

# **Alzheimer Disease**

## **New Drugs, Markets & Companies**

**by**

**Prof. K. K. Jain**  
MD, FRACS, FFPM  
**Jain PharmaBiotech**  
**Basel, Switzerland**

**January 2018**

**A Jain PharmaBiotech Report**

## **A U T H O R ' S   B I O G R A P H Y**

Professor K. K. Jain is a neurologist/neurosurgeon by training and has been working in the biotechnology/biopharmaceuticals industry for several years. He received graduate training in both Europe and US, held academic positions in several countries and is a Fellow of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians of UK. Currently he is CEO and consultant at Jain PharmaBiotech. Prof. Jain's 474 publications including 28 books (5 as editor + 23 as author) and 50 special reports, which cover important areas in biotechnology, cell/gene therapies and biopharmaceuticals. Recent books relevant to the nervous system include "Handbook of Neuroprotection" (Springer, 2011) and "Applications of Biotechnology in Neurology" (Springer 2013). In addition to the above, he has edited "Applied Neurogenomics" (Springer 2015).

**January 2018 (first edition in 2003)  
Copyright © 2018 by**

**Jain PharmaBiotech  
Bläsiring 7  
CH-4057 Basel  
Switzerland**

**Tel & Fax:       +4161-6924461  
Email:            info@pharmabiotech.ch  
Web site:        http://pharmabiotech.ch/**

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, or otherwise without the prior written permission of the Publisher. This report may not be lent, resold or otherwise traded in any manner without the consent of the Publisher. While all reasonable steps have been taken to ensure the accuracy of the information presented, the Publisher cannot accept responsibility for inadvertent errors or omissions.

# TABLE OF CONTENTS

<b>0. Executive Summary .....</b>	<b>17</b>
<b>1. Clinical Features, Epidemiology and Pathology .....</b>	<b>19</b>
<b>Introduction .....</b>	<b>19</b>
<b>Historical aspects .....</b>	<b>19</b>
<b>Clinical features of Alzheimer disease.....</b>	<b>20</b>
Seven stages of Alzheimer disease.....	22
AD as a terminal illness .....	24
Detection of AD in the preclinical phase .....	24
Differentiation of AD from other dementias .....	24
Differentiation of AD from non-dementing disorders .....	26
Cerebral insufficiency and AD .....	26
Memory deficits and preclinical AD .....	26
Sleep disorders and AD.....	27
<i>Circadian rhythms and sleep in AD .....</i>	<i>27</i>
Mild cognitive impairment .....	28
Evolution of diagnostic criteria of AD .....	29
Revised criteria for the clinical diagnosis of AD .....	31
<b>Epidemiology .....</b>	<b>32</b>
Epidemiology of aging .....	32
Epidemiology of dementia .....	34
Epidemiology of AD.....	35
<i>Prevalence of AD according to age .....</i>	<i>35</i>
<i>Mortality in AD.....</i>	<i>35</i>
<b>Pathophysiology of AD.....</b>	<b>35</b>
Cerebral atrophy and neuronal loss .....	35
Neuritic plaques and neurofibrillary tangles .....	36
See-through 3D imaging of the AD brain.....	36
Sp proteins as markers of neuronal death in AD.....	37
Role of tau in the pathogenesis of AD .....	37
RNA-binding proteins and AD .....	39
Amyloid precursor protein .....	40
<i>Relation of APP mutations to CNS disorders.....</i>	<i>40</i>
<i>Relation of APP to A<math>\beta</math> deposits and pathogenesis of AD .....</i>	<i>41</i>
<i>APP intracellular domain .....</i>	<i>42</i>
<i>Role of neprilysin in A<math>\beta</math> degradation .....</i>	<i>42</i>
<i>Role of secretases in amyloid cascade .....</i>	<i>42</i>
<i>Role of exosomal proteins .....</i>	<i>44</i>
<i>Role of nicastrin.....</i>	<i>44</i>
Neurotoxicity of A $\beta$ deposits.....	44
<i>A<math>\beta</math> production and clearance .....</i>	<i>45</i>
<i>Dysfunction of TGF-<math>\beta</math> signaling accelerates A<math>\beta</math> deposition .....</i>	<i>47</i>
<i>Interaction of A<math>\beta</math> with neuron-specific Na<sup>+</sup>/K<sup>+</sup>-ATPase <math>\alpha</math>3 subunit .....</i>	<i>47</i>
<i>Relation of A<math>\beta</math> deposits to synaptic activity.....</i>	<i>47</i>
<i>Role of TMP21 in presenilin complexes and A<math>\beta</math> formation .....</i>	<i>47</i>
<i>Role of A<math>\beta</math> dimers in the pathogenesis of AD.....</i>	<i>48</i>
<i>A<math>\beta</math>-mediated synaptic and cognitive deficits .....</i>	<i>48</i>
<i>Role of dsDNA breaks in neurodegeneration due to A<math>\beta</math>.....</i>	<i>49</i>
<i>Structure-neurotoxicity relationships of A<math>\beta</math> oligomers.....</i>	<i>49</i>
<i>Sequence of events in neurotoxicity of A<math>\beta</math>.....</i>	<i>50</i>
Impairment of mitochondrial energy metabolism .....	51
<i>A<math>\beta</math>-binding alcohol dehydrogenase links AD to mitochondrial toxicity .....</i>	<i>51</i>
Neural thread protein .....	51
Loss of synaptic proteins.....	52
<i>AD and Down syndrome.....</i>	<i>52</i>
<i>Overlapping pathologies of AD and Parkinson disease.....</i>	<i>53</i>
<i>AD and age-related macular degeneration.....</i>	<i>53</i>
<i>Myelin hypothesis of AD.....</i>	<i>53</i>
<i>Blood-brain barrier in AD .....</i>	<i>53</i>
<i>Blood vessel damage in AD .....</i>	<i>55</i>
<i>Loss of serotonin 1A receptors in the brain.....</i>	<i>55</i>
Factors in pathogenesis of AD.....	55
<i>Astrocytes and AD.....</i>	<i>55</i>
<i>Axonal transport failure in AD.....</i>	<i>56</i>
<i>Cell-cycle hypothesis .....</i>	<i>56</i>
<i>Chronic heart failure link with AD.....</i>	<i>57</i>
<i>Creatine and AD .....</i>	<i>57</i>
<i>Disturbances in brain metabolism in early AD.....</i>	<i>57</i>

<i>Disturbances of interaction of nervous system proteins</i> .....	58
<i>Disturbance of lipid metabolism in the brain</i> .....	58
<i>DENN/MADD expression and enhanced pro-apoptotic signaling in AD</i> .....	58
<i>Dopamine and AD</i> .....	58
<i>Gonadotrophins and AD</i> .....	59
<i>Glutamate transport dysfunction in AD</i> .....	59
<i>Herpes simplex virus type 1 and AD</i> .....	60
<i>Innate immune system and AD</i> .....	61
<i>Insulin, diabetes and AD</i> .....	61
<i>Mechanisms underlying cognitive deficits in AD</i> .....	62
<i>Microglia and AD</i> .....	63
<i>Monoamine oxidase and AD</i> .....	63
<i>Neuroinflammation and AD</i> .....	64
<i>Neurotransmitter deficits</i> .....	65
<i>Neurotrophic factors</i> .....	66
<i>NF-<math>\kappa</math>B signaling and the pathogenesis of neurodegeneration</i> .....	66
<i>Nitric oxide and AD</i> .....	66
<i>Nogo receptor pathway</i> .....	69
<i>Oxidative stress and AD</i> .....	69
<i>Prostaglandins and AD</i> .....	71
<i>Quinolinic acid and AD</i> .....	71
<i>Retromer deficiency</i> .....	71
<i>Serotonin and AD</i> .....	72
Spread of neurodegeneration.....	72
<i>Synaptic failure in AD</i> .....	72
<i>Transmission of AD</i> .....	73
<i>Ubiquitin-proteasome system in pathogenesis of AD</i> .....	74
Risk factors in the etiology of AD.....	75
<i>Aging and developmental abnormalities of the cholinergic system</i> .....	75
<i>Cholesterol, dietary lipids, and A<math>\beta</math></i> .....	76
<i>Exposure to magnetic fields</i> .....	77
<i>Family history of AD</i> .....	77
<i>Homocysteine and AD</i> .....	77
<i>Hypertension and AD</i> .....	78
<i>Level of education/type of job and risk of AD</i> .....	78
<i>Metals and AD</i> .....	79
<i>Obesity</i> .....	80
<i>Proneness to psychological distress and risk of AD</i> .....	81
<i>Reduced muscle strength</i> .....	81
<i>Sleep deprivation</i> .....	81
<i>Traumatic brain injury and AD</i> .....	82
<i>Vascular risk factors for AD</i> .....	83
<i>Vitamin B12 and folate</i> .....	84
AD versus non-dementing changes in the aging brain.....	85
AD and cognitive impairment with aging.....	85
Pathomechanism of memory impairment and AD.....	85
Concluding remarks on pathophysiology of AD.....	86
<b>Genetics of AD</b> .....	<b>87</b>
Familial AD.....	88
<i>Molecular genetics of familial AD</i> .....	88
<i>Presenilins and calcium channel pathogenesis of familial AD</i> .....	89
<i>Presenilin-1 mutations and familial AD</i> .....	89
Late onset AD.....	90
<b>Genomics of AD</b> .....	<b>90</b>
Introduction to genomics.....	90
Genes associated with Alzheimer disease.....	91
<i>AlzGene database</i> .....	92
<i>ApoE gene</i> .....	92
<i>ApoE genotype and nitric oxide</i> .....	94
<i>ApoE genotype modulates AD phenotype</i> .....	94
<i>APOE genotype and age-related myelin breakdown</i> .....	95
<i>ApoE receptor interaction with NMDA receptor</i> .....	95
<i>ApoE and ApoER2</i> .....	95
<i>ApoE receptor LR11 as regulator of A<math>\beta</math></i> .....	96
<i>Arctic mutation</i> .....	96
<i>BCHE gene</i> .....	96
<i>CALHM1 polymorphism and AD</i> .....	97
<i>CLU, CRI and PICALM</i> .....	97
<i>CYP46 and risk for AD</i> .....	97
<i>DAPK1 gene variants and AD</i> .....	98
Genetic variants associated with early-onset AD.....	98

Genetic variants associated with late-onset AD .....	98
<i>ApoE</i> polymorphisms associated with LOAD .....	98
Copy number variation (CNV) in LOAD .....	99
<i>LRRTM3</i> as a candidate gene for AD .....	99
<i>MTHFD1L</i> gene variant associated with AD .....	99
Mutation in <i>APP</i> gene with protective effect against AD .....	100
<i>OGG1</i> mutations associated with AD .....	100
<i>SORL1</i> gene in AD .....	100
<i>TOMM40</i> gene and risk of AD .....	101
<i>TREM2</i> variants in AD .....	101
International Genomics of Alzheimer's Project .....	101
Sequencing in Alzheimer disease .....	102
Molecular neuropathology .....	104
Role of microRNAs in AD .....	104
DNA methylation in AD .....	105
AD as a polygenic disorder .....	106
<b>Proteomics of AD .....</b>	<b>106</b>
Introduction .....	106
Application of proteomic technologies to study AD .....	106
Protein misfolding in AD .....	108
Common denominators of AD and prion diseases .....	109
<b>2. Diagnostic Procedures for Alzheimer Disease .....</b>	<b>111</b>
<b>Importance of the diagnosis of Alzheimer disease .....</b>	<b>111</b>
<b>Methods of diagnosis of AD .....</b>	<b>111</b>
Self-administered olfactory test .....	112
Neuropsychological testing .....	112
Assessment and evaluation .....	113
7-minute screen .....	113
15-point risk index .....	114
Activities of Daily Living .....	114
Alzheimer Disease Cooperative Study .....	114
CDR-SOB score .....	114
Clinician's Interview-Based Impression of Change .....	115
DETECT™ System .....	115
Measurement of aggregation in anterior segment of the eye .....	115
Resource Utilization in Dementia Battery .....	115
SymptomGuide™ .....	115
Electrophysiology .....	116
Quantitative EEG for investigation of early AD .....	116
EEG-based bispectral index .....	116
Event-related potentials .....	116
Correlation of electrical activity of the brain with cognition .....	117
Early detection of cataract associated with AD .....	117
Retinal imaging to detect A $\beta$ deposits .....	117
Laboratory methods for diagnosis of AD .....	118
Monitoring of synthesis and clearance rates of A $\beta$ in the CSF .....	119
Molecular diagnostics for AD .....	119
Genetic tests for AD .....	120
<i>ApoE</i> genotyping .....	121
Gene expression patterns in AD .....	121
Monoclonal antibody-based <i>in vitro</i> diagnosis of AD from brain tissues .....	121
Multi-tissue RNA signature of aging as diagnostic for AD .....	121
Biomarkers of AD .....	122
The ideal biomarker for AD .....	124
CSF biomarkers of AD .....	124
CSF sulfatide as a biomarker for AD .....	124
Glycerophosphocholine as CSF biomarker in AD .....	125
Protein biomarkers of AD in CSF .....	125
Tau proteins in CSF .....	127
Tests for the detection of A $\beta$ in CSF .....	127
Tests combining CSF tau and A $\beta$ .....	128
Concluding remarks about CSF biomarkers of AD .....	128
Urine tests for AD .....	129
Blood tests for AD .....	129
Blood A $\beta$ levels .....	129
Blood test for AD based on heme oxygenase-1 .....	130
Blood test for AD based on RNA hybridization .....	130
GSK-3 elevation in white blood cells .....	130
Lipid biomarkers for preclinical detection of AD .....	131
Lymphocyte Proliferation Test .....	131

<i>Metabolomic biomarker profiling</i> .....	131
<i>MGAT3 as biomarker for prognosis of AD</i> .....	132
<i>MicroRNA-based test for AD</i> .....	132
<i>Protein kinase C in red blood cells</i> .....	132
<i>Sphingolipids</i> .....	132
<i>Tests based on protein biomarkers in blood</i> .....	133
Skin test for early detection of AD .....	133
Saliva-based tests for AD .....	134
<i>Saliva A<math>\beta</math>42 level as a biomarker of AD</i> .....	134
Smell identification test .....	134
Nanotechnology to measure A $\beta$ -derived diffusible ligands .....	134
Simultaneous measurement of several biomarkers for AD .....	135
Nutritional biomarkers in plasma of AD patients .....	135
Plasma biomarkers of drug response in AD .....	136
A serum protein-based algorithm for the detection of AD .....	136
Concluding remarks about biomarkers for AD .....	136
<b>Imaging in AD</b> .....	<b>137</b>
Computed tomography .....	137
Magnetic resonance imaging .....	137
<i>Arterial spin labeling with MRI</i> .....	138
<i>Magnetic resonance microscopy</i> .....	138
<i>Magnetic resonance spectroscopy</i> .....	138
Single photon emission computed tomography and modifications .....	139
Positron emission tomography .....	140
In vivo imaging of A $\beta$ deposits by PET .....	141
<i>Pittsburgh compound B and PET</i> .....	142
<i>Florbetapir-PET</i> .....	143
<i>Florbetaben-PET</i> .....	144
<i>Flutemetamol-PET</i> .....	144
<i>Future prospects of the PET imaging in AD</i> .....	144
In vivo detection of A $\beta$ plaques by MRI .....	145
Imaging agents for A $\beta$ and neurofibrillary tangles .....	145
Hyperspectral Raman imaging of neuritic plaques in AD .....	146
Targeting of a chemokine receptor as biomarker for brain imaging .....	146
Radiiodinated cloquinol as a biomarker for A $\beta$ .....	147
Imaging neuroinflammation in AD .....	147
Preclinical diagnosis of AD .....	147
<i>Correlation of imaging with CSF biomarkers for early detection of AD</i> .....	148
Meta-analysis of literature on imaging in AD .....	148
Alzheimer Disease Neuroimaging Initiative .....	149
Computer aided diagnosis systems for AD based on imaging data .....	150
Concluding remarks on imaging for diagnosis of AD .....	150
<b>Diagnosis of MCI and prediction of AD</b> .....	<b>151</b>
Diagnosis of MCI .....	151
<i>Computer-Administered Neuropsychological screen for MCI</i> .....	151
<i>Infrared eye-tracking technology to detect MCI</i> .....	151
<i>MRI for detection of MCI</i> .....	152
<i>PET for detection of MCI</i> .....	152
<i>Role of APOE genotype in early MCI</i> .....	152
Presymptomatic detection of AD .....	153
<i>Biomarker changes in autosomal dominantly inherited AD</i> .....	153
<i>Blood test for preclinical diagnosis of AD</i> .....	154
<i>Gait analysis during cognitive tasks</i> .....	154
PredictAD project .....	154
Prediction of AD in patients with MCI .....	155
<i>Biochemical biomarkers in CSF for prediction of AD</i> .....	155
<i>Clinical and biochemical biomarkers for profiling prodromal AD</i> .....	155
<i>Combination of MMSE and a memory test for prediction of AD</i> .....	155
<i>Plasma protein biomarkers of conversion of MCI to AD</i> .....	156
<i>Structural MRI biomarkers for prediction of AD</i> .....	156
<i>Magnetoencephalography for detection of MCI and AD</i> .....	156
<i>MRI-based index to measure the severity of AD in MCI</i> .....	157
<i>Concluding remarks about prediction of AD in MCI</i> .....	157
<b>Criteria for diagnosis of AD</b> .....	<b>157</b>
Role of biomarkers in diagnosis of AD dementia .....	159
<b>Ethical aspects of diagnostics for AD</b> .....	<b>160</b>
Genetic testing for AD .....	160
Ethical issues of brain imaging in AD .....	160
Monitoring of treatment of AD .....	161
<i>Monitoring treatment of mixed AD and vascular dementia</i> .....	161
<b>Companies involved in diagnosis of AD</b> .....	<b>161</b>

<b>3. Management of Alzheimer Disease .....</b>	<b>163</b>
<b>Introduction .....</b>	<b>163</b>
<b>Cholinergic approaches.....</b>	<b>163</b>
Mechanism of action of cholinesterase inhibitors .....	164
Choline and lecithin.....	165
Donepezil.....	166
Rivastigmine .....	167
Galantamine.....	168
Duration of treatment with ChE inhibitors .....	169
<b>Comparative studies of ChE inhibitors .....</b>	<b>169</b>
Donepezil versus rivastigmine .....	170
Donepezil versus galantamine .....	170
Combination of cholinesterase inhibitors and a cholinergic precursor .....	170
An assessment and future prospects of anticholinergic therapies.....	171
<b>Neuroprotection in Alzheimer's disease.....</b>	<b>172</b>
Memantine.....	172
<i>Pharmacology of memantine .....</i>	<i>172</i>
<i>Clinical trials of memantine .....</i>	<i>173</i>
<i>Combination of memantine with ChE inhibitors .....</i>	<i>175</i>
Monoamine oxidase inhibitors.....	176
<i>Selegiline.....</i>	<i>176</i>
Synaptoprotection in AD .....	176
<b>Drugs for noncognitive symptoms in AD .....</b>	<b>177</b>
Antidepressants.....	177
Antipsychotics .....	177
ChE inhibitors for behavioral and psychological disorders in AD.....	178
Concluding remarks and other drugs for agitation in AD.....	178
Sensory stimulation .....	179
<b>Non-pharmacological treatments of AD .....</b>	<b>179</b>
Cerebrospinal fluid shunting .....	179
Deep brain stimulation .....	180
Exposure of the brain to electromagnetic fields for treatment of AD .....	181
<i>Application of electrical fields for improvement of cerebral function .....</i>	<i>181</i>
<i>High-frequency electromagnetic field treatment of AD .....</i>	<i>181</i>
<i>Transcranial magnetic stimulation .....</i>	<i>182</i>
Mental training for management of memory loss in AD .....	182
Microchip-based hippocampal prosthesis for AD .....	182
Omental transposition .....	183
Photo-induced inhibition of A $\beta$ accumulation in AD .....	183
Scanning ultrasound for removal of A $\beta$ .....	183
Vagal nerve stimulation .....	184
<b>Nutritional therapies for AD .....</b>	<b>184</b>
Axona.....	184
Cocktail of dietary supplements for AD .....	184
Docosahexaenoic acid.....	185
Magnesium .....	186
Nicotinamide for the treatment of AD .....	187
Omega-3 fatty acids.....	187
<b>Preventing decline of mental function with aging and dementia.....</b>	<b>188</b>
<b>Prevention of Alzheimer disease.....</b>	<b>189</b>
Mental training .....	190
Physical exercise.....	190
Higher level of conscientiousness and decreased risk of AD .....	191
Nutritional factors in prevention of AD and MCI.....	191
<i>Black and green teas.....</i>	<i>192</i>
<i>Caffeine.....</i>	<i>192</i>
<i>Caloric restriction.....</i>	<i>193</i>
<i>Cinnamon .....</i>	<i>193</i>
<i>Cocoa flavonol consumption .....</i>	<i>193</i>
<i>Grapes and red wine .....</i>	<i>193</i>
<i>Vitamin D and docosahexaenoic acid .....</i>	<i>195</i>
Drugs to prevent Alzheimer disease .....	195
Preimplantation genetic diagnosis of inherited Alzheimer disease .....	195
Presymptomatic detection of AD .....	195
<b>Management of mild cognitive impairment .....</b>	<b>196</b>
Slowing the progression of MCI to AD.....	196
<b>Management of Down syndrome.....</b>	<b>197</b>
<b>Guidelines for use of anti-dementia drugs in clinical practice .....</b>	<b>198</b>
Donepezil and/or memantine.....	198
<b>General care of the Alzheimer disease patients .....</b>	<b>199</b>
<b>Strategies for the management of Alzheimer disease .....</b>	<b>199</b>

<b>4. Research in Alzheimer Disease .....</b>	<b>201</b>
<b>Introduction .....</b>	<b>201</b>
<b>Animal models of Alzheimer disease.....</b>	<b>201</b>
Lesional models .....	201
<i>Cerebroventricular injection of A<math>\beta</math> in rats .....</i>	<i>201</i>
<i>Lentiviral vector-based models of amyloid pathology .....</i>	<i>202</i>
<i>AAV-mediated gene transfer to increase hippocampal A<math>\beta</math> .....</i>	<i>202</i>
Transgenic mouse models .....	202
<i>Quantitative assessment of amyloid load in transgenic models.....</i>	<i>203</i>
<i>In vivo magnetic resonance microimaging in transgenic models of AD .....</i>	<i>204</i>
<i>Transgenic model of AD with suppression of A<math>\beta</math> production.....</i>	<i>204</i>
<i>Transgenic AD11 anti-NGF mice.....</i>	<i>204</i>
<i>Genetically altered mice with deficiency of vesicular ACh transporter.....</i>	<i>205</i>
<i>Limitations of mouse models of Alzheimer disease .....</i>	<i>205</i>
<i>Improved mouse models of AD expressing human genes .....</i>	<i>206</i>
Cholesterol-fed rabbits as models for AD.....	206
Canine dementia as model for AD .....	206
Zebrafish model for AD .....	207
Transgenic invertebrate models of Alzheimer disease .....	208
<i>Drosophila model of AD .....</i>	<i>208</i>
<i>Caenorhabditis elegans Alzheimer disease model .....</i>	<i>208</i>
Correlation of studies in animal models and human clinical trials.....	209
<b>Cell systems for AD research .....</b>	<b>210</b>
In vitro neuronal cell Lines .....	210
Single-gene expression system for use in cell culture .....	210
Stem cells for testing efficacy of AD drugs .....	210
Transgenic cells .....	211
In silico models .....	211
<b>Estimation of progression rates of Alzheimer disease.....</b>	<b>212</b>
<b>Clinical trial methods in Alzheimer disease.....</b>	<b>212</b>
Molecular imaging as a guide to drug development .....	213
Use of MRI and PET in clinical trials .....	213
Cognitive-function assessment in clinical trials.....	214
Clinical trials in mild cognitive impairment.....	214
<b>Research in AD as a basis for future therapies.....</b>	<b>215</b>
Use of microarrays for studying pathogenesis of AD .....	215
Computational brain mapping in AD .....	215
Study of neurogenesis in AD .....	215
Study of 3D structure of A $\beta$ .....	215
Solid-state NMR to study precursors of A $\beta$ .....	216
<b>Research in Alzheimer disease at academic centers .....</b>	<b>216</b>
Role of NIH in AD research.....	216
NIH Clinical Trials Database for AD.....	216
Alzheimer Research Consortium.....	216
The National Institute on Aging and AD research .....	217
<b>5. Drug Discovery &amp; Development for Alzheimer Disease .....</b>	<b>219</b>
<b>Introduction .....</b>	<b>219</b>
<b>Categories of drugs in development for AD.....</b>	<b>219</b>
<b>Memory-enhancing drugs .....</b>	<b>221</b>
Enhancing memory by drugs that block eIF2 $\alpha$ phosphorylation .....	221
<b>Drugs based on cholinergic approaches.....</b>	<b>221</b>
AP2238.....	222
Butyrylcholinesterase inhibitors .....	222
Donepezil-tacrine hybrids.....	222
Drugs modulating gamma-aminobutyric acid receptors.....	223
Ganstigmina.....	223
Methanesulfonyl fluoride .....	223
Muscarinic receptor modulators .....	224
<i>Muscarinic M1 agonists .....</i>	<i>224</i>
<i>Muscarinic M2 antagonists.....</i>	<i>225</i>
Nicotine and nicotinic receptor modulators .....	225
<i>Nicotine .....</i>	<i>225</i>
<i>Nicotinic receptor modulators .....</i>	<i>226</i>
<i>GTS21 .....</i>	<i>228</i>
<i>Ispronicline .....</i>	<i>229</i>
<i>JWB1-84-1.....</i>	<i>229</i>
<b>Neuropeptide/neurotransmitters .....</b>	<b>229</b>
Somatostatin release enhancers .....	229
<b>Glutamate receptor modulators .....</b>	<b>230</b>
Physiology and pharmacology of glutamate receptors.....	230



NMDA receptor ion channel complex.....	230
Metabotropic glutamate receptors .....	231
Glutamate receptor modulators as potential therapeutics for AD .....	232
<i>N2OC</i> .....	233
<i>AMPA modulators</i> .....	233
Glutamate release inhibitors.....	234
<i>INI-0602</i> .....	234
<b>Drugs affecting multiple neurotransmitters.....</b>	<b>234</b>
Ensaculin .....	234
RS-1259 .....	234
Lecozotan .....	234
<b>Vaccines for AD.....</b>	<b>235</b>
Active immunization with A $\beta$ .....	235
<i>AN-1792 vaccine</i> .....	235
<i>Complications in clinical trials with AN-1792</i> .....	236
<i>Effects of A<math>\beta</math> vaccine on the brain</i> .....	236
Strategies to avoid undesirable effect of A $\beta$ vaccination .....	237
Passive immunization in AD.....	238
<i>Passive immunization with MAbs</i> .....	238
<i>Clinical trials of MAbs in AD</i> .....	239
<i>Delivery of the passive antibody directly to the brain</i> .....	240
<i>Systemic injection of MAbs to treat AD</i> .....	241
Combination of A $\beta$ immunotherapy and CD40-CD40L blockade.....	241
Shaping the immune responses elicited against A $\beta$ .....	241
Delivery of AD vaccines .....	242
<i>Gene vaccination</i> .....	242
<i>Modified A<math>\beta</math> nasal vaccine</i> .....	243
<i>Transdermal A<math>\beta</math> vaccination</i> .....	243
Other vaccines for AD.....	243
<i>Nasal vaccination with Proteosome™ adjuvant</i> .....	244
<i>T cell vaccination with glatiramer acetate adjuvant</i> .....	244
Early start of immunotherapy for clearing A $\beta$ plaques.....	244
Reversal of cholinergic dysfunction by anti-A $\beta$ antibody .....	244
Immune modulation via Toll-like receptors to reduce A $\beta$ .....	245
Mechanisms by which A $\beta$ antibodies reduce amyloid accumulation in the brain .....	245
Perspectives on vaccines for AD.....	246
Companies involved in AD vaccines .....	248
<b>Inhibition of amyloid precursor protein aggregation .....</b>	<b>248</b>
Secretase modulators.....	248
<i>Neuroprotection by <math>\alpha</math>-secretase cleaved APP</i> .....	249
<i>Inhibitors of <math>\beta</math>-secretase</i> .....	250
<i>Inhibitors of <math>\gamma</math>-secretase</i> .....	251
Amyloid-derived diffusible ligands .....	252
GABA receptor modulation by etazolate and APP processing .....	253
Depletion of serum amyloid P .....	253
<b>Drugs that inhibit the formation of A<math>\beta</math> .....</b>	<b>253</b>
22R-hydroxycholesterol .....	254
Acylaminopyrazole .....	254
Cadmium telluride nanoparticles prevent A $\beta$ fibril formation .....	254
Cannabinoids.....	254
Chelation therapy for AD.....	255
<i>Clioquinol and PBT2</i> .....	255
<i>Copper chelation by FKBP52</i> .....	257
<i>Zinc chelation from amyloid plaques</i> .....	258
<i>Next generation multifunctional chelating agents for AD</i> .....	258
Heparin and its derivatives.....	258
<i>A reassessment of the role of heparin in AD</i> .....	258
<i>Enoxaparin</i> .....	259
<i>Heparan sulfate</i> .....	259
Imatinib mesylate .....	259
Laminin .....	260
Masitinib .....	260
NSAIDs.....	260
<i>Flurbiprofen analogs with A<math>\beta</math>42-lowering action</i> .....	261
<i>Nitric oxide-donating NSAIDs</i> .....	262
<i>In vivo demonstration of the effects of NSAIDs on brain in AD</i> .....	262
Paclitaxel .....	263
Phenserine .....	263
<i>Tolserine</i> .....	264
Platinum-based inhibitors of A $\beta$ .....	264
Retro-inverso peptide inhibitor .....	264

Scyllo-cyclohexanehexol .....	264
Selective serotonin reuptake inhibitor .....	265
Small molecule drug discovery for inhibiting A $\beta$ aggregation.....	265
Trojan-horse approach to prevent build-up of A $\beta$ aggregates.....	265
Ubiquitin C-terminal hydrolase L1 .....	266
<b>Drugs to prevent the formation of NFTs.....</b>	<b>266</b>
<b>Tau suppression.....</b>	<b>267</b>
Anthraquinones .....	267
Anti-tau antibodies.....	267
Tau aggregation inhibitor rember™ .....	267
LMTX® .....	268
Microtubule stabilizers .....	268
<b>ApoE4 as a therapeutic target in AD .....</b>	<b>268</b>
<b>Strategies to prevent deposits and enhance clearance of A<math>\beta</math> .....</b>	<b>269</b>
4,5-dianilinophthalimide for disruption of A $\beta$ <sub>1-42</sub> fibrils.....	269
ABCA1 overexpression to lower amyloid deposits .....	270
ANAVEX 2-73 .....	270
Beta-sheet breakers .....	271
Bexarotene .....	271
Blocking ApoE/A $\beta$ interaction to reduce A $\beta$ plaques .....	272
CD33 inhibitors.....	272
Clearance of A $\beta$ across the blood-brain barrier.....	272
Enhanced PKC $\epsilon$ activity promotes clearance of A $\beta$ .....	273
Galantamine-induced A $\beta$ clearance.....	273
Hemopheresis .....	273
Inhibitors of A $\beta$ dehydrogenase .....	273
Intravenous immune globulin .....	274
Monoclonal antibodies for removal of A $\beta$ .....	275
<i>Crenezumab</i> .....	275
<i>Gantenerumab</i> .....	275
<i>Solanezumab</i> .....	276
Nanotechnology for removal of A $\beta$ deposits .....	276
Role of matrix metalloproteinases in clearance of A $\beta$ .....	276
Serum amyloid P component depletion .....	277
Small molecule DAPH for clearance of amyloid.....	277
<b>Companies developing A<math>\beta</math>-directed therapeutics for AD .....</b>	<b>277</b>
<b>Nootropics .....</b>	<b>278</b>
Acetyl-L-carnitine.....	279
Cerebrolysin .....	279
Ergot derivatives.....	280
<i>Lisuride</i> .....	280
<i>Dihydroergocryptine</i> .....	280
<b>Neuroprotective effect drugs not primarily developed for AD .....</b>	<b>280</b>
Antiepileptic drugs .....	281
<i>Lamotrigine</i> .....	281
<i>Levetiracetam</i> .....	281
Antiinflammatory and antimicrobial drugs .....	282
<i>Dapsone</i> .....	282
<i>Antimicrobial drugs against C. pneumoniae</i> .....	282
<i>PPAR-gamma agonists</i> .....	282
Antidiabetic drugs .....	283
<i>Insulin</i> .....	283
<i>Metformin</i> .....	283
<i>Rosiglitazone</i> .....	284
<i>Pioglitazone</i> .....	284
Antihypertensive drugs .....	285
<i>Angiotensin-converting enzyme inhibitors</i> .....	285
<i>Angiotensin receptor blockers</i> .....	285
Bexarotene .....	285
Dimebon.....	285
Drugs acting on estrogen receptors .....	286
<i>Estrogen</i> .....	287
<i>Raloxifene</i> .....	287
Inhibitors of neuroinflammation .....	288
<i>Ceramide</i> .....	288
<i>CSP-1103</i> .....	288
<i>Cyclophosphamide</i> .....	288
<i>Etanercept</i> .....	289
<i>Fingolimod</i> .....	289
<i>Interferon beta-1a</i> .....	289
<i>MW01-5-188WH</i> .....	290

Neurosteroids .....	290
<i>Pregnenolone sulfate</i> .....	290
<i>Dehydroepiandrosterone</i> .....	291
Lithium .....	291
MAO-B inhibitors.....	291
<i>Ladostigil tartrate</i> .....	292
Memoquin .....	292
Methylene blue .....	293
Nilotinib.....	293
Nimodipine.....	293
Rapamycin.....	294
Saracatinib.....	294
Statins.....	294
Testosterone .....	295
Valproic acid.....	296
Future prospects of neuroprotection in AD.....	296
<i>Targeting Cdk5 pathway</i> .....	297
<b>Antioxidants .....</b>	<b>297</b>
Colostrinin .....	298
Curcumin .....	298
Dehydroascorbic acid .....	299
Reservatrol .....	299
Synthetic catalytic scavengers .....	300
<b>Vitamins .....</b>	<b>300</b>
Vitamin E as antioxidant .....	300
Vitamin B for lowering homocysteine.....	300
Folic acid .....	301
<b>Aminopyridazines .....</b>	<b>301</b>
<b>Nanobody-based drugs for AD .....</b>	<b>302</b>
<b>Nitric oxide based therapeutics for AD.....</b>	<b>302</b>
Nitric oxide mimetics .....	302
iNOS inhibitors for AD.....	302
<b>Novel drugs for AD from natural resources.....</b>	<b>303</b>
Berberine chloride.....	304
Centella asiatica .....	304
Ginko biloba.....	304
Huperzine-A .....	305
Hyperforin.....	306
Melissa officinalis .....	306
Nostocarboline derived from cyanobacteria .....	306
Salvia.....	307
Securinega suffruticosa.....	307
Withania somnifera .....	307
ZT-1.....	307
<b>Cholesterol and AD .....</b>	<b>308</b>
ACAT inhibitors.....	309
Role of gene for cholesterol ester transfer protein .....	310
Cholesterol 24S-hydroxylase as a drug target for AD .....	310
Selectively increase of ApoA-I production.....	310
<b>Neurotrophic factors.....</b>	<b>310</b>
Brain derived neurotrophic factor .....	311
Insulin-like growth factor-1 .....	311
Nerve growth factor .....	312
Neotrofin (AIT-082).....	312
Limitations of the use of NTFs for AD.....	313
<b>Role of serotonin modulators in AD .....</b>	<b>313</b>
Xaliproden .....	313
5-HT <sub>1A</sub> receptor antagonists .....	313
5-HT <sub>6</sub> antagonists .....	314
5-HT <sub>4</sub> receptor agonists .....	314
<i>PRX-03140</i> .....	315
<i>Donecopride</i> .....	315
<b>Restoration of factors deficient in the aging brain .....</b>	<b>315</b>
Reversal of cognitive impairment in aging by activation of creb protein.....	315
Reversal of cognitive impairment in aging by GDF11 protein .....	316
Restoration of repressor element 1-silencing transcription factor.....	316
<b>Cell therapy for AD.....</b>	<b>316</b>
Stem cell transplantation for AD .....	317
<i>Potential benefits of grafting NSCs in AD</i> .....	317
<i>NSCs improve cognition in AD via BDNF</i> .....	317
<i>Drugs for enhancing neuronal differentiation of implanted NSCs</i> .....	318

Choroid plexus epithelial cells for AD .....	318
Implantation of encapsulated cells for delivering NGF .....	318
<b>Gene therapy for AD .....</b>	<b>318</b>
ApoE gene therapy .....	319
<i>APPsa gene transfer for rescuing synaptic failure in AD</i> .....	319
FGF2 gene transfer in AD .....	319
Humanin gene therapy .....	320
Neprilysin gene therapy .....	320
NGF gene therapy .....	320
Targeting plasminogen activator inhibitor type-1 gene .....	322
<b>Antisense approaches to AD .....</b>	<b>322</b>
Antisense PNA in AD .....	322
Antisense tau in AD .....	322
<b>RNAi approaches to AD .....</b>	<b>323</b>
<b>Combined therapeutic approaches to AD .....</b>	<b>324</b>
<b>Drug delivery for Alzheimer disease .....</b>	<b>324</b>
Delivery of biologicals across the BBB .....	325
Delivery of thyrotropin-releasing hormone analogs by molecular packaging .....	325
Nanoparticle-based drug delivery for Alzheimer's disease .....	326
Transdermal drug delivery in Alzheimer's disease .....	326
<i>Transdermal rivastigmine</i> .....	327
Intranasal delivery of therapeutics for AD .....	327
<i>Intranasal delivery of tacrine</i> .....	327
<i>Intranasal delivery of nerve growth factor to the brain</i> .....	327
Circadian rhythms and timing of cholinesterase inhibitor therapy .....	328
<b>Clinical trials for AD .....</b>	<b>328</b>
Drugs for AD that were discontinued in clinical trials .....	334
Concluding remarks on clinical trials of AD .....	337
<b>Drug discovery for AD .....</b>	<b>338</b>
Drugs acting on signaling pathways .....	338
<i>Activation of GTPase signaling by Cytotoxic Necrotizing Factor 1</i> .....	338
<i>Drugs to reverse inhibition of the PKA/CREB pathway in AD</i> .....	338
<i>Inhibition of the CD40 signaling pathway</i> .....	339
<i>JNK pathway as a target</i> .....	340
<i>Mitogen-activated protein kinase pathway as target</i> .....	340
<i>Protein kinase C activators</i> .....	340
Electrophysiological detection of drug target for neuroprotection in early AD .....	341
Genomics-based drug discovery .....	341
High through screening for AD drug candidates .....	341
New chemical entities for AD by combining galantamine and memantine .....	342
Novel rivastigmine-hydroxycinnamic acid hybrids for AD .....	342
Novels targets/receptors for AD drug discovery .....	342
<i>Activation of cerebral Rho GTPases</i> .....	342
<i>Activators of insulin-degrading enzyme</i> .....	343
<i>Blockade of TGF-<math>\beta</math>-Smad2/3 signaling in peripheral macrophages</i> .....	343
<i>Calcium channel blockers</i> .....	343
<i>Calpain inhibitors</i> .....	344
<i>Casein kinase 1</i> .....	344
<i>Cyclin-dependent kinase-5</i> .....	344
<i>Drugs against arginine deprivation and immune suppression in AD</i> .....	345
<i>Heat shock protein 90 inhibitors</i> .....	345
<i>Histone deacetylase inhibitors</i> .....	346
<i>Inhibition of PDK1 to slow progression of both AD and prion disease</i> .....	346
<i>Melatonin</i> .....	346
<i>Neurotrophic compound J147</i> .....	347
<i>NF-<math>\kappa</math>B inhibitors</i> .....	347
<i>Kinases and phosphatases as targets for AD therapeutics</i> .....	347
<i>Neutral sphingomyelinase inhibitors</i> .....	348
<i>Phosphodiesterase inhibitors</i> .....	348
<i>Pin 1 as a target in AD</i> .....	349
<i>Protein phosphatase 5 as a neuroprotective in AD</i> .....	349
<i>Single drugs for multiple targets in AD</i> .....	350
<i>Src homology-containing protein-1 inhibitors</i> .....	350
<i>Targeting GABAergic system</i> .....	350
<i>TSPO ligands</i> .....	350
Proteomics and drug discovery for AD .....	351
Small molecule compounds binding to neurotrophin receptor p75NTR .....	352
<i>Targeting Vav in tyrosine kinase signaling pathway</i> .....	353
<i>LM11A-31 as p75NTR ligand</i> .....	353
<b>Pharmacogenomics of Alzheimer disease .....</b>	<b>354</b>
Biomarkers and companion diagnostics for AD .....	354

Personalized therapy of AD .....	354
Genotyping and AD therapeutics .....	355
<b>Regulatory aspects of drug development for AD .....</b>	<b>356</b>
EMA guidelines for drug development for AD .....	356
FDA guidelines for drug development for AD.....	357
<b>Concluding remarks and future of AD research.....</b>	<b>358</b>
Future for AD therapeutics .....	358
<b>6. Markets &amp; Finances of AD Care .....</b>	<b>361</b>
<b>Introduction .....</b>	<b>361</b>
<b>Pharmacoeconomics of treatment of AD .....</b>	<b>361</b>
Quality of Life in relation to economics of AD.....	361
Costs associated with Alzheimer disease .....	361
Pharmacoeconomics of donepezil .....	362
Pharmacoeconomics studies using rivastigmine .....	362
Pharmacoeconomics studies using galantamine .....	363
Pharmacoeconomics studies using memantine.....	363
<b>Patterns of AD care in major markets .....</b>	<b>363</b>
Care of AD patients in the US .....	364
<i>Cost of care.....</i>	<i>364</i>
<i>Medicare and AD.....</i>	<i>365</i>
<i>Patterns of practice in AD care.....</i>	<i>366</i>
<i>Opinions of physicians' organizations on drugs for dementia.....</i>	<i>366</i>
Care of AD patients in the UK .....	367
<i>Cost of care.....</i>	<i>367</i>
<i>Patterns of practice in AD care.....</i>	<i>367</i>
<i>NICE recommendations to NHS.....</i>	<i>368</i>
Care of AD patients in Germany.....	369
Care of AD patients in France .....	370
Care of AD patients in Italy .....	370
Care of AD patients in Spain.....	370
Care of AD patients in Japan .....	371
<b>Markets for AD diagnostics .....</b>	<b>371</b>
<b>Markets for AD therapeutics .....</b>	<b>371</b>
Geographical markets for AD .....	371
Markets for currently approved drugs for AD .....	372
Markets for generic AD drugs .....	373
Statins.....	373
Future growth of AD market.....	373
<b>Limitations of AD drug development by the biotechnology industry .....</b>	<b>374</b>
<b>Unmet needs in the management of AD.....</b>	<b>375</b>
<b>Drivers of AD markets.....</b>	<b>376</b>
Increase of the aged populations .....	376
Increase in the number of approved drugs for AD .....	376
Limitations of the current therapies.....	377
Improvements in diagnosis .....	377
Increasing awareness of the disease .....	377
<b>7. Companies .....</b>	<b>379</b>
<b>Introduction .....</b>	<b>379</b>
<b>Profiles of companies.....</b>	<b>379</b>
<b>Collaborations.....</b>	<b>503</b>
<b>8. References.....</b>	<b>508</b>

## Tables

Table 1-1: Historical landmarks relevant to Alzheimer disease.....	19
Table 1-2: Clinical features of Alzheimer disease .....	20
Table 1-3: Non-Alzheimer dementias .....	25
Table 1-4: A guide to evaluation for MCI due to AD.....	29
Table 1-5: NINCDS-ADRDA Criteria for diagnosis of Alzheimer disease .....	30
Table 1-6: 2011 Revised criteria for diagnosis of dementia due to Alzheimer Disease .....	31
Table 1-7: Relation of mutations in amyloid precursor protein to CNS disorders.....	40
Table 1-8: Risk factors for Alzheimer's disease .....	75
Table 1-9: Genes linked to AD .....	91
Table 1-10: Abnormalities of expression of brain proteins in Down's syndrome and AD.....	107
Table 2-1: Classification of methods of diagnosis of Alzheimer disease .....	111
Table 2-2: Neuropsychological test batteries and scales for Alzheimer's disease .....	112
Table 2-3: Available molecular diagnostic tests for Alzheimer disease.....	120

Table 2-4: Biomarkers of AD in blood and CSF .....	122
Table 2-5: Characteristics of an ideal biomarker for Alzheimer disease .....	124
Table 2-6: Role of biomarkers in diagnosis of AD dementia .....	159
Table 2-7: Companies involved in the diagnosis/monitoring of Alzheimer disease .....	161
Table 3-1: Classification of treatments for Alzheimer disease .....	163
Table 3-2: Cholinergic approaches used in the treatment of Alzheimer disease .....	164
Table 3-3: Categories of neuroprotective agents for Alzheimer disease.....	172
Table 3-4: Strategies for prevention of Alzheimer disease.....	189
Table 3-5: Guidelines for the treatment of dementia .....	198
Table 4-1: Transgenic mouse models of Alzheimer disease .....	202
Table 4-2: Correlation of studies in animal models with human clinical trials .....	209
Table 5-1: Classification of therapies in development for Alzheimer disease .....	219
Table 5-2: Drugs for AD targeting nACh receptors .....	228
Table 5-3: Ionotropic glutamate receptors .....	230
Table 5-4: Classification of mGluRs .....	230
Table 5-5: Glutamate receptor modulators as potential therapeutic agents in AD.....	232
Table 5-6: Companies involved in developing vaccines for AD .....	248
Table 5-7: Preclinical studies of secretase modulators .....	249
Table 5-8: Secretase modulators in clinical trials .....	249
Table 5-9: Companies developing A $\beta$ -directed therapeutics for AD.....	277
Table 5-10: Innovative neuroprotective approaches for Alzheimer disease .....	280
Table 5-11: Herbal therapies for AD .....	303
Table 5-12: Novel drug delivery methods for Alzheimer disease therapies.....	324
Table 5-13: Clinical trials in Alzheimer disease .....	329
Table 5-14: Discontinued, failed or inconclusive clinical trials of Alzheimer disease .....	334
Table 6-1: Direct and indirect costs associated with Alzheimer disease .....	364
Table 6-2: Prevalence of AD in major markets 2016-2026 .....	372
Table 6-3: AD market values from 2016-2026 in major world markets .....	372
Table 6-4: Markets for currently approved AD drugs 2016-2026 .....	373
Table 6-5: Potential markets for drugs in development 2016-2026 .....	374
Table 6-6: Limitations of AD drug development by the biotechnology industry.....	374
Table 6-7: Factors that drive AD markets .....	376
Table 7-1: Major players in Alzheimer's disease therapeutics.....	379
Table 7-2: Collaborations relevant to Alzheimer disease .....	503

## Figures

Figure 1-1: Percentages of world population of people over the age of 65 according to more developed and less developed portions – 2000 to 2050. ....	32
Figure 1-2: Correlation between aging and AD in the US from 2000 to 2020 .....	33
Figure 1-3: Prevalence of different types of dementia.....	34
Figure 1-4: Structure of tau in a brain with AD .....	38
Figure 1-5: A $\beta$ deposits in the brain .....	45
Figure 1-6: Mechanisms of A $\beta$ clearance.....	46
Figure 1-7: Pathways for A $\beta$ -induced nerve cell death .....	50
Figure 1-8: Insulin signaling in Alzheimer disease and diabetes .....	62
Figure 1-9: Nitric oxide neurotoxicity and neuroprotection in relation to Alzheimer disease .....	68
Figure 1-10: Oxidative stress and Alzheimer disease .....	70
Figure 1-11: Role of proteasome inhibition in A $\beta$ generation and neurodegeneration .....	74
Figure 1-12: Cholesterol-related pathways to AD .....	76
Figure 1-13: Pathomechanism of AD .....	87
Figure 3-1: Metabolism of acetylcholine.....	165
Figure 3-2: Neuroprotective effective of galantamine in AD.....	169
Figure 3-3: Strategies for the management of Alzheimer disease.....	199
Figure 5-1: Activation of $\alpha$ 7 nicotinic acetylcholine receptors.....	227
Figure 5-2: NMDA receptor ion channel complex.....	231
Figure 5-3: Neurotoxicity due to misfolding of A $\beta$ 1-42 .....	270
Figure 5-4: Interactions of players in clinical trials of Alzheimer disease in the USA.....	329
Figure 5-5: Role of proteomics in drug discovery/development for Alzheimer disease .....	352
Figure 5-6: FDA industry interaction during drug development for AD .....	357
Figure 5-7: FDA's accelerated approval pathway in early Alzheimer disease .....	359
Figure 6-1: Unmet needs in the management of Alzheimer disease.....	375