Institution: University of Lincoln

Unit of Assessment: UOA6

Title of case study: Using chemical signals to prevent and treat problem behaviour in domestic pets (pheromonatherapy)

1. Summary of the impact

Our research on the use of synthetic analogues of naturally occurring chemical signals to help manage stress-related disorders in pets (pheromonatherapy), has transformed problem behaviour management internationally, with consequent welfare benefits for both owners and their animals. Specifically, our research has addressed ignorance and scepticism about the technique, identified new indications and underpinned the commercialisation of novel and more convenient delivery systems (plug-in diffuser and collar). The research is directly linked to the commercial registration and success of these products internationally where evidence of efficacy is required (e.g. Australia) and continued growth in sales elsewhere. As a result of the research "pheromonatherapy" is now a multimillion-pound global industry.

2. Underpinning research

The impacts reported here flow from the pioneering research undertaken by Professor Mills working with colleagues at Lincoln and visiting academics (e.g. Gandia Estelles - Spain, Ramos - Brazil, Braem – Switzerland) since 1998 aimed at increasing the evidence base for the practice of veterinary behavioural medicine, and especially pheromonatherapy, in association with the veterinary company *Sanofi Animal Health*, who became *Ceva Animal Health* in 1999.

Two pheromone mixtures are of particular importance here are the feline facial pheromone fraction F3 (Feliway®) and dog appeasing pheromone (DAP, Adaptil®). Our work is summarised in the research anthology "Adaptil Feliway Comprehensive References"[1], in which nearly half of the peer-reviewed journal publications are the Lincoln team's research. Our ten full journal publications have made a greater contribution than any other research group, and evidence our claim that we were at the heart of this radically new treatment regime. In addition, our research has made several distinct and pioneering contributions impacting on the acceptance and use of such interventions and their commercial significance, specifically:

- In 1997, we undertook the first long term follow-up study of any of these products[2].
- In 1999, we began working with the manufacturers to establish the efficacy of a novel delivery system based on a plug-in aerial diffuser for the home, in place of the less convenient topical spray, which had been used to date. This research provided the first publications relating to this treatment modality for both F3[3], and in 2003 for DAP[4].
- There was a need to be able to deliver the dog-based products outdoors, and so we again worked with the manufacturers to validate a collar-based system. In 2006 we were the first to publish a peer-reviewed journal publication relating to the use of an impregnated collar[5], based on work undertaken the previous year. This publication was also the first to statistically examine the diversity of motivations underlying travel-related problems and provided important insights into the potential mechanism of action and limitations of indication for DAP.
- We have also been the first to demonstrate new indications based on double-blind placebo controlled studies, including:
  - Adaptation to the new home by puppies[6], undertaken in 2003, which provided further insights into mechanism and limitations, based on differential effects.
  - Anxiety in the veterinary clinic[7], collaboration in 2003 with Hargrave (MSc student, Southampton University).
- Our four journal publications[1] on noise phobias in dogs, which is one of the biggest markets for DAP in the UK, remain the only clinical studies for this indication.
- In 2009, there were sufficient publications to include the use of F3 to treat urine spraying in the first meta-analysis of any intervention for problem behaviour in companion animals[8]. This was led by colleagues in Lincoln (Redgate who subsequently moved to Nottingham Trent University), with Landsberg from Canada acting as a second independent expert in the process of literature evaluation. This provides the most definitive evidence to date to indicate a treatment effect for Feliway beyond placebo (at level 1a, for definition see www.cebm.net/?o=1025).

3. References to the research

1. Adaptil Feliway Comprehensive References, available from University of Lincoln or Ceva Animal Health- contact Marie-Laure Loubiere: marie-laure.loubiere@ceva.com
2. Mills D.S., White J. (2000) Long-term follow-up on the spraying behaviour of cats with chronic non-sexual urine spraying treated with synthetic feline facial pheromone analogue. Veterinary Record 147:746-747
3. Mills D.S., Mills C.B. (2001) Evaluation of a novel method of delivering a synthetic analogue of feline facial pheromone (FFP) for the control of feline urine spraying Veterinary Record **149**: 197-199
4. Sheppard G., Mills D.S. (2003) Evaluation of dog appeasing pheromone as a potential treatment for dogs fearful of fireworks. Veterinary Record **152**: 432-436
5. Gandia Estelles M., Mills D.S. (2006) Signs of travel related problems in dogs and their response to treatment with dog appeasing pheromone. Veterinary Record. 159: 143-148.
6. Taylor K., Mills D.S. (2007) A placebo controlled study to investigate the effect of Dog Appeasing Pheromone and other environmental and managemental factors on the reports of disturbance and house soiling during the night in recently adopted puppies. Applied Animal Behaviour Science **105**: 358-368
7. Mills D.S. Ramos D., Gandia Estelles M., Hargrave C. (2006) A triple blind placebo controlled investigation into the assessment of the effect of Dog Appeasing Pheromone (DAP) on anxiety related behaviour of problem dogs in the veterinary clinic. Applied Animal Behaviour Science. **98**: 114-126
8. Mills D.S., Redgate S.E., Landsberg G.M. (2011) A meta-analysis of studies of treatment for feline urine spraying. PloS One **6** e18448 1-10

4. Details of the impact

Our impact strategy has focused on the need to apply established best-practice protocols for evidence based medicine to develop and protect the scientific credibility of the research, while working closely with commerce and practitioners to build acceptance of a novel approach to improving pet animal welfare. The success of this strategy is reflected in the recognition now being given to this work by well-respected international journalists critical of the lack of evidence to support other "calming" products[1]. Our research has underpinned the following specific impacts in the assessment period:

Professional Practice and Animal Welfare: Given his essential role in much of the research relating to the use of these products, Prof Mills has continued to lead the education of both behaviour specialists and the wider veterinary profession in this field. This has sustained and expanded the use of pheromonatherapy during the census period, with new users in important geographic regions globally and increased use where the products were already available. For example, direct engagement with practitioners and key-opinion leaders (such as through key-note addresses at major conferences and seminars, like FECAVA[2], the inaugural Russian Veterinary Behaviour Meeting (2011)[3] and Japanese relaunch of Feliway in 2012[3]) has given them the necessary confidence to change their behaviour and advise others accordingly in relation to the practice of pheromonatherapy. The need for this knowledge and expertise ultimately led to the recent production of the influential paper "Stress and Pheromonatherapy"[4], with more than 2,000 copies distributed globally with the assistance of Ceva Animal Health to meet the needs of practitioners[3]. This paper is particularly important, as behaviour management is generally an unfamiliar discipline for veterinarians who have not sought specialist professional development training.

An increasing number of both practitioners and carers are now able to manage a range of stress-related problems more effectively, without resort to specialists. For example, urine marking was the primary reason for feline behaviour referral (62% of cases) from veterinary practice to the Association of Pet Behaviour Counsellors in 1996, prior to the launch of Feliway®. This fell to 30% by 2002, prior to the introduction of the diffuser technology, after which it has fallen further and remained at just over 20% for the last three years[5]. This translates into obvious benefits for animal welfare, since effective treatment can be delivered sooner if it does not require prior referral.

The impact of our work on the profession has now reached the point that our research is routinely

included to support the specific indications for pheromonatherapy in standard reference texts for the profession such as the BSAVA Manual of Canine and Feline Behavioural Medicine[6] and Small Animal Formulary[7].

As the sole researchers to produce evidence of the efficacy of pheromonatherapy in relation to noise phobias, our research has clearly had a major impact on the opinion of professional bodies as well as practitioners. For example, BSAVA have a position statement relating to the management and treatment of firework phobias, which refers to the need to use "evidence-based therapies", before going on to specifically list "the use of pheromones" in this regard[8]. Practitioners also frequently refer to our work in client newsletters in relation to the management of seasonal noise fears, e.g. www.ivybankvet.com/Fireworks%20Phobias.pdf.

Public recognition: We have worked to educate the public about pheromonatherapy, e.g. by working with major charities such as the RSPCA to aid the dissemination of best practice, based on our research, e.g. www.rspca.org.uk/allaboutanimals/pets/general/fireworks. Pheromonatherapy is now widely accepted by society, e.g. a HeartBeat sample of social media in July 2013 reported 2175 mentions of Feliway® in the preceding 21 days, and 87% favourable rating[5]. The products are now also widely used by rehoming charities such as Dogs Trust and Woodgreen[3].

Commerce: During the census period, our research has been an integral part of the registration documents of the products in countries, such as Australia in 2010[3,9] where evidence of efficacy is legally required, and is widely referenced in associated marketing material internationally e.g. www.revivalanimal.com/Shared/images/PDF/DAP.pdf or used to underpin public advertising. Claims within national television advertising campaigns for Feliway® and DAP® in the UK, have been based directly on our research[10]. For both products the novel delivery systems developed with Lincoln are more popular, in terms of global sales, than the original spray[3]. [text removed for publication]

In summary, the group's research has had both broad and deep impact on the development and adoption of pheromonatherapy both in general through the creation of new delivery systems and in relation to the discovery of specific indications that have improved animal well-being and secured the commercial success of these products.

5. Sources to corroborate the impact

1. Johannes L. (2009) A scent to distress pets. Wall Street Journal, November 10; available at: online.wsj.com/news/articles/SB10001424052748704402404574525741353495708
2. Mills D.S. (2011) Effective use of pheromones in veterinary practice. 17th FECAVA Eurocongress/6th Turkish SAVA Congress "Modern Veterinary Practices" September 7-10 2011, Istanbul. Congress Book pp 96-97
3. Ceva Animal Health, Contact: Marie-Laure Loubiere marie-laure.loubiere@ceva.com
4. Mills D., Braem Dube M, Zulch H., (2012) Stress and Pheromonatherapy. Wiley Blackwell.
5. Data based on various sources including APBC member access area information, available upon request from Daniel Mills: dmills@lincoln.ac.uk.
6. Horwitz D.F. & Mills D.S., (2009) BSAVA Manual of Canine and Feline Behavioural Medicine 2nd edn BSAVA, Gloucester,
7. Ramsey I (ed) (2011) BSAVA Small Animal Formulary. 7th edn BSAVA, Gloucester. Editorial Panel (psychoactive medication)
8. BSAVA position statement on management and treatment of firework phobias. Available from: www.bsava.com/Resources/Positionstatements/Fireworks.aspx
9. Decision reported in Commonwealth of Australia Gazette. Australian Pesticides and Veterinary Medicines Authority 6 March 30 2010; available at: www.apvma.gov.au/publications/gazette/2010/06/gazette_2010-03-30_page_18.pdf, related product submission, including references to our research, available from Ceva Animal Health see reference 3 below

10. VetClick/News 31 August 2010. New TV Advertising And Marketing Campaign For DAP® And Feliway®; available at: www.vetclick.com/news/new-tv-advertising-and-marketing-campaign-for-dapreg-and-feliwayreg-p1075.php