

Drug Delivery in Central Nervous System Disorders

Technologies, Companies and Markets

By

Prof. K. K. Jain
MD, FRCSC, FRACS, FFPMM
Jain PharmaBiotech
Basel, Switzerland

November 2021

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 with specialist qualifications including Fellowships of the Royal Colleges of Surgeons in Australia and Canada. He has trained, practiced, and held academic positions in several countries including Switzerland, India, Iran, Germany, Canada, and USA. After retirement from neurosurgery, Prof. Jain remains a consultant in neurology. He is also working in the biotechnology/biopharmaceuticals industry and is a Fellow of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians of UK. Currently, he is the CEO of Jain PharmaBiotech.

A B O U T T H I S R E P O R T

The original report on Drug Delivery in CNS Diseases by the author was published by Decision Resources Inc in 2000 as an enlargement of the chapter on this topic in his report on Drug Delivery Technologies (1998), which was also published by Decision Resources. The second edition was rewritten and published at Jain PharmaBiotech in 2004 and is being constantly rewritten since then.

Prof. Jain's 492 publications include 35 books (6 as editor+ 29 as author) and 50 special reports, which have covered important areas in neurology, biotechnology, gene therapy and biopharmaceuticals, biomarkers: proteomics, molecular diagnostics, nanobiotechnology, and personalized medicine. Contributions to MedLink, an accredited continuing education program for neurologists, include 172 articles out of a total of 1250 articles by 500 authors. These articles are updated on a yearly basis.

Prof. Jain's earlier books were the first in the areas covered: "Handbook of Laser Neurosurgery" (Charles C. Thomas, Springfield, Ill, 1983) and "Textbook of Hyperbaric Medicine" (1st ed in 1990 and 6th ed by Springer, 2017). His "Textbook of Gene Therapy" was translated into Chinese in 2000. Recent books include "Handbook of Nanomedicine" (Springer 2008, Chinese edition by Peking University Press 2011, 3rd ed 2017), "Textbook of Personalized Medicine" (Springer 2009; Japanese ed 2012; 2nd ed Springer 2015, 3rd ed 2021), "Handbook of Biomarkers" (Springer 2010; Chinese ed, Chemical Industry Press 2016, 2nd ed 2017), "Drug-induced Neurological Disorders", 4th ed (Springer 2021), "Handbook of Neuroprotection" (Springer 2011, 2nd ed 2019), "Applications of Biotechnology in Cardiovascular Therapeutics" (Springer 2011), "Applications of Biotechnology in Neurology" (Springer 2013), and "Applications of Biotechnology in Oncology" (Springer 2014). He has also edited 3 editions of "Drug Delivery System" (Springer 2008, 20012 and 2020) and "Applied Neurogenomics" (Springer 2015). Lectures on personalized medicine given at Kazakh National Medical University, Kazakhstan were translated into Russian and published as a book "Essentials of Personalized Medicine" (LITERRA Publishing House, Moscow, 2019). Currently, he is writing "The Handbook of Alzheimer Disease" to be published by Springer in 2022.

November 2021 (constantly rewritten since first edition published in 2000 by Decision Resources Inc) Copyright © 2021 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.

T A B L E O F C O N T E N T S

0. Executive Summary	16
1. Basics of Drug Delivery to the Central Nervous System	18
Introduction	18
Historical evolution of drug delivery for CNS disorders.....	18
Neuroanatomical and neurophysiological basis of drug delivery.....	19
The cerebrospinal fluid	19
The lymphatic drainage system of the brain	20
The extracellular space in the brain	20
Neurotransmitters.....	21
Extracellular vesicles as drug delivery vehicles	23
Neuropharmacology relevant to drug delivery.....	23
Introduction to neuropharmacology.....	23
Pharmacokinetics.....	23
<i>Absorption and distribution of drugs.....</i>	23
<i>Drug metabolism and elimination.....</i>	24
Pharmacodynamics	24
<i>Receptors</i>	24
Sites of drug action in the CNS	24
<i>Receptors coupled to guanine nucleotide binding proteins</i>	25
<i>Acetylcholine receptor channels</i>	25
<i>Dopamine receptors</i>	25
<i>GABA receptor channels.....</i>	26
<i>Glutamate receptor channels.....</i>	26
<i>Non-competitive NMDA antagonists.....</i>	26
<i>Serotonin receptors.....</i>	27
<i>G-protein coupled receptors</i>	27
In vivo study of drug action in the CNS in human patients	27
<i>Electroencephalography</i>	27
<i>Brain imaging</i>	28
Chronopharmacology as applied to the CNS	28
Role of drug delivery in personalized therapy of CNS disorders	29
2. Blood Brain Barrier	30
Introduction	30
Features of the blood-brain barrier relevant to CNS drug delivery.....	30
The neurovascular unit	30
Functions of the BBB	31
<i>BBB as an anatomical as well as physiological barrier</i>	31
<i>BBB as a biochemical barrier</i>	32
<i>Glucose transporters at the BBB</i>	32
Role of shear stress on development of BBB	33
Genomics of BBB	33
Proteomics of BBB.....	34
Other neural barriers	34
Blood-cerebrospinal fluid barrier	34
Blood nerve barrier	35
Blood-retinal barrier	35
Blood-labyrinth barrier	35
Passage of substances across the blood-brain barrier	35
Transporters localized in the BBB.....	36
<i>Adenosine carrier.....</i>	37
<i>Amino acid transporters.....</i>	37
<i>Efflux transport systems</i>	38
<i>Glucose transporter.....</i>	39
<i>Ionic transporter.....</i>	39
BBB-specific enzymes.....	40
Receptor-mediated transcytosis	40
Lysophosphatidic acid-mediated increase in BBB permeability	41
Folate transport system	41
Transferrin receptor	41
Molecular biology of the BBB	41
Transport of peptides and proteins across the BBB	42
<i>Passage of leptin across the BBB.....</i>	42
<i>Passage of cytokines across the BBB</i>	42
<i>Passage of hormones across the BBB</i>	43
<i>Passage of enzymes across the BBB</i>	43

<i>Passage of omega-3 fatty acids across the BBB</i>	44
<i>Drugs that cross the BBB by binding to plasma proteins.....</i>	44
<i>Current concepts of the permeability of the BBB</i>	44
<i>BBB permeability in relation to disease</i>	44
<i>BBB permeability in relation to drug delivery</i>	45
Factors that increase the permeability of the BBB	46
<i>BBB disruption as an adverse effect of pharmaceuticals</i>	46
<i>BBB disruption as adverse effect of vaccines for CNS disorders</i>	47
CNS disorders and BBB	47
<i>Autoimmune disorders.....</i>	48
<i>Brain tumors</i>	48
<i>Primary brain tumors.....</i>	48
<i>Cerebral metastases.....</i>	48
<i>Central nervous system injuries.....</i>	48
<i>Cerebrovascular disease</i>	49
<i>Cerebral ischemia</i>	49
<i>Intracerebral hemorrhage</i>	49
<i>Epilepsy.....</i>	50
<i>Infections</i>	50
<i>Inflammation.....</i>	51
<i>Mitochondrial encephalopathies</i>	51
<i>Multiple sclerosis.....</i>	51
<i>Neurodegenerative disorders</i>	53
<i>BBB in Alzheimer disease</i>	53
<i>BBB in Parkinson disease</i>	54
<i>BBB in amyotrophic lateral sclerosis</i>	54
<i>West Nile virus infection</i>	54
Testing permeability of the BBB.....	55
<i>In vitro models of BBB.....</i>	55
<i>In vivo study of BBB.....</i>	56
<i>Brain imaging</i>	56
<i>In silico prediction of BBB</i>	57
<i>Relevance of the BBB penetration to pharmacological action</i>	58
<i>BBB penetration and CNS drug screening</i>	58
<i>BBB models for testing drug delivery</i>	59
<i>CERENSESM.....</i>	59
<i>In vivo brain distribution of P-glycoprotein</i>	59
<i>Transthyretin monomer as a marker of blood-CSF barrier disruption</i>	60
<i>Evaluation of BBB permeability by brain imaging</i>	60
<i>Biomarkers of disruption of blood-brain barrier</i>	60
Future directions for research on the BBB	61
<i>Use of neural stem cells to construct the blood brain barrier.....</i>	62
Strategies to cross the BBB.....	62
3. Methods of Drug Delivery to the CNS	64
Introduction	64
Routes of drug delivery to the brain	65
<i>Drug delivery to the brain via the nasal route</i>	65
<i>Devices for nasal administration of drugs for CNS</i>	67
<i>Role of nanobiotechnology in nasal drug drug delivery</i>	68
<i>Nasal mucosal patch to facilitate drug delivery across the BBB</i>	68
<i>Passage of viruses to the brain via the nasal route</i>	68
<i>Potential and limitations of nasal drug delivery to the brain</i>	69
<i>Drugs that can be delivered to the brain via the nasal route</i>	69
<i>Erythropoietin.....</i>	69
<i>Esketamine</i>	69
<i>Hypocretin</i>	70
<i>IFN beta-1b.....</i>	70
<i>Levetiracetam</i>	70
<i>Lysosomal enzymes</i>	71
<i>Midazolam</i>	71
<i>Neurotrophic factors</i>	71
<i>Thyrotropin-releasing hormone.....</i>	72
<i>Neuroprotective drugs for stroke.....</i>	72
<i>Transdermal drug delivery for neurological disorders</i>	73
<i>Drug delivery to the brain via inner ear</i>	73
<i>Drug delivery for disorders of the spinal cord.....</i>	73
<i>Intrathecal drug delivery.....</i>	73
<i>Anatomical & physiological aspects of intrathecal drug delivery</i>	74
<i>Advantages of intrathecal drug delivery</i>	74
<i>Drugs that can be delivered by intrathecal route</i>	75

<i>Pharmacokinetics of intrathecal drug delivery</i>	76
<i>Retrograde delivery to the brain via the epidural venous system.....</i>	77
Devices for drug delivery to the CNS	78
<i>Catheters for drug delivery to the CNS</i>	78
<i>Reservoirs and pumps for drug delivery to the CNS.....</i>	78
Invasive neurosurgical approaches.....	79
<i>Intraarterial drug delivery to the brain.....</i>	79
<i>Direct injection into the CNS substance or CNS lesions</i>	80
<i>Targeted delivery of biologicals to the spinal cord by microinjection</i>	80
<i>Intraventricular injection of drugs</i>	80
Strategies for drug delivery to the CNS across the BBB	81
Increasing the permeability (opening) of the BBB	81
<i>Osmotic opening of the BBB.....</i>	81
<i>Chemical opening of the BBB.....</i>	82
<i>Cerebral vasodilation to open the BBB</i>	82
<i>Modulation of vascular permeability by laser irradiation</i>	83
<i>Neurostimulation for opening BBB.....</i>	83
<i>Ultrasound-induced focal disruption of BBB</i>	84
<i>Ultrasound-induced delivery across BBB without focal disruption.....</i>	84
<i>Use of nitric oxide donors to open the BBB.....</i>	84
<i>Manipulation of the sphingosine 1-phosphate receptor system.....</i>	84
Pharmacological strategies to facilitate transport across the BBB	85
<i>2B-Trans™ technology.....</i>	85
<i>ABC efflux transporters and penetration of the BBB.....</i>	86
<i>Adenosine agonist-mediated drug delivery across the BBB</i>	86
<i>Carrier-mediated drug delivery across the BBB.....</i>	87
<i>Fusion of receptor-binding peptide from apoE with therapeutic protein</i>	87
<i>G-Technology®</i>	88
<i>Glycosylation Independent Lysosomal Targeting</i>	88
<i>Inhibition of P-glycoprotein to enhance drug delivery across the BBB</i>	88
<i>LipoBridge™ technology</i>	89
<i>Modification of the drug to enhance its lipid solubility</i>	89
<i>Monoclonal antibody fusion proteins</i>	90
<i>Neuroimmunophilins.....</i>	91
<i>Peptide-mediated transport across the BBB.....</i>	91
<i>Prodrug bioconversion strategies and their CNS selectivity.....</i>	92
<i>Transport of small molecules across the BBB</i>	93
<i>Transport across the BBB by short chain oligoglycerolipids</i>	93
<i>Transvascular delivery across the BBB</i>	93
<i>Trojan horse approach.....</i>	94
<i>Role of the transferrin-receptor system in CNS drug delivery.....</i>	95
<i>Use of receptor-mediated transcytosis to cross the BBB</i>	95
Cell-based drug delivery to the CNS	97
<i>Activated T lymphocytes</i>	97
<i>Microglial cells</i>	97
<i>Neural stem cells</i>	97
Drug delivery to the CNS by using novel formulations.....	98
<i>Crystalline formulations</i>	98
<i>Liposomes.....</i>	98
<i>Monoclonal antibodies</i>	99
<i>Microspheres</i>	100
<i>Microbeads.....</i>	100
Brain-targeted chemical delivery systems	101
Nanotechnology-based drug delivery to CNS	101
Nanoparticles for drug delivery across the BBB	101
<i>Nanovesicles for transport across BBB</i>	102
<i>Nanoparticle-based reservatrol delivery to the brain.....</i>	103
<i>Penetration of BBB by nanoparticles coated with polysorbate 80</i>	103
<i>Targeting nicotinic acetylcholine receptor.....</i>	103
<i>Transcytosis of transferrin-containing nanoparticles across the BBB</i>	104
<i>V-SMART® drug delivery platform</i>	104
Nanotechnology-based devices and implants for CNS	105
Biochip implants for drug delivery to the CNS.....	105
Controlled-release microchip	105
Nanoscaffold for delivering antiinflammatory molecules to the brain.....	106
Retinal implant chip	106
Convection-enhanced delivery to the CNS	106
Systemic administration of drugs for CNS effects	107
Sustained and controlled release drug delivery to the CNS	107
<i>Fast dissolving oral selegiline.....</i>	109
Choice of the route of systemic delivery for effect on the CNS disorders	109

Methods of delivery of biopharmaceuticals to the CNS	110
Delivery of biopharmaceuticals across the BBB	110
Methods of delivery of peptides for CNS disorders	110
<i>Alteration of properties of the BBB for delivery of peptides.....</i>	<i>111</i>
<i>Challenges for delivery of peptides across the BBB.....</i>	<i>111</i>
<i>CNS delivery of peptides via conjugation to biological carriers</i>	<i>111</i>
<i>Delivery of conopeptides to the brain.....</i>	<i>111</i>
<i>Direct delivery of neuropeptides into the brain.....</i>	<i>112</i>
<i>Molecular manipulations of peptides to facilitate transport into CNS</i>	<i>112</i>
<i>Transport to spinal cord motor neurons after peripheral injection.....</i>	<i>113</i>
<i>Transnasal administration of neuropeptides.....</i>	<i>113</i>
Delivery of neurotrophic factors to the nervous system.....	113
<i>Systemic administration of NTFs</i>	<i>115</i>
<i>Delivery systems to facilitate crossing of the BBB by NTFs</i>	<i>116</i>
<i>Direct application of NTFs to the CNS</i>	<i>116</i>
<i>Intracerebroventricular injection</i>	<i>117</i>
<i>Intrathecal administration</i>	<i>118</i>
<i>Implants for delivery of neurotrophic factors</i>	<i>118</i>
<i>Use of neurotrophic factor mimics</i>	<i>118</i>
<i>Use of microspheres for delivery of neurotrophic factors</i>	<i>120</i>
<i>Use of nanobiotechnology for delivery of neurotrophic factors.....</i>	<i>120</i>
Use of microorganisms for therapeutic entry into the brain.....	120
Bacteriophages as CNS therapeutics.....	121
Intracellular drug delivery in the brain	121
Local factors in the brain affecting drug action.....	121
Methods for testing drug delivery to the CNS.....	122
Animal models for testing drug delivery	122
Conducting preclinical studies of CNS drug delivery	122
Screening for drug-P-gp interaction at BBB	122
Translating from preclinical to clinical application	122
4. Delivery of Cell, Gene and Antisense Therapies to the CNS.....	124
Introduction	124
Cell therapy of neurological disorders	124
Methods for delivering cell therapies in CNS disorders	124
<i>Cerebrospinal fluid-stem cell interactions for therapy of CNS disorders</i>	<i>125</i>
<i>Engineered stem cells for drug delivery to the brain</i>	<i>125</i>
<i>Encapsulated cells.....</i>	<i>126</i>
<i>Intrathecal delivery of stem cells</i>	<i>126</i>
<i>Intraparenchymal delivery of stem cells to the spinal cord</i>	<i>127</i>
<i>Intravascular administration.....</i>	<i>127</i>
<i>Neural stem cells as therapeutic delivery vehicles</i>	<i>128</i>
Gene therapy techniques for the nervous system	128
Introduction	128
Methods of gene transfer to the nervous system	130
AAV vector mediated gene therapy for neurogenetic disorders.....	130
Ideal vector for gene therapy of neurological disorders	130
Promoters of gene transfer.....	131
Routes of delivery of genes to the nervous system	131
<i>Direct injection into CNS</i>	<i>131</i>
<i>Introduction of the genes into cerebral circulation</i>	<i>132</i>
<i>Introduction of genes into cerebrospinal fluid</i>	<i>132</i>
<i>Intravenous administration of vectors.....</i>	<i>133</i>
<i>Delivery of gene therapy to the peripheral nervous system</i>	<i>133</i>
Cell-mediated gene therapy of neurological disorders	133
<i>Neuronal cells.....</i>	<i>133</i>
<i>Neural stem cells and progenitor cells.....</i>	<i>133</i>
<i>Astrocytes.....</i>	<i>134</i>
<i>Cerebral endothelial cells</i>	<i>134</i>
<i>Implantation of genetically modified encapsulated cells into the brain.....</i>	<i>134</i>
<i>Genetically modified bone marrow cells</i>	<i>134</i>
Nanoparticles as nonviral vectors for CNS gene therapy	135
Applications of gene therapy for neurological disorders	135
Companies involved in cell/gene therapy of neurological disorders	136
Antisense therapy of CNS disorders	137
Delivery of antisense oligonucleotides to the CNS	138
Delivery of oligonucleotides cross the BBB	139
Cellular delivery systems for oligonucleotides	140
High-flow microinfusion into the brain parenchyma	140
Systemic administration of peptide nucleic acids	140
Introduction of antisense compounds into the CSF Pathways	141

Intrathecal administration of antisense compounds	141
Intracerebroventricular administration of antisense oligonucleotides.....	142
Nanoparticle-based delivery of antisense therapy to the CNS.....	142
Methods of delivery of ribozymes	143
Delivery aspects of RNAi therapy of CNS disorders.....	143
Delivery of siRNA to the CNS	143
Future drug delivery strategies applicable to the CNS	144
5. Drug Delivery for Treatment of Neurological Disorders	146
Introduction	146
Targeted drug delivery for neurological disorders	146
Parkinson's disease	146
Drug delivery systems for Parkinson's disease	148
<i>Methods of delivery of levodopa in PD</i>	149
<i>Duodenal levodopa infusion.....</i>	149
<i>Inhaled levodopa</i>	150
<i>Sublingual apomorphine</i>	150
<i>Transdermal drug delivery for PD.....</i>	150
<i>Transdermal dopamine agonists for PD</i>	150
<i>Transdermal administration of other drugs for PD</i>	152
<i>Intracerebral administration of GDNF</i>	152
Cell therapy for PD.....	153
<i>Human dopaminergic neurons for PD..</i>	154
<i>Graft survival-enhancing drugs</i>	154
<i>Xenografting porcine fetal neurons.....</i>	154
<i>Encapsulated cells for PD</i>	155
<i>Stem cells for PD</i>	155
<i>Engineered stem cells for drug delivery to the brain in PD.....</i>	157
<i>Human retinal pigment epithelium cells for PD.....</i>	157
<i>Delivery of cells for PD.....</i>	157
Gene therapy for Parkinson disease.....	158
<i>Rationale</i>	158
<i>Techniques of gene therapy for PD.....</i>	159
<i>Prospects of gene therapy for PD</i>	162
<i>Companies developing gene therapy for PD.....</i>	163
RNAi therapy of Parkinson's disease	163
Alzheimer disease.....	164
Drug delivery for Alzheimer disease	164
Blood-brain partitioning of an AMPA receptor modulator	165
Clearing amyloid through the BBB.....	166
Delivery of the passive antibody directly to the brain.....	166
Delivery of thyrotropin-releasing hormone analogs by molecular packaging.....	166
Exosome-based drug delivery in AD	166
Nanoparticle-based drug delivery for Alzheimer's disease.....	167
Perispinal etanercept	168
Slow release implant of an AChE inhibitor	168
Intranasal insulin in Alzheimer disease	168
Transdermal drug delivery in Alzheimer's disease.....	169
Trojan-horse approach to prevent build-up of A β aggregates.....	169
Cell and gene therapy for Alzheimer disease.....	169
<i>NGF gene therapy</i>	170
<i>Neprilysin gene therapy</i>	171
RNAi therapy of Alzheimer's disease	171
Huntington's disease	171
Treatment of HD	172
Gene therapy of HD	172
<i>Encapsulated genetically engineered cellular implants.....</i>	172
<i>Viral vector mediated administration of neurotrophic factors</i>	172
<i>RNAi therapeutics for the treatment of HD</i>	173
Amyotrophic lateral sclerosis.....	173
Treatment of ALS.....	173
Drug delivery in ALS.....	174
Delivery of stem cell therapy for ALS.....	175
Gene and antisense therapy of ALS	175
<i>Neurotrophic factor gene therapies of ALS.....</i>	176
<i>Antisense therapy of ALS</i>	177
<i>RNAi therapy of amyotrophic lateral sclerosis</i>	177
Cerebrovascular disease	178
Treatment of stroke	178
Drug delivery in stroke	179
<i>Intraarterial administration of thrombolytic agents in stroke.....</i>	179

Drug delivery for prevention of restenosis of carotid arteries	180
<i>In-stent restenosis</i>	181
<i>Targeted local anti-restenotic drug delivery</i>	181
<i>Catheter-based drug delivery for restenosis</i>	182
<i>Stents for prevention of restenosis</i>	182
<i>Drug-eluting stents</i>	183
<i>Antisense approach to prevent restenosis</i>	183
Drug-eluting stents for the treatment of intracranial atherosclerosis.....	184
Tissues transplants for stroke.....	184
<i>Transplant of encapsulated tissue secreting neurotrophic factors</i>	184
Methods for delivery of neurotrophic factors in stroke.....	184
Cell therapy for stroke	185
<i>Stem cell transplant into the brain</i>	185
<i>Immortalized cell grafts for stroke</i>	185
<i>Intravenous infusion of marrow stromal cells</i>	186
<i>Intravenous infusion of umbilical cord blood stem cells</i>	186
<i>Future of cell therapy for stroke</i>	186
Gene therapy of cerebrovascular diseases.....	187
<i>Gene transfer to cerebral blood vessels</i>	187
<i>NOS gene therapy for restenosis</i>	188
Gene therapy for cerebral ischemia	188
<i>Gene therapy of strokes with a genetic component</i>	190
Drug delivery to intracranial aneurysms.....	190
Drug delivery for vasospasm following subarachnoid hemorrhage	190
<i>Intrathecal tissue plasminogen activator</i>	192
<i>Gene therapy for vasospasm</i>	192
Drug delivery in multiple sclerosis.....	193
An electronic device for self injection of interferon beta-1a.....	193
Oral therapies for MS	194
Drug delivery for MS across the BBB	194
<i>Delivery of methylprednisolone across the BBB</i>	194
<i>Monoclonal antibodies for MS and the BBB</i>	194
Antisense and RNAi approaches to MS	195
Cell therapy for multiple sclerosis.....	195
<i>Hematopoietic stem cell transplantation for multiple sclerosis</i>	196
<i>Embryonic stem cells and neural precursor cells for MS</i>	196
Gene therapy for multiple sclerosis	196
Drug delivery in epilepsy	197
Routes of administration of antiepileptic drugs.....	197
<i>Controlled-release preparations of carbamazepine</i>	197
<i>Intravenous carbamazepine</i>	198
<i>Various routes of administration of benzodiazepines</i>	198
Methods of delivery of novel antiepileptic therapies	199
<i>Use of neuronal membrane transporter</i>	199
<i>Delivery of the antiepileptic conopeptides to the brain</i>	199
<i>Nasal administration of AEDs</i>	199
<i>Intracerebral administration of AEDs</i>	200
The role of drug delivery in status epilepticus	200
Cell therapy of epilepsy	201
Gene therapy for epilepsy	201
<i>Gene therapy for neuroprotection in epilepsy</i>	202
Concluding remarks on drug delivery in epilepsy	202
Drug delivery for pain.....	203
Intranasal delivery of analgesics	204
<i>Intranasal administration of morphine</i>	204
<i>Intranasal morphine derivatives</i>	205
<i>Intranasal fentanyl</i>	205
<i>Intranasal buprenorphine</i>	206
<i>Intranasal ketamine</i>	206
<i>Intranasal ketorolac</i>	206
Delivery of analgesics by inhalation	207
Delivery of analgesics to peripheral nerves.....	207
Spinal delivery of analgesics.....	208
<i>Epidural dexamethasone</i>	210
<i>Epidural morphine</i>	210
<i>Relief of pain by intrathecal ziconotide</i>	210
<i>Intrathecal neostigmine</i>	211
<i>Intrathecal prostaglandin antagonists</i>	211
<i>Intrathecal fadolmidine</i>	211
<i>Intrathecal siRNA for relief of neuropathic pain</i>	212
Concluding remarks on intrathecal delivery of analgesic agents	212

Intracerebroventricular drug delivery for pain.....	212
<i>Delivery of analgesics to the CNS across the BBB.....</i>	212
Drug delivery for migraine.....	213
Management of migraine	213
Novel drug delivery methods for migraine	214
<i>Nasal formulations for migraine</i>	215
<i>Sublingual spray for migraine</i>	216
<i>Needle-free drug delivery for migraine.....</i>	216
Drug delivery for traumatic brain injury	216
Cell therapy of traumatic brain injury	216
<i>Gene therapy for traumatic brain injury</i>	217
Drug delivery for spinal cord injury	217
Administration of neurotrophic factors for spinal cord injury	217
Cell therapy for spinal cord injury	218
<i>Transplantation of glial cells for SCI</i>	218
<i>Fetal neural grafts for SCI.....</i>	218
<i>Embryonic stem cells for SCI.....</i>	218
<i>Schwann cell transplants for SCI.....</i>	219
<i>Olfactory glial cells for SCI</i>	220
<i>Marrow stromal cells for SCI.....</i>	220
<i>Intravenous injection of stem cells for spinal cord repair.....</i>	220
<i>Combinatorial approach for regeneration in SCI.....</i>	221
<i>Cell therapy of syringomyelia</i>	221
<i>Gene therapy of spinal cord injury.....</i>	221
Drug delivery in CNS infections.....	221
Drug delivery in neuroAIDS.....	222
Drug delivery for miscellaneous neurological disorders.....	222
Drug delivery for CNS involvement in Hunter syndrome.....	222
<i>Trojan horse therapeutics to treat mucopolysaccharidosis types I & II</i>	223
Antisense therapy for spinal muscular atrophy.....	224
<i>Antisense gene splicing for SMA.....</i>	224
<i>Intrathecal antisense delivery.....</i>	224
Genetically modified stem cells for metachromatic leukodystrophy	225
Relief of spasticity by intrathecal baclofen	225
Drug delivery for retinal disorders.....	225
Age-related macular degeneration	226
<i>Squalamine</i>	226
<i>Combretastatin A4P for myopic macular degeneration</i>	226
<i>Gene therapy for AMD</i>	227
<i>Anti-VEGF approach to AMD</i>	227
<i>Delivery of pegaptanib for treatment of AMD</i>	227
<i>Stem cell therapy for retinitis pigmentosa</i>	228
<i>Proliferative retinopathies</i>	228
<i>Retinoblastoma.....</i>	229
Drug delivery for inner ear disorders	229
Delivery of stem cells for hearing loss.....	229
Auditory hair cell replacement by gene therapy	230
Future prospects of drug delivery to the inner ear	230
Drug delivery in psychiatric disorders.....	230
Delivery of antidepressants	231
<i>Transdermal delivery of antidepressants</i>	232
<i>Nasal delivery of antidepressants</i>	233
Delivery methods and formulations of antipsychotics	234
<i>Long-acting injectable antipsychotics.....</i>	234
<i>Transdermal haloperidol</i>	235
<i>Transdermal risperidone for treatment of schizophrenia</i>	235
<i>Transdermal olanzapine for treatment of schizophrenia</i>	235
<i>Transnasal oxytocin for schizophrenia</i>	236
Transdermal lithium for bipolar disorder	236
6. Drug delivery for brain tumors	238
Introduction	238
Methods for evaluation of anticancer drug penetration into brain tumor	238
Innovative methods of drug delivery for glioblastoma	238
Delivery of anticancer drugs across the blood-brain barrier	239
Anticancer agents with increased penetration of BBB.....	239
BBB disruption.....	240
Nanoparticle-based targeted delivery of chemotherapy across the BBB.....	241
Tyrosine kinase inhibitor increases topotecan penetration into CNS	243
Bypassing the BBB by alternative methods of drug delivery	243
Intranasal perillyl alcohol	243

Intraarterial chemotherapy	243
Enhancing tumor permeability to chemotherapy	244
PDE5 inhibitors for increasing BTB permeability	244
Local delivery of therapeutic agents into the brain	245
Biodegradable microspheres containing 5-FU.....	245
Carmustine biodegradable polymer implants	245
Fibrin glue implants containing anticancer drugs.....	246
Interstitial delivery of dexamethasone for reduction of peritumor edema	246
Magnetically controlled microspheres.....	246
Convection-enhanced delivery	247
CED for receptor-directed cytotoxin therapy	247
CED of topotecan	247
CED of a modified diphtheria toxin conjugated to transferrin	247
CED of nanoliposomal CPT-11.....	248
CED for delivery ^{131}I -chTNT-1/B MAb	248
Anticancer drug formulations for targeted delivery to brain tumors	248
Intravenous delivery of anticancer agents bearing transferrin.....	248
Liposomes for drug delivery to brain tumors.....	248
MAbs targeted to brain tumors	249
Targeted delivery of drug-peptide conjugates to glioblastoma.....	250
Multiple targeted drugs for brain tumors	250
Nanoparticles for targeted drug delivery in glioblastoma	251
Targeted antiangiogenic/apoptotic/cytotoxic therapies.....	252
Targeted drug delivery to gliomas using cholera toxin subunit B	252
Introduction of the chemotherapeutic agent into the CSF pathways	253
Intraventricular chemotherapy for meningeal cancer	253
Intrathecal chemotherapy	253
Photodynamic therapy for chemosensitization of brain tumors	254
Nanoparticles for photodynamic therapy of brain tumors.....	254
Innovative delivery of radiotherapy to brain tumors	254
GliaSite Radiation Therapy System.....	254
Boron neutron capture therapy for brain tumors	255
Cell therapy for malignant brain tumors	255
Chimeric antigen receptor T cells	255
Mesenchymal stem cells to deliver treatment for gliomas	256
Intra-cavity stem cell therapy for medulloblastoma	256
Gene therapy for glioblastoma	256
Antiangiogenic gene therapy	257
Anticancer drug delivery by genetically engineered MSCs.....	258
Intracerebroventricular delivery of gene therapy for gliomas by NSCs	258
Intravenous gene delivery with nanoparticles into brain tumors	259
Ligand-directed delivery of dsRNA molecules targeted to EGFR	259
MSC-based gene delivery	259
Neural stem cells for drug/gene delivery to brain tumors	259
Peptides targeted to glial tumor cells	260
RNAi gene therapy of brain cancer	261
Single-chain antibody-targeted adenoviral vectors	261
Targeting normal brain cells with an AAV vector encoding interferon- β	261
Poliovirus-based vaccine for glioblastoma.....	262
Treatment of medulloblastoma by suppressing genes in Shh pathway	263
Virus-mediated oncolytic therapy of brain cancer	264
<i>HIV-mediated Oncolysis.....</i>	<i>264</i>
<i>Autophagy by conditionally replicating adenoviruses.....</i>	<i>264</i>
<i>Reovirus-mediated Oncolysis.....</i>	<i>265</i>
<i>Measles virus-mediated oncolysis.....</i>	<i>265</i>
<i>Oncolytic virus targeted to brain tumor stem cells.....</i>	<i>265</i>
<i>Oncolysis with vesicular stomatitis virus</i>	<i>266</i>
<i>Future of viral-mediated oncolysis.....</i>	<i>266</i>
Vaccination for glioblastoma.....	266
7. Markets for Drug Delivery in CNS Disorders.....	268
Introduction	268
Methods of calculation of CNS drug delivery markets	268
Markets for CNS drug delivery technologies	268
Drug delivery share in selected CNS markets.....	269
CNS share of drug delivery technologies	269
Geographical distribution of CNS drug delivery markets	270
Impact of improved drug delivery on CNS drug markets.....	271
Neurodegenerative disorders	271
<i>Alzheimer disease</i>	<i>271</i>
<i>Parkinson disease</i>	<i>271</i>

Huntington disease	271
Amyotrophic lateral sclerosis	272
Epilepsy.....	272
Migraine and other headaches	272
Stroke	273
Central nervous system trauma	273
Multiple sclerosis.....	273
Brain tumors	274
Limitations of the current drug delivery technologies for CNS	274
Unmet needs in CNS drug delivery technologies	274
Regulatory considerations for drugs that cross the BBB	275
Public-private collaboration for transfer of research to the clinic	276
Future strategies for expanding CNS drug delivery markets	276
Education of neurologists	276
Demonstration of the advantages of the newer methods of delivery	277
Rescue of old products by novel drug delivery methods	277
Facilitation of the approval process of new drugs	277
8. Companies	278
Introduction	278
Profiles of companies.....	278
Collaborations.....	364
9. References.....	368

Tables

Table 1-1: Landmarks in the development of drug delivery to the CNS	18
Table 2-1: Proteins expressed at the neurovascular unit	31
Table 2-2: Transporters that control penetration of molecules across the BBB	36
Table 2-3: Enzymes that control the penetration of molecules across the BBB	40
Table 2-4: Factors that increase the permeability of the BBB.....	46
Table 2-5: Diseases with associated disturbances of BBB	47
Table 3-1: Various methods of drug delivery to the central nervous system	64
Table 3-2: Drugs available for intrathecal administration	75
Table 3-3: Investigational drugs administered by intrathecal route	75
Table 3-4: Strategies for drug delivery to the CNS across the BBB	81
Table 3-5: Specific inhibitors of P-glycoprotein in clinical development	89
Table 3-6: Molecules attached to Trojan horses injected intravenously for CNS effect.....	94
Table 3-7: Examples of controlled and sustained release drug delivery for CNS disorders	108
Table 3-8: Novel methods of delivery of drugs for CNS disorders	109
Table 3-9: Indications for the clinical applications of NTFs in neurologic disorders	114
Table 3-10: Methods for delivery of neurotrophic factors to the CNS	114
Table 4-1: Methods for delivering cell therapies in CNS disorders.....	125
Table 4-2: Classification of methods of gene therapy.....	129
Table 4-3: Methods of gene transfer as applied to neurologic disorders	130
Table 4-4: Potential indications for gene therapy of neurologic disorders	135
Table 4-5: Companies developing cell/gene therapies for CNS disorders	137
Table 4-6: Methods of antisense delivery as applied to the CNS	139
Table 5-1: Strategies for the treatment of Parkinson's disease	146
Table 5-2: Drug delivery systems for Parkinson's disease	148
Table 5-3: Types of cell used for investigative treatment of Parkinson's disease	153
Table 5-4: Status of cell therapies in development for Parkinson's disease	153
Table 5-5: Gene therapy techniques applicable to Parkinson disease	159
Table 5-6: Companies developing gene therapy for Parkinson's disease.....	163
Table 5-7: Classification of pharmacotherapy for Alzheimer disease	164
Table 5-8: Novel drug delivery methods for Alzheimer disease therapies	165
Table 5-9: Classification of neuroprotective agents for amyotrophic lateral sclerosis.....	173
Table 5-10: Methods of delivery of therapies in development for ALS	174
Table 5-11: Classification of treatments for stroke	178
Table 5-12: Treatments of stroke involving innovative drug delivery methods	179
Table 5-13: Drug delivery for prevention of carotid artery restenosis after angioplasty	181
Table 5-14: Gene transfer in animal models of carotid artery restenosis	187
Table 5-15: Neuroprotective gene transfer strategies in models of cerebral ischemia	189
Table 5-16: Gene Therapy for reducing cerebral infarction in animal stroke models.....	189
Table 5-17: Pharmacological agents for treatment of cerebral vasospasm	191
Table 5-18: Gene therapy strategies for vasospasm	192
Table 5-19: A classification of drug delivery methods used in management of pain	203
Table 5-20: Spinal administration of drugs for pain	208

Table 5-21: Investigational drugs for pain administered by intrathecal route	209
Table 5-22: Current management of migraine	214
Table 5-23: Novel drug delivery methods for migraine	214
Table 6-1: Innovative methods of drug delivery for glioblastoma	238
Table 6-2: Strategies for gene therapy of malignant brain tumors.....	256
Table 7-1: Share of drug delivery technologies in selected CNS markets: 2020-2030	269
Table 7-2: CNS market share of drug delivery technologies 2020-2030	270
Table 7-3: Value of CNS drug delivery in the major world markets from 2020-2030.....	270
Table 7-4: Limitations of the current drug delivery technologies for CNS.....	274
Table 8-1: Collaborations of companies in CNS drug delivery	364

Figures

Figure 1-1: Interaction of neurotransmitters with receptors	22
Figure 2-1: The neurovascular unit	30
Figure 2-2: Various forms of passage of substances across the blood brain barrier.....	36
Figure 2-3: Disruptive vs non-disruptive changes in BBB as response to disease.....	45
Figure 2-4: Role of BBB models for drug delivery in preclinical CNS drug development	59
Figure 3-1: Routes of drug delivery to the brain	65
Figure 3-2: Extracellular mechanism for drug transportation to the brain following intranasal administration.....	66
Figure 3-3: Penetration of CSF into spinal cord	74
Figure 3-4: Disposition of opioids after intrathecal administration	77
Figure 3-5: Use of receptor-mediated transcytosis to cross the BBB	96
Figure 3-6: Nanotechnology-based strategies for delivery of BDNF to the CNS	120
Figure 5-1: Oral versus transdermal administration of a drug in Parkinson's disease	151
Figure 5-2: Effect of tyrosine hydroxylase gene delivery on dopamine levels	160
Figure 5-3: Trojan horse approach for delivery of AGT-181 to the brain.....	224
Figure 6-1: A concept of targeted drug delivery to glioblastoma across the BBB	241
Figure 6-2: Mechanism of antitumor effects of poliovirus-based vaccine for glioblastoma.....	263
Figure 7-1: Unmet needs in the CNS drug delivery technologies	275