Mahidol University
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Emerging molecular therapy in dementia

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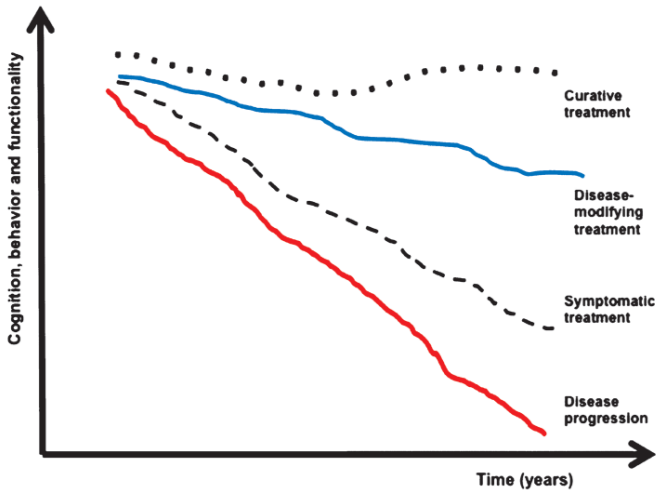


Fig. 1. Natural history of AD with treatment possibilities.

Indian J Med Res 138, October 2013, pp 449-460

Antisense oligonucleotides

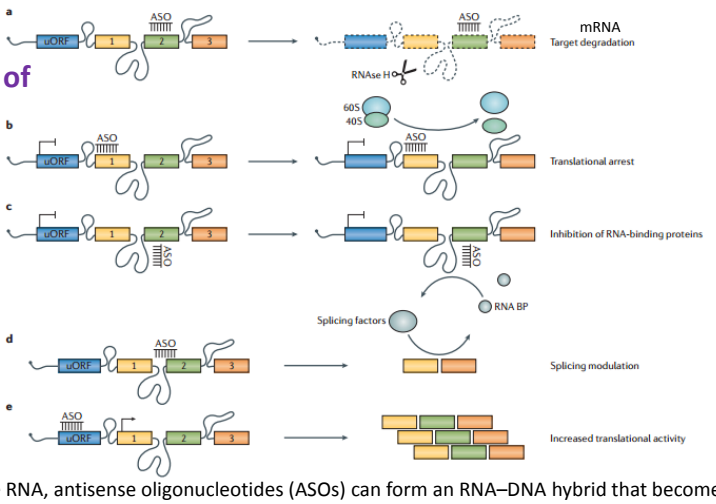
- Antisense oligonucleotides (ASOs) are short, synthetic single-stranded oligodeoxynucleotides tha can alter RNA and reduce, restore, or modify protein expression through severa distinct mechanisms
- Clinical trials using antisen oligonucleotides for neurological diseases

Drug	Target gene	Chemistry	Mechanism	Treatment route	Design (phase)	Clinical trials identifier
Duchenne muscular dystrophy						
Drisapersen	DMD (exon 51)	2′-OMe	Splicing modulation	Subcutaneous or intravenous	Open label (I–II)	NCT01910649 (REF. 200)
				Subcutaneous	Placebo-controlled (I)	NCT01128855 (REF. 201)
					Placebo-controlled (II)	NCT01153932 (REF. 202)
					Placebo-controlled (III)	NCT01254019 (REF. 203)
					Open label (III)	NCT01480245 (REF. 204)
					Placebo-controlled (II)	NCT01462292 (REF. 205)
					Open label (III)	NCT01803412 (REF. 206)
					Open label (III)	NCT02636686 (REF. 207)
Eteplirsen	DMD (exon 51)	PMO	Splicing modulation	Intravenous	Single blind (I–II)	NCT00159250 (REF. 208)
					Open label (I–II)	NCT00844597 (REF. 88)
					Placebo-controlled (II)	NCT01396239 (REF. 89)
					Open label (II)	NCT01540409 (REF. 209)
					Open label (III)	NCT02255552 (REF. 210)
					Open label (II)	NCT02286947 (REF. 211)
					Open label (II)	NCT02420379 (REF. 212)
PRO044	DMD (exon 45)	2′-OMe	Splicing modulation	Subcutaneous or intravenous	Open label (II)	NCT01037309 (REF. 213)
PRO045	DMD (exon 45)	2′-OMe	Splicing modulation	Subcutaneous	Open label (II)	NCT01826474 (REF. 214)
SRP-4045	DMD (exon 45)	PMO	Splicing modulation	Intravenous	Placebo-controlled (III)	NCT02500381 (REF. 215)
SRP-4053	DMD (exon 53)	PMO	Splicing modulation	Intravenous	Placebo-controlled (III)	NCT02500381 (REF. 215)
Spinal muscular atrophy						
Nusinersen	SMN2	2′MOE-PS	Splicing modulation	Intrathecal	Open label (I)	NCT01494701 (REF. 216)
					Open label (I–II)	NCT01703988 (REF. 217)
					Open label (I)	NCT01780246 (REF. 218)
					Open label (II)	NCT01839656 (REF. 34)
					Open label (I)	NCT02052791 (REF. 219)
					Sham-controlled (III)	NCT02193074 (REF. 220)
					Sham-controlled (III)	NCT02292537 (REF. 221)
					Open label (II)	NCT02386553 (REF. 222)
					Sham-controlled (II)	NCT02462759 (REF. 223)
					Open label (III)	NCT02594124 (REF. 224)
					Open label (III)	NCT02865109 (REF. 225)
Familial amyloid polyneuropathy						
IONIS-TTR$_{Rx}$	TTR	2′-MOE-PS	RNase H-mediated degradation	Subcutaneous	Placebo-controlled (III)	NCT01737398 (REF. 226)
Huntington disease						
IONIS-HTT$_{Rx}$	HTT	2′-MOE-PS	RNase H-mediated degradation	Intrathecal	Placebo-controlled (I–II)	NCT02519036 (REF. 227)
Amyotrophic lateral sclerosis						
IONIS-SOD1$_{Rx}$	SOD1	2′-MOE-PS	RNase H-mediated degradation	Intrathecal	Placebo-controlled (I)	NCT01041222 (REF. 35)
					Placebo-controlled (I–II)	NCT02623699 (REF. 228)

Myotronic dystrophy1

Nature Review Neurology 2018; 14: 9–21. doi:10.1038/nrneurol.2017.148

Functional mechanisms of ASOs.



Nature Review Neurology 2018; 14: 9–21. doi:10.1038/nrneurol.2017.148

a | Once bound to the RNA, antisense oligonucleotides (ASOs) can form an RNA–DNA hybrid that becomes a substrate for RNase H, which results in target mRNA degradation. b | ASOs targeting the AUG start site can block the binding of RNA binding protein complexes, such as ribosomal subunits, suppressing translation of target mRNA. c | In diseases caused by a toxic RNA gain-of-function mechanism, ASOs designed to bind complementarily with high-affinity to **untranslated regions** can prevent binding and sequestration of RNA-binding proteins by steric hindrance. d | ASO binding to splice sites or to exonic or intronic inclusion signals results in skipping or inclusion of the targeted exon. e | Translation of the upstream **open reading frames** (uORFs) typically inhibits the expression of the primary ORF. ASOs binding to the uORFs are able to increase the amounts of protein translated from a downstream ORF.

- **PD**-: Genetic ablation and pharmacological LRRK2 inhibition have demonstrated promise in blocking a-synuclein (a-syn) pathology - LRRK2 Antisense Oligonucleotidese(ASOs)
- **Tauopathies**. Human tau is encoded by MAPT: 3R tau , 4R tau. A treatment approach aimed at selectively modulating tau splicing to lower the levels of the 4R isoform has been proposed.

Molecular Therapy: Nucleic Acids 2017;8:508-519
Nature Review Neurology 2018; 14: 9–21. doi:10.1038/nrneurol.2017.148

- **C9orf72**. A GGGGCC hexanucleotide repeat expansion in the non-coding region of the C9orf72 gene accounts for ~40% of all inherited forms of ALS and FTD in studies of panEuropean, North American, and Australian patient populations. The proposed mechanisms of pathogenesis include loss of C9orf72 protein function. Another proposed mechanism of toxicity is the production and accumulation of aberrant dipeptiderepeat (DPR) proteins translated from the hexanucleotide repeat RNA.

In vivo administration of ASOs targeting the C9orf72 hexanucleotide expansion selectively reduced the repeatcontaining RNA levels via a RNase Hdependent mechanism, decreased both soluble and insoluble DPR proteins, and significantly attenuated the behavioural deficits in transgenic mice, but preserved levels of alternatively spliced C9orf72 proteinencoding isoforms that do not include the repeats

Molecular Therapy: Nucleic Acids 2017;8:508-519
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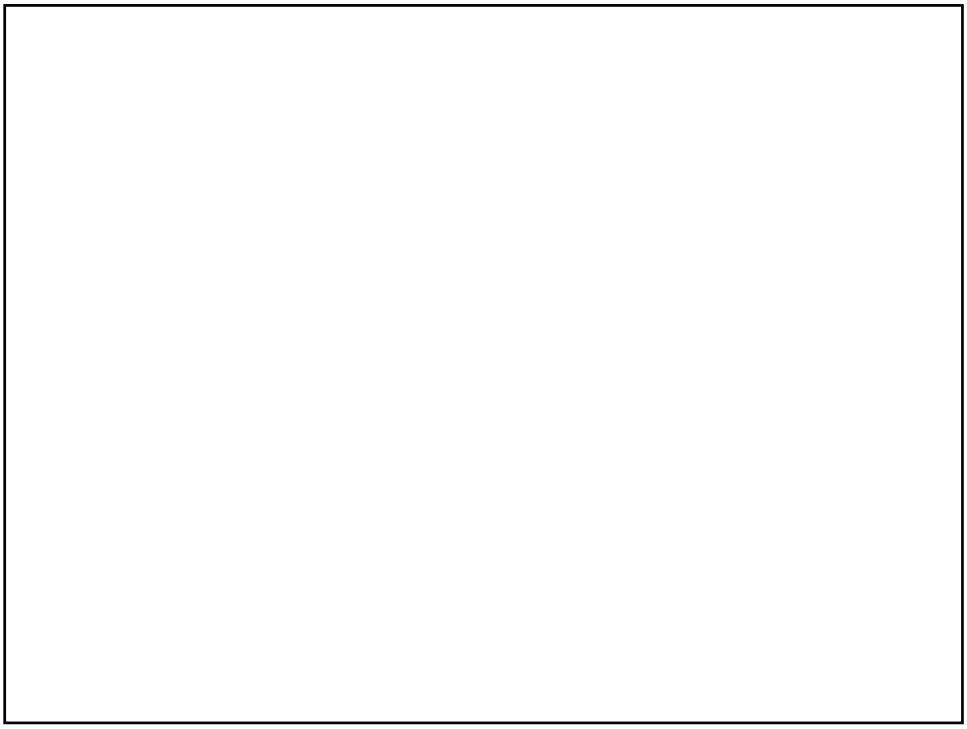
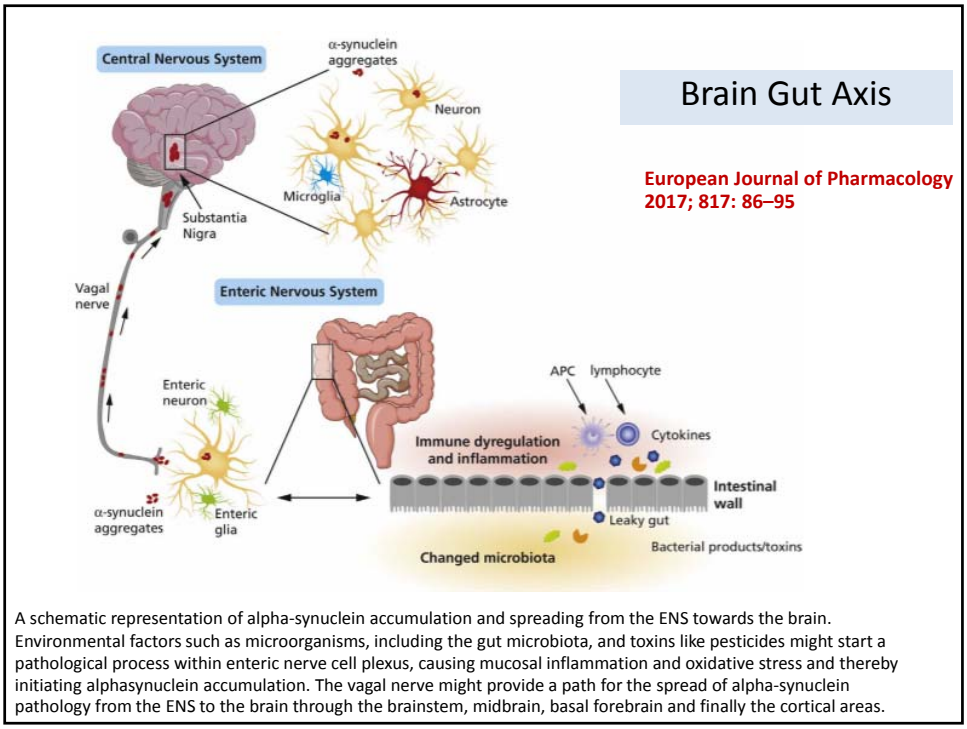
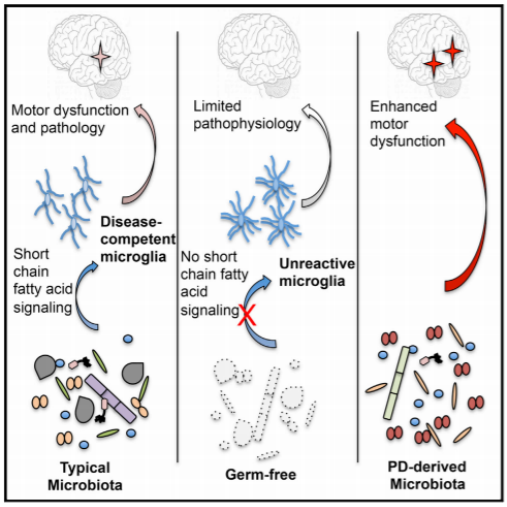




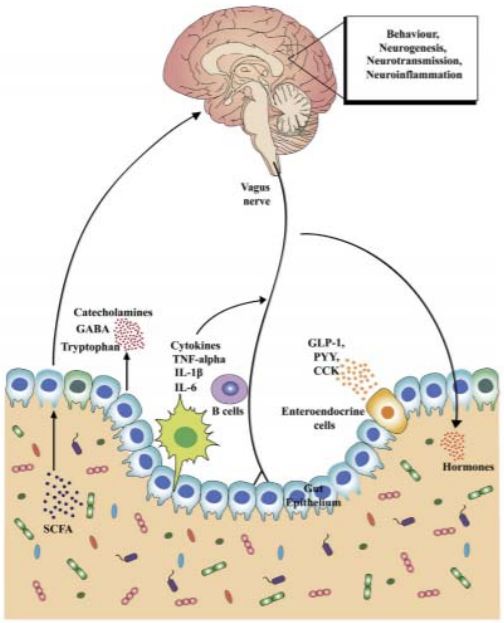
Brain Gut Axis

European Journal of Pharmacology 2017; 817: 86–95

A schematic representation of alpha-synuclein accumulation and spreading from the ENS towards the brain. Environmental factors such as microorganisms, including the gut microbiota, and toxins like pesticides might start a pathological process within enteric nerve cell plexus, causing mucosal inflammation and oxidative stress and thereby initiating alphasynuclein accumulation. The vagal nerve might provide a path for the spread of alpha-synuclein pathology from the ENS to the brain through the brainstem, midbrain, basal forebrain and finally the cortical areas.

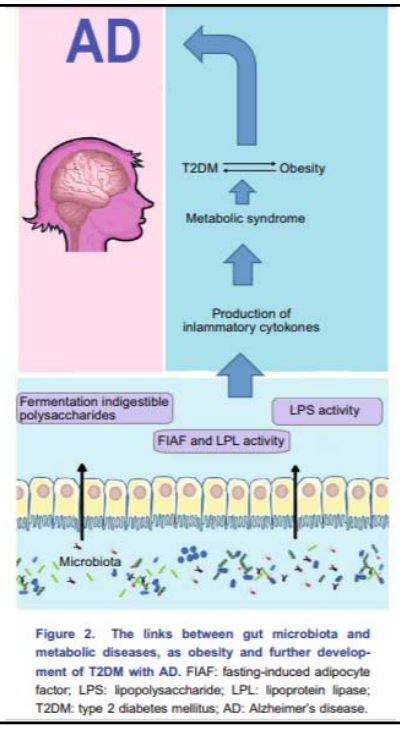


- Gut microbes promote a-synuclein-mediated motor deficits and brain pathology
- Depletion of gut bacteria reduces microglia activation
- SCFAs modulate microglia and enhance PD pathophysiology
- Human gut microbiota from PD patients induce enhanced motor dysfunction in mice



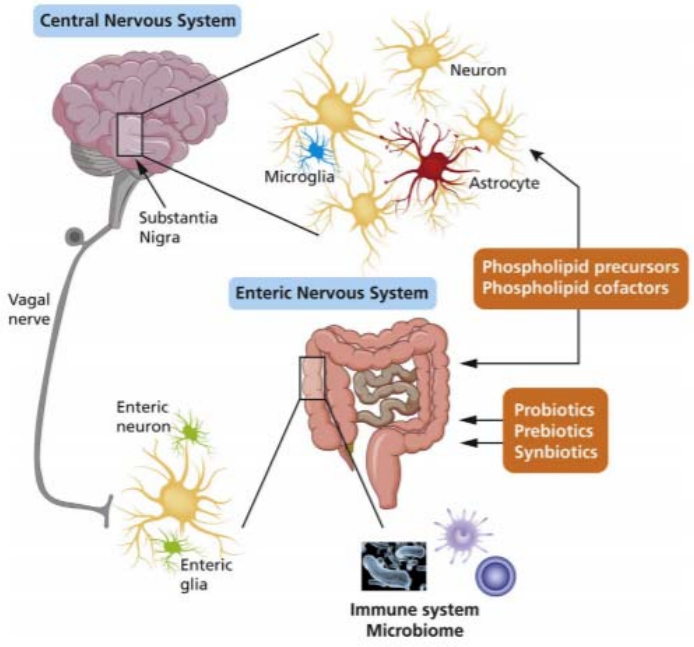
Neurobiology of Stress 2017; 7 : 124-136.

Key communication pathways of the microbiotaegutebrain axis. There are numerous mechanisms through which the gut microbiota can signal to the brain. These include activation of the vagus nerve, production of microbial antigens that recruit immune B cell responses, production of microbial metabolites (i.e. short-chain fatty acids [SCFAs]), and enteroendocrine signaling from gut epithelial cells (e.g., I-cells that release CCK, and L-cells that release GLP-1, PYY and other peptides). Through these routes of communication, the microbiotaegutebrain axis controls central physiological processes, such as neurotransmission, neurogenesis, neuroinflammation and neuroendocrine signaling that are all implicated in stress-related responses. Dysregulation of the gut microbiota subsequently leads to alterations in all of these central processes and potentially contributes to stressrelated disorders.
5-HT serotonin, CCK cholecystokinin, GABA g-aminobutyric acid, GLP glucagon-like peptide, IL interleukin, PYY peptide YY, TNF tumour necrosis factor.



Protein Cell 2017, 8(2):90–102

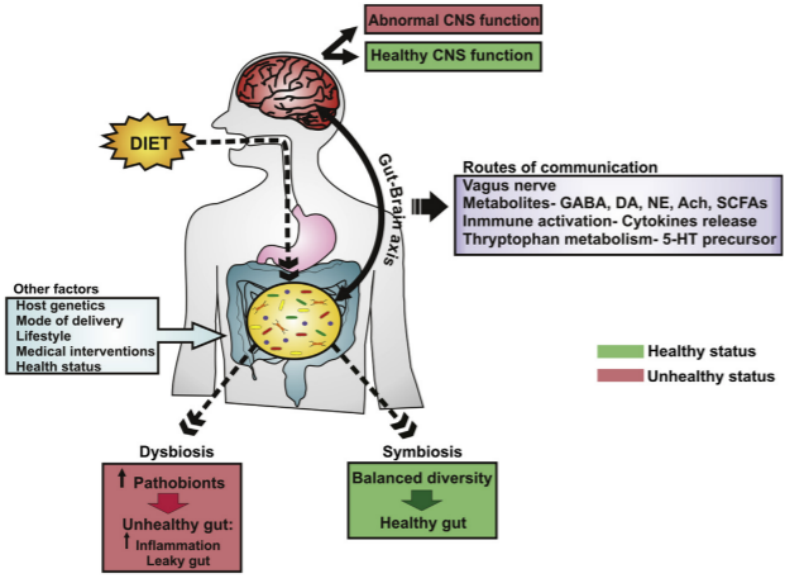
Figure 2. The links between gut microbiota and metabolic diseases, as obesity and further development of T2DM with AD. FIAF: fasting-induced adipocyte factor; LPS: lipopolysaccharide; LPL: lipoprotein lipase; T2DM: type 2 diabetes mellitus; AD: Alzheimer's disease.



Dietary phospholipid precursors and cofactors can increase neuronal membrane formation and function, and reduce inflammation, affecting both the ENS and CNS and reducing motor and non-motor abnormalities in PD. Probiotics, prebiotics and/or synbiotics might impact the gut microbiota composition, enhance intestinal epithelial integrity and reduce the pro-inflammatory response, impacting initiation or progression of the neurodegenerative process.

European Journal of Pharmacology 2017; 817: 86–95

Food for Thought



Clinical Nutrition Experimental 2016;6:25-38

Clinical and preclinical evidence for the antidepressant and anxiolytic properties associated with targeting the gut microbiota (modified from reference (Sh

	Behavioural outcomes	Physiological outcomes
Clinical evidence		
B-GOS	Increased cognitive processing of positive versus negative attentional vigilance	Reduced cortisol awakening response
Lactobacillus casei strain Shirota	Reduced anxiety scores in patients with chronic fatigue syndrome	Increased numbers of *Lactobacillus* and *Bifidobacterium* in faecal samples
	Improved mood in individuals with a low mood prior to taking the probiotic	NA
Probiotic formulation: *Lactobacillus helveticus* and *Bifidobacterium longum*	Reduced psychological distress as measured by the HADS	Reduced 24-h UFC levels
Multispecies probiotic formulation: *Lactobacillus* and *Bifidobacterium* species	Reduced cognitive processing of sad mood; decreased aggressive feelings and rumination	NA
Preclinical evidence		
Prebiotic- FOS and GOS	Antidepressant and anxiolytic-like effects in adult mice. Reversed the behavioural effects of chronic psychosocial stress in mice.	Increased BDNF, NR1 and NR2A mRNA, and protein expression in the dentate gyrus and frontal cortex Reduced acute and chronic stress-induced corticosterone release. Modified specific gene expression in the hippocampus and hypothalamus. Reduced chronic stress-induced elevations in pro-inflammatory cytokines levels
Prebiotic- 3'Sialyllactose and 6'sialyllactose	Anxiolytic effect in mice exposed to SDR	Prevented SDR-mediated reduction in the number of immature neurons
Prebiotic- GOS & polydextrose with lactoferrin (Lf) and milk fat globule membrane	Reduced immobility time of maternally separated rats in a forced swim test	Improves NREM Sleep, Enhance REM Sleep Rebound and Attenuate the Stress-Induced Decrease in Diurnal Temperature Attenuated exaggerated IL-6 response in maternally separated rats following concanavalin A stimulation
Bifidobacterium infantis	Improved depressive and anxiety-related behaviours in mice	No effect upon circulating corticosterone
Bifidobacterium breve	Anxiolytic effect in step-down inhibitory avoidance	Anxiolytic effect mediated via the vagus nerve
Bifidobacterium longum	Reduced immobility time and increased sucrose preference in ELS mice	Decreased basal and stress-induced circulating corticosterone levels; attenuated circulating TNF-α and IL-6 levels while increasing IL-10 levels in ELS mice
Lactobacillus plantarum PS128	Reduced immobility time in the forced swim test Decreased stress-induced anxiety-like behaviour	Decreased stress-induced circulating corticosterone secretion and altered central GABA receptor subunit expression Attenuated chronic stress-related activation of dendritic cells while increasing IL-10 + regulatory T cells
Lactobacillus rhamnosus	Reduced immobility time in the forced swim test Decreased stress-induced anxiety-like behaviour	Decreased stress-induced circulating corticosterone secretion and altered central GABA receptor subunit expression Attenuated chronic stress-related activation of dendritic cells while increasing IL-10 + regulatory T cells
Lactobacillus fermentum NS9	Reduced ampicillin-induced anxiety behaviour	Decreased ampicillin-induced corticosterone secretion and increased hippocampal mineralocorticoid receptor and NMDA receptor levels
Butyric acid	Reduced immobility time in Flinders sensitive line rats exposed to a forced swim test	Increased BDNF expression within the prefrontal cortex

Neurobiology of Stress 2017; 7 : 124-136

Table 1. Psychobiotics in Rodent Models of Dysfunction

Model	Induction	Psychobiotic	Species	Effects relative to comparison groups	R
Alzheimer's disease	A β_{1-42}-induced neurotoxicity	Prebiotic, chitosan oligosaccharide	Male Sprague–Dawley rats (n = 12)	↑ Cognitive function (Morris water maze), ↓ pro-inflammatory cytokines (tumour necrosis factor-α, interleukin-1β)	[↑
Amyotrophic lateral sclerosis	High level of mutant human $SOD1^{G93A}$ gene	Prebiotic, galacto-oligosaccharides	Male transgenic ALZ mice (n = 12)	↓ Motor neuron death, ↓ muscular atrophy, ↑ serum folate, ↑ vitamin B12, ↑ homocysteine	[↑
Autism spectrum disorder	Maternal immune activation	Probiotic, *Bacteroides fragilis*	Offspring of pregnant C57BL/6N mice (n = 9–75/group)	↑ Intestinal permeability, ↓ pro-inflammatory cytokines (interleukin-6), ↓ anxiety (open field test), ↓ repetitive behaviour (marble burying), ↑ communication (calling), ↑ sensorimotor gating (startle inhibition)	[↑

Trends in Neurosciences 2016;39(11): 763-781

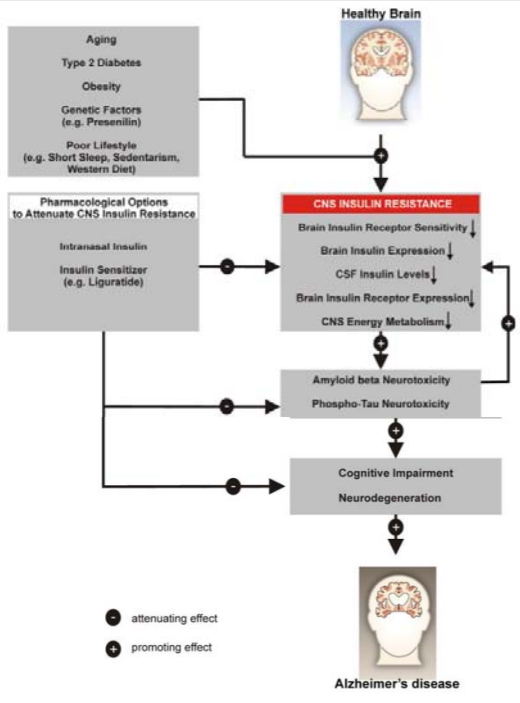
Table 2. Some methods that using to delay the process of neurodegeneration

Products	Description	Components	Foods contain them
Probiotic	Live microorganisms confer a health benefit and boost the host immunity	· *Lactobacillus acidophilus* · *Lactobacillus casei* · *Lactobacillus reuteri* · *Lactobacillus plantarum* · *Lactobacillus rhamnosus* · *Bifidobacterium animalis* · *Bifidobacterium infantis* · *Bifidobacterium lactis* · *Bifidobacterium longum*	Yogurt, Soy yogurt fermented dairy products Kombucha[a], Kimchi[b] Miso[c], Sauerkraut[d]
Prebiotic	Chemical substances, nondigestible foods that make their way through our digestive system and help good bacteria grow and flourish. Prebiotics help feed and keep beneficial bacteria healthy	Mostly come from carbohydrate fibers called oligosaccharides	Bananas, Onions, Garlic, Leeks, Asparagus, Whole wheat, Barley, Rye, Inulin[e]
NSAIDs	A drug class that groups together drugs: provide analgesic (pain-killing) and antipyretic (fever-reducing) effects, and, in higher doses, anti-inflammatory effects	Aspirin, indomethacin, ibuprofen, ketoprofen, diclofenac, piroxicam, celecoxib, nimesulid	Apples, Avocados, Blueberries, Broccoli, Cauliflower, Cherries, Chili peppers, Cucumbers, Dates, Eggplant, Figs…
GSPE[f]	An industrial derivative of whole grape seeds used as a dietary supplement with widespread health benefits	Catechin, gallic acid, epicatechin, proanthocyanidin dimers, larger oligomers	Grape seeds

[a] Kombucha—slightly effervescent drink that is brewed with tea and sugar and fermented into a liquid. This beverage originated in China nearly 2000 years ago.
[b] Kimchi—a traditional Korean lacto—fermented condiment made from cabbage.
[c] Miso is made by adding an enzymatic culture to a soybean base and often a grain.
[d] Sauerkrautis cabbage that has been salted and lacto-fermented over a period of weeks.
[e] Inulin is a natural prebiotic fiber that is found in over 36,000 plants worldwide.
[f] GSPE—grape seed polyphenol extract.

Protein Cell 2017, 8(2):90–102

Insulin Nasal Spray for Treating Cognitive Impairment



CNS Drugs 2013; 27:505–514

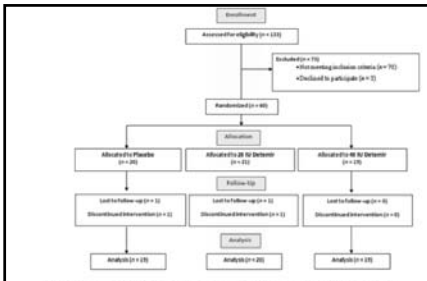


Fig. 1. Patient enrollment flowchart for the trial, which examines the effects of intranasal insulin detemir administration function in adults with amnestic mild cognitive impairment or Alzheimer's disease.

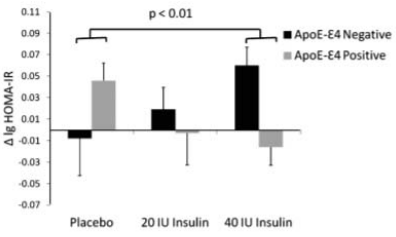


Fig. 5. Change in HOMA-IR from baseline to day 21, by treatment group and APOE-e4 carriage.

Journal of Alzheimer's Disease 2015;44: 897–906

Sixty adults diagnosed with MCI or mild to moderate AD received placebo (n = 20), 20 IU of insulin detemir (n = 21), or 40 IU of insulin detemir (n = 19) for 21 days, administered with a nasal drug delivery device. Results revealed a treatment effect for the memory composite for the 40 IU group compared with placebo ($p < 0.05$). This effect was moderated by APOE status ($p < 0.05$), reflecting improvement for APOE-4 carriers ($p < 0.02$), and worsening for non-carriers ($p < 0.02$). Higher insulin resistance at baseline predicted greater improvement with the 40 IU dose ($r = 0.54$, $p < 0.02$). Significant treatment effects were also apparent for verbal working memory ($p < 0.03$) and visuospatial working memory ($p < 0.04$), reflecting improvement for subjects who received the high dose of intranasal insulin detemir. No significant differences were found for daily functioning or executive functioning. In conclusion, daily treatment with 40 IU insulin detemir modulated cognition for adults with AD or MCI, with APOE-related differences in treatment response for the primary memory composite. Future research is needed to examine the mechanistic basis of APOE-related treatment differences, and to further assess the efficacy and safety of intranasal insulin detemir.

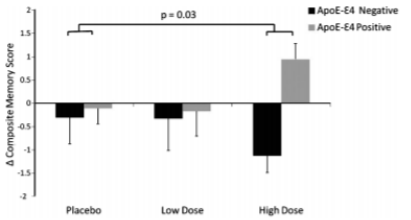


Fig. 2. Change in composite memory score from baseline to day 21, by treatment group and APOE-e4 carriage.

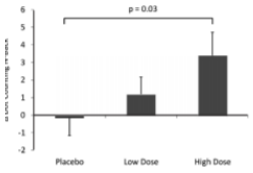


Fig. 3. Change in verbal working memory as measured by the Dot Counting N-Back Task from baseline to day 21, by treatment group.

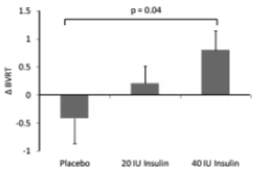
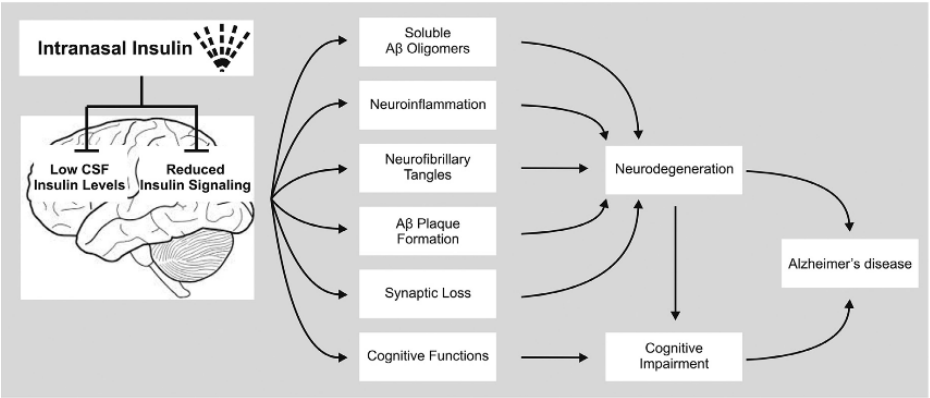


Fig. 4. Change in visuospatial working memory as measured by the BVRT from baseline to day 21, by treatment group.



Mechanisms involved in Alzheimer's disease that are likely promoted by brain insulin resistance and a lack of brain insulin and counteracted by intranasal insulintherapy Intranasal Insulin in Alzheimer's disease:

Neurophatmacology 2017:1-6

Table I. Compounds targeted to anti-beta-amyloid treatment

Compound	Target/treatment	Current phase
ANI 1792[21-23]	Vaccine – active immunization	Interrupted at phase I (severe side effects as meningoencephalitis)
CAD106[24]	Vaccine – active immunization	Phase I (ongoing)
Bapineuzumab[25]	Beta-amyloid monoclonal antibody	Phase III (ongoing)
Solanezumab[23]	Beta-amyloid monoclonal antibody	Phase III (ongoing)
Ponezumab[26]	Beta-amyloid monoclonal antibody	Interrupted at phase II (no efficacy)
Gantenerzumab[27]	Beta-amyloid monoclonal antibody	Phase I (ongoing)
Crenezumab[27]	Beta-amyloid monoclonal antibody	Phase I (ongoing)
Semagacestat[26]	Gamma-secretase inhibitor	Interrupted at phase III (no efficacy and risk for skin cancer)
Avagacestat[28]	Gamma-secretase inhibitor	Phase II (ongoing)
GRL-834[29]	Beta-secretase inhibitor	Ongoing
TAK-070[30]	Beta-secretase inhibitor	Ongoing
CHF5074[31]	Nonsteroid antinflammatory agent	Ongoing
DAPT [31]	Prototypal gamma-secretase inhibitor	Ongoing
Curcumin[22]	Anti-amyloid aggregator	Ongoing

DAPT, [N-(3, 5-Difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester

Indian J Med Res 138, October 2013, pp 449-460

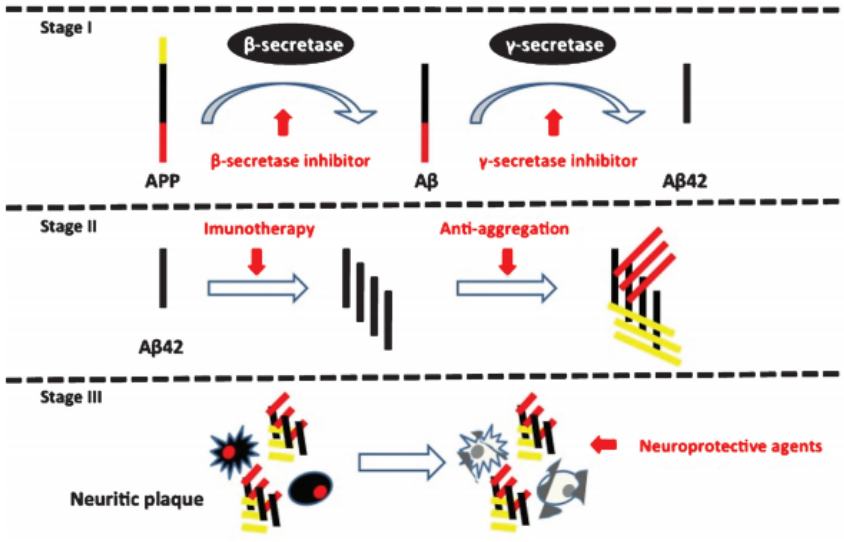


Fig. 2. Stages of amyloid (Aβ) beta production with possible targets for treatment. Red arrows indicate possible interventional targets with respective agent.

Indian J Med Res 138, October 2013, pp 449-460

Table II. Overall pharmacologic treatments other than anti-amyloid therapy under research for Alzheimer's disease[11,32,33]

Neurotransmitter-based	Agents under research
Acetylcholine	ST 101, AF 267B, ABT 089, AZD 3480, MEM 3454, EVP-6124, Posiphen, Huperzine
Serotonin	5-HT4 partial agonists, 5-HT1A agonists/antagonists, 5-HT6 antagonists
Norepinephrine/Dopamine	MAO A and MAO B inhibitors
GABA	$GABA_B$ antagonists
Glutamate	AMPA potentiators
Glycine	Partial agonists
Glial modulating drugs	
Direct glial target	G and GM CSF, Nitroflurbiprofen, ONO-2506, Tacrolimus
RAGE receptor antagonists	TTP 488
TNF alpha antagonists	Enbrel
Neuroprotection	
Antioxidants	Vitamin C and E, alpha lipoic acid, CoQ10
Miscellaneous	Phosphodiesterase inhibitors, PPARγ agonists and insulin, SIRT1 activators, Growth factors (BDNF and NGF), Dimebon
Anti-tau or tau modulators	
Microtubule stabilizers	NAP (AL-108) and Methylene blue (Rember)
Kinase inhibitors (GSK-3_α, GSK-3_β, CDK 5)	Lithium, AZD-1080, minocycline
Miscellaneous	Phosphodiesterase-4 inhibitors, immunotherapies

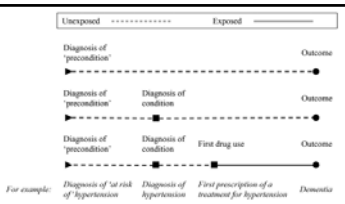
GABA, gamma-aminobutyric acid; RAGE, receptor for advanced glycation endproducts; TNF, tumor necrosis factor; GSK, glycogen synthase kinase; CDK, cyclin-dependent kinase; 5-HT (4, 1A and 6), 5-hydroxytryptamine (receptor subtypes); MAO (A and B), monoamine oxidase (A and B subtypes); AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; PPAR, peroxisome proliferator-activated receptors; SIRT1, sirtuin (silent mating type information regulation 2 homolog)-1; BDNF, brain-derived neurotrophic fator; NGF, nerve growth factor; NAP, neuronal microtubule-interacting agent (a peptide of eight amino acids, NAPVSIPQ)

Indian J Med Res 138, October 2013, pp 449-460

BMJ Open

Can commonly prescribed drugs be repurposed for the prevention or treatment of Alzheimer's and other neurodegenerative diseases? Protocol for an observational cohort study in the UK Clinical Practice Research Datalink

Venexia M Walker,[1,2] Neil M Davies,[1,2] Tim Jones,[3] Patrick G Kehoe,[4] Richard M Martin[1,2]



BMJ Open 2016;6: e012044. doi:10.1136/bmjopen-2016-012044

Table 2 The cohorts of type A, one for each treatment of interest

Cohort	Entry criteria
Treatments for hypertension	Patients who are 'at risk' of hypertension as indicated by one of the following: ▸ Medical code indicating a diagnosis of 'at risk' of hypertension. ▸ Recorded systolic blood pressure test result between 120 and 139 mm Hg. ▸ Recorded diastolic blood pressure test result between 80 and 89 mm Hg. In the case of no period 'at risk', patients who have hypertension as indicated by one of the following: ▸ Medical code indicating a diagnosis of hypertension. ▸ Product code indicating treatment for hypertension. ▸ Recorded systolic blood pressure test result of 140 mm Hg or more. ▸ Recorded diastolic blood pressure test result of 90 mm Hg or more. See online supplementary file 1 for code lists relating to hypertension.
Treatments for hypercholesterolaemia	Patients who are 'at risk' of hypercholesterolaemia as indicated by one of the following: ▸ Medical code indicating a diagnosis of 'at risk' of hypercholesterolaemia. ▸ Recorded test result where total cholesterol level is between 4 and 5 mmol/L. ▸ Recorded test result where LDL cholesterol level is between 2 and 3 mmol/L. In the case of no period 'at risk', patients who have hypercholesterolaemia as indicated by one of the following: ▸ Medical code indicating a diagnosis of hypercholesterolaemia. ▸ Product code indicating treatment for hypercholesterolaemia. ▸ Recorded test result where total cholesterol level exceeds 5 mmol/L. ▸ Recorded test result where LDL cholesterol level exceeds 3 mmol/L. See online supplementary file 2 for code lists relating to hypercholesterolaemia.
Treatments for type 2 diabetes	Patients who are 'at risk' of type 2 diabetes as indicated by a medical code. In the case of no period 'at risk', patients who have type 2 diabetes as indicated by one of the following: ▸ Medical code indicating a diagnosis of type 2 diabetes. ▸ Product code indicating treatment for type 2 diabetes. ▸ Medical code indicating a diagnosis of unspecified diabetes, first received over the age of 40. ▸ Product code indicating treatment with insulin, first received over the age of 40. This assumes that patients treated with insulin or receiving a diagnosis of unspecified diabetes after the age of 40 have type 2 diabetes. Patients with a recorded diagnosis of type 1 diabetes at any age will be excluded. See online supplementary file 3 for code lists relating to type 2 diabetes.

LDL, low density lipoprotein.

Box 1 The drug subclasses of interest for each treatment group with the control treatments indicated

Treatments for hypertension
- Beta-adrenoceptor blocking drugs (control)
- Angiotensin-converting enzyme inhibitors
- Thiazides and related diuretics
- Calcium channel blockers
- Loop diuretics
- Alpha-adrenoceptor blocking drugs
- Centrally acting antihypertensive drugs
- Angiotensin-II receptor antagonists
- Vasodilator antihypertensive drugs
- Potassium-sparing diuretics and aldosterone antagonists

Treatments for hypercholesterolaemia
- Statins (control)
- Fibrates
- Bile acid sequestrants
- Omega-3 fatty acid compounds
- Ezetimibe
- Nicotinic acid group

Treatments for type 2 diabetes
- Biguanides (control)
- Sulphonylureas
- Other antidiabetic drugs

Table 3 The expected number of events for the event used to define the start of follow-up presented with the minimum sample size and detectable HR (α=0.05, β=0.80) for the Cox regression analysis of cohorts B and C

Cohort	Start of follow-up	Expected number of events	Minimum sample size	Minimum detectable HR
B	Treatment for hypertension	1 018 519	269 808	0.968
	Treatment for hypercholesterolaemia	808 687	788 479	0.844
	Treatment for type 2 diabetes	200 800	158 775	0.943
C	Diagnosis of dementia (AD and NADD)	105 471	105 471	0.931
	Diagnosis of PD	20 686	20 686	0.870
	Diagnosis of ALS	2227	2227	0.600

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; NADD, Non-Alzheimer's disease dementias.

BMJ Open 2016;6: e012044. doi:10.1136/bmjopen-2016-012044

Epigenetics of Brain Disorders: The Paradigm of Alzheimer's Disease

- Over 80% of brain disorders are associated with multiple genomic defects in conjunction with environmental factors and epigenetic phenomena.
- Classical epigenetic mechanisms, including DNA methylation, histone modifications, and microRNAs (miRNAs) regulation, are among the major regulatory elements that control metabolic pathways at the molecular level, with epigenetic modifications controlling gene expression transcriptionally and miRNAs suppressing gene expression post-transcriptionally. Epigenetic modifications are related to disease development, environmental exposure, drug treatment and aging.
- Epigenetic changes are reversible and can be potentially targeted by pharmacological intervention

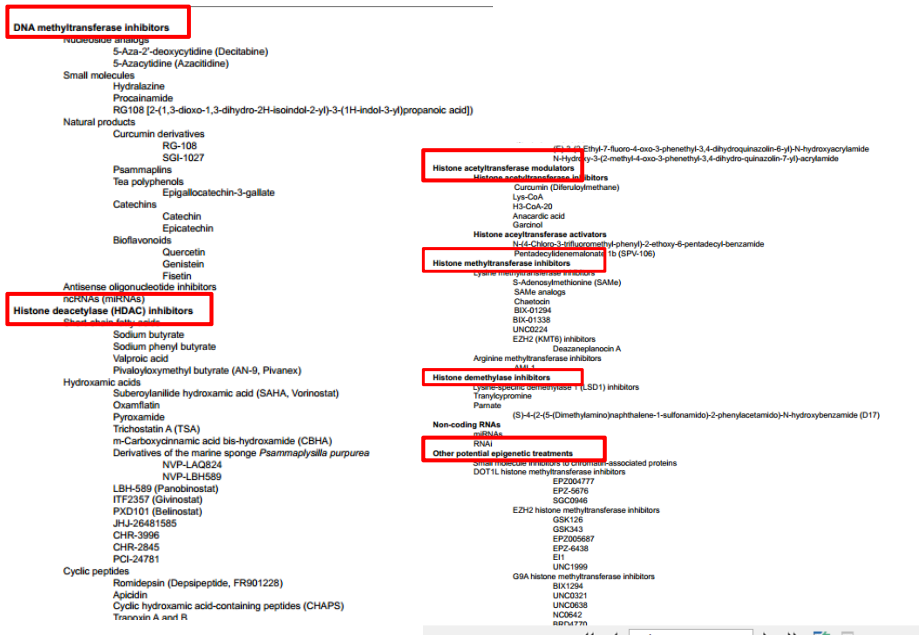
Cacabelos, J Alzheimers Dis Parkinsonism 2016, 6:2

Epigenetics of Brain Disorders: The Paradigm of Alzheimer's Disease

Pathogenic genes	Locus	Promoter length (bp)	3'UTR length	Defective protein	Methylation
APOE apolipoprotein E	19q13.32	996	--	apolipoprotein E	Hypomethylated
APP amyloid beta (A4) precursor protein	21q21.3	1086	1176	amyloid beta (A4) protein	Hypomethylated
BACE1 beta site APP cleaving enzyme 1	11q23.2-q23.3	987	3994	beta-secretase 1	Hypomethylated
CREB cAMP response element binding protein 1	2q33.3	1026	--	cAMP response element binding protein 1	Hypomethylated
MAPT microtubule-associated protein tau	17q21.31	1094	--	microtubule-associated protein tau	Hypermethylated
MTHFR methylene Tetrahydropholate reductase	1p36.22	959	--	methylene tetrahydropholate reductase	Hypermethylated
NCSTN nicastrin	1q22-q23	922	766	nicastrin	Hypermethylated
MME Membrane metallo- endopeptidase	3q25.1-q25.2	972	3330	neprilysin	Hypermethylated
PP2A protein phosphatase 2	9q34	981	1598	serine/threonine-protein phosphatase 2A activator	Hypomethylated
PSEN1 presenilin 1	14q24.2	929	1198	presenilin 1	Hypomethylated
S100A2 S100 calcium binding protein A2	1q21.3	902	400	protein S100-A2	Hypomethylated
SORBS3 sorbin and SH3 domain containing 3	8p21.3	972	939	vinexin	Hypermethylated
SPTBN4 spectrin beta nonerythrocytic 4	19q13.13	947	993	spectrin beta chain, non-erythrocytic 4	Hypermethylated
TBXA2R thromboxane A2 receptor	19p13.3	983	1335	thromboxane A2 receptor	Hypermethylated
TMEM59 transmembrane protein 59	1p32.3	1016	628	transmembrane protein 59	Hypomethylated

Table 1: Gene methylation patterns in Alzheimer's disease.

Cacabelos, J Alzheimers Dis Parkinsonism 2016, 6:2



Category	Gene	Locus	Promoter length (bp)	Pathology	Methylation
Phase I Drug Metabolism Genes	*ALDH1A2*	15q21.3	982	prostate cancer	Hypermethylated
	CYP1A1	15q24.1	1200	head and neck cancer prostate cancer fetal growth restriction (toxics) smoking-related	Hypermethylated Hypermethylated Hypomethylated Hypomethylated
	CYP1B1	2p22.2	1193	colorectal cancer prostate cancer hepatoma cell lines breast cancer	Hypermethylated Hypomethylated Hypermethylated Hypermethylated
	CYP24A1	20q13	945	vitamin D deficiency tumor-derived endothelial cells	Hypermethylated Hypermethylated
	CYP27B1	12q14.1	917	breast cancer choriocarcinoma lymphoma and leukemia	Hypermethylated Hypermethylated Hypermethylated
	CYP2A13	19q13.2	928	head and neck cancer	Hypermethylated
	CYP2C19	10q24	1048	Drug resistance	Hypermethylated
	CYP2E1	10q26.3	918	Parkinson's disease toluene exposure	Hypomethylated Hypomethylated
	CYP2R1	11p15.2	1026	vitamin D deficiency	Hypermethylated
	CYP2W1	7p22.3	934	colorectal cancer bladder, breast, thyroid cancer liver, stomach cancer	Hypomethylated Hypomethylated Hypomethylated
	CYP7B1	8q21.3	1052	prostate cancer	Hypomethylated
Phase II Drug Metabolism Genes	*GSTM1*	1p13.3	900	head and neck cancer	Hypermethylated
	GSTP1	11q13	958	toluene exposure hepatoma cells prostate cancer breast cancer	Hypomethylated Hypermethylated Hypermethylated Hypomethylated
	NAT1	8p22	2132	breast cancer	Hypomethylated
	SULT1A1	16p12.1	1086	breast cancer	Hypermethylated
	UGT3A2	5p13.2	1076	hepatoma cells	Hypermethylated
Phase III Transporter Genes	*ABCA7*	19p13.3	967	Alzheimer's disease	Hypomethylated
	ABCB1	7q21.12	906	breast cancer resistance to chemotherapy	Hypermethylated Hypomethylated
	ABCC6	16p13.1	975	bladder cancer	Hypermethylated
	ABCG2	4q22	1199	T-cell acute lymphoblastic leukemia cell lines	Hypomethylated
	SLC19A1	21q22.3	1040	CNS lymphomas	Hypomethylated
	SLC22A3	6q25.3	1034	prostate cancer	Hypermethylated
	SLC24A4	14q32.12	1029	Alzheimer's disease	Hypomethylated

Cacabelos, J Alzheimers Dis Parkinsonism 2016, 6:2

Current status of selected anti-Alzheimer's drugs in clinical trials.

Drug	Mechanism of action	Clinical stage	Status
AN-1792	Anti-Aβ vaccine	Phase II	Discontinued
CAD106	Anti-Aβ vaccine	Phase II	Terminated
ACC-001	Anti-Aβ vaccine	Phase II	Terminated
Bapineuzumab	Humanized monoclonal anti-Aβ antibody	Phase III	Discontinued
Solanezumab	Humanized monoclonal anti-Aβ antibody	Phase III and II/III	Ongoing
Gantenerumab	Humanized monoclonal anti-Aβ antibody	Phase II/III	Ongoing
Crenezumab	Humanized monoclonal anti-Aβ antibody	Phase II	Ongoing
IVIG	Human polyclonal anti-Aβ antibody	Phase III	Ongoing
GSK933776	Humanized monoclonal anti-Aβ antibody	Phase I	Terminated
BAN-21	Humanized monoclonal anti-Aβ antibody	Phase I/II	Ongoing
AADvac1	Anti-tau vaccine	Phase I	Ongoing
ACI-35	Anti-tau vaccine	Phase I	Ongoing
Semagacestat	γ-Secretase inhibitor	Phase III	Discontinued
Avagacestat	γ-Secretase modulator	Phase II	Discontinued
Begacestat	γ-Secretase modulator	Phase I	Terminated
NIC5-15	γ-Secretase modulator	Phase II	Ongoing
CHF-5074	γ-Secretase modulator	Phase II	Terminated
MK-8931	β-Secretase inhibitor	Phase II/III	Ongoing
LY2886721	β-Secretase inhibitor	Phase II	Discontinued
AZD 3293	β-Secretase inhibitor	Phase II/III	Ongoing
LY3314814	β-Secretase inhibitor	Phase II/III	Ongoing
E2609	β-Secretase inhibitor	Phase II/III	Ongoing
Tideglusib	GSK-3β inhibitor	Phase II	Terminated
Intranasal Humulin R	GSK-3β inhibitor	Phase II	Ongoing
Intranasal glulizine	GSK-3β inhibitor	Phase II	Terminated
Idalopirdine with donepezil	5-HT_6 receptor antagonist	Phase III	Ongoing
SB742457 with donepezil	5-HT_6 receptor antagonist	Phase II	Terminated
ABT-288	H_3 receptor antagonist	Phase II	Terminated
GSK239512	H_3 receptor antagonist	Phase II	Terminated
Azeliragon	RAGE inhibitor	Phase III	Ongoing
Encenicline	α7-nAChR inhibitor	Phase III	Ongoing
Nivaldipine	Calcium antagonist	Phase III	Ongoing

J. Godyn, et al. Pharmacological Reports 2016;68: 127–138

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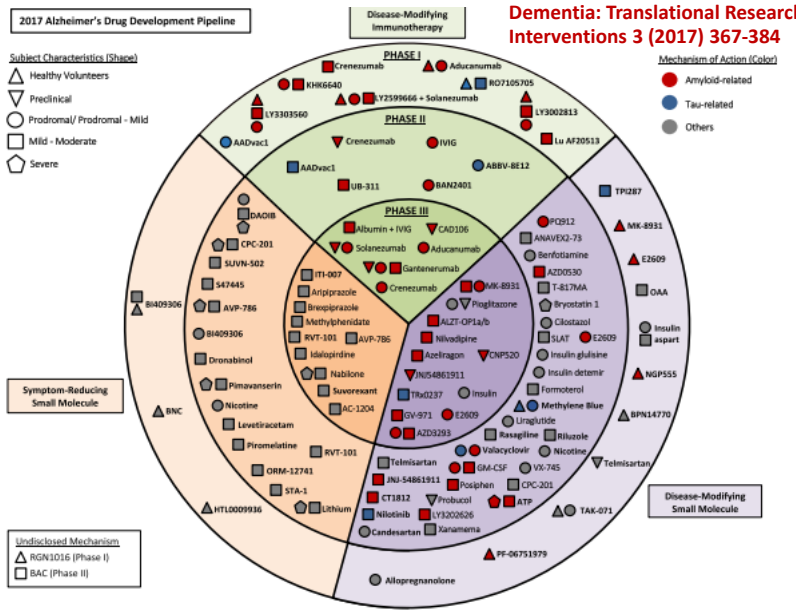

Fig. 1. Agents in clinical trials for the treatment of Alzheimer's disease in 2017 (from clinicaltrials.gov accessed 1/5/2017). Abbreviations: ATP, adenosine triphosphate; BNC, bisnorcymserine; GM-CSF, granulocyte-macrophage colony-stimulating factor; OAA, oxaloacetate; IVIG, intravenous immunoglobulin; SLAT, simvastatin + L-arginine + tetrahydrobiopterin.

Agents currently in phase I of Alzheimer's disease drug development (as of 1/5/2017) (*Continued*)

Agent	Agent mechanism class	Mechanism of action	Clinicaltrials.gov identifier	Status	Sponsor	Start date	Estimated end date
MK-8931 (verubecestat)	Anti-amyloid	BACE inhibitor	NCT01953601	Active, not recruiting	Merck	Nov-13	Mar-21
			NCT01739348*	Active, not recruiting	Merck	Nov-12	Jul-19
MK-4305 (suvorexant)	Neurotransmitter based	Dual orexin receptor antagonist	NCT02750306	Recruiting	Merck	May-16	Jul-17
Nabilone	Neurotransmitter based	Cannabinoid (receptor agent)	NCT02351882*	Recruiting	Sunnybrook Health Sciences Centre	Jan-15	Dec-17
Nilvadipine	Anti-Amyloid	Calcium channel blocker	NCT02017340	Active, not recruiting	St. James' Hospital Ireland, Alzheimer Europe, Archer Pharmaceuticals	Oct-12	Dec-17
Pioglitazone	Metabolic	PPAR-gamma agonist, anti-amyloid effect	NCT02284906	Recruiting, Extension	Takeda	Feb-15	Apr-21
			NCT01931566	Active, not recruiting	Takeda	Aug-13	Jul-19
RVT-101 (intepirdine)	Neurotransmitter based	5-HT6 antagonist	NCT02585934	Recruiting	Axovant Sciences	Oct-15	Oct-17
			NCT02586909	Recruiting, Extension	Axovant Sciences	Apr-16	Jun-18
Sodium Oligo-mannurarate (GV-971)	Anti-amyloid	Anti-amyloid agent	NCT02293915	Recruiting	Shanghai Greenvalley Pharmaceutical	Apr-14	May-17
Solanezumab	Anti-amyloid	Monoclonal antibody	NCT01760005*	Active, not recruiting	Washington University, Eli Lilly, Roche, NIA, Alzheimer's Association	Dec-12	Dec-19
			NCT02008357	Recruiting	Eli Lilly, ATRI	Feb-14	Oct-20
			NCT01127633	Active, not recruiting, Extension	Eli Lilly	Dec-10	Feb-17
			NCT01900665	Active, not recruiting	Eli Lilly	Jul-13	Feb-17
			NCT02760602	Recruiting	Eli Lilly	Jun-16	Apr-21
TRx0237	Anti-tau	Tau protein aggregation inhibitor	NCT02245568	Recruiting, Extension	TauRx Therapeutics	Aug-14	Sept-17
TTP488 (azeliragon)	Anti-amyloid, anti-inflammatory	Anti-amyloid RAGE antagonist	NCT02080364	Recruiting	vTv Therapeutics	Apr-15	Jan-19
			NCT02916056	Not yet recruiting		Dec-16	Nov-20

Abbreviations: ATRI, Alzheimer's Therapeutic Research Institute; BACE, β-site amyloid precursor protein cleaving enzyme; NIA, National Institute on Aging; PPAR, peroxisome proliferator-activated receptor; RAGE, receptor for advanced glycation end products.

NOTE. Twenty-eight agents in 42 phase III clinical trials as of January 5, 2017 according to clinicaltrials.gov.

*Phase II/III trials. Bolded = new entries into the 2017 phase III pipeline.

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Agents currently in phase II of Alzheimer's disease drug development (as of 1/5/2017)

Agent	Agent mechanism class	Mechanism of Action	Clinicaltrials.gov identifier	Status	Sponsor	Start date	Estimated end date
AADvac1	Anti-tau	Monoclonal antibody	NCT02579252	Recruiting	Axon Neuroscience	Dec-15	Feb-19
ABBV-8E12	Anti-tau	Monoclonal antibody	NCT02880956	Recruiting	AbbVie	Oct-16	Mar-21
ATP	Anti-amyloid	Inhibits amyloid misfolding and toxicity	NCT02279511	Active, not recruiting	Fundació Clínic per la Recerca Biomèdica, Spain	Nov-14	Nov-16
AD-SVF cells	Regenerative	AD-SVF cell infusion	NCT02912169*	Recruiting	Ageless Regenerative Institute	Nov-15	Dec-17
ANAVEX 2-73	Neuroprotective	Sigma-1 receptor agonist	NCT02244541	Active, not recruiting	Anavex Life Sciences	Dec-14	Oct-16
			NCT02756858	Recruiting, extension		Mar-16	Nov-18
Atomoxetine	Anti-amyloid	Adrenergic uptake inhibitor, SNRI	NCT01522404	Active, not recruiting	Emory University, NIA	Mar-12	Dec-17
AVP-786	Neurotransmitter based	Mixed transmitter effect	NCT02534038	Recruiting	Avanir	Oct-15	Mar-18
AZD0530 (saracatinib)	Anti-amyloid	Kinase inhibitor	NCT02167256	Active, not recruiting	Yale University, ATRI, AstraZeneca	Dec-14	Dec-17
BAC	Undisclosed	Undisclosed mechanism	NCT02886494	Not yet recruiting	Charsire Biotechnology	Nov-16	Nov-19
			NCT02467413	Not yet recruiting	Charsire Biotechnology, A2 Healthcare Taiwan Corporation	Mar-16	Dec-17
BAN2401	Anti-amyloid	Monoclonal antibody	NCT01767311	Recruiting	Eisai	Dec-12	Jul-18
Benfotiamine	Metabolic	Antioxidant	NCT02292238	Recruiting	Burke Medical Research Institute, Columbia University, NIA, ADDF	Nov-14	Nov-19
BI409306	Neuroprotective	Phosphodiesterase 9A inhibitor	NCT02240693	Recruiting	Boehringer Ingelheim	Jan-15	Oct-17
			NCT02337907	Recruiting	Boehringer Ingelheim	Jan-15	Oct-17
Bryostatin 1	Neuroprotective	Protein kinase C modulator	NCT02431468	Active, not recruiting	Neurotrope Bioscience	Jul-15	May-17
Candesartan	Neuroprotective, anti-inflammatory	Angiotensin receptor blocker	NCT02646982	Recruiting	Emory University	Jun-16	Sep-21
CB-AC-02 (Placenta derived-MSCs)	Regenerative	Stem cell therapy	NCT02899091*	Not yet recruiting	CHA Biotech Co.	Sep-16	Jun-18
Cilostazol	Neuroprotective	Phosphodiesterase 3 antagonist	NCT02491268	Recruiting	National Cerebral and Cardiovascular Center, Japan	Jul-15	Jul-18
CPC-201	Neuroprotective	Cholinesterase inhibitor + peripheral cholinergic antagonist	NCT02549196	Recruiting	Chase Pharmaceuticals	Oct-15	Dec-16
			NCT02434666	Active, not recruiting, Extension	Chase Pharmaceuticals	Jan-15	Dec-16
			NCT02860065	Not yet recruiting	Chase Pharmaceuticals	Sep-16	Jun-17
Crenezumab	Anti-amyloid	Monoclonal antibody	NCT01998841	Recruiting	Genentech, NIA, Banner Alzheimer's Institute	Dec-13	Sep-20
CT1812	Anti-amyloid	Sigma-2 receptor modulator	NCT02907567*	Recruiting	Cognition Therapeutics	Sep-16	May-17
DAOIB	Neurotransmitter based	NMDA enhancer	NCT02103673	Recruiting	Chang Gung Memorial Hospital, Taiwan	Feb-14	Sep-17
			NCT02239003	Recruiting	Chang Gung Memorial Hospital, Taiwan	Jan-12	Dec-17
Dronabinol	Neurotransmitter based	CB1 and CB2 endocannabinoid receptor partial agonist	NCT02792257	Not yet recruiting	Mclean Hospital, Johns Hopkins University	Aug-16	Dec-20
E2609	Anti-amyloid	BACE inhibitor	NCT02322021	Recruiting	Eisai, Biogen	Nov-14	Jan-18

(*Continued*)

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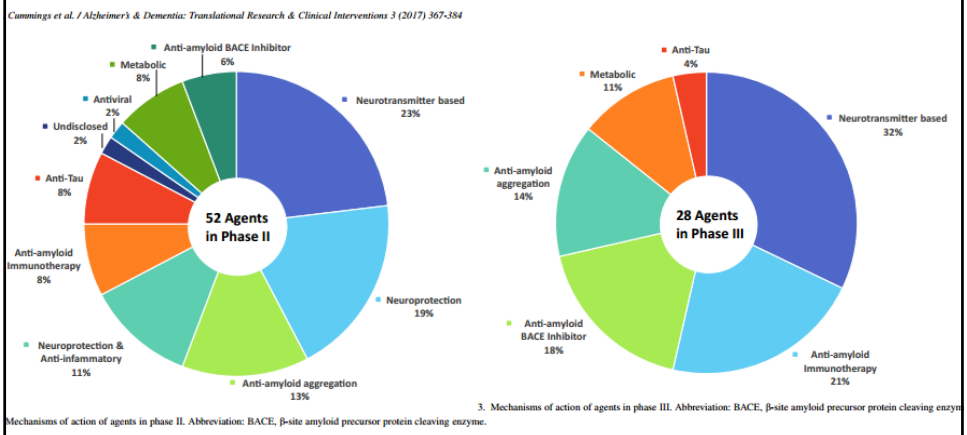

Mechanisms of action of agents in phase II. Abbreviation: BACE, β-site amyloid precursor protein cleaving enzyme.

3. Mechanisms of action of agents in phase III. Abbreviation: BACE, β-site amyloid precursor protein cleaving enzym

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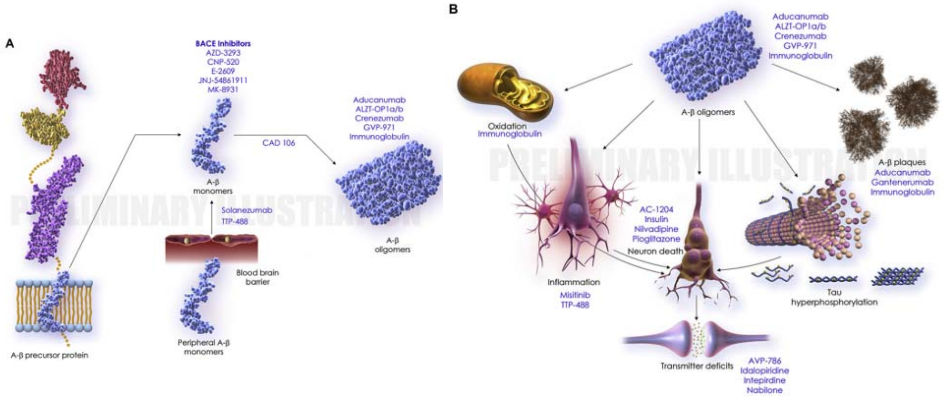

Ilustration of drug mechanism (phase III agents) and the proposed biology of Alzheimer's disease. (A) Amyloid cascade. (B) Downstream pathophysiology. Abbreviation: BACE, b-site amyloid precursor protein cleaving enzyme

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Table 5
Biomarkers as outcome measures in phase II and phase III trials for agents in the Alzheimer's disease drug development pipeline (clinicaltrials.gov; 1/5/2017)

	N of trials (%)	
Biomarker	Phase III	Phase II
CSF amyloid	12 (28.6)	17 (25.0)
CSF tau	13 (31.0)	16 (23.5)
FDG-PET	5 (11.9)	10 (14.7)
vMRI	9 (21.4)	6 (8.8)
Plasma amyloid	4 (9.5)	5 (7.4)
Plasma tau	0	1 (1.5)
Amyloid PET	13 (31.0)	6 (8.8)
Tau PET	1 (2.4)	0

Abbreviations: CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; PET, positron emission tomography; vMRI, volumetric magnetic resonance imaging.

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Table 6
BACE inhibitors in clinical trials for AD

BACE inhibitors currently in phase II or III of development

Agent (sponsor)	Clinicaltrials.gov identifier (trial name)	Phase	Population	Start date	Estimated end date
CNP520 (Novartis)	NCT02565511 (GENERATION)	II/III	Asymptomatic (homozygote *APOE* e4/e4)	11/2015	08/2023
E2609 (Eisai)	NCT02322021	II	MCI to moderate AD	11/2014	01/2018
	NCT02956486 (MISSION-AD1)	III	MCI to mild AD	10/2016	06/2020
JNJ54861911 (Janssen)	NCT02406027	II	MCI to mild AD	07/2015	10/2022
	NCT02569398	II/III	Preclinical (amyloid positive)	11/2015	05/2023
LY3202626 (Lilly)	NCT02791191 (NAVIGATE-AD)	II	Mild AD	06/2016	08/2018
LY3314814 (Lilly)	NCT02245737 (AMARANTH)	II/III	MCI to mild AD	9/2014	8/2019
	NCT02783573 (DAYBREAK ALZ)	III	Mild AD	7/2016	08/2021
Verubecestat (Merck)	NCT01739348 (EPOCH)	II/III	Mild to moderate AD	11/2012	06/2017

Abbreviations: AD, Alzheimer's disease; BACE, β-site amyloid precursor protein cleaving enzyme; MCI, mild cognitive impairment.

Table 4
Number of participants needed for AD clinical trials

Participant type	Phase I	Phase II	Phase III	Total
Healthy volunteers	864	120	0	984
Preclinical AD	66	323	7850	8239
Prodromal/prodromal-mild AD	597	3877	17,535	22,009
Mild-moderate AD	626	4528	17,099	22,253
Severe AD	0	568	20	588
Total	2153	9416	42,504	54,073

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Immunotherapies in clinical trials for AD (clinicaltrials.gov accessed 1/5/2017)

Agent	Sponsor	Target	Trial phase	Population
AADvac1	Axon Neuroscience	Anti-tau mAb	1	AD
AADvac1	Axon Neuroscience	Anti-tau mAb	2	Mild-moderate AD
ABBV-8E12	AbbVie	Anti-tau mAb	2	Early AD
Aducanumab	Biogen	mAb targeting multiple forms of Aβ	1	Healthy volunteers
Aducanumab	Biogen	mAb targeting multiple forms of Aβ	1	Prodromal-mild AD
Aducanumab	Biogen	mAb targeting multiple forms of Aβ	1	Mild-moderate AD
Aducanumab	Biogen	mAb targeting multiple forms of Aβ	3	Early AD
Aducanumab	Biogen	mAb targeting multiple forms of Aβ	3	Early AD
Albumin and immunoglobulin	Grifols	Polyclonal antibody targeting multiple forms of Aβ	3	Mild-moderate AD
BAN2401	Eisai	mAb targeting N terminal protofibrils	2	Early AD
CAD106	Novartis, NIA	$Aβ_{1–6}$, active vaccine	2	AD, at risk
Crenezumab	Genentech	mAb targeting soluble oligomer and fibrillar Aβ	1	Mild-moderate AD
Crenezumab	Genentech, NIA, Academic	mAb targeting soluble oligomer and fibrillar Aβ	2	ADAD
Crenezumab	Genentech	mAb targeting soluble oligomer and fibrillar Aβ	3	Prodromal-mild AD
Gantenerumab	Roche	mAb targeting aggregated Aβ	3	Mild AD
Gantenerumab	Roche	mAb targeting aggregated Aβ	3	Prodromal AD
Gantenerumab	Roche, Lilly, Alzheimer's Association	mAb targeting aggregated Aβ	2/3	AD, at risk
Solanezumab	Lilly, Roche, Alzheimer's Association	mAb targeting monomeric Aβ	2/3	AD, at risk
KH6640	Kyowa Hakko Kirin	mAb targeting aggregated Aβ	1	AD
Lu AF20513	Lundbeck		1	Mild AD
NewGam 10% IVIG	Sutter Health	Polyclonal antibody targeting multiple forms of Aβ	2	Amnestic MCI
LY2599666 & solanezumab	Lilly	Combination of BACE inhibitor and MAb targeting monomeric Aβ	1	MCI due to AD
LY3303560	Lilly		1	MCI due to AD-mild AD
LY30032813	Lilly		1	MCI due to AD
LY30032813	Lilly		1	Mild-moderate AD
RO7105705	Genentech	Anti-tau mAb	1	Mild-moderate AD
Solanezumab	Lilly	mAb targeting monomeric Aβ	3	Prodromal AD
Solanezumab	Lilly	mAb targeting monomeric Aβ	3	Preclinical AD
Solanezumab	Lilly	mAb targeting monomeric Aβ	3	AD
Solanezumab	Lilly	mAb targeting monomeric Aβ	3	Mild AD
UB-311	United Neuroscience	mAb targeting N terminal $Aβ_{1–14}$	2	Mild AD

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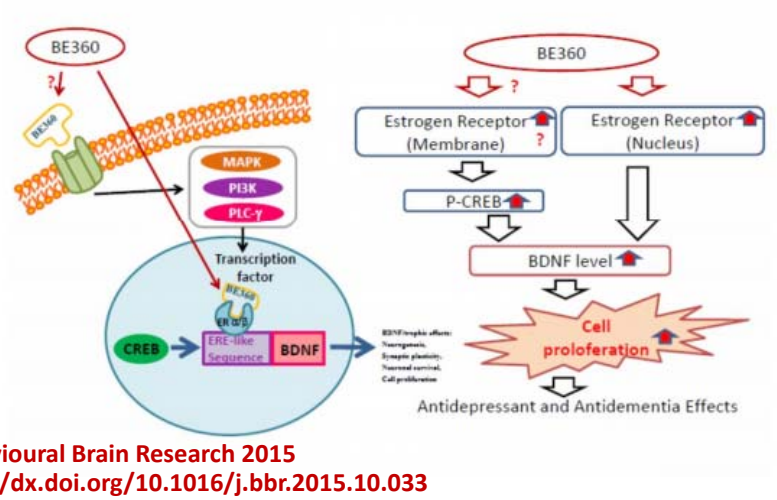
BE360, a new selective estrogen receptor modulator, produces antidepressant and antidementia effects through the enhancement of hippocampal cell proliferation in olfactory bulbectomized mice.



Behavioural Brain Research 2015
http://dx.doi.org/10.1016/j.bbr.2015.10.033

BE360 was administered subcutaneously to mice using a mini-osmotic pump for 2 weeks. Depressive-like behaviour was measured as the reduced intake of a sweet solution in the sucrose preference test. Short-term memory was assessed using the Y-maze test.

Cell proliferation was assessed by the analysis of cells expressing 5-bromo-2'-deoxyuridine (BrdU) uptake. The expression of phosphorylated cyclic-AMP response element binding protein (pCREB) and brainderived neurotrophic factor (BDNF) were measured by immunoblot. The depressive-like behaviour and memory impairment in OBX mice were improved by the chronic treatment with BE360.

Immunohistochemical analysis showed that the number of BrdU-positive

cells in the dentate gyrus of the hippocampus significantly decreased in OBX mice whereas they increased after the chronic treatment with BE360.

Immunoblotting studies revealed that pCREB and BDNF were significantly increased in the hippocampus of OBX mice treated with BE360.

The present study has shown that BE360 has antidepressant and antidementia effects characterized by hippocampal cell proliferation potentially activated via CREB/BDNF signaling pathways. These results indicate that BE360 may have valuable therapeutic potential against depression and neurodegenerative diseases.

Alzheimer's disease treatment

- Only 20–30% of patients with dementia respond appropriately to conventional drugs (tacrine, donepezil, rivastigmine, galantamine and memantine).
- Over 60% of Alzheimer's disease (AD) patients present concomitant disorders susceptible of further pharmacological treatment.
- The onset of ADRs imposes the additional administration of other drugs to neutralize side-effects, this multiplying the initial cost of the pharmacological treatment and the health risk for the patients.

Pharmacogenomics

- Approximately 60–70% of therapeutic outcomes depend upon pharmacogenomic criteria.
- Pharmacogenomic factors are responsible for 75–85% of the therapeutic response (efficacy/safety) in AD patients treated with conventional drugs.

Genes potentially involved in AD Pharmacogenomics

- Genes associated with AD pathogenesis and neurodegeneration (*APP*, *PSEN1*, *PSEN2*, *MAPT*, *PRNP*, *APOE* and others).
- Genes associated with the mechanism of action of drugs (enzymes, receptors, transmitters, messengers).
- Genes associated with drug metabolism (Phase I [*CYPs*] and Phase II reactions [*UGTs*, *NATs*]).
- Genes associated with drug transporters (*ABCs*, *SLCs*).
- Pleiotropic genes involved in multifaceted cascades and metabolic reactions (*APOs*, *ILs*, *MTHFR*, *ACE*, *AGT*, *NOS* and many others).

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Metabolic genes

- Over 75% of the Caucasian population is defective for the *CYP2D6+2C9+2C19* cluster.
- In AD, *CYP2D6* extensive (EM), intermediate (IM), poor (PM) and ultra-rapid metabolizers (UM) account for 56.38, 27.66, 7.45 and 8.51%, respectively.
- *CYP2C9*-PMs, -IMs and -EMs are 6.45, 37.64 and 55.91%, respectively.
- *CYP2C19*-EMs, -IMs and -PMs are 69.89, 30.11 and 0%, respectively.

Transporter genes

- The multidrug efflux transporters of the ABC family play important roles in limiting the movement of substances into and enhancing their efflux from the brain.
- Transporters cooperate with Phase I/Phase II metabolism enzymes by eliminating drug metabolites.
- Major features of transporters are their capacity to recognize drugs belonging to unrelated pharmacological classes, and their redundancy, by which a single molecule can act as a substrate for different transporters.
- Transporters exert efficient neuroprotection against xenobiotic invasions.
- The pharmacological induction of *ABC* gene expression is a mechanism of drug interaction, which may affect substrates of the upregulated transporter.
- Overexpression of transporters may confer resistance to CNS drugs.

Influence of the *APOE-TOMM40* region in AD pharmacogenomics

- Polymorphic variants in the *APOE-TOMM40* region on 19q13.2 influence AD pharmacogenomics.
- *APOE-4* carriers are the worst responders and *APOE-3* carriers are the best responders to conventional treatments.
- *TOMM40 poly T-S/S* carriers are the best responders, VL/VL and S/VL carriers are intermediate responders, and L/L carriers are the worst responders to treatment.
- The haplotype 4/4-L/L is probably responsible for early onset of the disease, a faster cognitive decline and a

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Epigenomics & pharmacoepigenomics

- Epigenetic changes (DNA methylation, histone remodeling, miRNA regulation) are common phenomena in AD.
- Genes associated with the pathogenesis of neurodegeneration in AD exhibit epigenetic changes, suggesting that epigenetics might contribute to the pathogenesis of dementia.
- Epigenetic modifications are associated with drug resistance.
- Epigenetic modifications are reversible and can be potentially targeted by pharmacological and dietary interventions.
- Epigenetic drugs can reverse epigenetic changes in gene expression and might open future avenues for the treatment of some forms of dementia.
- Pharmacoepigenomics deals with the influence that epigenetic alterations may exert on genes involved in the pharmacogenomic network responsible for the pharmacokinetics and pharmacodynamics of drugs (efficacy and safety), as well as the effects that drugs may have on the epigenetic machinery.

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