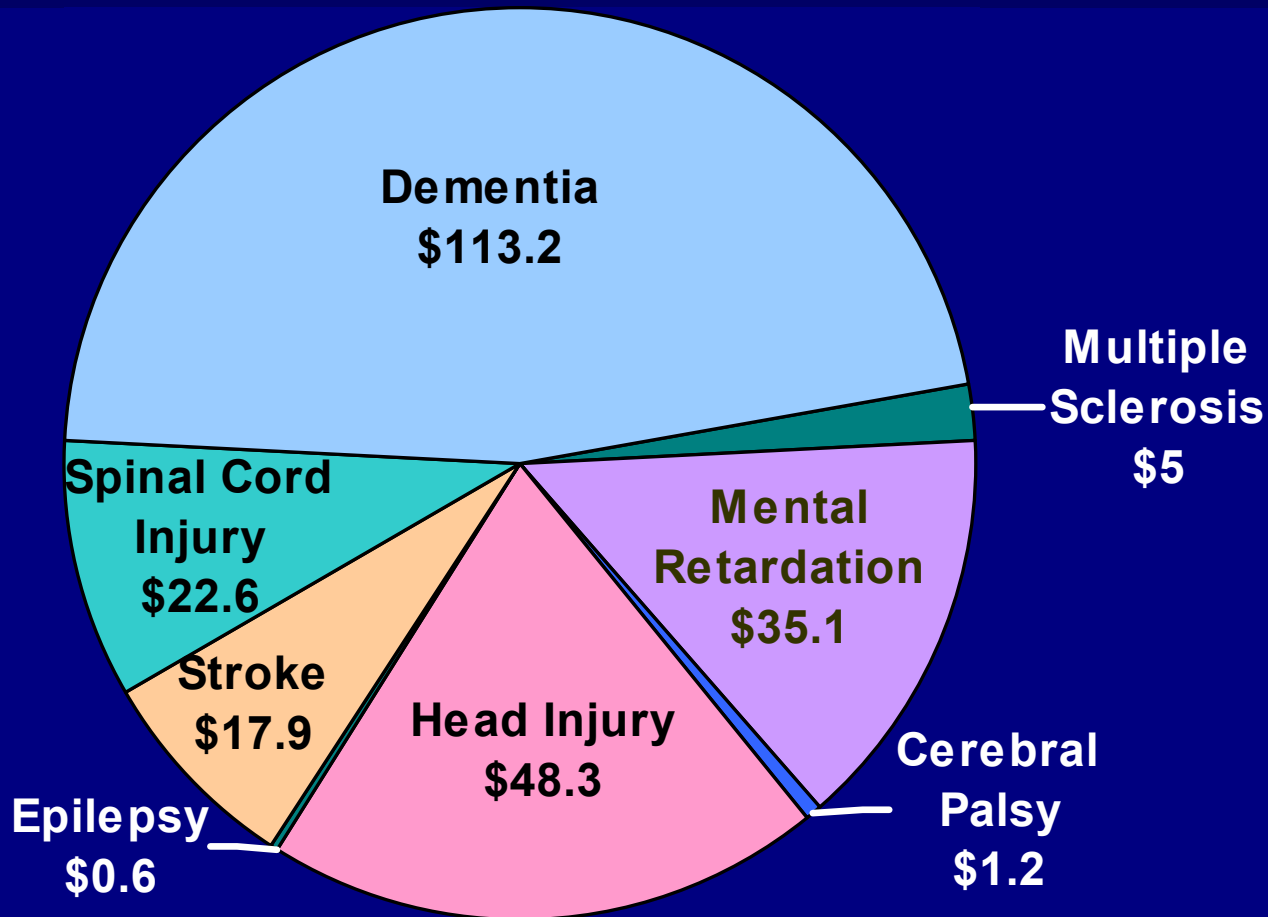
- I. “Burden” of neurologic disease
- II. Defining and special issues in measuring HRQOL for neurologic conditions
- III. Generic vs. disease-targeted HRQOL measures; examples of development for epilepsy and for peripheral neuropathy
- IV. Evidence for the value of disease-targeted HRQOL measures in neurology
- V. Evaluating meaningfulness of traditional clinical outcomes via application of HRQOL assessment

I. “Burden” of Neurologic Disease

Incidence and Prevalence of Various Neurologic Conditions

Condition	New cases/ 100,000/yr	Cases/ 100,000
Cerebrovascular	200	650
Seizures/Epilepsy	120	650
Peripheral neuropathy	100	
Dementia	50	250
Parkinsonism	20	200
Primary tumors	15	65
Spinal cord disorders	13	90
Trigeminal neuralgia	4	40
Multiple sclerosis	3	60
Motor neuron disease	1	6

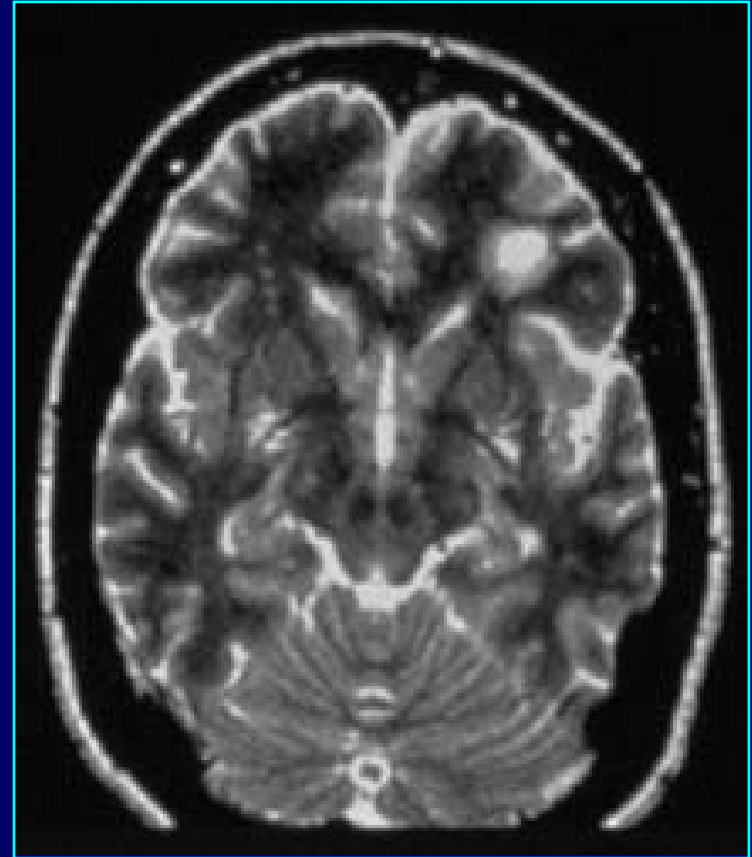
Cost (in Billions) of Neurologic Diseases of the Brain By Disease, in 1991 dollars



Includes direct and indirect costs; Source: Lewin-ICF

T2 Hyperintense Weighted Scans

- Traditional proton density/T2 scans
- Represent cumulative burden of disease
- Identification of heterogeneous lesions
 - “Footprint” of prior inflammatory event
 - Demyelination
 - Gliosis
 - Axonal loss



“Burden of Neurologic Disease”

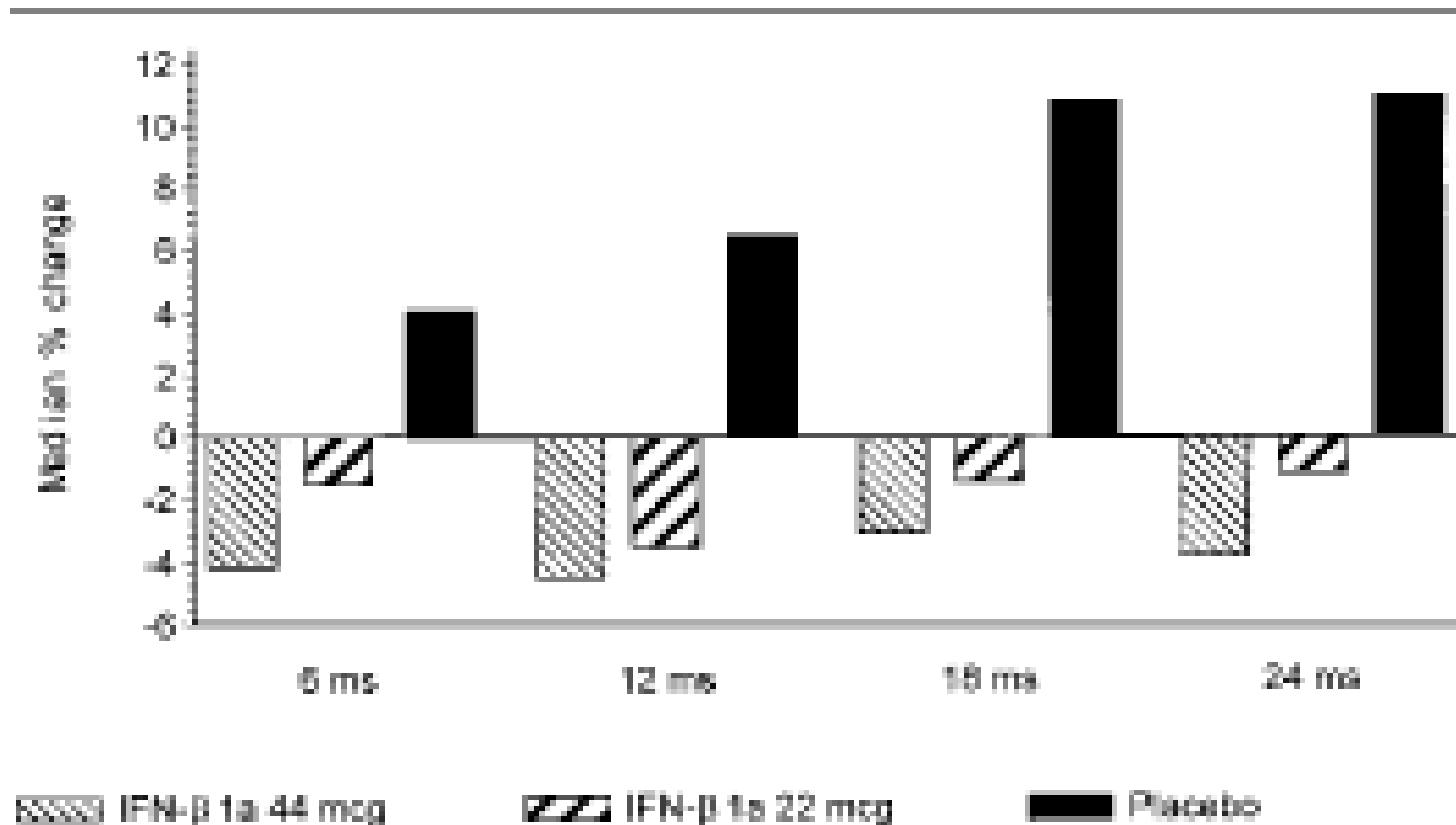


Fig 2. Burden of disease; median percentage change from baseline. IFN = interferon.

II. Defining and Special Issues in Measuring HRQOL for Neurologic Conditions

HEALTH OUTCOMES:

- **Mortality**
- **Disease/Symptoms/Status**
 - i.e. # of seizures per month, # of multiple sclerosis relapses per year, time to recurrent stroke
- **Health-related Quality of Life (HRQOL)**
 - i.e. Measures of functioning and well-being

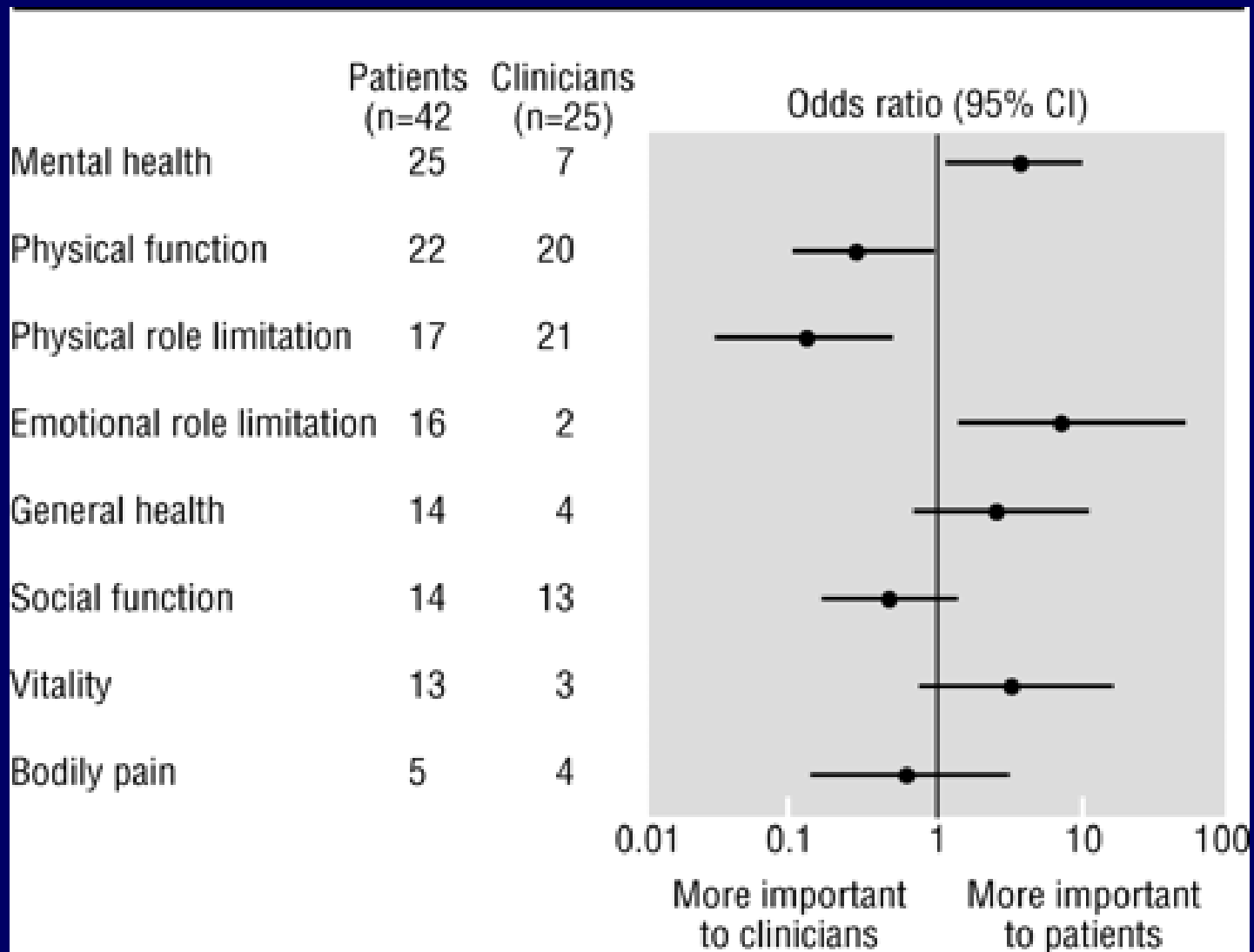
What is Health-Related Quality-of –Life (HRQOL)?

Perception of one's functioning and well-being based on multidimensional consideration of:

- Physical,
- Mental,
- Social, and
- General Health Status

Desired Characteristics of HRQOL Measures

- **Reliable and valid**
- **Comprehensive yet feasible to administer**
- **In some situations, may be desirable to have a disease-targeted component in addition to a generic core**
- **Self-report, where possible, for patient's perspective**



Frequency with which each of 8 domains of HRQOL in SF-36 were said to be among the three most important determinants of overall QOL by 42 patients with multiple sclerosis compared with frequency expected by 25 clinicians working in clinical neurosciences department (Rothwell et al, BMJ, 1997)

Special Issues in Assessing HRQOL for Neurologic Conditions

- **Considerable clinical heterogeneity**
- **Cognitive and/or language impairment**
- **Some conditions are characterized by episodic symptoms**
- **Traditional measures that have been used have considerable deficiencies in their psychometric characteristics**

Example: Expanded Disability Status Scale

- **Very commonly used outcome measure in multiple sclerosis trials**
- **Categories overlap and the same individual can be classified several ways depending on which criteria one uses**
- **Most studies have found mediocre interrater reliability**
- **Focus is on ambulation/mobility; other clinical manifestations of disease are not well-captured**

**III. Generic vs. Disease-
Targeted HRQOL
Measures; Examples
of Development for
Epilepsy and for
Peripheral Neuropathy**

Generic vs. Disease-Targeted HRQOL Measures

Generic:

Measure is relevant to individuals generally rather than specific to one condition; enables comparisons across diseases

Disease-targeted:

Measure is tailored to a particular disease; may enhance an instrument's ability to measure change in a particular population

Generic Item: Emotional Well-Being

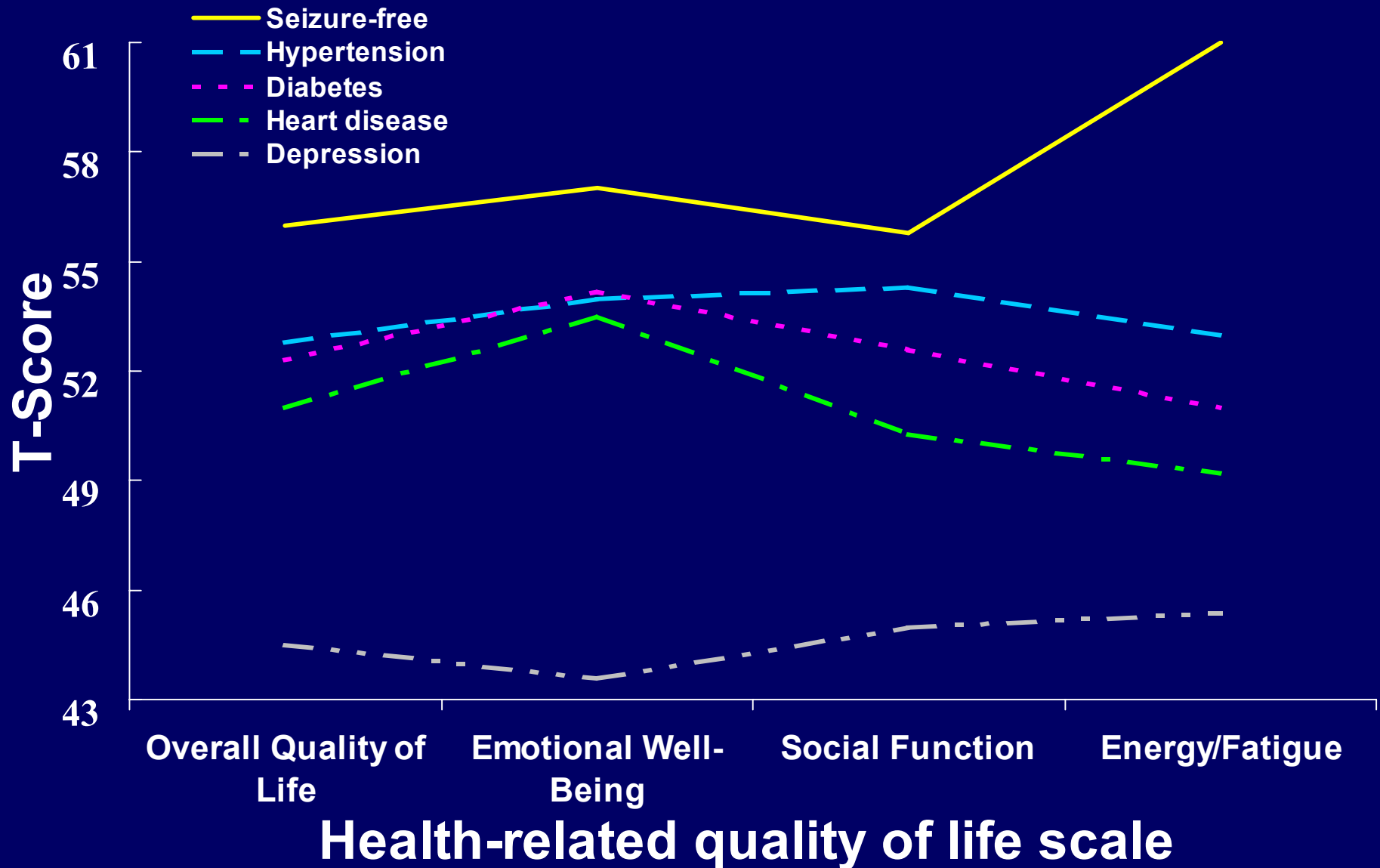
How much of the time during the past 4 weeks...

have you felt downhearted

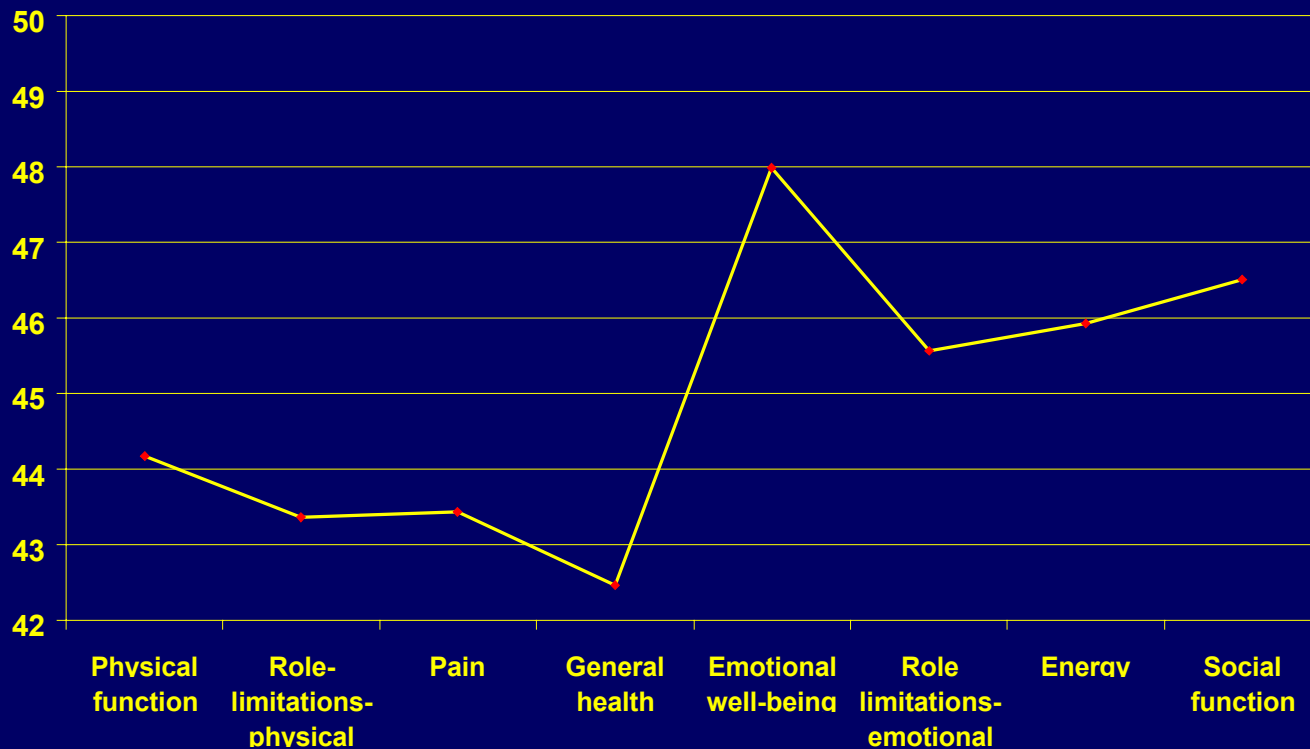
and blue?

1. All of the time
 2. Most of the time
 3. A good bit of the time
 4. Some of the time
 5. A little of the time
 6. None of the time
-

Seizure-Free Surgery Patients vs. Patients With Chronic Disease



T-scores of Peripheral Neuropathy Sample (N=80) Relative to General US Population



Disease-targeted Item

How much of the time during the past 4 weeks...

**have you worried about having
another seizure?**

1. All of the time
 2. Most of the time
 3. A good bit of the time
 4. Some of the time
 5. A little of the time
 6. None of the time
-

EXAMPLE:

**Development of an HRQOL
Measure to Evaluate
Outcomes of Surgical
Treatment of Epilepsy**

Rationale for Including HRQOL as an Outcome Measure

- Epilepsy is common
- Broad impact on HRQOL
- Seizures controlled in selected cases, but anecdotally, seizure control is not always accompanied by improved functioning
- Different definitions of seizure control
- Need valid measures to assess surgery outcome, overall impact

Desired Characteristics of HRQOL Measures

- **Reliable and valid**
- **Comprehensive yet feasible to administer**
- **In this situation, felt desirable to have a disease-targeted component in addition to a generic core**
- **Self-report, where possible, for patient's perspective**

Research Plan

Identify

- Relevant HRQOL areas
- Desired characteristics of measure

Assemble

- Group of Items
- Hypothesize placement in scales

Test

- Reliability and validity in patients

Content of SF-36 Health Survey

- **General health perceptions**
- **Energy/fatigue**
- **Social function**
- **Emotional well-being**
- **Role limitations – emotional**
- **Physical function**
- **Role limitations – physical**
- **Pain**
- **Change in health**

Epilepsy-Targeted Component

- **Cognitive function**
- **Role limitations due to memory problems**
- **Health perceptions (epilepsy-targeted)**
- **Overall quality of life**

ESI-55: Final Instrument Measures

11 HRQOL Dimensions

Scale	No. of Items
General	
Health perceptions	9
Energy/fatigue	4
Overall quality of life	2
Mental	
Emotional well-being	5
Cognitive function	6
Role limitations	
Emotional problems	5
Memory problems	5

ESI-55: Final Instrument (cont)

Scale	No. of Items
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Social

Social function	2
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Physical

Role limitations due to physical problems	5
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Physical function	10
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Pain	2
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Methods

Mailed questionnaire with cash payment

- ESI-55
- Profile of Mood States
- Age, gender, medication use
- Seizure occurrence over preceding 12 months

Response rate: 89%

Characteristics of Subjects

- Mean age: 34 years (range 18-66 yrs)
- 53% women
- Average time since evaluation: 5.6 years
- Surgery status %
 - Right TLE 38
 - Left TLE 35
 - Extratemporal 10
 - No surgery 17

Analysis Plan

Examine

- **Internal consistency reliability of scales in this sample**
- **Construct validity**
 - **Compare with POMS**
 - **Evaluate scale scores vs seizure control**

Internal Consistency Reliability

- **Cronbach's alpha ranged from 0.68 to 0.88**
- **All scales reliable for group comparisons**

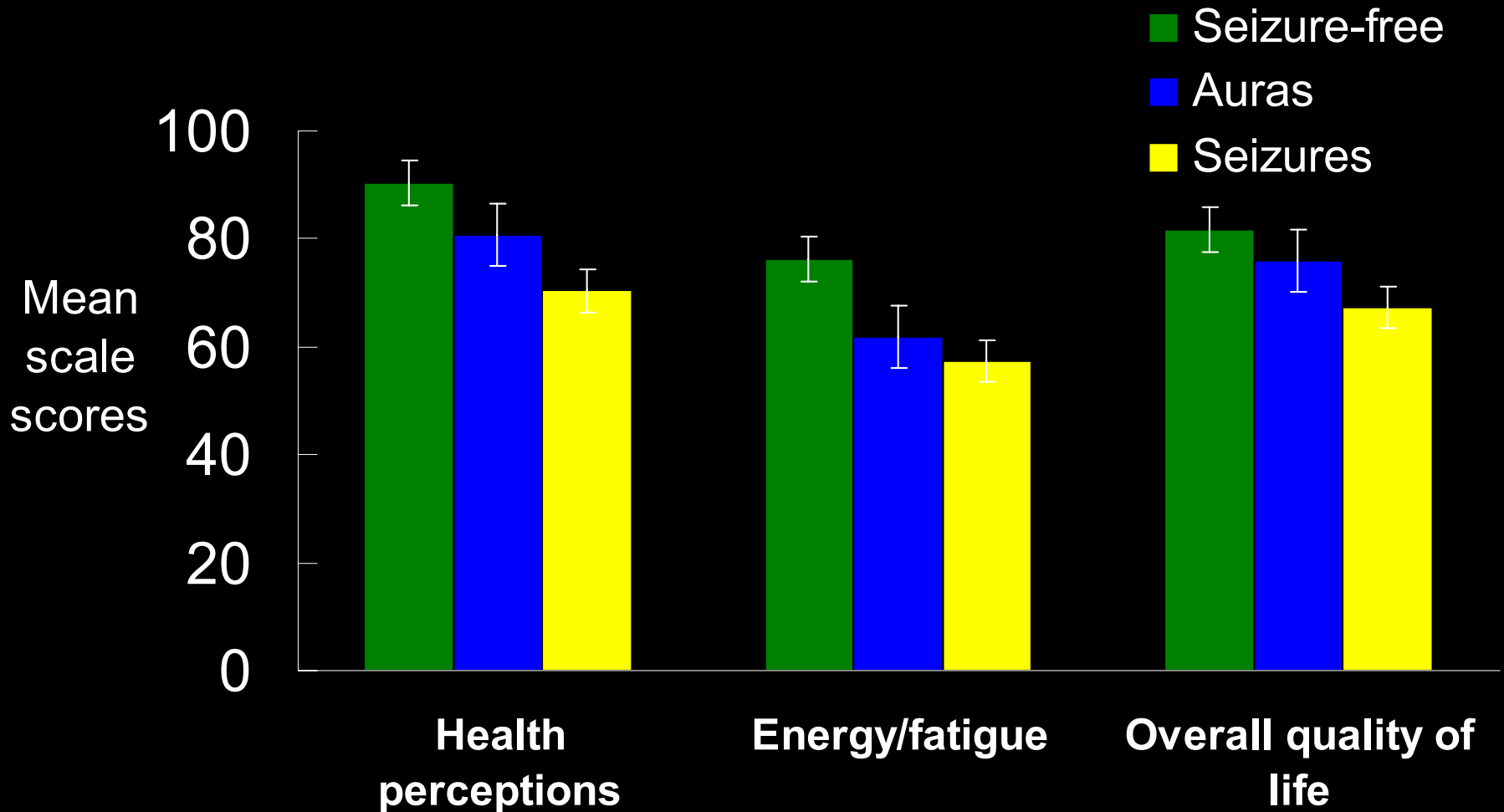
One Assessment of Construct Validity

ESI-55 Scales

POMS	Emotional well-being	Physical function
Depressed	-.68*	-.25*
Angry	-.67*	-.14
Cheerful	.57*	.19*

*Significant correlation ($p < 0.05$)

Assessment of Construct Validity: ESI-55 Scores by Seizure Control



Development of an HRQOL Measure for Peripheral Neuropathy

- To develop and evaluate a self-administered HRQOL measure for use as an outcome measure in peripheral neuropathy treatment trials**
- Peripheral neuropathies have a wide range of causes, with the commonality of damage to or degeneration of peripheral nerves; a very common cause in developed countries is diabetes**

Peripheral Neuropathy

- **The peripheral nervous system is composed of sensory fibers that communicate sensory information to the brain, like pain for example, and motor nerve fibers that send information to control muscles**
- **Peripheral neuropathy is damage or impairment of cells in the peripheral nervous system**

Potential Impacts of Peripheral Neuropathy on HRQOL

- **Range of clinical effects: weakness, pain, impaired sensation, and/or decreased autonomic function**
- **Anecdotally, potential HRQOL impacts include impairment of activities like bathing and dressing to more vigorous activities**
- **Other potential effects: anxiety, depression, low self-esteem, stigma**

Goals and Rationale

- **Goals:**
 - develop a measure that could be used for any chronic peripheral neuropathy
 - be able to compare HRQOL in neuropathy to that of other chronic conditions or to a general population
- We hypothesized that there would be important HRQOL areas not covered by generic measures, but literature review revealed sparse evidence

Methodologic Approach

- **Needed a methodologic approach to generate data to guide development of items in the disease-targeted component of the HRQOL measure**
- **Needed direct information from patients' perspective as to important areas of HRQOL not covered in generic instruments**

Focus Group Methodology

- Focus groups are designed to provide in-depth, fundamental information about experiences and perceptions in a “focused” area among people who share a common characteristics, such as peripheral neuropathy
- This methodology is useful for gaining an understanding of the essential ingredients of HRQOL for a targeted subgroup

Assembly and Conduct of Focus Groups

- **Conducted three focus groups of 22 adults (14 women and 8 men) with peripheral neuropathy**
- **Recruited from the practices of a general internist, an endocrinologist, and a neurologist, representing both academic and community practices in southern California**

Assembly and Conduct of Focus Groups (cont'd)

- **Semi-structured protocols were developed by study investigators as a focus group guide**
- **Audiotaped recordings were made**
- **Groups were run by the same, experienced moderator**

Characteristics of Focus Group Participants

- Two groups were people with diabetic neuropathy; another group had people with neuropathies of various etiologies, for example, Charcot Marie Tooth and paraprotein-related.
- Duration of neuropathy: 1 to 30 years
- Three participants used a wheelchair, three required a cane, and the remainder needed no assistance to walk

Focus Group Data Collection

- Information was elicited from the first two focus groups about:
 - daily activities as affected by neuropathy symptoms
 - feelings about neuropathy's effects on self-esteem and self-consciousness
 - impact of neuropathy on relationships
- Moderator's written summaries of the groups were reviewed by study investigators to identify content areas relevant to neuropathy

Findings from Focus Groups

- **Examples of neuropathy-targeted HRQOL topics identified from focus groups:**
 - **ambulation, balance, and fear of falling**
 - **ability to handle objects like change or utensils**
 - **numbness and hypersensitivity or pain in both upper and lower extremities**
 - **sleep disturbances**
 - **self-esteem**

Findings from Focus Groups

- **Participants in a third focus group completed a draft questionnaire containing questions developed by study investigators based on results of the previous focus groups, as well as items drawn from existing measures whose relevance was suggested by those focus groups**

Assembly of Field Test HRQOL Measure for Peripheral Neuropathy

- Based on the focus group data and on the available published literature**
- Chose SF-36 as generic core**
- Peripheral neuropathy-targeted component included items were created *de novo* or drawn from existing measures**

Content of Neuropathy- Targeted Field Test Items

- **Self-esteem**
- **Self-consciousness**
- **Optimism**
- **Stigma**
- **Control**
- **Social isolation**
- **Health distress**
- **Cognitive function**
- **Sleep**
- **Sexual function**

Content of Neuropathy- Targeted Field Test Items

Impact of neuropathy on:

- Daily activities**
- Work**
- Physical function**
- Pain**
- Energy**
- Sleep**
- Relationships**
- Social activities**
- Days of work or school missed in the prior month.**

Example Neuropathy- Targeted Items

- **Because of your peripheral neuropathy, how much difficulty have you had performing the following activities during the past 4 weeks:**
 - Working buttons, zippers, or laces?
 - Walking up a ramp?
 - Holding onto or using small objects such as keys, pens, or coins?
- **Because of your peripheral neuropathy, how much pain in your hands have you had during the past 4 weeks?**

Example Neuropathy- Targeted Items

- How TRUE or FALSE is each of the following statements for you?
 - I am embarrassed about how I look in public
 - I am comfortable in social situations
 - I avoid doing some things in public because of my peripheral neuropathy
 - I worry about falling in front of other people

Field Test Sample

- **80 adults (56 male, 24 female) enrolled in a multi-center, randomized trial of an experimental treatment for diabetic neuropathy**
- **Item placement into hypothesized scales; item analysis/reduction using multitrait scaling analysis**
- **Evaluation of reliability and construct validity**
- **Final instrument: 36 items of SF-36 and 61 neuropathy-targeted items**

IV. Evidence for the Value of Disease-targeted HRQOL Measures in Neurology

**Do Disease-Targeted HRQOL
Measures for Multiple Sclerosis
“Add Value” to HRQOL
Measurement in MS?**

SUBJECTS

- **227 consecutive patients at one university MS clinic**
- **170 (75%) completed both a mailed questionnaire and a phone interview**
- **mean age= 45 yrs; 72% female**
- **39% working for pay**
- **mean MS duration= 9.4 years**

HRQOL Measures: Generic

- **SF-36 (eight scales):**
 - General health perceptions
 - Energy/fatigue
 - Social function
 - Emotional well-being
 - Role limitations – emotional
 - Physical function
 - Role limitations – physical
 - Pain

HRQOL Measures: MS-Targeted

- **MS Activities of Daily Living Measure**
4 scales:
 - motor
 - communication
 - social activity
 - intimacy
- **Health distress scale from Medical Outcomes Study**

Two Criterion Variables for Analysis

1) overall MS symptom severity in prior year:

- none, mild, moderate, extreme

2) ambulation-related disability:

- walk unassisted, walk with assistance, wheelchair bound

Analyses

Forward stepwise linear regression analyses onto each criterion variable of

- 1) the 8 SF-36 scales, then**
- 2) the 8 SF-36 scales (required inclusion) + disease-targeted scales**

RESULTS: MS Symptom Severity

1) Scales entering stepwise regression (SF-36 only):

	<u>p-value</u>
Physical function	< 0.0001
Social function	0.02

Adj. $R^2 = 0.34$

RESULTS: MS Symptom Severity

2) Scales entering stepwise regression:

	<u>p-value</u>
SF-36 Phys. function	0.01
Health distress*	0.0004
Motor ADL*	< 0.0001

Adj. $R^2 = 0.44$ (↑) * = Disease-targeted

RESULTS: Ambulation Status

1) Scales entering stepwise regression (SF-36 only):

	<u>p-value</u>
Physical function	< 0.0001

Adj. R² = 0.51

RESULTS: Ambulation Status

2) Scales entering stepwise regression:

	<u>p-value</u>
SF-36 Phys function	< 0.0001
Motor ADL*	< 0.0001
Social ADL *	0.04

Adj. R² = 0.70 (↑)

* = Disease-targeted

**Do Disease-Targeted HRQOL
Measures for Epilepsy “Add
Value” to HRQOL
Measurement in Epilepsy?**

(Birbeck et al, 2000)

Responsiveness to Change

- **A measure of the degree to which an instrument is capable of detecting change over time**
- **Requires defining external criterion for clinically important change**
- **Several indices can be used to assess responsiveness, including effect size, AU-ROC, ANOVAs and others**

Responsiveness Index: Effect Size

- **Effect size: difference between 'changed' and 'unchanged' group divided by standard deviation at baseline**
- **Interpretation:**
 - **0.2** **small effect**
 - **0.5** **medium effect**
 - **0.8** **large effect**

Subjects

- RCT for add-on therapy of an AED vs placebo in adults with refractory epilepsy
- 142 subjects completed HRQOL measures at baseline and a 28-week follow-up
- Mean age 38.2 years (range 19-67)
- 48% male
- 85% Caucasian
- Complex partial \pm 2° generalization

HRQOL Measures Administered

- **Epilepsy-targeted measures:**
 - **QOLIE-31 Overall score**
 - **QOLIE-89 Overall, epilepsy-targeted, physical health, mental health**
- **Generic measures:**
 - **SF-36 Mental health, physical health**
 - **SF-12 Mental health, physical health**

Criterion Variable

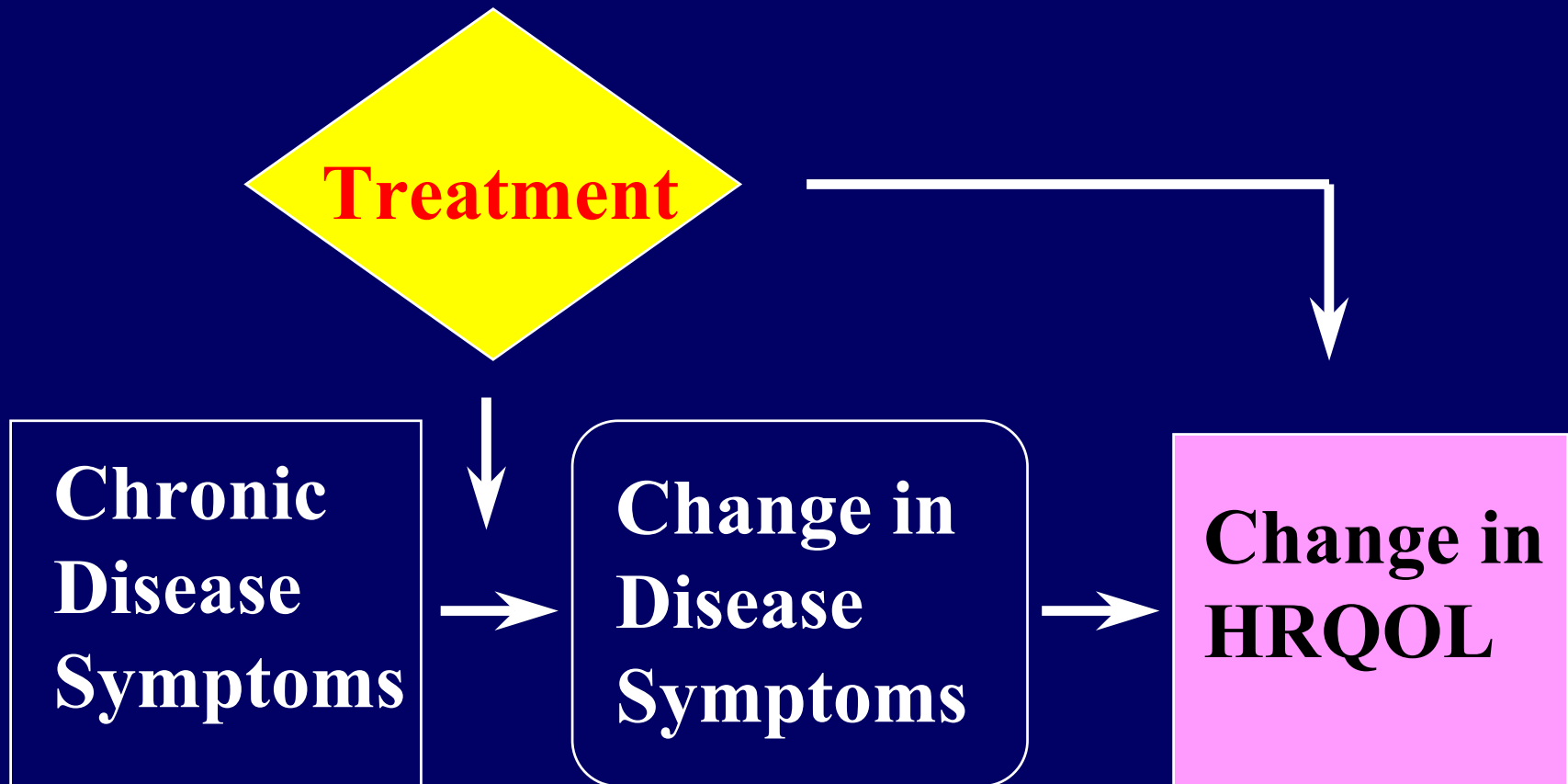
- **Two-category or greater improvement in patients' self-ratings of their overall condition from baseline to the 28-week follow-up = 'changed' (N=27)**
- **No difference from baseline to follow-up in the rating of overall condition = 'unchanged' (N=48)**

Results

Measure	Effect size	Interpretation
QOLIE-89 Epilepsy-Targeted	0.80	large
QOLIE-31 Overall	0.74	large
SF-36 Physical	0.30	medium
SF-36 Mental	0.41	medium
SF-12 Physical	0.17	small

**V. Evaluating the
Meaningfulness of
Traditional Clinical
Outcomes via
Application of HRQOL
Assessment**

Model of Relationship Between Disease Symptoms, Treatment, and HRQOL



VA Cooperative Comparative Study of Epilepsy Monotherapy

(Mattson et al, 1985)

- **10-center, double-blind, randomized trial**
- **Comparison of 4 antiepileptic drugs (AEDs) for partial and secondarily generalized tonic-clonic seizures**
- **N=622; 58% = no prior AED**
- **Followed for 1 to 6 years**
- **Primary end point: “length of time that the patient continued to take the randomly assigned drug”**
- **There was no difference across the 4 AEDs in mean or median seizure frequency**

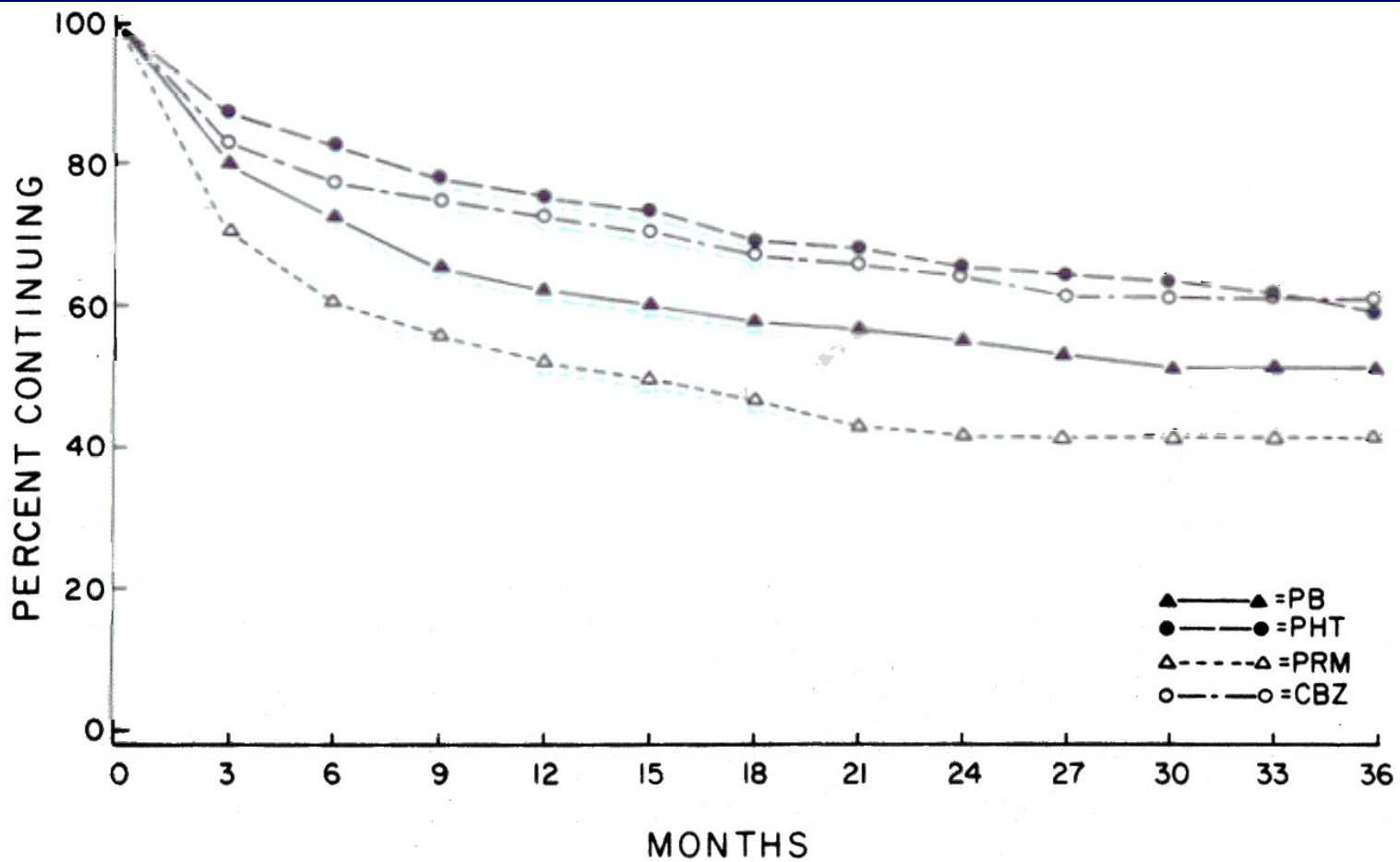


Figure 1. Cumulative Percentage of Patients Successfully Treated with Each Drug during 36 Months of Follow-up.

PB denotes phenobarbital, PHT phenytoin, PRM primidone, and CBZ carbamazepine. There were 275 patients at 12 months, 164 at 24 months, and 97 at 36 months.

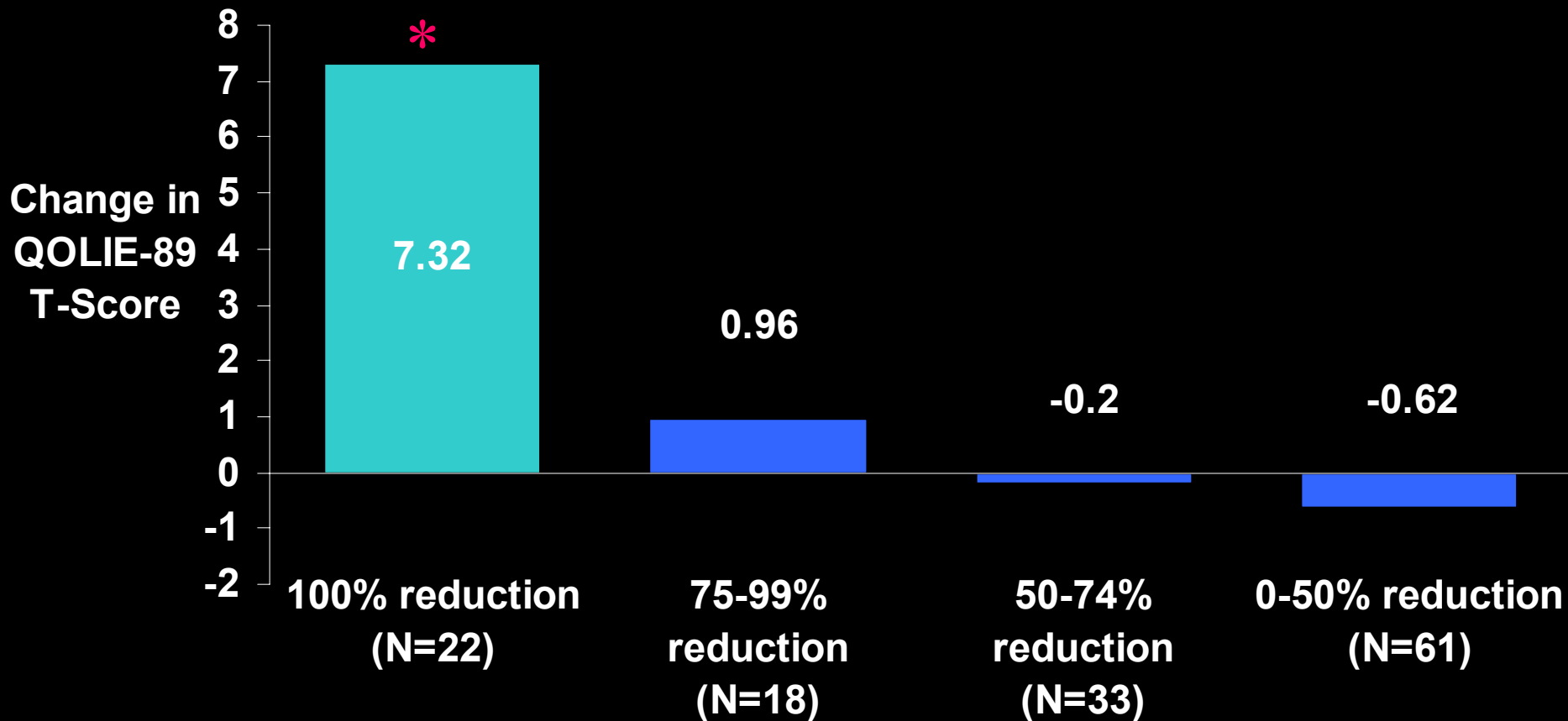
Epilepsy Treatment Outcomes

- **Outcomes of epilepsy treatment are often reported as a % reduction in seizures from before-to-after treatment, i.e., 90%, 75%, or 50% reduction**
- **Are these outcome categories meaningful?**

Subjects and Analysis

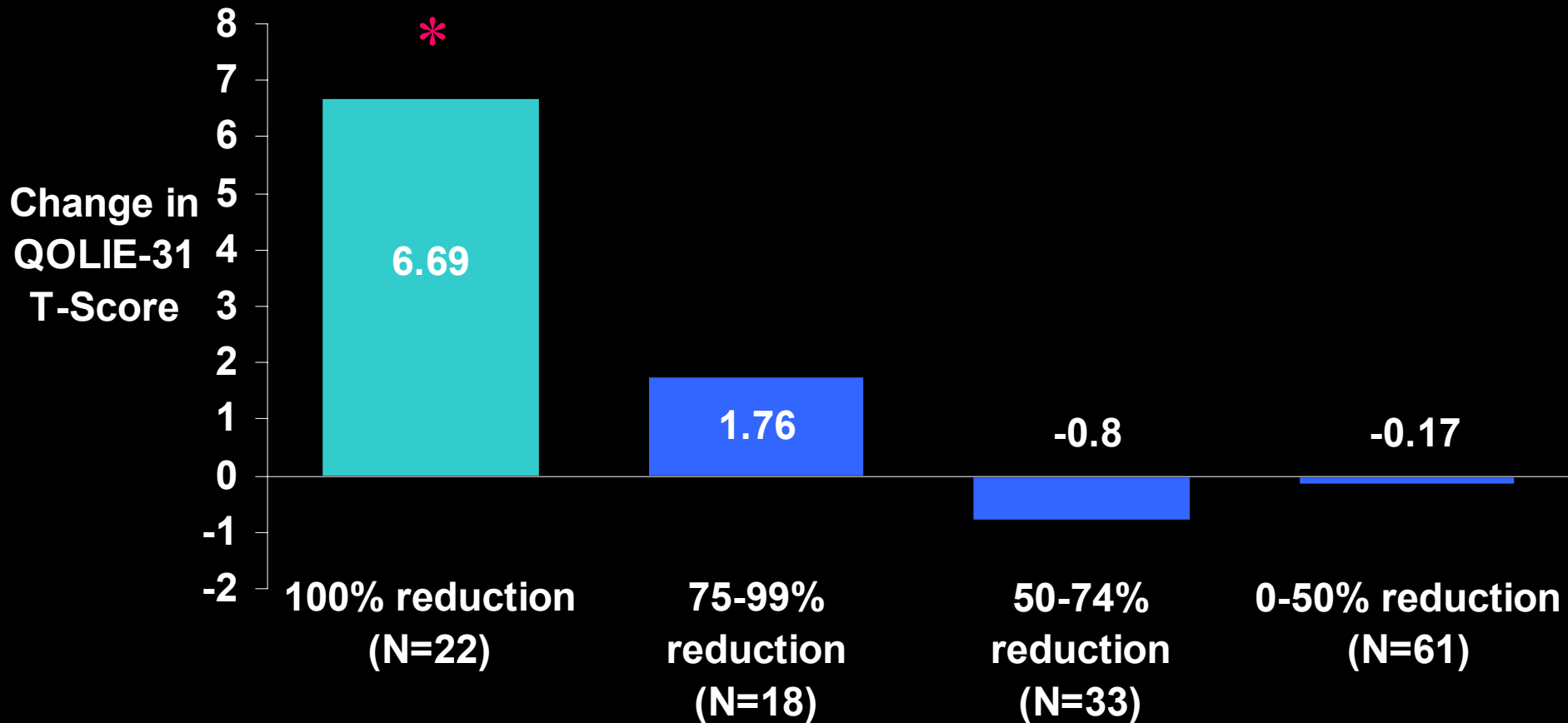
- RCT for add-on therapy of an AED vs placebo in adults with refractory epilepsy
- 142 subjects completed HRQOL measures at baseline and a 28-week follow-up
- In this analysis, subjects were classified by level of change in seizure frequency: 100%, 75-99%, 50-74% reductions, and 0-50% increase or decrease
- HRQOL was compared across groups

Mean change in QOLIE-89 T-score over 28 weeks by % change in seizure frequency



*F-value for ANOVA = 8.59 (p < 0.0001)

Mean change in QOLIE-31 T-score over 28 weeks by % change in seizure frequency



*F-value for ANOVA = 8.59 (p < 0.0001)

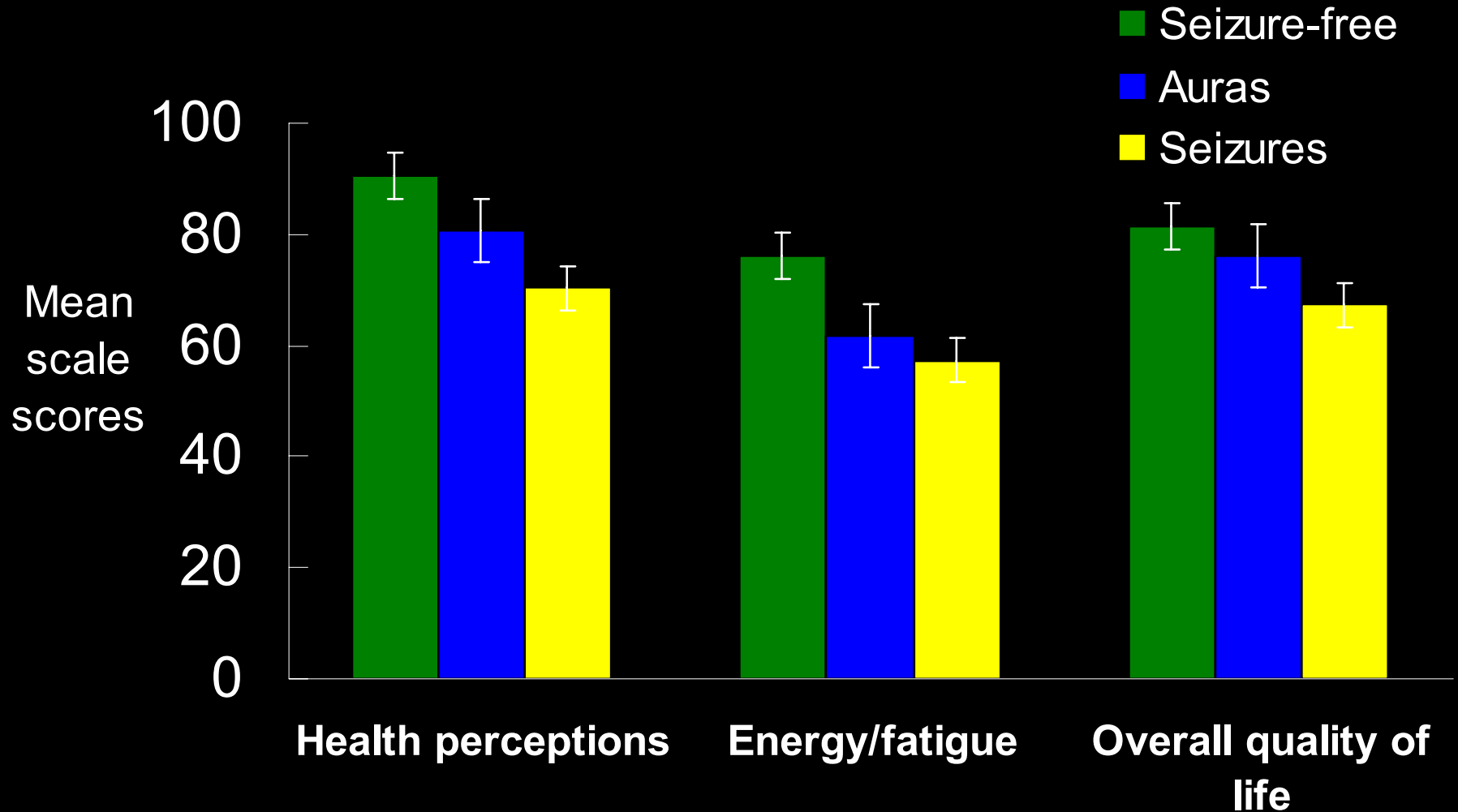
Epilepsy Treatment Outcomes

- **Most outcome reporting systems combine together people who become seizure free with those continuing to have auras**
- **Is HRQOL equivalent for people who are completely seizure free and those continuing to have auras?**

Analysis of Data from 142 Epilepsy Surgery Patients

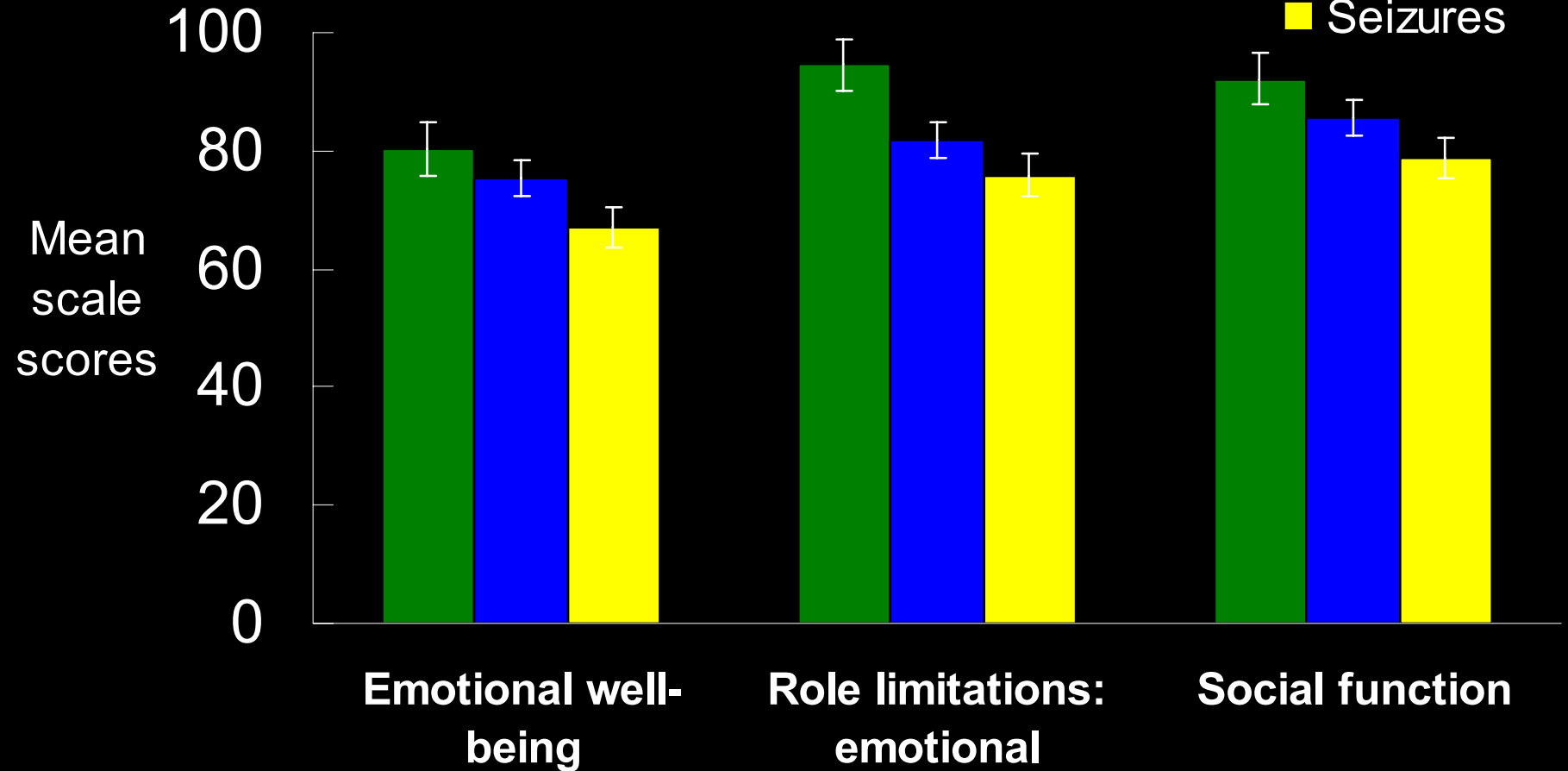
- Seizure control over the prior year categorized as
 - Completely seizure free (N=44)
 - Auras only (N=43)
 - At least one seizure with altered awareness (N=55)
- HRQOL scores compared across groups having different degrees of seizure control

Seizure Outcome vs General Health Measures

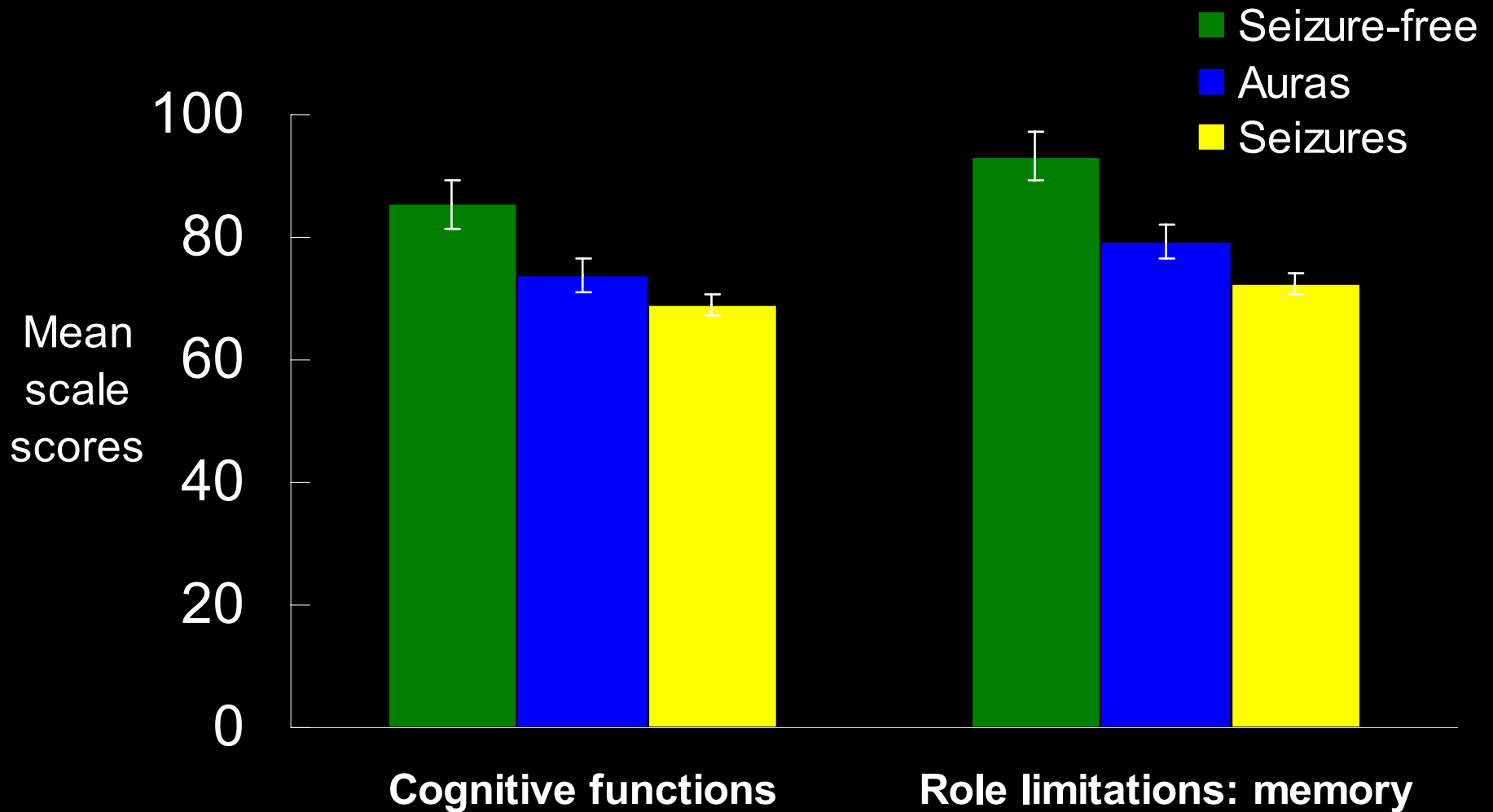


Seizure Outcome vs Mental Health Measures

■ Seizure-free
■ Auras
■ Seizures



Seizure Outcome vs Epilepsy-Specific Scales



Peripheral Neuropathy: HRQOL and Traditional Outcomes

- **Sample of 80 adults (56 male, 24 female) enrolled in a multi-center, randomized trial of an experimental treatment for diabetic neuropathy**
- **Subjects completed an HRQOL measure consisting of 36 items of SF-36 and 61 neuropathy-targeted items**
- **Symptom checklists, structured neurologic examinations, and nerve conduction velocity studies also obtained**

Symptoms of Peripheral Neuropathy

- Numbness, especially in the extremities (legs, feet, arms, and hands)
- Muscle weakness
- Tingling, burning, pricking, or tickling sensations
- Pain, especially in the extremities (legs, feet, arms, and hands)

Spearman Correlations Between Measures in Peripheral Neuropathy

HRQOL Scale	Sensory symptoms	Sensory exam	Sural nerve conduction amplitude
Mental Health	-0.11 p=0.35	0.09 p=0.45	0.04 p=0.71
Physical Health	-0.46 p<0.0001	-0.23 p=0.04	0.04 p=0.74

N ranged from 75 to 79

Spearman Correlations Between Measures in Peripheral Neuropathy

HRQOL Scale	Motor symptoms	Strength exam	Peroneal nerve conduction amplitude
Mental Health	-0.15 p=0.19	-0.11 p=0.32	-0.06 p=0.59
Physical Health	-0.47 p<0.0001	-0.18 p=0.11	-0.004 p=0.97

N ranged from 75 to 79

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