

Supplementary Material

Effect of Acetylcholinesterase Inhibitors on Cerebral Perfusion and Cognition: A Systematic Review

Supplementary Material 1. Search Strategy

PubMed

("patients"[mesh] OR "female"[mesh] OR "volunteers"[mesh] OR "Humans"[mesh] OR "men"[mesh] OR "Aged"[Mesh] OR patient[TI] OR patient[AB] OR patients[TI] OR patients[AB] OR human[ti] OR human[AB] or human being[ti] or human being[ab] or human body[ti] or human body[ab] or human race[ti] or human race[ab] or human subject [ti] or human subject [ab] or man[ti] or man[ab] or patient[ti] or patient[ab] or veterans[ti] or veterans [ab] or aged[ti] or aged[ab]) AND ("brain"[mesh] OR "brain/blood supply"[MeSH Terms] OR "Brain/blood supply"[MeSH Terms] OR "Brain/diagnostic imaging"[MeSH Terms] OR "Brain/drug effects"[MeSH Terms] OR "Brain/drug effects"[MeSH Terms] OR "Brain/pharmacology"[MeSH Terms] OR brain[ti] or brain[ab] or region[ti] or region[ab] or frontal[ti] or frontal[ab] or temporal[ti] or temporal[ab] or parietal[ti] or parietal[ab] or occipital[ti] or occipital[ab] or cholinergic[ti] or cholinergic[ab] or cognitive [ab] or cognitive[ti]) AND ("Perfusion"[Mesh:NoExp] OR "Perfusion"[Majr] OR "Cerebrovascular Circulation"[Mesh:NoExp] OR "Regional Blood Flow"[Mesh] OR "Regional Blood Flow"[Majr] OR "Tomography, Emission-Computed, Single-Photon"[Mesh] OR perfusion[TI] OR perfusion[AB] OR hypoperfusion[TI] OR hypoperfusion[AB] OR hyperperfusion[ti] OR hyperperfusion[AB] OR blood flow[ti] OR blood flow[ab] OR regional blood flow[ti] OR regional blood flow[ab] OR Cerebral Blood Flow[ti] OR Cerebral Blood Flow[ab] OR ASL[ab] OR PET[ab] OR MRI[ab] OR spect[ab]) AND ("Rivastigmine"[Mesh] or "Donepezil"[Mesh] or "Galantamine"[Mesh] or "Cholinesterase Inhibitors"[Mesh] OR Donepezil[TI] OR Donepezil[AB] or Aricept[TI] OR Aricept[AB] OR Galantamine[TI] OR Galantamine[AB] OR rivastigmine [TI] OR rivastigmine [AB])

Embase

('human'/de OR 'patient'/de OR 'male'/de OR 'female'/de) AND ('brain function'/de OR 'hemisphere'/exp OR 'central nervous system'/de OR 'brain blood vessel'/de) AND ('perfusion'/de

OR 'brain perfusion'/de OR 'blood flow'/exp OR 'hemodynamics'/de OR 'circulation'/de OR 'brain circulation'/de) AND ('cholinesterase inhibitor'/de OR 'donepezil'/de OR 'galantamine'/de OR 'rivastigmine'/de)

Web of Science

(TS=(human\$) OR TS=(human being) OR TS=(human body) OR TS=(human race) OR TS=(human subject) OR TS=(man) OR TS=(M?n) OR TS=(Modern Man) OR TS=(patient\$) OR TS=(sufferer\$) OR TS=(Client\$) OR TS=(individual) OR TS=(person) OR TS=(wom?n) OR TS=(volunteer\$) OR TS=(Volunteer) OR TS=(Voluntary Worker\$) OR TS=(Volunteer Worker\$) OR TS=(Volunteerism)) AND (TS=(frontal) OR TS=(occipital) OR TS=(temporal) OR TS=(parietal) OR TS=(cholinergic) OR TS=(alzheimer) OR TS=(dementia) OR TS=(MCI)) AND (TS=(perfusion) OR TS=(hyp*perfusion) OR TS=(microperfusion) OR TS=(blood flow distribution) OR TS=(blood flow) OR TS=(bloodflow) OR TS=(Regional Blood Flow\$) OR TS=(cerebrovascular circulation) OR TS=(Cerebral Circulation\$) OR TS=(Cerebral Blood Flow\$) OR TS=(cerebrovascular circulation)) AND (TS=(Donepezil) OR TS=(acetylcholinesterase inhibitor) OR TS=(Cholinesteraseinhibitor) OR TS=(Galantamine) OR TS=(Rivastigmine)) AND (TS=(PET) OR TS=(MRI) OR TS=(NMR) OR TS=(ASL) OR TS=(SPECT) OR TS=(PET))

Central

([mh "Humans"] OR [mh "Humans"] OR [mh "Human body"] OR [mh "Patients"] OR [mh "Men"] OR [mh "Female"] OR [mh "volunteers"] OR (human):ti,ab,kw OR (human being):ti,ab,kw OR (human body):ti,ab,kw OR (human race):ti,ab,kw OR (human subject):ti,ab,kw OR (humans):ti,ab,kw OR (man):ti,ab,kw OR (homo sapiens):ti,ab,kw OR (Man):ti,ab,kw OR (Modern Man):ti,ab,kw OR (human being):ti,ab,kw OR (Homo sapiens):ti,ab,kw OR (patient):ti,ab,kw OR (patients):ti,ab,kw OR (sufferer):ti,ab,kw OR (sufferers):ti,ab,kw OR (Patient):ti,ab,kw OR (Clients):ti,ab,kw OR (Client):ti,ab,kw OR (individual):ti,ab,kw OR (person):ti,ab,kw OR (men):ti,ab,kw OR (woman):ti,ab,kw OR (women):ti,ab,kw OR (volunteer):ti,ab,kw OR (volunteers):ti,ab,kw) AND ([mh "Cerebrum"] OR [mh "Nervous System"] OR [mh "Central Nervous System"] OR [mh "Head"] OR [mh "Cerebrum"] OR [mh "Basal Ganglia"] OR [mh "Cerebral Cortex"] OR [mh "Olfactory Cortex"])

OR [mh "Amygdala"] OR [mh "Corpus Striatum"] OR [mh "Substantia Innominata"] OR [mh "Hippocampus"] OR [mh "Limbic Lobe"] OR [mh "Neocortex"] OR [mh "Basal Forebrain"] OR [mh "Entorhinal Cortex"] OR [mh "Olfactory Tubercle"] OR [mh "Piriform Cortex"] OR [mh "Occipital Lobe"] OR [mh "Parietal Lobe"] OR [mh "Temporal Lobe"] OR [mh "Frontal Lobe"] OR [mh "Brain"] OR [mh "Rhombencephalon"] OR [mh "Diencephalon"] OR [mh "Telencephalon"] OR [mh "Myelencephalon"] OR [mh "Metencephalon"] OR [mh "Prosencephalon"] OR [mh "Mesencephalon"] OR [mh "Medulla Oblongata"] OR [mh "Pons"] OR [mh "Cerebellum"] OR [mh "Brain Stem"] OR [mh "Gray Matter"] OR [mh "White Matter"] OR [mh "Gyrus Cinguli"] OR (amygdala):ti,ab,kw OR (Angular Gyrus):ti,ab,kw OR (Annectant Gyrus):ti,ab,kw OR (Anterior Central Gyrus):ti,ab,kw OR (basal forebrain):ti,ab,kw OR (basal ganglia):ti,ab,kw OR (brain):ti,ab,kw OR (brain blood vessel):ti,ab,kw OR (brain cell):ti,ab,kw OR (brain frontal lobe):ti,ab,kw OR (brain occipital lobe):ti,ab,kw OR (brain parietal lobe):ti,ab,kw OR (brain region):ti,ab,kw OR (brain stem):ti,ab,kw OR (brain temporal lobe):ti,ab,kw OR (brain-stem):ti,ab,kw OR (Calcarine Fissure):ti,ab,kw OR (Calcarine Fissures):ti,ab,kw OR (Calcarine Sulcus):ti,ab,kw OR (caput):ti,ab,kw OR (Central Gyrus, Anterior):ti,ab,kw OR (central nervous system):ti,ab,kw OR (cerebellum):ti,ab,kw OR (cerebral):ti,ab,kw OR (cerebral cortex):ti,ab,kw OR (cerebral hemisphere):ti,ab,kw OR (cerebral hemispheres):ti,ab,kw OR (cerebrum):ti,ab,kw OR (CNS):ti,ab,kw OR (corpus striatum):ti,ab,kw OR (Cuneate Lobule):ti,ab,kw OR (Cuneate Lobules):ti,ab,kw OR (Cuneus):ti,ab,kw OR (Cuneus Cortex):ti,ab,kw OR (Cuneus Cortices):ti,ab,kw OR (Cuneus Gyrus):ti,ab,kw OR (diencephalon):ti,ab,kw OR (encephalon):ti,ab,kw OR (entorhinal cortex):ti,ab,kw OR (forebrain):ti,ab,kw OR (Frontal Cortex):ti,ab,kw OR (Frontal Cortices):ti,ab,kw OR (Frontal Eye Field):ti,ab,kw OR (Frontal Eye Fields):ti,ab,kw OR (frontal lobe):ti,ab,kw OR (Frontal Lobes):ti,ab,kw OR (frontal region):ti,ab,kw OR (Frontali, Lobus):ti,ab,kw OR (Frontalis, Lobus):ti,ab,kw OR (Fusiform Gyrus):ti,ab,kw OR (Fusiformi, Gyrus):ti,ab,kw OR (Fusiformis, Gyrus):ti,ab,kw OR (Gyrus Angulari):ti,ab,kw OR (Gyrus Angularis):ti,ab,kw OR (Gyrus Fusiformi):ti,ab,kw OR (Gyrus Fusiformis):ti,ab,kw OR (Gyrus Linguali):ti,ab,kw OR (Gyrus Lingualis):ti,ab,kw OR (Gyrus Precentrali):ti,ab,kw OR (Gyrus Precentralis):ti,ab,kw OR (Gyrus Supramarginali):ti,ab,kw OR (Gyrus Supramarginalis):ti,ab,kw OR (Gyrus Temporalis Superior):ti,ab,kw OR (Gyrus Temporalis Superiors):ti,ab,kw OR (Gyrus, Angular):ti,ab,kw OR (Gyrus, Annectant):ti,ab,kw OR (head):ti,ab,kw OR (hemisphere):ti,ab,kw OR

(hindbrain):ti,ab,kw OR (hippocampus):ti,ab,kw OR (Inferior Horn of Lateral Ventricle):ti,ab,kw OR (Inferior Horn of the Lateral Ventricle):ti,ab,kw OR (Intraparietal Sulcus):ti,ab,kw OR (Lateral Occipito Temporal Gyrus):ti,ab,kw OR (Lateral Occipitotemporal Gyrus):ti,ab,kw OR (Lateral Occipito-Temporal Gyrus):ti,ab,kw OR (left cerebral hemisphere):ti,ab,kw OR (limbic lobe):ti,ab,kw OR (Lingual Gyrus):ti,ab,kw OR (Lobus Frontali):ti,ab,kw OR (lobus frontalis):ti,ab,kw OR (lobus occipitalis):ti,ab,kw OR (lobus parietalis):ti,ab,kw OR (lobus temporalis):ti,ab,kw OR (Lunate Sulcus):ti,ab,kw OR (Marginal Sulcus):ti,ab,kw OR (Medial Occipitotemporal Gyrus):ti,ab,kw OR (medulla oblongata):ti,ab,kw OR (mesencephalon):ti,ab,kw OR (metencephalon):ti,ab,kw OR (myelencephalon):ti,ab,kw OR (neocortex):ti,ab,kw OR (nervous system):ti,ab,kw OR (Occipital Cortex):ti,ab,kw OR (Occipital Cortices):ti,ab,kw OR (Occipital Gyrus):ti,ab,kw OR (occipital lobe):ti,ab,kw OR (Occipital Lobes):ti,ab,kw OR (Occipital Region):ti,ab,kw OR (Occipital Regions):ti,ab,kw OR (Occipital Sulcus):ti,ab,kw OR (Occipitotemporal Gyrus):ti,ab,kw OR (olfactory cortex):ti,ab,kw OR (olfactory tubercle):ti,ab,kw OR (Parietal Cortex):ti,ab,kw OR (Parietal Cortices):ti,ab,kw OR (parietal lobe):ti,ab,kw OR (Parietal Lobes):ti,ab,kw OR (Parietal Lobule):ti,ab,kw OR (Parietal Lobules):ti,ab,kw OR (Parietal Region):ti,ab,kw OR (Parietal Regions):ti,ab,kw OR (piriform cortex):ti,ab,kw OR (Planum Polare):ti,ab,kw OR (Planum Polares):ti,ab,kw OR (pons):ti,ab,kw OR (Posterior Paracentral Lobule):ti,ab,kw OR (Posterior Paracentral Lobules):ti,ab,kw OR (Posterior Parietal Cortex):ti,ab,kw OR (Posterior Parietal Cortices):ti,ab,kw OR (Praecuneus):ti,ab,kw OR (Precentral Gyrus):ti,ab,kw OR (Precuneus):ti,ab,kw OR (Precuneus Cortex):ti,ab,kw OR (Precuneus Cortices):ti,ab,kw OR (Prelunate Gyrus):ti,ab,kw OR (prosencephalon):ti,ab,kw OR (regio frontalis):ti,ab,kw OR (regio occipitalis):ti,ab,kw OR (regio parietalis):ti,ab,kw OR (regio temporalis):ti,ab,kw OR (rhombencephalon):ti,ab,kw OR (right cerebral hemisphere):ti,ab,kw OR (substantia innominata):ti,ab,kw OR (Superior Temporal Gyrus):ti,ab,kw OR (Supplementary Eye Field):ti,ab,kw OR (Supplementary Eye Fields):ti,ab,kw OR (Supramarginal Gyrus):ti,ab,kw OR (telencephalon):ti,ab,kw OR (Temporal Cortex):ti,ab,kw OR (Temporal Cortices):ti,ab,kw OR (Temporal Gyrus):ti,ab,kw OR (Temporal Horn):ti,ab,kw OR (Temporal Horn of the Lateral Ventricle):ti,ab,kw OR (Temporal Horns):ti,ab,kw OR (temporal lobe):ti,ab,kw OR (Temporal Lobes):ti,ab,kw OR (Temporal Operculum):ti,ab,kw OR (Temporal Operculums):ti,ab,kw OR (Temporal Region):ti,ab,kw OR (Temporal Regions):ti,ab,kw OR (Temporal Sulcus):ti,ab,kw) AND ([mh "Perfusion"] OR [mh

"Regional Blood Flow"] OR [mh "Vascular Resistance"] OR [mh "Capillary Resistance"] OR [mh "Hemodynamics"] OR [mh "Blood circulation"] OR [mh "Cerebrovascular circulation"] OR [mh "Cardiovascular Physiological Phenomena"] OR (perfusion):ti,ab,kw OR (hypoperfusion):ti,ab,kw OR (hyperperfusion):ti,ab,kw OR (microperfusion):ti,ab,kw OR (blood flow distribution):ti,ab,kw OR (blood flow):ti,ab,kw OR (blood flow estimation):ti,ab,kw OR (blood stream):ti,ab,kw OR (blood vessel flow):ti,ab,kw OR (bloodflow):ti,ab,kw OR (flow):ti,ab,kw OR (regional blood flow):ti,ab,kw OR (vascular flow):ti,ab,kw OR (artery blood flow):ti,ab,kw OR (capillary flow):ti,ab,kw OR (vein blood flow):ti,ab,kw OR (Regional Blood Flows):ti,ab,kw OR (cerebrovascular circulation):ti,ab,kw OR (Cerebral Circulation):ti,ab,kw OR (Cerebral Circulations):ti,ab,kw OR (Cerebral Blood Flow):ti,ab,kw OR (hemodynamics):ti,ab,kw OR (circulation):ti,ab,kw OR (brain circulation):ti,ab,kw OR (brain blood circulation):ti,ab,kw OR (blood circulation):ti,ab,kw OR (brain circulation):ti,ab,kw OR (brain circulation model):ti,ab,kw OR (brain regional circulation):ti,ab,kw OR (cerebral blood circulation):ti,ab,kw OR (cerebral circulation):ti,ab,kw OR (cerebral circulations):ti,ab,kw OR (cerebrovascular circulation):ti,ab,kw OR (cerebral perfusion pressure):ti,ab,kw OR (cerebral perfusion pressures):ti,ab,kw) AND ([mh "Cholinesterase Inhibitors"] OR [mh "Galantamine"] OR [mh "Rivastigmine"] OR (Donepezil):ti,ab,kw OR (Aricept):ti,ab,kw OR (Aricept ODT):ti,ab,kw OR (donepezilium oxalate trihydrate):ti,ab,kw OR (doneliquid geriasan):ti,ab,kw OR (donepezil hydrochloride):ti,ab,kw OR (e2020):ti,ab,kw OR (e 2020):ti,ab,kw OR (E2020):ti,ab,kw OR (E 2020):ti,ab,kw OR (eranz):ti,ab,kw OR (memac):ti,ab,kw OR (memorit):ti,ab,kw OR (Donepezil Apotex):ti,ab,kw OR (Asenta):ti,ab,kw OR (Galantamine):ti,ab,kw OR (Galantamine hydrobromide):ti,ab,kw OR (Reminyl):ti,ab,kw OR (Razadyne):ti,ab,kw OR (Razadyne ER):ti,ab,kw OR (Razedyne):ti,ab,kw OR (Rivastigmine):ti,ab,kw OR (Exelon patch):ti,ab,kw OR (Rivastigmin):ti,ab,kw OR (Rivastigmine hydrogen tartrate):ti,ab,kw OR (Rivastigmine tartrate):ti,ab,kw OR (Prometax):ti,ab,kw OR (ENA 713):ti,ab,kw OR (SDZ ENA 713):ti,ab,kw OR (ENA713):ti,ab,kw OR (nimvastid):ti,ab,kw)

Supplementary Material 2. Risk of Bias

Study	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Antuono (2009)	●	+	●	+	+	+	-	●
Araki (2017)	-	+	+	-	+	-	+	●
Blin (1997)	-	+	-	+	●	+	+	●
Ceravolo (2004)	+	+	×	-	-	+	+	●
Ceravolo (2006)	×	×	-	-	×	-	×	×
Cerci (2007)	●	-	-	+	●	-	×	●
Chatterjee (1993)	●	-	+	+	+	+	-	●
Chaudhary (2012)	×	+	×	+	+	×	+	×
Chaudhary (2013)	-	×	-	×	×	+	-	×
Cho (2009)	●	●	+	+	●	+	+	●
Cho (2010)	●	×	-	-	●	-	×	●
Compagnone (2018)	●	+	●	+	+	+	-	●
Ettorre (2015)	●	-	-	+	●	×	+	●
Fong (2011)	-	×	+	+	×	+	+	●
Geaney (1990)	●	-	-	+	+	+	-	●
Gustafson (1993)	●	×	+	-	●	+	+	●
Iizuka (2007)	●	+	●	-	-	-	-	●
Kanaya (2012)	●	-	●	+	+	+	+	●
Li (2012)	●	+	-	+	?	+	-	●
Litvinenko (2007)	●	+	×	+	-	+	+	●
Lojkowska (2003)	●	+	●	-	+	+	●	●
Mori (2006)	●	-	+	+	●	-	+	●
Nakano (2011)	-	+	+	+	-	●	+	●
Nishida (2019)	●	×	●	+	×	-	+	●
Niwa (2006)	●	+	●	+	+	×	+	●
Nobili (2002)	●	×	+	+	-	+	+	●
Prohovnik (1997)	●	+	+	-	-	+	-	●
Rodriguez (2003)	●	-	+	+	+	+	+	●
Shimizu (2006)	-	×	+	-	+	-	+	●
Shimizu (2015)	-	-	-	+	+	-	+	●
Shirayama (2019)	●	-	+	-	×	×	+	●
Tateno (2008)	●	●	-	?	+	+	-	●
Tepmongkol (2019)	●	●	×	-	×	+	+	●
Ushijima (2006)	●	+	●	+	-	+	×	●
Venneri (2002a)	●	●	●	-	-	-	-	●
Warren (1998)	●	-	×	+	+	+	-	●
Yener (2005)	●	+	×	+	+	×	-	●
Yoshida (2007)	●	-	●	+	+	×	-	●
Yoshida (2010)	×	×	●	+	●	-	-	●

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
● Critical
● Serious
- Moderate
+ Low
? No information

Supplementary Table 1. Summary of the significant ($p < 0.05$) regional cerebral perfusion changes after long-term acetylcholinesterase-inhibitor treatment in patients with mild cognitive impairment, Alzheimer’s disease, Lewy body dementia, cerebellar cognitive affective syndrome, glaucoma, amnesia, akinesia, and Parkinson’s disease dementia.

Drug	D	Author	Brain region					
			Frontal	Parietal	Temporal	Occipital	ACC	PCC
Donepezil	3	Ushujima (2006)	●	●	●			
	4	Warren (1998)	●	●	●	●	●	●
	6	Yener (2005)	●	●				
		Yoshida (2010)			●			
	7	Cho (2010)	●		●	●		
	8	Ceravolo (2004)	● **	● **	● **		● **	
	12	Nakano (2011)						
		Niwa (2006)						
		Rodriguez (2003)				●		
		Ushujima (2006)	●	●	●			
	13	Nobili (2002)						
		Tateno (2008)			● *			
	14	Antuono (2009)						●
		Li (2012)						●
		Shimizu (2015)	●		●		●	●
	16	Fong (2011)	●	●	●	●		
	18	Shirayama (2019)	●	●			●	●
	24	Ceravolo (2006)	● **	● **	● **		● **	
		Kanaya (2012)	●	●	●	●		
	25	Chaudhary (2013)	●					●
Galantamine	4	Cho (2009)	●		●	●		
	6	Chaudhary (2012)	●					●
		Litvinenko (2007)	●				●	●
	12	Shimizu (2015)	●		●	●	●	●
	18	Shirayama (2019)	●	●			●	●
Rivastigmine	6	Chaudhary (2012)	●					●
	12	Ettorre (2015)	●	●	●			
		Lojkowska (2003)	●		●			
		Shimizu (2015)	●		●	●	●	●
	15	Cerci (2007)	●					

Legend

- Significant Perfusion ↓ compared to baseline ($p < 0.05$)
 - Significant Perfusion ↑ compared to baseline ($p < 0.05$)
 - No Significant Perfusion change compared to baseline ($p < 0.05$)
- * $p < 0.01$
** $p < 0.001$

D, duration follow-up (months); ACC, anterior cingulate cortex; PCC, posterior cingulate cortex