

Pain Therapeutics

Drugs, Markets & Companies

By

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

November 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 received graduate training in both Europe and US. He has held academic positions in several countries and is a Fellow of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians of UK. During his active neurosurgical career, Prof. Jain was involved in the management of pain. He has been working in the biotechnology/biopharmaceuticals industry for several years and currently is the CEO at Jain PharmaBiotech.

Prof. Jain is an Associate Editor of MedLink Neurology, an electronic encyclopedia of neurology published by Medlink Corporation (San Diego, California) where he is also the author in charge of writing and yearly update of 163 articles including those on treatment of pain.

Prof. Jain's 478 publications include 30 books (6 as editor + 24 as author) and 50 special reports which have covered important areas in biotechnology, gene therapy and biopharmaceuticals. He has also written a textbook of gene therapy, which is the first book on this subject to be translated into the Chinese language. A book on gene therapy companies was published in 2000 by John Wiley & Sons and the updated version has been incorporated into a report on Gene Therapy published by Jain PharmaBiotech in 2014. Prof. Jain has edited "Drug Delivery Systems" (Humana/Springer 2008, 2nd ed 2014, 3rd edn 2019 in preparation) and "Drug Delivery to the Central Nervous System" (Humana/Springer 2010). His other recent books include "Handbook of Nanomedicine" (Springer/Humana 2008; Chinese edition, Peking University Press 2011, 2nd ed Springer 2012, 3rd ed 2017), "Textbook of Personalized Medicine" (Springer 2009; Japanese ed 2012; 2nd ed Springer, 2015), "Handbook of Biomarkers" (Springer 2010; Chinese edition, Chemical Industry Press 2016, 2nd ed Springer, 2017), "Handbook of Neuroprotection" (Springer 2011, 2nd edn 2019, in preparation), "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 edited "Applied Neurogenomics" (Springer 2015).

The pain report is an update with inclusion of commercial information in an earlier publication titled "Pain Therapeutics: A strategic re-evaluation" published by Reuter's Business Insight/Datamonitor UK in 2000. Other reports written by Prof. Jain in the past have been published by PJB Publications, D & MD, Informa, and Decision Resources Inc. This is one of the in-house publications of Jain PharmaBiotech that are constantly updated.

November 2018
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

0. Executive Summary	18
1. Basic Aspects of Pain	20
Introduction	20
Historical aspects of pain	20
Pain definitions	22
A glossary of terms relevant to pain	23
Pain classification and description	23
Neuropathic pain	24
<i>Refractory neuropathic pain</i>	<i>25</i>
<i>Classification of neuropathic pain according to levels</i>	<i>25</i>
Cancer pain	26
<i>Bone pain in cancer</i>	<i>28</i>
Complex regional pain syndrome	28
Mechanisms of pain	29
Pain pathways	29
<i>Role of nociceptors in pain transmission</i>	<i>31</i>
Gate control and neuromatrix theories of pain	31
Pain mediators	32
Modulation of pain by pictures associated with social contacts	33
Modulation of pain by emotions	33
Role of the sympathetic nervous system in pain	33
Pathomechanism of inflammatory pain	33
Pathomechanism of visceral pain	34
Pathomechanism of neuropathic pain	35
<i>Role of intact nerve fibers in neuropathic pain</i>	<i>35</i>
<i>Chemokines as mediators of neuropathic pain</i>	<i>35</i>
<i>Chemotherapy-induced neuropathic pain</i>	<i>36</i>
<i>CNS innate immunity and neuropathic pain</i>	<i>36</i>
<i>Cytokines as mediators of neuropathic pain</i>	<i>36</i>
<i>Free radicals in generation of neuropathic pain</i>	<i>36</i>
<i>GABA deficiency in neuropathic pain</i>	<i>37</i>
<i>Genetic basis of neuropathic pain</i>	<i>37</i>
<i>Gene expression changes in neuropathic pain</i>	<i>37</i>
<i>Glial activation and neuropathic pain</i>	<i>38</i>
<i>Immune cell-derived opioids and neuropathic pain</i>	<i>38</i>
<i>Spinal leptin and neuropathic pain</i>	<i>38</i>
<i>Tetrahydrobiopterin regulates neuropathic pain sensitivity</i>	<i>39</i>
Pathomechanism of migraine	39
Role of the immune system in pain	40
Pain and itch	40
<i>Pathomechanism of itch</i>	<i>41</i>
<i>Clinical aspects of itch</i>	<i>42</i>
Molecular pathophysiology of pain	42
Role of ion channels in pain	42
<i>Acid-sensing ion channels</i>	<i>42</i>
<i>Calcium channels in pain</i>	<i>43</i>
<i>P2X3 ion channels</i>	<i>43</i>
<i>Potassium ion channels</i>	<i>44</i>
<i>Sodium ion channels in pain</i>	<i>44</i>
<i>TRP ion channels in pain</i>	<i>45</i>
Genetic basis of pain	46
<i>Alternative RNA splicing and pain</i>	<i>47</i>
<i>Study of genes in pain</i>	<i>47</i>
<i>Pain as a channelopathy</i>	<i>48</i>
Pain in the brain	48
<i>Effect of chronic pain on opioid receptors in the brain</i>	<i>49</i>
<i>Neuropathic pain-induced morphological changes in the brain</i>	<i>49</i>
Change from acute to chronic pain	49
<i>Acute versus chronic pain</i>	<i>49</i>
<i>Descending facilitatory modulation of pain</i>	<i>50</i>
<i>Development of chronic pain following severe accidental injury</i>	<i>50</i>
<i>Pain and transcriptional repressor DREAM</i>	<i>50</i>
<i>Role of neuronal plasticity in pain</i>	<i>51</i>
<i>Role of epigenetics in development of chronic pain</i>	<i>51</i>
<i>Concluding remarks on evolution of acute pain into chronic pain</i>	<i>51</i>
Neurochemistry of pain	52
<i>Molecular elements of pain in the peripheral nervous system</i>	<i>52</i>

<i>Molecular elements of pain in the central nervous system</i>	53
<i>Opioid receptors</i>	53
<i>Role of AMPA receptors in chronic pain</i>	54
<i>Kinins</i>	54
<i>Serotonin</i>	54
<i>Substance P</i>	55
<i>Excitatory amino acids</i>	55
<i>Role of nitric oxide in pain</i>	55
<i>Prostaglandins</i>	56
<i>Endocannabinoids</i>	57
<i>Protein kinase C</i>	57
<i>Adenosine and adenosine receptors</i>	57
<i>Vitamin D and pain</i>	58
<i>Vanilloid receptor</i>	58
<i>TRPA₁ and TRPV₁ receptors</i>	58
<i>Endothelin-B receptors</i>	60
<i>Nerve growth factor and pain</i>	60
<i>Adrenomedullin as a pain-related peptide</i>	60
Biomarkers of pain	61
<i>Biomarkers of visceral pain</i>	61
2. Assessment of Pain and Analgesics	62
Introduction	62
Animal models of pain	62
An overview	62
Selection of animal species as models for pain	62
Types of noxious stimuli	63
Animal models of neuropathic pain	63
Animal models of arthritis	63
Animal models of peripheral neuropathy	64
Limitations of current pain models	64
NeuroDigm GEL Model™ of neuropathic pain	65
Ethical issues concerning animal pain models	65
Medical evaluation of pain	65
Chronic pain as a manifestation of various diseases	65
Assessment of pain patients	66
Medical examination	66
Measurement of pain	67
Quality of pain intensity assessment in clinical research studies	68
Quantitative sensory testing	69
Pain measurement tools for neonates and children	69
Quantitative sensory testing	70
Microneurographic recordings	70
Psychological assessment of pain	71
Testing for in vivo pain processing	71
Brain imaging in pain	71
<i>fMRI for study of pain</i>	71
<i>PET for study of pain</i>	71
<i>PET correlated with fMRI and evoked potentials</i>	72
Patient outcomes and quality of life during treatment for chronic pain	72
Collection and analysis of data on pain patients	73
Evaluation of analgesics in humans	73
Early phase clinical trials of analgesics in humans	73
Design of clinical trials for pain	74
Assessment of neuropathic pain	75
Transdermal electrical stimulation for study of chronic pain	75
Placebo effect in pain	76
Role of electronic pain recording in determination of the placebo effect	76
Outcome measures for chronic pain trials	76
Pain, pain therapies and cognitive function	77
3. Pharmacotherapy of Pain	78
Introduction	78
Mechanism of action of currently used pain medications	78
Non-steroidal antiinflammatory drugs	79
COX-2 inhibitors	79
<i>Celecoxib</i>	80
<i>Metamizole</i>	81
<i>Nimesulide</i>	81
<i>Rofecoxib</i>	81
<i>Valdecoxib</i>	82

<i>Lumiracoxib</i>	82
<i>Side effects of COX inhibitors</i>	82
<i>Innovative COX-2 inhibitors in development</i>	84
Acetaminophen	85
Antioxidants as analgesics	85
Opiates and opioids	85
Morphine	86
Codeine	86
Tramadol	87
Innovations in opioid therapy	87
<i>Oral transmucosal fentanyl</i>	88
<i>Use of opioids for chronic non-cancer pain</i>	88
Opioid receptor modulation for visceral pain	88
Opiorphin	89
Sufentanil	89
N-methyl-D-aspartate receptor antagonists	89
Ketamine	89
CNS 5161	90
Triptans for treatment of non-migrainous pain	90
Capsaicin	91
NGX-4010	91
Local anesthetics	91
Topical application	91
Nerve blocks	92
<i>Injection of local anesthetics for analgesia</i>	92
<i>Ultrasound-guided nerve blocks</i>	92
Topical salicylates for the treatment of pain	92
Topical rubefaciants for acute and chronic pain in adults	93
Adjunctive analgesics	93
Antidepressants	93
<i>Mechanism of analgesic action of antidepressants</i>	94
Antiepileptic drugs	95
<i>Mechanism of action of antiepileptic drugs in neuropathic pain</i>	96
<i>Carbamazepine</i>	97
<i>Gabapentin</i>	97
<i>Lamotrigine</i>	97
<i>Phenytoin</i>	98
<i>Pregabalin</i>	98
<i>Topiramate</i>	99
<i>Valproic acid</i>	99
<i>Other antiepileptic drugs</i>	100
Clonidine	100
Baclofen	100
Corticosteroids	101
Calcitonin	101
Bisphosphonates	101
Botulinum toxins	102
Analgesic effect of botulinum toxin A	102
Engineered botulinum toxin	102
Analgesics from traditional medical systems	103
Herbs and other plants	103
Analgesics derived from cobra toxin	104
4. Management of Pain	106
Introduction	106
Sites for pain management	106
Self-medication at home	106
Physicians' offices	106
Major hospitals	106
Pain centers	107
Non-pharmacological approaches to pain	107
Alternative medicine	107
<i>Acupuncture</i>	108
<i>Aromatherapy</i>	108
<i>Self-Controlled Energo Neuro Adaptive Regulation</i>	109
Behavioral therapy	109
<i>Cognition and pain</i>	109
<i>Control over brain activation and pain by using functional MRI</i>	109
<i>Mindfulness meditation for relief of chronic pain</i>	110
<i>Thermal-grill illusion</i>	110
<i>Virtual reality therapy</i>	110

Local application of heat	110
Transcutaneous nerve stimulation	111
Non-invasive brain stimulation techniques for chronic pain	111
<i>Transcranial magnetic stimulation</i>	111
<i>Cranial electrotherapy stimulation</i>	112
Neurosurgery for pain relief	112
<i>Ablative procedures on the nervous system</i>	112
<i>Procedures on peripheral, spinal and cranial nerves</i>	112
<i>Vagal nerve stimulation for control of pain</i>	113
<i>Neuromodulation</i>	113
<i>Spinal cord stimulation</i>	114
<i>Brain stimulation</i>	115
<i>Implantation of drug delivery devices</i>	116
Management of special types of pain	116
Acute pain	116
<i>Management of acute renal colic: NSAIDs vs. opioids</i>	116
<i>Combination of opioids and NSAIDs for acute pain</i>	116
<i>Reasons for inadequate management of acute pain</i>	117
Perioperative pain management	117
<i>Devices for delivery of analgesics in the postoperative period</i>	118
<i>Drug combination for perioperative pain</i>	119
<i>Gabapentin for reduction of postoperative pain</i>	119
<i>Ketamine for perioperative pain</i>	119
<i>Opioids for perioperative pain</i>	119
<i>Perioperative pain in neurosurgery</i>	120
<i>Prolonged duration local anesthesia</i>	120
<i>Concluding remarks on the management of postoperative pain</i>	121
Pain in the intensive care unit	121
Pain associated with sports and exercise	122
Pain associated with trauma	122
Chronic pain and sleep	123
Chronic abdominal pain	123
Functional somatic syndromes	123
Fibromyalgia syndrome	124
<i>Pathomechanism of FMS</i>	124
<i>Management of FMS</i>	125
<i>Non-pharmacological therapies for FMS</i>	125
<i>Pharmacotherapy of FMS</i>	125
<i>Concluding remarks on management of FMS</i>	127
Erythromelalgia	127
Irritable bowel syndrome	127
<i>Opioids for IBS</i>	128
<i>Pregabalin for IBS</i>	129
<i>Tricyclic antidepressants for IBS</i>	129
<i>Serotonin-modulating drugs for IBS</i>	129
Musculoskeletal pain	129
Myofascial pain syndrome	130
<i>Non-pharmacological methods of treatment of MPS</i>	130
<i>Pharmacotherapy of MPS</i>	130
Osteoarthritis	131
<i>Pain aggravates osteoarthritis by crosstalk between CNS and the joint</i>	132
<i>Management of osteoarthritis</i>	133
Rheumatoid arthritis	134
<i>Management of pain in rheumatoid arthritis</i>	134
<i>Disease modifying therapies in rheumatoid arthritis</i>	134
<i>Resurgence of interest in gold-based treatments for RA</i>	136
Backache and sciatica	136
<i>Lumbar disc disease and sciatica</i>	137
<i>Management of back pain with analgesics</i>	138
<i>Miscellaneous medical therapies for backache and sciatica</i>	139
Neck pain	139
Chronic pelvic pain	140
<i>Prostatitis</i>	140
Cancer pain	140
<i>Adjuvant drugs for cancer pain</i>	141
<i>Alternative non-pharmacological methods</i>	141
<i>Anesthetic techniques</i>	142
<i>Management of bone pain in cancer</i>	142
<i>Non-opioid analgesics for cancer pain</i>	142
<i>Opioid treatment of cancer pain</i>	142
<i>Opioid breakthrough pains</i>	144

<i>Opioid-induced enhancement of cancer growth and its prevention</i>	144
<i>Opioids delivery methods for cancer pain</i>	144
<i>Opioid administration through implanted drug delivery devices</i>	145
<i>Radiation therapy</i>	145
<i>Surgical methods of cancer pain relief</i>	146
<i>Conclusions regarding management of cancer pain</i>	146
Chronic non-malignant pain.....	146
Headache.....	147
<i>Cluster headache</i>	148
<i>Chronic daily headache</i>	148
<i>Indomethacin-responsive headache</i>	149
<i>Occipital neuralgia</i>	149
<i>Paroxysmal hemicrania</i>	150
<i>Tension headache</i>	150
Migraine.....	150
<i>Management of acute migraine</i>	150
<i>Chronic migraine</i>	154
<i>Pediatric migraine</i>	155
<i>Status migrainosus</i>	155
<i>Migraine prophylaxis</i>	156
<i>Non-pharmacological approaches to migraine</i>	157
Trigeminal neuralgia.....	158
Dental pain.....	159
Neuropathic pain.....	159
<i>Pathogenesis of neuropathic pain</i>	159
<i>Chronobiology of neuropathic pain as guide to therapy</i>	160
<i>Management of neuropathic pain based on mechanism</i>	160
<i>Guidelines for the management of neuropathic pain</i>	161
<i>Pharmacotherapy of neuropathic pain</i>	161
<i>Evidence-based management of neuropathic pain</i>	163
Management of central neuropathic pain.....	164
<i>Neurosurgical approaches to central neuropathic pain</i>	164
<i>Management of neuropathic pain in syringomyelia</i>	165
<i>Neuropathic pain associated with spinal cord injury</i>	165
Management of peripheral neuropathic pain.....	165
<i>Truncal neuropathic pain</i>	166
<i>Management of postsurgical peripheral neuropathic pain</i>	166
<i>Management of chemotherapy-induced pain</i>	166
<i>Morton's neuroma</i>	167
<i>Management of peripheral diabetic neuropathy</i>	167
<i>Postherpetic neuralgia</i>	169
<i>Treatment of complex regional pain syndrome</i>	171
<i>An algorithm for the management of peripheral neuropathic pain</i>	172
Phantom limb pain.....	173
<i>Pathomechanism of phantom limb pain</i>	173
<i>Management of phantom limb pain</i>	173
Painful neuromas following amputation.....	175
Pain and depression.....	176
<i>Neurochemical link between pain and depression</i>	176
<i>Management of chronic pain and depression</i>	177
Miscellaneous painful conditions.....	177
<i>Burning mouth syndrome</i>	177
<i>Chronic unstable angina</i>	178
<i>Mastalgia</i>	178
<i>Ophthalmic pain</i>	179
<i>Pain in Parkinson's disease</i>	179
Pain in sickle cell disease.....	179
Management of chronic unexplained pain.....	180
Management of itching.....	180
<i>Topical applications for itching</i>	181
<i>Systemic therapies for itching</i>	182
<i>Non-pharmacological therapies for itch</i>	182
Management of pain in special population groups.....	182
Racial and ethnic differences in pain management.....	182
Pain in neonates.....	183
Management of pain in children.....	183
<i>Misuse of codeine in children</i>	185
Management of pain in the elderly.....	185
Management of pain in women.....	186
<i>Reasons for increased pain perception in women</i>	186
<i>Chronic pelvic pain in women</i>	187

<i>Gender differences in response to analgesics</i>	187
<i>Considerations for pain management in women</i>	187
Management of pain in neurologically handicapped persons.....	188
Management of pain in the cognitively impaired elderly people.....	188
Management of pain in brain-damaged minimally conscious patients.....	189
Management of pain in the terminally ill.....	189
Problems in the management of pain	189
Inadequate pain management.....	189
Problems with use of opioids.....	190
<i>Guideline for use of opioids</i>	191
<i>Opioid regulations</i>	192
<i>Opioids alternatives</i>	192
Excessive prescription of gabapentinoids.....	193
<i>Problems with use of gabapentinoids</i>	193
Patterns of analgesic consumption in France vs other European countries.....	193
Suggestions for improvement of pain management by healthcare providers.....	194
<i>Management of neuropathic pain refractory to first line treatment</i>	195
<i>Multidisciplinary approaches to pain management</i>	196
<i>Pain as the fifth vital sign</i>	196
<i>Reassessment of management of chronic pain</i>	196

5. Drug Delivery for Pain	199
Introduction	199
Intra-articular injection for relief of joint pain	200
Delivery of analgesics to peripheral nerves	200
Controlled release drug delivery for pain	201
Accelerating the effect of subcutaneous morphine.....	201
Controlled drug delivery at site of pain.....	201
Oral extended release opioids.....	202
<i>Extended release oral morphine</i>	202
<i>Controlled release oxycodone</i>	202
<i>Extended release oxymorphone</i>	202
<i>Oral extended release tramadol</i>	203
Extended release gabapentin.....	203
Use of nanotechnology for drug delivery for pain.....	203
Non-injection methods of delivery of analgesics	204
Topical applications for pain.....	205
<i>Topical local anesthetics</i>	205
<i>Topical NSAIDs</i>	205
<i>Topical and transdermal diclofenac</i>	206
<i>Topical application for postoperative pain</i>	206
Needle-free drug delivery for pain.....	206
<i>Glide SDI® solid dose injector</i>	207
<i>SUMAVEL™ DosePro™ needle-less injection</i>	207
Transdermal drug delivery for pain.....	207
<i>Relief of pain associated with minor medical procedures</i>	207
<i>Transdermal fentanyl</i>	208
<i>Transdermal ketoprofen</i>	209
<i>Transdermal nitroglycerine as an adjuvant to opioids</i>	210
<i>Transdermal buprenorphine</i>	210
<i>Transdermal trans-capsaicin</i>	210
<i>Powder Injection Systems</i>	210
Intranasal delivery of analgesics.....	211
<i>Intranasal morphine</i>	211
<i>Intranasal morphine derivatives</i>	212
<i>Intranasal fentanyl</i>	212
<i>Intranasal buprenorphine</i>	213
<i>Intranasal ketamine</i>	213
<i>Intranasal ketorolac</i>	213
<i>Nasal formulations for migraine</i>	214
Oral spray formulations for migraine.....	214
Delivery of analgesics by inhalation.....	214
Buccal transmucosal and sublingual delivery of analgesics.....	215
<i>Application for cancer pain</i>	215
<i>Application for non-cancer pain</i>	216
Pumps for drug delivery in pain.....	216
<i>Patient controlled analgesia</i>	216
<i>Postoperative pain pumps</i>	217
<i>Chronogestic (sufentanil) Pain Therapy System</i>	218
<i>PatchPump</i>	218
Intrathecal delivery of analgesics	219

Anatomical & physiological aspects of intrathecal drug delivery	219
Pharmacokinetics of intrathecal drug delivery	220
Epidural drugs	221
<i>Pharmacokinetics of analgesic drugs following epidural injection</i>	221
<i>Epidural glucocorticoids</i>	221
<i>Epidural etanercept</i>	222
<i>Epidural morphine</i>	222
Intrathecal drugs	222
<i>Intrathecal adenosine</i>	223
<i>Intrathecal baclofen</i>	224
<i>Intrathecal fadolmidine</i>	224
<i>Intrathecal lidocaine</i>	224
<i>Intrathecal magnesium sulfate</i>	225
<i>Intrathecal midazolam</i>	225
<i>Intrathecal opioids</i>	225
<i>Intrathecal neostigmine</i>	226
<i>Intrathecal octeoride</i>	226
<i>Intrathecal non-NMDA antagonists</i>	226
<i>Intrathecal prostaglandin antagonists</i>	227
<i>Intrathecal resiniferatoxin</i>	227
<i>Intrathecal ziconotide</i>	227
Combinations of intrathecal agents for relief of pain	228
Pumps for intrathecal delivery of analgesics	228
Complications of intrathecal delivery of analgesics	229
Concluding remarks on intrathecal delivery of analgesic agents	230
Intracerebroventricular morphine for pain	230
Development of drug delivery systems for pain therapy	230
Delivery of analgesics to the CNS across the blood brain barrier	230
Drug delivery systems in clinical trials	231
6. Drug Development for Pain.....	235
Introduction	235
Current research goals	235
An ideal analgesic	235
Challenges and prospects of pain therapeutic development	236
Priorities in pain research strategy in the US	236
Pain R & D goals in the pharmaceutical industry	237
Non-pharmacological therapies for pain	237
Drugs in development for pain.....	237
Drug targets in the spinal cord	238
Drug targets in the brain	238
Molecular targets for analgesic drugs	239
Activation of P2X7 receptors.....	239
Alfa2-adrenergic receptor agonists	239
Angiotensin II type 2 receptor	239
Anti-NGF strategies	240
Bradykinin antagonists	240
Cannabinoids.....	240
<i>Cannabinoid receptor agonists</i>	241
<i>Cannabidiol</i>	243
<i>Cannabinor</i>	243
<i>Nabilone</i>	244
Capsaicin and VR1 receptor-based analgesics	244
<i>Vanilloid (capsaicin) receptor antagonists</i>	245
<i>VR1 receptor agonists</i>	245
CCR2 receptor blockade.....	245
Cholecystokinin antagonists	245
Cholinergic receptor agonists.....	246
Conotoxins as analgesics	246
Corticotropin-releasing factor	247
FAAH inhibitors.....	248
<i>PF-3845</i>	248
<i>URB597</i>	248
FKBP51 as a target for treatment of chronic pain	249
Free radical scavengers as analgesics	249
<i>Superoxide dismutase mimetics</i>	249
GABA analogs.....	250
<i>Subtype-selective GABAergic drugs</i>	250
Glutamate receptor antagonists	250
<i>NMDA receptor modulation for neuropathic pain</i>	250
<i>Alternatives to direct blocking of NMDA receptors</i>	251

<i>Glycine antagonists</i>	251
<i>Metabotropic glutamate receptors</i>	251
Histogranin-like compounds for the management of pain	252
Ion channels as targets for analgesic drugs	252
<i>Acid-sensing ion channels as drug target</i>	253
<i>Calcium channel blockers</i>	253
<i>HCN1 channels as targets for propofol analogs for neuropathic pain</i>	254
<i>P2X ion channel receptor antagonists</i>	254
<i>Sodium channel modulation</i>	254
Mas-related GPCR agonists.....	255
Microsomal prostaglandin E synthase inhibitors	255
NAALADase inhibitors	256
Neuropeptide receptor antagonists for improving the efficacy of opioids.....	257
Neurotrophic factor-based pain therapeutics.....	257
<i>Glial cell line-derived neurotrophic factor</i>	257
<i>Nerve growth factor antagonists</i>	257
Newer COX inhibitors	258
<i>COX-3 inhibitors</i>	258
<i>Dual cyclooxygenase/lipoxygenase inhibitors</i>	258
Nicotinic acetylcholine receptors	259
<i>Mode of action of nACh/neural nicotinic receptor agonists</i>	259
<i>Potential of central nACh/neural nicotinic receptor agonists</i>	259
Nitric oxide-based analgesics.....	260
<i>Nitric oxide-releasing NSAIDs</i>	260
<i>Pharmacology of NO-SAIDs</i>	261
<i>COX-inhibiting nitric oxide donors</i>	261
<i>NO-donating structures to extend life cycle of existing analgesics</i>	262
<i>Nitric oxide mimetics</i>	262
<i>Neuronal nitric oxide synthase inhibitors</i>	262
Norepinephrine transporter inhibition	263
Opioid peptide receptors ligands	263
<i>Buprenorphine</i>	264
<i>Nociceptin</i>	264
<i>Opioids with unique receptor characteristics</i>	264
<i>Tapentadol</i>	265
Opioid analgesics acting outside the CNS	265
<i>Oliceridine</i>	265
<i>Opioid analgesics acting at peripheral receptors</i>	266
<i>Peripherally acting mu-opioid receptor agonists</i>	266
<i>Targeting of opioid peptide-containing immune cells</i>	266
<i>Advantages of peripherally selective opioid drugs</i>	267
Resolvins	267
Somatostatin analogs	267
Substance P and neurokinin receptor antagonists.....	268
Substance P-Saporin	268
Targeting prostanoid synthesis	269
Tetrodotoxin based analgesics	269
TRPV1 modulators.....	270
<i>TRPV1 antagonists</i>	270
<i>TRPV1 agonists</i>	271
<i>TRPV1-mediated entry of sodium channel blocker QX-314</i>	272
<i>TRPV1 receptors regulate longevity</i>	272
Tumor necrosis factor- α antagonists.....	272
Biological therapies for pain	273
Cell therapy for pain	273
Cells for delivery of antinociceptive molecules	274
Cell therapy for low back pain.....	274
Cell therapy for knee pain due to degenerative disorders	275
Cell therapy for peripheral neuropathic pain	275
Cell transplantation for relief of pain.....	275
<i>Transplantation of chromaffin cells</i>	275
<i>Transplantation of stem cells</i>	276
<i>Transplantation of astrocytes secreting enkephalin</i>	276
<i>Transplantation of cells for relief of neuropathic pain</i>	277
Concluding remarks on cell therapy for pain	277
Gene therapy for pain	278
Rationale of gene therapy for pain	278
<i>Gene therapy of peripheral neuropathy</i>	278
<i>Gene therapy targeted to neuroimmune component of chronic pain</i>	279
Methods of gene delivery for pain	279
Vectors for gene therapy of pain	280

<i>Vectors for endogenous analgesic production in cranial neuralgias</i>	280
Methods of gene delivery for pain	281
<i>Gene delivery by intrathecal route</i>	281
<i>Gene transfer to the dorsal nerve roots</i>	281
<i>Gene transfer by injections into the brain substance</i>	282
Antisense therapy for pain	282
RNAi-based approaches for pain therapy.....	283
Potential applications of gene therapy for management of pain.....	284
<i>Gene therapy for producing enkephalin to block pain signals</i>	284
<i>Gene therapy for upregulation of BMP in backache</i>	286
<i>Gene therapy for targeting nuclear factor-κB</i>	286
<i>Gene therapy for neuropathic pain</i>	286
<i>Zinc finger DNA-binding protein therapeutic for chronic pain</i>	287
Concluding remarks about gene therapy for pain	287
Preclinical development of pain drugs	288
NGF-blocking antibody.....	288
Prostatic acid phosphatase as a novel analgesic.....	289
Preclinical development of drugs for neuropathic pain.....	289
<i>5-HT receptor agonists</i>	290
<i>A-803467</i>	290
<i>α9α10 antagonists</i>	290
<i>AM1241</i>	291
<i>Artemin/Neuroblastin</i>	291
<i>Capsazepine</i>	292
<i>Central nACh receptor agonists</i>	292
<i>CGP 35024</i>	292
<i>Cortistatin</i>	293
<i>Drugs that suppress glial activation</i>	293
<i>Erythropoietin</i>	294
<i>NO donating GABA-agonist drugs</i>	294
<i>Resiniferatoxin</i>	294
<i>Targeting tumor necrosis factor</i>	295
Future targets for osteoarthritic pain	295
Pain drugs in clinical trials	295
Clinical trials of miscellaneous drugs for pain.....	295
<i>Alvimopan</i>	297
<i>Asimadoline</i>	298
<i>EN3202</i>	298
<i>Oxytrex</i>	298
Drugs in clinical trials for postsurgical pain.....	299
<i>Bicifadine</i>	299
<i>DepoMorphine</i>	300
Cox-2 inhibitors in clinical trials	301
Clinical trials of disease modifying therapies for arthritis	301
Drugs in clinical development for neuropathic pain.....	303
<i>Adenosine A1 agonists for neuropathic pain</i>	305
<i>Ajulemic acid</i>	305
<i>AVP-923 (dextromethorphan + quinidine)</i>	306
<i>Botulinum toxin type A</i>	306
<i>Carisbamate</i>	307
<i>CNV1014802</i>	307
<i>D-amino acid oxidase inhibitors</i>	307
<i>Glyx-13</i>	307
<i>IP-751</i>	307
<i>Lacosamide</i>	308
<i>Oxcarbazepine</i>	308
<i>Perampanel</i>	308
<i>Ralfinamide</i>	308
<i>Retigabine</i>	309
<i>SB-509</i>	309
<i>TC-6499</i>	309
<i>Tebancline</i>	309
<i>Tezampanel</i>	310
<i>Thalidomide</i>	310
<i>TRO19622</i>	310
<i>V3381 (indantadol)</i>	311
<i>XP-13512</i>	311
<i>Zonisamide</i>	311
Drug discovery and development for migraine.....	312
<i>Drugs in clinical development for treatment of migraine</i>	312
<i>Clinical development of preventive therapies for migraine</i>	316

<i>Monoclonal antibodies targeting CGRP for migraine prophylaxis</i>	316
Drug development for visceral pain	317
7. Safety, Regulatory and Legal issues of pain management	319
Safety issues of analgesics	319
Adverse effects of analgesics	319
Gastrointestinal adverse effects of NSAIDs	319
<i>Measures to reduce gastrointestinal adverse effects of NSAIDs</i>	319
Cardiovascular adverse effects of COX-2 inhibitors	319
Adverse effects of opioids	320
<i>Addiction and development of tolerance</i>	320
<i>Chronic pain and opioid addiction</i>	321
<i>Abuse-deterrent opioid products</i>	322
<i>Problems and limitations of abuse-deterrent opioids</i>	323
<i>Complications of opioid abuse in the elderly</i>	324
<i>Hyperalgesia associated with opioids</i>	324
<i>Narcotic bowel syndrome</i>	325
<i>Opioid use disorder</i>	325
<i>Opioid withdrawal</i>	326
<i>Opioid-associated constipation</i>	326
<i>Respiratory depression</i>	326
Role of opioid prescribing patterns of physicians	326
Adverse effects of use of opioids in non-malignant pain	327
<i>Pharmacogenetics of adverse effects of codeine</i>	327
<i>PEGylated naloxol</i>	328
<i>Innovative approaches to modify opioid pharmacology</i>	328
Adverse effects of miscellaneous non-narcotic analgesics	328
<i>Adverse effects of immunosuppressants used for relief of pain</i>	328
<i>Adverse effects of acetaminophen</i>	328
<i>Hyponatremia as an adverse effect of tramadol</i>	329
Regulatory issues	329
Opioids	329
DEA and use of opioids for pain relief in terminal care	329
Cannabinoids	330
FDA and COX-2 inhibitors	330
Legal issues of COX-2 inhibitors	331
Regulatory aspects of opioid safety and abuse	331
Opioid misuse and regulatory agencies	331
FDA measures for safety of opioid use	332
Misuse of fentanyl	333
Regulation of extended release and long-acting opioids	333
Pain relief as a legal right	334
Pain relief and the WHO	335
8. Pain Markets	336
Introduction	336
Epidemiological basis of pain markets	336
Cancer	337
Neuropathic pain	337
Trigeminal neuralgia	337
Arthritis	337
Backache	337
Migraine	338
Multiple sclerosis	338
Irritable bowel syndrome	338
Chronic pelvic pain	338
Chronic pain due to traumatic brain injury	338
Postsurgical pain	339
Economics of pain	339
Pain as a driver of healthcare costs	339
Disability and financial loss through pain	340
Pain markets based on painful conditions	340
The cancer pain market	340
The arthritis pain market	341
Postsurgical pain market	341
The backache market	341
The headache market	342
Neuropathic pain market	342
Fibromyalgia market	343
Pain markets based on drugs	343
Opioids	343

Nonsteroidal antiinflammatory drugs	344
Transdermal pain therapeutics.....	344
Anesthesia	344
Antiepileptic drugs as analgesics	345
Other drugs.....	345
Hospital vs retail share of pain market.....	345
<i>Hospital versus retail opioid market</i>	345
Devices for pain.....	345
Pain markets according to geographical areas.....	346
Cost effectiveness of various approaches	346
Unfulfilled R&D needs in pain therapy	347
Under treatment of pain	347
Unfulfilled needs in drug development for chronic pain	347
Strategies for developing pain markets	348
Finding alternatives to intrathecal administration for chronic pain	348
Development of other applications of analgesic drugs.....	348
Partnership of patients, pharmacists and companies.....	349
Factors that may influence future pain markets	349
Drivers of pain markets	349
Public surveys as indicators of impact of pain on people.....	350
Effect of regulatory reviews on markets for pain products	350
Novel versus older therapies for pain.....	351
9. Future of Pain Therapeutics.....	352
Introduction	352
Advances in the understanding of pain	352
Pathogenesis of chronic pain	352
Role of glia in neuropathic pain.....	352
Molecular and neurobiological techniques.....	353
Improved understanding of cancer pain	354
Advances in drug discovery and development for pain	354
Novel targets for drug discovery for pain	354
<i>PTH2 receptor</i>	354
<i>Modulators of endogenous cannabinoids</i>	355
Application of new technologies to pain therapeutics	355
<i>Application of nanobiotechnology to pain therapeutics</i>	356
<i>Technologies for the manufacture of analgesics</i>	357
Future trends and needs in pain management.....	357
Pain management in future healthcare systems	358
Systems biology approach to pain	358
Personalized management of pain	359
Genetic factors in response to pain.....	360
Genetic mutations with loss of pain	361
Genetic mutations and painful conditions	361
Mechanism-specific management of pain	361
Pharmacogenomics and pharmacogenetics of pain	362
Personalized management of pain with commonly used analgesics.....	362
<i>Pharmacogenomics and pharmacogenetics of opioids</i>	362
<i>Pharmacogenetics of NSAIDs</i>	363
Preoperative testing to tailor postoperative analgesic requirements.....	364
Role of conditioned pain modulation in personalized management of pain	364
Signature of pain on brain imaging.....	364
Strategies for improving pain management.....	365
Research on pain in Europe	365
10. Companies Involved in Pain Therapeutics.....	368
Introduction	368
Profiles of companies.....	368
Collaborations.....	548
11. References.....	554

Tables

Table 1-1: Landmarks in the history of pain therapeutics	21
Table 1-2: Classification of pain	23
Table 1-3: Classification of neuropathic pain	25
Table 1-4: Classification of chronic cancer pain according to cause.....	27
Table 1-5: Percentage of patients with pain according to the type of cancer	28
Table 1-6: Key molecular elements of pain in the peripheral nervous system	52
Table 1-7: Key molecular elements of pain in the central nervous system	53
Table 2-1: IASP guidelines for the use of animals in pain studies	65
Table 2-2: Chronic pain as a manifestation of other diseases.....	66
Table 2-3: Recommendations for assessing patient satisfaction with pain management	72
Table 3-1: Classification of some currently used pain medications according to mechanism.....	78
Table 3-2: Drugs used for the treatment of pain	78
Table 3-3: Selective COX-2 inhibitors in clinical use for pain.....	80
Table 3-4: Antiepileptic drugs with analgesic effect	95
Table 4-1: Non-pharmacological approaches to management of pain	107
Table 4-2: Companies involved in neuromodulation therapy for pain	113
Table 4-3: Reasons for the inadequate management of acute pain.....	117
Table 4-4: Monoclonal antibodies as disease modifying therapies in rheumatoid arthritis	134
Table 4-5: Causes of chronic backache	137
Table 4-6: Management of chronic pelvic pain	140
Table 4-7: Management of pain in cancer	141
Table 4-8: Definitions of tolerance, physiological dependence, withdrawal and addiction.....	147
Table 4-9: A simplified classification of headache	147
Table 4-10: Various methods for the management of acute migraine	151
Table 4-11: Prophylaxis and management of chronic migraine	154
Table 4-12: Evidence-based level of choice of drugs for prophylaxis of migraine	156
Table 4-13: Management of neuropathic pain based on mechanism and diagnosis	161
Table 4-14: Management of central neuropathic pain	164
Table 4-15: Current management of peripheral diabetic neuropathy	167
Table 4-16: Treatment strategies for postherpetic neuralgia.....	169
Table 4-17: Management of complex regional pain syndrome.....	171
Table 4-18: Methods of treating phantom limb pain	173
Table 4-19: Treatment of chronic unexplained pain due to central sensitization	180
Table 4-20: Anti-itching therapies.....	180
Table 4-21: Suggested improvements in the management of pain	194
Table 5-1: A classification of drug delivery methods used in management of pain.....	199
Table 5-2: Selected marketed non-injection drug delivery systems for pain	204
Table 5-3: Approved drugs for spinal administration for pain.....	222
Table 5-4: Off-label intrathecal use of drugs for for pain.....	222
Table 5-5: Experimental studies of intrathecal administration of drugs for analgesia	223
Table 5-6: Intrathecal drugs for pain in clinical trials	223
Table 5-7: Comparison of pharmacokinetics of lipophilic with hydrophilic opioids	225
Table 5-8: Delivery systems for pain (other than intrathecal) in clinical development	232
Table 6-1: Classification of drugs in development for pain.....	237
Table 6-2: Preclinical studies on cannabinoid (CB2) receptor agonists as analgesics.....	242
Table 6-3: Cannabinoid receptor agonists in clinical development as analgesics.....	242
Table 6-4: NO-related therapies for pain.....	260
Table 6-5: Major opioids receptors and their ligands	263
Table 6-6: Strategies to counteract pain at various levels at periphery and in the CNS	269
Table 6-7: Types of TRPV1 antagonists.....	270
Table 6-8: TRPV1 antagonists in clinical trials.....	271
Table 6-9: Biological therapies for pain.....	273
Table 6-10: Experimental gene therapy approaches for relief of pain.....	279
Table 6-11: Selected preclinical approaches to pain therapy.....	288
Table 6-12: Selected preclinical drugs for neuropathic pain	289
Table 6-13: Selected clinical trials of miscellaneous drugs for pain	296
Table 6-14: Selected clinical trials of drugs for postsurgical pain.....	299
Table 6-15: COX-2 inhibitors in clinical development.....	301
Table 6-16: Disease modifying drugs for arthritis in clinical trials	301
Table 6-17: Clinical trials of drugs for neuropathic pain	303
Table 6-18: Selected drugs in clinical development for migraine	312
Table 6-19: CGRP receptor antagonists in clinical development for acute migraine.....	314
Table 6-20: Clinical trials of anti-CGRP monoclonal antibodies for migraine prevention	317
Table 6-21: Therapeutic targets for treating visceral pain	317
Table 7-1: Abuse-deterrent opioid products	322
Table 7-2: Diagnostic criteria for an opioid-use disorder	325
Table 8-1: Market values for various painful conditions 2017-2027	340
Table 8-2: Changes in market shares of drugs for neuropathic pain 2017-2027	342
Table 8-3: Markets for pain according to therapies 2017-2027	343

Table 8-4: Distribution of value of pain therapeutics in major markets 2017-2027	346
Table 8-5: Distribution of value of opioids in major pain markets 2017-2027.....	346
Table 8-6: Distribution of value of NSAIDs in major pain markets 2017-2027.....	346
Table 8-7: Strategies for developing pain markets	348
Table 9-1: P450 isoforms in the metabolism of drugs used in the management of pain.....	362
Table 10-1: Top companies in pain therapeutics	368
Table 10-2: Product pipeline of Adolor Corporation	375
Table 10-3: Selected collaborations in the area of pain management	548

Figures

Figure 1-1: Afferent pain pathways	30
Figure 1-2: Evolution of the gate control theory	32
Figure 1-3: The body self-neurometric.....	32
Figure 1-4: Various ligands and receptors on the peripheral terminals of nociceptive nerve fibers	53
Figure 1-5: Prostaglandin biosynthesis pathway	57
Figure 2-1: Biopsychosocial factors that interact and modulate the experience of pain.....	67
Figure 2-2: Pain intensity scales	68
Figure 3-1: Pathway of metabolism of codein	87
Figure 4-1: The WHO step ladder for pain	143
Figure 4-2: An algorithm for the acute management of migraine	152
Figure 4-3: Neuroimmune activation events leading to sensitization of CNS	160
Figure 4-4: An algorithm for the management of peripheral neuropathic pain.....	172
Figure 4-5: Algorithm for management of patients with chronic pain and depression.....	177
Figure 5-1: Powder Injection Systems	211
Figure 5-2: Penetration of CSF into spinal cord	220
Figure 5-3: Disposition of opioids after intrathecal administration	221
Figure 6-1: Attributes of the ideal analgesic	235
Figure 6-2: Nerve targeting drug delivery system for gene therapy of pain	285
Figure 8-1: Unfulfilled needs in the treatment for chronic pain.....	347
Figure 9-1: Impact of new technologies on pain therapeutics	356
Figure 9-2: Essential components of personalized management of pain	359
Figure 9-3: Genetic and non-genetic factors affecting efficacy and side effects of opioids.....	363