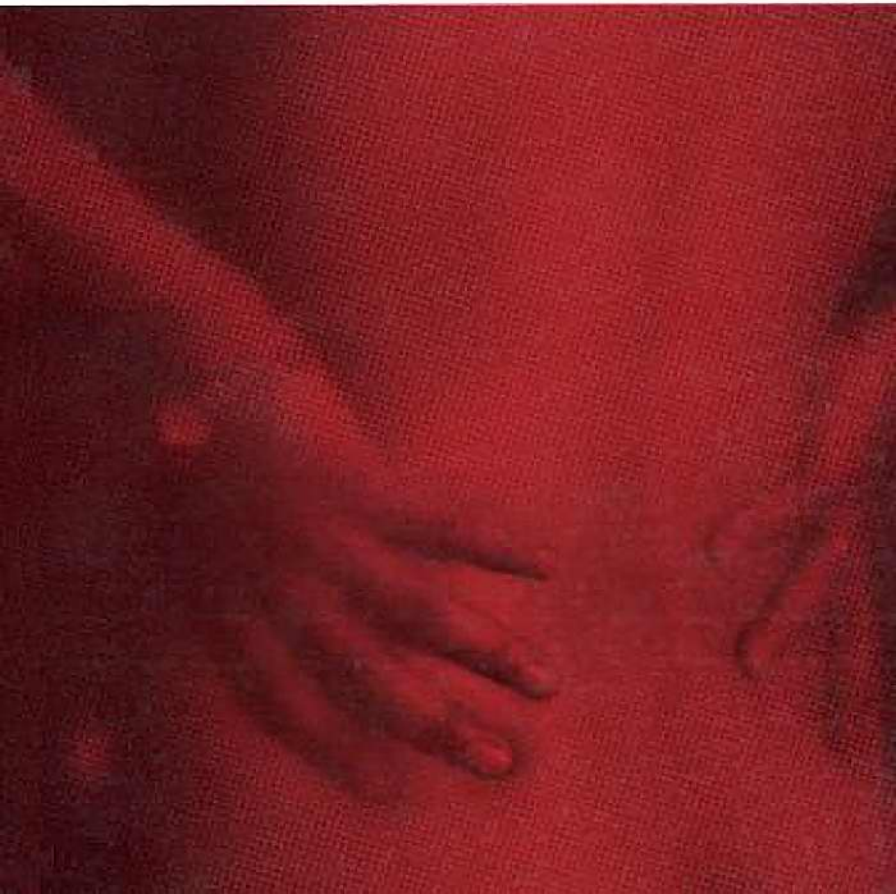
KEY TOPICS IN

CHRONIC PAIN

K M GRADY • A M SEVERN



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KEY TOPICS IN

CHRONIC PAIN

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BIOS SCIENTIFIC PUBLISHERS

First published 1997

A CIP catalogue record for this book is available from the British Library.

ISBN 1 859960 76 6

BIOS Scientific Publishers Ltd
9 Newtec Place, Magdalen Road, Oxford OX4 1RE, UK
Tel. +44 (0)1865 726286. Fax. +44 (0)1865 246823
World Wide Web home page: http://www.Bookshop.co.uk/BIOS/

DISTRIBUTORS

Australia and New Zealand
Blackwell Science Asia
54 University Street
Carlton, South Victoria 3053

India
Viva Books Private Limited
4325/3 Ansari Road, Daryaganj
New Delhi 110002

Singapore and South East Asia
Toppan Company (S) PTE Ltd
38 Liu Fang Road, Jurong
Singapore 2262

USA and Canada
BIOS Scientific Publishers
PO Box 605, Herndon
VA 20172-0605

Typeset by Chandos Electronic Publishing, Stanton Harcourt, UK.
Printed by Redwood Books, Trowbridge, UK.

CONTENTS

Introduction – evidence-based medicine in pain management	1
Assessment of chronic pain – history	3
Assessment of chronic pain – physical	6
Assessment of chronic pain – psychosocial	12
Back pain – assessment and medical management	16
Back pain – injections	22
Benign nociceptive pain – drug treatments	26
Botulinum toxin–haemagglutinin complex	32
Cancer – intrathecal and epidural infusions	35
Cancer – nerve blocks	40
Cancer – non-opioid drugs	44
Cancer – opioid drugs	48
Cancer pain – mechanisms and pathology	53
Cannabinoids	55
Central post-stroke pain	58
Complex regional pain syndromes I and II	62
Conduct of the pain clinic	67
Depression and pain	71
Digestive tract syndromes	74
Facial pain	77
Headache	81
Immunodeficiency disease and pain	86
Ketamine	89
Mechanisms in nociception	92
Mechanisms in peripheral and central neuropathic pain	94
Migraine	98
Multiple sclerosis	103
Musculoskeletal pain syndromes	108
Neck pain	111
Nerve blocks – autonomic	115
Nerve blocks – somatic	119
Neuromata and post-incisional pain	123
Neuropathic pain – drug treatments	128
Neurosurgery and pain[a]	133
Osteoporosis – generalized adult	138
Pelvic (gynaecological) and urinary tract pain	142
Peripheral neuropathies and neuralgias	147
Post-amputation pain	151
Post-herpetic neuralgia	154
Psychological management of chronic pain	157

Spinal cord injury and pain 160
Stimulation analgesia – spinal cord, deep brain and motor cortex stimulation[a] 164
Stimulation analgesia – TENS, TSE and acupuncture 175
Sympathetic nervous system and pain 179
Trigeminal neuralgia 183

Glossary 189

Index 191

[a] Contributed by Paul Eldridge (MA, MChir, FRCS), Consultant Neurosurgeon, Walton Centre for Neurology and Neurosurgery, Walton, Liverpool, UK.

ABBREVIATIONS

AIDS	acquired immune deficiency syndrome
b.d.	twice per day
CGRP	calcitonin gene-related peptide
CNS	central nervous system
CPPWOP	chronic pelvic pain without obvious pathology
CPSP	central post-stroke pain
CRPS	complex regional pain syndrome
CSF	cerebrospinal fluid
CT	computed tomography
DREZ	dorsal root entry zone
ESR	erythrocyte sedimentation rate
GABA	γ-amino butyric acid
GTN	glyceryl timitrate
HAD	hospital anxiety and depression index
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
5HT	5-hydroxytryptamine
5HT1D	5-hydroxytryptamine-1-delta
i.v.	intravenous
IASP	International Association for the Study of Pain
IBS	irritable bowel syndrome
IU	international units
LSD	lysergic acid diethylamine
MRI	magnetic resonance imaging
MS	multiple sclerosis
MVD	microvascular decompression
NGF	nerve growth factor
NMDA	*N*-methyl-D-aspartate
nocte	at night
NSAIDs	non-steroidal anti-inflammatory drugs
o.d.	once per day
o.n.	at night
p.r.	rectally
PHN	post-herpetic neuralgia
PVD	peripheral vascular disease
q.d.s	four times per day
s.c.	subcutaneously
SCS	spinal cord stimulation
SIP	sympathetically independent pain
SLR	straight-leg raise

SMP	sympathetically maintained pain
SSRI	selective serotonin re-uptake inhibitor
stat	immediately
t.d.s.	three times per day
TENS	transcutaneous electrical nerve stimulation
TGN	trigeminal neuralgia
TSE	transcutaneous spinal electroanalgesia
WHO	World Health Organisation

PREFACE

This latest volume in the Key Topics series aims to provide the health professional with up-to-date information about a range of issues in the management of chronic pain. It is not a substitute for the larger texts, nor is it an attempt to provide a comprehensive reference to palliative care or painful rheumatological and neurological conditions. It is a working manual of the common problems of management of the chronic pain sufferer, the patient in whom investigations have excluded treatable disease. The book is designed for specialist registrars, general practitioners, psychologists, nurses and physiotherapists. It is written by two hospital consultants responsible for running Pain Clinics in general hospitals, with two chapters provided by a colleague in a neurosurgical centre.

What is chronic pain?

A definition that describes a chronic condition as a long-standing acute condition is inadequate. Tissues involved in chronic inflammation, for example, can be distinguished microscopically from those with acute inflammation by changes of regeneration and repair. Once a condition becomes chronic, secondary changes make for an irremediable situation in which management involves treating complications of the condition rather than the condition itself. Thus it is with chronic pain. Chronic pain is not a symptom of an illness. It is an illness. It has its own symptoms, signs and complications. The professional caring for the chronic pain sufferer looks for complications of chronic pain and attempts to treat these. The original cause of the chronic pain may be irrelevant. If there is a possible cure the professional is advised to ascertain the degree to which the complications of chronic pain have become apparent: the complications themselves may seriously limit the benefit that might otherwise be obtained from treatment of the pain.

This book

The opening chapters explain the terms with which the professional should be familiar, and some of the practical problems encountered in Pain Clinic practice. They should be read as an introduction. Elsewhere the book is arranged according to topics in alphabetical order, in the format familiar to readers of the series. Cross-reference may be made to other chapters. The chapters on cancer pain are kept together.

We have attempted to organize our topics so that evidence-based medicine is afforded high priority. Yet we accept that much of our practice, and that of those with whom we meet regularly to share clinical problems, is based on precedent and experience. Our sources include comments made by colleagues in lectures at national and international meetings, and informally. It is impossible to acknowledge all of these sources.

The book is dedicated to our trainees and those other professionals who have laboured with us to build up our respective practices. In particular we acknowledge the support of Chris Glynn, Sara Severn, Frank Grady, Alan Severn and Barrie Tait.

Andrew Severn
Kathryn Grady

INTRODUCTION – EVIDENCE-BASED MEDICINE IN PAIN MANAGEMENT

Chronic pain patients present uniquely challenging management problems. Some of the problems can be described as follows:

- the placebo response to a treatment;
- a willingness to tolerate side-effects of medication if some benefit is achieved;
- insufficient training of specialists;
- specialists working in isolation from their peers;
- enthusiasm of some leading specialists for the treatments they have described.

Treatments may be accepted into routine clinical practice on the basis of case reports of successful outcome, tempered by warnings of potential serious side-effects. Evidence of efficacy may not be available, but, encouraged by a moderate success in an otherwise difficult clinical situation, the specialist may repeat the treatment next time the situation occurs.

Recently, there has been a move towards insisting on evidence for efficacy and safety in clinical practice. This move may be strengthened by a purchaser of a service adopting a similar critical view of any proposed treatment. It is important, therefore, that the pain clinician is aware of the evidence to support the use of particular treatments. The journal *Evidence Based Medicine*, a publication of the American College of Physicians, and its British counterpart, *Bandolier*, reviews and comments on clinical trials that satisfy criteria for evidence-based practice. The Cochrane Library is an electronic database of similar work.

Evidence-based medicine requires at the very least, the performance of an appropriately randomized controlled trial. The review of all available such trials is known as a systematic review. The systematic review is the 'gold standard' for evidence-based medicine. The authors have included in the references to the chapters systematic reviews where relevant. They have also included, where they are aware that work has been done, conclusions from randomized controlled trials. Similar work is identified as such in the references.

Where a *systematic review* of randomized controlled trials is reported it will be identified as

a ..... a

and a reference will be quoted at the end of the chapter. Some meta analysis is considered to be equivalent to a systematic review and will be identified as a systematic review.

Where work from a *randomized controlled* trial or meta analysis is reported it will be identified as

b ..... b

but not necessarily with a reference.

Where other *peer reviewed* work (reviews, uncontrolled studies, or case reports) is reported, it will be identified as

c c

but not necessarily with a reference.

In adopting this style we aim to serve two requirements of our readers, namely the provision of evidence where it exists, and information about treatments performed in pain clinics irrespective of whether there is adequate evidence for continuing practice. It should be recognized that our new and rapidly evolving speciality is still collecting the data from which randomized controlled trials and systematic reviews can be constructed.

A useful statistical concept which features in systematic reviews is the 'number to treat'. This is an estimate of the number of patients who do not respond to treatment for every patient who does respond. For the purposes of considering pain relief, treatment can be scored as successful if there is a 50% reduction in pain severity. The same concept can be used in assessing side-effects: a figure for 'number to treat' for side-effects can be calculated. A drug with a high therapeutic ratio has a difference between numbers to treat for efficacy and side-effects. Where the literature supports the fact, therapies described in this book will include 'numbers to treat' for efficacy and side-effects.

ASSESSMENT OF CHRONIC PAIN – HISTORY

In the pain clinic the history has purposes which are different from those of the history in other clinical settings. Pain must be assessed from a multidimensional perspective, determining physical, behavioural and psychosocial contributing factors and the disruption pain causes to normal function. The pain history concentrates on the biopsychosocial model rather than the biomedical model used for acute medical problems. To achieve this the context of history taking is wide: patients, patients' relatives and questionnaires, body drawings and pain diaries completed by patients all offer further information. Discussion of the pain with the patient allows psychological signs to be manifest. Although a diagnosis is less sought after in the pain clinic than in other settings, pathology better managed in other clinics has to be excluded.

The pain

1. The site of pain may indicate an underlying local cause, a referred origin, a dermatomal or peripheral nerve distribution or may bear no relationship to traditional neuroanatomical patterns. The site of pain should be recorded without prejudice.

2. Nature. Duration, rapidity of onset, whether a pain is intermittent or constant, how it varies in severity with time and circumstance and its overall progression or deterioration determine its nature.

3. The character of pain will point to its somatic, visceral or neuropathic component. Although there are characteristic descriptions of both nociceptive and neuropathic pain, they can be difficult to evaluate because of significant overlap of symptoms. The description can be of value in formulating a psychological diagnosis.

4. Alleviating and exacerbating factors offer specific information about aetiology. All factors which have a bearing on pain should be considered. The following should alert the clinician to specific pain problems. Pain relieved by going to bed has a high index of psychological dysfunction; pain affected by heat suggests a sympathetic nervous system component.

5. *The severity* of pain can be recorded from the history by a numerical analogue score.

The impact of pain

This offers preliminary assessment of disability and social and personal incapacity caused by pain. It attempts to identify all factors affected by pain. Assessment of impact can contribute to the psychological assessment where it reveals personal gain which results from continuing pain.

Treatments for pain

Details of all past treatments and their outcomes build a picture of the pain and avoid further futile attempts with the same modalities. However, history should determine whether treatment was effectively prescribed and whether compliance was adequate before considering it a failure. Current treatments and their effect should be noted. The patient may have beliefs about treatment which usefully contribute to psychological assessment, such as their condition being incurable because no treatment has ever worked, an unshakeable belief in a particular treatment and unreasonable expectations from treatments they have not yet tried.

Other medical history

Other symptoms or conditions can have a bearing on the pain itself or on proposed pain clinic treatments. Current medication for other conditions should be noted, especially anticoagulants.

Psychosocial history

An understanding of the patient's environment is central to understanding their pain.

(a) It assesses logistics of domestic and physical support which would be needed for treatments such as day case procedures, the application of transcutaneous electrical nerve stimulation (TENS) machines and coping with the side-effects of some drugs.

(b) It looks for psychological aspects of the pain. Psychological assessment begins at the first point of contact and does not require the skills of a psychologist initially. Details of personal, sexual and family relationships, source of income, occupation, ethnic origin, availability of social and psychological support can be sought from the history.

The patient is allowed to express beliefs about their condition and its progression and expectations of treatment. Symptoms of anxiety, depression or anger can emerge as causes or effects of pain. A profile of the patient's activities of daily living and questioning about interpersonal relationships demonstrates behavioural components to pain.

Outstanding litigation or compensation claims should be recorded. They can affect symptomatology and have bearing on reluctance to make improvement.

Further reading

Bonica JJ. Organization and function of a pain clinic. *Advances in Neurology,* 1974; **4:** 433–43.

Related topics of interest

Assessment of chronic pain – psychosocial (p.12)
Mechanisms in nociception (p. 92)
Mechanisms in peripheral and central neuropathic pain (p. 94)

ASSESSMENT OF CHRONIC PAIN – PHYSICAL

This chapter addresses the basics of physical assessment. In other areas of medicine, the physical examination helps to form a diagnosis. In chronic pain the physical assessment has several purposes.

Purpose

1. To exclude conditions better treated by other specialists. Some abnormal physical findings are indications of life-threatening or serious pathology which need to be referred appropriately.

2. To reassure the patient that their pain warrants no further investigation or surgery. This breaks the cycle of repeated investigation without findings to account for pain and unnecessary referral for further medical opinion.

3. To find physical signs associated with pain. Although visceral, neurological and orthopaedic components to pain have been investigated, signs of musculoskeletal tenderness or sensory signs such as allodynia, hyperalgesia and hyperpathia are frequently undocumented until the pain clinic physician's examination.

4. To define baseline signs and monitor changes. All physical signs should be documented at the outset to enable assessment of the affect of treatment or to allow monitoring of deterioration at subsequent physical examination.

5. To assess non-physiological response. Psychosocial assessment begins during the initial history. It continues throughout the physical examination looking at attitude, effect, behavioural adaptations and loss of function.

Back pain

The back

1. Inspection.

- Structural or postural abnormalities.
- Muscle spasm.
- Scars.

2. Palpation.

- Spinous processes.
- Area over facet joints.
- Paravertebral areas.

3. Range of movement.

- Determination of restriction.
- Attention to provocation of pain: flexion of lumbar spine causing leg pain.
- Rotation or extension of spine provoking pain from posterior structures.

Relevant neurological examination

Neurological examination distinguishes between back pain without root tension signs, back pain with simple root tension signs and back pain with neurological signs which needs to be assessed by a surgeon. For thoracic back pain, wasting and sensory abnormalities of the trunk should be excluded. For all back pain, neurological assessment of the legs and perineum should be made as follows:

1. Nerve root tension signs.

(a) Provocation of radicular pain by coughing or sneezing.

(b) Limited straight-leg raise. Each leg is examined separately. A positive finding on straight leg raise (SLR) is the reproduction of leg or buttock pain. The angle at which this occurs should be noted in degrees. SLR limited by the production of back pain does not necessarily imply nerve root tension. A SLR of less than 10° does not suggest nerve root tension.

(c) A positive sciatic stretch test is the exacerbation of radicular pain by dorsiflexion of the foot.
(d) Crossed leg pain is the provocation of pain in the symptomatic leg by straight raising of the other leg. It is highly suggestive of a prolapsed intervertebral disc.

2. *Muscle power is assessed by obvious wasting and grading of the following movements:*

- hip flexion dependent on L1 and L2 roots;
- knee flexion dependent on L5, S1 and S2 roots;
- knee extension dependent on L3 and L4 roots;
- ankle plantar flexion dependent on S1 root;
- ankle dorsiflexion dependent on L4 and L5 roots;
- extension of the big toe dependent on L5 and S1 roots.

3. *Sensation* to cotton wool and/or pin prick should be determined according to whether deficiency is in a dermatomal, peripheral nerve or other distribution, such as glove and stocking or whole limb. There may be signs of hyperexcitability such as allodynia, hyperalgesia or hyperpathia.

4. *Reflexes.* Patellar and ankle reflexes imply intact L3/L4 and S1/S2 nerve roots respectively. Up-going plantars and hyperreflexia need referral for the investigation of an upper motor neurone problem.

5. *Disc prolapses.* The majority of lumbar disc prolapses occur at the L5/S1 and L4/L5 levels. Compression of the S1 nerve root by the L5/S1 disc causes weakness of plantar flexion, reduced sensation in the S1 distribution and an absent or diminished ankle jerk. (Symmetrical loss of the ankle jerks is, however, common in the elderly without pathology.) Compression of the L5 nerve root by an L4/L5 disc causes weakness of the extensor hallucis longus,

reduced sensation in the L5 distribution but no changes in the reflexes.

Acute massive central disc prolapse is a surgical emergency:

- sudden onset of back pain radiating into the backs of both legs;
- paraesthesia of the legs and perineum;
- weakness of the bladder and bowel sphincters;
- weak or absent ankle power and absent ankle reflex.

Neck pain

The neck

1. *Inspection.*
- Deformities.
- Scars.
- Muscle atrophy.
- Abnormal vertebral contour.

2. *Palpation.*
- Tenderness.
- Muscle spasm.

3. *Range of movement in all parameters.*
- Determination of restriction.
- Attention to provocation of pain.

Relevant neurological examination

1. *Muscle power* is assessed by obvious wasting and grading of the following movements:
- arm abduction dependent on C5 root;
- elbow flexion dependent on C5 and C6 roots;
- elbow extension dependent on C7 root;
- wrist extension dependent on C6 root;
- wrist flexion dependent on C7 root;
- finger extension dependent on C7 root;
- finger flexion and adduction dependent on C8 root;
- finger abduction dependent on C8 and T1 roots.

2. *Sensation* is tested in the same way as in the legs during the neurological examination of the back.

3. *Reflexes.*
- Normal biceps reflex implies intact C5 root.
- Normal brachioradialis reflex implies intact C6 root.
- Normal triceps reflex implies intact C7 root.

Limb pain

The limb

1. *Inspection.*
- Deformity.
- Wasting.
- Discolouration.
- Oedema or trophic changes, such as loss of hair or shiny skin.

2. *Palpation.*
- Tenderness.
- Muscle spasm.
- Temperature change can be noted by comparison with the opposite limb.

3. *Range of movement.* Passive and active movement (with quantification of its limitation) estimates function, particularly of a joint.

Relevant neurological examination

- Weakness.
- Sensory changes.
- Abnormal reflexes.

For all pains of the upper limb examination should include head and neck. For all leg pain examination should include the back.

Head and face pain

Physical examination within the pain clinic is to reinforce that the referral of a face pain or headache is appropriate and does not require other specialist input.

Head and face

1. *Inspection.*
- Face;
- head;
- inside of mouth;
- external auditory meatus.

2. *Palpation.*
- Surface of head;
- temporal arteries;
- temporomandibular joints for tenderness and clicking on closure, areas of reported tenderness, trigger points or neuromata;
- facial sinuses.

Relevant neurological examination

- Neuralgias for nerve entrapment causing provocation of pain.
- Sensory testing for deficiencies and hyperexcitability.
- Cranial nerves where indicated.
- Fundoscopy where indicated.

Occlusal analysis

- Interincisal distance should be three finger breadths and closure should be smooth.
- There should be no side to side deviation or midline shift as maximum closure is approached.

Abdominal, pelvic and perineal pain

Visceral components to pains are investigated by general surgeons, urologists or gynaecologists.

The pain clinician assesses superficial tenderness or sensory abnormality. It is rarely appropriate to perform a rectal or vaginal examination. If appropriate this should be a chaperoned procedure.

Further reading

Rubenstein D., Wayne D. *Lecture Notes On Clinical Medicine*, Part I *The Clinical Approach.* Oxford: Blackwell Scientific Publications.

Related topics of interest

Assessment of chronic pain – physcial (p. 6)
Assessment of chronic pain – psychosocial (p. 12)
Back pain – assessment and medical management (p. 16)

ASSESSMENT OF CHRONIC PAIN – PSYCHOSOCIAL

Chronic pain is a multifaceted experience and any assessment of it must consider the impact of the pain on the sufferer. To consider it as no more than a nociceptive process which has run a longer than usual course is to miss the diagnosis of the disease called pain. The pain experience can be described as having five dimensions:

- the sensation of pain;
- the patients' attitudes and beliefs: the cognitive dimension;
- the patients' suffering and distress: the affective dimension;
- the patients' illness behaviour;
- the impact on the patient of the social environment.

Information about these is important in the assessment of the chronic pain sufferer. It is recommended that the contribution of psychosocial factors is considered at an early stage in non-specific low back pain, since intervention to abolish inappropriate illness behaviour or counter negative thoughts may prevent further morbidity.

Psychosocial assessment can be left to professional psychology personnel in those clinics which have the luxury of these staff. Their absence from other clinics, however, does not mean that the task can be ignored. A variety of psychological screening tests are available to the non-specialist and are easily administered: they take the form of multiple choice type questions which can be completed by the patient in the clinic. Their value in the clinic that does not have psychological support is three-fold: they may help to identify the patient whose psychological scores are well outside the normal variation for the population and may thus be unsuitable for the limited expertise available in the clinic; they allow progress to be charted; and they allow colleagues to share information using a common language. On the other hand, there is no evidence that the tests are of any diagnostic use on their own, and their use in quantifying the response to psychological treatments is disappointing.

In considering the psychosocial aspect, it is important for the clinician to distinguish between the multidimensional model and the concept of malingering. Illness behaviour is not a state of malingering nor even of conscious expression of disability. It is not a sign of abnormal psychological function, even though some of its more bizarre manifestations may cause wonder and, occasionally, amusement. Illness behaviour is a normal part of the experience of chronic pain. Its manifestation is subject to the principles governing human behaviour: attention to a behaviour, or rewarding it (by sympathy or taking on chores), encourages a repetition of the behaviour.

The subjective experience of pain

The nociceptive system for pain has, at the interface between the individual and the environment, nerve endings of simple structure whose physiological activity varies according to the local environment. Our current knowledge may help us to explain how some pains are experienced as a burning sensation, and others as an aching sensation. It does not, however, help us to understand how pain can be experienced as 'red hot barbed wire' or 'vice-like' or 'dreadful'. Yet terms like this are used commonly. The type of word used tells us something about the subjective experience of pain and its effect on the individual. The McGill scoring system offers a choice of words to describe the pain. Some of them (like 'aching' or 'burning') are straightforward symptoms of nociceptive or neuropathic pain. Others imply a degree of central nervous system integration of inputs.

Attitudes and beliefs

The traditional medical model explains the purpose of pain in that pain has a protective function, promoting rest of the injured part, and warning of environmental hazards. This is a belief that persists in the mind of the person who suffers persistent pain after an injury, and this belief is an important determinant of persistent disability. It can be made worse by casually worded medical terms that are misinterpreted by the sufferer. For example, someone to whom the word 'arthritis' is synonymous with a wheelchair-bound grandparent is not likely to try to exercise the spine that has been said to have 'arthritic changes'. The belief that there is an ongoing nociceptive cause and a continuing disease is an important determinant of the morbidity associated with attitudes and beliefs. This belief can be perpetuated by the professional adopting a purely biomedical view of the symptoms. Requests for investigations of increasing sophistication to find a cause for the pain are common. It is worth noting that if a patient expects that a test will show an abnormality, a normal result may worsen the patient's distress.

Suffering and distress

Depressive thoughts and loss of self esteem, even suicidal thoughts, are to be expected in a chronically painful condition. The premorbid state is relevant. In view of the common neurotransmitters involved in regulating mood and pain experience, there is good reason to view chronic pain and depression as diseases with features in common. There are several scoring systems which were developed for use in screening for depression but which have been successfully adapted for the chronic pain population. The hospital anxiety and depression index (HAD) and the modified Zung index are examples. 'Catastrophizing' is a technical term for 'fearing the worst' and refers to such emotions associated with thoughts such as "I can't go on" or "this pain is never going to get better". It can, as part of a detailed psychological evaluation, be assessed in a quantitative way. 'Locus of control' is the technical term for the patient's view of the responsibility for pain management. The patient who looks to the professional for a cure is 'externally controlled', the one who is prepared to consider responsibility for self-management is 'internally controlled'.

Illness behaviour

Illness behaviour is the way in which a sufferer communicates the experience. In its simplest, most easily observed form, this can take the form of grimacing or complaint on examination. The display of such behaviour is not governed entirely by the activity of nociceptors, but is influenced by cultural and social factors, and it can be altered by the actions of the person at whom this behaviour is directed. More subtle signs of illness behaviour include the wearing of a corset outside clothing, carrying crutches, or arriving in a clinic with a spouse who does all the talking. Certain aspects of illness behaviour can be quantitatively assessed with scoring systems. Unfortunately, the observation of illness behaviour is sometimes taken as 'evidence' that the patient is exaggerating the symptoms for personal gain.

The social environment

Management of the chronic pain patient involves rehabilitating the patient back into a meaningful role

in society. This may require a careful assessment of the work and social environment, so that activity, when it is resumed, is undertaken at a level compatible with ability. Significant amongst social influences is the financial factor. The patient who stands to lose all state benefits if he manages to overcome the powerful demotivating influences of cognitive, affective and behavioural complications of chronic pain may fall at the last hurdle unless this issue is addressed.

Further reading

Kendal NAS, Linton SJ, Main CJ. Guide to assessing psychosocial yellow flags in acute low back pain: risk factors for long term disability and work loss. Wellington, NZ: 1997. Accident Rehabilitation and Compensation Insurance Corporation of New Zealand and the National Health Committee, Ministry of Health,1997; 1–22.

Related topics of interest

Back pain – assessment and medical management (p. 16)
Depression and pain (p. 71)
Psychological management of chronic pain (p. 157)

BACK PAIN – ASSESSMENT AND MEDICAL MANAGEMENT

Low back pain currently accounts for more than half of all musculoskeletal disability; work loss due to back pain in the UK is approximately 52 million days per year. The disability of low back pain is of epidemic proportions although there is no increase in pathology. The cost of treating back pain is 1% of the total UK NHS budget.

Assessment of the back pain sufferer establishes:

- whether there is life-threatening disease;
- whether there is systemic disease or a serious disabling condition;
- whether there is nerve root involvement;
- whether there is a remediable medical or surgical problem.

It is intended that this assessment can be carried out in the acute stage of initial presentation and at regular intervals thereafter. In many cases assessment will allow the diagnosis of non-specific low back pain to be made by exclusion and with confidence. Once this diagnosis has been achieved, no further investigation is required.

Serious or systemic disease

The following factors should alert to the possibility of serious or systemic disease.

1. *History.*

- Bilateral or alternating symptoms;
- constant or progressive pain;
- night time pain;
- morning stiffness, relieved by exercise;
- acute onset in the elderly;
- history of cancer;
- fever or night sweats;
- immunosuppression;
- recent bacterial infection.

2. *Examination.*

- Tenderness on sacroiliac springing;
- multiple nerve root signs;
- symmetrical limitation of straight leg raising;
- spinal rigidity;
- absent lower limb pulses;
- abdominal mass.

In the presence of these symptoms or signs the following conditions should be considered as possible causes of back pain and appropriate investigation undertaken:

- aortic aneurysm;
- retroperitoneal fibrosis;
- tumour (primary or secondary);
- gynaecological pathology;
- ankylosing spondylitis;
- metabolic bone disease;
- infection;
- osteoporosis;
- Paget's disease;
- Potts' disease;
- myeloma.

Detailed discussion of investigation is beyond the scope of this book, but tests such as erythrocyte sedimentation rate (ESR), blood count, bone biochemistry, lumbar spine and sacroiliac joint X-ray or isotope bone scan can be easily organized in the pain clinic.

Back pain with nerve root signs

Nerve root symptoms and signs need to be distinguished from referred pain from the back. Nerve root problems need to be identified since there may be a surgical option.

Symptoms result from compression or irritation of the nerve root by either disc or bone: compression results in numbness and weakness in the appropriate dermatome and myotome, with loss of reflex at the corresponding root level; irritation results in pain in the appropriate dermatome, made worse by the manoeuvre of the sciatic or femoral stretch test. Interpretation requires that this should provoke pain in the leg, not just the back.

The cauda equina syndrome is an important example of nerve root compression. Its features are saddle anaesthesia, alteration of bladder function, and motor weakness, with perineal sensory loss and anal sphincter laxity being found on examination.

Compression of the nerve root in the lateral foramen may cause diagnostic confusion, with pain

referred to the front of the thigh. Neurogenic claudication (pain on walking associated with spinal stenosis) may be confused with intermittent claudication of vascular origin.

The indications for surgery in the patient with nerve root signs are:

- cauda equina syndrome: this is a surgical emergency;
- neurological deficit;
- deformity.

In the past, other indications for surgery included failed conservative management and repeated attacks of pain: these are no longer considered appropriate indications.

Non-specific low back pain

The diagnosis of non-specific low back pain is a diagnosis of exclusion. The optimal management of non-specific low back pain is the subject of debate: some consider that it is not a medical problem and there is no medical solution. It must be considered in the wider context of functional and psychosocial factors, with an overall aim of reducing the disability rather than controlling symptoms.

If a diagnosis of non-specific low back pain is entertained further observations may be valuable in defining an anatomical origin. However, for reasons explained above, the search for relevant pathology may be fruitless. The suggestion that radiological changes in the lumbar zygoapophyseal (facet) joints indicate a cause for the pain was first entertained in 1911, but there is no correlation between the X-ray appearance and the degree of pain. The idea of a specific 'facet syndrome' as a clinical diagnosis is by no means universally accepted. Where it is used, however it relates to a symptom complex that describes pain from the posterior structures of the vertebral column, and to be compared with other diagnoses.

1. *Facet syndrome.*

- Continuous pain;
- worsened by rotation and extension;

- radiation into the leg, particularly the gluteal area, in a non-dermatomal distribution;
- tenderness over the joints and paravertebral muscle spasm.

2. *Ligamentous pain.*
- Pain worsened by flexion and extension;
- tenderness is worse when the back muscles are relaxed.

3. *Pain from vertebral body.*
- Back pain radiating to buttock and leg;
- straight leg raising worsens the back pain but not the leg pain.

There is poor correlation between imaging studies and the pain and disability of low back pain. Even the new technology has not proved useful: intervertebral disc abnormalities are demonstrated in up to 30% of asymptomatic individuals in whom magnetic resonance imaging is undertaken. Indeed, the decision to investigate may confuse the patient and reinforce a belief that there is something seriously wrong.

The optimum medical management of back pain thus remains a controversial issue, and there has been much interest in multidisciplinary approaches involving input from physiotherapy, manipulative therapy, psychology and occupational therapy. The following conclusions are drawn from some of the literature on the subject.

[a] Bed rest delays recovery and return to work in acute back ache. Manual therapy for acute back ache may be more effective than conventional therapy in a selected group of patients, namely those with radiating pain and recurrent pain. [a]

[a] Manipulative therapy and conventional physiotherapy may offer comparable long-term results for the treatment of chronic back pain. Physical reconditioning can improve the level of function and comfort of chronic back pain. Relaxation and cognitive behavioural therapy improves long-term pain perception.[a]

[a] Group education alone provided short-term reduction in pain intensity in only one of four studies of patients with chronic back ache, and in one of two studies of patients with acute back ache, in which it also reduced sick leave duration. [a]

[a] Of 16 randomized control trials of the effectiveness of 'back schools' for low back pain sufferers, seven studies report the effectiveness of this particular approach, which consists of an education and skills programe with an exercise regime. The benefits are experienced over 3–6 months only, and are best achieved in the context of an intensive programme in a specialist centre. [a]

[a] Antidepressant medication has no proven benefit in reducing the severity of low back pain.[a]

[b] It is suggested that 'back schools' are more effective when combined with interventions such as cognitive behavioural therapy, operant conditioning, a worksite visit or an intensive physical training programme. [b]

[b] Normal activity is better than either extension/lateral bending exercises or bedrest for acute exacerbations of chronic back pain or a new episode of acute back pain. [b]

Further reading

Back Pain. *Report of a CSAG Committee on Back Pain* (Chaired by M. Rosen). London: HMSO, 1994.

Cohen JE, Goel V, Frank JW, Bombardier C, Peloso P, Guillemin F. Group education interventions for people with low back pain: an overview of the literature. *Spine,* 1994; **19:** 1214–22.

Evans G, Richards S. Low back pain: an evaluation of therapeutic interventions. University of Bristol, Health Care Evaluation Unit; p. 176.

Koes BW, Vantulder MW, Vanderwindt DAWM, Bouter LM. The efficacy of back schools: a review of randomised clinical trials. *Journal of Clinical Epidemiology,* 1994; **47:** 851–2.

Turner JA, Denny MC. Do antidepressant medications relieve chronic low back pain? *Journal of Family Practice,*1993; **37:** 545–53.

Related topics of interest

Assessment of chronic pain – psychosocial (p. 12)
Back pain – injections (p. 22)
Depression and pain (p. 71)
Psychological management of chronic pain (p. 157)

BACK PAIN – INJECTIONS

There are several targets for intervention techniques in the treatment of back pain. There are many nerve pathways implicated in the experience of back pain, and as many enthusiasts for one particular technique as there are uncontrolled reports of efficacy. The treatment of back pain, has however, to be seen in the light of other factors that influence its occurrence and prognosis, and it must be remembered that injections in general, with the possible exception of intrarticular steroid injections, do not alter a disease process.

Before considering any injection, diagnosis must be considered in the light of the multifactorial nature of non-specific low back pain. The disability caused by back pain is out of proportion to pathology. Patients with psychological distress or illness behaviour may have unrealistic expectations of treatment. Nerve blocks should be proceeded by advice on exercise and occupation. The difficulty in assessing the response to a specific nerve diagnostic block lies, in part, with the organization of spinal nociceptor input into the spinal cord: primary afferent fibres project to several segmental levels, this together with the proximity of other sensory nerves leads to difficulties in achieving specificity.

Anatomy

Spinal pain may originate from posterior or anterior structures. Pathology in each may coexist, for example disc pathology leading to strain on the posterior elements.

Posterior structures are innervated by the dorsal primary ramus of the spinal nerve. The structures are:

- facet joints;
- posterior part of the dura;
- ligaments;
- back muscles.

Anterior structures are innervated by networks of nerve plexi which enter the spinal nerve in the sympathetic communicating ramus and project to several levels of the spinal cord. The structures are:

- vertebral bodies;
- longitudinal ligaments;
- discs;
- anterior part of the dura;
- paravertebral muscles.

Of the available targets for nerve block, only the medial branch of the dorsal primary ramus can be described as providing a specific sensory supply to one particular part of the spine, in this case the facet joint. Each facet joint receives a nerve supply from the medial branch of the dorsal primary ramus above and below the joint. The anterior structures do not lend themselves to specific nerve block so easily.

Techniques

1. The posterior structures.

Two recognized techniques for treatment of pain from the lumbar facet joints are intra-articular injections of the facet joint and nerve blocks of the medial branch of the dorsal ramus of the spinal nerve. The two treatments are frequently confused in practice. [b] A distinction needs to be drawn, however, if only because the evidence for long-term benefit of intra-articular injections is not available, but that for radiofrequency destruction of the medial branch nerve is available [b]. Each technique has its enthusiasts. In the absence of any reliable clinical or radiological diagnostic fetaures of a 'lumbar facet syndrome', local anaesthetic blocks of either variety are of diagnostic importance, and may have value in planning surgery by localizing the site of pain. Depot steroids are also used for intra-articular injection.

The medial branch of the dorsal primary ramus can be blocked where it crosses the superior surface of the transverse process of the lumbar vertebra. X-ray imaging is reqiuired for localization. Imaging is also required for intra-articular facet joint injections, the X-ray beam being aligned obliquely to the patient to enable the joint space to be visualized. A therapeutic neurectomy of the medial branch nerve can be achieved with radiofrequency apparatus or a cryoprobe.

2. The anterior structures.

The anterior structures of the spinal column can be blocked by epidural and paravertebral injections. The spinal nerves and the cauda equina cannot of course be blocked by neurolytic substances without

causing havoc to the motor and sensory systems. Similarly, the communicating ramus serving the nerve plexus lies close to the spinal nerve exit foramen and is not accessible to selective nerve destruction. Paravertebral and epidural blocks block the communicating ramus. However, the sympathetic chain, which lies anterior to the plane of the spinal nerves, is accessible to selective block for diagnostic purposes and nerve destruction if appropriate. Injections into the disc itself are used for diagnostic and therapeutic purposes. [c] Radiofrequency lesions of the nerve supply to the disc can also be undertaken through a needle inserted into the disc [c].

The use of epidural steroid injections deserves special mention. The rationale for the use of epidural steroids is the presence of inflammation around nerve roots. There are many reports advocating the use of epidural steroids, but many of these are uncontrolled studies.[a] Of the 12 controlled trials to date, six support the use of epidural steroid for the short-term management of nerve root pain [a]. There is no indication for the treatment of non-specific low back pain with epidural steroids.

Epidural and intrathecal steroids have been used for conditions as diverse as multiple sclerosis, cluster headache, and postherpetic neuralgia. In 1987, some cases of nerve damage were blamed on epidural steroids and for a time the medico-legal advice, in Australia where these cases were reported, was that steroids should not be used. The allegations of nerve damage were not substantiated. The use of epidural depot steroid is discouraged by one of the manufacturers. Depot steroid preparations contain benzylalcohol and/or polyethylene glycol. Polyethylene glycol is a non-ionic detergent that can cause arachnoiditis after intrathecal injection.

There is no evidence to support the practice of repeated epidural injections for relapsing symptoms, although it is difficult to deny a patient who derives short-term relief. Patient and operator should be aware of the drug licence restriction. Every effort

should be made to ensure that the drug is deposited outside the dura.

There are various techniques which can be used in the management of neuropathic pain secondary to scarring in the epidural space. The use of a radiographic contrast medium in the epidural space, the so-called 'epidurogram' can demonstrate lesions around the nerves of the cauda equina. This technique enables the operator to observe the nerve root during injection of drugs into the epidural space, to target the drug to the radiological lesion and free the nerve from scar tissue by a hydrostatic pressure effect. Saline, local anaesthetic, steroids, [c] hyaluronidase and hypertonic saline have been used in this way [c]. A refinement of the technique involves the introduction of a fine catheter into the epidural space and its positioning adjacent to a scarred nerve root.

Further reading

Stolker RJ, Vervest ACM, Groen GJ. The management of chronic spinal pain by blockades: a review. *Pain,* 1994; **58:** 1–20.

Systematic review

Koes BW, Scholten RJPM, Mens JMA, Bouter LM. Efficacy of epidural steroid injections for low back pain and sciatica: a systematic review of randomized clinical trials. *Pain,* 1995; **63:** 279–88.

Related topics of interest

Back pain – assessment and medical management (p. 16)
Nerve blocks – somatic (p. 119)

BENIGN NOCICEPTIVE PAIN – DRUG TREATMENTS

Both opioid and non-opioid drugs are used to treat benign nociceptive pain. Mild pain is treated with aspirin or paracetamol. For more intense pain, non-steroidal anti-inflammatory drugs (NSAIDs), codeine preparations and combinations of codeine and paracetamol are used. [a] Codeine added to paracetamol provides a 5% increase in analgesia, comparable to the difference in analgesic effect between codeine and placebo. Combination preparations are more effective than paracetamol alone [a]. Failure of these drugs indicates a trial of stronger opioid, as discussed below. A failure of response to opioid indicates the possibility of neuropathic pain.

The response to each drug is variable, and different patients may respond to different drugs. It is worth changing drugs after a reasonable time (1 week) on one drug.

Aspirin

Aspirin is an acetylated salicylate with antipyretic activities. It reduces peripheral prostaglandin synthesis by the inhibition of cyclo-oxygenase which catalyses the conversion of arachidonic acid to prostaglandin. Because it causes irreversible inhibition of platelet function, it should be avoided in thrombocytopaenia and bleeding diatheses. It displaces warfarin from plasma binding, leading to an increased effect.

Paracetamol

Paracetamol is analgesic and antipyretic with little anti-inflammatory activity. It has little effect on either peripheral prostaglandin synthesis or platelet activity, although it does inhibit prostaglandin synthesis in the brain.

NSAIDs

NSAIDs are used where there is an inflammatory component to the pain. They have many possible actions:

- inhibition of peripheral prostaglandin synthesis;
- inhibition of spinal cyclooxygenase, thereby affecting spinal nociceptive processing;
- inhibition of the mechanism responsible for the 'windup' phenomenon;
- a central nervous system action independent of prostaglandin synthesis inhibition.

NSAIDs inhibit platelets reversibly, and should be avoided where there is a risk of provoking bleeding. Gastrointestinal effects are a major side-effect: [a] the use of NSAID confers a three-fold increased risk of serious side-effects such as bleeding or perforation, and is particularly dangerous in the elderly, where steroids are being used, or where there is a history of gastrointestinal problems [a]. Other side-effects include asthma and impaired renal function.

Choice of drug is determined in part by the side-effect profile. Ibuprofen has a low incidence (5–15%) of gastrointestinal effects and is a useful first choice as 200–800 mg thrice daily (t.d.s.). Diclofenac, as 50 mg t.d.s., has a higher incidence of gastric side-effects (up to 25%). Misoprostol protects against gastrointestinal side-effects and is available as a combination preparation with NSAID. Another approach to the prevention of side-effects is the specific targeting of the drug to the cyclooxygenase isoenzyme responsible for inflammation (COX2) rather than the isoenzyme responsible for the side-effects. [b] Meloxicam is a COX 2 inhibitor with a better side-effect profile [b]. [a] Tenoxicam is better tolerated than indomethacin [a].

Opioid drugs

Opioid drugs are analgesics the action of which is mediated via receptors in the central nervous system. Three types of receptors are involved in the analgesia of opioids: these are the μ, κ and δ receptors. Receptors are identified in the brain, the spinal cord, and afferent neurons. Receptor sensitivity may be enhanced by an inflammatory process. Some of the action of opioid drugs may be mediated indirectly via an action on adrenergic and serotoninergic modulation of the spinal cord. Presynaptic action on the primary afferent C fibre is believed to be an important site of action. There is evidence for a synergistic action of morphine and local anaesthetic, NSAID or ketamine in the prevention of the experimental condition known as 'windup phenomenon'.

Most clinically useful opioids are μ agonists, but some use has been made of partial agonists such as

buprenorphine and nalbuphine. Buprenorphine is a partial μ agonist, and nalbuphine a partial κ agonist which has antagonistic actions at the μ receptor. Tramadol is a μ, κ and δ agonist which stimulates the release of serotonin and inhibits the reuptake of noradrenaline.

It is useful to consider opioids as weak or strong depending on their relative efficacy. Codeine is a weak opioid, whose effects are maximum at about 200 mg/day. Strong opioids include morphine, its prodrug diamorphine, methadone and fentanyl. Fentanyl is available as a transdermal patch, providing 72 hours of continuous delivery.

Side-effects

The side-effects of opioids, in the context of the chronic pain sufferer, need careful consideration.

1. Respiratory depression can complicate the acute administration of opioids, but it can be ignored in the context of careful titration of dose in the chronic sufferer.

2. Sedation may complicate the chronic use of opioids, but it may resolve with the onset of tolerance.

3. Dependence is described as physical or psychological. Physical dependence is the potential for the development of an abstinence syndrome following abrupt dose reduction. Psychological dependence is a craving for drug on withdrawal and the associated drug-seeking behaviour. Dependence has been studied in volunteers who do not have pain, and in subjects who have a history of addiction to opioids. Dependence has not, however, been studied in a population of chronic pain sufferers. There is therefore no valid clinical reason to promote the idea that any one drug is better for chronic use than another on the basis of lack of street demand for the drug.

4. Tolerance is the diminution of effect of drug with time, or the need to increase dose to maintain

an effect. Tolerance is considered as a normal and expected response of no harmful significance. Tolerance extends the usefulness of the drug, since tolerance to side-effects also occurs. Tolerance is a result of several mechanisms:

- A pharmocokinetic action, such as the induction of enzymes, or the presence of metabolites with antagonist properties (e.g. morphine-3-glucuronide).
- A pharmacodynamic action that results from changes in the drug receptor.
- A psychological action, as a consequence of the behaviour of taking analgesia on an 'as required' (pain contingent) basis.

There are other reasons why drug effect may reduce with time. These include changes in modulatory processes, the effect of worsening pathology and the development of psychological distress or depression. They do not constitute tolerance.

5. *Constipation* remains a problem in patients on weak and strong opioids. Tramadol is said to cause fewer problems with constipation.

The management of chronic pain of non-malignant origin with opioids is controversial. There are no controlled trials to support the principle, but there are much published data supporting the practice. It is said that a properly designed trial would pose particularly difficult ethical and technical problems. [c] Significant benefit at doses of morphine up to 40 mg/day has been reported [c].

Argument for the use of opioids

In support of this view are observations that many patients can become stabilized on a dose of opioid after initial dose increases. Such patients do not develop dependence although they may become tolerant to the initial dose.

Argument against the use of opioids

The suggestion that neuropathic pain is poorly responsive to opioids is used to justify avoiding the use of opioids unless a nociceptive cause for the

pain is likely. Chronic pain is a multidimensional experience, and it is unlikely that all aspects of it will be addressed by a single drug. Taking any analgesic drug on 'as required (or pain contingent)' basis reinforces illness behaviour, and requires the patient to seek the help of external factors. This is particularly the case where the patient requires a nurse or partner to administer an injection. There is potential social harm in having a population of opioid users in the community.

Guidelines for the use of opioids in non-cancer pain

The prescriber should be aware that compound analgesics contain opioids such as codeine, and that the principles apply as much to codeine as they do to morphine.

The onus is on the prescriber to explain the purpose of using opioids, and to help the patient understand that relief of pain is less important than restoration of normal function and behaviour.

The patient should understand that the drug is not being used to provide complete pain relief, and that assessment of efficacy will be made in respect of function and behaviour as well as comfort.

Opioids should be prescribed on a time contingent (regular), rather than a pain contingent (as required) basis. This may minimize the risks of development of illness behaviour and psychological tolerance, and establishes a baseline level of analgesia alongside which coping strategies can be developed. A long-acting preparation such as methadone or slow-release morphine is appropriate for this strategy.

Dose can be titrated against response. In the same way that tolerance to the analgesic effects occurs, so it does to the side-effects. The response must consider whether the patient's disability is being relieved as a result of the action of the opioid. If it is not, then a further increase is not appropriate.

A *short* trial of drug is appropriate. The risks of physical or psychological dependence can be ignored if the patient selection has been appropriate.

Frequent review is important, and any other factors that might contribute to distress should be addressed before an increase in dose is sanctioned.

Indications for opioid administration in non-cancer pain	• A reasonable certainty that nociceptive factors are contributing to the pain. • Failure of all other reasonable treatments if neuropathic factors are contributing to the pain.
Contraindications to opioid administration in non-cancer pain	• Any history of substance abuse, either prescribed or illicit.

Further reading

Abramson S. Therapy with and mechanisms of non-steroidal anti-inflammatory drugs. *Current Opinion in Rheumatology,* 1991; **3:** 336–40.

Portenoy RK. Opioid tolerance and responsiveness: research findings and clinical observations. In: Gebbart GF, Hammond DL, Jensen TS (eds) Proceedings of the 7th World Congress on Pain, Progress in Pain Research and Management,Vol. 2. Seattle: IASP Press, 1994; pp. 595–620.

Systematic reviews

de Craen AJM, Di Giulio G, Lampe-Schoenmachers AJEM, Kessels AGH, Kleijnen J. Analgesic efficacy and safety of paracetamol codeine combinations versus paracetamol alone: a systematic review. *British Medical Journal,* 1996; **313:** 321–5.

Riedemann PJ, Bersinic S, Cuddy LJ, Torrance GW, Tugwell PX. A study to determine the efficacy and safety of tenoxicam versus piroxicam, diclofenac and indomethacin in patients with osteoarthritis: a metaanalysis. *Journal of Rheumatology,* 1993; **20** (12): 2095–103.

Watson MC, Brookes ST, Kirwan JR, Faulkner A. The comparative eficacy of non-aspirin non-steroidal antiinflammatory drugs for the management of osteoarthritis of the knee: a systematic review. In: Bombardier C, Nachemson A, Deyo R, de Bie R, Bouter L, Shekelle P, Waddell G, Roland M (eds). Musculoskeletal module of the Cochrane database of Systematic reviews. The Cochrane Library, The Cochrane Collaboration issue 1, Oxford. 1997.

Related topics of interest

Assessment of chronic pain – psychosocial (p. 12)
Cancer – opioid drugs (p. 48)
Ketamine (p. 89)
Mechanisms in nociception (p. 92)
Mechanisms in peripheral and central neuropathic pain (p. 94)

BOTULINUM TOXIN–HAEMAGGLUTININ COMPLEX

Botulinum toxin is licensed for the symptomatic treatment of blepharospasm and hemifacial spasm. It is used without licence to relieve pains due to other types of muscle spasm.

The pharmaceutical preparation contains botulinum toxin of the type A serotype, serum albumin and sodium chloride. The botulinum toxin was first isolated in 1895 from the food and victims of food poisoning. It was then first recognized as a neurotoxin.

Mechanism

The neurotoxic action reduces neuromuscular transmission thereby causing skeletal muscle weakness and inhibition of muscle spasm. Botulinum toxin selectively acts on peripheral cholinergic nerve endings. It enters the nerve terminal and causes localized chemical destruction. This prevents the release of acetylcholine at the neuromuscular junction. Efficient neuromuscular transmission depends on the release of acetylcholine from the axonal terminal and its binding to the postsynaptic receptors to effect the muscle action potential. Without the synthesis and release of acetylcholine the muscle action potential is prevented. After the nerve end plate has shrivelled it starts to regenerate by sprouting. When the sprouts reach the muscle surface a new neuromuscular junction has formed. Regeneration takes approximately 3 months. When it is complete, tone and muscle spasms recur. At that stage the injection of botulinum toxin can be repeated indefinitely. Tachyphylaxis has been shown.

Pharmacokinetics

Botulinum toxin is given intramuscularly to affected peripheral muscles. Its spread is dependent on the dose of drug and the volume of diluent. It is taken up by neuronal transport to the spinal cord where it is broken down to inactive metabolites.

Use

Botulinum toxin is available in single-patient use vials each containing 100 units. The preparation is freeze dried. It is recommended that it be reconstituted with normal saline although workers in

the USA are using local anaesthetic as solvent to enhance the speed of onset of effect. Diluted with normal saline the onset of action is at approximately 3 days and the effect peaks at 1–2 weeks post-administration. Injections are sometimes carried out under electromyographic control or with the use of radio-opaque dye and fluoroscopy.

The manufacturer's recommended maximum dose in the treatment of blepharospasm is 100 units per 12 weeks. The maximum dose used by workers in the USA for the relief of other muscle spasms is 400 units per 12 weeks. The LD_{50} for single use in a 70 kg person is 3000 units. Depending on the size and number of muscles needing treatment, doses as small as 1.25 units are used for blepharospasm and 30 units for painful conditions secondary to muscle spasm. Inhibition of muscle activity of 50% allows the performance of otherwise difficult physiotherapy. The physiotherapy brings further improvement in muscle function and pain.

The painful conditions in which botulinum toxin has been used are as follows.

1. Cervical dystonia. Over 70% have pain. [c] The injection of doses of botulinum toxin ranging from 100 to 236 units has given relief of spasm with consequent reduction in pain [c]. During the period of relief physiotherapy can be performed more easily.

2. Myofascial pains. [c] Botulinum toxin has been used to treat myofascial pains of the neck, shoulder and low back [c]. Injections have also been carried out to psoas and quadratus lumborum muscles.

3. Painful muscle spasms. [c] Muscle spasm precipitating pain in conditions such as multiple sclerosis has been treated [c].

4. Painful contractures. [c] Secondary contractures resulting from neurological deficit such as cerebrovascular accidents or from disuse as in the complex regional pain syndromes (CRPS) can be

relieved by botulinum toxin [c]. In CRPS particularly, the value of the period of inhibition of muscle spasm is the opportunity it provides for intensive physiotherapy.

5. Postural pains. [c] Pain caused by an abnormal posture forced by muscle spasm can be treated by botulinum toxin [c].

Side-effects

Local muscle weakness can occur from local spread of drug. Injections into the neck may thus affect swallowing. Misplaced injections can more extensively paralyse nearby muscle groups. Excessive doses may paralyse muscles distant to the site of injection. Spread is affected by both dose and volume of diluent. Generalized malaise, about which the patient should be informed, can follow the treatment.

Botulinum toxin is potent in reducing muscle spasm and although currently unlicensed for the purpose, there is a place for it in the relief of muscle spasm which causes pain. It has been found to have few side-effects. The established regeneration of nerve makes it acceptable in terms of no long-term destructive effect. It offers a useful addition to the pain clinician's armamentarium as a drug which not only relieves pain but also improves function.

Further reading

Jancovic J, Brin MF. Therapeutic uses of botulinum toxin. *New England Journal of Medicine*, 1991; **324**: 1186–94.

Related topics of interest

Complex regional pain syndromes I and II (p. 62)
Multiple sclerosis (p. 103)

CANCER – INTRATHECAL AND EPIDURAL INFUSIONS

Intrathecal and epidural infusions are used not only in cancer pain but also in acute pain and selected benign chronic pains. In chronic benign pain appropriate patient selection is very important and the importance of long-term commitment of both patient and physician should not be underestimated.

The principle of these routes of delivery is that small doses of analgesic drug are deposited in relatively high local concentrations, near to a spinal site of analgesic action. The need for systemic administration of drug is eliminated or reduced allowing sparing of systemic doses and consequent reduction in side effects. The delivery of two synergistically acting drugs allows further sparing of dosage. Worldwide it is estimated that 3–5% of cancer patients could benefit from this mode of administration.

Indications for these infusions are:

- uncontrolled nociceptive pain, despite adequate trials of drugs by other routes;
- uncontrolled neuropathic pain, despite adequate trials of drugs by other routes;
- intolerable side-effects such as drowsiness or hallucinations from the use of drugs by other routes making their continued use unacceptable;
- to allow a short period of respite from high-dose opioids in cases of apparent opioid resistance.

Contraindications are:

- lack of patient consent;
- coagulopathy (consider in the presence of liver disease);
- local sepsis or septicaemia;
- very limited life expectancy.

The relative merits of each route have to be considered in deciding between intrathecal or epidural infusions.

Advantages of epidural infusions

- Placement of an epidural line is technically easier.
- There is no leak of cerebrospinal fluid.
- Infection rates are lower.

Advantages of intrathecal infusions

- A smaller volume and dose of injectate is required so there is less systemic uptake of drug.
- Segmental analgesia is not a problem.
- Smaller volumes make it possible to use implanted reservoir systems as part of the technique.

- If infection is suspected, cerebrospinal fluid (CSF) can be sampled for microbiological investigation.

Drugs

Although the use of drugs for an unlicensed purpose is common practice in treatment of chronic and malignant pain it should not be undertaken lightly. With the exception of bupivacaine no drugs are licensed for epidural or intrathecal administration. Great care should be exercised in doing so and the patient should be informed of the risk undertaken. Particular attention should be paid to neurotoxicity of preparations.

Opioids are very commonly used. Hydrophilic drugs such as morphine are more likely to spread cephalad and to have systemic side-effects. Fentanyl and diamorphine are more commonly used. [c] Good results with spinal opioids have been seen in patients with deep, constant, intractable somatic pain. They do, however, have an effect on neuropathic pain [c].

Most often opioids are used in combination with local anaesthetics.

[b] Clonidine brings added relief in benign pain and is commonly used in malignant pain [b]. It is of use when pain remains uncontrolled despite infusions of both opioid and local anaesthetic. It is effective through agonist actions at the $\alpha 2$ receptors of the dorsal horn.

[c] Other drugs such as baclofen have been used effectively [c].

Technique

(a) Systemic opioids are reduced as opioid are introduced intrathecally or epidurally. An initial reduction in dose of at least 50% is recommended to minimize the risk of respiratory depression at the time of starting the infusion whilst still preventing a withdrawal syndrome. Amounts of fentanyl delivered from fentanyl patches must be reduced. As the half-life of a fentanyl patch is 17 hours, patch dose must be reduced several days before the commencement of intrathecal/epidural opiate infusion. Supplementary oral morphine must be given during the period when the fentanyl patches are being reduced and the patient awaits the procedure. Breakthrough doses of oral morphine may be needed after starting the infusion.

(b) Informed consent is taken.

(c) Conventionally catheters have been tunnelled subcutaneously. There are however conflicting views as to the usefulness of this in protecting against infection. The externalization site of the tunnelled catheter is planned and marked, giving consideration to positional factors such as sites of waist bands and stomata. Catheters are tunnelled to the abdominal wall or the anterior chest wall.

(d) Local anaesthetic cream is applied preoperatively to the skin beneath which tunnelling will take place (marked by the operator).
(e) Prophylactic antibiotics are recommended by some workers.
(f) Both the epidural and intrathecal placement of lines involve percutaneous access through an introducer needle (e.g. Tuohy needle).
(g) Epidural catheters are placed in the lumbar, thoracic or cervical region dependent on the level of pain.
(h) Intrathecal catheters are placed in the lumbar region and if required they are directed cephalad.
(i) The catheter can be connected to an external infusion pump/syringe driver via further tubing and filter(s).
(j) Intrathecal catheters can be attached to a subcutaneous injection port, a subcutaneous reservoir, a patient activated implanted reservoir system or a programmable implanted reservoir system.

Problems and solutions

Some problems are due to the placement and use of the catheter and some are due to the drugs infused.

Immediate

Local anaesthetic can cause hypotension, bradycardias, weakness or paralysis depending on the degree and height of sympathetic and motor block. Hypotension is treated by lying the patient flat, giving oxygen, intravenous fluids and where necessary vasopressors (ephedrine 3 mg intravenously (i.v.) increments, titrated against response). Bradycardia is treated with atropine increments of 0.3 mg i.v. Weakness affecting the muscles of respiration may necessitate ventilatory support. Opioids can cause respiratory depression or drowsiness. This can be treated by administering oxygen, naloxone 0.1 mg i.v. increments titrated against response and ventilatory support if necessary. Clonidine can cause hypotension and drowsiness.

Early

Throughout the time of infusion bupivacaine can cause numbness and weakness. It may be inevitable. It has to be balanced against the need for local anaesthetic to provide analgesia. Pruritus, urinary retention and nausea and vomiting are side-effects of opioid infusions. They are usually transient but should be dealt with symptomatically as they occur.

Pruritus can be treated with chlorpheniramine or naloxone.

Late

Infection is a serious consequence of these techniques. It may be heralded by pyrexia, leukocytosis or neurological deficit. The intrathecal line allows sampling of CSF for microscopy, culture and sensitivity determination before its removal. The suspicion of an infected epidural line necessitates its removal for microscopy culture and antibiotic sensitivity of the tip.

Tachyphylaxis to both local anaesthetics and opioids occurs requiring increasing doses to achieve the same effect.

Long-term management of lines

Once the patient is reasonably pain free and without side-effects, the catheter can be managed within the community. Support and backup from the hospital is maintained. Protocols for management are drawn up and training is given to carers.

Intrathecal infusions controlled by syringe drivers are infused at a rate of 10 ml/24 hours. This necessitates daily changing of the syringe, a task which can be undertaken by community nursing staff or relatives. Strict asepsis must be observed. Reservoirs are replenished by hospital staff.

Epidural infusions require much larger volumes. These tend to be made up by hospital pharmacies under aseptic conditions.

Regimes for the change of dressings for exteriorized lines must pay attention to infection control.

There should be daily inspection of exit sites or injection ports and daily recording of temperature, mobility and pain control.

Further reading

Anderson PE, Cohen JI, Everts EC, Bedder MD, Burchiel KJ. Intrathecal narcotics for relief of pain from head and neck cancer. *Archives of Otolaryngology – Head and Neck Surgery*, 1991; **117**: 1277–80.

Onofrio BM, Yaksh TL. Long term pain relief produced by intrathecal morphine infusion in 53 patients. *Journal of Neurosurgery*, 1990; **72**: 200–9.

Ventafridda V, Caraceni A, Sbanotto A. Cancer pain management in cancer pain. Pain Reviews, 1996; 3 (3): 153–79.

Related topics of interest

Cancer – non-opioid drugs (p. 44)
Cancer – opioid drugs (p. 48)
Cancer pain – mechanisms and pathology (p. 53)

CANCER – NERVE BLOCKS

The use of nerve blocks in cancer is less widespread than it has been. A better understanding of the use of morphine, less reluctance to use it for fear of dependence, and improvements in preparations of strong opioids, together with advances in psychological support, have resulted in an improvement in cancer symptom control. Nevertheless it was estimated, in 1989, that 10% of patients treated with morphine and similar drugs could not tolerate treatment, and a further 10% obtained no significant pain relief. Even with the introduction of alternative methods of opioid delievery, such as the spinal route, there remains a group of patients in whom a nerve block or nerve destruction procedure is appropriate which, if successful, will allow a substantial or total reduction in opioid dose and associated side-effects. Nerve destruction is optimally carried out after assessment of the response to a local anaesthetic block: this step may be omitted if urgency or logistics dictates and the indications for nerve destruction are obvious. A local block may be of value, however, in that a response to a block may outlast the pharmacological action of the local anaesthetic, and chemical neurolysis may be postponed while repeat local anaesthetic procedures are carried out.

Indications for nerve blocks Pain should be localized or unilateral. Many patients with cancer have more than one pain: in this case, the pain site that is considered for nerve block should be considered to be a major problem in its own right. Visceral and somatic pain is more appropriately treated with nerve blocks than neuropathic pain. Opioids should have been tried and found wanting, either because of failure to achieve analgesia or because of unacceptable side-effects.

Choice of method Block of the sympathetic ganglia or chain is effective for the treatment of visceral pain, and has the specific advantage over blocks of the somatic nerve roots of preserving bladder and bowel control and normal sensation and movement. The choice lies between somatic blocks: intrathecal, epidural, peripheral nerves, interpleural, and blocks of the sympathetic ganglia or the nerves travelling through them.

Specific techniques *1. Intrathecal injections.* The intrathecal route for neurolysis is particularly useful for unilateral pain

that is limited to the distribution of a few dermatomes. Major side-effects are sensory and motor loss, and loss of sphincter control. Intrathecal injections of neurolytic substances are used to destroy the dorsal (sensory) root of the spinal cord. The technique depends on the influence of gravity in distributing hypobaric and hyperbaric solutions of neurolytic substances through the cerebrospinal fluid, and the patient must be positioned accordingly. Furthermore, it is important to remember that the spinal cord is shorter than the spinal column and that for lesions of the lower thoracic roots, lumbar and sacral roots, the substance must be deposited at a more cephalald level than the exit foramen. Absolute alcohol is hypobaric, and the patient must be positioned with the target root uppermost. Phenol in glycerol is a hyperbaric solution which requires the patient to lie on the side of the lesion.

Side-effects are prevented by a technique which allows the cooperation of the patient to report untoward motor loss. Alcohol causes pain in the appropriate dermatomal distribution, phenol results in a sensation of warmth. These observations allow the conscious patient's position to be altered slightly if, after injection, the target for the lesion has been missed. The block can be repeated, avoiding the risk of using too great a volume of neurolytic substance at any one time.

2. *Epidural injections.* A more widespread pain than those treated by intrathecal neurolysis can be treated with epidural neurolysis. The placement of an epidural catheter allows the adequacy of a local anaesthetic block to be evaluated, and allows phenol (in aqueous solution) to be added on an incremental basis, thus minimizing the risk of motor block.

3. *Interpleural injections.* Relief of the pain of tumour in the pleura and chest wall following the interpleural injection of phenol has been reported. The greater splanchnic nerve can be blocked via the interpleural route, as an alternative to coeliac plexus block.

4. *Peripheral nerve injections.* Many possible clinical indications exist, for example the use of intercostal phenol to treat the pain of an isolated rib metastasis. An alternative is the use of a catheter technique for local anaesthetic infusions. Chemical neurolysis of a nerve trunk will produce motor block and sensory block: in the context in which it is administered (i.e. terminally ill and bed-bound) this may be a small price to pay for comfort.

5. *Coeliac plexus block.* This remains a useful method for the relief of visceral pain associated with cancer of pancreas and stomach. The efferent sympathetic block, in addition, results in an increase in gastric motility, with reduction in nausea and constipation. Following a successful coeliac plexus block, opioid consumption can be greatly reduced. Tumour may alter the anatomy of the region, making the block technically difficult. [a] Neurolytic coeliac plexus block has been shown to be effective in 90% of patients with pancreatic or non-pancreatic cancer pain [a].

6. *Hypogastric plexus block.* This has an application for the treatment of pain from pelvic malignancy, although, as above, anatomy may be distorted by tumour.

7. *Percutaneous anterolateral cordotomy.* This is a technique which is available in a few centres where it is offered to patients with unilateral pain. The technique involves the positioning of a radiofrequency lesioning probe in the spinothalamic tract at the level of the second cervical vertebra on the side opposite to the pain (the spinothalamic tract crosses the midline of the spinal cord just cephalad to the relevant dorsal horn). The procedure is performed with the patient lying supine and conscious, because the response to stimulation of the spinothalamic tract has to be noted. It is thus a major undertaking for the type of patient who could theoretically benefit most from it (chest wall pain

from lung cancer or mesothelioma). Lesions of the tract corresponding to the lumbar and sacral dermatomes are easier than those for the cervical dermatomes. Immediate complications include respiratory depression from phrenic nerve damage, late complications include central neuropathic pain.

Further reading

Carr D, Eisenberg E, Chalmers TC. Neurolytic celiac plexus block for cancer pain – a meta analysis. *Proceedings of the 7th World Congress on Pain, Paris.* Seattle: IASP Press, 1993; 338.

Stuart G, Cramond T. Role of percutaneous cordotomy for pain of malignant origin. *Medical Journal of Australia*, 1993; **158**: 667–70.

Related topics of interest

Cancer – opioid drugs (p. 48)
Mechanisms in peripheral and central neuropathic pain (p. 95)
Nerve blocks – autonomic (p. 115)
Nerve blocks – somatic (p. 119)

CANCER – NON-OPIOID DRUGS

These comprise treatments for neuropathic pain, non-narcotic analgesics, and a number of drugs with other principal activity but which are of recognized benefit to cancer pain. The management of neuropathic pain in the cancer patient is the same as in the patient with benign disease.

Non-narcotic analgesics

Non-narcotic analgesics such as paracetamol, the salicylates and the non-steroidal anti-inflammatory drugs (NSAIDs) are analgesics, anti-inflammatory treatments and antipyretics, with varying potencies for each of these actions.

The World Health Organisation (WHO) recommends a non-narcotic analgesic for mild to moderate pain and recommends NSAIDs as a supplement to opiates for bone pain or soft tissue invasion. NSAIDs are of particular use when there is an inflammatory component to the pain. The use of an NSAID may allow sparing of the dosage of morphine. NSAIDs have a ceiling effect so recommended doses should not be exceeded.

Individual toxicity and patient response governs choice of NSAID. Patient response to each drug is variable and lack of response to one does not imply lack of response to others. For analgesic effect the drug should be tried for up to 2 weeks and if it is not successful another should be tried. Treatment should start with those of lowest toxicity. Ibuprofen has a low incidence of gastrointestinal side-effects (5–15%) and is a useful first choice at 200–400 mg t.d.s. Diclofenac has up to 25% side-effects at a dose of 50 mg t.d.s. Misoprostol protects against gastrointestinal side-effects and is available in combination with an NSAID. Another approach to the prevention of side-effects is the targeting of the drug to the cyclooxygenase isoenzyme responsible for inflammation (COX2) rather than the isoenzyme responsible for side-effects (COX1). [b] Meloxicam is a COX2 inhibitor with a better side-effect profile[b]. [a] Tenoxicam is better tolerated than indomethacin[a].

Most NSAIDs are given orally but suppositories are available and ketorolac and diclofenac can be given parenterally. NSAID suppositories are used in the treatment of tenesmus. NSAIDs should not be given to patients with hepatic or renal impairment, or peptic ulcer disease and should be used with caution in the elderly. Side-effects include worsening of asthma, bleeding diatheses, dyspepsia or peptic ulceration and acute renal impairment.

Corticosteroids

[b] Pain with an inflammatory component can also be treated with corticosteroids[b]. These reduce perineural oedema and are therefore used in central nervous system

and spinal cord tumours. They are standard therapy for tumour-induced spinal cord compression. They are used in brachial or lumbosacral plexus invasion and can reverse early nerve compression. Pain from organ infiltration can benefit from corticosteroids. Pain from liver infiltration is improved by their effect in reducing capsular inflammation. They are given orally or intravenously. Suggested regimens are dexamethasone 2–24 mg/24 hours orally or a half to a third of this dose intravenously, or prednisolone 40–100 mg/24 hours orally. They should not be administered later than the early evening so sleep disturbance is avoided. Steroid enemas are used for the treatment of tenesmus.

Side-effects include adrenal axis suppression, sodium and water retention and hypertension, gastritis and peptic ulceration, reduced cell mediated immunity and increased risk of infection, mood alteration and psychoses, hyperglycaemia, increased requirements for insulin and weight gain, myopathy and osteoporosis.

Bisphosphonates

These are analogues of endogenous pyrophosphates which inhibit osteoclastic bone resorption.[c] They are effective in the treatment of cancer-associated hypercalcaemia[c]. Increasingly they are used to treat intractable bone pain, particularly in myeloma. Pamidronate and clodrinate may be effective in reducing malignant bone pain. Clodrinate can be given orally and intravenously. Pamidronate must be given by intravenous infusion. Other bisphosphonates with therapeutic potential are aminohexane, risedronate and alendronate.

Calcitonin

[c] This also inhibits osteoclastic resorption of bone and is used effectively in the treatment of hypercalcaemia of malignancy[c]. It has been said to be effective in the treatment of malignant bone pain at a dose of 100 IU b.d. subcutaneously.

Nifedipine

[c] Nifedipine at a dose of 5–10 mg t.d.s. is used for the treatment of painful oesophageal spasm and the relief of tenesmus [c].

Hyoscine butlybromide

[c] Colic due to malignant intestinal obstruction can be relieved by the smooth muscle relaxant hyoscine given 10–20 mg parenterally t.d.s. or 60–120 mg/24 hours by subcutaneous infusion[c].

Oxybutinin

[c] Painful bladder spasms may be relieved by oxybutinin. Patients should be warned of anticholinergic side-effects [c].

Baclofen

[c] The oral administration of baclofen, a γ-amino butyric acid (GABA) receptor agonist is used for the treatment of painful muscular spasms, 5 mg t.d.s. up to a maximum of 100 mg/day [c]. It has also been used experimentally spinally. Unpleasant side-effects such as sedation, fatigue and hypotonia occur.

Lignocaine

[c] The subcutaneous infusion of lignocaine titrated against response with attention to toxic doses has been of effect in cancer pain [c].

Nitrous oxide

A mixture of 50% nitrous oxide and 50% oxygen produces analgesia without loss of consciousness. It is self-administered using a demand valve. Excessive exposure by continuous use or frequent intermittent use causes megaloblastic anaemia from interference with vitamin B12 synthesis. This might be considered an acceptable risk in a patient of short life expectancy.

Chemotherapy/radiotherapy

Specific cancer therapy may relieve pain if the cause of pain is direct tumour involvement. Careful evaluation of overall potential benefit has to be made before undertaking what can be unpleasant treatment.

Further reading

Regnard CFB, Tempest S. *A Guide to Symptom Relief in Advanced Cancer*, 3rd edn. Haigh and Hochland, 1992; ISBN 1-869888-07-3.

Systematic reviews

Riedemenn PJ, Bersinic S, Cuddy LJ, Torrance GW, Tugwell PX. A study to determine the efficacy and safety of tenoxicam versus piroxicam, diclofenac and

indomethacin in patients with osteoarthritis: a meta-analysis. *Journal of Rheumatology,* 1993; **20** (12): 2095–103.

Watson MC, Brookes ST, Kirwan JR, Faulkner A. The comparative of non-aspirin non-steroidal anti-inflammatory drugs for the management of osteoarthritis of the knee: a systematic review. In: Tugwell P, Brooks P, Wells G, de Bie R, Busi-Ferraz M, Gillespie W (eds) *Musculoskeletal Model of the Cochrane Database of Systematic Reviews.* The Cochrane Library. The Cochrane Collaboration Issue 1, Oxford: Update Software; 1997.

Related topics of interest

Cancer – intrathecal and epidural infusions (p. 35)
Cancer – opioid drugs (p. 48)
Cancer pain – mechanisms and pathology (p. 53)
Neuropathic pain – drug treatments (p. 128)

CANCER – OPIOID DRUGS

Pain in advanced malignancy can usually be controlled by drugs. Opioids are the mainstay of treatment. They are used either alone or in combination with other analgesics. Pain may be uncontrolled despite the use of high-dose opioids. The principles of treatment of cancer pain are geared to optimizing treatment.

Principles of cancer pain treatment

1. Multiplicity. Most cancer patients have more than one pain; 80% have at least two pains.

2. Identification. Each pain must be clearly identified and treated separately.

3. Effectiveness of treatment should be regularly reviewed.

4. Efficacy. Not all pains are adequately treated by opioids. History, examination and investigation determine whether a pain is nociceptive and likely to respond to opioids or neuropathic and less likely to respond to opioid drugs and require antidepressants, anticonvulsants and other membrane-stabilizing drugs, etc. Other adjunctive treatments such as steroids may be needed. To ensure that a pain is still opioid sensitive, the breakthrough dose should be given (see later) and the patient reassessed for pain control after 20 minutes.

5. Doses of opioid should be increased for as long as the patient remains in pain and that pain responds to the opioid.

6. Side-effects. There must be close attention to and treatment of side-effects of opioid therapy, (e.g. constipation).

Choice of opioid drug

Guidance to the use of analgesics in cancer pain is given by the World Health Organisation as the 'analgesic ladder'. There is, however, no scientific evidence to support the use of drugs in this way.

1. *Step 1.* Non-opioid e.g. aspirin, paracetamol or non-steroidal anti-inflammatory drug (NSAID).

2. *Step 2.* Weak opioid e.g. codeine, with or without non-opioid.

3. *Step 3.* Strong opioid e.g. morphine, diamorphine or fentanyl, with or without non-opioid.

NSAIDs are the non-opioid of choice in steps 2 and 3 and are recommended in metastatic bone disease or soft tissue infiltration. Recommendations are ibuprofen 200–800 mg t.d.s. orally or diclofenac 50 mg t.d.s. orally.

Choice of route

1. Oral. The oral route is always preferable, unless precluded because of weakness, coma, dysphagia, vomiting or poor enteral absorption. Parenteral routes are not indicated simply because therapy is ineffective. Oral opioid treatment begins at step 2 of the analgesic ladder with codeine. Codeine is a prodrug of morphine. It is available in tablets of 30 mg and 60 mg and in various combinations with non-opioid analgesics. Most combined analgesics contain little codeine (8–10 mg). However Tylex, Kapake and Solpadol contain 30 mg of codeine plus 500 mg of paracetamol per tablet. Recommended dose of codeine is 30–60 mg 4-hourly. Codeine is very constipating. Laxatives must be prescribed. Pain uncontrolled by codeine should be treated at step 3.

The bioavailability of morphine may be as low as 20%. It is used in two main forms; one of immediate release and one of controlled or sustained release. Immediate release morphine is available in both liquid and tablet form. It has rapid onset, peak effect within 30–90 minutes, and short duration, usually of 4 hours. Controlled or sustained release morphine preparations have a different absorption profile. Modified release morphine tablets are prescribed on a 12-hourly basis and there are two newer preparations which are prescribed on a 24-hourly basis.

Assessment of requirements and adjustment of dose is accomplished using the immediate release preparation in the following way:

- start oral morphine sulphate solution regularly 4-hourly. Dose suggested for the elderly or frail is 2.5 mg, in others 5–10 mg;
- prescribe the same dose 2-hourly for breakthrough pain;
- if the regular dose is consistently inadequate or does not last 4 hours increase the 4-hourly dose by 30–50%;
- once the patient has been pain free for a period of at least 24 hours the morphine taken in the last 24 hour period should be totalled and prescribed in controlled release form, either as a twice daily dose of MST (total 24 hour dose divided by two) or as a once daily dose of the 24 hour preparations;
- one-sixth of the total daily dose of morphine should always be available as oral morphine sulphate solution for breakthrough pain;
- patients should be warned that drowsiness, dizziness and nausea may occur but wear off within a few days. Anti-emetics may be necessary. Constipation is the main persistent problem, so laxatives must be prescribed.

2. *Subcutaneous.* This route is used only when the oral route is not possible. Drugs are administered through a small cannula. Diamorphine is the drug of choice. (Hydromorphone is used outside Britain.) Its high solubility allows it to be dissolved in a very small volume of infusate. The potency of oral morphine to subcutaneous diamorphine is 3:1 so previous total daily oral morphine dose should be divided by three to give the 24 hour subcutaneous diamorphine dose. When infusing a volume of 10 ml/24 hours the subcutaneous site is effective for approximately 7 days. Breakthrough subcutaneous doses should be given at a sixth of the 24 hour dose. The subcutaneous route is unsuitable where there is oedema, erythema, soreness, a tendency to sterile

abscesses or a coagulopathy. Antiemetics and sedatives can be added to the infusate.

3. *Intravenous.* This may be necessary where subcutaneous infusions have failed.

4. *Rectal.* The oral preparations of immediate release morphine and MST tablets can be given p.r. Suppositories are also available.

5. *Transdermal.* Fentanyl is delivered transdermally in the fentanyl patch. It provides equivalent pain control to morphine on the following basis:

Oral morphine dose mg/24 hours	Fentanyl patch size μg/hour
<135	25
135–224	50
225–314	75
315–404	100
405–494	125
495–584	150
585–674	175
675–764	200
765–854	225
855–944	250
945–1034	275
1035–1124	300

The 25 μg/hour patch is a suitable starting point with breakthrough oral morphine to allow further assessment and titration. Patches come in doses of 25, 50, 75 and 100 μg/hour. To increase the dose above 100 μg/hour, combinations of patches are used. The fentanyl patch is effective and the patient does not need reminding of the need for medication. Each patch delivers the determined dose for 72 hours before it requires renewal. In a small number of patients the patch needs to be renewed after 48 hours. It can take 6–12 hours to achieve analgesic levels in the plasma and levels continue to rise for up to 24 hours. There is a slow fall in levels after the

patch has been removed. After 17 hours plasma levels are at 50%. These kinetics must be taken into consideration in changing from one form of opiate to another. Fentanyl patches have fewer side-effects than morphine, particularly constipation.

Tramadol has a relatively low affinity for μ opioid receptors and its analgesia is only partially inhibited by naloxone, a selective μ opioid receptor antagonist. It has a second analgesic mechanism. It inhibits reuptake of serotonin and noradrenaline, thus modifying the transmission of pain impulses by enhancing serotonergic and noradrenergic pathways. [c] The effects of the individual mechanisms in producing analgesia are modest, but in combination they are synergistic [c]. This allows sparing of μ2 opioid receptor side-effects. Tramadol is used as a transition between weak and strong opioids. It is said to be less constipating than other opioid drugs.

Further reading

Expert working group of the European Association for Palliative Care. Morphine in cancer pain: modes of administration. *British Medical Journal,* 1996; **312**: 823–27.

Lee CR, McTavish D, Surkin EM. Tramadol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in various acute and chronic pain states. *Drugs,* 1993; **46**: 313–40.

Payne R. Transdermal fentanyl: suggested recommendations for clinical use. *Journal of Pain and Symptom Management* (Fentanyl suppl), 1992; **7** (3S): 40–44.

Ventafridda V, Caraceni A, Sbanotto A. Cancer pain management. *Pain Reviews,* 1996; **3** (3): 153–79.

Related topics of interest

Cancer – non-opioid drugs (p. 44)
Cancer pain – mechanisms and pathology (p. 53)
Neuropathic pain – drug treatments (p. 128)

CANCER PAIN – MECHANISMS AND PATHOLOGY

Pain is a common symptom in cancer. Fifty per cent of cancer pain patients report pain at all stages of the disease. Some 3.5 million people worldwide are suffering cancer pain today. Four-fifths of these suffer pain of more than one type, and one-third pain of more than three types. Bone pain is the single most common type of cancer pain. The psychological consequences of chronic cancer pain can be devastating – in addition to the relentless progression of the disease, with increasing pain, the fear of severe disability and death contribute to an experience termed 'total pain'. The management of cancer pain is made more complicated by the observation that the public perception is of a disease in which pain is inevitable. It should be clear that no one pharmacological intervention will be effective in all cases.

Classification of pain

Pain can result from the direct result of the cancer, directly as a result of treatment, or as an indirect consequence of the treatment.

1. Pathology of clinical syndromes in cancer pain.

(a) Direct tumour involvement:

- bone – base of skull, vertebral body, generalized bone pain;
- nerve – peripheral nerve syndromes, plexopathies, spinal cord compression;
- viscera – costopleural syndrome;
- blood vessels;
- mucous membranes.

(b) As a consequence of therapy:

- post-operative – post-thoracotomy, post-mastectomy, post-amputation;
- post-chemotherapy;
- post-irradiation.

(c) Unrelated:

- post-herpetic neuralgia;
- osteoporosis.

Calcium balance in malignancy

Bone resorption and hypercalcaemia occur with and without evidence of metastases:

1. Humoral hypercalcaemia of malignancy results from bone resorption and tubular reabsorption of

calcium and is associated with the production of a protein with parathormone-like activity. Tumours differ in the extent to which each mechanism contributes to the debilitating condition of hypercalcaemia.

2. *Skeletal metastases* cause bone loss by activation of leukocytes which release osteoclast-activating factors. Tumour cells themselves may also have the ability to destroy bone. Skeletal metastases stimulate a local immune response. Skeletal metastases are blood borne. The presence of a single symptomatic metastasis implies that others are present.

Bone pain results from a combination of distortion, (of the bone itself or of a neighbouring nerve), invasion by metastases and release of chemical mediators of inflammation.

CANNABINOIDS

The cannabinoids are derived from the resin of the plant *Cannabis sativa*. The most important pharmacologically active constituent of the resin is 9-tetrahydrocannabinol (δ9-THC). Cannabinoids have a historical place in the management of chronically painful conditions and spasticity, but their use today is illegal.

The claims made for cannabinoids include the following:

- [c] Spasticity is reduced in patients with multiple sclerosis [c].
- [c] Antiemetic action is demonstrated in chemotherapy patients [c].
- [c] Analgesic actions have been demonstrated in humans [c].

There have also been claims that cannabinoids are useful in the treatment of chronic pain. [b] A double-blind comparison with placebo in a patient with prior history of cannabinoid use has demonstrated an opioid-sparing effect in chronic pain [b]. The ethical difficulties in undertaking a randomized controlled trial on patients who have not used cannabinoids in the past are considerable.

Mechanisms of action

The animal experimental evidence for a mechanism includes the following. The brain is probably the site of action, but there is evidence for a spinal cord site of action.

1. Opioid receptor agonism. Perinatal exposure to cannabinoids results in analgesia, morphine tolerance and an abstinence syndrome when given naloxone. Naloxone and other opioid receptor antagonists, specifically the κ1 antagonists block the antinociceptive actions of cannabinoids. They do not prevent the behavioural effects. An effect has been observed when the opioid receptor is blocked by spinal administration.

2. Cannabinoid receptor agonism. The identification and cloning of a specific cannabinoid receptor has been followed by the identification of an endogenous ligand called anandamide. Cannabinoid receptor activation reduces the amplitude of voltage-gated calcium currents, thereby decreasing excitability and neurotransmitter release. The finding of subclasses of receptors offers

potential for separating analgesic actions from the harmful psychotropic actions by the development of synthetic analogues. The spleen contains cannabinoid receptors.

3. Prostaglandin metabolism. Anandamide is an intermediate product of arachidonic acid metabolism. Synthetic cannabinoids have been shown to reduce arachidonic acid-induced inflammation, presumably by an action on inhibition of eicosanoid synthesis.

Pharmacokinetics

Δ 9-THC is highly lipid soluble and readily absorbed from the gastrointestinal tract and lungs. Bioavailability after oral ingestion is about 6%. It has, like other lipid soluble compounds, a large volume of distribution. It is metabolized to polar water-soluble compounds before excretion by the kidney, although intestinal elimination accounts for some of the drug.

Clinical effects

In addition to the actions described above, cannabinoids lower intraocular pressure. Inhalation of the drug is associated with carboxyhaemoglobin production, and intrauterine growth retardation and an increase in childhood leukaemia are features of the children of women who use cannabinoids in pregnancy. Psychiatric syndromes encountered with cannabinoid use include mania, anxiety and depression, and there is a six-fold greater incidence of schizophrenia in heavy users than in non-users.

Any potential clinical benefit in the management of chronic pain must be weighed against the hazards of the drug, and the potential harm that may result from widespread availability and social acceptability if legalization were undertaken.

Further reading

Doyle E, Spence AA. Cannabis as a medicine? *British Journal of Anaesthesia,* 1995; **74**: 359–61.

Holdcroft A, Smith M, Jacklin A, Hodgson H, Smith B, Newton M, Evans F. Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia,* 1997; **52**: 483–6.

Musty RE, Reggio P, Consroe P. A review of recent advances in cannabinoid research and the 1994 international symposium on cannabis and the cannabinoids. *Life Sciences,* 1995; **56** (23–4): 1933–40.

Related topic of interest

Mechanisms in nociception (p. 92)

CENTRAL POST-STROKE PAIN

Central pain is neuropathic pain due to central nervous system (CNS) damage. A CNS disorder must be identified to make a diagnosis of central pain. It is most commonly seen following stroke. It occurs in 2% of stroke victims. There may be a contribution to the pain from the sympathetic nervous system. Other causes of central pain are multiple sclerosis, spinal cord injury and syringomyelia. The central post-stroke pain (CPSP) syndrome was first recognized in 1906 and classically referred to as thalamic syndrome. Subsequently it was realized that lesions causing central pain are not necessarily within the thalamus but in any part of the CNS from spinal cord to cortex.

Pathophysiology

Any lesion of CNS can be implicated as the cause of central pain. No single area has to be involved and there are no patterns of symptomatology for any particular lesion. Loss of afferent input causes neuronal hyperpolarization and increased burst firing. Hyperpolarization of neurones normally involved in nociception signals the sensation of pain. Abnormal burst firing is influenced by the activity of several neurotransmitters including serotonin, noradrenaline, glutamate, γ-amino butyric acid (GABA) and histamine.

Clinical features

Pains presenting after stroke can be related to the stroke indirectly, directly related to the stroke or unrelated. Pains which are indirectly related are:

- nociceptive pain, due to muscular and skeletal problems secondary to paresis, discoordination and poor posture;
- peripheral neuropathic pain, due to postural problems causing nerve entrapment or due to coexisting conditions such as diabetic neuropathy.

Directly related to the stroke is a central neuropathic pain.

1. Central pain. No one pain is pathognomonic for central pain. Most commonly it is described as burning, aching, lancinating, pricking, lacerating or pressing. There may be a background of pain which is constant or intermittent with added paroxysms of

pain. It can be deep or superficial or both. It can be localized, for example to the hand or even only one side of the hand, or it may cover large areas such as the whole of the right or left side or the lower half of the body. Patients find it relatively easy to define the extent of the area of their pain. Sensory loss makes pain more likely. Allodynia or hyperalgesia are present in 75% of sufferers. The development of pain cannot be prevented. It may occur immediately or be noticed only several months after the stroke. Haemorrhages and infarcts are both associated with the syndrome.

2. *Psychological distress* may compound the presentation of pain.

Management

Not every pain in the victim of stroke is CPSP. Other pathology should be actively sought. Pains must be treated separately if necessary. Rehabilitation therapy, physiotherapy and psychosocial support are all necessary for the prevention and management of pain and disability. Psychological support is of particular value because of the autonomic instability of the pain and the predisposition of some stroke victims to emotional lability.

Treatments for central pain

1. Antidepressant drugs. [b] The tricyclic antidepressant drugs are the first line treatment for central pain. Between 50 and 70% of patients respond[b]. Results clearly demonstrate the better analgesic effect of antidepressant drugs compared with placebo. Pain may respond to one drug of the group but not to another. Trials of tricyclic drugs such as amitriptyline, dothiepin and imipramine should therefore be undertaken. Dose should be low initially, increasing as necessary so the benefits are not overcome by side-effects. Doses as low as 10–25 mg o.n. of amitriptyline or 25–50 mg o.n. of dothiepin may be appropriate There may be a place for selective serotonin reuptake inhibitors (SSRIs). [b] Chlorimipramine, a blocker of serotonin uptake is significantly more effective than nortryptiline, a blocker of noradrenaline uptake [b].

2. *Anticonvulsants.* [c] Sodium valproate, carbamezepine or phenytoin are used alone or in combination with the tricyclic antidepressant drugs[c].

3. *Membrane-stabilizing drugs.*

- [c] Patients who have failed to respond to adrenergic tricyclic antidepressant drugs have responded to mexiletine[c]. Unless precluded by dizziness and nausea, dosage is 400 mg stat, 200 mg 6-hourly for 3 days, thereafter 200 mg b.d. or t.d.s.
- The use of phenothiazine preparation should be guarded because of the potential for extrapyramidal side-effects in patients with existing CNS pathology.
- Calcium channel blockers may have a role but this is not clearly defined at present.
- Transcutaneous electrical nerve stimulation (TENS) machines are of limited use.
- Sympathetic nerve blocks are of some short-term use. Response to a diagnostic sympathetic nerve block suggests that drugs such as clonidine may be effective.
- Spinal cord stimulation may have a role and work on the stimulation of the motor cortex has been carried out.
- The suggested involvement of the neurotransmitters, glutamine and GABA in CPSP implies a role for ketamine and baclofen.
- Data about the use of naloxone is conflicting and there is no current clinical indication for its use in CPSP.

Further reading

Jensen TS, Lenz FA. Central post stroke pain: a challenge for the scientist and clinician. *Pain,* 1995; **61**: 161–4.

Related topics of interest

Ketamine (p. 89)
Mechanisms in peripheral and central neuropathic pain (p. 94)
Neuropathic pain – drug treatments (p. 128)
Spinal cord injury and pain (p. 160)
Stimulation analgesia – TENS, TSE and acupuncture(p. 175)
Sympathetic nervous system and pain (p. 179)

COMPLEX REGIONAL PAIN SYNDROMES I AND II

Complex regional pain syndrome type I (CRPS I) was formerly known as reflex sympathetic dystrophy or Sudeck's atrophy. Complex regional pain syndrome type II (CRPS II) was formerly known as causalgia. The former terms were used too loosely to be of value and many symptoms were not identified as the syndromes. Accurate diagnosis of the CRPS is important as early diagnosis and treatment may improve outcome. Diagnostic criteria were therefore laid down.

Diagnostic criteria

CRPS I

Of the following four criteria b, c and d must be present:

(a) an initiating noxious event or cause of immobilization;

(b) continuing pain, allodynia or hyperalgesia which is disproportionate to the inciting event;

(c) evidence at some time of oedema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain;

(d) diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

CRPS II

All of the following criteria must be present:

(a) continuing pain, allodynia or hyperalgesia following a nerve injury, not necessarily limited to the distribution of the nerve;

(b) evidence at some time of oedema, changes in skin blood flow or abnormal sudomotor activity in the region of the pain;

(c) diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

Involvement of the sympathetic nervous system (as defined by the beneficial effect of sympathetic nervous system blockade on pain) is not a synonym for CRPS. CRPS can be sympathetically maintained or sympathetically independent on clinical testing.

The sympathetically independent form tends to have a poorer prognosis.

Pathophysiology

This is unknown. There are several theories.

1. Autonomic nervous system. Classically the inappropriate reaction of the sympathetic nervous system was implicated. This is now challenged. Autonomic involvement is often a feature but is inconstant and varies with time. Abnormalities of blood flow are demonstrated on investigation. This may be attributed to the sympathetic nervous system causing reflex vasomotor spasm and subsequent loss of vascular tone. However, gross limb blood flow is also related to the degree of muscle inactivity. It is thought that increased blood flow may cause excessive bone resorption to account for secondary osteoporotic changes. The degree of osteoporosis is often disproportionate to the degree of disuse.

2. Inflammation. CRPS has signs in common with acute inflammatory processes, namely changes in colour and temperature and the presence of swelling and pain. There is experimental evidence of disturbance of mitochondrial oxygenation. Oxygen extraction in the affected region has been shown to be impaired. Free radicals may be involved in what is possibly an untoward inflammatory reaction.

3. Inactivity. Immobilization or reluctance to use the affected limb severely exacerbates the syndrome and results in secondary changes such as localized osteoporosis, muscle contractures and muscle atrophy. Immobility reduces blood circulation: poor flow may account for the trophic changes seen in skin and nails.

4. Central pain. [c] Although no clear mechanism has been defined, nor any clear link demonstrated, the development of CRPS in two patients following traumatic spinal cord injury and its incidence in stroke victims suggest there could feasibly be a central mechanism. This has been reinforced by

reports that electroconvulsive therapy has caused improvement in pain [c].

5. Psychological factors. Psychological factors significantly affect CRPS and its outcome.

Clinical features

Pain is localized to the limb and described as deep and burning. CRPS has been described as a 'funny pain in a funny looking limb'. The limb is painful to move and demonstrates allodynia and hyperalgesia. It is swollen and often shiny. There may be trophic changes in the nails and loss of hair. The affected limb may be abnormally warm or abnormally cool.

Although there are sophisticated tests which are used in experimental work, the diagnosis is a clinical one. History and examination findings are reinforced by the X-ray finding of localized osteoporosis. Diagnosis can however be made without X-ray findings.

Management

The unclear aetiology is reflected in the many treatments that are tried and their limited successes. The early recognition of the condition and its aggressive treatment is important with regard to outcome.

Relief from intravenous phentolamine (0.5–1.0 mg/kg infused over 20 minutes) suggests the pain is likely to respond to sympathetic blockade. Blockade of the sympathetic nervous system can be intravenous or regional neural sympathetic blocks. Classically intravenous sympathetic blockade is performed by the injection of guanethidine into a limb isolated with a tourniquet. [a] There is no evidence to support the use of intravenous regional sympathetic blockade [a]. However, anecdotal evidence is strong and the technique is often practised. Other drugs which have been used for intavenous regional sympathetic blockade are bretylium, ketanserin, droperidol and reserpine. [b] Ketanserin has been shown to provide relief [b].

[c] Systemic sympathetic blockade can be obtained from drugs such as clonidine, guanethidine or β-blockers [c].

Maintenance of mobility, driven either by the patient or more formally by physiotherapy, is central to improvement of CRPS and prevention of the secondary features. If pain is relieved by sympathetic nervous system blockade, a block can be used to give a period of analgesia during which physiotherapy can be intensive.

[c] Treatments used in other neuropathic pains such as antidepressants, anticonvulsants and other membrane stabilizers offer therapeutic possibilities. The use of capsaicin for a period of 3 weeks is reported to have given a temporary period of almost complete relief [c].

Psychosocial support is important to minimize disability which results from behavioural changes.

[c] Spinal cord stimulation relieved pain and reduced swelling in a small series of patients [c].

[b] Intranasal calcitonin has been used to reduce pain and improve mobility [b].

Recent work implies a role for free radical scavengers such as mannitol.

Further reading

International Association for the Study of Pain, Subcommittee on Taxonomy. Descriptions of chronic pain and definitions of pain terms. *Pain,* 1986; (suppl. 3) 28–30s.

Jang W, Stanton-Hicks H. (eds) *Reflex Sympathetic Dystrophy: a Re-appraisal.* Seattle: IASP Press, 1989.

Paice E. Fortnightly review: reflex sympathetic dystrophy. *British Medical Journal.* 1995; **310**: 1645–7.

Systematic review

Jadad AR, Carroll D, Glynn CJ, McQuay HJ. Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomised double-blind crossover study. *Journal of Pain and Symptom Management,* 1995; **10**: 13–20.

Related topics of interest

Botulinum toxin–haemagglutinin complex (p. 32)
Mechanisms in peripheral and central neuropathic pain (p. 94)
Neuropathic pain – drug treatments (p. 128)
Sympathetic nervous system and pain (p. 179)

CONDUCT OF THE PAIN CLINIC

Scope of the pain clinic

Chronic pain patients are a diverse group of patients, and there is no one recognized medical specialty that can truly claim the responsibility for managing pain. Historically the major impetus for the establishment of specialist pain clinics was cancer pain and the development of techniques for nerve destruction. However, improvements in medical management and overall nursing care of cancer patients has removed the burden of cancer pain from the shoulders of many pain specialists. At the same time the realization that pain clinics have a role in preventing the development of chronically disabling pain has encouraged an interest in behavioural medicine. The general hospital pain clinic manages cancer pain, nerve injury pain, chronic back problems and peripheral vascular disease. Its involvement may be for technical service reasons, such as a sympathectomy to improve blood flow to the ischaemic limb, or it may take the major responsibility for advising primary care about managing a complex medical and psychosocial problem.

The Royal College of Anaesthetists recognizes the specialty of 'pain management' and is responsible for the training of anaesthesia specialists and the recognition of consultant anaesthetist posts. The Pain Society, affiliated to the Association of Anaesthetists of Great Britian and Ireland but by no means the preserve of anaesthetists, is the UK chapter of the International Association for the Study of Pain (IASP) . Many specialties are represented in the worldwide membership of IASP.

Pain as a disease

The pain specialist treats symptoms of pain and a disease that is, for want of a better term, described as the 'chronic pain syndrome'. The chronic pain syndrome is the end result of a variety of pathological and psychological mechanisms that may have included, at some stage, tissue or nerve damage, and in which symptoms have failed to

resolve with healing or repair. The remit of the pain clinician is not dissimilar from that of the physician treating chronic liver disease, diabetes or epilepsy: a long-term management of the patient to ensure a reasonably full life and early recognition of specific complications. It is rarely possible to think in terms of a cure or total symptomatic relief.

Contractual considerations

The contract between purchaser and provider should reflect a rehabilitation role, rather than the type of contract undertaken for acute surgical work. The organization of the clinic must also consider this. Admissions for nerve blocks may be required on several occasions, and the cost of certain treatments may exceed those of major surgical operations. The relationship between primary care and hospital clinic should allow sharing of responsibility, and in many cases, discharge from hospital follow-up.

Pain clinic strategy

Short-term symptomatic relief is of less importance than the development of a strategy for long-term management. All treatments in which the patient plays a passive role must be used with caution, since they can lead to the pain sufferer becoming dependent on the attentions of a professional. In assessing the effectiveness of treatment the question is not 'did it hurt less ?' but 'did you manage to do more ?'. It is particularly important to adopt this approach if using techniques, such as acupuncture, which are minimally invasive, low cost procedures in which it is difficult to refuse further treatment to the patient who receives short-term benefit. It is important that the patient understands this role, and is made aware of his or her own responsibility to maintain any gains which have been achieved in the pain clinic.

Relationship with other medical specialities

Investigation of ongoing pathology is not the role of the clinic, although a working knowledge of the most expedient way of screening for and referral of rheumatological and neurological disease is required. This is best obtained by discussion with local specialists. Similarly, local negotiation will define the limits of responsibility for the

management of conditions such as headache, back pain, osteoporosis and cancer. In general terms, attendance at the pain clinic assumes that all reasonable attempts at diagnosis and management of ongoing disease have been addressed by relevant specialists. The type of referral accepted will vary from location to location: some clinics may see only referrals from other consultants, others may offer open access to general practice.

Relationship with non-medical bodies

The clinician is encouraged to extend influence beyond the immediate medical community to the self-help groups that meet in many village halls and community centres. Many of them understand the strategy of management of chronic pain; others may be justifiably labelled 'illness behaviour maintenance groups' in their campaigns for treatments that are inappropriate for the majority of their members.

Relationship with hospital management

Management of the chronic pain syndrome carries with it the responsibility for managing patients who have lost confidence in the medical profession. Illness behaviour can make the relationship between clinician and patient particularly challenging, and it is regrettable, although hardly surprising, that a small minority of patients will seek to apportion blame for failures of treatment or react to attempts to challenge illness behaviour by complaint. Pre-emptive action in the form of discussion with the Hospital Trust's medical director may prevent a crisis, membership of a recognized medical defence organization is invaluable if the crisis occurs.

Drug therapy

The pain clinic has a responsibility to be aware of applications for drugs licensed for other conditions, such as epilepsy and depression, to be used for pain management. Prescribing outside a manufacturer's product licence carries its own hazards. The consultant has a special responsibility for monitoring the patient on unlicensed medication that may be difficult to delegate to primary care or a trainee.

Outpatient procedures

Nerve block of a major nerve trunk requires facilities for resuscitation and monitoring, together with an aseptic environment. Such procedures are optimally undertaken in a day case operating theatre. X-ray imaging facilities are required for precise localization in many procedures. Sedation and general anaesthesia requires a comprehensive facility for monitoring, recovery, and of appropriately trained personnel to supervise the patient while the clinician undertakes the procedure. Very minor procedures, such as trigger point injection or greater occipital nerve block can be undertaken in the outpatient clinic.

Transcutaneous nerve stimulators

The continuing requirement for a supply of stimulators causes many pain clinics a problem. The cost of each unit is not high, but unless a specific budget can be assigned to machines, it will be impossible to supply every patient who responds to stimulation with a machine on a permanent basis. Short-term loans help the patient to assess the value of the treatment without cost to themselves. The cost of electrodes and batteries is considerable: unfortunately these disposables are not drugs and cannot be obtained on prescription.

DEPRESSION AND PAIN

Pain and depression are both seen in psychiatry and chronic pain clinics. Chronic pain causes depression. Chronic pain is a symptom of depression. Simple cause and effect is rare. Because pain and depression are often inextricably linked, the relative contribution and effect of each illness can be difficult to determine. Moreover psychiatrists and chronic pain clinicians lack the specialist skills to elucidate symptoms which fall outside their respective areas of expertise. The importance of a multidisciplinary approach is reinforced.

Chronic pain causes depression

An estimated 28% of patients attending pain clinics have a well-defined affective illness. A greater number are dysphoric. Factors which worsen mood in a patient suffering from chronic pain are the inability to work, the futility of medical intervention and suggestions of their malingering. Patients become depressed during the course of a painful illness when they have not been depressed previously.

Chronic pain is a symptom of depression

Over 50% of depressed men present with pain. Approximately half of all depressed patients have pain. In a series of depressed women, atypical facial pain was the most common presenting symptom in 66%. In a smaller proportion of both sexes, tension headache was the most common presenting symptom of depression. Sites of pains which can be symptoms of depression are, in order of frequency, face, head, low back, limbs and abdomen. Characteristics of patients in whom pain may be a symptom of depression are low self-esteem, disturbed family circumstances, a personal history of psychological problems or a family history of psychiatric illness.

Assessment of depressive symptoms in the chronic pain clinic

The additional presence of biological symptoms of depression such as loss of appetite and sleeplessness suggests that pain might be a symptom of depression. Scoring systems such as the Beck depression inventory, the Zung depression scale and the hospital anxiety and depression scale are used. These tests do not constitute a full assessment, nor a psychiatric diagnostic process. They are quick, simple tools.

The need to distinguish depression from chronic pain

The use of antidepressants to treat both depression and chronic pain has hampered the differentiation between the two illnesses. Analgesic effect is independent of antidepressant effect. This is supported by evidence of an analgesic effect in non-depressed patients, by the early response of chronic pain to amitriptyline compared to the later response of depression and by the effectiveness of amitriptyline in the treatment of chronic pain at doses much lower than those required to treat depression. It might be thought that the existence of a treatment effective in both would obviate the need to distinguish the symptomatology. The principle of chronic pain management is to consider pain an illness in itself and not a symptom of other disease. This is based on the assumption that other illnesses have been identified and optimally treated. If the primary illness is depression it must be identified and optimally treated. Antidepressants, particularly at some doses used in the treatment of chronic pain, may not provide optimal treatment. Established treatments for depression may be needed. Similarly, pain may not be optimally treated by antidepressants and may require specific treatment. The use of invasive pain management techniques in a patient who is primarily depressed puts the patient at iatrogenic risk. Proper assessment protects against futile or potentially damaging medical intervention.

Management of depressive symptoms in the chronic pain clinic

To facilitate the multidisciplinary approach, many pain clinics have enrolled the services of clinical psychologists, and some have liaison psychiatrists. A depressive illness without pain, or chronic pain which is clearly a symptom of depression should be managed by a psychologist or a psychiatrist. Psychologists are able to offer cognitive and behavioural treatments for depression. Negative cognitions can be challenged. If the patient's mood is very low, however, they may not be amenable to psychological treatment and need to be referred to a psychiatrist. Depression characterized by severe biological symptoms is best treated by psychiatrists.

Depression which is caused, either completely or mainly, by chronic pain can be treated in the pain

clinic. Specific pharmacological or physical treatments for pain can be effective in improving mood or the patient might benefit from coping strategies.

The link between pain and depression can require that both need to be treated to make an improvement in either (or both) of the illnesses.

Common mechanisms for pain and depression

A group of patients with pain without a physical explanation and not showing symptoms of depression were found to have an increased family history of depressive disorders. Their pain responded to the use of antidepressants. The relative contribution of the two overlapping conditions to the clinical picture is difficult to establish. Although at present distinctions are made in diagnosis and treatment, the interaction between pain and depression and the effectiveness of antidepressants in both illnesses suggests involvement of noradrenaline and 5HT in both. The role of common neurotransmitters suggests common pathology. This needs further research.

Related topics of interest

Assessment of chronic pain – psychosocial (p. 10)
Neuropathic pain – drug treatments (p. 128)

DIGESTIVE TRACT SYNDROMES

The series of painful disorders of the digestive tract include irritable bowel syndrome, non-ulcer dyspepsia, non-cardiac chest pain and burning mouth syndrome.

Irritable bowel syndrome

Irritable bowel syndrome (IBS) presents as crampy lower abdominal pain associated with either frequent loose stools or infrequent hard stools. Associated, distressing symptoms include bloating and a sensation of incomplete rectal emptying. Patients may complain of either diarrhoea or constipation.

The prolonged contractions of the colon which are suspected as being the major physiological alteration of IBS can be provoked by emotional factors. Stressful life events and a history of sexual abuse are worth noting as predisposing factors. IBS also occurs as a complication of infection of the gastrointestinal tract. The abnormal mechanoreceptor activation associated with a prolonged contraction may result in sensitization of primary afferents, and an exaggerated response to normally innocuous stimulation. This theory explains tenderness of the colon during palpation, and pain and spasm of bowel distension during sigmoidoscopy. The pain is therefore one of mechanical allodynia and hyperalgesia of viscera to non-painful and painful stimuli respectively. The mechanism may be either one of primary afferent and dorsal horn sensitization or reduction of tonic supraspinal inhibition of autonomic afferent activity. It is possible that both mechanisms are acting, leading to a 'positive feedback' loop in which peripheral afferents become increasingly sensitized by removal of supraspinal inhibition. More severe cases of IBS complain of constant symptoms that are not relieved by the passage of stool.

Non-cardiac chest pain and non-ulcer dyspepsia

Non-cardiac chest pain may account for up to 30% of admissions to coronary care units, and in view of the seriousness of the differential diagnosis of cardiac chest pain, may commit the physician to expensive, and risky, investigation (e.g. coronary angiography). Abnormalities of oesophageal peristalsis and acid reflux may be responsible for pain in some cases, but there remain a group where neither of these account for the pain. This group of patients may have abnormalities of muscle regulation of oesophageal diameter, a situation analagous to irritable bowel syndrome, and associated with visceral hyperalgesia. Non-ulcer dyspepsia is the term used to describe the manifestations of irritable bowel syndrome in the upper gastrointestinal tract.

Burning mouth syndrome

Bilateral symptoms of burning affecting all areas of the mouth are the predominant features. The condition is more common in women and its appearance is typically between 50 and 60 years. Symptoms may be due to local pathology, notably candidal infection, xerostomia and lichen planus. Diabetic microangiopathy may also be responsible. Candidiasis may be a symptom of immunodeficiency or diabetes. Other associations such as changes in rheumatoid factor and antinuclear titres, and vitamin B and iron deficiency, have been noted but not explained. Subtypes of the clinical syndrome, as follows, reflect the many possible aetiologies, though the pain clinician may meet the patient after all reasonable attempts to find a cause have failed.

Subtypes

- Type 1 worsens through the day, and may be associated with diabetes.
- Type 2 is present on awakening, persists through the day and may be associated with psychological problems.
- Type 3 runs a variable course, with days free from symptoms, a non-uniform distribution of symptoms, and may be associated with food allergy.

Management

Psychological approaches, particularly methods involving relaxation, have a role in the management of all these conditions. Explanation of the cause of the condition may reassure the patient who is convinced of the serious nature of the condition, and seeks reassurance from repeated examination or endoscopy. The following account of therapies of the various syndromes is not exhaustive:

Therapy

[b] Hypnotherapy is of value for IBS [b].

[b] A combination of ispaghula husk and propantheline relieves symptoms of IBS and maintains remission [b].

[b] Cognitive therapy reduces gastrointestinal symptoms in IBS and intensity of pain in burning mouth syndrome[b].

[b] The quaternary ammonium smooth muscle relaxant, pinaverium, reduces pain duration in IBS, and the antidiarrhoeal drug Lacteol, a preparation of *Lactobacillus* organisms (which works by acidifying the bowel contents) reduces pain and gastrointestinal symptoms. [b] Neither drug is available in the UK.

[b] Loperamide reduces overall pain intensity at the expense of increased night pain [b].

[c] Mast cell stabilizers (cromoglycate) and antihistamines (ketanserin and H2 blockers) have been described in the treatment of post-infectious IBS [c].

[c] Antidepressants have a role in IBS and burning mouth syndrome [c].

[c] A single study advocates the use of vitamins B1, B2 and B6 for burning mouth syndrome associated with deficiency of the same [c].

[c] Nitroglycerin, hydralazine, nifedipine and diltiazem have been described for treatment of non-cardiac chest pain. The rationale for use is the alteration of smooth muscle tone in the oesophagus [c].

Further reading

Mayer EA, Munakata J, Mertz H, Lembo T, Bernstein CN. Visceral hyperalgesia and irritable bowel syndrome. In: Gebhardt, GF (ed.) *Visceral Pain, Progress in Pain Research and Management*, Vol. 5. Seattle: IASP Press, 1995; 429–68.

Related topics of interest

Facial pain (p. 77)
Mechanisms in nociception (p. 92)

FACIAL PAIN

The density of anatomical structures in the face, the significant representation of facial sensation within the cerebral cortex and the role of the face in personal and social interaction account for there being many causes and types of face pain. The pains described below can be treated by either faciomaxillary surgeons with an interest in pain or by pain clinic physicians. Because of their often multifactorial aetiology and the frequent presence of discrete lesions, they are best treated by a combined or even multidisciplinary approach. A working diagnosis is sought to guide specific treatment.

Temporomandibular joint disease

This is taken to mean pain arising from the temporomandibular joint and the masticatory muscles. It can be classified into a disorder primarily of myofascial origin to be known as temporomandibular pain, and a disorder of the joint proper which will be referred to as internal derangement of the temporomandibular joint. It is appropriate to treat temporomandibular pain in the pain clinic. However the expertise of the faciomaxillary surgeon is often required initially to distinguish temporomandibular pain from pain due to internal derangement of the joint or other cause. Internal derangement of the temporomandibular joint should be managed by faciomaxillary surgeons. Temporomandibular joint disease occurs in a milder form equally in both sexes but those presenting for treatment (approximately 5–10% of the population) are female in a ratio of 8:1.

The validity of various aetiological theories such as occlusal derangement and bruxism remains unknown. Temporomandibular pain may be another form of musculoskeletal pain syndrome, and the sufferer may experience the same psychological consequences as the sufferer from one of these syndromes. The similarity between non-specific low back pain and temporomandibular pain has been mentioned by some authorities. The futility, and indeed danger, of adopting a purely biomedical view of the problem is the same – it leads to over investigation and unnecessary invasive treatment. These treatments have included prosthetic implants into the temporomandibular joint which have subsequently shown to be harmful.

Where the myofascial dysfunction is secondary to an occlusal problem, treatment of the underlying cause may benefit. The correction of occlusal abnormality resulting from an orthodontic problem or improperly filled tooth is necessary. [c] Splinting devices are commonly used to this end [c]. [a] The difficulties in proving the benefit of such appliances are considerable. In 1995, 26 randomized controlled trials of splint therapy subject had been identified, trialling 15 different devices for a variety of facial pain conditions. Inadequate study design and a high placebo response were noted; leading to a conclusion that it was unclear whether any one therapy was of benefit [a].

Temporomandibular pain

This is intermittent pain of the ear, angle of the mandible or temple or can be less well localized. It can be bilateral. It is more intense in the morning or afternoon. It is exacerbated by movement or clenching. It is associated with joint noises and reduced range of joint movement. There is tenderness of the joint capsule and muscles of mastication and trigger points can often be elicited. It lasts from weeks to years. Classically the pain is altered by the palpation of associated tender muscles and alleviated by the stretching of the muscle or the injection of local anaesthetic to the tender site.

Treatment

In addition to the management of occlusal problems (see above), the following approaches can be used to relieve muscle spasm.

[c] Injections to muscles of local anaesthetic alone are diagnostic but can be followed by the effective injection of steroid [c].

[c] Skeletal muscle relaxants such as baclofen at a dose of 5 mg t.d.s. are used beneficially [c].

[c] Local muscle relaxation techniques such as the injection of botulinum toxin, heat and massage can also be beneficial [c].

[c] Transcutaneous electrical nerve stimulation (TENS) and acupuncture are of use [c].

The faciomaxillary surgeon is able to offer treatment for discrete lesions, mechanical problems and other physically correctable causes of muscle dysfunction. Generalized muscle relaxation can be achieved by relaxation therapies and biofeedback techniques.

[a] Temporomandibular pain with and without symptoms of depression has been successfully treated with antidepressant drugs [a]. As with many chronic pains, because of its multifactorial nature, chronic facial pain must be addressed from a biopsychosocial perspective. To correct a physical disorder alone is frequently insufficient. Contributing psychological problems must be treated.

Internal derangement of the temporomandibular joint

This refers to distortion in the anatomy of the joint. Pain is exacerbated by jaw movement. There is

swelling and tenderness of the joint and overlying muscles. Joint noises are common.

The cause is usually anterior displacement of the disc as a result of trauma, ligament laxity or changes in the fluid environment of the joint.

Treatment

Treatment is conducted by faciomaxillary surgeons.

Atypical facial pain

It is difficult to classify atypical facial pain according to symptomatology. However pain tends to be present every day and lasts for most of the day. It can last from hours to months. It is a poorly localized, steady, deep burning or throbbing pain. It is unrelated to movement. It can migrate and has no anatomically defined distribution. It has no associated physical signs. Sufferers are frequently depressed or demonstrate obsessive personality traits. It is most common in females over the age of 45 years.

Treatment

It is most important to identify and treat the large contribution to pain from psychological, social and psychiatric factors.

[c] Small doses of β-blockers, such as propranolol 20 mg o.d., can be used to alter response to autonomic stimuli[c].

[a] Antidepressants are used to treat atypical face pain[a]. Antidepressants are effective in the absence of depression. [c] Chronic atypical facial pain has been shown to respond to the combination of tricyclic antidepressant and phenothiazine[c].

[c] Biofeedback and relaxation therapies are effective in some. TENS is used[c].

Facial neuralgias

These refer to trigeminal, glossopharyngeal and nervus intermedius neuralgias. They are uncommon.

Glossopharyngeal neuralgia is a milder disease than trigeminal neuralgia as indicated by the number of episodes, character and treatment of pain. The source of the pain is the anatomical base of the glossopharyngeal nerve (IX cranial nerve). Pain is felt unilaterally in the ear, base of the tongue, tonsils, pharynx or beneath the angle of the jaw. It is a stabbing pain. Its pathophysiology and time factors are the same as those for trigeminal neuralgia. The triggers for glossopharyngeal neuralgia are swallowing, yawning, eating, coughing or talking. Treatment is the same as the conservative treatment of trigeminal neuralgia.

Neuralgia of nervus intermedius is felt deep in the ear. Pain is paroxysmal and lasts for seconds or minutes. It is triggered by pressure in the external auditory meatus. Disorders of lacrimation, salivation and taste can accompany pain. Symptomatic treatment is as for the conservative management of trigeminal neuralgia.

Facial neuromata

Neuromata are common following facial trauma, particularly blow-out orbital fractures and Le Fort III fractures. They are frequently palpated at the site of exit of supraorbital infraorbital and mental nerves. Diagnostic local anaesthetic nerve blocks are performed. Subsequently, conservative treatment is the mainstay of treatment.

Other causes of face pain presenting to the pain clinic are post-herpetic neuralgia and central post-stroke pain.

Further reading

Classification Committee of the International Headache Society. Classification and diagnostic criteria for head disorders, cranial neuralgias and facial pain. *Cephalalgia,* 1988; **78** (suppl. 7): 1–97.

Systematic reviews

Antczak Bouckoms A, Marbach JJ, Glass EG, Glaros AG. Reaction Papers to Chapters 12 and 13. In: Sessle BJ, Bryant PS, Diohne RA (eds), Temporomandibular Disorders and Related Pain Conditions, Vol. 4. Seattle, JASP Press, pp. 237–45.

Onghena P, Van Houdenhove B. Antidepressant induced analgesia in chronic non-malignant pain: a meta analysis of 39 placebo controlled studies. *Pain,* 1992; **49** (2): 205–19.

Related topics of interest

Botulinum toxin–haemagglutinin complex (p. 32)
Central post-stroke pain (p. 58)
Depression and pain (p. 71)
Headache (p. 81)
Neuromata and post-incisional pain (p. 123)
Post-herpetic neuralgia (p. 154)
Trigeminal neuralgia (p. 183)

HEADACHE

Headache which is not due to intracranial or systemic pathology is described as primary headache. Primary headaches are appropriately treated in the pain clinic. A working diagnosis for primary headache is sought to decide on appropriate management. Diagnosis is made by history. Examination and investigations may be necessary to exclude secondary headache. Diagnostic criteria have been laid down by the Headache Classification Committee of the International Headache Society.

Cluster headache

This condition is otherwise known as migrainous neuralgia or Horton's syndrome.

Diagnostic criteria

(a) At least five attacks fulfilling criteria b–d.

(b) Severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes untreated.

(c) Headache is associated with at least one of the following signs which have to be present on the same side as the pain:

- conjunctival injection;
- lacrimation;
- nasal congestion;
- rhinorrhoea;
- forehead and facial sweating;
- miosis;
- ptosis;
- eyelid oedema.

(d) Frequency of attacks: from one every other day to eight per day.

History, examination and investigation must exclude another disorder which might account for the pain, or if such a disorder is present cluster headache should not occur for the first time in close temporal relation to the disorder.

Cluster headache occurs predominantly in men, in the fourth decade of life. Attacks occur in 'clusters' lasting 4–10 weeks. Most commonly they happen two to three times a day. Bouts of headaches often occur in early spring or early autumn. Clusters are interspersed by pain free periods of months to years, but rarely more than 2 years.

Headaches usually last about 45 minutes. They can occur at any time of day but typically start soon after the onset of sleep. The pain is burning in character. Classically sufferers have deep nasolabial folds and *peau d'orange* skin changes. Precipitating factors include alcohol and altitude.

Cluster headache is thought to have a vascular mechanism.

Management

[b] Intranasal capsaicin has been shown to reduce headache severity [b]. [b] Sumatriptan has been shown to be effective [b].

[c] Other treatments are:

- abstinence from alcohol;
- ergotamine 1–2 mg p.r. before the attack;
- methysergide 2 mg t.d.s.;
- verapamil 40–80 mg t.d.s.;
- oxygen for 15 minutes during the attack;
- sphenopalatine local anaesthetic block;
- sphenopalatine ganglion radiofrequency lesions;
- partial trigeminal nerve ablation[c].

Tension headache

Diagnostic criteria

(a) At least 10 previous headache episodes fulfilling criteria b–d. Less than 180 headaches per year; less than 15 per month.

(b) Headaches lasting 30 minutes to 7 days.

(c) At least two of the following:

- pressing, tightening, non-pulsating;
- mild or moderate;
- bilateral;
- no aggravation by routine physical activity.

(d) Both of the following:

- no nausea or vomiting; anorexia may occur;
- never both photophobia and phonophobia.

History, examination and investigation must exclude another disorder which might account for pain, or if such a disorder is present tension headache must not occur for the first time in close temporal relation to the disorder.

Headaches usually occur daily. There is a history of stress and depression may coexist. It is more common in women. Patients often abuse analgesics which aggravates the situation. Examination may reveal tender points.

Management

Depression should be treated if necessary. [a] Small doses of tricyclic antidepressants are also effective in those without clear signs of depression [a].

[b] Sumatriptan is also effective [b].

[c] Relaxation and cognitive strategies are used [c].

[c] Non-steroidal anti-inflammatory drugs (NSAIDs) are effective [c].

[c] Biofeedback techniques and hypnosis are of use [c].

Chronic paroxysmal hemicrania

This has the same features as cluster headache but attacks occur 15–20 times a day and last 3–15 minutes. It is more common in women and does not follow the onset of sleep.

Treatment

[c] Treatment is indomethacin 75–150 mg orally[c].

Cervicogenic headache

This is headache which originates in the structures in the neck. Pain from one or both sides of the neck radiates to the occiput, temples or frontal area. It is a dull pain, worse in the morning and exacerbated by movement or tension. Lateral flexion and rotational movements are restricted. Headache is often due to irritation of the C2 and C3 nerve roots and the greater occipital nerve.

Management

[c] Steroid injections to cervical facet joints gives temporary relief in 60–70%[c].

[c] Greater occipital nerve blocks have been used[c].

[c] Transcutaneous electrical nerve stimulation (TENS), acupuncture and physiotherapy are of use[c].

Occipital neuralgia

This is a paroxysmal jabbing pain in the distribution of the greater or lesser occipital nerves. Aching can persist between paroxysms and there may be altered sensation. The affected nerve is tender to palpation.

The pain is eased temporarily by local anaesthetic block of the appropriate nerve. [c] Subsequent injections of steroid are effective[c].

Analgesic headache

Large daily doses of aspirin, paracetamol or weak opioids taken for the treatment of headache can aggravate headache. The daily use of ergotamine for headache or sudden withdrawal from ergotamine induces headache. The withdrawal headache is thought to be due to vasodilatory counteracting mechanisms which have developed during the use of the drug but are left unopposed when the drug is withdrawn. Sumatriptan, used for the treatment of migraine causes the same problems.

Management

Recommendations for prevention are:

- analgesics should not be taken every day for the treatment of headaches;
- ergotamine should not be taken more than 10 times a month;
- there should be restrictions on the use of sumatriptan, to approximately 10 times a month;
- opioid drugs should not be used for the treatment of headache.

Idiopathic stabbing headache

This is stabbing pain, predominantly in the distribution of the first division of the trigeminal nerve. It lasts for a fraction of a second. It occurs as a single stab or a series of stabs, at irregular intervals.

Management

[c] Indomethacin 25 mg t.d.s. is used to treat[c].

Miscellaneous headaches

A number of primary headaches do not fit into these specific categories, such as those provoked by physical exertion, sexual activity, certain foods, very cold foods, coughing or restricting devices worn on the head. Avoidance of provoking factors should be advised where possible. [c] NSAIDs are used to treat [c].

Further reading

Classification Committee of the International Headache Society. Classification and diagnostic criteria for head disorders, cranial neuralgia and facial pain. *Cephalalgia,* 1988; **8** (suppl. 7): 1–96.

Connor HE. The aetiology of headache. *Pain Reviews,* 1994; **1** (2): 77–88.
Olesen J. Analgesic headache. *British Medical Journal,* 1997; **310**: 479–80.

Systematic review

Onghena P, Van Houdenhove B. Antidepressant induced analgesia in chronic non-malignant pain:a meta-analysis of 39 placebo controlled studies. *Pain,* 1992; **49** (2): 205–19.

Related topics of interest

Depression and pain (p. 71)
Facial pain (p. 77)
Migraine (p. 103)

IMMUNODEFICIENCY DISEASE AND PAIN

Pain is a common symptom suffered by patients with human immunodeficiency virus (HIV) disease. It is suggested that, as in the case of cancer patients, the severity of pain is underestimated. A recent multicentre study estimated the prevalence of pain as 62% in a population of inpatients. In common with cancer patients, patients with HIV disease may suffer from a number of pain syndromes, including an experience of 'whole body' pain, that is a feature of the psychological distress of a terminal illness. Pain syndromes in HIV disease may have underlying treatable causes, more often so than pain syndromes in malignant disease. Analgesia should not be withheld while causes are investigated.

Pain is experienced as a consequence of the infection and its complications, as a consequence of treatment, or for reasons unrelated to either. The principal causes of pain are gastrointestinal, neurological and rheumatological.

Detailed discussion of the investigation and treatment of the causes of pain in HIV disease is outside the scope of this book, but the following list, which is not exhaustive should demonstrate the problem of pain management in HIV disease.

1. *Gastrointestinal causes of pain:*
- oral and oesophageal candidiasis;
- dental abscess;
- aphthous ulceration;
- mouth ulceration due to cytomegalovirus and herpes virus infection;
- necrotizing gingivitis;
- oesophageal ulceration;
- gastrointestinal cramps asociated with *Shigella*, *Salmonella* and *Campylobacter* infection;
- small bowel obstruction and perforation, small bowel lymphoma;
- cytomegalovirus colitis;
- spontaneous peritonitis;
- cholecystitis or cholangitis due to *Cryptosporidium* or cytomegalovirus infection;
- proctitis and perianal abscess.

2. *Neurological causes of pain:*
- brain tumour;
- encephalitis;
- aseptic meningitis;
- cerebral toxoplasmosis;
- cryptococcal meningitis;
- painful symmetrical neuropathy due to direct action of HIV virus on peripheral nerves;

- cytomegalovirus infection of dorsal root ganglion;
- demyelinating polyneuropathy.

3. *Rheumatological causes of pain:*
- Reiter's syndrome;
- sacroiliitis;
- polyarthralgia associated with mononucleosis;
- psoriasis and psoriatic arthropathy;
- reactive arthritis;
- polymyositis.

4. *Iatrogenic causes of pain:*
- pancreatitis related to the use of the antibiotic pentamidine;
- opportunistic infection and growth of tumour as a result of steroid thearpy;
- myalgia related to the use of the antiviral agent zidovudine.

Management

The management of pain in HIV disease is similar in many respects to that of cancer pain. The analgesic ladder, as used for cancer pain, is a useful model. As with cancer patients, issues of emotional, psychological and spiritual concern must also be addressed. Pathological causes for pain are worth seeking as specific treatment may be available. Treatments of neuropathic pains with antidepressants and anticonvulsants are appropriate. Intra-articular steroid injections and occasionally (for intractable upper gastrointestinal tract pain) neurolytic sympathetic block procedures are appropriate. One particular concern that may need to be addressed is the requirement for strong opioids in patients who have abused opioids in the past. Another is the theoretical argument that opioids may promote replication of immunodeficiency virus. Zidovudine metabolism may be affected by the administration of non-steroidal anti-inflammatory drugs, and toxicity may occur.

Further reading

Larue F, Fontaine A, Colleau SM. Underestimation and undertreatment of pain in HIV disease: multicentre study. *British Medical Journal*, 1997; **314**: 23–9.

O'Neil W, Sherrard JS. Pain in human immunodeficiency disease: a review. *Pain*, 1993; **54**: 3–14.

Related topic of interest

Cancer pain – mechanisms and pathology (p. 53)

KETAMINE

Ketamine is an anaesthetic drug with a few notable features which have resulted in its introduction to pain clinic practice. The rationale for its use is supported by animal studies which allow tentative conclusions to be drawn about a mechanism of action. However, the extrapolation of animal data, based on electrophysiological and behavioural studies, to the human experience of pain is always difficult. The evidence to support the use of ketamine in chronic pain is necessarily limited. Ketamine is valuable for its excellent analgesic properties at subanaesthetic doses, and at anaesthetic doses for its freedom from the effects of cardiovascular and pharyngeal reflex depression which characterize other anaesthetic agents. As such it has a unique place for providing analgesia and anaesthesia for environments in which other agents would be difficult to use, for example at the site of a major accident or on the battlefield. The drug is limited by major side-effects, however, notably cardiovascular stimulation, increased cerebral blood flow, and psychological disturbance.

Mechanisms of action

The animal experimental evidence for a mechanism of action includes the following:

1. N-methyl D-aspartate receptor (NMDA) antagonism. NMDA receptors are believed to be involved in the spinal cord processing of nociceptive input, where they respond to excitatory amino acids released from the central processes of primary afferent nociceptors. Their activation by nociceptors is believed to result in a response, 'windup', which may outlast the duration of action of the activation impulse and stimulate the spinal cord cell to metabolic activity. Their inactivation by ketamine is suggested, but not proven, as a manoeuvre to prevent the development of a chronic pain syndrome. It is further suggested that the observed synergism between opioids and ketamine is mediated via a common action on the NMDA receptor. In animal models of neuropathic pain, ketamine appears to restore opioid responsiveness.

2. *Opioid receptor agonism.* Binding of ketamine to opioid receptors in central nervous system tissue has been observed.

3. Serotoninergic and adrenergic mechanisms. Synaptic uptake of serotonin and noradrenaline is inhibited, and the antinociceptive action of spinally administered ketamine can be reversed by phentolamine and serotonin receptor antagonists.

4. Cholinergic mechanisms. Physostigmine, a centrally acting anticholinesterase, can reverse the sedation and anaesthesia of ketamine, while 4-aminopyridine, an antagonist of competitive neuromuscular blockade, speeds recovery from ketamine anaesthesia.

Pharmacokinetics

Ketamine is metabolized in the liver to an active metabolite, norketamine, which has analgesic properties, but is believed to have fewer side-effects than ketamine. In this respect, oral treatment, despite a bioavailability of only 17%, may be preferred over parenteral treatment, where the benefits of the active metabolite are not obtained.

Pharmacodynamics

The incidence and severity of the two major side-effects are dose related. Cardiovascular side-effects include increases in heart rate, blood presure, cardiac output, systemic vascular resistance, and pulmonary artery pressure, and can be attenuated by benzodiazepines. Their origin is in the stimulation of the central nervous system by the drug, and because of this, the drug is contraindicated in the presence of raised intracranial pressure or seizures. The psychological disturbances take the form of alterations of mood or body image, feelings of spatial disorientation, vivid dreams, hallucinations and pleasant or unpleasant illusions, and complicated emergence from anaesthesia. They can occur with the use of ketamine by infusion for analgesia. Their occurrence can be reduced by the use of slow infusion rates. [c] Intravenous midazolam is effective in countering the side-effects observed after intravenous ketamine [c]. This is used at doses between 2.5 and 15 mg/day, as an infusion. Alternatives are the use of oral midazolam, 0.5 mg/kg, or diazepam 5–10 mg. Haloperidol 2–4 mg is an alternative.

Clinical uses in chronic pain

No oral preparation is available, and imagination has to be used to improve the oral acceptability of the parenteral preparation. Despite this constraint there is ample literature on the usefulness of ketamine for [c] premedication, post-herpetic neuralgia, and cancer pain. A suggested oral dose is 50 mg, t.d.s.[c].

For cancer pain, ketamine has been used for incident pain, painful cutaneous lesions, bone pain, tenesmus, and neuropathic pain, including the pain of spinal cord compression. Its use is best considered as an alternative or adjunct to opioid where this form of therapy has proven ineffective or poorly tolerated.[c] Subcutaneous and intravenous infusions at rates of between 40 and 500 mg/24 hours have given relief: there is a wide variation in response which requires the titration of drug to achieve a response [c]. The subcutaneous route is complicated by the presence of a skin reaction in 20% of patients, which requires regular resiting of the subcutaneous cannula.

[c] Severe phantom limb pain and postherpetic neuralgia have been reported to respond to parenteral ketamine [c] . The single dose for intravenous response is reported between 0.125 and 0.3 mg/kg, or as an infusion at 0.2 mg/kg/hour.

Further reading

Idvall J. Ketamine, a review of clinical applications. *Anaesthetic Pharmacology Review,* 1995; **3**: 82–9.

Luczak J, Dickenson AH, Kotlinska-Lemieszek A. The role of ketamine, an NMDA receptor antagonist, in the management of pain. *Progress in Palliative Care,* 1995; **3**: 127–34.

Mercadante S. Ketamine in cancer pain: an update. *Palliative Medicine,* 1996; **10**: 225–30.

Related topics of interest

Mechanisms in nociception (p. 92)

Mechanisms in peripheral and central neuropathic pain (p. 94)

MECHANISMS IN NOCICEPTION

The sensory system for pain consists of a population of receptors, primary afferent neurons, neurons of the dorsal root of the spinal cord and a pathway to the midbrain, thalamus and cortex via the spinothalamic tract on the opposite side of the spinal cord. Knowledge of the anatomy of pain pathways (a result of studies of cases with damage to nerve pathways and experimental observation) is detailed, but understanding of how the behaviour of the sensory system for pain changes with nerve damage or persistent stimulation is rudimentary. In contrast to the other sensory systems, pain is not a line labelled, modality specific, hard wired system, but one in which the relationship between input (stimulus) and output (response) is variable.

Receptors which respond to painful stimuli are termed nociceptors. They are simple nerve endings devoid of the elaborate organization found in the sensory systems for pressure and position sense. They respond to strong thermal and mechanical stimuli. Despite their similar ultrastructural appearance, they are not a homogeneous population, and their ability to propogate nerve impulses changes with their environment. Some nociceptors, notably in joints and in the urinary tract, are inactive, and cannot be stimulated unless tissue damage or chemical mediators of inflammation are present. They are referred to as silent nociceptors. It is believed that although 'silent' from the perspective of nerve impulse propagation, these nociceptors are providing the sensory system with continuous data about the tissue environment.

Primary afferent fibres are described as A or C fibres on the basis of microscopic appearance and velocity of conduction of electrical impulses. A fibres are larger, are well insulated by myelin, and conduct impulses at high velocity. C fibres are smaller, poorly insulated and conduct impulses slowly. The population of A fibres seen in a microscopic preparation of a nerve is subdivided by size into:

- $A\alpha$ – motor nerves;
- $A\beta$ – sensory nerves for light touch and vibration;
- $A\gamma$ – motor nerves;
- $A\delta$ – sensory nerves for pain.

Activation of nociceptors leads to a two-phase response. There is a fast response due to $A\delta$ activation. This is acute pain which is well localized. There is a slow response due to C fibre activation. This has a different quality, does not localize the site of injury, and persists after withdrawal of the stimulus. The proportion of fibres of each type in a sensory nerve varies. C fibres predominate in the sensory innervation of the viscera, where localization of pain serves no biological function.

The 'gate control' theory describes the relationship between nociceptive and tactile afferents in the dorsal horn as an electronic switch in order to explain the variability between input and output in the sensory system for pain. According to

this model Aβ afferents inhibit dorsal horn neurons from responding to Aδ and C fibre inputs. Thus pain can be relieved by rubbing. Such a model does not explain how pain can persist to become a chronic condition. To understand this it is necessary to consider changes which occur with persistent nociceptive stimulation. One such change is neuronal sensitization.

Neuronal sensitization

The clinical features of sensitization are:

- heightened sensitivity to painful stimulation – hyperalgesia;
- pain in response to light touch – allodynia;
- hypersensitivity of uninjured sites – secondary hyperalgesia.

Hyperalgesia results from a change in the receptive properties of the nociceptor to tissue injury. Secondary hyperalgesia is a consequence of the temporal and spatial summation of nociceptor input into the spinal cord.

Peripheral sensitization is the term used to describe the change in primary afferent fibres as a result of a change in the local receptor environment. There are several possible mediators of the process of sensitization, and they are present in areas of inflammation. They may act alone or in combination, and by direct action on the nerve ending or by a process of sensitizing the nociceptor to mechanical and thermal stimuli.

The mediators include:

- H^+ ions;
- K^+ ions;
- bradykinin;
- serotonin;
- prostaglandins;
- neurokinins.

A consequence of the process of sensitization is that myelinated Aβ fibres, those which form part of the gate control model, change their activity, and by a mechanism which is poorly understood, cease to function as inhibitors of dorsal horn activity.

A and C fibres have different actions at the dorsal horn of the spinal cord. A fibres cause transient changes at the synapse between primary afferent and spinal cord neuron. C fibres cause prolonged, progressive and ultimately irreversible changes. The increased excitability of the dorsal horn neuron that results from chronic repetitive C fibre stimulation has been studied in isolated spinal cord preparations and termed 'windup'.

Related topic of interest

Mechanisms in peripheral and central neuropathic pain (p. 94)

MECHANISMS IN PERIPHERAL AND CENTRAL NEUROPATHIC PAIN

The traditional neuroanatomical model of the sensory system for pain fails to explain a variety of pain syndromes that are associated with damage to the sensory nerve, or the pathways through dorsal horn to cortex. Syndromes include:

- scar pain;
- the complex regional pain syndromes;
- post-herpetic neuralgia;
- the polyneuropathies;
- demyelination;
- prolapsed intervertebral disc;
- spinal cord injury;
- central post-stroke pain.

Nerve damage at any point of the sensory system may result in any of the following features:

- spontaneous pain, which may be paroxysmal;
- quality described as burning, shooting, numb;
- severe pain in response to a noxious stimulus (hyperalgesia);
- severe pain in response to a stimulus which is not normally noxious (allodynia);
- severe pain in response to stimulation despite sensory impairment (hyperpathia).

A common complaint is of an area of skin which 'hurts though it is numb'. Other, unusual and graphic descriptions may be offered for the pain which is experienced as a familiar, but unexplicable, sensation. Similar clinical entities may produce different symptoms in different patients.

Peripheral mechanisms in neuropathic pain

Peripheral nerve damage, regardless of aetiology, results in damage to nociceptor and mechanoreceptor fibres as well as damage to the efferent motor and autonomic nerves. Axons themselves are not normally sensitive to pressure but will become so in the presence of inflammation or tissue damage. The dorsal root ganglion has its own nerve supply of nociceptors which respond to stimuli in the vicinity of the nerve root.

The damaged primary afferent fibre demonstrates three electrophysiological features:

- spontaneous activity;
- exaggerated response to stimulus;
- sensitivity to catecholamines.

Spontaneous activity can develop at the site of damage, at a site of demyelination, or within the cell body of the damaged neurone in the dorsal root ganglion. Where damage to a neuron is incomplete the primary afferent terminal itself may become spontaneously active. Spontaneous activity is influenced by the local environment: inflammatory mediators and noradrenaline increase the level of activity.

As well as the ultrastructural changes that can be observed in damaged nerves, other disturbances of function are noted. These changes are associated with the production of neurokinins such as nerve growth factor. There are other biochemical changes, most notably reduction of substance P and calcitonin gene-related peptide (CGRP) synthesis, and increased neurosubstance y and vasoactive intestinal peptide synthesis. An inflammatory response occurs. Undamaged nerve fibres are themselves sensitized by changes in adjacent damaged fibres: some of the more painful neuropathies are partial nerve lesions.

Central mechanisms in neuropathic pain

1. The spinal cord. The changes in the spinal cord neurons after nerve damage are similar to those that occur with constant low intensity C fibre nociceptive input. The common end result of each mechanism is a state of hyperexcitability of the dorsal horn neurone. The technical term for this is central sensitization, and it has been studied in experimental models of both nociceptive and neuropathic pain. 'Windup' refers to the specific action of C fibres (i.e. nociceptive input) on the dorsal horn neurone. It results in a state of hyperexcitability that is so similar to that resulting from a peripheral neuropathic cause that it is helpful to consider it here. It is not known whether windup is a normal protective response or a pathological one, and therefore whether it can be classed in its own right as a cause of 'neuropathic' pain. What is clear however, is that under certain circumstances,

unremitting nociceptive stimulation of the spinal cord leads to irreversible changes in the synaptic and cellular organization of the dorsal horn that persist after withdrawal of the stimulus.

The physiology of windup is as follows: C fibres release peptides (substance P and neurokinin A) and amino acids (glutamate and aspartate) on to dorsal horn neurones. There are two types of receptor at the dorsal horn, a neurokinin receptor and *N*-methyl-D-aspartic acid (NMDA), a receptor for amino acids. The binding of amino acids to the NMDA receptor depends upon its prior activation. Activation is accomplished by binding of substance P to the neurokinin receptor. Thus the release of substance P may lead to the recruitment of a second receptor type (NMDA) and an exaggerated response to further stimulation. The sensitized cell undergoes other biochemical changes, as indicated by the expression of the gene c-*fos*. Products of c-*fos* expression are involved in the regulation of neurotransmitter and nerve growth factor synthesis. In this way, persistent noxious stimulation may result in changes in the cells of the spinal cord.

2. *The brain.* Any model which tries to explain brain mechanisms in neuropathic pain must consider the diverse and detailed sensations of which a patient with a complete transection of the spinal cord lesion can complain. Such descriptions support the theory of a central pain generating area, part of a 'neuromatrix' within the brain responsible for both the sensation and its associated emotional and psychological sequelae, but triggered by nociceptive stimuli or inappropriate neuropathic stimuli. Thus a patient with a spinal cord transection may not only be aware of a phantom sensation such as bicycling, but may also suffer phantom muscle cramps and fatigue with time if the sensation persists.

An understanding of the concept, if not the details, of sensitization is important in understanding the chronic pain sufferer. The idea of pain being generated by abnormal nerve activity at spinal cord level or within the brain can be helpful

to the patient and the professional who is exasperated by the failure of conventional explanations for pain. It is of note that the analgesic drug ketamine is an antagonist of the NMDA receptor, although it is not known, for reasons discussed above, whether such a drug has a role in the prophylaxis of neuropathic pain.

Further reading

Fields HL, Rowbotham MC. Multiple mechanisms of neuropathic pain: a clinical perspective. In: Gebhart GF, Hammond DL, Jensen TS (eds) *Proceedings of the 7th World Congress on Pain, Paris.* Seattle: IASP Press, 1994; pp. 437–54.

Melzack R. Central pain syndromes and theories of pain. In: Casey KL (ed.) *Pain and Central Nervous System Disease: The Central Pain Syndromes.* New York: Raven Press, 1991; 59–64.

Related topics of interest

Complex regional pain syndromes I and II (p. 62)
Mechanisms in nociception (p. 92)
Neuromata and post-incisional pain (p. 123)
Post-herpetic neuralgia (p. 154)
Spinal cord injury and pain (p. 160)

MIGRAINE

Migraine is a headache which is not secondary to another medical condition. It is therefore defined as a primary headache. Diagnosis is made from the history. Investigation may be required to exclude headache of other aetiology.

Pathophysiology

There is no animal model for migraine. Experimental work has therefore been limited. However in establishing the pathophysiology of migraine, agonists for a subtype of 5-hydroxytryptamine receptor known as 5HT1 agonists have been useful. There are vascular and neural hypotheses. The ophthalmic division of the trigeminal nerve supplies painful structures within the head. Stimulation of the trigeminal ganglion releases a peptide from trigeminal neurones which innervate the cranial circulation. This peptide is called calcitonin gene-related peptide (CGRP). It is a powerful vasodilator. It is thought CGRP also causes neurogenic inflammation. 5HT1 agonists block the release of CGRP through presynaptic 5HT1D autoreceptors. The 5HT1 receptor has its own subpopulation of receptors, one of which, known as 5HT1δ, is involved in the mechanism of CGRP action.

Diagnostic criteria were laid down by the Headache Classification Committee of the International Headache Society in 1988.

Migraine is classified as migraine without aura and migraine with aura. Most patients have attacks without aura.

Diagnostic criteria for migraine without aura

(a) At least five attacks fulfilling criteria b–d.

(b) Headache lasts 4–72 hours, untreated or unsuccessfully treated.

(c) Headache has at least two of the following characteristics:

- unilateral location;
- pulsating quality;
- moderate or severe intensity (inhibits or prohibits daily activities);
- aggravation by walking up/down stairs, or similar routine physical activity;

(d) during headache at least one of the following:

- nausea and/or vomiting;
- photophobia and phonophobia.

History, examination and investigation must exclude another disorder which could account for the headache. If such a disorder is present, diagnosis of migraine requires that attacks do not occur for the first time in close temporal relation to that disorder.

Premonitory symptoms can occur before an attack of migraine without aura. They usually consist of hyper- or hypoactivity, depression, craving for particular foods or repetitive yawning.

Aura is a complex of neurological symptoms which can initiate or accompany an attack. Symptoms are localizable to the cerebral cortex or brain stem. Typical aura are visual disturbances, sensory symptoms, weakness or dysphasia. Migraine aura can be unaccompanied by headache.

Migraine can be triggered by factors such as stress, withdrawal from caffeine, dietary factors such as the ingestion of chocolate, cheese, wines and seafood, and hormonal changes due to the menstrual cycle or hormonal medication. Stress and hormonal factors are each identified triggers in 60% of migraine sufferers. Dietary factors have been implicated in approximately 20%. Frequently there is a family history of migraine.

Treatment

Management is by prevention of attacks and intermittent treatment of attacks. The choice between preventive therapy and the use of only abortive treatments depends on the frequency, severity and impact of acute attacks. Failure to relieve attacks necessitates prophylactic treatment.

Prevention

Drug therapy used for prevention aims to reduce the frequency of attacks by 50% and that attacks should be less severe when they do occur. The effect of the drug on the headache and its associated symptoms should be closely monitored. All drugs have side-effects and their benefits need to be accurately compared to their disadvantages.

Explanation and reassurance reduce the incidence and severity of attacks. Patients should be educated to avoid triggers where possible.

[a] Calcium channel-blocking drugs are effective in the prophylaxis of migraine. Flunarizine, nimodipine, verapamil, nifedipine and diltiazem are all equally as effective. A reduction in migraine frequency of approximately 50% can be expected after 2 months treatment with any of these drugs. 'Systemically active' calcium blockers caused predominantly vascular and gastrointestinal problems, whilst 'cerebro-specific' calcium blockers cause behavioural and muscular side-effects [a].

[a] Anticonvulsant drugs are effective in migraine prophylaxis but are associated with adverse effects [a]. This suggests a neural mechanism for migraine. They are thought to work via γ–amino butyric acid (GABA) enhancement of inhibitory pathways.

β-Blockers (e.g. propranolol 80–240 mg daily in divided doses) are thought to have some activity at 5HT subreceptors. [a] Propranolol yielded a 43% reduction in migraine headache activity in the average patient. When improvements were assessed using further outcomes they were found to be 20% greater [a]. [a] Propranolol 160 mg daily yielded a 44% reduction in migraine activity when daily headache recordings were used to assess outcome. With less conservative outcome measures there was a 65% reduction in migraine activity [a].

[a] The non-pharmacological treatments of relaxation and thermal biofeedback training yielded an initial reduction in migraine headache activity of 43% which was estimated to be 20% greater at further assessment [a].

[c] Tricyclic antidepressant drugs such as amitriptyline and dothiepin may be useful as an adjuvant therapy, particularly if headache is a major feature of attacks [c]. It is advisable to start at doses perhaps as low as amitriptyline 10 mg o.n. and dothiepin 25 mg o.n. to minimize anticholinergic side-effects.

[c] Pizotifen, a 5HT antagonist has been used at a dose of 0.5 mg t.d.s. [c]. It side-effects are consistent with its anticholinergic and antihistaminic effects.

[c] Methysergide another 5HT antagonist has been effective at a dose of 2mg t.d.s. [c] . It has serious side-effects and should be prescribed and monitored under hospital supervision.

Treatment of attacks

[c] Biofeedback techniques, hypnosis and acupuncture have also been used for the treatment of acute attacks. They are best used early [c].

[c] Non-steroidal anti-inflammatory drugs (NSAIDs) can be effective. They are given with anti-emetics to successfully treat a relatively mild attack. They have the advantage of being available in parenteral and suppository forms should nausea occur and preclude the oral route [c].

[c] Ergotamine is effective, in a dose of 2 mg initially with 1 mg half hourly thereafter up to 5 mg [c]. It is a powerful vasoconstrictor and should not be given to those with peripheral, cerebral or coronary vascular disease, nor to the pregnant patient or the known drug abuser.

[b] Sumatriptan an effective abortive treatment [b]. It is a 5HT1D agonist. Its major advantages are rapid onset and high efficacy. Given orally at a dose of 50 or 100 mg the attack is relieved in half to two thirds of patients. If the symptoms are not relieved a subsequent dose should not be taken. If symptoms are relieved but later recur a further dose can be taken, up to a maximum of 300 mg in 24 hours. The subcutaneous injection of 6 mg relieves 88% of attacks. Headache settles in approximately 30 minutes. It should be used with caution in patients with a history of cardiovascular disease.

Further reading

Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia,* 1988; **8** (suppl. 7): 1–96.

Goadsby PJ, Olesen J. Fortnightly review: Diagnosis and management of migraine. *British Medical Journal*, 1996; **312**: 1279–83.

Systematic reviews

Holroyd KA, Penzien DB. Pharmacological versus non-pharmacological prophylaxis of recurrent migraine headache: a meta-analytic review of clinical trials. *Pain,* 1990; **42** (1): 1–13.

Holroyd KA, Penzien DB, Cordingley GE. Propranolol in the management of recurrent migraine: a meta-analytic review. *Headache*, 1991; **31** (5): 333–40.

McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. *British Medical Journal,* 1995; **311**: 1047–52.

Solomon GD. Comparative efficacy of calcium antagonist drugs in the prophylaxis of migraine. *Headache,* 1985; **25** (7): 368–71.

Related topics of interest

Headache (p. 81)
Mechanisms in nociception (p. 93)

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a progressive disease. It is characterized by initial destruction of myelin and eventually axons and cell bodies. It can affect any part of the central nervous system (CNS). It is well established that MS can be associated with pain. Reports of the incidence of pain in MS vary from 13% to 82%, but it is now generally accepted that pain occurs in over half of MS sufferers. Pain from MS is predominant in females at a ratio higher than the female predominance of MS itself. The incidence of pain due to MS increases with age.

Of those with pain:

- 48% have more than one pain;
- 40% are never pain free;
- 23% have pain at the time of onset of MS;
- 33% report pain as their most distressing symptom.

Types of pain

Musculoskeletal pains

These are caused by postural and musculoskeletal abnormalities arising from paresis, spasm and discoordination. An estimated 39% of those who suffer pain have persistent aching low back pain secondary to spasm and posture changes.

Neuropathic pains

1. Central neuropathic pains. An estimated 17–66% of MS patients have central pain. Lesions anywhere from dorsal horn to cerebral cortex may be the cause of central pain. Lesions of the spinal cord, lower brain stem and periventricular areas of the forebrain are more likely to be the cause of pain but there is no one pathognomonic lesion. Although the demyelinating process of MS causes conduction block, secondary reorganization of membrane electrical properties occurs causing hyperexcitability and pain.

There are no typical symptoms but central pain due to MS has been identified as:

(a) Persistent pain. This tends to be extensive. It occurs frequently in the legs but may be present in more than one area of the body. It is usually described as burning and has associated

allodynia, hyperalgesia and abnormalities of temperature sensibility. Visceral efferents can intensify this pain.

(b) Paroxysmal pains.

- Tightening painful sensations of the extremities.
- Pain due to tonic seizures or spasms of the legs. Patients with spasticity are more likely to suffer from these pains.
- Pain in a radicular or girdle distribution occurring acutely in the absence of obvious nerve compression. This may be due to demyelination of root entry zones and is perceived as burning pain.
- Lhermitte's sign. This sign refers to the occurrence of an electrical sensation passing from the back to the legs on flexion of the neck. It is reported at some time in up to 25% of MS patients. It is related to disease involving the dorsal columns and cervical nerve roots. It is not always painful.

(c) Pain from optic neuritis

(d) Trigeminal neuralgia. This may be caused by demyelination of the brain stem. It occurs in up to 5% of MS sufferers. It differs from primary trigeminal neuralgia in that there is a constant background of pain with superimposed spasms of pain, typical of classical trigeminal neuralgia, it occurs in a younger population, and is more likely to be bilateral. Of those with bilateral trigeminal neuralgia, 18% have MS.

(e) Abdominal pain occurs in 2% of MS patients.

2. *Peripheral neuropathic pains.* Nerve compression secondary to musculoskeletal deformities can cause neuropathic pain.

Significant exacerbation of pain by psychological factors is rare. Although depressive symptoms and cognitive disturbances are recognized in MS sufferers the incidence of such symptoms does not differ between MS sufferers with pain and MS sufferers without pain.

Treatments

It is important to identify individual pains and to treat each separately if necessary. Careful assessment is therefore the key.

Musculoskeletal pain

The cause of musculoskeletal pain should be determined and removed or corrected by physiotherapy and rehabilitation appliances. Pain can be treated with simple analgesics, non-steroidal anti-inflammatory drugs, transcutaneous electrical nerve stimulation (TENS), acupuncture and possibly intra-articular injection therapy.

Neuropathic pain

There are many groups of drugs used in the treatment of neuropathic pain. It is fortunate, particularly where central and peripheral neuropathic pains coexist, that in general, treatments apply to both. Central pain in MS is probably the most difficult of all pain to treat. Expectations on the part of both patient and physician should be realistic.

1. [c] *Persistent neuropathic* pain should be treated with antidepressants, of choice amitriptyline or dothiepin at low dosage initially [c]. These drugs are however less effective in MS than in central post-stroke pain. [c] Mexiletine has been of benefit in reducing painful tonic seizures [c].

2. [c] *Paroxysmal pains* of MS respond well to the anticonvulsant drugs, the first line treatment being carbamezepine. Carbamezepine 200 mg daily increasing every other day by 200 mg to a daily maximum of 1200 mg or as side-effects permit produces dramatic relief of painful tonic seizures [c]. Carbamezepine is, however, not well tolerated in MS patients.

[c] Epidural clonidine has been shown to have a place in the reduction of painful spasms [c].

[c] Baclofen (a γ-amino butyric acid (GABA) receptor agonist) has been used with some success in the treatment of spasticity [c].

[c] Treatment of all pains but especially pain due to Lhermitte's sign has been successful using extracranial picotesla range pulsed electromagnetic fields [c]. This modality of treatment, however, is unusual and requires further validation.

[c] Spinal cord stimulation has been demonstrated to reduce spasticity and provide relief, particularly of lower extremity pain, although again, it is not well established in the treatment of painful MS [c].

Anecdotal evidence suggests a use for cannabis in the alleviation of painful muscle spasms.

3. *Painful optic neuritis* may respond to drugs used to treat neuropathic pain.

4. [a] *Trigeminal neuralgia* secondary to MS is best treated with anticonvulsant drugs [a]. [c] Reports vary from 38% to 88% complete relief following percutaneous retrogasserian glycerol rhizotomy [c]. The technique is not as successful as in those with primary trigeminal neuralgia, but low reported morbidity, effectiveness and repeatability make it feasible in MS sufferers. [c] Radiofrequency percutaneous trigeminal ganglion rhizotomy has been used with success. Balloon compression rhizolysis has also been employed. Trigeminal neuralgia due to MS is rarely relieved by microvascular decompression although success increases dramatically with the experience of the operator [c].

5. *Abdominal pain* may be improved by sympathetic blockade or pharmacological treatments for neuropathic pain.

6. *Peripheral neuropathic pain.* The treatment of peripheral neuropathic pain depends on its cause. Nerve entrapment may be amenable to surgical treatment. Radicular pain can be treated by the epidural injection of steroids.

[c] Relief of leg pain has been achieved by the use of intrathecal morphine infusions. Intrathecal baclofen has been used to treat painful spasticity [c]. Careful patient selection is required. Since there are medicolegal considerations surrounding the use of regional block techniques in patients with a progressive neurological disorder.

Further reading

Clifford DB, Trotter JL. Pain in multiple sclerosis. *Archives of Neurology,* 1984; **41**: 1270–2.

Kassirer MR, Osterberg DH. Pain in chronic multiple sclerosis. *Journal of Pain and Symptom Management,* 1987; **2** (2): 95–7.

Stenager E, Knudsen L, Jensen K. Acute and chronic pain syndromes in multiple sclerosis. *Acta Neurologica Scandinavica,* 1991; **84**: 197–200.

Systematic review

McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for the management of pain: a systematic review. *British Medical Journal,* 1995; **311**: 1047–52.

Related topics of interest

Back pain – injections (p. 22)

Cannabinoids (p. 55)

Mechanisms in nociception (p. 92)

Mechanisms in peripheral and central neuropathic pain (p. 94)

Neuropathic pain – drug treatments (p. 128)

Stimulation analgesia – spinal cord, deep brain and motor cortex stimulation (p. 164)

Trigeminal neuralgia (p. 183)

MUSCULOSKELETAL PAIN SYNDROMES

The musculoskeletal pain syndromes include the syndromes termed fibromyalgia and myofascial pain syndrome. Non-specific low back pain may be usefully considered as a variant of these syndromes.

The syndromes have as common features symptoms of regional or widespread tenderness.

The wisdom of using separate diagnostic criteria, implying distinct patholgy, is questionable. There is a risk that, in focusing on specific pain complaints in the search for symptom relief, the strategy of reducing disability will be ignored.

Some authorities have considered the concept of a condition such as fibromyalgia so unhelpful that they have suggested an alternative name, the 'irritable everything syndrome'. One interpretation is that musculoskeletal pain syndromes are overlapping syndromes, variants of muscle pains that otherwise healthy individuals suffer.

Definitions

Given the limitations above, attempts to define individual syndromes are as follows:

1. Fibromyalgia. Widespread pain: this means bilateral pain, and pain below and above the waist, in addition to neck or back pain.

Pain on digital palpation, using a standard force (4 kg) in 11 of 18 possible sites. The sites are described bilaterally in the following positions and are by convention referred to as 'tender points':

- suboccipital muscle insertions;
- anterior aspect of transverse process c5–c7;
- midpoint of upper border of trapezius;
- on the medial border of the spine of the scapula;
- costochondral junction of second rib;
- distal to the lateral epicondyle;
- the upper outer quadrant of the buttock;
- posterior to the greater trochanter of femur;
- medial aspect of lower end of femur.

Three-quarters of patients with tenderness in 11 or more of these sites complain of fatigue, sleep disturbance or morning stiffness, and over half complain of headache or pain 'all over'. Sleep disturbance, as described in association with tender points and widespread pain has particular electrophysiological features.

2. *Myofascial pain syndrome.* There is no requirement for the pain to be widespread. Areas where pain is experienced on palpation are, by convention, called trigger points. Trigger points are specific for particular muscles. Pain is experienced in a characteristic regional distribution when trigger points are stimulated. Trigger points are described as occurring within one area of a taut band of muscle fibres, which if snapped in a transverse direction is associated with a local twitch response.

Pathophysiology

It has not proved possible to identify a peripheral source of abnormal nociceptor activity in these conditions, although attractive theories concerning metabolic origins for areas of taut muscle fibres abound. Histological and biochemical studies have so far failed to prove these theories. Lowering of threshold to electrical stimulation is not restricted to tender or trigger points identified clinically, but is part of a widespread disorder, and therefore one of central processing.

Management

Initial management requires reassurance that serious or systemic pathology is not causing the problem.

The following factors should alert to the possibility of serious or systemic disease:

- morning stiffness;
- tenderness over the superficial temporal artery;
- joint tenderness or swelling.

Regional pain may be described in the referred dermatomal distribution of visceral pathology, persisting after the visceral problem has ceased to be a medical problem. Where there is history of trauma, consideration should be given to the spectrum of disorders known as 'complex regional pain syndrome'.

Trigger points can be treated with precise needling of the point. The nature of any substance injected is less important than the mechanical disruption of the taut band that is achieved by needling. Local anaesthetic, steroids and neurolytic substances have their advocates. Longitudinal stretching of taut bands can be performed by the

therapist or the patient. However, symptom control is no more important than advice about exercise and posture to prevent recurrence.

The evidence for any particular treatment of fibromyalgia syndrome is difficult to assess. The diversity of symptoms and the number of potential outcome measurements that could be made mean that it is difficult to interpret the data from randomized controlled trials. [a] There is no consensus for the use of particular outcome measures: one of the more popular measures, a simple physician rated scale of global improvement, demonstrates improvement in several drug trials. The use of amitryptiline is supported by two out of four randomized controlled trials, using measures of patient-reported pain, physician-reported pain and patient overall (global) assessment, and two out of three trials assessing patients' sleep [a].

Formal psychosocial and functional assessment with appropriate cognitive/behavioural approaches may be required for patients who do not respond to the measures outlined above.

Systematic review

White KP, Harth M. An analytical review of 24 controlled trials for fibromyalgia syndrome. *Pain,* 1996; **64**: 211–7.

Related topics of interest

Assessment of chronic pain – psychosocial (p. 12)
Back pain – assessment and medical management (p. 16)
Digestive tract syndromes (p. 74)

NECK PAIN

Painful neck syndromes are a heterogeneous group of conditions in which many mechanisms may be acting, but in which attention has in particular been directed to two sites of possible pathology: these are the cervical discs and the facet joints. The use of diagnostic nerve blocks has allowed the relative contribution of each site to persistent pain to be determined. In addition to pain arising from joints or discs, there may be muscular pain and pain due to irritation or compression of the cervical or brachial plexus. Secondary hyperalgesia may complicate the clinical presentation and make the precise diagnosis of origin of pain very difficult. Furthermore, other conditions, such as the musculoskeletal pain syndromes and headache syndromes include neck pain amongst the symptoms.

Cervical spine trauma and pain

Pain after cervical spine trauma is frequently seen as a consequence of a rear end impact in a road traffic impact, where it is colloquially termed a 'whiplash' injury. It is estimated that some 20% of victims subjected to this mechanism of injury will develop symptoms. It appears to be more common in women.

Pathophysiology

Acute muscle injury occurs and may be the cause of pain in the acute stages, but other significant injuries include cervical spine fracture, prevertebral haematoma and damage to the recurrent laryngeal nerve. Muscle spasm of the scalene muscles may be responsible for some of the neurological symptoms referred to the arms, including a functional thoracic outlet syndrome. Primary brain injury may also occur, and be responsible for a psychological disturbance in the chronic syndrome.

There is a substantial body of opinion which believes that the primary pathological mechanism is an arthritic process in the cervical facet joint, with pain referred to dermatomes according to the level of injury. [c] An autopsy report attributes neck pain that led to suicide on a single, badly arthritic cervical facet joint [c]. The idea that the pain syndrome in its entirety can be explained by one mechanism is, however, controversial and not universally accepted.

Other mechanisms which have been suggested to be of importance in the symptom complex include:

- damage to the sympathetic autonomic supply to the head;
- the cilio-spinal reflex (neck pain associated with ipsilateral pupillary dilatation);
- altered proprioceptive information from abnormally active cervical efferents leading to disordered vestibular function;
- reflex inhibition of muscles supplied by segmental levels which receive nociceptive inputs.

Clinical presentation

The principal symptom is of a pain in the back of the neck which is worsened by movement and may radiate to the head, shoulder, arm or interscapular region. The headache is suboccipital and radiates anteriorly. There are other symptoms which may confuse and perhaps lead the unwary into considering them as signs of psychological distress. These are:

- visual disturbance;
- vestibular difficulties;
- weakness and heaviness of the arms;
- paraesthesiae of medial side of hand;
- dysphagia/hoarseness;
- auditory disturbance.

Investigation

No investigation is needed to confirm the clinical diagnosis of whiplash injury, but the circumstances of the injury usually require that a lateral X-ray of the cervical spine is taken anyway. Fractures of the cervical spine can occur without impact, and specialized views e.g. laminar and pedicle views with computed tomography (CT) examination may be needed to exclude these with confidence. [c] Diagnostic block of the medial branch of the cervical dorsal ramus has shown that over 50% of patients have pain arising from cervical facet joints [c].

Treatment

There have been many approaches attempted to treat the acute symptoms and those of the chronic syndrome. The evidence in favour of many approaches is limited to uncontrolled trials and case reports. [b] The exception is the use of selective local

anaesthetic block followed , if successful, by radiofrequency lesion of the sensory supply to the cervical facet joint, the medial branch of the primary ramus of the appropriate cervical root [b]. The technique involves the prior identification of patients who respond in the short-term to a selective local anaesthetic block. Pain relief of greater than 6 months is reported. In contrast, intra-articular injections of the facet joints may provide short-term pain relief of diagnostic significance, [b] but no advantage is conferred by the addition of steroid to the local anaesthetic [b].

[c] Other treatments that have been tried and reported include:

- local heat, soft collar and physiotherapy;
- occipital nerve blocks, diagnostic and neurolytic;
- cervical epidural injections;
- sympathetic nerve blocks [c].

Attempts to prevent the onset of a chronic condition have been unsuccessful: on present evidence it is assumed that spontaneous remission of symptoms after 3 months is unlikely. [c] The link between ongoing litigation and persistence of symptoms is not proven: in one study 45% continued to have symptoms 2 years after settling of claims [c].

Cervical spondylosis

Pathophysiology

This diagnosis describes the changes caused by narrowing of the cervical nerve root foramina by bone or cartilage from ostephytes and hypertrophic facet joints. Such a definition supposes that the nerves in the foramina undergo pathological change, and it is to be expected that the sufferer would present with radicular symptoms.

Clinical presentation

The pain syndromes associated with cervical root involvement are well described and consistent, although symptoms in adjacent nerve root territory may compound the clinical picture. Pain in the distribution of the nerve tends not to involve the

hand, although paraesthesiae may be experienced. Upper cervical root compression is experienced as pain over the occciput and mastoid area. Nerve root compression is agggravated by axial loading, and by coughing, sneezing, jugular vein compression and extension of the neck.

Investigation

The diagnosis of cervical spondylosis is a radiological one. As with other chronically painful conditions of the spine, however, there is a poor correlation between the radiological appearance, and the symptoms. Magnetic resonance imaging (MRI) allows the contribution of abnormalities of cervical discs to be assessed.

Management

The contribution of the cervical facet joints to the overall pain syndrome can be assessed by specific diagnostic nerve blocks (medial branch of dorsal primary ramus) or intra-articular steroid injection. Cervical epidural steroid and paravertebral injections may be used for pain with radicular features. The greater occipital nerve, a continuation of the dorsal ramus of the second cervical nerve, can be blocked just lateral to the external occipital protuberance. It is always worth, however, considering those aspects of the pain which are of muscular origin, and looking for and treating tender points and trigger points in the first instance. As with any other painful musculoskeletal condition, the contribution of psychological factors, such as those engendering a fear of movement should be addressed.

Further reading

Barnsley L, Lord S, Bogduk N. Whiplash injury. *Pain,* 1994; **58**: 283–307.

Related topics of interest

Assessment of chronic pain – psychosocial (p. 12)
Back pain – injections (p. 22)
Musculoskeletal pain syndromes (p. 108)
Nerve blocks – somatic (p. 119)
Stimulation analgesia – TENS, TSE and acupuncture (p. 175)

NERVE BLOCKS – AUTONOMIC

Nerve blocks of the sympathetic nervous system are indicated for the control of pain where nociceptive afferents travel with the nerves of the autonomic system, or where an effect of blockade of the efferent autonomic nervous system is required. Efferent autonomic blockade has two major effects:

- removal of the influence of catecholamines from nociceptors;
- increased blood flow.

The analgesic effects of sympathetic block can be usefully considered as direct and indirect effects. Direct effects result from the removal of a nociceptive pathway, and indirect effects from the modulation of the nociceptive pathway, such that it is less sensitive to the effects of stimulation.

The sympathetic nervous system arises from the spinal roots of the thoracic and lumbar segments. Pre-ganglionic fibres exit from the spinal nerve as the white communicating ramus and pass to ganglia on the paravertebral sympathetic chain. Some fibres pass through the ganglion as pre-ganglionic fibres and synapse in more distal ganglia, from which fibres are distributed along blood vessels. Others form synapses within the ganglion, and post-synaptic fibres form the grey communicating ramus which joins the mixed spinal nerve. Visceral afferents are not themselves technically part of the sympathetic nervous system although their fibres pass through the ganglia.

The anatomy of the sympathetic nervous system lends itself to selective nerve blockade, which can be achieved without motor or somatic sensory loss. Successful local anaesthetic blockade may be followed with chemical neurolysis.

Description of sympathetic nerve blocks is described with reference to the major anatomical landmarks of the sympathetic nervous system.

Stellate ganglion

Three cervical sympathetic ganglia are formed from the fibres which originate from the upper thoracic nerve roots. The lowest of these fuses with the first thoracic ganglion to form the stellate ganglion, which lies superficial to the prevertebral fascia overlying the prominent anterior tubercle of the sixth cervical vertebra. An anterior approach, facilitated by retracting the carotid sheath laterally is possible at this level. Local anaesthetic block results in a block of the sympathetic supply to the cerebral vasculature, the eye and the upper limb, as evidenced by a Horner's syndrome and warmth in the upper limb. Complications include accidental injection into the vertebral artery, the epidural space

and the subarachnoid space. These risks require that the procedure is performed where there are facilities for resuscitation. The proximity of the recurrent laryngeal nerve and the cervical nerve roots accounts for the minor inconvenience of block of these nerves.

Thoracic paravertebral chain

Direct approach to the thoracic sympathetic chain is complicated by the close proximity of the pleura to the chain, and the risk of pneumothorax.[c] However, the interpleural technique of nerve block, involving the positioning of a catheter between visceral and parietal pleura affords one way of achieving block of the thoracic chain and the nerves associated with it, namely the greater, lesser and least splanchnic nerves [c].

Coeliac plexus

The coeliac plexus lies anterior to the aorta and surrounds the coeliac artery. It consists of three paired ganglia in which fibres from the greater and lesser splanchnic nerves form synapses, and through which visceral afferent fibres pass. The technique of coeliac plexus block involves the passage of needles, either side of the aorta, at the level of the body of the first lumbar vertebra, using a posterolateral approach. Needles are advanced from a point 6–7 cm from the midline under X-ray control, to a position in front of the first lumbar vertebral body. [c] Several variations of the technique have been described, including a transaortic approach, in which the needle is passed through the aorta, transcrural and a retrocrural approach, and the use of computed tomography imaging to aid needle localization[c]. The most notable complication, and one which limits the application of an effective technique to patients with limited life expectancy, is the development of paraplegia as a result of damage to the arterial supply to the spinal cord. This complication has been variously attributed to direct needle damage, arterial spasm, direct injection of neurolytic solution or spread of neurolytic solution. [a] Side-effects of coelaic plexus block have been analysed in a meta analysis as follows: local pain in 72%, diarrhoea in

41% and hypotension in 36%, with the incidence of more serious side-effects occurring in 3% [a].

Lumbar sympathetic chain

The lumbar sympathetic chain can be interrupted where it lies in the paravertebral gutter. In this position it lies conveniently separated from the lumbar plexus by the psoas muscle. The percutaneous approach to the sympathetic chain involves passage of a needle from a position some 7–8 cm lateral to the midline. With this approach, the transverse process may not be encountered. The classical technique sought the transverse process as a landmark and then reintroduced the needle to pass to the anterior aspect of the vertebral body. Using X-ray control, a mandatory requirement, the landmark of the transverse process can be ignored. X-ray contrast should be seen to be dispersed medially when the needle is in the paravertebral gutter: lateral spread implies injection into or posterior to the psoas muscle, with the risk of damage to the lumbar plexus.

Superior hypogastric plexus

The superior hypogastric plexus lies retroperitoneally at the junction of the fifth lumbar vertebra and the sacrum, and is a bilateral structure. The technique of approach is analagous to that of percutaneous block of the lumbar sympathetic chain, except that the needle is advanced caudally to pass between the transverse process of the fifth lumbar vertebra and the sacral ala. This can be very difficult to achieve, particularly as the gap between the two may be very narrow and the fifth lumbar nerve is in close proximity.[c] Successful treatment of a variety of pelvic pain syndromes, including cancer, has been reported [c].

Clinical indications for sympathetic nerve block

Blockade and destruction of visceral afferent nociceptors is valuable in the treatment of visceral pain arising from the structures served by the appropriate ganglia.

Blockade of the efferent sympathetic nervous system is useful in the diagnosis of 'sympathetically maintained pain', a condition of neuropathic pain described in complex regional pain syndromes, post-

herpetic neuralgia and cases of peripheral nerve damage. Where a reasonable result is obtained from the action of local anaesthetic, a chemical neurolysis is indicated if technically feasible. Chemical neurolysis of the stellate ganglion carries with it the risk of a long term Horner's syndrome and other nerve damage.

Blockade of the sympathetic nervous system is useful for the treatment of limb ischaemia and Raynaud's phenomenon.

Further reading

Plancarte R, Amescua C, Patt RB, Aldrete A. Superior hypogastric plexus block for pelvic cancer pain. *Anesthesiology*, 1990; **73**: 236–9.

Systematic review

Carr D, Eisenberg E, Chalmers TC. Neurolytic celiac plexus block for cancer pain – a meta analysis. In: *Proceedings of the 7th World Congress on Pain, Paris.* Seattle: IASG Press, 1993; 338.

Related topics of interest

Cancer – nerve blocks (p. 40)
Complex regional pain syndromes I and II (p. 62)
Pelvic (gynaecological) and urinary tract pain (p. 142)
Post-herpetic neuralgia (p. 154)

NERVE BLOCKS – SOMATIC

Sensory nerve blocks are widely used in chronic pain management for diagnostic and therpaeutic purposes. Local anaesthetic agents and neurolytic substances such as phenol, alcohol, or glycerol can be used, depending on the indication. Radiofrequency (heating) or cryotherapy (freezing) probes can be used to cause a lesion in a nerve after precise localization with X-ray and nerve stimulation. Drugs with differing mechanisms of action, such as depot steroids, clonidine and opioids can be added to local anaesthetic. Historically, nerve block procedures were the cornerstone of pain clinic practice: their role is being redefined in the light of controlled trials.

Diagnostic nerve blocks

A diagnostic nerve block seeks evidence of pain relief following local anaesthetic block of a sensory nerve. The purpose of a diagnostic block is the identification of an anatomical lesion responsible for pain so that definitive treatment can be planned. This lesion may be of either nociceptive, or peripheral neuropathic origin. Diagnostic blocks require precise localization of nerve to be of value. Inaccurate needle positioning gives a false indication of the likely pathology, and an overoptimistic interpretation of the results of nerve destruction or surgical treatment. Even when a needle placement is satisfactory, there are several problems associated with the interpretation of diagnostic blocks, as follows:

- the placebo reponse;
- a patient who is eager to please the therapist;
- needle placement is accurate but local anaesthetic has spread;
- the patient is responding to the systemic action of local anaesthetic;
- the nerve block includes the sympathetic nerve fibres and the block is not specific.

In an attempt to improve the accuracy of diagnostic block various recommendations have been made to overcome these problems. These are:

- assessment is made by an observer who is unaware of the treatment used;

- the duration of pain relief should be similar to the action of the local anaesthetic;
- pain relief that outlasts the anaesthetic duration may be due to other mechanisms;
- the response to a specific sympathetic block should be ascertained first;
- low volumes of local anaesthetic agent are used;
- the procedure is undertaken on more than one occasion;
- the patient understands the nature and purpose of the block.

Even when diagnostic nerve blocks are performed with attention to the above details, there can be further problems if it is assumed that nerve destruction or surgery will take away the pain:

- pain relief can be obtained by nerve block in the area of referred pain;
- pain relief in practice may outlast the pharmacological action of local anaesthetic;
- the dorsal horn will respond to nerve destruction by becoming sensitized.

Despite these limitations, and in addition to the principal indication, diagnostic nerve block of a somatic sensory nerve serves two other functions if a negative result is obtained:

- it may convince a patient of the futility of nerve destruction or surgery;
- it may indicate to the clinician that a central component to the pain exists.

It is also worth noting the comment of an authority on the subject who states that the practice of making a psychological assessment on the strength of a negative response to a diagnostic nerve block is 'an arrogance evolved from ignorance'.

Therapeutic nerve blocks

Therapeutic nerve blocks include local anaesthetic, neurolytic and other drugs. Local anaesthetic on its own can break the 'vicious circle' of chronic pain. Once pain and spasm around a joint has been

relieved, movement may become possible, and relief of disability and pain may outlast the pharmacological action of the anaesthetic. Successful procedures may be repeated on an occasional basis. Short-term relief from repetitive C fibre input may allow the neurons of the dorsal horn to restore their normal sensitivity. Referred pain is, according to traditional neuroanatomy, the result of branching of primary afferents and converging of inputs onto a dorsal horn cell. It can be relieved by local anaesthetic to the site of referred pain. The success of this approach is due to block of tonically active nerve impulses which increase excitability of dorsal horn neurons. Some phenomena of referred pain are difficult to explain but may be treated by imaginative use of local anaesthetic. Examples include pain from angina referred to a recent thoracic vertebral fracture, and pain from sinusitis referred to recently filled teeth. Both visceral and musculoskeletal pains can be treated with therapeutic local anaesthetic nerve blocks of areas of referred pain.

Nerve lesions and neurolytic therapeutic injections of somatic sensory nerves should be performed only after a properly conducted diagnostic trial, as described above, unless clinical urgency (advanced malignancy) makes this approach inhumane or impractical. The major hazards of nerve destruction techniques are:

- permanent motor block;
- neuropathic pain as a consequence of dorsal horn sensitization;
- accidental damage to structures adjacent to the target nerve.

Motor block may be avoided if a specific lesion is made of the dorsal (sensory) root of the mixed spinal nerve. The technical term for this procedure is rhizotomy. Alternatively, a neurotomy of a nerve serving little or no motor function is possible.

Further reading

Boas RA, Cousins MJ. Diagnostic neural blockade. In: Cousins MJ, Bridenbaugh PO (eds) *Neural Blockade in Clinical Anaesthesia and Management of Pain*, 2nd edn. Philadelphia: JB Lippincott Company, 1988; pp. 885–98.

Related topics of interest

Back pain – injections (p. 22)
Cancer – nerve blocks (p. 40)
Mechanisms in nociception (p. 92)
Nerve blocks – autonomic (p. 115)
Neuromata and post-incisional pain (p. 123)
Sympathetic nervous system and pain (p. 179)

NEUROMATA AND POST-INCISIONAL PAIN

Neuromata

Neuropathic pain is a disease of neuronal membrane excitability and the neuroma is the animal model for neuropathic pain. In humans neuromata can cause pain. Neuromata develop following partial transection of a nerve. The initial pain is from Aδ and C fibres firing. An increase in neuronal excitability causing spontaneous discharge of action potential can occur following nerve transection. Ongoing pain, accompanied by allodynia, hyperalgesia and hyperpathia then occur.

Pathophysiology

(a) When a nerve axon is cut the part which is still attached to the cell body forms a swelling (end bulb). Elongating processes are sprouted from the end bulb as an attempt to regenerate. Regeneration occurs if the axonal sprouts reach their target peripheral receptors and normal function is restored. If the processes do not reach their target sprouting continues and when their forward progress is blocked sprouts become entangled to form a neuroma. Sprouts cause disruption of the myelin sheath. Secondary reorganization of membrane electrical properties takes place, causing neuronal hyperexcitability. This may be due to an increase in number of sodium channels in the proximal axonal membrane.

(b) Disruption of the myelin sheath produces ectopic foci of electrical activity locally and in sites as remote from the damage such as the dorsal root ganglion.

(c) In undamaged nerves individual afferent fibres conduct independently, insulated by myelin. Where demyelination has occurred, nerves cross-excite each other electrically. This is termed as ephaptic transmission or neuronal cross-talk. When nociceptive afferents cross-excite each other, amplification of pain occurs. However, coupled fibres can be of different types; nociceptor afferents may be activated by afferents for light touch such that allodynia occurs. Ephaptic transmission occurs between afferents and efferents.

(d) Neuromata are chemically sensitive, for example, to adrenaline and noradrenaline.
(e) Neuromata discharge abnormally into the central nervous system (CNS) from the periphery. This may cause a phenomenon of central sensitization.

Clinical features

Neuromata are present in sites where the perineurium has been breached but not at all sites where nerves have been cut. Pain from neuromata is variable and may be governed, amongst other things, by genetic factors. Neuromata are often, but not necessarily, palpable as discrete tender lumps. Several neuromata can be found, trapped at a suture line because the regenerating nerve fibres are unable to sprout across it.

- Pain is most intense during the first 2 weeks of its development, continuing beyond then but less sustained.
- Pain from neuromata may be spontaneous or provoked. Pressure on the neuromata may provoke pain through contiguous areas.
- Pain is augmented by percussion of the neuromata. The neuromata may demonstrate allodynia, hyperalgesia or hyperpathia.
- Temperature, metabolic and chemical factors can excite ectopic discharge in animal models.

Treatments

- [c] Systemic administration of drugs acting on the sodium channel can prevent electrical firing. First-line treatment is with anticonvulsants. Local anaesthetics and antiarrythmics are also used [c].
- [c] Calcium channel blockers may also have a role in reducing excitability but have not yet been clinically evaluated [c].
- [c] Surgical excision of neuromata can be effective but in susceptible individuals neuromata recur [c].
- [c] Mechanically sensitive neuromata can be surgically embedded in deep tissue and in bone marrow away from factors which may encourage nerve growth factor (NGF) production [c].
- [c] Injections to neuromata of local anaesthetic can have effects outlasting the pharmacological duration of local anaesthetic [c].

- Colchicine and vincristine both reduce the transport of NGF. They have the unfortunate effect of causing peripheral neuropathies and currently have no established role in the treatment of neuromata.
- In animal models, electrical discharge from neuromata can be decreased by noradrenaline depletion with agents such as guanethidine or bretylium.
- Topical steroids and topical glycerol suppress ectopic neural discharge in experimental neuromata.

Post-incisional pain

Although it is recognized that long-term chronic pain following surgery can be isolated to a scar, the more usual clinical finding is pain in and around the operation site. It is more likely after the following surgical procedures:

- lateral thoracotomy;
- inguinal herniorrhaphy;
- radical neck dissection;
- cholecystectomy via a subcostal incision;
- nephrectomy via a flank incision;
- pelvic surgery via a Pfannensteil incision;
- episiotomy;
- stripping of the long saphenous vein;
- radical mastectomy.

Post-incisional pain can occur, however, after any surgery. Post-incisional pain following limb amputation constitutes a separate clinical syndrome.

Clinical features

Neuropathic pain, allodynia, hyperalgesia and hyperpathia occur along the line of the scar, nearby or deep to it. The chronic neuropathic pain is usually as an extension of the immediate post-operative pain. However, pain may develop after a pain free period.

History and examination should also identify the presence of keloid scarring, hypertrophic skin scars or a complex regional pain syndrome (CRPS).

Pathophysiology

Spontaneous or provoked pain very localized to a scar can be due to single or multiple neuromata.

Pain nearby and deep to the incision is caused by damage to both large and small afferent nerves. This can occur from surgical trauma or infection. Absence of Aβ fibre input to the dorsal horn causes loss of regulation of pain afferents. Hypertrophic and keloid scars can be bulky and uncomfortable.

Treatment

Neuromata should be treated as described above. Hypertrophic scars regress with time. Gross keloid scars may be suitable for excision. Excision is however almost always followed by a recurrence. [c] Steroid creams and pressure on scars have been used to prevent recurrence. Steroid injections may be more effective. Revision of painful scars is not always successful in producing pain relief and should be undertaken with reservation [c]. It is suggested but not proven that prevention of secondary CNS changes by local anaesthetic block can result in less pain after surgery.

[c] Transcutaneous electrical nerve stimulation may be of use in single nerve neuralgias such as intercostal neuralgia in thoracotomy pain [c].

[a] Topical application of capsaicin cream 0.075%, has been successful in the treatment of postmastectomy pain [a].

[c] Infiltration of the scar with local anaesthetic and steroid (e.g. bupivacaine 0.25–0.5% with depomedrone 20–40 mg with attention to local anaesthetic toxic doses) has been reported as effective [c].

[c] Cryotherapy to the scar is effective in isolated scar pain [c].

Benefit from sympathetic nerve blocks suggests that a pain may have a sympathetic component. Subsequent treatments are repeated sympathetic nerve blockade and the use of adrenergically active drugs.

[c] Tricyclic adrenergic antidepressant drugs, anticonvulsants and membrane-stabilizing agents are all used [c].

Radiofrequency lesioning locally to the scar, to the dorsal root ganglion and to the dorsal root entry zone (DREZ lesioning) may be of benefit.

Further reading

Bennett GJ. Neuropathic pain. In: Wall PD, Melzack R (eds) *Textbook of Pain*, 3rd edn. Edinburgh: Churchill Livingstone, 1994; 201–24.

Devor M. The pathophysiology of damaged peripheral nerves. In: Wall PD, Melzack R (eds) *Textbook of Pain*, 3rd edn. Edinburgh: Churchill Livingstone, 1994; 79–100.

Systematic review

Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin: a meta-analysis. *European Journal of Clinical Pharmacology,* 1994; **46**: 517–22.

Related topics of interest

Complex regional pain syndromes I and II (p. 62)
Mechanisms in nociception (p. 92)
Mechanisms in peripheral and central neuropathic pain (p. 94)
Neuropathic pain – drug treatments (p. 128)
Post-amputation pain (p. 151)
Sympathetic nervous system and pain (p. 179)

NEUROPATHIC PAIN – DRUG TREATMENTS

There is much debate about whether responsiveness to opioids depends on whether the pain is nociceptive or neuropathic. [b] In general, neuropathic pain tends to be less responsive to opioid, although there is evidence to support at least partial effectiveness [b]. Drug treatments for nociceptive pain are simple analgesics, the non-steroidal anti-inflammatory drugs and the stronger opioid.

Several categories of drug are available for the treatment of neuropathic pain. They are referred to, however, as coanalgesics as, conventionally they do not have analgesic action and are licensed for other uses. For the sake of completeness, references to systematic reviews include the role of these drugs in other conditions. In general, it is more difficult to relieve neuropathic pain than nociceptive pain. A single drug may not adequately treat a pain. Several drugs within the same category may have to be tried in sequence. Drugs from different categories may have to be used in combination. It has to be defined whether a pain is sympathetically maintained or sympathetically independent. The following are drugs used in the treatment of sympathetically independent neuropathic pain. Particular caution should be exercized in prescribing those which are being used without license.

Antidepressants

[a] There is evidence for an antidepressant-induced analgesic effect. In the great majority of studies, there is a statistically significant pain decrement and a statistically significant difference between antidepressant and placebo. The average chronic pain patient who receives an antidepressant is better than 74% of chronic pain patients who receive placebo. Patients suffering from pain in the head region appear to benefit more than other pain patients [a].

The role of antidepressants in the management of low back pain remains controversial. [a] On the one hand pain relief is not consistently obtained. On the other hand associated symptoms and functional ability may be improved. [a]

[a] Although all types of antidepressant have been postulated for use in the treatment of neuropathic pain, amitriptyline is the drug most frequently studied. Tricyclic drugs are more efficient than heterocyclic drugs [a]. Secondary amine tricyclics are associated with fewer anticholinergic, sedative, cardiovascular and central nervous system (CNS) side-effects and therefore with improved compliance and safety. [b] Amitryptiline and desipramine have been shown to relieve painful diabetic neuropathy [b].

[a] Analgesic effect has been shown to be independent of their effect on mood [a]. However additional benefit may be accrued from the effect of antidepressants on the reactive component of pain. [b] Patients with a substantial physical basis for their back pain responded to desipramine as well as patients who did not have a physical basis [b].

[a] The size of the analgesic effect is not significantly different for pain with an organic or a psychological basis. The size of analgesic effect is not significantly different in the presence or absence of depression. The size of analgesic effect is not significantly different in doses smaller than those usually effective in treating depression and in normal doses [a].

Analgesic response occurs much faster (within 1 week) than antidepressant response (usually after 2 weeks). Both serotonin and noradrenaline may be involved in the analgesic effect of antidepressants. Tricyclic antidepressants prevent the reuptake of endogenous noradrenaline and serotonin. Serotonin and noradrenaline within the CNS enhance the action of the descending inhibitory neural pathways at spinal cord level. To spare anticholinergic side-effects such as drowsiness and dry mouth, small doses such as amitriptyline 10 mg o.n. in the elderly or 25 mg o.n. in the more robust or imipramine 25–50 mg b.d. are used. Patients should be encouraged that side-effects reduce over time. As side-effects allow, dose can be increased at weekly intervals to achieve further therapeutic effect. Sedating antidepressants such as amitriptyline should be considered in patients who have sleeping problems. [b] Amitriptyline has proven analgesic efficacy with a median preferred dose of 75 mg in a range of 25–150 mg daily [b].

[b] Selective serotonin reuptake inhibitors (SSRIs) have been successfully used in chronic pain, but experience of them is limited and consistent results are hard to achieve [b]. They act to elevate 5-hydroxytryptamine (5HT) levels alone. [c] Paroxetine at a dose of 40 mg daily has been used to treat painful diabetic neuropathy [c]. [a] However, drugs inhibiting the monoamines less selectively do better than selective drugs, in line with pharmacological evidence that both serotonin and noradrenaline are involved in the analgesic effect of antidepressants [a].

A newer antidepressant, venlafaxine is a potent inhibitor of both 5HT and noradrenaline uptake. In contrast with the tricyclics it has negligible effects on muscarinic, α adrenergic and histamine receptors.

[a] Systematic review recommends non-selective antidepressants to be used for depressed patients with pain complaints if antidepressants are a suitable treatment for the depression, for patients with pain of organic basis where other treatments have failed and for patients with chronic pain in the head region [a]. It is important for the sake of the patient's confidence in the doctor that the patient is aware he has been prescribed an antidepressant albeit for a different indication.

Membrane stabilizing agents

Repetitive firing in afferent fibres depends on influx and efflux of sodium through sodium channels. Sodium channel blockers are therefore membrane stabilizers. Ectopic peripheral nervous system discharge is suppressed to provide relief from some neuropathic pains. Three classes of drug block sodium channels; the local anaesthetics, some anticonvulsants and some antiarythmics.

Anticonvulsants

Anticonvulsants are membrane stabilizing agents. They reduce neural excitability in the spinal cord and inhibit neuronal firing of the central nervous system. Those used in the treatment of chronic pain are carbamezepine, phenytoin, sodium valproate, clonazepam, lamotrigine and gabapentin. They are effective in a population smaller than those with neuropathic pain successfully treated with antidepressants.

[a] For the treatment of trigeminal neuralgia, carbamezepine had a combined number needed to treat of 2.6 for effectiveness, 3.4 for adverse effects and 24 for severe side-effects[a].

[a] For migraine prophylaxis anticonvulsants had a combined number needed to treat of 1.6 for effectiveness, 2.4 for adverse effects and 39 for severe side-effects. Phenytoin had no effect on irritable bowel syndrome and carbamezepine had little effect on pain after stroke. In summary, anticonvulsants were effective for trigeminal neuralgia, diabetic neuropathy and migraine prophylaxis [a].

Specific toxicities, side-effects and idiosyncratic reactions govern the choice of drug. [a] Minor adverse effects occur as often as benefit [a]. Carbamezepine causes bone marrow suppression, drowsiness and ataxia. Regular monitoring of haematological variables and liver function tests should be carried out.

Anticonvulsants for the treatment of pain are prescribed at similar dose and by similar regimes as in the treatment of epilepsy. Carbamezepine is started at 100–200 mg b.d. increasing if necessary to 1600 mg daily in four divided doses. Phenytoin is given at 300–500 mg o.d. and valproate at 200–400 mg q.d.s. Clonazepam at doses as small as 0.5 mg o.n. may be effective where the other anticonvulsants have failed.

Antiarythmics

The antiarythmics used in chronic pain are mexiletine, flecainide and tocainide. Response to mexiletine can be predicted by assessing improvement in pain following the intravenous

administration of lignocaine 3–5 mg/kg at a rate of 10 mg/minute.

Tocainide has a high incidence of side-effects compared to benefit which significantly limits its use.

Drugs affecting cholinergic transmission

The cholinergic system is involved in pain. Experimentally acetylcholinesterase inhibitors and muscarinic cholinergic antagonists given spinally and systemically increase pain thresholds. The clinical place of these drug has not yet been determined.

N-methyl D-aspartate antagonists

[c] The *N*-methyl D-aspartate (NMDA) antagonist ketamine is reported to have been effective in the treatment of neuropathic pain [c]. Dextromoraphan has no clinical role.

Capsaicin

Capsaicin is a cream which depletes substance P from primary afferent C fibre endings in the periphery and the dorsal horn. It thereby inhibits central transmission of pain. It is believed to be transported in neurotubules and neurofilaments from the periphery to the dorsal horn. The 0.075% cream is applied to the painful area liberally four times a day for the treatment of a variety of painful conditions of the skin. [a] In painful diabetic neuropathy, for every four patients treated with capsaicin, one would have had pain relieved who would not if they had been treated with placebo. In the treatment of osteoarthritis, for every three patients treated with capsaicin one had the pain of osteoarthritis relieved which would not have been relieved had they been treated with placebo. It has also been used in post-mastectomy pain [a].

An adequate trial is 8 weeks. A burning sensation can occur with application. This can be prevented by the concurrent application of lignocaine 5% ointment.

Phenothiazines

Phenothiazines are used in the treatment of neuropathic pain with little evidence as to their mechanism. They may well work by α adrenergic blockade, suggesting they would be more effective in sympathetically maintained pain.

Baclofen

Baclofen is a γ-amino butyric acid (GABA) receptor agonist. [b] It is useful for relaxing muscle where this is contributing to pain [b]. It has been used in the treatment of lightning pain.

Further reading

McQuay HJ, Moore RA. Antidepressants and chronic pain. *British Medical Journal,* 1997; **314**: 763–4.

Watson CP. Antidepressant drugs as adjuvant analgesics (Review). *Journal of Pain and Symptom Management.* 1994; **9** (6): 392–405.

Systematic reviews

McQuay H, Carroll D, Jadad AR, Wiffen P, Moore RA. Anticonvulsant drugs for the management of pain – a systematic review. *British Medical Journal,* 1995; **311**: 1047–52.

Onghena P, Van Houdenhove B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. *Pain,* 1992; **49** (2): 205–19.

Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin: a meta-analysis. *European Journal of Clinical Pharmacology*, 1994; **46**: 517–22.

Related topics of interest

Depression and pain (p. 71)
Ketamine (p. 89)
Mechanisms in peripheral and central neuropathic pain (p. 94)

NEUROSURGERY AND PAIN

This topic is not intended as a comprehensive account of all the neurosurgical procedures for pain; rather it is intended to explain the rationale of neurosurgery for pain, and illustrate some of its potential. Procedures may involve quite specialized techniques drawn from different areas of neurosurgery such as spinal neurosurgery or stereotactic and image-guided techniques. The 'pain' neurosurgeon thus requires considerable general and specialist expertise. A fully equipped neurosurgical facility is of course required, preferably with facilities for intra-operative neurophysiological monitoring.

Neurosurgery for the relief of persistent pain began in the last century with root sections and later cordotomy. Pain relief was dominated by these methods until the second half of this century when advances in analgesics, including anti-convulsants, psychotropics and specific opioid preparations, were associated with the rapid development of pain clinics and hospices. There was then a virtual cessation in the practice of neurosurgery for pain relief.

In the last 20 years, the development of more precise, safe, effective and low-morbidity techniques has resulted in a renewed interest in neurosurgery for the relief of pain when medication has proved inadequate or intolerable. These advances include percutaneous techniques and non-destructive augmentative techniques such as electrical stimulation or the implantation of sophisticated devices for drug delivery. The percutaneous techniques were particularly suited to an anaesthetic training, from which specialty many pain practitioners came.

The neurosurgical procedures performed can be divided into three. **1. Correct structural problem:** Microvascular decompression for TGN, spinal fusions for instability, discectomy, tumour resections; **2. Non-destructive or augmentative such as electrical stimulation:** At many sites in the nervous system (*see* Stimulation analgesia: spinal cord, deep brain and motor cortex stiumulation); at its most sophisticated this includes stimulation of deep brain structures; **3. Destructive procedures:** Radio-frequency lesioning, root sections, open cordotomy, commisurotomy, DREZ, medullary tractotomy, thalamotomy and pituitary ablation.

In the first category, apart from MVD (see below), the examples may appear unrelated to the specialty of pain. However, one of the most important roles of a neurosurgeon involved in surgery for pain is to be certain that surgically remediable pathology has not been missed – in the case of 'chronic' sciatica this may be a simple lumbar disc prolapse – more rarely 'trigeminal neuralgia' may represent the facial pain from an acoustic or even trigeminal schwannoma.

The distinction between destructive and non-destructive procedures is important since destructive procedures are most appropriate for treatment of persistent pain due to malignancy, and are little used for non-malignant pains. The reason for this is that relapse rates are high after destructive procedures; there is a risk of neurological deficit and therefore disability; and new syndromes (particularly dysaesthetic type

pains) may arise after destruction of the nervous system at either peripheral or central levels, though more particularly after peripheral lesions.

Another underlying and related philosophy is that low-risk procedures are to be attempted before high-risk procedures even if the success rate of the former is poor; thus deep brain lesions or stimulation tend to be last resort options. Finally, it is important that a multidisciplinary approach occurs: in the authors unit this is achieved by joint ward rounds and clinics between anaesthetic, neurological and neurosurgical pain specialists, and involving nurse specialists, and the pain management team, supported by an active research unit.

Two examples illustrate these points.

Dorsal root entry zone (DREZ) lesion

There are a number of destructive lesions of the spinal cord designed to alleviate pain. The DREZ lesion is unusual in that it is used for chronic pain due to 'benign' pathology. This may be because in distinction to cordotomy or commissural myelotomy grey matter is targeted rather than tracts; in this case the dorsal root entry zone. Cordotomy and commissural myelotomy certainly have relapse rates, and like DREZ carry risk of significant physical disability – they are reserved almost exclusively for pains due to malignancy. Although cervical cordotomy can be performed percutaneously in the neck, elsewhere an open laminectomy is needed.

Historical

It was first introduced by Sindou in 1972 as a treatment for neuropathic pain and spasticity. He coined the term microsurgical selective posterior rhizotomy. The lesion was also popularized by Nashold in 1976, who used radiofrequency technology to create the lesion in the dorsal root entry zone – hence the acronym 'DREZ' particularly for brachial plexus lesions.

Syndromes

The best indications seem to be brachial plexus avulsion injuries; well-localized cancer pain (as in Pancoast syndrome); cauda equina and spinal cord lesions for pain corresponding to segmental lesions, peripheral nerve lesions, amputations and herpes zoster, provided the predominant component of the pain is paroxysmal and associated with allodynia. It can also be used for spasticity, and for hyperactive neuropathic bladder.

Operation

This is an open neurosurgical procedure requiring a laminectomy with opening of the dura to expose the spinal cord. The DREZ region is identified from the

position of the dorsal rootlets. The target for the lesion, whether performed by incision with subsequent coagulation (Sindou), radiofrequency or laser (Nashold), is immediately anterior to this point. A lesion of depth 2–3 mm is created, affecting Rexed layers I–IV. This may be difficult to identify when the roots have been avulsed, as is the case in brachial plexus injuries. Some employ intra-operative neurophysiological monitoring of somato-sensory evoked potentials in order to guard against unintentional damage to the dorsal columns.

Risks

The main complication is ipsilateral leg weakness, although there may also be ipsilateral loss of sensation. Some subjective loss of sensation and/or weakness may occur in as many as 60% of cases and be significant in up to 10%. Loss of bladder control can occur, albeit rarely. For these reasons, DREZ lesion is often only attempted as a last resort; it may follow attempts at spinal cord stimulation, even if this is thought not likely to succeed.

Outcomes

For brachial plexus lesions, success rates of 70% are reported with long-term follow-up of 1–8 years. Rates of 50–70% are found for other indications; where relief is obtained it does seem to be maintained. However, the experience in the author's unit is for a tendency to relapse with time, a finding in keeping with most other ablative or destructive techniques for the treatment of pain.

Results for post-herpetic neuralgia are much less encouraging. Although initial success rates of about 60% are observed, this falls to only 25% with longer follow-up.

Microvascular decompression for trigeminal neuralgia

Here a structural abnormality is corrected; the outcome may be compared with that for radiofrequency lesioning, where there is a significant recurrence rate and risk of anaesthesia dolorosa. Recurrence with a high incidence of late dysaesthetic pains is the rule following peripheral nerve lesions by avulsion or alcohol injection.

Historical

Microvascular decompression for trigeminal neuralgia was popularized by Janetta in the late 1960s but first carried out by Walter Dandy in the 1930s.

Causes of trigeminal neuralgia

The cause of TGN is unknown. However, in approximately 90% of cases a vessel, usually an artery, is found in contact with the trigeminal nerve as it exits the pons. The transition between the central nervous system and the peripheral nervous system occurs at this point: the root entry zone. Sometimes this contact may groove the nerve. It is not clear how such contacts cause TGN, but sensory malfunction can be detected in the laboratory (albeit not clinically), as can abnormalities of the trigeminal somatosensory-evoked response. Normalization of neurophysiology and sensation occurs following microvascular decompression, and the usual outcome from the procedure is instantaneous pain relief.

Investigations

Until recently it was not possible to detect vascular compression of the nerve pre-operatively, so all of the early procedures were carried out 'blind'. More recently, advances in magnetic resonance imaging (MRI) have allowed the detection of vessels pre-operatively. MRI to detect such vessels is now routine in the author's practice.

Fitness for surgery

Because MVD involves craniotomy, and TGN occurs in elderly people, fitness for surgery has been a major issue in the past. With modern anaesthesia very few patients are unsuitable for this procedure, and the choice between percutaneous radiofrequency lesioning and MVD can be based on the outcomes of the procedures. It is worth remembering that radiofrequency lesioning also involves anaesthesia.

Operation

This is performed via a retro-mastoid craniectomy; the subsequent approach is over the surface of the cerebellum until the nerve is identified. Arteries must be dissected free and held clear from the nerve using small pieces of Ivalon sponge or Teflon. If a vein is the cause, it may be coagulated and divided. If no vessel is found, a partial sensory rhizotomy gives good relief.

Risks

In most published series, the serious morbidity (death or major stroke) is significantly below 1%. The operation, being performed near to the acoustic nerve, also carries a risk of hearing impairment, possibly due to traction on the nerve whilst

retracting structures to gain access to the deeper trigeminal nerve. Since brain stem auditory-evoked responses have been used as a monitoring device peroperatively, the risk of unintentional hearing deficit has been almost eradicated.

Outcomes

Overall, of those with clear arterial compression, a long-term cure will be obtained in about 90%, of whom some 70% are completely pain-free. Results of venous compression are less good, as are the outcomes following partial rhizotomy – approximately 60–70% at 2 year follow-up.

Choice of technique

The risk of all destructive lesions is anaesthesia dolorosa. Whilst the amount of pain relief is related to the amount of damage to the nerve, so unfortunately is the risk of anaesthesia dolorosa. Recent evidence suggests that MVD is followed by normalization of trigeminal somatosensory physiology and cutaneous sensation; thus, while trauma to the nerve can be effective (e.g. partial rhizotomy), MVD itself should be regarded as a non-destructive procedure for pain relief. Increasingly, therefore, MVD is being viewed as the treatment of choice, especially since the results of arterial decompression are so good, and this state can be demonstrated pre-operatively by MRI.

Further reading

Barker FG II, Janetta PJ, Bissonette DJ, Larkins MV, Jho HD. The long-term outcome of microvascular decompression for trigeminal neuralgia. *New England Journal of Medicine*, 1996; **334:** 1077–83.

Meaney JF, Eldridge PR, Dunn LT, Nixon TE, Whitehouse GH, Miles JB. Demonstration of neurovascular compression in trigeminal neuralgia with magnetic resonance imaging. *Journal of Neurosurgery*, 1995; **83:** 799–805.

Miles JB, Eldridge PR, Haggett CE, Bowsher D. Sensory effects of microvascular decompression in trigeminal neuralgia. *Journal of Neurosurgery*, 1997; **86**(2): 193–6.

Sindou M. Microsurgical DREZotomy (MDT) for pain spasticity and hyperactive bladder: a 20-year experience. *Acta Neurochirugia (Wien)*, 1995; **137:** 1–5.

Related topics of interest

Mechanisms in peripheral and central neuropathic pain (p. 94)

Post-herpetic neuralgia (p. 154)

Trigeminal neuralgia (p. 183)

OSTEOPOROSIS – GENERALIZED ADULT

Bone is metabolically active. It is continually formed and resorbed. Osteoporosis occurs when resorption exceeds formation. This causes loss of bone, with a consequent susceptibility to fractures, loss of normal architecture of bones, postural deformities and soft tissue changes. All result in pain. A clinical definition is made by standardized bone density measurements.

Osteoporosis can be idiopathic, with recognized risk factors, or secondary to other conditions such as cancer, liver impairment, coeliac disease or gastric surgery. Sex hormones have a significant effect on the skeleton. High-risk factors include early surgical menopause and early natural menopause. Other risks are steroid therapy, family history, thinness, lack of weight-bearing exercise, smoking and alcoholism.

Calcium is an important element of bone mineral. Adequate calcium intake and the calcium-regulating hormones, vitamin D and calcitonin protect against osteoporosis.

Chronic pain in osteoporosis is caused by several factors.

Acute vertebral crush fractures

The severity of pain is variable depending on the degree of collapse. Collapse starts as increased biconcavity of the horizontal surface of the vertebral bodies, often with loss of height. Pain at this stage is absent or mild and may be the result of microfractures or ligament or muscular strain. As the vertebral body collapses further and becomes visibly wedge-shaped, localized back pain occurs, with or without radicular pain depending on whether there is associated nerve compression. There can be associated pain from spasm of paraspinal muscles. Complete vertebral body crush causes severe back pain often accompanied by radicular and muscle spasm pain. Pain from crush fractures subsides within weeks. However repetitions of these fractures occur.

Back pain

Back pain occurs in an estimated 70% of osteoporotic patients. In the absence of radiological lesion other than the osteoporosis itself, it can be attributed to microfractures of the trabeculae or to generalized degenerative changes producing associated strain of interspinous ligaments and tenderness of paraspinal muscles. Osteoporotic changes may cause facet joint disease, sacroiliac

arthritis or nerve compression with associated radiculopathy.

Postural pains

Loss of bone architecture causes many deformities. The most troublesome is kyphosis caused by wedging or complete collapse of vertebral bodies. Sufferers develop a stiff painful neck from hyperextending in an attempt to hold up their head. As dorsal kyphosis progresses, undue effort is needed from cervical extensor muscles. Eventually the splenius capitis muscles become weak and the head can then only be lifted passively.

Neck pain frequently causes cervicogenic headache.

Inability to lift the neck causes the chin to be in constant contact with the chest wall. This causes soreness of the chin.

In order to look ahead, severely kyphotic patients flex the knees to enhance their angle of vision, thereby putting painful strain on to their knees.

Dorsal kyphosis causes the lower rib to painfully abut the top of the pelvis.

Treatments

Pain arises as a complication of progressive osteoporosis, not from osteoporosis *per se*. The first-line approach should be the prevention of further deterioration and the treatment of the osteoporosis itself. Symptomatic treatment of pain is second-line. Government attention has recently been given to osteoporosis with the result that designated physicians have been nominated in many centres. Advice is now, therefore widely available and coordinated approaches should be made to empirical treatment and the appropriateness of symptomatic treatment.

1. Lifestyle factors. Advice as to appropriate exercise, diet and exposure to sunlight should be given. Dietary supplements of calcium and vitamin D may be necessary. A synthetic precursor of vitamin D is available.

2. *Empirical treatments*

(a) Hormone replacement therapy (HRT). Following an early natural or surgical menopause the risk of osteoporosis is high. [b] It is well established that small doses of oestrogen given for several years starting at the time of the menopause will reduce the likelihood of post-menopausal osteoporosis [b]. Where the uterus remains, there is an increased risk of endometrial cancer from the administration of oestrogens so cyclical progestogen is added to prevent cystic hyperplasia of the endometrium and its progression to carcinoma. Hormone replacement is administered in preparations of conjugated oestrogen and progestogen or oestrogens alone for those without a uterus. HRT is recommended at least until the age of 50 and possibly for a further 10 years or more, although this is a subject of debate. Because of considerable first-pass metabolism, endogenous hormone levels are better mimicked by transdermal patches or subcutaneous implants.

(b) Bisphosphonates. [c] Established vertebral osteoporosis is treated with bisphosphonates [c]. Two in current use are etidronate and alendronate. Risedronate, ibandronate, zolendronate and tiludronate also offer therapeutic potential. Bisphosphonates are analogues of endogenous pyrophosphates. They bind tightly to the surface of trabecular bone and inhibit its resorption. They also modify the behaviour of resorption cells. By preventing bone loss they increase bone mass over 2–3 years, significantly reduce the incidence of bone fractures and are often markedly effective in pain. They are only given for short periods because they are considered toxic, as they remain in bone for a long time.

(c) Calcitonin. This inhibits bone resorption by osteoclasts. b Osteoporotic patients are not deficient in calcitonin but a synthetic form is quick and successful in relieving pain in post-menopausal osteoporosis b.

3. *Symptomatic treatments*

(a) Acute vertebral crush fractures. [b] Salmon calcitonin injections have been shown to improve pain relief [b]. Bed rest may be necessary because of the pain associated with movement. Analgesics such as codeine or morphine should be given for limited periods. [c] Transcutaneous electrical nerve stimulation (TENS), acupuncture and massage may be beneficial [c]. [c] Epidural injections have been shown to be of value where the fracture is not too far from the epidural injection site [c]. [c]Epidural steroid injections and paravertebral steroid injections improve pain of root compression [c].

(b) Acupuncture, TENS, and pain management programmes. The treatment of back pain depends on the anatomical component likely to be involved. Analgesics for both nociceptive and neuropathic components, physiotherapy, injections, acupuncture TENS and pain management programmes all have their place.

(c) Postural pains. Occupational therapy and physiotherapy support for activities of daily living can relieve some of the misery. Thoracolumbar supports have been shown to reduce back pain.

Further reading

Dequeker J, Geusens P. Treatment of established osteoporosis and rehabilitation: current practice and possibilities. *Maturitas,* 1990; **12**: 1–36.

Related topics of interest

Back pain – injections (p. 22)
Complex regional pain syndromes I and II (p. 62)
Neuropathic pain – drug treatments (p. 128)
Stimulation analgesia – TENS, TSE and acupuncture (p. 175)

PELVIC (GYNAECOLOGICAL) AND URINARY TRACT PAIN

This group of conditions is considered together because a number of syndromes with non-specific symptoms and overlapping features are described. Common nociceptive mechanisms are implicated. Difficulties in diagnosis of the patient presenting with pain in the lower abdomen may lead to extensive investigation of the genitourinary system. Further confusion may be the consequence of the pain being referred from, or referred to the musculoskeletal system. Iatrogenic causes may confuse. An empirical approach to symptom control, such as the use of frequent courses of antibiotics for symptoms of pain on micturition, may lead to painful candidiasis, and the unguarded use of opioids for undiagnosed urinary tract pain may have its own problems.

Investigation may reveal pathology to account for the problem. The indication for, and the possible findings of investigation is outside the scope of this book. Conventionally, symptoms that corelate with pathology are referred to as 'secondary'. Thus secondary dysmenorrhoea refers to painful periods attributed to a condition such as endometriosis in which treatment of the condition is appropriate along with treatment of the symptom. Laparoscopy has made the diagnosis of painful pelvic conditions more specific. It has not, however, answered some essential questions, in the same way that magnetic resonance imaging of the spine has not helped the management of many back conditions. The unanswered questions are those about the poor corelation between abnormal laparoscopic, cystoscopic, laboratory findings and the symptoms of pain. Any attempt to explain how patients with normal pelvic organs continue to experience pain has to consider that an incomplete diagnosis has been made, that the disturbance is physiological rather than pathological, or that psychological factors are playing a part. [c] The existence of a painful 'phantom pelvis' following pelvic exenteration is evidence of the complexity of the mechanisms maintaining pain [c].

Pathophysiology

The sensory innervation of visceral organs is notable for three important reasons:

(a) The anatomical organization is complicated, with primary afferent nociceptive fibres entering the spinal cord via fibres which pass with efferent nerves of both the sympathetic (thoracic and lumbar spinal nerve roots) and parasympathetic (sacral nerve roots) divisions of the autonomic nervous system.

(b) The segmental representation of each system is wide and receptive fields for dorsal horn neurons large such that a clinical diagnosis of origin of pain is not easy.

(c) The population of primary afferents contains a substantial proportion of fibres that do not conduct electrical impulses unless sensitized by a change in the local environment, such as occurs with tissue damage, or by an alteration in the spinal cord modulating process, such as occurs after spinal cord injury. It is believed that these 'silent' nociceptors serve a monitoring function, and by an as yet incompletely understood mechanism (one which involves axonal transport mechanisms), 'sample' the environment near the nerve ending.

The somatic and the autonomic system are both involved in nociception. Somatic innervation to the perineum is the pudendal nerve which projects to sacral (S2–S4) roots. The parietal peritoneum is innervated by intercostal and subcostal nerves. In the female the autonomic nerves provide a source of visceral afferent sensation, and project to the spinal cord between T9 (for ovary) and L1 (for bladder and cervix). Ovarian afferents access the lower thoracic spinal roots via the lumbar sympathetic chain, whilst bladder and cervical afferents access the lumbar roots as the presacral nerves or hypogastric plexi. In both sexes there is identified a number of nerve plexi (named after the target organ) through which the sympathetic fibres pass to the spinal cord: the distribution of the sympathetic fibres to and from these plexi follows the blood supply to the organ. The pelvic splanchnic nerves (S2–S4) are parasympathetic sensory and motor to cervix, lower uterine segment, muscular stroma of prostate, distal urethra and bladder. The relative contribution of the two divisions of the autonomic nervous system to nociception in health and disease is unknown.

The environment of the uterine nociceptor is subject to change with the physiological processes of ovulation and menstruation. Afferents are sensitized by prostaglandins and leukotrienes, and become sensitive to pressure or ischaemia when the uterus contracts. Similarly, chemical irritation of the peritoneum by pathology (e.g. endometriosis) may sensitize and stimulate afferents.

Uterine veins have been implicated in the pathophysiology of pelvic pain. The uterine venous system is unique in its abiliy to accommodate huge increases in its blood flow (in pregnancy), and in keeping with this, is a valveless system, in which distension may occur in the upright position. The finding of distended uterine veins at venography was said, prior to the era of laparoscopy, to be diagnostic of a specific condition of pelvic congestion.

Menstruation is a painful condition in many women, and prior experience of painful menstruation may influence the psychological state of the woman who presents with pelvic pain.

Clinical presentation

Chronic pelvic pain without obvious pathology (CPPWOP)

In a series of studies conducted in 1976–1979, pain was the commonest presentation at a gynaecological outpatient clinic. It was the commonest indication

for laparoscopy. In one study, laparoscopy was normal in 65% of patients investigated for pain. Such findings have resulted in the description of a syndrome termed 'chronic pelvic pain without obvious pathology' (CPPWOP). Although the syndrome, as defined today, requires a laparoscopic exclusion of other pathology, it seems reasonable to equate it with the pelvic congestion syndrome described above. It presents as a dull ache, worsening before menses, and having a symmetrical distribution. Examination reveals tenderness over the ovarian point, a cyanotic cervix and tender adnexae.

Psychological examination reveals anxiety, feelings of being sexually unattractive, inability to sustain relationships, and stressful life events prior to symptoms. It is helpful to consider the condition as either a psychological disorder in which noxious stimulation plays a part, or a painful physiological disturbance. It is conveniently described as a disorder of the autonomic nervous system in which abnormal afferent activity (nociception) and efferent activity (altered blood flow) coexist.

[c] Non-steroidal anti-inflammatory drugs and oral contraceptives prevent the synthesis of prostaglandins and may be useful in treating pelvic pain that results from chemical sensitization. A hypoestrogenic state is helpful for the control of the pain of endometriosis and is used for the control of pelvic pain without obvious pathology, using progesterone containing contraceptives [c].

[c] Successful treatment of appropriate cases of benign pain can result from blocking the presacral nerve anterior to the lumbosacral junction. Sphincter control is preserved as the sacral nerve roots are not affected by this nerve block [c].

The contribution of psychological factors to the experience of pelvic pain is important to assess. General cognitive/behavioural approaches may be of value, but particular problems with issues involving sexual difficulties may need specialist attention.

Pelvic adhesions

A diagnosis of this pathology can be made at laparoscopy, but a diagnosis cannot explain how

some patients with dense adhesions (from pelvic inflammatory disease, endometriosis or previous surgery) have no pain and how some patients are incapacitated with pain despite few findings. Similarly, surgical division of adhesions has a variable success rate.

Haematuria /loin pain syndrome

The diagnosis is made by exclusion of organic causes to account for recurrent attacks of unilateral or bilateral loin pain associated with haematuria, but not explained by other pathology. Renal biopsy may show a number of features, such as mesangial proliferation, and immune complement C3 deposition in the arterioles, and arteriolar abnormalities may be demonstrated at renal arteriography, but these changes are non-specific and inconsistent. Psychological disturbance may complicate the presentation.

[c] Ureteric catheterization with instillation of a solution of capsaicin into the renal calyx and ureter has been described: this is said to result in a depletion of substance P from the nociceptors of the urothelium. The procedure may require prolonged epidural anaesthesia [c].

[c] Denervation of the kidney by removal of the renal capsule may afford relief, but the long-term results are disappointing. Pain returns or affects the opposite side [c].

[c] Autotransplantation has been reported to achieve good long-term results [c].

Interstitial cystitis

A history of suprapubic pain, frequency, dysuria and urgency in the absence of infection, and cystometric findings of small bladder capacity and painful catheterization are features of this condition. Cystoscopic findings include petechial haemorrhages and occasionally ulceration. An increase in the number of Mast cells in the bladder wall has been noted in sufferers of the condition. The condition occurs predominantly in middle aged women and may be associated with irritable bowel syndrome. Many patients have had a hysterectomy prior to diagnosis, such that it has been suggested that this operation has been performed because of

complaints of pelvic pain that were those of interstitial cystitis.

[c]Steroids and non-steroidal anti-inflammatory drugs, anti-histamines, heparin, long-term antibiotics, local anaesthetics, and tricyclic antidepressants have been reported to be of benefit in medical management of interstitial cystitis [c].

[c] Surgical management, with ablation of the vesicoureteric plexus has been reported to provide long-term relief [c].

[c] Behavioural therapy, aimed at reducing the level of distress and associated illness behaviour has been reported to be of value [c].

Further reading

Beard RW, Pearce S. Gynaecological pain. In: Wall PD, Melzack R (eds) *Textbook of Pain*, 2nd edn. New York: Churchill Livingstone, 1993; 467–8.

Related topics of interest

Mechanisms of nociception (p. 92)
Musculoskeletal pain syndromes (p. 108)
Nerve blocks – autonomic (p. 115)
Psychological management of chronic pain (p. 157)

PERIPHERAL NEUROPATHIES AND NEURALGIAS

A neuropathy refers to dysfunction in a nerve secondary to nerve damage. It can affect a single nerve (a mononeuropathy) or many nerves (a polyneuropathy). It may or may not be painful. A bilateral symmetrical neuropathy is usually of systemic cause. A painful mononeuropathy is often referred to as a neuralgia.

Pathophysiology

Localized or systemic damage and disease can cause demyelination of nerves and less frequently axonal degeneration. Consequently there is a barrage of afferent impulses to the dorsal horn of the spinal cord. This proceeds to a central windup mechanism. Ectopic impulse generation occurs both at the sites of damage and from associated degeneration in the dorsal root ganglion and the spinal cord. Damaged axons become hypersensitive to mechanical and chemical stimuli. Different nerves are affected by different types of damage. Damage may be non-selective, may affect only large fibres or may affect only small fibres. The type of fibre affected has bearing on the symptoms. Although the presence of pain is not related to fibre size alone damage to smaller fibres more often tends to cause pain. Rapid degeneration is more likely to cause painful neuropathy. Ephaptic transmission (neural cross-talk) causes the provocation of pain by normally non-painful stimuli such as touch.

Painful polyneuropathies

Painful polyneuropathies tend to have a systemic cause. They are most frequently due to toxic agents, metabolic disorders or vitamin deficiencies. They present various patterns of sensory, motor or autonomic deficit. The lower limbs are usually affected, with sensory symptoms prevailing over motor symptoms. The more common ones are described below.

Diabetic neuropathy

This is caused by small fibre damage. Sensorimotor deficiency and autonomic instability occur. Pain is tingling, burning, stabbing or shooting. Pain may also be due to peripheral vascular disease, joint disease or the development of ulcers secondary to reduced sensation.

Alcoholic neuropathy

This is compounded by concurrent dietary insufficiencies. Non-selective damage occurs causing a sensory and motor deficit. Pain is burning with tenderness of the feet and legs.

Nutritional deficiency neuropathy

Vitamin B1 and niacin deficiencies cause peripheral neuropathy. An associated condition, burning feet syndrome, does not necessarily have the clinical signs of peripheral neuropathy but responds to dietary enhancement of the B vitamins.

Isoniazid neuropathy

This is the most well known of the toxic substance neuropathies. It is characterized by spontaneous pain and paraesthesiae, worse at night. It is due to large fibre damage. Other toxic causes are certain chemotherapy agents, arsenic and mercury.

Painful peripheral neuropathies also occur in hypothyroidism, myeloma, amyloid, Fabry's disease, acquired immunodeficiency syndrome (AIDS) and as a dominantly inherited form. The peripheral neuropathy of chronic renal failure is often painless but there may be troublesome paraesthesiae or restless legs.

Painful mononeuropathies and neuralgias

Damage to single nerves results from direct trauma, invasion by tumour, past surgery and compression or entrapment.

Examples include carpal tunnel syndrome, cranial, facial and intercostal neuralgias, radicular pain and meralgia paraesthetica. Within the distribution of the nerve there is pain with associated numbness, hyperpathia or allodynia. Some neuralgias develop into complex regional pain syndrome II.

Management

History and examination gives pointers to the aetiology of neuropathies and neuralgias. The clinical suspicion of an undiagnosed systemic disease or a systemic disease which is suboptimally treated might warrant investigation and treatment outside the pain clinic. Dietary neuropathies improve with supplements. Myeloma neuropathy can improve with antineoplastic treatments. Similarly entrapment neuropathies may warrant the opinion of a surgeon.

The treatments specifically for pain follow similar principles for both poly- and mono-neuropathies and neuralgias. However extensive areas of involvement in the polyneuropthies often make the use of topical treatments impractical.

1. Physiotherapy. Exercise and use is important to maintain central input from non-nociceptor afferents.

2. Nerve blocks. A sympathetic component to the pain should be sought. Sympathetically maintained pain should be treated by either a series of sympathetic nerve blocks to the affected area or by α adrenergic antagonists, $\alpha 2$ adrenergic agonists, β adrenergic antagonists and calcium antagonists as appropriate. Somatic nerve blocks have a place in the treatment of sympathetically independent mononeuropathies and neuralgias.

3. Topical treatments. [a] Capsaicin 0.075% cream applied four times daily for 4–8 weeks is effective in the treatment of painful diabetic neuropathy [a]. [c] Other topical treatments include the infiltration of the affected nerve with steroid, glycerol injections or the topical application of local anaesthetic or creams. The application of TENS to stimulate nerves proximal to the areas of damage can be useful [c].

4. Systemic treatments. Polyneuropathies tend to need systemic treatments. [a] Anticonvulsants are effective for trigeminal neuralgia and diabetic neuropathy [a]. [b] Painful diabetic neuropathy has also been shown to respond to the selective serotonin re-uptake inhibitor (SSRI) paroxetine [b]. [b] Desipramine relieves pain caused by diabetic neuropathy with efficacy similar to amitryptiline. Fluoxitine has not been shown to be any more effective than a placebo [b]. [c] The newer SSRI vanlafaxine offers potential. The tricyclic antidepressants and other membrane stabilizing

agents such as the antiarrhythmic drugs mexiletine and flecainide are of use [c].

Further reading

Devor H. The pathophysiology of damaged peripheral nerves. In: Wall PD, Melzack R (eds) *Textbook of Pain*, 3rd edn. New York: Churchill Livingstone, 1994; pp. 79–100.

Scadding JW. Peripheral neuropathies. In: Wall PD, Melzack R (eds) *Textbook of Pain*, 3rd edn. New York: Churchill Livingstone, 1994; pp. 667–84.

Systematic reviews

McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. *British Medical Journal*, 1995; **311**: 1047–52.

Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin: a meta-analysis. *European Journal of Clinical Pharmacology*, 1994; **46**: 517–22.

Related topics of interest

Complex regional pain syndromes I and II (p. 62)
Mechanisms in nociception (p. 92)
Mechanisms in peripheral and central neuropathic pain (p. 94)
Neuromata and post-incisional pain (p. 123)
Neuropathic pain – drug treatments (p. 128)
Sympathetic nervous system and pain (p. 179)

POST-AMPUTATION PAIN

Pain following amputation can be stump pain or phantom limb pain. Phantom limb pain is often confused with phantom limb sensation, which is the perception of the continued presence of the amputated part. It is not painful. Most commonly it is an awareness of the amputated part or a feeling of its altered position. Phantom limb sensation occurs in almost all amputees in the first month after surgery and abates with time. It has been described following surgical removal of breast, nose, tongue and penis but is most commonly described in relation to limb amputation.

Stump pain

Stump pain occurs in approximately 50% of early amputees. It improves with time.

Aetiology

Stump pain can be caused by prominent bony spurs, vascular insufficiency or neuromata within the amputation scar. Badly fitting prostheses cause superficial inflammation, ulceration and pain. This discourages the patient from wearing the prosthesis, thereby further impeding their rehabilitation.

Clinical features

Pain is localized to the stump but not necessarily within the scar. It is spontaneous or provoked. It is commonly described as sharp or stabbing but sometimes as burning. Pressure aggravates pain. Examination can reveal signs of vascular insufficiency or the presence of tender bony spurs, myofascial trigger points or neuromata. Allodynia may be a feature.

Management

Prostheses must be fitted correctly. Surgery may be required to remove bony spurs, revascularize or refashion the stump. The attempt to treat pain is, however, only worth one re-exploration of the stump. Neuromata can be surgically embedded although this does not have significant success. They can also be treated conservatively. Local anaesthetic injections improve tender trigger points. [b] The topical application of local anaesthetic or the regular application of 0.075% capsaicin cream can be of benefit [b]. A physiological hypersensitivity can be helped by repeated touch to desensitize, and by reassurance and encouragement to persevere with the use of the prosthesis.

Phantom pain

Phantom pain occurs in up to 85% of amputees. It is more likely following extensive amputation.

Aetiology

The mechanism of phantom pain is unclear.

1. The gate theory. This suggests pain occurs because neuronal derangement at the time of amputation causes reduced Aβ mechanoceptor firing which in turn reduces the normal inhibition of pain transmission in the spinal cord.

2. Windup. The development of phantom limb pain is apparently related to the amount of pain before amputation. Phantom limb pain has been reported to respond to ketamine, an *N*-methyl D-aspartate antagonist. It has been suggested that pain has a central component. Sensitization of the dorsal horn neuron by persistent nociceptor input (windup) may be a mechanism.

Clinical features

Phantom pain is perceived to originate in the amputated portion. It is constant or more likely intermittent and brief. It is spontaneous, but the frequency and intensity of pain is exacerbated by physical and emotional stimuli. Pain is variably described as cramping, crushing, burning, stretching or squeezing. It can be associated with spasms or jerking in the stump.

Phantom pain can begin immediately after surgery or the onset can be delayed. Its duration and intensity improves and the frequency of attacks reduces with time.

Emotional distress arising from physical loss and disability is compounded by the pain itself and what is misinterpreted by the patient as an unnatural phenomena.

Management

Phantom pain can be difficult to treat. Vigorous attempts are therefore made to prevent it. Whether the development and severity of phantom pain is correlated with the presence and severity of preoperative pain is debated. Effort is made to pre-

empt phantom pain by aggressively treating pain preoperatively. Epidural local anaesthetic infusion for a 72 hour period pre-operatively has been shown to reduce the incidence of phantom pain in the first post-operative year. Once pain has developed better results are achieved if it is treated early.

Antidepressant drugs are used on the basis that they are effective in other neuropathic pains. They are of no proven benefit in phantom pain. [c] There are reports of the effectiveness of carbamezepine at a dose of 400–600 mg daily [c]. [c] There are reported cases of relief from a daily dose of propranolol of 80 mg [c]. Opioid drugs are generally ineffective [c]. There are anecdotal reports of success using lysergic acid diethylamine (LSD). [b] Intravenous salmon calcitonin IU has been demonstrated to be effective [b].

[c] Long-term subcutaneous ketamine infusions at 0.125–0.25 mg/kg/hour have given excellent relief [c].

[c] Results vary from good to excellent using transcutaneous electrical nerve stimulation (TENS) [c].

[c] Dorsal column stimulation gives 25% reduction in pain in 65% of patients [c]. Patient selection is important and cost is an issue.

[c] Lesions of the dorsal root entry zone (DREZ lesions) have been reported to provide long-term relief [c].

Psychological factors contributing to pain and other psychological problems must be addressed.

Further reading

Hord AH. Phantom limb pain. *Pain Digest,* 1992; **2** (3): 193–200.

Related topics of interest

Ketamine (p. 89)
Mechanisms in nociception (p. 92)
Neuromata and post-incisional pain (p. 123)
Neuropathic pain – drug treatments (p. 128)
Neurosurgery and pain (p. 133)
Stimulation analgesia – TENS, TSE and acupuncture (p. 175)

POST-HERPETIC NEURALGIA

Post-herpetic neuralgia (PHN) is a chronic pain which can occur following acute herpes zoster infection (shingles). Herpes zoster infection results from reactivation of the varicella zoster virus, dormant in perineural tissues following a primary chickenpox infection. Acute herpes zoster infection is painful. PHN is pain persisting after the pain of the acute infection. The demarcation between pain due to acute infection and the pain of PHN is not defined. Some define pain persisting beyond the crusting of acute infective lesions as PHN; others, pain after specified periods from 4 weeks to 6 months since the eruption of acute infective skin lesions. There is therefore no clear definition of PHN.

Pathophysiology

Acute inflammation and ischaemia during the acute infection cause a necrotizing reaction in the dorsal root, the dorsal root ganglion and the dorsal horn. Large myelinated fibres are more extensively damaged and are reduced in number. This allows increased transmission of nociceptive information at the dorsal horn and thereby pain. The elderly have fewer large myelinated fibres. Further reduction in number by disease process explains the susceptibility of the elderly to the development of PHN. Usually only a single dermatomal segment is affected. Damage occurs to both sensory and motor nerves but the effect on motor nerves is subclinical.

Clinical features

If PHN is defined as pain persisting at 1 month, the incidence varies from 9% to 14%. It has been found to be only 3% at 1 year and tends to gradually improve and eventually remit. More severe pain lasts longer. PHN develops almost exclusively in people over the age of 50. It occurs in up to 65% of those over the age of 60. Acute herpes zoster causes pain in a dermatomal distribution. The pain of PHN is in the dermatomal distribution of the acute infection. The commonest sites for PHN are thoracic dermatomes and the ophthalmic division of the trigeminal nerve. It is less common with lumbar dermatomal involvement. It is frequently unilateral.

Pain is a constant aching, burning or itching. There are paroxysms of severe stabbing or lancinating pain. Allodynia, hyperalgesia and hyperaesthesia often occur. There is scarring and

pigmentation in the affected dermatomal distribution with a wider area of sensory change.

Pain can be severe enough to cause lethargy, anorexia, sleep disturbance, loss of libido and consideration of suicide.

Management

1. Prevention. [a] Currently there is no proven useful therapy for the prevention of PHN. The benefits of acyclovir and corticosteroids require further evaluation [a]. Therefore vigorous efforts must be made to prevent acute herpes zoster infection by vaccination programmes, etc. Opinion is divided as to the role of nerve blocks. [c] Amitriptyline has been suggested as a prophylactic drug [c].

2. Treatment. [a] Tricyclic antidepressants are the only agents of proven benefit for the treatment of PHN [a]. [a] The number needed to treat to achieve at least 50% pain relief after 3–6 weeks compared with placebo was 2.3. This means that two patients in five will achieve this high level of relief who would not have done so with placebo [a]. Several drugs of the same category may need to be tried. Amitriptyline is recommended at an initial dose of 10 mg nocte in the over 65 age group and at 25 mg nocte under 65. [c] The combination of tricyclic antidepressant and phenothiazine has been effective [c].

[a] Use of a 0.075% Capsaicin cream three or four times daily for 6 weeks resulted in pain relief in four of 16 patients with capsaicin compared with one of 16 patients with placebo [a].

[b] There is supportive evidence for at least partial effectiveness of opioid drugs in PHN. Morphine has been shown to significantly relieve PHN and results are favourable for the new, as yet unlicensed, strong opioid agonist, oxycodone [b].

Prognostic trials of intravenous fentanyl or morphine are of value.

[c] Phenytoin 100 mg t.d.s.–q.d.s. and carbamezepine 500–1000 mg daily have been effective [c].

[c] Daily subcutaneous injections of local anaesthetic have given relief. Their effect is cumulative. Repeated somatic nerve blocks have

limited success. Sympathetic nerve blocks give better relief albeit short term [c].

[c] Transcutaneous electrical nerve stimulation (TENS) has been used with good effect [c].

Allodynia can be prevented by the simple measure of the application of household 'cling film' to the affected area.The topical application of aspirin, non-steroidal anti-inflammatory drugs and local anaesthetics is being evaluated. Psychological support is necessary for many sufferers.

Further reading

Johnson RW. Neurogenic pain. Aspects of postherpetic neuralgia. Can we zap ZaP? *Pain Reviews,* 1996; **3** (2): 117–35.

Lee JJ, Gauci CAG. Postherpetic neuralgia: current concepts and management. *British Journal of Hospital Medicine,* 1995; **52** (11):565–68.

McQuay H, Moore RA. Antidepressants and chronic pain. *British Medical Journal,* 1997; **314**: 763–4.

Systematic reviews

Lancaster T, Silagy C, Gray S. Primary care management of acute herpes zoster: systematic review of evidence from randomised controlled trials. *British Journal of General Practice,* 1995; **45**: 39–45.

McQuay HJ, Tramer M, Nye BA, Carroll D, Wiffen PJ, Moore RA. A systematic review of antidepressants in neuropathic pain. *Pain,* 1996; **68**: 217–27.

Schmader KE, Studenski S. Are current therapies useful for the prevention of postherpetic neuralgia? A critical analysis of the literature. *Journal of General Internal Medicine,* **4** (2): 83–9.

Volmink J, Lancaster T, Gray S, Silagy C. Treatments for postherpetic neuralgia: a systematic review of randomized control trials. *Family Practice,* 1996; **13** (1): 84–91.

Zhang WY, Li Wan Po A. The effectiveness of topically applied capsaicin: a meta-analysis. *European Journal of Clinical Pharmacology,* **46**: 517–22.

Related topics of interest

Mechanisms in nociception (p. 92)

Mechanisms in peripheral and central neuropathic pain (p. 94)

Stimulation analgesia – spinal cord, deep brain and motor cortex stimulation (p. 164)

Stimulation analgesia – TENS, TSE and acupuncture (p. 175)

PSYCHOLOGICAL MANAGEMENT OF CHRONIC PAIN

The aim of psychological management is one of changing the perception of sufferers, so that rather than considering themselves to be suffering from chronic illness, they consider themselves to be well and coping, and responsible for the maintenance of their own health.

The psychological management of pain addresses those features of the chronic pain syndrome described as cognitive and behavioural features. It does not attempt to provide relief from pain. For this reason, psychological management is sometimes deferred until all possible medical treatments have been concluded. This approach has the advantage that the sufferer cannot approach psychological treatments with an ambivalent attitude. It has the disadvantage that distinction is made between an orthodox medical view about the cause of the pain and the psychosocial view that symptoms are part of a multidimensional dysfunction. It has been suggested that psychosocial features are of relevance to the outcome of painful conditions within a short time of initial presentation, and that early intervention might prevent progression to a chronic pain syndrome.

Interview and questionnaires may decribe the sufferer in terms of affective, cognitive, behavioural or functional impairment, and individualized treatment plans can be designed. An efficient use of resources is a Pain Management Programme which provides psychological management within a group setting. An advantage of this approach is the peer pressure that can be applied on members of the group. Programmes are typically outpatient activities, occurring over a period of weeks, but inpatient programmes are suitable for isolated areas or where the patients are most disabled. The precise subject matter of programmes varies with the skill-mix and interest of the staff, but in general terms the treatment is described as cognitive behaviour therapy. Cognitive behaviour therapy works in [a] chronic back pain [a], [b] irritable bowel syndrome [b] and other conditions in which a pain syndrome may coexist, such as the [b] chronic fatigue syndrome [b]. The topics covered in a cognitive behaviour programme are as follows.

Information

An explanation of the nature of chronic pain is necessary to overcome fears that pain is a sign of harm that requires rest. The concept of chronic pain as a disease as distinct from a symptom is difficult to grasp. Inadequate explanations or the unguarded use of medical jargon may result in false beliefs about the presence of progressive disease. Inadequate understanding of the nature and purpose of investigations and treatment lead the pain sufferer to expect further tests or surgery. It is helpful to

have an explanation from an expert about the limitations of medical treatment. Explanations about the role of analgesics, in particular about the hazards of using a 'pain contingent' dosing strategy, are also useful.

Coping skills

Strategies for dealing with exacerbations of pain can be introduced. The gate control theory of pain modulation can be used as a model to explain that many factors influence the perception of pain. Distraction techniques encourage the use of intensive mental or pleasurable activity, including relaxation techniques, to overcome the pain experience. Distraction techniques encourage the patient to develop an 'internal' way of managing distress, rather than relying on 'external' factors, such as analgesics or the physical attentions of a partner or health professional.

Mood modification

The effect of mood on the pain experience can be addressed by encouraging patients to challenge negative thoughts which accompany disability or an exacerbation of pain.

Activity modification

Inappropriate expectations of ability and fear of activity are features of the pain experience that need specific attention. The two concepts introduced are goal setting and pacing. Goal setting refers to a target for physical activity that is agreed between patient and professional, and pacing is the tactic by which this target is achieved. In the case of the patient who undertakes excess activity when pain is controlled and is then disabled by pain as a consequence of this activity, paced activity demands a disciplined approach to rest breaks and exercise. Activity goals during a programme are agreed by mutual consent: the patient is encouraged to start activity at a level compatible with pre-existing fitness and to increase this level progressively.

Behaviour modification

The psychological management of pain addresses those behaviours that cause the sufferer to become dependent on others. The overprotective partner is encouraged to allow the pain sufferer to undertake activities, and needs education about all the issues

outlined above. Pain behaviour can be a threat to normal social functioning. It can be reduced by responses which pay little attention to the behaviour. This approach sees pain behaviours as responses that have been reinforced by inappropriate attention, such as encouragement to rest, continued investigation to find non-existent pathology, and continued attempts to cure the pain.

The result of psychological intervention is measured, not as pain relief, but as an alteration in the variables such as disability and distress which made the basis for the initial assessment. It is of interest that pain relief, as well as reduction in medication use, is sometimes reported.

Further reading

Luscombe FE, Wallace L, Williams J, Griffiths PDG. A District General Hospital pain management programme. *Anaesthesia*, 1995; **50:** 114–7.

Systematic review

Evans G, Richards S. Low back pain: an evaluation of therapeutic interventions. University of Bristol, Health Care Evaluation Unit, 1996; 176.

Related topics of interest

Benign nociceptive pain – drug treatments (p. 26)
Digestive tract syndromes (p. 74)
Musculoskeletal pain syndromes (p. 108)

SPINAL CORD INJURY AND PAIN

Pain is a common symptom is patients with spinal cord injuries and contributes significantly to the morbidity of the condition. In some studies, it has been the pain, rather than the paraplegia, which has been the reason for inability to work. Pain may be nociceptive or neuropathic.

Pathophysiology

The physiology of pain sensation after spinal cord injury has to explain the varied and distressing syndromes that are observed. The clinical picture may be confused by the presence of an incomplete lesion, or a second lesion at a lower segment of the cord. Traditional neuroanatomy has described the effects of partial spinal cord section: in the Brown–Sequard syndrome, selective modalities are lost because the spinothalamic pathway (temperature and pain) crosses the midline near the level of the spinal root and the dorsal column (proprioception and mechanoreceptor) does not. Similarly, the development of a syrinx, a cystic lesion within the spinal cord, has its own symptomatology, which can be explained by reference to nerve pathways.

Explanations based on gross anatomical findings do not, however, explain other phenomena. Central pain syndromes occur even in the absence of a spinal cord. They can be extraordinarily complicated in their presentation, with the patient 'experiencing' not only pain, but movement and related phenomena, such as fatigue. Inhibition of modulating descending pathways accounts for some, but not all, of the increased activity of dorsal horn neurones immediately above the level of injury. In an animal experimental spinal cord preparation, abnormal activity in visceral afferents to non-noxious stimulation is due to this mechanism, and may be responsible for the exaggerated cardiovascular response that is seen with bladder distension and catheterization. Dorsal horn sensitization by nerve damage and continuing nociceptive stimulation may account for some of the changes.

Clinical features

The spinally injured patient may present with a complete or incomplete lesion. Careful evaluation will sometimes reveal a second lesion at a lower level of the cord than the primary lesion. This may be the site of specific symptoms that would confuse the unwary. There are thus many ways in which the spinally injured patient can present.

Nociceptive pain may be overlooked as a cause of pain, unless there is an obvious other injury to account for it. The assumption that nociceptive pain will not be experienced distal to a spinal cord lesion is a dangerous one, for it fails to consider the situation with an incomplete lesion, and the effect of central disinhibition of nerve pathways which enter the cord above the level of the lesion. The causes of nociceptive pain include:

- soft tissue trauma;
- spinal fractures;
- mechanical instability of the spine;
- osteoporotic vertebral collapse;
- pressure areas;
- overuse of upper limbs to compensate for disability;
- painful muscle spasm.

Neuropathic pain presents as segmental pain at the level of injury, with an area of hyperalgesia at the boundary between normal and abnormal sensation. The level of lesion is rarely precise and subtle differences in modality loss may be detected for several segments above the clinical level of the lesion. Rarely, changes of a type I complex regional pain syndrome (CRPS I) may be apparent in the dermatomal distribution corresponding to the site of the lesion. The author has seen one case in which CRPS developed after minor surgery on the toe. In the case of an incomplete lesion, a root lesion at a lower level may be symptomatic.

Causes of neuropathic pain include:

- compression of nerve roots;
- compression of spinal cord by bone fragments, haematoma, and scar tissue;

- syrinx development within the spinal cord;
- changes within the brain itself (central pain).

Central pain is of insiduous onset and occurs week to months after the injury. Central pain may have a visceral quality. It is experienced as a burning sensation below the level of the lesion, though poorly localized, and alterations of pain and temperature sensitivity (indicative of spinothalamic tract involvement) are noticed on examination.

Management

Treatment of pain after spinal injury requires accurate diagnosis. Abdominal causes should be excluded before the pain is assumed to be of central origin. Visceral stimulation, either by abdominal pathology or physiological processes is dangerous when the spinal cord injury has removed the inhibitory influence on spinal reflexes. It can lead to fatal hypertension or arrhythmias.

With the exception of selective destruction of the dorsal root entry zone for intractable segmental pain, procedures to destroy nerves are not appropriate. Surgical removal of the diseased spinal cord may result in central pain, and less drastic destruction procedures prevent the patient taking advantage of future surgical advances. Spinal decompression and stabilization is appropriate in some cases, and prevents further injury to the cord. Counter-stimulation techniques (transcutaneous electrical nerve stimulation and spinal cord stimulation) can be used when dorsal column nerve tracts remain intact. Tricyclic antidepressants and anticonvulsants are routinely used to suppress spontaneous activity of dorsal root and dorsal horn neurones and modify descending inhibitory pathways. Painful muscle spasm and other nociceptive pains can be treated symptomatically. General and psychological support for the victim of spinal injury has a role to play in preventing the morbidity of chronic pain. Pain relief has in the past received relatively little attention, and the low frequency of reports of pain has been said to be due to patients and carers adopting a stoical attitude to an inexplicable and untreatable complication.

Related topics of interest

Central post-stroke pain (p. 58)
Mechanisms in peripheral and central neuropathic pain (p. 94)
Multiple sclerosis (p. 103)
Stimulation analgesia – spinal cord, deep brain and motor cortex stimulation (p. 164)

STIMULATION ANALGESIA – SPINAL CORD, DEEP BRAIN AND MOTOR CORTEX STIMULATION

Historical

The recent use of electrical stimulation to relieve pain dates back to 1967, when spinal cord stimulation (SCS) was first attempted by Shealy and co-workers, the logic for this following on from Melzack and Wall's gate control theory for pain published in 1965.

Methods and sites

The most common site for stimulation is the spinal cord. Stimulation can also be delivered to sites within the brain (such as the thalamus) or occasionally over the motor cortex of the brain. Stimulation can be used for control of conditions other than pain, such as spasticity, bladder control in multiple sclerosis (MS), peripheral vascular disease, angina, movement disorders and even epilepsy. Since the last two indications are not related to pain they will not be discussed further; the others have pain as one of their symptoms, and in helping the underlying condition, pain may also be relieved.

Transcutaneous electrical stimulation of peripheral nerves (TENS) is considered elsewhere in this volume.

Spinal cord stimulation

Physiology

The mechanism of SCS is unknown. Three possible mechanisms have been suggested. Stimulation using currents, voltages and frequencies typically in use is shown to activate the dorsal column fibres. Larger fibres are preferentially activated, though the spinal sympathetic pathways are also activated.

- In the first of these mechanisms it is suggested that anti-dromic activation of dorsal column fibres 'closes the gate'. This was the original logic behind the development of the use of SCS.

- The second mechanism involves supraspinal pathways. Stimulation passes up the dorsal columns to the anterior pre-tectal nuclei in the brain stem, and is relayed back down to the spinal cord via the dorsal longitudinal funiculus, where the pain pathways are modulated.
- Lastly, spinal cord stimulation acts by stimulating adrenergic sympathetic neurones. This probably accounts for the effects on blood flow seen in peripheral vascular disease and angina, and on bladder function seen in multiple sclerosis.

However none of these mechanisms have been proven, and all may be important. The effects on blood flow seem separate from the effects on pain. The dorsal columns are important as pain relief is not obtained unless parasthesiae are produced in the affected area; indeed the precise position of the electrode is crucial to success of the technique. The observation that parasthesiae must be perceived by the patient argues for a supra-spinal mechanism. Some studies have been made of neurochemical changes resulting from SCS; most of these are inconsistent, although rises in noradrenalin, substance P and 5-hydroxytryptamine have been observed. In contrast with TENS, the action of SCS is unaffected by naloxone.

Methods

An electrode array is positioned over the midline of the spinal cord in the epidural space. The usual minimum surface area of the electrodes is about 6–8 mm^2. At least two electrodes of opposite polarity are required, but it is more usual to use an array of four or more electrodes. The current trend is to use an increasing number of electrodes. There must be at least one electrode of each polarity but thereafter any combination of polarity, and number of electrodes in use is possible. The electrodes are activated in one of two ways. The more usual practice is to connect the electrodes to a receiver implanted subcutaneously (usually the flank). This receiver is powered by induction from an external transmitter, using an aerial attached to a battery-

powered transmitter. Alternatively a battery-powered internal transmitter is used. Each system can be programmed in detail; programmable parameters include varying frequency of stimulus, amplitude, duration of stimulus pulse and which electrode in the array is active and its polarity. The considerable advantage of the external systems is that control of the system is much more in the hands of the patient (a version of 'patient-controlled analgesia'), though there is a training period whilst the complexities of the system are appreciated. The vast majority of patients will use such a system successfully; however, a totally implanted system may be useful in patients who do not cope. Typically these may be those with peripheral vascular disease in whom simultaneous cerebrovascular impairment has taken its toll. The implanted systems lack flexibility and must be reprogrammed by the implanting service.

Surgical procedure

Electrodes can be implanted percutaneously, or at open operation. Whatever the method, positioning of the electrode is crucial. Paraesthesiae must be elicited in the area of the pain, and there should not be over-stimulation of areas unaffected by pain as such stimulation can prove unpleasant. As frequency, pulse width and amplitude of stimulus increase so does the area covered.

1. Percutaneous method. Percutaneously the electrode is passed down a Tuohy needle into the epidural space. Current designs mean that this electrode must be cylindrical so that the electrode contacts run in a line. Once the electrode is in position, the remainder of the system can be implanted making a subcutaneous tunnel from the back round to the flank where the receiver is usually positioned. The whole procedure can be carried out under local anaesthetic. The advantage of this system is that it is less invasive and, because it is carried out under local anaesthetic, the correct position of the electrode can be confirmed by stimulation during the procedure. The major

disadvantage is that it is difficult to keep such electrodes in a constant position, and this is particularly true in the neck. Movement may then result in sudden and unpredictable decreases or increases in stimulation; the latter are extremely unpleasant for the patient. The method is used when patient is unfit for general anaesthesia (e.g. SCS for angina), or when expertise necessary to carry out surgical implantation is unavailable.

2. *Surgical implantation.* An open operation under general anaesthesia, and partial laminectomy is required when surgical electrodes are to be implanted. Position is held much better, and because a larger electrode surface is available the system provides better and more controllable stimulation. Accurate positioning of the electrode relies upon information from a pre-operative trial, or from placing an electrode with a large enough array so that a given combination of electrodes will stimulate the desired area. If electrodes are placed in a partly transverse direction, then two or more electrodes can be programmed from the four available, in most arrays, to stimulate the desired area.

Trial procedures

Because a major procedure may be involved, and because the stimulator equipment is quite costly, many, though not all practitioners, will undertake a trial of stimulation prior to permanent implantation. An electrode is passed into the epidural space under local anaesthesia using a Tuohy needle and brought out through the skin to an external power source. The position of the electrode can be adjusted at stimulation and also by staged withdrawal in the ward. The trial normally lasts 5–7 days, but can under certain circumstances last several weeks. It may be necessary to send the patient home to ensure an accurate trial; this may be particularly important in Raynaud's disease as the subject may need to experience a cold environment to provoke the symptoms.

The case against a trial procedure is that it may not accurately predict a responder, and that in certain circumstances the likelihood of success is so high

that it is unnecessary. The author undertakes trial procedure routinely, as this allows consideration of cases in whom clinical predictors of success are low.

Indications

In treating any form of chronic persistent pain it is important that a diagnosis is made. It is important that conditions with successful alternative therapies are not missed (e.g. unrecognized recurrent prolapse of disc following back surgery), and in addition one of the best predictive indicators for successful stimulation is the diagnostic category.

Indication	Success rate
Angina Ischaemic limb pain	Almost certain response
Regional pain syndrome Complex regional pain syndrome Peripheral nerve lesion[1] Brachial plexus damage[1] Cauda equina damage[1] Nerve root avulsion[1] Amputation stump pain	Success rate ≈ 70–80%
Failed back surgery; arachnoiditis Partial spinal cord lesion Phantom limb pain Post-herpetic neuralgia	Moderate success ≈ 40–50%
Nociceptive pain including cancer Central post-stroke pain Vaginal, penile and peri-anal pain Intercostal neuralgia	Low chance of success
Facial anaesthesia dolorosa Atypical facial pain Complete cord lesion Abdominal pain	Do not respond

[1]If there is nerve injury with preserved, though disordered sensation (dysaesthesia) then success is likely; if there is established neurological deficit then response is unlikely.

Some of these categories prove difficult to treat for technical reasons. For example it is difficult to achieve effective stimulation of midline areas such as the peri-anal area; however, when stimulation is obtained pain relief can be excellent. Another problem in such cases is unwanted excessive stimulation in surrounding areas. Another area which is difficult to access is head and neck, particularly scalp. Since it is a non-destructive technique it is particularly suitable for non-malignant pains, and should take preference over destructive techniques (e.g. dorsal root entry zone; DREZ) even if the chance of success is less, since most destructive techniques have a high delayed relapse rate, and may cause neurological deficit (e.g. DREZ again).

Case selection

It may be considered under three headings: diagnosis, influences on the pain and response to trial.

1. *Diagnosis:* as discussed above.

2. *Influences on the pain.* Most of these can be elucidated in the history in out-patients. If the pain is susceptible to external influence it is more likely to respond to spinal cord stimulation. Examples are the response of the pain to changes in temperature, to rubbing and to distraction. A reduction in pain indicates a high chance of stimulation being effective. However, there may be an increase in pain due to allodynia which can also predict a good response, though this is not as hopeful a predictor as when there is pain relief. Some practitioners use a test to provoke counter-irritation such as the injection of hypertonic saline into the interspinous ligament. This produces an intense local irritation; if this irritation substantially reduces or abolishes the pain then SCS is predicted to be effective. Using these clinical criteria, those with positive features produce an excellent outcome after permanent stimulation in approximately 60% of cases.

3. *Response to trial.* A positive response indicates a high likelihood of success, though not a certainty. In the audit referred to below, a positive trial predicted a 90% chance of success (86% excellent outcomes); however, it is not perfect and 10% of responders ultimately prove to be failures.

It can be seen that the percutaneous trial is particularly important in the groups where success is predicated to be 40–50% or less. For cases with a poor chance of success it would seem to this author to be mandatory.

Outcome

In Liverpool a series of 192 cases referred for consideration of SCS for pain were audited [i.e. not peripheral vascular disease (PVD) or angina]. Only 46% ultimately were implanted, 22% were rejected altogether (predicted to be poor responders), and 22% were treated in other ways (TENS, medical analgesics). Eight per cent required a different surgical procedure (e.g. removal of recurrent disc) and 2% refused implantation. Out of the 88 cases implanted, 79 (90%) were adjudged successful (good or excellent pain relief) and 10% failures (poor relief or none) with a minimum follow-up of 1 year. Few studies exist showing long-term outcome. However, in series that do exist there is a reduction in success rate with time.

Post-operative management and follow-up

Following successful implantation good results are only obtained when there is adequate follow-up. In the author's unit this is achieved by a specialist nurse running 'stimulator clinics'. This individual has expertise in pain management techniques in addition to knowledge of stimulator hardware, programming and surgical techniques so that a comprehensive support service is available.

SCS for vascular disease

SCS is extremely effective in treating these conditions. The action seems to be different to that of pure pain relief in that the mechanism appears to be an inhibition of the descending sympathetic pathway in the spinal cord. This is believed to prevent sympathetically mediated vasoconstriction. Supraspinal pathways are probably not involved and

are certainly less important than in simple pain relief.

1. Angina. SCS is effective in over 80% of cases. There is excellent pain relief, and the patients' usage of GTN declines. The inhibition of sympathetic vasoconstriction also appears to improve myocardial function, and it may be that this provides pain relief. At higher exercise levels the patients still experience angina, so this is not felt to be an unsafe treatment. In uncontrolled studies, survival seems to be improved compared to predictions from actuarial tables.

2. PVD. SCS is highly effective in treating the pain of intermittent claudication due to PVD. It is more effective in the early stages of the disease. Due to the sympathetic inhibition increases in skin temperature, signals from laser–Doppler, and transcutaneous oxygen measurements occur with stimulation. By implication it is argued that there are parallel increases in muscle blood flow although there is no good evidence for this, and it could be argued that flow drops due to steal to superficial tissues. Overall, 80% of cases notice an improvement in pain control; 65% an improvement in walking distance and in 30% this improvement will be significant. These percentages improve if end-stage disease is excluded. Improvements in ulcer healing are also claimed and there may be a reduction in the amputation rate. Unlike the case of angina it appears that the effect on pain is separate from that on flow, as by stimulating at higher levels in the spine (T8 vs T12 in the cases of lower limb problems) decreases in blood flow may occur, although pain relief is still maintained.

In addition to peripheral vascular disease due to atherosclerosis it can help in vasospastic conditions such as Raynaud's disease. It is worth trying in diabetics although the peripheral neuropathy which occurs in such patients, being quite severe, may preclude a response in respect of pain relief, and the widespread peripheral arterial disease secondary to

diabetes often is not amenable. There are, however, enough responders to mean that the treatment should be offered.

SCS for diabetic neuropathy Painful diabetic neuropathy can be difficult to treat. However of 10 patients assessed by trial stimulation eight responded at the trial stage and were implanted. Of these, six obtained long-term relief (>6 months); one did not and one died from a cause unrelated to the pain. There was relief of both the neuropathic pain and exercise tolerance.

SCS for MS Approximately 25% of cases of MS experience some form of central pain syndrome (excluding trigeminal neuralgia, which occurs in about 5%). These syndromes may respond to SCS. An additional benefit is that improvements in bladder control may result in up to 70–80% of patients.

Deep brain stimulation

Indications Severe chronic pain in face, arms or legs, often due to partial nerve injury such as may occur in amputation or stroke. It can be used in cases of central post-stroke pain. Many patients will be reluctant to undergo this form of surgery for a chronic pain condition; it is, of course, the case that any procedure invasive to the brain carries risk of stroke and to life, albeit very small.

Methods Under local anaesthetic a burr hole is made in the skull and an electrode passed stereotactically to the intended target, normally within the thalamus, although some have tried other sites such as peri-aqueductal grey matter. A trial of stimulation is performed to make sure the electrode is in the desired physiological target, and then there is a trial of the therapeutic effect over a few days. After a few days, and provided the trial is successful, a permanent device is implanted and connected to this electrode. The technique has increased in popularity recently with improvements in electrode design. A trial stage is required because a significant number

of patients will turn out to be non-responders for whom a stimulator is inappropriate.

Outcomes Only 50% of patients will respond and be implanted.

Motor cortex stimulation

Indications The main indication is for central post-stroke pain where the referred area in which the pain is felt comprises upper limb or face. The leg motor cortex is difficult to target, being mainly in the interhemispheric fissure, which is a large area; hence it cannot be considered when the syndrome covers half the sensorium.

Methods A craniotomy is performed and electrodes placed over the motor cortex. Intra-operative neurophysiology and/or sophisticated image guidance techniques may be necessary to locate the part of the brain which is the motor cortex. A trial is performed before a permanent device is used, as the percentage of patients who prove to be responsive to this form of therapy is small. If the cortex is stimulated too vigorously there is a risk of either focal or generalized seizures. Unlike stimulation of the sensory pathways there are no parasthesiae to indicate function of the stimulator, so over-stimulation is a real risk. Since it is an intracranial procedure there must also be risk of stroke (and therefore to life) from haemorrhage or infection and a risk of epilepsy, however low these risks must be.

Outcomes These have not been encouraging overall. Currently the method should be regarded as unproven.

Further reading

Jacobs MJ, Jorning PJ, Beckers RC, Ubbink DT, van Kleef M, Slaaf DW, Reneman RS. Foot salvage and improvement of microvascular blood flow as a result of epidural spinal cord electrical stimulation. *Journal of Vascular Surgery,* 1990; **12:** 354–60.

North RB, Roark GL. Spinal cord stimulation for chronic pain. *Neurosurgery Clinics of North America,* 1995; **6:** 145–55.

North RB, Kidd DH, Zahurak M, James CS, Long DM. Spinal cord stimulation for chronic, intractable pain: experience over two decades. *Neurosurgery,* 1993; **32:** 384–95.

Rees G. Mechanism of action of spinal cord stimulation. *Pain Reviews,* 1994; **1:** 184–98.

Simpson BA. Spinal cord stimulation. *Pain Reviews,* 1994; **1:** 199–230.

Related topics of interest

Central post-stroke pain (p. 58)
Neurosurgery and pain (p. 133)
Stimulation analgesia – TENS, TSE and acupuncture (p. 175)

STIMULATION ANALGESIA – TENS, TSE AND ACUPUNCTURE

Transcutaneous electrical nerve stimulation (TENS)

The transcutaneous electrical stimulation of peripheral nerves through intact skin is effective in controlling some pains. This is achieved by the placement of two electrodes over the painful area and the passage of a small current through the electrodes. The current is generated from a portable battery-operated device. Stimulation of low threshold afferents, (Aβ mechanoceptors) causes inhibition of the passage of high-threshold pain fibre impulses (Aδ and C fibres) at spinal cord level. High-frequency current selectively stimulates larger afferent fibres. It may also increase the refractory period and reduce firing rate in smaller afferent pain fibres. Low frequency stimulation (Aδ mechanism) can produce analgesia in patients who have failed to respond to the more conventional high-frequency stimulation. This is thought to work by activating inhibitory descending neuronal influence in the dorsal horn of the spinal cord.

Uses

[a] TENS appears to reduce pain and improve the range of movement in chronic low back pain patients [a]. A trial of TENS is appropriate for most pains which have some physical basis. Its success in the treatment of central pain depends on whether dorsal columns and medial lemniscal pathways are intact. [c] TENS can treat the pain of mild post-herpetic neuralgia. Where afferent fibre destruction is extensive it may aggravate the pain. [c] TENS has been effective in facial pain, myofascial pain, mechanical back pain, post-amputation pain and peripheral nerve injury, particularly when there is paraesthesia. TENS can be effective in visceral, neuropathic or metastatic pain of cancer. Twenty-five per cent of radicular pain responds to TENS [c].

Practicalities

Electrode pads are made of a size which minimizes current density. Good contact with skin is necessary and is achieved by adhesiveness of the pads or the application of conducting gel underneath the pads. TENS should be used for at least 30 minutes at a time. It can be used for longer periods. Some patients gain relief only for the period that the machine is in use. Others feel relief beyond the

period of use. Sites of application should be rotated to avoid skin irritation. TENS should not be used whilst asleep or whilst driving. Electrode pads are applied to the painful area. They should not be applied to an insensate area. For the treatment of radicular pain electrode pads are placed over the dermatomal distribution of the affected root. Electrodes should not be placed on the anterior surface of the neck, lest they affect the carotid sinus. Constant high frequency stimulation is the normal mode of use, most patients preferring a rate of 40–70 Hz. Those who fail to get relief from this mode may respond to stimulation at a frequency of 2–4 Hz. This requires a higher intensity and may cause uncomfortable muscle contractions. Some machines therefore have a modulation facility which allows switching of current and frequency at short intervals.

Limitations

TENS is relatively safe with few side-effects. It should not be used in pregnancy until the onset of labour. It should not be used in the patient with a cardiac pacemaker. Side-effects are limited to skin irritation and scorching under the pads. This may be severe if electrode pads have wrongly been applied to an insensate area. Patients may encounter difficulty in placing electrodes at awkward sites.

Transcutaneous spinal electroanalgesia (TSE)

TSE is a non-invasive method of stimulating the area over spinal cord to produce analgesia. Surface electrodes are used to stimulate. The passage of current across 5 cm of tissue reduces its amplitude by 90%. To elicit adequate voltage gradients at the distance of spinal cord from skin surface requires amplitudes at the skin surface which would be painful. Pulses of less than 10 μsec duration do not cause the same level of pain as produced by longer duration pulses of the same amplitude. At a subthreshold level for tingling, a sensation of continuous light pressure is felt deeply in the spinal region. Analgesia is being produced without peripheral nerve stimulation.

Uses

[c] Many chronic pains have been improved by TSE, including musculoskeletal, visceral and neuropathic pain [c].

Practicalities

Two surface electrodes are applied to the midline over the spinous processes of T1 and T12 for the treatment of pain below the neck. For pain in the neck or head electrodes are applied to the transverse processes of C3, C4 or C5. The electrodes are connected to a portable battery-operated machine. The relief of pain occurs within minutes and lasts for several hours following a single treatment. Repeated treatments cause a cumulative effect. Pain can be relieved for months.

Limitations

Evidence as to the effectiveness and long-term effect is lacking. TSE is of no benefit in the treatment of acute pain.

Acupuncture

Acupuncture is an ancient Chinese medical art which has gained momentum in the West over the past 25 years. Traditionally the understanding of mechanism was based on the concept that the body requires a balance of energy factors to be in good health. The balance of the energy factors, Yin and Yang was thought to be restored by acupuncture. Energy flowing along intangible meridians to and from vital organs was believed to be effected by sharp objects applied at certain points along the meridians. The rationale of acupuncture in Western medical practice is that high-threshold mechanoceptors are activated by low-frequency high-intensity stimulation. They in turn affect descending inhibition in the spinal cord.

Electroacupuncture is the augmentation of the mechanical needle stimulus by using electricity.

Uses

Acupuncture lends itself to the treatment of many painful conditions. It is of particular use in myofascial pain, low back pain and neuralgias. [a] A meta-analysis found that results favourable to acupuncture were obtained significantly more often than chance alone would allow [a].

Practicalities

Asepsis is important and needles should not be positioned in infected-looking areas. Needles should be carefully placed to avoid the complications of pneumothorax, cardiac tamponade, damage to nervous tissue or the piercing of blood vessels.

Limitations

Improvement is short-term and repeated treatments are necessary to sustain pain relief. However, as with other passive short term treatments, the

attendant risks are patient request for treatment which outstrips resource and no improvement of function. Acupuncture has to be incorporated into an overall strategy of pain management.

Further reading

Alexander JR, Macdonald T, Coates W. The discovery of transcutaneous spinal electroanalgesia and its relief of chronic pain. *Physiotherapy,* 1995; **81** (11): 653–61.

Ernst E, White A. Acupuncture: safety first. *British Medical Journal,* 1997; **314:** 1362.

Systematic reviews

Gadsby JG, Flowerdew MW. The effectiveness of transcutaneous electrical nerve stimulation (TENS) and acupuncture-like transcutaneous electrical nerve stimulation (ALTENS) in the treatment of patients with chronic low back pain. In: Bombardier C, Natchemson A, Deyo R, de Bie R, Bouter L, Shekelle P, Waddell G, Roland M (eds) *The Cochrane Collaboration Issue 1.* Oxford: The Cochrane Library, 1997.

Patel M, Gutzwiller F, Paccaud F, Marrazi A. A meta-analysis of acupuncture for chronic pain. *International Journal of Epidemiology,* 1989; **18** (4): 900–6.

Related topics of interest

Conduct of the pain clinic (p. 67)
Mechanisms in nociception (p. 92)

SYMPATHETIC NERVOUS SYSTEM AND PAIN

Peripheral nociceptor activity causes an increase in efferent sympathetic discharge, but under usual circumstances sympathetic activity has no impact on the discharge of nociceptive neurones. When nociceptors appear to be under the influence of the sympathetic nervous system, pain is described as sympathetically maintained pain (SMP). When nociception is unaffected by the sympathetic nervous system the pain is described as sympathetically independent (SIP). The sympathetic nervous system can be involved in pain at any part of the neuraxis. Sympathetic nerve blocks affect pain which has a sympathetic component. Adrenergically active drugs applied to the periphery, the spinal cord or centrally affect pain which has a sympathetic component. SMP includes some neuropathic pains and the complex regional pain syndromes (CRPS). Not all neuropathic pains are sympathetically maintained. CRPS has signs directly associated with the sympathetic nervous system and is a more complex clinical picture than SMP.

Mechanisms

The mechanisms for pain which responds to sympathetic nerve blockade are:

- peripheral nociceptors which are sensitive to noradrenaline;
- sympathetic efferent activity producing low grade ongoing activity in nociceptors;
- sprouting of sympathetic nerve fibres in dorsal root ganglia;
- the stimulation of α receptors in the dorsal horn;
- the altered levels of centrally acting monoamines.

Diagnosis

A diagnosis of SMP is made by response to various manipulations of the sympathetic nervous system.

1. The intravenous phentolamine test. Phentolamine is an $\alpha 1$ and $\alpha 2$ adrenergic antagonist. It prevents excitation of noradrenaline sensitive nociceptors. Phentolamine in normal saline (30 mg/100 ml) is infused over 20 minutes. If pain is relieved it is likely that the pain is sympathetically maintained.

2. Sympathetic local anaesthetic blocks, by preventing efferent sympathetic activity also allow

an assessment of the place of the sympathetic nervous system in the maintenance of the pain. Although local anaesthetics preferentially block preganglionic sympathetic fibres, false positive results can be produced by blocking nociceptive afferents but sensory testing will alert to this.

3. Intravenous regional sympathetic blockade using a guanethidine tourniquet technique helps diagnosis. Guanethidine in normal saline (10–20 mg/20–50 ml) is injected into a limb which has been exsanguinated and to which a tourniquet has been applied. The technique has been adapted by some to inject guanethidine in a prilocaine solution to enhance patient comfort during the procedure.

4. Sympathomimetic drugs. SMP can be provoked by sympathomimetic drugs.

Treatments

1. Intravenous regional sympathetic blockade. This technique is widely used for the treatment of sympathetically maintained pain. It comprises the injection of a drug, most commonly guanethidine although sometimes ketanserin or bretylium to an exsanguinated limb, isolated by a tourniquet. [a] Systematic review showed no significant difference in the treatment of complex regional pain syndrome between guanethidine and placebo. Two reports, one using ketanserin and one using bretylium showed some advantage of the technique over controls [a]. Despite this conclusion, and the suggestion leading from this, that the technique is of little value, intravenous guanethidine sympathetic block is commonly performed, and its use is believed to be justified by the past success of uncontrolled trials.

2. Guanethidine. Guanethidine displaces noradrenaline from nerve endings. When it is used in intravenous regional sympathetic blockade, pain can transiently worsen as displacement initially increases circulating amounts of noradrenaline. Allodynia has been demonstrated during the block.

The worsening of pain and the allodynia can be protected against by adding prilocaine to guanethidine for injection. Guanethidine is also available in tablet form.

3. Clonidine. Clonidine is an α2 adrenergic agonist. [c] Experimentally and clinically it has been shown to have an antinociceptive effect. It is effective in treating sympathetically maintained pain [c]. The understanding of its mechanism suggests a further role in the treatment of noradrenaline sensitive neuromata.

Clonidine has a spinal and supraspinal action. It inhibits the release of noradrenaline from primary afferents both in the dorsal horn and at higher centres. This is a presynaptic α2 action. Clonidine also effects cholinergic transmission and inhibits acetylcholinesterase.

[b] Clonidine is effective intrathecally and epidurally in cancer patients who are not adequately treated by opioids [b]. It enhances analgesia and allows sparing of local anaesthetic and opiate dosage. [b] In non-malignant chronic pain, epidural clonidine is equally as effective as morphine in producing short-term analgesia [b]. Clonidine caused fewer side-effects and the analgesia was longer lasting. [c] Clonidine is effective in many resistant neuropathic pains, including pains of spinal cord injury, multiple sclerosis, painful diabetic neuropathy and complex regional pain syndromes [c].

Clonidine is available as an oral preparation, licensed for the treatment of hypertension. Tablets are also used in the treatment of chronic pain, at doses of 50–150 μg t.d.s. The absence of neurotoxicity allows intrathecal and epidural use.

Consistent with the mechanism of its main use, clonidine causes hypotension. Rebound hypertension can occur. Bradycardia occurs. Sedation, anticholinergic effects and respiratory depression are recorded.

4. Dexmedetomidine. Clonidine is selective for α2 receptors at a ratio of 200:1. It demonstrates a

ceiling effect. Dexmedetomidine has an eight times greater affinity for α2 receptors and does not have a ceiling effect. It is therefore more potent and may be associated with fewer side-effects. As yet a clinical role has not been defined and no preparation is available for human use.

5. *Phenoxybenzamine.* Phenoxybenzamine is a long-acting, powerful α adrenergic antagonist with many side-effects. It is available in capsules.

6. *Adrenergic β-antagonists.* [c] Propranolol, a β2 antagonist has been reported effective in phantom limb pain and painful diabetic neuropathy [c].

7. *Neuroleptic drugs.* These work through post-synaptic α blockade. [c] Although their use is not common they have been reported to be of use as single preparations and in combination use with amitriptyline [c].

Further reading

Dickenson E. Spinal cord pharmacology of pain. *British Journal of Anaesthesia,* 1995; **75**: 193–200.

Glynn C, Dawson D, Sanders R. A double-blind comparison between epidural morphine and epidural clonidine in patients with chronic non-cancer pain. *Pain,* 1988; **34**: 123–8.

Peden CJ, Roberts CP. Dexmedetomidine – a powerful adjunct to anaesthesia? *British Journal of Anaesthesia,* 1992; **68**: 123–5.

Systematic review

Jadad AR, Carroll D, Glynn CJ, McQuay HJ. Intravenous regional sympathetic blockade for pain relief in reflex sympathetic dystrophy: a systematic review and a randomised, double-blind crossover study. *Journal of Pain and Symptom Management,* 1995; **10** (1):13–20.

Related topics of interest

Mechanisms in nociception (p. 92)

Mechanisms in peripheral and central neuropathic pain (p. 94)

TRIGEMINAL NEURALGIA

Trigeminal neuralgia is pain in the distribution of one or more of the divisions of the trigeminal nerve. It was formerly known as 'tic douloureux' because in addition to pain it can cause reflex facial muscle spasms. Historically, trigeminal neuralgia was defined as idiopathic or secondary to systemic disease. Eighty-eight per cent were described as idiopathic. However, two-thirds of the idiopathic group have been found to have an abnormal vascular loop around the root entry zone. There remains a proportion in whom no cause can be found. Clinical features differ depending on whether the pain is secondary to other disease or whether it is from the former 'idiopathic' group, which will be referred to as primary trigeminal neuralgia.

Anatomical background

The trigeminal nerve is the sensory nerve of the face, a large area of the scalp, the teeth and the oral and nasal cavities. It is the motor nerve of the muscles of mastication. It divides into ophthalmic, maxillary and mandibular branches. The trigeminal nerve leaves the ventral surface of the pons as a large sensory root and a smaller motor root. It passes forward to a recess at the apex of petrous temporal bone called the trigeminal cave. Here the sensory root expands to form the trigeminal ganglion. The three branches of the nerve arise from the anterior border of the ganglion. The ganglion lies at the posterior aspect of the zygomatic arch, at its mid-point. The ganglion is approached percutaneously through the foramen ovale which is slightly inferior and anterior to the ganglion.

Pathophysiology

In the majority the lesion is demyelination. This is caused by compression of the root entry zone at the junction between central and peripheral myelin. Compression which occurs in the posterior fossa is usually by the superior cerebellar artery or inferior cerebellar arteries or veins. Pain results from neuronal sensitization and repetitive discharge from the demyelinated axons.

In trigeminal neuralgia symptomatic of other conditions, pain is caused by:

- direct pressure from anatomical lesions such as tumours (acoustic neuroma) or angioma (6% of all cases of trigeminal neuralgia);

- the demyelination of multiple sclerosis (6% of all cases of trigeminal neuralgia) or other diseases;
- central lesions such as brain stem infarcts.

Clinical features

These differ according to whether the disease is the primary or secondary form. Prevalence in the primary group is greater in females and onset tends to be after the age of 50 years. When secondary to other conditions the demographic features are as for those diseases.

Features common to both types and all aetiologies are:

- unilateral face or frontal pain, limited to one or more divisions of the trigeminal nerve, usually one. Most commonly involved is the mandibular division alone, then maxillary alone, then mandibular and maxillary in combination, then ophthalmic and maxillary and most rarely the ophthalmic division alone;
- pain never crosses to the opposite side but occurs bilaterally in 3–5 %. Of those with bilateral pain 18% have multiple sclerosis;
- pain of abrupt onset lasting from a few seconds up to 2 minutes. Paroxysms vary in frequency and regularity but can occur many times a day or remit for several weeks;
- pain is intense and superficial, lancinating, sharp or stabbing in quality;
- pain may be spontaneous or triggered. Trigger zones are around the mouth, nose or face, or within the nasal or oral cavities. Triggers are otherwise innocuous stimuli such as talking, washing, shaving, brushing of the teeth, chewing or the sensation of draught or wind on the trigger zone. Behavioural changes take place to avoid triggers, and can result in social isolation, depression and a tendency to suicide;
- attacks are stereotyped in the individual patient;
- pain may remit spontaneously. Remissions that occur soon after onset may last for years.

Clinical features which differentiate are:

- the patient with the primary form is entirely asymptomatic between paroxysms. The patient with other disease can have a persistent ache between attacks within the distribution of the paroxysmal pains. The optimal treatment of a persistent pain is with antidepressant medication;
- with the rare exception of involuntary muscle spasm, in the primary form there are no abnormal physical signs on examination. Those with the secondary form may have sensory impairment in the distribution of the affected division and signs consistent with their underlying disease. Abnormal physical signs in the absence of other known disease warrant neurological investigation.

Treatment

Vascular loops can be identified by magnetic resonance angiography. In such cases the root entry zone can be surgically decompressed. The alternative medical and invasive procedures are detailed below. Suitability for surgery or access to it will determine the type of management.

Treatment in the pain clinic

1. Pharmacological treatments are effective in 75% of cases. The mainstay of treatment is the anticonvulsant group.

[a] Anticonvulsant drugs reduce pain in trigeminal neuralgia. Carbamezepine had a combined number needed to treat of 2.6 for effectiveness, 3.4 for adverse effects and 24 for severe effects [a].

Carbamezepine is the most commonly used drug. It can be effective alone or given with phenytoin, baclofen or clonazepam. Combination allows sparing of dosage and reduced potential side effects. Carbamezepine dosage requirement varies considerably so a small dose is given initially, increasing by 100–200 mg/day each week as pain control requires and side-effects allow, to a maximum of 1600 mg daily. In the elderly an initial dose should be 100 mg b.d. Most patients are controlled on 200 mg t.d.s. or q.d.s. Side-effects include dizziness, drowsiness, ataxia, fatigue and

nausea. These often abate with time or with a reduction of dose. Pain can become refractory to treatment.

Phenytoin should only be used if carbamezepine is ineffective or cannot be tolerated. Dose requirement varies considerably. Side-effects are ataxia, nystagmus, slurred speech, discoordination and mental confusion. Initial dose is 3–4 mg/kg/day with increases no more frequently than every 7 days.

Clonazepam is effective in some, initially at a dose of 1 mg/day in two to three divided doses (may need as little as 0.5 mg/day in the elderly). Sedation can occur.

Sodium valproate may offer alternative single therapy at a dose of 20 mg/kg/day. Liver dysfunction can occur so liver function tests are suggested at the start of therapy and at regular intervals after commencement.

Lamotrigine is an anticonvulsant drug which can be given alone or in combination with anticonvulsants. It should be used with caution in combination with sodium valproate. It offers potential for improvement in medical management.

[c] Baclofen has given relief at a dose of 5–10 mg t.d.s.[c]

2. *Minor percutaneous invasive procedures.*

(a) Percutaneous retrogasserian glycerol rhizotomy. Glycerol (0.1–0.3 ml) is injected to the trigeminal cave, percutaneously, under radiological control. Correct positioning of the needle is verified by the drainage of cerebrospinal fluid and the injection of radio-opaque dye. The injection of glycerol can be preceded by the diagnostic injection of local anaesthetic. Glycerol rhizotomy can relieve pain for an average of 2 years. Loss of facial sensation with associated discomfort complicates the technique.

(b) Percutaneous trigeminal ganglion rhizolysis. Radiofrequency lesioning of the ganglion, percutaneously can give immediate relief for

months to several years. Electrical stimulation down the needle allows the needle to be manoeuvred so the part of the ganglion pertaining to the affected division is selectively lesioned. Sedation or general anaesthesia are required to introduce the needle and to make the lesion. Between these times the patient must be alert to ascertain correct positioning. Repeated administration of short-term acting anaesthetic agents make this technique possible. Anaesthesia dolorosa and other sensory deficits occur in 1–2%.

(c) Balloon compression rhizolysis.

Further reading

Barker FG II, Jannetta PJ, Bissonette DJ, Larkins MV, Jho HD. The long term outcome of microvascular decompression for trigeminal neuralgia. *New England Journal of Medicine,* 1996; **334**: 1077–83.

Fields HL. Treatment of trigeminal neuralgia. *New Engand Journal of Medicine,* 1996; **334**: 1125–6.

Walkenbach R, Voormolen JHC. Surgical treatment for trigeminal neuralgia. *British Medical Journal*, 1996; **313**:1027–8.

Systematic review

McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for the management of pain: a systematic review. *British Medical Journal,* 1995; **311**:1047–52.

Related topics of interest

Mechanisms in nociception (p. 92)
Multiple sclerosis (p. 103)
Neuropathic pain – drug treatments (p. 128)
Neurosurgery and pain (p. 133)

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GLOSSARY

The glossary is not exhaustive: basic understanding of pharmacology is assumed, and the reader is referred to basic pharmacology textbooks for familiarization with drugs and their modes of action. The list below explains some of the anatomical and technical terms for which it might be otherwise difficult to find a definition. The definitions apply to the context in which they are found in the book.

Allodynia: pain in response to light touch.

Anaesthesia dolorosa: spontaneous neuropathic pain in an area where the skin sensation is altered.

Bioavailability: fraction of drug available for a clinical effect once the effects of first pass metabolism have been considered.

Biofeedback: the use of a biological signal (e.g. electromyogram) as an aid to monitoring relaxation.

Biomedical model: the conventional medical model that considers complaints as symptoms of an underlying pathological process.

Biopsychosocial model: the model that considers complaints to be part of a condition to which social and psychological factors contribute.

Caudad: away from the head.

Cephalad: towards the head.

Co-analgesics: drugs which have useful analgesic actions in addition to their normal commonly used actions.

Dysaethesia: abnormal sensation.

Dysphoria: sense of unease.

Electrophysiology: the science of measurement of electrical discharges from neurone tissue.

Ephaptic transmission: direct electrical contact between nerves as a consequence of failure of the normal insulation.

Epidurogram: the use of X-ray contrast material in the epidural space.

Functional: a physiological, as opposed to a pathological process.

Horner's syndrome: ptosis, miosis, anhydrosis and enopthalmos resulting from block of the sympathetic supply to the head.

Hyperalgesia: heigthtened sensitivity to painful stimulus.

Hyperpathia: severe pain in response to stimulation despite sensory impairment.

Iatrogenic: resulting from treatment.

Keloid: scarring as a result of abnormal collagen deposition beyond the boundaries of the wound.

Le Fort fracture: classification system for the fractures of the facial bones.

Malingerer: one who feigns symptoms for gain.

Meta analysis: statistical technique in which the results of several studies are combined.

Modality specific: the concept that different pain sensations are transmitted by different pain receptors.

Neuralgia: mononeuropathy of a named nerve.
Neurectomy: surgical removal or destruction of a nerve.
Neurolytic: destruction of nerve.
Neuromatrix: the complex series of neuronal connections in the central nervous system that is responsible for pain.
Neuropathy: nerve damage.
Neurotomy: interruption of a mixed nerve.
Nociceptive: resulting from tissue damage.
Nociceptor: nerve ending stimulated by tissue damage.
Operant conditioning: the use of reward or punishment to alter the behaviour of a subject.
Opioid: drug or endogenous substance having similar pharmacological properties to opium.
Parenteral: bypassing the oral route (intramuscular, subcutaneous, transdermal and intravenous administration).
Peau d'orange: 'orange peel' appearance of the skin as a result of dermal infiltration by pathological process.
Preemptive analgesia: administration of analgesic agent before noxious stimulus to prevent the sensitization of the dorsal horn.
Prodrug: inactive precursor of a drug that is activated by metabolism.
Radiofrequency lesion: the use of radiofrequency current to generate heat in tissue and destroy C fibres.
Receptive field: the peripheral area from which neural stimulation will elicit a neurophysiological response in a central neurone.
Retrogasserian: anatomical description of the trigeminal cistern in which lies the gasserian or trigeminal ganglion.
Rhizolysis: destruction of a nerve root.
Rhizotomy: interruption of a nerve root.
Sensitization: increased activity in a nerve as a result of alteration of the chemical environment or action of other nerves.
Substance P: neurotransmitter found in the terminals of C fibres which plays a major role in nociception.
Sympathectomy: interruption of the sympathetic nervous system.
Syringomyelia: degenerative neurological condition in which a cystic lesion develops in the spinal cord.
Syrinx: a cystic lesion in the grey matter of the spinal cord.
Systematic review: the collation of all relevant literature pertaining to a subject and the conclusions derived from this.
Tachyphylaxis: acute tolerance to a drug.
Tenesmus: sensation of rectal fullness.
Windup: a change in the activity of the dorsal horn of the spinal cord as a consequence of persistent noxious stimulation.

INDEX

Acupuncture, 68, **177**
Adhesions, **144**
Adrenergic agonists,
clonidine, 36, 37, 64,105, 119, **181**
Adrenergic antagonists
alpha, 131, 149, 179, 182
beta, 64, 79, 100, 149, 153, 182
Allodynia, 6, 8, 59,62, 74, 93, 94,123, 124, 125, 134, 148, 151, 154, 156, 169, 180, 189
Ankylosing spondylitis, 17
Anticonvulsants, 60, 100, 105, 124, 126, 133, 149, 153, 155, 162, 185
carbamazepine, 60, 105, 130, 153, 155, 185
Antidepressants, 20, 72, 76, 79, 83,126, 128, 146, 153, 162
amitryptiline, **72**, 100, 105, 110, 128, 155
SSRI, 59, **129**, 149
Arachnoiditis, 24, 168
Arterial disease
coronary, 74, 164, 168, **171**
peripheral vascular, 67, 118, 147, 164, 168, **170–171**
Raynaud's phenomenon, 171
stroke, 33, **58–60**, 94, 130, 136, 168, 173
Arthritis, 13, 87
osteo, **131**
Aspirin, **26**, 49
Atypical facial pain, 78, 168

Back pain, 7, **16–21**, 22–25,67, 69,108, 138, 157, 175, 177
Baclofen, 36, 46, 78,105, 132, 168, 185, 186
Behaviour
effects of drugs, 28, 29, 55, 89
illness, 3, 5, 6, 12, **14**, 22, 29, 30, 69,146, 184
therapy, 12, 19, 20, 75,110, 144, 146, **157–159**
Biofeedback, 79, 100–101, 189
Bisphosphonates, **45**, **140**
Bladder, 134, 135, 145, 165, 172 (*see also Cystitis, Interstitial*)
Botulinum toxin, **32–34**, 78
Bradykinin, 93

C-fos, 88
Calcitonin, **45**, 65, 138, **140–141**, 153
gene related peptide, 95, 98
Calcium
balance, **53–54**, 88
channel blocker, **45**, 76, 82, 100, 124, 149
Cancer, 16,**35–54**, 69,117, 121, 134, 138, 148, 175
Candida, 86, 142
Cannabinoids, **55–57**, 106
Capsaicin, 65, 126, 131, 145, 149, 151, 159
Cauda equina, 9, 18, 25, 134, 168
Causalgia (*see Syndrome: complex regional pain*)
Central pain, 43 , **58**, **162**, (*see also Neuropathic pain, Physiology*)
Cervical spondylosis, **113–114**,
C fibre, 27, 92–96,121
Chemotherapy, 46
Clonidine, 36, 37, 64, 105, 119, **181**
Cognitive problems (*see Behaviour, Illness*)
Cognitive/behavioural therapy (*see Behaviour, Therapy*)
Coping skills, **158**
Cordotomy, 42,133, 134
Cryotherapy, 119, 126
Cyclooxygenase inhibition, 26, 27, 44
Cystitis, interstitial, 145

Deep brain stimulation, **172–173**
Dependence, **28**
Depression, 5,14, 29, 56, **71–73**, 78, 104, 129
Diabetes, 58, 75, 128, 131, 147, 149, 171, 172, 181
Dorsal root entry zone, 126, **133–135**, 153, 162, 169
Dysmennorrhoea, 142

Electrophysiology, 89, 94, 108, 135, 137
Endometriosis, 142–144
Epidural
space, 25, 115, 165, 167
steroid, **24**, 25, 106, 141, 145, 153
injection, 24, 35, 36, 40, 181
Ergotamine, 84, 101

Facet joint
cervical, 83, 111–114
lumbar, 7, 18, **22–23**, 138
Fibromyalgia, **108**

Gate control theory, **92–93**, 152, 158, 164
Guanethidine, 64, 125, 180

Headache
analgesic, 84
cervicogenic, **83**, 112, 139
cluster, 81
idiopathic, **84**
migraine, **98–102**, 130
paroxysmal hemicrania, 82
tension, 71

Hormone replacement therapy, **140**
Hydralazine
Hyoscine, 45
Hyperalgesia, 6, 8, 58, 66, 74, 93, 94, 111, 123, 124, 125, 154, 189
Hyperpathia, 6, 8, 94, 123, 124, 125, 148, 189
Hypnotherapy, 75, 101

Immunodeficiency, **86–88**, 148
Immunosuppression, 16
Intervertebral disc, 8, 17, 22, 94,133

Ketamine, 27, **89–91**, 97, 131, 152, 153

Litigation, 5, 113
Local anaesthetics, 109, 120, 121, 124, 146, 151, 155, 166, 179
  bupivacaine, 36, 37, 126
  lignocaine, 46, 131

Magnetic resonance, 19, 114, 136, 142, 185
Malingering, 12, 71, 189
Manipulative therapy, 19
McGill scoring system, 13
Membrane stabilizing agents
  antiarrhythmic-mexilitine, 105, 130, 150
  antiarrhythmics, 124, 126, **130**, 150
  anticonvulsants, **60**, **130** (*see also Anticonvulsants*)
Menstrual cycle, 99, 144
Mesothelioma, 43
Misoprostol, 27, 44 (*see also Non-steroidal antiinflammatory drugs*)
Mononeuropathy, **148** (*see also Neuralgia*)
Motor cortex stimulation, 173
Multiple sclerosis, 33, 55, **103–107**, 164, 172, 181
Myofascial, 33, 77, 109, 175, 177

N-methyl-D-aspartate, **89**, **96**, 97, 131
Nerve block
  coeliac plexus, 42, 87, **116**
  epidural, (see *Epidural*)
  intercostal, 42
  interpleural, 41, 116
  intrathecal, 24, 35, 36, 40, 107, 181
  intravenous regional, 64, 180
  medial branch of dorsal primary ramus, (*see Facet joints*)
  occipital, 70, 83, 113,114
  paravertebral, 114
  retrogasserian, 106, 186, 190
  sphenopalatine, 82
  splanchnic, 116
  stellate ganglion, 113, **115**, 118
  superior hypogastric/p, 24, 42, 65, **117**, 144, 126
  sympathetic chain, **117**, 24, 65, 126
Neuralgia
  glossopharyngeal, 79
  nervus intermedius, 79
  occipital, 83
  postherpetic, 53, 91,94, 118, 134, **154–157**, 168
  trigeminal, 104, 106,130, 133, **135–137**, **183**,
Neurogenic claudication, 18
Neurokinins, 95, 96
Neuroma, 79, **123–125**
Neuromatrix, 96, 190
Neuropathic pain
  physiology, 89, **95–98**, 160 , 161, 58
  treatments, 25, 26, 29, 31, 35, 40, 44, 91, **103**, 105, 119, 123–127, **128–132**, 161
Nitrates, 76, 171
Nitrous oxide, 46
Nociceptive pain
  physiology, 13, 58, 89, **92–93**, 95, 112, 142, 161
  treatments, **26–31**,35, 115
Non-cardiac chest pain, **74**
Non-steroidal antiinflammatory drugs
  diclofenac, 27, 44, 49
  ibuprofen, 49
  indomethacin, 27, 82
  side effects, 27, 87 (*see also Cyclooxygenase inhibitors*)
  uses, **26–28**, 44, 49 82, 84, 101, 105, 144, 146
Non-ulcer dyspepsia, 74
Number to treat, 2, 130, 155, 185

Opioid
  receptors, 28, 52, 89, 153
Opioids, 26–28, 48–52 119, 133, 142, 155, 190
  codeine, 26, 49
  diamorphine, 28, 36, 49, 50
  fentanyl, 28, 36, 49, **51**, 155
  methadone, 30
  morphine, 28, 30, 40, 49, 50, 155
  nalbuphine, 28
  spinal, **36**, 107
  tramadol, 28, 29, **52**
Osteoporosis, 17, 53, 56, 69, **138–141**, 161
Oxybutinin, 45

Pain management programme, 141, **157**
Paracetamol, **26**, 44, 49
Phantom pain, **91**, 142, 151, **152–153**, 168
Phenothiazines, 13, 11, 55
Phentolamine, 64, 179
Phrenic nerve, 43
Physiotherapy, 17, 33, 59, 65,83, 141, 149, **158**
Plexus
  brachial, 134, 135, 168
Polyneuropathy, 86–87, **147–148**

Post-incicional pain, **125–127**
Product licence, 24, 69, **128**
Prostaglandin, 26 (*see also Non-steroidal Antiinflammatory Drugs*)
Psychological assessment, **12–15** (*see Behaviour, Illness*)

Radiofrequency, 23, 24, 42, 82, 106, 113, **119**, 126, 133, 134, 136, 187, 190
Radiotherapy, 46
Reflex sympathetic dystrophy (*see Syndrome: Complex Regional Pain*)

Sacroiliitis, 87
Self-help groups, 69
Sensitization
  central, **92–93**, 95, 120, 124, 143, 144, 152, 160, 190
  peripheral, **93**,143
Serotonin
  antagonists, 90, 100, 101
  agonists-sumatriptan, 82, 83, 98, 101
Sleep disorder, 108
Spinal cord,
  anatomy/physiology, 42, 89, 92, 93, 94, 95,134–135, 143
  injury, 96, 116, 143, **162–163**, 168, 181
  stimulation, 106, 153, 162, **164–172**
Spinothalamic tract, 92
Steroids
  epidural, **24**
  injections, 22, 23, 83, 84, 87, 109, 114, 113, 119, 126, 149
  systemic therapy, 27, **44**, 87, 146, 155
Straight leg raise, 7
Stroke, **58–60**
Stump pain, (*see Phantom pain*)
Substance P, 95, 96, 145, 165, 190
Sudeck's atrophy (*see Syndrome: Complex regional pain)*
Suicide, 111, 155, 184
Sympathetic nervous system, **115–118**, 143
Sympathetically independent pain, 62,128, 149, 179
Sympathetically maintained pain, 62, 117, 128, 131, 149, 179
Syndrome
  Brown Sequard, 160
  burning mouth, **74**
  chronic fatigue, 157
  complex regional pain, 33, **62–66**, 94, 109, 117, 125, 148, 161, 168, 179, 181
  CPPWOP, **143**
  Horner's, 115, 118, 189,81
  Horton's, **81**
  irritable bowel, **74**, 130, 145, 157
  loin pain/haematuria, **145**
  Pancoast, 134
  Raynaud's,118, 167, 171
  Reiter's, **87**
Syrinx, 160, 190

Temporomandibular joint, **77**
Tolerance, **28–30**
Transcutaneous nerve stimulation, 4, 70,78, 79,83, 105, 126, 141, 149, 153, 156, 162, **175–178**,
Transcutaneus spinal electroanalgesia, **176–177**

Vitamins, 75–76, 147, 148

Whiplash, **111**
Windup, 26, 27, 89, 93, **95–96**, 147, 152, 190

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