Indonesian Journal of Veterinary Science
Vol. 4. No. 2. September 2023, Page. 61-75
DOI:10.22146/ijvs.v4i2.106709, ISSN 2722-421X (Online)
Available online di https://journal.ugm.ac.id/ijvs

Off-Label Use of Human Over-the-Counter (OTC) Products in Veterinary Medicine: A Literature Review on Effects, Risks, and Safety Precautions

Ida Fitriana[1]*, Antasiswa Windraningtyas Rosetyadewi[1], Ika Nindya Irianti[1,2], Agustina Dwi Wijayanti[1]*

[1] Department of Pharmacology, Faculty of Veterinary Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia
[2] Grha Petcare Animal Clinic Yogyakarta
**Corresponding author,* email: ida.fitriana@ugm.ac.id

Received: May 10, 2023, Accepted: July 20, 2023, Published: September 1, 2023

Abstract

The off-label use of human over-the-counter (OTC) medications in veterinary medicine is a common but potentially hazardous practice, particularly in regions where access to veterinary-approved drugs is limited. While some OTC agents, such as diphenhydramine or melatonin, may offer therapeutic benefits under veterinary supervision, many others pose significant risks due to species-specific differences in drug metabolism, narrow safety margins, and the presence of toxic excipients such as xylitol, pseudoephedrine, or acetaminophen. This literature review examines the rationale behind such practices, the most commonly used OTC drug classes, and the associated pharmacological and toxicological risks. It also highlights critical considerations in clinical decision-making, including appropriate dosing, contraindications, and alternative treatment options. Additionally, the role of veterinary pharmacists, interprofessional collaboration, and pharmacovigilance systems are discussed as essential components in mitigating risks and promoting safe usage. The review emphasizes the importance of client education and the need for veterinarians to rely on species-specific products whenever available. Ultimately, the off-label use of OTC medications in animals should be approached with caution, guided by evidence-based practice, and employed only when clinically justified and accompanied by rigorous safety monitoring.

Keywords: off-label drug use; over-the-counter medications; veterinary pharmacy; drug safety; pharmacovigilance

Introduction

The use of human over-the-counter (OTC) products in veterinary medicine, particularly in an off-label capacity, has become increasingly prevalent worldwide (FDA, 2023a; Tomanic et al., 2021). This is especially true in areas with limited access to veterinary-specific formulations, such as rural regions, low-resource settings, or developing countries where the availability, affordability, or approval status of veterinary drugs may be restrictive (FDA, 2023a; James A. Budde, 2023; Myers et al., 2022; Tomanic et al., 2021). OTC medications, by virtue of their widespread availability and familiarity among pet owners, are often perceived as convenient substitutes for veterinary therapeutics. However, this practice is fraught with clinical, pharmacological, and regulatory challenges that can compromise animal health and complicate treatment outcomes.

Off-label use refers to the administration of drugs in a manner not explicitly approved by the regulatory agency (such as the FDA in the U.S. or EMA in Europe), including use in a different species, indication, dose, route of administration, or frequency than specified in the product label. Although off-label drug use is legally permissible under guidelines such as the Animal Medicinal Drug Use Clarification Act (AMDUCA) in the U.S., it requires a valid veterinarian-client-patient relationship (VCPR) and should be based on sound clinical

judgment (FDA, 2023a; James A. Budde, 2023). The unregulated or unsupervised use of OTC medications, particularly by laypersons or through anecdotal advice, can pose serious risks due to species-specific differences in drug absorption, metabolism, and elimination (Gehring et al., 2006). For instance, the inability of cats to glucuronidate certain compounds (e.g., acetaminophen) or the MDR1 mutation in some dog breeds that alters drug sensitivity highlights the critical importance of interspecies pharmacokinetics (Court, 2013; Lautz et al., 2021; Siroká, 2012).

Moreover, many OTC drugs contain inactive excipients, sweeteners (e.g., xylitol), or combination ingredients that may be safe for humans but highly toxic to animals (Pottel et al., 2020; Thomazini et al., 2024). This is compounded by the potential for underdosing (leading to therapeutic failure) or overdosing (causing toxicity) when human doses are inappropriately extrapolated for animals. Clinical signs of toxicity may range from gastrointestinal irritation and CNS depression to hepatotoxicity, nephrotoxicity, or life-threatening organ failure. Despite these risks, the continued reliance on OTC products in veterinary contexts reflects broader issues related to drug accessibility, economic pressures on pet owners, and gaps in veterinary pharmacological education among non-veterinarians. It also underscores the need for clearer guidance, pharmacovigilance systems, and interprofessional collaboration between veterinarians, pharmacists, and public health stakeholders to mitigate misuse.

This literature review aims to systematically examine the scope and impact of OTC drug use in animals. It synthesizes existing reports, toxicological data, and clinical experiences to identify commonly used OTC agents, evaluate their pharmacological suitability and associated adverse effects, and propose evidence-based precautionary principles for both veterinary professionals and the general public. By clarifying the boundaries and risks of this practice, this review contributes to a safer, more informed framework for therapeutic decision-making in veterinary medicine.

Definition of OTC Products and Off-Label Use

Over-the-counter products are medications that are legally available to consumers without a prescription (FDA, 2023b; Lynch, 2023; NIDA, 2017). In human healthcare, they are often used for self-limiting conditions such as pain, fever, allergies, or gastrointestinal symptoms. These products are deemed safe and effective when used as directed by the manufacturer and have undergone regulatory approval for human use.

Extra-label use means using an approved human or animal drug in a way that isn't listed on the drug's label. It's sometimes called off-label because the use is "off the label." Off-label use, in veterinary medicine, refers to the use of a drug in a manner not specified in the approved labeling (FDA, 2023a; James A. Budde, 2023). This can include use in a different species, for an unapproved indication, at a different dosage, or via a different route of administration. Although off-label use is legally permitted in many countries under veterinary discretion (e.g., the U.S. under AMDUCA), it comes with professional responsibility to ensure efficacy and safety based on scientific or empirical evidence. When applied to OTC products, off-label use often lacks the rigorous testing and species-specific data needed for informed decision-making.

1. Reasons for Off-Label OTC Use in Animals

There are several practical drivers behind the off-label use of OTC drugs in animals: 1) **Cost-effectiveness:** Veterinary drugs, especially those approved for chronic or specialty care, can be prohibitively expensive. OTC products, in contrast, are widely available and often cheaper, especially in generic forms. 2) **Access limitations:** In rural or underserved regions, veterinary clinics may lack sufficient pharmaceutical inventories. Pet owners or para-veterinary workers may turn to human pharmacies or household medications as substitutes. 3) **Convenience and familiarity:** Many OTC products are well known to the public, and owners may feel more confident using something familiar to treat minor ailments in pets. Additionally, some formulations (e.g., syrups or tablets) may be easier to administer or more palatable to animals. 4) **Perceived**

mildness or safety: OTC status in humans may be wrongly interpreted by pet owners as an indication of safety in animals, leading to unsupervised use without consideration of species-specific pharmacology (Miller, 2014; Taylor et al., 2023).

2. Common OTC Drug Classes Used Off-Label in Animals

OTC drug classes commonly used in veterinary settings without label approval reflect a combination of clinical necessity, owner-driven interventions, and accessibility of human pharmaceuticals. While some drugs have proven utility in specific circumstances, others present significant toxicological or pharmacokinetic risks, particularly in species such as cats, which have limited metabolic capacities.

2.1 Analgesics and Antipyretics

OTC analgesics and antipyretics, including acetaminophen (paracetamol), ibuprofen, naproxen, and aspirin, are commonly used to manage fever, pain, and inflammation (James A. Budde, 2023). Pet owners often extrapolate these indications to their animals, particularly in cases of musculoskeletal pain, fever of unknown origin, or post-traumatic discomfort. This behavior is frequently driven by the accessibility and familiarity of these medications, as well as a desire to provide immediate relief in the absence of veterinary access. However, this class of drugs poses some of the highest toxicity risks when used off-label in animals, especially without veterinary oversight.

In veterinary clinical settings, aspirin is occasionally used in dogs for its antithrombotic effects, such as in cases of heartworm-associated thromboembolism or immune-mediated hemolytic anemia, albeit with narrow safety margins (Griebsch et al., 2022; James A. Budde, 2023). However, acetaminophen, ibuprofen, and naproxen are not recommended for routine veterinary use, particularly in cats, due to severe and often fatal adverse effects. The use of these NSAIDs in veterinary species is complicated by species-specific metabolic pathways, notably deficiencies in detoxification enzymes and heightened sensitivity of the gastrointestinal mucosa and kidneys.

Acetaminophen is especially lethal to cats, even at small doses (as low as 50–100 mg/kg), due to their lack of glucuronyl transferase enzymes required for hepatic conjugation and elimination (Allen, 2003; Court, 2013). This leads to the accumulation of toxic metabolites that cause methemoglobinemia (oxidized hemoglobin incapable of oxygen transport), hepatocellular necrosis, facial edema, cyanosis, and death. Although dogs have a slightly higher tolerance to acetaminophen, its safety margin remains narrow, and liver damage is a major concern.

Ibuprofen and naproxen, while effective in humans, are highly toxic to dogs, with the toxic dose of ibuprofen beginning around 25 mg/kg (Dunayer, 2004; G. Osweiler, et al. , 2011). Adverse effects include gastrointestinal ulceration, renal tubular necrosis, and in severe cases, central nervous system depression and seizures. Even low-dose, repeated use can lead to cumulative toxicity. Naproxen has an even longer half-life in dogs, which increases the risk of persistent toxic effects and complicates management (Butty et al., 2022).

Aspirin, though sometimes prescribed under veterinary supervision, carries risks of gastric mucosal injury, coagulopathy, metabolic acidosis, and nephrotoxicity, especially at anti-inflammatory doses. Its use is generally limited to short-term or low-dose protocols and should be avoided in animals with pre-existing renal or gastrointestinal disease (Griebsch et al., 2022).

2.2 Antihistamines

Antihistamines are one of the few classes of OTC medications that are relatively well-tolerated and frequently utilized in veterinary medicine, particularly for managing allergic reactions, insect bites, vaccine-associated hypersensitivity, and in some cases, motion sickness or mild sedation (James A. Budde, 2023). Among these, diphenhydramine is the most widely accepted and studied antihistamine used off-label in dogs and cats. It functions primarily as an H1 receptor antagonist, blocking the effects of histamine released during allergic responses. Other first-generation antihistamines, such as chlorpheniramine, also have a veterinary application, particularly in felines, where it

is often used for chronic allergic dermatitis or upper respiratory inflammation (Hsieh & Beets, 2020; Mueller et al., 2021; Rossbach et al., 2016).

In clinical veterinary practice, diphenhydramine is generally considered safe when administered at appropriate doses, typically 2–4 mg/kg every 8–12 hours (Shipstone, 2022). It has mild sedative effects due to its ability to cross the blood-brain barrier, which can be beneficial in certain anxious or travel-stressed animals. Similarly, chlorpheniramine is valued in cats for its lower sedative profile and effectiveness in treating skin-related allergic conditions. Loratadine, a second-generation antihistamine with reduced sedative effects, is sometimes explored in dogs for chronic allergies, although its efficacy in animals is less well established and compounded by variability in absorption and metabolism (Hsieh & Beets, 2020; Rossbach et al., 2016; Shipstone, 2022).

Despite their relative safety, antihistamines are not without risk, particularly in cases of overdose or misidentification of combination products. Excessive dosing of diphenhydramine or chlorpheniramine can result in central nervous system depression, disorientation, ataxia, hyperexcitability, tremors, or seizures, as well as anticholinergic effects such as dry mouth, urinary retention, tachycardia, and constipation. These effects are more pronounced in small or geriatric animals and those with underlying cardiovascular or neurological conditions (Borowy CS, 2023; Church & Church, 2011). A more serious and often overlooked risk arises when pet owners administer combination antihistamine products that include decongestants, such as pseudoephedrine or phenylephrine, which are commonly found in human cold and flu preparations (C., 2012; James A. Budde, 2023; Walden, 2021). These sympathomimetic agents are highly toxic to animals, especially dogs and cats, even in small amounts. Ingestion can lead to severe hypertension, cardiac arrhythmias, hyperthermia, tremors, seizures, and potentially fatal outcomes (C., 2012; James A. Budde, 2023; Walden, 2021). Unfortunately, product labeling may not always clearly distinguish these combinations, increasing the likelihood of unintentional poisoning.

2.3 Antidiarrheals and Gastrointestinal (GI) Agents

OTC antidiarrheal medications such as loperamide and bismuth subsalicylate are often used off-label in veterinary settings to manage acute, self-limiting diarrhea in dogs and, less frequently, in cats (Dowling, 2023; Howe, 2023; Krista Williams, 2023). Pet owners may administer these medications without veterinary consultation, guided by prior experiences, anecdotal reports, or online sources recommending their use. While these agents can offer symptomatic relief when used correctly, they pose significant risks if improperly dosed, used in contraindicated species or breeds, or given over extended periods (Howe, 2023).

Loperamide, a peripherally acting μ-opioid receptor agonist, slows intestinal motility and enhances water reabsorption, making it effective for non-infectious, mild diarrhea (Sobczak et al., 2014). It is sometimes used off-label in dogs at doses of 0.08 mg/kg, peroral, TID-QID, typically for short durations (Dowling, 2023). However, loperamide crosses the blood-brain barrier in animals with a defective MDR1 (ABCB1) gene, commonly found in herding breeds such as Collies, Australian Shepherds, and Shetland Sheepdogs (Beckers et al., 2022; Long et al., 2017; Sartor et al., 2004). In these dogs, the lack of a functional P-glycoprotein efflux pump leads to CNS accumulation of the drug, resulting in ataxia, profound sedation, coma, or even death. Genetic testing for the MDR1 mutation is crucial before considering its use in these breeds. Additionally, overdose in any breed may cause severe central nervous system depression, bradycardia, hypotension, and respiratory compromise (Fecht & Distl, 2008; Mealey et al., 2023; Schulz et al., 2023).

Bismuth subsalicylate, the active ingredient in Pepto-Bismol, has a dual mechanism: bismuth acts as a gastroprotectant with antimicrobial properties, while salicylate has anti-inflammatory effects that can help reduce intestinal secretion and irritation (Pitz et al., 2015). It may be used under veterinary supervision in dogs for mild gastrointestinal upset, often in cases of dietary indiscretion. However, its use is contraindicated in cats due to the salicylate content, which is a derivative of aspirin. Cats have limited

hepatic glucuronidation capacity, making them especially vulnerable to salicylate toxicity, which can cause gastric mucosal damage, melena, hematemesis, metabolic acidosis, and renal impairment (Cafer et al., 2024; Dowling, 2023).

2.4 Cough/Cold Medications

Cough and cold OTC medications, particularly those containing dextromethorphan or guaifenesin, are occasionally used off-label in veterinary medicine to address non-productive coughing in conditions such as canine infectious tracheobronchitis (kennel cough), tracheitis, or bronchitis (Brooks, 2024; Kuehn, 2018). These drugs are selected based on their common use in humans and the assumption that symptomatic relief of cough in animals will follow similar pharmacological principles. However, this approach is controversial, as efficacy in animals is inconsistent, and the risk of toxicity from combination formulations is substantial.

Dextromethorphan, a non-opioid antitussive, acts on the cough center in the medulla to suppress the cough reflex. It is structurally related to opioids but lacks analgesic or addictive properties in therapeutic doses (Dowling, 2022a). In veterinary practice, it is occasionally used in dogs at 1–2 mg/kg for dry, irritating coughs, especially when coughing disrupts rest or recovery (G. D. Osweiler, 2011). Nonetheless, its clinical effectiveness in dogs remains poorly substantiated, and its use is often empirical rather than evidence-based. Furthermore, at higher doses, dextromethorphan can lead to CNS side effects such as ataxia, sedation, disorientation, vomiting, and, paradoxically, hyperexcitability or stimulation due to its action on NMDA receptors (Chyka et al., 2007; Rogasch et al., 2020; Taylor et al., 2016).

Guaifenesin, a commonly used expectorant in human medicine, is often misunderstood in the veterinary context. While marketed for mucus clearance in humans, in animals, especially horses and ruminants, guaifenesin is primarily used as an intravenous muscle relaxant and adjunct to general anesthesia, not as an oral mucolytic (Dowling, 2022b; Wiegand, 2024). Its utility as an expectorant in dogs or cats is minimal to negligible, and its inclusion in OTC cough syrups intended for small animals offers little therapeutic benefit (Dowling, 2022b).

The greatest concern surrounding the use of OTC cold medications in animals lies in their combination formulations. Many human cough products combine dextromethorphan or guaifenesin with potentially toxic ingredients such as acetaminophen (hepatotoxic in cats), pseudoephedrine or phenylephrine (vasoconstrictive and cardiotoxic), caffeine (neurostimulant), antihistamines, or ethanol. These additional agents can easily lead to serious or fatal toxicity, even at low doses in small animals. For instance, ingestion of pseudoephedrine at doses as low as 2–3 mg/kg in dogs can result in tachycardia, hypertension, seizures, and hyperthermia (Chyka et al., 2007; Dowling, 2022b; James A. Budde, 2023; G. D. Osweiler, 2011; Wiegand, 2024). In addition, OTC syrups often contain alcohol, artificial sweeteners (e.g., xylitol), or flavoring agents that are unsuitable or dangerous for pets. These excipients can further contribute to gastrointestinal upset, hypoglycemia (in the case of xylitol), or CNS depression, particularly in small or compromised animals (Thomazini et al., 2024).

2.5` Topical Antimicrobials and Antifungals

Topical antimicrobials and antifungals, such as bacitracin-neomycin-polymyxin (commonly known as triple antibiotic ointment), miconazole, and clotrimazole, are among the most accessible and widely used OTC products (FDA, 2023b; Krista Williams, 2023; NIDA, 2017). They are frequently applied by pet owners to treat minor wounds, superficial bacterial skin infections, or fungal dermatitis in companion animals, often without prior veterinary guidance. The appeal of these products lies in their easy availability, familiarity, and perceived safety in human use factors, which unfortunately do not always translate to veterinary appropriateness. In clinical veterinary medicine, triple antibiotic ointments may be used judiciously on small, non-infected or mildly contaminated wounds, particularly in dogs. The combination provides broad-spectrum antibacterial coverage, and its application can help prevent superficial infection

in abrasions or lacerations. However, neomycin, one of the components, is a sensitizer known to cause contact dermatitis or allergic reactions, especially in repeated or prolonged use.

Miconazole and clotrimazole, both imidazole antifungals, are effective against a range of superficial fungal pathogens, including dermatophytes and Malassezia spp., and are commonly used in otitis externa formulations or topical creams. Their use in veterinary medicine is often safe when applied externally and under supervision. These antifungals are particularly useful in treating Malassezia otitis in dogs, often in combination with corticosteroids or antibiotics in commercial veterinary otic preparations (Hobi et al., 2024; Peano et al., 2012).

Despite their apparent safety when used topically, several risks arise from off-label or unsupervised use in animals: 1) Licking or ingestion of the product is a major concern, particularly in cats and dogs with accessible wounds. This can result in gastrointestinal upset, vomiting, or diarrhea, and may potentially expose the animal to toxicity from absorbed active ingredients or excipients (e.g., preservatives or mineral oil bases). 2) The use of non-sterile human topical products in or near the eyes, a common mistake when treating conjunctivitis or corneal injuries, can lead to corneal irritation, ulceration, or secondary infections. The eye is an immunologically privileged and highly sensitive site, and products not labeled for ophthalmic use may contain particulates or preservatives that damage the ocular surface. 3) Cats are particularly sensitive to topical medications, due to their frequent grooming behavior and increased dermal and mucosal absorption relative to body weight. Certain ingredients, even when applied externally, can be systemically absorbed and lead to toxicity, especially when used over large surface areas or in occluded environments like the ear canal.

2.6 Supplements and Vitamins

OTC supplements and vitamins, including melatonin, vitamin D, multivitamins, and probiotics, are increasingly used off-label in veterinary settings, often driven by the rising popularity of holistic health trends and the perception that natural products are inherently safe. Pet owners may administer these products to animals based on anecdotal evidence, online forums, or assumptions of similarity in physiological needs between humans and animals. While some supplements may provide benefits under veterinary supervision, their unregulated use poses substantial risks due to differences in species-specific metabolism, narrow safety margins, and inconsistent product quality (Finno, 2020).

Among these, melatonin is one of the few supplements with documented veterinary utility. In dogs, it is used for the management of alopecia-X (seasonal flank alopecia), anxiety-related disorders, and sometimes to influence reproductive cycles, particularly in ferrets or seasonal breeders. Dosages typically range from 1 to 6 mg, depending on the size of the animal, and timing of administration is important due to melatonin's circadian regulatory effects. However, melatonin products vary widely in concentration and may contain xylitol, a common sweetener that is highly toxic to dogs, leading to hypoglycemia and hepatic failure (Minich et al., 2022).

Probiotics are also commonly given to support gut health, especially during or after antibiotic therapy or in animals with gastrointestinal disturbances. While some strains (e.g., Enterococcus faecium, Lactobacillus spp.) are safe and effective, the use of human-targeted formulations may result in inadequate colonization, or worse, introduce pathogenic or unverified strains into the animal's gut. Veterinary probiotics are typically species-specific and undergo stricter quality control for use in animals.

In contrast, vitamin D supplements present a significant danger. Animals, especially dogs and cats, have a much narrower therapeutic index for vitamin D compared to humans. Even slight over-supplementation can lead to hypercalcemia, resulting in vomiting, lethargy, muscle tremors, arrhythmias, kidney failure, or death. Toxicity has been reported from both acute ingestion and chronic low-level exposure to OTC human vitamin D supplements or vitamin-enriched foods (e.g., fortified cereal or rodenticide ingestion) (Minich et al., 2022).

Multivitamins, particularly those containing

iron, pose another major toxicity risk. Iron, while essential, is highly toxic in overdose, especially in chewable pediatric formulations. In animals, ingestion can lead to corrosive gastrointestinal injury, followed by hepatic necrosis, metabolic acidosis, cardiovascular collapse, and death. Moreover, many multivitamin products include other minerals, fat-soluble vitamins, and herbal additives, whose safety in veterinary species is unknown or untested (Thomazini et al., 2024). A critical concern with OTC supplements is the lack of regulatory oversight and variability in product quality. Studies have shown that many human supplements contain inconsistent ingredient levels, unlisted substances, or contaminants, especially in unregulated herbal or dietary supplements. This inconsistency can result in underdosing, overdosing, or exposure to toxic compounds, particularly when pet owners use multiple products simultaneously.

3. Excipients of Concern in OTC Products Used in Animals

While the active ingredients in OTC medications often receive the greatest attention, the inactive ingredients or excipients can pose equally significant threats to animal health when these products are used off-label in veterinary patients. Many excipients are considered GRAS (Generally Recognized as Safe) for human use but lack safety data or are known to be toxic or poorly tolerated in non-human species. Species-specific differences in enzymatic pathways, hepatic metabolism, and gastrointestinal physiology mean that substances benign in humans may result in idiosyncratic or dose-dependent adverse effects in animals. This section highlights the most clinically relevant excipients found in OTC medications that should raise concern in veterinary practice.

3.1 Sweeteners and Flavoring Agents

Excipients such as artificial sweeteners and sugar alcohols are frequently used in chewable tablets, syrups, and lozenges to improve palatability for humans, but several of these agents are toxic to animals. Xylitol, in particular, is a highly toxic sugar substitute for dogs (Thomazini et al., 2024). It induces a rapid insulin release, resulting in hypoglycemia, and at higher doses, causes acute hepatic necrosis. Toxic effects have been observed at doses as low as 75–100 mg/kg, and even small quantities can be lethal. Unfortunately, xylitol is often unlisted on labels or disguised under other terms such as "sugar alcohol." Other sugar alcohols, such as sorbitol and mannitol, may be less acutely toxic but can lead to osmotic diarrhea, bloating, or abdominal discomfort, especially in sensitive or small animals. Propylene glycol, a common solvent and humectant, is considered safe in small quantities for dogs, but cats lack the enzymes necessary to metabolize it effectively, leading to Heinz body anemia and oxidative red cell damage with chronic exposure.

3.2 Preservatives and Antimicrobials

Preservatives are essential in extending the shelf-life of pharmaceutical products, but several agents are poorly tolerated by animals. Benzalkonium chloride (BAK) is frequently found in ophthalmic and nasal sprays. Although effective as an antimicrobial, BAK is cytotoxic to corneal epithelial cells, and repeated exposure in animals can cause ocular irritation, delayed healing, and corneal ulceration. Its use in non-veterinary ophthalmic products presents a notable risk when misapplied to animal eyes (Thomazini et al., 2024). Parabens, a class of preservatives used in topical and oral formulations, exhibit estrogenic activity and have been implicated in endocrine disruption. While considered low-risk in short-term exposure, chronic or cumulative exposure, particularly in small or developing animals, raises concerns about reproductive and hormonal effects, especially given the lack of dose-specific veterinary safety data (Torfs & Brackman, 2021).

3.3 Coloring Agents

Artificial dyes such as FD&C Red No. 40 and other synthetic colorants are routinely added to human products for visual appeal. Although not overtly toxic, some dyes have been linked to hypersensitivity reactions, behavioral changes, or immune-mediated responses in sensitive animal breeds, particularly in dogs predisposed to skin allergies or food sensitivities. While their effects are subtle and often cumulative, unnecessary dye exposure through off-label

OTC use should be avoided (Thomazini et al., 2024).

3.4 Solvents and Vehicles

Ethanol, commonly found in liquid formulations and syrups, poses a significant risk of CNS depression, hypothermia, hypoglycemia, and respiratory failure in small animals, especially neonates and toy breeds. Animals metabolize ethanol differently, and even small volumes can cause intoxication. Moreover, ingestion of ethanol-containing cold remedies or tinctures can be fatal if untreated. Polyethylene glycol (PEG) is a solvent and laxative used in various oral and topical preparations. Though generally considered safe in low doses, renal-compromised or dehydrated animals may be more susceptible to GI irritation or hypersensitivity reactions, particularly if PEG is absorbed systemically (Thomazini et al., 2024).

3.5 Emulsifiers and Thickeners

Polysorbates, especially Polysorbate 80, are used to stabilize emulsions but have been associated with hypersensitivity reactions, particularly in parenteral (injectable) formulations. Reactions range from mild urticaria to anaphylaxis, particularly when administered intravenously or absorbed over damaged skin (Thomazini et al., 2024). Carrageenan, derived from red seaweed and used as a thickener in lozenges and liquid suspensions, has been linked to intestinal inflammation and ulceration in some experimental models (Borsani et al., 2021). While evidence in veterinary species is limited, its inclusion in long-term oral therapies for pets remains a potential concern, particularly in animals with chronic GI conditions.

3.6 Miscellaneous Concerns

Several other excipients found in OTC products pose serious veterinary hazards. Caffeine, often included in cold and headache remedies or topical pain rubs, is a potent central nervous system stimulant in animals. Dogs and cats are highly sensitive to methylxanthines, and ingestion can lead to tachycardia, hyperactivity, tremors, seizures, and death. Menthol and camphor, common in balms, rubs, and decongestants, are rapidly absorbed through the skin and mucous membranes, particularly in cats and small dogs. These substances can cause neurotoxicity, presenting as salivation, vomiting, tremors, or seizures when ingested or applied over large surface areas (Thomazini et al., 2024).

4. Clinical Decision-Making and Risk Assessment

The off-label use of OTC products in animals requires careful and structured clinical decision-making, particularly given the potential for toxicity, inappropriate dosing, and lack of species-specific safety data (FDA, 2023a). Veterinarians must base their decisions not only on the pharmacological profile of the drug but also on contextual factors such as the animal's species, size, health status, and the availability of safer veterinary-approved alternatives. This section outlines the critical components of decision-making and risk assessment when considering OTC medications for veterinary patients.

Factors Influencing the Decision to Use OTCs in Animals

Several factors may drive veterinarians or sometimes pet owners themselves to consider the use of OTC products in animals. These include: a) **Drug availability:** In regions where veterinary formulations are not accessible due to supply chain limitations or regulatory constraints, practitioners may have no choice but to consider human medications. b) **Cost considerations:** Veterinary drugs may be unaffordable for some clients, especially for chronic conditions. OTC products are often cheaper and more readily available in pharmacies. c) **Owner insistence or prior use:** Some pet owners may request specific human products they've used before or seen recommended online, leading to pressure on the veterinarian to validate or approve their use. d) **Emergency situations:** In acute scenarios, such as allergic reactions, diarrhea, or minor injuries, practitioners may resort to OTC drugs when time-sensitive treatment is necessary. While these factors may justify the consideration of OTC products, they should never override the need for scientific judgment, patient safety, and legal compliance (FDA, 2023a).

Consideration of Alternative Veterinary-Approved Treatments

Before prescribing or recommending an OTC product, the clinician must assess whether a veterinary-approved equivalent or superior option exists. Veterinary drugs are specifically formulated to match species-specific pharmacokinetics, dosing requirements, and palatability, and they undergo regulatory scrutiny for safety and efficacy in the target animal. Examples include veterinary NSAIDs (e.g., carprofen, meloxicam) that are safer alternatives to ibuprofen or aspirin, or veterinary-formulated antihistamines and probiotics (FDA, 2023a, 2023b; Krista Williams, 2023; Lynch, 2023).

Additionally, compounding pharmacies may offer custom-formulated veterinary drugs that replicate the therapeutic intent of a human product in a safer, tailored format. Choosing veterinary-specific treatments also reduces the risk of inappropriate excipients, incorrect dosages, and adverse drug reactions.

Dosage Calculations and Treatment Planning

If the decision is made to use an OTC product, precise dose calculation is essential (Shugg, 2022). Human dosing instructions cannot be directly extrapolated to animals, as metabolic rates, volume of distribution, and elimination half-lives differ significantly between species. Doses must be calculated based on the animal's weight (mg/kg), age, organ function (particularly hepatic and renal), and breed-specific metabolic traits (e.g., MDR1 mutation in herding breeds) (Fecht & Distl, 2008; Mealey et al., 2023; Sartor et al., 2004).
In addition to dosing, treatment planning should include route of administration (e.g., oral vs. topical), duration of therapy, expected onset of action, monitoring protocols for adverse effects or clinical response, drug interactions, especially in patients receiving multiple medications. Labeling of the dispensed product should be customized with veterinary instructions to avoid confusion and ensure compliance (Shugg, 2022).

Risk-Benefit Analysis in Clinical Scenarios

Ultimately, the decision to use an OTC product in an animal should involve a thorough risk-benefit analysis. This involves weighing the potential therapeutic gain against the likelihood and severity of adverse outcomes. Key questions to guide this analysis include: 1) Is the animal's condition self-limiting or life-threatening? 2) Are there safer, veterinary-labeled alternatives available? 3) What is the margin of safety for the OTC drug in the species being treated? 4) Are there toxic excipients in the formulation? 5)Can the owner reliably monitor the animal and report adverse events?. In low-risk, short-term cases (e.g., using diphenhydramine for mild allergic reactions in dogs), the benefit may outweigh the risk (Walden, 2021). However, in cases involving cats, exotic species, polypharmacy, or chronic administration, the risk often outweighs the potential benefit unless the product has been thoroughly vetted for veterinary use.

5. Guidelines and Precautionary Principles

The off-label use of OTC products in animals presents significant clinical and ethical challenges. To mitigate potential risks and ensure patient safety, it is essential to establish clear guidelines and precautionary principles for veterinarians, animal owners, and other stakeholders (Dresser & Frader, 2009; Van Norman, 2023). These principles should emphasize veterinary oversight, client education, and structured clinical decision-making tools that promote responsible medication use in animal patients.

Best Practices for Veterinarians: Supervision, Dosing, Monitoring

Veterinarians play a critical role in ensuring the safe application of OTC medications in animals. Supervision is non-negotiable; no OTC product should be recommended for animal use without a thorough evaluation by a qualified professional. Best practices include: Individualized dosing based on mg/kg body weight, not extrapolated from human doses or packaging; Verification of active and inactive ingredients, especially to identify toxic excipients (e.g., xylitol, pseudoephedrine, propylene glycol); Selection of single-agent products whenever possible to reduce the risk of adverse interactions; Development of a monitoring plan, including parameters to assess efficacy (e.g.,

resolution of diarrhea, reduction in pruritus) and safety (e.g., signs of toxicity, bloodwork if needed); Documentation of the rationale, dose, frequency, duration, and informed consent for off-label use in the medical record (Muñoz et al., 2023; Thomazini et al., 2024; Tomanic et al., 2021).

Education for Pet Owners and Livestock Handlers

One of the most important strategies in preventing OTC misuse is proactive education. Pet owners often lack understanding of species-specific drug sensitivities and may mistakenly believe that OTC products labeled "mild" or "natural" are universally safe (Dresser & Frader, 2009; Tomanic et al., 2021; Van Norman, 2023). Veterinarians and animal health professionals should: Emphasize that human-safe does not mean animal-safe; Encourage clients to consult a veterinarian before administering any OTC product, even for minor conditions; Provide written instructions and verbal counseling when dispensing or approving OTC use; Warn about dangerous combinations, especially cold medications with multiple active ingredients; For livestock handlers, include information on residues and withdrawal periods, which are particularly relevant for food-producing animals. Educational outreach can also include clinic brochures, posters, infographics, and social media content focused on common OTC drug dangers.

Red Flags and Contraindications

Certain scenarios should immediately contraindicate the use of OTC products in animals. Red flags include: 1) Use in cats: due to unique metabolic vulnerabilities, especially with acetaminophen, propylene glycol, or salicylates; 2) Presence of combination ingredients, such as decongestants, antihistamines, and analgesics, which increase the risk of unintended toxicity; 3) Patients with comorbidities, such as hepatic, renal, or cardiovascular disease, where drug clearance is impaired; 4) Use in neonates, geriatrics, or pregnant animals: populations with altered pharmacokinetics and greater sensitivity; and 5) Breeds with known mutations, such as the MDR1 gene mutation in Collies, which predisposes to loperamide toxicity. Any OTC product containing unknown, unlisted, or unverified ingredients should never be used in veterinary patients.

Decision Trees or Checklists for Safe Use

To support rational decision-making, veterinarians and pharmacists can implement decision-support tools such as 1) Checklists to confirm species suitability, safe dosage, and excipient screening; and 2) Decision trees that guide clinicians through a structured process: Is there a veterinary-approved alternative?, Is the species compatible with the active and inactive ingredients?, Is there a clear therapeutic indication?, Can proper dosing and monitoring be ensured?, Are owners capable of identifying adverse effects?. Such tools not only reduce the risk of human error but also help in standardizing care across practitioners and improving accountability in clinical documentation.

6. The Role of Veterinary Pharmacists and Interprofessional Collaboration

As the off-label use of human over-the-counter (OTC) medications in animals becomes more common, the need for collaboration between veterinarians, pharmacists, and pet owners becomes increasingly important (Dresser & Frader, 2009; FDA, 2023a; Van Norman, 2023). Veterinary pharmacists play a critical role in ensuring medication safety, especially when human products are used in veterinary contexts (Immonen et al., 2023; Plaza et al., 2022). Effective interprofessional communication and coordination across these disciplines can significantly reduce errors, enhance therapeutic outcomes, and support a culture of pharmacovigilance in animal healthcare.

Counseling and Screening by Pharmacists

Pharmacists, particularly those trained in veterinary pharmacology, serve as a first line of defense when pet owners seek human medications for animal use. Given that many OTC products are purchased without prescriptions, community pharmacists are in a key position to: Screen for inappropriate or harmful ingredients, such as xylitol, pseudoephedrine, or NSAIDs

that are toxic to animals; Advise against the use of combination products with unclear or dangerous excipients; Verify dosing questions based on animal weight and species, especially for common requests like diphenhydramine or loperamide; Recommend the proper veterinary-labeled alternatives, where available; Encourage clients to consult their veterinarian before administering any human medication to pets. By offering this level of oversight, pharmacists help prevent unintentional toxicity and promote rational drug use across species boundaries (Immonen et al., 2023; Plaza et al., 2022).

Communication Between Veterinarians, Pharmacists, and Clients

Currently, there are not many pharmacists in Indonesia who work in animal health facilities, so there is no communication between veterinarians, pharmacists, and clients. In fact, seamless communication among veterinarians, pharmacists, and clients is essential for safe off-label use of OTC drugs in animals (FDA, 2023a; Immonen et al., 2023; Plaza et al., 2022). Interprofessional collaboration can: Clarify dosing instructions and species compatibility, especially when pharmacists dispense medications that may be intended for animals; Ensure the accurate interpretation of prescriptions, particularly when drugs need to be compounded or adjusted for animal use; Promote shared responsibility in monitoring for side effects, particularly during extended therapy; and Help reconcile polypharmacy issues by identifying interactions between veterinary and human medications. Veterinarians should maintain open channels with local pharmacists, especially in rural or underserved areas, to build trust and establish standardized protocols for verifying the safety of human medications in animals.

Pharmacovigilance and Adverse Event Reporting Systems

A cornerstone of safe medication use, whether human or veterinary, is pharmacovigilance, the active monitoring and reporting of adverse drug reactions (Davies et al., 2022; Mekasha et al., 2024). Veterinary pharmacists and clinicians are jointly responsible for: Identifying unexpected adverse events following the use of OTC medications in animals; Submitting reports to relevant authorities such as the FDA Center for Veterinary Medicine (CVM) in the United States or EudraVigilance Veterinary in Europe; Participating in post-marketing surveillance efforts that collect real-world data on drug safety across species; and Educating clients on what signs to watch for, how to report adverse effects, and the importance of follow-up care. Improved reporting not only enhances the safety of individual patients but also contributes to larger databases that inform regulatory policies, labeling changes, and veterinary education.

In summary, veterinary pharmacists are indispensable allies in the responsible use of OTC products in animal health. Their expertise in pharmacology, product screening, and client education complements the clinical judgment of veterinarians. By fostering strong interprofessional collaboration and a robust culture of pharmacovigilance, we can significantly reduce the risks associated with off-label OTC drug use and promote safer, evidence-based veterinary care.

Conclusion

In conclusion, while the off-label use of human over-the-counter (OTC) products in veterinary medicine may offer practical benefits such as cost-effectiveness and accessibility, it also carries substantial risks due to species-specific pharmacokinetic differences, toxic excipients, inappropriate dosing, and the potential for adverse reactions. This literature review highlights the critical importance of veterinary oversight, informed clinical decision-making, and interprofessional collaboration to ensure safe and effective use of these products in animals. Education of pet owners, adherence to evidence-based guidelines, and the promotion of pharmacovigilance are essential to minimizing harm and optimizing therapeutic outcomes when OTC drugs are considered for veterinary patients.

Acknowledgement

The authors declare that no external funding was received for the completion of this study.

References

Allen, A. L. (2003). The diagnosis of acetaminophen toxicosis in a cat. *Can Vet J*, *44*(6), 509-510.

Beckers, E., Casselman, I., Soudant, E., Daminet, S., Paepe, D., Peelman, L., & Broeckx, B. J. G. (2022). The prevalence of the ABCB1-1Δ variant in a clinical veterinary setting: The risk of not genotyping. *PLoS One*, *17*(8), e0273706. https://doi.org/10.1371/journal.pone.0273706

Borowy CS, M. P. (2023). *Antihistamine Toxicity*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK482318/

Borsani, B., De Santis, R., Perico, V., Penagini, F., Pendezza, E., Dilillo, D., Bosetti, A., Zuccotti, G. V., & D'Auria, E. (2021). The Role of Carrageenan in Inflammatory Bowel Diseases and Allergic Reactions: Where Do We Stand? *Nutrients*, *13*(10). https://doi.org/10.3390/nu13103402

Brooks, W. (2024). *Kennel Cough in Dog*. Veterinary Partner.

Butty, E. M., Suter, S. E., Chalifoux, N. V., Lynch, A. M., Mauro, K. D., Moyle, R. B., Ehrhardt, C. M., Robertson, J. B., Culler, C. A., Londoño, L. A., Vigani, A., Ueda, Y., & Labato, M. A. (2022). Outcomes of nonsteroidal anti-inflammatory drug toxicosis treated with therapeutic plasma exchange in 62 dogs. *Journal of Veterinary Internal Medicine*, *36*(5), 1641-1647. https://doi.org/https://doi.org/10.1111/jvim.16507

C., W. (2012). *Toxicology brief: phenylephrine ingestion in dogs: what's the harm?* . DVM360.

Cafer, S., Bilgiç, B., & Or, M. E. (2024). Is acetylsalicylic acid use in cats contra-indicated or limited indicated? *Journal of Toxicological Studies*, *2*(2), 1486. https://doi.org/10.59400/jts.v2i2.1486

Church, D. S., & Church, M. K. (2011). Pharmacology of antihistamines. *World Allergy Organ J*, *4*(3 Suppl), S22-27. https://doi.org/10.1097/WOX.0b013e3181f385d9

Chyka, P. A., R., E. A., S., M. A., Gwenn, C., L., B. L., S., N. L., D., W. A., J., C. D., Martin, C. E., J., S. E., & and Troutman, W. G. (2007). Dextromethorphan poisoning: An evidence-based consensus guideline for out-of-hospital management. *Clinical Toxicology*, *45*(6), 662-677. https://doi.org/10.1080/15563650701606443

Court, M. H. (2013). Feline drug metabolism and disposition: pharmacokinetic evidence for species differences and molecular mechanisms. *Vet Clin North Am Small Anim Pract*, *43*(5), 1039-1054. https://doi.org/10.1016/j.cvsm.2013.05.002

Davies, H., Pinchbeck, G., Noble, P. M., Diesel, G., Pirmohamed, M., Anderson, N., & Killick, D. R. (2022). UK veterinary professionals' perceptions and experiences of adverse drug reaction reporting. *Vet Rec*, *191*(6), e1796. https://doi.org/10.1002/vetr.1796

Dowling, P. M. (2022a, 2022/01). *Antitussive Drugs in Animals*. MSD Veterinary Manual. https://www.msdvetmanual.com/pharmacology/systemic-pharmacotherapeutics-of-the-respiratory-system/antitussive-drugs-in-animals

Dowling, P. M. (2022b, 2022/01). *Expectorants and Mucolytic Drugs in Animals*. MSD Veterinary Manual. https://www.msdvetmanual.com/pharmacology/systemic-pharmacotherapeutics-of-the-respiratory-system/expectorants-and-mucolytic-drugs-in-animals

Dowling, P. M. (2023, 2023/05). *Drugs Used to Treat Diarrhea in Monogastric Animals*. MSD Veterinary Manual. https://www.msdvetmanual.com/pharmacology/systemic-pharmacotherapeutics-of-the-digestive-system/drugs-used-to-treat-diarrhea-in-monogastric-animals

Dresser, R., & Frader, J. (2009). Off-label prescribing: a call for heightened professional and government oversight. *J Law Med Ethics*, *37*(3), 476-486, 396. https://doi.org/10.1111/j.1748-720X.2009.00408.x

Dunayer, E. (2004). Ibuprofen toxicosis in dogs, cats, and ferrets. *Toxicology Brief*

FDA, U. (2023a). *The Ins and Outs of Extra-Label Drug Use in Animals: A Resource for Veterinarians*.

FDA, U. (2023b). *Over-the-Counter OTC | Nonprescription Drugs*. US. Food and Drug Administration.

Fecht, S., & Distl, O. (2008). Review of prevalence, genetic aspects and adverse effects of the mdr1-1Delta mutation in dogs. *Dtsch Tierarztl Wochenschr*, *115*(6), 212-219.

Finno, C. J. (2020). Veterinary Pet Supplements and Nutraceuticals. *Nutr Today*, *55*(2), 97-101. https://doi.org/10.1097/nt.0000000000000399

Gehring, R., Baynes, R. E., & Riviere, J. E. (2006). Application of risk assessment and management principles to the extralabel use of drugs in food-producing animals. *J Vet Pharmacol Ther*, *29*(1), 5-14. https://doi.org/10.1111/j.1365-2885.2006.00707.x

Griebsch, C., Hall, E., & Barrs, V. R. (2022). Effectiveness of aspirin vs. clopidogrel in dogs with immune mediated haemolytic anaemia evaluated by serial thromboelastography and platelet mapping. *Vet J*, *287*, 105882. https://doi.org/10.1016/j.tvjl.2022.105882

Hobi, S., Bęczkowski, P. M., Mueller, R., Tse, M., & Barrs, V. R. (2024). Malassezia dermatitis in dogs and cats. *The Veterinary Journal*, *304*, 106084. https://doi.org/https://doi.org/10.1016/j.tvjl.2024.106084

Howe, S. (2023). *Imodium® For Dogs: Can You Give Dogs Imodium?* PetMD.

Hsieh, B. M., & Beets, A. K. (2020). Coughing in Small Animal Patients [Review]. *Frontiers in Veterinary Science*, *Volume 6 - 2019*. https://doi.org/10.3389/fvets.2019.00513

Immonen, H., Raekallio, M. R., & Holmström, A. R. (2023). Promoting veterinary medication safety - Exploring the competencies of community pharmacy professionals in veterinary pharmacotherapy. *Vet Anim Sci*, *21*, 100310. https://doi.org/10.1016/j.vas.2023.100310

James A. Budde, D. M. M. (2023). *Plumb's Veterinary Drug Handbook, 10th Edition*. Wiley-Blackwell.

Krista Williams, M. W., Lynn Buzhardt (2023). *Over-the-Counter (OTC) Medications That May Be Safe for Dogs*. VCA Animal Hospital.

Kuehn, N. F. (2018, 2018/06). *Tracheobronchitis (Bronchitis) in Dogs*. MSD Veterinary Manual. https://www.msdvetmanual.com/dog-owners/lung-and-airway-disorders-of-dogs/tracheobronchitis-bronchitis-in-dogs

Lautz, L. S., Jeddi, M. Z., Girolami, F., Nebbia, C., & Dorne, J. L. C. M. (2021). Metabolism and pharmacokinetics of pharmaceuticals in cats (Felix sylvestris catus) and implications for the risk assessment of feed additives and contaminants. *Toxicology Letters*, *338*, 114-127. https://doi.org/https://doi.org/10.1016/j.toxlet.2020.11.014

Long, W. M., Sinnott, V. B., Bracker, K., & Thomas, D. (2017). Use of 20% intravenous lipid emulsion for the treatment of loperamide toxicosis in a Collie homozygous for the ABCB1-1Δ mutation. *J Vet Emerg Crit Care (San Antonio)*, *27*(3), 357-361. https://doi.org/10.1111/vec.12562

Lynch, S. S. (2023, 2025/03). *Overview of Over-the-Counter Medications*. MSD Manual. https://www.msdmanuals.com/home/drugs/over-the-counter-medications/overview-of-over-the-counter-medications

Mealey, K. L., Owens, J. G., & Freeman, E. (2023). Canine and feline P-glycoprotein deficiency: What we know and where we need to go. *J Vet Pharmacol Ther*, *46*(1), 1-16. https://doi.org/10.1111/jvp.13102

Mekasha, Y. T., Nigussie, S., Mekonen, A. W., Berrie, K., Mulaw, A., & Feleke, M. G. (2024). A narrative review of

veterinary pharmacovigilance situations and prospects in East African countries. *Front Vet Sci*, *11*, 1430587. https://doi.org/10.3389/fvets.2024.1430587

Miller, L. (2014). Assuring Quality Care for Animals – Youth Food Animal Quality Assurance Curriculum Guide In

Minich, D. M., Henning, M., Darley, C., Fahoum, M., Schuler, C. B., & Frame, J. (2022). Is Melatonin the "Next Vitamin D"?: A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients*, *14*(19). https://doi.org/10.3390/nu14193934

Mueller, R. S., Nuttall, T., Prost, C., Schulz, B., & Bizikova, P. (2021). Treatment of the feline atopic syndrome – a systematic review. *Veterinary Dermatology*, *32*(1), 43-e48. https://doi.org/https://doi.org/10.1111/vde.12933

Muñoz, J., Nasaré, A., Cruz, B., Sousa, J., Messanelli, J., Leoni, L., Oliveira, T., Lopes, B., Nascimento, F., Novais, S., Serrano, B., Waziry, P., & Fukushima, A. (2023). Feline toxicology: quick guide for consultation. *12*, 43-49. https://doi.org/10.15406/jdvar.2023.12.00321

Myers, J., Hennessey, M., Arnold, J. C., McCubbin, K. D., Lembo, T., Mateus, A., Kitutu, F. E., Samanta, I., Hutchinson, E., Davis, A., Mmbaga, B. T., Nasuwa, F., Gautham, M., & Clarke, S. E. (2022). Crossover-Use of Human Antibiotics in Livestock in Agricultural Communities: A Qualitative Cross-Country Comparison between Uganda, Tanzania and India. *Antibiotics (Basel)*, *11*(10). https://doi.org/10.3390/antibiotics11101342

NIDA. (2017). *Over-the-Counter Medicines DrugFacts*. National Institute on Drug Abuse.

Osweiler, G., et al. . (2011). *Blackwell's five-minute veterinary consult clinical companion. Small Animal Toxicolog*.

Osweiler, G. D. (2011). *Blackwell's five-minute veterinary consult clinical companion: Small animal toxicology*. Wiley-Blackwell.

Peano, A., Beccati, M., Chiavassa, E., & Pasquetti, M. (2012). Evaluation of the antifungal susceptibility of Malassezia pachydermatis to clotrimazole, miconazole and thiabendazole using a modified CLSI M27-A3 microdilution method. *Veterinary Dermatology*, *23*, 131-135, e129. https://doi.org/10.1111/j.1365-3164.2011.01025.x

Pitz, A. M., Park, G. W., Lee, D., Boissy, Y. L., & Vinjé, J. (2015). Antimicrobial activity of bismuth subsalicylate on Clostridium difficile, Escherichia coli O157:H7, norovirus, and other common enteric pathogens. *Gut Microbes*, *6*(2), 93-100. https://doi.org/10.1080/19490976.2015.1008336

Plaza, P. I., Wiemeyer, G. M., & Lambertucci, S. A. (2022). Veterinary pharmaceuticals as a threat to endangered taxa: Mitigation action for vulture conservation. *Science of The Total Environment*, *817*, 152884. https://doi.org/https://doi.org/10.1016/j.scitotenv.2021.152884

Pottel, J., Armstrong, D., Zou, L., Fekete, A., Huang, X. P., Torosyan, H., Bednarczyk, D., Whitebread, S., Bhhatarai, B., Liang, G., Jin, H., Ghaemi, S. N., Slocum, S., Lukacs, K. V., Irwin, J. J., Berg, E. L., Giacomini, K. M., Roth, B. L., Shoichet, B. K., & Urban, L. (2020). The activities of drug inactive ingredients on biological targets. *Science*, *369*(6502), 403-413. https://doi.org/10.1126/science.aaz9906

Rogasch, N. C., Zipser, C., Darmani, G., Mutanen, T. P., Biabani, M., Zrenner, C., Desideri, D., Belardinelli, P., Müller-Dahlhaus, F., & Ziemann, U. (2020). The effects of NMDA receptor blockade on TMS-evoked EEG potentials from prefrontal and parietal cortex. *Sci Rep*, *10*(1), 3168. https://doi.org/10.1038/s41598-020-59911-6

Rossbach, K., Strattner, A., & Meurer, D. (2016). The use of H1-antihistamines in veterinary medicine. *97*, 1012-1020.

Sartor, L. L., Bentjen, S. A., Trepanier, L., & Mealey, K. L. (2004). Loperamide toxicity

in a collie with the MDR1 mutation associated with ivermectin sensitivity. *J Vet Intern Med*, *18*(1), 117-118. https://doi.org/10.1892/0891-6640(2004)18<117:ltiacw>2.0.co;2

Schulz, J. A., Hartz, A. M. S., & Bauer, B. (2023). ABCB1 and ABCG2 Regulation at the Blood-Brain Barrier: Potential New Targets to Improve Brain Drug Delivery. *Pharmacol Rev*, *75*(5), 815-853. https://doi.org/10.1124/pharmrev.120.000025

Shipstone, M. (2022, 2022/04). *Antihistamines for Integumentary Disease in Animals*. MSD Veterinary Manual. https://www.msdvetmanual.com/pharmacology/systemic-pharmacotherapeutics-of-the-integumentary-system/antihistamines-for-integumentary-disease-in-animals

Shugg, R. (2022). *Which Over-the-Counter Human Medications Are Safe for Dogs?* PetMD.

Siroká, Z. (2012). [Important toxic and undesirable effects of medicaments in animals from the pharmacists viewpoint]. *Ceska Slov Farm*, *61*(5), 222-228. (Významné toxické a nežádoucí účinky léků u zvířat z pohledu lékárníka.)

Sobczak, M., Sałaga, M., Storr, M. A., & Fichna, J. (2014). Physiology, signaling, and pharmacology of opioid receptors and their ligands in the gastrointestinal tract: current concepts and future perspectives. *Journal of Gastroenterology*, *49*(1), 24-45. https://doi.org/10.1007/s00535-013-0753-x

Taylor, C. P., Traynelis, S. F., Siffert, J., Pope, L. E., & Matsumoto, R. R. (2016). Pharmacology of dextromethorphan: Relevance to dextromethorphan/quinidine (Nuedexta®) clinical use. *Pharmacology & Therapeutics*, *164*, 170-182. https://doi.org/https://doi.org/10.1016/j.pharmthera.2016.04.010

Taylor, J. G., Ayosanmi, S., & Sansgiry, S. S. (2023). Consumer Impressions of the Safety and Effectiveness of OTC Medicines. *Pharmacy (Basel)*, *11*(2). https://doi.org/10.3390/pharmacy11020051

Thomazini, V. C., da Cunha, G. M., Guimarães, N. M., Saleme, S. D., de Melo, R. C. G., de Paula, G. A., Carvalho, S. G., Chorilli, M., Dos Santos Giuberti, C., & Villanova, J. C. O. (2024). Impact of concerning excipients on animal safety: insights for veterinary pharmacotherapy and regulatory considerations. *Daru*, *32*(1), 289-305. https://doi.org/10.1007/s40199-023-00486-8

Tomanic, D., Stojanovic, D., Belić, B., Davidov, I., Novakov, N., Radinovic, M., Kladar, N., & Kovacevic, Z. (2021). Off label use of human approved drugs in treatment of dogs in the Republic of Serbia. *Pol J Vet Sci*, *24*(3), 399-407. https://doi.org/10.24425/pjvs.2021.138731

Torfs, E., & Brackman, G. (2021). A perspective on the safety of parabens as preservatives in wound care products. *Int Wound J*, *18*(2), 221-232. https://doi.org/10.1111/iwj.13521

Van Norman, G. A. (2023). Off-Label Use vs Off-Label Marketing of Drugs: Part 1: Off-Label Use-Patient Harms and Prescriber Responsibilities. *JACC Basic Transl Sci*, *8*(2), 224-233. https://doi.org/10.1016/j.jacbts.2022.12.011

Walden, L. A. (2021). *Cold and Flu Medications Dangerous for Pets*. Mallard Creek Animal Hospital.

Wiegand, T. J. (2024). Guaifenesin. In P. Wexler (Ed.), *Encyclopedia of Toxicology (Fourth Edition)* (pp. 93-97). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-12-824315-2.00825-3