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1338 • PAIN AND PALLIATIVE CARE velocity and are responsible for transmitting diffuse and poorly localised pain, as well as other sensations (Box 34.1). Sensory neurons (also known as primary afferent neurons) connect the spinal cord to the periphery and supply a defined territory or a dermatome, which can be used to identify the position of a nerve lesion (see Fig. 25.10, p. 1071). In healthy individuals dermatomes have distinct borders, but in pathological pain syndromes these may become blurred as the result of neuronal plasticity, which means that pain may be felt in an area adjacent to that supplied by a specific nerve root. Autonomic neurons also contain pain fibres and are responsible for transmitting visceral sensations, such as colic. In general, visceral pain is diffuse and less well localised than pain transmitted by sensory neurons. Anatomical features of the afferent pain pathway are illustrated in Figure 34.2. Pain signals are transmitted from the periphery to the spinal cord by sensory neurons. These have the following components: • A cell body, containing the nucleus, which is situated in the dorsal root ganglion close to the spinal cord. The cell body is essential for survival of the neuron, production of neurotransmitters and neuronal function. • The nerve fibre (axon) and peripheral nerve endings, which are located in the periphery and contain a range of receptors in the neuronal membrane. • Specialised receptors in the periphery, consisting of bare nerve endings known as nociceptors or pain receptors, which are activated by various mediators. They are situated mainly in the epidermis. • The central termination, which travels to the dorsal horn of the spinal cord to form the first central synapse with neurons that transmit pain sensation to the brain. When a noxious stimulus is encountered, activation of nociceptors leads to generation of an action potential, which travels upwards to the dorsal root ganglion and also stimulates the release of neurotransmitters that have secondary effects on surrounding neurons. Spinal cord Sensory neurons, through their central termination, synapse with second-order neurons in the dorsal horn of the spinal cord. There is considerable modulation of pain messages at Fig. 34.1 The biopsychosocial model of pain. The perception of pain as a symptom is dependent not only on sensory inputs but also on the individual’s cognitive

reaction to the pain, their emotional state, their underlying disease and their social and cultural background. Illness and pain behaviour (underlying disease, impact on quality of life, fear avoidance) Social and cultural (socioeconomics, religion, family) Affect and emotional state (mood, self-efficacy) Cognition (catastrophising, acceptance) Sensory (genetic, anatomical, biomedical) 34.1 Types of nerve fibre Fibre type Diameter (μm) Conduction velocity (ms−1) Function Large myelinated Aα 12–20 70–120 Proprioception Motor to muscle fibres Aβ 5–12 30–70 Light touch, pressure A3–6 15–30 Motor to muscle spindles Small myelinated A 2–5 12–30 Well-localised pain Thermal sensation B < 3 3–15 Pre-ganglionic autonomic Unmyelinated C 0.4–1.3 0.5–3 Diffuse pain Poorly localised thermal sensation Post-ganglionic autonomic Pain Pain is defined as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'. It is one of the most common symptoms for which people seek health-care advice. Our understanding of the mechanisms of pain has evolved considerably from Hippocrates' suggestion in 450 BC that pain arose as a result of an imbalance in vital fluids. We now know that pain is a complex symptom that is influenced and modified by many social, cultural and emotional factors, as illustrated in Figure 34.1. The sensation of acute pain that occurs in response to inflammation or tissue damage plays an important role in protection from further injury. Chronic pain serves no useful function but results in significant distress and suffering for the patient affected, as well as having a wider societal impact. Functional anatomy and physiology The functional anatomy of the somatosensory system is shown in Figures 25.3 and 25.6 (pp. 1065 and 1068). Here, discussion will focus on the mechanisms and mediators that are involved in pain processing. Peripheral nerves Peripheral nerves contain several types of neuron. These can be classified into two groups, depending on whether or not they are surrounded by a myelin sheath. Myelinated neurons have a fast conduction velocity and are responsible for transmission of various sensory signals, such as proprioception, light touch, heat and cold, and the detection of localised pains, such as pin-prick. Unmyelinated fibres have a much slower conduction

of structures in the brain, where sensory, cognitive and emotional aspects are integrated. This is termed the pain neuromatrix (Fig. 34.2). Signals within the neuromatrix are multidirectional in nature, involving modulation of incoming messages by the cerebral cortex (top-down regulation), as well as a complex network of connections between other subcortical structures. Under normal conditions, there is a degree of descending inhibition from the brainstem that reduces input from peripheral stimuli. It is thought that chronic widespread pain (CWP) and opioid-induced hyperalgesia may result, at least in part, from abnormalities in central processing of pain signals. It has also been suggested that variations in the levels of descending inhibition between individuals may make some people more vulnerable than others to developing chronic pain. Over recent years, there has been increasing interest in the role that glial cells (see Fig. 25.1, p. 1064) play in pain processing. Both astrocytes and microglial cells can become activated in chronic pain states and release this site, both from local neurons within the spinal cord and from neurons that descend from the brain, as depicted in Figure 25.11 (p. 1072). Several neurotransmitters are involved in pain processing at this level and these are summarised in Box 34.2. They include amino acids, such as glycine and γ-aminobutyric acid (GABA), which are inhibitory, and glutamate, which is excitatory; neuropeptides, such as substance P and calcitonin gene-related peptide (CGRP); and endorphins. Whether or not they increase or decrease pain perception depends on the connectivity of the neurons on which they act. Central processing of pain The signals transmitted by second-

order neurons in the spinal cord are relayed to the sensory cortex by third-order neurons, which synapse with second-order neurons in the thalamus. At this site, perception of pain is influenced by interactions between a range Fig. 34.2 Ascending and descending pain pathways. Ascending pathways are shown in blue and descending in red. Pain signals are detected in the periphery by nociceptors, which are activated by chemicals, changes in pH and cytokines. The signal is transmitted by the primary afferent neuron to the spinal cord, where there is a synapse with a second-order neuron, which transmits the signal onwards to the thalamus. Thereafter, the pain signal is transmitted to the cerebral cortex. The intensity of pain signals is subject to extensive modulation at several levels within the nervous system. Cognitive influences derived from the frontal lobe, coupled with sensory influences from cortex and emotional influences from the amygdyla, affect pain perception in the mid-brain around the periaqueductal gray matter (PAG) and the rostroventrolateral medulla (RVM) in the medulla. These structures form part of the descending modulatory systems, which, under normal circumstances, inhibit pain perception. In some chronic pain states, however, dysfunction of the descending pathways can occur, increasing pain. Primary afferent neuron Second-order neuron First central synapse Spinothalamic tract Dorsal root ganglion Peripheral input Spinal cord Medulla Mid-brain Cell body C fibre Nociceptors: chemicals, changes in pH, cytokines Thalamus PAG RVM Synapse Hypothalamus Amygdala Emotional Cognitive Sensory Sensory Emotional Cerebral cortex

1340 • PAIN AND PALLIATIVE CARE channels on nociceptors of primary afferent neurons (Fig. 34.3). The signalling pathways activated by these mediators generate action potentials, which are transmitted by sensory neurons to the spinal cord. If these pain-provoking stimuli persist, the activation threshold of sensory neurons is reduced, resulting in an increased transmission of pain signals to the spinal cord. Central sensitisation Sensitisation may also take place at the level of the spinal cord in response to a sustained painful stimulus. It can occur acutely and rapidly, such as immediately after surgery, or may progress to chronic changes, such as chronic infection, cancer, repeated surgery or multiple traumatic episodes. Glutamate, acting via the N-methyl-D-aspartate (NMDA) receptor complex, plays a key role in central sensitisation (Fig. 34.4). In response to a sustained peripheral painful stimulus, increased amounts of glutamate are released in the spinal cord, overcoming the inhibitory action of magnesium ions and resulting in activation of the NMDA receptor. This initiates a cascade of intracellular signalling events that lead to prolonged modifications of somatosensory processing, with amplification of pain responses within the spinal cord and continued neuronal firing, even after the noxious stimulus has stopped. This phenomenon is termed ‘after-discharge’. In neuropathic pain, prolonged activation of the NMDA pathway results in a decrease in the number of inhibitory interneurons, which further potentiates pain. Genetic determinants of pain perception There are marked ethnic and individual variations in how people respond to painful stimuli and studies in twins have estimated pro-inflammatory cytokines, as well as altering re-uptake of excitatory neurotransmitters such as glutamate, which can influence pain perception considerably. As our understanding of these processes improves, there is increasing potential to develop novel therapies targeted at these mediators, with some early clinical studies in neuropathic pain. Sensitisation Sensitisation is one of the key features of pain processing. It refers to the fact that both peripheral and central nervous systems adapt rapidly to the presence of pain, especially in response to tissue damage. This adaptive process is called neuronal plasticity. In some situations, neuronal plasticity can lead to prolonged changes in the pathways that are involved in detecting and processing nociceptive stimuli, resulting in chronic pain syndromes. The specific changes in key neurotransmitters and receptors differ between chronic pain states, with

implications for the efficacy of treatments. For example, μ-opioid receptors are down-regulated in neuropathic pain, potentially leading to limited opioid responsiveness. Peripheral sensitisation Peripheral sensitisation can occur in association with a variety of clinical conditions, including sepsis, cancer, inflammatory disease, injury, surgery and obesity. The final common pathway by which sensitisation takes place in all of these conditions is inflammation. Inflammation is accompanied by increased capillary permeability and tissue oedema with the release of a diverse range of mediators, including bradykinin, hydrogen ions, prostaglandins and adenosine, which bind to receptors and ion 34.2 Neurotransmitters and receptors involved in pain processing in the spinal cord Neurotransmitter Receptor(s) Receptor type Comments* Amino acids Glutamate AMPA Ion channel Excitatory; permeable to cations: can be Ca2+, Na+ or K+, depending on subunit structure NMDA Ion channel Excitatory; blocked by Mg2+ in the resting state; block can be altered if membrane potential changes; permeable to Ca2+, Na+ and K+ Kainate Ion channel Post synaptic – excitatory Gp I GPCR Pre-synaptic – inhibitory through GABA release; permeable to Na+ and K+ Gp II GPCR Activates a range of signalling pathways; long-term effects on synaptic excitability Gp III GPCR Probably inhibitory; can decrease cAMP production; pre-synaptic; decreases glutamate release Glycine GlyR Ion channel Mainly inhibitory; permeable to Cl−; blocked by caffeine GABA GABAA Ion channel Mainly inhibitory in spinal cord; permeable to Cl−; indirectly modulated by benzodiazepines (increased ion channel opening); not specifically involved in nociception, generally depressant effect on spinal cord activity GABAB GPCR Predominantly inhibitory; activated by baclofen Neuropeptides Substance P Neurokinin receptors GPCR Mainly excitatory; increased in inflammation, decreased in neuropathic pain Cholecystokinin CCKRs1–8 GPCR Excitatory; clinical trials of antagonists in progress Calcitonin gene-related peptide CALCRL GPCR Excitatory; slows degradation of substance P; implicated in migraine Opioids Dynorphin OP1 (kappa) GPCR Excitatory?; may be pro-nociceptive β-endorphin OP3 (mu) GPCR Inhibitory Nociceptin ORL-1 GPCR Inhibitory; also expressed by immune cells *Excitatory = increased pain; inhibitory = reduced pain. (AMPA = α-amino 3-hydroxy, 5-methyl, 4-isoxazole propionic acid; CALCRL = calcitonin receptor-like receptor; cAMP = cyclic adenosine monophosphate; GABA = γ-aminobutyric acid; Gp = group; GPCR = G-protein-coupled receptor; NMDA = N-methyl-D-aspartate; OP = opioid; ORL = opioid-like receptor)

occur as the result of a single gene disorder, as summarised in Box 34.3. Most are due to mutations affecting ion channels that play a key role in neurotransmission (see Fig. 34.3), but other causes include mutations in the NTKR1 gene, which encodes the receptor for nerve growth factor, and mutations in the PDRM12 transcription factor, which is involved in neuron development. that the heritability of CWP ranges between 30% and 50%. In the general population, the individual variants in response to pain and perception of pain are most likely due to a complex interaction between genetic and environmental influences. Few variants have been identified with robust evidence of association with CWP. Several rare syndromes have been described, however, in which insensitivity to pain or heightened pain responses Fig. 34.3 Mechanisms of peripheral sensitisation. A Sensory nerve terminating with nociceptor in skin. B Peripheral nociceptors express various receptors and ion channels that act as mediators of pain. They include sodium channels implicated in congenital pain syndromes; the purinergic 2X (P2X) receptor for adenosine triphosphate (ATP); members of the transient receptor potential (TRP) superfamily of ion channel receptors, which detect changes in osmolality and temperature; acid-sensing ion channel (ASIC) receptors, which detect hydrogen

ions; G-protein-coupled receptors, which detect bradykinin (BK), prostaglandins and ATP; and the neurotrophic tyrosine kinase 1 (NTRK1) receptor, which detects nerve growth factor (NGF). C Activation of these receptors by ligands, hydrogen ion [H+] and high temperature (> 42°C) amplifies action potentials, which increase pain signals and cause peripheral sensitisation. Adapted from Bennett DL, Woods CG. Painful and painless channelopathies. Reprinted with permission from Elsevier (The Lancet Neurol 2014; 13:587–599). Stimulus ATP Temperature or low pH Osmosis Cold or limitants Cool Low pH Mechanical Bradykinin Prostanoids ATP NGF Transducer P2X TRPV1/2 TRPV4 TRPA1 TRPM8 ASIC Unknown BK1/2 EP P2Y NTRK1 Kv HCN2 Nav1.7 Sensitisation Stimulus Agonists [H+] Receptors Response Nav1.8 Nav1.9 B A C Fig. 34.4 Mechanisms of central sensitisation. Post-synaptic activation of the N-methyl-D-aspartate (NMDA) receptor requires the amino acids glycine and glutamate, which bind to the NR1 and NR2 subunits, respectively; these amplify pain signals at the level of the spinal cord. In contrast, magnesium ions block receptor activation. Glutamate Amino acids (and other neurotransmitters) Pain signal Amplified signal Kinase Dorsal root ganglia Neurotransmitter changes Glycine NR1 NR2 Mg2+ Regulation of pain response NMDA receptor

1342 • PAIN AND PALLIATIVE CARE Nerve conduction studies Nerve conduction studies can be helpful in demonstrating and quantifying a definitive nerve lesion, either peripherally or centrally. They can be used to help differentiate between central and peripheral neuropathic pain. They do not, however, effectively examine small nerve fibre function. Nerve blocks Performing a nerve block with infiltration of a local anaesthetic such as 1% lidocaine can be used diagnostically, in assessing whether a pain syndrome is due to involvement of a specific nerve or nerve root. Where inflammation and or swelling may be contributing to the underlying pain – for example, if there is compression of a nerve root – then a mixture of local anaesthetic Fig. 34.5 Equipment for bedside sensory testing. Cotton wool Neurology pin Allodynia Warm and cool thermal rollers Increased or decreased thermal sensation Hyperalgesia 34.3 Genetic regulators of pain perception Gene (protein) Mutation (inheritance) Protein function Phenotypes SCN9A (Na,1.7) LoF (AR) Ion channel Absent pain, hypohydrosis, anosmia SCN9A (Na,1.7) GoF (AD) Ion channel Erythromelalgia, paroxysmal pain, burning pain, autonomic dysfunction SCN11A (Na,1.9) GoF (AD) Ion channel Absent pain, hyperhydrosis, muscular weakness, gut dysmotility SCN10A (Na,1.8) GoF (AD) Ion channel Burning pain, autonomic dysfunction TRPA1 (TRPA1) GoF (AD) Ion channel Absent pain PDRM12 (PDRM12) LoF (AR) Transcription factor; neuron development Absent pain NTRK1 (high-affinity NGF receptor) LoF (AR) Tyrosine kinase; promotes neuron development Absent pain; anhydrosis, mental retardation, increased cancer risk (AD = autosomal dominant; AR = autosomal recessive; GoF = gain of function; LoF = loss of function; NGF = nerve growth factor) Investigations Pain can be a presenting feature of a wide range of disorders and the first step in evaluation of a patient with pain should be to perform whatever investigations are required to define the underlying cause of the pain, unless this is already known. However, with most chronic pain syndromes, such as fibromyalgia, complex regional pain syndrome and CWP, investigations are negative and the diagnosis is made on the basis of clinical history and exclusion of other causes. Specific investigations that are useful in the assessment of selected patients with chronic pain are discussed below. Magnetic resonance imaging Magnetic resonance imaging (MRI) can be helpful in the assessment of an underlying cause in patients with focal pain that follows a nerve root or peripheral nerve distribution. Imaging is seldom helpful in individuals with CWP. Blood tests Blood tests are not generally helpful in the diagnosis of chronic pain, except in patients with peripheral neuropathy; in this case, a number of blood tests may be required to investigate the underlying

causes of the neuropathy. Full details are provided in Box 25.86 (p. 1139). Genetic testing may be of value in patients with clinical features that point to an inherited disorder of pain processing (Box 34.3). Quantitative sensory testing Quantitative sensory testing can be helpful in the detailed assessment of patients with chronic pain. A simple set of tools can be used in the clinical setting (Fig. 34.5). Lightly touching the skin with a brush, swab or cotton-wool ball can be used to test for abnormalities of fine touch (allodynia). Assessing the patient's response to a pin-prick can be used to test for abnormalities in mechanical hyperalgesia. Finally, touching the patient's skin with warm and cool thermal rollers can be used to test for abnormalities of thermal sensation. An unaffected area of skin should be tested first, to establish normal sensation, before testing the affected area.

The past medical and medication history should be recorded and specific enquiry made about substance misuse and any previous history of physical or mental abuse. It is also useful to enquire specifically about the patient's beliefs as to what is causing their pain, as well as what their expectation of treatment is; unless these are addressed, management may be less effective. There are some patient populations in whom particular challenges arise, often related to differences in communication ability. Strategies that can be used to overcome these difficulties are summarised in Box 34.5. Examination The patient's general appearance should be noted, including ability to walk and use of a walking aid. In those with focal pain, neurological examination should be performed, focusing particularly on any areas of abnormal sensation, reflexes and evidence of muscle wasting. A general examination should be carried out to determine whether there is any evidence of an underlying physical disorder that can account for the pain. In addition to the use of investigations to find the underlying cause of pain, patients with persistent or chronic pain may benefit from sensory testing or diagnostic nerve blocks to explore the underlying mechanisms and direct treatment. For example, a combined femoral and sciatic nerve block may be used in a patient with lower limb amputation to assess whether the pain is predominantly peripherally or centrally generated. If the pain is not improved by an effective nerve block, then peripherally directed therapies are unlikely to be effective. and depot glucocorticoid may be helpful in alleviating pain. Nerve blockade can also be used to determine whether more radical therapies, such as nerve ablation, might be helpful in controlling pain, particularly that related to cancer. Pain scoring systems Various questionnaires and other instruments have been devised to localise pain, rate its severity and assess its impact on quality of life. Some of the most widely used are listed in Box 34.4. The distribution of pain can be documented on a diagram of the body, on which the patient can mark the sites that are painful. Similarly, other methods have been developed with which to assess the severity of pain using verbal, numerical and behavioural rating scales. Visual scoring systems employing different facial expressions may be of value in paediatric patients and those with cognitive impairment. Documenting changes in pain scores using questionnaires can be helpful in indicating to what extent drug treatments have been successful and can reduce the time taken to achieve pain control. Principles of management Effective management of chronic pain depends in part on the underlying cause but some general principles can be applied. In general terms, the treatment goals are to: • educate the patient • promote self-management • optimise function • enhance quality of life • control pain. Clinical history Biopsychosocial assessment A full biopsychosocial assessment should be performed in all patients with chronic pain. Although this is time-consuming, the time invested is likely to pay dividends in improving the long-term outcome for patients. A biopsychosocial assessment takes account of the underlying neurobiology of the

condition in the context of wider influences, including cognition and beliefs, emotions, and social and cultural factors. For example, an individual with abdominal pain might respond differently if a close relative had recently died of gastric cancer than if a colleague had been off work with gastric upset. An accurate clinical history is important, taking note of the duration of pain, any precipitating and relieving factors, its location and, if the pain is located at more than one site, which site is the one that impacts most on the patient's quality of life. The characteristics of the pain should be documented, by assessing whether it is described as dull, sharp, aching or burning. Associated features, such as hypersensitivity to fine touch or temperature, numbness, paraesthesia, tingling and formication (the feeling of insects crawling over the skin), should be noted. It is important to determine to what extent the pain is interfering with normal daily activities, such as work, leisure pursuits and sleep. The patient's social circumstances and cultural background should be documented, including any caring responsibilities, employment status and social and family support. The intensity of pain should also be recorded, preferably using a validated questionnaire (Box 34.4). The patient's mood should be assessed and, if evidence of low mood is detected, a suicide risk assessment should be considered (see Box 28.12, p. 1187). 34.4 Instruments used in the assessment of pain and its impact Instrument Comments Brief Pain Inventory Developed for use in cancer pain, validated and widely employed for chronic pain; based on 0–10 ratings of pain intensity and the impact of pain on a range of domains, including sleep, work and enjoyment of life Pain Detect, s-LANSS, DN-4 A number of screening questionnaires to aid diagnosis of neuropathic pain Pain Catastrophising Scale Developed to assess individual levels of catastrophising, encompassing three different domains: helplessness, rumination and magnification Tampa Scale of Kinesiophobia Measures how much an individual is fearful of movement Pain Self-efficacy Questionnaire Assesses individual beliefs about self-efficacy in the context of chronic pain, and how this impacts on function Visual analogue scale (VAS) Patient marks pain intensity on a horizontal line Localisation of pain Body chart, allowing the patient to indicate where pain is situated Beck Depression Inventory Assesses emotional function SF-36/EQ-5D Assesses health-related quality of life (DN-4 = Douleur Neuropathique questionnaire; EQ-5D = EuroQol 5-Domain questionnaire; SF-36 = Short Form 36; s-LANSS = self-completed Leeds Assessment of Neuropathic Signs and Symptoms)

 to the individual patient. A successful exercise programme can help overcome 'fear avoidance', a well-recognised problem in chronic pain, where patients associate activity with an increase in pain and therefore do progressively less activity, with resultant deconditioning. Because of this it is important to pace physical activity to ensure that patients do not cycle from over-activity, with a flare in pain, to fatigue and deconditioning. This can be done by working with patients to establish their baseline level of activity and using an individually tailored, graded exercise programme (Box 34.6). This may include normal household activities, as well as targeted exercises and stretches. Manual therapy covers a variety of hands-on treatments, including manipulation, mobilisation and massage. Manual therapy can be provided by a range of therapists, including physiotherapists, osteopaths and chiropractors. There is some evidence of shortterm benefit for manual therapy but limited evidence of long-term efficacy. Pharmacological therapies A range of analgesics can be used in the management of chronic pain but, for most of these, the evidence of long-term benefit is limited. In general, it is advisable to use a multimodal approach in the treatment of chronic pain, choosing different drugs to target pain processing at multiple points (Box 34.7). By employing different classes of analgesic, it is possible to use lower doses of each, thereby improving the side-effect profile. There is considerable inter-

individual variability in response to analgesics, even within the same class. There are many reasons for this, including genetic variations in the enzymes that metabolise drugs. For example, the CYP2D6 gene encodes for a liver enzyme, cytochrome P450 2D6, which metabolises a number of commonly used analgesics. Genetic variation in CYP2D6 can influence circulating levels of many drugs, depending on whether Interventions Probably the most effective mode of treatment for pain is to identify the underlying cause. Examples include the use of immunosuppressive medication in inflammatory disease, chemotherapy, radiotherapy or hormone therapy in cancer, and antimicrobial therapy in patients with infection. There are many circumstances, however, in which the underlying cause of pain cannot be treated or the treatments available are incompletely effective. Under these circumstances, several management options are available. In all cases, a multidisciplinary approach is necessary that combines pharmacological management with supported self-management, and other specific interventions when appropriate. Supported self-management Self-management strategies are useful in the treatment of chronic pain. Self-management works best if the patient has some understanding of their chronic pain, and acceptance that it is unlikely to resolve completely. The aim is for patients to maximise their quality of life and function despite ongoing pain. Support for self-management can be delivered by health-care professionals, patients who suffer from the same condition or lay people, either on an individual basis, in a group setting or, increasingly, through web-based resources. There is a strong educational component to supported self-management, which seeks to generate an interaction between patient and tutor. The key aspects include: • increasing activity levels, while understanding and practising pacing techniques (not overdoing things and cycling between over- and under-activity) • using relaxation and mindfulness techniques as part of daily management • using medication when appropriate • having a plan to manage pain flares. There are a number of useful online self-help resources (see ‘Further reading’). Physical therapies There is strong evidence that exercise can help in the management of chronic pain. Several types of exercise have been successfully used delivered in various ways, through physiotherapists, exercise classes or individual tuition. In choosing a form of exercise therapy, it is important to tailor the approach most likely to be acceptable 34.6 Physical therapies for chronic pain Land-based • Walking • Gym work • Exercise classes • Yoga • Pilates • Tai-chi Water-based • Hydrotherapy • Swimming • Exercise classes 34.5 Challenges in pain assessment in particular patient populations Patient population Challenges Solutions Paediatric Assessment needs to be appropriate to developmental stage Consider visual tools to aid pain assessment Elderly May have impaired cognitive function Cultural factors may reduce self-reporting of pain Risk of adverse effects of medication increased Consider formal assessment of cognitive function Consider non-verbal assessment Consider visual tools to assess pain Employ a number of tools assessing pain behaviours Cognitive impairment Reporting and expression of pain may change Increased sensitivity to central nervous system effects of analgesics Perform formal assessment of cognitive function Use non-verbal assessment: facial expressions, vocalisations, body movements, changes in social interactions Substance misuse Response to analgesics altered Increased tolerance Increased risk of addiction Substance misuse may affect reporting of pain Seek specialist support early Ensure prescribing is safe

be employed with caution in elderly patients and those weighing less than 50 kg. Non-steroidal anti-inflammatory drugs Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of inflammatory pain and osteoarthritis. These drugs can be given systemically or locally

and are discussed in more detail on page 1002. They are also useful in the management of pain in cancer patients, as discussed later in this chapter (p. 1350). Although widely prescribed, there is limited high-quality evidence of long-term efficacy in chronic pain, with a need for further studies in this area. Topical analgesics Topical capsaicin cream (0.025 or 0.075%) has some efficacy for osteoarthritis and may be used for neuropathic pain, although evidence of benefit is limited. A single application (done by a trained health-care professional) of a high-dose 8% capsaicin patch can give around 12 weeks of pain relief for neuropathic pain and can be repeated thereafter. Capsaicin is an agonist at the transient receptor potential vanilloid 1 (TRPV1) ion channel, found on some C fibres. Capsaicin activates the channel, causing an initial sensation of heat, but an analgesic effect subsequently results due to desensitisation of the channel. Lidocaine 5% patches can also be helpful in focal neuropathic pain and should be applied for 12 hours out of 24 hours, with up to 4–6 weeks before maximum benefit is seen. The mode of action is blockade of sodium channels in primary afferent neurons and nociceptors, which reduces peripheral input to the spinal cord. Adjuvant analgesics Adjuvant analgesics is the term used to cover a range of agents that are used in the treatment of neuropathic pain, usually in combination with classical analgesics. Typically, these agents 34.7 Pharmacological management of chronic pain Drug or class of drug Mechanism of action Paracetamol Central inhibition of COX-1 and COX-2 enzymes Mechanisms of action incompletely understood Non-steroidal anti-inflammatory drugs Inhibition of prostaglandin production Opioids Agonists at OP3 receptors at multiple levels in the central nervous system Blockade of ascending pain pathways Ketamine Antagonist of NMDA receptors Reduction of central sensitisation Gabapentin Pregabalin Inhibition of glutamate release by primary afferent neurons at first central synapse Decrease of excitatory neuronal activity Tricyclic antidepressants Inhibition of serotonin and noradrenaline (norepinephrine) re-uptake at synapses in the spinal cord, and also potential effects in the limbic system Inhibition of Na+ channels in neurons Serotonin (5-hydroxytryptamine, 5-HT) and noradrenaline (norepinephrine) re-uptake inhibitors Inhibition of serotonin and noradrenaline re-uptake at synapses in the spinal cord, and also potential effects in the limbic system Lidocaine patches Inhibition of Na+ in sensory neurons Capsaicin patch Activation of TRPV1 channels on subset of C fibres, causing selective pharmacological denervation, with a decrease in intra-epidermal nerve fibre density Nerve blocks with lidocaine and glucocorticoids Temporary denervation due to blockade of Na+ channels in sensory neurons Local anti-inflammatory effect (COX = cyclo-oxygenase; NMDA = N-methyl-D-aspartate; OP = opioid; TRPV1 = transient receptor potential vanilloid 1) someone is a rapid or poor metaboliser. This is particularly important if metabolites are active, as is the case with codeine and tramadol, which are metabolised to morphine. Genetic variations have also been described in the opioid receptors and downstream pathways that they affect, with good pre-clinical evidence that variations in mu opioid receptors alter analgesic response to different opioids. Because of this there is a good rationale to try different drugs, even ones from the same class, if there is an inadequate response or there are unacceptable side-effects with one agent. Whatever drug or combination of drugs is chosen, the key to successful pharmacological management is careful assessment and review, aiming for an acceptable balance between the benefits of treatment in providing pain relief, maximising function, and improving quality of life and adverse effects. Specific drug treatments are described below. Non-opioid analgesics Paracetamol Paracetamol is widely used in the treatment of mild to moderate pain. Its mechanism of action is incompletely understood but it is known to be a weak inhibitor of the cyclo-oxygenase type 1 (COX-1) and cyclo-oxygenase type 2 (COX-2) enzymes, providing weak anti-inflammatory properties. There is also some of evidence that it activates inhibitory descending spinal pathways, via a serotonergic mechanism. Other postulated

mechanisms include endocannabinoid re-uptake inhibition, and inhibition of nitric oxide and tumour necrosis factor alpha. For migraine and tension-type headache it has moderate efficacy at a dose of 1000 mg. It is used widely for musculoskeletal disorders and osteoarthritis, with very little high-quality evidence that it is much better than placebo, even at doses of up to 4000 mg per day. Acute liver failure is a well-recognised complication of paracetamol overdose but this risk may also be increased with long-term use, even within the recommended dose range. In view of this, it should

1346 • PAIN AND PALLIATIVE CARE potassium permeability of neurons. Opioids are traditionally divided into subclasses of weak opioids, such as codeine and dihydrocodeine, and strong opioids, such as morphine and oxycodone. While tramadol is a weak agonist at the mu opioid receptor, it is classified as a strong opioid in some countries. The dosages and characteristics of commonly prescribed opioids are shown in Box 34.9. There has been a large increase in the use of strong opioids for chronic pain over the last 10–20 years. A number of factors contribute to this, including a rising incidence of chronic pain with an ageing population, reluctance to use NSAIDs because of cardiovascular and gastrointestinal adverse effects, changes in patient expectation, societal attitudes and availability of new formulations of opioids. There is evidence of short- to medium-term benefit for strong opioids in low back pain and osteoarthritis but there have been very few good-quality studies of long-term use. Additionally, there is increasing concern about potential harm from long-term use. This includes addiction, dependence, opioid-induced hyperalgesia, endocrine dysfunction, fracture risk (especially in the elderly), overdose and cardiovascular do not produce an immediate reduction in pain, but rather exert an analgesic effect over a longer timeframe through their effects on central processing of pain. They are of particular value when used in combination in the management of pain with a neuropathic component but require careful dose titration over a number of weeks, to reach a dose that balances efficacy with side-effects. While the response to individual agents is variable, it is often possible to find an agent or combination of agents that works for most patients. Opioid analgesics Opioids are a class of drugs that target opioid receptors. The original receptor classification was based on pharmacological activity (mu, delta, kappa), with the more recent International Union of Basic and Clinical Pharmacology (IUPHAR) classification being generally accepted in current use (Box 34.8). Opioid receptors are G-protein-coupled receptors. Ligand binding activates several intracellular signalling pathways, increasing cyclic adenosine monophosphate (cAMP) levels, as well as altering calcium and 34.8 Opioids and opioid receptors Endogenous ligand Receptor (IUPHAR) Alternative classification Potential sites Pharmacological effects Endomorphin 1 and 2 Met-enkephalin Dynorphin A Dynorphin B MOP Mu; OP3 Brain, spinal cord, peripheral nerves, immune cells Analgesia, reduced gastrointestinal motility, respiratory depression, pruritus Leu-enkephalin Met-enkephalin β-endorphin DOP Delta; OP1 Brain, spinal cord, peripheral nerves Analgesia, cardioprotection, thermoregulation Dynorphin A Dynorphin B β-endorphin KOP Kappa; OP2 Brain (nucleus accumbens, neocortex, brainstem, cerebellum) Analgesia, neuroendocrine (e.g. on hypothalamic–pituitary axis), diuresis, dysphoria Orphanin FQ (nociceptin) NOP Orphan; ORL-1; OP4 Nucleus raphe magnus, spinal cord, afferent neurons Opioid tolerance, anxiety, depression, increased appetite (IUPHAR = International Union of Basic and Clinical Pharmacology; OP = opioid; ORL = opioid-like receptor) 34.9 Commonly used opioids Opioid Typical starting dose Route Oral morphine equivalent Comments Morphine 10 mg Oral 10 mg Most widely used Codeine 100 mg Oral 10 mg Metabolised to morphine Dihydrocodeine 100 mg Oral 10 mg Semi-synthetic Tramadol 100 mg Oral 10 mg Synthetic Oxycodone 6.6 mg Oral 10 mg More predictable bioavailability than

morphine Buprenorphine 5 µg/hr Transdermal 30 mg/day Patch change usually every 7 days (frequency of change dependent on manufacturer and dose); advantages in impaired renal function Fentanyl 12 µg/hr Transdermal 30 mg/day Use with care in opioid-naïve patients; patch change usually every 72 hrs Tapentadol 50 mg Oral 20 mg Use with care in opioid-naïve patients Hydromorphone 2 mg Oral 10 mg Semi-synthetic; hepatic metabolism Diamorphine 3 mg Subcutaneous, intramuscular, intravenous 10 mg Mainly used for acute pain or palliative care

34.10 Use of opioids in chronic pain Step Factors to take into account Comment

1. Assess suitability for opioids Type of pain Neuropathic pain less likely to respond Likelihood of dependence History of substance or alcohol misuse, including stimulant misuse Co-morbidity Avoid use in conditions where adverse effects more likely: Chronic obstructive pulmonary disease Chronic liver disease Chronic kidney disease
2. Discuss with patient Discuss potential benefits Improvement in pain Improvement in function Discuss adverse effects Nausea Constipation Drowsiness Establish treatment goal Improvement in function
3. Plan treatment trial Set timescale Define duration of treatment Agree frequency of review Agree on dose Aim for lowest effective dose Set upper dose limit Agree on stopping rules Consider stopping if: Treatment goal is not met There is no dose response Tolerance develops rapidly events, with many of these adverse effects being dose-related. There is evidence that doses of more than 120 mg morphine equivalents per day are associated with increased harm, and regular review to assess ongoing benefit is needed in this patient group. A suggested strategy for using strong opioids in chronic pain is shown in Box 34.10. Psychological therapies The aims of psychological therapy are to increase coping skills and improve quality of life when facing the challenges of living with chronic pain. There are a range of ways in which psychological therapies can be delivered, including individual one-to-one sessions, group sessions, multidisciplinary pain management programmes, or web-based or telephone-based programmes. There is a good evidence for the use of a cognitive behavioural therapy (CBT)-based approach for chronic pain, delivered either individually or in a group. The overall aim is to reduce negative thoughts and beliefs, and develop positive coping strategies. The interaction between thoughts, behaviours and emotions is explored, and a problem-focused approach is used in therapy delivery. Relaxation techniques, such as biofeedback and mindfulness meditation, require a degree of stillness and withdrawal, with regular practice required for sustained benefit (see ‘Further information’). Acceptance and commitment therapy (ACT) is based on CBT principles but also uses components of mindfulness to improve psychological flexibility in the context of living with chronic pain. Stimulation therapies These range from minimally invasive procedures like acupuncture and transcutaneous electrical nerve stimulation (TENS) to more invasive techniques such as spinal cord stimulation. Acupuncture (Fig. 34.6) has been used successfully in Eastern medicine for centuries. The mechanisms are incompletely understood, although endorphin release may explain, in part, Fig. 34.6 Acupuncture. the analgesic effect. Acupuncture is particularly effective in pain related to muscle spasm, with some evidence of short-term benefit for patients with low back pain. Similar mechanisms probably apply to TENS, which is worth

considering in many types of chronic pain. Neuromodulation, using implanted electrodes in the epidural space (or, more recently, adjacent to peripheral nerves), has been shown to be an effective option for neuropathic pain, including failed back surgery syndrome and chronic regional pain syndrome (see below). Specialist assessment and ongoing support is necessary, as there are many potential complications, including infection, malfunction and battery failure. The likelihood of success is increased when this technique is used within the context of multidisciplinary assessment and management.

1348 • PAIN AND PALLIATIVE CARE Complementary and alternative therapies Complementary techniques, such as herbal medicines, vitamins, homeopathy and reflexology, have been used for the treatment of chronic pain but with little evidence of efficacy. It should be noted that herbal medications may interact with conventional drugs, causing adverse effects as the result of drug–drug interactions. St John's wort (Hypericum perforatum) interacts with many drugs, including many antidepressants used in chronic pain, with increased serotonergic effects. Grapefruit may also increase the risk of serotonergic effects with some antidepressants. Ginkgo biloba may interact with paracetamol to increase bleeding time. Nerve blocks and nerve ablation The use of specialist nerve blocks and nerve ablation therapy can be considered for pain that is unresponsive to less invasive approaches. If these are being considered, they should form part of a multidisciplinary management plan, with the aim of restoring function and reducing pain. Local anaesthetic with or without depot glucocorticoid (non-particulate for neuraxial administration) can be effective in some circumstances. Examples include occipital nerve blocks for migraine or cervicogenic headache and trigger point injections for myofascial pain. If there is limited compression of a spinal nerve root, the nerve root injections into the epidural space may help settle symptoms and avoid the need for surgical intervention. Neurodestructive procedures can also be employed for intractable pain but are rarely used outside the palliative care setting. Chronic pain syndromes Chronic pain is a feature of several recognised syndromes, which are discussed in more detail below. Neuropathic pain Neuropathic pain is defined as 'pain associated with a lesion or disease of the somatosensory nervous system'. Neuropathic pain may be acute, such as in sciatica, which occurs as the result of a prolapsed disc, but is most problematic when it becomes chronic. Neuropathic pain causes major morbidity; in a recent study, 17% of those affected rated their quality of life as 'worse than death'. The clinical features of neuropathic pain are summarised in Box 34.11. The diagnosis is easily missed and so careful assessment is vital, in order to make the diagnosis in the first place and then to direct management appropriately. An algorithm for the management of neuropathic pain is provided in Figure 34.7. It is important to recognise the negative impact of neuropathic pain on quality of life, which has been shown to be greater than with other types of chronic pain. As a result, appropriate support and multidisciplinary management should always be considered in addition to pharmacological therapies. Complex regional pain syndrome Complex regional pain syndrome (CRPS) is a type of neuropathic pain that affects one or more limbs. It was previously termed reflex sympathetic dystrophy (RSD), reflecting the fact the disease is thought to be caused in part by an abnormality in the autonomic nervous system. It is a rare syndrome, occurring in about 20 per 100 000 individuals, and is more common in females, typically presenting between the ages of 35 and 50. It is classified into type I CRPS, which may be precipitated by a traumatic event Fig. 34.7 Algorithm for pharmacological management of neuropathic pain. (SNRI = serotonin noradrenaline (norepinephrine) re-uptake inhibitor) Adapted from SIGN 136 and NeuPSIG recommendations (Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and

meta-analysis. Reprinted with permission from Elsevier (The Lancet Neurol 2015; 14:162–173)). Are there clinical features of neuropathic pain? (Box 34.11) Assess likelihood of neuropathic pain Tricyclic antidepressant Gabapentin or pregabalin SNRI First line (moderate to high evidence; strong recommendation) Probable Possible Definite Response? Continue Yes Capsaicin patch Lidocaine patch Tramadol Second line (moderate evidence; weak recommendation) No Yes Response? Continue Botulinum toxin Strong opioids Third line (moderate evidence; weak recommendation) No Yes 34.11 Clinical features of neuropathic pain Characteristic Symptom or clinical feature* Descriptive term Spontaneous pain No stimulus required to evoke pain Positive sensory disturbance Light touch painful Dynamic allodynia Pressure painful Punctate allodynia Increased pain on pin-prick Hyperalgesia Cool and warm temperatures painful Thermal allodynia Negative sensory disturbance Numbness Loss of sensation Tingling Paraesthesia Loss of temperature sensitivity Other features Feeling of insects crawling over skin Formication Affected area feels abnormal Dysaesthesia *Symptoms may cluster, with a predominance of either positive or negative symptoms, or a mixture of both, reflecting differences in underlying mechanisms.

Fibromyalgia is a subtype of CWP in which there are myofascial trigger points, and is often associated with sleep disturbance. Clinical features and management of fibromyalgia are discussed in more detail on page 1018. Joint hypermobility syndrome Hypermobility can be associated with chronic musculoskeletal pain that often targets the joints and periarticular tissues. It is thought to be caused by abnormal stresses being placed on the joints and surrounding soft tissues due to ligament laxity, although the mechanisms are poorly understood since many people with hypermobile joints do not suffer pain. It is described in more detail on page 1059. Palliative care Palliative care is the term used to describe the active total care of patients with incurable disease. It can be distinguished from end-of-life care, which refers to the care of patients with far advanced, rapidly progressive disease that will soon prove fatal. The focus of palliative care is on symptom control alongside supportive care. While palliative care can and should be delivered at any stage of an incurable illness alongside optimal disease control, the focus of end-of-life care is on quality of life rather than prolongation of life or cure. Palliative care encompasses a distinct body of knowledge and skills that all good physicians must possess to allow them to care effectively for patients. Palliative care is traditionally seen as a means of managing distress and symptoms in patients with cancer, when metastatic disease has been diagnosed and death is seen as inevitable. There is, however, a growing recognition that the principles of palliative care and some of the interventions it uses are equally applicable in other conditions. Palliative may therefore be applied to any chronic disease state. For conditions other than cancer, the challenge is recognising when patients have entered the terminal phase of their illness, as there are fewer clear markers and the course of the illness is much more variable. Different chronic disease states progress at different rates, allowing some general trajectories of illness or dying to be defined (Fig. 34.8). These trajectories are useful in decision-making for individual patients and also in planning services. such as a fracture but is not associated with peripheral nerve damage, and type II CRPS, which is associated with a peripheral nerve lesion. The diagnosis is primarily clinical, based on the features shown in Box 34.12. Imaging with MRI or radionuclide bone scan may provide support for the diagnosis of type I CRPS in showing bone marrow oedema or increased tracer uptake localised to an affected site (p. 1055). Prompt diagnosis and early treatment with physiotherapy may prevent progression of symptoms. Management is as for neuropathic pain, additional approaches including

graded motor imagery. Bisphosphonates have been used empirically for treatment but the evidence base for efficacy in controlling pain is weak. If medical management is incompletely effective, consideration should be given to the appropriateness of a spinal cord stimulator. Phantom limb pain Phantom limb is a common complication of amputation, occurring in up to 70% of patients. It is a form of neuropathic pain but can be particularly distressing, as the pain is felt in the area where the absent limb was previously. Although usually presenting after limb amputation, reports of phantom pain in other body parts have been reported, such as phantom breast pain following mastectomy. It is very often associated with phantom sensations, which are described as non-painful sensations in the absent body part and pain in the stump. Diagnostic nerve blocks may be helpful in directing therapy, with use of anti-neuropathic medications as outlined in Box 34.7. If there is a definite neuroma at the stump site that is interfering with prosthesis use, surgical review may be necessary. Chronic widespread pain Chronic widespread pain (CWP) is often associated with other features, such as fatigue and irritable bowel syndrome. *The diagnosis of CRPS type 1 can be made if a patient has at least one symptom in at least three out of the four categories and at least one sign in two out of the four categories, and no other diagnosis can explain the symptoms. 34.12 Criteria for diagnosis of complex regional pain syndrome (CRPS) type 1* Category Symptom or sign Sensory Allodynia to: Temperature Light touch Deep somatic pressure Movement Hyperalgesia to pin-prick Vasomotor Temperature asymmetry Skin colour change and asymmetry Skin colour asymmetry Oedema/sudomotor Oedema Sweating change or asymmetry Motor/trophic Reduced range of motion Motor dysfunction: Weakness Tremor Dystonia Trophic changes: Hair Nails Skin Fig. 34.8 Archetypal trajectories of dying. Reproduced from Murray SA, Kendall M, Boyd K, et al. Illness trajectories and palliative care. BMJ 2005; 330:7498; reproduced with permission from the BMJ Publishing Group. High Death Cancer Organ failure Physical and cognitive frailty Function Low Time

 Management: pharmacological treatments Pharmacological treatments are the mainstay of management in cancer-associated pain. A stepwise approach is adopted, following the principles of the World Health Organisation (WHO) analgesic ladder (Fig. 34.9), in which analgesia that is appropriate for the degree of pain is prescribed first. Patients with mild pain should be started on a non-opioid analgesic drug, such as paracetamol (1 g 4 times daily) or an NSAID (step 1). If the patient fails to respond adequately or has moderate pain, a weak opioid, such as codeine (60 mg 4 times daily), should be added (step 2). This can be prescribed separately or in the form of the compound analgesic co-codamol. If pain relief is still not achieved or if the patient has severe pain, a strong opioid should be substituted for the weak opioid (step 3). If the pain is severe at the outset, strong opioids should be prescribed and increased or titrated according to the patient's response. It is important not to move 'sideways' (change from one drug to another of equal potency), which is a common problem during step 2 of the analgesic ladder. Opioids Opioid analgesia plays a key role in patients with moderate to severe pain. Its successful use depends on appropriate assessment and a detailed explanation to the patient and carer about the benefits and potential side-effects of therapy. Morphine The 'rapid decline' trajectory following a gradual decline, as occurs in cancer, is the best-recognised pattern of the need for palliative care, although a similar trajectory may be observed in other conditions, such as motor neuron disease can. Many traditional hospice services are designed to meet the needs of people on this trajectory. Over recent years, improvements in management of malignant disease mean that some types of cancer may follow an erratic or intermittent decline trajectory. Many chronic diseases, such as advanced chronic obstructive pulmonary disease (COPD) and intractable congestive heart failure,

carry as high a burden of symptoms as cancer, as well as psychological and family distress. The ‘palliative phase’ of these illnesses may be more difficult to identify because of periods of relative stability interspersed with acute episodes of severe illness. However, it is still possible to recognise those patients who may benefit from a palliative approach to their care. The challenge is that symptom management needs to be delivered at the same time as treatment for acute exacerbations. This leads to difficult decisions as to the balance between symptom relief and aggressive management of the underlying disease. The starting point of need for palliative care in these conditions is the point at which consideration of comfort and individual values becomes important in decision-making, often alongside management of the underlying disease. The third major trajectory is categorised by years of poor function and frailty before a relatively short terminal period; it is exemplified by dementia but is also increasingly true for patients with many different chronic illnesses. As medical advances extend survival, this mode of dying is being experienced by increasing numbers of people. The main challenge lies in providing nursing care and ensuring that plans are agreed for the time when medical intervention is no longer beneficial. In a situation where death is inevitable and foreseeable, palliative care balances the ‘standard textbook’ approach with the wishes and values of the patient and a realistic assessment of the benefits of medical interventions. This often results in a greater focus on comfort, symptom control and support for patient and family, and may enable withdrawal of both futile and burdensome interventions. In cases of prognostic uncertainty, open, honest and gentle communication with the patient and family is important. The most common symptoms in palliative care are discussed in the next section. Presenting problems in palliative care Pain Pain is a common problem in palliative care. It has been estimated that about two-thirds of patients with cancer experience moderate or severe pain, and a quarter have three or more different sites of pain. Many of these are of a mixed aetiology and about half of patients with cancer-associated pain have a neuropathic element. Clinical assessment Careful evaluation to identify the likely mechanisms of pain is important so that the most appropriate treatment can be given. Clinical features and suggested management strategies for common types of pain in cancer are shown in Box 34.13. The majority of patients with cancer-associated pain can be effectively managed using a stepwise approach, as outlined below. 34.13 Common types of pain in cancer Type of pain Features Management options Bone pain Tender area over bone Possible pain on movement NSAIDs Bisphosphonates Radiotherapy Increased intracranial pressure Headache, worse in the morning, associated with vomiting and occasionally delirium Glucocorticoids Radiotherapy Codeine Abdominal colic Intermittent, severe, spasmodic, associated with nausea or vomiting Antispasmodics Hyoscine butylbromide Liver capsule pain Right upper quadrant abdominal pain, often associated with tender enlarged liver Responds poorly to opioids Glucocorticoids Neuropathic pain Spontaneous pain Light touch, pressure and temperature changes are painful; increased pain on pin-prick Numbness, tingling or loss of temperature sensation Skin feels abnormal Anticonvulsants: Gabapentin Pregabalin Antidepressants Amitriptyline Duloxetine Ketamine Ischaemic pain Diffuse, severe, aching pain associated with evidence of poor perfusion Responds poorly to opioids NSAIDs Ketamine Incident pain Episodic pain usually related to movement or bowel spasm Intermittent short-acting opioids Nerve block (NSAIDs = non-steroidal anti-inflammatory drugs)

that psychological dependence is rare when opioids are used for cancer pain, unless a pre-existing dependence problem exists. Pharmacological tolerance is not usually a clinically relevant problem;

however, physical dependence, which is physiological, as manifest by a physical withdrawal syndrome, can occur if opioids are suddenly discontinued. Nearly all types of cancer pain respond to morphine to some degree but there is a spectrum of response, such that in some patients the dose of opioid required to control neuropathic pain and all elements of metastatic bone pain may be high and associated with unacceptable side-effects. In these situations, other methods of analgesia, both pharmacological and nonpharmacological, should be explored and considered at an early stage. The most effective and appropriate route of morphine administration is oral but transdermal preparations of strong opioids (usually fentanyl) are useful in certain situations, such as in patients with dysphagia or those who are reluctant to take tablets on a regular basis. Diamorphine is a highly soluble strong opioid used for subcutaneous infusions, particularly in the last few days of life, but is only available in certain countries. Opioid-related adverse effects Adverse effects are a common problem with opioids, especially on initiating treatment and on increasing the dose. The most common side-effects are nausea, drowsiness, constipation and dry mouth, as summarised in Box 34.14. Nausea and vomiting can occur initially but usually settle after a few days. Drowsiness is usually transient at opioid initiation and dose increase. If it is persistent, an alternative opioid and/or a non-opioid should be considered. In acute dosing, respiratory depression can occur but this is rare in patients on regular opioids or in those starting on small, regular doses with appropriate titration. Tolerance usually develops to nausea, vomiting and drowsiness but not to constipation or dry mouth. All patients should therefore be prescribed a laxative, unless suffering from diarrhoea, and have access to an antiemetic and good mouth care, along with rationalisation of any concomitant medication that might exacerbate drowsiness. Newer developments include the use of preparations in which opioids are combined with opioid is the most commonly prescribed strong opioid, although there are several alternatives, as outlined in Box 34.9. Oral morphine takes about 20 minutes to exert an effect and usually provides pain relief for 4 hours. Most patients with continuous pain should be prescribed oral morphine every 4 hours initially, as this will provide continuous pain relief over the whole 24-hour period. Controlled-release morphine lasts for 12 or 24 hours, depending on the formulation, and if clinical circumstances dictate, a controlled-release formulation can be used to initiate and titrate morphine. The median effective morphine equivalent dose for cancer pain is about 200 mg per 24 hours. In addition to the regular dose of morphine, an extra dose of immediate-release (IR) morphine should be prescribed ‘as required’ for the treatment of breakthrough pain that has not been controlled by the regular prescription. As a rule of thumb, this additional dose should be one-sixth of the total 24-hour dose of opioid. The frequency of breakthrough doses should be dictated by their efficacy and any side-effects, rather than by a fixed time interval. A patient may require breakthrough analgesia as frequently as hourly if pain is severe, but this should lead to early review of the regular prescription. The patient or carer should note the timing of any breakthrough doses and the reason for them. These should be reviewed daily and the regular 4-hourly dose increased for the next 24 hours on the basis of: • the frequency of and reasons for breakthrough analgesia • the degree and acceptability of side-effects. The regular dose should be increased by adding the total of the breakthrough doses over the previous 24 hours, unless there are significant problems with unacceptable side-effects. When the correct dose has been established, a continuous release (CR) preparation can be prescribed, usually twice daily. Breakthrough analgesia used for movement-related pain is generally not included in background opioid dose titration. Attempts to control movement-related pain with background opioid dose will usually lead to over-medication and opioid-related side-effects. This can be a risk in metastatic bone pain. Some patients may have concerns about using opioids and it is vital for these to be explored. Patients should be reassured

Fig. 34.9 The WHO analgesic ladder. From WHO. Cancer pain relief, 2nd edn. Geneva: WHO; 1996. Opioid for moderate to severe pain ± non-opioid ± adjuvant Opioid for mild to moderate pain ± non-opioid ± adjuvant Non-opioid ± adjuvant Pain persisting or increasing Pain persisting or increasing Freedom from cancer pain Pain 34.14 Opioid side-effects Side-effect Management Constipation Regular laxative Opioid/naloxone oral combination, in resistant constipation Dry mouth Frequent sips of iced water, soft white paraffin to lips, chlorhexidine mouthwashes twice daily, sugar-free gum, water or saliva sprays Nausea/vomiting Oral haloperidol 0.5–1 mg at night, oral metoclopramide 10 mg 3 times daily or oral domperidone 10 mg 3 times daily If constant, haloperidol or levomepromazine may be given parenterally to break the nausea cycle Sedation Explanation is very important Symptoms usually settle in a few days Avoid other sedating medication where possible Ensure appropriate use of adjuvant analgesics that can have an opioid-sparing effect May require an alternative opioid

1352 • PAIN AND PALLIATIVE CARE analgesic should be considered, the choice depending on the type of pain. Management: non-pharmacological treatments Neurodestructive interventions Neurodestructive techniques have an important role in the management of cancer pain, where life expectancy is limited. They should be used as part of an overall management plan and considered when the response to drug treatment has been inadequate. Intrathecal analgesia, delivered via either an external pump or a fully implanted device, is a good option, particularly where life expectancy is more than 3 months. Coeliac plexus blocks can be helpful for visceral pain, such as in pancreatic cancer. Lateral cordotomy to disrupt the spinothalamic tracts (either open or percutaneous) may be considered for unilateral chest wall pain, such as may occur in mesothelioma, where life expectancy is limited. Radiotherapy Radiotherapy is the treatment of choice for pain from bone metastases (see Box 34.13) and can also be considered for metastatic involvement at other sites. All patients with pain secondary to bone metastases should be considered for palliative radiotherapy, which can usually be given in a single dose. Physiotherapy Physiotherapy has a key role in the multidisciplinary approach to a wide spectrum of cancer-related symptoms, including the prevention and management of pain, muscle spasm, reduced mobility, muscle wasting and lymphoedema. Rehabilitation in palliative care has expanded and now includes pre-habilitation, which involves the use of proactive focused exercise to maintain muscle mass during cancer chemotherapy and in other chronic conditions such as COPD. Psychological techniques As with chronic pain, there is increasing use of psychological techniques in cancer pain management, which train the patient antagonists, such as naloxone. The naloxone is poorly absorbed and does not antagonise the systemic analgesic effect but rather acts locally to block opioid receptors in the gut, thereby reducing opioid-related constipation. Vivid dreams, visual hallucinations (often consisting of a sense of movement at the periphery of vision), delirium and myoclonus are typical of opioid-related toxicity and, if present, require urgent reassessment of the opioid dose. Biochemistry should also be checked to exclude renal impairment, dehydration, electrolyte disturbance or hypercalcaemia. Since opioid toxicity can occur at any dose, side-effects should be assessed regularly, but particularly after a dose increase. Pain should be reassessed to ensure that appropriate adjuvants are being used. Parenteral rehydration is often helpful to speed up excretion of active metabolites of morphine. The dose of opioid may need to be reduced or the opioid changed to a strong alternative. Different opioids have different side-effect profiles in different people. If a patient develops side-effects, switching to an alternative strong opioid may be helpful. Options include oxycodone, transdermal fentanyl, alfentanil, hydromorphone and occasionally methadone, any of which may produce a better balance of benefit against side-effects.

Fentanyl and alfentanil have no renally excreted active metabolites and may be particularly useful in patients with renal failure. It is possible to switch between opioids but great care must be taken when doing so to make sure the dose is correct and to avoid prescribing too much or too little opioid. Adjuvant analgesics An adjuvant analgesic is a drug that has a primary indication other than pain but which provides analgesia in some painful conditions and may enhance the effect of the primary analgesic. Commonly used adjuvant analgesics in the palliative care setting are shown in Box 34.15. Some adjuvant analgesics may enhance the side-effect profile of the primary analgesic, and dose reductions of opioids may be required when an adjuvant analgesic is added. At each step of the WHO analgesic ladder, an adjuvant 34.15 Adjuvant analgesics in cancer pain Drug Example Indications Side-effects* NSAIDs Diclofenac Bone metastases, soft tissue infiltration, liver pain, inflammatory pain Gastric irritation and bleeding, fluid retention, headache Caution in renal impairment Glucocorticoids Dexamethasone 8–16 mg per day, titrated to lowest dose that controls pain Raised intracranial pressure, nerve compression, soft tissue infiltration, liver pain Gastric irritation if used together with NSAID, fluid retention, proximal muscle myopathy, delirium, Cushingoid appearance, candidiasis, hyperglycaemia Anticonvulsants Evidence strongest for: Gabapentin Pregabalin Duloxetine Neuropathic pain of any aetiology Mild sedation, tremor, delirium Exacerbation of opioid-related side-effects Tricyclic antidepressants Amitriptyline Neuropathic pain of any aetiology Sedation, dizziness, delirium, dry mouth, constipation, urinary retention Avoid in cardiac disease Exacerbation of opioid-related side-effects NMDA receptor blockers Ketamine Severe neuropathic pain (only under specialist supervision) Delirium, anxiety, agitation, hypertension *In old age, all drugs can cause delirium. (NMDA = N-methyl-D-aspartate; NSAIDs = non-steroidal anti-inflammatory drugs)

drugs. Vomiting related to raised intracranial pressure is worse in the morning. Different receptors are activated, depending on the cause or causes of the nausea (Fig. 34.10). For example, dopamine receptors in the chemotactic trigger zone in the fourth ventricle are stimulated by metabolic and drug causes of nausea, whereas gastric irritation stimulates histamine receptors in the vomiting centre via the vagus nerve. Reversible causes, such as hypercalcaemia and constipation, should be treated appropriately. Drug-induced causes should be considered and the offending drugs stopped if possible. As different classes of antiemetic drug act at different receptors, antiemetic therapy should be based on a careful assessment of the probable causes and a rational decision to use a particular class of drug (Box 34.16). to use coping strategies and behavioural techniques. Other issues related to the specific experience of a cancer diagnosis and cancer treatment may be complex, and individual therapy in addition to group-based approaches can be helpful. Stimulation therapies Acupuncture and TENS are low-risk stimulation therapies that may be useful in palliative care for management of pain and nausea. Complementary and alternative therapies Palliative care patients often seek symptom relief from both complementary and alternative therapies. While the evidence base is poorly developed, individual patients can gain significant benefits from the complementary therapies outlined on page 1348. It is critically important that patients are encouraged to discuss any alternative medicines they are considering, given the potential interactions with other therapies. Breathlessness Breathlessness is one of the most common symptoms in palliative care and is distressing for both patients and carers. Patients with breathlessness should be fully assessed to determine whether there is a reversible cause, such as a pleural effusion, heart failure or bronchospasm; if so, this should be managed in the

normal way. If symptoms persist, additional measures may be necessary. There are many potential causes of dyspnoea in cancer patients and in other chronic diseases; apart from direct involvement of the lungs, muscle loss secondary to cachexia, anxiety and fear can all contribute. A cycle of panic and breathlessness, often associated with fear of dying, can be dominant. Exploration of precipitating factors is important and patient education about breathlessness and effective breathing has been shown to be effective. Non-pharmacological approaches that include using a hand-held fan, pacing, and following a tailored exercise programme can help. There is no evidence to suggest that oxygen therapy reduces the sensation of breathlessness in advanced cancer any better than cool airflow, and oxygen is indicated only if there is significant hypoxia. Opioids, through both their central and their peripheral action, can palliate breathlessness. Both oral and parenteral opioids are effective. A low dose should be used initially and titrated against symptoms, unless opioids are already being prescribed for pain, in which case the existing dose can be increased further. If anxiety is considered to be playing a significant role, a quick-acting benzodiazepine, such as lorazepam (used sublingually for rapid absorption), may also be useful. Cough Persistent unproductive cough can be helped by opioids, which have an antitussive effect. Troublesome respiratory secretions can be treated with hyoscine hydrobromide (400–600 µg every 4–8 hours), although dry mouth is a common adverse effect. As an alternative, glycopyrronium can be useful and is given by subcutaneous infusion (0.6–1.2 mg in 24 hours). Nausea and vomiting The presentation of nausea and vomiting differs depending on the underlying cause, of which there are many (p. 780). Large-volume vomiting with little nausea is common in intestinal obstruction, whereas constant nausea with little or no vomiting is often due to metabolic abnormalities or adverse effects of Fig. 34.10 Mechanisms of nausea. (ACh = acetylcholine; D2 = dopamine; 5-HT = 5-hydroxytryptamine, serotonin; H1 = histamine) Higher centres Vestibular input Vomiting centre H1, ACh, 5-HT Chemotactic trigger zone D2, 5-HT Vagal afferents Metabolic toxins Chemoreceptors Mechanoreceptors Retroperistalsis Gastric pyloric contraction Abdominal and thoracic wall contraction Peripheral circulation 34.16 Receptor site activity of antiemetic drugs Area Receptors Drugs Chemotactic trigger zone Dopamine2 5-HT Haloperidol Metoclopramide Vomiting centre Histamine1 Acetylcholine Cyclizine Levomepromazine Hyoscine Gut (gastric stasis) Metoclopramide Gut distension (vagal stimulation) Histamine1 Cyclizine Gut (chemoreceptors) 5-HT Levomepromazine (5-HT = 5-hydroxytryptamine, serotonin)

1354 • PAIN AND PALLIATIVE CARE Delirium and agitation Many patients become confused or agitated in the last days of life. It is important to identify and treat potentially reversible causes (p. 183), unless the patient is too close to death for this to be feasible. Early diagnosis and effective management of delirium are extremely important. As in other palliative situations, it may not be possible to identify and treat the underlying cause, and the focus of management should be to ensure that the patient is comfortable. It is important to distinguish between behavioural change due to pain and that due to delirium, as opioids will improve one and worsen the other. The management of delirium is detailed on page 209. It is important, even in the care of the actively dying patient, to treat delirium with antipsychotic medicines, such as haloperidol, rather than to regard it as distress or anxiety and use benzodiazepines only. Dehydration Deciding whether to give intravenous fluids can be difficult when a patient is very unwell and the prognosis is uncertain. A patient with a major stroke, who is unable to swallow but is expected to survive the event, will develop renal impairment and thirst if not given fluids and should be hydrated. On the other hand, when a patient has been deteriorating and is clearly dying, parenteral hydration needs very careful consideration and it is very important to manage this on an individual basis. Comfort and

avoidance of distress in the family are the primary aims. Where a patient and family are happy with meticulous oral hygiene and care to reduce the sensation of dryness in the mouth, this is usually more appropriate and effective at the end of life than parenteral hydration, which by itself will not necessarily improve the sensation of dryness. In some patients, parenteral hydration will simply exacerbate pooling of secretions, causing noisy and distressing breathing. Each decision should be individual and discussed with the patient's family. Death and dying Planning for dying There have been dramatic improvements in the medical treatment and care of patients with cancer and other illnesses over recent years but the inescapable fact remains that everyone will die at some time. Planning for death should be actively considered in patients with chronic diseases when the death is considered to be foreseeable or inevitable. Doctors rarely know exactly when a patient will die but are usually aware that an individual is about to die and that medical interventions are unlikely to extend life or improve its quality significantly. Most people wish their doctors to be honest about this situation to allow them time to think ahead, make plans and address practical issues. A few do not wish to discuss future deterioration or death; if this is felt to be the case, avoidance of discussion should be respected. For doctors, it is helpful to understand an individual's wishes and values about medical interventions at this time, as this can help guide decisions about interventions. It is important to distinguish between interventions that will not provide clinical benefit (a medical decision) and those that do not confer sufficient benefit to be worthwhile (a decision that can only be reached with a patient's involvement and consent). A common example of this would be decisions about not attempting cardiopulmonary resuscitation. The subcutaneous route is often required initially to overcome gastric stasis and poor absorption of oral medicines. Gastrointestinal obstruction Gastrointestinal obstruction is a frequent complication of intra-abdominal cancer. Patients may have multiple levels of obstruction and symptoms may vary greatly in nature and severity. Surgical mortality is high in patients with advanced disease and obstruction should normally be managed without surgery. The key to effective management is to address the presenting symptoms – colic, abdominal pain, nausea, vomiting, intestinal secretions – individually or in combination, using parenteral drugs that do not cause or worsen other symptoms. This can be problematic when a specific treatment worsens another symptom. Cyclizine improves nausea and colic responds well to anticholinergic agents, such as hyoscine butylbromide, but both slow gut motility. Nausea will improve with metoclopramide, although this is usually contraindicated in the presence of colic because of its prokinetic effect. There is some low-level evidence that glucocorticoids (dexamethasone 8 mg) can shorten the length of obstructive episodes. Somatostatin analogues, such as octreotide, will reduce intestinal secretions and therefore large-volume vomits. Occasionally, a nasogastric tube is required to reduce gaseous or fluid distension. Weight loss Patients with cancer lose weight for a variety of reasons, including reduced appetite or the effects of drug treatment, or as a consequence of low mood and anxiety. There is, however, a particularly challenging syndrome associated with weight loss, which is known as cancer cachexia. This results from an alteration of metabolism caused by a complex interaction of tumour-related factors and the body's response to these factors, resulting in muscle loss, along with anorexia. Treatment involves prescribing exercise to maintain muscle mass and strengthen muscles, ensuring that there is an adequate calorie intake and providing nutritional supplements. Anti-inflammatory medication to attenuate systemic inflammation is the subject of research and many patients self-medicate with fish oil. Glucocorticoids can temporarily boost appetite and general well-being but may cause false weight gain by promoting fluid retention. Their benefits need to be weighed against the risk of side-effects, and glucocorticoids should generally be used on a short-term basis only. Anxiety and depression Anxiety and depression are common in

palliative care but the diagnosis may be difficult, since the physical symptoms of depression are similar to those of advanced cancer. It is therefore important to realise that these symptoms are not inevitable in advanced cancer. Patients should still expect to look forward to things and to enjoy them, within the context of the situation. Simply asking the question ‘Do you think you are depressed?’ can be very useful in deciding with the patient whether antidepressants or psychological interventions may be of benefit (p. 1199). In this regard, psycho-oncology has been evolving rapidly and there is now good evidence for the role of ‘talk therapy’ in palliative care, along with other appropriate management of anxiety and depression. If antidepressants are required, citalopram and mirtazapine are good choices since they are generally well tolerated in patients with advanced disease.

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for their care. Trust in the whole team will come through a solid lead working with a team who are appropriately informed and in sympathy with the patient’s situation, each having a clear role. Families and other carers are often unprepared for the challenge of caring for a dying person. It can be an exhausting experience, both emotionally and physically, and without a critical number of carers battle fatigue can ensue, resulting in urgent admissions. With much discussion about advance directives, we should not lose sight of the reality of changing circumstances and wishes. Good anticipatory care means not just providing for new physical symptoms, but also planning for any time when care at home becomes no longer possible. Capacity and advance directives The wishes of the patient are paramount in Western societies, whereas in other cultures the views of the family are equally important. If a patient is unable to express their view because of communication or cognitive impairment, that person is said to lack ‘capacity’. In order to decide what the patient would have wished, as much information as possible should be gained about any previously expressed wishes, along with the views of relatives and other health professionals. An advance directive is a previously recorded, written document of a patient’s wishes (p. 1307). It should carry the same weight in decisionmaking as a patient’s expressed wishes at that time, but may In general, people wish for a dignified and peaceful death and most prefer to die at home. Families also are grateful for the chance to prepare themselves for the death of a relative, by timely and gentle discussion with the doctor or other health professionals. Early discussion and effective planning improve the chances that an individual’s wishes will be achieved. There are two important caveats: firstly, wishes can and do change as the terminal situation evolves, and secondly, planning in general can only be done over time as patients form a relationship with professionals and evolve an understanding of the situation in which they find themselves. Structures for assessment and planning around end-of-life care are for guidance only and the focus should evolve with the individual patient. Diagnosing dying When patients with cancer or other conditions become bedbound, semi-comatose, unable to take tablets and only able to take sips of water, with no reversible cause, they are likely to be dying and many will have died within 2 days. Doctors are sometimes poor at recognising this and should be alert to the views of other members of the multidisciplinary team. A clear decision that the patient is dying should be agreed and recorded. Management of dying Once the conclusion has been reached that a patient is going to die in days to a few weeks, there is a significant shift in management (Box 34.17). Symptom control, relief of distress and care for the family become the most important elements of care. Medication and investigation are justifiable only if they contribute to these ends. When patients can no longer drink because they are dying, intravenous fluids are usually not necessary and may

cause worsening of bronchial secretions; however, this is a decision that can be made only on an individual basis. Management should not be changed without discussion with the patient and/or family. Medicines should always be prescribed for the relief of symptoms. For example, morphine or diamorphine may be used to control pain, levomepromazine to control nausea, haloperidol to treat delirium, diazepam or midazolam to treat distress, and hyoscine hydrobromide to reduce respiratory secretions. Side-effects, such as drowsiness, may be acceptable if the principal aim of relieving distress is achieved. It is important to discuss and agree the aims of care with the patient's family. Poor communication with families at this time is one of the most common reasons for family distress afterwards and for formal complaints. Ethical considerations The overwhelming force in caring for any patient must be to listen to that patient and family and take their wishes on board. Patients know when health-care professionals are just receiving the information, as opposed to receiving and understanding the information in the context of the patient, their illness and needs, their carers and the socioeconomic context. It is impossible to provide holistic care for a patient without this comprehension. Every patient is unique and it is important to avoid slipping into a tick-box mentality in addressing items that should be covered in patients with advanced, incurable disease. While the key to successful palliative care is effective interdisciplinary working, every patient needs to know who has overall responsibility 34.17 How to manage a patient who is dying Patient and family awareness • Assess patient's and family's awareness of the situation • Ensure family understands plan of care Medical interventions • Stop non-essential medications that do not contribute to symptom control • Stop inappropriate investigations and interventions, including routine observations Resuscitation • Complete Do Not Attempt Cardiopulmonary Resuscitation (DNACPR) form • Deactivate implantable defibrillator Symptom control • Ensure availability of parenteral medication for symptom relief Support for family • Make sure you have contact details for family, that you know when they want to be contacted and that they are aware of facilities available to them Religious and spiritual needs • Make sure any particular wishes are identified and followed Ongoing assessment • Family's awareness of condition • Management of symptoms • Need for parenteral hydration Care after death • Make sure family know what they have to do • Notify other appropriate health professionals

1356 • PAIN AND PALLIATIVE CARE Further information Websites breathworks-mindfulness.org.uk An online resource to support learning the use of mindfulness to deal with pain, illness or stress. cuh.org.uk/breathlessness Information and resources from Cambridge University Hospital on managing breathlessness. hospiceuk.org A resource from UK hospices. mdanderson.org Brief Pain Inventory (Short Form) questionnaire. nhmrc.gov.au Australia and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute pain management: scientific evidence, 3rd edn; 2010. npcrc.org Short-form McGill Pain questionnaire. paintoolkit.org Pain toolkit self-help resource for managing pain. palliativecareguidelines.scot.nhs.uk Regularly reviewed, evidence-based clinical guidelines. palliativedrugs.com Practical information about drugs used in palliative care. sign.ac.uk SIGN guideline 136 – Management of chronic pain. Journal articles Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015; 14:162–173. A comprehensive, high-quality review of the current evidence for the pharmacological management of neuropathic pain. not be sufficiently specific to be used in a particular clinical situation. The legal framework for decision-making varies in different countries. Euthanasia In the UK and Europe, between 3% and 6% of dying patients will ask a doctor to end their life. Many of these requests are transient; some are associated with poor control of physical symptoms or a depressive illness. All expressions of a wish to die are an opportunity to help the patient discuss and address unresolved issues and problems. Reversible

causes, such as pain or depression, should be treated. Sometimes, patients may choose to discontinue life-prolonging treatments, such as diuretics or anticoagulation, following discussion and the provision of adequate alternative symptom control. However, there remain a small number of patients who have a sustained, competent wish to end their lives, despite good control of physical symptoms. Euthanasia is now permitted or legal under certain circumstances in some countries but remains illegal in many others; public, ethical and legal debate over this issue is likely to continue and is often influenced by many complex non-palliative care issues. The European Association for Palliative Care does not see euthanasia or physician-assisted suicide as part of the role of palliative care physicians.

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