认知障碍(腦退化)症患者的药物治疗

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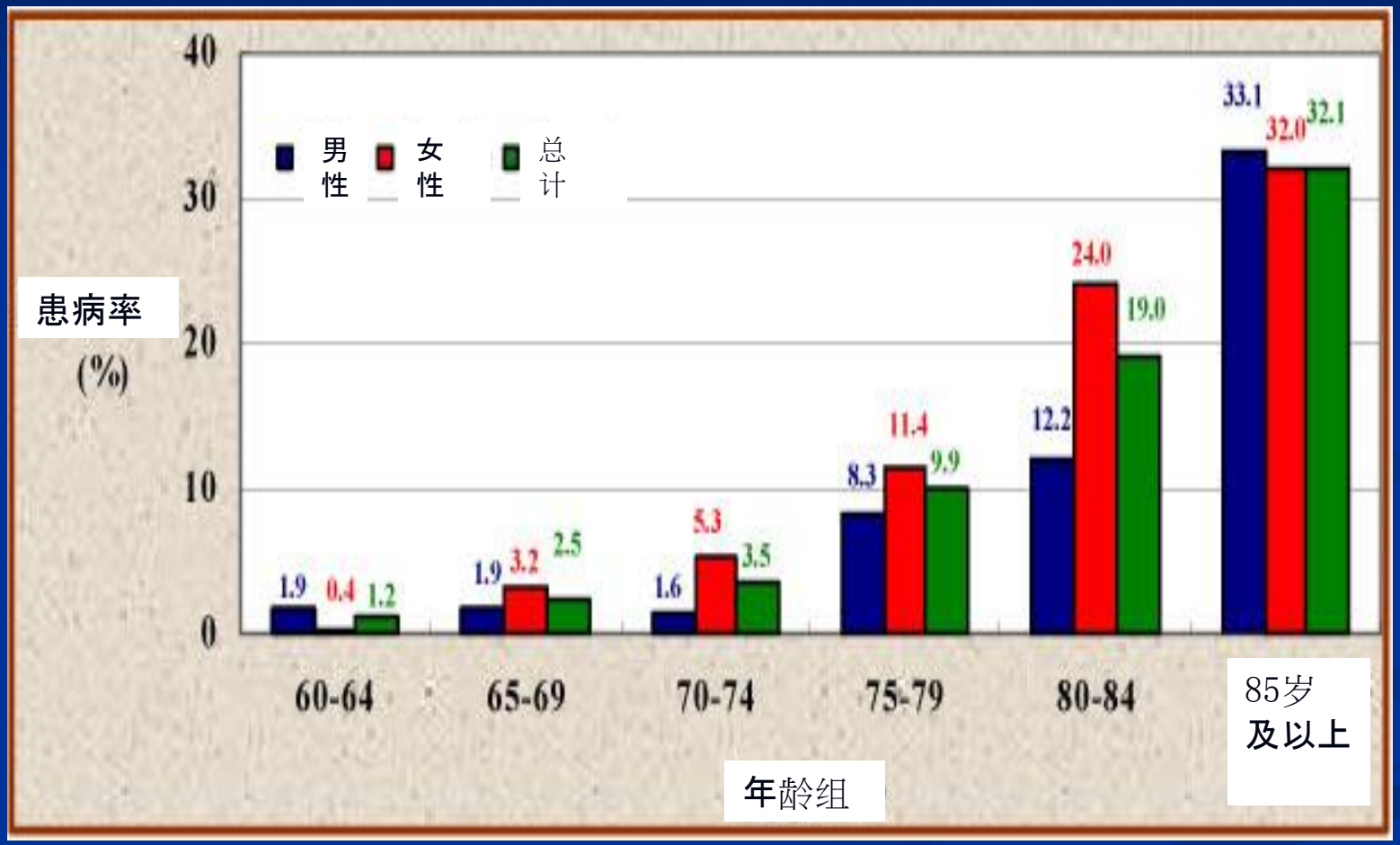
社区腦退化患病率



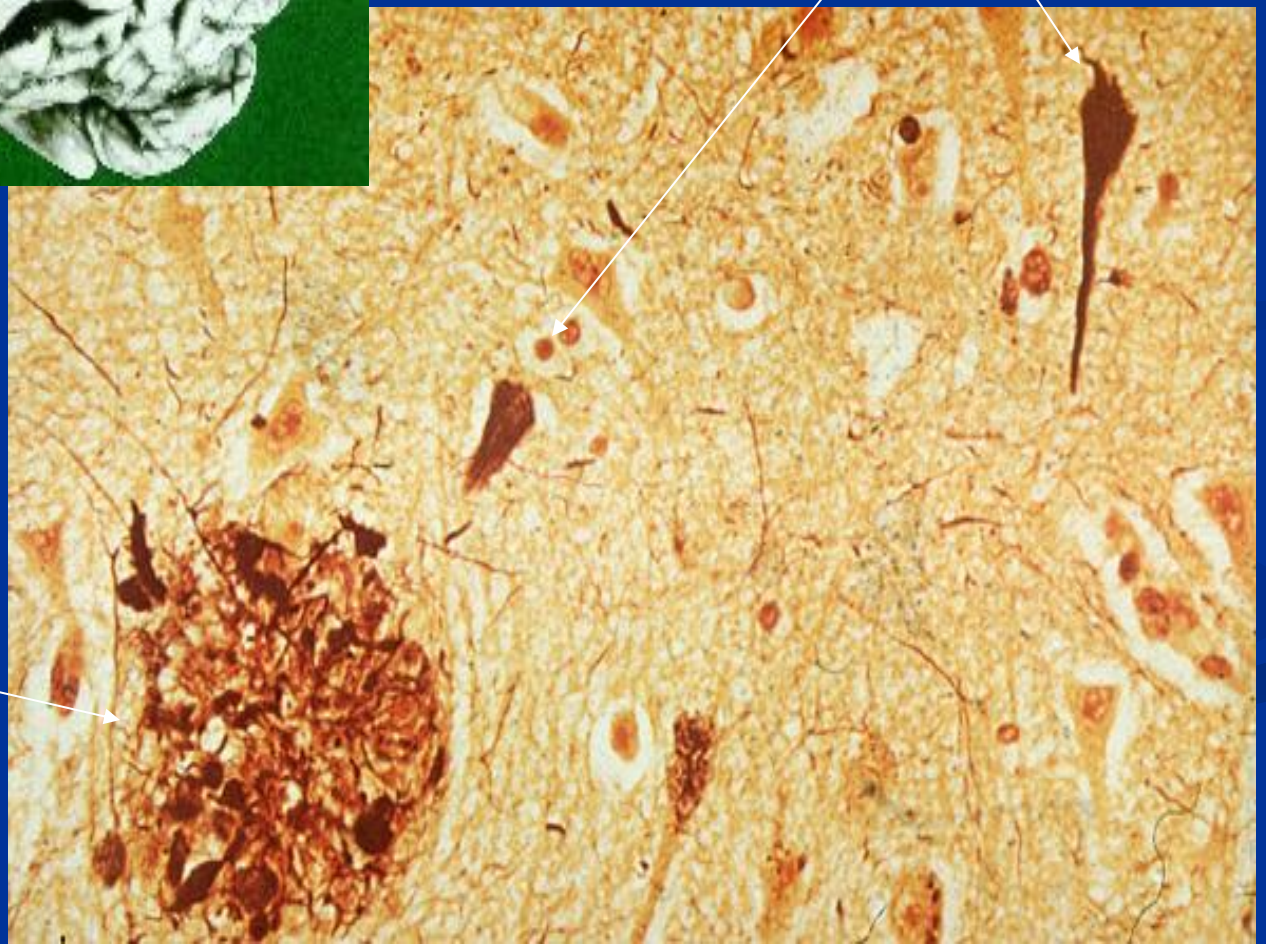
Centre for Health Protection (2006). Aware (Newsletter). Volume 3, Issue 12

阿尔茨海默病

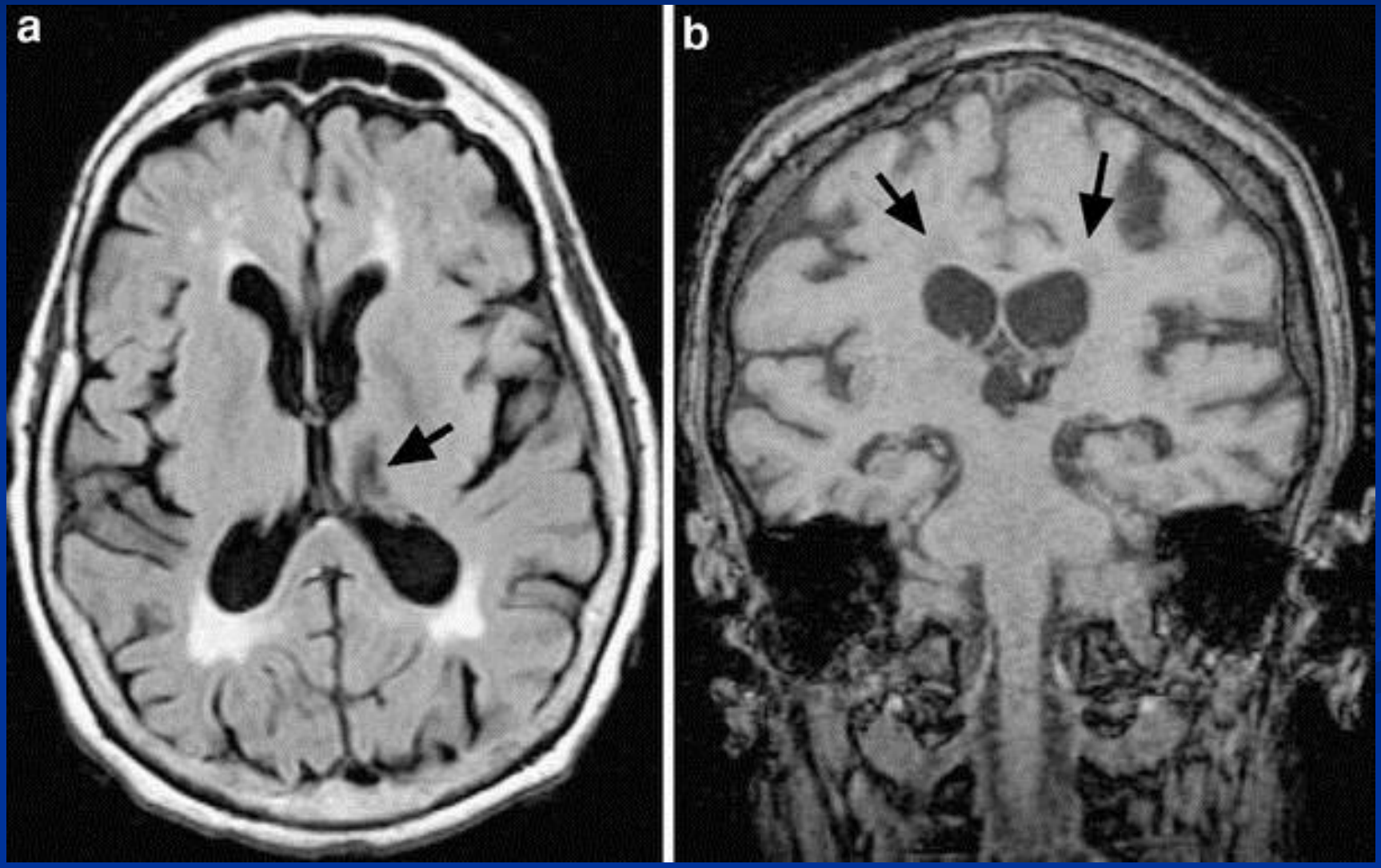
萎缩

缠结

斑块



混合性腦退化的病变



早期

- 高级ADL能力受损
- 自知力
- 焦虑、抑郁
- 社会关系障碍
- 对药物/生活方式不依从
- 营养障碍
- 财物管理
- 居家安全

中期

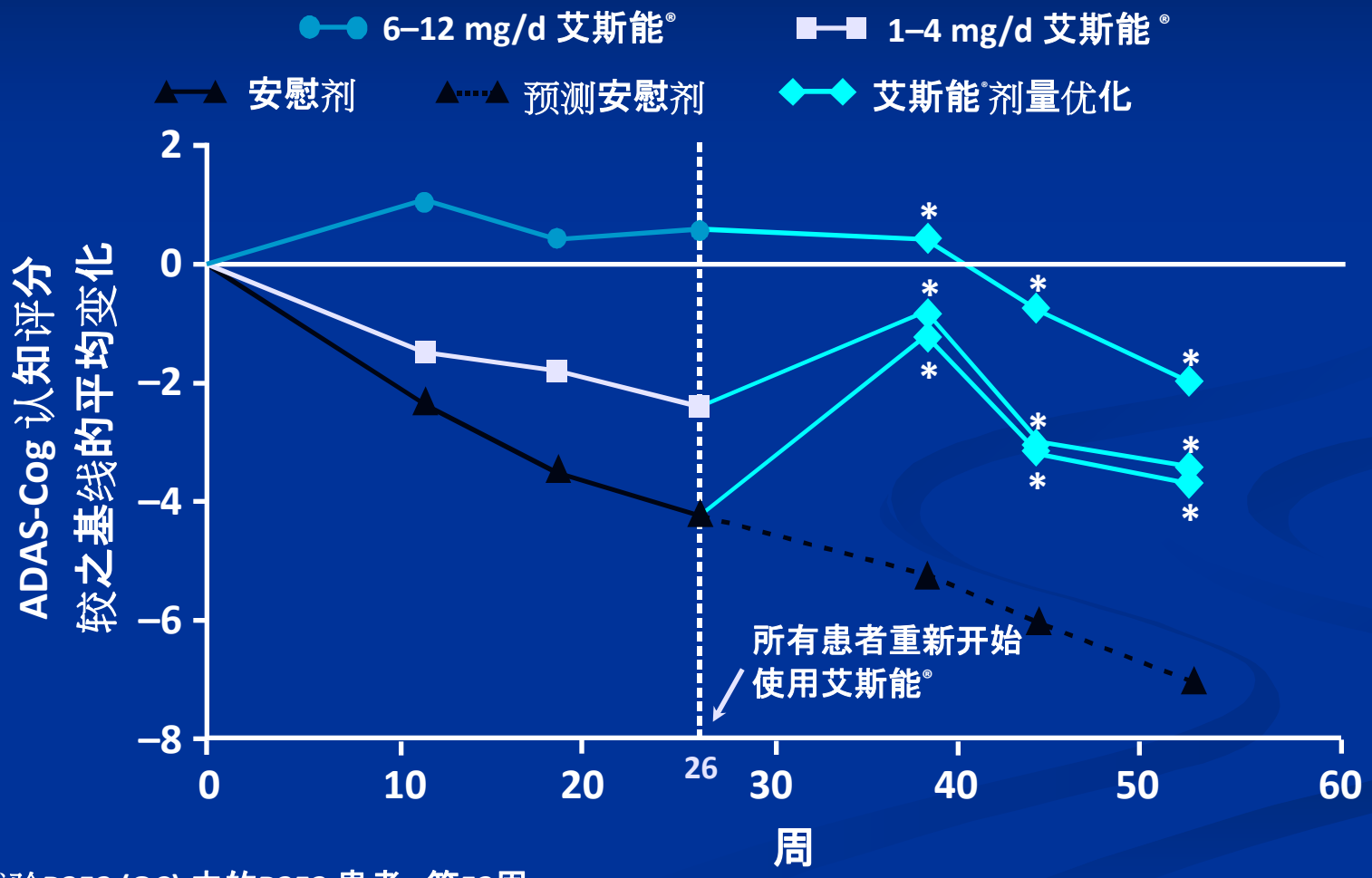
- 基本ADL能力受损
- 居家安全
- 照护者支持
- 行为障碍
- 抑郁
- 精神病
- 自知力损害

晚期

- 躯体依赖
- 嗜睡
- 进食障碍
- 精神障碍
- 临终问题

AD的药物治疗

胆碱酯酶抑制剂(cholinesterase inhibitor)对认知功能的影响



试验B353 (OC) 中的B352 患者，第52周
*p<0.05 vs 统计学预测的安慰剂

Messina et al., 2000

胆碱酯酶抑制剂(cholinesterase inhibitors)的不良反应

- 恶心 (11%)
- 厌食 (10%)
- 呕吐 (5%)
- 失眠 (9%)
- 眩晕 (8%)
- 肌肉痉挛 (5%)
- 做恶梦 (高达 10%)

胆碱酯酶抑制剂的不良反应

- 大部分患者不会出现不良反应
- 副作用呈剂量依赖性
- 如采用滴定法逐步增加剂量，可降低副作用的发生频率
- 通常可随时间逐渐缓解，或者减量后即可缓解
- 艾斯能贴片的消化道症状可能更少

Rationale for Transdermal Patch in AD

Reduce side effects

- Reducing side effects by providing smooth, continuous drug delivery over 24 h for long duration action[1]
- Avoiding first-pass effect[1]

Achieve high dose

- Improved tolerability allowing easier and faster access to higher doses with better efficacy[2]
- Preserving existing quality of life for as long as possible[3]

Improve compliance

- Helping family members to monitor treatment compliance (visual reassurance)[4]
- Simplifying treatment for elderly patients often taking many other medicines[4]
- Administration independent of food intake[4]

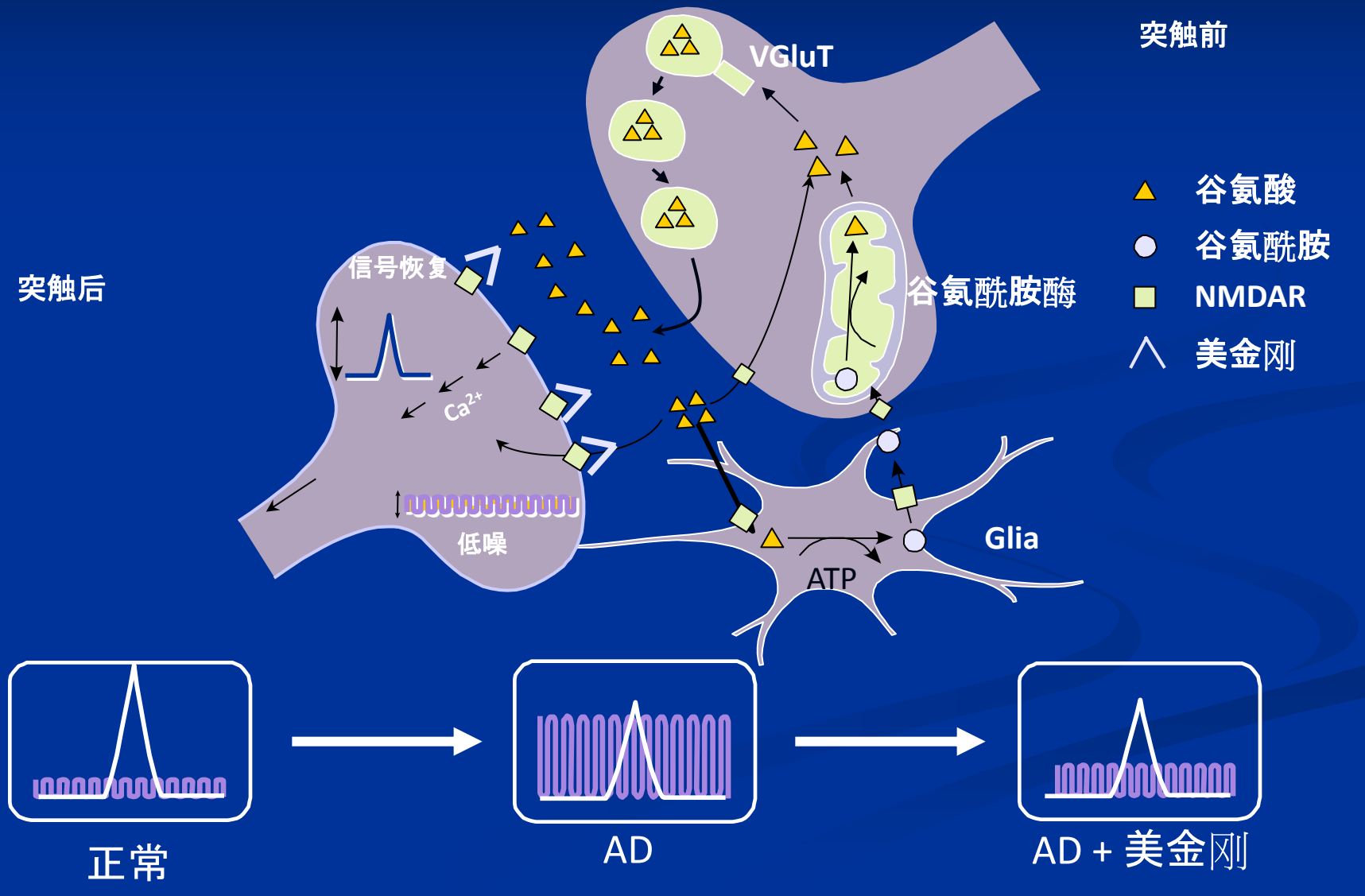
1. Cummings & Winblad, *Expert Rev Neurotherapeutics* 2007;7:1457–63; 2. Cumming J et al., *Dementia* 2012;33:341-53; 3. Small G & Bollock R, *Alzheimer's & Dementia* 2011;7:177-84; 4. Exelon ® Patc Monograph, 2012

NOVARTIS

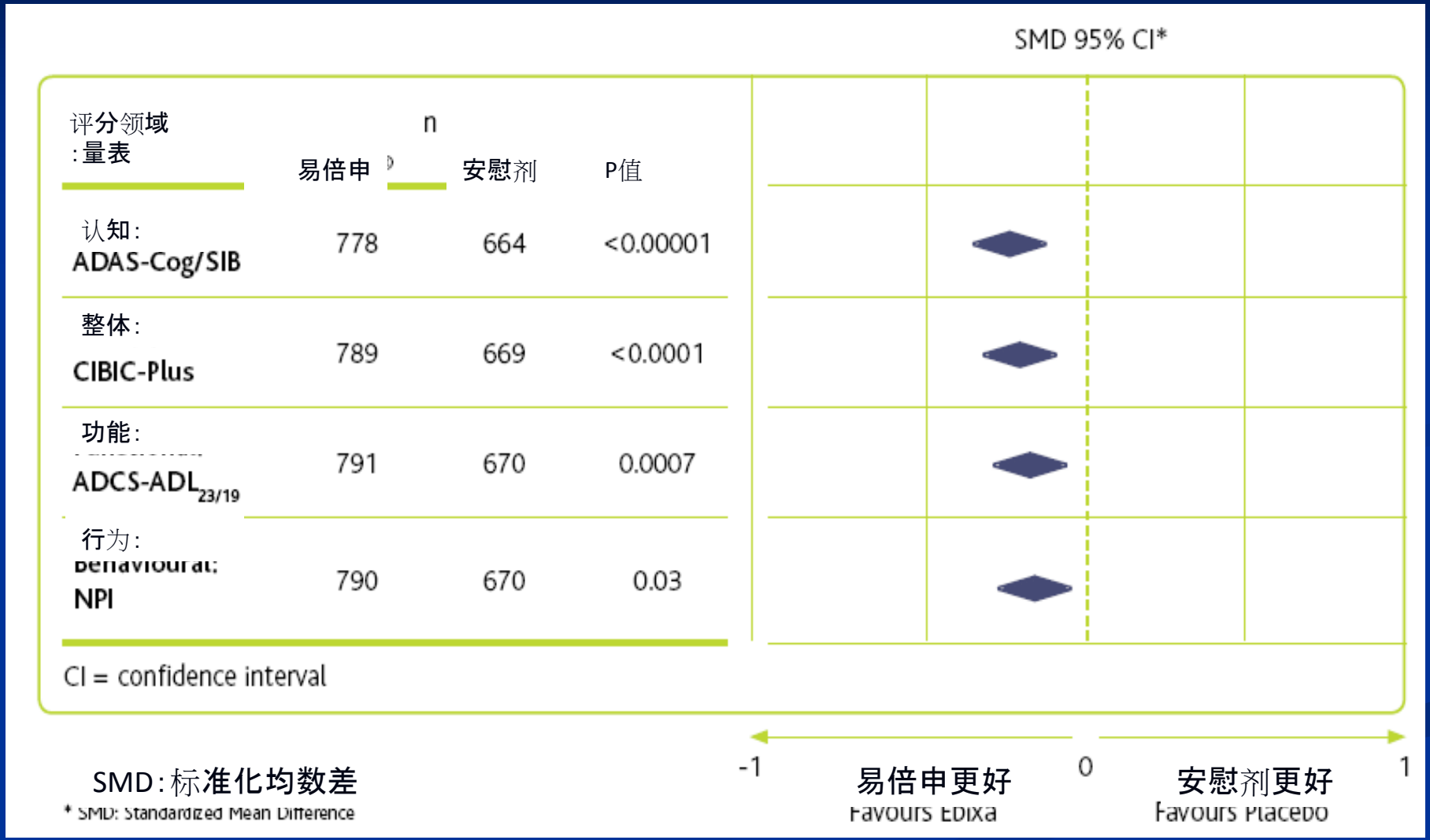
易倍申 (美金刚)(memantine)

- 非竞争性NMDA受体拮抗剂
- 可有效治疗AD和血管性认知障碍(VaD)
- 耐受良好
- 疗效和安全性已获得FDA & EMEA的肯定 (中度/重度AD)
- 有片剂 (10mg b.d.)

AD的谷氨酸-谷氨酰胺循环

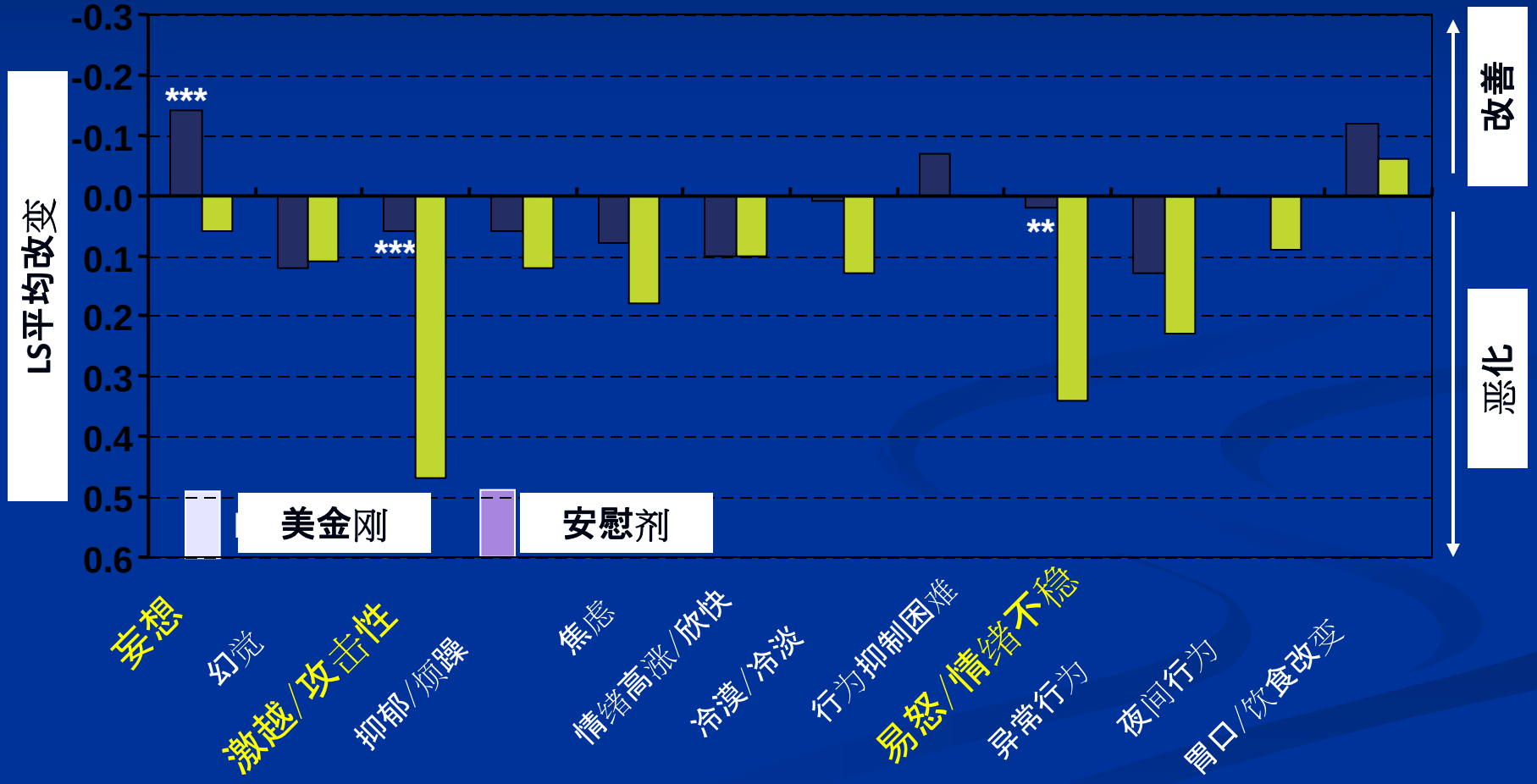


易倍申对阿尔茨海默病各方面症状的显著影响



Winblad et al. Dement Geriatr Cogn Disord 2007;24:20-27

美金刚对行为的影响
来自6项III期安慰剂对照研究的汇总数据



**p<0.01; ***p=0.001

Gauthier et al. Poster at ICAD 2006

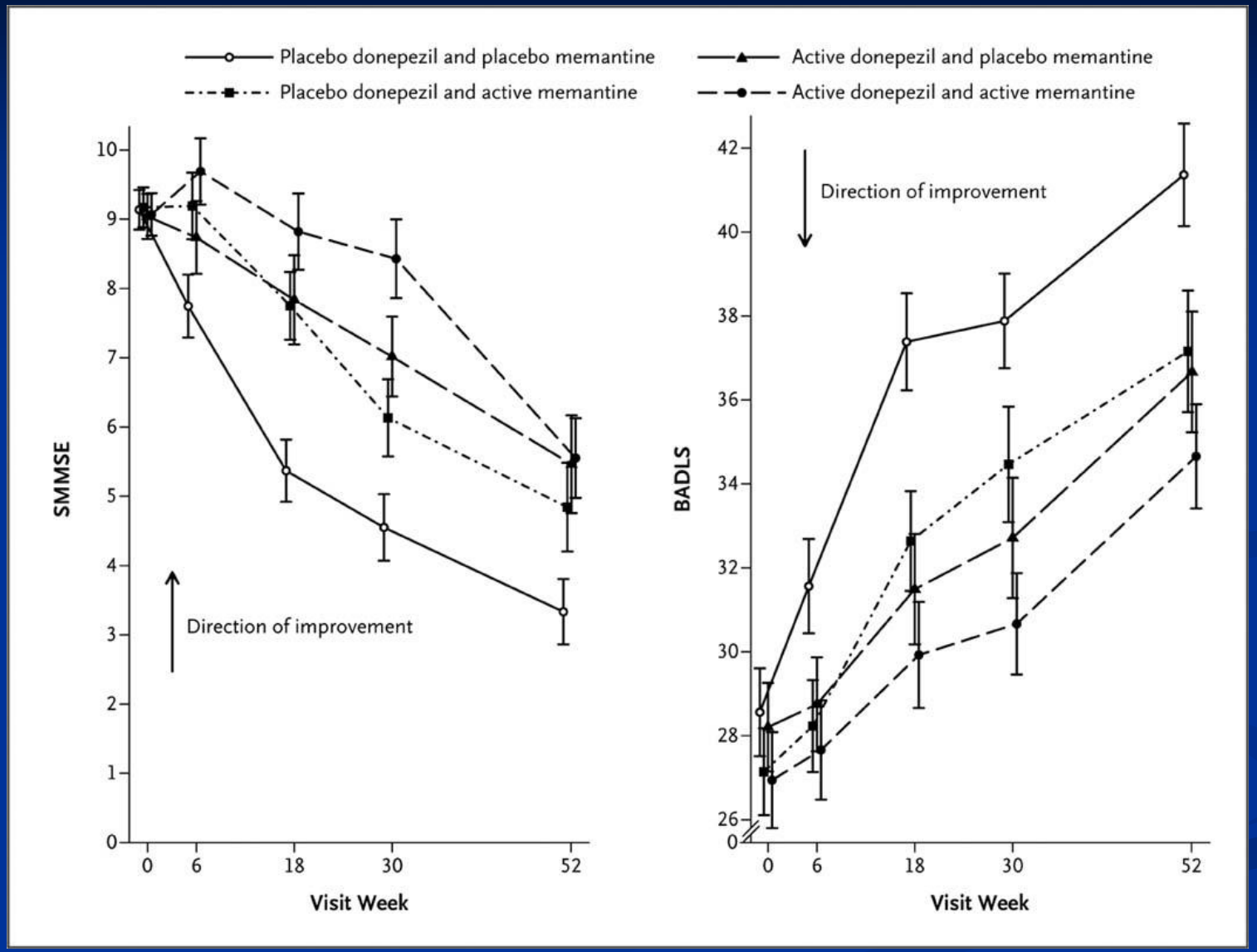
Common questions

- Are there any differences among the three cholinesterase inhibitors
- Do memantine and cholinesterase inhibitor have additive effects ?
- When to stop AD drugs?

Randomized trial of Donepezil ± Memantine in moderate/severe AD on Donepezil

	Placebo (N=72)	Memantine (N=74)	Donepezil (N=73)	Both (N=72)
Age (yr)	77.7	76.2	77.2	77.5
Female (%)	64	61	70	67
MMSE	9.1	9.2	9.0	9.1
NPI	22.9	23.1	22.3	20.3

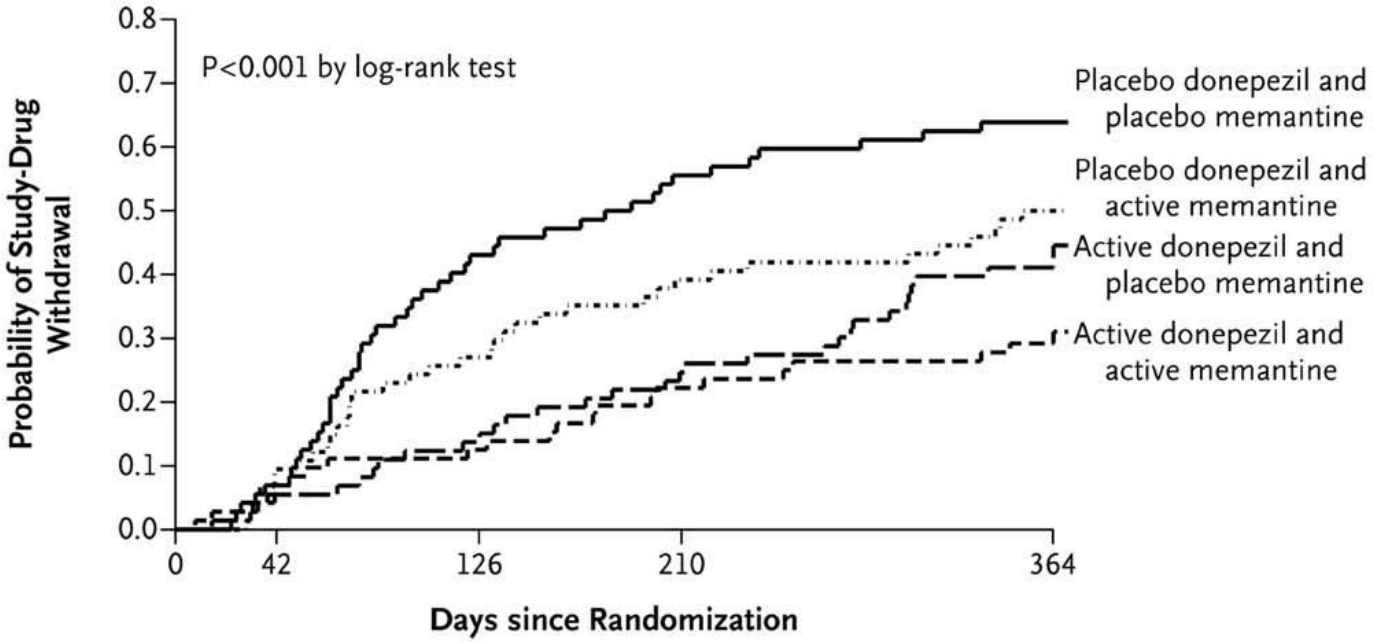
Mean Scores on the Standardized Mini–Mental State Examination (SMMSE) and the Bristol Activities of Daily Living Scale (BADLS), According to Visit Week and Treatment Group.



Howard R et al. N Engl J Med 2012;366:893-903

The NEW ENGLAND JOURNAL of MEDICINE

Cumulative Probability of Withdrawal from Study Drug



No. of Patients Still Receiving Study Drug					
Placebo donepezil and placebo memantine	72	67	41	32	20
Placebo donepezil and active memantine	74	67	54	45	27
Active donepezil and placebo memantine	73	69	63	55	34
Active donepezil and active memantine	72	68	63	56	38

Howard R et al. N Engl J Med 2012;366:893-903

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Estimated average effect of donepezil and memantine over one year

	MMSE (N=284-217)	ADL (N=284-218)	NPI (N=283-217)
Donepezil vs placebo	1.9 (1.3 to 2.5)	-3.0 (-4.3 to -1.8)	-2.3 (-5.7 to 1.1)
Memantine vs placebo	1.2 (0.6 to 1.8)	-1.5 (-2.8 to -0.3)	-4.0 (-7.4 to -0.6)

重點

- Stopping treatment in patients with moderate or severe AD resulted in more cognitive and functional decline
- Both donepezil and memantine significantly improved cognitive function and daily functioning
- Memantine had a significant modest effect on behavioral problems
- Memantine and donepezil may not have significant additive effect, but may complement each other

The NEW ENGLAND JOURNAL of MEDICINE

行为障碍

- 情绪爆发
- 指责他人偷窃/不忠
- 无目的徘徊
- 拒绝洗澡
- 随地大小便
- 性骚扰
- 妄想/幻觉
- 日夜颠倒

巴月安抑制劑(Dopamine antagonists)

- 常用于“控制” AD患者的行为问题
- 没有证据证明其对于痴呆患者有效
- 研究表明利培酮 (risperidone) 能改善谵妄 in the short term
- 有证据显示其可能 stroke risk以及死亡率增加
- 副作用包括帕金森综合症、过度镇静、跌倒

改善脾气和攻击性的替代药物

- SSRI
- 曲唑酮 (trazodone)
- 美金刚 (memantine)
- 丙戊酸钠 (sodium valproate)

日间护理

- 团体与个人的活
- 家庭照护者的支持

賽馬會耆智園
Jockey Club Centre for Positive Ageing

家庭照护者网站 (adcarer.com)

Funded by Kao's walkathon 2010, Knowledge transfer grant (CUHK)

耆智同行

一个专为脑退化症患者的家属而设的网站

结论

- 对于腦退化患者，需仔细权衡药物的风险与效益
- 护理的持续性以及家庭照护者的支持非常重要
- 認知活動減緩認知能力下降和改善腦退化患者的行为问题