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1 **Summary**

2 The inability to talk does not diminish an animal's ability to experience pain, though it may
3 hinder the recognition and therefore lead to the under-treatment of pain. Pain assessment and
4 treatment in horses has advanced considerably recently with the publication of numerous
5 research papers in this area. This review will summarise recent research findings and suggest
6 how advances in knowledge of peri-operative pain management can be implemented in
7 equine clinical practice.

8

9 **Introduction**

10 Unresolved stress or pain behaviour was recently identified as one of the four priority welfare
11 challenges facing horses in the UK (Horseman, 2017). It is imperative that equine clinicians
12 both assess pain in horses presented for veterinary attention and ensure that pain management
13 protocols are optimised as far as possible for individual horses.

14 The understanding of the physiology of pain has evolved from the concept of a simple reflex
15 arc to one that involves many complex interactions at all levels of the peripheral and central
16 nervous system (Livingston and Chambers, 2000). Acute pain usually results from a specific
17 injury or disease and has a biologic function whereas chronic pain can be considered as a
18 disease entity in itself (Lamont et al., 2000). In chronic pain synaptic plasticity of the central
19 nervous system results in increased transmission of pain and a reduction in pain thresholds
20 at the site of original injury and also areas distant to it (Ji et al., 2003). The difference pain
21 and nociception is relevant when evaluating results of clinical and experimental studies
22 investigating analgesics. Pain is defined by the International Association for the Study of Pain
23 (IASP) as "*An unpleasant sensory and emotional experience associated with actual or*
24 *potential tissue damage, or described in terms of such damage*" (<https://www.iasp->

25 pain.org/Taxonomy). Measuring pain in animals is challenging so studies often measure
26 nociceptive responses using electrical, mechanical or thermal stimuli (Moens et al., 2003)
27 Nociceptive threshold testing is a useful technique but does not replicate the complete pain
28 experience that is seen in clinical cases and this disparity can lead to differences in response
29 to a drug in an animal presenting with clinical pain compared to an experimental model.

30 The treatment of pain is dependent upon the recognition of pain. Horses in pain may show
31 “*low*’ and/or ‘*asymmetrical*’ ears, an angled appearance of the eyes, a withdrawn and/or
32 tense stare, mediolaterally dilated nostrils and tension of the lips, chin and certain facial
33 muscles” (Gleerup et al., 2015) along with changes in behaviour (Price et al., 2003).

34 Generalised behavioural changes occur regardless of the type of pain stimulus, but these are
35 often accompanied by more specific localising pain behaviours or physiological changes
36 (Gleerup and Lindegaard, 2016). An increase in composite pain scale (CPS) and horse
37 grimace scale (HGS) has been seen in ponies following castration (Dalla Costa et al., 2014),
38 with similar results following arthroscopic surgery (Price et al., 2003). An association
39 between CPS score and survival without complication has been found in horses after
40 emergency gastrointestinal surgery (van Loon et al., 2014).

41 A review on the recognition and quantification of pain in horses along with a practical guide
42 to the implementation of pain assessment protocols in horses was recently published in this
43 journal and should be consulted for an in depth discussion of this topic (Gleerup and
44 Lindegaard, 2016).

45 The finding that surgery is painful is unsurprising, yet in 2005 only 36.9% of UK equine vets
46 provided analgesia following castration (Price et al., 2005). Hopefully, with increasing
47 awareness of equine pain behaviours and more data regarding the use of analgesics in horses
48 this under-treatment will have improved. The reluctance to use analgesics is not limited to the

49 UK. In New Zealand 55% of veterinarians have morphine available for the treatment of
50 horses, but 13% only use it (Waran et al., 2010). In an international survey of veterinarians
51 who perform equine anaesthesia 81.2% of respondents used methadone and 77% morphine
52 “rarely” or “not at all” (Wohlfender et al., 2015). The tendency towards older analgesics is
53 also highlighted with 69% of equine vets using Phenylbutazone or Flunixin either “as
54 standard” or “frequently” (Wohlfender et al., 2015), with 95% of UK equine veterinary
55 surgeons prescribing Phenylbutazone or Flunixin. This is in contrast to small animal practice
56 where there is a move towards more recently licenced treatments (Hunt et al., 2015).

57 An effective perioperative analgesic plan starts before the procedure and should be
58 appropriate to the diagnosis, planned surgery and duration of expected postoperative
59 discomfort. Pre-emptive analgesia will result in clinically effective drug concentrations
60 before surgery begins. An understanding of drug pharmacology and pain pathways is
61 essential and assists with the formulation of an individualized multimodal drug protocol
62 which targets the pain pathways at multiple levels (Muir, 2010). The theory behind the use of
63 a multi-modal technique is that lower doses of individual drugs can be used by taking
64 advantage of additive and synergistic effects that certain drugs show when given together
65 with a consequent reduction in side effects (Lamont, 2008).

66 Locoregional anaesthesia plays an important role in equine pain management protocols and
67 should be used with systemic analgesia whenever possible.

68 The horse is classified as a food producing animal within the EU, and therefore medicines
69 mentioned in this article should be prescribed in accordance with BEVA guidelines
70 (www.beva.org.uk). Medicines prescribed for competition horses should be checked against
71 the Equine Prohibited Substance List ([https://inside.fei.org/fei/cleansport/ad-h/prohibited-](https://inside.fei.org/fei/cleansport/ad-h/prohibited-list)
72 [list](https://inside.fei.org/fei/cleansport/ad-h/prohibited-list)). Commonly used analgesic drug doses are listed in Table 1.

73 **Systemic Analgesics**

74 **Alpha-2 adrenoceptor agonists**

75 Alpha-2 adrenoceptor agonists produce sedation by acting on the locus coeruleus in the
76 brain and analgesic effects via actions on supra- and spinal tissues (Murrell and Hellebrekers,
77 2005). The antinociceptive properties of the alpha-2 adrenoceptor agonists have been
78 demonstrated using both visceral and mechanical pain models (Moens et al., 2003, Muir and
79 Robertson, 1985). However, in clinical cases their sedative effects can confound the
80 interpretation of their analgesic effects, particularly as the sedative effects outlast the
81 analgesic properties (Chambers et al., 1993). Increased alpha-2 adrenoceptor selectivity
82 should theoretically lead to increased analgesic efficacy, especially as alpha-1 adrenoceptor
83 agonist activity has been found to interfere with alpha-2 adrenoceptor mediated analgesia (Gil
84 et al., 2009). The alpha-1:alpha-2 selectivity is 1:160 for xylazine, 1:260 for detomidine,
85 1:360 for romifidine and 1:1620 for (dex-) medetomidine (Sinclair, 2003, Scheinin et al.,
86 1989). Other mechanisms of analgesia may play a role as the in vivo analgesia does not
87 precisely follow the increasing alpha-2 adrenoceptor selectivity, with detomidine providing
88 better analgesia than romifidine against electrical stimulation of cutaneous regions (Moens et
89 al., 2003). This finding may not translate precisely to clinical manifestation of pain (Hamm et
90 al., 1995, Moens et al., 2003).

91 Constant rate infusions of alpha-2 adrenoceptor agonists are commonly used for sedation in
92 standing horses and to supplement inhalant anaesthetic techniques (partial intravenous
93 anaesthesia). Following an initial loading dose the aim is to administer the drug by infusion
94 to achieve stable plasma drug concentrations. This should avoid peaks and troughs in
95 analgesia or sedation and potentially lead to fewer side effects. The pharmacokinetic profile
96 of (dex-) medetomidine makes it a good choice for intraoperative continuous rate infusion

97 (CRI) (Bettschart-Wolfensberger et al., 1999)., A significant reduction in isoflurane
98 requirement is seen with medetomidine CRI (K Neges et al., 2003), and dexmedetomidine is
99 associated with improved recovery scores with only limited cardiopulmonary effects
100 (Marcilla et al., 2012). The use of a CRI of an alpha-2 adrenoceptor agonist results in a
101 subjectively more stable plane of anaesthesia and less requirement for additional anaesthetic
102 top-ups (K Neges et al., 2003) although it is not clear whether this is a result of their
103 antinociceptive effects or as a consequence of MAC reduction. Dexmedetomidine or
104 medetomidine do not have a Marketing Authorisation for administration to horses making
105 their routine use difficult to justify. Romifidine and detomidine are licensed alternatives and
106 also have an isoflurane-sparing effect (del Barrio 2017).

107 Although the alpha-2 adrenoceptor agonists lead to a reduction in intestinal motility the
108 precise effect of an intraoperative CRI on postoperative gastrointestinal function is not clear
109 and their effects on postoperative analgesia requirements have not yet been established. Their
110 use may contribute to a multimodal protocol but they should not be relied upon as the sole
111 analgesic.

112 **Ketamine**

113 Ketamine is a phencyclidine derivative and is the most commonly used agent for the
114 induction of general anaesthesia horses (Wohlfender et al., 2015). Sub-anaesthetic doses
115 produce analgesia by interacting with NMDA receptors. In chronic pain states NMDA
116 receptor antagonism limits the development of central sensitisation by inhibiting temporal
117 summation and secondary mechanical hyperalgesia (Woolf, 2011). Ketamine is commonly
118 presented as a racemic mixture of the R(-) and S(+) enantiomers though enantiopure
119 preparations containing the S(+) isomer are available. S(+)-Ketamine is twice as potent as the
120 racemic mixture and is associated with faster recovery times. These possible benefits have led

121 to preliminary investigations into its use in the horse (Canola et al., 2015, Casoni et al., 2015,
122 Larenza et al., 2009) though this preparation does not have a veterinary Marketing
123 Authorisation.

124 In healthy patients, after administration of ketamine direct stimulation of the central nervous
125 system leads to increased sympathetic tone and subsequent increases in blood pressure and
126 heart rate. In sick patients the direct depressant effects of ketamine on the myocardium may
127 become apparent due to depletion of catecholamine stores within the sympathetic system. A
128 MAC sparing effect of 37% was found under halothane anaesthesia when ketamine was
129 given by CRI whilst increasing cardiac output (Muir and Sams, 1992). Low dose ketamine
130 infusion (20 mcg/kg/min) in conscious experimental horses reduces the response to electrical
131 cutaneous stimulation (Peterbauer et al., 2008). The same can be found in clinical cases;
132 horses with naturally occurring laminitis that received 0.6mg/kg/hr ketamine for six hours
133 once daily for three days, alongside tramadol twice daily, had increased forelimb loading
134 both during and after treatment and this was attributed to ketamine's effect on central
135 sensitization (Guedes et al., 2012). The same laminitic horses also had lower concentrations
136 of circulating inflammatory prostaglandins TNF- α and thromboxane B(2) indicating an anti-
137 inflammatory effect of systemic ketamine use. Clinical experience suggests that a low dose
138 ketamine CRI may have some benefit in cases that involve orthopaedic and integument pain
139 that is not responding to conventional treatment with opioids and NSAIDs, though it may be
140 of less use in visceral pain (Matthews et al., 2004).

141 **Opioids**

142 Opioids, particularly butorphanol, are often included in sedation protocols though
143 perioperative use of opioids is still limited in equine practice (Wohlfender et al., 2015). This
144 may be related to apprehension over possible side effects, with the potential for excitability

145 following intravenous injection and decreased intestinal motility following general
146 anaesthesia being commonly stated concerns (Clutton, 2010).

147 Horses that received a morphine bolus followed by a CRI during halothane anaesthesia had
148 similar haemodynamic variables to those that did not (Clark et al., 2005) and the
149 administration of morphine was also associated with the need for less additional anaesthetic
150 agent, fewer attempts to stand and shorter times to standing (Clark et al., 2005, Clark et al.,
151 2008, Love et al., 2006). The optimal dose of morphine for analgesia in clinical cases has not
152 yet been established. The early dose-response studies investigated relatively high doses of
153 morphine in small numbers of pain-free, healthy horses using experimental threshold testing
154 assays rather than clinical pain (Kalpravidh et al., 1984b, Roger et al., 1985). (Kalpravidh et
155 al., 1984b). In horses undergoing airway surgery 0.2 mg/kg bwt had no additional benefits
156 over 0.1 mg/kg bwt on the duration or quality of recovery following anaesthesia although the
157 surgery performed was relatively non-invasive (compared to orthopaedic surgery) and post-
158 operative pain was not assessed (Love et al., 2006). Conflicting results on the association of
159 post anaesthetic colic and the use of morphine may lead to difficulties when deciding on its
160 use. In one retrospective study the use of morphine was associated with a four-fold increase
161 in the risk of colic following orthopaedic surgery (Senior et al., 2004), however another
162 retrospective study found no increased incidence of post anaesthetic colic in horses that
163 received morphine compared to those that did not (Andersen et al., 2006). Morphine is
164 associated with an increase in locomotor activity in healthy pain free horses (Carregaro et al.,
165 2007). This increase in locomotor activity is less likely to be seen in horses having surgery or
166 those that are already experiencing pain (Mircica et al., 2003, Muir, 1981), with horses that
167 received 0.1 mg/kg bwt morphine for sedation for standing surgery showing no intraoperative
168 ataxia or locomotor activity (Potter et al., 2016). The conflicting arguments presented above
169 highlight the different findings that may be seen in experimental and clinical studies and

170 explain why the use of systemic morphine in horses is controversial. More data is available to
171 support the use of morphine by the epidural or intraarticular routes in horses.

172 Buprenorphine has a marketing authorisation in the UK for postoperative analgesia in horses.
173 It produces antinociception to thermal stimuli (Love et al 2012) and these experimental
174 findings were provided more effective postoperative analgesia than butorphanol after elective
175 surgical procedures performed under general anaesthesia without detrimental effects (Taylor
176 et al., 2016, , . The use of buprenorphine in combination with Detomidine via CRI for
177 standing surgery resulted in more complications than the use of morphine (Potter et al.,
178 2016). All horses that received buprenorphine showed box walking and tremors/shivering,
179 half of the horses were hypersensitive to noise in the postoperative period. No horses that
180 received morphine showed complications, though only a small sample size of four horses per
181 group was used. This increased incidence of side effects in the buprenorphine group may be
182 due to the effect that detomidine has on the excretion of drugs administered at the same time
183 resulting in a higher plasma concentration than that achieved when buprenorphine is given
184 alone (Pakkanen et al., 2015). In order to investigate this hypothesis plasma samples would
185 have needed to be taken for buprenorphine concentration determination. In addition local
186 anaesthetic blocks were used as part of the analgesic protocol – if these were effective the
187 requirements for buprenorphine would have been reduced. Sublingual use of buprenorphine
188 has been reported in a five month old thoroughbred filly with a cervical vertebral fracture
189 (Walker, 2007). A dose of 0.006 mg/kg bwt was given twice daily with onset of analgesia
190 and sedation subjectively assessed to occur 45 minutes after administration into the
191 interdental space. Mucosal absorption of buprenorphine following sublingual administration
192 may provide a practically easy method of providing longer duration postoperative analgesia.

193 Butorphanol is the most commonly used opioid in equine practice (Wohlfender et al., 2015).
194 In nociceptive studies of visceral and superficial pain 0.2 mg/kg bwt was suggested as the

195 optimal dose (Kalpravidh et al., 1984a). The duration of analgesia for visceral pain was 4
196 hours after 0.22 mg/kg bwt, compared to 1 hour of visceral analgesia after 0.66 mg/kg bwt
197 morphine (Kalpravidh et al., 1984b). Despite this, no improvement in recovery quality or a
198 reduction in inhalational requirement has been seen during anaesthesia (Bettschart-
199 Wolfensberger et al., 2011, Dias et al., 2014). Postoperative CRI of butorphanol at 13
200 mg/kg/hr was associated with lower plasma cortisol concentrations, improved behaviour
201 scores and less bodyweight loss (Sellon et al., 2004). This finding is consistent with the
202 horses receiving butorphanol CRI postoperative experiencing less pain. It has been
203 demonstrated to be an ineffective sole analgesic following castration (Love et al., 2009).

204 Methadone has a UK Marketing Authorisation for use in cats and dogs. A dose of 0.2 mg/kg
205 bwt has been demonstrated to have an antinociceptive effect to mechanical, thermal and
206 electrical stimulus when administered in combination with acepromazine or detomidine to
207 horses, with the combination of methadone and detomidine having the greatest effect (Lopes
208 et al., 2016). In a lipopolysaccharide induced synovitis model methadone was found to
209 produce analgesia with less reduction in gastrointestinal sounds than morphine (Carregaro et
210 al., 2014). If this finding is found to be consistent in clinical cases this may alleviate some of
211 the concerns of postoperative ileus after morphine. Studies on the analgesic effect of
212 methadone on animals experiencing clinical pain are currently limited.

213 Transdermal fentanyl patches have been used to treat horses with pain non-responsive to
214 NSAID treatment, application of either one or two 10mg fentanyl patches to the
215 antebrachium was found to reduce pain but not lameness scores. Uptake of drug is varies
216 between sites of application; the thorax or groin results in greater systemic absorption with
217 shorter lag time than the limb (Mills and Cross, 2007). The method used to prepare the area
218 for transdermal drug administration has an effect on the systemic absorption as does variation
219 in skin thickness between sites (Mills and Cross, 2006, Mills et al., 2004). The time taken to

220 reach analgesic serum concentrations varies from 1 to 14 hours (Thomasy et al., 2004,
221 Maxwell et al., 2003), and in one study plasma concentrations of fentanyl failed to reach
222 analgesic levels in 33% of horses (Orsini et al., 2006). Transdermal patches were found to be
223 easy to apply and well tolerated in foals, but similar to adults systemic absorption was
224 variable with no assessment of analgesic provision (Eberspacher et al., 2008). Based on the
225 studies when placing a transdermal fentanyl patch the skin should be clipped and prepared
226 with alcohol and chlorhexidine solution (Mills and Cross, 2006). The most appropriate site
227 to apply the patch is the thorax. Due to impracticalities of keeping the patch in position use of
228 a limb is better suited for keeping the patch in contact with the skin. The variable lag time
229 and systemic absorption means that the use of transdermal fentanyl patches requires close
230 attention to the monitoring of pain scores, but may be useful for long lasting analgesia of
231 outpatients postoperatively.

232 **Lidocaine**

233 Lidocaine is often used systemically for its prokinetic properties in horses with colic, its
234 analgesic properties have also been shown in horses undergoing castration (Murrell et al.,
235 2005), and its use is associated with a reduction in the use of inhalational agents (Schuhbeck
236 et al., 2012). Its use in standing horses resulted in analgesia to a thermal stimulus but not to
237 colorectal distension, suggesting a possible role in managing somatic pain (Robertson et al.,
238 2005).

239 The potential for adverse effects should be considered when lidocaine is used systemically,
240 neurological signs of toxicity include rapid blinking, anxiety, visual disturbance and ataxia
241 and may be seen at doses of 30 µg/kg/min (Meyer et al., 2001). Horses that had a 1.5 mg/kg
242 bwt loading bolus developed clinical signs earlier than those horses that did not, with
243 cardiovascular signs of toxicity not apparent at doses causing neurological signs. The

244 systemic dose needed to produce toxic side effects may be reduced in compromised patients
245 due to a slower hepatic clearance of the drug. General anaesthesia may make recognition of
246 toxicity harder. A bolus of lidocaine before CRI is often used, but this may not be required as
247 no inhalant sparing effect or difference in cardiopulmonary parameters and recovery scores
248 was found between horses that did or did not receive a loading bolus whilst under isoflurane
249 anaesthesia (Nannarone et al., 2015). Not giving a loading bolus may reduce the potential for
250 reaching a toxic threshold.

251 Intraoperative administration of lidocaine may have a negative impact on quality of recovery
252 from general anaesthesia (Schuhbeck et al., 2012, Valverde et al., 2005) so it is recommended
253 that the lidocaine CRI should be stopped at least 30 minutes before transfer to the recovery
254 box and also that additional sedation in recovery may be required (Valverde et al., 2005).

255 One study supports the therapeutic role of lidocaine in horses with ileus by reduction in
256 reflux and shorter length of hospitalisation (Malone et al., 2006), however a more recent
257 study found no effect of lidocaine administration on total reflux volume or duration, or on
258 postoperative survival (Salem et al., 2016). Equivocal results on its use for analgesia and
259 reduction of postoperative ileus mean that lidocaine should not be relied upon to provide
260 post-operative analgesia and other analgesics should be administered concurrently.

261 **Non-Steroidal Anti Inflammatory Drugs**

262 NSAIDs remain the mainstay of analgesia in horses and, unless there is a contra-indication to
263 their administration, should be included in the analgesic protocols of horses undergoing
264 surgery . The variety of formulations and their long duration of action make them an
265 attractive choice, with phenylbutazone and flunixin the most commonly used drugs
266 (Wohlfender et al., 2015, Price et al., 2002). Clinical experience and familiarity probably
267 form the basis of NSAID selection in clinical practice. Clinicians often express a preference

268 for the use of Phenylbutazone in horses with orthopaedic pain and Flunixin for horses with
269 visceral pain, though this is not supported by the evidence (Johnson et al., 1993). Pre-emptive
270 administration of NSAIDs may also help to reduce the likelihood of development of central
271 sensitisation as has been shown with opioid and NSAID administration in other species
272 (Lascelles et al., 1998, Lascelles et al., 1997) and timing their administration so that they are
273 given before surgery means that they will be having an analgesic effect when the effects of
274 anaesthesia are waning.

275 NSAIDs act by inhibition of cyclo-oxygenase (COX-1 and -2) enzymes, resulting in a
276 reduction in the production of prostaglandins and thromboxane. COX-2 selectivity was
277 thought to be preferential with COX-1 being a constitutive enzyme required for coagulation,
278 protection of gastric mucosa and maintenance of renal blood flow. It is now known that
279 COX-2 is also a constitutive enzyme in the eye, central nervous system and kidney, with
280 COX-2 required for the healing of gastric ulcers. Potential adverse effects reported for
281 NSAID use at therapeutic doses in the horse include gastric ulceration, renal dysfunction and
282 right dorsal colitis (Andrews and McConnico, 2009).

283 Meloxicam is a COX-2 selective NSAID that is licenced for the treatment of acute and
284 chronic musculoskeletal disorders and colic. Evidence also exists to suggest a beneficial
285 effect on healing of the intestinal mucosa following ischaemic injury when meloxicam is
286 used (Little et al., 2007). When compared to flunixin for provision of postoperative analgesia
287 following surgery for strangulating small intestine, meloxicam showed no difference in
288 analgesia based upon clinical evaluation, however when pain scores were compared horses
289 that received flunixin had significantly lower scores (Naylor et al., 2014)..

290 Firocoxib is licenced for the treatment of pain associated with osteoarthritis, and vedaprofen
291 for the treatment of postoperative pain. Firocoxib has shown to work as well as both

292 Phenylbutazone and Vedaprofen for treatment of osteoarthritis without treatment related side
293 effects (Doucet et al., 2008, Koene et al., 2010).

294 The use of topical NSAID creams and gels is reported clinically, with a cream containing 1%
295 diclofenac sodium available outside the UK. There is a lack of evidence to support the
296 clinical use of these preparations.

297 **Other Systemic Analgesics**

298 The use of gabapentin is documented in case reports for the treatment of neuropathic pain
299 unresponsive to other treatments (Davis et al., 2007), and management of severe hoof pain in
300 combination with other systemic analgesics (Dutton et al., 2009). Tramadol co-administered
301 with a low dose of ketamine was successfully used as part of an analgesic protocol in a horse
302 with pain due to laminitis (Guedes et al., 2012). Tramadol 5mg/kg bwt orally every 12 hours
303 for 1 week gave limited analgesia for three days only. The addition of a ketamine infusion at
304 0.6 mg/kg/hr, for 6 hours on the first three days of treatment, significantly increased the level
305 and duration of analgesia. An experimental study reported a lack of anti-nociceptive effects
306 against thermal, electrical or pinprick stimulation following administration of tramadol at 2
307 mg/kg bwt i.v. (Dhanjal et al., 2009, Seo et al., 2011) although the duration of antinociception
308 following xylazine administration was extended by the concurrent use of tramadol (Seo et al.,
309 2011) suggesting that it may play a useful role as part of a multimodal analgesic protocol.

310 The use of paracetamol as an adjunct treatment for laminitis has also been described in a
311 pony (West et al., 2011). Further research is needed before routine use of these drugs can be
312 recommended although their use can be considered on an individual case basis.

313 **Locoregional Techniques**

314 **Local Anaesthesia**

315 The use of local anaesthetics for the diagnosis of lameness in horses is commonplace; the
316 same techniques and drugs can also be used for the provision of effective perioperative
317 analgesia. The versatility of this class of drug means that it can be used in multiple different
318 ways, with a technique available for most situations. Local anaesthetics stop the transmission
319 of the pain signal by binding to and blocking Na⁺ channels when they are in the open or
320 inactivated state, for this reason nerves of high firing frequency are most likely to be blocked.
321 One limitation of the local anaesthetics is their reduced performance in infected tissues, this
322 is due to the altered pH of the tissue affecting the fraction of unionised drug (Ueno et al.,
323 2008). In this instance a nerve block at a site remote from the infected tissue may be of
324 benefit.

325 The use of nerve blocks to facilitate dental and ophthalmic procedures in the standing and
326 anaesthetised horse is well described. The inferior alveolar (mandibular) block will
327 desensitise the mandible and lower dental arcade (Harding et al., 2012) and the maxillary
328 block desensitises most structures of the maxilla including the rostral maxilla, paranasal
329 sinuses and upper dental arcade (Bardell et al., 2010). Accidental blockade of the lingual
330 nerve has been reported to occur with blockade of the mandibular nerve resulting in self
331 trauma of the tongue (Caldwell and Easley, 2012). When performing nerve blocks of the
332 horse's eye it should be remembered that the auriculopalpebral/palpebral nerve supplies only
333 motor function and, although a block of this nerve will aid in examination of the eye, it does
334 not desensitise any structures. Blockade of the frontal, lacrimal, zygomatic and infratrochlear
335 nerves will desensitise the periorbital region. A retrobulbar block will facilitate enucleation,
336 but may need to be accompanied by an auriculopalpebral block for immobilising the upper
337 eyelid.

338 Infiltration of local anaesthetic into the testicle, cord and subcutaneously before castration in
339 standing, sedated horses is routine; this technique is also useful in anaesthetised horses and

340 may reduce the incidence of movement as well as requirement for supplemental doses of
341 anaesthetics (Portier et al., 2009). Subcutaneous infiltration of local anaesthetic is easy to
342 perform before wound closure.

343 Increasingly, orthopaedic surgery is being performed in standing, sedated horses and nerve
344 blocks can improve surgical conditions and reduce the requirements for additional chemical
345 restraint. In standing, sedated horses distal limb blocks should be performed before
346 arthroscopy or fracture repair, with specific nerve blocks often being used alongside a ring
347 block (Payne and Compston, 2012). Intravenous regional techniques for delivery of
348 antimicrobials is commonly implemented in equine practice and the same technique can be
349 used to desensitise the distal limbs. Desensitization of the limb being operated on with local
350 anaesthesia can also be considered in horses having the procedures done under general
351 anaesthesia. Careful thought should be given to the individual case as ataxia and effects on
352 control of the limb are potential hazards during recovery from anaesthesia.

353 Intraarticular injection following arthroscopic procedures can contribute to postoperative
354 analgesia. Morphine, local anaesthetics and the alpha-2 adrenoceptor agonists all provide
355 analgesia for inflamed joints (van Loon et al., 2010). Caution must be used as systemic
356 uptake of the drugs still occurs and systemic side effects can still be seen (Di Salvo et al.,
357 2014). Concern over chondrotoxicity of the local anaesthetics has been a topic of discussion
358 in recent years. In an in vitro cell culture preparation of equine chondrocytes mepivacaine
359 was the least chondrotoxic, with bupivacaine showing the most chondrotoxicity to equine
360 cartilage (Park et al., 2011). However, in vivo effects do not always mimic the changes seen
361 in laboratory cell culture preparations and the method of delivery of the local anaesthetic
362 probably has a significant impact on the effects of local anaesthetics on chondrocytes since in
363 people continuous infusion of local anaesthetic into the joint has a more deleterious effect
364 than would be expected from a drug effect alone (Dragoo et al., 2008). A single injection of a

365 low concentration of local anaesthetic would appear to be safe, whereas the effects of a
366 continuous infusions require further investigation (Webb and Ghosh, 2009).

367 When morphine (0.05 mg/kg) is given intraarticularly, to horses with lipopolysaccharide
368 induced synovitis, it is detectable within the synovial fluid for 24 hours and results in less
369 swelling and lameness than the same dose of morphine given IV (Lindegaard et al., 2010a,
370 Lindegaard et al., 2010b, Lindegaard et al., 2010c). The reduced swelling of the joint when
371 morphine was given intraarticularly supports morphine having a peripheral anti-inflammatory
372 effect as well as a central mechanism of action. Despite a reduction in lameness there was no
373 difference in pain score between the two routes of administration (Lindegaard et al., 2010c).

374 Paravertebral thoracolumbar anaesthesia in horses having standing laparoscopic procedures
375 produces good to excellent anaesthesia in 80% of cases (Moon and Suter, 1993).

376 **Epidural and Subarachnoid Anaesthesia and Analgesia**

377 Epidural anaesthesia was first described in the horse almost 100 years ago (Pape and
378 Pitzschk, 1925). Use of both a single injection and repeated dosing via an epidural catheter
379 are options for both intra-operative and post-operative analgesia. Local anaesthetics, opioids
380 and alpha-2 adrenoceptor agonists can all be administered via the epidural space, though it
381 must be remembered that systemic uptake of the drugs will occur and side effects of may
382 become apparent for example, sedation and ataxia Epidural injections are most commonly
383 performed via the first intercoccygeal space, with location of the space most practically
384 identified by repeatedly raising and lowering the tail.. Subarachnoid injection, where the drug
385 is injected into the cerebrospinal fluid rather than the epidural space, can be performed at the
386 lumbar-sacral (L7-S1) space, though this technique is more challenging and often resented by
387 the horses (Natalini and Driessen, 2007) which limits its use clinically.

388 Opioids, most commonly morphine, are used for epidural analgesia. Opioid receptors are
389 found extensively in the dorsal horn of the spinal cord, and opioid agonists can provide
390 effective and long-lasting pain relief (Valverde et al., 1990, Cousins and Mather, 1984).
391 Analgesia can be achieved as far cranially as the thoracic dermatomes after a single epidural
392 injection of morphine diluted to a volume of 20mL (Natalini and Robinson, 2000). Another
393 potential benefit is that morphine administered into the epidural space has also been found to
394 inhibit the development of hyperalgesia in an experimental model of synovitis (van Loon et
395 al., 2012).

396 Concern over side effects is similar when administering opioids in the epidural space as when
397 they are given systemically although the dose administered epidurally is usually lower than
398 that given systemically which should reduce the risk or intensity of side effects. In healthy
399 horses morphine reduced gastrointestinal transit times in healthy horses but not when used for
400 provision of analgesia for laparoscopic castration (Sano et al., 2011, Martin-Flores et al.,
401 2014) indicating differences in effects between healthy and painful horses.

402 Both methadone and buprenorphine also provide effective analgesia when given epidurally.
403 Methadone provides effective analgesia but with a shorter duration than that reported for
404 morphine (Olbrich and Mosing, 2003). In horses undergoing bilateral stifle arthroscopy
405 epidural buprenorphine plus detomidine produced analgesia of similar intensity and duration
406 to that provided by morphine and detomidine (Fischer et al., 2009).

407 Combining a local anaesthetic with an opioid extends the duration of analgesia compared to
408 the use of an opioid alone (Hendrix et al., 1996). However, care should be taken with the
409 volume of local anaesthetic used as cranial spread can impair the function of the pelvic limbs
410 and cause ataxia or even paralysis. If an epidural including a local anaesthetic is to be
411 administered consider restraining the horse in stocks and ensure that everyone working with

412 the horse is aware that ataxia is a potential risk. The total volume used will depend on the size
413 and conformation of the horse and the drug or combination of drugs used. Less than 10mL
414 total volume should be used in adult horses if a combination including a local anaesthetic is
415 used, as cranial spread of volumes greater than this may cause hindlimb paralysis and
416 recumbency of the patient (Natalini and Driessen, 2007).

417 Alpha-2 adrenoceptor agonists administered epidurally can increase both the sensory and
418 motor blockade compared to an opioid or local anaesthetic used alone. Speed of onset is
419 quicker and an extended duration of action is also seen (Grubb et al., 1992). Doses of other
420 drugs given at the same time should be reduced. Systemic uptake of the drug also occurs and
421 signs of sedation, ataxia and cardiovascular changes such as bradycardia and atrioventricular
422 block may become apparent.

423 **Adjunctive Therapies**

424 When devising a perioperative analgesia plan the use of non-drug therapy should also be
425 considered. Good nursing care is imperative and in addition the use of cold packs on inflamed
426 tissues and physiotherapy when appropriate will also help. Although acupuncture is
427 frequently employed by equine veterinarians in the treatment of chronic pain (Bergenstrahle
428 and Nielsen, 2016) its efficacy for treatment of acute pain and in the perioperative period is
429 unknown. Its use for the treatment of colic pain has been shown to be less effective than
430 butorphanol in one method (Skarda and Muir, 2003) and ineffective in another (Merritt et al.,
431 2002).

432 **Conclusion**

433 The ability to recognise pain behaviours in horses is an essential skill of the equine
434 veterinarian. The publication of clinically useful pain scales for this species will further aid in
435 the recognition of pain in the perioperative period. Careful consideration should be given to

436 the mechanism of the pain stimulus when planning a surgery and an analgesic plan. Table 2
437 suggests when each therapy should be used. The use of multimodal analgesia utilising drugs
438 from different classes and given both systemically and locoregionally will improve outcomes
439 and the welfare of patients.

440

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