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Nicotine for Alzheimer's disease (Review)

López-Arrieta J, Sanz FJFJS

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[Intervention Review]

Nicotine for Alzheimer's disease

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ABSTRACT

Background

Nicotine is a cholinergic agonist that also has a presynaptic effect in releasing acetylcholine. It has been shown to reverse spatial memory deficits produced in rats by lesions in the medial septal nucleus of their brains, and, in aged monkeys, nicotine administration improves memory and alertness to visual stimuli. Observational studies have suggested a protective effect of smoking against Alzheimer's disease, but recent studies have called this into question. Smoking is a risk factor for stroke and so, possibly, for vascular dementia. Because nicotine has adverse effects, it is important to conduct a systematic review to assess its clinical efficacy and safety for people with Alzheimer's disease.

Objectives

To evaluate the efficacy and safety of nicotine, administered in any way or form, for people with Alzheimer's disease.

Search methods

ALOIS, the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG), *The Cochrane Library*, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS and other sources were searched on 25 March 2010.

The latest search performed in March 2010 retrieved four new studies for consideration; none of these met the inclusion criteria for the review.

Selection criteria

All unconfounded, double-blind, randomized trials in which treatment with nicotine patches, or administration of nicotine intravenously, or in any other way or form, was administered for more than a day and compared with placebo for people with Alzheimer's disease.

Data collection and analysis

The one included trial did not present results suitable for inclusion in the review.

Main results

There were no results available from the one included study.

Authors' conclusions

This review is not able to provide any evidence that nicotine is or is not a useful treatment for Alzheimer´s disease.

PLAIN LANGUAGE SUMMARY

No evidence of the efficacy of nicotine for Alzheimer's disease

Nicotine has been related to recovery of memory in humans and animal models and some observational studies have been compatible with a protective effect of nicotine inhalation against Alzheimer's disease. At present, there is great controversy over this possible effect of tobacco use, and evidence is inconclusive. This review found no evidence on which to recommend nicotine for Alzheimer's disease.

BACKGROUND

Alzheimer's disease is a progressive disease of the brain leading to loss of neurons and eventually to the clinical syndrome of dementia. It is the commonest cause of dementia in Western societies. The cognitive impairment produced by Alzheimer's disease is associated with deficits in cholinergic systems of neurotransmission in the brain (Whitehouse 1982; Blessed 1968). This has provided the rationale for the development of acetylcholinesterase inhibitors such as tacrine (López-Arrieta 1998), donepezil (Birks 2003), rivastigmine (Anand 1997), and galantamine (Loy 2004) for treatment of the cognitive and behavioural manifestations of Alzheimer's disease.

Acetylcholine has two important types of receptors - muscarinic and nicotinic. Neuronal nicotinic receptors are widely distributed in central nervous system and the two most abundant subtypes are those containing α4β2 and α7 subunits (Gotti 1997).
The prototypical agonist of the nicotinic acetylcholine receptor is nicotine, an alkaloid derived from the leaves of tobacco plants (Nicotiana tabacum and Nicotiana rustica). Nicotinic receptor densities are further attenuated in age-associated neurodegenerative disorders in the elderly, such as Alzheimer's disease (Graham 2002).

Nicotine is a cholinergic agonist that acts both post-synaptically and pre-synaptically to release acetylcholine (Araujo 1988). Most anticholinesterase anti-dementia drugs have been presumed to exert their effect essentially through the muscarinic cholinergic system, only galantamine has nicotinic allosteric modulation activity as well.
Numerous investigations, both in vivo and in vitro, indicate that nicotine acting via neuronal nicotinic receptors, both α4β2 and α7 subtypes, can enhance neurone survival in response to a range of neurotoxic insults (Zanardi 2002). Nicotine has been shown to reverse spatial memory deficits in rats with lesions in the medial septal nucleus (Decker 1992) and to improve memory in aged monkeys (Buccafusco 1991). Nicotine also exerts an effect on other transmitters including serotonin (5HT), dopamine, and GABA.

Acute nicotinic blockade with single oral doses of mecamylamine, a central and peripheral nicotinic antagonist, produces cognitive impairment in healthy male non-smokers (Newhouse 1990; Newhouse 1992). Nicotinic cholinergic stimulation can activate pituitary hormonal secretion in the human and nicotinic cholinergic stimulation may constitute an important part of cholinesterase inhibitor-induced endocrine stimulation and behavioural activation (Newhouse 1990).

Published studies in humans have reported the effects of intravenous or subcutaneous nicotine administration on people with Alzheimer's disease. Significant improvements were reported in several cognitive tasks such as free recall, visual attention and perception (Jones 1992; Newhouse 1990), and in mood (Gentry 2000) although not on memory (Sahakian 1989). These results suggest that central nicotinic cholinergic stimulation deserves further investigation as a possible treatment for Alzheimer's disease. There is also the possibility that nicotine might have a preventive action on Alzheimer's disease, delaying the onset of clinical dementia by reducing the rate of neuronal loss or mitigating its functional consequences (Howe 2001).

The effects of smoking on dementia in general and Alzheimer's disease in particular are controversial, and the issue is inevitably tinged by ideological considerations (Boyd 2000, Calinas 2000) that might hinder objective investigation. Nicotine readily crosses the blood-brain barrier, and some studies support the notion that smoking reduces the risk of Alzheimer's disease (Graves 1991; Lee 1994). Some other studies show opposite results (Launer 1999; Ott 1998; Shaji 1996) and yet others find no statistical association between smoking and dementia (Doll 2000). One population-based study demonstrated a significantly increased risk of developing AD in smokers (Ott 1998), although this was only so in individuals not carrying the apolipoprotein e4 allele (ApoE e4). In ApoE e4 carriers, tobacco smoking tended to reduce the risk of AD, consistent with a previous case control study (van Duijn 1995). There is also evidence that chronic nicotine in vivo and tobacco use is capable in reducing brain Aß in elderly individuals although bthe mechanism of action remain uncertain (Court 2005).

On the other hand, because nicotine has been related with adverse effects, especially concerning cardiovascular risks in elderly people, and also on sleep and behaviour (Parrott 1989), it is important to conduct a systematic review of the efficacy and safety of nicotine in people with Alzheimer's disease.

OBJECTIVES

To evaluate the efficacy and safety of nicotine, administered in any way or form, for people with Alzheimer's disease.

METHODS

Criteria for considering studies for this review

Types of studies

All unconfounded, double-blind, randomized, placebo-controlled trials of longer than one day were considered for inclusion. Trials in which the allocation to treatment or placebo was not randomized, or in which treatment allocation was not concealed were excluded. Prior knowledge of treatment allocation may lead to bias (Schulz 1995).

Types of participants

People with Alzheimer's disease as diagnosed by ICD, DSM-III-R (Diagnostic Statistical Manual: Mental Disorders, third revised edition) DSM-IV (Diagnostic Statistic Manual: Mental Disorders, fourth edition) or NINCDS-ADRDA (National Institute of Neurological, Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders) criteria (McKhann 1984).

Types of interventions

Nicotine, or a pharmacologically equivalent derivative, in any dose and by any method of administration, without any other drug, compared with placebo with the same appearance, without any other drug.

Types of outcome measures

The primary of outcomes of interest are:
1. Cognitive performance such as: attention, recent memory, recognition, learning
2. Acceptability of treatment as measured by withdrawal rate from trial

3. Safety as measured by the incidence of adverse effects leading to withdrawal

Biological outcomes such as plasma levels, activity or ECG monitoring to be noted but not assessed as efficacy measures.

Search methods for identification of studies

We searched ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Group's Specialized Register on 25 March 2010. The search term used was: nicotine

ALOIS is maintained by the Trials Search Co-ordinator and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy. The studies are identified from:

1. Monthly searches of a number of major healthcare databases: Medline, Embase, Cinahl, Psycinfo and Lilacs
2. Monthly searches of a number of trial registers: meta Register of Controlled Trials; Umin (Japan's Trial Register); WHO portal (which covers ClinicalTrials.gov; ISRCTN; Chinese Clinical Trials Register; German Clinical Trials Register; Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others)
3. Quarterly search of *The Cochrane Library*'s central register of controlled trials (CENTRAL)
4. Monthly searches of a number of grey literature sources: ISI Web of Knowledge - Conference Proceedings; Index to Theses; Australasian Digital Theses

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS website.

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, CENTRAL and conference proceedings can be viewed in the 'methods used in reviews' section within the editorial information about the Dementia and Cognitive Improvement Group.

Additional searches in each of the sources listed above to cover the timeframe from the last searches performed for the Specialized Register to March 2010 to ensure that the search for the review was as up-to-date as possible. The search strategies used can be seen in Appendix 1.

When the information from a report was unclear, trial investigators were asked to provide additional information on methodological issues such as randomization, blinding and data from the first period of any cross-over study. One trialist responded and sent original data, but unfortunately in an incomplete form (Snaedel 1996).

The latest search performed on 25 March 2010 retrieved 4 new studies for consideration. None of those studies met the inclusion criteria for the review.

Data collection and analysis

Selection of studies

A single reviewer (JLA) discarded citations deemed irrelevant on the basis of the title of the publication and its abstract. All other citations were retrieved for further assessment.

Two reviewers (JLA and FJSS) independently selected the trials for inclusion in the review from the culled citation list.

Quality assessment

Two reviewers (JLA and FJSS) assessed the methodological quality of each selected trial. Quality was rated according to the criteria of the Cochrane Collaboration Handbook (Higgins 2005).

Empirical research has shown that lack of adequate allocation concealment is associated with bias. Trials with unclear concealment measures have been shown to yield more pronounced estimates of treatment effects than trials that have taken adequate measures to conceal allocation schedules, but less pronounced than inadequately concealed trials (Chalmers 1983; Schulz 1995). Thus trials were included if they conformed to categories A or B; those falling into category C were excluded.

Data extraction

The one included study did not report the results with enough detail and they were not extracted for the review.

Data analysis

There were no data to analyse.

RESULTS

Description of studies

The one qualifying study, White 1999, randomized eight people with mild to moderate Alzheimer's disease, diagnosed using NINCDS-ADRDA criteria, to one of two arms of a cross-over design against placebo. None of the participants had smoked during the preceding year even if they had been smokers previously. None suffered from a serious disease or disability. During the nicotine phase, the drug was delivered using a nicotine patch (Nicotrol®) that released the drug over 16 hours of the day. For the first week, the dose was 5 mg/day, for weeks two and three 10 mg per day, and for week four 5 mg per day. The two treatment periods were separated by a two-week wash-out period. One subject dropped out during the nicotine period, but the reason is not reported.

The participants were examined on eight separate occasions over the 10 weeks of the study. The outcomes were assessed using the tests or scales listed.

1. The primary cognitive test was the cognitive part of the Alzheimer's Disease Assessment Scale (ADAS-cog) (Rosen 1984). ADAS-cog comprises 11 individual tests, spoken language ability (0-5), comprehension of spoken language (0-5), recall of test instructions (0-5), word finding facility (0-5), following commands (0-5), naming object (0-5), construction drawing (0-5), ideational praxis (0-5), orientation (0-8), word recall (0-10) and word recognition (0-12). The total score ranges from 0-70, the high score indicating greater impairment.
2. The Progressive Deterioration Scale (PDS) (De Jong 1989) is an instrument with 29 items, assessing the activities of daily living as rated by a carer. Each item is scored on a visual analogue scale of 0-100, and the total score is the mean item score. The score of 0-100 decreases with severity of dementia.
3. The Clinical Global Impression of Change (CGIC) (Guy 1976) is a global rating of all domains of an individual's current condition in comparison with his or her state at baseline. It is a seven-point scale, from 1 (very much improved) to 7 (very much worse), 4

indicating no change. The assessment is conducted by the same clinician at both time points with input from relatives or carers.
4. Basic and instrumental activities of daily living were assessed using the ADL scale (Lawton 1969)
5. To assess neuropsychological performance six computerized tests from the Automated Neuropsychological Assessment Metrics (ANAM) (Reeves 1993) were used.

Risk of bias in included studies

Although it is reasonable to choose a cross-over design for a small study, there are problems associated with the analysis and interpretation of the data. In studies of dementia, crossover designs are controversial, reflecting concerns about temporal stability of disease, confounding of treatment effects with period by treatment interactions and carryover effects (Putt 2002). The included study does not deal with the possible decline of the participants.

Effects of interventions

Update 2005
The 2005 search identified one new paper (White 2004) that was excluded; the study population did not suffer from Alzheimer's Disease but Age Associated Memory Impairment (AAMI). Thus the results and conclusions remain unchanged.

The results from an analysis combining results from both phases of a cross-over study are not considered reliable. No data were available from the first phase alone.

Update 2008
The first update search performed in January 2008 retrieved three new studies for consideration; none of these met the inclusion criteria for the review.

Update 2010

The latest update search of March 2010 retrieved four new studies for consideration; none of these met the inclusion criteria for the review.

DISCUSSION

There are no adequate randomized double-blind controlled trials of nicotine for treatment of people with Alzheimer's disease. Evidence from studies excluded because of methodological inadequacies is inconclusive. Some have reported improvement on nicotine, some no improvement, and others worsening compared with placebo. Nicotine has been claimed to improve attentional performance (Jones 1992; Sahakian 1994; White 1999), learning (Wilson 1995) and behavioural symptoms (Newhouse 1988; Newhouse 1990) in people with Alzheimer's disease, but these findings are not replicated in other studies in which nicotine did not improve memory or behaviour (Snaedel 1996; White 1999; Wilson 1995). In a recent double-blind placebo crossover study where nicotine was tested on AAMI patients, the authors claimed some benefit in clinical global impression and in attention performance (White 2004). Although cohort data suggest that individuals who meet criteria for AAMI are at substantially greater risk for developing overt dementia than are individuals who do not have AAMI (Goldman 2001), this concept depends on which particular test is used, and so when using a difficult memory test such as the Auditory Learning Test, 90% of otherwise normal elderly subjects would qualify for AAMI (Smith 1991). Hence we cannot extrapolate data from cognitive impairment-no dementia population studies (where participants have AAMI or mild cognitive impairment (MCI)) to demented subjects. This point has been illustrated in recent galantamine and donepezil studies which do not have the same efficacy in patients with MCI as in those with dementia.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence from randomized controlled trials to support the use of nicotine as a treatment for Alzheimer's disease.

Implications for research

The possible role for nicotine in the treatment of Alzheimer's disease is an important issue. There is a need for well-designed trials that are of randomized, double-blind, placebo-controlled parallel-group design. Trial treatments need to last at least six months with outcomes to include valid and reliable measures of cognitive status, activities of daily living, institutionalization and mortality, and adverse effects.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

White 1999

Methods	Randomized double-blind placebo-controlled crossover study 2 x 4 weeks separated by a 2 week washout period
Participants	Country: USA 8 participants (3 male 5 female) diagnosis: probable Alzheimer's disease NINCDS-ADRDA criteria mild to moderate dementia MMSE 10-26 mean 19 (5) Exclusion : uncontrolled hypertension cardiac disease stroke renal insufficiancy seizure syncope alcohol or drug abuse active skin disease sensitivity to medical dressings major depression tacrine or donepezil

White 1999 *(Continued)*

	liver disease Parkinson's disease
Interventions	1. placebo patch 2. nicotine patch (Nicotrol) (5mg/day for 1 week , 10mg/day for 2 weeks, 5mg/day for the 4th week)
Outcomes	ADAS-Cog ADL PDS CGI ANAM
Notes	

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Jones 1992	This study was not double-blind and no method of randomization was specified.
Knott 2000	This study was confounded: 6 out of 13 were receiving a cholinesterase inhibitor. No method of randomization was stated and it was unclear whether it was double blinded.
Knott 2002	Single-dose, pseudo-randomized cross-over design
Newhouse 1988	Single-blind and not randomized
Newhouse 1990	Not double-blind or randomized
Parks 1994	The study is not randomized. AD patients compared with normal controls.
Sahakian 1989	Single-blind study, placebo-controlled study. No randomization
Sahakian 1994	Single-blind, placebo-controlled study. No randomization
Snaedel 1996	Two studies reported: First was an open trial with an unsatisfactory method of randomization. In the second trial, there is no mention of randomization and the design is unclear from the details available.
White 2004	The study population did not suffer from AD but AAMI. Cross-over design with no data from the first phase
Wilson 1995	No mention of randomization. Cross-over design with no data from the first phase

APPENDICES

Appendix 1. Sources searched and search strategies used

Source searched	Search strategy
MEDLINE In-process and other non-indexed citations and MEDLINE 1950-present	1. exp Nicotine/
	2. nicotine.mp.
	3. 1 or 2
	4. alzheimer*.mp.
	5. exp Alzheimer Disease/
	6. dement*.mp.
	7. exp Dementia/
	8. or/4-7
	9. 3 and 8
	10. randomized controlled trial.pt.
	11. controlled clinical trial.pt.
	12. randomized.ab.
	13. placebo.ab.
	14. drug therapy.fs.
	15. randomly.ab.
	16. trial.ab.
	17. groups.ab.
	18. or/10-17
	19. (animals not (humans and animals)).sh.
	20. 18 not 19
	21. 9 and 20
	22. 2008*.ed.
	23. 2009*.ed.
	24. 2010*.ed.
	25. or/22-24
	26. 21 and 25
EMBASE	1. exp nicotine/
1980-2010 week 11	2. nicotine.mp.
	3. *smoking/
	4. or/1-3
	5. exp Alzheimer disease/
	6. alzheimer*.mp.

(Continued)

	7. exp dementia/
	8. dement*.mp.
	9. or/5-8
	10. 4 and 9
	11. randomized controlled trial/
	12. random*.ti,ab.
	13. trial.ti,ab.
	14. placebo.ti,ab.
	15. groups.ab.
	16. or/11-15
	17. 10 and 16
	18. 2008*.em.
	19. 2009*.em.
	20. 2010*.em.
	21. or/18-20
	22. 21 and 17
PSYCINFO	1. exp Nicotine/
1806-March week 4 2010	2. nicotine.mp.
	3. smoking.mp.
	4. or/1-3
	5. exp Alzheimers Disease/
	6. alzheimer*.mp.
	7. exp Dementia/
	8. dement*.mp.
	9. or/5-8
	10. 4 and 9
	11. random*.mp.
	12. trial.mp.
	13. placebo.ti,ab.
	14. groups.ab.
	15. exp Clinical Trials/
	16. "control group".ab.
	17. or/11-16
	18. 10 and 17

(Continued)

	19. 2008*.up.
	20. 2009*.up.
	21. 2010*.up.
	22. or/19-21
	23. 18 and 22
CINAHL (EBSCOhost)	S1 (MH "Nicotine") or (MM "Nicotinic Agonists") or (MM "Nicotinic Antagonists") or (MM "Cholinergic Agents")
	S2 TX nicoti*
	S3 S1 or S2
	S4 (MH "Alzheimer's Disease")
	S5 TX alzheimer*
	S6 (MH "Dementia+") or (MH "Delirium, Dementia, Amnestic, Cognitive Disorders")
	S7 TX dement*
	S8 S4 or S5 or S6 or S7
	S9 S3 and S8
	S10 TX random*
	S11 TX placebo
	S12 (MH "Clinical Trials")
	S13 AB groups
	S14 TX trial
	S15 TX "control group"
	S16 S10 or S11 or S12 or S13 or S14 or S15
	S17 S9 and S16
	S18 EM 2008
	S19 EM 2009
	S20 EM 2010
	S21 S18 or S19 or S20
	S22 S17 and S21
CENTRAL	#1 MeSH descriptor Nicotine explode all trees
The Cochrane Library	#2 nicotin*
	#3 (#1 OR #2)
	#4 MeSH descriptor Alzheimer Disease explode all trees
	#5 alzheimer*
	#6 MeSH descriptor Dementia explode all trees

(Continued)

	#7 dement* #8)#4 OR #5 OR #6 OR #7) #9 (#3 AND #8) #10 (#9), from 2008 to 2010 [Clinical Trials]
LILACS (BIREME)	(nicotine OR nicotina) AND (Alzheimer$ OR dementia OR demencia)
ALOIS www.medicine.ox.ac.uk/alois	Advanced search: [Study aim] Treatment Dementia AND [Study Design] RCT AND [Intervention] (starts with) nico
Umin (Clinical Trial Register of Japan)	Free keyword: nicotine
Clinicaltrials.gov	Interventional Studies | alzheimer OR alzheimers OR alzheimer's OR dementia | nicotine OR nicotinic | Adult Senior | received from 01/01/2008 to 03/25/2010
ICTRP Search Portal	Advanced search: [Condition:(alzheimer OR alzheimers OR alzheimer's OR dementia)] AND [Intervention: nicotine] AND [date rec: 01/01/2008 to 25/03/2010]
ISI Web of Knowledge - all databases	Topic=(nicotin*) AND Topic=(alzheimer* OR dement*) AND Topic=(random* OR trial OR placebo OR study OR "control group") AND Year Published=(2007-2010)

WHAT'S NEW

Date	Event	Description
25 March 2010	New search has been performed	An update search was performed for this review on 25 March 2010. No new studies were identified for either inclusion or exclusion within the review

HISTORY

Protocol first published: Issue 3, 1998
Review first published: Issue 3, 1999

Date	Event	Description
5 November 2008	Amended	Converted to new review format.
18 February 2008	New search has been performed	January 2008: A new update search was run. Three trials for consideration were retrieved; none of these met the inclusion criteria.
26 February 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

-Jess López Arrieta did the core work of the review: search, identification and selection of studies, data extraction, analysis and writing.

-Jose Luis Rodríguez and Francisco Sanz contributed to the first review and they have participated in the identification and selection of studies and both have criticized the review. 12/06/03: Francisco Sanz has contributed in the the critical appraisal of studies and review update

-CDCIG contact editor: Jacqueline Birks
-Consumer editor: Angela Clayton Turner (UK)
-This review has been peer reviewed anonymously (November 2003)

DECLARATIONS OF INTEREST

None known.

NOTES

No new studies have been found, so the review conclusions remains the same as the former version.

INDEX TERMS

Medical Subject Headings (MeSH)

Alzheimer Disease [*drug therapy]; Double-Blind Method; Nicotine [adverse effects] [*therapeutic use]; Nicotinic Agonists [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans