Efficacy and Effectiveness models

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EMA Workshop: Ensuring safe and effective medicines for an ageing population
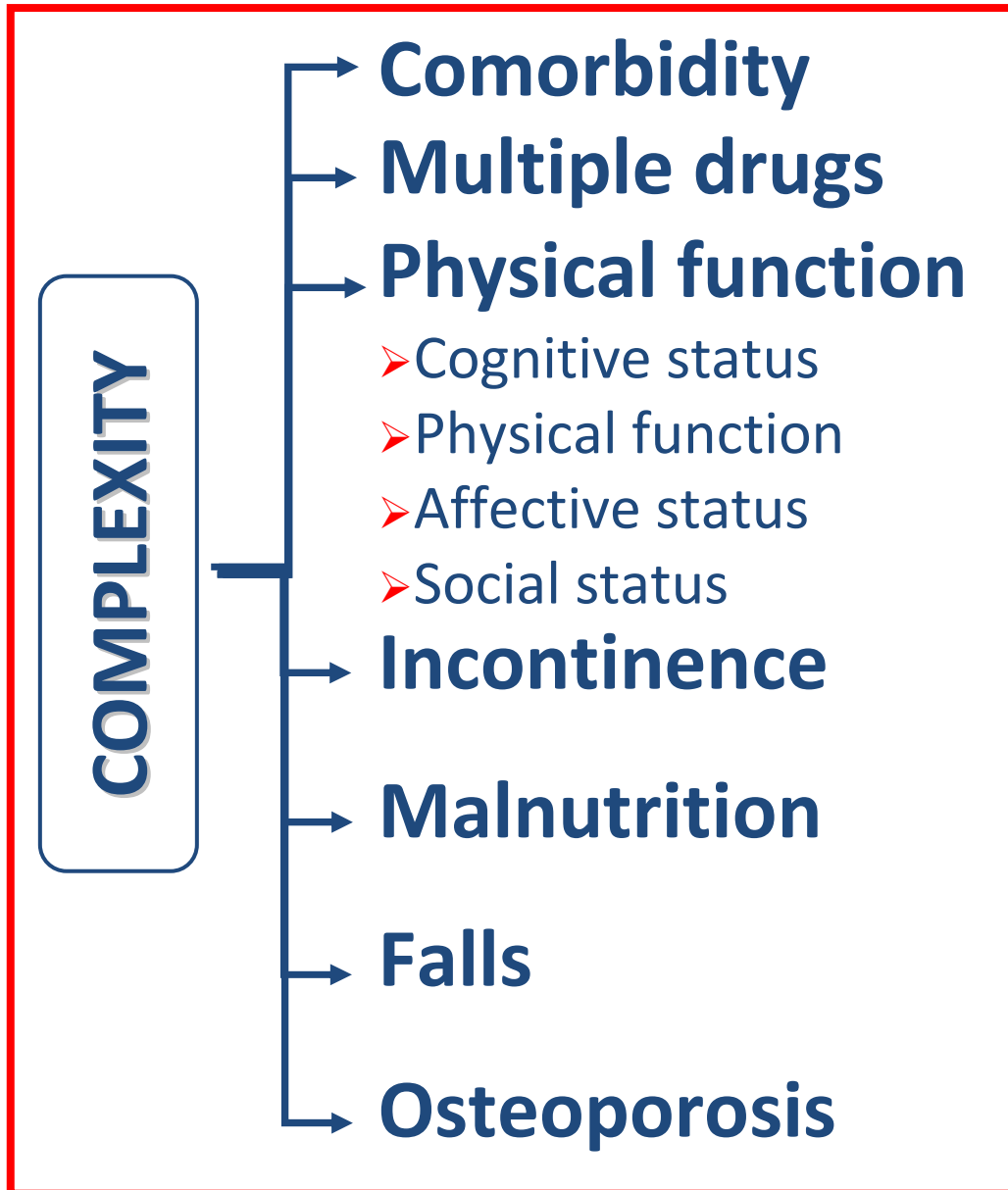
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Definition

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?

COMPLEXITY

→ **Comorbidity**
→ **Multiple drugs**
→ **Physical function**
  ➤ Cognitive status
  ➤ Physical function
  ➤ Affective status
  ➤ Social status
→ **Incontinence**
→ **Malnutrition**
→ **Falls**
→ **Osteoporosis**

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

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.

Efficacy and Effectiveness research

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

    1. Population (sample)

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)
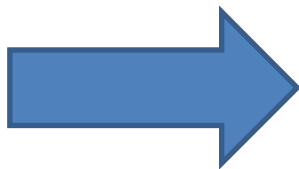
+ Generalizability

- 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

Population

Efficacy research	Effectiveness research
Population with single disease, no complexity	Population that consumes the most health care (comorbidity, behavioral and physical conditions, different settings)
+ Retention/adherence	+ Generalizability
- Generalizability	- Heterogeneity Retention/adherence

Leukotriene Antagonists as First-Line or Add-on Asthma-Controller Therapy

Design: Two parallel, pragmatic trials to evaluate effectiveness of LTRA

Study 1: LTRA vs inhaled glucocorticoid for first-line asthma-controller therapy

Study 2: LTRA vs a long-acting beta2- agonist as add-on therapy in patients already receiving inhaled glucocorticoid therapy.

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Leukotriene Antagonists as First-Line or Add-on Asthma-Controller Therapy

Study 1

	LTRA	Glucocorticoid
Retention	92%	
Adherence	65%	41%

Study 2

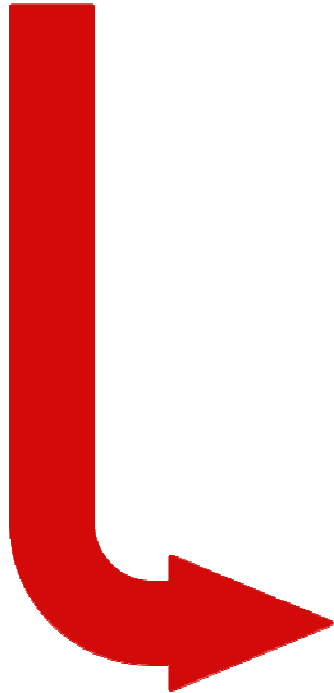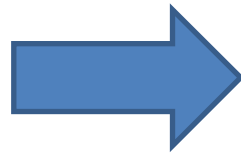|	LTRA	Beta2-agonist
Retention	97%	
Adherence	74%	46%

Poor adherence
Poor retention

→ Dilution of the effect

↓
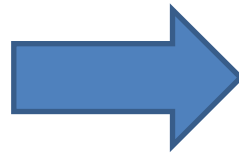
Need of large sample size

Data analysis: '... an ***intention to treat analysis*** will provide a valid comparison of treatment strategies.'
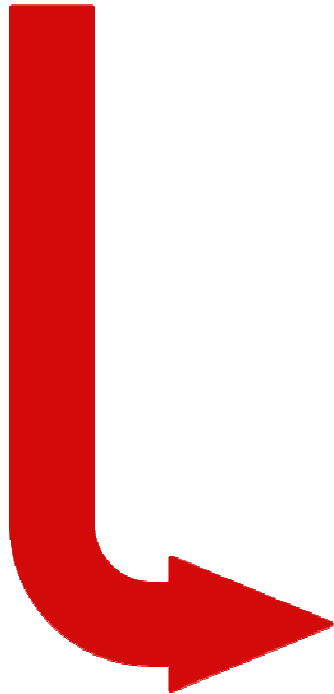
NEJM FREE FULL TEXT Ware JH NEJM 2011
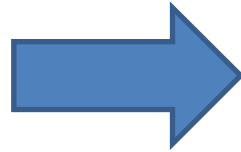
Poor adherence

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'
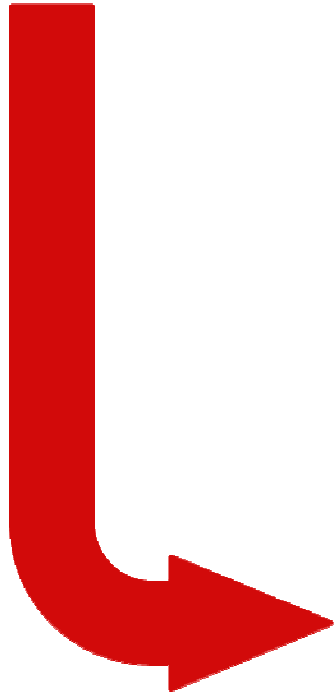
Poor adherence

Poor retention

Dilution of the effect

Need of large
sample size

Data analysis: '... a pragmatic
equivalence trial with a substantial rate
on nonadherence may not demostrate
equivalence robustly.'

Ware JH NEJM 2011

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%**

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

Efficacy and Effectiveness research

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

    1. Population (sample)

    2. Interventions

Intervention

Efficacy research

Placebo comparison
Blinded

Effectiveness research

Head to head comparisons
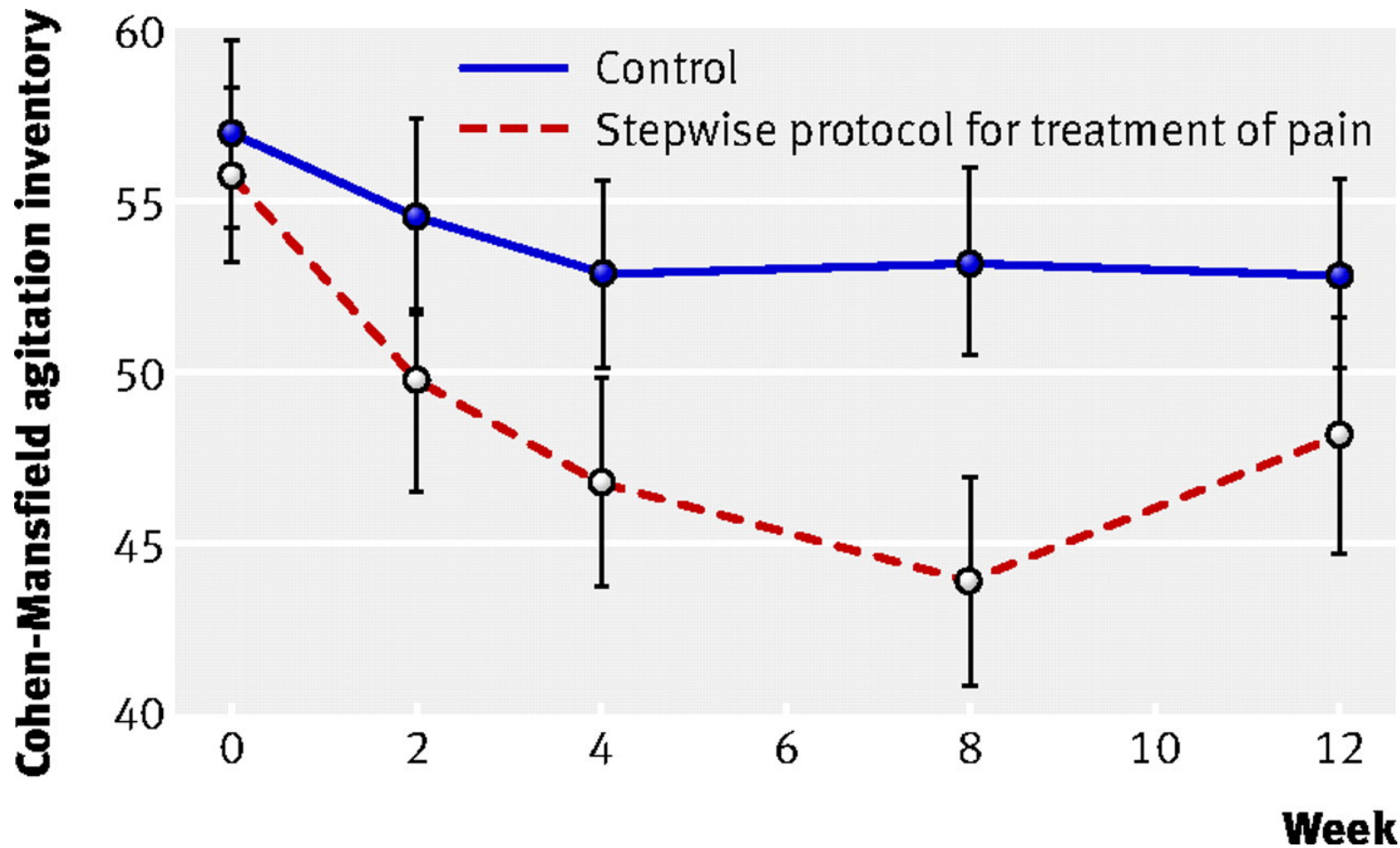Pharmacological and non-pharmacological interventions
Unblinded

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

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;

Exercise and dietary weight loss in obese older adults with knee osteoarthritis: the ADAPT study

	6-minute walk distance, meters			
Study group	Baseline	6 months	18 months	Change from baseline at 18 months (95% confidence interval)
Healthy lifestyle	434.61 ± 10.96	428.56 ± 12.88	429.89 ± 12.77	$-4.72\ (-29.75, 20.31)$
Diet only	425.98 ± 10.89	433.68 ± 11.94	435.63 ± 12.88	$9.65\ (-15.79, 35.09)$
Exercise only	424.15 ± 11.42	465.04 ± 12.13	$472.73 \pm 13.12\dagger$	$48.58\ (22.87, 74.29)$
Diet plus exercise	416.15 ± 11.34	482.37 ± 12.65	$477.76 \pm 13.12\dagger$	$61.61\ (35.90, 87.32)$

Messier SP Arthritis Rheum 2004

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;

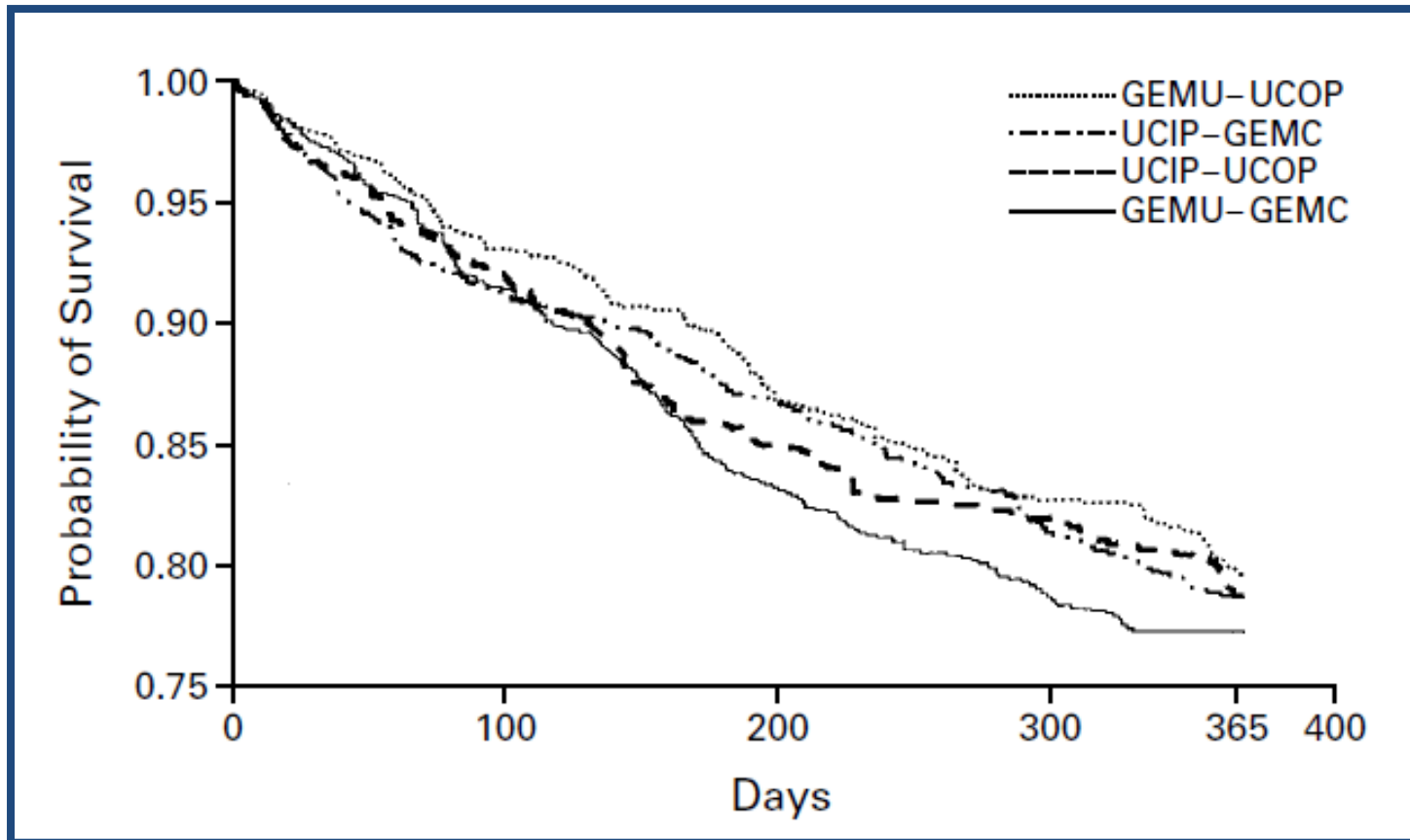3. Combination of pharmacological and non-pharmacological treatments;

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

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. Comparison of models of care

A RCT of Inpatient and Outpatient Geriatric Evaluation and Management

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).

Efficacy and Effectiveness research

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

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2. Interventions

3. Outcomes

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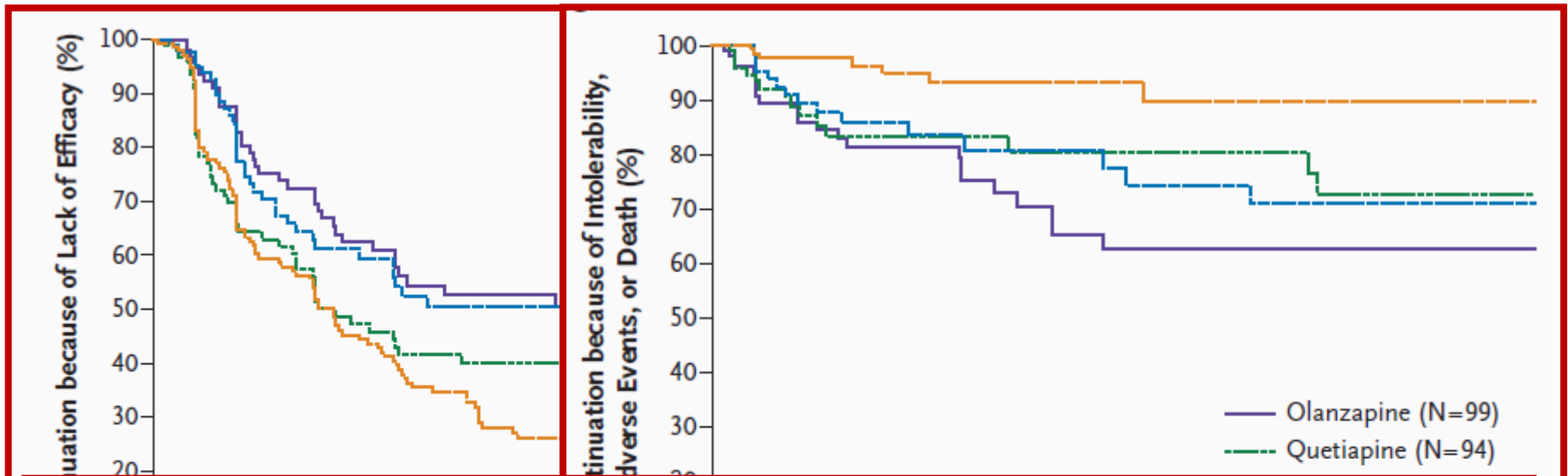
15 trials met selection criteria … a total of 3,353 patients were randomized to drug and 1,757 to placebo.

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
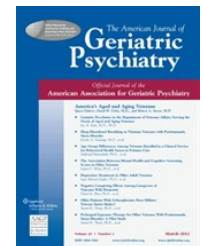
Antipsychotics – CATIE-AD

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

Schneider LS NEJM 2006

Outcomes

Efficacy research

Disease oriented (occurrence of a single disease or exacerbation of a single chronic condition)
Rating scales/test measures

- People at risk for multiple adverse outcomes

Effectiveness research

Universal health outcomes (symptoms burden, function, health related quality of life, active life expectancy)
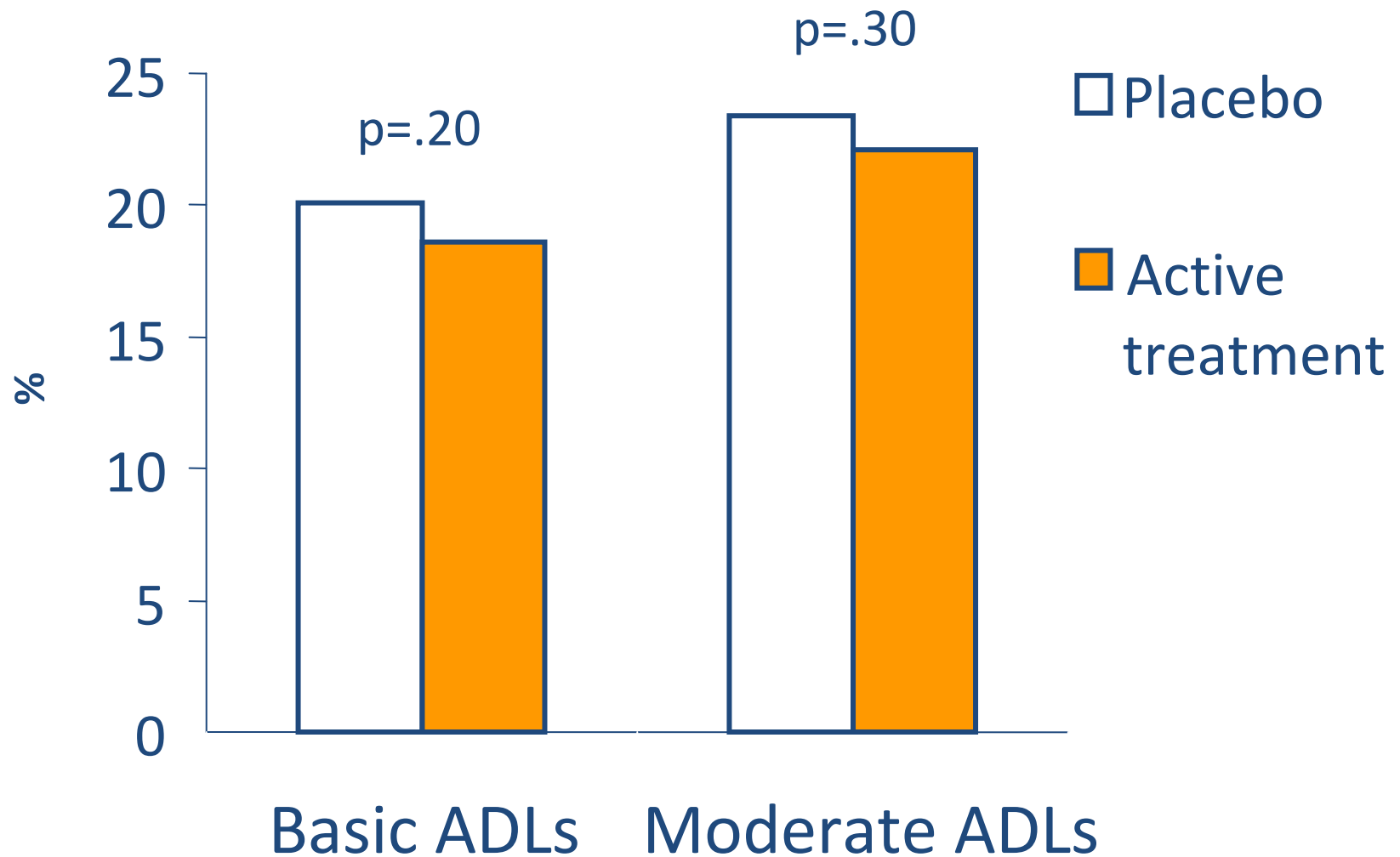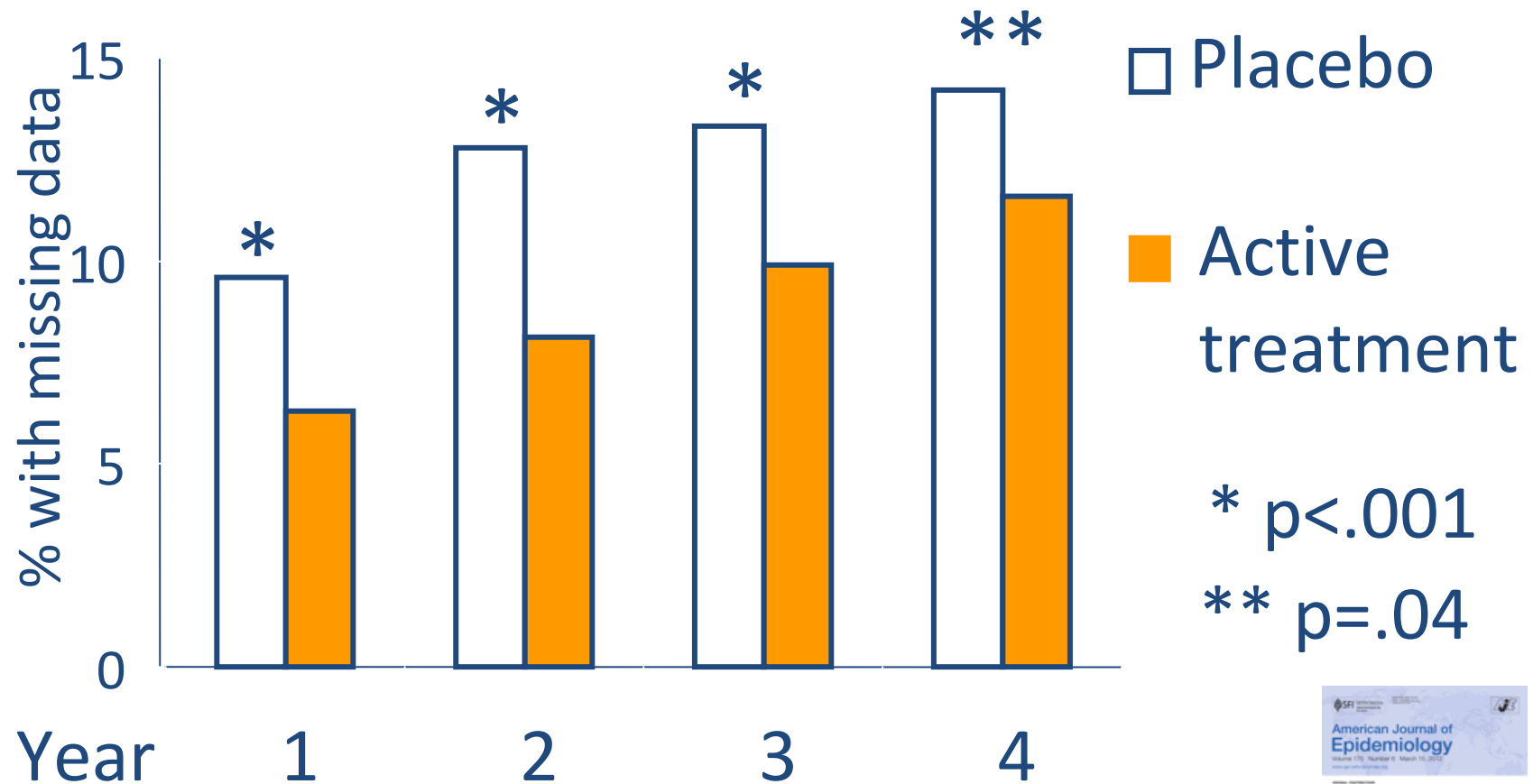***Real-world measure of clinical practice***

+ Informative

- Harder to collect

SHEP -Chlortalidone versus placebo

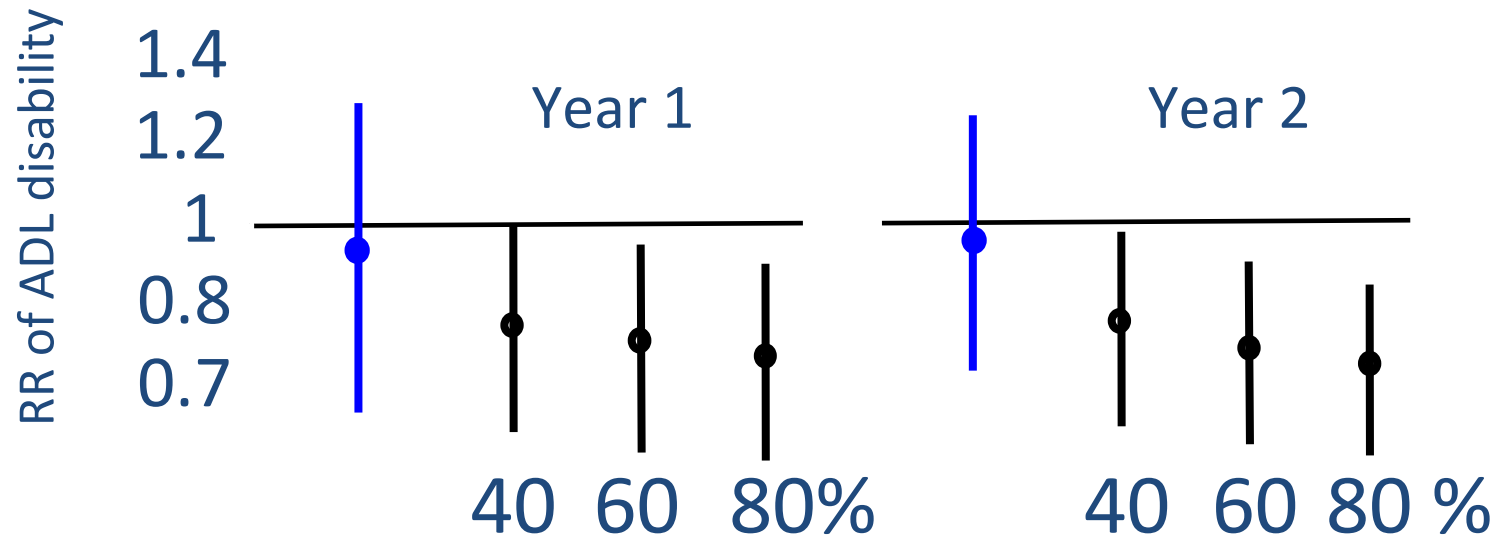| Outcome	RR	95% CI
Stroke	0.67	0.56-0.80
CHF	0.46	0.33-0.65
CHD	0.75	0.60-0.94
Any CVD	0.68	0.58-0.79

Deterioration of ADLs in SHEP

Missing disability assessments in SHEP

Di Bari Am J Epidemiol 2000

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

Di Bari Am J Epidemiol 2000

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.

Ware JH NEJM 2011