

Impact case study (REF3b)

Institution: University of Glasgow
Unit of Assessment: Unit 6; Agriculture, Veterinary and Food Science
Title of case study: Advancing clinical assessment of acute pain in companion animals
<p>1. Summary of the impact</p> <p>The Glasgow Composite Measure Pain Scale (CMPS) has provided the first validated pain questionnaire for the rapid assessment of acute pain in dogs in surgical and clinical settings. Developed by the University of Glasgow School of Veterinary Medicine, the scale aids clinical decisions on appropriate pain relief intervention and has been freely downloaded by over 3,000 clinical users since its launch in 2008. In addition, it has been used extensively by veterinary healthcare companies to successfully obtain regulatory approval for analgesic drugs and in marketing support materials. The University of Glasgow researchers have been instrumental in developing international pain guidelines with the World Small Animal Veterinary Association, which represent more than 180,000 veterinarians worldwide, and has thereby promoted awareness of pain management in companion animals.</p>
<p>2. Underpinning research</p> <p>Pain and the resulting reduction in quality of life are both subjective experiences unique to each individual. The assessment and treatment of pain in animals has long been a controversial and often overlooked issue. For the past 15 years, the University of Glasgow School of Veterinary Medicine Pain and Welfare group, led by Professors Andrea Nolan and Jacky Reid, have conducted comprehensive studies to identify the underlying pathophysiology and pharmacology of pain in animals, establishing how pain can be practically assessed and managed by veterinarians.</p> <p><i>Revealing the pathophysiology and pharmacology of pain in animals</i></p> <p>The research group characterised the presence of pain and its underlying mechanisms using two models of disease in sheep: a clinical model of pain – sheep foot rot; and the experimental sheep model using injection of an inflammatory and pain sensitising agent (carrageenan). Through these translational research studies Professor Nolan (along with Dr Dolan, now Glasgow Caledonian University) identified spinal cord glutamate receptors in pain pathways that could be directly targeted by analgesic drugs,¹ and described two glutamate receptor subtypes (group I and II), which each had a different response threshold to mechanical stimulation.² In contrast to sheep with experimentally-induced pain, sheep with clinical pain induced by foot rot were shown to have higher levels of two additional glutamate receptor subtypes (mGluR₃ and mGluR₅) in the spinal cord.³ The group also examined the expression of two genes (<i>cyclooxygenase-2</i> and <i>Egr-1</i>) that are markers of neuronal changes in spinal cord tissue taken from animals with clinical pain induced by persistent inflammation.⁴ Pain treatment reduced changes in these genes, thereby preventing the evolution of chronic pain. Nolan’s group was the first to show altered levels of glutamate receptors in the sheep spinal cord after surgery, and to demonstrate that treatment with non-steroidal anti-inflammatory drugs after surgery could increase subsequent pain thresholds.</p> <p><i>Development of a robust and validated pain assessment questionnaire for dogs</i></p> <p>Aware of the McGill pain scale – an objective scale for assessing pain in humans - and the absence of a similar scale in veterinary medicine, the University of Glasgow researchers worked to develop a questionnaire for assessing acute pain in dogs. At that time, pain management in veterinary medicine was a much neglected field, and there were no valid tools to assess pain in any animal species. The questionnaire was developed between 1997 and 2007 in collaboration with Professor Marian Scott (University of Glasgow School of Mathematics & Statistics). The group adopted a psychometric approach to tool development. They surveyed 69 practising veterinarians to provide words and expressions that represented their observational assessment of a dog experiencing pain. A total of 279 words obtained were reduced to 47 and refined into seven behavioural categories. A second group of 75 veterinary surgeons allocated intensity values to the range of words within each category and the resulting product was named the Glasgow Composite Measure Pain Scale (CMPS). The group then optimised the CMPS into a form that was practically quick and easy to use. The CMPS short form (CMPS-SF) contained 30 word descriptors within six</p>

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categories of behaviour in dogs (vocalisation, attention to painful area, mobility, response to touch, demeanour and posture/activity). Each category was numerically ranked according to associated pain severity. The sum of the rank scores yielded the composite total pain score out of 24 (or 20 if it was not possible to assess mobility). The CMPS-SF was applied by a group of veterinary surgeons from 3 international, English speaking sites to a total of 122 dogs post-surgery. These individuals were also asked to indicate the level at which they felt the dog required analgesia based on their clinical judgement. A score equal to or greater than 6/24 (or 5/20) indicated the point at which animals were experiencing significant pain levels. Importantly, the CMPS-SF was the first validated pain scale to define a threshold for intervention with analgesics in dogs.⁶

Together, the underpinning research for the CMPS/CMPS-SF was supported by over £400,000 of funding from Pfizer animal health and the BVA welfare trust.

Key researchers: Andrea Nolan (Professor of Veterinary Pharmacology [1998-present], Vice Principal (VP) Learning & Teaching [2004-2009], Senior VP & Deputy Vice-Chancellor [2009-July 2013]); Jacky Reid (Professor of Veterinary Anaesthesia [1998-2006], Honorary Senior Research Fellow [2006-present]); Marian Scott (Professor of Environmental Statistics [2000-present]).

3. References to the research

1. Dolan S & Nolan AM. [N-methyl D-aspartate induced mechanical allodynia is blocked by nitric oxide synthase and cyclooxygenase-2 inhibitors.](#) *Neuroreport* 1999; 10, 449-452. [no doi available, PDF available on request]
2. Dolan S & Nolan AM. [Behavioural evidence supporting a differential role for group I and II metabotropic glutamate receptors in spinal nociceptive transmission.](#) *Neuropharmacology* 2000; 39, 1132-1138. doi:10.1016/S0028-3908(99)00200-2
3. Dolan S, *et al.* [Up-regulation of metabotropic glutamate receptor subtypes 3 and 5 in spinal cord in a clinical model of persistent inflammation and hyperalgesia.](#) *Pain* 2003; 106, 501-512. doi:10.1016/j.pain.2003.09.017
4. Dolan S, *et al.* [Co-induction of cyclooxygenase-2 and early growth response gene \(*Egr-1*\) in spinal cord in a clinical model of persistent inflammation and hyperalgesia.](#) *Mol Pain* 2011; 7, 91. doi:10.1186/1744-8069-7-91
5. Holton L, *et al.* [Development of a behavioural-based scale to measure acute pain in dogs.](#) *Vet. Record.* 2001;148, 525-531 doi:10.1136/vr.148.17.525
6. Reid J, *et al.* [Development of the short-form Glasgow Composite Measure Pain Scale \(CMPS-SF\) and derivation of an analgesic intervention score.](#) *Animal Welfare* 2007; 16, 97-104

4. Details of the impact

The Glasgow CMPS-SF

Assessing pain in animals is a challenge for veterinarians because of the inherent communication difficulties and because different animals and species have varying responses to pain. An animal will experience acute pain immediately after a traumatic injury (e.g. after breaking a bone or following surgery) and appropriate intervention with pain relief can significantly enhance recovery and minimise the risk of chronic pain developing. The CMPS-SF is the first statistically validated scale to incorporate a structured and objective approach to pain assessment in dogs. This behaviour-based assessment provides an accurate, unbiased indication of the pain level experienced by the animal. The assessment is easy and quick to perform with results available in 3–4 minutes. Uniquely, the CMPS-SF provides a threshold for analgesic intervention, thereby enabling clinical decision making on pain relief provision.

A practical resource for veterinarians to guide clinical decisions

The CMPS-SF is available for open-access download from the University of Glasgow website. Since 2008, the CMPS-SF has been downloaded by 3266 non-academic users worldwide - 3109 and 157 of whom stated their intended use was in veterinary practice and industry, respectively.^a However, once downloaded the CMPS-SF can be copied; download data are, therefore, likely to underestimate total usage. The CMPS-SF is further disseminated and used within the veterinary profession through its inclusion in textbooks, establishing it as a standard reference for measuring pain for both teaching and veterinary practice. The CMPS-SF has featured in key pain

management handbooks for practitioners such as 'Anesthesia for Veterinary Technicians' (2010) and 'Practical Emergency and Critical Care Veterinary Nursing' (2013), with global sales of 2,600 and 750 respectively.^b

Impacts on the veterinary healthcare industry

As detailed below, the CMPS-SF has been used by the following market-leading veterinary healthcare companies since 2008: Merial, Novartis Animal Health Inc., Nexcyon Pharmaceuticals Inc., Vetoquinol, Dechra and Animalcare.

Use of the CMPS-SF in clinical trials and regulatory application for novel analgesics

Before new analgesic drugs for animals can be made available on the market, they must gain regulatory approval, a process that relies on robust clinical trial data that demonstrate a drug's effectiveness in the target species using validated pain measurement scales. The following applications have gained regulatory approval based on data obtained with the CMPS-SF:^c

- 2008, Merial Ltd.— approval from the US Food and Drug Administration for 'previcox' chewable tablets in dogs following orthopaedic surgery.
- 2011 – approval from the European Medicines Agency for 'Recuvyra' in dogs following orthopaedic surgery.
- 2011 Novartis Animal Health US Inc. – approval from the FDA for 'DERAMAXX' chewable tablets in dogs following dental surgery.
- 2012, Nexcyon Pharmaceuticals Inc. – approval from the FDA for 'Recuvyra' in dogs following general surgery.

Use of the CMPS-SF by veterinary healthcare for promotion of analgesics

Vetoquinol is the 10th largest veterinary pharmaceutical company in the world, with reported sales of €17M for the first half of 2013. Since mid-2012, its UK subsidiary has used the CMPS-SF as marketing support for its pain medications (including *Cimalgex*[®]—the fastest growing non-steroidal anti-inflammatory drug for dogs in the UK and Ireland).^d The company has reproduced the original copy and layout of the CMPS-SF on Vetoquinol branded pads containing 50 leaves of the questionnaire (see example sheet). Vetoquinol specifically chose the CMPS-SF acute pain scale because:

'it is scientifically validated and well known in the UK whilst being simple to use....it was recommended to us by various veterinary surgeons throughout the UK'^e

Almost 2,000 copies of the pad have been distributed (100,000 individual copies of the acute pain scale) to complement Vetoquinol products. The Vetoquinol CMPS-SF marketing supporting materials were a major focus of *Cimalgex*[®] promotional activities at the London Vet Show (November 2012) and British Small Animal Veterinary Association Congress exhibition (April 2013)^d — these prominent events were attended by over 3300 and 4000 veterinary professionals respectively.

Since 2010, Animalcare have employed a similar use of the CMPS-SF to support their analgesic products. The company have distributed the CMPS-SF in pads (50 sheets) to veterinary surgeons and nurses across the 4,000 practices in their UK territory through their 'lunch and learn' programme. During these sessions the territory managers inform staff on 'why and how' to use the CMPS-SF thus '*[promoting] awareness of the scale to vets and nurses (many of whom have limited time and finances to attend external CPD).'*'^e



The image shows a sample of the 'SHORT FORM OF THE GLASGOW COMPOSITE PAIN SCALE'. It includes fields for 'Dog's Name', 'Sex/Breed', 'Date/Time', 'Hospital Number', 'Procedure or Condition', and 'Referral'. The scale consists of several sections: 'A. Look at dog in kennel', 'B. Pick up dog and hold out of the kennel', 'C. If dog is sound or alert area including previous 2 inches of the scale', 'D. Overall', and 'E. In the Pad'. A 'Total score (0-18) = A+B+C+D' is calculated at the bottom. The Vetoquinol logo is visible at the bottom right.

In spring 2013 the Dechra UK Marketing Team confirmed the key inclusion of the Glasgow CMPS-SF in its new UK-wide marketing campaign of *Comfortan*[®] (the UK's only veterinary licenced methadone) via distribution of the CMPS-SF in a laminated form with the product. Prior to spring 2013 Dechra had been directing customers to the CMPS-SF download at the University of Glasgow website. The decision to formally incorporate the Glasgow CMPS-SF into the marketing material was taken following an internal recommendation of the scale by Dechra's technical team

who highlighted the CMPS-SF as ‘*the most recognisable system*’ and one which was ‘*easy to use*’, ‘*familiar to most vets and nurses*’ and ‘*known internationally by [Dechra’s] other international territories*’.^f

Recognition of the University of Glasgow CMPS-SF

In 2009, the University of Glasgow research team was awarded the Universities Federation for Animal Welfare (UFAW) inaugural Companion Animal Welfare Award for the development of the CMPS-SF acute pain scale. This award is given in recognition of ‘*outstanding innovation in animal welfare science to the benefit of companion animals*’.^g

Raising awareness of animal pain in the veterinary community – The Global Pain Council

In 2011, Professor Nolan was recruited as one of only two European experts on the World Small Animal Veterinary Association (WSAVA) Global Pain Council (eight members in total).^h Professor Nolan’s appointment to the committee resulted from her reputation as a world-leading authority on pain, and her pioneering research track record in the field of the pathophysiology of pain in small animals (detailed in section 2), as well as the pain assessment tools.ⁱ The council has produced comprehensive practical guidelines that raise awareness of animal pain around the world and provide tools to manage pain in animals, with the aim of providing a resource that veterinarians worldwide can tailor for pain management strategies in companion animals. Professor Nolan has had particular input towards the guidelines on recognising acute and chronic presentations of pain. The protocols are specifically written for international audiences, providing tiered options for analgesic therapies that recognise the variable availability of drugs across the individual countries of the world. These guidelines, in which the CMPS-SF was reprinted, were presented at the World Congress of WSAVA, March 2013 with 1500 delegates from over 50 countries in attendance.^{ij}

5. Sources to corroborate the impact

- a. University of Glasgow website ‘[Acute pain questionnaire – download the CMPS-SF form](#)’
- b. Textbooks reproducing CMPS-SF:
 - Wiseman-Orr ML *et al.* (2008) Quality of life issues. In *Handbook of Veterinary Pain Management, 2nd Edition*. Eds James S. Gaynor, and William W. Muir, III. St Louis: Mosby Elsevier. ISBN 978-0-323-04679-4,
 - Bryant S (2010) Pain Assessment. In *Anesthesia for Veterinary Technicians*, Wiley-Blackwell. ISBN 978-0-8138-0586-3 and
 - Aldridge P & O’Dwyer L (2013) *Practical Emergency and Critical Care Veterinary Nursing*, Wiley-Blackwell. ISBN 978-0-470-65681-5

Sales for the 2010 and 2013 books were obtained directly from the publisher and copies are available on request
- c. Regulatory approval (the following documents all cite the CMPS-SF as ‘Glasgow Composite Pain Scale [GCPS]’)
 - Merial Ltd.– [FDA approval for ‘previcox’](#) - GCPS is referenced in ‘*Measurements and observations*’ section c.5) on p3 with a full description of the scale on p4
 - [EMA marketing authorisation for ‘Recuvyra’](#) – GCPS is referenced in ‘*Orthopaedic surgery*’ on p12
 - Novartis Animal Health US Inc. – [FDA approval for ‘DERAMAXX’](#) – GCPS is referenced in ‘*Parameters measured*’
 - Nexcyon Pharmaceuticals Inc. – [FDA approval for ‘Recuvyra’](#) – GCPS is referenced in section 8 ‘*Measurement and Observations*’ p12
- d. Information obtained from Product Manager at Vetoquinol (available on request).
- e. Information obtained from Director of Technical Affairs at Animalcare (available on request).
- f. Information obtained from Brand Manager at Dechra (available on request).
- g. [UFAW Companion Animal Welfare Award](#) – University of Glasgow team award is listed under the ‘Past Winners’ section
- h. The World Small Animal Veterinary Association (WSAVA) [Global Pain Council website](#) listing Professor Nolan as one of nine members
- i. Supporting statement obtained from the WSAVA Vice President
- j. WSAVA 38th Annual congress, 6-9 March, NZ– WSAVA Press release, ‘[Global Pain Treatise launched by the WSAVA’s Global Pain Council](#)’ 5 March 2013