Mechanisms of Vascular Disease:

A Reference Book for Vascular Specialists

22

Edited by Robert Fitridge and Matthew Thompson

Completely Updated Edition 2011

Barr Smith Press

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BARR SMITH PRESS
An imprint of
The University of Adelaide Press

Published in Adelaide by

The University of Adelaide, Barr Smith Press
Barr Smith Library
The University of Adelaide
South Australia 5005
press@adelaide.edu.au
www.adelaide.edu.au/press

The University of Adelaide Press publishes peer-reviewed scholarly works by staff via Open Access online editions and print editions.

The Barr Smith Press is an imprint of the University of Adelaide Press, reserved for scholarly works which are not available in Open Access, as well as titles of interest to the University and its associates. The Barr Smith Press logo features a woodcut of the original Barr Smith Library entrance.

This CIP cataloguing for this work is as follows;

Mechanisms of vascular disease : a reference book for vascular surgeons / Robert Fitridge, Matthew Thompson, [editors].

1. Blood vessels, Diseases.
2. Blood vessels, Surgery.

I. Fitridge, Robert
II. Thompson, M. M.

For the full Cataloguing-in-Publication data please contact National Library of Australia:
cip@nla.gov.au

ISBN (paperback) 978-0-9871718-2-5

Book design: Midland Typesetters
Cover design: Emma Spoehr, based on a diagram by Dave Heinrich of the Medical Illustration and Media Unit, Flinders Medical Centre
Paperback edition printed by Griffin Press, South Australia

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Acknowledgements

The Editors gratefully acknowledge the outstanding contributions of each Author involved in this reference book. We would also like to acknowledge the invaluable efforts of Ms Sheona Page who has worked tirelessly on this project. We would also like to thank Prue Cowled PhD and Ms Cayley Wright for their assistance.

Abbreviation List

a1-PI	a1-protease inhibitor
5-HT	5-Hydroxytryptamine/Serotonin
AAA	Abdominal aortic aneurysm
AAS	Acute aortic syndrome
AAV	Adeno-associated viruses
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ACS	Abdominal compartment syndrome
ACTH	Adrenocorticotropic hormone
ADAMTS	A disintegrin and metalloproteinase with thrombospondin motifs
ADP	Adenosine diphosphate
AIDS	Acquired immune deficiency syndrome
ALI	Acute lung injury
AMP	Adenosine monophosphate
AMPA	α-amino-3 hydroxy-5-methylisoxazole
ANA	Anti-nuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibody
AOD	Aortic occlusive disease
AP1	Activated protein 1
APC	Activated protein C
APC	Antigen presenting cell
APLAS	Antiphospholipid antibody syndrome
ApoAI	Apolipoprotein AI
ApoE	Apolipoprotein E
APS	Antiphospholipid antibody syndrome
APTT	Activated partial thromboplastin time

ARDS	Acute respiratory distress syndrome
AT	Antithrombin
ATP	Adenosine triphosphate
AVP	Ambulatory venous thrombosis
β2-GPI	β2-glycoprotein Ib
bFGF	Basic fibroblast growth factor
BKCa	Large conductance calcium activated potassium channel
BMPs	Bone morphogenetic proteins
BMS	Bare metal stent
CAD	Coronary artery disease
CaM	Calmodulin
CAM	Cell adhesion molecule
cAMP	Cyclic adenosine monophosphate
CCK	Cholecystokinin
cGMP	Cyclic guanine monophosphate
CD	Cluster of differentiation
CD40L	Cluster of differentiation 40 ligand
CEA	Carotid endarterectomy
CETP	Cholesteryl ester transfer protein
CFD	Computational fluid dynamics
CG	Cationized gelatin
CGRP	Calcitonic gene regulated peptide
CHD	Coronary heart disease
CI	Confidence interval
CIMT	Carotid intimal-media thickness
c-JNK	c-Jun N-terminal kinase
CK-MB	Creatinine kinase (Myocardial specific)
CNCP	Chronic noncancer pain
cNOS	Constitutive nitric oxygen synthase enzyme
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CROW	Charcot restraint orthotic walker
CRRT	Continuous renal replacement therapy

CRP	C-reactive protein
CRPS	Complex regional pain syndromes
CT	Computational tomography
CTA	Computed tomographic angiography
CTD	Connective tissue disorders
CTGF	Connective tissue growth factor
CYP	Cytochrome P450
CVD	Cardiovascular disease
CVI	Chronic venous insufficiency
DAG	Diacylglycerol
DES	Drug-eluting stent
DRG	Dorsal root ganglion
DNA	Deoxyribonucleic acid
DSA	Digital subtraction arteriography
DTS	Dense tubular system
DVT	Deep vein thrombosis
EC	Endothelial cell
ECM	Extracellular matrix
EDCF	Endothelium-derived contracting factor
EDH	Endothelium-dependent hyperpolarisation
EDS	Ehlers-Danlos syndrome
EET	Epoxyeicosatrienoic acids
ELAM-1	Endothelial-leukocyte adhesion molecule-1
ELG	Endoluminal grafts
ELISA	Enzyme linked immunosorbent assay
E_K	Equilibrium potential
E_M	Membrane potential
eNOS	Endothelial nitric oxide synthase enzyme
EPC	Endothelial progenitor cells
EPCR	Endothelial protein C receptor
ePTFE	Expanded polytetrafluoroethylene
ERK	Extracellular signal-regulated kinase
ESR	Erythrocyte sedimentation rate

ET	Essential thrombocytosis
ET-1	Endothelin 1
EVAR	Endovascular aortic aneurysm repair
EVLA	Endovenous LASER ablation
FDA	Food and drug administration
FDPs	Fibrin degradation products (soluble)
FGF	Fibroblast growth factor
FGF-2	Fibroblast growth factor 2
FMN	Flavin mononucleotide
FVL	Factor V Leiden
GABA	Gamma-aminobutyric acid
GABA B	Gamma-aminobutyric acid subtype B
G-CSF	Granulocyte colony stimulating factor
GMCSF	Granulocyte-macrophage colony stimulating factor
GP	Glycoprotein
GPCR	G-protein coupled receptor
GSV	Great saphenous vein
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
HIF	Hypoxia inducible factor
HIT	Heparin induced thrombocytopenia
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMG Co-A	Hydroxymethylglutaryl coenzyme-A
HMW	High molecular weight
HPETE	Hydroperoxyeicosatetraenoic acid
HETE	Hydroxyeicosatetraenoic acids
HR	Hazard ratio
hsCRP	High-sensitive C-reactive protein
HSP	Heat shock protein
HUV	Human umbilical vein
IAH	Intra-abdominal hypertension

IAP	Intra-abdominal pressure
IAPP	Intra-abdominal perfusion pressure
ICAM-1	Inter-cellular adhesion molecule-1
ICAM-2	Inter-cellular adhesion molecule-2
ICP	Intra-compartmental pressure
ICU	Intensive care unit
IFN	Interferon
IGF-1	Insulin-like growth factor-1
IHD	Ischemic heart disease
IL	Interleukin
IL-1	Interleukin-1
IL-1α	Interleukin-1 alpha
IL1-β	Interleukin-1 beta
IL-6	Interleukin-6
IL-8	Interleukin-8
ILT	Intraluminal thrombus
IKCa	Intermediate conductance calcium-activated potassium channels
IMH	Intramural haematoma
IMP	Inosine monophosphate
iNOS	Inducible nitric oxide synthase enzyme
IP(3)	1,4,5-inositol triphosphate
IRI	Ischemia reperfusion injury
IVIG	Intravenous pooled immunoglobulin
IVUS	Intravascular ultrasound
KGF	Keratinocyte growth factor
KGF-2	Keratinocyte growth factor-2
LAP	Latency associated peptide
LCS	Limb compartment syndrome
LDL	Low density lipoprotein
LDS	Loeys-Dietz syndrome
LLC	Large latent complex
LEC	Lymphatic endothelial cells

LFA-1	Lymphocyte function-associated antigen-1
LO	Lipoxygenase
LOX	Lysyl oxidase
LOPS	Loss of protective sensation
LPA	Lysophosphatidic acid
LPS	Lipopolysaccharide
LTA	Lipoteichoic acid
LTGFBP	Latent TGF binding protein
MAC-1	Macrophage-1 antigen
MAPK	Mitogen activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
M-CSF	Macrophage-colony stimulating factor
MFS	Marfan syndrome
MHC	Major histocompatibility
MI	Myocardial infarction
MIP-1	Macrophage inflammatory protein-1
MLC_{20}	Myosin light $chain_{20}$
MLCK	Myosin light chain kinase
MLCP	Myosin light chain phosphatase
MMP	Matrix metalloproteinase
MODS	Multiple organ dysfunction syndrome
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MRSA	Methicillin resistant *Staphylococcus aureus*
MRSE	Methicillin resistant *Staphylococcus epidermidis*
MRTA	Magnetic resonance tomographic angiography
MTHFR	Methylenetetrahydrofolate reductase
MT-MMP	Membrane-type MMP
MVPS	Mitral valve prolapse syndrome
NADPH	Nicotinamide adenine dinucleotide phosphate
NGF	Nerve growth factor

NFκB	Nuclear factor kappa B
NiTi	Nitinol
NJP	Non-junctional perforators
NMDA	N-methyl-D-aspartate
NNH	Number needed to harm
NNT	Number needed to treat
NO	Nitric oxide
NOS	Nitric oxide synthase enzyme
NSAID	Non-steroidal anti-inflammatory drug
NV	Neovascularisation
OCP	Oestrogen/progesterone contraceptive pill
OPN	Osteopontin
OPG	Osteoprotegerin
OR	Odds ratio
OxLDL	Oxidised low density lipoprotein
PAD	Peripheral arterial disease
PAF	Platelet activating factor
PAI	Plasminogen activator inhibitor
PAI-1	Plasminogen activator inhibitor-1
PAR	Protease activated receptor
PAR-1	Protease activated receptor-1
PAR-4	Protease activated receptor-4
PAU	Penetrating aortic ulcer
PC	Protein C
PCA	Poly (carbonate-urea) urethane
PCI	Percutaneous coronary intervention (angioplasty)
PCWP	Pulmonary capillary wedge pressure
PDGF	Platelet-derived growth factor
PDGFβ	Platelet-derived growth factor-β
PDS	Polydioxanone
PECAM-1	Platelet-endothelial cell adhesion molecule-1
PEDF	Pigment epithelium-derived factor
PES	Paclitaxel-eluting stent

PET	Positron emission tomography
PF4	Platelet factor 4
PGI_2	Prostacyclin
PGG_2	Prostaglandin G_2
PGH_2	Prostaglandin H_2
$PGEI_2/PGI_2$	Prostaglandin I_2
PGN	Peptidoglycan
PHN	Postherpetic neuropathy
PHZ	Para-anastomotic hyper-compliant zone
PI3K	Phosphatidylinositol 3-kinase
PIP2	Phosphatidylinositol 4,5-bisphosphate
PLC	Phospholipase C
PLOD	Procollagen lysyl hydroxylase
PMCA	Plasma membrane Ca^{2+} APTases
PMN	Polymorphonuclear leukocyte
POSS	Polyhedral oligomeric silsesquioxanes
PPAR	Peroxisomal proliferation activating receptor
PPI	Proton pump inhibitor
PRV	Polycythaemia rubra vera
PS	Protein S
PSGL-1	P-selectin glycoprotein ligand-1
PT	Prothombin time
PTCA	Percutaneous coronary angioplasty
PTFE	Polytetrafluoroethylene
PTS	Post-thrombotic syndrome
PUFA	Polyunsaturated fatty acid
PVI	Primary valvular incompetence
rAAA	Ruptured AAA
Rac	Ras activated cell adhesion molecule
RANTES	Regulated upon activation, normal T cell expressed and secreted
RAS	Renin angiotensin system
RCT	Randomised controlled trial

RF	Rheumatoid factor
RFA	Radiofrequency ablation
rhAPC	Recombinant human activated protein C
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RR	Relative risk
RSD	Reflex sympathetic dystrophy
S1P	Sphingosine-1-phosphate
SAPK	Stress-activated protein kinase
SCF	Stem cell factor
SCS	Spinal cord stimulation
ScvO2	Superior vena cava venous oxygen saturation
SDF-1	Stromal-cell-derived factor-1
SERCA	Sarco/endoplasmic reticulum CaATPases
SEP	Serum elastin peptides
SES	Sirolimus-eluting stent
SEPS	Subfascial endoscopic perforator surgery
SFA	Superficial femoral artery
SFJ	Sapheno-femoral junction
SIRS	Systemic inflammatory response syndrome
SKCa	Small conductance calcium-activated potassium channels
SLE	Systemic lupus erythematosus
SMA	Smooth muscle alpha actin
SMC	Smooth muscle cell
SMP	Sympathetically maintained pain
SNARE	Soluble N-ethylmaleimide-sensitive factor activating protein receptors
SNP	Single nucleotide polymorphisms
SNRI	Serotonin/Noradrenaline reuptake inhibitors
SPJ	Sapheno-popliteal junction
SPP	Skin perfusion pressure
SR	Sarcoplasmic reticulum
SSRIs	Selective serotonin re-uptake inhibitors
SSV	Small saphenous vein

SVT	Superficial thrombophlebitis
STIM1	Stromal interacting molecule 1
TαCE	TNFα converting enzyme
TAAD	Thoracic aortic aneurysm disease
TAD	Thoracic aortic dissection
TAFI	Thrombin-activatable fibrinolysis inhibitor
Tc-99 MDP	Technetium-99 methylene diphosphonate
TCA	Tricyclic antidepressant
TCC	Total contact cast
TCR	T-cell receptor
TENS	Transcutaneous electrical nerve stimulation
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TGF	Transforming growth factor
TGF-α	Transforming growth factor-alpha
TGF-β	Transforming growth factor-beta
TGL	Triglycerides
Th	T helper
TIA	Transient ischemic attack
TIMP	Tissue inhibitors of metalloproteinase
TLR	Toll-like receptors
TNF	Tumour necrosis factor
TNF-α	Tumour necrosis factor-alpha
tPA	Tissue-type plasminogen activator
TRP	Transient receptor potential
TRPC	Transmembrane receptor potential canonical
TRPV1	Transmembrane receptor potential Vanilloid-type
TXA2	Thromboxane A2
uPA	Urokinase
UT	University of Texas
VCAM	Vascular cell adhesion molecule
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor

VEGF-R	Vascular endothelial growth factor receptor
VIP	Vasoactive intestinal peptide
VLA-1	Very late activating antigen-1
VOCC	Voltage operated calcium channels
VPT	Vibratory perception threshold
VSMC	Vascular smooth muscle cells
VTE	Venous thromboembolism
VV	Varicose veins
vWF	von Willebrand factor
XO	Xanthine oxidase

22 • Treatment of Neuropathic Pain

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INTRODUCTION

Neuropathic pain is defined by The International Association for the Study of Pain (IASP) as pain following a primary lesion or dysfunction of the nervous system.[1] It is caused either by peripheral damage with lesions involving peripheral nerves, dorsal root ganglia and the dorsal roots (peripheral neuropathic pain) or by central damage, which may involve injury caused by infarction or trauma of spinal cord or brain (central neuropathic pain).

Neuropathic pain results in persistent pain syndromes that have no biological function, but are difficult to treat and cause great distress to the individual. Neuropathic pain is also referred to as neurogenic pain, deafferentation pain, neuralgia, neuralgic pain and nerve pain.

Neuropathic pain may develop immediately after a nerve injury or after a variable interval. It may be maintained by factors different from the initial cause. It can persist for a long time and is frequently not explained by underlying pathology. Patients are frequently seen by many different specialists and their treatment often fails to resolve the pain. As the pain persists other factors such as environmental, psychological and social stressors become relevant contributors to the overall presentation.

PRINCIPLES OF TREATMENT

Treatment of neuropathic pain is not straightforward. The pain is often refractory to conventional analgesic regimens such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Opioids have only limited efficacy in neuropathic pain as outlined later in this chapter; therefore so called co-analgesics, medications which are not typically used as analgesics, are often the first-line treatment of neuropathic pain.

Increasingly, data from randomised controlled trials (RCTs) and meta-analyses are leading to improvements in management and a more evidence-based approach. A number of recent evidence-based guidelines have been published by various societies and organisations. Of particular value are the guidelines published by the European Federation of Neurological Societies (EFNS)[2] and by the Special Interest Group Neuropathic Pain of the IASP (NeuPSIG).[3]

It is important that patients have realistic expectations regarding treatment efficacy and potential side effects in order to improve

compliance with medication.[4] A balance between these should be achieved on an individual basis. A single drug therapy should be tried before combinations of drugs are started. Non-pharmacological treatments are available that may be appropriate for certain cases. For optimal results a multidisciplinary approach to treatment should be adopted that addresses affective and behavioural changes and disability.

PHARMACOLOGICAL TREATMENT

Opioids

The use of opioids to treat neuropathic pain is controversial. In 1988 a study implied that patients with neuropathic pain did not experience pain relief from opioids.[5] However, this study has been criticised for possible selection bias as most non-responders had previously used morphine without effective results and there was no individual titration of morphine. A number of reasons have been suggested for the relative opioid resistance; these include among others, down-regulation of peripheral and spinal opioid receptors[6,7] and physiological antagonism with up-regulation of cholecystokinin.[8] There is also evidence in animal experiments that long term use of opioids induces a state of CNS hyperexcitability implying that tolerance to opioids may have a pharmacology similar to hyperalgesia.[9] Studies in humans have so far not confirmed these experimental data.

Since then multiple RCTs in neuropathic pain have been conducted with morphine, fentanyl, oxycodone and other opioids. The general consensus is that pain intensity may be relieved by opioids titrated for that individual. This concept was confirmed in a study in which dose responses of opioids in nociceptive and neuropathic pain were compared and higher doses were indeed required in neuropathic pain.[10] A Cochrane Review of the multiple RCTs confirmed significant efficacy of opioids in neuropathic pain.[11]

Recommendations for clinical use of opioids in neuropathic pain

There is now a general consensus that a subset of patients with neuropathic pain benefit from treatment with opioids.[12] However, current guidelines for neuropathic pain treatment do not recommend opioids as a first-line option due to the potential adverse effects and risks of these drugs.[2,3] If a decision to use opioids is made, then the approach to identify these patients and manage their treatment should follow guidelines for the use of opioids in chronic noncancer pain (CNCP).[13,14]

Summarising such guidelines is beyond the scope of this chapter; in brief they usually include a past/present history of drug addiction as a relative contraindication, the need for regular follow-up visits and opioids to be prescribed and supervised by the same doctor. Legal issues with opioid prescriptions are associated with their controlled status, the risk of addiction and abuse and the potential for diversion into illegal channels by selling or passing on to others.[15] Methadone, due to its additional monaminergic and NMDA receptor effects, might be a particularly useful opioid in the setting of neuropathic pain.[16,17]

Tramadol

Mechanism of action

Tramadol is a centrally acting synthetic analogue of codeine; however it is not a conventional opioid as it has relatively low affinity for μ-opioid receptors and is classified by the FDA as an atypical centrally acting analgesic. Tramadol together with its primary active metabolite has

three synergistic mechanisms of action to provide analgesia. It combines weak effects on opioid receptors with monoaminergic mechanisms. Reuptake inhibition of 5-HT and noradrenaline contribute to the anti-nociceptive action of tramadol.[18,19] Tramadol is a racemic mixture with opioid receptor activity and 5-HT reuptake inhibition mainly associated with the (+)-tramadol enantiomer, whereas (-)-tramadol is a reuptake inhibitor of noradrenaline.[20,21] The monaminergic effects suggest a higher analgesic potency of tramadol in neuropathic than in nociceptive pain states; this has been recently confirmed by our group.[22]

Efficacy

Tramadol has been investigated for the treatment of chronic pain in the past. A number of RCTs of tramadol in patients with neuropathic pain have been completed. The first involved 131 patients with diabetic neuropathic pain, 37% patients withdrew, more from adverse effects in the tramadol group and more from lack of efficacy in the placebo group. The tramadol group had significantly more pain relief than placebo.[23] In a subsequent randomised placebo-controlled crossover trial 45 patients with neuropathic pain were studied. Significant reductions in spontaneous and touch-evoked pain were achieved with tramadol.[24]

A meta-analysis of these and other RCTs identified tramadol as an effective treatment for neuropathic pain; or with number needed to treat (NNT) for 50% pain relief of 3.8 with therapeutic effects on paraesthesia and allodynia and a number needed to harm (NNH) of 8.3.[25]

Adverse effects

Tramadol causes less respiratory depression[26] and constipation[27] than conventional opioids. Physical dependence to tramadol use is extremely rare[28] and occurs in the range of 1:100,000 users.[29] Similarly, tramadol has a low abuse potential[30] and its risk of addiction has been rated in the range of 1:100,000.[29,31] For these reasons, tramadol is not under special regulatory control in most countries. Phase IV clinical trials have reported the overall incidence of side-effects from tramadol to be 15.3%.[32] The majority of side-effects were found to be dose dependent.

Recommendations for clinical use of tramadol in neuropathic pain

Experimental evidence and a meta-analysis have shown tramadol to be a particularly useful analgesic in neuropathic pain with a low incidence of adverse effects, mainly of a benign nature. In our experience (and that of many other pain clinics) it is the preferred opioid-like drug in this indication, in particular as a background analgesic in a slow-release preparation. However, it is not a first-line drug in neuropathic pain.[2,3]

Antidepressants

Tricyclic antidepressants (TCAs)

In 1960 Paoli *et al* made the incidental discovery that the tricyclic antidepressant (TCA) imipramine had an analgesic effect.[33] Since then other TCAs and other antidepressants have been evaluated and used for the treatment of neuropathic pain. TCAs are the first class of medication to be proven to be effective for neuropathic pain in a double blind placebo controlled trial.[34] The role of TCAs in the treatment of neuropathic pain is now well established and has the best documented evidence.[35] The overall NNT for neuropathic pain is 3.6 with better efficacy in diabetic neuropathy than in postherpetic neuralgia (PHN).

Amitriptyline is established as the 'gold standard' as it has the most evidence available, especially for the treatment of painful diabetic neuropathy and PHN.[36] However,

amitriptyline and other TCAs have also been evaluated for the relief of pain in peripheral neuropathies and central post stroke pain. In comparative trials no single TCA has been found to be superior for neuropathic pain except in PHN where amitriptyline was found to be superior to maprotiline.[34]

Mechanism of action

Initially it was thought that the analgesic action of TCAs was related to their antidepressant activity. However, it is now clear that there is an independent specific analgesic effect, as the doses used to relieve neuropathic pain are smaller and the onset of analgesic efficacy is faster than an antidepressant effect and analgesia does not appear to depend upon mood improvement in depressed patients.[37,38] In addition, pain relief was found to be independent of any sedative effect.

TCAs are inhibitors of the reuptake of monoaminergic transmitters and this mechanism mediates their analgesic effect by the following presumed mechanisms: [36]

1) Central blockade of monoamine re-uptake, particularly serotonin and noradrenaline, leads to enhancement of the descending inhibitory monoaminergic pathways in the dorsal horn of the spinal cord.
2) Anticholinergic activity reduces firing of central neurones involved in pain, especially after deafferation.

Additionally there may be a number of other contributing mechanisms: moderation of NMDA receptor activity, opioid receptor activity, increase in dopamine or endorphin levels, blockade of central or peripheral histamine receptors, sodium channel blockade and blockade of adrenergic receptors on regenerating sprouts.[36,39]

Adverse effects

The optimum analgesic dose of TCAs can often not be reached due to unpleasant side effects. A systematic review of randomised controlled trials of TCAs used to treat neuropathic pain found that out of 100 patients, 30 had significant pain relief, 30 had minor side effects and 40 had to discontinue their therapy due to side effects.[40] These include:

1) Anticholinergic: dry mouth, constipation, urinary retention and blurred vision.
2) Antihistaminergic: confusion and sedation (the latter may be of benefit)
3) Anti α-adrenergic: postural hypotension and sexual dysfunction.

Cardiac conduction abnormalities may also arise due to the muscarinic anticholinergic actions. Patients at risk should have a pre-treatment ECG as cardiac conduction defects are a contraindication to treatment with TCAs. Another potential problem is overdose where TCAs are more dangerous than other groups of antidepressants and maybe fatal due to severe cardiac arrhythmias and convulsions.

Desipramine, imipramine and nortriptyline are more specific to noradrenergic blockade and are associated with less anticholinergic and antihistamine side effects. They may be useful in patients who are not able to tolerate amitriptyline, before progressing to another class of drug. In PHN and painful diabetic neuropathy, they were both found to be as effective as amitriptyline,[34,37,41] but associated with less side effects. Physical withdrawal reactions have been described for most antidepressants, but psychological addiction is not an issue.[36]

Selective serotonin re-uptake inhibitors (SSRIs)

Selective serotonin re-uptake inhibitors such as fluoxetine and paroxetine have only

limited efficacy in neuropathic pain.[35] They alter serotonergic (5-HT) far more than noradrenergic (NE) neurotransmission. However, due to their selectivity they do not interfere as much with adrenergic, histaminergic or muscarinic receptors and therefore have fewer side effects. There is currently insufficient evidence to make generalisations regarding their use in this indication.[42]

Serotonin/Noradrenaline reuptake inhibitors (SNRIs)

Venlafaxine and duloxetine are novel antidepressants, which belong to the class of SNRIs. They have similar mechanisms of action as TCAs, but no anticholinergic effects. While data on venlafaxine are currently inconclusive, duloxetine has indications in the treatment of diabetic polyneuropathy (NNT = 6) and fibromyalgia (NNT = 8) and is approved for this indication in some countries.[43] There are no direct comparisons to other antidepressants published, but SNRIs are thought to be better tolerated than TCAs.

Recommendations for clinical use of antidepressants as analgesics

Evidence-based decisions to use antidepressants in neuropathic pain states are usually based on a NNT approach:[35,43,44]

- TCAs for PHN: NNT 2.7
- TCAs for atypical face pain: NNT 2.8
- TCAs for diabetic neuropathy: NNT 1.3
- Duloxetine for diabetic neuropathy: NNT 5.8 - 6

It is difficult to generalise a dosage regimen for antidepressants in neuropathic pain, due to significant inter-individual variability.[45] McQuay *et al* have demonstrated a dose response relationship for amitriptyline with a greater analgesic response at 75mg/d than 25 or 50mg/d.[46]

Current recommendations for prescribing TCAs are:[4]

1) Start with a low dose (5–10mg/d) especially in the elderly and increase this weekly to analgesic efficacy or unacceptable side effects.
2) Once the optimal dose is achieved analgesic efficacy usually takes up to a week to achieve.
3) There have not been any trials conducted for longer than 6 weeks, so there is no evidence base for optimum duration of treatment. The current practice is to continue the same effective dose for several months and then to try and reduce it.
4) If a therapeutic dose of a TCA fails to provide pain relief, other antidepressants are also likely to fail.
5) If a TCA provides pain relief at the expense of unacceptable side effects then other antidepressants (in particular SNRIs) with a lower side effect profile should be tried.
6) If due to contraindications or unacceptable side effects a patient is unable to be treated with TCAs, other antidepressants (in particular SNRIs) should be tried before excluding this drug category.

Anticonvulsants

In the 1960s phenytoin was found to have an analgesic effect in the treatment of painful diabetic neuropathy.[47] Since then anticonvulsants have been evaluated and used in neuropathic pain states, including old agents: carbamazepine, sodium valproate, phenytoin and newer agents: gabapentin, lamotrigine, felbamate and pregabalin. Anticonvulsants have a specific indication in the treatment of trigeminal neuralgia with carbamazepine the first line therapy. They

may prove effective in conditions that have proved intractable to other treatments.

Mechanism of action

The neuronal hyperexcitability and corresponding molecular changes in neuropathic pain have many features in common with the cellular changes in certain forms of epilepsy.[48] The pain relieving effect of anticonvulsants is thought to be due to dampening of abnormal central nervous activity that follows nerve damage.[49] This may occur by: [50,51]

1) Sodium channel blockade resulting in a reduction of ectopic firing in both peripheral nerves and the dorsal root ganglion
2) Indirect or direct enhancement of inhibitory GABAergic neurotransmission
3) Inhibition of excitatory glutaminergic neurotransmission

Overall effects may be due to a combination of these mechanisms and longer term neuroplastic effects.[51] The process of ectopic impulse generation is so sensitive to sodium channel blockade that these agents have an action at much lower concentrations than that required to block normal neuronal transmission.[52]

Individual medications

Clonazepam

Clonazepam is a benzodiazepine anticonvulsant acting as a GABA agonist. Lorazepam, nitrazepam and diazepam have also been used in chronic pain. They have anxiolytic and anticonvulsant properties. However, with the exception of clonazepam, benzodiazepines are not generally felt to have specific analgesic activity and their use is not encouraged for this purpose due to their addictive nature, tolerance and cognitive impairment.[53]

However, for clonazepam several studies suggest a role in lancinating neuropathic pain. The old cross-over trial by Swerdlow shows clonazepam to be superior to carbamazepine, phenytoin and sodium valproate with regard to efficacy in neuropathic pain and adverse effects.[54]

This reflects our past clinical experience, where clonazepam was an easy to use agent with excellent efficacy and minimal side effects, in particular sedation. However, clonazepam is a benzodiazepine and thereby closely linked to risks of tolerance, dependence and addiction/abuse and should no longer be used as a first-line agent in neuropathic pain.

Gabapentin

Gabapentin is a relatively new anticonvulsant, available in the USA since 1995. It is a lipophilic GABA analogue but does not interact with $GABA_A$ or $GABA_B$ receptors or directly affect GABA uptake.[55] It is now clear that this drug has a modulating effect on the $\alpha 2\text{-}\delta$ subunit of voltage-gated calcium channels, an unexpected pharmacological target.[56] By modulating the calcium influx into hyperexcitable primary afferent neurons, gabapentin reduces the release of excitatory amino acids, in particular glutamate, and thereby reduces the excitation of secondary neurons. This explains its effects in neuropathic pain, but also in other conditions presenting with hyperalgesia and allodynia including fibromyalgia, even postoperative[57] and burns pain[58] and its anxiolytic effect with efficacy in generalised anxiety disorder. Large scale RCTs have demonstrated efficacy in PHN and diabetic neuropathy at target doses of 3600mg/day.[59-61]

The Cochrane review reports NNT of 3.9 in PHN and 2.9 for painful diabetic neuropathy.[62] Results indicate a similar efficacy of gabapentin and TCAs.[63]

A case report cited a significant improvement with gabapentin treatment in a patient with central post stroke pain that had failed

to respond to a variety of analgesics.[64] Gabapentin was also effective in the treatment of central neuropathic pain after spinal cord injury.[65]

The most commonly reported side effects are somnolence, fatigue, ataxia and dizziness. A dose adjustment is required in renal failure, but not in hepatic disorders as gabapentin is excreted unchanged by the kidneys.

The effective analgesic dose of gabapentin is variable, with some patients responding at low doses and others requiring high doses (more than 3600mg/day) for the same benefit. This is partially due to uptake by an active carrier process, showing saturation kinetics. It has been suggested that treatment failure maybe due to inadequate dosage, although rapid dose escalation can be responsible for the high incidence of CNS side effects.[66] The development of pregabalin with better kinetics and higher efficacy has reduced the usage of gabapentin.

Pregabalin

Pregabalin, an analogue to gabapentin, has been developed with an indication for neuropathic pain. It has a similar pharmacodynamic effect to gabapentin, i.e. modulates the $\alpha 2$-δ subunit of voltage-gated calcium channels and thereby reduces excitatory amino acid release.[56] It differs from gabapentin insofar as it has a higher potency, a better bioavailability, linear absorption kinetics and a longer half-life permitting twice instead of three times daily dosing.

Pregabalin is used successfully in a number of neuropathic pain states of peripheral and central origin including PHN, diabetic neuropathy (NNT 3.24)[67] and spinal cord injury pain.[68] It has also been used successfully in fibromyalgia[69] and generalised anxiety disorder[70] and has these three conditions as an indication in many countries. It is not only superior to gabapentin from a pharmacokinetic point of view, but also in clinical practice achieving better pain relief and quality of life.[71]

Adverse effects of pregabalin include sedation, drowsiness, disturbance of balance and unexplained peripheral oedema. However, these adverse effects are often mild and can be partially avoided by slow and careful titration of the dose. Starting doses of 75mg in ambulatory patients (with 25mg in the frail), starting with an evening dose and higher evening than morning doses are useful recommendations for the titration process.

The efficacy of pregabalin and its mild adverse effects have made it a viable first-line alternative to antidepressants in the setting of neuropathic pain. An interesting aspect from a surgical perspective is its perioperative use, which leads to improved postoperative pain, reduced opioid consumption and opioid side effects.[57] Two more recent studies suggest further benefit from its perioperative use by improving recovery after laminectomy[72] and reducing chronic neuropathic pain after knee joint replacement.[73]

Carbamazepine

Carbamazepine has been the first line treatment for trigeminal neuralgia for many years.[74] A recent Cochrane review found that three placebo-controlled trials of carbamazepine in trigeminal neuralgia demonstrated a combined NNT of 2.5.[75] It has not however been shown to be efficacious in PHN or central pain and its use in other neuropathic states has been reported only in small uncontrolled studies. Evidence shows carbamazepine inhibits spontaneous and evoked responses of spinal neurones and increases brain serotonin. Doses of up to 1200mg/day can be used.

Side effects are the main limitation to its use and include sedation, ataxia, drug interactions and liver dysfunction.[76] Serious but rare side effects are irreversible aplastic anaemia and Stevens-Johnson-Syndrome.

With carbamazepine therapy regular haematological and liver function monitoring is required. Occasional monitoring of serum sodium is also recommended because hyponatraemia can occur. The sustained release preparations of carbamazepine may limit the side effects.

Sodium valproate

This is structurally unrelated to other anticonvulsants and does not block sodium channels. The exact mechanism of action is unknown but may be related to increased GABA synthesis and release and hence potentiated GABAergic inhibition. In addition valproate attenuates the neuronal excitation caused by glutamate activation of NMDA receptors.[77] There is evidence for its use in migraine prophylaxis[78] and some for second line therapy in trigeminal neuralgia.[79] It can be used in doses up to 800mg/day.

Again side effects and the risk of serious toxicity limit its use. These include sedation, gastrointestinal disturbance, altered liver function with potentially fatal hepatotoxicity, decreased platelet aggregation and other haematological effects and drug interactions. Close follow up is mandatory.

Phenytoin

Phenytoin can be of help in patients with neuropathic pain but less so than carbamazepine. It has fallen from favour mainly due to its extensive side effect profile, complex kinetics and drug interactions and a lack of supportive studies.

Side effects include sedation, gingival hypertrophy, hirsutism and coarsening of facial features. At high blood levels neurotoxicity occurs and cardiac conduction is affected and thus close blood drug level monitoring is required. Results from RCTs have shown an analgesic effect in diabetic neuropathy and Fabrys disease.[80,81] The Cochrane review found that NNT for diabetic neuropathy with phenytoin was 2.1.[75]

Lamotrigine

This new anticonvulsant appears to act on voltage-gated cation channels (calcium and potassium) as well as inhibiting glutamate release.[82] Studies (open and double blind) have indicated that lamotrigine can be effective in diabetic neuropathy, central post stroke pain, HIV associated polyneuropathy and trigeminal neuralgia.[48,53,83] It may be useful in cases of trigeminal neuralgia that have proven refractory to carbamazepine and phenytoin, in doses of 50–400mg/day.[53] However, other evidence suggests that it may not be more effective than placebo in many other cases of neuropathic pain.[82]

Side effects have restricted the use of lamotrigine: dizziness, constipation, nausea, somnolence and diplopia.[53] Lamotrigine is associated with Steven-Johnson-Syndrome with 1:1000 patients requiring hospitalisation and can be rarely fatal. These side effects can be lessened and the incidence of rash significantly decreased by slow titration of lamotrigine, starting at a dose of 12.5 to 25 mg per day and slowly increasing to 100 to 200 mg per day over 1 to 2 months.

Recommendations for clinical use of anticonvulsants as analgesics

Anticonvulsants are typically used for neuropathic pain that has a shooting, burning or lancinating character. Empirically they are often used in combination with a TCA, although the evidence for using both classes of drug in combination is not strong.

For peripheral neuropathic pain and spinal cord injury pain pregabalin is the anticonvulsant of choice.[2] For trigeminal neuralgia only, carabamazepine is the first choice.[2] Although few trials exist for the treatment of central post-stroke pain, current opinion is that lamotrigine and gabapentin may be helpful.[84]

As with antidepressants, titration should start with low doses, gradually increasing to

a dose that either produces analgesic efficacy or unacceptable side effects.

Local anaesthetics and antiarrhythmics

In 1948 systemic procaine was identified as beneficial in the treatment of neuropathic pain. This led to the evaluation of other local anaesthetics for the treatment of neuropathic pain.

Mechanism of action

The mechanism of analgesic action is thought to be due to membrane stabilising effects by blockade of voltage-dependent sodium channels and hence reduced ectopic activity in damaged afferent nerves.[50] In addition there maybe a central action on sodium channels and at the spinal level, blocking the actions of glutamate.[85,86]

Lignocaine

Over the last 35 years there have been reports of analgesic efficacy of intravenous lignocaine in a wide range of neuropathic pain states, including diabetic neuropathy, peripheral nerve lesions, PHN and central pain.[87-92] Sakuri and Kanazawa have reported its effectiveness in multiple sclerosis associated pain.[93] There is large variation in reported duration of analgesic effect, varying from no residual effect to 20 weeks benefit in patients with central pain. A beneficial response to a lignocaine infusion may suggest a similar benefit from oral mexiletine, but does not predict this reliably.[94]

Mexiletine

This antiarrhythmic is an oral analogue of lignocaine that has been used in neuropathic pain with mixed results. Some effectiveness has been demonstrated in treating pain after peripheral nerve injuries and painful diabetic neuropathy, although these findings are not consistent and the effects are less than that provided by TCAs and anticonvulsants with an NNT of 10.[95] Optimal dosing may be a problem with a poor therapeutic ratio and potential cardiotoxicity.[4] Mexiletine should only be regarded as a last resort in the treatment of neuropathic pain.

Recommendations for clinical use of lignocaine and mexilitine in neuropathic pain

Side effects of both substances are CNS (dizziness, nausea, perioral numbness, convulsions & coma) and CVS effects (arrhythmias). Contraindications therefore include, cardiac conduction abnormalities, left ventricular failure and ischaemic heart disease. An ECG should be obtained before and during treatment to monitor any cardiac effects. If there is a question regarding safety in a patient, a cardiologist's opinion should be sought, prior to starting treatment.

For lignocaine the recommended starting dose is 1 –1.5mg/kg as a slow IV bolus; this is an ideal agent for the neuropathic pain emergency. Maintenance is by IV infusion of 1-3mg/min with measurement of blood concentrations.The recommended starting dose for mexiletine is 150mg three times a day with a slow increase to 600mg to 1200mg per day to optimal results.

N-methyl-D-aspartate-receptor (NMDA) antagonists

NMDA receptors are activated by the excitatory neurotransmitter glutamate. NMDA antagonists are thought to play an important role in the development of central sensitisation following a peripheral nerve lesion. They may block this hyperactivity responsible for the maintenance of the pain. Drugs with NMDA receptor antagonist activity include ketamine, dextromethorphan, memantine and amantadine.

Ketamine

Ketamine is the most commonly used NMDA antagonist. Its original use was as an anaesthetic agent, particularly 'in the field' and other difficult locations and situations. It has also been used for the treatment of severe asthma and for sedation. However, ketamine is known to have analgesic properties at subanaesthetic doses.[96]

Analgesic efficacy of ketamine has been demonstrated in RCTs for PHN, peripheral nerve injuries, phantom limb pain and post stroke central pain.[96] In peripheral[97] and central neuropathic pain states,[98] low-dose IV ketamine was superior to IV lignocaine. Ketamine may in part provide analgesia by reversing opioid tolerance.[99] In opioid-tolerant patients low-dose ketamine improves postoperative analgesia and reduces opioid requirements.

Unpleasant side effects limit its use, although they occur rarely with the low doses commonly used to treat neuropathic pain. These are mostly psychomimetic: sedation, hallucinations, dysphoria, unpleasant sensations (dissociation) and paranoid feelings. It is important to warn patients in advance of these potential effects; they can be reduced by co-prescribing benzodiazepines such as midazolam if needed. The pharmacokinetics of a sublingual and oral dosing form have been documented[100] and a nasal spray of ketamine is under development.[101]

Other NMDA antagonists

Dextromethorphan, amantidine and memantine have been shown to have weaker actions than ketamine. In a blinded trial, Nelson *et al* demonstrated an analgesic effect with high dose dextromethorphan in painful diabetic neuropathy,[102] but this has not been reproduced in other neuropathic pain states.[103] Memantine was also shown to be ineffective in phantom limb pain treatment;[104] its routine use in neuropathic pain can currently not be recommended.[105]

Miscellaneous compounds for systemic use

Clonidine

Clonidine is an α_2-agonist with analgesic activity. Its analgesic action is thought to occur centrally and at a spinal level, mediated by activation of α_2-adrenoceptors in the dorsal horn of the spinal cord. This results in direct inhibition of postsynaptic spinal dorsal horn neurones or by decreasing the release of noradrenaline from sympathetic nerve terminals.

Efficacy

Only a small number of studies have been conducted to look at a potential role in the treatment of neuropathic pain. Significant improvement was reported in patients with PHN treated with clonidine.[106] Transdermal clonidine (0.1 to 0.3mg per day) has been used with success in patients with diabetic neuropathies.[107,108] A double blind crossover study in 20 chronic pain patients, comparing epidural clonidine and an epidural combination of morphine and lignocaine found epidural clonidine to be as effective as epidural morphine in 20 chronic pain patients.[109] It is registered in the USA as an adjuvant in combination with epidural local anaesthetics and opioids for resistant neuropathic pain. Side effects include drowsiness, dizziness and dry mouth.

Baclofen

Baclofen is a gamma-aminobutyric acid (GABA) receptor agonist, capable of crossing the blood-brain barrier. It is an agonist at GABA-B receptors and has presynaptic action in the spinal cord preventing the release of excitatory neurotransmitters.[110]

Baclofen causes muscle relaxation and is used to treat muscle spasticity. It has been shown to have antinociceptive action and has been used to treat neuropathic pain.[111] It was

first used for this purpose to treat trigeminal neuralgia.[112] Its efficacy has not however been confirmed in other neuropathic pain conditions.[113] Baclofen has been administered intrathecally and may be useful for pain related to spinal cord injuries.[114] Side effects include sedation, nausea, confusion, convulsions, hypotension, GI upset, visual disturbances and occasionally hepatic impairment (A to Z). After prolonged use, baclofen requires a gradual dose reduction in order to minimise the risk of a withdrawal syndrome.[110]

Levodopa

Ertas *et al* found levodopa to be better than placebo in treating painful diabetic neuropathy.[115] A review of placebo-controlled trials by Sindrup and Jensen in patients with diabetic neuropathy showed that NNT was 3.4 for levodopa, compared with 6.7 for SSRIs.[95] A placebo-controlled trial has demonstrated efficacy in acute herpes zoster pain.[116]

Cannabinoids

There has been increasing interest in the use of cannabis and cannabinoids as analgesics in chronic pain. Cannabinoid receptors are located in the central and peripheral nervous system. Animal models have shown that cannabinoid receptors do not undergo down-regulation after nerve lesions (unlike opioid receptors) and that cannabinoids may attenuate the associated sensory changes.[8]

Cannabis has been used for thousands of years for medicinal and recreational purposes. There is much interest surrounding its legalisation and its potential role as an analgesic. The data situation here remains unclear; however, overall there is a trend to show some efficacy by some cannabinoids in some neuropathic pain states. A meta-analysis found efficacy in neuropathic pain states including multiple sclerosis.[117] Similarly, a randomised trial of smoked cannabis in neuropathic pain reduced pain intensity and improved sleep quality.[118] However, a trial in spinal cord injury pain failed to show efficacy.[119] Adverse effects associated with cannabinoids are common, the main being sedation, disorientation, ataxia, memory impairment, dry mouth and blurred vision.

Larger blinded, randomised controlled trials are required before it can be ascertained whether cannabinoids are efficacious in neuropathic pain. The development of new safe and effective agonists that separates the psychotropic effects from the therapeutic ones would improve trial designs.

Topical treatments

Allodynia is frequently a feature of neuropathic pain especially in PHN, traumatic neuropathies and causalgia. It may therefore be helpful to consider the use of topical medications for the treatment of cutaneous hyperalgesia in these cases. There are a few options in the form of capsaicin, local anaesthetics (and NSAIDs with some reports of good pain relief from post herpetic neuralgia with topical aspirin preparations).[120-122]

Lignocaine 5% medicated plaster

In patients with PHN, success has been reported using lignocaine patches or topically applied gel to painful areas.[52,123,124] The mechanism of action is thought to involve suppression of ectopic discharges from sensory afferents and from providing mechanical protection to underlying allodynic skin.[125] In 1999 the FDA approved the use of 5% topical lignocaine patches for treatment of PHN. It is recommended as a first-line approach for this indication and other localised neuropathic pain states.[126] A meta-analysis showed superiority of the plaster over capsaicin and pregabalin and

similar efficacy to gabapentin, however with significantly fewer systemic side effects.[127]

The advantages of this route of administration are its effectiveness, duration of analgesia, ease of application without dose titration and lack of systemic side effects. The safety profile is particularly advantageous in the elderly population whom are most affected by PHN. The area of pain has however to be of limited size for practical application.

Capsaicin

Capsaicin is the pungent component to chilli peppers. The chilli pepper has been recognised by various cultures for many years for its medicinal qualities.[128] It is neurotoxic and has analgesic properties. When capsaicin is applied topically it initially causes a burning sensation and heat hyperalgesia that decreases with subsequent applications.

Mechanism of Action

Capsaicin acts on receptors at the terminals of primary nociceptive afferents. In 1997 a specific receptor on C fibres was cloned, a vanilloid receptor, the VR-1 receptor. When capsaicin binds to this receptor, it induces initial activation of the nociceptors, hence the burning sensation. It depletes substance P from the sensory nerve terminals of peripheral nociceptors. With repeat or prolonged application, this is followed by desensitisation and inactivation of the receptive terminals of the nociceptors.[129] There is also evidence that it causes depletion of substance P in epidermal nerve fibres.[130]

Efficacy

In a meta-analysis of RCTs, low-dose capsaicin cream (0.075%) repeatedly administered had an NNT of 6.6 for any pain relief.[131] A commercially available patch with high-dose capsaicin (8%) had an NNT of 12 for 30% pain relief. These not very impressive results have to be seen in the context of a potentially high placebo effect, as the burning feeling after administration results in the patient effectively being unblinded. This criticism is confirmed by one double blind trial using a placebo with a similar burning sensation and finding no difference in analgesic efficacy between placebo and capsaicin.[132]

The use of capsaicin has been limited by this unpleasant burning sensation occurring in 60–70% patients, need for frequent applications and uncertain efficacy.[4] Co-administration of lignocaine gel has been used in order to improve compliance.[4]

Capsaicin can only be seen as an adjuvant treatment and second line therapy.

NON PHARMACOLOGICAL THERAPY

Transcutaneous electrical nerve stimulation (TENS)

This technique applies cutaneous electrodes to stimulate peripheral nerves to relieve pain. [133] This is based on the gate control theory of pain transmission, so that by stimulating Aβ and Aδ fibres pain transmission by C-fibres is inhibited. It utilises a pulse generator that provides a range of currents, frequencies and pulse widths. The surface electrodes are placed on either side of the painful area or alternatively over the nerves supplying that area. The current is then increased until a tingling sensation is felt in the painful area, the timing and duration of pulses is a matter of titration to maximal response. TENS may reduce analgesic requirements.[134] A meta-analysis shows improvement in neuropathic symptoms in patients with diabetic polyneuropathy.[135]

It has few side effects and complications, allergic dermatitis may occur at the contact sites and its use is contraindicated in patients with pacemakers. Its efficacy can be assessed

quickly (there is a significant placebo effect) and can therefore be easily trialled for any potential benefit to an individual.[136] Unfortunately tolerance may develop resulting in loss of previously effective analgesia, changing the stimulation variables can sometimes attenuate this.

Spinal cord stimulation (SCS)

This technique requires an implantable device with electrodes positioned under direct vision at open laminectomy or via a needle in the epidural space percutaneously. The electrodes are placed above the level of the pain and connected to an inductance coil placed on the abdominal wall; an implantable power source can also be used. The mechanism of action is not yet clear, but it seems to be not effective in nociceptive pain, but only in neuropathic pain.[137] It seems that this device can be as useful for a variety of neuropathic and chronic pain states.[138] A systematic review describes efficacy in refractory neuropathic back and leg pain, failed back surgery syndrome and chronic regional pain syndrome (CRPS) Type 1.[139]

Complications include infection, bleeding, dural puncture and hardware failure; decisions on use of this invasive and expensive approach should be made ideally by a multidisciplinary team experienced in the use of such techniques. Deep brain stimulation and motor cortex stimulation have also been used to treat neuropathic pain.[140]

Sympathetic nerve blocks

The diagnosis of sympathetically maintained pain can be confirmed by the response to a sympatholytic procedure. This may be helpful, if there is a significant sympathetic component to the patient's pain. A patient should receive sustained pain relief after administration of a sympathetic chain or sympathetic plexus local anaesthetic block or accumulative relief from a number of procedures. If the patient fails to respond, a systematic pharmacological approach is tried. However, a block may be incorrectly thought to be successful. This can happen for one of two reasons: either, the local anaesthetic is absorbed and provides a systemic analgesic effect or it diffuses locally and acts on nearby somatic nerves.[141]

In case of effectiveness, progression to a sympatholytic procedure can be chosen. Techniques then involve the use of neurolytic substances or radiofrequency ablation; regrettably the current scientific basis for this approach is poor.[142]

Neurosurgical destructive techniques

There has been increasing awareness that destructive techniques may in fact increase pain in the long term due to the plasticity of the nervous system, sometimes resulting in incapacitating side effects. Therefore these techniques, which include neurectomy and dorsal root entry zone lesions, are now rarely used.[143] The exception being in the treatment of trigeminal neuralgia, which has proved refractory to pharmacological treatments. In this situation a variety of surgical procedures can provide rapid pain relief, the most effective option being microvascular decompression. Recurrence is still a risk but appears to be more frequent after percutaneous radiofrequency rhizotomy or compression with a percutaneously positioned balloon than the more invasive microvascular decompression technique.[144]

Cognitive-behavioural therapy

Chronic neuropathic pain is best managed in a multidisciplinary pain clinic.[145] This is because the patient often has cognitive,

affective and behavioural factors influencing their pain; however new understandings of the physiology of cortical reorganisation in chronic pain might also lead to new psychological approaches.[146] A multidisciplinary approach will address both the somatic and psychological aspects of the patient's condition. The main methods are cognitive-behavioural therapy and operant conditioning.

The cognitive-behavioural approach aims to identify and modify the patient's thoughts, feelings, beliefs and behaviour. Common problems are anxiety, depression and the development of fear-avoidance. Behavioural therapy procedures are utilised to bring about change. The aims are to enable patients to take a positive and active role in coping with their pain and to change maladaptive behaviour that may be aggravating the problem.

Operant conditioning uses firstly continuous re-enforcement to encourage positive behaviour from the patient that is then stepped down later on. This is based on the belief that the consequence of certain behaviour determines whether it is likely to recur.

Psychotherapy may increase levels of activity and decrease medication requirements but an actual reporting in pain reduction may be more modest. In addition the therapy may need to be extended to the carers of the patient in order to change their response to the patient's beliefs and behaviour. The current data situation on this approach to neuropathic pain is insufficient to draw any conclusions on efficacy.[147]

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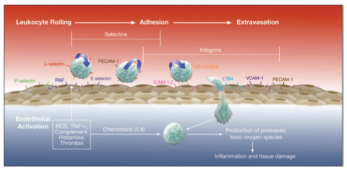

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