Direction of care management for person with cognitive impairment

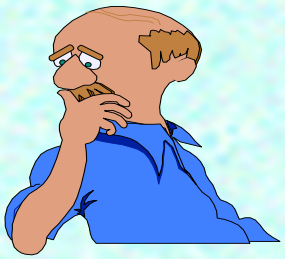
พ.ญ.สิรินทร ฉันศิริกาญจน
หน่วยเวชศาสตร์ผู้สูงอายุ
ภาควิชาอายุรศาสตร์โรงพยาบาลรามาธิบดี

Contents

- Cognitive function
- Cognitive impairment
- Comprehensive care
- Direction of care
- Prepare for the nation

Cognitive function

- memory
- perceiving
- reasoning
- judgment
- imagining
- thinking



Definition

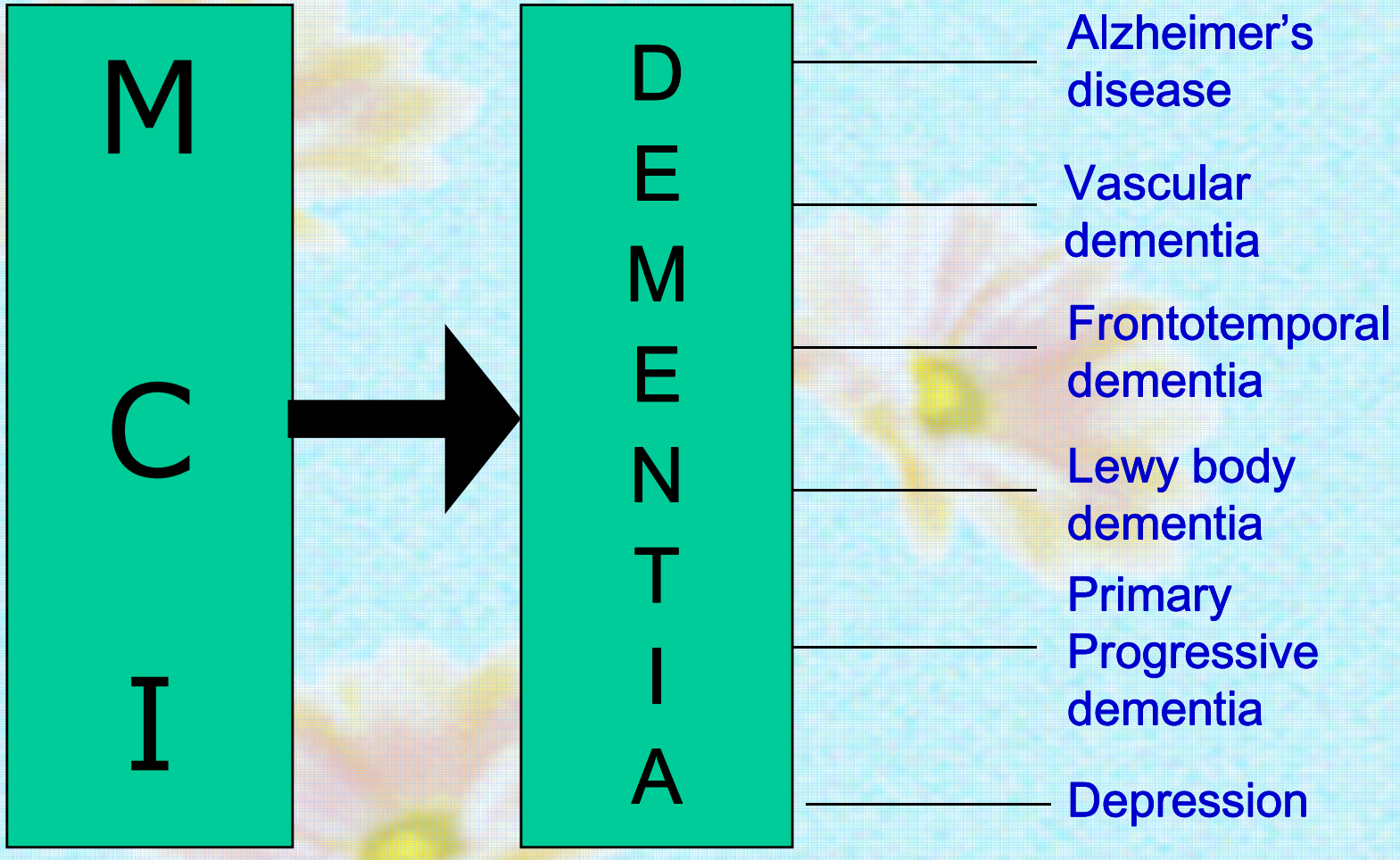
- Syndrome of impaired cognition
- Multiple cognitive deficits
- Behavioral functions
- Progressive course
- Disabling
- Not when patient develops delirium

มีปัญหาทางพฤติกรรม อารมณ์ หรือ บุคลิกภาพ behavioral and psychological symptoms of dementia

- ไม่เข้าใจตำแหน่งของตนเมื่อเปรียบเทียบกับสิ่งแวดล้อมรอบตัว มิติสัมพันธ์ = visuospatial
- คิด วางแผน จัดลำดับไม่ได้ ไม่เข้าใจเหตุผล = reasoning and justment/executive function
- พูดไม่ถูก เรียกไม่ถูก พูดไม่ได้ = language
- มีปัญหาเรื่องความจำ = memory
- ไม่มีสมาธิ ไม่จดจ่อสิ่งใด = attention

Normal Cognitive Aging

- Cognitive changes associated with truly healthy aging
  - Memory
  - Learning new information
- Compensatory strategies – enable to function independently
- Severity of cognitive changes – minimal and non-disabling



Mild cognitive impairment as a prodromal state for dementia that ultimately differentiates into a variety of clinical and pathological condition

Mild Cognitive Impairment (MCI)

- Subjective memory impairment, preferably corroborated by an informant
- Objective memory impairment when compared with persons of similar age and education
- Normal general cognitive function
- Normal competence for activities of daily living
- Impairment not serious enough to meet criteria for dementia-DSMIV, NIN CDS/ADRDA

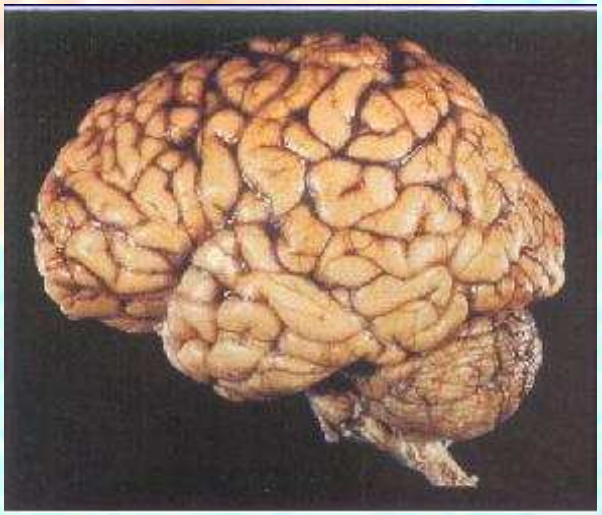
Causes of Dementia

- **Primary Dementia**
  - Neurodegenerative Diseases
  - Neurogenetic Diseases
- **Secondary dementia – Reversible /Arrestable**
  - Cerebrovascular disease
  - Toxic-Metabolic-Nutritional-Encephalopathy
  - Infectious disorders
  - Space occupying lesion
  - Pseudodementia

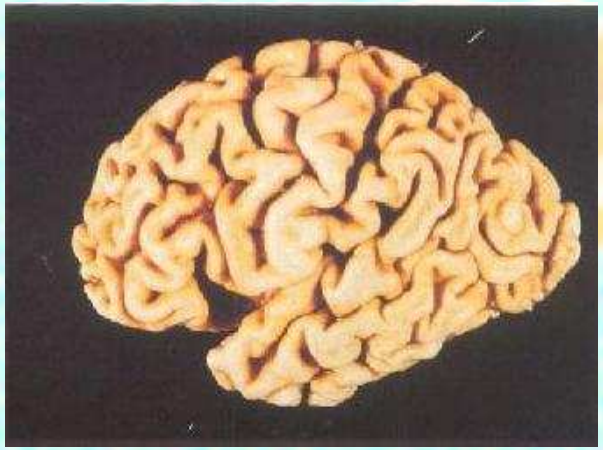
Neurodegenerative Disorders

- Alzheimer's disease
- Frontotemporal dementia
  - Pick's disease
  - Frontotemporal lobe degeneration
- Dementia with Lewy bodies
- Parkinson's disease
- Tauopathy
- Multiple system atrophy
- Huntington's disease

สมองปกติ



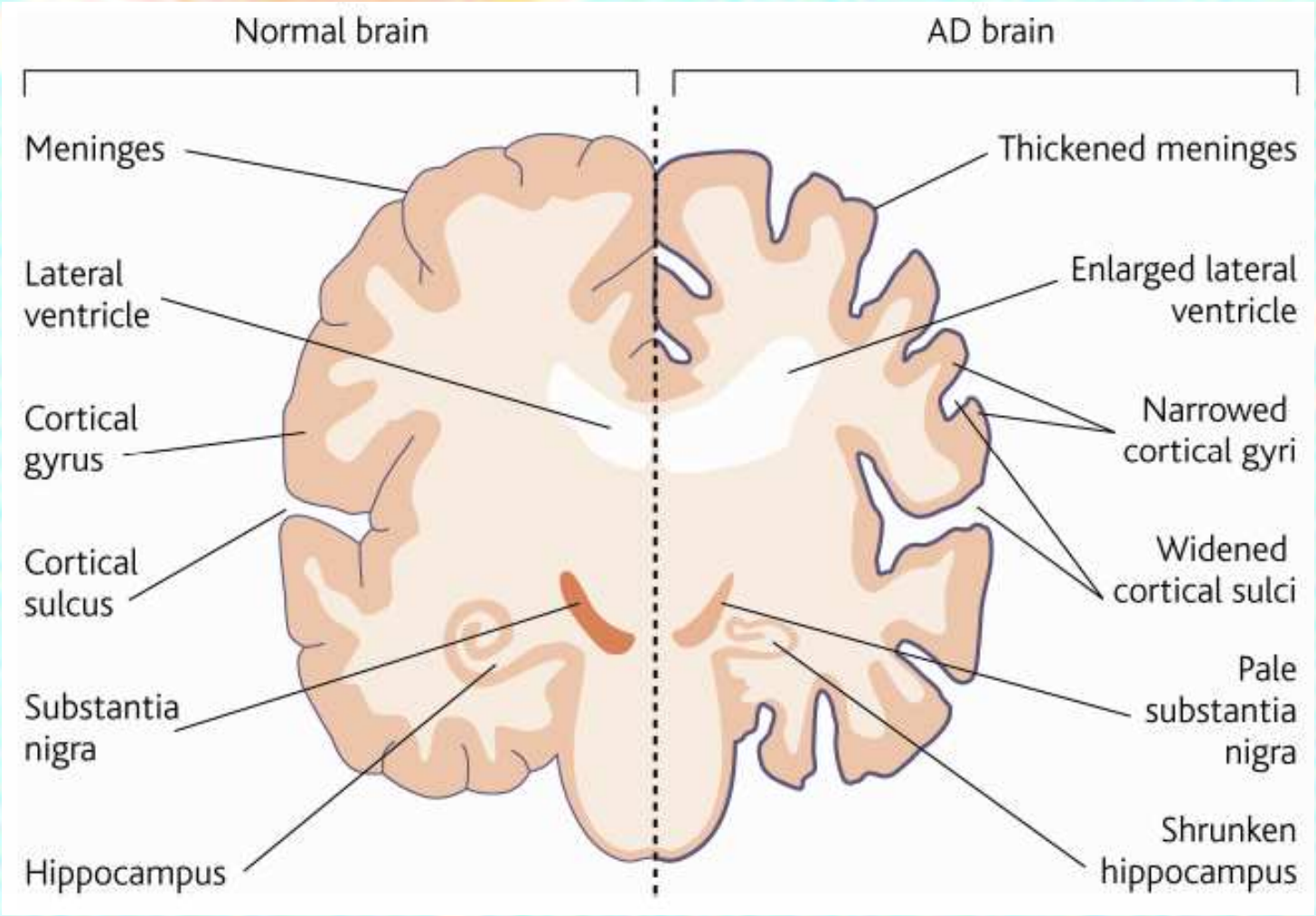
สมอง Alzheimer



AD

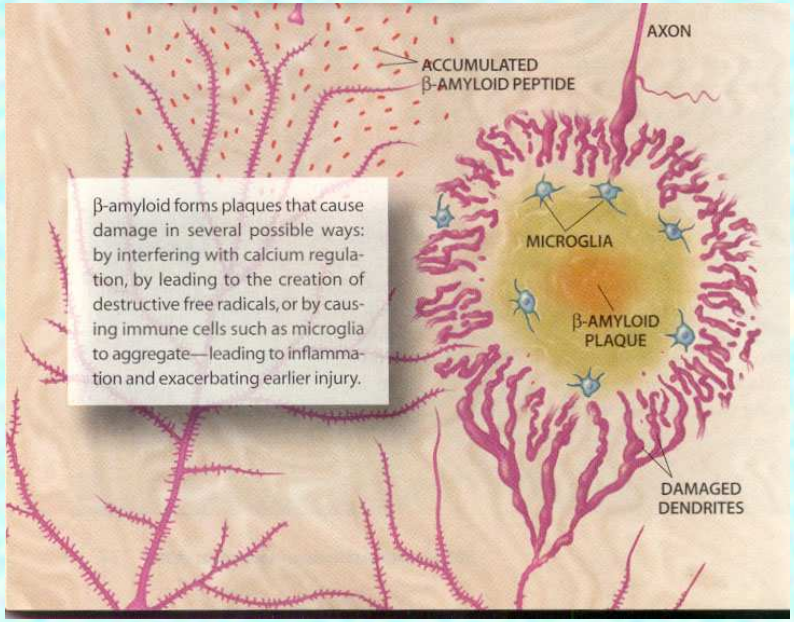
- Symptoms
  - cognitive impairment
  - aphasia
  - visuospatial disorientation

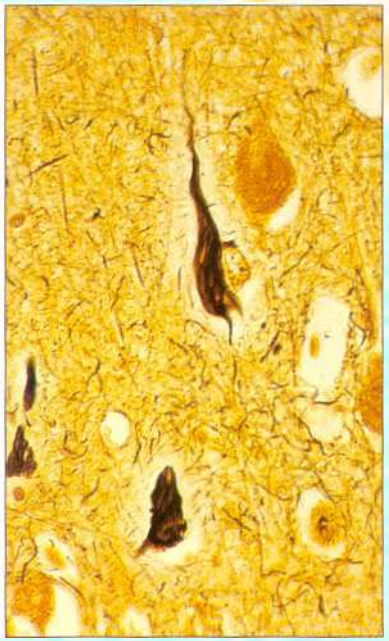
AD pathology

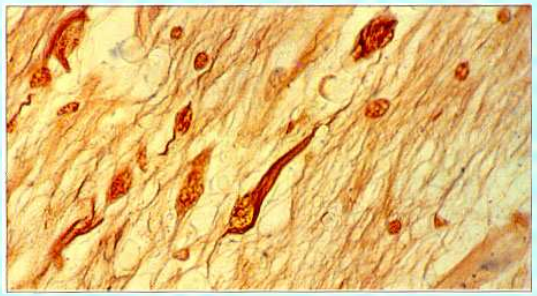


Pathology of AD

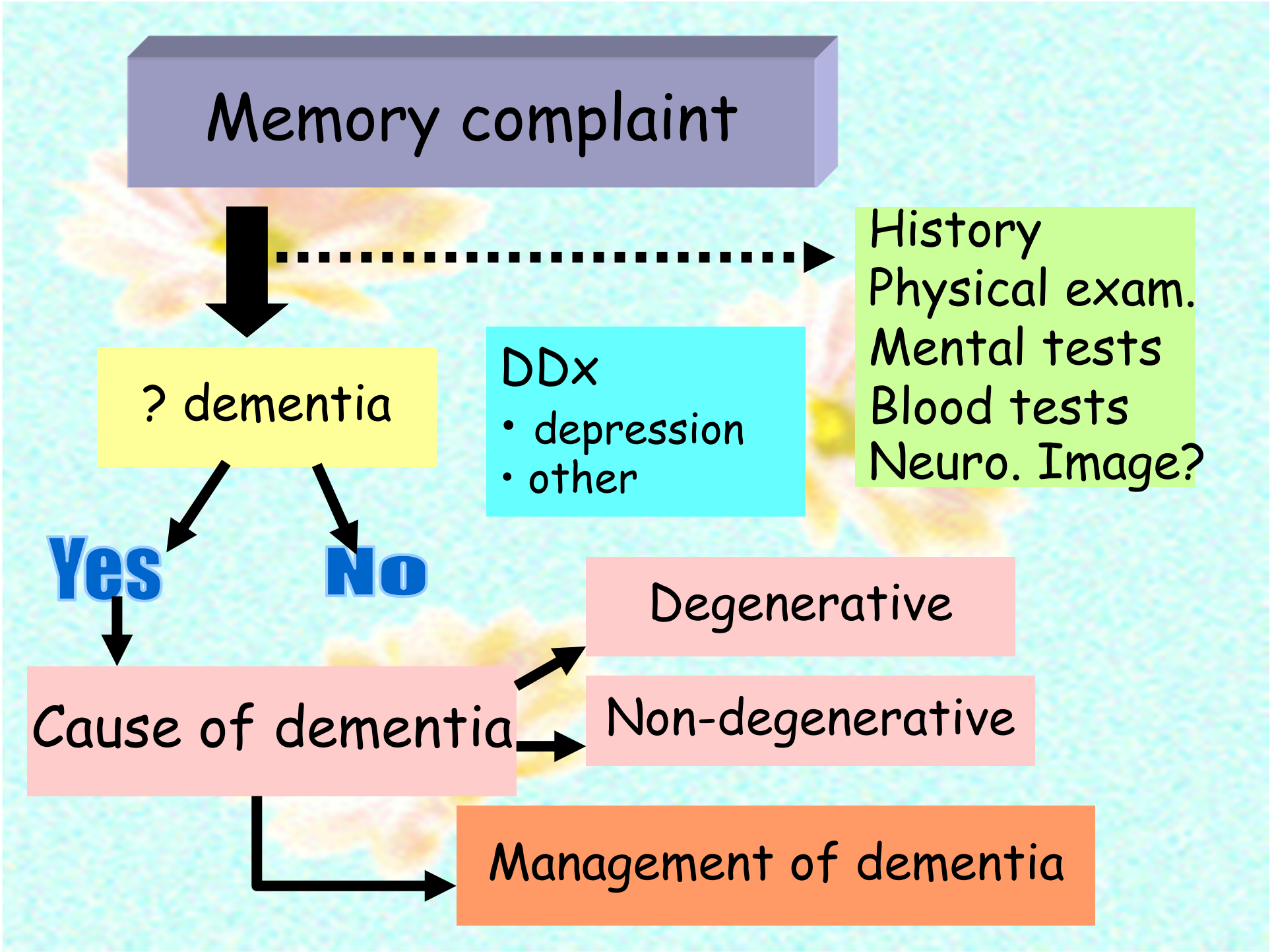
- **Outside : amyloid (senile) plaque**
- **Inside : neurofibrillary tangle**







Management of Dementia


Memory complaint
History
Physical exam.
Mental tests
Blood tests
Neuro. Image?
? dementia
DDx
• depression
• other
Yes
No
Degenerative
Cause of dementia
Non-degenerative
Management of dementia

Dementia

- cognitive impairment
- behavioral changes
- psychological symptoms

ABC: the key symptom domains of dementia

สมองเสื่อม

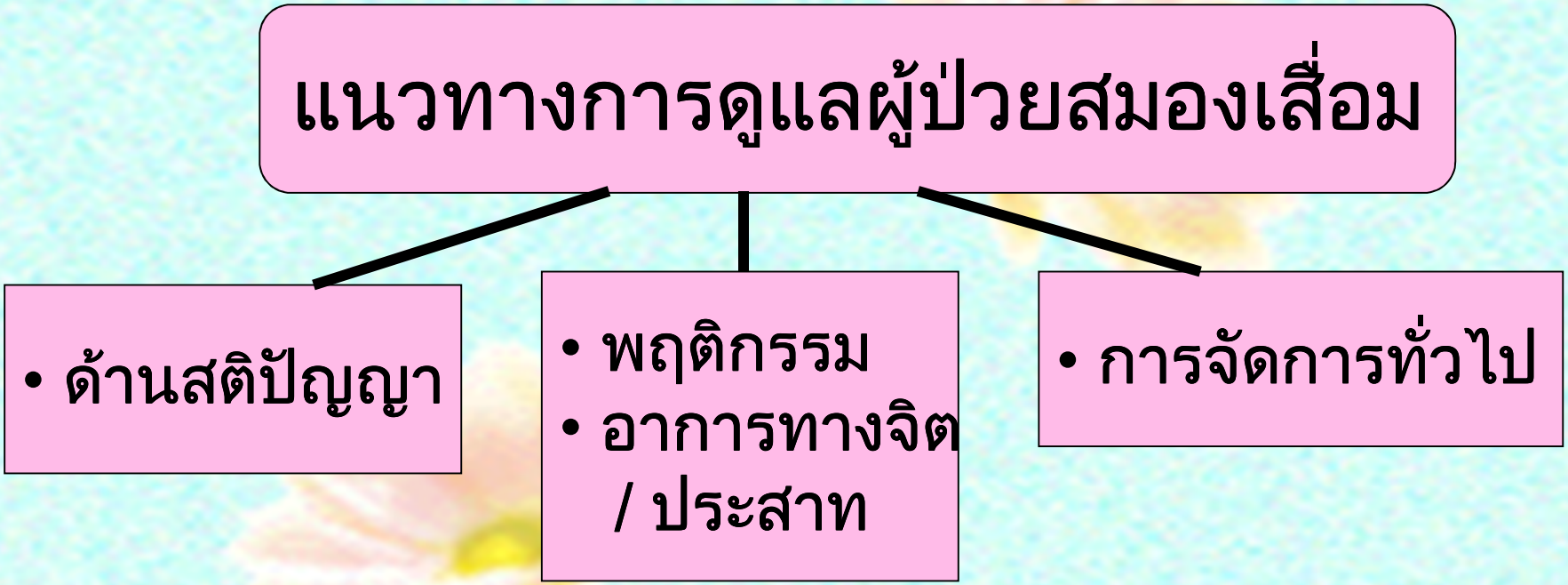
บกพร่อง

- สติปัญญา
- ความรู้
- ความคิด
- กาตัดสินใจ
- อารมณ์

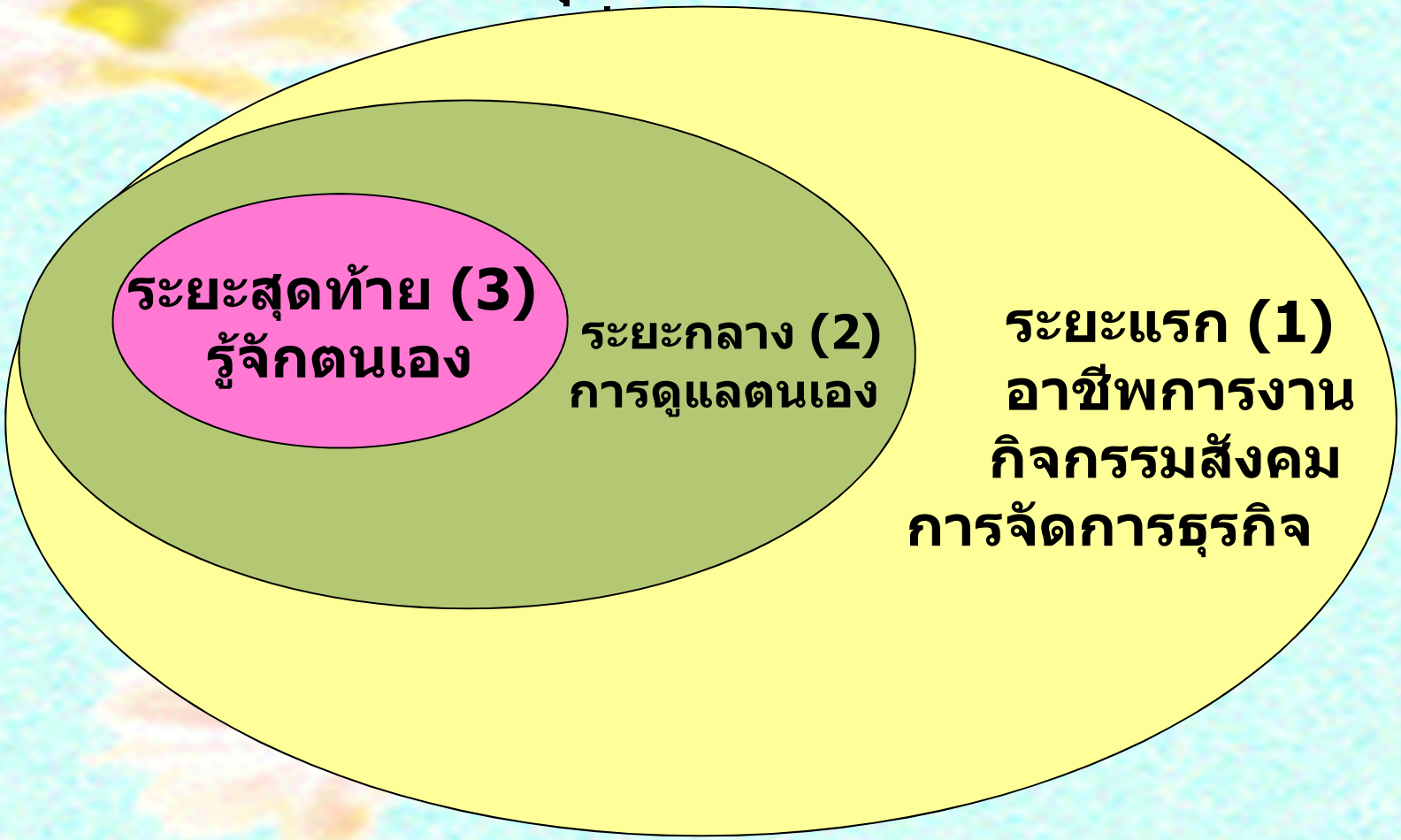
- บุคลิกภาพ
- พฤติกรรม
- อาการทางจิต / ประสาท

- กิจวัตรประจำวัน
- การดูแลตนเอง

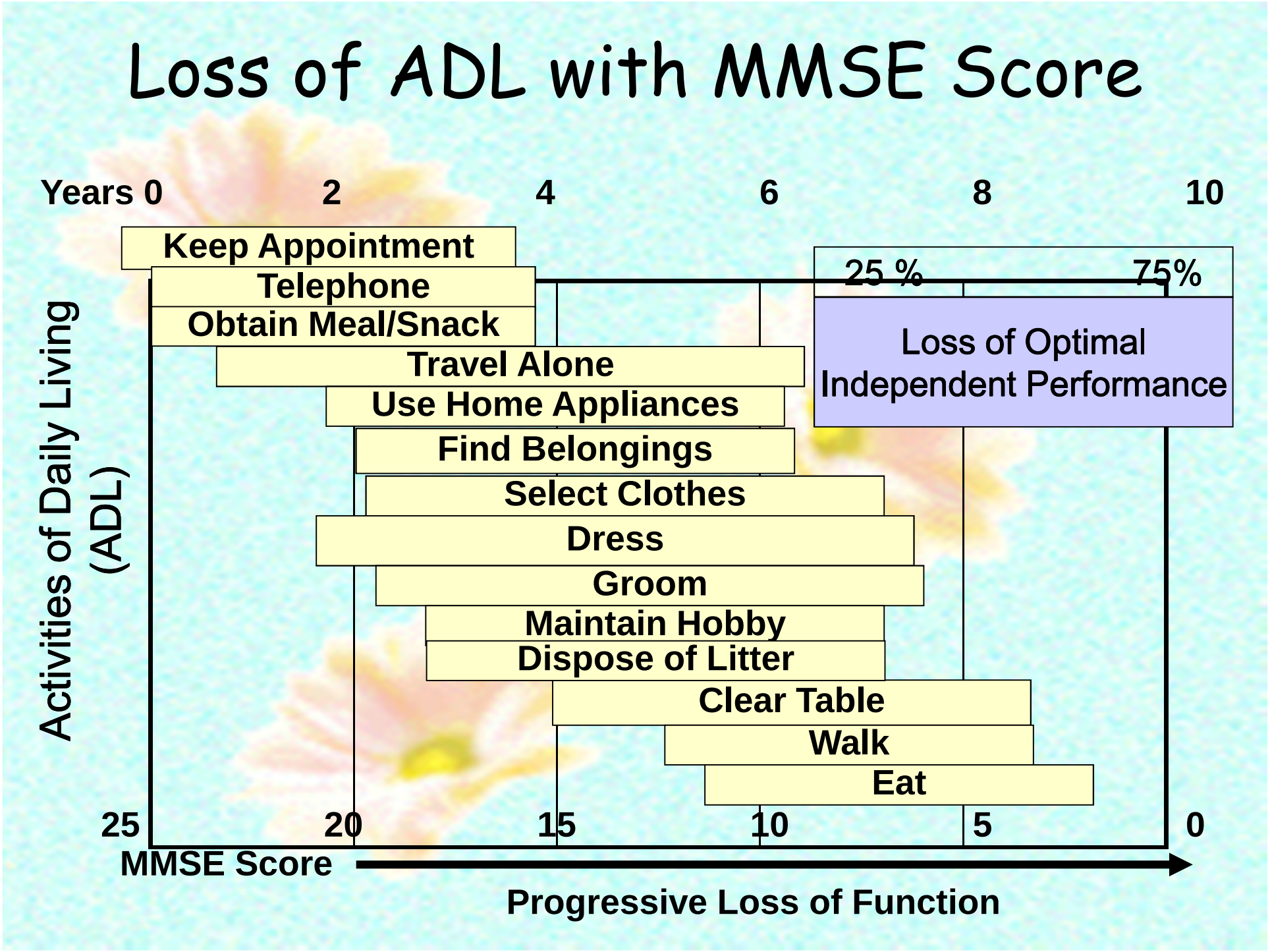
สมองเสื่อม


แนวทางการดูแลผู้ป่วยสมองเสื่อม
• ด้านสติปัญญา
• พฤติกรรม
• อาการทางจิต / ประสาท
• การจัดการทั่วไป

แสดงระยะการถดถอยของ กิจวัตรประจำวัน ตามระยะความรุนแรงของโรคสมอง

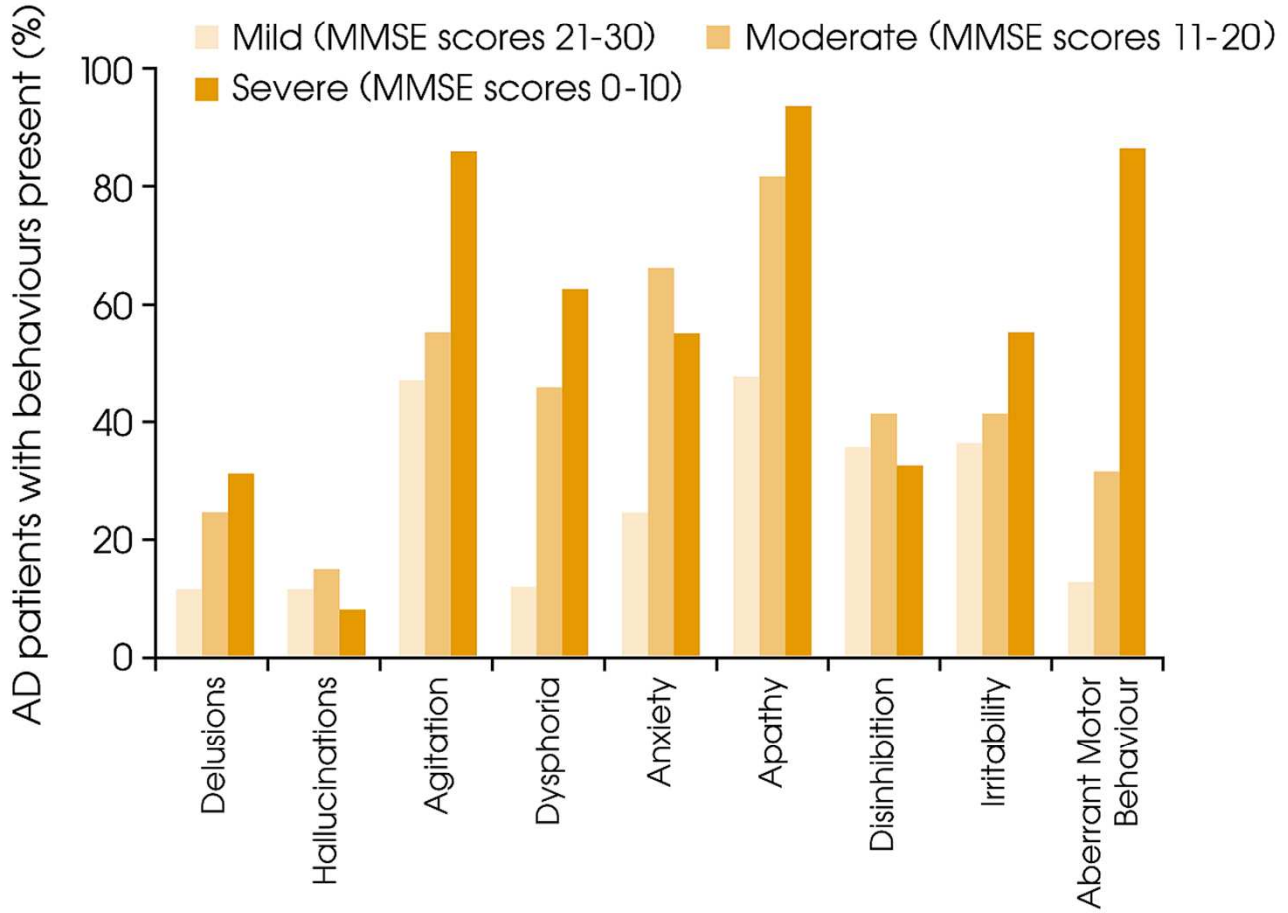


Loss of ADL with MMSE Score



Behavioral & Psychological Symptom of Dementia (BPSD)

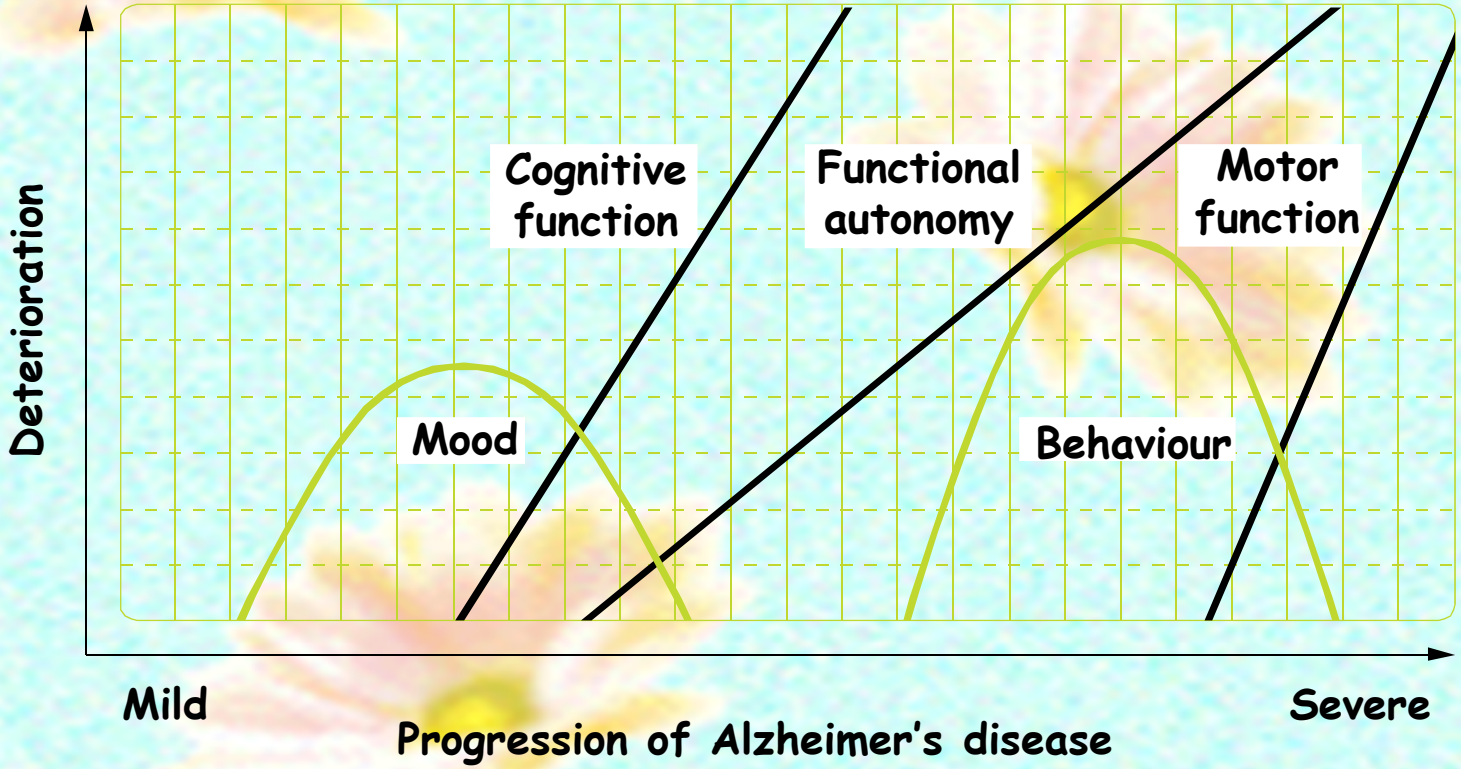
Presence of neuropsychiatric symptoms in patients with AD according to severity of disease



Robert, 2002

Progression and symptoms of AD

Pattern of symptoms over time in patients with AD



ปัญหาพฤติกรรมที่พบบ่อย

- ก้าวร้าว
- ชอบเที่ยว / เดินเรื่อยเปื่อย
- ปัญหาเกี่ยวกับการกิน
- การนอนเปลี่ยนแปลง
- ถามซ้ำซาก เล่าแล้วเล่าอีก
- ติดตามเหมือนเงา

อาการทางจิต

- หลงผิด
- ภาพหลอน
- หวาดระแวง
- ซึมเศร้า
- วิตกกังวล
- ทึกทักผิดคน ผิดของ

Neurochemical changes in AD

- Several changes in neurotransmitter balance accompany the microscopic changes in the AD brain
- The two neurotransmitters that have gained most prominence in recent years are:
  - Acetylcholine
  - Glutamate
- Other neurotransmitters affected by AD are:
  - Noradrenaline
  - Dopamine
  - Serotonin

Gsell et al. Curr Pharm Des 2004; 10: 265-293

Acetylcholine

- Levels of acetylcholine are substantially reduced in AD
- Levels of the acetylcholine regulatory enzymes are reduced:
  - Choline acetyltransferase (ChAT)
  - Acetylcholinesterase (AChE)
- Acetylcholine receptors are also affected – reduction in the number of nicotinic receptors
- Treatment with AChE inhibitors aims to increase acetylcholine levels

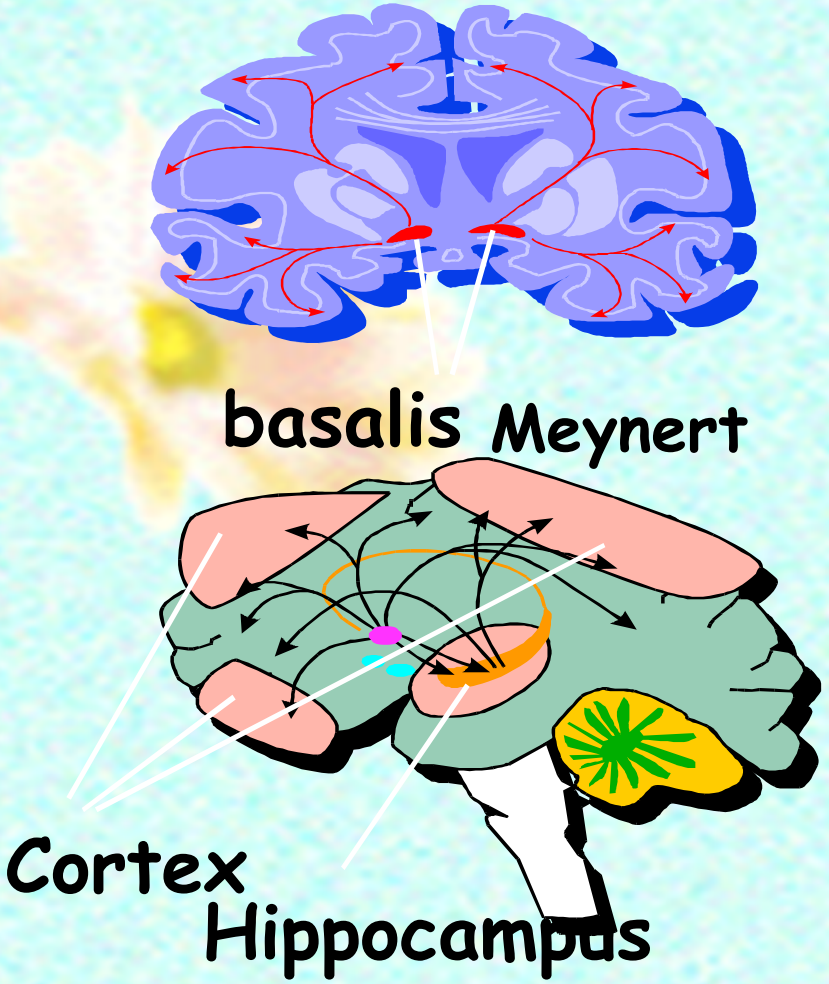
Glutamate

- Glutamate accounts for ~70% of excitatory neurotransmission
- The NMDA glutamate receptor is involved in long-term potentiation (LTP), responsible for learning and memory
- In AD, glutamate release and reuptake is dysfunctional, and a tonic elevation of synaptic glutamate levels is observed
- The tonic elevation of glutamate impairs effective signal transmission, thus impairing learning and memory
- In addition, over-activity of glutamatergic synapses causes excitotoxicity and consequent neurodegeneration

Müller et al. Pharmacopsychiat 1995; 28: 113-124

The Cholinergic Deficit in AD Underlies the Clinical Symptomatology

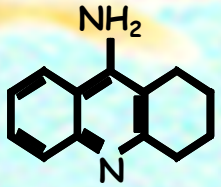
- Cholinergic deficit
  - progressive loss of cholinergic neurones
  - progressive decrease in available Ach
  - impairment in ADL, behaviour and cognition



Bartus et al., 1982; Cummings and Back, 1998, Perry et al., 1978

Cholinesterase Inhibitors:

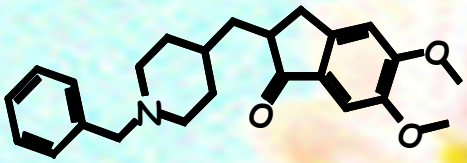
A Rational Therapeutic Approach in AD



Tacrine

Mechanism: AChE/BuChE-I

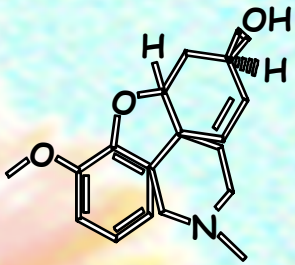
Inhibition: reversible



Donepezil

Mechanism: AChE-I

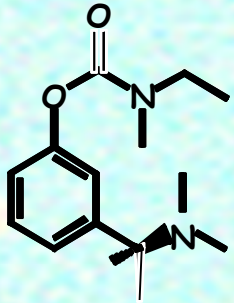
Inhibition: reversible



Galantamine

Mechanism: AChE-I

Inhibition: reversible



RIVASTIGMINE

Mechanism: AChE/BuChE-I

Inhibition: pseudo-irreversible

Weinstock, 1999

Cholinesterase Inhibitors: Two Classes Exist for the Treatment of AD

Class	Inhibit
Dual ChE inhibitors	
Rivastigmine	Both AChE
Tacrine	and BuChE
Single ChE inhibitors	
Donepezil	AChE
Galantamine	AChE + Nicotinic Receptor Modulation

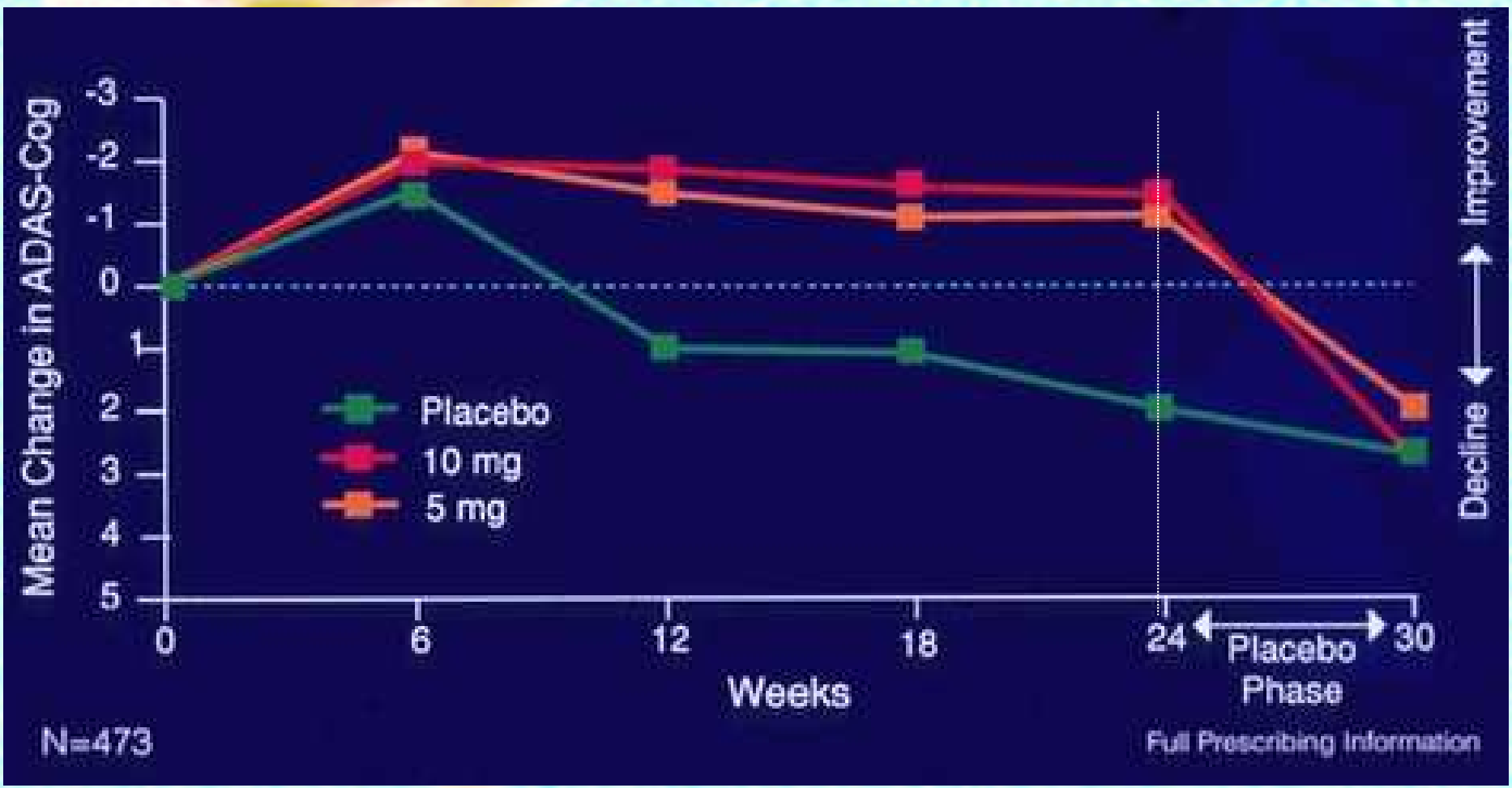
Weinstock , 1999

Comparison of Cholinesterase inhibitors

Attributes	Donepezil	Rivastigmine	Galantamine
NNT(Number needed to treat) with 95% CI -ADAS-Cog(> 4 points) -Clinical Global Rating	11 (8-14) 11 (7-15)	14 (8-20) 12(8-17)	7 (5-10) 7 (5-12)
The National Institute for Clinical Excellence (UK guideline by Wessex Institute for Health Research and Development www.nice.org.uk	Benefit in terms of -global outcome(CIBIC-plus) -cognitive outcome(ADAS)	Benefit in terms of -global outcome(CIBIC-plus)	Benefit in terms of -global outcome(CIBIC-plus) -cognitive outcome(ADAS) -functional outcome (ADL)
Comparison of Pharmacoeconomic Outcomes -condition:same daily cost	-Cost increased with Donepezil 5 mg -Cost decreased with Donepezil 10 mg	-Cost increased with Rivastigmine 1-4 mg, 6-12 mg	Cost decreased with Galantamine 16, 24 mg

Ref: Evidence-based Dementia Practice ; 2002: 473- 493

Effect of donepezil on mean changes in ADAS-Cog

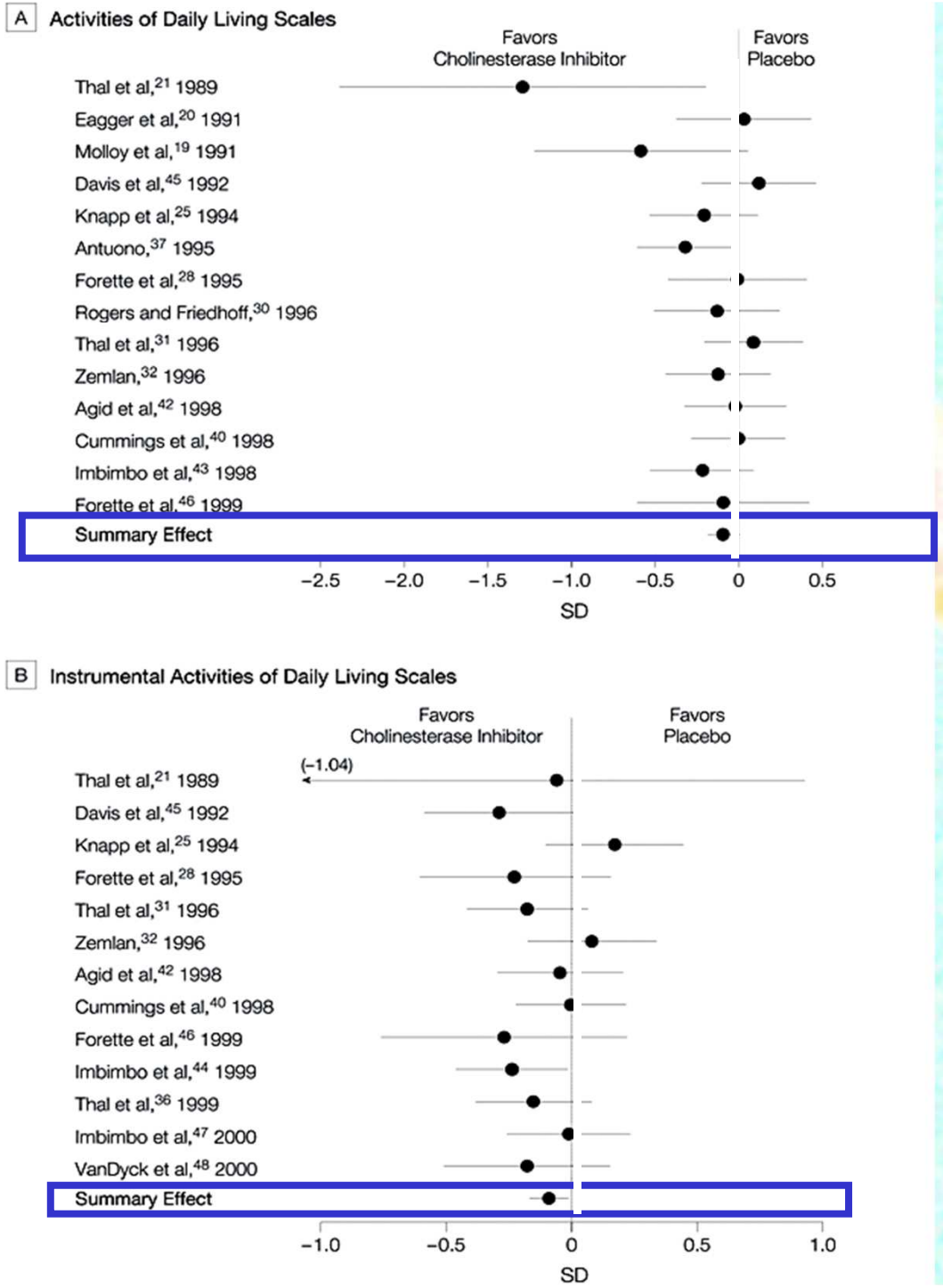


Rogers SL *et al.* Neurology 1998; 50: 136-45.

ADAS-cog weighted mean difference after 6 months' treatment versus placebo

Treatment	Dose (mg)	ADAS-cog WMD (95% CI)
Donepezil	5	−1 · 85 (−2 · 6, −1 · 11)
	10	−2 · 90 (−3 · 65, −2 · 15)
Rivastigmine	1–4	−0 · 84 (−1 · 48, −0 · 19)
	6–12	−2 · 09 (−2 · 65, −1 · 54)
Galantamine	8	−1 · 30 (−2 · 75, −0 · 02)
	16	−3 · 10 (−4 · 12, −2 · 07)
	24	−3 · 28 (−3 · 92, −2 · 65)

Lancet Neurology 2003;2:539-4



ADL

meta-analysis

JAMA 2003;289:210-6.

Glutamate neurotransmission and NMDA receptors

- Glutamate accounts for ~70% of excitatory neurotransmission

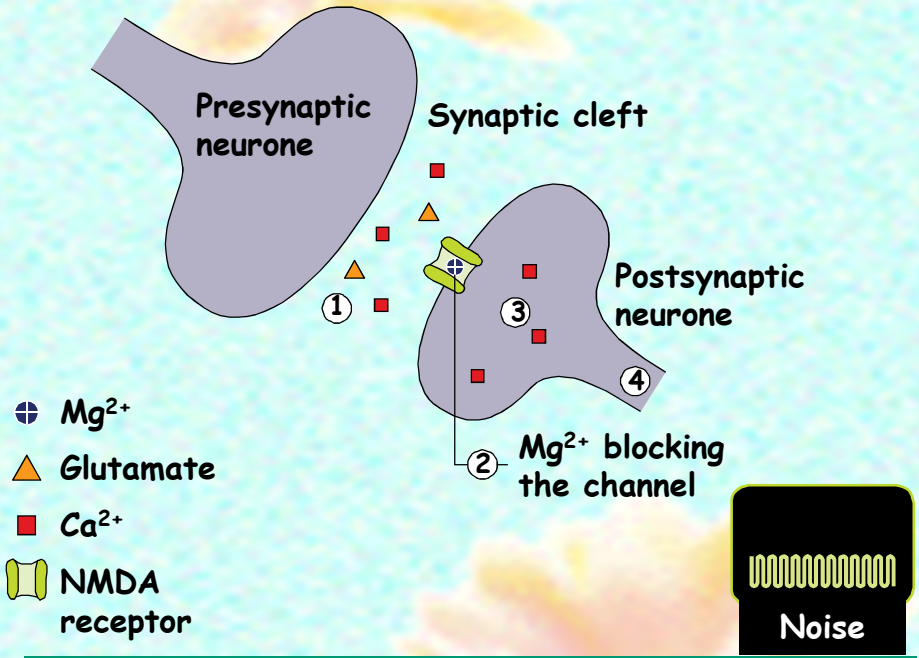
- Glutamate receptors include NMDA receptors
  - Membrane-spanning ion channels
  - High Ca^{2+} permeability
  - Voltage-dependent blockade by Mg^{2+} ions
  - Closely connected with learning and memory

- Under normal conditions, presynaptic release of glutamate determines NMDA receptor activation

Dingledine et al. Pharmacol Rev 1999; 51 (1): 7–61; Parsons et al, FP Graham Publishing Co. 2002;
Müller et al. Pharmacopsychiat 1995; 28: 113–124; 10: 265–293;
Parsons et al. Drug News Perspect 1998; 11: 523–569

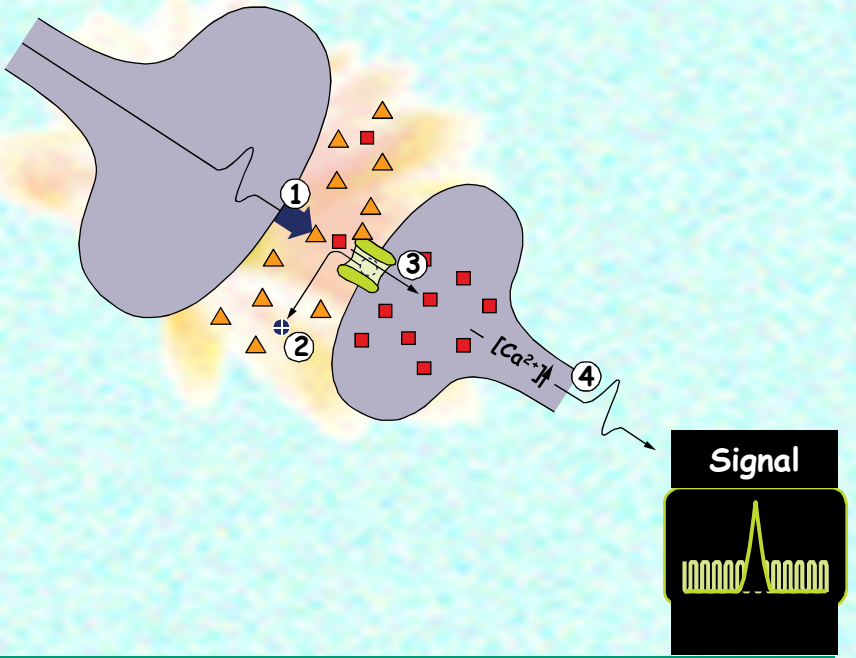
Normal glutamate neurotransmission and long-term potentiation

a) Glutamatergic neurone at rest



1. At rest, low background level of glutamate in the synaptic cleft
2. Mg^{2+} ions block the ion channels
3. Intracellular Ca^{2+} levels in the postsynaptic neurone are low
4. Low Ca^{2+} levels result in low background noise

b) Stimulated glutamatergic neurone



1. During learning and memory, impulses in presynaptic neurone result in glutamate being released
2. Glutamate binds to the postsynaptic receptors and the membrane is depolarised – release of the Mg^{2+} ions
3. Ca^{2+} ions now flow into the postsynaptic neurone
4. Raised Ca^{2+} levels initiate a signalling cascade, ultimately facilitating learning and memory

Glutamatergic neurotransmission in AD

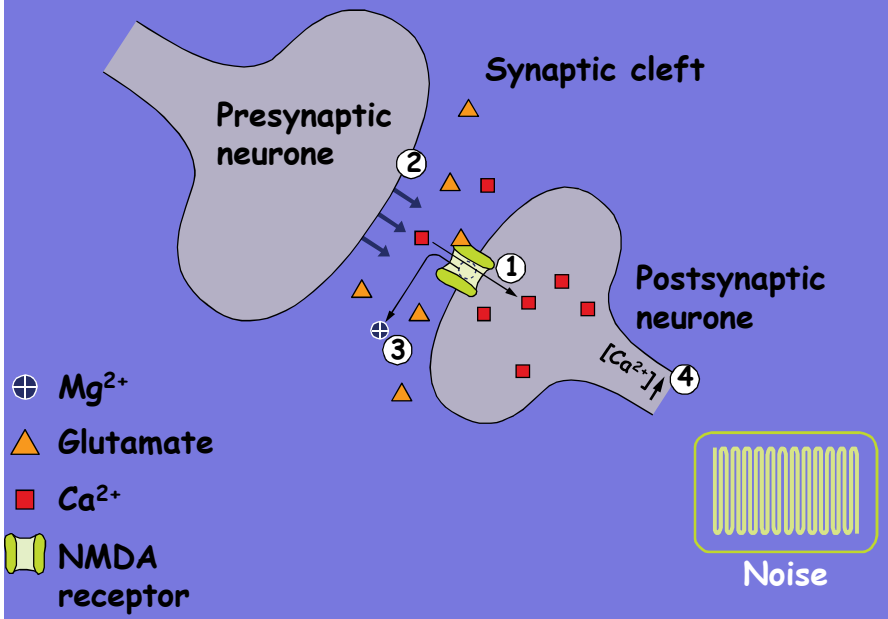
- **Glutamate release and reuptake are chronically dysfunctional in AD**
- **Raised glutamate levels partially depolarise the post-synaptic neurones. Other contributing factors include oxidative stress, free radicals, energy deficit, Aβ, etc**
- **The abnormally high intracellular concentrations of Ca^{2+} trigger:**
  - **Formation of free radicals**
  - **Changes in nuclear chromatin**
  - **Changes in DNA fragmentation**

…Resulting in excitotoxicity – damage to, or death of, neurones – implicated in AD neurodegeneration

Cacabelos et al. Int J Geriatr Psychiatry 1999; 14: 3–47; Danysz et al. Neurotoxicity Res 2000; 2: 85–97

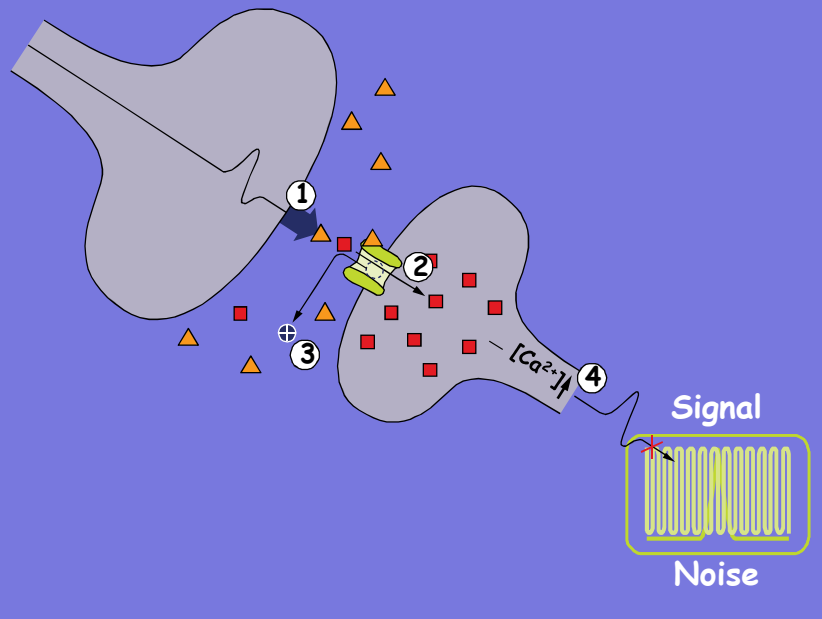
Dysfunctional glutamatergic neurotransmission in AD

a) Glutamatergic neurone at rest



1. Dysfunctional glutamate release and reuptake leads to raised background levels of glutamate
2. Mg^{2+} ions are displaced from the NMDA receptors
3. Ca^{2+} ions flow into the postsynaptic neurone
4. Prolonged exposure to raised Ca^{2+} levels can trigger excitotoxicity

b) Stimulated glutamatergic neurone



1. During learning and memory, more glutamate is transiently released from the presynaptic neurone
2. Mg^{2+} ions are displaced from NMDA receptors
3. Increasing the flow of Ca^{2+} ions through the NMDA receptor channels
4. Peak Ca^{2+} levels are not detected, thus neuronal plasticity and, consequently, learning and memory, are impaired

Mechanism of action of memantine

- **Voltage-dependent, moderate-affinity, uncompetitive NMDA receptor antagonist**
- **Selective for NMDA receptors in the brain**
- **Blocks NMDA receptors in a concentration-dependent manner**
- **Prevents the effects of tonic pathologically elevated levels of glutamate that may lead to neuronal dysfunction**

Danysz et al. Neurotoxicity Res 2000; 2: 85–97; Kornhuber et al. J Neural Transm 1994; Suppl 43: 91–104;
Parsons et al. Neuropharmacology 1993; 32: 1337–1350; Chen et al. J Neurosci 1992; 12: 4427–4436;
Bresink et al. Br J Pharmacol 1996; 119: 195–204

Summary – mechanism of action of memantine

- **Memantine is a voltage-dependent, moderate-affinity, uncompetitive NMDA receptor antagonist**

- **The intermediate voltage-dependency and fast receptor-binding kinetics of memantine enable it to:**

Summary – effect of memantine on behaviour and cognition in AD

- **In animal models of behavioural and cognitive symptomatic effects, memantine was shown to:**
  - **Provide significant efficacy against specific behavioural symptoms**
  - **Prolong LTP**
  - **Improve memory retention**
  - **Reverse deficits in learning and cognition**
  - **Prevent progressive decline in cognitive functioning**

Summary – memantine's neuroprotective potential

- **Memantine's preclinical neuroprotective potential:**
  - **Protects neurones from excitotoxicity**
  - **Induces 'functional rescue' of neurones exposed to an excitotoxin**
  - **Reduces lethality and brain damage in a model of hypoxia–ischaemia**
  - **Reverses the abnormal hyperphosphorylation of tau**
  - **Protects against neuronal degeneration induced by Aβ**
  - **Prevents chronic neuroinflammation of cholinergic cells**

Ebixa® in moderate to severe AD

– individual study results

Author (Study No.)	MMSE inclusion, range (mean)	Duration/design	N	Outcomes – Ebixa® produced benefits (vs placebo) in:
Reisberg 2003 (MRZ-9605)	3–14 (7.9)	28-week, double-blind, placebo-controlled, Ebixa® 20 mg/day	252	• Global status (CIBIC-Plus, p=0.03) • Function (ADCS-ADL$_{19}$, p=0.003) • Cognition (SIB, p=0.002) • Caregiving time (p=0.02) • Time to institutionalisation • Patient autonomy
van Dyck 2007 (MD-01)	5–14 (10.1)	24-week, double-blind, placebo-controlled, Ebixa® 20 mg/day	350	• Function (ADCS-ADL$_{19}$, NS) • Cognition (SIB, Week 12: p=0.008)
Winblad 1999 (M-Best)	<10 (6.3)	12-week, nursing home, Ebixa® 10 mg/day	79*	• Global status (CGI-C, p=0.005) • Function (BGP care-dependency subscale, p=0.002) • Cognition (BGP cognition subscale, p=0.004)

*AD subgroup; NS=not significant

Reisberg et al. N Engl J Med 2003; 348: 1333–1341; van Dyck et al. Alzheimer Dis Assoc Disord 2007; 21 (2): 136–143; Winblad & Poritis. Int J Geriatr Psychiatry 1999; 14 (2): 135–146

Ebixa® in moderate to severe AD

Single item benefits for Ebixa® (versus placebo)

- **Cognitive single items (SIB subscales):**
  - **Memory ($p<0.001$)**
  - **Visuospatial ability ($p=0.013$)**
  - **Language ($p=0.052$)**
  - **Praxis ($p=0.059$)**
- **Functional single items (ADCS-ADL_{19}):**
  - **Pay attention to conversation'($p<0.05$)**
  - **Clear dishes from table after meal ($p<0.05$)**
  - **Dispose of garbage or litter ($p<0.05$)**
  - **Use a telephone ($p<0.10$)**
  - **Get around outside of his/her home ($p<0.10$)**

Schmitt et al. J Neural Transm Suppl 2002; 62: 135-148;
Doody et al. Dement Geriatr Cogn Disord 2004; 18 (2): 227-232

Ebixa® in moderate to severe AD – specific symptom benefits

- **Behavioural single items (NPI):**
  - **Agitation/aggression (p=0.008)**
  - **Delusions (p=0.04)***
  - **Depression/dysphoria (p=0.07)**
  - **Emergence** of agitation/aggression (p<0.01)**

*** The Ebixa® group had a significantly higher prevalence of delusions at baseline versus placebo**

**** i.e., patients without 'agitation/aggression' at baseline**

Gauthier et al. Int J Geriatr Psychiatry 2005; 20 (5): 459-464

Donepezil in moderate to severe AD

– individual study results

Author	MMSE inclusion, range (mean)	Duration/design	N	Outcomes – Donepezil produced benefits (vs placebo) in:
Winblad, 2006; Black, 2007; Homma, 2008	1–12 (7)	6-month, double-blind, placebo-controlled, donepezil 10 mg/day (3 studies, pooled)	736 total	• Global status ($p<0.0001$) • Cognition (SIB; $p<0.0001$) • Function (ADCS-ADL_{19}; $p=0.03$) • Behaviour (NPI; NS)
Feldman, 2001	5–17 (12)	24-week, double-blind, placebo-controlled, donepezil 10 mg/day	290	• Global status (CIBIC-Plus; $p<0.0001$) • Cognition (SIB; $p<0.0001$) • Function (DAD; $p<0.0001$) • Behaviour (NPI; $p=0.0005$) • Caregiver stress • Caregiving time ($p=0.004$)

NS=not significant; DAD=Disability Assessment for Dementia

Winblad et al. Lancet 2006; 367 (9516): 1057–1065; Black et al. Neurology 2007; 69 (5): 459–469;
Homma et al. Dement Geriatr Cogn Disord 2008; 25 (5): 399–407;
Winblad et al. Curr Med Res Opin 2009; 25 (11): 2577–2587;
Feldman et al. Neurology 2001; 57 (4): 613–620; Feldman et al. J Am Geriatr Soc 2003; 51 (6): 737–744

Donepezil in moderate to severe AD

Single item benefits for donepezil (versus placebo)

- Cognitive single items (SIB subscales):
  - improvements from baseline on memory, language, orientation, attention, praxis, visuospatial, and social interaction
- Functional single items ($ADCS\text{-}ADL_{19}$):
  - Grooming ($p<0.05$)
  - Obtaining beverage ($p<0.05$)
- Behavioural single items (NPI):
  - Depression/dysphoria ($p<0.05$)
  - Anxiety ($p<0.05$)
  - Apathy/indifference ($p<0.05$)

Winblad et al. Curr Med Res Opin 2009; 25 (11): 2577–2587;
Gauthier Set al. Int Psychogeriatr 2002; 14 (4): 389–404

Ebixa®/donepezil monotherapy

Summary

- Ebixa®/donepezil monotherapy in patients with moderate to severe AD shows benefits over placebo in the treatment of cognitive, functional, and behavioural symptoms, and global measures

- The specific symptom benefits of both drugs complement each other
  - Ebixa® benefits agitation/aggression and language/ communication
  - Donepezil benefits apathy and memory

การจัดการทั่วไป

กิจวัตรประจำวัน

- การแต่งตัว
- การกินอาหาร
- การอาบน้ำ
- การขับถ่าย
- การใช้ห้องน้ำ
- การเคลื่อนย้าย
- ตารางกิจกรรม
- การส่งเสริมสุขภาพ

ผู้ดูแล

- บทบาทหน้าที่
- การช่วยเหลือผู้ดูแล

สิ่งแวดล้อม

- ความปลอดภัย
- บรรยากาศภายในห้อง
- การย้ายที่อยู่

Outcome of dementia care

- Early diagnosis
- Proper medication at early stage of disease
- General health and nutritional status
- Care giver
  - Understanding of the disease
  - Attitude
  - Adaptation
  - Health status
  - Support from family and others

Direction of care in AEC

- Risk reduction
- Delay the onset of symptom toward active aging
- Strengthen the family and community
- Local authority as the manager of care

Prepare for the nation 1

- Public awareness of the disease and problems
- Active & comprehensive risks reduction
- Emerge medical and social welfare
- Encourage and support person at risk to be active in physical, social and cognitive aspect

Prepare for the nation 2

- Plan for developing health care professionals, social workers, psychologist, volunteers and people in community authority as specialist in dementia care
- Patient registration and drug accessibility

Prepare for the nation 3

- Family and person aspect
  - Be healthy in physical, mental and spiritual
  - Be rich in many aspects
  - Be open mind for the technology and changes
  - Pay attention for person in the family more than economy or incomes


Thank you