Surgery Not Required: Current and Future Options in Fertility Control of Dogs and Cats

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Mission: To expedite the successful introduction of methods to non-surgically sterilize dogs and cats and to support the distribution and promotion of these products to humanely control cat and dog populations worldwide.

acc-d.org
Priorities for Non-Surgical Fertility Control

- Safe and effective
- Permanent or long-term
- Deliverable in a single injection or treatment
- Approaches for dogs and cats / male and female
- Documented effects on behavior and health
- Affordable
ACC&D Resources

February 2013

Product Profile and Position Paper

ESTERILSOL™/ZEUTERIN™

ESTERILSOL™/ZEUTERIN™ is a non-surgical sterilant for male dogs delivered via intratesticular injection. The active ingredient is zinc gluconate neutralized by arginine. This formulation causes permanent infertility in one treatment. It is also known as “one-shot sterilization.”
Why nonsurgical sterilization instead of traditional spay/neuter?
SURGICAL SPAY/NEUTER
To save more lives.....

...we need more options.
Let’s explore the options.

- On the horizon
- Available now

How is ACC&D paving the way for these options?
Michelson Prize and Grants Program in Reproductive Biology

Founded in 2009
$50M available for research grants to develop a non-surgical sterilant for male and female dogs and cats.
“A nonsurgical sterilant could reduce the global population of homeless dogs and cats, but there hasn’t been money to develop one—until now.”
Goal

- Reduction or elimination of deaths of healthy shelter cats and dogs in the United States
- Successful product will likely be made available worldwide for feral cat and dog control
Research Approaches

Immunocontraception

High dose, long-term GnRH agonists

Targeted delivery of cytotoxins

Gene silencing/gene therapy
Michelson Grant Funding
December 2014

TOTAL since 2009: >30 projects in 7 countries
$25M Prize

- Single-dose, permanent, nonsurgical sterilant
- Safe and effective in male and female cats and dogs
- Ablates sex steroids and/or their effects
- Suitable for administration in a field setting
- Viable pathway to regulatory approval
- Reasonable manufacturing process and cost

[Images of a cat and a dog]
Reproductive Control

Hypothesis

Gonadotropin Releasing Hormone (GnRH)

Pituitary Gland

Luteinizing Hormone (LH)
Follicle Stimulating Hormone (FSH)

Gametes

Hormones

• Testosterone
• Estrogen
• Progesterone

Negative Feedback
Reproductive Control

**Hypothalamus**
- Gonadotropin Releasing Hormone (GnRH)
- Luteinizing Hormone (LH)
- Follicle Stimulating Hormone (FSH)

**Pituitary Gland**

**Hormones**
- Testosterone
- Estrogen
- Progesterone

**Gonads**

**Gametes**

**Negative Feedback**

GnRH Vaccines
gnRH Agonists
Slimmy receives a rabies vaccine.

Her body makes antibodies against the virus.

If exposed to the virus, circulating antibodies bind it. The virus does not reach its receptor.

Slimmy is not infected.
Slimmy receives a GnRH vaccine.

Her body makes antibodies against her own GnRH.

When her hypothalamus releases GnRH, antibodies bind it.

GnRH does not reach its receptors in the pituitary.

FSH and LH are not released.

Slimmy is contracepted.

Yay!
GonaCon

• Overview:
  – Developed by USDA-NWRC
  – EPA registered for use in white-tailed deer (2009) and wild horses and burros (2013)
  – Contraceptive effect in several other species
Dr. Levy’s studies demonstrated safety, efficacy & suppression of sexual behaviors in male & female laboratory cats.

Photo: Julie Levy
Results in Male Cats

• Single dose GonaCon
• 24 adult male cats – 2 studies
  – Antibody titer, testosterone and semen analysis
  – Secondary sex characteristics
• Breeding trial – mean time to successful breeding was 12 mos. for responders
• 3-year follow-up; no injection site issues
Secondary Male Sex Characteristics

Testicle shrinkage

Loss of penile spines

Slide: Courtesy of Dr. Julie Levy, Maddies’ Shelter Medicine Program, University of Florida College of Veterinary Medicine.
Results in Female Cats

• 20 adult female cats
• Single dose GonaCon
• Monthly measurements
  – GnRH antibody titers
  – Estrogen, progesterone
• Breeding trial
• 5-year follow-up

Photo: Julie Levy
GonaCon treated female cats:
Median time to pregnancy 39.7 mos.

Slide: Courtesy of Dr. Julie Levy, Maddie’s Shelter Medicine Program, University of Florida College of Veterinary Medicine
Injection-Site Reactions

• Non-painful granulomatous masses
• Late onset (~24 months) in 6/20 cats

Slide: Courtesy of Dr. Julie Levy, Maddies’ Shelter Medicine Program, University of Florida College of Veterinary Medicine.
Why we are excited about GonaCon

• Contraceptive vaccine safe & effective in female cats
  – 3+ year average duration; suppression of sexual behaviors

• Practical for field administration

• Potentially very affordable
ACC&D is working to realize GonaCon’s potential for free-roaming cats.
Deslorelin / Suprelorin®
VIRBAC, formerly Peptech Animal Health

- GnRH agonist
- Delivered by implant
- Approved in Australia, New Zealand and EU for male dogs
- FDA-indexed product to treat adrenal tumors in ferrets
Dogs with No Names

Dr. Judith Samson-French and her team implant dogs on First Nations Reserves with Suprelorin.

Give female dogs a “pregnant pause”
Chemical sterilization

The use of chemical compounds which destroy and/or render ineffective essential component(s) of the reproductive system

• Current approaches are for males
  – Zinc gluconate neutralized by arginine
    • Zeuterin®
  – Calcium chloride
Reproductive Control

Hypothalamus

Gonadotropin Releasing Hormone (GnRH)

Pituitary Gland

Luteinizing Hormone (LH)
Follicle Stimulating Hormone (FSH)

Gonads

Gametes

Hormones
- Testosterone
- Estrogen
- Progesterone

Negative Feedback

Zinc Gluconate
Calcium Chloride

• Testosterone
• Estrogen
• Progesterone
New York Times

December 2, 2013

“New Strides in Spaying and Neutering”
“Too Many Dogs: A Simple Solution”
Calcium Chloride

Results: Testicles of dogs treated with CaCl$_2$ in either diluent significantly decreased in size. After administration of CaCl$_2$ in lidocaine solution, sterility was achieved for at least 12 months in 75% of treated dogs. However, optimal long-term contraceptive effectiveness was achieved with CaCl$_2$ in alcohol, which resulted in azoospermia over the 12-month study period.

Testosterone levels significantly decreased following treatment with CaCl$_2$, and sexual activity disappeared. Although testosterone returned to baseline levels by 12 months for the group treated with CaCl$_2$ in lidocaine, dogs injected with CaCl$_2$ in alcohol had a 63.6% drop in testosterone level, which remained at the low end of physiological range throughout the study. No adverse effects were noted.
Changes in testicular width after intratesticular injection of CaCl$_2$. At 12 months (T3) after treatment with CaCl$_2$ (group A and group B), significant reductions in testicular width were observed (*P < 0.001), as compared with no or minimal changes seen in the control (C) group.
Calcium Chloride

Effects of intratesticular injection of CaCl$_2$ on serum testosterone levels over time. Following the injection of CaCl$_2$ in lidocaine solution (group A), testosterone decreased significantly (\( F = 0.47; P < 0.003 \)) for up to 6 months, although testosterone levels at 12 months returned to baseline. After injection of calcium chloride in alcohol (group B), testosterone levels decreased significantly (\( F = 65.1, P < 0.001 \)) throughout the 12-month follow-up period.
ACC&D Position Statement on Calcium Chloride:

- To our knowledge, CaCl$_2$ has not been reviewed or approved by any regulatory agency for use as an animal sterilant.
- ACC&D believes that the current use of intratesticular CaCl$_2$ as a sterilant should be considered experimental.
Zeuterin™

Zinc Gluconate Neutralized by Arginine is the only FDA approved non-surgical sterilant for male dogs

A single, virtually painless injection to neuter a male dog, permanently

Courtesy Ark Sciences
Zeuterin™ Highlights

Male dogs 3-10 months of age (older pending)

One-time injection into each testicle

Safe & Effective

Permanent and Irreversible

Reduces Testosterone

Courtesy Ark Sciences
Efficacy

- Proven safe and effective
- 99.6% Efficacy
- FDA clinical trial: 223/224 dogs age 3 to 10 months
How do we know Zeuterin is permanent?

Epididymis from untreated dog (100x)

Epididymis from Zeuterin treated dog (100x)

At 30 days post-injection
How do we know Zeuterin is permanent?

Epididymis from untreated dog (100x)  Epididymis from Zeuterin treated dog (100x)

At 24 months post-injection
How do we know Zeuterin is permanent?

Testicle from untreated dog (100x)

Testicle from Zeuterin treated dog (100x)

At 24 months post-injection

Courtesy Ark Sciences
Research Behind FDA Approval

- Twelve years of scientific research
- Dosage determination study
- Animal Safety Study
- Clinical Trial 224 dogs 3-10 months old
- Follow-up of dogs in original study

Courtesy Ark Sciences
**Adverse Reactions Observed During FDA Trial**

<table>
<thead>
<tr>
<th>Local Reactions</th>
<th>No. of Dogs (n = 270)</th>
<th>Percent (%)</th>
<th>Systemic Reactions</th>
<th>No. of Dogs (n = 270)</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scrotal Pain*</td>
<td>17</td>
<td>6.3%</td>
<td>Neutrophilia</td>
<td>17</td>
<td>6.3%</td>
</tr>
<tr>
<td>Scrotal Irritation</td>
<td>3</td>
<td>1.1%</td>
<td>Vomiting**</td>
<td>12</td>
<td>4.4%</td>
</tr>
<tr>
<td>Biting and Licking</td>
<td>2</td>
<td>0.7%</td>
<td>Anorexia</td>
<td>11</td>
<td>4.1%</td>
</tr>
<tr>
<td>Scrotal Swelling</td>
<td>2</td>
<td>0.7%</td>
<td>Lethargy</td>
<td>6</td>
<td>2.2%</td>
</tr>
<tr>
<td>Scrotal Irritation/Dermatitis</td>
<td>2</td>
<td>0.7%</td>
<td>Diarrhea</td>
<td>5</td>
<td>1.9%</td>
</tr>
<tr>
<td>Scrotal Ulceration</td>
<td>1</td>
<td>0.4%</td>
<td>Leukocytosis</td>
<td>2</td>
<td>0.7%</td>
</tr>
<tr>
<td>Scrotal Infection</td>
<td>1</td>
<td>0.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry Scrotal Skin</td>
<td>1</td>
<td>0.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scrotal Bruising</td>
<td>1</td>
<td>0.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preputial Swelling</td>
<td>1</td>
<td>0.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scrotal Sore</td>
<td>1</td>
<td>0.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* No NSAIDs were used and most scrotal pain was reported on the first two days after injection.

** Vomiting was most commonly seen on the day of the injection, between 1 minute and 4 hours post-injection.

Courtesy Ark Sciences
Expected Reactions

- Injection technique is critical to prevent adverse reactions
- Normal reactions include:
  - Generally non-painful swelling for 24-48 hours
  - Listlessness for the first 24 hours
  - May or may not vomit during the first 24 hours
  - Should return to normalcy within 24 hours
How do we know Zeuterin is painless?

“How pain receptors are considered to be present in the tunicae testis and it would seem reasonable to suppose that, as in other solid organs, the acute pain experienced in testicular injury is due in part to stretching of the capsule.”

Long Term Effects

- 30 six-month old dogs treated with Zeuterin were followed for 2 years
- 2 years of routine observations and clinical evaluations
- Permanent reduction of circulating testosterone of 41-52%
- 24 months post injection - necropsy concluded all vital organs normal
- Epididymides, testicles and prostate had all reduced in size
Long Term Effects

Zinc Neutering spares the testosterone producing function of Leydig cells, keeping the critical endocrine system intact.

Without spermatogenesis, the testosterone production goes down by 41-52%.

Testosterone production remains available for other metabolic functions of the dog.
Long Term Effects of Surgical Neutering Show Benefits and Detriments
(Source: Determining the optimal age for gonadectomy of dogs and cats, Margaret V. Root Kustritz, DVM, PhD, DACT)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
<th>Substantial morbidity?</th>
<th>Specific breeds at risk?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testicular neoplasms</td>
<td>0.9%</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>BPH or prostatitis</td>
<td>75%–80% by 6 years of age</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Detriments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complications of surgery</td>
<td>6.1%</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prostatic neoplasms</td>
<td>0.2%–0.6%</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>TCC</td>
<td>1.0%</td>
<td>No</td>
<td>Yes*</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>0.2%</td>
<td>Yes</td>
<td>Yes†</td>
</tr>
<tr>
<td>Hemangiosarcoma</td>
<td>0.2%</td>
<td>Yes</td>
<td>Yes‡</td>
</tr>
<tr>
<td>CCL rupture</td>
<td>1.8%</td>
<td>Yes</td>
<td>Yes§</td>
</tr>
<tr>
<td>Obesity</td>
<td>2.8%</td>
<td>No</td>
<td>YesII</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.5%</td>
<td>No</td>
<td>Yes¶</td>
</tr>
</tbody>
</table>

* Airedale Terrier, Beagle, Collie, Scottish Terrier, Shetland Sheepdog, West Highland, White Terrier, and Wire Fox Terrier.
† Doberman Pinscher, Great Dane, Irish Setter, Irish Wolfhound, Rottweiler, and Saint Bernard.
‡ Boxer, English Setter, German Shepherd Dog, Golden Retriever, Great Dane, Labrador Retriever, Pointer, Poodle, and Siberian Husky.
§ Akita, American Staffordshire Terrier, Chesapeake Bay Retriever, German Shepherd Dog, Golden Retriever, Labrador Retriever, Mastiff, Neapolitan Mastiff, Newfoundland, Poodle, and Saint Bernard.
II Beagle, Cairn Terrier, Cavalier King Charles Spaniel, Cocker Spaniel, Dachshund, Labrador Retriever.

JAVMA, Vol 231, No. 11, December 1, 2007
Does Zeuterin™ Change Behavior?

Behavior changes may be observed after zinc neutering:

“My observation as an Animal Caretaker for the dogs is that the male dogs treated with Zinc Gluconate are much calmer than as compared to the intact male dogs.”
– FDA Clinical Trial, Progeny Testing and Sexual Behavior Study

“Max stopped urine marking and now sits on my lap”
– Dee Ann, Dog Owner

“Tank stopped digging the garden and became cuddly”
– Kari, Dog Owner

Courtesy Ark Sciences
Spaying and neutering makes pets better, more affectionate companions.

Female dogs, like males, have an increased risk of aggression if left intact.

Unneutered dogs are often more aggressive and territorial (urine marking, fighting), but these traits should not be confused with loyalty and protection of their home and family.

Altered pets are less aggressive toward other dogs and cats, are less likely to urine mark and wander, and generally have better personalities.

Unsterilized animals often exhibit more behavior and temperament problems than do those who have been spayed or neutered.

What We Think We Know

(Quotes from websites of veterinary clinics, humane societies, trainers & animal shelters)

Courtesy Dr. James Serpell
Behavior Conclusions

- Surgical neutering may reduce specific male hormone-dependent behaviors (e.g. sexual mounting, roaming, urine-marking, and aggression directed toward other (intact) males) in dogs that have already learned these behaviors.
- Surgical spay/neuter may increase other undesirable behaviors (e.g. owner-directed aggression, touch sensitivity, fearfulness, etc.) in otherwise behaviorally normal dogs.
- Definitive conclusions will require prospective, controlled studies.
Does Zeuterin™ Change Behavior?

The FDA behavior position statement:

“As with surgical castration, secondary male characteristics (roaming, marking, aggression, or mounting) may be displayed.”
Zeuterin Administration

Measure the testicular width

Gently cleanse and disinfect the scrotum
Zeuterin Administration

Pass the needle from the cranial aspect of the testicle, just ventral to the head of the epididymis.

Position the needle along the long axis of the testicle in the center of the testicular parenchyma.
Zeuterin vs. Neutersol
What has changed?

Injection technique modified – strict adherence to protocol is important to minimize potential adverse reactions

✓ Three 28 gauge needles, ½ to 1 inch length
✓ 1 needle to draw solution – 2 needles to inject
✓ Timed injection (slow)
Zeuterin vs. Neutersol
What has changed?

Injection technique modified – strict adherence to protocol is important to minimize potential adverse reactions

✓ Do not aspirate prior to injecting
✓ Wait when done injecting prior to withdrawal
✓ Do not massage the testicles after injecting
How Do We Identify a Zinc Neutered Dog?

Microchipping
• Microchip tracking companies will record the Zinc Neutered status of dog

Tattooing
• A “Z” tattoo between the genitals and inner thigh is the standard sign for zinc neutering

Unique Collar Tag
• Every dog is given a unique identification number collar tag with the website address to verify neutering status

Courtesy Ark Sciences
Changing Perception

Evidence-based decision making

- Conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.

- De-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research.
When I was in vet school, I was told, "Half of what you learn here will turn out to be wrong. But no one knows which half."

So true! One of the things we may have gotten wrong was in looking at the health impacts of neutering.

Dr Marty Becker
“America’s Veterinarian”
The Evolution of Neutering

zeuterin™
Zinc Gluconate Neutralized by L-Arginine is the only FDA Approved Non-surgical Sterilant

A single, virtually painless injection into each testicle will sterilize a male dog, permanently.
“The greatness of a nation and its moral progress can be judged by the way its animals are treated.”

Mahatma Gandhi
Projects to pave the way...
Population Models for Free-Roaming Cats

Figure 6. Stochastic population growth rate under different FRC management strategies.

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0113553
Marking and identification of free-roaming populations of dogs and cats
International Society of Feline Medicine
2015 Feline Veterinary Congress

• Pre-Congress Day: “Feline Fertility and Population Control”
• Special issue of Journal of Feline Medicine and Surgery
acc-d.org

✓ E-book
✓ Product profile & position papers
✓ Legislative information
✓ FAQs
✓ Much more
Thank you for exploring the options with us.
Surgery Not Required: Current and Future Options in Fertility Control of Dogs and Cats

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