Advancing Farm Animal Management with Improved Methods to Recognize and Manage Pain

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Kansas State University

Credit: Yann Arthus-bertrand
Current Disclosures (last 3 years)

- **Funded Research**

- **Consulting**
  - Boehringer Ingelheim; Bayer Animal Health; Merck Inc.; Midwest Veterinary Services Inc., and Zoetis

- **Sponsored CE**
  - Local and State Veterinary Medical Associations

- **Patents**

- **Ethical Oversight:** all studies cited had local IACUC approval
What are we going to discuss today?

1. Why is pain management in farm animals important?
2. What are the barriers to implementation of pain management strategies in livestock?
3. What are the new advances in pain assessment and pain management in livestock?
4. What are the unmet pain management needs?
1. What are the pain challenges in livestock production systems?

**Elective Procedures**
- Castration, tail docking (pigs/sheep), dehorning (calves/goats), branding, abdominal surgery, beak trimming (Poultry)

**Pain associated with livestock management**
- Lameness, calving, lambing, farrowing, infectious diseases

Why are these procedures necessary?

- Castration reduces aggression and unplanned breeding events, and improves meat quality.
- In pigs, castration reduces “boar taint”, an unpleasant taste that occurs during cooking pork from non-castrated male pigs after they reach puberty.
- Dehorning reduces injury to other animals and caregivers.
- Branding is used for animal identification especially in Western states.

https://timesoftexas.wordpress.com/tag/austin/
Why is pain management critical for farm animal welfare?

Pain management is a key part of assuring animal well-being.

Brambell Report, 1965
Pain mitigation is becoming a consumer expectation

Food makers encourage dairy farms to end painful dehorning practice, breed hornless cattle

Progress! Dannon Works to End Dehorning of Calves

The animal welfare policy of Dunkin' Brands, which owns Baskin-Robbins ice cream, asks its suppliers to "support industry-wide efforts to promote the humane treatment of cattle, including the responsible use of polled breeding." And dining chain Denny's released a policy in February indicating a "purchase preference" for milk from polled dairy cattle.

Fair Oaks Farms in Indiana, a Kroger supplier and one of the nation's largest dairy farms with 36,000 cows, is phasing out horned milk cows. About a quarter of its newborn calves are hornless due to selective use of bulls with the polled gene, CEO Gary Corbett said. It began to do so after genetics in polled bulls improved and there was proof that good traits like milk production weren't being lost.
How have food processors and retailers responded to consumer concerns about pain in livestock?

It is noteworthy that there are currently no FDA-approved drugs labeled for pain relief in pigs.
Current trends and attitudes towards pain management in cattle

Change in All Respondents’ (n=1,187) use of Pain Management in Their Operations or Practices in Last 10 Years

<table>
<thead>
<tr>
<th>Use of Pain Management</th>
<th>% total (n)</th>
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<tbody>
<tr>
<td>No Response</td>
<td>1.10% (n=13)</td>
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<tr>
<td>Increased Use</td>
<td>57.49% (n=679)</td>
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<tr>
<td>Stayed the Same</td>
<td>36.75% (n=434)</td>
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<tr>
<td>Decreased Use</td>
<td>4.66% (n=55)</td>
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</tbody>
</table>

- **75%** of respondents agree that cattle benefit from receiving analgesic drugs as part of their treatment
- **33%** of respondents agree that analgesics may mask deterioration in the animal’s condition
- **48%** of respondents agree that the benefits of analgesia outweigh the costs
- **64%** of respondents agree that FDA regulations limit their ability to use analgesic drugs in cattle
2. What are the barriers to the widespread adoption of pain management in livestock?

1. Pain assessment is difficult in livestock
2. Currently there is only one drug approved for pain management in cattle
   → Label does not include castration, dehorning and tail-docking pain
   → There are no drugs labeled for pain management in pigs
3. Time delay between drug administration and onset of activity (e.g. local anesthesia) → requires repeated handling that increases labor costs
4. Inconvenient routes of drug administration (IV, IM with large injection volumes)
5. Short duration of drug activity requires repeated injections
6. Cost of drugs and meat withhold periods
7. Nothing works well for treating chronic pain (Lameness/ tail docking)
Why has the approval of pain management drugs for livestock in the USA been challenging?

VI. LABELING

2. Pain

“We (FDA) **recommend** that this indication be based on the **control of clinical signs of pain associated with a disease**. We encourage the use of **validated methods of pain assessment** in the target species”.

FDA Guideline No. 123
DEVELOPMENT OF TARGET ANIMAL SAFETY AND EFFECTIVENESS DATA TO SUPPORT APPROVAL OF NSAIDS FOR USE IN ANIMALS

Banamine transdermal® is the only approved drug for relief of pain specifically associated with infectious lameness in cattle.
Currently pain management in livestock in the United States requires Extralabel Drug Use (ELDU)?

- The analgesics must be prescribed by a veterinarian
- The analgesic must be manufactured in an FDA-inspected facility
- The producer must keep a record of ELDU administration
- Drug administration in feed is prohibited
- A veterinarian must provide withdrawal period recommendations

Under AMDUCA, veterinarians are responsible for ensuring that drug residues arising from ELDU, do not pose a risk to consumers
How do we know if it hurts?

This research was supported by the Agriculture and Food Research Initiative Competitive Grant no. 2008-35204-19238 from the USDA National Institute of Food and Agriculture.
MODERATE

UNIVERSAL PAIN ASSESSMENT TOOL

This pain assessment tool is intended to help patient care providers assess pain according to individual patient needs. Explain and use 0-10 Scale for patient self-assessment. Use the faces or behavioral observations to interpret expressed pain when patient cannot communicate his/her pain intensity.

<table>
<thead>
<tr>
<th>Verbal Descriptor Scale</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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<tbody>
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<td>NO PAIN</td>
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WONG-BAKER FACIAL GRIMACE SCALE

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<thead>
<tr>
<th>Verbal Descriptor Scale</th>
<th>Alert Smiling</th>
<th>No humor serious</th>
<th>Furrowed brow</th>
<th>Wrinkled nose</th>
<th>Slow blink</th>
<th>Eyes closed</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO PAIN</td>
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<td>CAN BE IGNORED</td>
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<td>INTERFERES WITH TASKS</td>
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<td>INTERFERES WITH CONCENTRATION</td>
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<td>INTERFERES WITH BASIC NEEDS</td>
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<td>REDREST REQUIRED</td>
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ACTIVITY TOLERANCE SCALE

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<thead>
<tr>
<th>Verbal Descriptor Scale</th>
<th>NADA DE DOLOR</th>
<th>UNPOQUITO DE DOLOR</th>
<th>UN DOLOR LEVE</th>
<th>DOLOR FUERTE</th>
<th>DOLOR DEMASIADO FUERTE</th>
<th>UN DOLOR INSOPORTABLE</th>
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<tbody>
<tr>
<td>SPANISH</td>
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<td>TAGALOG</td>
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<td>CHINESE</td>
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<td>KOREAN</td>
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<td>PERSIAN (Farsi)</td>
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<td>VIETNAMESE</td>
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<td>JAPANESE</td>
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**Verbal Descriptor Scale**
- **0**: NO PAIN
- **1-2**: MILD PAIN
- **3-5**: MODERATE PAIN
- **6-7**: MODERATE PAIN
- **8**: SEVERE PAIN
- **9**: WORST PAIN POSSIBLE

**Wong-Baker Facial Grasmace Scale**
- **0**: NO PAIN
- **1-2**: CAN BE IGNORED
- **3**: INTERFERES WITH TASKS
- **4**: INTERFERES WITH CONCENTRATION
- **5**: INTERFERES WITH BASIC NEEDS
- **6**: REDREST REQUIRED

**Activity Tolerance Scale**
- **SPANISH**: NADA DE DOLOR
- **TAGALOG**: Walang Sakit
- **CHINESE**: 不痛
- **KOREAN**: 통증 없음
- **PERSSIAN (Farsi)**: بدون درد
- **VIETNAMESE**: Không Đau
- **JAPANESE**: 痛みがない

- **UNPOQUITO DE DOLOR**: UN DOLOR LEVE
- **Katamangang Sakit**: Matinding Sakit
- **中度**: 中度
- **약한 통증**: 보통 통증
- **ارد معتدل**: درد معتدل
- **軽微**: 軽微
- **軽度**: 軽度

- **UN DOLOR FUERTE**: DOLOR FUERTE
- **DOLOR DEMASIADO FUERTE**: DOLOR DEMASIADO FUERTE
- **されない痛み**: 非常嚴重
- **痛い**: 痛い
- **다른 드립**: 느겁
- **Muy fuerte**: Muy fuerte
- **ND Withdrawal**: ND Withdrawal

- **UN DOLOR INSOPORTABLE**: UN DOLOR INSOPORTABLE
- **피곤**: 負荷
- **超級**: 超級
- **하이**: 高度
3. Advances in pain assessment and pain management in livestock

- Electrodermal Activity
- Chute Exit Speed
- Growth & Performance
- Accelerometers
- Behavior & Location in a pen
- Heart Rate Determination
- Plasma Cortisol
- Plasma Substance P
- EEG
- Algometers measuring MNT
- Thermography
- Pressure mat analysis
Thermography

- Detects thermographic differences associated with changes in cutaneous perfusion
- Pain causes alterations in sympathetic tone
  - Results in changes in superficial vascular blood supply.
  - Gives rise to quantifiable changes in localized body temperature
This research was supported by the Agriculture and Food Research Initiative Competitive Grant no. 2008-35204-19238 from the USDA National Institute of Food and Agriculture.
Impact of transmammary meloxicam on skin temperature of piglets

Higher skin temperatures in piglets nursing on medicated sows
Electroencephalography (EEG)

- Measurement of electrical activity on the scalp produced in brain
- **Effects of Age:** EEG responses in lambs undergoing castration under light halothane anesthesia varied with age.
- **Effects of Method:** EEG differences are seen with tonic pain (surgical castration) and phasic pain (non-surgical castration)
- **Preemptive Analgesia:** Quantitative EEG analyses are used to quantify anesthetic drug effects.
Electroencephalography (EEG)

6 week old calves
Electroencephalography (EEG)

6 month old calves
How do we objectively measure lameness?

- Walkway with two sensor mats in series
- Computer software allows real-time recording of all phases of stride
  - the duration of stride,
  - length of stride,
  - force throughout the stride,
  - force distribution, and
  - moment of inertia.
- This allows complete characterization of how much weight is being carried on each foot.
Research funded by the Agriculture and Food Research Initiative Competitive Grant no. 2008-35204-19238 directly supported the approval of the first drug for pain relief in livestock in the United States.

Table II.5: Site 1 Results

<table>
<thead>
<tr>
<th>Primary variable</th>
<th>Control group</th>
<th>Flunixin transdermal solution-treated group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lameness score improvement success (number of animals classified as a treatment success/number in treatment group)</td>
<td>6.67% (1/15)</td>
<td>100% (15/15)</td>
<td>0.0263*</td>
</tr>
<tr>
<td>Mean change in maximum force (kg-force) between enrollment and 6 hours post-treatment (95% confidence interval)</td>
<td>-4.14 kg-force (-19.82;11.54)</td>
<td>43.08 kg-force (30.65;55.52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean change in contact area (cm²) between enrollment and 6 hours post-treatment (95% confidence interval)</td>
<td>-2.70 cm² (-8.19;2.80)</td>
<td>16.76 cm² (11.48;22.04)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* The p-value is from a sensitivity analysis in which one success in the flunixin transdermal solution-treated group was artificially changed to a failure. The original model did not converge because there were no failures in the flunixin transdermal solution-treated group.
This technology could this also be a “validated method of pain assessment” for use in pigs?
Work in Progress- Using genetic biomarkers for pain detection

Untargeted gene expression profiling after lameness and pain relief in goats
3. What can we do to minimize pain? The 3 S’s

- **SUPPRESS** the source of pain
  - Hornless “Polled” genes to eliminate dehorning
  - Sexed Semen to reduce need for castration
  - Selection (boar taint, lameness, temperament)

- **SUBSTITUTE** with less painful alternative
  - Optimize timing and methods used to perform painful procedures
  - Immunocastration

- **SOOTHE** pain with an analgesic drug
  - Cost and convenience will determine if use of pain management becomes routine
How have we lowered barriers to on-farm analgesic use in livestock production systems?

With support from USDA-NIFA we identified oral meloxicam as an effective pain relief drug for use in cattle and pigs

- Meloxicam is a prescription-only NSAID used to treat arthritis in people
- **Meloxicam tablets are rapidly absorbed from the gut of animals**
- Human generic tablets are very inexpensive (< $0.50/calf)
- Pain relieving effects of oral meloxicam lasts for several days after a single administration
How have we lowered barriers to on-farm analgesic use in livestock production systems?

- Providing pain relief improved weight gain in calves for 10 days after dehorning.
- Pain relief reduced the number of calves requiring antibiotic treatment for pneumonia.
Transmammary drug delivery of pain relief to reduce pain in piglets

- Reduces the need to inject every piglet before surgery
- Caregivers only handle each piglet only once at processing
- Fewer needle sticks
- Less stress on both pigs and workers
- Long acting and potentially cost effective
- Piglets nursing medicated sows have increased growth rates
Non-pharmaceutical alternatives for reducing pain in livestock

- SUBSTITUTE with less painful alternative
  - Immunocastration vaccine
  - With support received from USDA (2017-67015-27124) we have developed a novel ear implant that releases vaccine over the lifetime of the animal
  - The implant would eliminate the need for surgical castration
  - The implant also eliminates any risk to the operator of accidental self-injection
What are the unmet needs for pain management in livestock?

- We currently do not have any drugs with FDA-approval to relieve pain in pigs.
- We currently do not have any drugs with FDA-approval to relieve pain associated with castration, dehorning and branding in cattle.
- Identification and validation of robust pain biomarkers.
- The absence of analgesic drug approvals places a regulatory burden on veterinarians and livestock producers who are responsible, under AMDUCA, to ensure that drug residues do not enter the food supply.
**Take Home Messages**

- **Considerable progress has been made in validating methods of pain assessment**
  - With financial support from USDA, considerable progress has been made towards developing biomarkers of pain in livestock to support analgesic drug approvals
  - Oral meloxicam provides a convenient and cost effective approach to providing analgesia in livestock

- **Analgesic drug approvals in food animals are urgently needed**
  - Routine use of pain management is rapidly becoming a consumer expectation
  - The absence of FDA-approved analgesic drugs for use in livestock is a significant barrier to the widespread adoption of analgesic drug protocols on farms
  - Incentives, such as waiving ADUFA user fees, may encourage pharmaceutical companies to pursue analgesic drug approvals in livestock
  - Alternatives to painful procedures are an area of ongoing investigation
Acknowledgements

• This research was supported by the Agriculture and Food Research Initiative Competitive Grants no. 2008-35204-19238; 2009-65120-05729; 2013-67015-21332 and #017-67015-27124 from the USDA National Institute of Food and Agriculture.
Questions?

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