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Clinical Endpoints in Long-Term Studies in Alzheimer's Disease: Daily Functioning

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Assessment of Daily Functioning in AD

- The Premise
- Common Scales
- Measurement and Analysis Issues
- Future Directions

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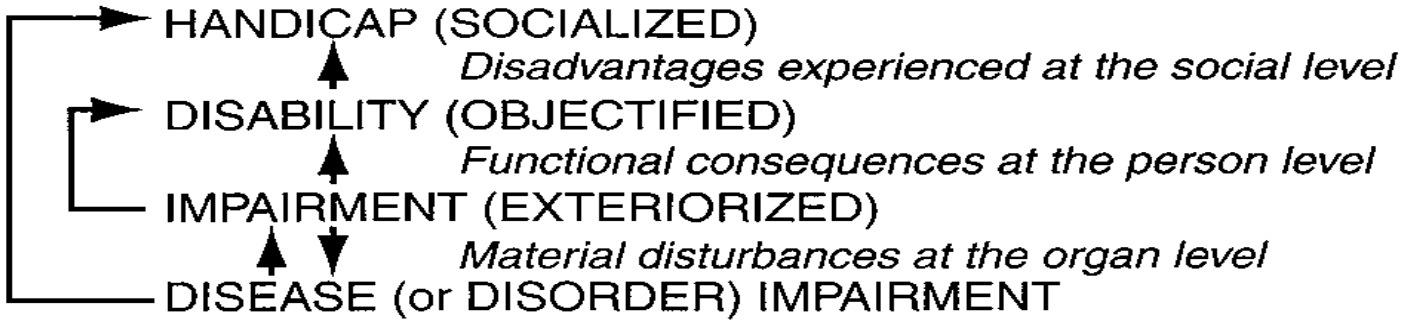
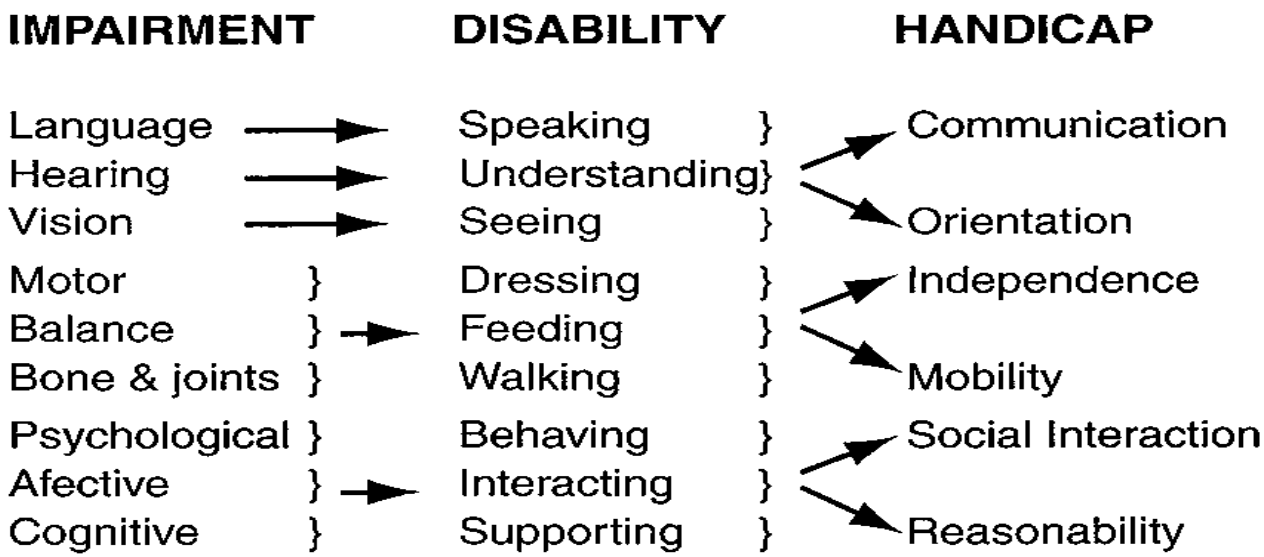
Premise

1. Functional behavior is the central outcome in health care. In AD, the preservation of functional independence is an essential objective of treatment.

2. Measurement of change in patient function is therefore key to evaluation of clinically meaningful outcomes of treatment for AD.

- Terms
  - Impairment
  - Disability
  - IADLs
  - BADLs





Gauthier, et al. (1999); Orgogozo (1994)

- **International Working Group on Harmonization of Dementia Drug Guidelines (IWGHDDG)**
- IADL and ADL Disability
- IADL loss precedes ADL loss
- Executive Function behaviors of initiation and planning related to performance of I/ADL

Gauthier, et al. (1997)

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Common I/ADL Measures

- **Generic**
  - Katz Index (BADL)
  - Refined ADL Assessment (BADL)
  - Physical Self-Maintenance Scale (BADL)
  - Lawton IADL
  - Structured Assessment of Independent Living Scale (IADL / ADL)
  - Performance Test of ADL (IADL and ADL)
  - Bayer ADL (IADL / ADL)

- **Disease-specific (dementia-specific)**

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Common I/ADL Measures

Assessment Measure	Function	Type	Advantages	Disadvantages
Direct Assessment of Functional Abilities	IADL	P	Useful in clinic-based setting	Time consuming
Direct Assessment of Functional Status	IADL and ADL	P	Sensitive to change over time	Time consuming
Functional Activities Questionnaire	IADL	I	Easy to use	Not useful for advanced dementia
Progressive Deterioration Scale	IADL and ADL	I	Can be used as quality-of-life scale	Time consuming
Interview for Deterioration in Daily Living Activities in Dementia	IADL and ADL	I	Initiative also evaluated	Time consuming
Disability Assessment for Dementia scale	IADL and ADL	I	Useful in antidementia drug trials	Time consuming
Bristol-ADL	IADL and ADL	I	Sensitive to change	Time consuming
Cleveland Scale for ADL	IADL and ADL	I	Useful in antidementia drug trials	Time consuming
Alzheimer's Disease Cooperative Study-ADL Inventory	IADL and ADL	I	Useful in antidementia drug trials	Time consuming
Dependence Scale	IADL and ADL	I	Useful from mild to most advanced stages	Time consuming
Alzheimer's Disease ADL-International Scale	IADL and ADL	I	Cross-nationally relevant	Time consuming

Desai, Grossberg and Sheth (2004). Activities of daily living in patients with dementia. CNS Drugs: 18 (13), 853-875.

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Key Question: Which measure is most sensitive to change?

Some Basic Considerations:

1. What assessment methods influence this?
2. What study design features influence this?
3. Is the measure appropriate to the patient's disease state?
4. Is the measure appropriate to the patient's culture?
5. Impact of individual differences on rating?
6. Study burden and respondent burden of measurement?

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AD Stage	Examples of I/ADL Scales
Mild (mostly IADL tasks)	ADCS-ADL Scale (Galasko, et al., 1997) IADL Scale (Lawton and Brody, 1999) Progressive Deterioration Scale (DeJong, et al.,1989)
Mild to Moderate (balance IADL and BADL)	Cleveland Scale for ADL (Patterson, 1992) Disability Asst for Dementia (Gelinas, et al., 1999) Modified Interview for Deterioration in Daily Living Activities in Dementia (Teunisse, et al., 1991)
Moderate to Severe (mostly BADL)	ADCS-ADL severe (Galasko, et al., 2005) Physical Self-Maintenance Scale (Lawton and Brody, 1969) Barthel Index (Mahoney and Barthel, 1965) Katz ADL Scale (Katz, et al., 1963; 1970; 2000)

Adapted from Gauthier, et al. (1999)

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Psychometric, Study Design and Analysis Considerations:

1. Measurement reliability (assuming validity)
2. Generic vs. Disease-specific measure
3. Floor and Ceiling Effects
4. Opportunity for recovery of performance once lost (habituation)
5. Method variance
   - caregiver/informant report and characteristics (over- and under-estimation; different informant at asst time point; caregiver burden, stress, morbidities)
   - clinician interview (standardization and drift)
6. Cross-cultural assessment issues
7. Subgroup differences
   - w/in Ss differences in rate of decline and responsiveness to Tx
8. Time of follow-up period (eg, “dependence” and FTC / NH admission)
9. Desynchrony between biomarker, cognitive, behavioral and functional assessment measures (response channel variation)
10. Dilution of Tx effect by modeling an IADL/ADL single score of “the average bear”
11. Clinical Meaningfulness of observed changes

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Future Directions:

1. **Further development of standardized functional scales**
   - ADCS Prevention Instrument Project
   - Item banking and "smart tree" assessment systems?
2. **Individualized assessment approach**
   - Goal Attainment Scaling?
3. **Cross-cultural measurement**
   - Cultural adaptation of functional concepts and response scaling
4. **Functional endpoint operational definition**
   - Time to milestones (eg, "dependence" and FTC / NH admission)
   - Time in health state
   - Proportion of "responders" AUC analysis
5. **Regulatory collaboration**
   - Alzheimer's Research Forum (June 2007)
   - Identified need for Working Group on functional scales
   - Evidentiary requirements in context of a regulated claim

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Expert Working Group

- Jeffrey Cummings
- Howard Feldman
- Serge Gauthier
- Roy Jones
- Oscar Lopez
- Rachel Schindler
- Elias Schwam
- Gunhild Waldemar
- David Wilkinson
- Yikang Xu
- Richard Zhang

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Creation of Standardized Functional Score (SFS)

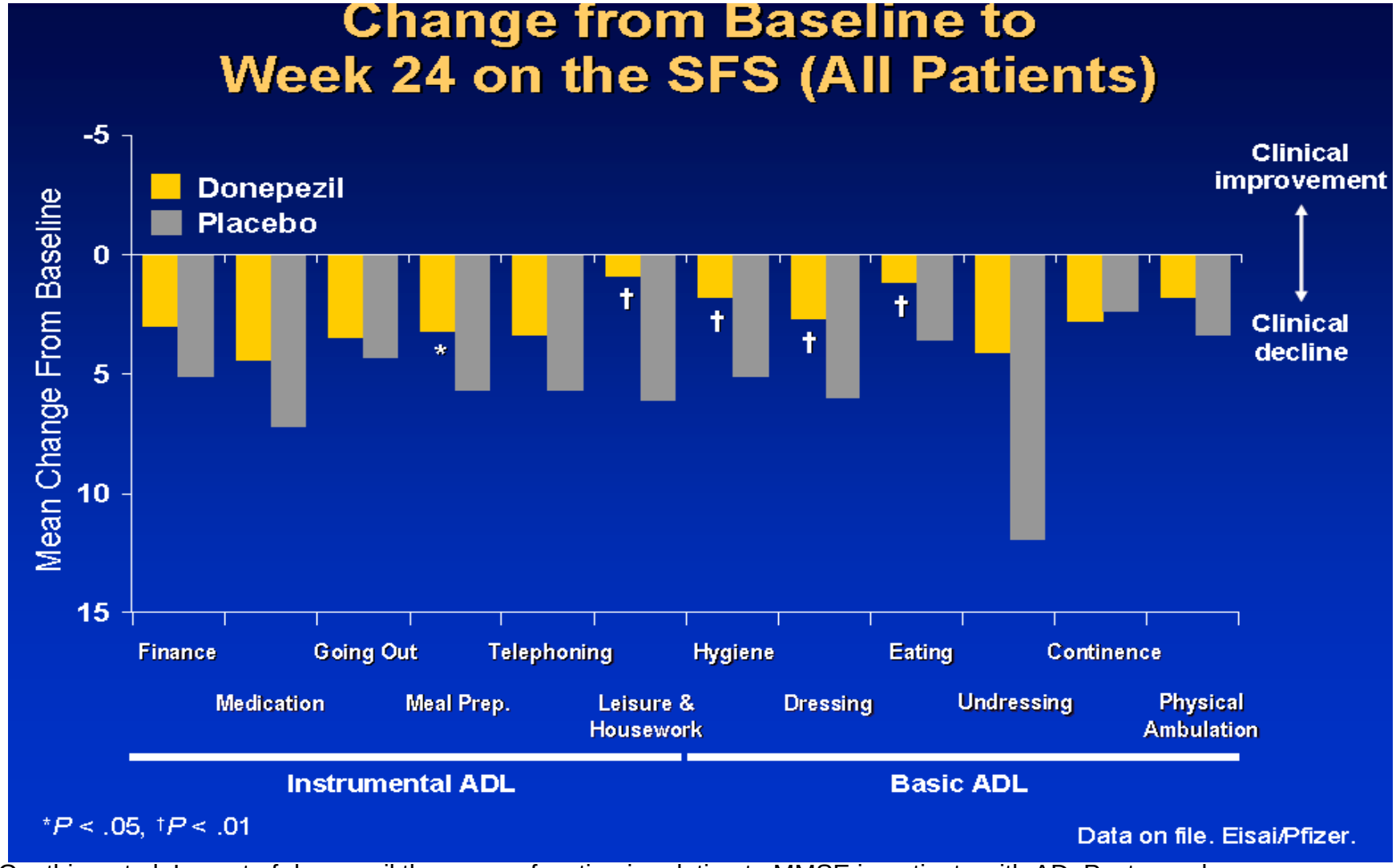
	STUDY					
	201	304	311	312	324	96-001
Function Measure	Uniform ADL	IDDD	PSMS	ADFACS	IADL PSMS* DAD	IADL PSMS

*physical ambulation item only

- Items from each scale matched to corresponding items on DAD scale
- The sum of each item score was transformed to a score ranging from 0 (complete independence) to 100 (total dependence)

IDDD = Interview for Deterioration in Daily living activities in Dementia ;
ADFACS = Alzheimer's Disease Functional Assessment and Change Scale .

Data on file. Eisai/Pfizer.



Gauthier, et al. Impact of donepezil therapy on function in relation to MMSE in patients with AD. Poster and Symposium. ICAD 2008.

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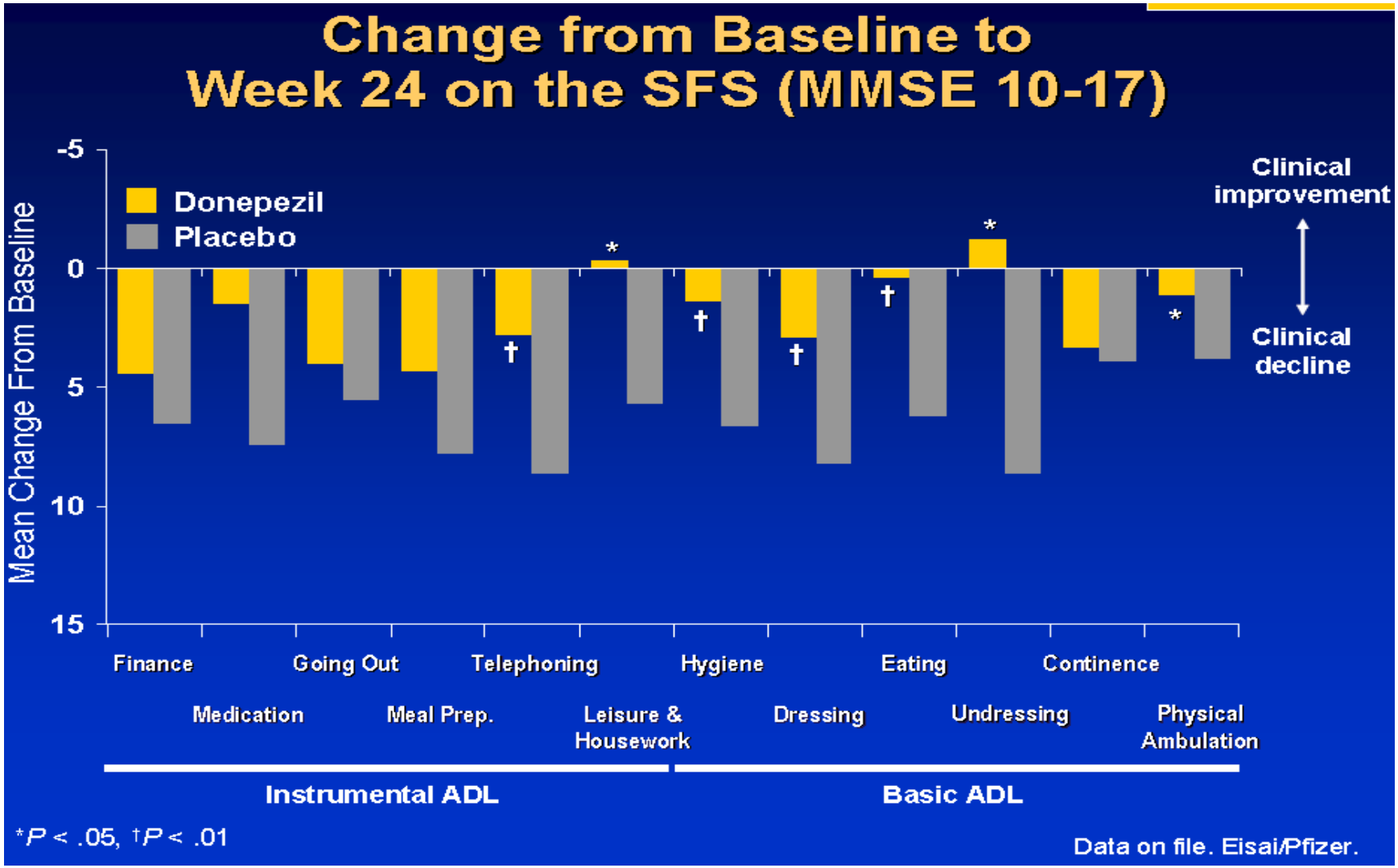

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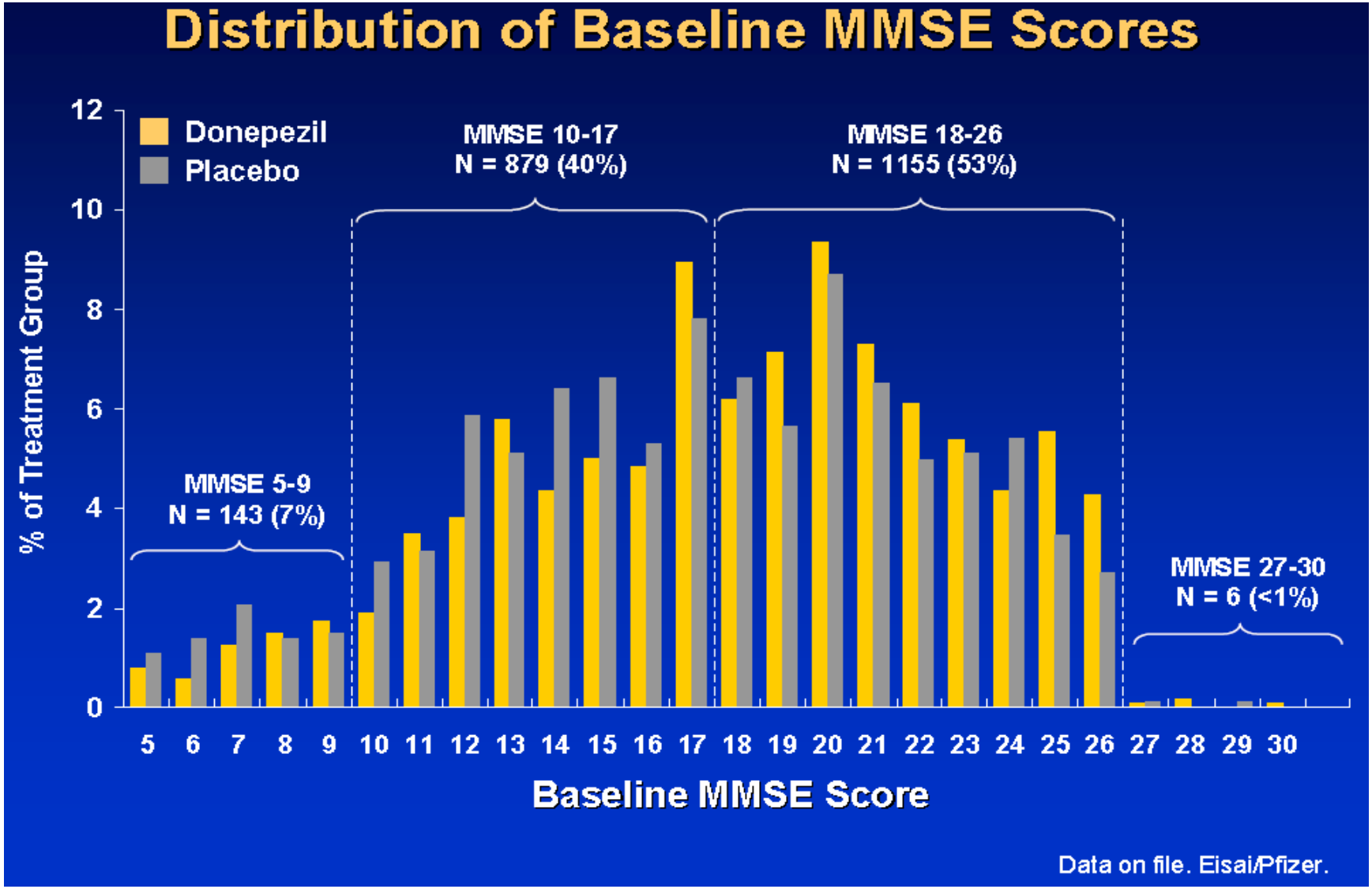
Distribution of Baseline MMSE Scores



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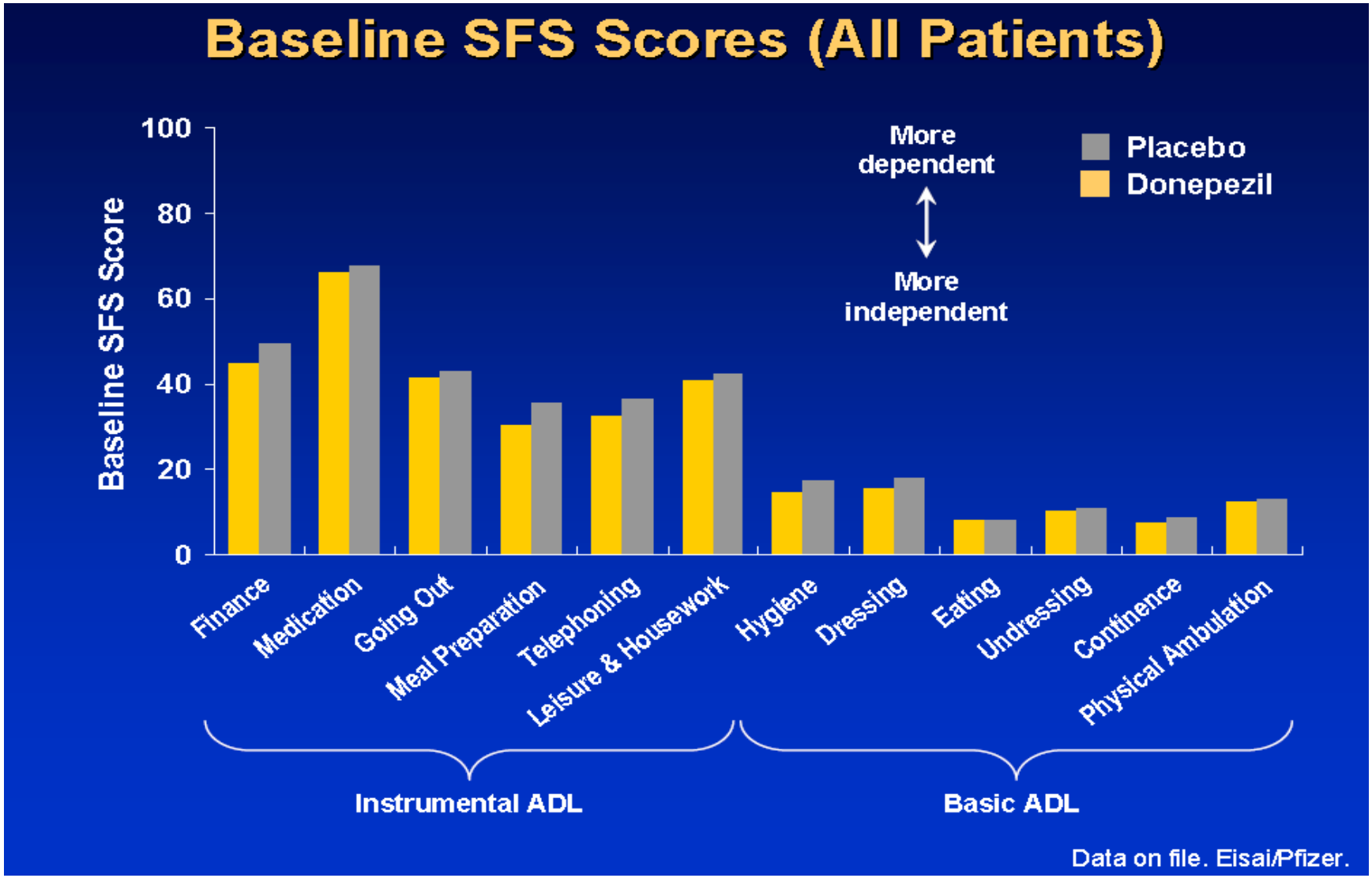
Baseline SFS Scores (All Patients)
Baseline SFS Score
100
80
60
40
20
0
More dependent
More independent
Placebo
Donepezil
Finance
Medication
Going Out
Meal Preparation
Telephoning
Leisure & Housework
Hygiene
Dressing
Eating
Undressing
Continence
Physical Ambulation
Instrumental ADL
Basic ADL
Data on file. Eisai/Pfizer.