Médicaments et Cognition

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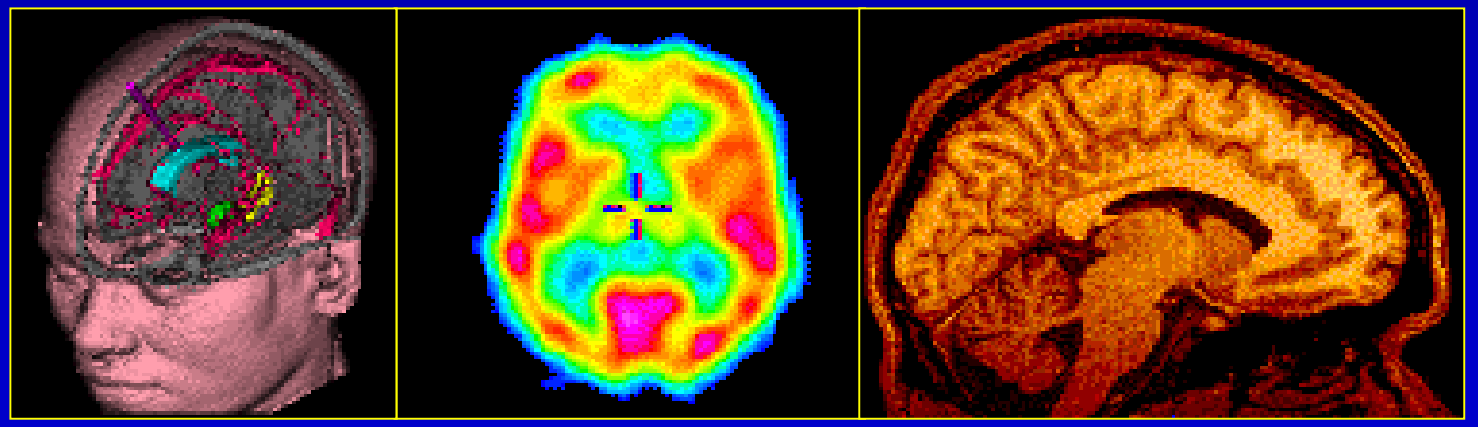

Médicaments et Cognition chez le sujet âgé

En gériatrie, 11 à 30% des cas de troubles cognitifs sont liés aux médicaments ***(Moore et al, Drugs Aging, 1999)***

Les médicaments anticholinergiques , médicaments atropiniques

Antiparkinsoniens, antispasmodiques, médicaments de l'incontinence urinaire, bronchodilatateurs, antitussifs, AD imipraminiques, antihistaminique H1, neuroleptiques, antiarythmiques, antihypertenseurs, analgésiques…

- Résidence de sujets agés USA (Feinberg et al, 1993) :
30% ont plus de 2 atropiniques
5% ont plus de 5 atropiniques

- 51% de la population générale âgée (USA) utilise des atropiniques (Mulsant et al, 2003)

Les médicaments anticholinergiques , médicaments atropiniques

Les effets à court terme

Clinical Interventions in Aging

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ORIGINAL RESEARCH

The cognitive impact of anticholinergics: A clinical review

27 études, MMSE

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Context: The cognitive side effects of medications with anticholinergic activity have been documented among older adults in a variety of clinical settings. However, there has been no systematic confirmation that acute or chronic prescribing of such medications lead to transient or permanent adverse cognitive outcomes.

Objective: Evaluate the existing evidence regarding the effects of anticholinergic medications on cognition in older adults.

Data sources: We searched the MEDLINE, OVID, and CINAHL databases from January, 1966 to January, 2008 for eligible studies.

Study selection: Studies were included if the anticholinergic activity was systematically measured and correlated with standard measurements of cognitive performance. Studies were excluded if they reported case studies, case series, editorials, and review articles.

Data extraction: We extracted the method used to determine anticholinergic activity of

Reference	CI	Delirium
Ancelin et al[12]	+ (Stockholm)	N/A
Chew et al[15]*	+ (MMSE, SIB)	N/A
Flacker et al[16]	N/A	+ (CAM, DSI)
Flacker et al[17]	N/A	+ (CAM)
Golinger et al[18]	N/A	+ (DSM-III)
Mach et al[23]	N/A	+ (DSM-III-R)
Miller et al[25]	– (MMSE)	+ (SDC)
Mondimore et al[27]	+ (MMSE)	N/A
Mulsant et al[6]	+ (MMSE)	N/A
Mussi et al[28]	N/A	+ (CAM)
Nebes et al[29]	+ (DSM-IV)	N/A
Nebes et al[30]	+ (Verbal N Back test)	N/A
Plaschke et al[32]	N/A	– (CAM-ICU)
Rovner et al[34]*	+ (MMSE, DSM-III)	N/A
Thienhaus et al[35]*	+ (MMSE)	N/A
Tollefson et al[5]*	+ (MMSE, BCRS, WMS)	+ (SDC)
Tune et al[10]	N/A	+ (Clinical)

Association positive entre altération cognitive et médicaments atropiniques

- ↓ temps de réaction
- ↓ attention
- ↓ rappel différé
- ↓ fonction visuospatiale
- ↓ language (fluence)

Les médicaments anticholinergiques , médicaments atropiniques

Les effets à long terme

Non-degenerative mild cognitive impa
use of anticholinergic drugs: longitud

Marie L Ancelin, Sylvaine Artero, Florence Portet, Anne-Marie D

2006

Abstract

Objective To assess the potential of anticholinergic drugs as a cause of non-degenerative mild cognitive impairment in elderly people.

Design Longitudinal cohort study.

Setting 63 randomly selected general practices in the Montpellier region of southern France.

Participants 372 people aged >60 years without dementia at recruitment.

Suivi 2 ans

Batterie cognitive

Consommation de med atropiniques : facteur prédictif de survenue de MCI : OR 5,12 (IC 1,94-13,51; p =0,001)

Table 1 List of anticholinergic drugs used by study participants. All drugs had an anticholinergic burden classification of 3 (see Methods for details) unless stated otherwise

Compound	Drug class	Application
Aceprometazine	Neuroleptic, antihistamine (phenothiazine)	Psychiatry
Acepromazine	Neuroleptic (phenothiazine)	Psychiatry
Alimemazine*	Antihistamine, sedative (phenothiazine)	Allergy relief, psychiatry
Alprazolam	Anxiolytic (benzodiazepine)	Psychiatry
Alverine*	Antispasmodic	Analgesia and anti-inflammatory
Amitriptyline	Tricyclic antidepressant	Psychiatry
Amoxapine	Tricyclic antidepressant	Psychiatry
Belladonna alkaloids	Antispasmodic	Analgesia and anti-inflammatory
Chlorphenamine	Antihistamine	Analgesia and anti-inflammatory
Clomipramine	Tricyclic antidepressant	Psychiatry
Clorazepate	Anxiolytic (benzodiazepine)	Psychiatry
Codeine*	Analgesic, antipyretic	Analgesia and anti-inflammatory
Colchicine	Anti-hyperuricemic, anti-inflammatory	Rheumatology
Dexchlorpheniramine	Antihistamine	Allergy relief
Digoxin	Antiarrhythmic, cardiotonic	Cardiology
Furosemide	Diuretic, antihypertensive	Cardiology
Hydroxyzine	Anxiolytic, antihistamine	Psychiatry
Imipramine	Tricyclic antidepressant	Psychiatry
Levomepromazine	Neuroleptic (phenothiazine)	Psychiatry
Maprotiline	Tetracyclic antidepressant	Psychiatry
Opipramol	Tricyclic antidepressant	Psychiatry
Orphenadrine	Antiparkinsonian	Neurology
Oxybutynin	Antispasmodic	Urology
Theophylline*	Bronchodilator, antiasthmatic	Pneumology
Trihexyphenidyl	Antiparkinsonian	Neurology
Trimipramine	Tricyclic antidepressant	Psychiatry
Tropatepine	Antiparkinsonian	Neurology

Les médicaments anticholinergiques , médicaments atropiniques

Les effets à long terme

Anticholinergic Medication Use and Cognitive Impairment in the Older Population: The Medical Research Council Cognitive Function and Ageing Study

Chris Fox, MD,[a] Kathryn Richardson,* MSc,[b] Ian D. Maidment, MA,[cd] George M. Savva, PhD,[e] Fiona E. Matthews, PhD,[f] David Smithard, MD,[gh] Simon Coulton, MSc,[d] Cornelius Katona, MD,[i] Malaz A. Boustani, MD, MPH,[jklm] and Carol Brayne, MD[be]*

OBJECTIVES: To determine whether the use of medications with possible and definite anticholinergic activity increases the risk of cognitive impairment and mortality in older people and whether risk is cumulative.

DESIGN: A 2-year longitudinal study of participants enrolled in the Medical Research Council Cognitive Function and Ageing Study between 1991 and 1993.

13004 participants
Base de données > 65 ans
MMSE baseline et suivi
Recueil des med atropiniques

Age moyen : 75 ± 6,8 ans
48% (6010) prenaient des médicaments atropiniques

Les médicaments atropiniques

Augmentent le déclin cognitif de 0,33 point sur le MMSE (IC 95% 0,03-0,64; p=0,03)

Augmentent la mortalité sur 2 ans : OR =1,68 (IC 95% 1,30-2,16; p<0,001)

Les médicaments atropiniques ont des effets à court terme sur les fonctions cognitives et des effets à long terme (déclin cognitif)

Les benzodiazépines

En France : 30% des > 65 ans consomment des BZD ***(Fourrier et al, 2001)***

Effet à court terme : sédation, diminution de l'attention, déficit mémoire anterograde… ***(Buffett-Jerrott et al, 2002)***

Effet à long terme : risque de démence ??? Résultats contradictoires : études positives ***(Lagnaoui et al, 2002; Wu et al, 2009; 2011)*** **et études négatives** ***(Fastbom et al, 1998;Lagnaoui et al, 2002)***

Risque de démence plus élevé chez les consommateurs de BZD

Benzodiazepine use and risk of dementia: prospective population based study

OPEN ACCESS *BMJ, 2012*

Sophie Billioti de Gage *PhD student*[1 2], Bernard Bégaud *professor*[1 2 3], Fabienne Bazin *researcher*[1 2], Hélène Verdoux *professor*[1 2 4], Jean-François Dartigues *professor*[1 5 3], Karine Pérès *researcher*[1 5], Tobias Kurth *director of research*[1 6 7], Antoine Pariente *associate professor*[1 2 3]

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Abstract

Objective To evaluate the association between use of benzodiazepines and incident dementia.

Design Prospective, population based study.

Setting PAQUID study, France.

Participants 1063 men and women (mean age 78.2 years) who were free of dementia and did not start taking benzodiazepines until at least the third year of follow-up.

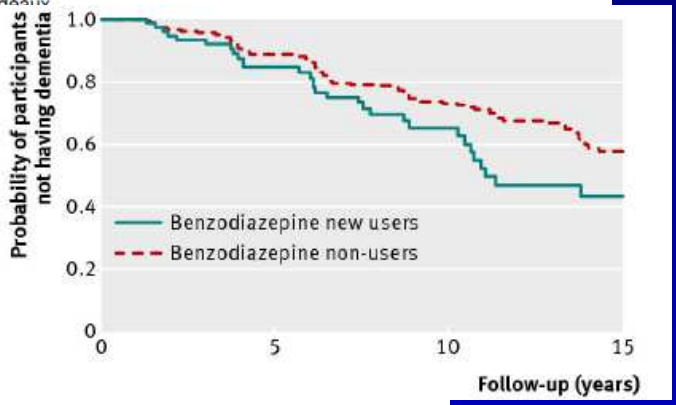


Table 2| **Association between new use of benzodiazepine with incident dementia in PAQUID study. Values are numbers (percentages) unless stated otherwise**

	Incident dementia	No dementia during follow-up	Hazard ratio (95%CI)
Analysis adjusted for age*	**(n=253)**	**(n=810)**	
Benzodiazepine non-users	223 (88)	745 (92.0)	1.00
Benzodiazepine new users	30 (12)	65 (8.0)	1.59 (1.09 to 2.34)
Main analysis†	**(n=240)**	**(n=766)**	
Benzodiazepine non-users	211 (88)	708 (92.4)	1.00
Benzodiazepine new users	29 (12)	58 (7.6)	1.60 (1.08 to 2.38)
Complementary analysis††‡	**(n=231)**	**(n=752)**	
Benzodiazepine non-users	203 (88)	695 (92.4)	1.00
Benzodiazepine new users	28 (12)	57 (7.6)	1.62 (1.08 to 2.43)

Et les Hypnotiques ???

OPEN ACCESS Freely available online

2012

PLOS ONE

Risk of Dementia in Patients with Insomnia and Long-term Use of Hypnotics: A Population-based Retrospective Cohort Study

Pin-Liang Chen[1☯], Wei-Ju Lee[2,3,4☯], Wei-Zen Sun[5], Yen-Jen Oyang[1,7], Jong-Ling Fuh[3,6*]

Table 3. Hazard ratios of dementia in patients with and without hypnotic usage stratified by age and sex.

Group	Hypnotic Users, No. (%) (N = 5693)		Hypnotic Nonusers, No. (%) (N = 28,465)		HR	(95% CI)	*P* Value
All	220/5473	(3.86)	424/28041	(1.49)	2.34	(1.92–2.85)	<.001
Sex							
Male	97/2423	(3.85)	183/12417	(1.45)	2.28	(1.68–3.10)	<.001
Female	123/3050	(3.88)	241/15624	(1.52)	2.39	(1.85–3.09)	<.001
Age							
50–65	27/2758	(0.97)	22/13903	(0.16)	5.22	(2.62–10.41)	<.001
>65	193/2715	(6.64)	402/14138	(2.76)	2.33	(1.90–2.88)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio.
All models are analyzed by Cox regression adjusted for hypertension, diabetes, hyperlipidemia, and stroke.
doi:10.1371/journal.pone.0049113.t003

Les patients insomniaques traités par hypnotiques ont deux fois plus de risque de développer une démence

Autres psychotropes

Les antidepresseurs *Hindmarch et al, 2009*

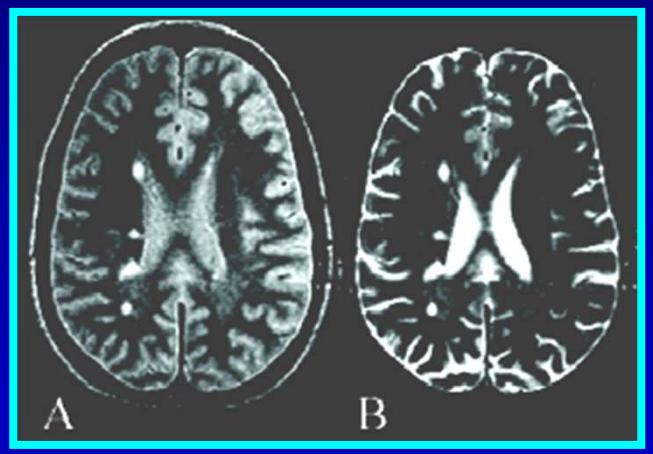
Table 3 Proportional impairment ratios for within-class comparisons of drugs used in the treatment of SAD

Drugs and classes	Dose ranges studied (mg)	No. of studies analysed	No. of psychometrics impaired	Total no. of psychometric assessments	% Cognitive impairment	Within class PIR	References
Selective serotonin reuptake inhibitors							
Fluvoxamine	50–100	5	2	167	1.2	0.08	28,29,31,58,60
Paroxetine	20–30	4	2	49	4.1	0.44	42,43,57,68
Escitalopram	20	1	1	18	5.6	0.67	70
Fluoxetine	20–60	3	4	30	13.3	1.63	41,55,61
Sertraline	100–400	2	29	183	15.8	5.33	49,59
Tricyclic antidepressants							
Dothiepin (V)	50–150	3	10	54	18.5	0.45	33,41,55
Clomipramine	75–150	1	4	18	22.2	0.56	23
Imipramine (V)	75–150	2	13	45	28.9	0.74	60,66
Amitriptyline (V)	25–150	11	86	184	46.7	2.04	35,41,42,44,46, 48,49,51,54,64,68
Other antidepressants							
Moclobemide	100–400	4	7	102	6.9	0.19	35,46,56,64
Venlafaxine	37.5–150	2	6	69	8.7	0.27	51,53
Bupropion	50–100	2	2	22	9.1	0.30	44,54
Mirtazepine	15–45	3	23	65	35.4	1.30	48,57,70
Nefazodone	200–400	1	6	16	38.0	1.36	66
Mianserin (V)	10–60	6	59	87	67.8	4.25	28,29,42,44,53,56
Benzodiazepines							
Diazepam (V)	5–15	4	18	60	30.0	0.58	32,38,39,48
Clonazepam	0.5–2	2	8	26	30.8	0.62	34,65
Bromazepam	3–18	2	16	36	44.4	0.90	25,64
Oxazepam (V)	15	2	13	22	59.1	1.04	30,31
Alprazolam	0.5–3	7	88	175	50.3	1.23	23,31,37,45,52,63,67
Lorazepam (V)	1–2.5	9	60	98	61.2	1.36	22,34,36,40,43,47,50,67,70

Les médicaments anti-HTA

Effet cognitif à court terme ?

HTA favorise les anomalies de la substance blanche responsables d'hypoperfusion chronique

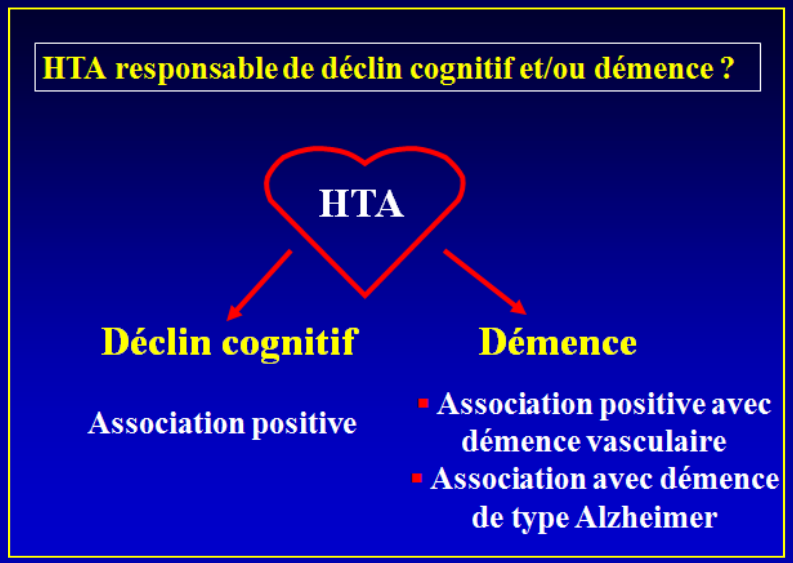


Une baisse de PA peut aggraver l'hypoperfusion chronique

Effet à court terme : peu d'effet cognitif ***(Muldoon et al, 2002)***

Les médicaments anti-HTA

Effet cognitif à long terme ?



Effet Préventif des médicaments anti-HTA sur le déclin cognitif et /ou la démence ?

Résultats contradictoires : études positives ***(Forette et al, 1998; Starr et al, 1996)*** **et études négatives** ***(Peters et al, 2008; Prince et al, 1996)***

Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis

Natacha Levi Marpillat[a,b,c,d], Isabelle Macquin-Mavier[a,b], Anne-Isabelle Tropeano[e], Anne-Catherine Bachoud-Levi[a,b,d,f], and Patrick Maison[a,b,c,d]

Journal of Hypertension, 2013

19 études (18 515) : effet des med anti HTA sur la cognition (suivi médian de 6 mois)

11 études (4 RCT et 7 observationnelles) (n = 831 674) : incidence de démence (suivi médian de 3 ans)

Comparaison des différentes classes médicamenteuses ?

Les anti HTA ont un effet positif sur les fonctions cognitives

Study or subgroup	Mean Difference	SE	Weight	IV, random, 95% CI
MRC 1996 † [8]	–0.417	0.0869	3.7%	–0.42 [–0.59, –0.25]
MRC 1996 # [8]	–0.2669	0.0747	3.7%	–0.27 [–0.41, –0.12]
SCOPE 2003 § [5]	–0.2079	0.0285	4.0%	–0.21 [–0.26, –0.15]
Callender 1986 [16]¤	–0.0739	0.2586	2.2%	–0.07 [–0.58, 0.43]
Skinner 1992 # [37]	–0.0713	0.3019	1.9%	–0.07 [–0.66, 0.52]
Fogari 2003 # [38]	–0.0512	0.1362	3.3%	–0.05 [–0.32, 0.22]
SHEP 1991 † [6]	–0.0012	0.0208	4.0%	–0.00 [–0.04, 0.04]
Callender 1986 # [16]	0.0333	0.2583	2.3%	0.03 [–0.47, 0.54]
Syst-Eutrial 1998 [3]¤	0.0454	0.0407	3.9%	0.05 [–0.03, 0.13]
Fogari 2004 § [39]	0.049	0.1207	3.4%	0.05 [–0.19, 0.29]
PROBE 2006 * [14]	0.0698	0.118	3.4%	0.07 [–0.16, 0.30]
Louis 1999 † [22]	0.0833	0.2504	2.3%	0.08 [–0.41, 0.57]
Skinner 1992 [37]¤	0.0852	0.2677	2.2%	0.09 [–0.44, 0.61]
Louis 1999 * [22]	0.0931	0.2505	2.3%	0.09 [–0.40, 0.58]
Blumenthal 1990 * [15]	0.1129	0.259	2.2%	0.11 [–0.39, 0.62]
HOPE 1996 * [4]	0.1226	0.1697	3.0%	0.12 [–0.21, 0.46]
Perez-Stable 2000 # [23]	0.1639	0.1406	3.2%	0.16 [–0.11, 0.44]
Hyvet-Cog 2008 † [7]	0.1749	0.0347	3.9%	0.17 [0.11, 0.24]
HOPE 1996 † [4]	0.2071	0.1733	3.0%	0.21 [–0.13, 0.55]
Blumenthal 1990 * [15]	0.2278	0.2615	2.2%	0.23 [–0.28, 0.74]
Dimsdale 1992 # [19]	0.298	0.2555	2.3%	0.30 [–0.20, 0.80]
Madden 1988 # [20]	0.3182	0.489	1.1%	0.32 [–0.64, 1.28]
Tedesco 1999 † [21]	0.3402	0.1979	2.7%	0.34 [–0.05, 0.73]
Fogari 2004 * [39]	0.3567	0.1207	3.4%	0.36 [0.12, 0.59]
PROBE 2006 § [14]	0.3749	0.1195	3.4%	0.37 [0.14, 0.61]
Croog 1986 # [18]	0.408	0.0818	3.7%	0.41 [0.25, 0.57]
Dimsdale 1992 # [19]	0.4381	0.1343	3.3%	0.44 [0.17, 0.70]
Croog 1986 * [18]	0.4749	0.0784	3.7%	0.47 [0.32, 0.63]
Madden 1988 # [20]	0.8258	0.5391	0.9%	0.83 [–0.23, 1.88]
Croog 1994 # [17]	0.9779	0.1413	3.2%	0.98 [0.70, 1.25]
Croog 1994 [17]¤	1.0145	0.1343	3.3%	1.01 [0.75, 1.28]
Fogari 2003 § [38]	1.2044	0.174	3.0%	1.20 [0.86, 1.55]
Tedesco 1999 § [21]	1.3088	0.2102	2.6%	1.31 [0.90, 1.72]
Croog 1994 * [17]	1.5226	0.1623	3.1%	1.52 [1.20, 1.84]
Total (95% CI)			100.0%	0.29 [0.17, 0.40]

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 484.07$, df = 33 ($P < 0.00001$); $I^2 = 93\%$
Test for overall effect: $Z = 4.86$ ($P < 0.00001$)

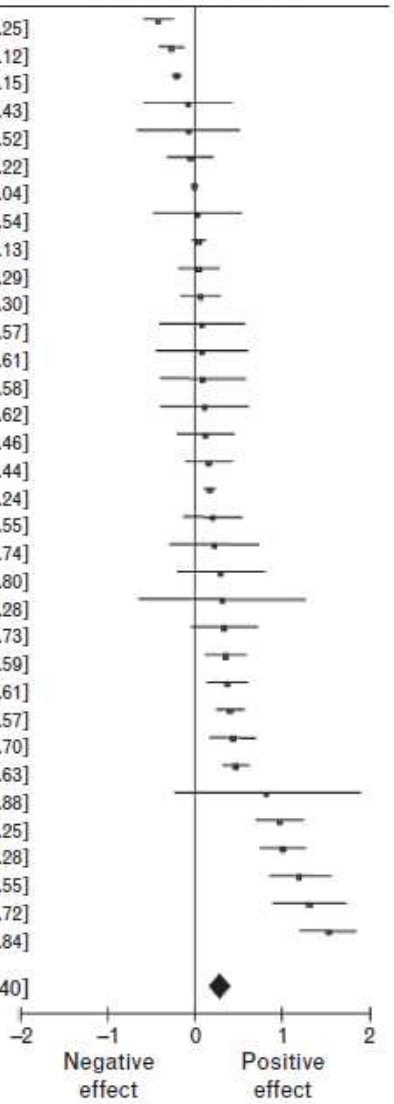


FIGURE 2 Effects of antihypertensive treatment on overall cognition in randomized controlled trials. Boxes represent the individual study estimates, the size being proportionnal to the study weight; lines, the 95% confidence interval; and the diamond, the overall effect with a 95% confidence interval. † indicates diuretics, ‡: angiotensin-converting enzyme inhibitors, ¥: angiotensin receptor blockers, *: β-blockers and §: calcium channel blockers.

Les médicaments anti HTA diminuent de 9% le taux incident de démence

Study or subgroup	log[Hazard ratio]	SE	Weight	Hazard ratio IV, random, 95% CI
Syst-Eur trial 1998 [3]	–0.713	0.364	2.0%	0.49 [0.24, 1.00]
BLSA 2005 [43]	–0.462	0.362	2.0%	0.63 [0.31, 1.28]
Cache County Study 2006 [44]	–0.446	0.227	4.4%	0.64 [0.41, 1.00]
Kungsholmen1999 [40]	–0.357	0.08	13.2%	0.70 [0.60, 0.82]
Rotterdam 2001 [41]	–0.274	0.194	5.5%	0.76 [0.52, 1.11]
US Veteran 2010 § [46]	–0.269	0.051	15.9%	0.76 [0.69, 0.84]
SHEP 1991 [6]	–0.174	0.225	4.4%	0.84 [0.54, 1.31]
Hyvet-Cog 2008 [7]	–0.116	0.13	9.0%	0.89 [0.69, 1.15]
CSHA 2002 [42]	–0.094	0.179	6.1%	0.91 [0.64, 1.29]
US Veteran 2010* [46]	–0.061	0.017	18.1%	0.94 [0.91, 0.97]
CHS 2009 [45]	0.0099	0.076	13.6%	1.01 [0.87, 1.17]
SCOPE 2003 [5]	0.08	0.186	5.8%	1.08 [0.75, 1.56]
Total (95% CI)			100.0%	0.84 [0.75, 0.93]

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 36.43$, df = 11 ($P = 0.0001$); $I^2 = 70\%$

Test for overall effect: $Z = 3.25$ ($P = 0.001$)

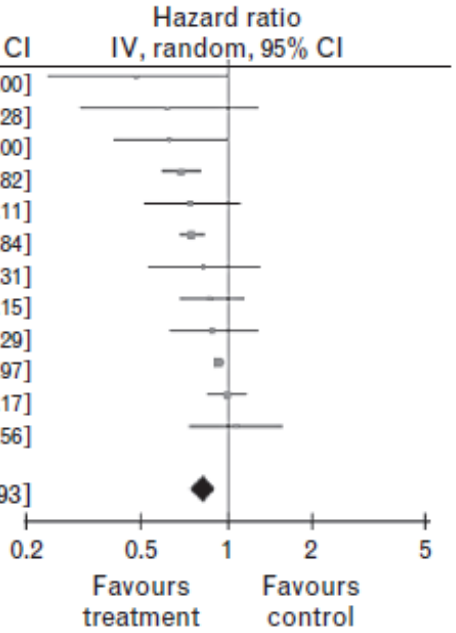


FIGURE 3 Effect of antihypertensive treatment on the incidence of all-cause dementia. Boxes represent the individual study estimates, the size being proportional to the study weight; lines, the 95% confidence interval; and the diamond, the overall effect with a 95% confidence interval. * and § relate to ACEI and ARBs groups, respectively.

Comparaison des différentes classes médicamenteuses sur les fonctions cognitives

Treatment \ Comparison group	Placebo	CCBs	ACE inhibitors	β-blockers	Diuretics
ARBs	0.60 ± 0.18 (*P* = 0.02)	0.57 ± 0.24 (*P* = 0.06)	0.47 ± 0.17 (*P* = 0.04)	0.67 ± 0.18 (*P* = 0.01)	0.54 ± 0.19 (*P* = 0.04)
CCBs	0.02 ± 0.19 (*P* = 0.91)	–	–0.11 ± 0.22 (*P* = 0.65)	0.10 ± 0.17 (*P* = 0.58)	–0.03 ± 0.24 (*P* = 0.89)
ACE inhibitors	0.13 ± 0.17 (*P* = 0.49)		–	0.21 ± 0.15 (*P* = 0.23)	0.07 ± 0.17 (*P* = 0.70)
β-blockers	–0.08 ± 0.13 (*P* = 0.59)			–	–0.13 ± 0.19 (*P* = 0.50)
Diuretics	0.06 ± 0.17 (*P* = 0.76)				–

Les antagonistes des R de l'angiotensine > placebo et aux autres classes médicamenteuses

Au total, chez des patients HTA sans ATDC cardiovasculaires

- Les médicaments anti HTA améliorent les fcts cognitives et réduisent le risque de démence.

- Les antagonistes des récepteurs de l'angiotensine +++

Chez des patients avec ATCD cardiovasculaires : pas de bénéfice sur les fonctions cognitives !

Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies

Lancet Neurol, 2011

Craig Anderson, Koon Teo, Peggy Gao, Hisatomi Arima, Antonio Dans, Thomas Unger, Patrick Commerford, Leanne Dyal, Helmut Schumacher, Janice Pogue, Ernesto Paolasso, Nicolaas Halwerda, Irina Chazova, Azan Binbrek, James Young, Salim Yusuf, for the ONTARGET and TRANSCEND Investigators.

Les Statines

Les Statines diminuent la production de β Amyloide chez modèle animal de Maladie d'Alzheimer ***(Refolo et al, 2001)***

Et chez l'homme ???

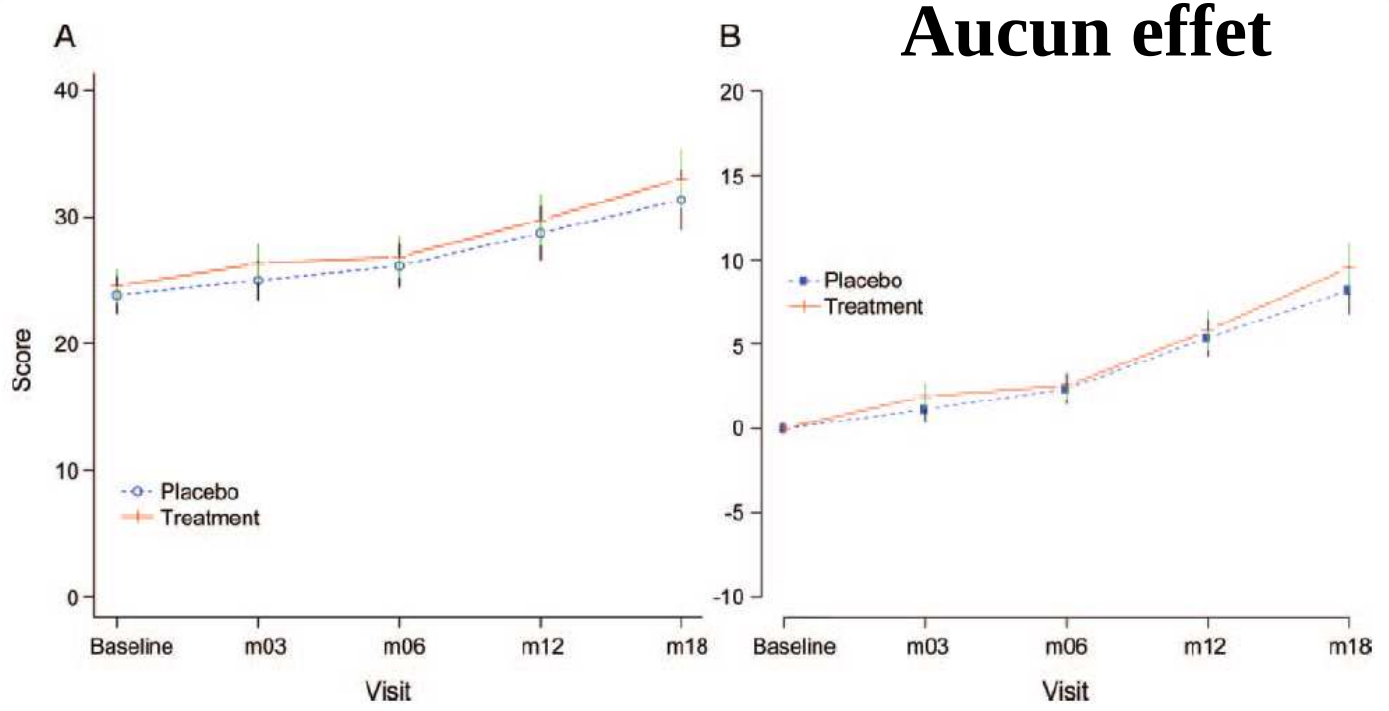
- Malade : atteint de maladie d'Alzheimer
- Sain : en prévention

A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease

Neurology, 2011

Figure 2 Effect of treatment on the primary outcome measures

Aucun effet



Mean of ADAS-Cog = Alzheimer's Disease Assessment Scale–cognitive portion total score (A) and change score (B) by treatment and visit. Presented with 95% confidence intervals.

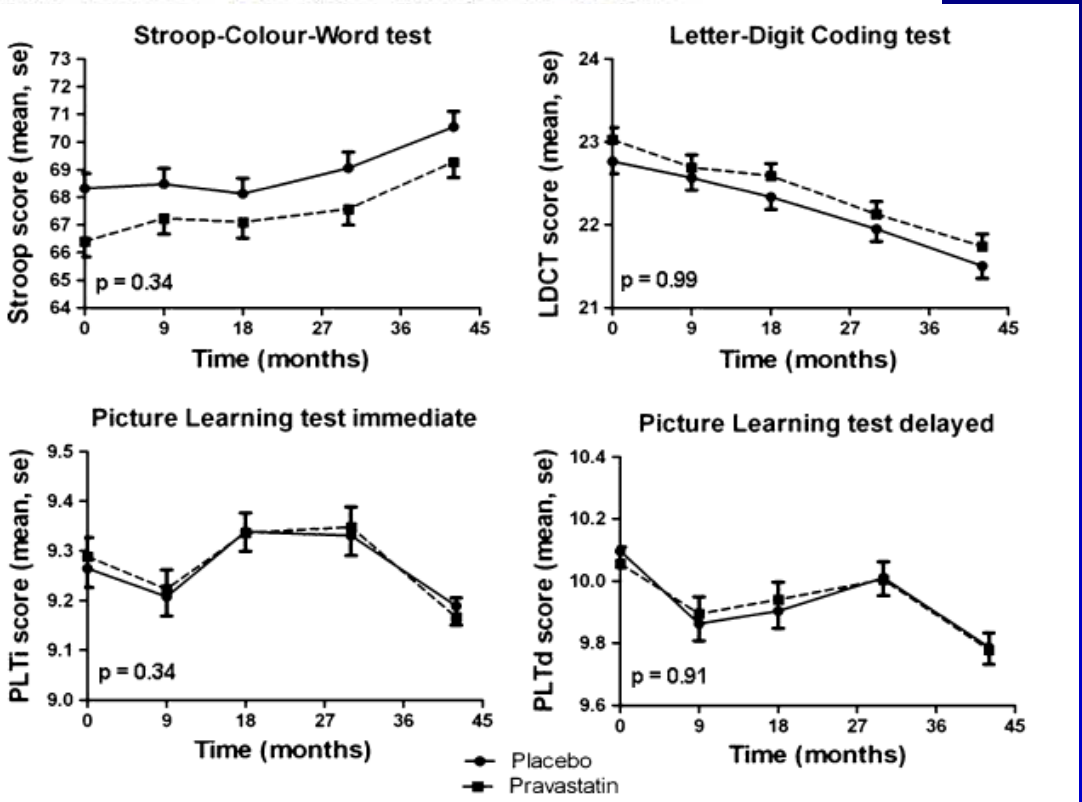
Chez des sujets non déments

J Neurol (2010) 257:85–90
DOI 10.1007/s00415-009-5271-7

ORIGINAL COMMUNICATION

Pravastatin and cognitive function in the elderly. Results of the PROSPER study

Stella Trompet · Peter van Vliet · Anton
Michael B. Murphy · Ian Ford · Peter
David J. Stott · Jim Shepherd · Eduard
Rudi G. J. Westendorp



Essai clinique :
5804 sujets (70 -82 ans) à risque cardiovasculaire

Pas d'effet sur la cognition

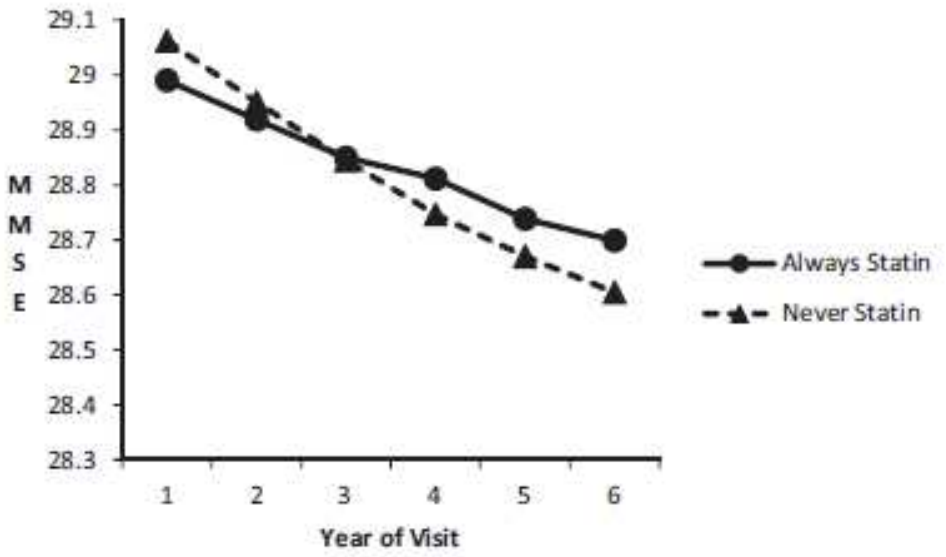
Chez des sujets non déments

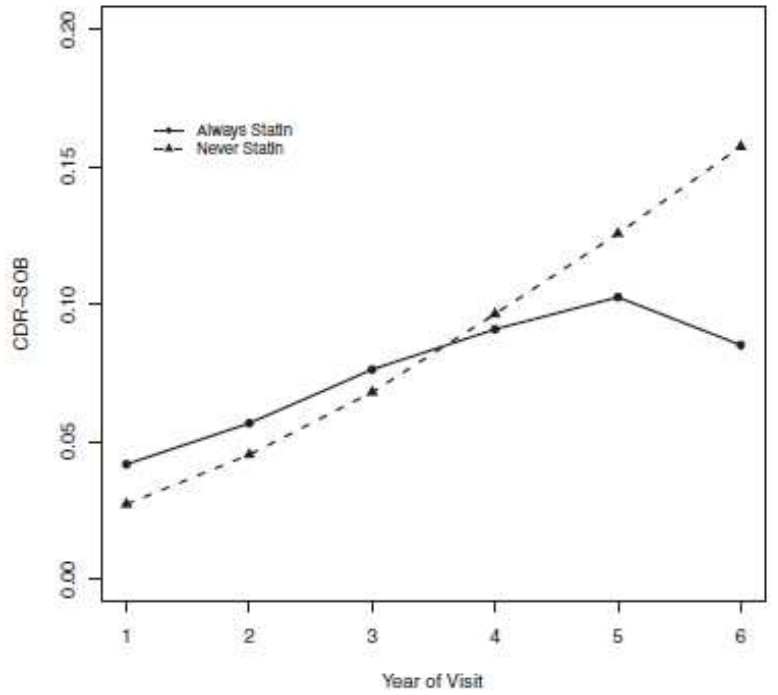
Etudes observationnelles : résultats contradictoires :
études positives ***(Bettermann et al, 2012; Steenland et al, 2013)*** **et**
études négatives ***(Ancelin et al, 2012; Zandi et al, 2005)***

Statins and Cognitive Decline in Older Adults with Normal Cognition or Mild Cognitive Impairment

Kyle Steenland, PhD, Liping Zhao, MS,† Felicia C. Goldstein, PhD,‡ and Allan I. Levey, MD, PhD‡*

1244 utilisateurs statines
2363 non utilisateurs





Nécessité d'autres essais cliniques

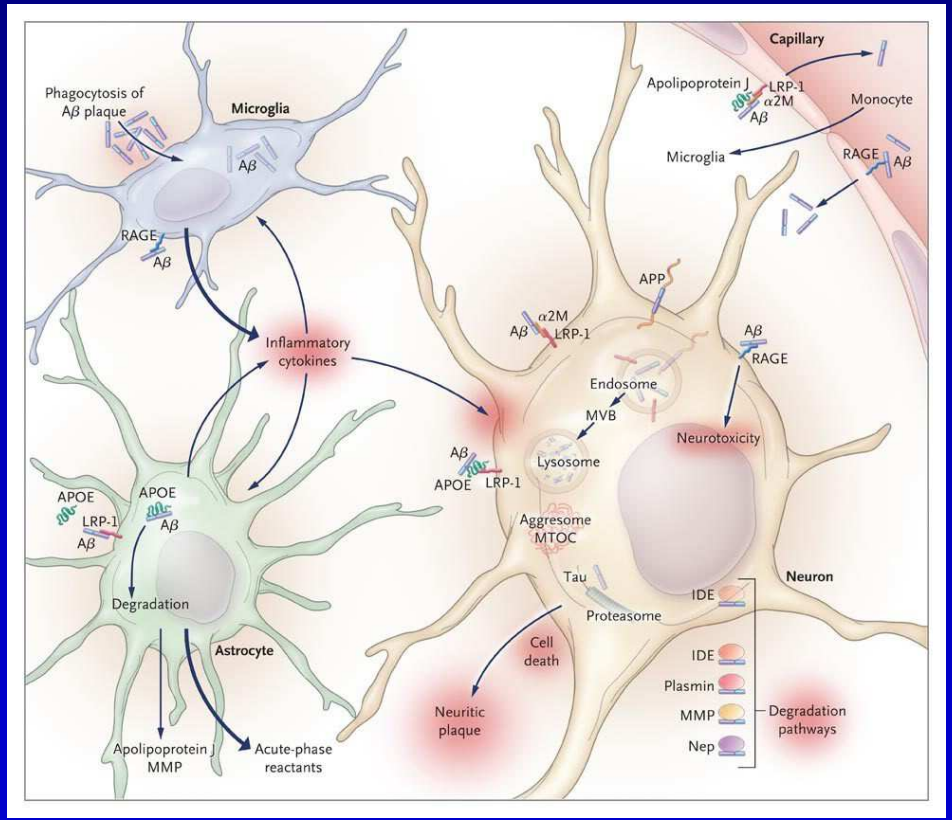
Les Antalgiques

- **Paracétamol : pas d'effet**

- **Médicaments morphiniques : effets sédatifs, confusion, altération mémoire, attention**

- AINS et AIS ?

Inflammation est impliquée dans les troubles cognitifs et la démence ***(Gorelick, 2010)***



Les Anti Inflammatoires Non Stéroidiens (AINS)

Chez des patients atteints de maladie d'Alzheimer

Effects of Rofecoxib or Naproxen vs Placebo on Alzheimer Disease Progression

A Randomized Controlled Trial

JAMA, 2003

Paul S. Aisen, MD
Kimberly A. Schafer, MS
Michael Grundman, MD, MPH
Eric Pfeiffer, MD
Mary Sano, PhD
Kenneth L. Davis, MD
Martin R. Farlow, MD

Context Laboratory evidence that inflammatory mechanisms contribute to neuronal injury in Alzheimer disease (AD), along with epidemiological evidence, suggests that nonsteroidal anti-inflammatory drugs (NSAIDs) may favorably influence the course of the disease.

Objective To determine whether treatment with a selective cyclooxygenase (COX) -2 inhibitor (rofecoxib) or a traditional nonselective NSAID (naproxen) slows cognitive decline in patients with mild-to-moderate AD.

Design Multicenter, randomized, double-blind, placebo-controlled, parallel group trial, with 1-year exposure to study medications.

351 sujets AD, suivi 1 an
Résultats : pas d'effet significatif

Les Anti Inflammatoires Non Stéroidiens (AINS)

Chez des patients atteints de maladie d'Alzheimer

Rofecoxib *Neurology, 2004*

No effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study

S.A. Reines, MD; G.A. Block, MD; J.C. Morris, MD; G. Liu, PhD; M.L. Nessly, MS; C.R. Lines, PhD; B.A. Norman, BS; and C.C. Baranak, MA, on behalf of the Rofecoxib Protocol 091 Study Group

692 sujets AD, suivi 1 an
Résultats : Pas d'effet significatif

Pasqualetti et al, 2009 : A randomized controlled study on effects of ibuprofen on cognitive progression of Alzheimer's disease

Résultats : Pas d'effet significatif

Les Anti Inflammatoires Non Stéroidiens (AINS)

Chez des sujets non déments : prévention

Cognitive Function Over Time
in the Alzheimer's Disease
Anti-inflammatory Prevention Trial (ADAPT)

ARCHIVES EXPRESS

Results of a Randomized, Controlled Trial of Naproxen and Celecoxib

*ADAPT Research Group**

Arch Neurol, 2008

2528 sujets > 70 ans ayant un parent (1 degré) avec une AD
Bilan cognitif normal
3 groups naproxen, celecoxib et placebo
Suivi 3 ans

Résultats

Table 3. Longitudinal Effect of Treatment on Cognitive Function

Measure	Celecoxib vs Placebo		Naproxen Sodium vs Placebo	
	β (95% Confidence Interval)	*P* Value	β (95% Confidence Interval)	*P* Value
Global summary score	−0.01 (−0.05 to 0.02)	.47	−0.05 (−0.09 to −0.01)	.02
Adjusted 3MS-E score	−0.32 (−0.62 to −0.02)	.04	−0.36 (−0.68 to −0.04)	.03
GVF score	−0.27 (−0.73 to 0.19)	.24	−0.54 (−1.01 to −0.07)	.02
RBMT delayed recall score	−0.09 (−0.32 to 0.15)	.47	−0.18 (−0.42 to 0.06)	.14
BVMT-R delayed recall score	0.03 (−0.15 to 0.21)	.75	−0.12 (−0.31 to 0.07)	.22
Adjusted HVLT-R trial 4 score	0.08 (−0.11 to 0.27)	.4	−0.10 (−0.30 to 0.10)	.34
Digit Span score, forward	−0.06 (−0.20 to 0.08)	.42	−0.04 (−0.19 to 0.10)	.55
Digit Span score, backward	0.03 (−0.11 to 0.17)	.67	−0.11 (−0.26 to 0.03)	.13

Abbreviations: BVMT-R, Brief Visuospatial Memory Test–Revised; GVF, generative verbal fluency; HVLT-R, Hopkins Verbal Learning Test–Revised; RBMT, Rivermead Behavioral Memory Test; 3MS-E, Modified Mini-Mental State Examination.

Le Naproxen et le celecoxib n'améliorent pas la cognition
Le naproxen a un effet aggravant

Les Anti Inflammatoires Non Stéroidiens (AINS)

Chez des sujets non déments : prévention

Low dose aspirin and cognitive function in middle aged to elderly adults: randomised controlled trial

BMJ, 2008

Jackie F Price,[1] Marlene C Stewart,[1] Ian J Deary,[2] Gordon D Murray,[1] Peter Sandercock,[3] Isabella Butcher,[1] F Gerald R Fowkes,[1] on behalf of the AAA Trialists

Performance on cognitive function tests at follow-up*

	Aspirin group (n=1139)		Placebo group (n=1186)		
Test of cognition	No of participants	Mean (SD) score; 95% CI	No of participants	Mean (SD) score; 95% CI	P value
General cognitive factor score (summary cognitive score)†	1109	0.00 (1.01); −0.06 to 0.06	1153	−0.01 (0.99); −0.06 to 0.05	0.83
Raven's progressive matrices (5 sets of 12 item tests; maximum possible score 60)	1110	34.3 (9.5); 33.8 to 34.9	1153	34.4 (9.3); 33.9 to 35.0	0.83
Auditory verbal learning, trials I-V (sum of five trials with same list; maximum possible 75 words)	1118	63.0 (16.7); 62.1 to 64.0	1159	63.0 (16.9); 62.0 to 64.0	0.93
Digit symbol (total No of symbols matched correctly in 90 second test; maximum possible score 93)	1126	40.0 (11.7); 39.3 to 40.7	1170	40.0 (11.7); 39.4 to 40.7	0.92
Verbal fluency (total No of words generated in three 1 minute tests)	1117	37.6 (12.8); 36.9 to 38.4	1156	37.1 (12.7); 36.3 to 37.8	0.27
Trail making (seconds to completion)‡	1122	4.6 (0.4); 4.6 to 4.6	1167	4.6 (0.4); 4.6 to 4.6	0.90
Mini-mental state examination (total score, maximum possible 30)	1131	28.6 (1.7); 28.5 to 28.7	1178	28.5 (1.8); 28.4 to 28.6	0.20

Suivi à 5 ans Aucun effet !

Les Anti Inflammatoires Non Stéroidiens (AINS)

Chez des sujets non déments : prévention

ELSEVIER

Alzheimer's & Dementia 8 (2012) 219–226

Alzheimer's & Dementia

Nonsteroidal anti-inflammatory drug use and the risk of cognitive impairment and Alzheimer's disease

Sharlène Côté[a,b], Pierre-Hugues Carmichael[a], René Verreault[a,b], Joan Lindsay[a,c], Jean Lefebvre[d], Danielle Laurin[a,d,*]

5276 sujets non déments

Cohorte population Canadienne > 65 ans

Suivi 10 ans

Résultats : l'utilisation des AINS est associée à un risque plus faible de survenue de démence HR = 0,80; IC95% 0,70-0,92

Les Anti Inflammatoires Stéroidiens (AIS)

ELSEVIER

Neurobiology of Aging 33 (2012) 2082–2090

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Steroid and nonsteroidal anti-inflammatory drugs, cognitive decline, and dementia

Marie-Laure Ancelin[a,b,1,*], Isabelle Carrière[a,b,1], Catherine Helmer[c], Olivier Rouaud[d], Florence Pasquier[e], Claudine Berr[a,b], Isabelle Chaudieu[a,b], Karen Ritchie[a,b,f]

Etude prospective observationnelle chez 7234 sujets > 65 ans (The 3C study group) non déments sur 7 ans

352 (147 H et 205 F) étaient sous AIS (5%)
Chez les femmes : ↑ déclin cognitif (OR = 1,76; IC95% 1,14-2,71) sur fonctions exécutives.
Pas d' ↑ du risque de démence

En Synthèse : Médicaments et cognition

Médicaments	Effet à court terme	Effet à long terme chez le dément	Effet à long terme chez le sujet sain
Atropiniques	↑ Trouble cognitif	↑ Trouble cognitif	↑ Déclin cognitif
BZD Hypnotiques	↑ Trouble cognitif	↑ Trouble cognitif	Contradictoire ? ↑ risque démence
Antidépresseurs	↑ Trouble cognitif	?	?
Antihypertenseurs	≈ 0		↓ déclin cognitif ↓ risque démence
Statines		Pas d'effet	RCT : pas d'effet Epidémio : contradictoire ?
AINS		Pas d'effet	RCT : pas d'effet Epidémio : ↓ risque démence ?
AIS			↑ Déclin cognitif

Les cognitivo stimulants ???

Table 1. Summary of the effects of some drugs frequently used as cognitive enhancers

Cognitive enhancer	Neuromodulatory mechanism	Cognitive functions improved	Known brain systems most affected	Currently recommended clinical use
Methylphenidate, amphetamine	Dopamine and noradrenaline reuptake inhibitors	Response inhibition, working memory, attention, vigilance	Frontoparietal attentional systems, striatum, default mode networks	ADHD, wake-promoting agent
Caffeine	Non-selective adenosine receptor antagonist	Vigilance, working memory, incidental learning	Frontal lobe attentional systems	–
Nicotine	Nicotinic cholinergic receptor agonist	Working memory, episodic memory, attention	Fronto-parietal attentional systems, medial temporal lobe, default mode networks	–
Modafinil	Unknown, but effects on dopamine, noradrenaline and orexin systems proposed	Working memory, episodic memory, attention	Frontal lobe attentional systems	Wake-promoting agent
Atomoxetine, reboxetine	Noradrenaline reuptake inhibitors	Response inhibition, working memory, attention	Frontoparietal attentional systems	ADHD, depression
Donepezil, galantamine, rivastigmine (AChEI)	Blocks enzymatic breakdown of acetylcholine	Episodic memory, attention	Frontal lobe attentional systems	Alzheimer's disease, PDD, DLB
Memantine	Noncompetitive, low-affinity, open channel blocker of the NMDA receptor	Episodic memory, attention	Frontal and parietal lobe	Alzheimer's disease

Mais aussi utilisés chez des étudiants, chez les militaires, chez les personnes âgés ….

Chez les sujets sains

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Modafinil and methylphenidate for neuroenhancement in healthy individuals: A systematic review

Dimitris Repantis[a,*], Peter Schlattmann[b,1], Oona Laisney[a], Isabella Heuser[a]

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

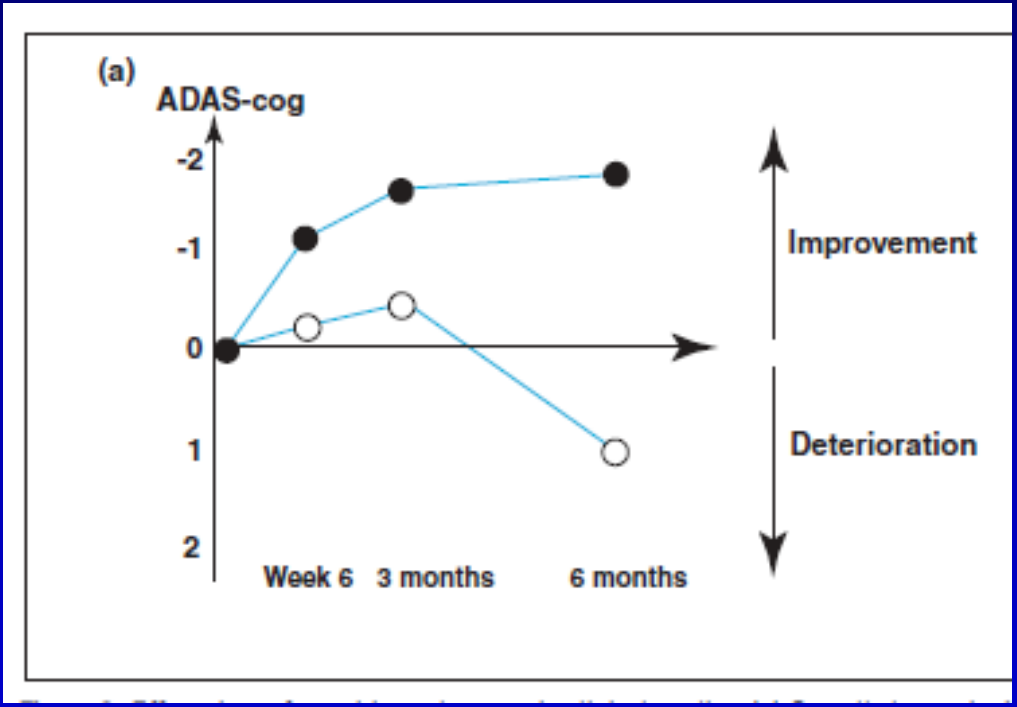
Acetylcholinesterase inhibitors and memantine for neuroenhancement in healthy individuals: A systematic review

Dimitris Repantis*, Oona Laisney, Isabella Heuser

Les effets sur la cognition ne sont pas significatifs !

Chez les sujets déments : Maladie d'Alzheimer

Les anticholinesterasiques :
Les essai cliniques à 6 mois



Taille de l'effet minime !!!

Chez les sujets déments : Maladie d'Alzheimer

Les anticholinesterasiques :
Les essai cliniques à 3 ans

Ne retardent pas l'institutionnalisation

Ne retardent pas la perte d'autonomie

Doit on continuer à les prescrire ?

Conclusion : Médicaments et cognition

Chez le patient dément :

Eviter les médicaments !

Chez le sujet âgé sain en prévention :

si hypertendu : anti HTA (sartan ?)

Eviter les atropiniques, les BZD, les AIS

Il n'existe pas de médicament « protecteur »