Alzheimer's Disease Progression Healthy-Year Equivalents: Stated Risk-benefit Trade-off Preferences

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OBJECTIVE

To estimate the willingness of older Americans to forgo life expectancy in exchange for modifying the course of Alzheimer's disease (AD) using two difference measures, maximum acceptable risk (MAR) and healthy-year equivalents (HYEs).

BACKGROUND

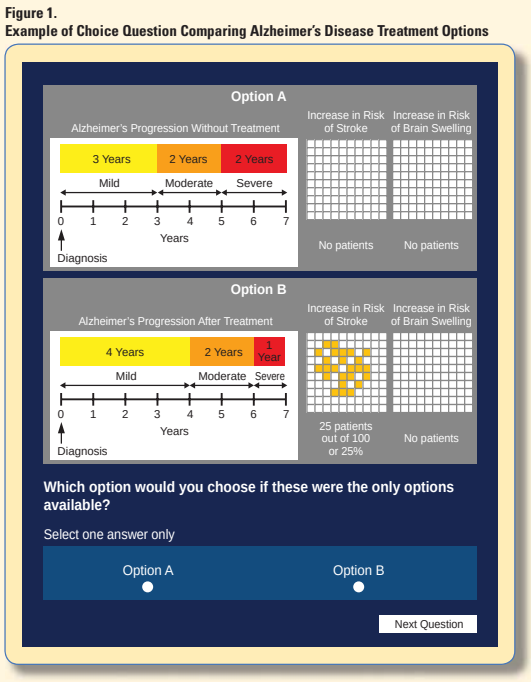
- AD is a progressive, fatal condition with rising prevalence.
- Results from a recent study indicate that older Americans fear AD more than any other disease[1]; however, few studies have quantified the extent to which these people are willing to sacrifice to avoid AD and its consequences.
- Previous research has shown that older Americans were willing to accept significant increases in the risk of death or disability in exchange for treatments that modify the course of AD.[2,3]
- Because maximum acceptable risk (MAR) estimates represent the risk of treatment-related death people are willing to accept to achieve therapeutic benefits, these measures can be used to quantify the amount of life expectancy older Americans are willing to forego to achive the benefits of AD treatments.
- Changes in life expectancy involve years in multiple disease states. Comparisons thus require a method for calculating quality equivalents for differerent disease-progression patterns.
- Data on hypothetical treatment tradeoffs can be used to estimate healthy-year equivalents (HYEs) to compare the perceived relative seriousness of alternative disease progression profiles by older, healthy Americans.

METHODS

Survey Instrument

- Web-enabled survey instrument:
  - Knowledge Networks (KN) online consumer panel,
    - Representative, probability-based sample of the US population,
- Discrete-choice experiment or stated-choice (SC) survey method:
  - Elicits subject tradeoffs among alternatives with varying attribute levels,
  - Is the most valid and reliable technique available for quantifying preferences[4,5,6,7]
- Ten choices between pairs of treatment options (Figure 1):
  - Option A: Reference condition with no adverse event risks,
  - Option B: Treatment with improved AD progression profile and specified adverse event risk,
  - Varying levels of serious adverse event risks:
    - Death or severe disability from stroke,
    - Death or severe disability from brain swelling (encephalopathy),
  - Treatment begins at diagnosis with fixed life expectancy,
- Subjects assume physician informed them today that they had mild AD.
- AD staging:
  - Defined using clinical input and the Clinical Dementia Rating (CDR)[8] scale for mild, moderate, and severe AD stages,
  - Stage durations sum to 7 years (average life expectancy of patients newly diagnosed with AD[9,10]).

Figure 1.
Example of Choice Question Comparing Alzheimer's Disease Treatment Options



ANALYSIS

- Estimate a nonlinear SC utility function using random-parameters logit:
  - SC Utility = β_1·MILD Years
    + β_2·(MILD Years × MODERATE Years)
    + β_3·SEVERE Years
    + β_4·STROKE Risk
- Evaluate the AD progression profiles outlined in Table 1.

Table 1. Alternative Alzheimer's Disease Progression Profiles

Progression Profile	Years		
	Mild AD	Moderate AD	Severe AD
Reference condition	3	2	2
Changing 1 year moderate to 1 year early stage/mild	4	1	2
Changing 1 year severe to 1 year moderate	3	3	1
Changing 1 year severe to 1 year early stage/mild	4	2	1
Slowing	5	2	0
Halting	7	0	0

AD = Alzheimer's disease.

Calculate MAR of stroke for changes in disease progression:

- Measure of risk tolerance, the maximum risk subjects are willing to accept in exchange for treatment benefits,
- MAR is the increase in treatment risk that would exactly offset any treatment benefit.

$$MAR = \frac{\text{SC Utility Gain from Treatment}}{\text{SC Utility Loss from 1\% Increase in Treatment Risk}}$$

Calculate mild-year equivalents (MYE)[11,12] for disease progression profiles:

- MYE_k is the time with mild AD (the best possible health state in the survey) that yields the same SC utility as disease progression profile k.
  - SC utility for MYE_k mild years = SC utility for 7 years with AD progression profile k.
- MYE incorporates both quantity and quality of life, estimated jointly.

Chaining calculations:

- While clinically relevant, MYE does not scale utility between perfect health and death – the most common convention in health economics.
- HYE_k is the time in perfect health that yields the same SC utility as disease progression profile k.
- Chaining calculations approximate perfect-health HYEs by adjusting the MYE for the difference between mild AD and perfect health. We also evaluate assumptions about whether permanent severe disability from stroke is better or worse than death.[14]
- The mild chaining calculation is based on a published health-state utility for mild AD[13] (Table 2) and assumes SC utility for severe disability from stroke = 0 (same as death).

$$HYE_k = (\text{Mild AD health state utility}) \times MYE_k$$

- We also calculate HYE using two health-state utility estimates of stroke disability, one greater than zero and one less than zero (Table 2).[14]

$$HYE_k = [(\text{Mild AD utility}) \times MYE_k] \times (1 - \text{Stroke disability utility}) + (\text{Stroke disability utlity} \times 7 \text{ years})$$

- The HYE estimates indicate the potential gains from modifying AD progression scaled in perfect-health-year equivalents.

Table 2. Health-State Utilities Used for Chaining Calculations

Measure	Value
Mild AD (HUI2)[13]	0.69
Stroke worse than death[14]	-0.20
Stroke better than death[14]	0.32

RESULTS

- Overall, 2,146 American adults over age 60 with no diagnosis of dementia completed the survey.
- MYE and HYE estimates for each progression profile are presented in Figures 2 and 3.

Figure 2. Mild-Year Equivalents of Alzheimer's Disease Progression Profiles

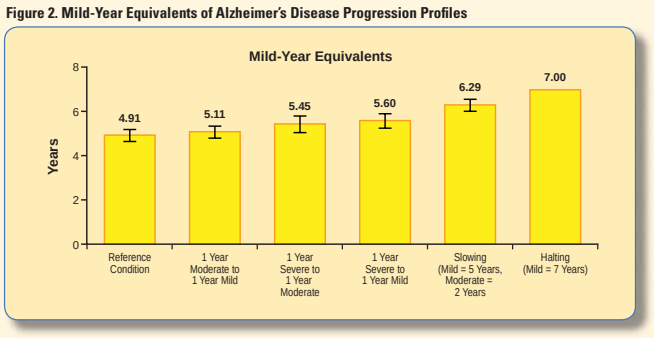


Figure 3. Healthy-Year Equivalents of Alzheimer's Disease Progression Profiles Using Chaining Calculations

Figure 3a. Worst Outcome is Death

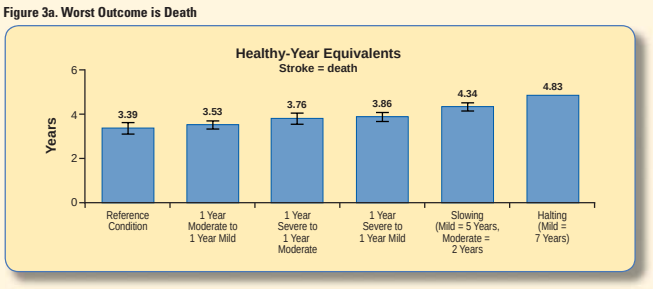


Figure 3b. Worst Outcome is Worse Than Death

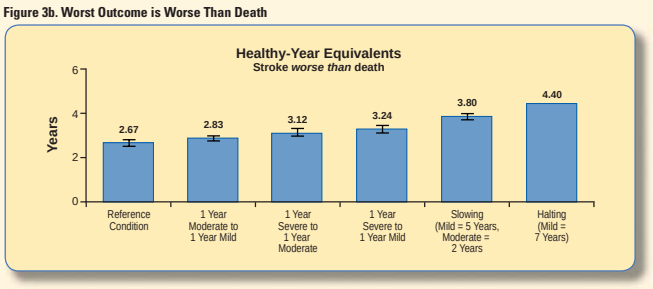
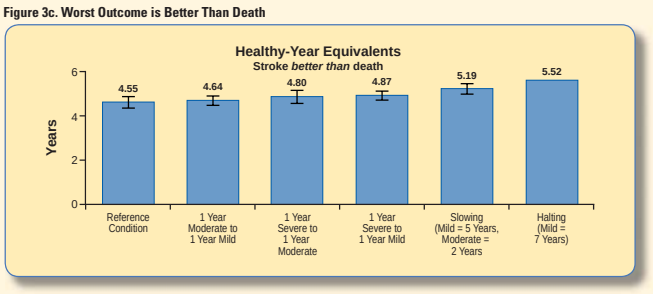


Figure 3c. Worst Outcome is Better Than Death



LIMITATIONS

- Subjects evaluate hypothetical treatments:
  - Intended to simulate clinical decisions but do not have the same clinical, financial, and emotional consequences of actual decisions,
  - Differences can arise between stated and actual choices.
- We provided numeric and graphical representations of adverse-event risks, however:
  - Numeracy skills in the general population are poorly developed,
  - Subjects may have applied simplifying heuristics in comparing probabilities that are inconsistent with actual numeric magnitudes.

CONCLUSIONS

- Clinically relevant tradeoffs between hypothetical treatment efficacy and increased treatment risks indicate that older Americans regard AD as a very serious condition, and therapies that could delay worsening from mild AD to moderate and severe stages could yield substantial increases in well-being.
- MAR and MYEs provide consistent evidence that the magnitude of the impact of disease modifying therapies is substantial.
- Approximating HYEs from MYEs yields significantly different results depending on chaining assumptions used.
- MAR and MYE provide more informative estimates of the value of treating AD in all stages, including later, more severe stages.

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DISCLOSURE

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