U.S. FOOD & DRUG ADMINISTRATION

ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop

Pain Assessment in Human and Animal Studies

Virginia Recta, PhD
Mathematical Statistician
Office of New Animal Drug Evaluation
FDA Center for Veterinary Medicine
September 25, 2019

www.fda.gov

Outline

- Definition, kinds of pain
- Pain evaluation in non-verbal human patients
  - Outcome measures
  - Advances and challenges in clinical trial design
- Pain evaluation in animals
  - Outcome measures
  - Advances and challenges in clinical trial design
- Summary

2

Definition

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage

- From the International Association for the Study of Pain

3

Acute vs Chronic Pain

- Acute pain can arise from (1) medical procedures, (2) surgeries, (3) injuries, and (4) acute exacerbations of disease-related pain
- Chronic – long standing pain conditions and not those present for a specific time period

4

Pain Assessment in Non-verbal Human Patients

- Special populations
  - Neonates and infants (acute pain)
  - Non-verbal geriatric, sedated, or critically ill patients (acute or chronic pain)
- Assessment by observation (proxies: caregiver, family member)

5

Pain Assessment Tools for Infants (examples)

Pain Scale	Variables/components
Face, legs, activity, crying, and consolability (FLACC) scale	Facial expression, leg position, activity, crying, and consolability
Premature Infant Pain Profile (PIPP)	Heart rate, oxygen saturation, facial actions
COMFORT Scale	Movement, calmness, facial tension, alertness, respiration rate, muscle tone, heart rate, blood pressure

6

Pain Assessment Tools for Non-verbal Adults (examples)

Pain Scale	Variables/components
Behavioral Pain Scale (BPS)	Facial expression, movement of upper limbs, vocalization (or compliance with mechanical ventilation)
Checklist of Non-verbal Pain Indicators (CNPI)	Verbal vocalizations, nonverbal vocalizations, grimacing, bracing, rubbing, and restlessness
Multidimensional Observational Pain Assessment Tool (MOPAT)	Behavioral: Restlessness, tense muscles, frowning/grimacing, and patient Sounds Physiologic: Blood pressure, heart rate, respiration rate, and diaphoresis

7

Advances in Pain Evaluation

- Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)*
  - Consensus: Core outcome domains and measures for pediatric pain clinical trials (PedIMMPACT, 2008)
    - 6 acute and 8 chronic pain domains
  - to promote (1) standardization of domains and measures for clinical trials in pediatric pain, and (2)evidence-based treatment

*Activities are now under Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION).

8

PedIMMPACT

- Systematic review (2018): 337 POP trials
- Median no. of outcomes collected is 5 (1-11)
- Median no. of PedIMMPACT outcomes collected is 2 (0-6)
  - pain intensity (93%), symptoms and AEs (83%), the others, 4 (30%)
- Pediatric POP trials insufficiently applied the recommendations

Boric et al, European J Pain, 2019

9

Typical analgesic clinical trial

10

Considerations for Design of Pediatric Analgesic Trials

- Randomized, placebo controlled, parallel group clinical trial
- "Add-on" design with opioid-sparing as primary endpoint rather than pain scores
- American Academy of Pediatrics (2010) – Guidelines for ethical conduct of studies to evaluate drugs in pediatric populations

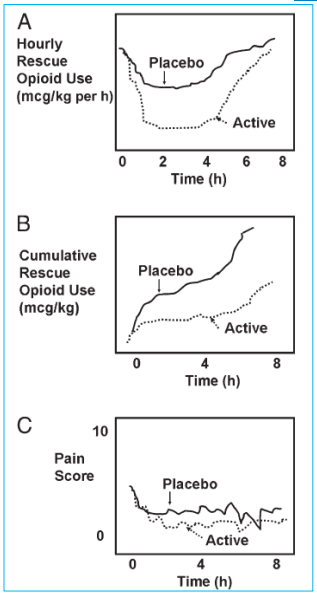


Image: Berde at al., Pediatrics 2012.

11

Pain in Animals

- Postoperative pain (POP)
  - Orthopedic, soft tissue, castration, dehorning
- Osteoarthritis (OA) pain
- Dental pain
- Neuropathic pain
- Cancer pain, foot rot, others

Images: Petvax.com

Owner Assessments for Chronic Pain in Dogs and Cats

	Pain Scale	Domains
Dogs	American College of Veterinary Surgeons Canine Orthopedic Index (COI)	Gait, function, Quality of Life (QOL)
	Canine Brief Pain Inventory (CBPI)	Pain severity Pain interference with function
	Helsinki Chronic Pain Index (HCP)	Chronic pain
	Liverpool OA in dogs (LOAD)	Mobility
Cats	Client Specific Outcome Measures (CSOM)	Activities of daily living
	Feline Musculoskeletal Pain Index (FMPI)	Mobility, agility, and disposition

Adapted from Lascelles, et al (2019) Measurement of chronic pain in companion animals: Discussions from the Pain in Animals Workshop (PAW) 2017. The Veterinary Journal 250: 71-78.

13

Instruments to Measure Acute Pain in Dogs and Cats

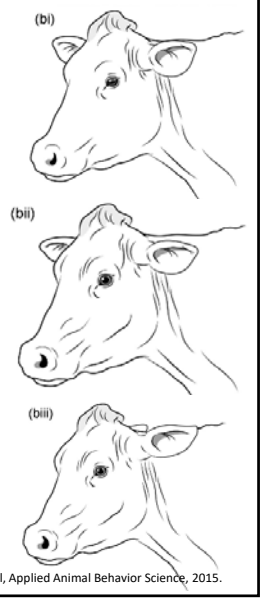
	Pain Scale	Domains
Dogs	University of Melbourne Pain Scale	Behavioral, physiological
	Glasgow Composite Measure Pain Scale (Glasgow CMPS)	Behavioral
Dogs & Cats	Colorado State Acute Pain Scale	Behavioral
Cats	UNESP –Botucatu Multidimensional Composite Pain Scale	Behavioral, physiological
	Glasgow CMPS - Feline	Behavioral

Adapted from Reid, et al (2018) Measuring pain in dogs and cats using structured behavioural observation. The Veterinary Journal 236: 72-79.

14

Pain Assessment Tools for Horses, Cattle

Pain Scale	Description
Horse Composite Pain Scale (CPS)	Composite scale for acute POP after GI surgery
Horse Grimace Scale	Pain scale based on 6 facial parameters
Cow Pain Scale (CPS)	Composite scale based on 6 behaviors
UNESP-Botucatu unidimensional CPS for cattle (surgical castration)	Based on 8 behaviors



Images: Gleerup et al, Applied Animal Behavior Science, 2015.

Outcome Measures in Canine OA

Systematic review of outcome measures reported in canine OA research

- 3697 screened, 117 eligible
- 618 outcome measures (median =4 /publication)
- Of 618 outcome measures, 491 were assessed for uniqueness
  - 348 (71%) were unique to a single publication

- Belshaw et al. Veterinary Surgery 2016

16

Typical Pain Effectiveness Field Study Design

- Multi-site, 4-15 sites
- Client owned animals, enrolled over time
- Randomized, parallel groups
- Placebo controlled
- Primary endpoint: treatment success or failure
  - For POP, success=no rescue pain medications

17

Ongoing Work

Measurements from automated and electronic systems

- Gait analysis, pressure mats
- Biosensors
- Accelerometers
- Videography

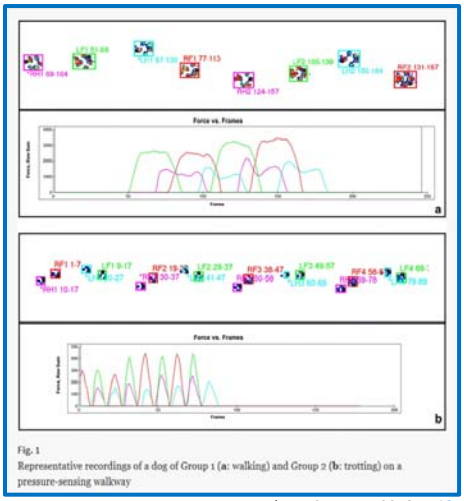


Fig. 1
Representative recordings of a dog of Group 1 (a: walking) and Group 2 (b: trotting) on a pressure-sensing walkway

Image: Kano et al., BMC Vet Res, 2016

18

Challenges in clinical trials for pain (humans and animals)

Recruitment and retention in placebo controlled studies

- Fear of harm to patients
- Risk of pain when there are available effective treatments
- Few study sites, can take years to enroll

19

Challenges in clinical trials for pain (humans and animals)

Design and interpretation

- Accuracy of pain assessments
- Clinical relevance of detected differences
  - Mean comparison using continuous outcomes
  - Clinically interpretable cut points
- Heterogeneous pain conditions, patients
- High placebo effects
  - 53-57% in pediatric migraine (Palermo et al., Pain Reports, 2019)

20

Placebo effect - Approval Study

Table 3: Percentage of Owners Rating Improvement in Dog's Quality of Life

Day	Number of animals rated as "improved" by owners compared with Day 0 / Total number of animals rated by owners: DERAMAXX	Placebo
Day 14	50/91* (54.9%)	32/90 (35.6%)
Day 28	53/88* (60.2%)	35/88 (39.8%)
Day 42	58/89* (65.2%)	35/87 (40.2%)

* Statistical significance compared with the placebo group at $p<0.05$

https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/718

21

Placebo effect – Approval Studies

Table 8. Summary of the Statistical Analysis of the Primary Effectiveness Outcome

Treatment Group	N	Number of Treatment Successes	% Success†	SEM[a]	P-value of Treatment Effect
Meloxicam	170	123	72.62%	4.11	0.0030
Placebo	88	42	46.85%	6.08	

†Percent success values were back-transformed from the logistic regression.
[a]SEM Standard Error of the Mean

Table 3: Success on Day 28 compared to Day 0.

Success	GALLIPRANT (grapiprant tablets) N = 131	Vehicle Control (tablets minus active ingredient) N = 131
% success (n)	48.1 (63)	31.3 (41)
p-value*	0.0315	

*p-value derived by a generalized linear mixed model assuming a binomial distribution and a logit link. The model included treatment group as a fixed effect and site and treatment by site interaction as random effects.

https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/903
https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/941

22

Summary

- Discussed pain assessment in non-verbal humans and animals
- Identified challenges common to human and animal analgesic assessments
- Similar areas of development (developing consensus, standardization, study designs)

23

Joint (animal/human) Work

- Pain in Animals Workshop 2017
  - advances and roadblocks in chronic pain measurement in animals from the perspective of veterinary therapeutic development **and also translational research**
  - consensus list of priorities for future research
  - Lascelles et al, The Veterinary Journal, 2019
- Pain in Animals Workshop, Oct. 2-3, 2019
  - Same as above, for acute pain

24

When it comes to pain, humans and animals have more in common than we think.

www.fda.gov

THANK YOU


FDA
U.S. FOOD & DRUG
ADMINISTRATION