

In Practice

Managing orthopaedic pain in horses

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Introduction

Orthopaedic pain is a broad term applied to pathology of the musculoskeletal system, potentially involving bones, joints, tendons, ligaments and muscles and consequently incorporating both soft and hard tissues. When thinking in terms of appropriate therapeutics, it may therefore be more useful to define it as deep somatic pain to distinguish it from superficial (cutaneous) somatic pain and visceral pain.

Musculoskeletal pain may result from trauma (including planned surgical intervention), overuse, inflammation, infection, neoplasia, osteolysis, ischaemia or neuronal damage. Common equine orthopaedic conditions such as degenerative joint disease, navicular syndrome and laminitis often present several of these aspects in combination and can be challenging to manage. Difficulty can be compounded by occurrence of acute-on-chronic flare-ups (see Box 1 for some definitions associated with pain).

The nature, severity and types of pain all must be taken into consideration when deciding how to provide effective analgesia.

Pain recognition

One of the biggest challenges in veterinary medicine is the recognition and quantification of pain. Assessment of pain in non-verbal species (and non-verbal humans) is difficult and subjective, typically relying on a combination of physiological variables, behaviour assessment and a degree of anthropomorphism. Several attempts have been made to devise pain scales for use in horses to identify the site and type of pain, but as yet none of these has been fully validated. This is further complicated by the fact that horses as a species tend not to be overtly demonstrative of pain unless

1
2
3 it is moderate to severe, show considerable variation in the way they respond and alter their
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5 behaviour in the presence of an observer. Different assessors may therefore attribute very different
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7 levels of pain to the same animal, leading to very different assessments of the requirement for
8
9 analgesia. In the current context, lameness scores are crude but clinically useful and widely
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11 employed. Manifestation of musculoskeletal pain may be obvious in the case of a single limb
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13 lameness, less so in mild multiple limb lameness, post surgically, or in cases of axial rather than
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15 appendicular pathology.
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Box 1.**Types of Pain**

Acute pain - Acute pain is the normal physiological response to application of a noxious stimulus. It is designed to be protective, being linked to the withdrawal reflex, preventing further tissue damage and triggering behavioural changes intended to maximise healing. This type of pain is typically of short duration, persisting only as long as the original insult. This is the type of pain associated with the early stages of tissue injury or surgery and is relatively easy to treat.

Chronic pain – this is pain that persists beyond the time frame expected for the relevant condition, a period of three to six months is often quoted. Thus may be due to acute injury or disease that is not resolving, ongoing degenerative conditions such as arthritis, or failure to manage acute pain adequately in the early stages of treatment. Achieving satisfactory analgesia can be extremely difficult in chronic pain states as the nervous system undergoes maladaptive changes – a process called neuroplasticity. This can result in sensitisation of the nervous system, when normally innocuous sensory input becomes perceived as painful (termed allodynia) or an exaggerated response to normally painful stimuli (termed hyperalgesia). Sensitisation may occur in both peripheral and central components of the nervous system and involves increased reactivity of peripheral nociceptors and central pain neurons, recruitment of additional nociceptors to generate pain signals and upregulation of pain receptor expression, so reinforcing the pain transmission pathways. In cases where chronic pain develops, pain ceases to become simply an indicator of a disease process and becomes part of the disease process itself. The longer pain is left untreated or inadequately controlled the more difficult it becomes to obtain a satisfactory outcome.

Neuropathic pain – this is pain caused by direct peripheral or central nerve injury resulting in hyperalgesia, allodynia and chronic, spontaneous ectopic generation of pain signals in the absence of any external stimuli.

Strategic Analgesia

A good analgesic plan will consist of systemically administered drugs, if possible in combination with local or regional analgesic techniques. Drugs chosen should ideally be those licensed for analgesia in the horse by the prescribed route, however licensed drugs administered by an unlicensed route, or unlicensed drugs may on occasion be indicated and appropriate. The key is in understanding the types of pain that may be present, the mode of action of the drugs that are available and how these drugs may be employed to maximise their effect on the case in question. In this way a multi-modal therapeutic plan can be formulated, incorporating the most appropriate drugs, designed to target as many aspects of the pain pathway as accurately as possible.

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3 **Systemic administration** of analgesic agents in the short term is typically by the intravenous (IV) or
4
5 intramuscular (IM) route, with oral medication often being relied on for more protracted courses of
6
7 treatment. Whilst a combination of these routes will probably prove adequate in the majority of
8
9 cases, other methods of drug delivery may allow for more effective provision of analgesia in specific
10
11 cases.

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13
14 The **oral-transmucosal** (OTM) absorption of some drugs can result in rapid uptake and high
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16 bioavailability as it avoids first pass metabolism which enterally absorbed drugs administered per os
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18 (PO) are subject to. Although potentially very effective, drugs administered this way may be
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20 swallowed or spat out, resulting in imprecise dosing, restricting this method to either highly
21
22 concentrated formulations or highly potent drugs, where a small total volume can be given.
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24 Although several drugs can be effectively administered this way, only the alpha 2 agonist detomidine
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26 has a formulation licenced specifically for this route.
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30 **Transdermal** drug delivery systems have been developed for a number of classes of drugs in the
31
32 human market and include patches, creams and gels for external application designed to have either
33
34 systemic or local effects. Transdermal drug absorption avoids first pass metabolism and gives the
35
36 potential for prolonged drug administration with minimal patient handling. However drug uptake is
37
38 highly dependent on sustained contact with the skin and that the area of application is healthy and
39
40 has a good blood supply. Several human preparations have been evaluated in veterinary species and
41
42 a specific veterinary formulation of fentanyl (licenced for use in dogs) is now available.
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46 **Epidural** drug administration (Fig 1) provides the opportunity for a more targeted effect and is
47
48 becoming more commonly employed. Use of local anaesthetics, alpha 2 agonists, opioids, ketamine
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50 and tramadol has been reported in the horse by this route. Depending on the characteristics of the
51
52 drug, there will be varying systemic uptake, and onset and duration of effect may differ significantly
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54 from those familiar from conventional systemic administration, which can be advantageous. For
55
56 prolonged analgesia, epidural catheters can be placed which facilitate provision of extended
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3 targeted pain management (Fig 2). Commercial kits (Fig 3) for this procedure are available (B Braun
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5 Medical Ltd, Yorkshire, UK; Smiths Medical, Kent, UK) and have been used successfully in several
6
7 cases at the author's hospital. These catheters require very careful management, with maintenance
8
9 of patency and sterility being the main problems, however with proper management it is possible to
10
11 maintain these in situ for up to 10 days in clinical cases.
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13
14 **Diffusion (soaker) catheters** offer the potential for prolonged, precise administration of local
15
16 anaesthetic agents. Their potential has yet to be fully realised and they are discussed in more detail
17
18 below with local anaesthetic drugs.
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22 With the high prevalence of developmental, degenerative and traumatic disease affecting the joints
23
24 of horses, as well as the frequency of diagnostic and therapeutic surgical procedures involving joints
25
26 and other synovial structures, **intra-synovial** administration of analgesic agents is an attractive and
27
28 effective method of achieving targeted pain relief. Administration of a number of drugs by this route
29
30 has been described, including morphine, corticosteroids and local anaesthetic agents.
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33 34 35 36 **Non-Steroidal Anti-inflammatory Drugs (NSAIDs)**

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39 There are several non-steroidal anti-inflammatory drugs licenced for use in horses in the UK and
40
41 these often form the first line and mainstay of analgesia provision. Action is by inhibition of cyclo-
42
43 oxygenase enzymes both peripherally and centrally, thereby interrupting the arachidonic acid
44
45 cascade that results in production of prostacyclin, prostaglandins and thromboxanes. These
46
47 substances are potent inflammatory mediators, which result in sensitisation and recruitment of
48
49 peripheral nociceptors and transmission of central pain pathways. Many disease processes and
50
51 certainly surgical interventions will induce an inflammatory response, so incorporating an anti-
52
53 inflammatory drug is eminently appropriate.
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3 Many are available for administration by IV injection and as powders and/or pastes for oral
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5 administration, making them convenient for both acute and chronic pain management, although
6
7 palatability may be problematic with some of the powdered preparations designed to be mixed with
8
9 food. Choice largely comes down to familiarity, availability and cost. Anecdotally, some horses will
10
11 respond better to one than another so it may be worth trying an alternative if response to one is
12
13 unsatisfactory. Data sheets tend to advise leaving 24 hours between dosing if changing to an
14
15 alternative to avoid inadvertent overdose. The potential for toxicity also need to be considered in
16
17 the context of long term treatment, particularly as this may be continued by the owner of the horse
18
19 for extended periods, outside the direct control of the veterinary surgeon. Doses should be carefully
20
21 calculated and dosing regimes clearly stipulated. Toxicity may manifest as blood dyscrasias and
22
23 gastrointestinal ulceration, with the glandular region of the stomach, proximal duodenum and right
24
25 dorsal colon being particularly affected. Renal papillary necrosis has also been reported in horses
26
27 receiving clinically relevant doses of phenylbutazone (Read 1983). This is particularly relevant as the
28
29 aminoglycoside antimicrobial gentamicin, commonly used as a first line treatment in cases of
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31 synovial sepsis is also known to be nephrotoxic.
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39 **Paracetamol (acetaminophen)**

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41 Veterinary licensed oral preparations of paracetamol are available for dogs (in combination with
42
43 codeine) and pigs in the UK, but not horses. This is not a typical NSAID and the exact mechanism of
44
45 action is undetermined but thought to act centrally on serotonergic, opioid, nitric oxide and
46
47 cannabinoid pathways as well as effects on prostaglandin production (Sharma and Mehta 2013). Its
48
49 successful use as an adjunctive analgesic medication has been reported (20mg/kg PO twice daily) in
50
51 a laminitic pony showing pain refractory to NSAIDs, lidocaine and morphine analgesia (West and
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53 others 2011).
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Corticosteroids

Corticosteroids act by inhibiting both cyclo-oxygenase and lipoxygenase pathways of the arachidonic acid cascade, exerting potent anti-inflammatory activity as well as a wide range of other effects.

Most commonly utilised when discrete foci of inflammation can be precisely targeted using small volumes, such as vertebral or limb synovial or ligamentous structures. Methylprednisolone and dexamethasone are licenced for systemic and intra-synovial use in horses. Data sheets invariably carry warnings about the risk of inducing or exacerbating laminitis and total dose and frequency of administration should be carefully considered. Triamcinolone although not licenced is also frequently used.

Opioids

This is a versatile group of drugs offering IV, IM, OTM, transdermal, epidural and intra synovial routes of administration. Action is primarily by central modulation of the pain pathways although opioid receptors are also present outside the central nervous system in tissues such as the myenteric plexus and synovial membranes, with expression being upregulated in inflammatory states.

Butorphanol, pethidine and buprenorphine are licensed for use in horses in the UK and all demonstrate different receptor activity and affinity.

Pethidine (meperidine) is a mu receptor agonist, making it potentially the most efficacious of the licenced options. Used at 1mg/kg IM it was shown to improve experimentally induced foot lameness, but only at 2-3hrs post administration (Foreman and Ruemmler 2013). Despite its theoretical promise, several factors limit its clinical utility. It is only licenced as a visceral analgesic, IV administration is contra-indicated due to potential for histamine release and seizure-like activity, it can cause pain on IM injection and large volumes need to be injected due to its low potency. It is also a Schedule 2 Controlled Drug, with the associated administrative requirements. Epidural

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2
3 administration of pethidine (0.8mg/kg) has been reported, giving a fast onset (12 minutes) and 4 to 5
4
5 hour duration of action (Skarda and Muir 2001).
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8 Buprenorphine (a Schedule 3 Controlled Drug) is a partial mu agonist, with some potentially
9
10 attractive attributes and is licenced for post-operative analgesia at a dose of 10µg/kg IV. It is highly
11
12 potent, requiring small volumes of administration and somatic analgesia of 6hrs duration (assessed
13
14 experimentally using thermal threshold testing) is reported at this dose (Carregaro and others 2007).
15
16 Buprenorphine also shows very good absorption by the OTM route, facilitating administration to
17
18 needle shy horses. A sublingual dose of 6µg/kg is reported to have produced effective sedation and
19
20 analgesia lasting up to 12hrs in a case of trauma-associated musculoskeletal pain (Walker 2007). The
21
22 author has used it with apparent good effect by this route. Data sheet recommendations state
23
24 buprenorphine should only be administered after an intravenous sedative agent and cardiovascular
25
26 stimulation and locomotor excitement lasting for over 12hours have been reported following the
27
28 recommended dosing regimen (Carregaro and others 2006, 2007) and the author has seen horses
29
30 compulsively box-walking following use in clinical cases.
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34 Butorphanol is a mu receptor antagonist and kappa receptor agonist. Whilst analgesia is reported as
35
36 excellent or good in clinical colic cases (Stout and Priest 1986), it does not perform so well for
37
38 somatic pain. In experimental horses Kalpravidh and others (1984a, 1984b) demonstrated only
39
40 moderate analgesia lasting 15-30 minutes, assessed using thermal threshold testing. Increased heart
41
42 rate and locomotor activity may also be seen, although in the author's experience this is not as
43
44 marked as that seen following buprenorphine administration. Epidural administration of
45
46 butorphanol failed to produce detectable analgesia (Natalini and Robinson 2000), suggesting that
47
48 horses do not possess kappa receptors in the spinal cord. It is then logical to assume that kappa
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50 agonists will only have a supraspinal effect.
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57 Unlicenced opioids.
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3 In the author's hospital, morphine (0.1-0.3mg/kg) is routinely given systemically (IM and IV) for
4
5 perioperative analgesia and managing pain not controlled by NSAID administration. Morphine and
6
7 methadone are also administered regularly by the epidural route for painful hindlimb orthopaedic
8
9 conditions. Epidurally, morphine (0.1–0.2 mg/kg) (Sysel and others 1996, Goodrich and others 2002)
10
11 shows a slow onset (up to 6 hours) and a duration of action of around 5 hours (Natalini and
12
13 Robinson 2000), but can possibly last up to 12 - 18 hours. Epidural methadone (0.1mg/kg) has an
14
15 onset of around 15 minutes and lasts about 5 hours (Olbrich and Mosing 2003). In the author's
16
17 hospital it is routine to combine methadone and morphine (0.1mg/kg of each) to obtain the
18
19 theoretical advantage of providing rapid onset of analgesia with extended duration in the acute
20
21 setting. Methadone also has activity at the N-methyl-D-aspartate (NMDA) receptor, therefore has an
22
23 additional mechanism for contributing to analgesia. Where sustained provision of targeted analgesia
24
25 is required, morphine can be administered at 0.1-0.2mg/kg twice daily via an indwelling epidural
26
27 catheter. It is important to ensure strict aseptic technique and that preservative free solutions are
28
29 used where possible.
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34 Intra-synovial administration of 0.05mg/kg morphine has also been demonstrated to provide
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36 analgesia for potentially 24 hours in experimentally induced radio-carpal joint synovitis (Lindgaard
37
38 and others 2010a and 2010b).
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41 The availability of fentanyl patches offers the attractive prospect of providing extended opioid
42
43 analgesia with minimal intervention. Maxwell and others (2003) showed rapid uptake by the
44
45 transdermal route with all horses exceeding the 1ng/mL plasma level consistent with that reported
46
47 to provide analgesia in other species, which was maintained for 32 hours. Orsini and others (2006)
48
49 examined the pharmacokinetics of transdermal fentanyl using commercially available patches
50
51 targeted to deliver 60µg/kg and found a large variation in onset of absorption (up to 5 hours), time
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53 to peak concentration (8.5-14.5 hours) and maximum plasma concentration achieved (0.67-
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55 5.12ng/mL). One third of horses failed to achieve the 1ng/mL plasma concentration considered to be
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3 analgesic. A large variation in onset, maximum concentration (0.1-28.7ng/mL) and time to maximum
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5 concentration (8-24 hours) has also been reported in neonatal foals treated with fentanyl patches
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7 designed to deliver 100µg/hr (Eberspacher and others 2008). The site of patch application is known
8
9 to affect the rate and uptake of transdermally delivered fentanyl (Mills and Cross 2007).

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11 Combination therapy with NSAIDs has been reported in clinical cases refractory to NSAID treatment
12
13 alone (Thomasy and others 2004). Again, a large variation in maximum concentration and time to
14
15 achieve this were reported, but some, although weak, evidence of analgesic effect was claimed. A
16
17 solution of fentanyl (50mg/mL) is licenced for transdermal use in dogs where it is claimed to provide
18
19 analgesia for a minimum of 4 days post-application, but this has not been evaluated in horses at the
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21 time of writing.
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24 25 26 27 28 **Alpha 2 adrenergic agonists**

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30 Frequently used as sedative agents, alpha 2 agonist compounds also provide analgesia by a
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32 mechanism similar to, and synergistic with, that of the opioids (Hellyer and others 2003). Duration
33
34 and quality of analgesia is controversial (England and Clarke 1996), but appears to be better for
35
36 visceral, rather than somatic pain. Some authors have reported no detectable influence on somatic
37
38 analgesia (Elfenbein and others 2009), whilst others have found that the effect depends not only on
39
40 the drug used, but also on the type of stimulus applied (Moens and others 2003, Rohrbach and
41
42 others 2009). Given systemically, analgesia is best considered to be of short duration, peaking later
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44 than sedative effects and not lasting as long, making them of most use during surgical procedures.
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49 All alpha 2 agonists have profound effects on the cardiovascular system which should also be taken
50
51 into account, as should the difficulty of assessing adequate analgesia in a sedated animal.
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54 Epidurally, xylazine (0.17mg/kg up to 0.25mg/kg) is safe and effective (LeBlanc and Carron 1990;
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56 Skarda and Muir 1996; LeBlanc and others 1998). Detomidine (30µg/kg) in combination with
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3 0.2mg/kg morphine produces analgesia (Skarda and Muir 1996, Sysel and others 1996, Goodrich and
4
5 others 2002) and reduces post-operative lameness after hindlimb surgery (Sysel and others 1996,
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7 Goodrich and others 2002). High lipid solubility facilitates systemic absorption from the epidural
8
9 space, especially of detomidine (Skarda and Muir 1996), causing sedation following epidural
10
11 administration. Loss of tail and perineal muscle tone may become evident due to local anaesthetic-
12
13 like properties (particularly with xylazine). Onset is rapid (approximately 12 minutes) and duration of
14
15 effect is 2.5-3.5 hours (LeBlanc and others 1998, Skarda and Muir 1996).
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21 **Local Anaesthetic Agents**

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24 Local anaesthetics have the potential to completely abolish pain by interrupting neuronal signal
25
26 transmission, rather than just obtunding it. They affect both sensory and motor neurons,
27
28 consequently their use will not be appropriate for all sites of pain or surgery, but where applicable
29
30 they offer considerable benefit. They can be administered topically, perineurally, epidurally, intra-
31
32 synovially, systemically and directly infiltrated into tissues. Mepivacaine, lidocaine and procaine are
33
34 all licenced for use in horses in the UK. Of these, only mepivacaine is supplied without adrenaline or
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36 preservative and is licensed for infiltration, perineural, intra-articular and epidural administration,
37
38 making it an extremely versatile preparation. Lidocaine without adrenaline is also available from
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40 pharmaceutical suppliers as a 2% solution for injection and as a 0.2% solution in 5% glucose for IV
41
42 infusion, but not licenced for use in horses.
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47 Lidocaine administration has been described by continuous IV infusion (loading dose of up to
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49 2mg/kg followed by infusion at 50µg/kg/minute). Its use in this manner is most often associated
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51 with gastrointestinal tract surgery, however somatic analgesia as assessed by thermal threshold
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53 testing has been demonstrated experimentally (Robertson and others 2005).
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3 Epidurally, care needs to be taken with the total volume injected to avoid cranial spread which may
4
5 impair motor function to the hindlimbs (Goodrich and others 2002, Olbrich and Mosing 2003).

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7 Preservative free preparations of bupivacaine 0.5%, lidocaine 2% and mepivacaine 2% solutions (5-
8
9 10mL) have been used by the author.

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11
12 Transdermal patches containing 5% lidocaine are used to treat a range of chronic neuropathic and
13
14 musculoskeletal pain in humans, with systemic uptake having been proven. Application of two
15
16 700mg patches to the limbs of horses for 12 hours failed to demonstrate systemic uptake in a study
17
18 by Bidwell and others (2007). Doubling the number of patches for 24 hours gave variable systemic
19
20 uptake (Andreoni and Giorgi 2009). If the skin was subjected to an alcohol scrub prior to patch
21
22 placement there was a tendency for a more rapid and pronounced, but less sustained uptake.

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24 Antinociceptive effects assessed by pricking the skin under the patch at removal showed no
25
26 difference in sensation between horses which had had a patch applied and control animals. This
27
28 application therefore appears to be of little benefit.

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32 Diffusion catheters (Fig 4) are another method of providing targeted pain relief. These are available
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34 commercially (Mila International Inc, Kentucky, USA) or can be improvised from narrow gauge plastic
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36 tubing or intravenous cannulae. The use of these for prolonged perineural administration of
37
38 lidocaine, mepivacaine and bupivacaine to the palmar metacarpal nerves has been investigated
39
40 experimentally in horses (Driessen and others 2008). Although regional anaesthesia was achieved,
41
42 significant oedema developed, necessitating discontinuation of the infusions, limiting their clinical
43
44 potential. Alternatively, catheter implantation during wound closure, allowing local anaesthetic to
45
46 be instilled directly at the surgical site for post-operative pain management has been described in
47
48 small animals (Abelson and others 2009) with no associated risk of wound complications and has
49
50 been successfully used in horses at the author's hospital to provide analgesia for 48 hours following
51
52 surgical resection of thoracolumbar spinous processes (Fig 5).

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2
3 Prolonged intra-synovial administration of local anaesthetic agents in human patients has been
4
5 associated with chondrolysis, with bupivacaine appearing to exhibit the greatest degree of
6
7 chondrotoxicity. This effect appears to be dose and time dependent, being particularly pronounced
8
9 with formulations containing adrenaline. Consequently a number of local anaesthetic agents have
10
11 been tested in animal models and chondrocyte cultures, with mixed results; *in vitro* results not
12
13 always supporting *in vivo* ones (Webb and Ghosh 2009; Dragoo and others 2010). An *in vitro* study of
14
15 bupivacaine, lidocaine and mepivacaine on equine chondrocyte cultures showed mepivacaine to be
16
17 the least chondrotoxic, with cell viability on exposure to this agent approaching that of the saline
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19 control (Park and others 2011). Single intra-synovial injection of local anaesthetic solution is
20
21 performed regularly at the author's hospital to provide targeted pain relief following arthroscopic
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23 surgery, with no apparent problem.
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30 Ketamine

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33 Used at sub-anaesthetic doses, this NMDA receptor antagonist has potent analgesic properties and
34
35 may counteract central sensitization, so making it potentially useful in the management of chronic as
36
37 well as acute pain. Infusions of 0.4 and 0.8mg/kg/hour have been shown to be tolerated well in
38
39 conscious horses, with excitement seen at 1.6mg/kg/hour, although no somatic analgesia was
40
41 demonstrated (Fielding and others 2006). Peterbauer and others (2008) however, did demonstrate
42
43 analgesic properties in conscious horses after 0.6mg/kg IV bolus followed by 20µg/kg/minute
44
45 infusion. Analgesia is mainly somatic rather than visceral and is mediated by a number of
46
47 mechanisms in addition to NMDA receptor activity. In addition to infusion administration, IM bolus
48
49 dosing at 0.2-0.5mg/kg has been practiced by the author to manage acute episodes of pain, or
50
51 acute-on-chronic episodes in cases of laminitis or following surgical intervention. Epidural
52
53 administration (0.5, 1.0 and 2.0mg/kg) has been shown to provide analgesia lasting 30 to 75 minutes
54
55 (De Segura and others 1998).
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Tramadol

Tramadol is a synthetic analogue of codeine which has been used in the management of acute and chronic moderate to severe pain in humans. It is a centrally acting analgesic that has agonist activity at mu opioid receptors and also inhibits the reuptake of noradrenaline and serotonin. Although not licenced in the horse, the pharmacokinetics and pharmacodynamics of intravenously, intramuscularly and orally administered tramadol have been investigated in this species (Shilo and others 2007, Cox and others 2010, Dhanjal and others 2009, Knych and others 2013a 2013b, Giorgi and others 2007, Stewart and others 2011). Minimum plasma tramadol levels which provide analgesia in people vary greatly between 100 and 600ng/mL, with much of the analgesic effect of tramadol being attributed to the M1 metabolite (O-desmethyltramadol) which has 200 times the affinity for the mu opioid receptor than the parent drug. In people there is genetically predetermined variation in the ability to produce this metabolite, making some individuals poorly responsive to the drug. It is unknown whether this is also true in horses, although a large individual variation in plasma concentrations of M1 (and several other metabolites) has been demonstrated (De Leo and others 2009, Knych and others 2013a, 2013b, Giorgi and others 2007). Oral bioavailability following a 5mg/kg dose has been reported as approximately 65% in fasted horses, increasing to approximately 85% in fed horses (Giorgi and others 2007), whilst Shilo and others (2007) reported only 3% following 2mg/kg administered to fasted horses. Knych and others (2013a) used doses of 3, 6 and 9mg/kg PO which showed a very wide variation in plasma levels, with only the 9mg/kg dose consistently achieving plasma concentrations within the human analgesic range. No adverse events were reported apart from mild signs of colic and increased pacing behaviour in 1 horse at the higher dose. Intramuscular administration of 2mg/kg resulted in rapid and complete absorption with attainment of useful plasma concentrations and no adverse effects (Shilo and others 2007). Cox and others (2010) and Shilo and others (2007) reported side effects including ataxia, muscle twitching

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3 and sweating for 15 minutes after 2mg/kg IV and Giorgi and others (2007) reported confusion,
4
5 agitation, tremor and tachycardia after 5mg/kg IV but not PO. Dhanjal and others (2009) reported
6
7 side effects following 2mg/kg IV and were unable to demonstrate an antinociceptive effect using a
8
9 noxious thermal stimulus. Guedes and others (2012) administered 5mg/kg PO twice daily to horses
10
11 with chronic laminitic pain and showed only weak evidence of analgesia, whilst ketamine showed a
12
13 much greater effect. Epidural administration of 1mg/kg tramadol produced analgesia after 30
14
15 minutes with effects lasting for 4 hours (Natalini and Robinson 2000).
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21 **Gabapentin**

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24 Originally used as an adjuvant anticonvulsant, gabapentin was subsequently shown to be effective in
25
26 treating a range of chronic pain syndromes in people. It is a structural analogue of the inhibitory
27
28 neurotransmitter γ -aminobutyric acid (GABA) but neither parent drug nor metabolites show affinity
29
30 for, or activity at GABA_A or GABA_B receptors. The major mechanism of action is currently thought to
31
32 be via voltage dependent calcium channels, thereby reducing neurotransmitter release (Kong and
33
34 Irwin 2007). Pharmacokinetics of a single dose of 5mg/kg PO (Dirikolu and others 2008) and 20mg/kg
35
36 PO and IV (Terry and others 2010) have been evaluated in horses. No adverse events were noted
37
38 after either dose or route of administration although sedation was evident for 1 hour after the IV
39
40 dose. Rapid but poor absorption (compared with humans, rats, dogs and monkeys) followed PO
41
42 administration with a bioavailability of only 16% following the higher dose. Gabapentin is not
43
44 licensed for veterinary species but there are case reports of its use in horses. Davis and others (2007)
45
46 describe its use in a heavily pregnant mare with suspected neuropathic pain at 2.5mg/kg PO every 8
47
48 hours, increasing dosing interval over 6 days, with apparent beneficial effect and no detriment to the
49
50 foetus. It is also reported as a component of a multimodal approach to provision of analgesia in the
51
52 management of severe laminitis associated hoof pain, at doses between 3.3mg/kg every 8 hours and
53
54 2mg/kg every 12 hours PO (Dutton and others 2009).
55
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Bisphosphonates

Bisphosphonates have been shown to reduce pain in human patients with osteoarthritis and cancer pain and improve joint mobility. These drugs inhibit osteoclast proton secretion, reducing the acidity of the microenvironment associated with bone resorption, so reducing activation of acid sensitive ion channels in sensory neurons. A direct anti-inflammatory effect is also demonstrated by inhibiting osteoblast secretion of vascular endothelial growth factor, reducing cytokine release from activated macrophages (Silvina and Barbara 2014). Tiludronic acid is licenced for treatment of inflammatory and degenerative joint disease in horses at a dose of 1mg/kg by intravenous infusion over 30 minutes. Improvement of lameness in horses suffering from bone spavin (Gough and others 2010) and navicular disease (Denoix and others 2003) has been demonstrated in tiludronate treated horses.

Isoxsuprine hydrochloride is licenced for the treatment of navicular disease in horses. Its action causes vasodilation, lowers blood viscosity and inhibits platelet aggregation, thereby potentially improving circulation in the affected area. Some, but inconsistent evidence of clinical efficacy has been shown (Rose and others 1983; Turner and Tucker 1989).

Conclusion

The World Health Organisation 'pain ladder' (Fig 6) describes a graded approach to administration of analgesic agents, combined with adjunctive therapies and provides a useful framework to follow for pain management. Originally designed to provide guidance managing cancer pain in people, is now much more widely applied. The number of drugs available for use in horses is limited, however by understanding the action of what is available and adopting a multi-modal approach, additive or synergistic activities can be exploited to maximise effect whilst minimising the risk of side effects. Adjunctive therapies can equally be vital in achieving a successful outcome (Fig 7). These range from

1
2
3 simple bandaging, hot and cold compresses or using ice, physiotherapy, acupuncture, corrective or
4
5 remedial farriery up to surgical interventions such as hoof wall resection, and salvage procedures
6
7 such as neurectomy (sometimes in conjunction with fasciotomy) and arthrodesis. Novel attributes
8
9 of drugs used for other indications can also be exploited for good effect, for example the use of
10
11 tricyclic antidepressants for chronic pain management in people and small animals. However
12
13 evidence of safety and efficacy in the horse in this regard is often lacking.
14
15

16
17 Quiz

- 18
19
20 1. In addition to being a general anaesthetic agent, ketamine provides profound analgesia via
21
22 its action at NMDA receptors. Which of the following drugs also has NMDA receptor activity?
23
24 a) Gabapentin
25
26 b) Methadone
27
28 c) Paracetamol
29
30 d) Tramadol
31
32
33
34
35 2. Which of the following statements is **true** of alpha 2 agonists?
36
37 a) They provide reliable somatic analgesia
38
39 b) The analgesia they provide lasts as long as the sedative effects
40
41 c) They are all licensed for administration by the oral transmucosal route
42
43 d) It is possible to achieve sedation by administering them into the epidural space
44
45
46
47
48 3. The following classes of drugs can effectively be administered epidurally, **except** for which
49
50 one?
51
52 a) Alpha 2 agonists
53
54 b) Non-steroidal anti-inflammatories
55
56 c) Opioids
57
58
59
60

1
2
3 d) Local anaesthetics
4
5
6

7 4. Which of the following statements is **true** regarding intra-synovial administration of
8 analgesic agents?
9

- 10 a) Local anaesthetics should never be used due to their chondrotoxic effects
11
12 b) There are no drugs licenced for use by this route in the horse
13
14 c) Total dose of corticosteroids should be restricted due to the potential for adverse
15
16 systemic side effects
17
18 d) There are no opioid receptors present in synovial tissue therefore these drugs will not be
19
20 effective by this route
21
22
23
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25
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27 Answers: 1 b), 2 d), 3 b), 4 c).
28
29

30 Contributorship

31 The author is the sole contributor to this article and accepts responsibility for its content.
32
33

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24 **Further reading**
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3 **Figure 1.**
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5 Epidural injection (here shown being performed at the sacro-coccygeal/first inter-coccygeal space) is
6
7 a useful technique for achieving more targeted drug delivery. It is important to observe good
8
9 hygiene and where possible to use preservative free drugs.
10

11
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13
14 **Figure 2.**
15

16 Epidural catheter placed at the sacro-coccygeal/first inter-coccygeal space. Note the bacterial filter
17
18 and sterile dressing to maintain cleanliness. With appropriate care, these can be maintained for
19
20 several days for extended pain management without the requirement for repeated needle puncture.
21
22

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24
25 **Figure 3.**
26

27 Commercially available epidural catheter kits. Several makes are available and contain all the
28
29 necessary components.
30
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32
33 **Figure 4.**
34

35 Commercially available wound diffusion catheters. These are available with different diffusion
36
37 lengths so can be chosen to suit the extent of the surgical field. Home-made ones can be
38
39 constructed from long intravenous cannulae or dog urinary catheters.
40
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44 **Figure 5.**
45

46 Commercial wound diffusion catheter in-situ following spinous process resection. The catheter is
47
48 placed during wound closure and exited through a stab incision distant from the surgical site. Note
49
50 the bacterial filter to preserve sterility of injected local anaesthetic agent.
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Figure 6.

World Health Organisation 'Pain Ladder'. Originally designed for guidance in managing cancer pain in people, it describes a logical, progressive approach to provision of analgesic agents when managing many types of clinical pain.

Figure 7.

Severe case of laminitis. These cases can be extremely challenging to manage, often presenting with complex pain that is refractory to conventional analgesic protocols. Adjunctive approaches are as important as pharmacological therapy, with hoof wall resection and provision of adequate mechanical support illustrated here.

Managing orthopaedic pain in horses

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Introduction

Orthopaedic pain is a broad term applied to pathology of the musculoskeletal system, potentially involving bones, joints, tendons, ligaments and muscles and consequently incorporating both soft and hard tissues. When thinking in terms of appropriate therapeutics, it may therefore be more useful to define it as deep somatic pain to distinguish it from superficial (cutaneous) somatic pain and visceral pain.

Musculoskeletal pain may result from trauma (including planned surgical intervention), overuse, inflammation, infection, neoplasia, osteolysis, ischaemia or neuronal damage. Common equine orthopaedic conditions such as degenerative joint disease, navicular syndrome and laminitis often present several of these aspects in combination and can be challenging to manage. Difficulty can be compounded by occurrence of acute-on-chronic flare-ups (see Box 1 for some definitions associated with pain).

The nature, severity and types of pain all must be taken into consideration when deciding how to provide effective analgesia.

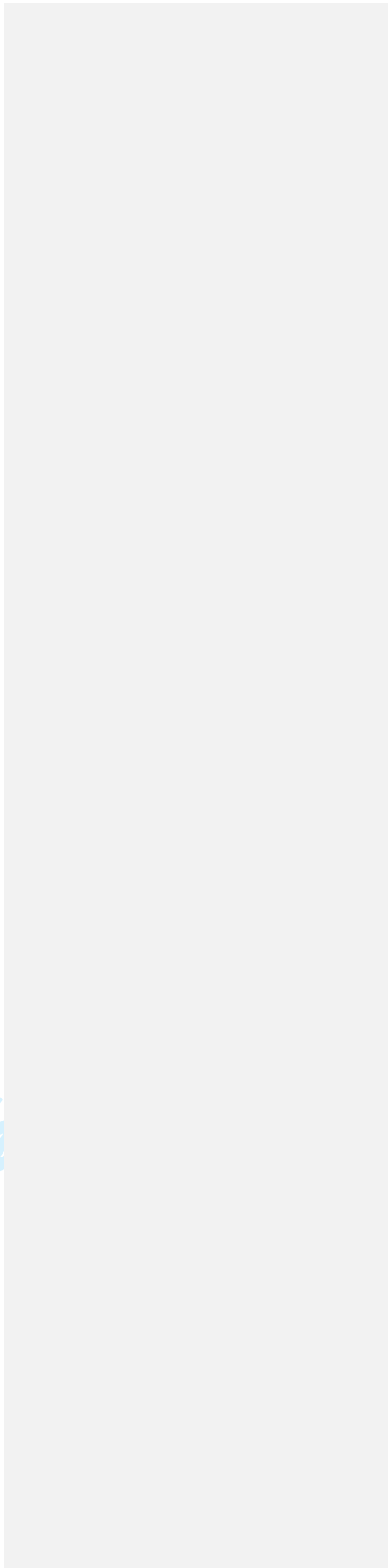
Pain recognition

One of the biggest challenges in veterinary medicine is the recognition and quantification of pain. Assessment of pain in non-verbal species (and non-verbal humans) is difficult and subjective, typically relying on a combination of physiological variables, behaviour assessment and a degree of anthropomorphism. Several attempts have been made to devise pain scales for use in horses to identify the site and type of pain, but as yet none of these has been fully validated. This is further complicated by the fact that horses as a species tend not to be overtly demonstrative of pain unless

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it is moderate to severe, show considerable variation in the way they respond and alter their behaviour in the presence of an observer. Different assessors may therefore attribute very different levels of pain to the same animal, leading to very different assessments of the requirement for analgesia. In the current context, lameness scores are crude but clinically useful and widely employed. Manifestation of musculoskeletal pain may be obvious in the case of a single limb lameness, less so in mild multiple limb lameness, post surgically, or in cases of axial rather than appendicular pathology.

Confidential: For Review



Box 1.**Types of Pain**

Acute pain - Acute pain is the normal physiological response to application of a noxious stimulus. It is designed to be protective, being linked to the withdrawal reflex, preventing further tissue damage and triggering behavioural changes intended to maximise healing. This type of pain is typically of short duration, persisting only as long as the original insult. This is the type of pain associated with the early stages of tissue injury or surgery and is relatively easy to treat.

Chronic pain – this is pain that persists beyond the time frame expected for the relevant condition, a period of three to six months is often quoted. This may be due to acute injury or disease that is not resolving, ongoing degenerative conditions such as arthritis, or failure to manage acute pain adequately in the early stages of treatment. Achieving satisfactory analgesia can be extremely difficult in chronic pain states as the nervous system undergoes maladaptive changes – a process called neuroplasticity. This can result in sensitisation of the nervous system, when normally innocuous sensory input becomes perceived as painful (termed allodynia) or an exaggerated response to normally painful stimuli (termed hyperalgesia). Sensitisation may occur in both peripheral and central components of the nervous system and involves increased reactivity of peripheral nociceptors and central pain neurones, recruitment of additional nociceptors to generate pain signals and upregulation of pain receptor expression, so reinforcing the pain transmission pathways. In cases where chronic pain develops, pain ceases to become simply an indicator of a disease process and becomes part of the disease process itself. The longer pain is left untreated or inadequately controlled the more difficult it becomes to obtain a satisfactory outcome.

Neuropathic pain – this is pain caused by direct peripheral or central nerve injury resulting in hyperalgesia, allodynia and chronic, spontaneous ectopic generation of pain signals in the absence of any external stimuli.

Strategic Analgesia

A good analgesic plan will consist of systemically administered drugs, if possible in combination with local or regional analgesic techniques. Drugs chosen should ideally be those licensed for analgesia in the horse by the prescribed route, however licensed drugs administered by an unlicensed route, or unlicensed drugs may on occasion be indicated and appropriate. The key is in understanding the types of pain that may be present, the mode of action of the drugs that are available and how these drugs may be employed to maximise their effect on the case in question. In this way a multi-modal therapeutic plan can be formulated, incorporating the most appropriate drugs, designed to target as many aspects of the pain pathway as accurately as possible.

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7 **Systemic administration** of analgesic agents in the short term is typically by the intravenous (IV) or
8 intramuscular (IM) route, with oral medication often being relied on for more protracted courses of
9 treatment. Whilst a combination of these routes will probably prove adequate in the majority of
10 cases, other methods of drug delivery may allow for more effective provision of analgesia in specific
11 cases.
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16 The **oral-transmucosal** (OTM) absorption of some drugs can result in rapid uptake and high
17 bioavailability as it avoids first pass metabolism which enterally absorbed drugs administered per os
18 (PO) are subject to. Although potentially very effective, drugs administered this way may be
19 swallowed or spat out, resulting in imprecise dosing, restricting this method to either highly
20 concentrated formulations or highly potent drugs, where a small total volume can be given.
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22 Although several drugs can be effectively administered this way, only the alpha 2 agonist detomidine
23 has a formulation licenced specifically for this route.
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30 **Transdermal** drug delivery systems have been developed for a number of classes of drugs in the
31 human market and include patches, creams and gels for external application designed to have either
32 systemic or local effects. Transdermal drug absorption avoids first pass metabolism and gives the
33 potential for prolonged drug administration with minimal patient handling. However drug uptake is
34 highly dependent on sustained contact with the skin and that the area of application is healthy and
35 has a good blood supply. Several human preparations have been evaluated in veterinary species and
36 a specific veterinary formulation of fentanyl (licenced for use in dogs) is now available.
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44 **Epidural** drug administration (Fig 1) provides the opportunity for a more targeted effect and is
45 becoming more commonly employed. Use of local anaesthetics, alpha 2 agonists, opioids, ketamine
46 and tramadol has been reported in the horse by this route. Depending on the characteristics of the
47 drug, there will be varying systemic uptake, and onset and duration of effect may differ significantly
48 from those familiar from conventional systemic administration, which can be advantageous. For
49 prolonged analgesia, epidural catheters can be placed which facilitate provision of extended
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7 targeted pain management (Fig 2). Commercial kits (Fig 3) for this procedure are available (Fig 3, B
8 [Braun Medical Ltd, Yorkshire, UK; Smiths Medical, Kent, UK](#)) and have been used successfully in
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10 several cases at the author's hospital. These catheters require very careful management, with
11
12 maintenance of patency and sterility being the main problems, however with proper management it
13
14 is possible to maintain these in situ for up to 10 days in clinical cases.

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17 **Diffusion (soaker) catheters** offer the potential for prolonged, precise administration of local
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19 anaesthetic agents. Their potential has yet to be fully realised and they are discussed in more detail
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21 below with local anaesthetic drugs.

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23 With the high prevalence of developmental, degenerative and traumatic disease affecting the joints
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25 of horses, as well as the frequency of diagnostic and therapeutic surgical procedures involving joints
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27 and other synovial structures, **intra-synovial** administration of analgesic agents is an attractive and
28
29 effective method of achieving targeted pain relief. Administration of a number of drugs by this route
30
31 has been described, including morphine, corticosteroids and local anaesthetic agents.

32 33 34 35 **Non-Steroidal Anti-inflammatory Drugs (NSAIDs)**

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38 ~~The first line and mainstay of analgesia provision, t~~here are several [non-steroidal anti-inflammatory](#)
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40 [drugs](#) licenced for use in horses in the UK [and these often form the first line and mainstay of](#)
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42 [analgesia provision](#). Action is by inhibition of cyclo-oxygenase enzymes both peripherally and
43
44 centrally, thereby interrupting the arachidonic acid cascade that results in production of
45
46 prostacyclin, prostaglandins and thromboxanes. These substances are potent inflammatory
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48 mediators, which result in sensitisation and recruitment of peripheral nociceptors and transmission
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50 of central pain pathways. Many disease processes and certainly surgical interventions will induce an
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52 inflammatory response, so incorporating an anti-inflammatory drug is eminently appropriate.
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7 Many are available for administration by IV injection and as powders and/or pastes for oral
8 administration, making them convenient for both acute and chronic pain management, although
9 palatability may be problematic with some of the powdered preparations designed to be mixed with
10 food. Choice largely comes down to familiarity, availability and cost. Anecdotally, some horses will
11 respond better to one than another so it may be worth trying an alternative if response to one is
12 unsatisfactory. Data sheets tend to advise leaving 24 hours between dosing if changing to an
13 alternative to avoid inadvertent overdose. The potential for toxicity also need to be considered in
14 the context of long term treatment, particularly as this may be continued by the owner of the horse
15 for extended periods, outside the direct control of the veterinary surgeon. Doses should be carefully
16 calculated and dosing regimes clearly stipulated. Toxicity may manifest as blood dyscrasias and
17 gastrointestinal ulceration, with the glandular region of the stomach, proximal duodenum and right
18 dorsal colon being particularly affected. Renal papillary necrosis has also been reported in horses
19 receiving clinically relevant doses of phenylbutazone (Read 1983). This is particularly relevant as the
20 aminoglycoside antimicrobial gentamicin, commonly used as a first line treatment in cases of
21 synovial sepsis is also known to be nephrotoxic.
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38 **Paracetamol (acetaminophen)**

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40 Veterinary licensed oral preparations of paracetamol are available for dogs (in combination with
41 codeine) and pigs in the UK, but not horses. This is not a typical NSAID and the exact mechanism of
42 action is undetermined but thought to act centrally on serotonergic, opioid, nitric oxide and
43 cannabinoid pathways as well as effects on prostaglandin production (Sharma and Mehta 2013). Its
44 successful use as an adjunctive analgesic medication has been reported (20mg/kg PO twice daily) in
45 a laminitic pony showing pain refractory to NSAIDs, lidocaine and morphine analgesia (West and
46 others 2011).
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Corticosteroids

Corticosteroids act by inhibiting both cyclo-oxygenase and lipoxygenase pathways of the arachidonic acid cascade, ~~these drugs~~ exerting potent anti-inflammatory activity as well as a wide range of other effects. Most commonly utilised when discrete foci of inflammation can be precisely targeted using small volumes, such as vertebral or limb synovial or ligamentous structures.

Methylprednisolone and dexamethasone are licenced for systemic and intra-synovial use in horses. Data sheets invariably carry warnings about the risk of inducing or exacerbating laminitis and total dose and frequency of administration should be carefully considered. Triamcinolone although not licenced is also frequently used.

Opioids

This is a versatile group of drugs offering IV, IM, OTM, transdermal, epidural and intra synovial routes of administration. Action is primarily by central modulation of the pain pathways although opioid receptors are also present outside the central nervous system CNS in tissues such as the myenteric plexus and synovial membranes, with expression being upregulated in inflammatory states.

Butorphanol, pethidine and buprenorphine are licensed for use in horses in the UK and all demonstrate different receptor activity and affinity.

Pethidine (meperidine) is a mu receptor agonist, making it potentially the most efficacious of the licenced options. Used at 1mg/kg IM it was shown to improve experimentally induced foot lameness, but only at 2-3hrs post administration (Foreman and Ruemmler 2013). Despite its theoretical promise, several factors limit its clinical utility. It is only licenced as a visceral analgesic, IV administration is contra-indicated due to potential for histamine release and seizure-like activity, it can cause pain on IM injection and large volumes need to be injected due to its low potency. It is

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7 also a Schedule 2 Controlled Drug, with the associated administrative requirements. Epidural
8 administration of pethidine (0.8mg/kg) has been reported, giving a fast onset (12 minutes) and 4 to 5
9 hour duration of action (Skarda and Muir 2001).

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12 Buprenorphine (a Schedule 3 Controlled Drug) is a partial mu agonist, with some potentially
13 attractive attributes and is licenced for post-operative analgesia at a dose of 10µg/kg IV. It is highly
14 potent, requiring small volumes of administration and somatic analgesia of 6hrs duration (assessed
15 experimentally using thermal threshold testing) is reported at this dose (Carregaro and others 2007).

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18 Buprenorphine also shows very good absorption by the OTM route, facilitating administration to
19 needle shy horses. A sublingual dose of 6µg/kg is reported to have produced effective sedation and
20 analgesia lasting up to 12hrs in a case of trauma-associated musculoskeletal pain (Walker 2007). The
21 author has used it with apparent good effect by this route. Data sheet recommendations state
22 buprenorphine should only be administered after an intravenous sedative agent and cardiovascular
23 stimulation and locomotor excitement lasting for over 12hours have been reported following the
24 recommended dosing regimen (Carregaro and others 2006, 2007) and the author has seen horses
25 compulsively box-walking following use in clinical cases.

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28 Butorphanol is a mu receptor antagonist and kappa receptor agonist. Whilst analgesia is reported as
29 excellent or good in clinical colic cases (Stout and Priest 1986), it does not perform so well for
30 somatic pain. In experimental horses Kalpravidh and others (1984a, 1984b) demonstrated only
31 moderate analgesia lasting 15-30 minutes, assessed using thermal threshold testing. Increased heart
32 rate and locomotor activity may also be seen, although in the author's experience this is not as
33 marked as that seen following buprenorphine administration. Epidural administration of
34 butorphanol failed to produce detectable analgesia (Natalini and Robinson 2000), suggesting that
35 horses do not possess kappa receptors in the spinal cord. It is then logical to assume that kappa
36 agonists will only have a supraspinal effect.

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7 Unlicensed opioids.

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9 In the author's hospital, morphine (0.1-0.3mg/kg) is routinely given systemically (IM and IV) for
10 perioperative analgesia and managing pain not controlled by NSAID administration. Morphine and
11 methadone are also administered regularly by the epidural route for painful hindlimb orthopaedic
12 conditions. Epidurally, morphine (0.1–0.2 mg/kg) (Sysel and others 1996, Goodrich and others 2002)
13 shows a slow onset (up to 6 hours) and a duration of action of around 5 hours (Natalini and
14 Robinson 2000), but can possibly last up to 12 - 18 hours. Epidural methadone (0.1mg/kg) has an
15 onset of around 15 minutes and lasts about 5 hours (Olbrich and Mosing 2003). In the author's
16 hospital it is routine to combine methadone and morphine (0.1mg/kg of each) to obtain the
17 theoretical advantage of providing rapid onset of analgesia with extended duration in the acute
18 setting. Methadone also has activity at the N-methyl-D-aspartate (NMDA) receptor, therefore has an
19 additional mechanism for contributing to analgesia. Where sustained provision of targeted analgesia
20 is required, morphine can be administered at 0.1-0.2mg/kg twice daily via an indwelling epidural
21 catheter. It is important to ensure strict aseptic technique and that preservative free solutions are
22 used where possible.
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36 Intra-synovial administration of 0.05mg/kg morphine has also been demonstrated to provide
37 analgesia for potentially 24 hours in experimentally induced radio-carpal joint synovitis (Lindgaard
38 and others 2010a and 2010b).
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41 The availability of fentanyl patches offers the attractive prospect of providing extended opioid
42 analgesia with minimal intervention. Maxwell and others (2003) showed rapid uptake by the
43 transdermal route with all horses exceeding the 1ng/mL plasma level consistent with that reported
44 to provide analgesia in other species, which was maintained for 32 hours. Orsini and others (2006)
45 examined the pharmacokinetics of transdermal fentanyl using commercially available patches
46 targeted to deliver 60µg/kg and found a large variation in onset of absorption (up to 5 hours), time
47 to peak concentration (8.5-14.5 hours) and maximum plasma concentration achieved (0.67-
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7 5.12ng/mL). One third of horses failed to achieve the 1ng/mL plasma concentration considered to be
8 analgesic. A large variation in onset, maximum concentration (0.1-28.7ng/mL) and time to maximum
9 concentration (8-24 hours) has also been reported in neonatal foals treated with fentanyl patches
10 designed to deliver 100µg/hr (Eberspacher and others 2008). The site of patch application is known
11 to affect the rate and uptake of transdermally delivered fentanyl (Mills and Cross 2007).
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16 Combination therapy with NSAIDs has been reported in clinical cases refractory to NSAID treatment
17 alone (Thomasy and others 2004). Again, a large variation in maximum concentration and time to
18 achieve this were reported, but some, although weak, evidence of analgesic effect was claimed. A
19 solution of fentanyl (50mg/mL) is licenced for transdermal use in dogs where it is claimed to provide
20 analgesia for a minimum of 4 days post-application, but this has not been evaluated in horses at the
21 time of writing.
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30 **Alpha 2 adrenergic agonists**

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33 Frequently used as sedative agents, ~~these~~alpha 2 agonist compounds also provide analgesia by a
34 mechanism similar to, and synergistic with, that of the opioids (Hellyer and others 2003). Duration
35 and quality of analgesia is controversial (England and Clarke 1996), but appears to be better for
36 visceral, rather than somatic pain. Some authors have reported no detectable influence on somatic
37 analgesia (Elfenbein and others 2009), whilst others have found that the effect depends not only on
38 the drug used, but also on the type of stimulus applied (Moens and others 2003, Rohrbach and
39 others 2009). Given systemically, analgesia is best considered to be of short duration, peaking later
40 than sedative effects and not lasting as long, making them of most use during surgical procedures.
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48 All alpha 2 agonists have profound effects on the cardiovascular system which should also be taken
49 into account, as should the difficulty of assessing adequate analgesia in a sedated animal.
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7 Epidurally, xylazine (0.17mg/kg up to 0.25mg/kg) is safe and effective (LeBlanc and Carron 1990;
8 Skarda and Muir 1996; LeBlanc and others 1998). Detomidine (30µg/kg) in combination with
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10 0.2mg/kg morphine produces analgesia (Skarda and Muir 1996, Sysel and others 1996, Goodrich and
11
12 others 2002) and reduces post-operative lameness after hindlimb surgery (Sysel and others 1996,
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14 Goodrich and others 2002). High lipid solubility facilitates systemic absorption from the epidural
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16 space, especially of detomidine (Skarda and Muir 1996), causing sedation following epidural
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18 administration. Loss of tail and perineal muscle tone may become evident due to local anaesthetic-
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20 like properties (particularly with xylazine). Onset is rapid (approximately 12 minutes) and duration of
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22 effect is 2.5-3.5 hours (LeBlanc and others 1998, Skarda and Muir 1996).
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26 **Local Anaesthetic Agents**

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29 Local anaesthetics have the potential to completely abolish pain by interrupting neuronal signal
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31 transmission, rather than just obtunding it. They affect both sensory and motor neurons,
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33 consequently their use will not be appropriate for all sites of pain or surgery, but where applicable
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35 they offer considerable benefit. They can be administered topically, perineurally, epidurally, intra-
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37 synovially, systemically and directly infiltrated into tissues. Mepivacaine, lidocaine and procaine are
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39 all licenced for use in horses in the UK. Of these, only mepivacaine is supplied without adrenaline or
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41 preservative and is licensed for infiltration, perineural, intra-articular and epidural administration,
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43 making it an extremely versatile preparation. Lidocaine without adrenaline is also available from
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45 pharmaceutical suppliers as a 2% solution for injection and as a 0.2% solution in 5% glucose for IV
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47 infusion, but not licenced for use in horses.

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49 Lidocaine administration has been described by continuous IV infusion (loading dose of up to
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51 2mg/kg followed by infusion at 50µg/kg/minute). Its use in this manner is most often associated
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53 with gastrointestinal tract surgery, however somatic analgesia as assessed by thermal threshold
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55 testing has been demonstrated experimentally (Robertson and others 2005).
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7 Epidurally, care needs to be taken with the total volume injected to avoid cranial spread which may
8 impair motor function to the hindlimbs (Goodrich and others 2002, Olbrich and Mosing 2003).

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10 Preservative free preparations of bupivacaine 0.5%, lidocaine 2% and mepivacaine 2% solutions (5-
11 10mL) have been used by the author.

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14 Transdermal patches containing 5% lidocaine are used to treat a range of chronic neuropathic and
15 musculoskeletal pain in humans, with systemic uptake having been proven. Application of two
16 700mg patches to the limbs of horses for 12 hours failed to demonstrate systemic uptake in a study
17 by Bidwell and others (2007). Doubling the number of patches for 24 hours gave variable systemic
18 uptake (Andreoni and Giorgi 2009). If the skin was subjected to an alcohol scrub prior to patch
19 placement there was a tendency for a more rapid and pronounced, but less sustained uptake.

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21 Antinociceptive effects assessed by pricking the skin under the patch at removal showed no
22 difference in sensation between horses which had had a patch applied and control animals. This
23 application therefore appears to be of little benefit.

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26 Diffusion catheters (Fig 4) are another method of providing targeted pain relief. These are available
27 commercially (Fig 4 Mila International Inc, Kentucky, USA) or can be improvised from narrow gauge
28 plastic tubing or intravenous cannulae. The use of these for prolonged perineural administration of
29 lidocaine, mepivacaine and bupivacaine to the palmar metacarpal nerves has been investigated
30 experimentally in horses (Driessen and others 2008). Although regional anaesthesia was achieved,
31 significant oedema developed, necessitating discontinuation of the infusions, limiting their clinical
32 potential. Alternatively, catheter implantation during wound closure, allowing local anaesthetic to
33 be instilled directly at the surgical site for post-operative pain management has been described in
34 small animals (Abelson and others 2009) with no associated risk of wound complications and has
35 been successfully used in horses at the author's hospital to provide analgesia for 48 hours following
36 surgical resection of thoracolumbar dorsal spinous processes (Fig 5).

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7 Prolonged intra-synovial administration of local anaesthetic agents in human patients has been
8 associated with chondrolysis, with bupivacaine appearing to exhibit the greatest degree of
9 chondrotoxicity. This effect appears to be dose and time dependent, being particularly pronounced
10 with formulations containing adrenaline. Consequently a number of local anaesthetic agents have
11 been tested in animal models and chondrocyte cultures, with mixed results; *in vitro* results not
12 always supporting *in vivo* ones (Webb and Ghosh 2009; Dragoo and others 2010). An *in vitro* study of
13 bupivacaine, lidocaine and mepivacaine on equine chondrocyte cultures showed mepivacaine to be
14 the least chondrotoxic, with cell viability on exposure to this agent approaching that of the saline
15 control (Park and others 2011). Single intra-synovial injection of local anaesthetic solution is
16 performed regularly at the author's hospital to provide targeted pain relief following arthroscopic
17 surgery, with no apparent problem.
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30 Ketamine

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32 Used at sub-anaesthetic doses, this NMDA receptor antagonist has potent analgesic properties and
33 may counteract central sensitization, so making it potentially useful in the management of chronic as
34 well as acute pain. Infusions of 0.4 and 0.8mg/kg/hour have been shown to be tolerated well in
35 conscious horses, with excitement seen at 1.6mg/kg/hour, although no somatic analgesia was
36 demonstrated (Fielding and others 2006). Peterbauer and others (2008) however, did demonstrate
37 analgesic properties in conscious horses after 0.6mg/kg IV bolus followed by 20µg/kg/minute
38 infusion. Analgesia is mainly somatic rather than visceral and is mediated by a number of
39 mechanisms in addition to NMDA receptor activity. In addition to infusion administration, IM bolus
40 dosing at 0.2-0.5mg/kg has been practiced by the author to manage acute episodes of pain, or
41 acute-on-chronic episodes in cases of laminitis or following surgical intervention. Epidural
42 administration (0.5, 1.0 and 2.0mg/kg) has been shown to provide analgesia lasting 30 to 75 minutes
43 (De Segura and others 1998).
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Tramadol

Tramadol is a synthetic analogue of codeine which has been used in the management of acute and chronic moderate to severe pain in humans. It is a centrally acting analgesic that has agonist activity at mu opioid receptors and also inhibits the reuptake of noradrenaline and serotonin. Although Not

licensed in the horse, ~~but~~ the pharmacokinetics and pharmacodynamics of intravenously,

intramuscularly and orally administered tramadol ~~in horses~~ have been investigated in this species

(Shilo and others 2007, Cox and others 2010, Dhanjal and others 2009, Knych and others 2013a

2013b, Giorgi and others 2007, Stewart and others 2011). ~~Tramadol is a synthetic analogue of~~

~~codeine which has been used in the management of acute and chronic moderate to severe pain in~~

~~humans. It is a centrally acting analgesic that has agonist activity at mu opioid receptors and also~~

~~inhibits the reuptake of noradrenaline and serotonin.~~ Minimum plasma tramadol levels which

provide analgesia in people vary greatly between 100 and 600ng/mL, with much of the analgesic

effect of tramadol being attributed to the M1 metabolite (O-desmethyltramadol) which has 200

times the affinity for the mu opioid receptor than the parent drug. In people there is genetically

predetermined variation in the ability to produce this metabolite, making some individuals poorly

responsive to the drug. It is unknown whether this is also true in horses, although a large individual

variation in plasma concentrations of M1 (and several other metabolites) has been demonstrated (De

Leo and others 2009, Knych and others 2013a, 2013b, Giorgi and others 2007). Oral bioavailability

following a 5mg/kg dose has been reported as approximately 65% in fasted horses, increasing to

approximately 85% in fed horses (Giorgi and others 2007), whilst Shilo and others (2007) reported

only 3% following 2mg/kg administered to fasted horses. Knych and others (2013a) used doses of 3,

6 and 9mg/kg PO which showed a very wide variation in plasma levels, with only the 9mg/kg dose

consistently achieving plasma concentrations within the human analgesic range. No adverse events

were reported apart from mild signs of colic and increased pacing behaviour in 1 horse at the higher

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7 dose. Intramuscular administration of 2mg/kg resulted in rapid and complete absorption with
8 attainment of useful plasma concentrations and no adverse effects (Shilo and others 2007). Cox and
9 others (2010) and Shilo and others (2007) reported side effects including ataxia, muscle twitching
10 and sweating for 15 minutes after 2mg/kg IV and Giorgi and others (2007) reported confusion,
11 and sweating for 15 minutes after 2mg/kg IV and Giorgi and others (2007) reported confusion,
12 agitation, tremor and tachycardia after 5mg/kg IV but not PO. Dhanjal and others (2009) reported
13 side effects following 2mg/kg IV and were unable to demonstrate an antinociceptive effect using a
14 noxious thermal stimulus. Guedes and others (2012) administered 5mg/kg PO twice daily to horses
15 with chronic laminitic pain and showed only weak evidence of analgesia, whilst ketamine showed a
16 much greater effect. Epidural administration of 1mg/kg tramadol produced analgesia after 30
17 minutes with effects lasting for 4 hours (Natalini and Robinson 2000).
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25 26 27 28 **Gabapentin**

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31 Originally used as an adjuvant anticonvulsant, ~~it~~ gabapentin was subsequently shown to be effective
32 in treating a range of chronic pain syndromes in people. It is a structural analogue of the inhibitory
33 neurotransmitter γ -aminobutyric acid (GABA) but neither parent drug nor metabolites show affinity
34 for, or activity at GABA_A or GABA_B receptors. The major mechanism of action is currently thought to
35 be via voltage dependent calcium channels, thereby reducing neurotransmitter release (Kong and
36 Irwin 2007). Pharmacokinetics of a single dose of 5mg/kg PO (Dirikolu and others 2008) and 20mg/kg
37 PO and IV (Terry and others 2010) have been evaluated in horses. No adverse events were noted
38 after either dose or route of administration although sedation was evident for 1 hour after the IV
39 dose. Rapid but poor absorption (compared with humans, rats, dogs and monkeys) followed PO
40 administration with a bioavailability of only 16% following the higher dose. ~~Not~~ Gabapentin is not
41 licensed for veterinary species but there ~~is~~ are case reports of its use in horses. Davis and others
42 (2007) describe its use in a heavily pregnant mare with suspected neuropathic pain (Davis and others
43 2007) at 2.5mg/kg PO every 8 hours, increasing dosing interval over 6 days, with apparent beneficial
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7 effect and no detriment to the foetus. It is also reported as a component of a multimodal approach
8 to provision of analgesia in the management of severe laminitis associated hoof pain, at doses
9 between 3.3mg/kg every 8 hours and 2mg/kg every 12 hours PO (Dutton and others 2009).
10
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13 14 15 **Bisphosphonates**

16
17 Bisphosphonates have been shown to reduce pain in human patients with osteoarthritis and cancer
18 pain and improve joint mobility. These drugs inhibit osteoclast proton secretion, reducing the acidity
19 of the microenvironment associated with bone resorption, so reducing activation of acid sensitive
20 ion channels in sensory neurons. A direct anti-inflammatory effect is also demonstrated by inhibiting
21 osteoblast secretion of vascular endothelial growth factor, reducing cytokine release from activated
22 macrophages (Silvina and Barbara 2014). Tiludronic acid is licenced for treatment of inflammatory
23 and degenerative joint disease in horses at a dose of 1mg/kg by intravenous infusion over 30
24 minutes. Improvement of lameness in horses suffering from bone spavin (Gough and others 2010)
25 and navicular disease (Denoix and others 2003) has been demonstrated in tiludronate treated
26 horses.
27
28

29
30 **Isoxsuprine hydrochloride** is licenced for the treatment of navicular disease in horses. Its action
31 causes vasodilation, lowers blood viscosity and inhibits platelet aggregation, thereby potentially
32 improving circulation in the affected area. Some, but inconsistent evidence of clinical efficacy has
33 been shown (Rose and others 1983; Turner and Tucker 1989).
34
35
36

37 38 39 **Conclusion**

40
41 The World Health Organisation 'pain ladder' (Fig 6) describes a graded approach to administration of
42 analgesic agents, combined with adjunctive therapies and provides a useful framework to follow for
43 pain management. Originally designed to provide guidance managing cancer pain in people, is now
44 much more widely applied. The number of drugs available for use in horses is limited, however by
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7 understanding the action of what is available and adopting a multi-modal approach, additive or
8 synergistic activities can be exploited to maximise effect whilst minimising the risk of side effects.
9
10 Adjunctive therapies can equally be vital in achieving a successful outcome (Fig 7). These range from
11 simple bandaging, hot and cold compresses or using ice, physiotherapy, acupuncture, corrective or
12 remedial farriery up to surgical interventions such as hoof wall resection, and salvage procedures
13 such as neurectomy (sometimes in conjunction with fasciotomy) and arthrodesis. Novel attributes
14 of drugs used for other indications can also be exploited for good effect, for example the use of
15 tricyclic antidepressants for chronic pain management in people and small animals. However
16 evidence of safety and efficacy in the horse in this regard is often lacking.
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23 Quiz

- 24
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26
27 1. In addition to being a general anaesthetic agent, ketamine provides profound analgesia via
28 its action at NMDA receptors. Which of the following drugs also has NMDA receptor activity?
29
30 a) Gabapentin
31
32 b) Methadone
33
34 c) Paracetamol
35
36 d) Tramadol
37
38
39
40 2. Which of the following statements is **true** of alpha 2 agonists?
41
42 a) They provide reliable somatic analgesia
43
44 b) The analgesia they provide lasts as long as the sedative effects
45
46 c) They are all licensed for administration by the oral transmucosal route
47
48 d) It is possible to achieve sedation by administering them into the epidural space
49
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52 3. The following classes of drugs can effectively be administered epidurally, **except** for which
53 one?
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7 a) Alpha 2 agonists
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9 b) Non-steroidal anti-inflammatories
10
11 c) Opioids
12
13 d) Local anaesthetics
14

15
16 4. Which of the following statements is **true** regarding intra-synovial administration of
17 analgesic agents?
18

- 19
20 a) Local anaesthetics should never be used due to their chondrotoxic effects
21
22 b) There are no drugs licenced for use by this route in the horse
23
24 c) Total dose of corticosteroids should be restricted due to the potential for adverse
25 systemic side effects
26
27 d) There are no opioid receptors present in synovial tissue therefore these drugs will not be
28 effective by this route
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33 Answers: 1 b), 2 d), 3 b), 4 c).
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36 Contributorship

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38 The author is the sole contributor to this article and accepts responsibility for its content.

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12 **Figure 1.**

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14 Epidural injection (here shown being performed at the sacro-coccygeal/first inter-coccygeal space) is
15 a useful technique for achieving more targeted drug delivery. It is important to observe good
16 hygiene and where possible to use preservative free drugs.
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21 **Figure 2.**

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23 Epidural catheter placed at the sacro-coccygeal/first inter-coccygeal space. Note the bacterial filter
24 and sterile dressing to maintain cleanliness. With appropriate care, these can be maintained for
25 several days for extended pain management without the requirement for repeated needle puncture.
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31 **Figure 3.**

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33 Commercially available epidural catheter kits. Several makes are available and contain all the
34 necessary components.
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38 **Figure 4.**

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40 Commercially available wound diffusion catheters. These are available with different diffusion
41 lengths so can be chosen to suit the extent of the surgical field. Home-made ones can be
42 constructed from long intravenous cannulae or dog urinary catheters.
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48 **Figure 5.**

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50 Commercial wound diffusion catheter in-situ following ~~dorsal~~ spinous process resection. The
51 catheter is placed during wound closure and exited through a stab incision distant from the surgical
52 site. Note the bacterial filter to preserve sterility of injected local anaesthetic agent.
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12 **Figure 6.**
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14 World Health Organisation 'Pain Ladder'. Originally designed for guidance in managing cancer pain in
15 people, it describes a logical, progressive approach to provision of analgesic agents when managing
16 many types of clinical pain.
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21 **Figure 7.**
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23 Severe case of laminitis. These cases can be extremely challenging to manage, often presenting with
24 complex pain that is refractory to conventional analgesic protocols. Adjunctive approaches are as
25 important as pharmacological therapy, with hoof wall resection and provision of adequate
26 mechanical support illustrated here.
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Epidural injection (here shown being performed at the sacro-coccygeal/first inter-coccygeal space) is a useful technique for achieving more targeted drug delivery. It is important to observe good hygiene and where possible to use preservative free drugs.

149x107mm (150 x 150 DPI)

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Epidural catheter placed at the sacro-coccygeal/first inter-coccygeal space. Note the bacterial filter and sterile dressing to maintain cleanliness. With appropriate care, these can be maintained for several days for extended pain management without the requirement for repeated needle puncture.

159x119mm (150 x 150 DPI)

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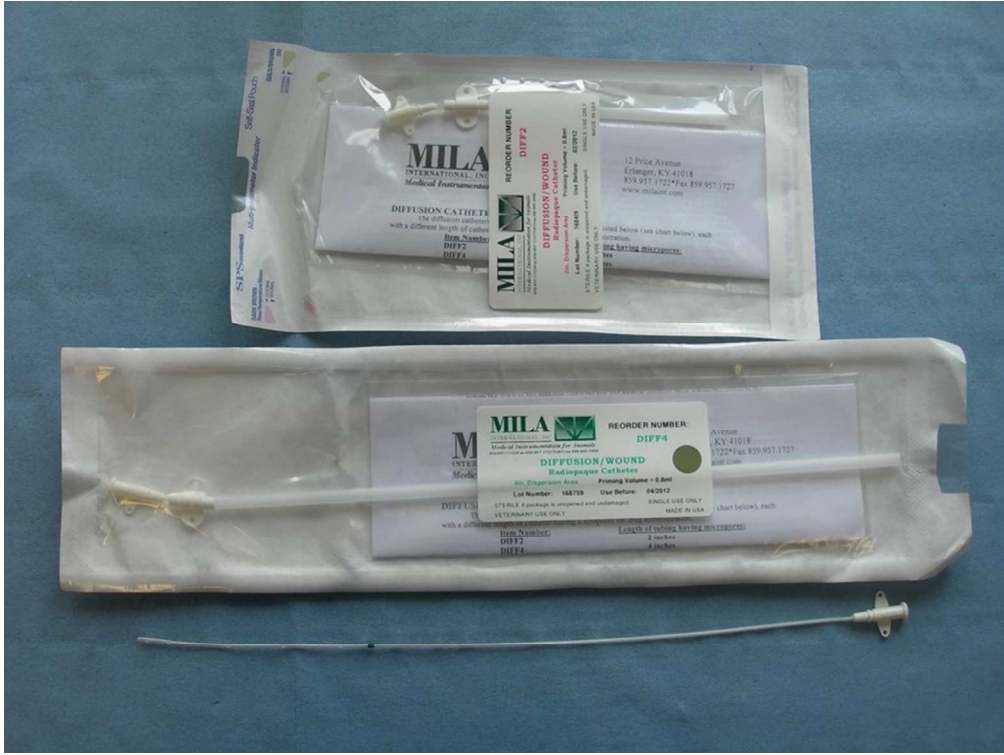


Commercially available epidural catheter kits. Several makes are available and contain all the necessary components.

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Commercially available wound diffusion catheters. These are available with different diffusion lengths so can be chosen to suit the extent of the surgical field. Home-made ones can be constructed from long intravenous cannulae or dog urinary catheters.

159x119mm (150 x 150 DPI)

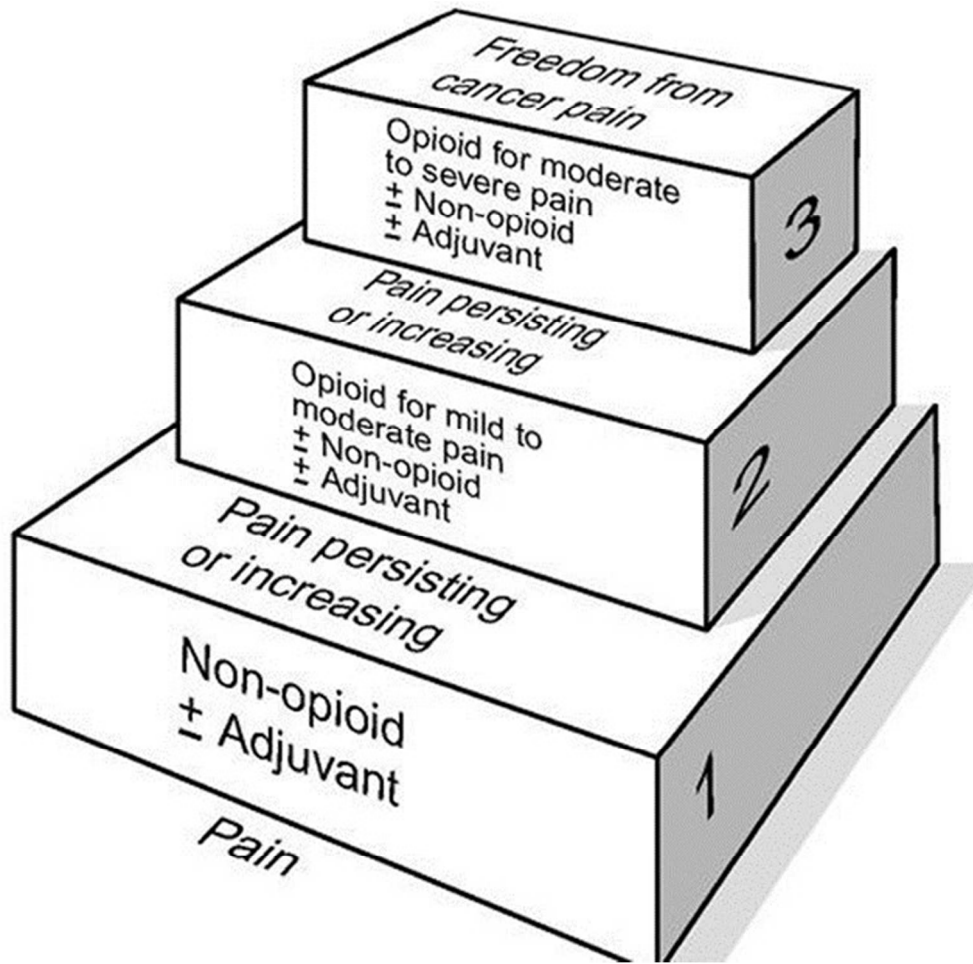


Commercial wound diffusion catheter in-situ following spinous process resection. The catheter is placed during wound closure and exited through a stab incision distant from the surgical site. Note the bacterial filter to preserve sterility of injected local anaesthetic agent.

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World Health Organisation 'Pain Ladder'. Originally designed for guidance in managing cancer pain in people, it describes a logical, progressive approach to provision of analgesic agents when managing many types of clinical pain.

109x104mm (150 x 150 DPI)

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Severe case of laminitis. These cases can be extremely challenging to manage, often presenting with complex pain that is refractory to conventional analgesic protocols. Adjunctive approaches are as important as pharmacological therapy, with hoof wall resection and provision of adequate mechanical support illustrated here.

159x119mm (150 x 150 DPI)

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