63° CONGRESSO NAZIONALE SIGG

GLI ANZIANI:
LE RADICI DA PRESERVARE

ROMA 28 novembre 01 dicembre 2018

LA SPERIMENTAZIONE FARMACOLOGICA CLINICA IN ETÀ GERIATRICA

Trial clinici nell'anziano: efficacy or effectiveness?

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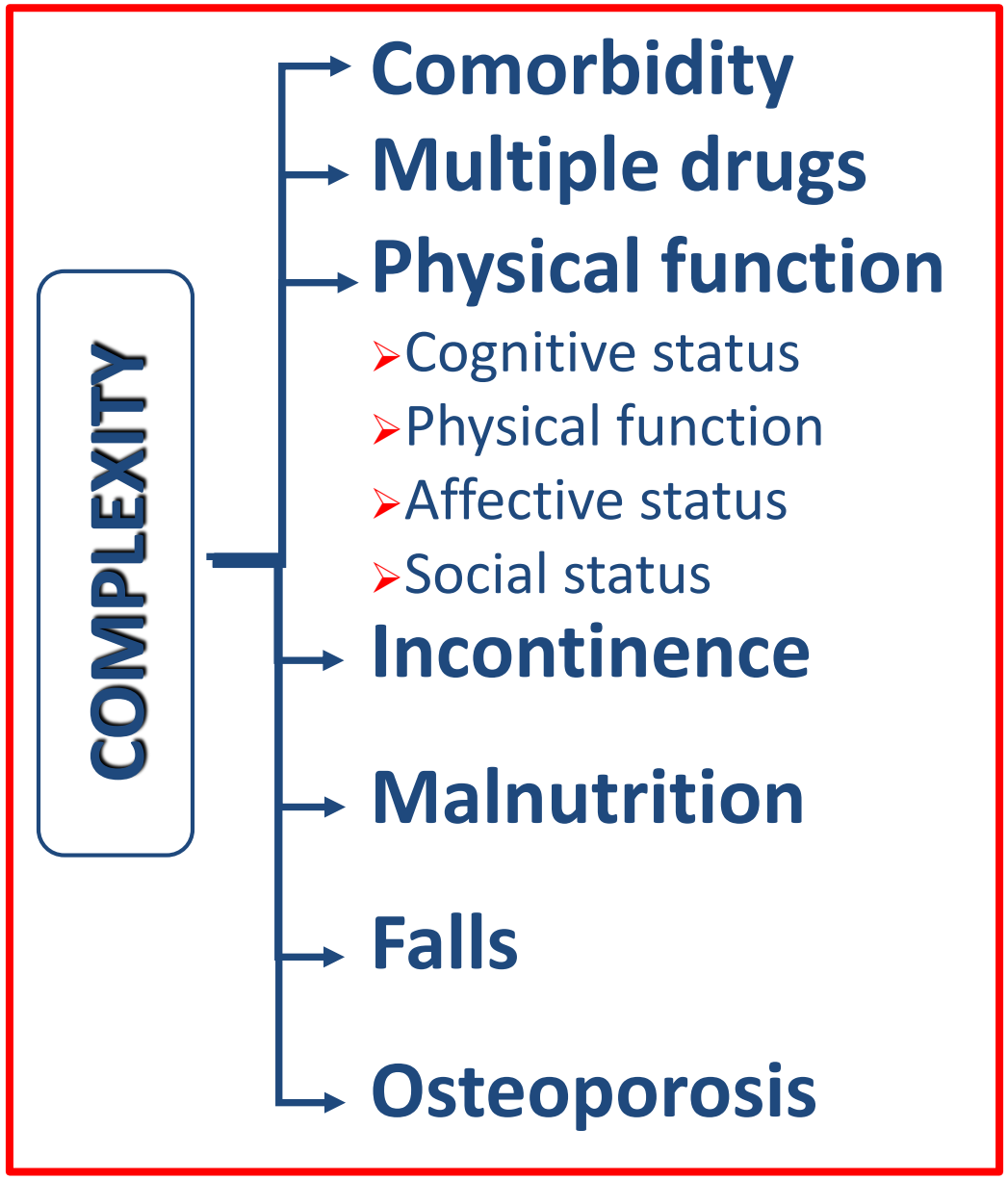
Definition

Efficacy is the capacity to produce an effect. In medicine, it is the ability of an intervention or drug to produce a desired effect in expert hands and ***under ideal circumstances***.

Effectiveness is the capability of producing a desired result. In medicine, effectiveness relates to ***how well a treatment works in practice***, as opposed to efficacy, which measures how well it works in RCT or laboratory studies.

Ideal or real patient?



Researchers have largely shied away from the complexity of multiple chronic conditions — avoidance that results in expensive, potentially harmful care of unclear benefit.

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Efficacy and Effectiveness research

Effectiveness research addresses practical questions about an intervention as it would occur in routine clinical practice, preserving the *'ecology'* of care: hypothesis and study design are formulated based on information needed to make a decision.

Efficacy research is aimed to better understand how and why an intervention works.

FULL text at JAMA Tunis SR. JAMA 2003

Efficacy and Effectiveness research

3 key features differentiates effectiveness (***pragmatic or practical trials***) and efficacy research (***explanatory trials***):

1. Population (sample)

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Population

Efficacy research

Population with single disease, no complexity

- Generalizability

Effectiveness research

Population that consumes the most health care (comorbidity, behavioral and physical conditions, different settings)

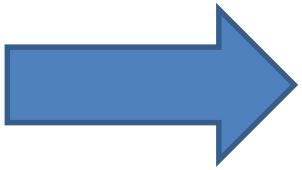
+ Generalizability

- Heterogeneity

Heterogeneity

Heterogeneity resulting from:

- patients' initial level of risk for a given outcome;
- responsiveness to treatment;
- vulnerability to adverse effect



Treatments compared within homogeneous risk strata

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Population

Efficacy research

Population with single disease, no complexity

+ Retention/adherence

- Generalizability

Effectiveness research

Population that consumes the most health care (comorbidity, behavioral and physical conditions, different settings)

+ Generalizability

- Heterogeneity
  Retention/adherence

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Design: Pragmatic clinical trial (ROCKET AF)

Sample: 14,264 patients with nonvalvular atrial fibrillation

Study groups: rivaroxaban vs. dose-adjusted warfarin

NEJM FREE FULL TEXT

Patel MR NEJM 2011

Adherence – Rocket AF

Inclusion criteria: history of stroke, transient ischemic attack, or systemic embolism, heart failure or a left ventricular ejection fraction of 35% or less, hypertension, an age of 75 years or more, or the presence of diabetes mellitus

Mean **CHADS score 3.5**

Warfarin dosing evaluated by **time in therapeutic range (TTR) = 55%**

NEJM FREE FULL TEXT Patel MR NEJM 2011

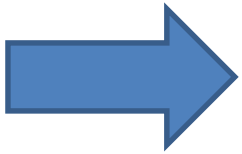
FDA Advisory Decision Highlights Some Problems Inherent in Pragmatic Trials

…findings were ***not adequate to determine whether rivaroxaban was as effective compared with warfarin when the existing treatment is used skillfully*** … The FDA said the median TTR for warfarin in general use is about 65%, but in ROCKET AF, the ***TTR was only a "relatively poor" 55%***

FULL text at JAMA Mitka M JAMA 2011

Poor adherence

Poor retention



Dilution of the effect

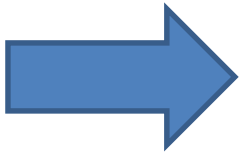
Need of large sample size

Data analysis: '… an ***intention to treat analysis*** will provide a valid comparison of treatment strategies.'

NEJM FREE FULL TEXT Ware JH NEJM 2011

Poor adherence

Poor retention



Dilution of the effect

Need of large sample size

Data analysis: '… in equivalence trials it can create a bias toward a finding of equivalence'

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Efficacy and Effectiveness research

3 key features differentiates effectiveness (***pragmatic or practical trials***) and efficacy research (***explanatory trials***):

1. Population (sample)
2. Interventions

NEJM FREE FULL TEXT Tinetti M. NEJM2011

Intervention

Efficacy research

Placebo comparison

Blinded

Effectiveness research

Head to head comparisons

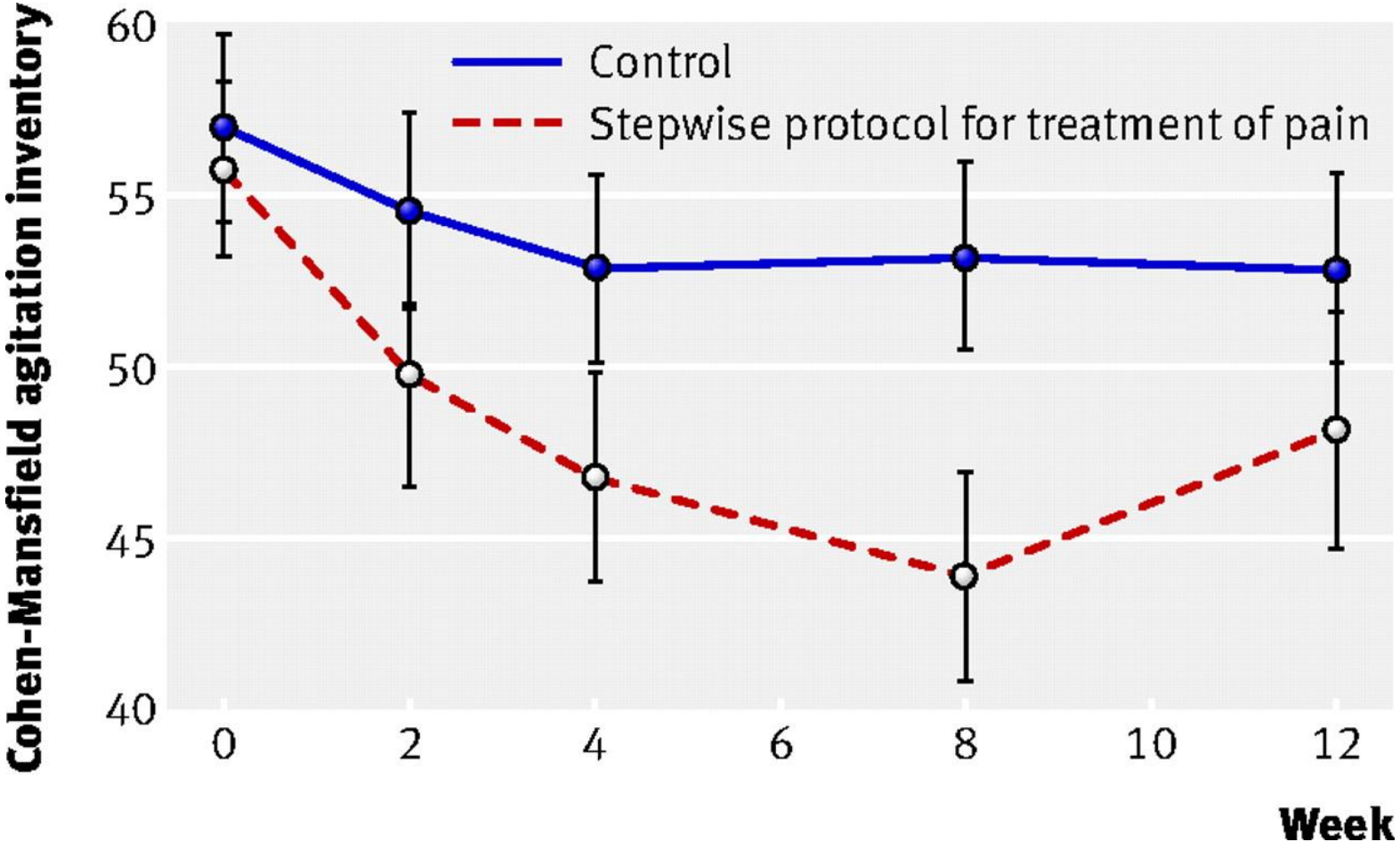
Pharmacological and non-pharmacological interventions

Unblinded

Interventions in effectiveness research

1. Examination of treatments for common pairs of diseases in which treatment of one may exacerbate or improve the other;

Treatment of pain and behavioural symptoms in NH residents with dementia



BMJ Husebo B BMJ 2011

Interventions in effectiveness research

1. Examination of treatments for common pairs of diseases in which treatment of one may exacerbate or improve the other;
2. Testing interventions that can affect simultaneously multiple conditions;

Comprehensive geriatric assessment for older adults admitted to hospital: meta-analysis of RCT

Outcomes	Impact/RR or SMD (95% CI)
Living at home	1.16 (1.05 to 1.28)
NH admission	0.78 (0.69 to 0.88)
Mortality	0.76 (0.64 to 0.90)
Improved cognition	0.08 (0.01 to 0.15)
Costs	↓
Caregiver distress	↓

Ellis G et al. BMJ 2011

BMJ

Interventions in effectiveness research

1. Examination of treatments for common pairs of diseases in which treatment of one may exacerbate or improve the other;
2. Testing interventions that can affect simultaneously multiple conditions;
3. Combination of pharmacological and non pharmacological treatments;

ROT combined with cholinesterase inhibitors in Alzheimer's disease

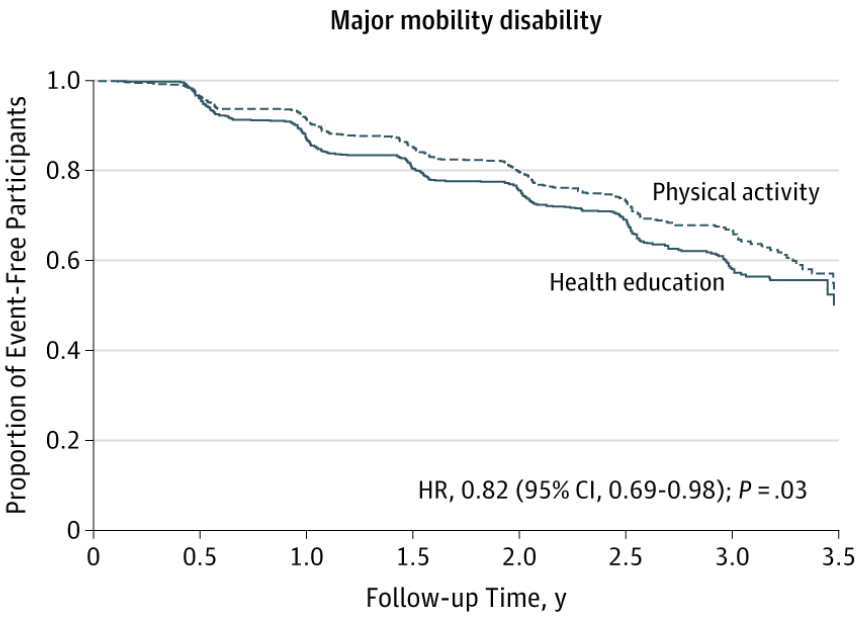
	Mean change in score (standard error)[1]		P
	Treatment group (*n*=70)	Control group (*n*=67)	
Patients			
MMSE	0.2 (0.4)	−1.1 (0.4)	0.02
ADAS–Cog	0.4 (0.8)	−2.5 (0.8)	0.01
Neuropsychiatric Inventory	0.9 (1.9)	−2.5 (2.1)	0.23
Barthel Index	−0.9 (1.0)	−2.9 (1.0)	0.18
Number of impaired IADL	0.0 (0.2)	−0.2 (0.2)	0.34
Caregivers			
Hamilton Rating Scale for Depression	−0.9 (0.4)	−1.0 (0.4)	0.83
Hamilton Anxiety Scale	−0.3 (0.4)	−0.5 (0.4)	0.80
Caregiver Burden Inventory	−2.0 (1.4)	−1.3 (1.5)	0.72
SF–36	−1.3 (1.4)	−1.1 (1.4)	0.90

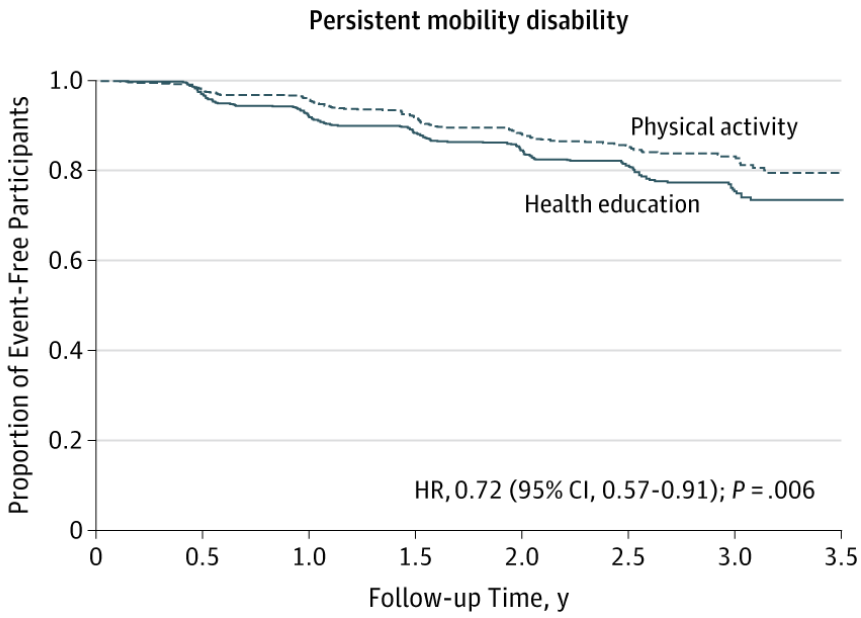
BJPsych Onder G. Br J Psychiatry 2005

Interventions in effectiveness research

1. Examination of treatments for common pairs of diseases in which treatment of one may exacerbate or improve the other;
2. Testing interventions that can affect simultaneously multiple conditions;
3. Combination of pharmacological and non pharmacological treatments;
4. Tested against gold standards

Physical activity and disability - LIFE





Pahor M et al. JAMA 2014 JAMA

Intervention

Efficacy research

Placebo comparison
Blinded

- Not informative

Effectiveness research

Head to head comparisons
Pharmacological and non-pharmacological interventions
Unblinded

+ Informative for users

- Blindness

Blindness and outcomes

… the combination of unblinded treatment and patient self-assessment undermines an important element of efficacy trials, creating a ***potential for bias***: patients' expectations may influence their outcomes report … Effectiveness trials are stronger when they include both ***objective*** (e.g., survival, test results) and ***subjective outcome measures*** (e.g., quality-of-life surveys).

NEJM FREE FULL TEXT Ware JH NEJM 2011

Efficacy and Effectiveness research

3 key features differentiates effectiveness (***pragmatic or practical trials***) and efficacy research (***explanatory trials***):

1. Population (sample)
2. Interventions
3. Outcomes

NEJM FREE FULL TEXT Tinetti M. NEJM2011

Outcomes

Efficacy research

Disease oriented (occurrence of a single disease or exacerbation of a single chronic condition)

Rating scales/test measures

Effectiveness research

Universal health outcomes (symptoms burden, function, health related quality of life, active life expectancy)

Real-world measure of clinical practice

Antipsychotics - Outcomes

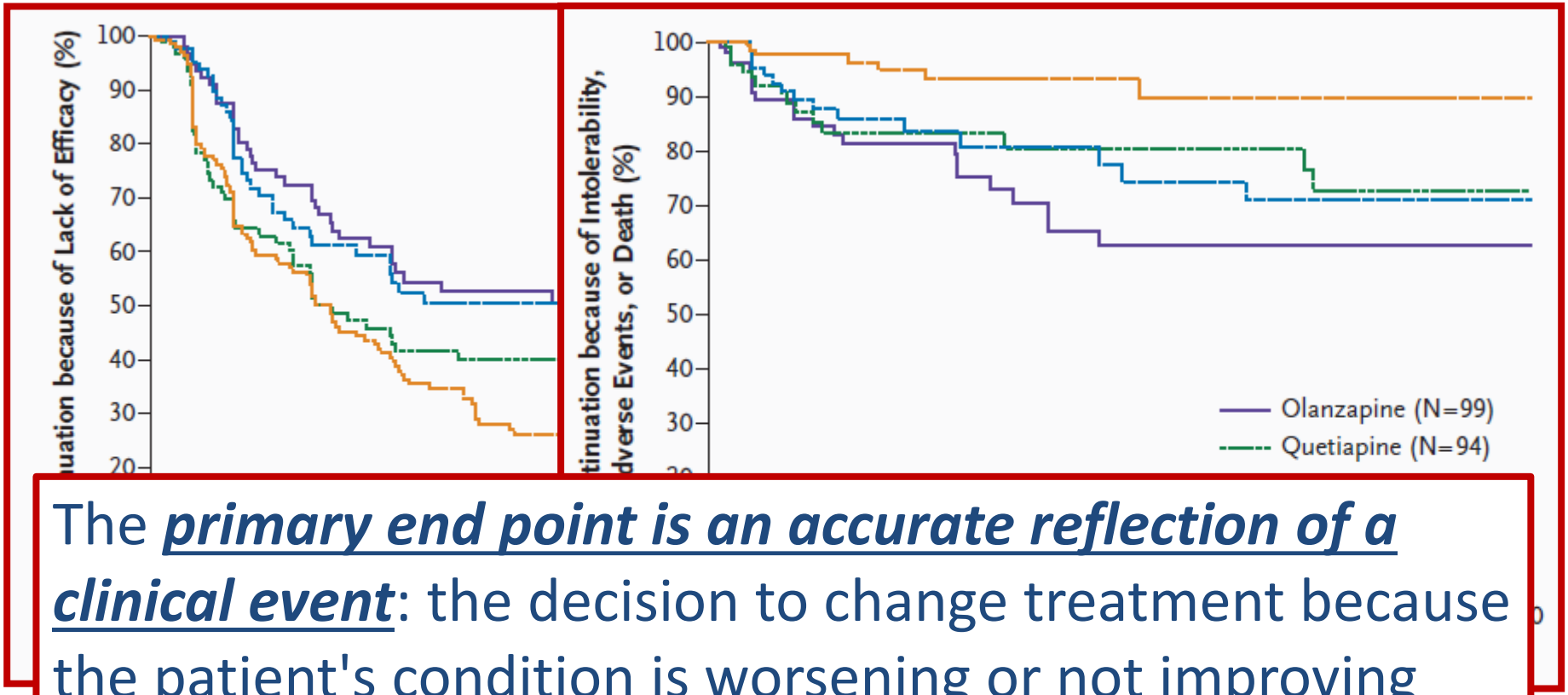
Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials.

15 trials met selection criteria … a total of 3,353 patients were randomized to drug and 1,757 to placebo.

Results: ***Efficacy on rating scales*** was observed by meta-analysis for aripiprazole and risperidone, but not for olanzapine.

Schenider LS Am J Geriatr Psychiatry 2006

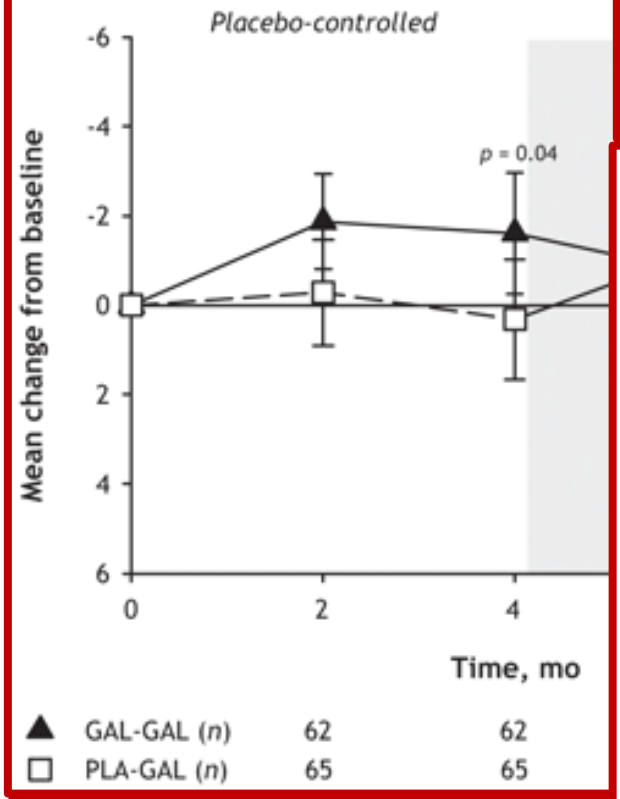
Antipsychotics – CATIE-AD



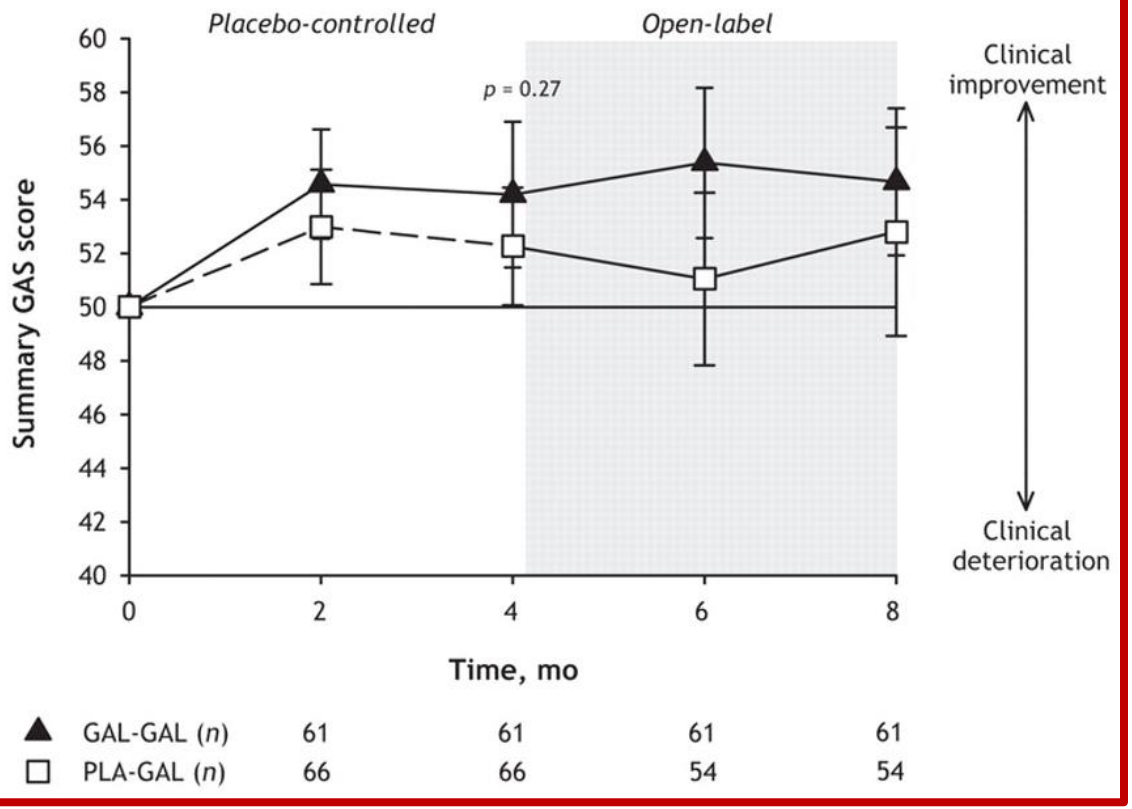
The ***primary end point is an accurate reflection of a clinical event***: the decision to change treatment because the patient's condition is worsening or not improving sufficiently … The CATIE-AD study is an exemplar of the clinical trial's revolutionary role in shaping therapeutics

NEJM FREE FULL TEXT Schneider LS NEJM 2006

Attainment of treatment goals by people with Alzheimer's disease receiving galantamine: a randomized controlled trial



Change in patient-caregiver **Goal Attainment Scaling**



Change in AdasCOG

CMAJ 2013

Effect of T supplementation on functional mobility, cognition, and other parameters in older men

	Mean (SD)					
	Baseline		Final Visit			
	Testosterone (n = 113)[a]	Placebo (n = 110)[a]	Testosterone (n = 113)[a]	Placebo (n = 110)[a]	Change Difference (95% CI)	*P* Value
Functional Mobility						
Health Assessment Questionnaire score (0-3)	0.02 (0.1)	0.06 (0.2)	0.05 (0.1)	0.07 (0.2)	0.01 (–0.02 to 0.04)	.61
Isometric grip strength, kg						
Left	43.0 (9.7)	44.4 (11.6)	42.3 (8.8)	42.7 (8.2)	0.7 (–1.6 to 3.0)	.54
Right	44.6 (8.7)	46.5 (9.5)	43.0 (7.5)	43.4 (7.7)	1.3 (–0.5 to 3.2)	.16
Isometric leg extension strength, N						
Left	78.8 (29.4)	84.5 (36.3)	73.3 (25.0)	75.2 (24.8)	3.5 (–6.4 to 13.5)	.83
Right	79.8 (29.0)	84.3 (35.9)	73.2 (24.3)	77.0 (26.0)	1.1 (–8.6 to 10.7)	.48
Timed get up and go test, s	4.24 (0.9)	4.24 (1.0)	4.27 (0.7)	4.34 (1.0)	–0.04 (–0.02 to 0.04)	.70
Body Composition						
Body mass index[b]	27.4 (3.8)	27.3 (3.9)	27.5 (3.8)	27.4 (3.9)	0 (–0.2 to 0.3)	.76
Total mass, kg						
Fat	23.2 (7.9)	22.9 (7.2)	22.2 (8.1)	22.8 (7.1)	–1.3 (–1.8 to –0.8)	<.001
Lean mass	58.9 (6.8)	58.3 (7.6)	60.0 (6.6)	58.0 (7.5)	1.2 (0.7 to 1.7)	<.001
Fat mass percentage, %	27.7 (6.0)	27.8 (5.4)	26.4 (6.2)	27.8 (5.4)	–1.7 (–2.1 to –1.1)	<.001
Fat ultrasound, cm						
Intra-abdominal	8.3 (2.3)	8.2 (2.0)	8.6 (2.5)	8.5 (2.1)	0 (–0.4 to 0.4)	.98
Subcutaneous	2.6 (0.8)	3.5 (0.8)	2.5 (0.8)	2.7 (0.8)	0.7 (–0.8 to 2.4)	.34

Emmelot-Vonk et al. JAMA 2008 JAMA

Outcomes

Efficacy research

Disease oriented (occurrence of a single disease or exacerbation of a single chronic condition)

Rating scales/test measures

+ Good for homogeneous populations

- People at risk for multiple adverse outcomes

Effectiveness research

Universal health outcomes (symptoms burden, function, health related quality of life, active life expectancy)

Real-world measure of clinical practice

+ Informative

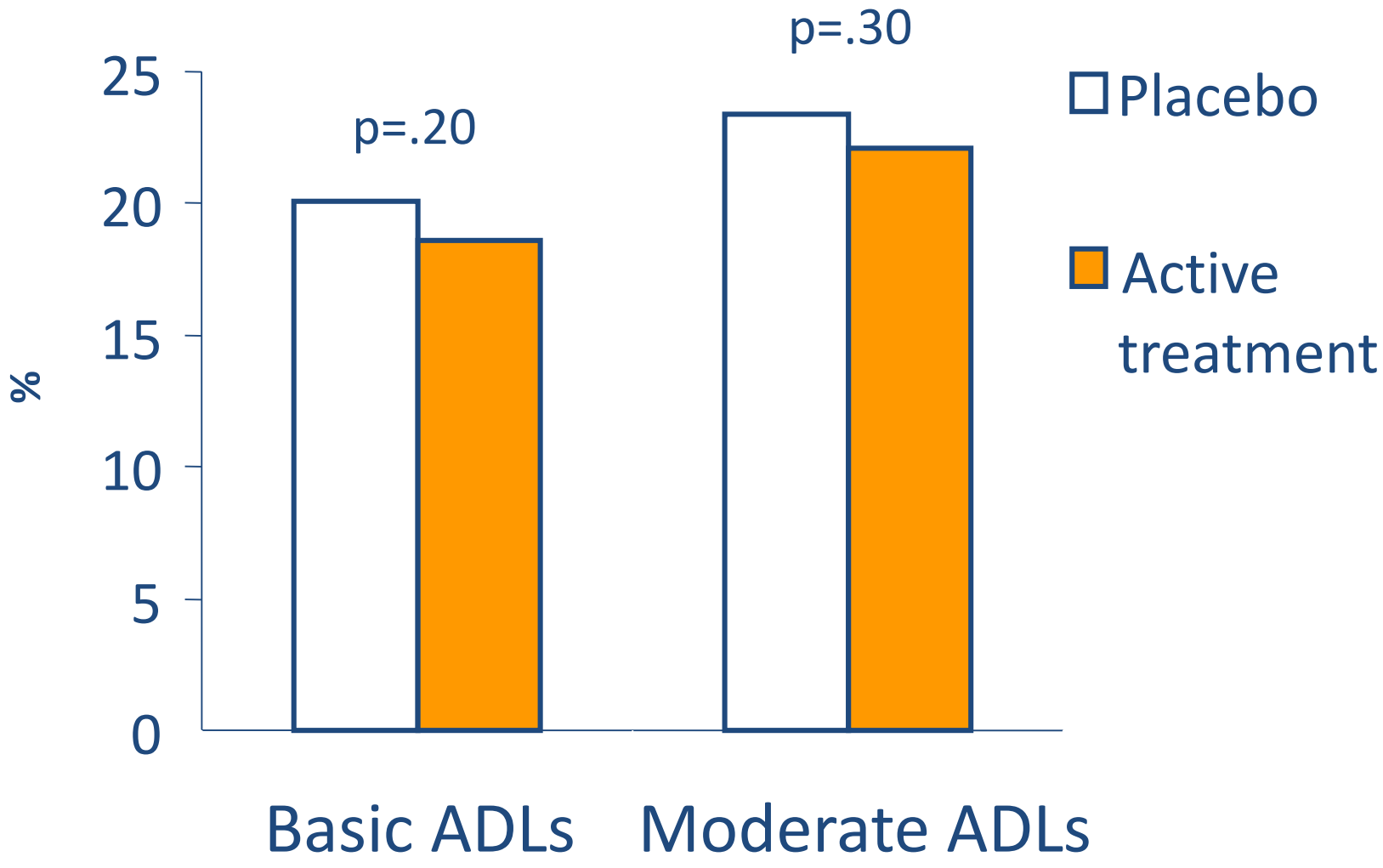
- Harder to collect

SHEP -Clortalidone versus placebo

Outcome	RR	95% CI
Stroke	0.67	0.56-0.80
CHF	0.46	0.33-0.65
CHD	0.75	0.60-0.94
Any CVD	0.68	0.58-0.79

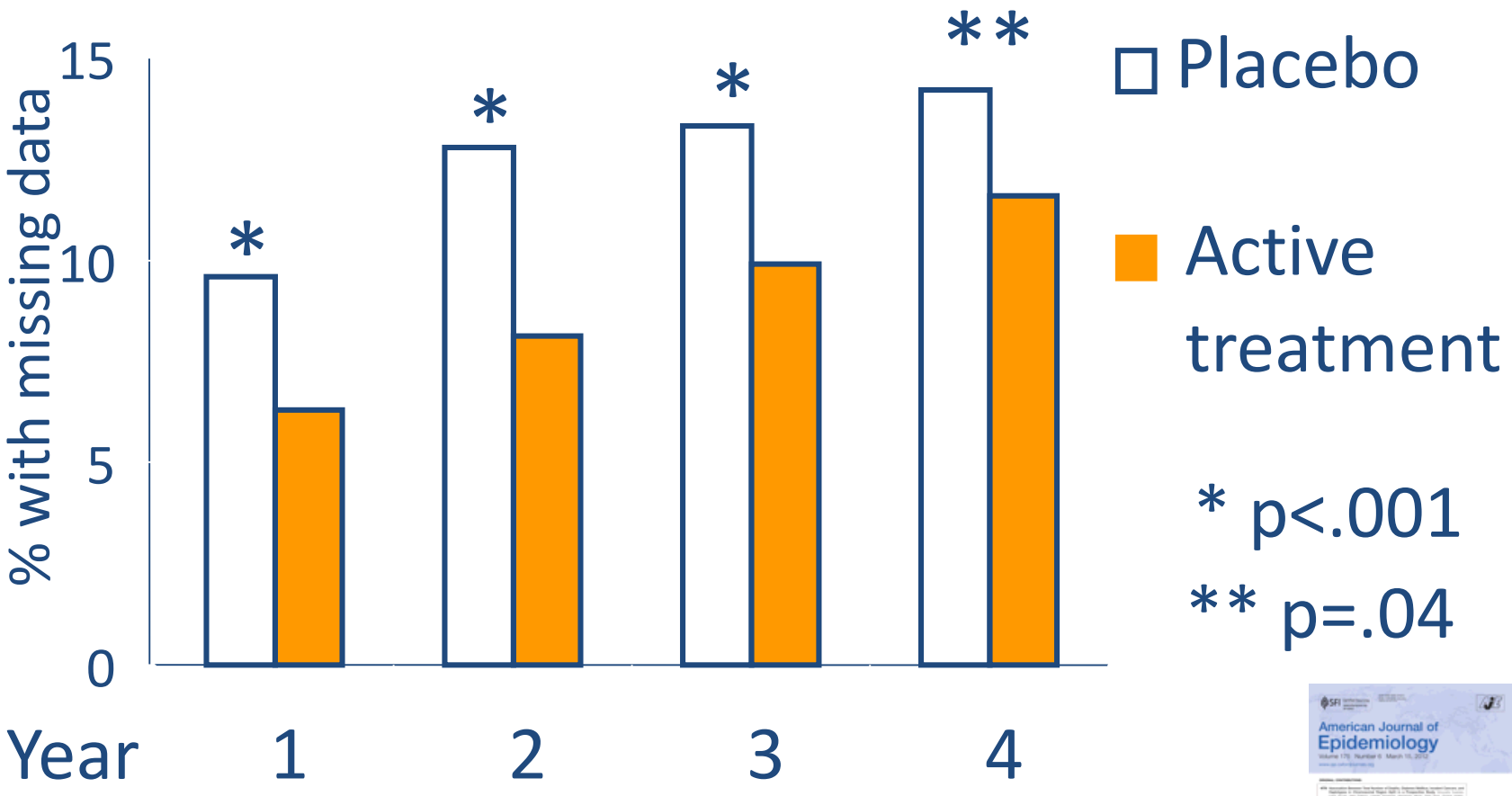
FULL text at JAMA SHEP JAMA 1991

Deterioration of ADLs in SHEP



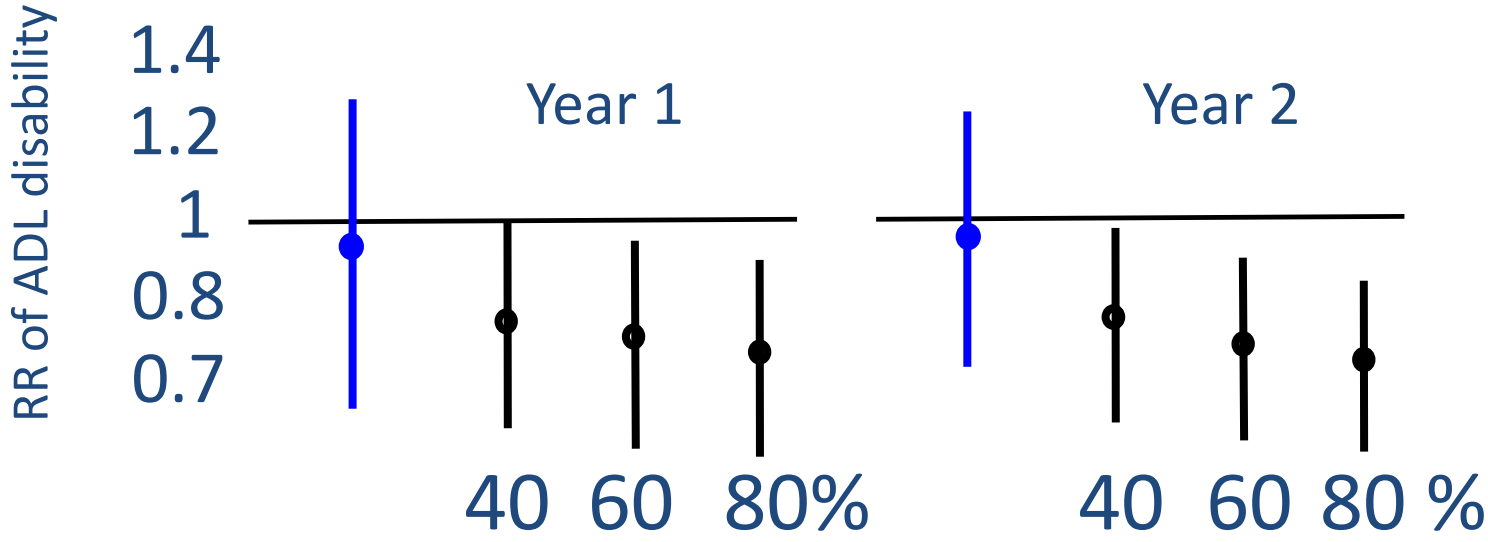
ARCHIVES OF INTERNAL MEDICINE Applegate W Arch Intern Med *1994*

Missing disability assessments in SHEP



Di Bari Am J Epidemiol 2000

SHEP sensitivity analyses - RR of ADL disability for active treatment vs placebo



- Reported
- Sensitivity analysis: % disability among missing data

Di Bari Am J Epidemiol 2000

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STATISTICS IN MEDICINE

Pragmatic Trials — Guides to Better Patient Care?

James H. Ware, Ph.D., and Mary Beth Hamel, M.D., M.P.H.

Pragmatic trials are designed to study real-world practice and therefore represent less-perfect experiments than efficacy trials; ***they sacrifice internal validity to achieve generalizability***.

The challenge is to ***keep the balance right*** so that the findings are likely to be both correct and applicable to clinical practice or health care delivery.

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