[연수강좌]

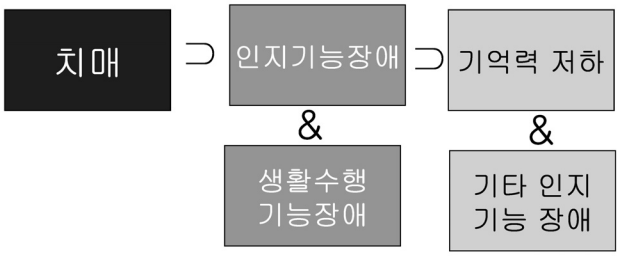
기억력 감퇴를 호소하는 환자

이 상 현

일산병원

기억력저하와 여러상황들

"선생님,
기억력이 떨어지는데요?"



치매란?

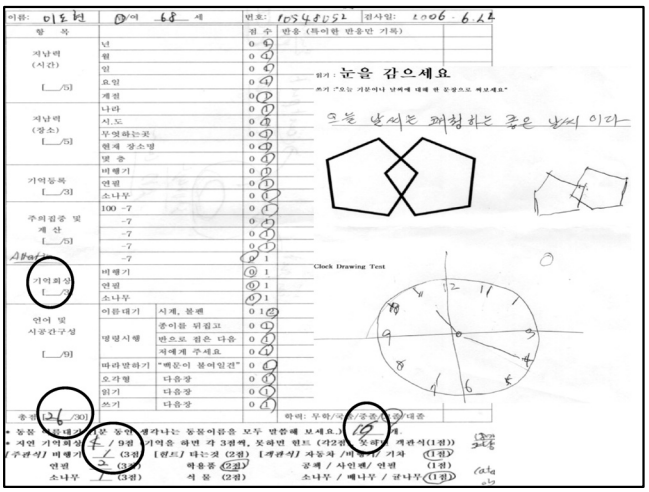
노인성 건망증

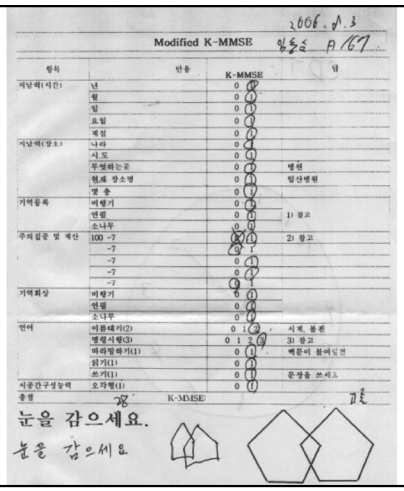
- 용어?
  - Benign Senescent Forgetfulness (Kral, 1962)
  - Age-associated Memory Impairment (Crook, 1986, NIMH)
  - Age-associated Cognitive decline (Levy, 1994)
- 비교기준은?
  - 젊었을 때보다 기억이 떨어진다?
- 왜?
  - 기억력의 주요부위인 해마의 기능저하보다는
  - 전두엽의 기능저하에 의한 인지처리속도 저하 (psychomotor speed)

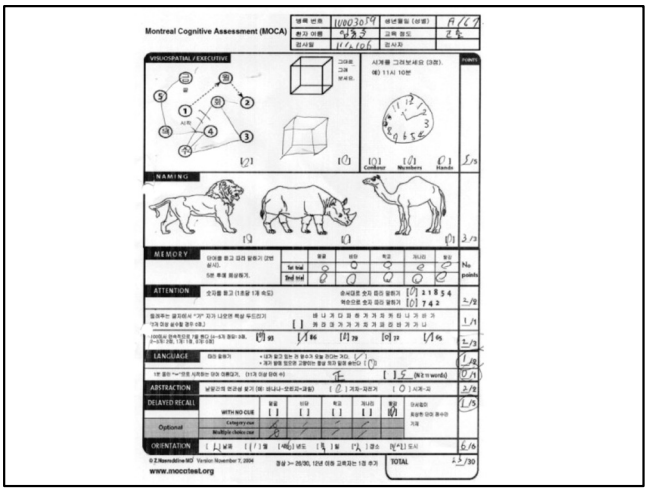
경도인지장애
(Mild Cognitive Impairment)

- 주관적 기억력 저하 호소, 본인 또는 보호자
- 기억력 검사상 객관적 기억력 저하가 있어야 함
  (같은 교육수준, 같은 나이에 비해 떨어짐 <1.5 SD)
- 그 외 다른 인지기능저하 없음
- 일상생활수행능력은 정상
- 따라서 치매는 아닌 경우

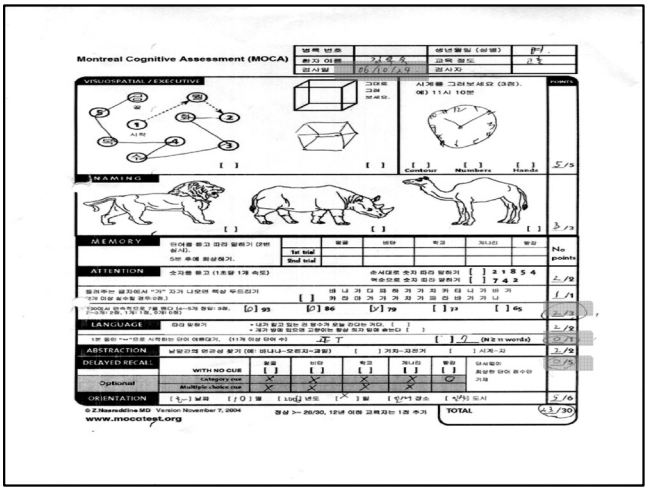
Cf: Amnestic MCI, Petersen, 2002

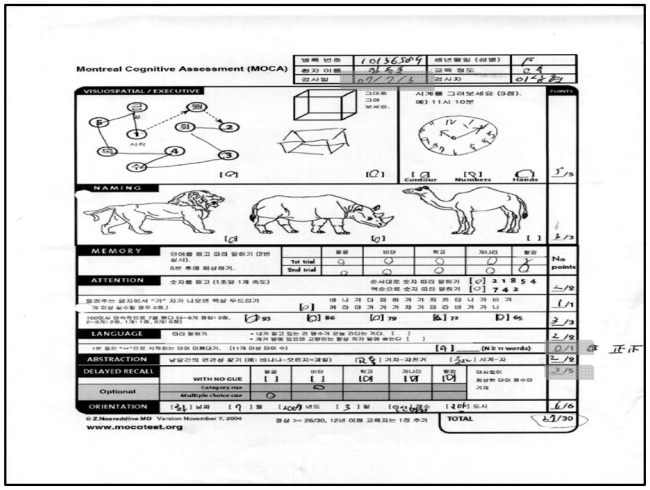






F/U 해 보면 나빠지나….





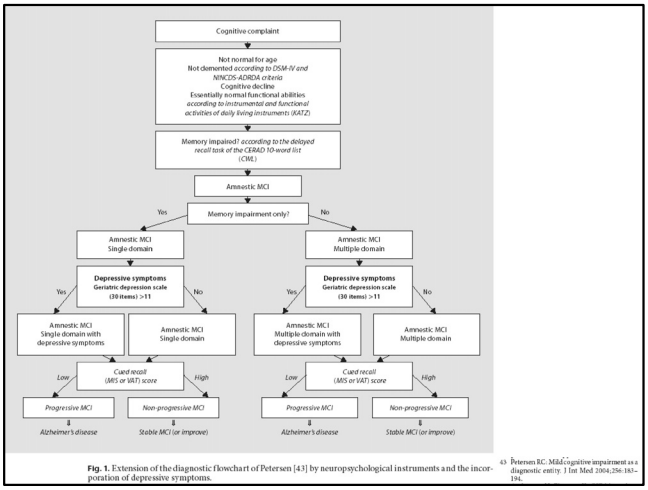
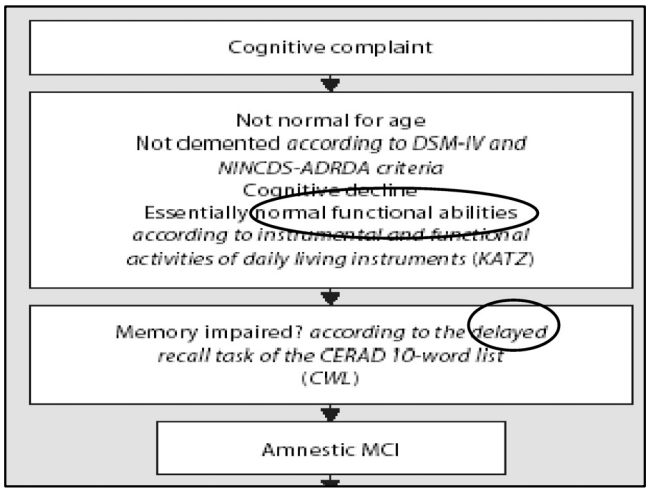
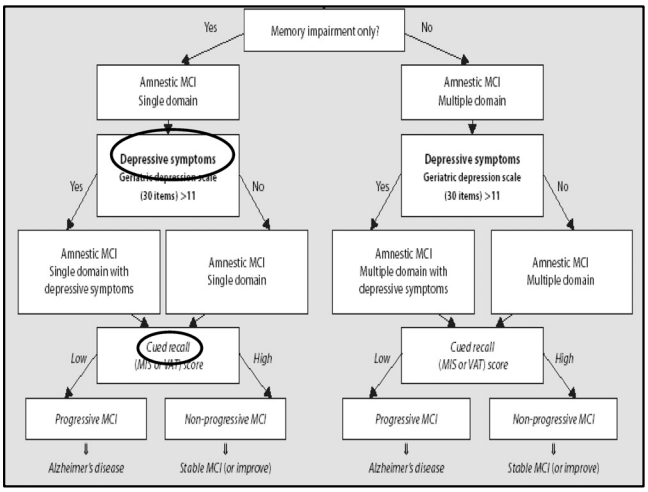


Fig. 1. Extension of the diagnostic flowchart of Petersen [43] by neuropsychological instruments and the incorporation of depressive symptoms.

43 Petersen RC: Mild cognitive impairment as a diagnostic entity. J Int Med 2004;256:183–194.





Delayed recall

- **Free Recall**
  - "제가 기억하라고 불러드린 것이 무언인지 말씀해 보시겠어요?" 주관식 => 3점
- **Cued Recall**
  - Categories 힌트 (타는 것, 학용품, 식물) => 2점
- **Recognition**
  - 선택 => 1점
  - 자동차, 비행기, 기차
  - 공책, 사인펜, 연필
  - 소나무, 배나무, 잣나무

2차 재시험
With 힌트 / 객관식

- If difficulty, ***Storage problem*** (eg;Cortical D. AD)
- If OK, (storage is OK but ***Retrieval problem***.
  - (eg: subcortical D, PD MCI)

- **Best predictor** of conversion to AD.
- **Best discriminator** between normal aging and mild AD.

What?

무슨 약물로 시작할 것인가?

Is one cholinesterase inhibitor better than the others?

- *Cochrane Review 2006*
- *10 RCT of dementia for 6mo*
  - *MMSE 호전 -2.7점*
- *More A/E in pt with ChEI than placebo.*

GI S/E
- Rivastigmine & Galantamine with food

Wt loss
- Rivastigmine

Drug interaction
- Donepezil & Galantamine
  - metabolized by hepatic cytochrome P450 isoenzyme
  - SSRI와 함께 투여시 농도증가 , 항경련제는 농도 감소
- Rivastigmine
  - hydrolyzed by brain esterases

Insomnia

Pharmacologic Agents for the Treatment of Alzheimer's Disease

	Cytochrome p450	Initial Dose	Does Escalation	Adverse Effects
Donepezil	+	5mg	increase to 10mg after 4 weeks	Nausea, fatigue, diarrhea, vomiting
Rivastigmine	- / BuChE	1.5mg	increase by 1.5mg bid every 2-4 weeks up to toal daily dose of 9-12mg	Nausea, weight loss, diarrhea
Galantamine (ER)	+/ Nicotine	4mg	increase 80 mg bid after 4weeks; on additional increase to 12mg bid may be considered 4 weeks later	Nausea, vomiting, anorexia, diarrhea
Memantine*	-	5mg	increase by 5mg weekly to total of 20mg daily(5mg qd, 5mg bid, 10mg in AM and 5mg in PM, 10mg bid)	Headache, dizziness, constipation

ER = extended-release. 국내보험기준 MMSE 10-26 & (CDR 1-2 or GDS 3-5), *MMSE <=14

AchI를 투약하면 정말 좋아지는가?

Yes or No?

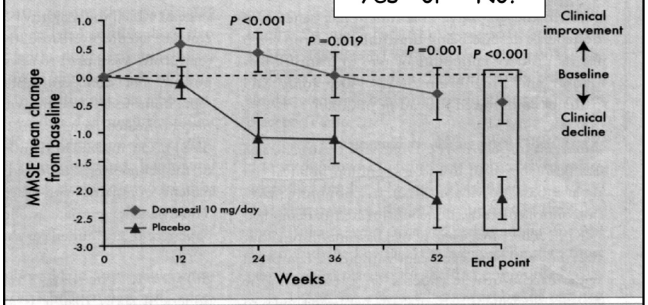


Figure 2. Long-term benefits of donepezil in a 1-year, placebo-controlled trial.

Reprinted with permission from Winblad B, Engedal K, Soininen H, et al; Donepezil Nordic Study Group. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. Neurology 2001;57(3):489-495.

When?

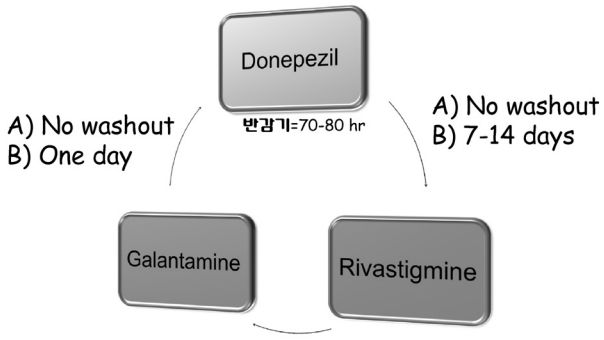
언제 약을 바꾸고,
언제까지 투약할 것인가?

교체 기준

A. 3개월째 인지기능 평가
- 좋아지거나 비슷하면 => 약물 효과
- 나빠지면 => 교체 고려
- (AD 평균 MMSE 점수 감소는 3.3점/년)

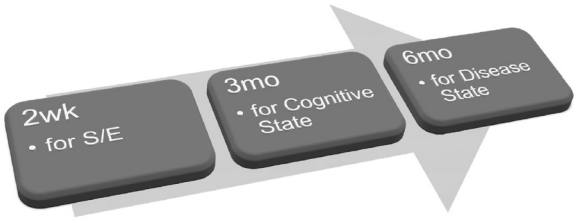
B. 부작용

Switching ChEI



어떻게 F/U하며 언제까지 투여할 것인가?

Monitoring Point



6-mo should elapse before any definite decision regarding the efficacy.

Response should not be judged in a single domain.

언제까지 사용할 것인가?

- 연구결과들 (AchI)
  - 초기 : 인지기능/ 일상생활 활동 호전
  - 9-12개월 : 위약군보다는 좋지만 투여전 상태
  - 5년 추적결과 : 치료군이 상대적 차이를 보임
- 결론
  - 지속적 투여가 도움
  - 언제까지?
    - 치매말기
      - 한두단어 말, 대소변 식사 전적 의존, 운동기능 상실
  - Cf: 약 끊고서 급속히 악화되면 재투약 고려

	Normal Aging	Alzheimer's Disease
Memory Impairment	Retrieval deficit type	Amnestic type
Word finding	Minor delay	Anomia
Visuospatial function	Retained	Impaired
Insight	Retained	Loss
ADL	No change	Compromised
Social engagement	Retained	Apathy, withdrawal

Farlow MR. AJM 2007

Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

Ronald C. Petersen, Ph.D., M.D., Ronald G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H., David Bennett, M.D., Rachelle Doody, M.D., Ph.D., Steven Ferris, Ph.D., Douglas Galasko, M.D., Shelia Jin, M.D., M.P.H., Jeffrey Kaye, M.D., Allan Levey, M.D., Ph.D., Eric Pfeiffer, M.D., Mary Sano, Ph.D., Christopher H. van Dyck, M.D., and Leon J. Thal, M.D., for the Alzheimer's Disease Cooperative Study Group*

ABSTRACT

BACKGROUND
Mild cognitive impairment is a transitional state between the cognitive changes of normal aging and early Alzheimer's disease.

METHODS
In a double-blind study, we evaluated subjects with the amnestic subtype of mild cognitive impairment. Subjects were randomly a… of donepezil daily, or placebo for thre… ble or probable Alzheimer's disease; s…

Method : 769명 Vit E 2000 IU & 10 mg of donepezil for three years. (n=769)
The primary outcome = AD
Secondary outcomes = cognition and function.

RESULTS
A total of 769 subjects were enrolled, … veloped in 212. The overall rate of pro… heimer's disease was 16 percent per … were no significant differences in the … in the vitamin E group (hazard ratio, 1… P=0.91) or the donepezil group (haza… to 1.13; P=0.42) during the three yea… ment effects at 6-month intervals showed that as compared with the placebo group, the donepezil group had a reduced likelihood of progression to Alzheimer's disease during the first 12 months of the study (P=0.04), a finding supported by the secondary outcome measures. Among carriers of one or more apolipoprotein E ϵ4 alleles, the benefit of donepezil was evident throughout the three-year follow-up. There were no significant differences in the rate of progression to Alzheimer's disease between the vitamin E and placebo groups at any point, either among all patients or among apolipoprotein E ϵ4 carriers.

CONCLUSIONS
Vitamin E had no benefit in patients with mild cognitive impairment. Although donepezil therapy was associated with a lower rate of progression to Alzheimer's disease during the first 12 months of treatment, the rate of progression to Alzheimer's disease after three years was not lower among patients treated with donepezil than among those given placebo.

From the Mayo Clinic College of Medicine, Rochester, Minn. (R.C.P.); University of California, San Diego, San Diego (R.G.T., D.G., S.J., L.J.T.); Elan Pharmaceuticals, San Diego (M.G.); Rush University Medical School, Chicago (D.B.); Baylor College of Medi-…

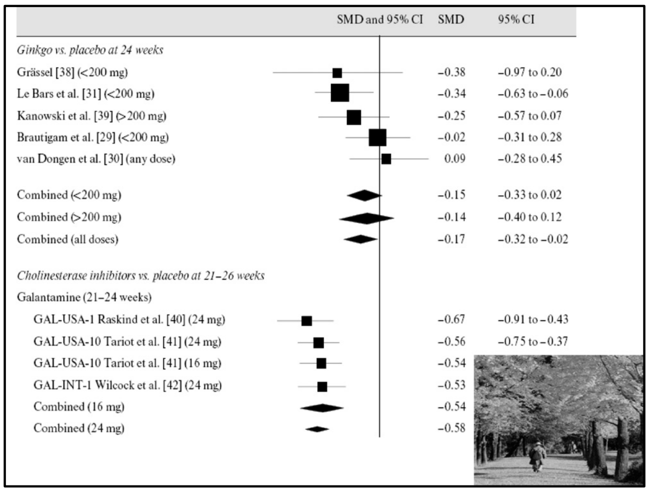
This article was published at www.nejm.org on April 13, 2005.

N Engl J Med 2005;352:2379-88.
Copyright © 2005 Massachusetts Medical Society.

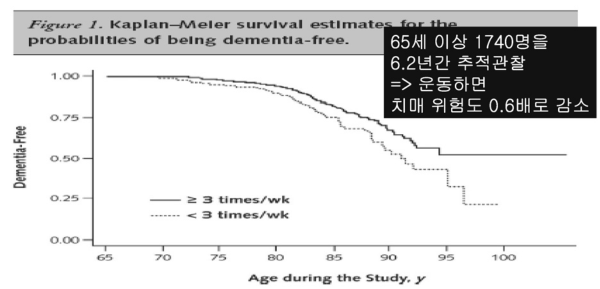
Table 3. **Hazard Ratios for the Risk of Progression to Alzheimer's Disease in the Donepezil and Vitamin E Groups as Compared with the Placebo Group.***

Interval	All Subjects		*APOE* ϵ4 Carriers	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Donepezil vs. placebo				
First 12 mo	0.42 (0.24–0.76)	0.004	0.34 (0.16–0.69)	0.003
First 24 mo	0.64 (0.44–0.95)	0.03	0.54 (0.35–0.86)	0.009
All 36 mo	0.80 (0.57–1.13)	0.21	0.66 (0.44–0.98)	0.04
Vitamin E vs. placebo				
First 12 mo	0.83 (0.52–1.32)	0.43	0.78 (0.46–1.34)	0.37
First 24 mo	0.95 (0.67–1.36)	0.79	0.95 (0.64–1.41)	0.79
All 36 mo	1.02 (0.74–1.41)	0.91	0.95 (0.66–1.36)	0.77

* CI denotes confidence interval. P values were not adjusted for multiple comparisons. In the donepezil group, when corrected for multiple comparisons, the P value at 24 months for all subjects became nonsignificant (P=0.052), and the P value at 36 months for *APOE* ϵ4 carriers also became nonsignificant (P=0.078).

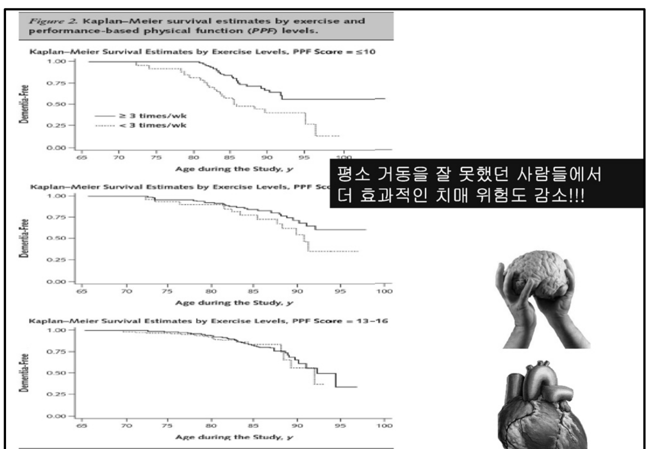


운동하면 정말 치매가 예방되나?



Persons who exercised 3 or more times per week were more likely to be dementia-free than those who exercised fewer than 3 times per week.

Ann Intern Med. 2006;144:73-81



Persons who exercised 3 or more times per week had a higher probability of being dementia-free than those who exercised fewer than 3 times per week if their PPF score was less than 13. This relative risk reduction of dementia by exercise was greater among persons with lower PPF scores than among those with higher PPF scores.