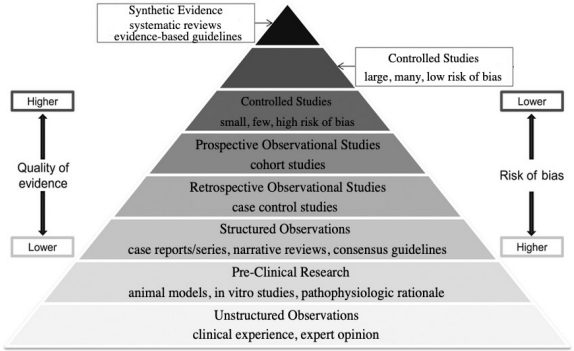
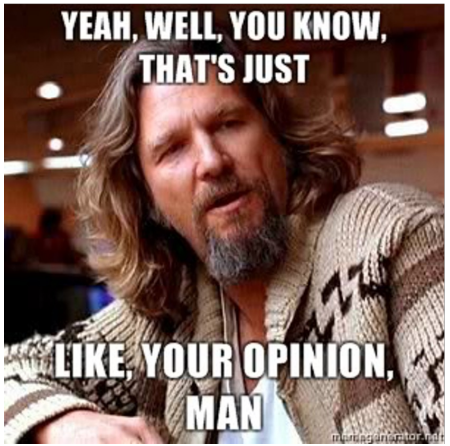


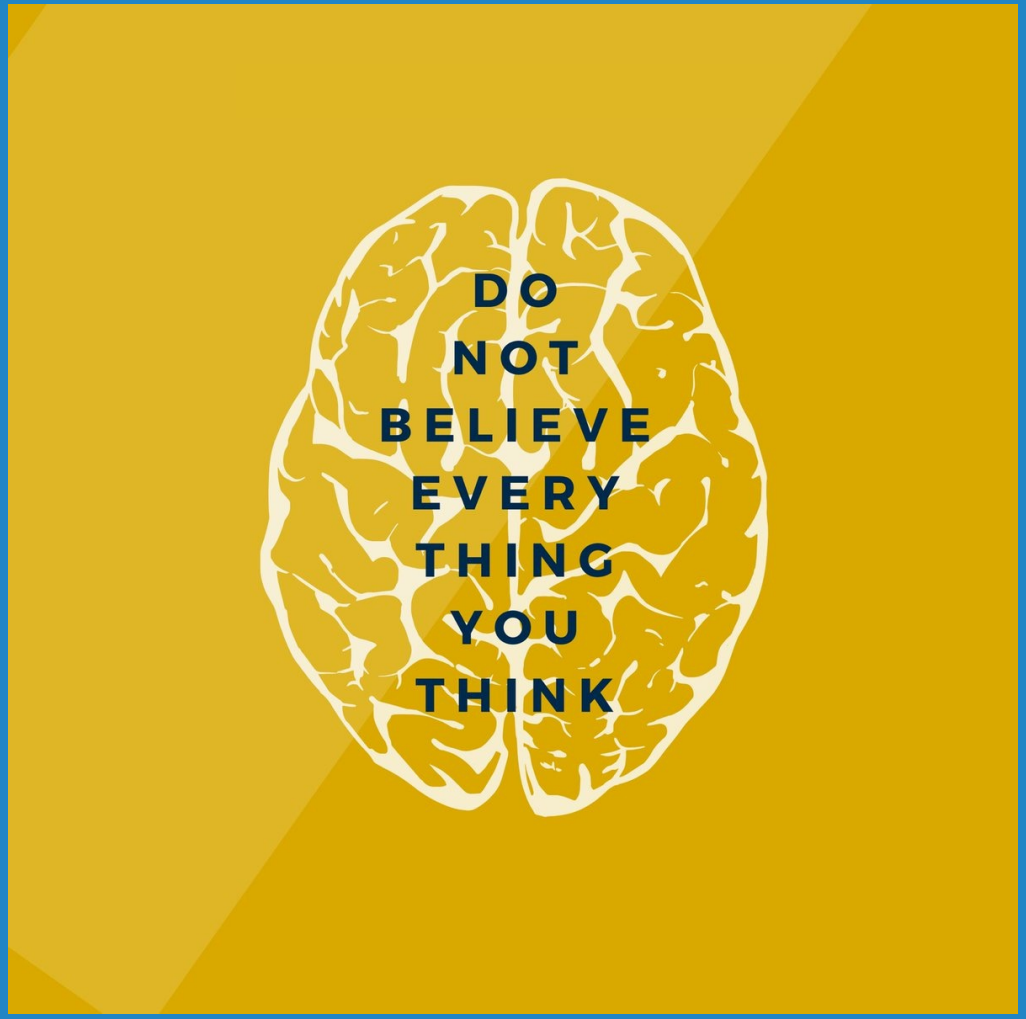
Evidence-based Medicine

vs



Choosing Wisely

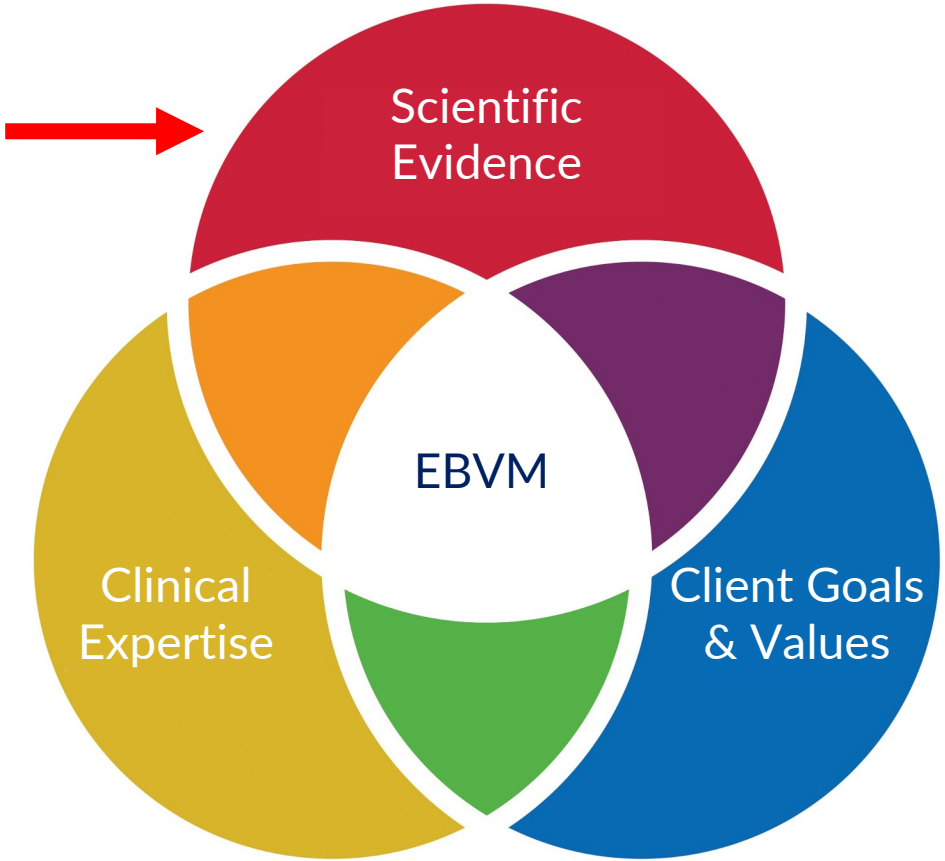
Things to Stop Doing in Your Practice (Maybe)


DO
NOT
BELIEVE
EVERY
THING
YOU
THINK

What is EBVM?

"the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients…integrating individual clinical expertise with the best available external clinical evidence from systematic research."

Sackett, DL. et al. Evidence based medicine: what it is and what it isn't


Scientific Evidence
EBVM
Clinical Expertise
Client Goals & Values

“The real purpose of the scientific method is to make sure Nature hasn’t misled you into thinking you know something you actually don’t know.”

Robert Pirsig
Zen and the Art of Motorcycle Maintenance

“Be very, very careful what you put in that head, because you will never, ever get it out.”

Thomas Cardinal Wolsey

1.

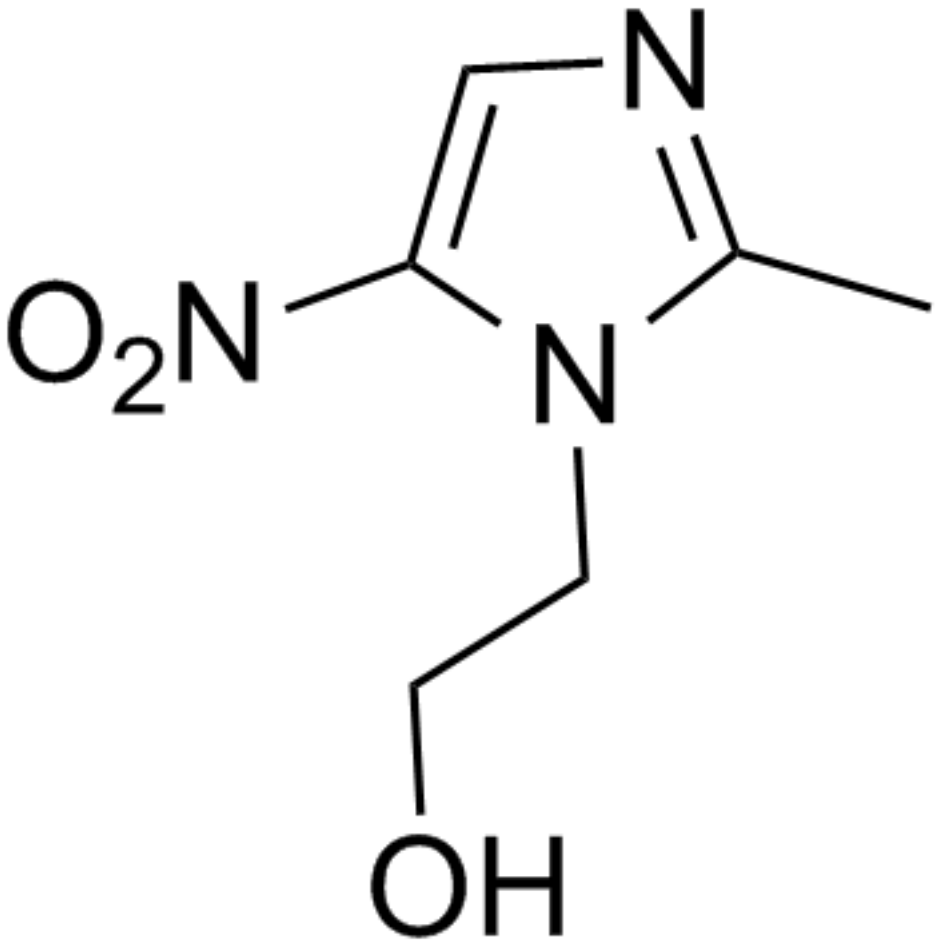
Metronidazole

For Acute Idiopathic Diarrhea

What is Metronidazole?

- Antibiotic
- Antiprotozoal
- Anti-inflammatory & Immunomodulator
- Old (1950s)
- Cheap
- AE- neuro, GI, dysbiosis

- Anti-diarrheal???????????????



Metronidazole for Diarrhea

- Giardia
  - 13-20% of symptomatic dogs
  - 5-25% of symptomatic cats
  - Developing resistance
    - Often still useful
    - Variable efficacy
    - Combo Tx probably better

Metronidazole for Diarrhea

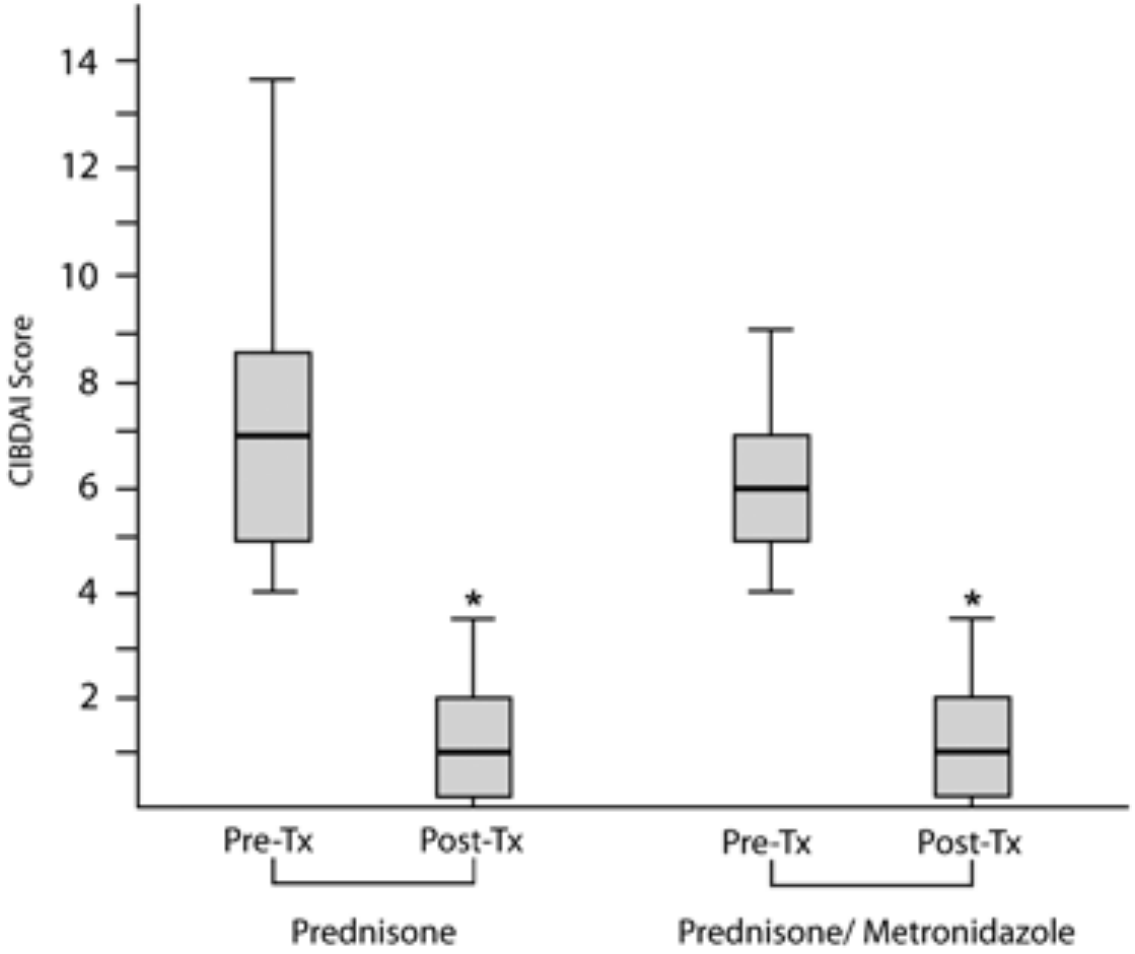
- Bacterial Enteritis (e.g. Clostridium)
  - 0-40% of dogs with diarrhea test +
  - Similar rates in asymptomatic dogs
  - Causal role often difficult to determine

Metronidazole for Diarrhea

- Bacterial Enteritis (e.g. Clostridium)
  - AHDS (prev HGE)
    - AB not indicated in most cases
    - Reserve for those with signs of sepsis/translocation
    - No benefit when MET added to clavamox
    - (but that doesn't work either)

Metronidazole for Diarrhea

- Inflammatory Bowel Disease
  - No benefit when added to prednisolone


CIBDAI Score
14
12
10
8
6
4
2
*
*
Pre-Tx
Post-Tx
Pre-Tx
Post-Tx
Prednisone
Prednisone/ Metronidazole

Metronidazole for Diarrhea

- Inflammatory Bowel Disease
  - No benefit when added to prednisolone
  - Not recommended in human guidelines

Metronidazole for Diarrhea

- Acute Idiopathic
  - Usually self-limiting (<1 week)
  - Minimal symptoms and risk
  - Little evidence of benefit

Metronidazole for Diarrhea

Shmalberg, 2019

MET- 4.6 +/- 2.4 days

PRO- 3.5 +/- 2.2 days
PLC- 4.8 +/- 2.9 days

(p=0.17)

Langlois, 2020

MET- 2.1 +/- 1.6 days

PLC- 3.6 +/- 2.1 days

(p=0.04)

Rudinsky, 2022

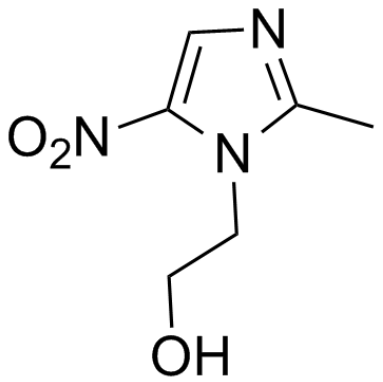
Bland+MET- 8.5 days (7-12)

Bland+PLC- 5 days (4-10)

Bland+Fiber- 5 days (3-6)

(p<0.01)

Metronidazole for Diarrhea



Pros

- Happy Clients
- $$
- Small benefit??
- Small risk??

Cons

- Probably ineffective
- Possible Risks
  - Toxicity
  - AB resistance
  - Dysbiosis
- Ethics?

Bottom Line

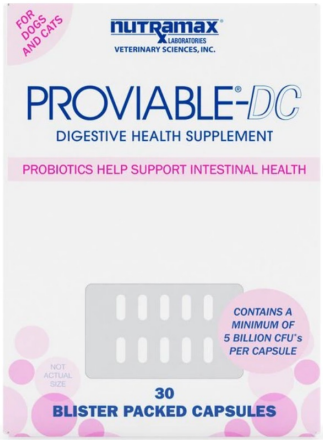
- **Probably doesn’t work**
- **Some risks**
- **Misleading clients**

Metronidazole for Diarrhea

- What Else?
  - Other AB?
    - Clavamox prob doesn't work
    - Tylosin?
    - Similar pros and cons to MET

Metronidazole for Diarrhea

- What Else?
  - Probiotics
    - Not an AB
    - Microbiome health
    - Limited evidence
    - Which? How Much? How Long? Quality Control



Metronidazole for Diarrhea

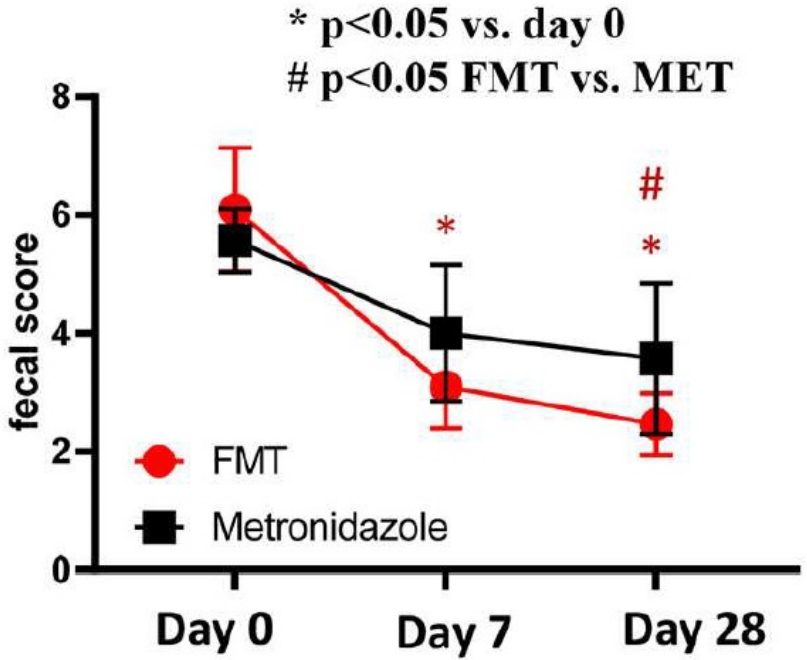
- What Else?
  - Diet
    - Low-residue
    - Fiber

Metronidazole for Diarrhea

- What Else?
  - Loperamide- Who knows?!

Metronidazole for Diarrhea

- What Else?
  - FMT (Chaitman, 2020)



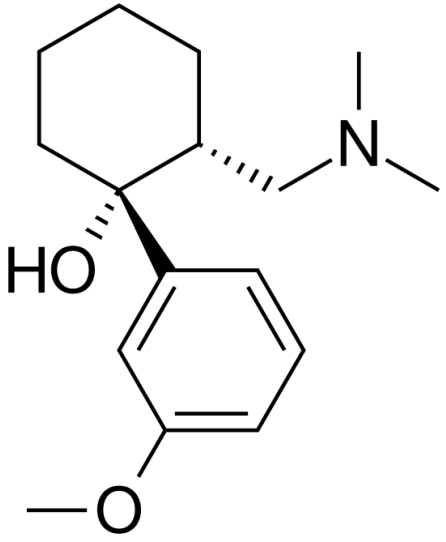
2.

Tramadol

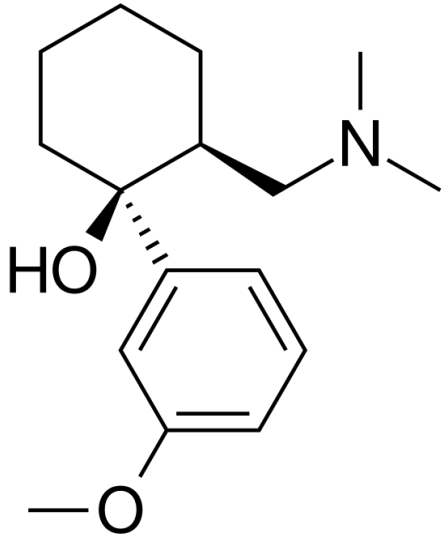
Oral Analgesia

What is Tramadol?

- Opioid and serotonin agonist
- Pro-drug
- Useful for many types of pain in humans
- Old (1970s)
- Cheap
- Schedule IV since 2014



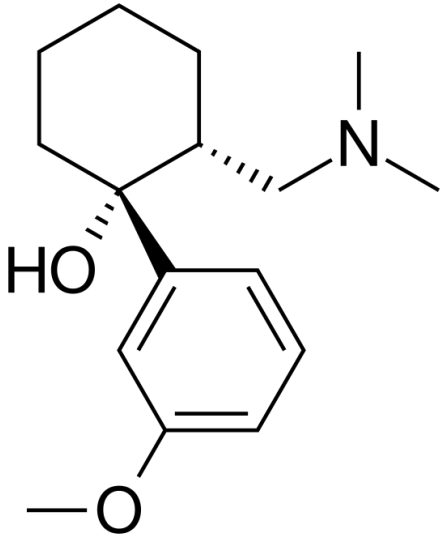
(1*R*,2*R*)-tramadol



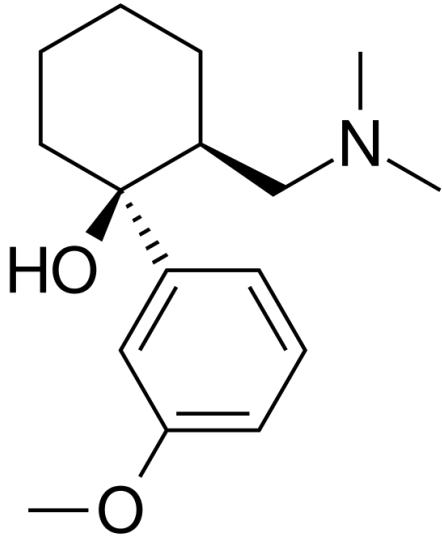
(1*S*,2*S*)-tramadol

What is Tramadol?

- AE
  - GI
  - Serotonin syndrome
  - Decreased Sz threshold
  - Dependance/withdrawal



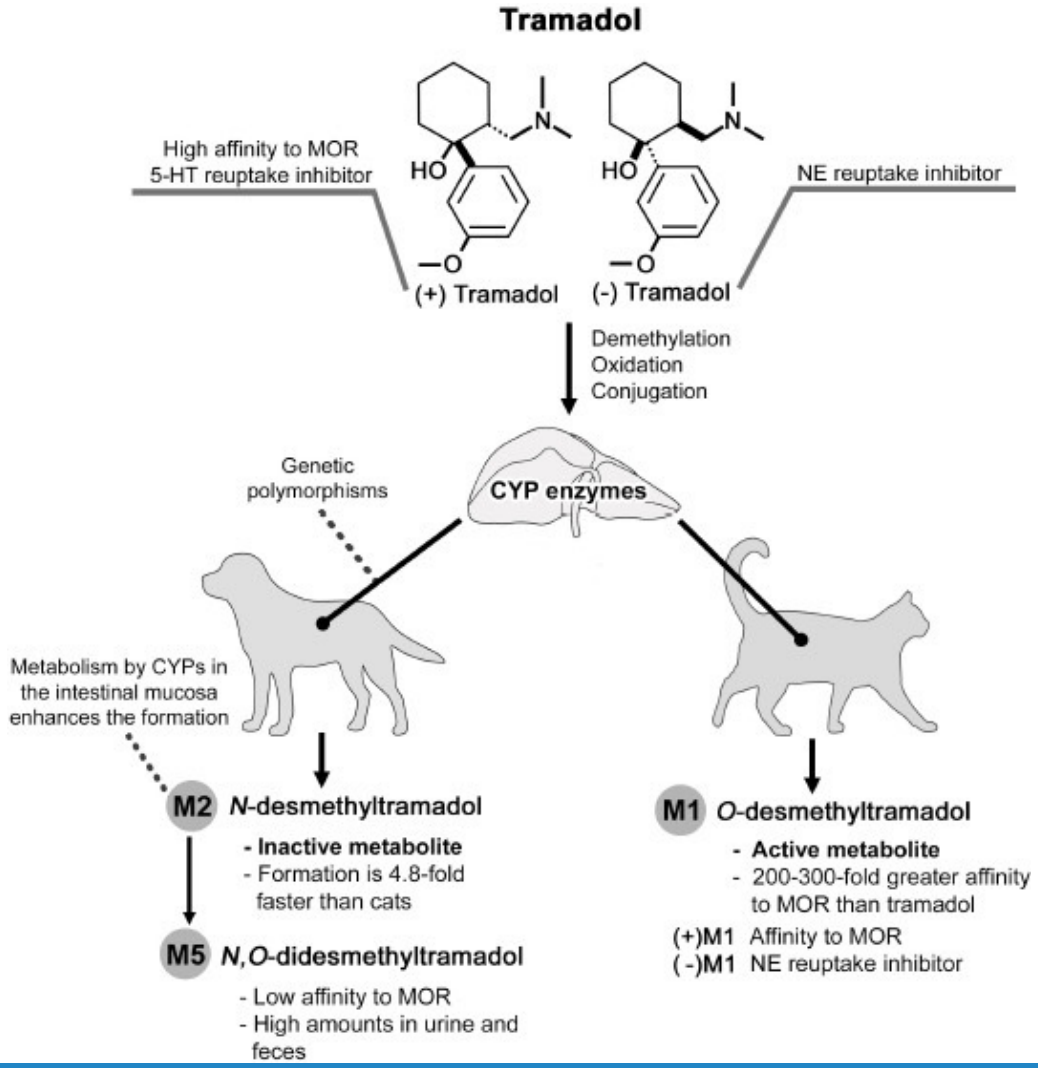
(1*R*,2*R*)-tramadol



(1*S*,2*S*)-tramadol

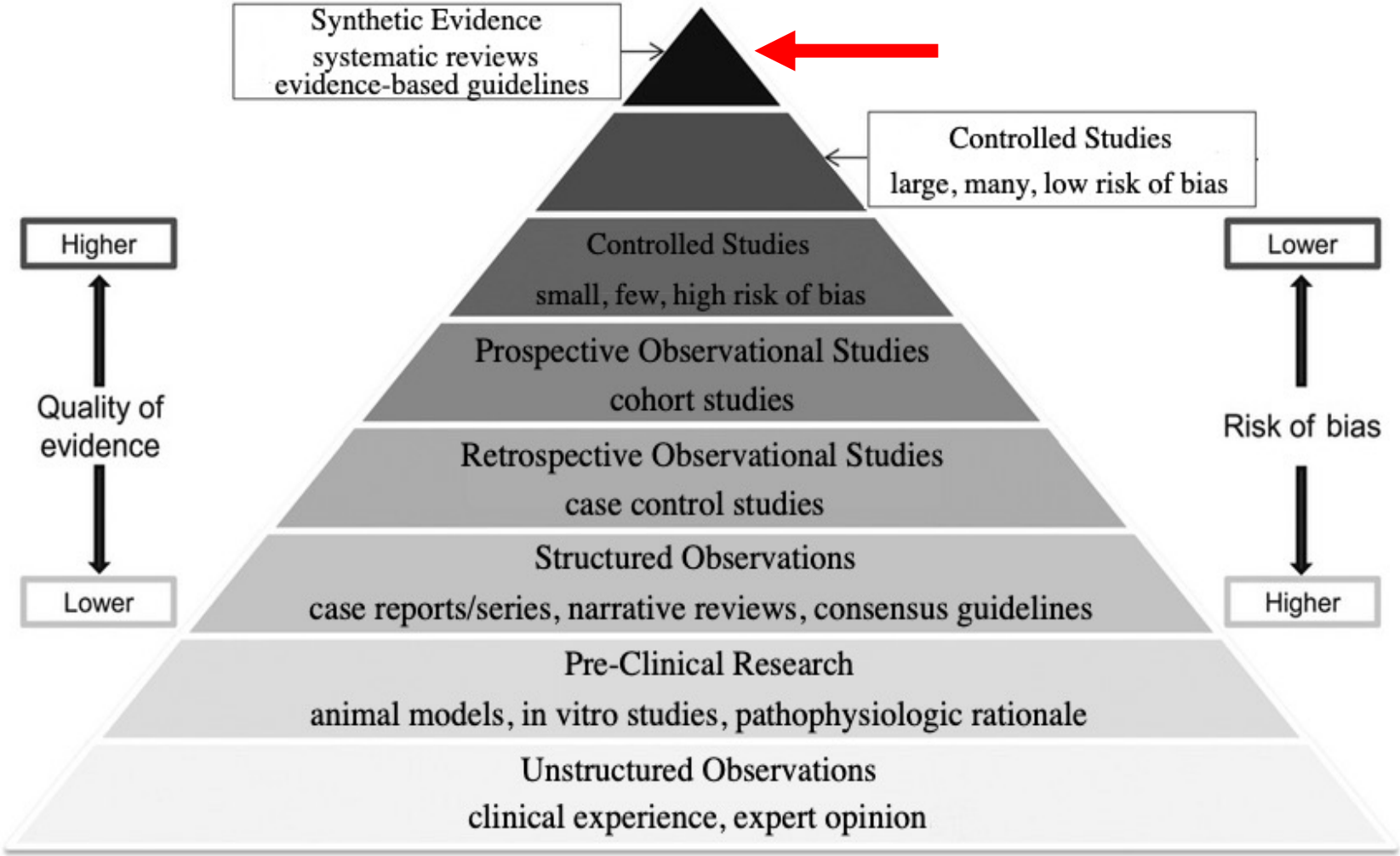
Tramadol for Pain- Dogs

- Pre-clinical Studies
  - Poor & variable conversion to active metabolite


Tramadol
High affinity to MOR
5-HT reuptake inhibitor
NE reuptake inhibitor
HO
N
O
(+) Tramadol
(-) Tramadol
Demethylation
Oxidation
Conjugation
Genetic
polymorphisms
CYP enzymes
Metabolism by CYPs in
the intestinal mucosa
enhances the formation
M2 N-desmethyltramadol
- Inactive metabolite
- Formation is 4.8-fold
faster than cats
M5 N,O-didesmethyltramadol
- Low affinity to MOR
- High amounts in urine and
feces
M1 O-desmethyltramadol
- Active metabolite
- 200-300-fold greater affinity
to MOR than tramadol
(+)M1 Affinity to MOR
(-)M1 NE reuptake inhibitor

Tramadol for Pain- Dogs

- Clinical Studies
  - Systematic Review with metanalysis


Synthetic Evidence
systematic reviews
evidence-based guidelines
Controlled Studies
large, many, low risk of bias
Higher
Quality of evidence
Lower
Controlled Studies
small, few, high risk of bias
Prospective Observational Studies
cohort studies
Retrospective Observational Studies
case control studies
Structured Observations
case reports/series, narrative reviews, consensus guidelines
Pre-Clinical Research
animal models, in vitro studies, pathophysiologic rationale
Unstructured Observations
clinical experience, expert opinion
Lower
Risk of bias
Higher

[Confidence] regarding the efficacy of tramadol on postoperative analgesia in dogs compared with other analgesic agents or no treatment is currently low or very low.

*In comparison with **no treatment**, tramadol administration **probably** results in a reduced number of dogs requiring analgesic rescue.*

Tramadol for Pain- Cats

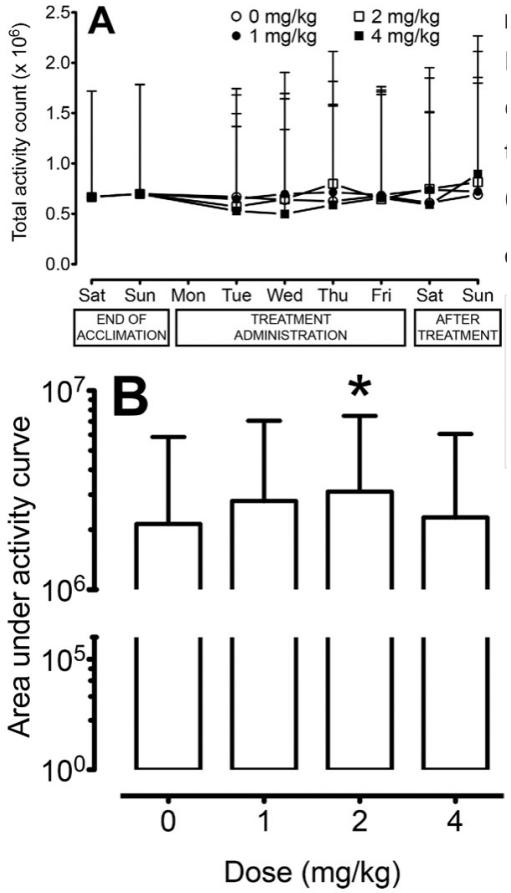
- Pre-clinical Studies
  - Active metabolite produced
  - Antinociceptive effects- PO & IM, SQ?

Tramadol for Pain- Cats

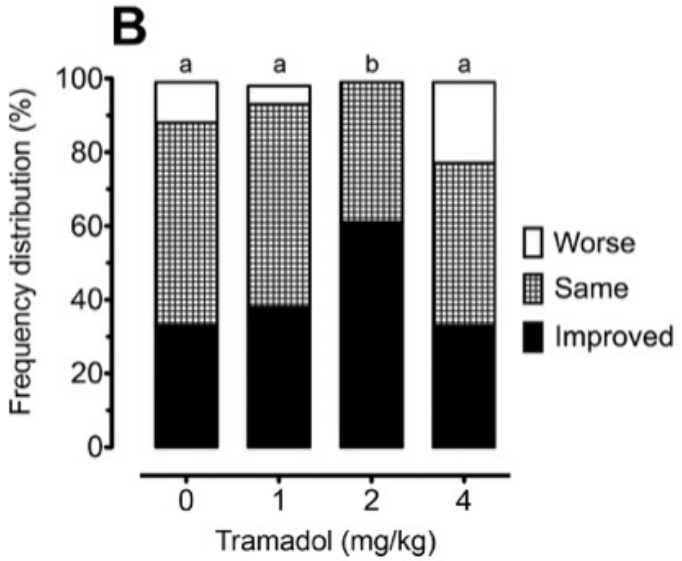
- Clinical Studies
  - Generally positive effects in OVH, castration, dentistry
    - Mostly parenteral
    - Variable methods (dose, pain measurement, etc.)
    - Comparator sometimes placebo

Tramadol for Pain- Cats

- Clinical Studies- oral
  - Possible beneficial effects
  - Significant limitations
  - AEs common
    - Refusal
    - GI signs
    - Behavior



Activity Monitor



CSOM

Tramadol for Pain- Cats

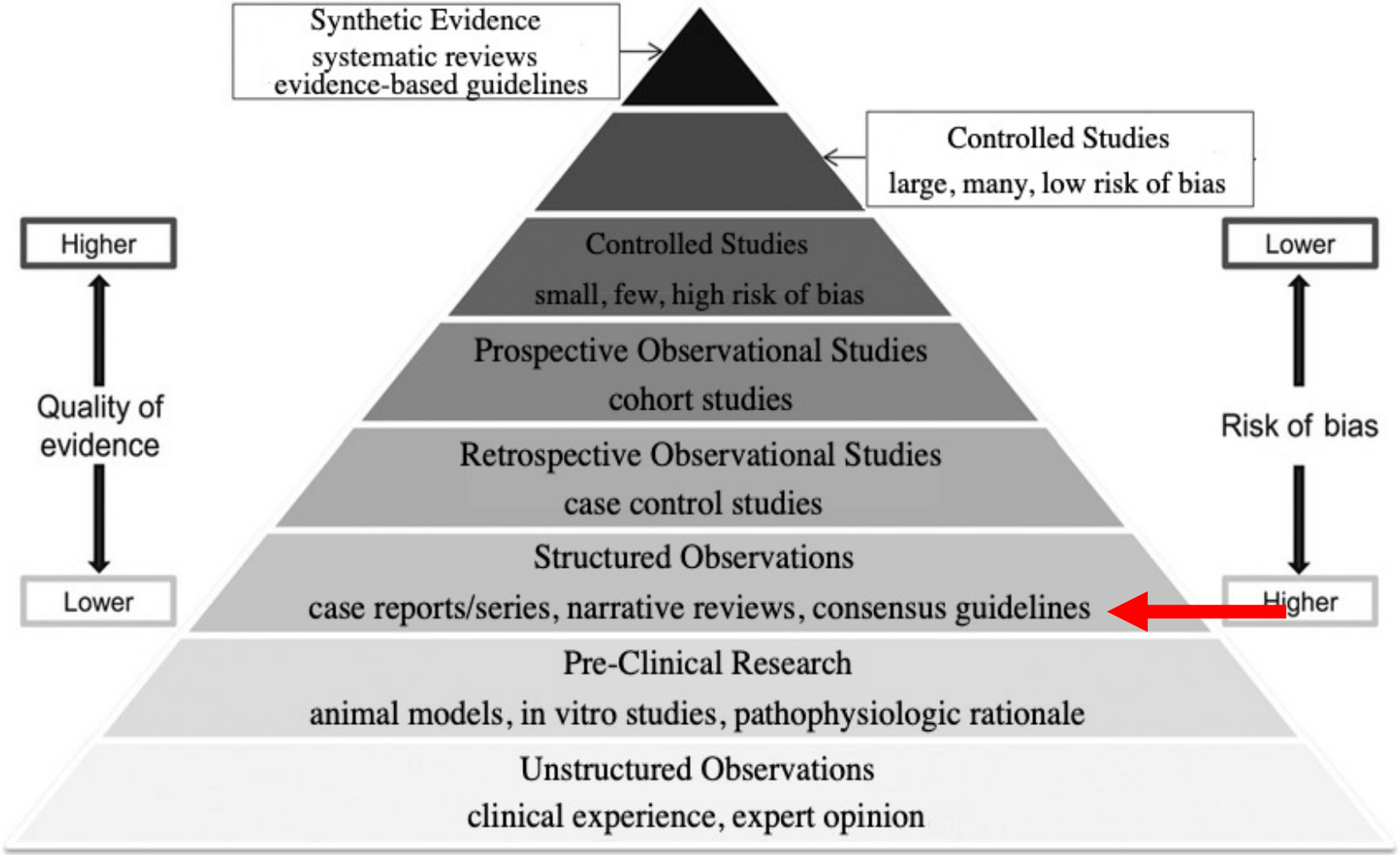
- AEs common
  - Placebo- 0/21
  - 1mg/kg- 2/21 9.5%
  - 2mg/kg- 6/18* 33.3%
  - 4mg/kg- 8/19* 42%

Bottom Line

- **Negligible benefits for dogs**
- **Some benefit for cats**
- **Significant AEs for cats**

- **Probably better options**

3.
Gastroprotectants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clinical experience, expert opinion
Lower
Risk of bias
Higher

ACVIM consensus statement: Support for rational administration of gastrointestinal protectants to dogs and cats

Stanley L. Marks[1] | Peter H. Kook[2] | Mark G. Papich[3] | M. K. Tolbert[4] | Michael D. Willard[4]

The practice of inappropriate prescription of acid suppressants is commonplace in veterinary medicine

ACVIM consensus statement: Support for rational administration of gastrointestinal protectants to dogs and cats

Stanley L. Marks[1] | Peter H. Kook[2] | Mark G. Papich[3] | M. K. Tolbert[4] | Michael D. Willard[4]

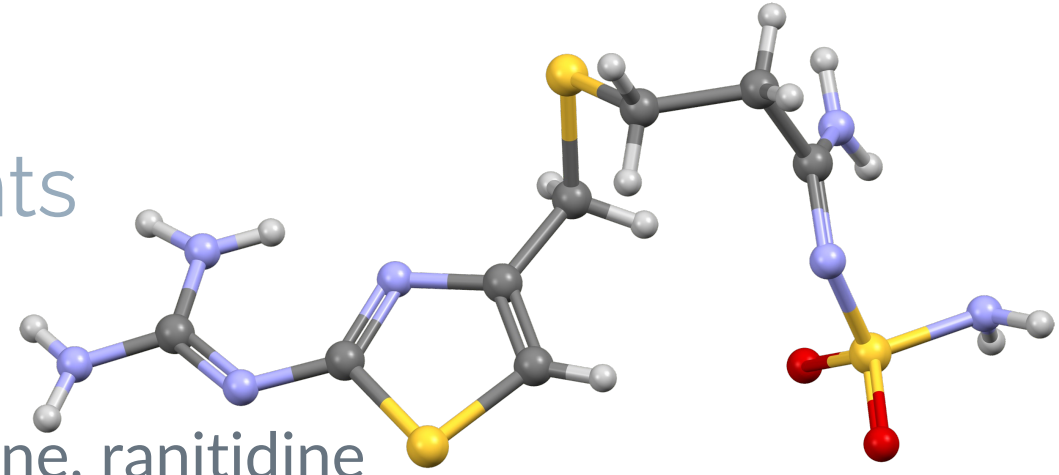
This report challenges the dogma and clinical practice of administering GI protectants for the routine management of

- *gastritis*
- *pancreatitis*
- *hepatic disease*
- *renal disease*

Gastroprotectants

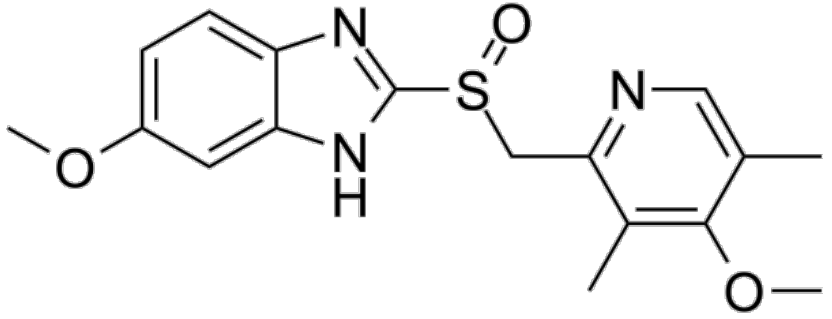
- Antacids
  - e.g. $AL(OH)_3$, $CaCO_3$
  - Local secretory & barrier effects
  - Do NOT neutralize gastric acid
  - Probably not very effective
  - Difficult to achieve adequate frequency (e.g. 6x/day)

Gastroprotectants



- H_2RAs
  - e.g. famotidine, ranitidine
  - Rapid development of tolerance (3-13 days)
  - Rebound hyperacidity when d/c
  - Slightly better than placebo
  - Not as effective as PPIs

Gastroprotectants



- PPIs
  - e.g. omeprazole, pantoprazole
  - Maximal effect in 2-4 days
  - Initial IV Tx induces faster effects

Prospective observational study of the use of omeprazole and maropitant citrate in veterinary specialist care

Rachel McCormack, Louise Olley, Barbara Glanemann & James W. Swann

Scientific Reports **10**, Article number: 15727 (2020) | Cite this article

> We find omeprazole and maropitant are administered to a large proportion of dogs, including to many of those with no presenting signs suggestive of gastrointestinal disease.

Prospective observational study of the use of omeprazole and maropitant citrate in veterinary specialist care

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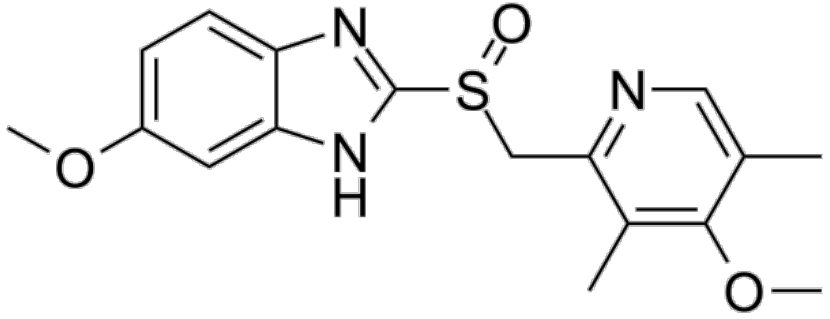
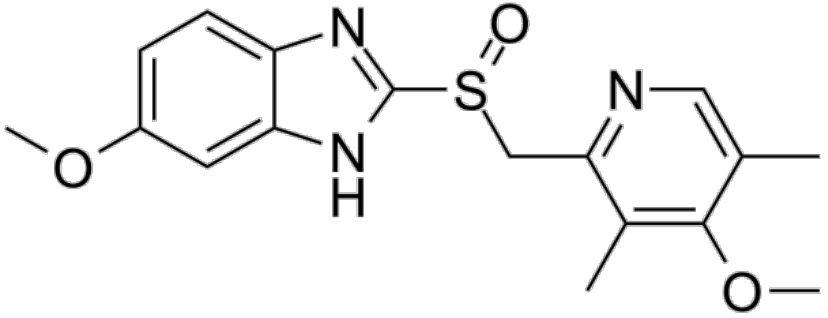
- prescribing clinicians consider both drugs safe but often underestimate their financial cost.
- omeprazole is often administered outside dosing recommendations
- frequently administered for aims that are unlikely to be achieved when considering their known biological effects

Gastroprotectants



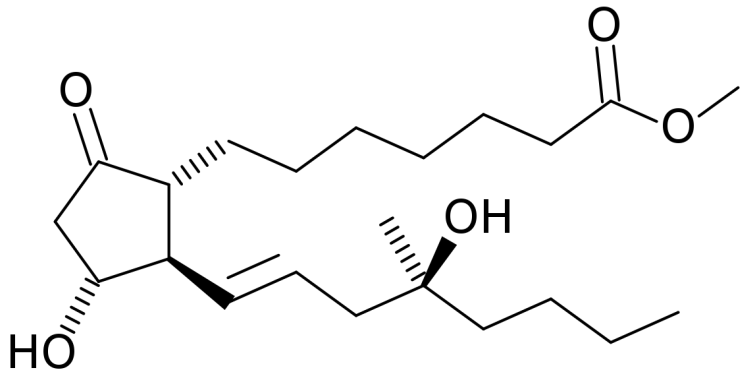
- PPIs
  - Drug interactions
    - Less effective if H_2RAs are given
    - Antifungals, clopidogrel?
    - CYP450 effects?

Gastroprotectants



- PPIs
  - AEs
    - Diarrhea (dogs)
    - Dysbiosis

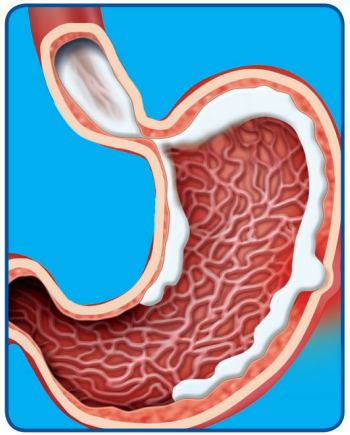
Gastroprotectants



- Misoprostil
  - Prostaglandin analogue
  - Protective in ASA model
  - NSAIDs?
  - Not protective with steroids

Gastroprotectants

- Sucralfate
  - Binds to proteins in damaged gastric mucosa
  - pH buffering, decreases pepsin
  - May be beneficial with esophagitis
  - Probably should use suspension



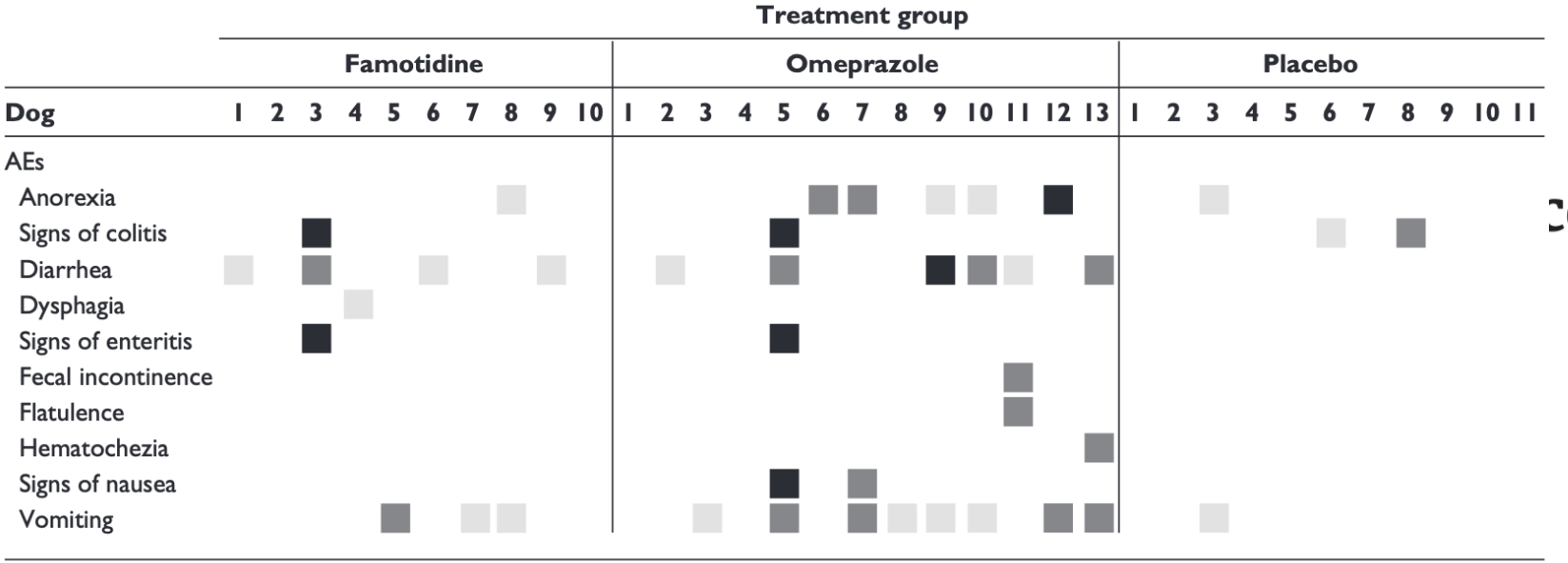
Gastroprotectants

J Am Vet Med Assoc. 2021 Aug 15;259(4):385-391. doi: 10.2460/javma.259.4.385.

A prospective, randomized, placebo-controlled, double-blinded clinical trial comparing the incidence and severity of gastrointestinal adverse events in dogs with cancer treated with piroxicam alone or in combination with omeprazole or famotidine

Marejka H Shaevitz, George E Moore, Christopher M Fulkerson

Gastroprotectants



A shaded box indicates that a dog had a GI AE, with the shade indicating the severity of the GI AE on the basis of the Veterinary Comparative Oncology Group's Common Terminology Criteria for Adverse Events.[25]

White = no AE. Light gray = grade 1 AE. Medium gray = grade 2 AE. Black = grade 3 AE.

Gastroprotectants

The effect of combined carprofen and omeprazole administration on gastrointestinal permeability and inflammation in dogs

Susan M. Jones, Ann Gaier, Hiroko Enomoto, Patricia Ishii, Rachel Pilla, Josh Price, Jan Suchodolski, Joerg M. Steiner, Mark G. Papich, Kristen Messenger, M. Katherine Tolbert ✉

First published: 07 September 2020 | https://doi.org/10.1111/jvim.15897 | Citations: 8

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▷ *Omeprazole prophylaxis **induces fecal dysbiosis** and **increases intestinal inflammatory markers** when co-administered with carprofen to otherwise healthy dogs with no other risk factors for GI bleeding.*

Gastroprotectants

- When to use them
  - GUE
    - Neoplasia (gastric and pancreatic)
    - PPI > H_2RA, sucralfate, misoprostil

Gastroprotectants

- When to use them
  - Hepatic Dz
    - Weak evidence
  - Stress
    - e.g. illness, performance dogs
    - Weak evidence

Gastroprotectants

- When to use them
  - GER associated w/ GA
    - PPI > H_2RA, sucralfate, misoprostil

Gastroprotectants

- When **NOT** to use them
  - Acute gastritis
  - IRIS CKD Stages 1-3, 4?
  - Pancreatitis
  - With NSAIDs
  - With steroids

Bottom Line

Probably Useful

- GUE
- GA GER
- GI & pancreatic neoplasia

Bottom Line

Probably NOT Useful

- Acute gastritis
- Pancreatitis
- CKD
- Steroids

Vitamin C for Sepsis

- HAT
  - Hydrocortisone (low-dose)
  - Ascorbic acid (Vit C)
  - Thiamine
  - 94 subjects

CHEST®

Volume 151, Issue 6, June 2017, Pages 1229-1238

Original Research: Critical Care

Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study

Vitamin C for Sepsis

- HAT
  - Failure to replicate
    - Over a dozen systematic reviews
    - Thousands of patients
    - Negligible benefits
  - Fraud allegations
  - Lawsuits, politics

Decline Effect

Initial effect sizes decline with further research.