WeMeReC
Welsh Medicines Resource Centre
Canolfan Adnoddau Moddion Cymru

Bulletin
"Independent prescribing information for NHS Wales"

February 2017

Palliative care – pain and symptom control

Palliative care is defined by the World Health Organisation (WHO) as, "An approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual."[1] While it is recognised that the provision of palliative care extends beyond pharmacological treatment, this bulletin primarily concentrates on the use of medicines for the control of pain and other symptoms in adult patients.

Identifying patients

In Wales, the Identify, Prepare, Ask, Document, Share (wIPADS) approach is suggested to help to identify those patients who might benefit from supportive or palliative care, and advance care planning (ACP).[2] It is perhaps easier to identify patients as suitable for ACP or palliative care when they have a clear diagnosis of a progressive, life-limiting illness, specifically when this disease is metastatic cancer. However, other triggers for healthcare professionals to initiate ACP are also suggested by the *Identify* step of wIPADS:[2]

- a diagnosis, or shift of treatment focus, in a 'terminal illness' e.g. metastatic cancer, severe chronic obstructive pulmonary disease (COPD).
- multiple hospital admissions.
- "Would not be surprised if patient died in next 6-12 months."

It may be possible to identify such patients in primary care at general practice palliative care meetings. A more detailed identification tool and further information on wIPADS is available from the *Advance Care Planning* section of http://wales.pallcare.info.

Pain management

It has been estimated that up to two thirds of patients with metastatic disease, and a similar proportion of patients with other progressive conditions, experience pain requiring a strong opioid.[3] Unrelieved pain can be psychologically devastating and the goal of management is that no patient lives or dies in pain.

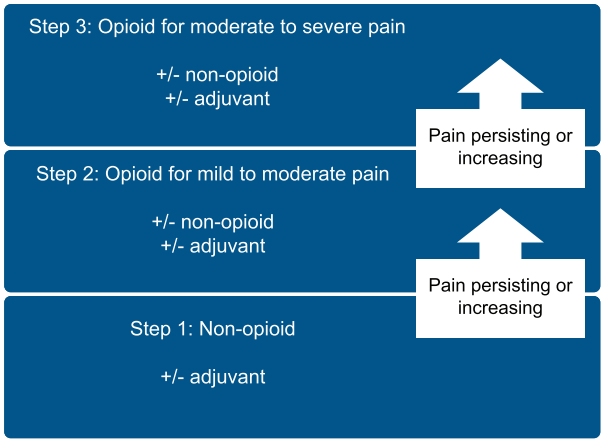
The concept of total pain, first described 50 years ago, is recognised as being central to the philosophy of palliative care. It is known that physical, psychological, social, emotional, and spiritual components all contribute to a patient's personal experience of pain and it is vital that each component is separately evaluated and addressed to facilitate appropriate management. Here we concentrate on the pharmacological management of physical pain, recognising that this is just one facet of pain management.

A regular evaluation of the cause/s of pain should be undertaken and all appropriate factors should be addressed. The PQRST tool (Table 1) may be useful to assess and determine the cause/s of pain, e.g. nociceptive, neuropathic, etc., and therefore help to guide treatment.[4] For people with cognitive disabilities or communication difficulties, other tools such as the Abbey Pain Scale (available via www.wales.nhs.uk) may be more appropriate.

Table 1. The PQRST pain evaluation tool[4]
Provocation/Palliation – provoking or relieving factors What makes it better/worse? Does analgesia help?
Quality – establish type of pain Sharp, dull, stabbing, throbbing, deep-seated, etc.
Region/Radiation – location and extent Where exactly is the pain? Does it move/radiate? If so: where, when?
Severity – pain scale to establish severity of pain For example, on a scale of 0-10 where zero is no pain and 10 the worst imaginable pain.
Timing – establish precise timings Onset? Constant or intermittent? Morning, night, etc.?

Regular, 'by the clock' analgesia is the foundation of appropriate management. This may be augmented with various regular or acute adjuncts and the provision of rescue analgesia for 'breakthrough' and/or 'incident' pain. When used correctly, the WHO analgesic ladder controls cancer pain in 80-90% of patients.[3] Medication should be initiated from the step appropriate for the pain. Increases in analgesic potency should be in accordance with the ladder; if pain severity increases, a step up should not be delayed by the use of different medication from the same step.[5]

Figure 1. The WHO ladder for cancer pain[6]



Step 1 The regular use of paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) is often effective. NSAIDs may also be useful as an adjunct at any step, particularly if an inflammatory cause is suspected, e.g. in bone or pleuritic pain.

Step 2 Where Step 1 analgesia has failed or pain has progressed, **codeine** may be added to the previous analgesia at an adequate dose, e.g. 30-60mg four times daily. Single-ingredient preparations allow flexibility of dosing, but combination products may be more convenient for some patients. **Dihydrocodeine** is a much less frequently used alternative. Its use is not encouraged, but may be appropriate in some circumstances. **Tramadol** is usually not appropriate for palliative use and should not be regarded as more advantageous than codeine unless there is a compelling clinical reason. Extra-opioid effects, e.g. lowered seizure threshold, etc., should be carefully considered, both before initiation and during therapy.

There has been some recent debate suggesting the complete omission of Step 2 of the WHO analgesic ladder in palliative care, in order to expedite appropriate pain management. This approach is not universally accepted, although a pragmatic clinical approach may well take this path in certain circumstances. Careful patient counselling is required whenever a Step 3 opioid is initiated.

Step 3 Where possible, when offering treatment with a strong opioid, it is recommended that patients are asked about concerns over addiction, tolerance, adverse effects, and fear that this signals the final stage of life. Any issues should then be addressed.[3] Experience in palliative care suggests that dependence and addiction are rarely a problem.

Adverse effects of opioids should be anticipated. Whereas nausea and sedation will likely diminish over time, constipation will always require active management (see Pages 4-5).[5]

Respiratory rate is a good indicator of toxicity; other signs include twitching and pinpoint pupils.[5] Specialist advice should be sought before prescribing strong opioids for people with moderate-severe hepatic or renal impairment.[3] Doses given below are for people without such impairment/s.

Oral **morphine** is the first-line strong opioid; a clear reason should be documented if any other strong opioid is to be used first.[5] Patient preference should guide the decision on whether to use an immediate- or sustained-release preparation initially,[3] although the classical approach is to begin with immediate-release, determine the 24-hour dosage when the pain is stable, and then switch to sustained-release. Immediate-release morphine should be available for breakthrough pain whichever approach is taken.[3]

During the titration phase, a daily dose of 20-30mg of morphine is usually suitable for opioid-naive patients, or 40-60mg for those switching from a regular weak opioid.[3,7] A suitable rescue dose is typically one-tenth to one-sixth of the total daily dose.[7] The total daily dose should be adjusted until there is a good balance between analgesic efficacy and adverse effects. If this cannot be achieved within a few dose adjustments, then specialist advice is recommended.[3]

There is no evidence that any other strong opioid offers superiority over morphine in terms of efficacy or adverse effect profile in the majority of patients.[8] However, in certain circumstances, e.g. where adverse effects of morphine are intolerable, etc., other opioids should be considered, based on specific clinical requirements.

Oxycodone may be an option if a patient has effective pain relief with morphine but cannot tolerate its adverse effects. Elderly patients and those with poor renal function may be at increased risk of such effects, but this is by no means certain to be the case.

Diamorphine administered subcutaneously via a syringe driver is considered to be first-line treatment when oral opioid medication is unsuitable, especially when pain is changing or unstable.[3] **Morphine** delivered by the same route is an alternative, although it is less soluble in water and so comparatively larger volumes are required.[7] **Oxycodone** may also be an option via syringe driver, as above.

Fentanyl or **buprenorphine** administered via transdermal patch should only be used in stable pain and where there is a good clinical reason to do so, e.g. in dysphagic patients (such as those with head and neck cancers or who are post-stroke) or those with intractable vomiting.[3]

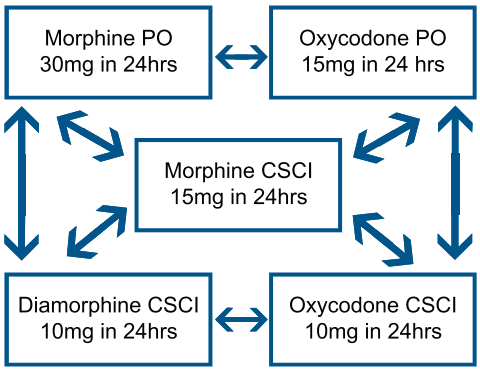
Transdermal patches have a slow onset of action and true effectiveness can only be evaluated when a patch has been worn for 24 hours (or 72 hours in the case of BuTrans).[7] Dose titration can therefore be time-consuming. If a patient has been taking oral morphine, the last 12-hourly dose should be given at the time of patch application and suitable rescue medication should remain available at all times.[9] It should be further noted that, due to differing receptor effects, both fentanyl and buprenorphine have the potential to precipitate morphine withdrawal upon their initiation. Due to their long duration of action, patients should be monitored for any adverse effects for up to 30 hours after the last patch is removed.[7] Fever or external heat sources may increase drug absorption from patches.[7] Appropriate patch disposal should be ensured to prevent accidental exposure, particularly in children.[10]

Various formulations of **fentanyl** are available for use as a rescue therapy. In general, due to their short duration of action, these products are considered less useful than immediate-release morphine for breakthrough pain and they are not first-line therapies.[3] They may sometimes be useful for 'incident pain', e.g. where a patient is to undergo a procedure which may be painful for a very short period, e.g. a dressing change. Products are not interchangeable and patients switched between formulations will require re-titration.[7]

Dose equivalences

Dose equivalences are not straightforward calculations due to intra- and inter-patient variability and incomplete cross-tolerance.[7,9] Doses should be confirmed before use and clinical judgement must be exercised. Some sources suggest reducing equivalent doses by 25-50% upon conversion to take account of incomplete cross-tolerance, especially at higher doses.[9] However, this must be balanced against providing adequate pain relief and the patient should be monitored carefully. A very useful online dose calculator/converter is available at http://book.pallcare.info.[9]

Figure 2. Approximate opioid equivalent doses



PO = oral dose in **24 hours**
CSCI = continuous subcutaneous infusion in **24 hours**

Table 2. **Approximate** oral morphine to transdermal fentanyl equivalence[7]	
Oral morphine 30mg **in 24 hours**	Fentanyl patch 12micrograms **per hour**
Oral morphine 60mg **in 24 hours**	Fentanyl patch 25micrograms **per hour**
Oral morphine 120mg **in 24 hours**	Fentanyl patch 50micrograms **per hour**
Oral morphine 180mg **in 24 hours**	Fentanyl patch 75micrograms **per hour**
Oral morphine 240mg **in 24 hours**	Fentanyl patch 100micrograms **per hour**

Buprenorphine patches allow lower equivalent doses of morphine to be administered transdermally and so may be advantageous in some situations.

Table 3. **Approximate** oral morphine to transdermal buprenorphine equivalence[7]	
Oral morphine 12mg **in 24 hours**	BuTrans **7-day** patch 5micrograms **per hour**
Oral morphine 24mg **in 24 hours**	BuTrans **7-day** patch 10micrograms **per hour**
Oral morphine 48mg **in 24 hours**	BuTrans **7-day** patch 20micrograms **per hour**
Oral morphine 84mg **in 24 hours**	Transtec **4-day** patch 35micrograms **per hour**
Oral morphine 126mg **in 24 hours**	Transtec **4-day** patch 52.5micrograms **per hour**
Oral morphine 168mg **in 24 hours**	Transtec **4-day** patch 70micrograms **per hour**

Adjunctive treatment for pain

Some pains are less responsive to opioids than others and different approaches are required. In addition, many patients will have mixed aetiologies of pain. An adjunct may be added at any stage of the analgesic ladder to treat a specific pain. They may have an opioid-sparing effect and, where adjuncts are used, opioid doses should be kept under review.

Bone pain: An **NSAID** or a **corticosteroid** is often of use in bone pain.[7] Referral for **radiotherapy** may be one of the most effective interventions for bone metastases. **Bisphosphonate** treatment can also be useful in chronic or acute bone pain and may help to reduce long-term skeletal complications.[5] **Denosumab** is an alternative in certain circumstances.[11] Oncological management with newer agents is a developing field; advice can be obtained from an appropriate specialist.

Neuropathic pain: A tricyclic antidepressant is often recommended as the first-line adjunct. **Amitriptyline** may be given at a dose of 10mg at night, increasing to 75mg to achieve pain control.[7] Higher doses may be used under specialist supervision. The patient should be monitored for antimuscarinic adverse effects. **Duloxetine** may be an alternative for some people.[12]

Certain antiepileptic drugs may be added or substituted if pain persists. **Gabapentin** given at a dose of 300mg on day 1, 300mg bd on day 2, 300mg tds on day 3, (or initiated at 300mg tds) and titrated in steps of 300mg every 2-3 days to a maximum of 3.6g daily is recommended.[7] However, many practitioners titrate more slowly and to a lower maximum dose.[5] Dose reductions are required in renal impairment.[7] An alternative is **pregabalin**, which may be useful in patients who have difficulty swallowing since it has a smaller unit size, but it is many times more expensive.[12] Other antiepileptic drugs, such as **lamotrigine**, may sometimes be used in specialist care.[5]

Management of other symptoms

In addition to pain control, the control of other symptoms is essential to a patient's quality of life. Anticipating issues, establishing causation, and addressing reversible causes are vital. It is useful to consider whether a symptom is the result of:

- the cancer itself, e.g. increasing tumour mass
- the treatment, e.g. opioid-induced constipation
- something else, e.g. an infection.

First-line, pharmacological approaches to common issues are discussed here. If these fail it is advisable to contact your local palliative care team. Non-pharmacological approaches should also be considered alongside, or before, a pharmacological approach.

Gastrointestinal symptoms

Mouth care: Routine mouthcare, including gentle teeth or denture brushing is essential. **Dry mouth** is common, and is often caused by the antimuscarinic effects of medicines or a combination of medicines (including strong opioids), hypercalcaemia, dehydration, or diuretics. Fluid intake should be increased or the offending medicine stopped where possible. If this is not feasible, sucking on ice chips, preferably sugar-free ice lollies or sweets, or fruit segments may help. Artificial saliva products are also available. **Sore mouth**, often caused by dryness, ill-fitting dentures, ulceration, or infection, may be treated with a mouthwash, such as benzydamine hydrochloride or even systemic analgesia if needed. Fungal infections should be treated appropriately with nystatin, miconazole, or systemically with fluconazole if required.[5]

Nausea and vomiting: These symptoms are estimated to be present in 40% of chemotherapy and radiotherapy patients (despite prophylactic regimens), between 30% and 60% of cancer patients no longer receiving cancer treatment, up to 43% of patients with chronic kidney disease, and 48% of patients with end stage heart failure.[13]

Causes such as hypercalcaemia, infection, gastritis, constipation (see below), raised intracranial pressure, intestinal obstruction, and uraemia should be specifically managed. If a specific medicine or treatment is suspected, it may sometimes be feasible to stop it. The nausea and vomiting associated with strong opioids is often self-limiting, but some patients will continue to be affected and will require continued anti-emetic treatment (often haloperidol) or, in some cases, a change in analgesic therapy.

There may be more than one cause of nausea and vomiting, but it is helpful to base the choice of anti-emetic on the likely mechanism where this can be established (see Table 4). Combinations of anti-emetics may be required and sometimes subcutaneous administration will be useful until vomiting has been brought under control.

Table 4. Causes of nausea/vomiting and choice of anti-emetic[7]

Direct or central – effects on the gastrointestinal tract or vomiting centre (VC)	
Cyclizine Acts mainly on the VC. Useful with haloperidol in raised intracranial pressure or intestinal obstruction.	50mg tds
Chemical – via the chemoreceptor trigger zone (CTZ) – predominantly nausea often with little vomiting	
Haloperidol Acts mainly on the CTZ. Useful for most chemical causes, e.g. opioids or uraemia.	1.5mg nocte or bd (max. 5-10mg/24h)
Mechanical – delayed gastric emptying – predominantly vomiting	
Metoclopramide Acts mainly as a prokinetic. Some central activity at higher doses.	10mg tds*
Domperidone Acts almost entirely as a prokinetic.	10mg tds*

*increased doses may be used in specialist care[5]

Levomepromazine is a 'broad spectrum' anti-emetic and may be useful if first-line therapy fails. However, postural hypotension and sedation may limit its use. Potential drug-drug interactions with other therapies and the adverse effects of the anti-emetics themselves should also be borne in mind, e.g. antimuscarinic effects with cyclizine, neurological problems with metoclopramide, and cardiac issues with domperidone.[7]

Constipation: Affects the vast majority of patients taking opioids and so should be anticipated and actively managed with regular laxatives.[5,7] Other causes include dehydration, antimuscarinic medicines, hypercalcaemia, intestinal obstruction, and spinal cord compression. If present, these causes should be individually addressed where possible.

Therapy should usually include a stimulant (e.g. senna, bisacodyl, dantron, docusate sodium) **and** a faecal softener or osmotic laxative (e.g. magnesium hydroxide or lactulose).[5] Macrogols may be a useful alternative, but bulk-forming laxatives are rarely suitable in palliative care. Naloxegol is a possible alternative where laxatives have produced an inadequate response in opioid-induced constipation.[14] Methylnaltrexone is not recommended.[15]

Intestinal obstruction: Often characterised by large-volume, foul-smelling vomits, abdominal discomfort, and colic. Chemotherapy may help sensitive tumours (e.g. in ovarian cancer) and surgery or stenting may help with single-site obstruction. In advanced cancer, multiple sites are often affected and medical management is required, often with a combination of anti-emetics. An antisecretory agent, such as octreotide may decrease the volume of vomit.[16] In such cases, specialist advice is appropriate.

Respiratory symptoms

Breathlessness/dyspnoea: This is common in the last weeks of life and can be disturbing for patients and their carers. Reversible causes such as infection, bronchospasm, pleural effusion, pulmonary emboli, large airway obstruction, or heart failure, should be considered and treated if appropriate. Oxygen is not usually helpful unless a patient is hypoxic; a trial use of a fan is advised.[5] In COPD, target saturations should be low to prevent hypercapnic respiratory failure.[5]

Table 5. Treatment for breathlessness/dyspnoea

General	
Morphine	2.5-5mg 4 hourly, carefully titrated as for pain[5,7]
With associated anxiety	
Diazepam	5-10mg daily[7] (or 2-5mg bd)[5]
Lorazepam	0.5-1mg 6-8 hourly sublingually[5]
In terminal phase	
Midazolam	5-15mg in 24 hours CSCI[5]
Bronchospasm/obstruction	
Dexamethasone	4-8mg daily (one week trial, stop if no improvement)[5,7]

Cough: Can be associated with breathlessness, haemoptysis, pain, incontinence, insomnia, and social isolation. Reversible precipitants, such as infection, obstruction/asthma, angiotensin-converting enzyme inhibitors, smoking, etc., should be assessed and addressed where possible. Depending on location, some tumours may be responsive to radiotherapy. Symptomatic treatment includes anti-tussives (e.g. simple linctus) and suppressant opioids (e.g. codeine, pholcodine, morphine). Patients with COPD may respond to a mucolytic such as carbocysteine.

Central nervous system

Depression and anxiety: May go undiagnosed and lack of effective treatment can affect quality of life and exacerbate pain. In depression, response to therapy, including psychological support, can be very good. Some patients benefit from an appropriate antidepressant. In the case of anxiety, talking therapy is often effective; benzodiazepines may be used in the terminal phase but, as anxiety may be a presenting symptom of depression, this should also be considered.

Delirium: Has many causes, including dementia, hypercalcaemia, urinary retention, infection, dehydration, and antimuscarinic, sedative, and opioid medication. Offending medication should be stopped or changed if possible. If other causes are eliminated but confusion continues and the patient is not distressed, treatment may be unnecessary. If other, possibly treatable causes, e.g. transient ischaemic attacks, etc. are suspected, advice regarding therapy may be sought from the palliative care team.

Other symptoms

Hypercalcaemia: Can be responsible for a wide range of other symptoms. Patients can appear seriously unwell, but the problem is often reversible (especially at first presentation) and should be actively investigated. Significant symptoms often only appear at levels above 3mmol/l; levels above 4mmol/l will cause death in a few days if left untreated.[5] Rehydration and intravenous bisphosphonates are usually effective.

Raised intracranial pressure (ICP): Symptoms may include headache, vomiting, confusion, blurred vision, and focal neurological signs. Dexamethasone (16mg daily for 4-5 days, reduced to 4-6mg daily thereafter – give before 6pm to reduce the risk of insomnia, monitor blood glucose) can be effective.[7] New presentations of raised ICP should be referred.

Spinal cord compression: If suspected, oral dexamethasone 16mg should be given immediately and the patient should be referred without delay.[5]

Anticipatory prescribing

Palliative Care Emergency Medicine Packs or **'Just in Case' (JIC)** boxes exist to support home care of patients by improving access to palliative medicines, particularly out of hours. JIC medication can be prescribed by a GP on a WP10 form and dispensed at a participating community pharmacy (check for local availability) for use when deterioration in symptoms requires it. A standard **full set** of medication should be prescribed as shown in Table 6, including controlled drug (CD) requirements. See also Table 7 for doses and indications in the last days of life.

Table 6. Prescribing for a JIC box[17]
Diamorphine 10mg x 2 (two) amps 10mg as directed for pain
Diamorphine 30mg x 2 (two) amps 30mg as directed for pain
Midazolam 10mg/2ml x 4 (four) amps 10mg as directed
Cyclizine 50mg/ml x 3 amps Use as directed
Hyoscine hydrobromide 400micrograms/ml x 3 amps Use as directed
Water for injection 10ml x 2 amps Use as directed

The JIC box is not intended for immediate use and patient education and understanding on this point is essential. Verbal consent should be obtained from the family and carers. Documentation for notification, supply, and administration should be completed. Further information and guidance is available from the *Anticipatory Prescribing* section of http://wales.pallcare.info.[17] Several health boards also have their own repositories of information. Where patients are already taking high doses of oral morphine, if they are taking oxycodone, or if the circumstances of deterioration can be foreseen, a more individualised approach (sometimes known as **'Targeted Anticipatory Prescribing'**) will be required.[17]

Care in the last days of life

It is often difficult to be certain that a person is entering the last days of life. The National Institute for Health and Care Excellence (NICE) recommend reviewing any reported investigations and assessing for:[16]

- signs – agitation, Cheyne-Stokes breathing, decreasing consciousness, mottled skin, noisy respiratory secretions, weight loss.
- symptoms – increased fatigue, loss of appetite.
- function – changes in communication, decreased mobility or functional status, social withdrawal.

In Wales, the Care Decisions for the Last Days of Life toolkit emphasises the principles of good symptom control, good communication with patients and those close to them, and holistic and individualised care. It is recommended that wherever possible, medical and nursing professionals carry out a joint clinical assessment and that plans are carefully documented.[18] Resources are available from the *Last Days of Life* section of http://wales.pallcare.info.

Some recommendations in this bulletin are for off-label doses and/or routes. Summaries of Product Characteristics (SPCs) should be consulted for full prescribing information.

The **subcutaneous** doses and indications for commonly-used 'as required' or 'prn' medicines used at the end of life are listed in Table 7.[18] Conversion equivalences from oral to sub-cutaneous opioids can be found in Figure 2. To calculate the subcutaneous prn opioid dose, divide the 24 hour subcutaneous dose by 6; the answer may need to be rounded up or down.[18]

Table 7. Subcutaneous 'as required' medicines[18]	
Pain	
Diamorphine	Dose tailored to patient, 2 to 4 hourly
Morphine	Dose tailored to patient, 2 to 4 hourly
Nausea/vomiting	
Cyclizine	50mg 4 hourly (max. 150mg/24h)
Haloperidol	1.25-1.5mg 4 hourly
Anxiety/distress	
Midazolam	2.5mg or 5mg 2 hourly
Respiratory secretions	
Hyoscine hydrobromide	400micrograms 4 hourly (max. 2.4mg/24h)
Glycopyrronium	200micrograms 4 hourly (max. 1.2mg/24h)

'Do not attempt cardio-pulmonary resuscitation' (DNACPR) decisions

Although CPR may, in theory, be attempted on any person following a cardiac arrest, the clinical outcome depends on the clinical factors leading to the arrest. Inappropriate CPR can lead to distress and suffering for patients, their families, and carers. A decision not to attempt CPR should be based on a properly informed discussion with patients and those close to them.[19]

A trigger for a CPR discussion may be where the harms of CPR will clearly exceed the benefit or if the clinician envisages a possible cardiac arrest as a consequence of the underlying condition, e.g. in the urgent acute setting, following the rapid irreversible deterioration of a known condition, or, in less acute situations, a gradual decline in well-being where the death might be regarded as clinically inevitable (a natural, anticipated, and accepted death – NAAD).[19]

A senior responsible clinician, usually a consultant or a general practitioner, must be available in all settings – documentation and communication with the patient, carers, and other members of the healthcare team needs to be meticulous. A DNACPR decision review should take place at the request of the patient or if the patient's overall condition significantly improves.[19] The full policy, information for patients and carers, and other appropriate documentation is available from the *DNACPR* section of http://wales.pallcare.info.

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