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Exploring the Crossroads of Animal Medicine: Assessing its Potential Impact on Human Health – A Comprehensive Mixed-Methods Investigation through Systematic Literature Review, Pharmacovigilance Approaches, and Netnographic Analysis

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Abstract

The misuse of veterinary drugs has emerged as a significant public health concern with growing evidence of their infiltration into both illicit drug markets and recreational use. This study aimed to investigate veterinary drug misuse through various methodologies, including systematic literature review, pharmacovigilance data approaches, and social media analysis. The systematic review of 66 articles identified 28 veterinary drugs being misused by humans, primarily α-2 and β-2 adrenergic receptor agonists, GABAergic modulators, opioid receptor agonists, NSAIDs, and NMDA receptor antagonists. These drugs were misused for purposes such as recreational use, pain relief, weight loss, bodybuilding, and stress-related self-medication, with common routes of administration being parenteral, oral, and inhalation. The motivations for their misuse ranged from affordability and accessibility to the ease of obtaining multiple prescriptions from various veterinary sources. Veterinary workers and individuals with access to animals were particularly prone to misuse.

A pharmacovigilance analysis using the FAERS database analysed 21 veterinary drugs, retrieving 38,756 adverse events. A total of 9566 fatalities were recorded for the specific veterinary drugs, with the highest number of reports from the United States (13,532), followed by Canada (2869), and the United Kingdom (1400). For the eight drugs licensed exclusively for animals, most reports were related to levamisole, pentobarbital, and xylazine. Polysubstance use was evident in 90% of the drugs examined, with benzodiazepines (BZDs)/Z-drugs and opioids constituting the most prevalent co-used drug classes. Drugs such as xylazine, pentobarbital, phenylbutazone, and acepromazine were particularly concerning due to their rising use in these contexts, due to being animal drugs identified on a human-centric reporting system.

A netnographic, dual-method analysis of social media discussions on Reddit revealed significant trends related to the misuse of xylazine, carfentanil, medetomidine, pentobarbital, phenylbutazone, and acepromazine. Common themes included motivations for misuse, adverse effects, and public perceptions. The combination of manual and AI-driven analysis provided deeper insights into these discussions, understanding the need for proactive monitoring of online platforms as early indicators of emerging drug misuse trends.

Collectively, this research emphasises the increasing misuse of veterinary drugs and the need for heightened vigilance in both healthcare and public health policy to address the growing risks of overdose, dependence, and illicit drug adulteration.

Declarations and Statements

Declaration

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

Signed: Josie Dunn
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Statement 1

This thesis is the result of my own investigations, except where otherwise stated. Where correction services have been used, the extent and nature of the correction are clearly marked in a footnote(s).

Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

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Statement 2

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Abbreviations

AAS- Anabolic Androgenic Steroids

ACMD – Advisory Council on the Misuse of Drugs

AE – Adverse Event

AI – Artificial Intelligence

BNF- British National Formulary

BZD – Benzodiazepine

CDC – Centre for Disease Control and Prevention

CFSRE – Centre for Forensic Science Research and Education

CNS – Central Nervous System

DEA – Drug Enforcement Administration

EUDA – European Union Drug Agency

FAERS – FDA Adverse Events Reporting System

FDA – Food and Drug Association

IMF – Illicitly Manufactured Fentanyl

I.V. – Intravenous

MDMA – 3,4-Methylenedioxymethamphetamine

MeDRA – Medical Dictionary for Regulatory Activities

NSAID – Non-Steroidal Anti-Inflammatory Drug

NSDUH – National Survey on Drug Use and Health

NSFW – Not Safe For Work

PKA – Protein Kinase A

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PT – Preferred Term

ROBIS – Risk Of Bias in Systematic Reviews

ROR – Reporting Odds Ratio

SLR – Systematic Literature Review

SNRI – Selective Norepinephrine Reuptake Inhibitor

SUD – Substance Use Disorder

THC - Tetrahydrocannabinol

U.K – United Kingdom

U.S – United States

VPM – Veterinary Prescription Medications

WEDINOS – Welsh Emerging Drugs and Identification of Novel Substances

Chapter 1: Introduction and Background

The misuse of drugs is a multifaced public health issue that has evolved with changing patterns of substance use and availability. According to the World Drug Report 2024 (United Nations, 2024), drug use has surged to 292 million people globally, marking a 20% increase over the past decade. This rise in drug use has been accompanied by a troubling increase in drug-induced deaths. In Europe, the peak of drug-induced deaths occurred in 2017 with 7,113 fatalities. Although there was a slight decline between 2018 and 2021, the number of drug-induced deaths rebounded significantly from 6,568 in 2021 to 6,959 in 2022, reflecting a 6% increase (EUDA, 2024b).

While human medications have traditionally been the primary focus of substance misuse research, emerging evidence suggests that veterinary drugs are increasingly being used outside of their intended purposes (Anand & Hosanagar, 2021; Lehnus et al., 2023). The manufacturing and regulation of drugs of misuse often resemble a continuous and dynamic struggle, where advancements in drug production are frequently met with regulatory efforts to control and mitigate their impact. This emerging trend presents unique challenges for public health, law enforcement, and healthcare professionals, as veterinary drugs often display potent pharmacological effects yet are not controlled and regulated in the same way medications of misuse are for humans. Currently, several medications used in both human and animal medicine are controlled under the misuse of drugs legislation (United Kingdom, 2001), including ketamine, buprenorphine, diazepam, tramadol, gabapentin, carfentanil, and fentanyl. However, the increasing misuse of veterinary drugs by humans means that adverse effects and fatalities may arise well before these emerging substances are identified and brought under control. This trend has been observed with the veterinary tranquiliser xylazine, which has been seen to proliferate across the United States (US), where it was described as the ‘deadliest drug threat’ the US has ever faced (DEA, 2022b). In the United Kingdom (UK), xylazine has been detected in 16 cases with 11 fatalities (ACMD, 2024), along with identification in various drug samples including tetrahydrocannabinol (THC) vapes (WEDINOS, 2024).

Although the same drugs are used in both humans and animals, due to differences in pharmacological properties and potency of some of these drugs, the dosages can be very different. Drug metabolism is a crucial function of pharmacokinetics, and the variation in expression and activity of drug-metabolising enzymes between humans and animals will play a crucial role in why doses are tailored to different species. For example, ketamine is approved for both use in humans and animals but due to pharmacokinetic and pharmacodynamic differences, veterinary formulations can be 10 times stronger than human formulations (McReynolds, 2023). Carfentanil, a potent opioid used in veterinary medicine, is known to be 10,000 times more potent than morphine, with the 2mg used to tranquilise an elephant being enough to kill around 50 people (Veterans Health Administration, 2022).

With the rising prevalence of veterinary medications as adulterants (CFSRE, 2023a; CFSRE, 2023b; CFSRE, 2023c; CFSRE, 2024a; CFSRE, 2024b), heightened vigilance and monitoring are crucial. This trend contributes to polysubstance misuse and severe adverse effects, as users unknowingly consume these potent drugs. The combination of veterinary medications with other commonly misused drugs like heroin and fentanyl can result in serious or even fatal outcomes, often leaving healthcare and emergency workers unaware of the presence of these substances.

Due to the recent emergence of these medications, instances of their misuse are under-reported, and research on the issue remains limited. Through a systematic literature review, pharmacovigilance approaches, and a social media analysis, a more comprehensive understanding can be established. Published data on this topic remains limited and significant research gaps hinder our understanding and response to this issue. Limited data on the prevalence and health impacts of such misuse, alongside insufficient awareness in healthcare settings, pose challenges in addressing this public health threat.

The aims of this project are:

1. To investigate the potential transfer or misuse of medications developed for animals in human contexts.
2. Analyse the existing literature on the subject through a systematic literature review to identify key trends, knowledge gaps and potential concerns.
3. Implement pharmacovigilance approaches to assess the safety and efficacy of these cross-species medicinal applications and to analyse any adverse effects.
4. Employ netnographic analysis techniques to study online communities and discussions related to the use of animal medicines in human health, and to understand public perceptions and potential risks.
5. Provide insights into the potential risks and dangers of using animal medicines in human health, with a focus on enhancing awareness and informing regulatory and healthcare decisions.

The objectives of this project are:

1. To conduct a systematic literature review to explore and identify articles already published within the area of animal medicine misuse.
2. To employ pharmacovigilance methods to monitor and evaluate adverse effects associated with the misuse of animal medicines in humans.

3. To explore and analyse online discussions and communities related to the misuse of animal medicines in human health, gain insights into public perceptions, practices, and concerns, and retrieve data on how the public may misuse animal medicine.
4. To provide recommendations for regulatory agencies, healthcare providers, and the public on the responsible and safe use of animal medicines in human healthcare.
5. To contribute to the overall understanding of the potential risks of the misuse of animal medicines in human contexts, and to help bridge the gap between veterinary and human medicine.

Research Questions:

1. What type of animal medications are being commonly misused by humans and in what context are they being misused?
2. What are the potential risks of using animal medications in humans?
3. What adverse effects can occur when humans consume animal medications?
4. How can pharmacovigilance approaches help monitor and evaluate the safety and effectiveness of animal medicines in human applications?
5. How do public perceptions and attitudes towards the use of animal medicines in human health vary?
6. How can netnographic analysis of online communities provide insights into the misuse of animal medications and answer specific questions regarding how they are misused, where they are obtained and why they are misused?

Chapter 2: Exploring the Confluence of Animal Medicine and its Implications for Human Health: A Systematic Literature Review

2.1. Introduction

As the global crisis of prescription drug misuse continues to escalate, individuals grappling with substance use are relentlessly seeking new avenues to satisfy their cravings. According to the National Survey on Drug Use and Health (NSDUH), diversion of prescription medicines is defined as 'use without a prescription or in ways not intended by the prescriber' (Schepis et al., 2020). This issue has been characterised as a “public health disaster, killing hundreds of people and ruining the lives of millions” by Harry Shapiro, the Head of the addiction charity DrugWise, during a 2016 meeting of the All-Party Parliamentary Group for Prescribed Drug Dependence (Claire Wilson, 2016).

In 2022-23, the expenditure on prescription items dispensed in England reached £10.4 billion, reflecting a 3% increase from the previous year (NHSBSA Statistics and Data Science, 2023). Among the array of prescription drugs subject to abuse are opioids, benzodiazepines (BZDs), stimulants, antidepressants, and steroids. The mounting misuse of these medications has prompted medical professionals and policymakers to label it a global health crisis, with misuse reaching alarming proportions (Preston, 2022). In the United Kingdom (UK), deaths associated with codeine and tramadol surged by over fivefold among males and nearly eightfold among females between 1998 and 2021. Moreover, opioids were implicated in approximately 50% of drug poisoning cases reported in the UK in 2021, accounting for 45.7% of cases, equating to 2219 deaths (ONS, 2022).

In an increasingly interconnected world, the diversion of veterinary and human medicine is gaining prominence as a pivotal focal point. Veterinarians, who annually treat numerous animals and have the authority to prescribe controlled substances, are often overlooked as potential contributors to prescription drug misuse (Anand & Hosanagar, 2021). A survey conducted in 2023 explored the perspectives of UK veterinarians regarding the potential misuse of veterinary prescription medications (VPMs). The findings revealed that 88% of participants recognised the risk of abuse associated with certain VPMs. Furthermore, 30% of respondents reported suspicions of pet owners misusing VPMs, while 20% expressed concerns about misuse among veterinary staff (Lehnus et al., 2023). The growing inclination towards acquiring medications through healthcare providers, such as veterinarians, is a familiar trend owing to the perception of these drugs being safer than those obtained through illicit channels, as well as being more cost-effective (Health Canada, 2006). Additionally, the purchase of veterinary medicines online in the UK is reportedly on the rise (VMD, 2014). The practice of "vet shopping" involves soliciting veterinarians for prescription medications intended for animals, without the intention of administering them to the animals in question (AVMA, 2019). This behaviour

significantly contributes to the escalating global issue of substance misuse, as individuals gain access to additional drug supplies through veterinarians. A study conducted in 2022 revealed a threefold increase between 2014 and 2019 in the number of clients obtaining prescriptions for any class of controlled substances from four or more veterinarians (Chua et al., 2022). The surge in acquiring medications through veterinarians prompted the United States Food and Drug Administration (US FDA) to express concerns in 2018, highlighting the significant risk posed by the prescription of opioids by veterinarians. Like opioid medications intended for human use, these drugs hold the potential for addiction, abuse, and overdose when diverted for personal use (FDA, 2020). News articles have reported novel methods employed by individuals to access these controlled substances, such as harming their pets to obtain analgesics (Herzog, 2018) and training their dogs to simulate symptoms to receive hydrocodone cough syrup (Burke, 2002).

The issue extends beyond the misuse of prescription drugs approved for human use; there has been a concerning increase in the misuse of medications exclusively approved for animal use. This trend is alarming as drugs approved solely for animal use have not undergone testing on humans, potentially resulting in a range of adverse effects due to anatomical, physiological, and pharmacokinetic differences. Unlike in human development, pre-clinical trials for animal medicine are not necessarily utilised, meaning human safety is not a focus (Woods Consulting, n.d.). The administration of larger doses in animals, owing to variations in hepatic metabolism (LeBourgeois et al., 2002), increases the risk of toxic effects when these medications are misused in humans. For example, veterinary ketamine formulations can be ten times stronger than human formulations (Cohen, 2024). Recreational ketamine use and associated fatalities are on the rise (Corkery et al., 2021), with the prevalence of ketamine use in the last year increasing by 3.8% (ONS, 2023). Conversely, carfentanil, approved only for animal use due to its potency being 100 times higher than fentanyl (Swanson et al., 2017), was the second most frequently reported synthetic opioid in the United States between 2016 and 2017 (Zawilska et al., 2021), prompting the World Health Organisation to declare it a serious threat to public health.

Given that prescription drug misuse in veterinary settings remains an underestimated and under-researched area (Anand & Hosanagar, 2021), this study aims to enhance understanding regarding the types of veterinary medications that are misused, the intentions behind their misuse, and the methods of acquisition.

2.2 Methodology

A systematic review involves meticulous analysis of well-defined research questions employing a systematic and explicit methodology to identify, select, and critically evaluate pertinent research, as well as to analyse the data derived from the studies incorporated (Moher, 2019). To ensure objectivity and rigour in study selection, a systematic and structured approach was adopted. Preferred Reporting

Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009) were adhered to, providing consistency and transparency in the collection of suitable studies. This method facilitated a clear and structured approach to data collection. In November 2023, a systematic search was conducted using PubMed (NCBI), Web of Science (Clarivate), and Scopus (Elsevier) databases. The aim was to identify the most appropriate scientific databases for this study. PubMed was praised for its convenience, speed, and user-friendliness, particularly significant for clinicians and researchers (Falagas et al., 2008). It also affirmed that Scopus covers a broader range of journals compared to PubMed and Web of Science. Additionally, it highlighted Google Scholar's utility in retrieving less mainstream information, albeit with the drawback of infrequent updates.

Boolean operators (AND/OR) were utilised to combine two groups of words into the final string utilised in all three databases. An iterative process of optimisation and refinement was utilised to ensure the retrieval of pertinent and comprehensive articles. Initially, various combinations of the search thread were explored to determine their effectiveness in capturing relevant literature. Further adjustments were made to the search strategy until a final search thread was determined. The string (("veterinary drug" OR "veterinary medication" OR "veterinary prescription drug") AND ("misuse" OR "abuse")) was entered into the three scientific databases. We established clear inclusion and exclusion criteria to ensure a selection of papers relevant to our research questions and the aims of the study. Specifically, we included articles that addressed the misuse or diversion of veterinary medicine regarding human consumption. This encompassed literature reviews, case studies, and reports focusing on the unauthorised use, misuse, or non-medical consumption of veterinary drugs. Conversely, we excluded papers that did not explicitly reference the misuse or diversion of veterinary pharmaceuticals in humans. The risk of bias was assessed using the risk of bias in systematic reviews (ROBIS) tool (University of Bristol, 2019), where each study was individually evaluated by JD and peer-reviewed by the principal supervisor. A thematic approach was employed to analyse the existing literature. This type of analysis aided in the identification of specific themes present within the literature. Following a systematic review of all articles, the data was organised based on categories including drug class, classification as human or animal drugs, and controlled substance status. The search was not restricted by time or geographical limitations, and all languages were included in the search results. Identification of grey literature was conducted between November and December 2023, involving examination of government reports and manual scrutiny of supplementary articles through Google Scholar. Microsoft Excel (Version 16.79.1 (23111614)) served as a tool to eliminate duplicate articles. A supplementary cross-reference search was conducted on the remaining studies to mitigate the risk of overlooking relevant articles in the systematic search.

2.3 Results

Initially, a total of 338 records were identified, encompassing both database searches and various sources of grey literature. After completing the screening process, 66 articles were found to be relevant to the current study and met all the points of the inclusion criteria. A total of 272 articles were excluded as they did not meet the inclusion criteria. Within this body of literature, 28 distinct veterinary drugs were identified as being misused by humans or posing a risk to human health. Figure 1 provides a summary of the process through which records were identified, screened, and assessed for eligibility. Subsequently, each remaining article underwent further analysis, and the main findings from the selected articles and reports are summarised in Supplementary Information (SI). This Table (in SI) provides an insight into the off-label use and indication for each of the diverted veterinary medicines identified in this literature review, as well as the dose consumed, the routes of administration, and where each medicine was obtained from.

One of the primary objectives of the systematic literature review was to identify the types of veterinary medications susceptible to misuse by humans or currently being misused. The primary classes of drugs identified included α-2- and β-2-adrenergic receptor agonists, NMDA antagonists, opioid receptor agonists, GABAergic receptor modulators, and non-steroidal anti-inflammatory drugs (NSAIDs). Table 1 provides a summary of the veterinary drugs obtained from the literature, along with the primary reasons for their misuse in humans.

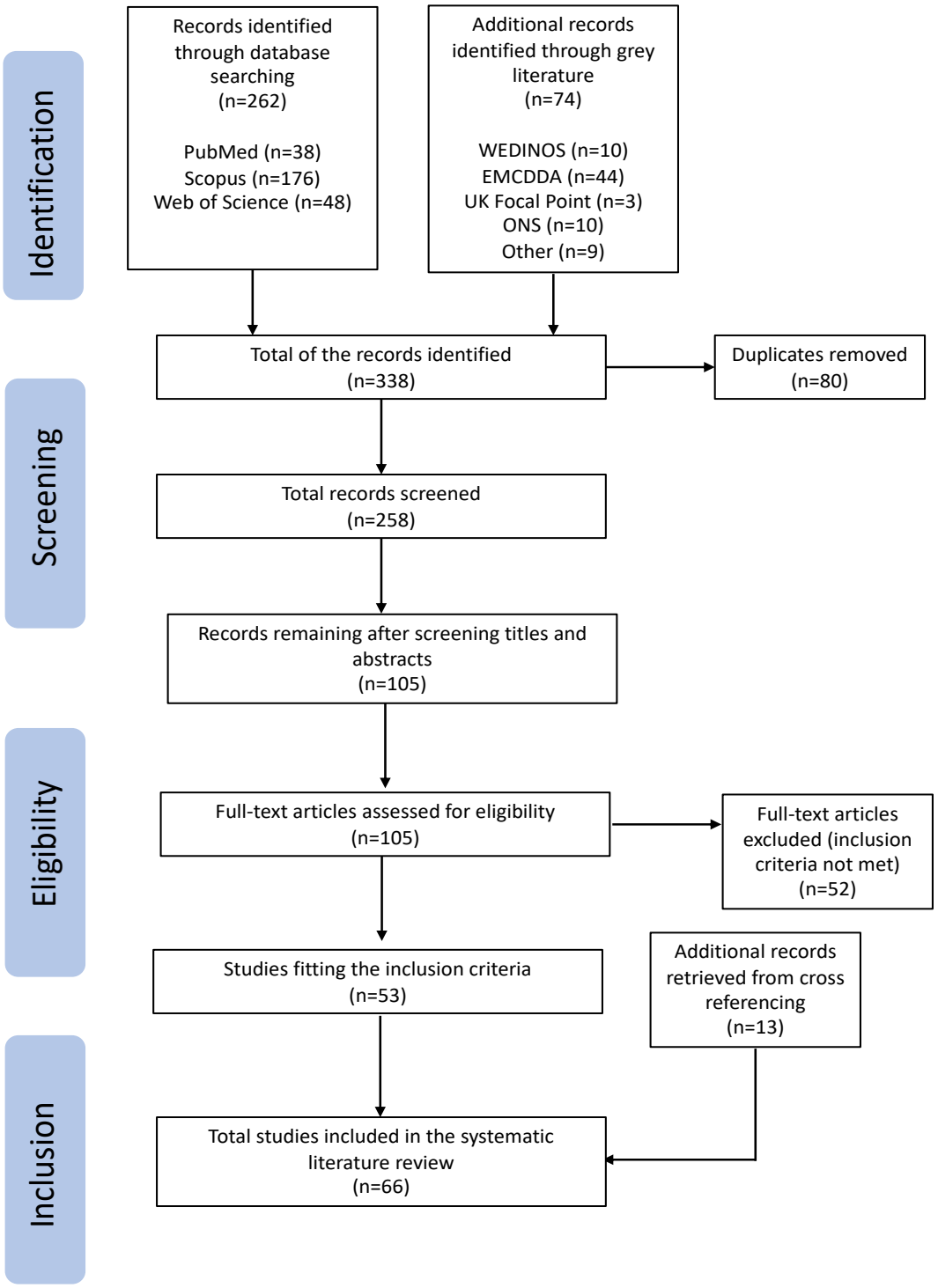

Figure 1 - PRISMA flow diagram of included studies assessing the effects of veterinary medication use by humans on their health (*Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS), European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (now known as the European Union Drug Agency))

Table 1 - Drugs identified through the systematic literature search and their potential reasons for their misuse in humans.

Drug Class	Name of Drug	Reason for Misuse in Humans
Adrenergic Receptor Agonists		
	Xylazine	Sedation/Analgesia
	Medetomidine	Sedation/Analgesia
	Dexmedetomidine	Sedation/Analgesia
	Clenbuterol	Performance Enhancement
NDMA Antagonists		
	Ketamine	Analgesia/Dissociation/Sedation
	Telazol (Zolazepam/Tiletamine)	Anaesthesia/Sedation/Sedation
Opioid Receptor Agonists		
	Carfentanil	Analgesia/Euphoria
	Tramadol	Analgesia/Sedation/Euphoria
	Butorphanol	Analgesia/Sedation/Euphoria
GABAergic Receptor Modulators		
	Diazepam	Sedation/Muscle Relaxation
	Clorazepate	Sedation/Muscle Relaxation
	Pentobarbital	Suicidal Indications/Sedation
	Phenobarbital	Sedation/Anticonvulsant/Hypnotic Effects
Other Drugs		
	Acepromazine (Phenothiazines)	Sedation/Muscle Relaxation
	Levamisole (Anthelminthic)	Bulking agent
	Pheniramine (Antihistamine)	Sedation
	Stanozolol (Anabolic Steroid)	Performance Enhancement
	Levothyroxine (Thyroid Hormone)	Weight loss Supplement
	Furosemide (Loop Diuretic)	Weight loss Supplement
	Amitriptyline (Tricyclic Antidepressant)	Antidepressant Properties
	Tilmicosin (Macrolide Antibiotic)	Suicidal Indications
	Embutramide/Mebezonium (Euthanasia Compound)	Suicidal Indications
	Dinoprost (Prostaglandin)	Abortion
	Cloprostenol (Prostaglandin)	Abortion
	Phenylbutazone (NSAID)	Analgesia/Anti-Inflammatory
	Flunixin (NSAID)	Analgesia/Anti-Inflammatory
	Carprofen (NSAID)	Analgesia/Anti-Inflammatory
	Vitamin ADE Compound	Performance Enhancement

Among the drugs identified, those approved exclusively for animal use constituted 54% of the total drugs retrieved from the literature (15 out of 28). The remaining 13 drugs were approved for both human and animal use, although some were administered at higher doses that were licensed for animal use only. Table 2 outlines the approved/ licensed usage of each veterinary drug identified, and its legal classification in both the UK and the US.

Table 2 - The veterinary drugs identified from the literature review, their licensed usage and legal classification in both the UK and the US.

Drug Name	Approved Usage (Humans or Animals)	Status: UK	Status: FDA
Xylazine	Animals	Not Controlled	Not Controlled
Medetomidine	Animals	Not Controlled	Not Controlled
Dexmedetomidine	Both	Not Controlled	Not Controlled
Clenbuterol	Both	Class C, Schedule 4	Not Controlled
Ketamine	Both	Class B, Schedule 2	Schedule III
Telazol (Zolazepam/ Tiletamine)	Animals	Not Controlled	Not Controlled
Carfentanil	Animals	Class A	Schedule II
Tramadol	Both	Class C, Schedule 3	Schedule IV
Butorphanol	Both	Not Controlled	Schedule IV
Diazepam	Both	Class C, Schedule 4	Schedule IV
Clorazepate	Both	Class C, Schedule 4	Schedule IV
Pentobarbital	Animals	Class B, Schedule 3	Schedule II
Phenobarbital	Both	Class B, Schedule 3	Schedule IV
Acepromazine (Phenothiazines)	Animals	Not Controlled	Not Controlled
Levamisole (Anthelminthic)	Animals	Not Controlled	Not Controlled
Pheniramine (Antihistamine)	Both	Not Controlled	Not Controlled
Stanozolol (Anabolic Steroid)	Both	Class C, Schedule 4	Schedule III
Levothyroxine (Thyroid Hormone)	Both	Not Controlled	Not Controlled
Furosemide (Loop Diuretic)	Both	Not Controlled	Not Controlled
Amitriptyline (Tricyclic Antidepressant)	Both	Not Controlled	Not Controlled
Tilmicosin (Macrolide Antibiotic)	Animals	Not Controlled	Not Controlled
Embutramide/Mebezonium (Euthanasia Compound)	Animals	Not Controlled	Not Controlled
Dinoprost (Prostaglandin)	Animals	Not Controlled	Not Controlled
Cloprostenol (Prostaglandin)	Animals	Not Controlled	Not Controlled
Phenylbutazone (NSAID)	Animals	Not Controlled	Not Controlled
Flunixin (NSAID)	Animals	Not Controlled	Not Controlled
Carprofen (NSAID)	Animals	Not Controlled	Not Controlled
Vitamin ADE Supplement	Animals	Not Controlled	Not Controlled

Among all medicines identified as misused by humans, 68% (19 out of 28) are not classified as controlled substances. Examination of the regulatory status of these drugs in both the UK and the US reveals significant similarities, with only two drugs having different classifications between the two countries. Specifically, while clenbuterol is not considered a controlled substance in the US, it falls under controlled status in the UK. Conversely, butorphanol is not classified as a controlled substance in

the UK. Notably, only 13% (2 out of 15) of drugs approved strictly for animal use only (carfentanil and pentobarbital) are classified as controlled drugs in both countries.

2.4. Discussion

The primary objective of this systematic review was to delve into the spectrum of veterinary medications prone to misuse or capable of fostering drug-seeking behaviour and dependence in humans, while also exploring the motivations behind individuals resorting to substances intended for animal use. To our knowledge, this marks the first systematic literature review analysing the harms associated with veterinary drug misuse in humans.

Of all drugs identified as misused by humans, over half (57% (n=15/28)) are exclusively approved for animal use. Through a comprehensive literature review, we identified 28 distinct veterinary medications being misused by humans. Among these, 15 were solely approved for animal use, while the remaining 13 held approval for both species. Despite certain drugs being approved for both humans and animals, distinct dosages are mandated for each species due to variable biochemical and functional systems, thereby altering the pharmacokinetics of different drugs (Nair & Jacob, 2016). Drug metabolism, a crucial aspect of pharmacokinetics, is influenced by the variation in expression and activity of drug-metabolising enzymes between humans and animals, thereby necessitating tailored doses for different species.

Among the 28 drugs identified, their primary effects are attributed to analgesic and sedative properties, indicating potential for misuse. The main drug classes identified in the literature include α-2- and β-2-adrenergic receptor agonists (n=4 drugs), GABAergic receptor modulators (n=4 drugs), opioid receptor agonists (n=3 drugs), NSAIDs (n=3 drugs), and NMDA receptor antagonists (n=2 drugs). Literature findings reveal that veterinary drugs are primarily obtained by individuals working in veterinary settings or those with easy access to the drugs (Alleva et al., 2015; de la Peña & Cheong, 2016; Perrin, 2014; Ruiz-Colon et al., 2014), as well as through the practices of "vet shopping" and malingering by using animals as proxies (LeBourgeois et al., 2002; Russell et al., 2018). Parenteral injection emerged as the primary route of administration for veterinary drugs, followed by oral ingestion and inhalation by humans. Only 32% of identified veterinary drugs fall under the category of controlled substances (in the UK), with the remaining 68% not subject to the stringent regulations, monitoring, and legal restrictions applied to the prescribing and supply of controlled drugs. The absence of such strict oversight may contribute to increased accessibility and growing misuse of these non-controlled drugs.

The α-2-adrenergic agonists, particularly xylazine, have emerged as a potential contributor to increasing drug-related deaths globally. Xylazine, known for its central nervous system (CNS) depressant effects,

is commonly used for sedation, muscle relaxation, analgesia, and anaesthesia in veterinary practice (Greene & Thurmon, 1988). However, its misuse, often in conjunction with opioids, has potentially led to a surge in fatalities, drawing attention to its alarming presence as an adulterant in illicit drug markets. Studies have documented a sharp increase in xylazine-related deaths by 276% in the US, particularly in combination with illicitly manufactured fentanyl (IMF), indicating a concerning trend in substance misuse (Sibbesen et al., 2022). The co-consumption of xylazine and opioids can lead to synergistic effects, exacerbating CNS depression and increasing the risk of fatalities (Acosta-Mares et al., 2023). Recent data underscores the growing prevalence of xylazine in drug-related fatalities, prompting public safety alerts in several countries (CDC, 2023a; DEA, 2022b). Notably, xylazine-associated deaths have been reported in the UK and Europe, indicating its infiltration into the European illicit drug supply (Rock et al., 2023). A study found that stimulants were present in 53% of xylazine-positive cases, cannabinoids in 30% and BZDs in 26% (Kacinko et al., 2022). Other drugs detected in xylazine-related death cases include morphine, cocaine, paracetamol, pregabalin, THC, diazepam, methadone, alcohol, and heroin (Johnson et al., 2021; Rock et al., 2023). Other drugs identified in xylazine-positive syringes included protonitazene, metonitazene, isotonitazene, and carfentanil (EUDA, 2023a; EUDA, 2023b). The new mixtures of novel BZDs and opioids, with xylazine, have been reported in Estonia (EUDA 2023f) and have the potential to seriously impact public health (EUDA, 2023e).

Xylazine misuse encompasses various scenarios, including recreational use, adulteration of other drugs, drug-facilitated crimes, and intentional poisoning (Teoh et al., 2022). Its combination with opioids, termed "tranq dope," has been reported to enhance the euphoric effects of fentanyl and prolong its duration of action (Friedman et al., 2022). Moreover, physical dependence on xylazine, coupled with withdrawal symptoms, has been observed, further complicating its misuse dynamics (Torruella, 2011). Synergistic effects of the combination of opioids with xylazine have been reported to enhance sedation and analgesia in the veterinary setting (Leonardo et al., 2016), where greater sedation is observed using the combination than the α-2-agonist alone. Known for inducing painful ulcers, xylazine misuse has been fuelled by its ability to alleviate pain from injection site ulcers it causes, creating a negative drug-use cycle. Research shows that α-2 adrenergic agonists, like xylazine, can partially block withdrawal symptoms in opioid users. This suggests individuals may combine xylazine with opioids to manage withdrawal discomfort. Similarly, clonidine, another α-2 agonist, is used to treat withdrawal from various substances by modulating noradrenergic activity. This inhibition of norepinephrine release may explain why xylazine is misused with other drugs. The route of administration for xylazine primarily involves parenteral injection, with males being disproportionately affected by xylazine-related overdoses and fatalities (CDC, 2023b; Forrester, 2016; Ruiz-Colon et al., 2014).

Medetomidine and dexmedetomidine, α-2-adrenergic agonists primarily used for sedation and analgesia in dogs, have recently emerged as substances of misuse. While dexmedetomidine is approved for both

human and animal use, medetomidine is restricted to veterinary use. A toxic adulterant alert (CFSRE, 2023c) identified medetomidine in drug samples containing fentanyl, xylazine, heroin, and cocaine, raising concerns due to its potency and selectivity as an agonist. While xylazine was previously the primary drug in this class associated with diversion and abuse, recent misuse of medetomidine and dexmedetomidine has been observed. Like xylazine, these drugs diminish opioid withdrawal symptoms, potentially explaining their misuse alongside opioids. Additionally, α-2-adrenergic receptors, targeted by these drugs, play a role in modulating symptoms of nicotine and alcohol withdrawal syndromes. Notably, there are no further documented instances of medetomidine or dexmedetomidine misuse in humans beyond the mentioned alert.

Clenbuterol, a β-2-adrenergic receptor agonist, activates adenylyl cyclase and thus, protein kinase A (PKA) to promote the relaxation of smooth muscles (Witkowska-Piłaszewicz et al., 2021). It is primarily used as a bronchodilator in horses and asthma treatment in humans (Lust et al., 2011). Despite its exclusive veterinary approval in the US, clenbuterol has become prevalent in illegal markets and is marketed as a weight loss supplement. The dosages consumed by athletes often far exceed therapeutic levels, reaching up to 200mg daily, posing significant health risks (Moriarty & Attar, 2020). The addictive potential of clenbuterol misuse stems from its ability to activate the brain's reward system, leading to dopamine release and habit formation (NIDA, 2022). Moreover, the physical effects associated with bodybuilding, such as enhanced athletic performance, increased rate of muscle protein deposition and reduced appetite, contribute to its addictive behaviour (Lust et al., 2011; Moriarty & Attar, 2020). Salbutamol, a similar β-2 agonist, is also misused for performance enhancement, although clenbuterol exhibits a higher abuse potential due to its potency and pharmacokinetic properties (Milano et al., 2018).

In addition to its misuse in bodybuilding, clenbuterol is increasingly being mixed with opioids and BZDs, posing grave health risks. The concurrent use of clenbuterol with depressants like opioids and BZDs can lead to unpredictable interactions, exacerbating cardiovascular and respiratory complications (Wingert et al., 2008). Furthermore, co-ingestion with stimulants like cocaine heightens the risk of cardiovascular distress and central nervous system overstimulation (Wingert et al., 2008). The widespread availability of clenbuterol online has also fuelled its misuse, with reports of increased exposure to poison control centres (Brett et al., 2014; Schifano et al., 2018). The alarming trend of clenbuterol intoxication showed the presence of heroin, cocaine, fentanyl, BZDs, and methadone (Wingert et al., 2008). Opioids and BZDs depress both cardiovascular and respiratory functions while inducing sedation in the CNS. In contrast, clenbuterol has opposing effects, boosting heart and respiratory rates while triggering anxiety and tremors in the CNS. Such differing effects can result in unpredictable interactions and heightened risks when these substances are used together. Conversely, cocaine shares similar stimulating effects on the cardiovascular and CNS systems with clenbuterol,

escalating the chances of heart complications and CNS overstimulation when these substances are co-consumed.

For the NMDA receptor agonists/antagonists, Telazol, a veterinary anaesthetic (licensed for cats and dogs) compound composed of an equal ratio of zolazepam, a benzodiazepine, and tiletamine, an NMDA receptor antagonist, has raised concerns regarding its misuse in humans despite its safe use in veterinary medicine (de la Peña & Cheong, 2016). The potent nature of tiletamine, akin to ketamine, combined with zolazepam's BZD properties, poses a risk of misuse and dependence (Lin et al., 1992). Instances of Telazol misuse, resembling recreational drugs like ketamine and diazepam, underscore its potential for abuse, particularly among those with easy access to veterinary settings (de la Peña & Cheong, 2016). Despite its controlled status in the US, Telazol remains unregulated in the UK, amplifying concerns regarding its public health impact (EUDA, 2009). In 2003, the UK's Threat Assessment of Serious and Organised Crime raised concern about the rising abuse of ketamine and further stated that its restriction may lead to Telazol being used as a replacement in the future (NCIS, 2009). Most cases involved individuals with easy access to the veterinary drug combination, indicating a heightened risk within veterinary settings. Telazol misuse by a veterinarian to reduce heroin consumption (Lee et al., 2009a) corroborates with research showing that most Telazol abusers also use other psychoactive drugs, often through cross-addiction, wherein users are more likely to misuse drugs with similar anaesthetic/depressant effects that act on the NMDA/GABA receptors (de la Peña & Cheong, 2016). This pattern of polydrug misuse was evident in a case where a patient was found unresponsive, with Telazol, BZDs, and cannabinoids detected in urine analysis (Quail et al., 2001). Tiletamine (a component of Telazol) exhibits significantly higher potency than ketamine, and zolazepam (the other component of Telazol) is 5-10 times more potent than diazepam (Chung et al., 2000). Tiletamine, an NMDA receptor antagonist, produces rewarding and reinforcing effects, potentially leading to dependence and addiction (Bryan et al., 2012). Like ketamine, tiletamine induces hallucinogenic, dissociative effects, possibly contributing to its recreational misuse (Lee et al., 2009a). Furthermore, NMDA receptor antagonists stimulate the mesolimbic dopamine system and directly inhibit dopamine reuptake, highlighting the role of the reward pathway in drug dependence (Bryan et al., 2012; Smith et al., 1977). Exposure to zolazepam also increases dopamine levels by hyperpolarising GABA neurons, leading to dopamine neuron inhibition (Tan et al., 2011).

Although ketamine is widely known to be a veterinary anaesthetic, its diversion from medical settings is a contributing factor to its recreational use (EUDA, 2002). The misuse of ketamine as 'pink cocaine' has been associated with increased levels of serotonin, dopamine, and norepinephrine (Lindefors et al., 1997; EUDA, 2023b), possibly driving its misuse as individuals seek mood enhancement and altered states of consciousness fuelled by the heightened activity of these neurotransmitters. Despite its therapeutic potential in pain management and depression treatment, ketamine's recreational misuse

remains a significant health concern (Gao et al., 2016). The escalating prevalence of ketamine misuse, highlighted by its emergence as a prevalent substance in drug markets, underscores the urgent need for public health interventions (EUDA, 2022b; GOV.UK, 2021). The poly-drug misuse of ketamine, particularly in combination with stimulants like cocaine and 3,4-methylenedioxymethamphetamine (MDMA), poses grave risks, including cardiovascular complications and serotonin syndrome (Francescangeli et al., 2019). Ketamine's pharmacokinetic characteristics include a broad hepatic CYP P-450 induction, which may potentiate the toxicity of other drugs in the hepatobiliary system by increasing the production of harmful metabolites (Lee et al., 2009b). Despite its therapeutic benefits, ketamine's accessibility, low cost, and potent dissociative effects contribute to its widespread misuse (Beerten et al., 2023).

Opioid agonists identified include carfentanil, tramadol, and butorphanol. Despite its exclusive approval for veterinary use, carfentanil has emerged as a prevalent opioid misused by humans, often disguised as heroin in illicit drug markets (DEA, 2016). Its potency, estimated to be thousands of times greater than morphine, poses severe health risks, contributing to numerous deaths and poisonings worldwide (Bever et al., 1976). Carfentanil's increasing presence in illicit drug markets, combined with its potency, makes it particularly dangerous, with users often unaware of its inclusion in street drugs (EUDA, 2018). The mixture of carfentanil with other substances like cocaine exacerbates these risks, leading to unintended side effects and fatalities (Prekupec et al., 2017). The lack of data on its abuse liability and dependence potential underscores the urgent need for further research and public health interventions (Wei et al., 2023).

Tramadol, a controlled substance approved for both human and animal use, is susceptible to misuse, particularly due to its accessibility through veterinary prescriptions (Anand & Hosanagar, 2021). Its relatively low cost compared to other opioids and its dual action as an opioid agonist and serotonin-norepinephrine reuptake inhibitor (SNRI) contribute to its abuse potential (Miotto et al., 2017; Russell et al., 2018). Tramadol's unique pharmacological profile results in distinctive withdrawal symptoms and an increased risk of dependence (Babalonis et al., 2013; Miotto et al., 2017). Despite its partial agonist and antagonist activity, making dependence less likely than with traditional opioids, butorphanol misuse has been documented, often through deceptive means such as malingering by animal proxy (Heel et al., 1978; LeBourgeois et al., 2002). In contrast to other opioids abused by humans, butorphanol demonstrates partial agonist and antagonist activity (Heel et al., 1978), potentially resulting in a reduced likelihood of dependence compared to opioids like morphine. Limited information exists on butorphanol misuse, highlighting the need for further research and surveillance in veterinary settings.

GABAergic receptor modulators/positive allosteric modulators identified include diazepam, clorazepate, phenobarbital, and pentobarbital. While not commonly discussed in the context of misuse,

diazepam stands out as the most prescribed BZD in veterinary settings (Anand & Hosanagar, 2021). Its accessibility in veterinary medicine raises concerns about potential misuse by pet owners, given its addictive properties and associated withdrawal symptoms. Instances of "vet shopping" and malingering by animal proxy have been documented, illustrating the acquisition of clorazepate from veterinary sources for personal use (LeBourgeois et al., 2002). As a controlled substance with addictive potential, monitoring its use in veterinary settings is essential, particularly considering the growing concern over BZD misuse (Votaw et al., 2019). Used primarily for seizure management in both humans and animals, phenobarbital has been misused, leading to fatal overdoses in some cases (Alleva et al., 2015). Its accessibility in veterinary medicine poses a risk, especially when individuals with substance use disorders (SUDs) seek to alleviate withdrawal symptoms (Alleva et al., 2015). Like phenobarbital, pentobarbital misuse has been reported, particularly among individuals associated with veterinary practices (Perrin, 2014). Its potential for habit formation and toxic effects underscores the need for vigilance, especially in professions where access to veterinary medications is common (Johnson & Sadiq, 2021). Recent cases of pentobarbital adulteration in counterfeit fentanyl tablets highlight the potentially lethal consequences of combined drug use (CFSRE, 2024).

Several veterinary medications, not fitting into previously mentioned categories, have been identified for misuse by humans. Among these are acepromazine, pheniramine, and others.

Acepromazine emerged as a notable focus in five retrieved papers (Algren & Ashworth, 2014; Anand & Hosanagar, 2021; de Lima & de Araujo, 2023; Perrin, 2014). This commonly used phenothiazine tranquiliser is administered to mitigate stress and excitement during various veterinary procedures (Schneiders et al., 2012). Originally approved for treating schizophrenia in humans, acepromazine is now exclusively licensed for veterinary use, although it is not classified as a controlled substance. Its pharmacological profile includes antagonistic effects on dopaminergic and serotonin receptors, as well as antagonism of histamine, muscarinic acetylcholine, and α-1 receptors (Algren & Ashworth, 2014). A case study detailed a woman who intentionally ingested 950mg of her dog’s acepromazine, with a medical history notable for depression, anxiety, and hypothyroidism. Despite several reports of acepromazine poisonings, including instances of drug-facilitated sexual assaults and suicides, detection remains challenging due to rapid metabolism (de Lima & de Araujo, 2023). A case where a survey of veterinary practitioners revealed misuse of veterinary acepromazine for stress management (Erramouspe et al., 2002). In these cases, acepromazine misuse appeared to be associated with mental health conditions such as stress, anxiety, and depression, possibly linked to its antagonism of dopamine and serotonin receptors. Two additional suicide cases involving acepromazine were documented (Perrin, 2014), both involving female individuals. One case involved a veterinary worker, while the source of acepromazine for the other patient remained unclear. In both instances, acepromazine was

implicated in completed suicides, with one dose totalling 2500mg. To our knowledge, the misuse of its analogue promazine has not been documented and is not known.

Pheniramine, an antihistamine, is approved for use in both humans and animals, primarily targeting allergic conditions. Antihistamines, easily accessible over the counter, rank among the most abused drugs (Kamath et al., 2022). A study revealed that 14.7% of overdose deaths in the US between 2019 and 2020 involved antihistamines, with opioids implicated in 83% of these cases (Dinwiddie et al., 2022). However, despite this concerning trend, the UK has not analysed antihistamine-related mortalities in over 40 years (Oyekan et al., 2021), and reports on pheniramine misuse are scarce. Notably, a high proportion (80%) of patients hospitalised due to pheniramine poisoning had a history of drug or alcohol abuse, with 61% exhibiting an antihistamine abuse history (Buckley et al., 1994). Although not a controlled substance, one documented case highlights veterinary-grade pheniramine misuse, where a user intravenously mixed 100 mg of heroin with 15 ml of injection pheniramine, 4-5 times daily, in an attempt to manage sleep issues (Tyagi et al., 2022). Co-administration of pheniramine with opioids like heroin can lead to life-threatening outcomes, given the additive effects of antihistamines with CNS depressants (Oyekan et al., 2021). In this case, the user exhibited signs of heavy pheniramine addiction, experiencing withdrawal symptoms such as insomnia, restlessness, and tremors upon attempts to reduce dosage (Tyagi et al., 2022). Psychological tolerance and physical withdrawal symptoms to pheniramine misuse have been documented (Tyagi et al., 2022). It remains unclear how the veterinary-grade pheniramine was obtained in this case, but a 100 ml bottle labelled "NOT FOR HUMAN USE. FOR ANIMAL TREATMENT ONLY" was reported. Given its source outside traditional pharmacies, it's plausible that this veterinary product was purchased online. A study addressing the illicit veterinary medicine market highlighted the distribution of such medications through illegal online pharmacies, online marketplaces, and social media platforms, posing significant regulatory and enforcement challenges (Pons-Hernandez et al., 2022).

Stanozolol, an anabolic steroid, holds licenses for use in both human and veterinary medicine and is classified as a Class C controlled substance (United Kingdom, 2001). It ranks among the most abused anabolic androgenic steroids (AAS), particularly among young adults and professional athletes, who often seek to enhance physical appearance and performance (Ozcagli et al., 2018). A case study documented an individual's attempt to procure stanozolol, without an accompanying animal, from a veterinary facility (LeBourgeois et al., 2002). While the extent of the individual's dependence on the AAS remains unclear, studies have indicated the potential for dependency due to the self-administration stimulation observed in animal models (Kanayama et al., 2010). Although users do not experience immediate intoxication, dependence on AAS may develop, particularly in individuals grappling with body image disorders like "muscle dysmorphia" (Kanayama et al., 2009).

Both levothyroxine and furosemide were found to be utilised inappropriately for weight loss (Erramouspe et al., 2002; LeBourgeois et al., 2002). Levothyroxine, typically prescribed for hypothyroidism, was acquired from a veterinary source by a veterinary worker for off-label use as a weight loss aid. It was apparent that in this instance, the individual engaged in 'vet shopping', obtaining multiple prescriptions for levothyroxine from different veterinary clinics. Similarly, misuse of furosemide, a loop diuretic, was reported by veterinarians to be misused for weight management (Erramouspe et al., 2002). Furosemide has been recognised for its misuse in sports due to its ability to induce rapid weight loss (Cadwallader et al., 2010).

A single case of veterinary amitriptyline misuse was identified. Amitriptyline, a tricyclic antidepressant, is licensed for use in both humans and animals. A detailed incident wherein an anxious pet owner specifically requested amitriptyline for her dog (LeBourgeois et al., 2002). The prescribed three-week medication supply was depleted within a mere 10 days, prompting suspicion of misuse by the owner. Notably, a study revealed that 25% of amitriptyline users aimed to achieve euphoria (Cohen, 1978), highlighting the potential for dependence and abuse. This may be attributed to the drug's synergistic antihistamine and anticholinergic effects (Umaharan et al., 2021).

Two articles documented the misuse of the veterinary antibiotic tilmicosin. While this antibiotic serves as a calcium-channel blocker and lacks approval for human use, it has been implicated in suicide cases. Tilmicosin poses a significant risk to certain animal species, including pigs, primates, and horses, due to its cardiotoxicity (Lust et al., 2011). However, it is deemed appropriate for treating specific infectious diseases in cattle and sheep. Despite many exposures being accidental, there have been 25 recorded deaths, with 16 suspected suicides (AVMA, 2017). The primary exposure route in all tilmicosin cases was parenteral (Perrin, 2014), with intentional misuse in humans attributed to its widespread availability. In 2017, the FDA issued a warning regarding the dangers of tilmicosin, noting its lack of antidote and its toxic effects on the heart (AVMA, 2017).

The use of Tanax® has been implicated in suicide cases. Tanax® is a veterinary drug comprising three ingredients: embutramide (a general anaesthetic), mebezonium iodide (a neuromuscular blocking agent), and tetracaine hydrochloride (a local anaesthetic), known to potentially encourage abuse due to its hypnotic effects (Lajtai et al., 2016). Before 2014, eight documented fatalities resulted from self-administration of mebezonium and embutramide (Perrin, 2014). Notably, 50% of these cases involved individuals with convenient access to euthanasia agents, including veterinarians. Forensic and clinical toxicological analyses revealed embutramide in two cases in 2013 (Lajtai et al., 2016). In the first case, embutramide was detected in the urine of a man who had murdered his ex-wife, along with alprazolam. The second case involved a 16-year-old hospitalised for severe symptoms, experiencing recurrent episodes of unconsciousness, bradycardia, and diplopia over several months. While research (Lajtai et

al., 2016) indicated that this drug combination had not previously been associated with abuse, both cases underscored the need for heightened attention to the misuse of veterinary medications.

Dinoprost and cloprostenol are both classified as veterinary medications with potential hazards for humans. Dinoprost, a synthetic form of prostaglandin F2 alpha, is not approved for human use and is primarily employed for inducing abortion in cattle (Lust et al., 2011). However, concerns have been raised regarding its potential misuse for terminating unwanted pregnancies in humans. There are reports of a case of dinoprost misuse for this purpose (Erramouspe et al., 2002). In contrast, it was noted that human exposure to dinoprost is typically accidental, often occurring through occupational exposure (Lust et al., 2011). Similarly, cloprostenol, another synthetic prostaglandin used in veterinary medicine, is not licensed for human use and shares concerns about potential misuse for inducing abortion.

Interestingly, phenylbutazone emerged as the most frequently misused veterinary medication, constituting 57% of all reported cases involving NSAIDs (Erramouspe et al., 2002). While primarily intended for animal use, phenylbutazone is approved for treating ankylosing spondylitis in humans. However, its human usage is associated with gastrointestinal toxicity, renal dysfunction, and aplastic anaemia (Erramouspe et al., 2002). Concerningly, instances of phenylbutazone adulterating illicit drugs, particularly those containing heroin, fentanyl, and/or fentanyl derivatives, have been on the rise (CFSRE, 2023a). This trend is troubling given that phenylbutazone was largely discontinued for human consumption due to associated fatalities. Since 2016, Pennsylvania alone has reported 116 positive samples containing phenylbutazone as an adulterant (CFSRE, 2023a). Flunixin, another NSAID, was identified as a medication misused in a study analysing veterinarians' perceptions of the misuse of veterinary medications in humans (Erramouspe et al., 2002). While NSAIDs were the most frequently reported class of drugs in this study, flunixin accounted for 24% of these cases. Adverse outcomes associated with flunixin's misuse in humans, including gastrointestinal toxicity and renal dysfunction, were documented (Erramouspe et al., 2002). The study highlighted the potential for severe human overdose due to the oral formulations of flunixin used for horses. Similarly, carprofen, another veterinary NSAID, was recognised as being misused by humans in the same study (Erramouspe et al., 2002). Although NSAIDs were the most misused drug class identified, carprofen ranked as the third most misused drug within this category (13%). However, no additional reports of flunixin or carprofen misuse were found in the literature. In general, over-the-counter NSAIDs are known with an increasing potential for misuse (Hudson, 2019), due to their availability and overuse.

Finally, the misuse of a veterinary vitamin supplement containing vitamins A, D, and E was used to enhance muscle volume, with the oily vehicle of the supplement contributing to this effect (Ronsoni et al., 2017). Over four months preceding the case presentation, a parenteral application of 150 mL, containing 20,000,000 IU of vitamin A, 5,000,000 IU of vitamin D3, and 6,800 IU of vitamin E per 100

mL vial, was administered. Despite being restricted for veterinary use only, this vitamin combination is becoming increasingly popular in Brazil due to its non-anabolic classification, easy accessibility, and affordability (Ronsoni et al., 2017). Although not inherently addictive, users may misuse the supplement due to observable physical changes and may develop psychological dependence to achieve fitness goals. Several other studies also document the misuse of the veterinary ADE supplement for bodybuilding purposes (De Francesco Daher et al., 2017; Rocha et al., 2011). However, all reported cases are from South America, and it remains unclear whether similar misuse occurs in the UK.

The findings presented shed light on a concerning trend of increasing misuse of veterinary medications, reflecting a complex interplay of factors driving this phenomenon. While most data primarily focus on misuse in the US and UK, there are significant reports of carfentanil misuse across Northern Europe (EUDA, 2023h). Additionally, the detection of xylazine has extended to Estonia, Latvia, and France (EUDA, 2024a), demonstrating that this issue is widespread. The accessibility and affordability of these drugs, coupled with lax prescribing oversight, have rendered them attractive to a diverse range of users for various purposes, from recreational use to self-medication and even illicit drug adulteration. However, the underreporting of such instances highlights a significant gap in our understanding of the scope and implications of veterinary drug misuse. Furthermore, the diverse motivations behind this misuse, including recreational, therapeutic, and criminal intents, underscore the need for multifaceted interventions to address this issue effectively. Strengthening monitoring protocols within the veterinary industry and enhancing public awareness and education are crucial steps towards mitigating the risks associated with veterinary drug misuse. Additionally, healthcare professionals must remain vigilant to the unique challenges posed by poly-substance use involving veterinary medications, necessitating the development of targeted treatment and intervention strategies. Ultimately, concerted efforts across multiple sectors are essential to address this emerging public health concern and safeguard both human and animal welfare.

2.5 Limitations

As the misuse of veterinary medicines in humans is an emerging phenomenon, a limitation of this study includes the lack of substantial evidence in this subject area. Although a risk of bias assessment was conducted, there were a large amount of case report studies. These studies carry a higher risk of bias and may affect the interpretation of the findings. Further research is needed to gain a better understanding of this developing trend.

2.6 Conclusions

This comprehensive literature review aimed at evaluating the prevalence and motivations underlying the misuse of veterinary medications reveals a troubling trend. Veterinary drugs are increasingly appealing to drug users due to their affordability and ease of access, stemming from less rigorous

prescribing oversight. However, despite this surge in usage, instances of veterinary medication misuse remain largely underreported, with scant data available for research. The review revealed various rationales driving this misuse, ranging from recreational use to pain relief, self-medication, suicide, drug-facilitated crimes, pregnancy termination, bodybuilding, and weight loss. Of particular concern is the frequent use of veterinary drugs as adulterants in illicit drug samples, often unclaimed to consumers, leading to unintended exposures and potential health hazards. There exists an urgent need for veterinary professionals to bolster monitoring protocols for their products, aiming to curtail overdose incidents among staff and associated personnel, while also ensuring that animal owners procure these drugs for legitimate purposes. Concurrently, healthcare practitioners must exercise heightened vigilance regarding the diverse effects that may manifest in emergency room scenarios due to poly-substance use, exacerbated by the lack of necessary antidotes for many veterinary products. To effectively address these challenges, a multi-pronged approach is imperative. This includes bolstering public awareness and education efforts to elucidate the risks associated with veterinary medications. Furthermore, stricter regulatory measures are warranted alongside the development of more robust treatment and intervention strategies to mitigate the burgeoning misuse of these medications.

Chapter 3: Exploring Human Misuse and Abuse of Veterinary Drugs: A Descriptive Pharmacovigilance Analysis Utilising the Food and Drug Administration's Adverse Events Reporting System (FAERS)

3.1 Introduction

The problem of drug misuse and its contribution to the rising number of drug-related deaths has been a recognised issue for the last few decades. Official statistics show that drug-related deaths in England and Wales have risen for the 11th year in a row, reaching their highest since records began in 1993 (Iacobucci, 2023; ONS, 2023). However, it has been noted that prescription and over-the-counter medication misuse is a significantly under-recognised problem, affecting a range of vulnerable individuals (Coombes & Cooper, 2019). Dependence on prescription drugs, particularly opioids and other controlled substances, represents an increasing public health and clinical challenge both in the UK and internationally (Coombes & Cooper, 2019). This growing dependency drives individuals to explore innovative and often risky methods to satisfy their need for these drugs. With more drugs of misuse being controlled and recognised, veterinary medication misuse has become an emerging issue. It is unclear why drug users have increasingly turned to veterinary medications, but it has been observed that most prescription drug misuse is facilitated through healthcare providers (Hughes et al., 2016). Given that veterinary clinics can serve as alternative sources of medications, they may become targets for those seeking to misuse prescription drugs outside traditional healthcare channels.

Data regarding veterinary prescription drug misuse is sparse in the UK, yet veterinary prescription medications in the US have increasingly been identified as sources of misuse, primarily due to easy access and availability (Lehnus et al., 2023). Veterinarians are frequently overlooked as potential contributors to prescription drug misuse (Anand & Hosanagar, 2021), although there is gaining interest in seeking medications through veterinarians, due to the perception of them being safer and cheaper than street drugs (Health Canada, 2006). Between 2014 and 2019, it was documented that the number of patients with prescriptions for any class of controlled substances from four or more veterinarians increased 3-fold (Chua et al., 2022), with reports suggesting that individuals harmed their pets to obtain veterinary analgesics (Herzog, 2018). As veterinarians do not fall under the same monitoring and control constraints as general practitioners, there is potential for increased opportunities for drug diversion and misuse. As such, Russel et al., (2018) documented that 75% of a sample of veterinarians were aware of working with someone with a substance abuse problem.

In addition to users obtaining veterinary drugs directly through clinics, there has also been a rise in adulteration of common drugs of misuse with veterinary products, mainly heroin and fentanyl. Veterinary medicines including xylazine, carfentanil, dexmedetomidine, pentobarbital, and levamisole

have all been identified in seized fentanyl tablets in the US (CFSRE, 2024). This poses a significant concern as users may unknowingly ingest these veterinary substances, leading to potentially serious harm. In 2023, it was reported by the Centres for Disease Control and Prevention (CDC) that the monthly percentage of deaths involving xylazine, a veterinary tranquiliser, in the context of IMF increased by 276%, rising from 2.9% in January 2019 to 10.9% in June 2022 (CFSRE, 2023). The escalating fatalities associated with xylazine misuse in the US raised concerns that a similar trend may emerge in the UK, akin to the opioid crisis. As polydrug consumption increases, the challenges of developing effective responses to reduce drug overdose deaths and drug-related poisonings rise (EUDA, 2023c), where mixtures containing novel opioids and BZDs have been found to contain xylazine. This increase in diversity in drug supply was described by the EUDA to pose new challenges for drug policy and healthcare in Europe, with these mixtures having the potential to impact European health (EUDA, 2023b). Xylazine use has been increasing rapidly over the last few years, causing the US to announce a public safety alert in 2022 and an announcement in 2023, describing it as an "emerging threat" – with this type of report being a first in US history (DEA, 2022b; The White House, 2023). Although xylazine deaths remain significantly lower in the UK, there is evidence that xylazine has been detected in the UK illicit drug supply, with eleven fatalities documented between May 2022 and August 2023 (ACMD, 2024). Ketamine and carfentanil are two other popular veterinary medications to be misused by humans, with both these drugs being listed as veterinary products with significant health hazards to human health (Lust et al., 2011). The latest Focal Report on the UK drug situation in 2019 reported that ketamine usage has reached its peak, at 0.8% (GOV.UK, 2019), with a simultaneous rise in deaths attributed to recreational ketamine misuse (Corkery et al., 2021). Carfentanil's misuse is also believed to be under-reported because of its exclusion from most routine drug screenings, as well as its dose regimens and abuse liability being unknown, due to it not being licensed for humans (EUDA, 2018). Despite the lack of data regarding carfentanil, 92% of syringes collected in Lithuania contained carfentanil (EUDA, 2023c).

To the best of our knowledge, there is no current study that investigated veterinary misuse using pharmacovigilance approaches informed by a systematic literature review. Therefore, this study aims to analyse the Food and Drug Association Adverse Events Reporting System (FAERS) for Adverse Events (AEs) associated with selected veterinary products that have been identified from a systematic literature review (Dunn et al., 2024 (*in press*)).

3.2 Methodology

3.2.1 Prior Research

A systematic literature review (SLR) exploring the confluence of animal medicine and its implications for human health was conducted by the research group to investigate which specific veterinary

medications are currently being misused. Results from this study found 28 distinct veterinary products, including xylazine, medetomidine, dexmedetomidine, clenbuterol, ketamine, telazol (zolazepam/ tiletamine), carfentanil, tramadol, butorphanol, diazepam, clorazepate, pentobarbital, phenobarbital, acepromazine, levamisole, pheniramine, stanozolol, levothyroxine, furosemide, amitriptyline, tilmicosin, embutramide/ mebezonium, dinoprost, cloprostenol, phenylbutazone, flunixin, carprofen, and veterinary vitamin ADE compound (Dunn et al., 2024 (*in press*)). Commonly misused drugs like diazepam were identified through the SLR but were excluded from the study due to a lack of evidence for veterinary-grade diazepam misuse or diversion through veterinary clinics for human misuse.

3.2.2 Search Strategy

The FAERS Public Dashboard (U.S. Food & Drug Association (FDA), 2020) is an online database, free to use by consumers, healthcare professionals, and manufacturers to report and view adverse events associated with drug products. The database currently has 28,655,483 total reports, dating back to 1968. The year 2022 had the highest number of reports, with a total of 2,338,998. It is important to note that FAERS is based on the reporting parties' observations and assessments, which may not include laboratory confirmation or toxicological analysis. However, the reports in FAERS are evaluated by clinical reviewers to monitor the safety of products after they are approved by the FDA.

In line with previous studies that have conducted similar analyses of AEs associated with drugs of misuse (Chiappini et al., 2023), we employed a pharmacovigilance approach to systematically retrieve and analyse data on AEs associated with these veterinary products. The database encompasses valuable data on AEs, medication errors, and patient demographics, making it a crucial asset for regulatory science (Fang et al., 2014). Trends and patterns can be identified as the FDA database contains a vast amount of data that reflects real-world outcomes related to drug use. By combining both the systematic literature review with the FAERS data analysis, novel data can be retrieved regarding the emerging problem of veterinary medicine misuse in humans.

3.2.3 Selected Preferred Terms

In pharmacovigilance, 'misuse' denotes the intentional and improper utilisation of a product, diverging from prescribed guidelines, while 'abuse' involves the deliberate non-therapeutic use of a product, motivated by presumed rewards (Chiappini et al., 2023). Preferred Terms (PTs) were designated from the Medical Dictionary for Regulatory Activities (MeDRA), a recognised set of terms relating to medical conditions and medicines (Medical Dictionary for Regulatory Activities, 2023). Terms selected and deemed relevant for this study were: overdose, intentional overdose, accidental overdose, drug abuse, substance abuse, off-label use, intentional product misuse, product use in an approved indication, prescription drug used without prescription, toxicity to various agents, poisoning, dependence, substance dependence, drug withdrawal syndrome, withdrawal syndrome, drug diversion, completed

suicide, suspected suicide, suicide attempt, and suspected suicide attempt. No date limits or geographical limitations were imposed, encompassing AE reports up to the Q4 of 2023, with no instances of duplicate cases identified.

3.2.4 Analysis

The drug names used in the FDA database corresponded to those listed in the British National Formulary (BNF) (National Institute for Health and Care Excellence, 2023). For the drugs that were not included on the BNF, such as clenbuterol, the selection was based on FDA database entry with the highest number of reports, ensuring the most relevant drug profile was chosen. The parameters analysed include sex, age, indications of use, country of origin, year of report, reporter type, and the outcomes (e.g. hospitalisation, death, life-threatening outcome). To investigate polydrug use, a separate list of commonly misused drugs was created. This list was separated into drug classes (see Supplementary Information (SI) Table 2), including opioids (e.g. hydrocodone, tramadol and oxycodone), BZDs (e.g. alprazolam, bromazolam and flunitrazepam), stimulants (e.g. cocaine, amphetamine and methylphenidate), and CNS depressants (e.g. alcohol, GHB and medetomidine). Common drugs of misuse that did not align with the drug groups were listed under 'other drugs of misuse' (e.g. cannabis, ayahuasca, gabapentin and promethazine). Common brand names (e.g. Xanax, Adderall and Ambien) of these drugs were also cross-referenced to ensure comprehensive data collection. Subsequently, these drugs were extracted from the dataset if they were identified as being concurrently used with the drugs of interest in this current study. A descriptive analysis was then conducted to analyse the AEs associated with the veterinary products extracted from the literature. The reporting odds ratio (ROR) for the drugs analysed in this study was not calculated due to their diverse classification across different drug classes. Since the drugs under investigation belonged to varying groups, comparing their adverse event reporting frequencies using ROR may not yield meaningful results. Of all the drugs included in this study, eight drugs (xylazine, pentobarbital, carfentanil, levamisole, acepromazine, tilmicosin, carprofen, and phenylbutazone) are exclusively approved for animals only. Unmasking techniques were employed to analyse the specific effects of the drug of interest in isolation. This involved examining AEs where no other drugs were identified, thereby isolating the AEs attributed solely to the drug in question. By filtering out cases involving polysubstance use, this method allowed for a clearer understanding of the drug's independent impact. Data analyses were performed using Microsoft Excel (Version 16.83 (24031120)). Ethical approval was not required for this study as all data reported to the FDA was anonymous.

3.3. Results

3.3.1 Querying FAERS Database for AEs

The FAERS was queried in January 2024 for AEs related to the veterinary drugs that were retrieved from the systematic literature review (Dunn et al., 2024 (*in press*)). Due to the human-centric nature of

the FAERS, data for specific veterinary products was unavailable for analysis as it was not included in the FAERS database. Consequently, some drugs were excluded from this study as no associated AE reports were found. These included the veterinary compound telazol, embutramide/ mebezonium, cloprostenol, medetomidine, and the veterinary ADE vitamin compound. Flunixin data was available on the FAERS, however it did not include data relevant to this study. Diazepam was also not included in this study due to the absence of reports on human misuse of veterinary-grade diazepam diverted from clinics.

3.3.2 Overview of AEs and Mortality

From the 21 drugs that were included in this study, there were a total of 198,640 adverse events reported to the FDA up until 31st December 2023. Among these, 38,756 (20%) adverse events related to the selected PTs were reported for the same 21 drugs. There was a total of 9566 (25%) deaths associated with the PTs for all drugs included in this study.

Figure 2 demonstrates the general increase in the number of reports received by the FDA for the last 10 years for the chosen drugs. Carprofen and tilmicosin were excluded from this total as they have not had any relevant reports in the last 10 years.

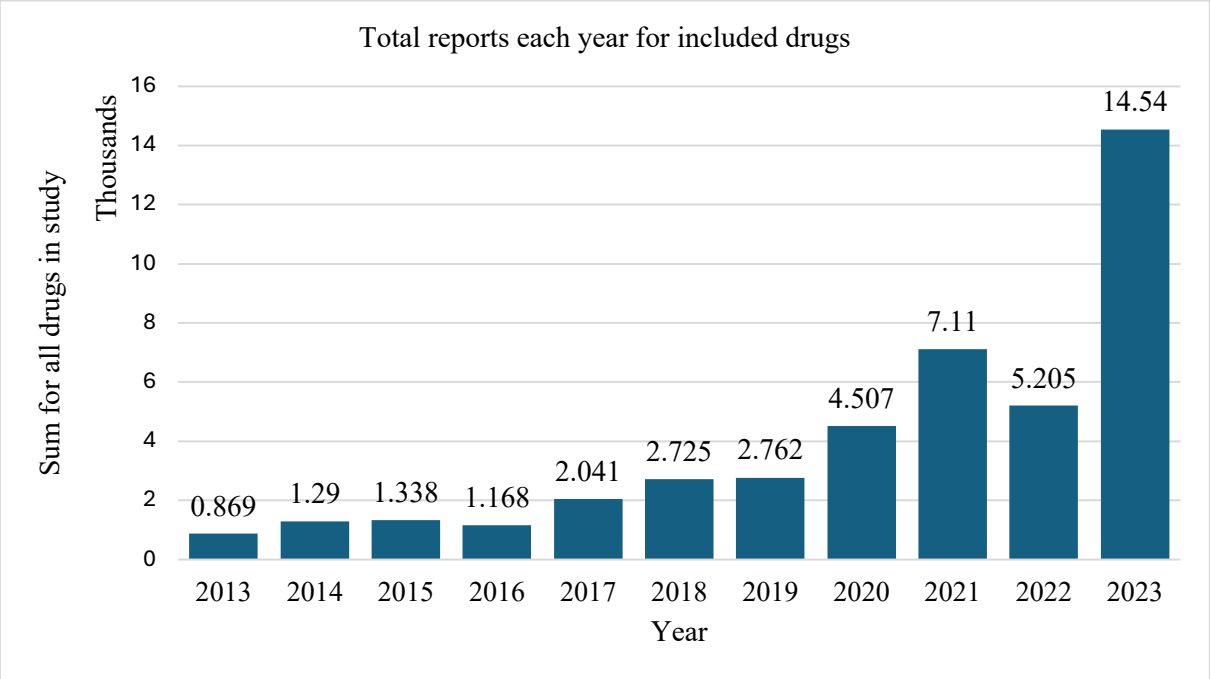

Figure 2 - The total number of reports for the selected PTs for all drugs included in the study, per year

3.3.3 Reporting Trends and Demographics

Examining the eight drugs exclusively approved for animal use, there is a noticeable overall increase in the number of reports for levamisole, pentobarbital, and xylazine. Carfentanil's reports to FAERS peaked in 2021 (41 reports) and slightly decreased in 2022 (19), with only three reports in 2023. Acepromazine had the highest number of reports in 2017 (33), yet reports have remained low since then. Phenylbutazone has received just seven reports since 2017, with only one report in 2023. Figure 3 demonstrates the number of reports of drugs approved for animals only, over the last decade.

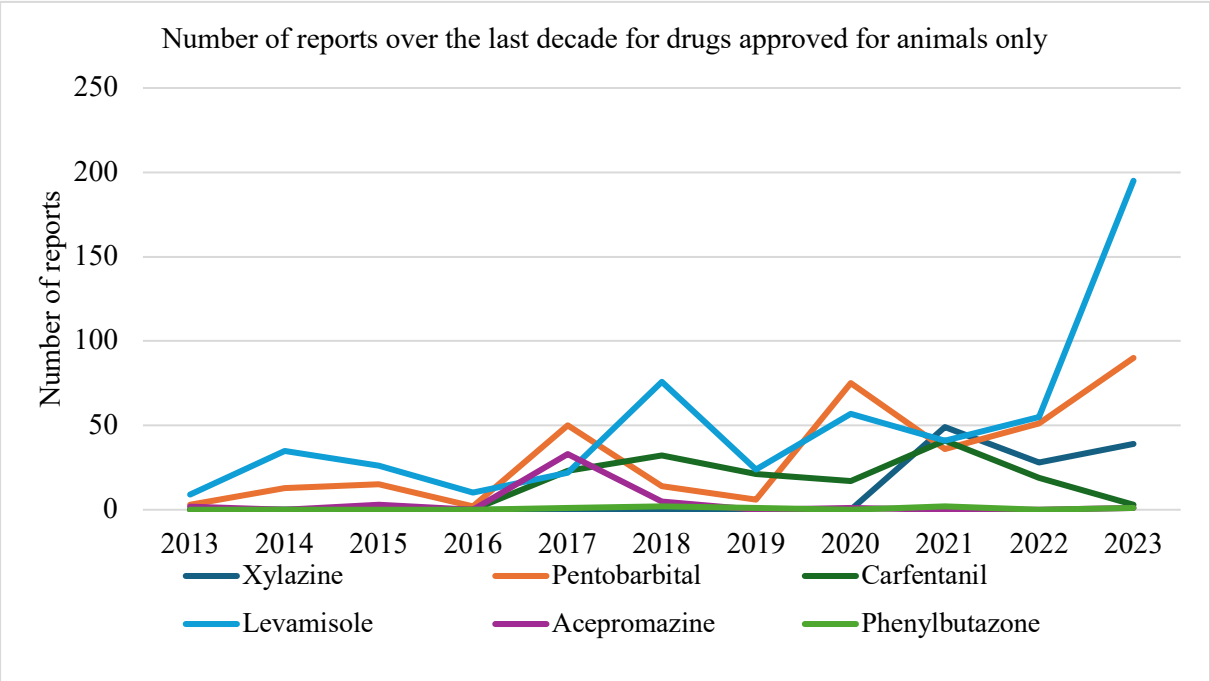

Figure 3 - A graph demonstrating the number of reports for the last ten years for drugs approved for animals only.

Of the 21 drugs analysed, 12/21 (57%) demonstrated a higher number of reports from males, whereas 9/21 (43%) exhibited a greater number of reports from females. Although more drugs had males as the more common reporter, the total number of reports for all 21 drugs was higher for females. Females contributed to a total of 16076 (50%) reports, whereas males reported 15927 (50%) altogether. From the total number of reports, the 'not specified' age group accounted for 17002 reports. Excluding the cases where the age was not classified, there were a total of 21,755 reports that were separated by age group. Of these, the age group 18-64 years accounted for 14766 (68%) reports. The 18-64 age group had the highest number of reports for 20 out of 21 drugs, with furosemide having the highest number of reports in the 65-84 age category. This is summarised in Figure 4.

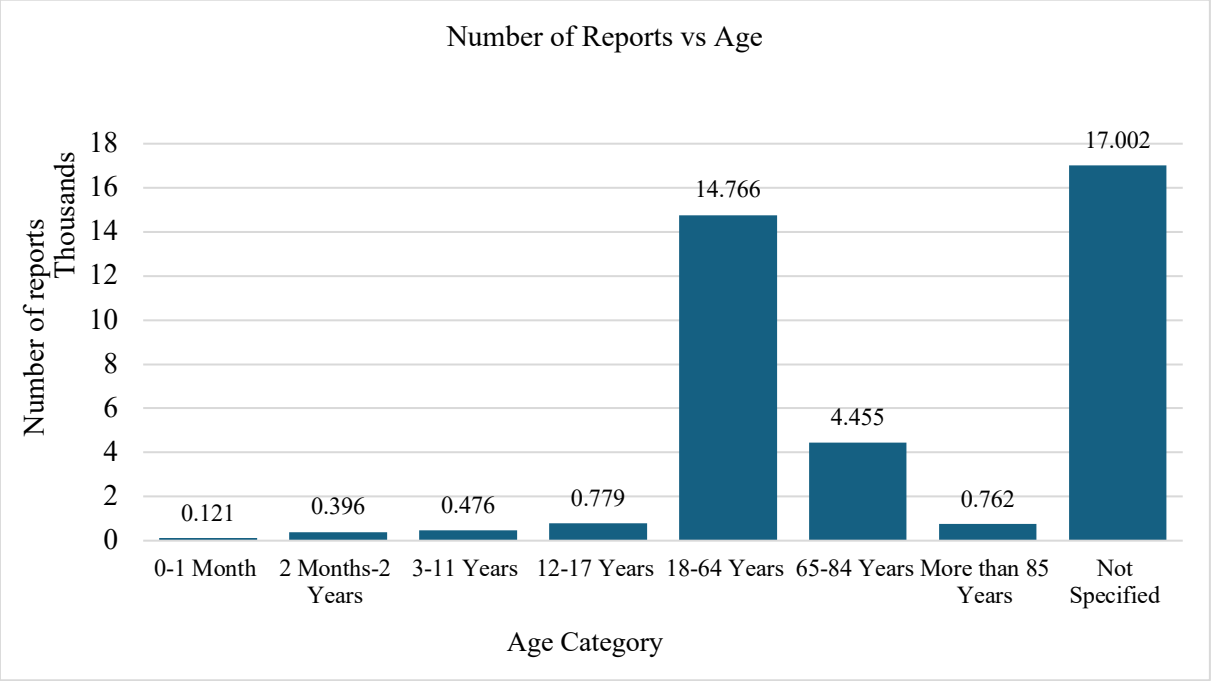

Figure 4 - The number of reports (in thousands) for each age category

Healthcare professionals submitted 20431 (53%) total reports, while consumer reports accounted for 16804 reports (44%). The reporter type for the remaining 1512 (4%) of reports was unspecified. After excluding reports categorised as an 'unknown outcome', hospitalisation emerged as the most common outcome with 12447 reports (44%), followed by death as the secondary outcome with 9566 reports (34%). Non-serious outcomes represented only 5% (1553) of reports. This is summarised in Figure 5.

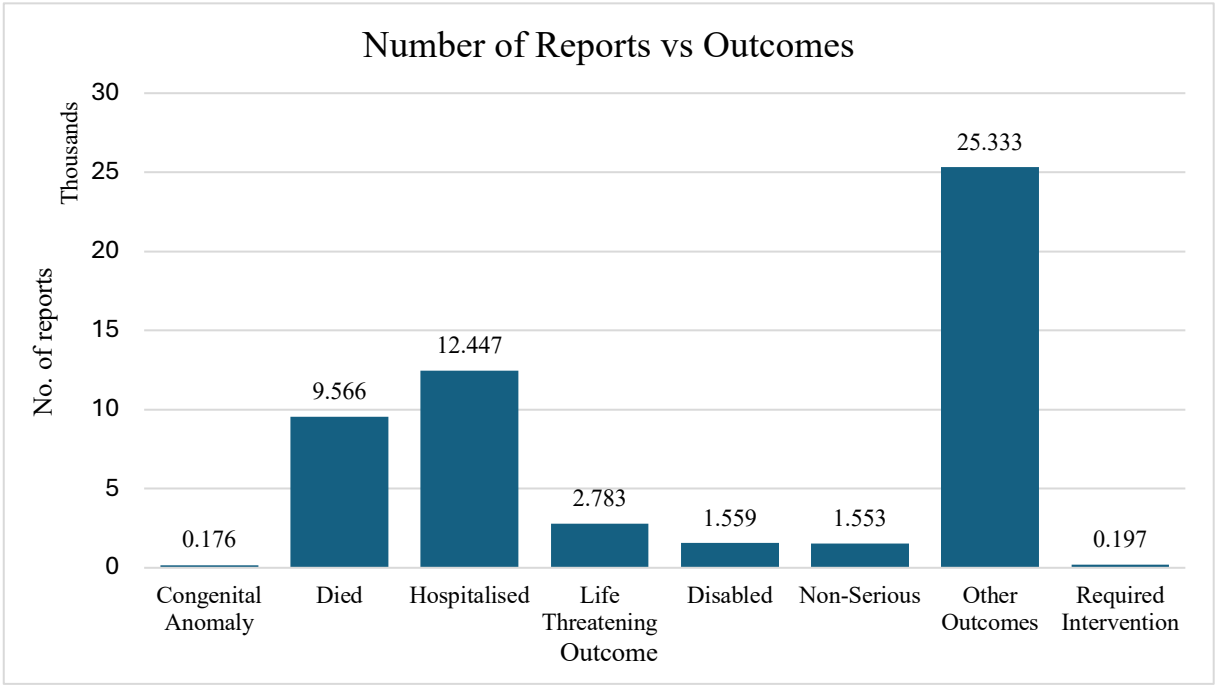

Figure 5 - Number of reports and the associated outcomes

3.3.4 Adverse Reactions

Of the 21 selected PTs, 'overdose' was the most reported reaction, followed by 'dependence' and 'toxicity to various agents', with reports of 8647 (16%), 7555 (14%) and 6711 (12%), respectively (figure 6). Although 'overdose' had the highest number of total reports across all 21 drugs in the study, it is noteworthy to add that 'toxicity to various agents' emerged as the most reported reaction for six specific drugs (xylazine, pentobarbital, carfentanil, levamisole, furosemide, and amitriptyline). In these cases, this reaction had the highest number of reports among all reactions associated with those drugs individually.

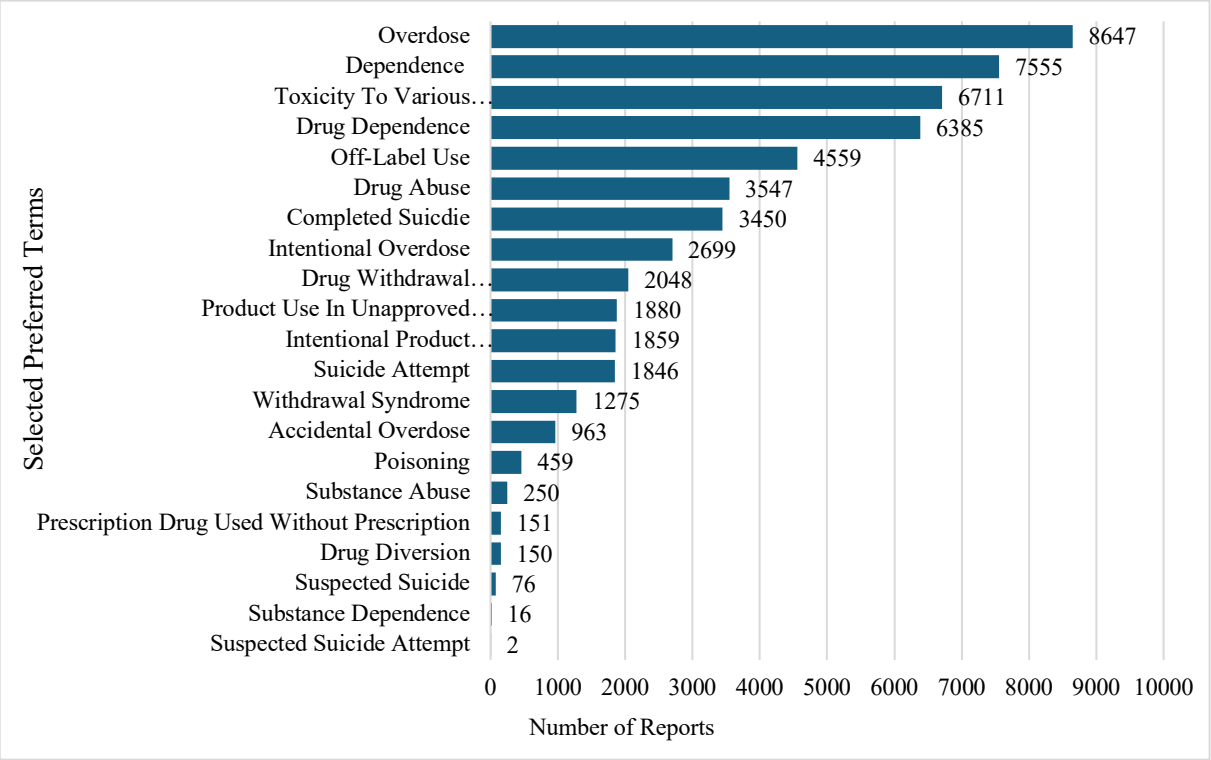

Figure 6 - The number of reports associated with the selected PTs

3.3.5 Polysubstance Misuse

Out of all the drugs included in this study, 90% had reports of co-use with other drugs of misuse (19/21). BZDs/Z-Drugs and opioids were implicated in AEs associated with 62% (13/21) of drugs analysed. Stimulants were implicated in AEs associated with 57% (12/21), CNS depressants in 57% (12/21) and 67% of the drugs under study were found to have been used concomitantly with drugs of misuse categorised as 'other'. Figure 7 summarises this.

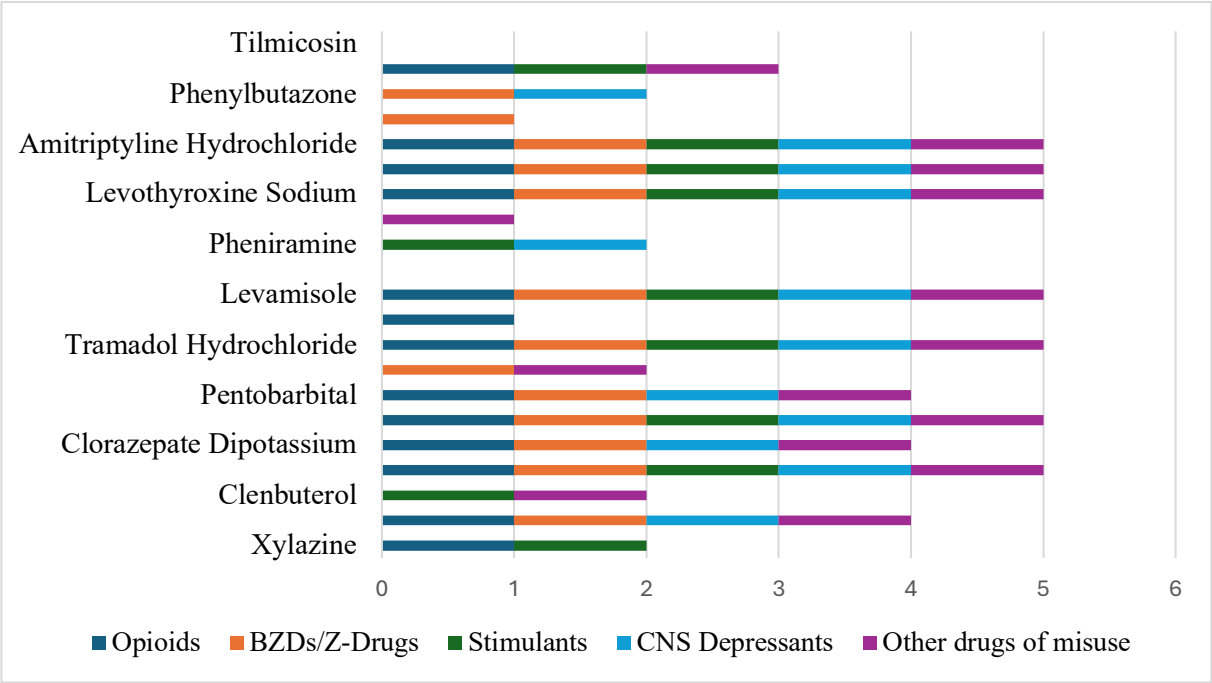

Figure 7 - A stacked bar chart showing poly-substance use

3.3.6 Reactions Associated with Animal-Only Drugs

Quantitative analysis was performed on the reactions associated with the eight drugs exclusively approved for animal use (xylazine, levamisole, pentobarbital, carfentanil, phenylbutazone, acepromazine, tilmicosin, and carprofen), revealing a total of 27 reactions through unmasking techniques. Carfentanil, acepromazine, tilmicosin, and carprofen did not have any data. Using a frequency analysis of adverse events identified through unmasking techniques, this analysis quantified the number of distinct adverse reactions reported for each drug, focusing on reactions that were isolated from cases involving other drugs. This ensured that the reported effects were attributed solely to the drug of interest, excluding any influence from the concurrent use of other drugs. The unmasking of these drugs revealed that 'intentional overdose' and 'overdose' were the most reported reactions associated with these drugs when taken alone, with seven reports each (26%). Other reactions included 'accidental overdose' with four reports (15%) and 'toxicity to various agents' with three reports (11%). 'Completed suicide' received two reports (7%) and 'intentional product misuse', 'withdrawal syndrome', 'drug withdrawal syndrome', and 'suicide attempt' all received one report (4%) each. For the eight animal-only drugs, 63% (5 out of 8) had 'died' as the most common outcome, these drugs included xylazine (81 reports, 74%), levamisole (280 reports, 71%), carfentanil (92 reports, 84%), tilmicosin (one report, 100%), and carprofen (12 reports, 86%). For the eight drugs licensed for animals only, further analyses were conducted and are summarised in Table 3.

Table 3 - A breakdown of the animal drugs and their demographics, with unmasking techniques applied

Drugs	Total ADRs	ADRs associated to PTs	Most common reactions	Gender	Age	Reporter	Outcome	Concomitant drugs
Xylazine	109	95 (87%)	Toxicity to Various Agents = 68 (58%) Drug Abuse = 26 (22%) Overdose = 9 (8%)	F=20 (30%) M=67 (77%)	18-64 = 74 (91%) 3-11 = 5 (6%)	Healthcare professional = 90 (95%) Consumer = 5 (5%)	Died = 81 (74%) Hospitalisation = 16 (15%) Life Threatening = 9 (8%)	Opioids = morphine, codeine, tramadol, methadone. Stimulants = amphetamine, cocaine
Levamisole	510	372 (73%)	Toxicity to Various Agents = 216 (37%), Drug Abuse = 134 (23%) Completed Suicide = 48 (8%)	F= 94 (28%) M = 236 (72%)	18-64 = 305 (95%) 12-17 = 10 (3%)	Healthcare Professional = 334 (95%) Consumer = 17 (5%)	Died = 280 (71%) Hospitalised = 87 (22%) Life Threatening = 25 (6%)	Opioids = carfentanil, morphine. Stimulants = caffeine, cocaine, nicotine. BZDs/Z-drugs = diazepam, temazepam. CNS depressants = alcohol. Others = gabapentin, pregabalin
Pentobarbital	486	220 (45%)	Off Label Use = 75 (27%), Toxicity to Various Agents = 69 (25%) Completed Suicide = 48 (17%)	F = 114 (56%) M = 90 (44%)	18-64 = 126 (65%) 3-11 = 30 (15%) 12-17 = 16	Healthcare professional = 202 (95%) Consu	Died = 109 (37%) Hospitalised = 113 (39%) Life Threateni	Opioids = fentanyl, tramadol, loperamide. BZDs/Z-drugs = diazepam, oxazepam,

					(8%) 2 month -2 = 10 (5%)	mer = 11 (5%)	ng = 52 (18%)	nordazepam, valium, clonazepam, lorazepam, clobazam, flunitrazepam, midazolam, dalmane, zolpidem. CNS Depressants = phenobarbital, dexmedetomidine. Others = ketamine, gabapentin, dextromethorphan
Carfentanil	118	104 (88%)	Toxicity to Various Agents = 79 (54%) Drug Abuse = 27 (19%), Overdose = 15 (10%)	F = 48 (48%) M=52 (52%)	18-64 = 97 (99%) 12-17 = 1 (1%)	Healthcare professional = 90 (95%) Consumer = 5 (5%)	Died = 92 (84%) Hospitalised = 15 (14%) Life Threatening = 3 (3%)	Opioids = codeine
Phenylbutazone	953	32 (3%)	Overdose = 12 (36%) Intentional overdose = 5 (15%) Accidental overdose = 4 (12%) Completed suicide = 4 (12%)	F = 12 (41%) M = 17 (59%)	18-64 = 18 (75%) 12-17 = 2 (8%) 65-84 = 2 (8%)	Healthcare Professional = 19 (59%) Consumer = 13 (41%)	Died = 10 (40%) Hospitalised = 12 (48%) Life Threatening = 3 (12%)	BZDs/Z-drugs = diazepam. CNS depressants = alcohol

Aceprom azine	42	31 (74%)	Overdose = 16 (41%) Drug Abuse = 7 (18%) Intentional Overdose = 3 (8%) Completed Suicide = 3 (8) Suicide Attempt = 3 (8%)	F = 19 (66%) M = 10 (34%)	18-64 = 29 (100 %)	Healthc are Professi onal = 30 (100%)	Died = 9 (20.45%) Hospitali sed = 21 (48%) Life Threateni ng = 14 (32%)	N/A
Tilmicosi n	1	1 (100%)	Completed Suicide = 1 (100%)	F = 1 (100%)	18-64 = 1 (100 %)	N/A	Died = 1 (100%)	BZDs/Z-drugs = Zopiclone
Carprofe n	24	12 (50%)	Completed Suicide = 8 (53%) Toxicity to Various Agents = 7 (47%)	F = 12 (100%)	18-64 = 12 (100 %)	Healthc are Professi onal = 10 (100%)	Died = 12 (85.71%) Hospitali sed =2 (14%)	Opioids = Hydromorpho ne. Stimulants = Amphetamine Sulfate. Others = Promethazine

3.4 Discussion

This article examined the FAERS AEs related to veterinary drug misuse, specifically, the 21 drugs identified from the systematic literature review (Dunn et al., 2024 (*in press*)). With the increasing misuse of prescription drugs being described as a modern epidemic (Roberts & Richards, 2023), veterinary prescription drugs are also becoming more apparent in the illicit drug market and increasing use can be associated with the lack of stringent regulations, easy access, and low cost, rendering them an appealing option for misuse. The analysis confirmed that veterinary medicines can be subject to diversion, misuse, and dependence, as well as be used for acts of suicide. The growing body of evidence and rising number of reports on the misuse and abuse of veterinary drugs highlight this area as a significant cause of concern, which lacks current, up-to-date research. A total of 38,756 cases from FAERS were identified for the 21 drugs detected in the systematic literature search conducted before this study. To our knowledge, this is the first study utilising the FAERS database to gain data regarding the growing misuse of veterinary products.

The results of this study reveal a significant increase in the number of adverse event reports associated with veterinary products. When analysing the groups of drugs, it was found that the year 2023 accounted for over one-third (14,540, 33%) of the total reports across the last decade (43555). For the 21 drugs analysed, nine (ketamine, clenbuterol, butorphanol, tramadol, levamisole, stanozolol, levothyroxine, furosemide and amitriptyline) exhibited an increase of over 1000% in reports over the past five years, highlighting a significant rise in potential misuse and increased awareness and reporting. Additionally, six drugs demonstrated a percentage increase between 500-999% (dexmedetomidine, clorazepate, phenobarbital, pentobarbital, carfentanil and phenylbutazone) over the same period. Reports of pheniramine rose by 300%, xylazine by 136%, and acepromazine by 21%. The remaining three drugs (dinoprost, carprofen and tilmicosin) did not show any percentage increase over the last five years, suggesting a potentially low risk of misuse. However, given that these drugs are primarily intended for veterinary use, human reports are inherently low as they are not commonly prescribed drugs in human medicine.

3.4.1 Drugs approved for animals only

Of the 21 drugs identified from the systematic literature review, eight of these are exclusively licensed for animal use only (xylazine, pentobarbital, carfentanil, levamisole, acepromazine, tilmicosin, carprofen and phenylbutazone). Notably, recent documentation from the CFSRE (2024) highlights the presence of xylazine, pentobarbital, and levamisole in counterfeit fentanyl tablets. Furthermore, research by O'Donnell et al. (2017) indicates that carfentanil, a fentanyl analogue, is increasingly prevalent in opioid overdose deaths. These instances underscore the growing use of veterinary products as adulterants in illicit drugs. The FAERS database primarily focuses on human products that have been

approved and licensed by the FDA. Although it does include data on unapproved products, data regarding veterinary products is sparse. The inclusion of data on animal-only drugs in the FAERS database indicates a noticeable rise in their usage, as individuals and healthcare reporters are increasingly documenting adverse effects linked to these medications. Two animal-only drugs (carprofen and tilmicosin) did not receive any reports related to the specific PTs in the last decade.

Examining the remaining six drugs approved exclusively for animal use, xylazine, levamisole, and pentobarbital have shown an upward trend in reports up until 2023. Xylazine's upward trend correlates with its increasing presence in illicit drug markets in the US, with the UK now demonstrating a small rise in cases also. In 2022, 98% of xylazine-related deaths involved fentanyl (Sibbesen et al., 2022), leading to the US recognising fentanyl-associated xylazine as an emerging threat (The White House, 2023). Similarly, the UK's Advisory Council on the Misuse of Drugs (ACMD) released a statement in 2024 advising xylazine to be controlled with increased vigilance and monitoring, after evidence of xylazine detections in sixteen people with eleven fatalities (ACMD, 2024). After its first reports to the FDA in 2021 (49), there have been an additional 67 reports relating to the PTs specific to this study. The majority of xylazine's total reports (87%) are for the specific PTs, indicating a significant number of reports related to misuse. The main motivations behind xylazine misuse are not fully understood, and most users do not intentionally seek out xylazine (Spadaro et al., 2023). However, one study found a group of people who intentionally sought after xylazine and its desirable effects, including prolonging the duration of the high when taken with opioids (Spadaro et al., 2023).

Over the last 10 years, there have been 550 reports of levamisole use, with a significant spike in 2023 with 195 reports, marking a dramatic increase from the previous year's 55 reports. The high reports for levamisole correlate to its prevalence in cocaine samples, where the DEA (2018) stated that 87% of cocaine bricks contained the veterinary anti-helminthic. Cocaine is the second most illicitly used drug after cannabis (Conrad et al., 2021), and its frequent adulteration with levamisole has become a public health concern. This contamination poses serious risks, including vasculitis, a dangerous condition that can lead to organ failure as a result of levamisole poisoning (Lee et al., 2012). Its various pharmacological properties contribute to its use as an adulterant, as it enhances neurotransmitter release by acting on dopamine, serotonin, and norepinephrine transporters. Additionally, it extends the effects of cocaine and influences neurotransmitter reuptake after cocaine is metabolised (Hofmaier et al., 2014).

Since 2013, there has been a fluctuation in the number of reports concerning the barbiturate, pentobarbital. However, since 2021, there has been a constant increase with the number of reports rising from 36 (2021) to 90 (2023). Notably, 2023 saw the highest number of FDA reports regarding pentobarbital to date, where an increase in reports could be associated with its rising identification of counterfeit fentanyl samples in the US (CFSRE, 2024). Although historically used in humans to treat

insomnia and manage seizures, pentobarbital's main uses are as a euthanasia agent in veterinary medicine. Reports suggest that media coverage describing pentobarbital as a peaceful method of suicide (Druda et al., 2019) has led to increased interest in acquiring the drug from regions where it is less regulated. These reports align with findings from this study, where pentobarbital had 48 reports of 'completed suicide', this being its third most reported reaction after 'off-label use' (75 reports) and 'toxicity to various agents' (69 reports).

In contrast, carfentanil, acepromazine, and phenylbutazone have exhibited relatively fewer reports in 2023 (3, 1, and 1 report, respectively). Carfentanil's initial spike in reports, from zero in 2016 to 23 in 2017, aligns with findings indicating that carfentanil ranked as the second most frequently reported synthetic opioid in the U.S. between 2016-2017, and was the most frequently seized drug among synthetic opioids in 2017 for the years 2015-2018 (Zawilska et al., 2021). Additionally, in 2017, the World Health Organisation (WHO) recommended that carfentanil be moved to the most stringent level of international control due to the high potential for harm and dependence (WHO, 2017). Although recent reports to the FDA may be low for carfentanil, it was documented that there is growing evidence that "carfentanil may be making a comeback" as there was a 3400% increase in detection from 2022 to 2023 (Randox Toxicology, 2023). Given the extreme potency of this medication, it is crucial to allocate attention and effort to prevent an increase in reported cases.

Furthermore, the CFSRE (2023b) predicted acepromazine (phenothiazine) and phenylbutazone (NSAID) as the 'next xylazine', emphasising the need for monitoring and testing due to their use as toxic adulterants, albeit the relatively low number of cases. The CFSRE (2023a) reported that there were 116 seized drug samples from Pennsylvania between 2016 and 2021 containing phenylbutazone, raising concerns about its potential nationwide spread, mirroring the pattern observed with xylazine. These samples predominantly included heroin, fentanyl, and xylazine. There is limited data available regarding the misuse of phenylbutazone but there were 32 cases related to this study's PTs, with 32 reports of overdose (36%) and 4 reports of completed suicide (12%). It is known to be a very potent NSAID with serious adverse effects on human health, including gastrointestinal bleeding, liver and kidney damage, and blood disorders (CFSRE, 2023a). Acepromazine has no approved use for humans and like phenylbutazone, data regarding its misuse is sparse. There were 31 cases retrieved for acepromazine, with 16 reports of overdose (41%), seven cases of drug abuse (18%) and three cases of completed suicide (8%). It has been reported that CNS and respiratory depression are possible if ingested by humans (CFSRE, 2023b). Despite the relatively low cases of phenylbutazone and acepromazine, recent detection and a lack of scheduling means monitoring is warranted.

3.4.2 Demographics and Reporting of Drug AEs

Our analysis revealed notable disparities in the distribution of reported AEs among countries. The US exhibited the highest number of reported AEs (13,532), followed by France (3459), Canada (2869), and the UK (1400). These findings may reflect differences in veterinary medication usage patterns, regulatory practices, and healthcare reporting requirements across counties. The high number of reports from the US is consistent with expectations, given that the FAERS is a US-based database. Additionally, the significant prevalence of SUDs in the U.S., with 46.8 million Americans (over age 12) battling SUDs in 2022, underscores the widespread nature of the issue. Reports associated with the eight animal drugs were documented by 18 different countries, underscoring the emerging widespread, global problem of misuse of animal medications worldwide.

For every drug included in the whole FAERS database, females contributed to over five million more AE reports than males. This aligns with findings that female AE reports outnumber male AE reports across the world, in all age groups, although male reports more often contain more serious and fatal reports (Watson et al., 2019). UK statistics in 2022 also demonstrated this pattern, where there were 1143.3 drug-related deaths registered per million among males (3240 deaths), compared with 55.8 deaths per million among females (1667 deaths) (ONS, 2023). These statistics correspond to reports stating males have higher rates of use/dependence on illicit drugs than females (NIDA, 2020) and males die from overdose at an approximately 2-3 times greater rate than females for opioids and stimulants (Butelman et al., 2023). In this study, although 57% (12/21) of drugs had more cases from males, the overall total of reports had slightly more from females (50%). For all drugs in this study, there was a higher number of deaths associated with females with 4529 deaths reported (53%), with 4005 death reports attributed to males (47%).

In the UK for the last 25 years, the age group with the highest rate of drug misuse deaths were those aged 40-49 (ONS, 2023). As expected, the age group with the highest number of reports associated with the selected PTs were 18-64 years, contributing 14766 (68%) of reports. Worryingly, 1772 reports were from children under 18 (8%), with 893 (4%) reports from those aged 0-11 years. It is unknown how these children gained these drugs and whether exposure was accidental or intentional. Various physiological differences between children and adults lead to significant variations in pharmacokinetics and pharmacodynamics, including gastric pH, first-pass metabolism, renal clearance, protein binding, protein concentration, and enzyme activities (Garg et al., 2021). The ONS (2023) reported 2734 drug poisonings from the years 1993-2022 for those aged under 20, with 1562 (57%) of these reports being classified as drug misuse.

‘Overdose’ emerged as the most common reaction reported, with 8647 reports (16%), suggesting a clinical public health concern associated with increasing misuse of these products. The high overdose rates could be linked to the potency of these medications, as drugs approved for animals will be tailored to their differing pharmacology. For example, carfentanil and phenylbutazone, two veterinary-only products, received 15 and 12 overdose reports, respectively. Carfentanil lacks approved medical applications in human healthcare settings. Its reported cases of overdose may stem from the considerable challenge of accurately dosing the substance (Jalal & Burke, 2020). Additionally, limited data on appropriate dosage schedules and abuse potential contribute to the ambiguity surrounding its usage (EUDA, 2018). Overdose emerged as the predominant report for phenylbutazone, possibly due to its toxic properties, leading to it being discontinued from human use after reports of death (CFSRE, 2023a).

A higher percentage of reports coming from healthcare professionals (53%) indicates these drugs could have a higher risk, requiring medical intervention. Consumer reports may be slightly lower due to multiple reasons. Individuals who frequently misuse drugs or have SUDs may have acquired them illegally, leading to a reluctance to report AEs out of fear of legal repercussions, this fear potentially acts as a deterrence to engage with formal reporting systems. Additionally, they may be hesitant to disclose information about their history of drug use, further reducing their likelihood of reporting AEs.

The prevalence of hospitalisation as the highest outcome underscores the severity of the harms and risks associated with veterinary medication. The high rate of hospitalisation (44%) suggests these drugs have a high toxicity profile which could be due to the differences in dosing between human and animal medicine, as well as differences in metabolism and tolerance. Certain veterinary medications, which are also approved for humans, may vary in dosage. For instance, veterinary ketamine formulation can be ten times stronger than medicinal ketamine for humans (Cohen, 2024). For medicines approved for animals only, dosages can be increasingly more potent for human drugs within the same class, such as the differences in potency between carfentanil and morphine, with carfentanil being 10,000 more potent than morphine (Bever et al., 1976).

Worryingly, death was the second most reported event for the drugs included in this study, with 9566 reports (34%). Unfortunately, it remains uncertain whether these fatalities resulted from intentional or accidental actions, and the specific dosages involved are also unknown. Hospitalisation and death rates may also be associated with the increasing adulteration using veterinary medication. As adulteration increases, users are more exposed and are at increased risk of harm as they are ingesting multiple drugs that can have additive or synergistic effects. When xylazine is combined with fentanyl or other synthetic opioids, xylazine can increase the potential of fatal overdoses, due to increased respiratory depression (DEA, 2022). Adulteration of drugs using veterinary medication is increasing, where more potent drug

mixtures are being identified and illicit drug production in Europe continues to grow (EUDA, 2023a). Individuals struggling with drug addiction may resort to seeking more potent substances to fulfil their cravings, and turning to veterinary medications is the way drug manufacturers are targeting these problematic users.

3.4.3 Polysubstance Use

The simultaneous consumption of multiple drugs is a common behaviour among many drug users and was a trend observed within this study also. Polysubstance use disorder has been identified as a significant factor in the public health crisis of overdose toxicity (Pergolizzi Jr. et al., 2021), where it may be utilised to enhance a drug's effects, where additive or synergistic effects are often desired. Xylazine is infrequently found on its own and is rarely the primary purchase purpose of buyers (Spadaro et al., 2023); nonetheless, data has demonstrated that is becoming more common in drug samples as a co-detected drug. Recent data from the ACMD presented that 100% of xylazine detection in the UK also included other drugs of misuse, with most samples including more than six other drugs, including heroin, cocaine, bromazolam, fentanyl, ketamine, metonitazene, and protonitazene (ACMD, 2024). WEDINOS have received samples of xylazine from 2020, and since then they have received 48 samples, where 100% were not the buyer's purchase intent. Of these, 31 (65%) samples contained two or more other substances, including synthetic opioids (metnitazene) and designer benzodiazepines (bromazolam). Alarmingly, there were two cases of a THC vape containing xylazine (WEDINOS, 2024). The polysubstance use of xylazine with other drugs of misuse exacerbates the risk of overdose and fatalities, where increased CNS depression and respiratory depression are often observed. Moreover, the clandestine nature of xylazine's presence in drug samples, often without the knowledge of the user, can further complicate the diagnosis and understanding of a patient's conditions. While naloxone, an opioid antagonist, has been deemed ineffective in reversing the effects of xylazine (DEA, 2022), it is recommended for administration due to the frequent co-occurrence of xylazine with opioids (Ayub et al., 2023). However, recent research utilising rat models has reported xylazine to be a full kappa-opioid receptor agonist and was shown to be responsive to the antidote naloxone (Bedard et al., 2024). Although the polysubstance effect of xylazine's role in opioid-induced deaths is largely unknown, one report shows a connection between xylazine and opioid co-use and effects on brain oxygenation and brain temperature (Choi et al., 2023), implying that xylazine exacerbates the life-threatening effects of opioids by worsening brain hypoxia. Polysubstance use data in this study revealed that 90% (19/21) of drugs analysed had reports of concurrent use with common drugs of misuse, where BZDs/Z-drugs and opioids were the most popular. Interestingly, it was discovered that the veterinary drugs we examined were also co-used with other veterinary drugs included in this study. For example, there were reports of ketamine being used alongside dexmedetomidine, clenbuterol, phenobarbital, and pentobarbital. Additionally, pentobarbital was co-used with dexmedetomidine and there was one report of levamisole with carfentanil. Other common drugs of misuse were also commonly reported alongside

the drugs of interest, including cocaine, heroin, alprazolam, pregabalin, fentanyl, flunitrazepam, and etizolam. This high level of polysubstance misuse can directly relate to significant risks to drug users, where there are increased risks of overdose and severe medical complications. The increasing rate of using veterinary compounds as adulterants is of significant concern to public health as testing for these products is extremely limited, leading to treatment that is not precise and accurate for the patient's specific needs. This can lead to challenges in managing overdose events and underscores the importance of expanding testing capabilities and increasing awareness among healthcare providers about the emerging presence of veterinary products as adulterants. Notably, within this study, overdose emerged as the most prevalent reported reaction, further highlighting the urgency of these measures.

3.5 Limitations

While the findings of this study offer valuable insights into the misuse of veterinary medicines, there are limitations present that must be acknowledged. The FAERS database is a spontaneous reporting system that, despite its global reach inherently suffers from underreporting, incomplete case information, and potential bias towards the reporting of only severe or unexpected adverse events (Yin et al., 2022). Due to FAERS being a US-based database, the findings of this study cannot be generalised to regions outside of the US. It is also important to note that changes in reporting practices, such as increased awareness or regulatory changes, might lead to spikes in reports that do not necessarily correlate with actual increases in misuse or AEs. Other limitations of FAERS include the broad age range classification (18-64), which complicates the reporting and analysis of age-specific demographics, as well as the lack of detailed information on factors such as dosages and routes of administration. Due to FAERS being a human-based reporting system, data for specific drugs (e.g. medetomidine) were not available to analyse. The focus of the study was veterinary medicines, meaning formulations of drugs (e.g. intranasal ketamine) were also not included in the study. Specific statistical analysis, such as the ROR, could also not be conducted for this analysis due to the drugs' diverse classification across different drug classes. As the drugs belonged to varying drug groups, comparing their adverse event reporting frequencies may not yield meaningful results.

3.6 Conclusions

This descriptive pharmacovigilance study aimed at analysing the adverse event reports associated with drugs commonly used in veterinary medicine. The FDA database is a human-drug reporting system, therefore the reporting of AEs of animal-only medications is alarming and demonstrates an increasing misuse rate. This method of investigating veterinary drug use is important as instances of veterinary medication misuse remain largely underreported. This analysis reveals a rising trend of veterinary product misuse and its associated reporting, as indicated by the year 2023 accounting for approximately one-third of all reports for these products during the previous decade. Socio-demographic findings showed that overall, for all 21 drugs, females had a slightly higher number of reports than males, the

age group 18-64 demonstrated the highest number of total reports and healthcare professionals contributed to 53% of all reports. Hospitalisation was the most common outcome reported and non-serious outcomes only accounted for 5% of cases, although death was the most common outcome when observing animal-only products. Overdose was the most reported reaction overall, yet unmasking techniques of the drugs exclusively approved for animals only revealed that intentional overdose was the most reported reaction.

It is pivotal to draw attention to this emerging issue to ensure all healthcare professionals are equipped with the necessary knowledge to address the increasing utilisation of veterinary products. It is also crucial that drug users are aware of the risks associated with this type of drug consumption, particularly with the growing prevalence of adulteration involving veterinary products.

Chapter 4: From Veterinary Medicine to Illicit Drug Supply: Utilising Social Media to Explore the Rising Emergence of Veterinary Medicines in Human Health

4.1 Introduction

In 2022, England and Wales experienced the highest number of deaths related to drug poisoning since 1993, with an increased rate every year since 2012 (ONS, 2023). This growing issue could be attributed to the ever-growing drug market, targeting problematic users who are constantly chasing their next 'high'. As the drug market expands globally, scientific knowledge regarding the potency, purity, and combinations of drugs and their health impacts remains limited (EUDA, 2024a). In 2021, drug misuse in the veterinary setting was described as an 'under-recognised avenue', where veterinarians were represented to be often overlooked as a source of prescription drug misuse (Anad & Hosanagar, 2021). This oversight persists despite their ability to prescribe, administer, stock, and dispense drugs with misuse potential (Mason et al., 2018). Individuals with SUDs frequently attempt to acquire medications to satisfy their cravings, with reports of intentional pain inflicted on animals to obtain veterinary analgesics (Herzog, 2018). Accessing multiple prescriptions from various veterinary clinics (vet shopping) has been observed, where it has been documented that the number of patients obtaining any class of controlled substances from four or more veterinarians increased 3-fold between 2014 and 2019 (Chua et al., 2022).

Human misuse of veterinary medications is not a new topic, where reports of xylazine exposure in humans date back to the 1970s (Bradford et al., 2024). However, in the last few years, reports of this potent veterinary tranquilliser have proliferated, especially across the US where the South experienced a 193% increase in xylazine identifications from 2020 to 2021 (DEA, 2022). This trend of xylazine identification has recently emerged in the UK, where there was evidence of xylazine detections in sixteen people, including eleven fatalities (ACMD, 2024). Between May 2022 and August 2023, xylazine was frequently detected in the UK in combination with other drugs of misuse, including opioids (heroin, fentanyl), BZDs (bromazolam) and other drugs of misuse such as ketamine and pregabalin (ACMD, 2024). Although information regarding its misuse is relatively sparse in the UK, WEDINOS have identified over 50 samples where xylazine was identified from January 2020 to June 2024, with 100% of these samples including xylazine as a drug that was not the intended purchase (WEDINOS, 2024). For the first time, xylazine was also detected in two THC vape samples in the UK in 2022, highlighting its emergence and associated risks as an adulterant (WEDINOS, 2024). Medetomidine, a veterinary non-selective alpha-2-agonist like xylazine, has also been gaining recognition as an adulterant across the recreational opioid drug supply in the US. It is yet to be identified in the UK illicit supply (as of July 2024), yet it has been reported to be rapidly proliferating across the

USA and Canada in samples also containing heroin, fentanyl, xylazine, and cocaine (CFSRE, 2023c; Krotulski et al., 2024). Medetomidine's increasing prevalence is concerning due to it being a more potent, selective and specific a-2-agonist, exhibiting increased sedation compared to xylazine (Rioja et al., 2008). Alongside medetomidine, two other veterinary medications—acepromazine (a phenothiazine) and phenylbutazone (an NSAID)—were identified as potential toxic adulterants and predicted to be the "next xylazine" (CFSRE, 2023b). Although acepromazine reports remain relatively low, phenylbutazone has been identified in 116 seized drug samples between 2016-2021, alongside heroin, fentanyl, xylazine, tramadol, and cocaine (CFSRE, 2023a). Pentobarbital, a veterinary euthanasia agent, has also been detected in seized samples across the US (CFSRE, 2024a; CFSRE, 2024b), although it is classified as a Class B Schedule 3 drug. These five drugs' pharmacological profiles have made them valuable tools in veterinary medicine, yet it is these same properties that influence the dangerous outcomes in humans. The lack of control or scheduling of these drugs may contribute to their increased availability and prevalence, leading to their rise as adulterants in the illicit opioid supply.

Carfentanil is described as an ultrapotent, selective agonist of the μ-opioid receptor, with a potency 100x greater than fentanyl (Zawilska et al., 2021). In 2022, 14 countries reported seizing a total of 6.5 kg of carfentanil, accounting for 273 seizures across Europe (EUDA, 2024b). Although this represents a slight decrease from the 308 seizures reported in 2020 (EUDA, 2022), carfentanil misuse is believed to be underreported due to its exclusion from routine screenings and limited information on its abuse liability and dependence (EUDA, 2018a). Unlike other veterinary medications, carfentanil is scheduled under the Misuse of Drugs Act 1971 and the Misuse of Drugs Regulations 2001, as a Class A, Schedule 2 substance (United Kingdom, 2001). This classification demonstrates it is recognised as a drug with a high potential for harm and abuse in the UK. Nonetheless, due to its extreme potency and high risk of harm, it is crucial to allocate attention and effort to preventing cases of overdose.

Due to the relatively new emergence of these veterinary medications as adulterants, research needs to be conducted to gain novel and valuable information regarding their misuse and prevalence. This study aims to employ a social media listening method to retrieve real-life data of user's thoughts and experiences related to the selected drugs of interest.

4.2 Methodology

The social media platform Reddit has 52 million daily active users and over 138,000 active topical communities known as "subreddits" (Proferes et al., 2021), and was chosen to be analysed for this study. Reddit offers a unique opportunity for anonymous discussions, which is particularly valuable when researching sensitive topics such as drug misuse. Users can freely share experiences and advice without

the fear of stigma, a concern often present in face-to-face interviews or surveys. While traditional studies involving patients provide valuable insights, they are not always feasible or efficient for capturing the diverse perspectives and emergent trends seen in online communities. As such, Reddit serves as an accessible and rich data source for understanding contemporary issues in drug misuse. Although a netnographic study analysing veterinary drugs has never been conducted, prompts utilised for this analysis were adapted from previous research conducted on the topic of drug misuse (Arillotta et al., 2023).

4.2.1 Primary Data Search

Initial research was conducted to identify the main slang words for the drugs of interest (e.g. “tranq dope”), given the use of social media as a source of data collection. Reddit posts and comments were screened using the web-scraping software Apify (Apify, 2024) between June - July 2024. Specific search terms for each drug were included to retrieve optimal posts and comments, summarised in Table 4. All the boxes were ticked to allow the scraper to search for posts, comments, communities and users. The search included NSFW (not safe for work) content, which is content that refers to any explicit or inappropriate material, including topics related to drug misuse. The number entered for maximum post and comment count was set to 9999 to ensure all data was retrieved. Subreddits were not predefined; Apify collected all threads and comments containing the specified keywords without filtering for subreddit relevance. The collected raw data were imported into Microsoft Excel Spreadsheets (Version 16.86 (24060916)) via a function on Apify that enabled downloading the data as an Excel file. Inclusion and exclusion criteria for Reddit posts and comments are shown in Table 5.

Table 4 - Drugs and their associated keywords inputted into Apify

Drug	Keywords used in Apify
Xylazine	“xylazine”, “tranq”, “tranq dope”, “zombie drug”
Carfentanil	“carfentanil”, “carfentanyl”, “carf”, “wildnil”, “serial killer drug”, “drop dead drug”
Medetomidine	“medetomidine”
Phenylbutazone	“phenylbutazone”
Pentobarbital	“pentobarbital”
Acepromazine	“acepromazine”

Table 5 - Inclusion and exclusion criteria for Reddit posts

Inclusion Criteria	Exclusion Criteria
Posts and comments posted in English	Posts and comments posted in a language other than English
Posts and comments discussing the use/misuse of the specified veterinary products	Posts not related to the use/misuse of the specified veterinary drugs
Publicly available posts and comments	Posts and comments not publicly accessible
Posts and comments including information regarding the human consumption of the specific drugs	Posts and comments not including information regarding human consumption of the specific drugs
Posts and comments from any region, regardless of the user's age, gender, religion, or race (if this information was provided in the post or comment)	No exclusions based on these demographic factors
Posts and comments describing/discussing the dose/route/method of acquisition of the specified drugs	Posts and comments falling outside the inclusion criteria

4.2.2 Data Screening and Cleaning

The data cleaning and screening process were performed manually. Any posts or comments not containing the specific keywords were removed. Duplicate posts and comments were also removed using the 'remove duplicates' function on Excel. The remaining posts and comments were then screened for relevance to the research aims and any data that did not fit the inclusion criteria was removed. The data screening process was conducted by JD and regular discussions were held with supervisor AG to ensure consistency and agreement on the inclusion and exclusion criteria. Although specific keywords were entered into Apify for data collection, a review of the extracted dataset in Excel revealed duplicate entries, demonstrating a possible error with the Apify software, where these duplicates likely resulted from repeated instances of the same content. While specific keywords were used to retrieve posts and comments, Apify also captured posts where the comments contained these keywords, even if the posts themselves did not. This led to the inclusion of unrelated content, such as posts about war, as the keyword 'tranq' was often associated with guns in video games. As a result, additional filtering was required to exclude irrelevant posts and ensure that the dataset was accurate for the intended purpose of the study.

4.2.3 Data Analyses

For each of the selected keywords, the most prevalent themes identified were analysed manually. Themes were identified through an inductive approach, emerging naturally from the data rather than being predefined. A colour-coding method was utilised to distinguish between the various posts and comments within each theme. Any data that fell into multiple themes was included in each associated theme. A separate, manual search of Reddit posts and comments was also conducted to ensure Apify did not miss important data. This was performed by taking the keywords used in the scraping method and inputting them into the Reddit search bar. By analysing the most represented posts and comments on Reddit for relevance to the study, the posts and comments that met the inclusion criteria, and were not captured by Apify, were then incorporated into the study and put into their according themes. If a post or comment contained references to multiple drugs of interest, it was attributed to the drug that was specified as the keyword during the data retrieval in Apify.

4.2.4 Artificial Intelligence Analysis

In addition to conducting a manual thematic analysis, artificial intelligence (AI) tools were employed to enhance the analysis process, using the two programmes numerous.ai (Numerous.ai, 2024) and ChatGPT (ChatGPT, 2024). The AI method was integrated to minimise researcher bias during the manual thematic analysis (Mullin et al., 2024), and to act as a complementary method to provide an additional layer of validation. The extracted posts and comments for each drug were sampled in groups of ten on Google Sheets (Google Sheets, 2024). The following term was then inputted [=AI("Please act as an expert in qualitative content analysis with a focus on public health issues. Analyse the following text specifically for themes related to the misuse of drugs. Identify these themes and present them in bullet points. Also, consider any biases or contextual factors that may impact the analysis. Ensure that the analysis is conducted with sensitivity and neutrality.")]. The numerous.ai results were then exported into Windows NotePad (Microsoft, 2024) documents in preparation for the ChatGPT analysis. For accurate ChatGPT analysis, the themes created by numerous.ai were analysed by ChatGPT in groups of 20. The following term was inputted into ChatGPT ["I have a chunk of thematic analysis data for (drug name). Each post has several bullet points summarising themes and biases. Please analyse the following data and identify the top five most common themes and biases, ranked in order of prevalence."]. All ChatGPT responses were captured into a new Excel Spreadsheet for analysis.

4.2.5 Ethical Considerations

Ethical approval was not required for this study as all the Reddit data was publicly available, however, ethical considerations regarding the use of public data were adhered to in this study. The identity of the users remained anonymous throughout the entirety of the study with a focus on ensuring secure data handling and confidentiality. No attempts to identify or trace the users were made from the anonymous

data and only the data necessary for this research was extracted to respect user privacy. To minimise any potential impact on the users who wrote the extracted posts, no negative stereotypes or harmful generalisations will be concluded, thereby avoiding any stigma associated with drug misuse. Ethical approval for this study was granted by the Department of Pharmacy Ethics Committee at the University of Hertfordshire (protocol number aLMS/SF/UH/02951(5)).

Figure 8 represents a schematic flowchart that outlines the process of extracting the relevant posts and comments from Reddit.

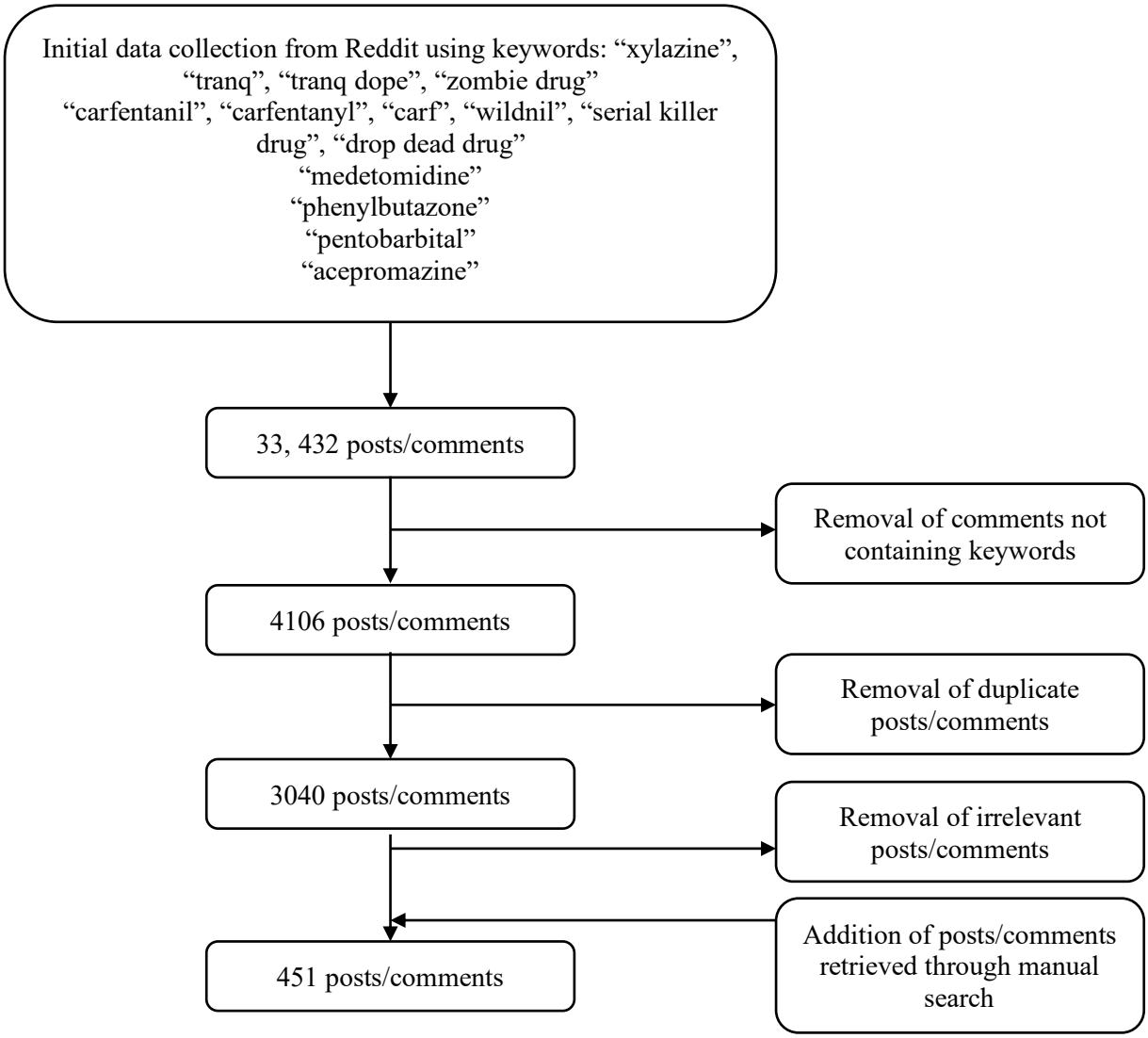

Figure 8 - A schematic flowchart outlining the data collection process of extracting posts and comments

4.3 Results

4.3.1 Manual Analysis

After the collected data was screened, 451 posts/comments were deemed relevant for this study. The keywords related to the drug xylazine gained the highest number of relevant posts and comments with 250 results after the data was cleaned and screened, followed by carfentanil (83 results), pentobarbital (82 results), medetomidine (24 results), phenylbutazone (six results) and acepromazine (six results). The most frequently discussed theme was 'motivations for misuse', accounting for 92 related posts and comments. This was followed by "public experience/perceptions", with 70 entries, and 'adverse effects', with 63. Discussions around 'route, dose, and appearance' had 51 posts, while both 'polysubstance misuse' and 'advice and support' were featured in 50. 'Education and awareness' received 45 mentions, 'method of acquisition' had 40, and 'seizures' appeared in only two posts.

Both positive and negative posts and comments regarding veterinary drugs were encountered, with users often demonstrating why they like misusing these drugs and the motivations behind their misuse. On the other hand, other Reddit users came to social media to display their worries and concerns about the growing trend of veterinary misuse. For example, a handful of positive xylazine-related posts included *"Yes I enjoy tranq"* and *"I prefer xylazine"*, with users describing the reasons for the rise in misuse due to *"tranq gives fent legs…it helps fent subjectively last longer",* with the longer high experienced making users *"feel more like you got your money's worth".* Carfentanil was described as *"the most euphoric substance",* with a user displaying a desire for the substance, stating, *"I need some of that carfentanyl right now".* Pentobarbital was described as *"pleasant and abusable"* and as a *"more intense high overall and lasted for a longer duration of time*", as well as *"the holy grail", "glorious"* and *"blissful".*

Conversely, comments such as *"evil"* and *"I hate tranq"* were used to describe xylazine. The term *"poison"* was also used to describe xylazine and medetomidine, although one user demonstrated a liking towards medetomidine, stating it was *"the best dope I've ever seen it had that met stuff in".* Despite the positive comments about pentobarbital, there were many posts and comments where users described their intentions for use as suicidal intentions (e.g. *"I want to get access to pentobarbital and sodium thiopental, to take it and die"),* where one user described it as *"the gold standard for a quick and painless suicide".* Whilst there were very few comments regarding the misuse of acepromazine and phenylbutazone, a user stated they misused phenylbutazone due to joint pain. The posts associated with the adverse effects of veterinary drugs were more commonly for xylazine and carfentanil, where xylazine was described to *"destroy any part of your body you put it into*" and carfentanil to make a user feel as if they *"should have been dead"* and having *"no idea how I'm still here".* Polysubstance misuse data was retrieved from the study for five of the six veterinary drugs, with various dangerous

combinations being identified. Xylazine was posted to be found in a sample with *"Lidocaine, Fentanyl, Tramadol, DXM, Niacinamide"* and *"Xanax and mdma"*. A harmful sample, named *"smurf dope"* was noted to include "*either methamphetamine or heroin that has been laced with fentanyl. Perhaps not just fentanyl but carfentanil"*. In addition to this, a different sample, *"Super Mario",* was described to contain *"xylazine, fentanyl, DPH, heroin, carfentanil"*. Different routes of administration were encountered in the study, including intravenous (I.V.) (carfentanil, xylazine), insufflation (xylazine), inhalation (xylazine), and oral ingestion (xylazine, pentobarbital).

Table 6 provides a summary of selected posts and comments with their corresponding drug and theme chosen. The brand name for pentobarbital, Nembutal, was often used by users on Reddit when discussing pentobarbital, despite it not being a keyword used in the data collection. It is important to note that Table 6 may include spelling errors and informal language, reflecting its social media origin.

4.3.2 AI-Driven Thematic Analysis

The two AI software's, Numerous.ai and ChatGPT, were utilised to obtain the top occurring themes for each veterinary drug. Each drug was analysed independently and the top five themes for each drug are summarised in Table 7. Although Numerous.ai applied filters to remove content related to suicide or promoting drug use, some relevant posts remained in the dataset, such as those associated with the suicidal intent of using pentobarbital.

Table 6 - The themes identified through the manual analysis of the veterinary drugs

	1. Motivation for Misuse
Xylazine	*e.g., "(…) so you get that shouldn't be injected in humans constantly, like a drug addict does, that is extrememly cheap and easy to source"*
	e.g., "Fent and xylazine are wayyyy cheaper to produce and have flooded the US from China"
	e.g., "And people are doing it purposefully. "Tranq gives fent legs," it helps fent subjectively "last longer" as heroin users switch to fent, which has a shorter half life."
	e.g., "Fent high is significantly shorter than heroin. The xylazine cut extends that high so you don't have to keep hustling non-stop. Ultimately, it is more profitable because it is more popular."
	e.g., "(…) You get the brief window of being high from the fent, then you stay zoned out for hours later like a zombie from the Xylazine. No real high, you're just incredibly tranquilized, but you feel more like you got your money's worth"

	e.g., "Yes I enjoy tranq"
	e.g., "It's get too a point where even pure fentanyl doesn't do nothing too you so I just look at tranq as the next step if you wanna still get high so yea I enjoy it now I just tell my dealer don't put too much or I buy it separately and do small portions I'm in the tranq capital btw."
	e.g., "Dealers are lacing the fentanyl with xylazine nowadays. It makes the user nod harder, so they end up thinking the dope is really strong and will buy from them again"
	e.g., "(...) dealers who are now selling tranq as a stand alone drug because so many people are addicted to it that they are requesting it"
	e.g., "I've always wanted to try xylazine on its own"
	e.g., "(...) And tbh....I prefer xylazine....whe asking what stamp is hot on the bloxk...i ask for heavy trank. The shots I did which I believe were mostly trank (xylazine) it was like ketamine...."
Carfentanil	*e.g., "(...) I was looking for Carfentanil because it is very potent, and small doses can be used"*
	e.g., "(...) apart from the fact that I am violently addicted to injecting heron cut with carfent but it's basically a plant so it doesn't really affect me in any bad way"
	e.g., "(...) Carfentanyl alone is shit just like regular fentanyl. It just knocks you out with no euphoria. That's why I mix it with regular H. So I can feel it.."
	e.g., "Carfentanyl is the most euphoric substance I have ever had. You haven't had carfentanyl in your possession if you claim it knocks you out without euphoria. I had highly pure carfentanyl oxolate. Carfent alone is good shit…"
	e.g., "I need some of that carfentanyl right now."
Medetomidine	*e.g., "Dope is now being found with medetomidine which is similar to xylazine. I guess now that states are banning xylazine they have now switched to this crap."*
Pentobarbital	*e.g., "(...) a study in 2020 found that 47% of the vet suicides they looked at in the US used poisoning as the method and more than half of them were attributed to pentobarbital"*
	e.g., "(...) I've been looking into pentobarbital as a method of finally putting myself out of my misery, but it's damn near impossible to find"
	e.g., "(...) Pentobarbital is considered to be more pleasent and abuseable."
	e.g., "Some people would be willing to pay thousands of dollars for a bottle of pentobarbital. It's the gold standard for a quick and painless suicide."

Phenylbutazone	*e.g., "(…) My joints are in a lot of pain and I have to wait over 3 months for an appointment with a doctor. In the meantime I'm not sure how I'm alive because I've been overdosing myself with Tylenol and Advil. (Please don't think I'm crazy but I've also taken phenylbutazone which is not available to humans it's a horse med)"*
	2. Personal Experiences/Public Perception
Xylazine	*e.g., "(…) Xylazine is, and I rarely use this word, evil."*
	e.g., "That's all there is out in my area anymore fentanyl cut with tranq ...I hate tranq"
	e.g., "(…) And you'll KNOW when you get regular fetty once you're addicted to tranq because you will go into the WORST withdrawal of your LIFE in no time.. xylazine sickness cold turkey is the worst thing I have ever been thru in my 29 years"
	e.g., "(…) xylazine should NEVER be in the human body, and the withdrawals it causes last weeks and are the worst thing I've ever been through in my life"
	e.g., "The withdrawal for Trang aka xylazine is horrendous I speak from experience. It is the worst thing I ever went through"
Carfentanil	*e.g., "I thought carfent was stronger than fent ive overdosed on both"*
	e.g., "(…) I've come to the conclusion that a lot of the strong shit I've been getting lately has been partly or entirely carfentanil. Tastes basically the same as regular fetty but is way stronger. I've asked dealers their opinions and they've agreed"
Medetomidine	*e.g., "(…) Medetomidine can cause some side effects that are alot worse then xylazine. They are still both poison though."*
	e.g., "Medetomidine is just a anesthestic/analgesic it's not that dangerous unless you're a drug addict taking random cocktails"
	e.g., "(…) I had a sample tested but ironicslly it was like THE BEST dope I've ever seen it had that met stuff in"
Pentobarbital	*e.g., "Only experience ive had is with pentobarbital, and yea, it sucked."*
	e.g., "(…) Pentobarbital is a slightly more intense high overall and lasted for a longer duration of time too"
	e.g., "As someone who has used both, phenobarbital is SHIT and pentobarbital is the holy grail"
	e.g., "(…) i want to try pentobarbital once in my lifetime"
	e.g., "(…) pure Pentobarbital is absolutely blissful, I had the chance to try it one year ago"

	e.g., "Pentobarbital is beyond awesome. Have fun"
	e.g., "I happen to love the way Pentobarbital (Nembutal) makes me feel. I take prescribed Xanax multiple times a day. Nembutal hits hard and fast you will feel and seem basically drunk but with a tingly body and complete relaxation"
	e.g., "Honestly I loved pentobarbital way to much I would take it and just flat out cold pass out for 4 hours straight"
	e.g., "I tried new veterianry pentobarb and it was GLORIOUS…it felt like the best benzo body high one could get, very warm and super anxiolytic-confidence boosting effects. As for the negative side, it was just too addictive, as soon as I got it I began using every day..."
	3. Adverse Effects
Xylazine	*e.g., "(…) I'm still dealing with blisters and tissue damage in my nose and throat. Pretty sure it fucked my molars up too. Stuff is a poison and will destroy any part of your body you put it into"*
	e.g., "(…) And traq wds can kill now with the dehydration and insane blood pressure and irregular heart beats this shit causes."
	e.g., "(…) that's another thing the tranq makes me have vivid lucid dreams even nightmares like really weird sleep paralysis too sometimes"
	e.g., "My mom nearly lost her whole entire leg due to xylazine. She has had several grafts. It has taken nearly two years to get to a stable healing point. It had also started eating holes in her heart. She is very lucky to have survived through all of it and it's because she got and stayed sober. If it doesn't cause an OD it WILL eventually cause severe health issues."
	e.g., "(…) the tranq is making their bodies shut down; slow breathing, lethargy, low heart rate, but they're resisting the natural urge to sleep in that state because going to sleep wastes the high. So they stand there, barely awake, while their whole bodies shuts down, fighting the urge to nod out"
	e.g., "(…) Could never breathe out of my nose, and it was always hitting, and bleeding. Even after I stopped, it took months for my nose to heal, and it's still not as open as it was before."
Carfentanil	*e.g., "Carfentanil had me literally hallucinating/tripping. Almost like fever dreams where you're nodded and just seeing the craziest shit."*
	e.g., "I was doing these bags before it hit the news. They literally knocked me out."
	4. Route/Dose/Appearance

Xylazine	*e.g., "(...) I smoked my tranq and i ended up having a bunch of black sludge come out of my lungs."*
	e.g., "Well I'm trying to snort it I've snorted it twice today but people are scaring me cuz it can fuck their nose"
	e.g., "Can xylazine cause those sores if you don't shoot, smoke or sniff? The only consumption method I use is orally."
	e.g., "(...) I was only snorting it, and it still decided to eat my legs up!"
	e.g., "Xylazine is only "flesh eating" if injected. It can be reltively safely taken orally to taper but it's almost impossible to determine what dose you'd need without knowing how much was in your dope."
Carfentanil	*e.g., "A few micrograms of carfentanil will help."*
	e.g., "Was surprised to learn that carfentanil is the safest opiate there is, since the multiple of a therapeutic dose needed for an overdose is so high. So, if you can accurately measure it, you'd need to 'accidentally' put like 5 times the amount you planned into someone to cause OD."
	e.g., "I smoke about 2 grams of street fentanyl daily but I hate the way carfentanyl taste but I would start at about a tenth of gram daily"
Medetomidine	*e.g., "(...) I've been slowly increasing my doses and I'm up to a little over 100mcg"*
Pentobarbital	*e.g., "Do it orally if you do 200mg is a very nice dose"*
	e.g., "(...) 75-150mg Pentobarbital is quite nice orally with onset at 35min, peak hits at 40 -45 min."
	e.g., "I feel that oral route would be risky as first pass metabolism is really unpredictable. It would feel like a slow death. IV pentobarbital would be quick and easy."
	e.g., "If I had had access to more I would definitely have used them every day in high quantities"
	5. Polysubstance use
Xylazine	*e.g., "(...) Lab analysis showed: Lidocaine, Fentanyl, Tramadol, DXM, Niacinamide, Xylazine Experience Note: 'Knocked out in one minute, \[non-fatal\] overdose'"*
	e.g., "Yea, my last near fatal OD the dope did not only have xylazine in it, it also had carfentanil in it and two other fentanyl analogues that were all several times more potent than just actual fentanyl. As If just straight fentanyl wasn't already way too potent itself. It did however contain some amount of

	diacetylmorphine (actual heroin) in it also. Cocaine too which boggles my mind"
	e.g., "(...) Also when I toom drug test I came up for fetty tranq Xanax and mdma. All I was doing was the fetty powder. Stuffs horrible"
	e.g., "(...) When you mix xlazine with opiates like heroin or fentanyl they work together (synergize) and make the user feel much, much higher. The mixture makes people act and look just like zombies."
	e.g., "What would happen if xylazine and K2 Spice was mixed, put into a vape pen and smoked?"
	e.g., "Has anyone done tranq-dope with mdma? Any side effects? I want to take molly for new years but I do tranq-dope and idk if that's gonna cause bad side effects. Has anyone done it and how was your experience?"
Carfentanil	*e.g., "(...) It doesn't do anything but that's because I was doing fentanyl, xylazine and "trace amounts" of heroin and carfentanil."*
	e.g.," i overdosed on laced xanax and my pee tested positive for carfentanil"
	e.g., "(...) SMURF DOPE :"It has vibrant blue color. Either methamphetamine or heroin that has been laced with fentanyl. Perhaps not just fentanyl but carfentanil," said Brad Brewer, a Harm Reduction Specialist with the Kentucky River District Health Department."
	e.g., "My very last near fatal OD, and the last time I used, was in mid 2019. I bought it as "heroin" supposedly but of course I knew better. Once what I had left of that bag was tested it came out to be, in this order, furanylfentanyl, Acrylfentanyl, Carfentanil, Remifentanil, diacetylmorphine (acetylated morphine) 4-ANPP, cocaine, xylazine, and mannitol."
	e.g., "Carfentanyl + clonazolam should do the trick."
	e.g., "Drug users of Reddit, what is the shrooms and carfentanil combo like?"
	e.g., "NY Public Health Alert: "Super Mario" stamped bags contain xylazine, fentanyl, DPH, heroin, carfentanil"
Medetomidine	*e.g., "Sample came back from lab as xylazine/fent/medetomidine"*
	e.g., "mixing a dangerous chemical sedative called medetomidine into fentanyl"
	e.g., "(...) they found she had butorphanol, azaperone, and medetomidine in her system."
	e.g., "Dope is now being found with medetomidine which is similar to xylazine. I guess now that states are banning xylazine they have now switched to this crap"

Pentobarbital	*e.g., "(…) Pentobarbital is one of the least cyp inducing barbiturates as apposed to Seconal for instance. That's why it was perfect to mix Nembutal and Codeine together."*
	e.g., "I need: a powerful sedative, a neuromuscular blocker, a potassium ion-donating agent. For the sedative I could use fentanyl or pentobarbital + tramadol mix."
Acepromazine	*e.g., "What I want to know is if I took 4.8 g propranolol, 60 mg acepromazine, 8g trazodone and weed as an antiemetic would I die? And how painful would it be?"*
	6. Advice/Support
Xylazine	*e.g., "I'm developing gross, necrotic-looking, very, very itchy xylazine ulcers all over my legs. More so, in injection sites where a "miss" took place. My skin itches like crazy, flakes, and these lesions form. Anyone else experience this phenomenon?"*
	e.g., "Yes I know this is a fent group but idk where else to ask… I only hear bad things about tranq… No euphoria, skin lesions, blacking out, horrible withdrawals… does anyone actually like tranq dope and actively search it out???"
	e.g., "I swear everything in my area and surrounding areas is flooded and I mean FLOODED with nasty tranq dope ! And I mean I hate it like to the point where I really don't wanna get high anymore. It's such a unenjoyable high. Anyone else feel like this ?"
	e.g., "I just came into possession of a bottle of xylazine and I was wondering how mich I load into a syringe for a nice, regular experience?"
Carfentanil	*e.g., "I was addicted to IV carfentanil, so I would totally use it, however I recommend you have a tolerance first!"*
	e.g., "(…) so if ur gonna reduce the ham, you need to provide alternatives, like carfentanyl, which has been proven to not be addictive and also cure cancer and hiv. so stop with the weed, and reduce ham"
	e.g., "I wonder if carfentanil (trace) would be deadly. I have no idea how much "trace" is."
Pentobarbital	*e.g., "any information on these and what to expect? (pentobarbital)"*
	e.g., "You're right, I think pentobarbital would do the trick!"
Phenylbutazone	*e.g., "Toxic dose phenylbutazone What would a toxic dose of bute be? Also what would be symptoms and treatment in a human? Just curious"*

	e.g., "I was wondering what does a horse drug such as phenylbutazone aka "bute" or also called equipalazone do if a human were to consume it? Would it also relive pain, is it harmful, what would the negative effects be? How much should be consumed?"
Acepromazine	*e.g., "Has anyone here ever taken their dog's or cat's acepromazine?"*
	e.g., "Can I take Acepromazine? So I recently ran into a couple of 25mg pills of acepromazine…just want to know how much/if I can take these! Any advice helps."
	7. Awareness/Education
Xylazine	*e.g., (…) Once using regularly the odds of fatality exponentially increase due to OD, open sores causing infections, or related complications such as malnutrition/dehydration that occur with substance abuse. There is no "safe" dose of this approved for human comsumption.*
	e.g., (…) High doses cause individuals to become nonresponsive via a shutdown of the CNS and overdoses can be fatal. It does NOT respond to narcan. They are, however, producing xylazine test strips that I highly recommend any users purchase or get ahold of. Many community harm reduction groups are giving them out as well. Please, guys, test your supply every time.
	e.g., The ease of access to Fentanyl and its analogs, along with xylazine, is truly alarming…why isnt this a global issue?
	e.g., Xylazine is not safe
	e.g., Fake tranq accords going around the UK….my friend bought 100 boxes of what appeared to be accord codeine phosphates….i was having weird hallucinations and felt incredibly weird and sleepy….i sent them to a lab to get tested and got xylazine test strips...they were just xylazine and nothing else.
Carfentanil	*e.g., I live in Cuyahoga county now, but just a heads up that carfentanil is making a comeback out our way. If you know anyone doing any type of hard drugs, please encourage them to at least get a test kit for their stuff.*
	e.g., Also trace amount of carfent lol which I'm surprised to be popping back up after 5yrs
	e.g., (…) but there have actually been a lot of reports coming up for carfent again, surprisingly.
Medetomidine	*e.g., (…) Experts say the chemical, mixed into counterfeit pills and powders sold on the street, slows the human heart rate to dangerous levels. It's impossible for drug users to detect*

	e.g., (...) The one they're warning about now is fentanyl cut with medetomidine, which is a surgical analgesic. Different, but still devastating.
	e.g., "PINK FENTANYL" *Batches are popping up all around Ohio! - A Chunky Powdery substance, likely colored in some variation of Pink & thought to be packaged in paper.* *Altho... Contains little to no Fentanyl.* *Suspected to be a *Veterinary anesthetic|sedative substance combo*.* *Known as *Xylazine|Medetomidine*. With **severe** side effects!*
	8. Method of Acquisition
Xylazine	*e.g., Do you know where I can find it any serious people hit me up I am overseas looking for xylazine*
	e.g., You can buy a lot of large animal drugs online, from catalogues, and in feed stores - including xylazine. It's actually kinda horrifying how many prescription drugs you can just buy in feed stores without a prescription.
	e.g., Where and how to obtain xylazine? Looking for info on how to obtain tranq
	e.g., Willing to pay high in the five figures to a clandestine chemist that can produce xylazine
Carfentanil	*e.g., Was it like really pure shit? Where do u even find carfentanil at Darkweb*
	e.g., (...) I was looking on the darknet some days ago and I came across the listing on a market of "Carfentanil pure powder" 50g for 1000$, I messaged the seller and he said that he can send me 1 g for 50$ or 3 for 90$.
	e.g., Where does one get this carfentanil or fentanyl stuff?
Pentobarbital	*e.g., Honestly, I'm SO jelous of everyone who got Pentobarbital. Despite I generally cheer for people.Those who managed to get it and don't use it ...* *LET ME BUY IT FROM YOU AND USE IT MYSELF.*
	e.g., (...) I'm thinking of ordering pentobarbital, the drug they used on him, online.
	e.g., I just want a place where I can get pentobarbital delivered that's all
	e.g., (...) These popular media reports of pentobarbital being a peaceful method of suicide have led to increased interest in obtaining it from jurisdictions where it is less regulated.
	e.g., Is pentobarbital available for purchase from pet stores in Tijuana? If not where should I look?
	e.g., (...) I'd like to know how to get my hands on some Pentobarbital.
	e.g., (...) Mypeacefulend.com are the leading supplier of nembutal and other barbiturates online.

	9. Seizures
Carfentanil	*e.g., A dealer in drugs and guns sentenced to 20 years after the country's largest seizure of the deadly drug carfentanil has been granted bail by a judge of Ontario's highest court, pending an appeal. Maisum Ansari was convicted in February of possession for the purpose of trafficking after police seized 33 firearms and 26.5 kilograms of carfentanil from a basement apartment he owned.*
Phenylbutazone:	*e.g., (…) In a review of case data from NMS Labs from 2016-2021, 116 seized drug samples from Pennsylvania were identified as containing phenylbutazone.*

Table 7 - The top 5 themes identified through the AI-driven analysis

Drug	**Top 5 Occurring Themes**	**Post Examples**
Xylazine	1. Negative Health Effects/ Consequences 2. Poly Substance Use 3. Public Health Concerns 4. Addiction/ Withdrawal/ Dependence 5. Public Perception/ Experiences	1. *e.g., "(...) It's primarily the Xylazine that causes these people to sleep on the sidewalk or walk about in a stupor, the Xylazine is also responsible for the horrendous skin abscesses that rapidly progress into full blown infections often leading to amputation."* 2. *e.g., " (...) My mom nearly lost her whole entire leg due to xylazine. She has had several grafts. It has taken nearly two years to get to a stable healing point. It had also started eating holes in her heart."* 3. *e.g., "(...) we found out later it was meth, xylazine, and fentanyl"* 4. *e.g., "(...) it's causing homelessness, open drug use in some parts of Philly, and a huge public health issue with all the physically damaging effects of the drug"* 5. *e.g., "(...) These things that are flooding the streets scare me more than coke or heroin: this is going to be devastating."* 6. *e.g., "(...) The problem is how fucking bad you feel when you aren't, so you keep chasing just desperately trying to escape how shit you feel when you're off the crap."* 7. *e.g., "(...) xylazine should NEVER be in the human body, and the withdrawals it causes last weeks and are the worst thing I've ever been through in my life"* 8. *e.g., "I'm developing gross, necrotic-looking, very, very itchy xylazine ulcers all over my legs. More so, in injection sites where a "miss" took place. My skin itches like crazy, flakes, and these lesions form. Anyone else experience this phenomenon?"*
Carfentanil	1. Drug Misuse 2. Potency 3. Personal Experiences	1. *e.g., "I was doing these bags before it hit the news. They literally knocked me out."*

	4. Public Health Concerns 5. Poly Substance Use	2. *e.g., "I was looking for Carfentanil because it is very potent, and small doses can be used and because it had been studied pretty well"* 3. *e.g., "Got carfentanyl thinking it was regular fentanyl. Just told it was stronger. Woke up hours later without being narcanned somehow because I was alone. I should have been dead. No idea how I'm still here."* 4. *e.g., "Didn't know carfent was being found more frequently as of recently."* 5. *e.g., "(...)SMURF DOPE: "It has vibrant blue color. Either methamphetamine or heroin that has been laced with fentanyl. Perhaps not just fentanyl but carfentanil""*
Medetomidine	1. Misuse of Medetomidine 2. Public Health Concerns 3. Lack of Antidote or Detection 4. Poly Substance Use 5. Need for Awareness and Education	1. *e.g., "(...) have personally used both substances and even though they are both alpha 2 drugs the side effects greatly vary but of course they do have some similar side effects. Medetomidine can cause some side effects that are alot worse then xylazine."* 2. *e.g., "Dope is now being found with medetomidine which is similar to xylazine. I guess now that states are banning xylazine they have now switched to this crap"* 3. *e.g., "(...) Experts say the chemical, mixed into counterfeit pills and powders sold on the street, slows the human heart rate to dangerous levels. It's impossible for drug users to detect."*" 4. *e.g.," (...) The sedative was found in combination with opioids such as fentanyl, nitazenes and heroin, as well as with tranq and the anti-anxiety drug alprazolam (Xanax)."* 5. *e.g., "(...) no one knows what long-term health effects this new cocktail of chemicals will cause in the human body."*
Pentobarbital	1. Motivations for Misuse 2. Personal Experiences	1. *e.g., "(...) a study in 2020 found that 47% of the vet suicides they looked at in the US used poisoning as the method and more than half of them were attributed to pentobarbital"*

	3. Acquisition of Drugs 4. Poly Substance Use 5. Public Perception	*e.g., "I want to get access to pentobarbital and sodium thiopental, to take it and die."* 2. *e.g., "(...) pure Pentobarbital is absolutely blissful, I had the chance to try it"* *e.g., "I tried new veterianry pentobarb and it was GLORIOUS…it felt like the best benzo body high one could get, very warm and super anxiolytic-confidence boosting effects. As for the negative side, it was just too addictive, as soon as I got it I began using every day"* 3. *e.g., "Lots of people find ways to buy pentobarbital online and they use that as a "softer" means to end their life."* *e.g., "I need help. I need to order 12ml of pentobarbital. I would consider the darknet but idk how to trust what i get. Anyone know of a serious supplier? Thanks in advance."* 4. *e.g., "(...) I'm thinking of trying to go to Tijuana and getting pentobarbital and maybe Xanax and heroin too"* 5. *e.g., "Pentobarbital these days is pretty popular among those with terminal illness"*
Phenylbutazone	1. Toxicity and Adulteration 2. Misuse of Phenylbutazone 3. Comparative Analysis with Other Drugs 4. Curiosity and Inquiry into Drug Effects 5. Potential Damage and Health Implications	1. *e.g., "(...) 116 seized drug samples from Pennsylvania were identified as containing phenylbutazone"* 2. *e.g., "(...) I've also taken phenylbutazone which is not available to humans* 3. *Simple google search shows phenylbutazone is not good for humans. Ketamine should not be referred to as a horse drug as it is widely and regularly used in human medicine."* 4. *e.g., "I was wondering what does a horse drug such as phenylbutazone aka "bute" or also called equipalazone do if a human were to consume it? Would it also relive pain, is it harmful, what would the negative effects be? How much should be consumed?"*

		5. *e.g., "(...) The serious adverse effects of phenylbutazone can include gastrointestinal bleeding, liver and kidney damage, and blood disorders"*
Acepromazine	1. Misuse of Veterinary Drugs 2. Polysubstance Use 3. Mental Health and Suicidal Ideation 4. Lack of Knowledge and Uncertainty About Safe Drug Use 5. Negative Health Impacts	1. *e.g., "Has anyone here ever taken their dog's or cat's acepromazine?"* 2. *e.g., "What I want to know is if I took 4.8 g propranolol, 60 mg acepromazine, 8g trazodone and weed as an antiemetic would I die?"* 3. *e.g., "What I want to know is if I took 4.8 g propranolol, 60 mg acepromazine, 8g trazodone and weed as an antiemetic would I die?"* 4. *e.g., "Can I take Acepromazine? So I recently ran into a couple of 25mg pills of acepromazine…just want to know how much/if I can take these! Any advice helps."* 5. *e.g., "(...) It can cause significant organ damage in humans."*

4.4 Discussion

To the best of our knowledge, this is the first article utilising social media as a source of novel information concerning the rising emergence of veterinary drugs in human health. Leveraging specific AI techniques, a thematic analysis was conducted to explore the most common themes related to veterinary drug misuse in Reddit discussions. Xylazine, carfentanil, medetomidine, pentobarbital, phenylbutazone, and acepromazine were chosen to investigate based on prior work (Dunn et al., 2024 *(in press)*), where these specific veterinary drugs were found to be emerging threats to public health.

Of the six drugs analysed in this study, only two (carfentanil and pentobarbital) are listed as controlled drugs in the United Kingdom (United Kingdom, 2001), leaving xylazine, medetomidine, phenylbutazone, and acepromazine uncontrolled and unregulated. Despite xylazine being identified as a public health threat in the UK due to its penetration in the illicit drug market (Copeland et al., 2024), regulatory measures for this veterinary medicine have yet to be established. There were 35 cases of xylazine detection in the UK by the end of August 2023, through different measures of toxicology, drug screening, and drug seizure techniques (Copeland et al., 2024), with 11 reports of fatality (ACMD, 2024). In the US, xylazine detection is still increasing, where xylazine was the most frequently detected adulterant found with a positivity rate of 15.8%, nearly double what it was in the previous data round collection (8%) in 2018 (CFSRE, 2024c). Despite the lack of evidence of medetomidine misuse in the

UK, its emergence in the US has raised concerns among healthcare professionals. In May 2024, a public alert was issued due to the rising number of hospitalisations and overdose events incidents (Krotulski et al., 2024). Here, medetomidine was identified across several states and has been found alongside fentanyl and xylazine, as well as heroin, in the absence of xylazine. Similar to xylazine, medetomidine misuse is likely under-represented due to a lack of testing and effective detection techniques. Phenylbutazone, an NSAID, has been a recognised adulterant in seized drug material, where 116 seized drug samples from Pennsylvania were identified (CFSRE, 2023a) alongside heroin, fentanyl, xylazine, and cocaine. Acepromazine, commonly used in veterinary medicine for pre-medication anaesthesia, was recognised by the CFSRE when predicting the next xylazine, where it was noted that monitoring is crucial due to it being uncontrolled and widely available (CFSRE, 2023b). Pentobarbital is a veterinary barbiturate medicine often used for animal euthanasia and is currently a Class B Schedule 3 drug. Despite low reports of adulteration, it is still noteworthy that it is identified in seized counterfeit tablets in the US. Between 2020 and 2023, pentobarbital was identified in 1% of 1219 seized samples (CFSRE, 2024b). Regardless of the low identification percentage, this drug must be monitored due to its toxicity, where one gram of pentobarbital is considered a toxic dose (CFSRE, 2024b). Carfentanil, a potent synthetic opioid classified as a Class A Schedule 2 controlled drug, is used in veterinary medicine for tranquilising large animals and has no approved use in humans. There were 31 deaths attributed to carfentanil in the UK between February 2017 and June 2017, which aligns with the World Health Organisation's (WHO) recommendation that carfentanil be moved to the most stringent level of international control in 2017 (WHO, 2017).

Comparing both the manual analysis and AI-driven analysis, it is apparent that there are several recurring themes in social media discussions about the human misuse of veterinary medications. Both manual and AI analyses identified themes such as the negative health effects of veterinary drugs, personal experiences with their use, polysubstance use, the routes of administration, doses and associated toxicities, as well as the motivations driving the misuse of these drugs.

The manual analysis categorised 451 posts and comments into nine distinct themes. This analysis demonstrates that the misuse of veterinary drugs is driven by various motivations, such as accessibility, cost, and desired effects, with users often sharing personal experiences, with the theme of 'motivations of misuse' and 'public perception/experiences' being the two most frequent themes, with 92 and 70 entries, respectively. Despite these motivations, a significant number of users report adverse effects (63 posts/comments), highlighting the risks associated with the misuse of veterinary products. Different routes of administration were encountered in the study with 51 posts/comments, including intravenous (I.V.) (carfentanil, xylazine), insufflation (xylazine), inhalation (xylazine), and oral ingestion (xylazine, pentobarbital).

Polysubstance misuse was represented by 50 posts and comments, demonstrating the risky behaviours of people who misuse drugs. This practice is particularly dangerous due to the heightened toxicity from drug interactions, additive and synergistic effects, and increased risk of severe health implications, such as respiratory depression. The posts and comments demonstrated that veterinary drugs are often used with other drugs of misuse, with one post displaying the misuse of pentobarbital with codeine, stating that *"it was perfect to mix Nembutal and Codeine together".* One user posted about a recent drug test result, where *"fetty tranq Xanax and mdma"* was identified.

Other posts that were analysed presented that users often took to Reddit to ask about specific combinations of veterinary drugs with other drugs of misuse, for example, *"What would happen if xylazine and K2 Spice was mixed, put into a vape pen and smoked?"* and *"what is the shrooms and carfentanil combo like?".* In addition to this, polysubstance misuse with veterinary drugs and other veterinary drugs was apparent. This type of polysubstance misuse was mainly due to drug adulteration, where posts demonstrated xylazine, fentanyl and medetomidine, as well as the "*Super Mario"* mixture, containing xylazine, fentanyl, diphenhydramine, heroin, and carfentanil.

The posts and comments of users seeking advice and support related to veterinary drug misuse could suggest a lack of resources or medical guidance for these specific products, leading them to seek help from online communities instead. The substantial number of posts related to the themes of 'education/awareness' (45 posts) and 'method of acquisition' (40 posts) suggests that users are leveraging social media to both inform others about emerging dangerous drugs and to discuss new public health concerns. However, a drawback of social media in the context of drug misuse is that it also allows users to anonymously seek information on how and where to obtain these drugs.

4.4.1 Xylazine

The analysis of social media posts and comments surrounding xylazine misuse yielded insightful themes, both from the manual and AI-driven thematic analysis. The manual analysis highlighted that the most prevalent theme, with 59 mentions, was 'motivations for misuse'. Users frequently cited the affordability and accessibility of xylazine, with comments describing it as *"extremely cheap and easy to source"* and *"way cheaper to produce"*. Additionally, users noted that combining xylazine with fentanyl ("tranq") was popular due to the way xylazine extends the effects of fentanyl, described as giving the *"fent legs"* or making the high last longer. This combination was seen as providing better value for money and increasing dealer profits, with one user commenting that it makes the drug appear stronger, encouraging repeat purchases. Despite some positive posts regarding xylazine, such as *"yes, I enjoy tranq"* and *"I prefer tranq*", the majority of experiences shared were negative, with xylazine being labelled as *"evil"* and *"poison".*

The AI-driven analysis of xylazine-related posts complements these findings by identifying that negative health effects were the most common theme, reflecting the adverse effects reported in the manual analysis. Users frequently discussed the severe withdrawal symptoms and graphic descriptions of xylazine-associated wounds. Extensive tissue damage and physical harm, including tissue destruction in the nose and throat, amputations, and severely infected wounds were reported.

Withdrawal of xylazine was a frequently discussed topic, with users often sharing their negative experiences. It was described as *"the worst withdrawal of your life", "the worst thing I've ever been through",* and *"near lethal".* The lack of effective treatments for xylazine withdrawal or long-term therapy for xylazine addiction (Papudesi et al., 2023) is particularly concerning, given the severe withdrawal symptoms reported by users. The AI analysis also identified polysubstance misuse as the second most frequently discussed theme, consistent with manual observations that xylazine was used alongside fentanyl, tramadol, carfentanil, heroin, alprazolam, cocaine, and methamphetamine. This aligns with reports of xylazine rarely being identified alone, where 100% of toxicology cases in the UK detected xylazine with other common drugs of misuse (Copeland et al., 2024). Although xylazine is rarely sought out intentionally (Spadaro et al., 2023), posts and comments reveal that some users actively seek to obtain it, with examples such as "*where and how to obtain xylazine? Looking for info on how to obtain tranq"* and *"I am overseas looking for xylazine".* Worryingly, users turned to social media for advice on how to use xylazine, indicating it remains a drug of choice. One user, for example, mentioned having *"just come into possession of a bottle of xylazine"* and sought guidance on *"how much to load into a syringe for a nice, regular experience."* Moreover, the AI analysis noted public health concerns as a significant theme, aligning with user posts describing xylazine *"a huge public health issue with all the physically damaging effects of the drug".* User testimonials on Reddit reveal both the allure and the dangers of xylazine, showing a stark contrast between its perceived benefits and the reality of its harmful impact. This discrepancy underscores the need for increased awareness and intervention to address the misuse of xylazine. The patterns observed in the discussions and experiences shared online emphasise the urgent need for targeted public health strategies and regulatory measures to mitigate the harmful effects of xylazine.

4.4.2 Carfentanil

The two analyses for carfentanil yielded slightly different results, with the manual analysis having the most prevalent theme with polysubstance misuse (20 posts/comments), followed by discussions on routes/dosages (14 posts/comments), and advice/support (11 posts/comments). In contrast, the AI analysis identified the misuse of carfentanil as the most common theme, with potency and personal experiences being the next most frequently discussed topics. Both analyses identified polysubstance misuse as a prevalent theme, with this theme ranked fourth out of five identified themes in the AI analysis. Users reported events where their drug samples, Xanax and fentanyl, were adultered with

carfentanil, as well as organisations warning Reddit users of "Super Mario", stamped bags containing xylazine, fentanyl, diphenhydramine (DPH), heroin, and carfentanil. "Super Mario" has been documented by US news articles as an urgent health alert (Cassidy Morrison Senior, 2024; Misiaszek, 2024) where it was described as a 'deadly cocktail of drugs.' This health alert aligns with a post, where a user states they were *"doing fentanyl, xylazine and "trace amounts" of heroin and carfentanil"*. In 2019, carfentanil was reported to be identified as an adulterant in counterfeit prescription opioids (DEA, 2019), as well as to falsify other prescription drugs such as OxyContin (oxycodone) and Xanax (alprazolam) (EUDA, 2018b; Misailidi et al., 2017). Despite the observed spike in carfentanil reports in 2017 (Jalal & Burke, 2020), a slight decrease in reports has been observed. In 2022, there were 273 reported seizures of carfentanil, with three syringes containing both carfentanil and xylazine (EUDA, 2024b). In comparison, 333 carfentanil seizures were reported to the EU Early Warning System in 2021 (EUDA, 2023). Reddit users voiced concerns about the recent resurgence of carfentanil, with remarks like *"(...) which I'm surprised to be popping back up after 5 years"*, *"(...) surprised it's making a comeback"*, and *"(...) but there have actually been a lot of reports coming up for carfent again, surprisingly"*. These posts highlight the growing apprehension expressed by users, suggesting a collective awareness of the dangers associated with carfentanil. The fact that carfentanil may be resurfacing after a period of decline indicates a troubling trend in the drug's availability, which could lead to accidental overdoses and severe adverse effects. Carfentanil is known for its extreme potency, with it being the most potent of the commercially available fentanyl analogues (Misailidi et al., 2017), with these attributes being desirable to a user – *"I was looking for carfentanil because it is very potent, and small doses can be used"*. It was observed that users took to social media to offer advice, with comments such as *"carfentanil can easily be used in humans. Obviously don't dose it at elephant levels"* and *"I was addicted to IV carfentanil, so I would totally use it, however I recommend you have a tolerance first"*. Others asked for guidance on Reddit, *"But does carfentanil feel good?"*. These examples highlight both the advantages and drawbacks of drug-related discussions on social media. The benefits of these discussions allow for the dissemination of information about dangerous adulterations, warning users to exercise caution and potentially preventing adverse events from these new mixtures. However, it is evident that these discussions can also encourage or promote the use of these dangerous substances.

4.4.3 Medetomidine

Medetomidine was less frequently identified through the social media analysis, with 26 posts/comments retrieved through the manual analysis. The lack of social media posts may be because this veterinary medicine is relatively novel to the illicit drug supply, with cases first being reported in 2022 (Krotulski et al., 2024). The manual analysis revealed 'education and awareness' as the most prevalent theme, which aligns with the AI analysis, where public health concerns emerged as the second most common theme. Like with xylazine and carfentanil, users are increasingly turning to social media to express their

concerns and issue warnings about the recent emergence of medetomidine. One post stated that *"(…) experts say the chemical, mixed into counterfeit pills and powders sold on the street, slows the heart rate to dangerous levels. It's impossible for users to detect"*, with this post serving as a warning to others about the dangers associated with medetomidine. The misuse of medetomidine was a theme detected by the AI analysis, where one user posted about xylazine and medetomidine, stating he has *"used both substances and even though they are both alpha 2 drugs the side effects greatly vary….medetomidine can cause some side effects that are a lot worse then xylazine"*. Another user also posted about their experience with medetomidine, stating they have *"been slowly increasing my doses and I'm up to a little over 100mcg",* suggesting they use *"it to get the sleep, but sometimes, especially with an opiate, it's quite nice to stay awake and read or watch tv until I pass out"*. This post illustrates the concerning trend of using this potent veterinary tranquiliser, raising safety concerns due to the casual approach to mixing it with opioids. Polysubstance misuse was identified by the dual analysis of medetomidine, where it was posted that a *"sample came back from the lab as xylazine/fent/medetomidine"*. Another post warned about *"pink fentanyl"*, which was described to *"be a veterinary anaesthetic sedative combo known as xylazine medetomidine. With severe side effects"*. This trend of combining medetomidine with other substances aligns with reports from 2022-2023, where five patients with suspected opioid overdose were found to have also used a mix of opioids (fentanyl, mitragynine, heroin, tramadol, N-pyrrolidino etonitazene), BZDs (bromazolam, clonazolam, etizolam), stimulants (methamphetamine, cocaine) and others (xylazine, olanzapine, quinine, lidocaine) (Schwarz et al., 2024). These findings demonstrate the complexity of substance misuse patterns, as 100% of medetomidine samples were found in conjunction with other drugs of misuse. The presence of medetomidine with multiple other illicit compounds may complicate the clinical management of overdoses and the associated withdrawal symptoms experienced afterwards. The identification of medetomidine with other illicit drugs in human samples corresponds with seized medetomidine samples, where it was also found alongside fentanyl, xylazine, para-flurofentanyl, tetracaine, and diphenhydramine (Krotulski et al., 2024).

Although there have been no published case reports of acute toxicity related to the use of medetomidine in the UK (ACMD, 2024), medetomidine must be monitored due to its emergence in drug samples in the US and Canada. Early monitoring can help to detect trends before they become widespread, allowing for timely public health responses.

4.4.4 Pentobarbital

Two of the most prevalent themes for pentobarbital were 'motivations for misuse' and 'methods of acquisition' which were picked up through both analyses. Users often turned to social media to inquire about ways to obtain this drug, commonly used as a euthanasia agent in veterinary practice and previously utilised in human medicine for managing seizures and insomnia (CFSRE, 2024a). Due to its

use as a euthanasia agent, a common theme encountered was people seeking to obtain it for suicidal intentions, where users stated that *"lots of people find ways to buy pentobarbital online and they use that as a "softer" means to end their life"* and that *"some people would be willing to pay thousands of dollars for a bottle of pentobarbital. It's the gold standard for a quick and painless suicide"*. It was observed that there were links for users to buy pentobarbital online, with the post stating they *"sell pentobarbital at the best rates you will find online"*. One user posted they *"would consider the darknet"* as they wanted to *"order 12ml of pentobarbital"*. Similarly, it was reported by one user that *"a study in 2020 found that 47% of the vet suicides they looked at in the US used poisonings as the method and more than half of them were attributed to pentobarbital"*.

Self-poisoning using pentobarbital is not a novel phenomenon, with lots of previous reports (Druda et al., 2019; Solbeck et al., 2018), where pentobarbital was found to be purchased online, although it was reported that suicide attempts via pentobarbital are uncommon (Crellin & Katz, 2016), yet may occur in those who have access to veterinary medications. Veterinary professionals have a high suicide risk compared to the general population (Witte et al., 2019), where pentobarbital was the main method of suicide for veterinarians when analysing suicides among veterinary professionals. In contrast to its intentional use in suicide reports, pentobarbital has recently been identified as an adulterant in drug seizures across the U.S., where it was present in 1% of samples (CFSRE, 2024b). The identification of pentobarbital in counterfeit tablet drug seizures across the U.S. raises significant concerns, particularly as users may unknowingly ingest it alongside other dangerous substances, where it was detected alongside fentanyl, methamphetamine, xylazine, para-Flurofentnayl, and metamizole (CFSRE 2024b). The unintentional consumption can lead to severe health risks including respiratory and CNS depression, as well as the increased risk of adverse effects when combined with other drugs like opioids or stimulants. The combinational effects of pentobarbital with opioids and BZDs can lead to increased sedation and synergistic respiratory depression (Johnson & Sadiq, 2019), as well as increasing the risk of overdose and death.

Other users took to Reddit to share their positive experiences using pentobarbital, where it was described as *"glorious"* and that *"it felt like the best benzo body high one could get, very warm and super anxiolytic-confidence boosting effects"*. Other positive posts and comments related to the misuse of pentobarbital included *"overall yes a very good drug lucky I got to try it", "took 2 just slightly relaxed and no anxiety not much effect",* and *"if I had access to more I would definitely have used them every day in high quantities*". Alongside pentobarbital's general misuse demonstrated through Reddit posts and comments, users also described the polysubstance misuse they demonstrated, with comments suggesting *"pentobarbital is one of the least cyp inducing barbiturates…that's why it was perfect to mix Nembutal and Codeine together. With both you get more relief than using just one of the drugs"*. Another user stated that they needed a *"powerful sedative"* and wrote they *"could use fentanyl or*

pentobarbital + tramadol mix…this ingredients aren't hard to get, tramadol (where I live) is a over the counter drug, pentobarbital it's sold in veterinary shops".

Despite pentobarbital's relatively low detection in recent counterfeit drug samples, its potential for toxic effects underscores the need for vigilance, where toxic doses of pentobarbital occur at approximately 1g (Johnson & Sadiq, 2019). Healthcare professionals need to be aware of the combinational effects of pentobarbital alongside other drugs of misuse, such as opioids and xylazine.

4.4.5 Phenylbutazone and Acepromazine

The decision to analyse phenylbutazone and acepromazine stemmed from their recent detection in seized drug material (CFSRE 2023b), indicating their potential involvement in illicit drug mixtures, as well as being two veterinary drugs retrieved from prior work conducted before this research (Dunn et al., 2024 *(in press)*). However, the Reddit analysis revealed only six posts/comments for each substance, suggesting a relatively low level of discussion and awareness about these specific veterinary drugs on social media platforms. For the six posts related to phenylbutazone, the predominant theme identified in the manual analysis was 'advice/support,' accounting for three posts. The remaining themes, 'motivations for misuse,' 'personal experiences,' and 'seizures,' were each represented by one post. In contrast, the AI-driven analysis recognised 'toxicity and adulteration' and 'misuse of phenylbutazone' as the two most prevalent themes. Similarly, acepromazine's most common themes identified through the manual analysis were 'advice/support,' with three posts, followed by 'personal experiences' with two posts, and 'polysubstance misuse' with one post. Acepromazine's AI analysis demonstrated 'misuse of veterinary drugs' as the most common theme, followed by 'polysubstance misuse'. Asking for advice regarding the misuse of phenylbutazone was apparent, with one user asking what would happen *"if a human were to consume it"* and asked, *"would it also relieve pain, is it harmful, what would the negative effects be, how much should be consumed?"* Another user asked, *"what is better for recreational purposes"* and listed *"phenylbutazone (75mg)"* in their list of drugs. Subsequently, another user presented misusing phenylbutazone for joint pains, *stating "my joints are in a lot of pain…I'm not sure how I'm alive because I've been overdosing myself with Tylenol and Advil (Please don't think I'm crazy but I've also taken phenylbutazone which is not available to humans it's a horse med)".* Phenylbutazone was once used in human medicine in the early 1950s to treat arthritis and other inflammatory musculoskeletal disorders (Worboys & Toon, 2018), although the mid-1980s banned it due to safety concerns. Between 2016 and 2021, phenylbutazone was detected in 116 seized drug samples, frequently observed with heroin, fentanyl, and xylazine (CFSRE, 2023a). The CFSRE issued a 'toxic adulterant alert' regarding its presence, raising concerns about its spread across the US, originating from Pennsylvania, similar to xylazine. It has been made clear that phenylbutazone may be present in illicit drug samples, especially those containing heroin and fentanyl, and that the adverse effects of phenylbutazone include liver and kidney damage, gastrointestinal bleeding, and blood disorders (CFSRE, 2023a).

Discussions surrounding the misuse of acepromazine were evident in users seeking advice on its consumption. One user inquired*, "Can I take acepromazine? Just want to know how much/if I can take these!"*. Similarly, another asked, *"Has anyone here ever taken their dog's or cat's acepromazine?"*. These posts highlight the concerning trend of individuals turning to social media for guidance on misusing veterinary medications, underscoring the need for better awareness of the potential dangers associated with consuming drugs intended for animals. Similar to pentobarbital, one user demonstrated taking acepromazine for suicidal ideation, asking *"if I took 4.8 g propranolol, 60 mg acepromazine, 8g trazodone and weed as an antiemetic would I die? And how painful would it be? How long would it take?"*. This polysubstance misuse illustrates the potential for harmful consequences when veterinary drugs are misused and combined with other common drugs. Reports of the misuse of acepromazine are rare, although one report documented toxicity related to the intentional ingestion of her dog's acepromazine, resulting in CNS and respiratory depression (Algren & Ashworth, 2014). Due to a lack of regulation, there are concerns that this could increase its availability and prevalence (2023b), making acepromazine recognised as "the next xylazine".

It is important to acknowledge that despite the small amounts of data regarding phenylbutazone and acepromazine, it is crucial to prioritise enhanced monitoring and awareness efforts. Given the potential for severe health consequences, it is imperative for health authorities, researchers, and policymakers to address these issues proactively.

The findings of this study demonstrate that these specific drugs, aimed at animals, possess potent pharmacological properties, resulting in dangerous outcomes when taken by humans. Two of the most common themes presented within the thematic analysis were regarding the negative health effects and polysubstance misuse, demonstrating both the dangerous outcomes associated with these products, whether that is intentional or unintentional intake. The deliberate use of these animal medicines is a cause for concern, as users are actively searching for higher-potency drugs to satisfy their desires. As individuals develop dependence and tolerance to commonly misused drugs, there may be an increasing desire for more potent substances. This heightened demand for stronger drugs, including certain veterinary medications, could lead to a rise in their production and distribution to meet the evolving needs of users. Polysubstance misuse increases the exposure to multiple substances, increasing the chances of unintentional exposure to veterinary medicines. Due to the potency of animal medicines, such intentional consumption can lead to severe and unpredictable health outcomes. Results from the study demonstrate that adulteration using veterinary medicines is present within a wide range of illicit drugs, such as alprazolam, methamphetamine, heroin, and fentanyl. As adulteration using veterinary medicines increases, the potential harm beyond a single demographic of drug users broadens.

4.5 Limitations

Although valuable findings related to online communities and behaviours can be established from this study, several limitations exist. Firstly, social media users do not represent the wider population of drug users and lots of drug users do not take to social media to share their experiences. This leads to an incomplete picture, where offline behaviours remain underrepresented. The pseudonymous nature of Reddit participation presents challenges in accurately assessing demographic information, as users are not required to disclose their age, gender, or other personal details. This limitation restricts the ability to contextualise findings across different demographic groups (Proferes et al., 2021). Additionally, the study relied on data reported by anonymous social media accounts, where information can be inaccurate or deliberately misleading. When conducting the AI analysis, it became apparent that the inclusion of certain posts and comments was limited due to the nature of its content, where certain posts included terms associated with suicide were removed. Although the AI-driven analysis filtered out these specific posts, the manual analysis did not. Despite the benefits of using an AI analysis, this tool has not been specifically trained on this dataset or subject matter. This limitation of AI may have caused posts and comments to be categorised into themes based on the AI's own criteria, leading to potential biases or misattributions. Conducting an exploratory analysis has its downfalls, as no statistical testing or hypothesis has been performed. Despite this, this study sheds light on the recent trends of emerging veterinary drug use and will further help inform relevant policies and future interventions to reduce drug-related harm. It is important to recognise that this work serves as a foundation for more extensive, confirmatory research to be carried out.

4.6 Conclusions

This study has shed light on emerging trends of veterinary drug misuse as discussed on the social media platform, Reddit. The six veterinary drugs identified from previous work (Dunn et al., 2024 *(in press)*) were analysed through a series of posts and comments to investigate several factors regarding their adverse effects, specific routes and doses, polysubstance misuse, how they are obtained, and the main motivations for misuse. Combining the dual method of a manual and AI-driven thematic analysis allowed for a more comprehensive, accurate, and insightful understanding of social media discussions around veterinary drug misuse. These findings highlight the potential of social media as a powerful tool for identifying emerging drug misuse trends, offering valuable insights that can inform public health policies and intervention strategies. It is important to acknowledge that this study reflects only the experiences shared by social media users and is not representative of the wider population, particularly those who do not engage online. This study demonstrates that xylazine, medetomidine, carfentanil, and pentobarbital have the potential for misuse, whilst phenylbutazone and acepromazine do not appear to be commonly misused. However, the latter two drugs have been identified in the illicit drug supply recently, making ongoing monitoring essential.

Chapter 5: Conclusions, Implication in Practice, and Future Work

Upon completion of this thesis, all research questions were answered, providing a comprehensive understanding of the misuse of veterinary medications and their implications for human health. The work carried out in this thesis aimed at investigating and analysing the emerging trend of veterinary drug misuse and its impact on human health, research that is yet to be conducted. Through the three different types of analysis, it was clear that this is a current issue that needs to be addressed appropriately.

This work demonstrated the rising appeal towards veterinary drugs, for reasons such as their affordability and ease of access, recreational use, self-medicating, pain relief, suicide, and to enhance the effects of other drugs of misuse. Of the 28 drugs identified through the systematic literature review, 19 were not controlled and 13 were approved exclusively for animal use, highlighting the extensive range of different animal drugs that are being misused. From the systematic literature review, specific drugs were analysed on the FAERS database to gain a more in-depth understanding of the veterinary products. The pharmacovigilance study confirmed that veterinary drug misuse is becoming more prevalent, where a large increase in reports was documented in 2023, with nine drugs exhibiting an increase of over 1000% in the last five years. Hospitalisation was the most common outcome overall whilst death was the most common outcome for the drugs approved only for animals, presenting the serious effects these medications impose. Looking more specifically at the drugs approved for animal use only, a social media analysis was employed and allowed for a deeper insight into the public's perceptions of this issue, where it was revealed that the most common themes were regarding the negative health effects, their personal experiences, polysubstance misuse, and the motivations driving the misuse. This work provides the necessary foundations to fill the current knowledge gaps and provide an appropriate starting point for future research.

Following the ACMD's recommendations set out in February 2024 (ACMD, 2024), it was announced that xylazine is due to be a Class C controlled drug by 2025 in September 2024 (Home Office, 2024), underscoring the relevance and timeliness of this work. This decision reflects the growing governmental concern regarding the misuse of veterinary medications, aligning with the findings of this research. The acknowledgement of xylazine's potential for abuse by regulatory bodies not only validates the significance of the issues identified in this study but also highlights the need for continued research and intervention in this area. Consequently, other new emerging veterinary drugs may receive similar attention and follow the same path as xylazine and become controlled and regulated. Expanding control measures to include a broader range of veterinary drugs could mitigate misuse and improve monitoring. Policymakers should consider implementing policies that address the growing trend of veterinary drug

misuse. Increased awareness must be performed to ensure the risks associated with veterinary drugs are known to both the public and healthcare professionals. This can include educational campaigns to target both the public and specific high-risk groups, spreading important information which in turn could help reduce misuse and associated harm. Healthcare professionals, including hospital staff, pharmacists, and veterinary professionals should receive ongoing education and training about the risks of veterinary drug misuse and how to prevent it. Improving training and education strategies could help staff recognise the signs of misuse, how to treat overdoses containing specific veterinary drugs, and ensure medications are dispensed responsibly. The current gaps in veterinary drug misuse highlight the need for more comprehensive research, where research is needed to better understand the health impacts, prevalence, and patterns of this type of drug misuse.

Future work recommendations should focus on further exploration of under-reported, uncontrolled veterinary drugs, aiming to explore their misuse potential and any associated health effects. This can inform healthcare professionals of potential emerging drugs before they rise in prevalence. Educational programs and accessible resources should be developed to inform professionals in the field, including veterinary workers, pharmacists, hospital staff, and harm reduction workers, about the misuse of these substances. Further laboratory research is needed to enhance our understanding of the pharmacological properties of these drugs in humans, as existing data predominantly pertains to their use in animals.

Supplementary Information (SI)

Supplementary Table 1 - The articles obtained through the systematic literature review

Type of publication	Main Findings	Specifics - illicit indication	Dose	Route	Source	References
Case Study https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4371025/	950mg of a woman's dog's acepromazine was ingested intentionally, resulting in central nervous system and respiratory depression. Her past medical history included depression, anxiety and hypothyroidism.	Potential self-medication to treat anxiety/depression	950mg	Oral	Pet's own prescription	Algren & Ashworth, 2014
Case Study https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9249150/	A 29-year-old male reported misuse of injected 100mg heroin mixed with 15ml veterinary-use pheniramine maleate, 4-5 times a day. Misuse started due to sleep problems and decreasing the dose led to insomnia, restlessness, and tremulousness. The likelihood for addiction potential is due to stimulation of dopamine. Case report concluded pheniramine has a dependence potential.	Initially misused for sleep problems	100mg heroin with 15ml pheniramine	Parenteral injection	Online Source	Tyagi et al., 2022
Case Study https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7473675/	Myocardial injury is one of the life-threatening complications due to the misuse of clenbuterol. Although used in veterinary medicine, it's misuse has been increasing due to the illegal marketing as a weight loss supplement. There is no reported antidote for clenbuterol misuse.	Anabolic effects for bodybuilding	40mg (dosing frequency unknown)	Oral	N/A	Moriartry & Attar, 2020
Case Study https://pubmed.ncbi.nlm.nih.gov/18713522/	Discussed 12 clenbuterol cases of intoxication. Heroin was present in 8/12 cases with the remaining 4 cases indicating a history of heroin misuse due to the presence of morphine. Multi-drug use was popular with fentanyl	Anabolic effects for bodybuilding	Case 1 - 76 ng/mL (Blood) Case 2 - Present (Urine), Trace (Blood) Case 3 - 7.6ng/mL (Blood) Case 4 - Present	N/A	N/A	Wingert et al., 2008

	present in 3 cases, cocaine in 4, ethanol and benzodiazepines in 2, and methadone present in 1 case.		(Urine), Trace (Blood) Case 5 - Present (Urine), ND (Blood) Case 6 - 10ng/mL (Blood) Case 7 - 5.5ng/mL (decomposition fluid), 12ng/g (Spleen) Case 8 - Present (Urine), ND (Blood) Case 9 - Present (Urine), Trace (Blood) Case 10 - Present (Urine), ND (Blood) Case 11 - Present (Urine), 6.3ng/mL (Blood) Case 12 - Present (Urine), 20ng/mL (Blood)			
Case Study https://onlinelibrary.wiley.com/doi/10.1111/1556-4029.13010	1/3 of Tanax's components, Embutramide, was identified in the urine of a man who murdered his ex-wife, along with alprazolam. The second case study reported a 16-year-old who was hospitalised, where embutramide, drotaverine (antispasmodic) and alprazolam was found. This patient suffered with severe symptoms and was hospitalised 4 more times in the following 4 months due to the same symptoms, being periods of unconsciousness, bradycardia and diplopia.	Suicide attempt (case 1) & general drug misuse (case 2)	2.36 µg/mL (in urine (case 1)) & 2.83µg/mL (in urine (case 2))	Case 1 - N/A Case 2 - Inhaled	Case 1 - User was a veterinarian so had own access Case 2 - N/A	Lajtai et al., 2016
Case Study https://pubmed.ncbi.nlm.nih.gov/29319776/	Veterinary concentrations of vitamin A, D and E were misused and injected into patient's arms twice a month. This veterinary vitamin combination is popular in Brazil due to its availability and low cost, and due to not	Muscle swelling for body building	150mL of vitamin ADE (20,000,000 IU Vitamin A, 5,000,000 IU Vitamin D3, 6,800 Vitamin E per 100mL vial) in the previous 4 months	Parenteral injection	N/A	Ronsoni et al., 2017

	being classed as an anabolic steroid.					
Case Study https://www.sciencedirect.com/science/article/pii/S07356757090001 02?via%3Dihub	A 35-year-old veterinarian was hospitalised with movement disorder due to the misuse of Zoletil (Telazol) - a fixed ratio combination of zolazepam (tranquiliser) and tiletamine (anaesthetic). The accessibility of scheduled drugs and health care professionals was highlighted in this case.	To reduce the amount of heroin misused	N/A	N/A	User was a veterinarian so had own access	Lee et al., 2009a
Case Study file:///C:/Users/2009986/Downloads/Phenobarbitaltoxicityfromahighlyconcentratedveterinaryformulation-reviewandcasereport%20(1).pdf	Case of intoxication of a high concentration of veterinary acquired phenobarbital, complicated by ethanol abuse. The co-ingestion caused significant central nervous system depressants.	Patient had a history of substance misuse	124mcg/mL initial serum concentration (consumption amount unknown)	N/A	User was an assistant horse trainer with access to equine phenobarbital	Alleva et al., 2015
Case Study https://academic.oup.com/jat/article/25/4/245/779255?login=true	The dose of xylazine used for animals ranges from 0.5-5.0mg/kg. A 27-year-old farmer attempted suicide with an ~75mL 2% aqueous solution xylazine by intramuscular injection.	Suicide attempt	75mL 2% aqueous solution	Intramuscular	User was a farmer	Hoffmann et al., 2001
Case Study https://pubmed.ncbi.nlm.nih.gov/12539907/	5 cases of malingering my animal proxy were reported by veterinarians. Case 1 involves a dog noise phobia case in order to receive clorazepate (benzodiazepine) for the owner's use. Case 2 includes a false reporting of malnutrition in a dog to obtain stanozolol. In case 3, the client was seeing multiple veterinary clinics to misuse levothyroxine for weight loss. Case 4 involved falsely	Case 1 - Benzodiazepine (Clorazepate) misuse Case 2 - Anabolic steroid use for body building Case 3 - Levothyroxine misuse for weight loss Case 4 - Opioid (Tobuterol)	Case 1 - 7.5mg Case 2 - N/A Case 3 - N/A Case 4 - 7- to 10-day 5mg Case 5 - 30mg every 12 hours for 21 days	Case 1 - Oral Case 2 - N/A Case 3 - N/A Case 4 - Oral Case 5 - Oral	Prescribed from veterinary clinic	LeBourgeoi et al., 2002

	reporting a dog's cough to receive opioids. Case 5 involved amitriptyline for the owner to misuse as an antidepressant.	misuse Case 5 - Self-medication for anxiety using amitriptyline				
Case Study https://pubmed.ncbi.nlm.nih.gov/29098704/	Describes three cases where xylazine was used in human poisoning events with criminal intent via drink spiking. This report suggests xylazine should be classified as a controlled drug.	Intentional poisoning with criminal intent	Case 1 - N/A Case 2 - 0.294 µg/mL (urine) & 0.057 µg/mL (serum) Case 3 - 0.533 µg/mL (urine)	Oral ingestion	N/A	Krongvorakul et al., 2017
Case Study https://pubmed.ncbi.nlm.nih.gov/11527235/	A 30-year-old zoo employee, found unresponsive, tested positive for benzodiazepines and cannabinoids and revealed a history of Telazol misuse.	Patient revealed history of Telazol recreational misuse	N/A	Parenteral injection	User was a veterinary worker	Quail et al., 2001
Case Study https://pubmed.ncbi.nlm.nih.gov/10872580/	A 22-year-old male was found dead with 28 needle marks where it was suspected illicit drugs were used. Upon analysis, tiletamine and zolazepam were identified. This drug combination is common in veterinary medicine as an anaesthetic.	N/A	Exact doses unknown Concentration in blood = 0.85mg/L (tiletamine) & 3.3mg/L (zolazepam) Concentration in tissue injection site = 25.2mg/L (tiletamine) & 23.3mg/L (zolazepam)	Parenteral injection	N/A	Chung et al., 2000
Case Study https://pubmed.ncbi.nlm.nih.gov/12670006/	A case study in which xylazine was detected on its own in a suicide by hanging.	Suicide due to history of depression	2.3 mg/L in heart blood, 2.9 mg/L in peripheral blood, 6.3 mg/L in bile, 0.01 mg/L in urine, 6.1 mg/kg in the liver, and 7.8 mg/kg in the kidney.	Parenteral injection	User was a veterinary worker	Moore et al., 2003

Case Study https://pubmed.ncbi.nlm.nih.gov/37236142/	The first drug-related death in the UK/Europe associated with Xylazine was reported to the National Programme on Substance Abuse Deaths (NPSAD) on the 31/12/22. Other drugs present in urine/blood samples of the deceased included cocaine, fentanyl, morphine, paracetamol, pregabalin, THC, diazepam, methadone and alcohol.	Illicit drug misuse - also found cocaine, fentanyl, diazepam and alcohol in tissue	Blood concentration of xylazine = 38ng/ml and urine = 135ng/ml	N/A	N/A	Rock et al., 2023
Government Article https://www.legislation.gov.uk/uksi/2001/3998/introduction	The UK Government Misuse of Drugs Regulations 2001	N/A	N/A	N/A	N/A	United Kingdom, 2001
Government Report https://www.gov.uk/government/publications/united-kingdom-drug-situation-focal-point-annual-report/uk-drug-situation-2019-summary	The current rate of ketamine use among adults in England and Wales is the highest ever recorded, reaching 0.8%.	N/A	N/A	N/A	N/A	GOV.UK, 2021
Informative poster https://www.avma.org/sites/default/files/2019-11/Opioids_Vet-Shopping-Drug-Diversion_Guide-for-Veterinarians_flyer.pdf	Describes behaviour associated with 'vet shoppers' and ways to minimise drug diversion in a veterinary setting.	N/A	N/A	N/A	N/A	American Veterinary Medical Association, n.d.

Journal Article https://pubmed.ncbi.nlm.nih.gov/27341080/	Reviewed 7 cases of human exposure to the veterinary tiletamine-zolazepam combination. In 6/7 cases, administration was intentional and the use of the drug combination in 5/7 cases was for recreational purposes. It was shown that human misuse of veterinary medications is more prevalent than previously thought. The majority of people who misuse the TZ combo also use or abuse other psychoactive substances.	Case 1 - Recreational use Case 2 - Substitute for heroin Case 3 - To get high Case 4 - N/A Case 5 - To get high Case 6 - Suicidal purposes Case 7 - Recreational use	Case 1 - 200mg-100mg tiletamine, 100mg zolazepam Case 2 - N/A Case 3 - 500mg Case 4 - 875mg tiletamine, 875mg zolazepam Case 5 - 1125mg tiletamine, 1125mg zolazepam (over 9 days) Case 6 - N/A Case 7 - N/A	Case 1 - Injection Case 2 - N/A Case 3 - Ingestion Case 4 - Injection Case 5 - Injection Case 6 - Injection Case 7 - Injection	2/7 patients were veterinarians, 1/7 works in a veterinarian's office, 1/7 is a zoo employee	de la Peña & Cheong, 2016
Journal Article https://pubs.rsc.org/en/content/articlelanding/2023/ay/d3ay00815k#!	Acepromazine poisonings have been reported, including suicide reports and drug-facilitated sexual assaults, however it is difficult to detect due to rapid metabolism.	N/A	N/A	N/A	N/A	de Lima & de Araujo, 2023
Journal Article https://medic.upm.edu.my/upload/dokumen/2022071815362726_MJMHS_1600.pdf	Xylazine can be misused in several ways including as a recreational drug, an adulterant, in drug-facilitated crime/sexual assault and as a source of accidental and intended poisoning.	Recreational drug, adulterant, drug facilitated crime and sexual assault, doping agent in animal sport	N/A	Inhaled/snorted/ injected	N/A	Teoh et al., 2022
Journal Article https://pubmed.ncbi.nlm.nih.gov/20221861/	Levamisole, an anti-parasitic is used as an adulterant in a high percentage of cocaine samples. This may be because it is a bulky white powder, similar to cocaine. Other theories include to increase profit and the idea of levamisole adulterated cocaine effecting the ability to be detected by dogs/analytical methods. It was reported that levamisole was found to affect the endogenous opiate levels, including codeine and morphine.	Adulterant	N/A	N/A	N/A	Wiegand, 2010

Journal Article https://pubmed.ncbi.nlm.nih.gov/33403403/	Currently, there is insufficient information regarding veterinary prescription drug misuse to estimate the severity. 398 veterinarians reported in a study that they suspected 23% of pet owners misuse animal drugs on themselves. A different study found that 13% of veterinarians were conscious of an animal owner that injured their pet to gain opioids, and 12% were aware of staff opioid misuse. Opioid prescribing is increasing in the veterinary setting.	N/A	N/A	N/A	Veterinary setting	Anand & Hosanagar, 2021
Journal Article https://jamanetwork.com/journals/jama/fullarticle/2805530	Xylazine was found in every street opioid sample tested by the Philadelphia Department of Public Health in January 2023. The FDA have issued an import alert, restricting unlawful importation of xylazine, in February 2023. In April 2023, the White House Office of National Drug Control Policy declared xylazine mixed with fentanyl as an "emerging threat to the United States".	N/A	N/A	Injection	Illicit drug supply	Rubin, 2023
Journal Article https://pubmed.ncbi.nlm.nih.gov/20045604/	There is a need for increased awareness of the potential hazards of veterinary medications in humans. The veterinary products with significant health hazards to humans are carfentanil, clenbuterol, ketamine, tilmicosin, testosterone/estradiol, dinoprost and cloprostenol.	N/A	N/A	N/A	N/A	Lust et al., 2011
Journal Article https://pubmed.ncbi.nlm.nih.gov/25404261/	Examined which veterinary compounds are misused in human suicide. The drugs found were veterinary-grade pentobarbital, xylazine, tilmicosin (antibiotic), acepromazine and euthanasia	Pentobarbital - Suicide Acepromazine - Suicide	Lethal blood concentration of 2mg/L of pentobarbital reported, 2500mg acepromazine, 21mg/kg tilmicosin	Parenteral/oral consumption	50% of cases involved either veterinarian /those who had	Perrin, 2014

	preparations (mebezonium and embutramide).				easy access due to their employment. Reports of people with no association with veterinary medicine being able to successfully buy veterinary-grade pentobarbital.	
Journal Article https://pubmed.ncbi.nlm.nih.gov/29733092/	In America, veterinarians are a unique source of prescription opioid analgesics as many states do not need to report their prescribing of them. There are no limits on the amounts of opioids veterinarians can prescribe, influencing diversion/misuse. 75% of a sample (of US veterinarians) were aware of working with someone with a substance abuse problem.	N/A	N/A	N/A	Veterinary setting	Russell et al., 2018
Journal Article https://pubmed.ncbi.nlm.nih.gov/12135152/	Analgesic, anti-inflammatory, anti-arthritis, systemic antibiotics and topical corticosteroids were the most frequently reported veterinary drugs misused. Veterinarians stated the most likely reason for veterinary drug misuse include lower cost, convenient availability and the belief that veterinary medications are stronger than comparable human medications.	Low cost and the belief that veterinary medications are stronger than comparable human medications	N/A	N/A	People involved in animal sport, those who work in healthcare	Erramouspe et al., 2002

Journal Article https://pubmed.ncbi.nlm.nih.gov/21481268/	There is a notable gap in the understanding of how xylazine was diverted into the illicit drug market, the specific context of its use, and the chronic health implications associated with its consumption. It was common for consumers in Puerto Rico to be able to control the ratio of heroin:xylazine themselves, as it was usually sold not mixed. 'Speedball' was a mix of heroin, xylazine and cocaine and when sold, each substance were kept separate so the user could tailor to their own liking. Skin ulcers, due to xylazine, promoted further xylazine use to help manage the pain.	N/A	N/A	Parenteral injection	N/A	Torruella, 2011
Journal Article https://www.sciencedirect.com/science/article/pii/S0736467916303547	There were 76 cases of xylazine exposures reported to Texas poison centres between 2000-2014. 93% of patients were over the age of 20 and 54% were male. Injection accounted for 51% of exposures and ingestion for 28%. 64% of exposures were unintentional and 32% were intentional. Drowsiness/lethargy (47%), bradycardia (20%), hypotension (11%), hypertension (9%), puncture/wound (8%) and slurred speech (8%) were the most common clinical effects.	31.6% of exposures were intentional, of which 15.8% were suspected suicide attempt, 13.2% were drug abuse	N/A	Parenteral injection (51.3%), Ingestion (15.8%), Dermal Route (14.5%), Ocular Route (2.6%), Inhalation (2.6%).	N/A	Forrester, 2016

Journal Article https://pubmed.ncbi.nlm.nih.gov/24769343/	From 1966 to 2013, 43 cases of intoxication were reported, of which 51% resulted in fatalities. Of the 22 fatal instances, 17 had xylazine usage as a contributing factor. Males made about 60% of the intoxication cases. In 82% of cases, xylazine deaths were accidental, whereas 9% were suicide-related. Xylazine was employed in 17/18 unintentional occurrences as an adulterant. Parenteral (intramuscular, subcutaneous, and intravenous) administration was the primary mode of delivery. 33% of intoxications were individuals that had easy access to the drug, including veterinarians (and assistants), farmers and horse trainers.	Horse doping agent, a drug of abuse, for attempted sexual assault, as a source of accidental or intended poisonings	Toxic doses varied from 40 to 2400ng	Inhaled, intramuscular, intravenous, ocular exposure, oral administration, subcutaneous, self-administration	Individuals who had easy access (veterinarians /farmers/horse trainers)	Ruiz-Colon, 2014
Journal Article https://pubmed.ncbi.nlm.nih.gov/37009344/	Of the 59 documented occurrences of xylazine intoxication, 21 had fatal results; of these, 17 included the combination of xylazine and other substances. 1,200mg was the average fatal dose, 525mg was the average dose in non-fatal cases.	Drug abuse	525mg = non-fatal average dose 1,200 mg = fatal average dose Doses ranged from 40mg-4300mg	Intravenous, subcutaneous, intramuscular, inhalation	N/A	Ayub et al., 2023
Journal Article https://pubmed.ncbi.nlm.nih.gov/35770859/	Every stimulant-containing xylazine-positive case also included an opioid. Stimulants were present in 53% of cases, cannabinoids in 30% and benzodiazepines in 26%. Xylazine's geographic distribution and prevalence grew during the study period.	N/A	450mg (injected) - for one case studied	Injection Inhalation Dermal Exposure Ingestion	N/A	Kacinko et al., 2022

Journal Article https://injuryprevention.bmj.com/content/injuryprev/27/4/395.full.pdf	Between 2010 and 2015, xylazine was found in less than 2% of fatal heroin and/or fentanyl overdose cases; in 2019, it was found in 262 (31%) of the 858 cases of fatal heroin and/or fentanyl overdose. Of the 262 fatal cases, 76% were male. 100% of these fatal cases in 2019 were positive for fentanyl, as well as xylazine.	People stated eurphoric effects lasted longer, like heroin before it was replaced with fentanyl	N/A	Injection	N/A	Johnson et al., 2021
Journal Article https://pubmed.ncbi.nlm.nih.gov/30485426/	In Kentucky, cocaine and methamphetamine were the main controlled substances and levamisole was the most prevalent adulterant detected (17.5%). Xylazine was present as a cutting agent in 4.6% of heroin samples, 11% of fentanyl samples and 2.6% of cocaine samples.	As an adulterant	N/A	N/A	N/A	Fiorentin et al., 2018
Journal Article https://www.sciencedirect.com/science/article/pii/S27726320230005 82	In 2023, xylazine addiction has rapidly grown into a global concern and misuse has increased alarmingly. Serious repercussions have been seen in 2023 due to xylazine quickly growing into a global concern. Between 2019-2021, fatal overdoses in New York increased by more than 80%.	Drug of abuse, drug of sexual assault attempt, accidental/ intentional poisoning	N/A	Oral administration, inhaled, sniffed, injected	Online Source	Debnath & Chawla, 2023
Report https://www.cfsre.org/images/content/reports/public_alerts/Medetomidine_Public_Health_Alert__Final.pdf	A toxic adulterant alert sent out in December 2023 due to medetomidine/dexmedetomidine being identified as an adulterant in illicit drug material. Medetomidine (potent veterinary anaesthetic) has frequently been observed in samples containing fentanyl and xylazine and also heroin and cocaine.	N/A	N/A	N/A	N/A	CFSRE, 2023b

Retrospective, Secondary Data Analysis https://pubmed.ncbi.nlm.nih.gov/36504413/	An increase of xylazine deaths in West Virginia have gone from 1% (2019) to 5% (2021). Deaths involving xylazine had more coin toxicants, compared to non-xylazine deaths. 98% of xylazine deaths involved fentanyl. There was a greater history of drug/alcohol use with xylazine decedents.	N/A	N/A	N/A	N/A	Sibbesen et al., 2022
Journal Article https://pubmed.ncbi.nlm.nih.gov/37700329/	Xylazine-related overdoses in the United States have been escalating rapidly and show little indication of decelerating, posing a significant public health crisis. The 'speedball' mixture of heroin, cocaine and xylazine is obtainable for $8. Monthly rates of fentanyl mixed with xylazine overdose deaths increased nearly fourfold (from 2.9% to 10.9%) between January 2019 - June 2022.	N/A	N/A	Injection (84.5%), inhalation (14.1%), smoking (1.4%)	N/A	Zhu, 2023
Report https://www.dea.gov/sites/default/files/2022-12/The%20Growing%20Threat%20of%20Xylazine%20and%20its%20Mixture%20with%20Illicit%20Drugs.pdf	The prevalence of xylazine is increasing although limited scientific research has been conducted on the effects of the drug in the body. The Centre for Disease Control and Prevention does not include xylazine-positive overdose deaths meaning it's prevalence is widely underestimated. A significant jump in xylazine deaths in the US from 2020-2021 has been reported. Northeast US has experienced a 103% increase, South - 1127% increase, Midwest - 516% increase and West - 750% increase.	N/A	N/A	N/A	N/A	DEA, 2022a
Report https://www.cdc.gov/mmwr/volumes/72/	In 21 US jurisdictions, the monthly percentage of deaths involving xylazine in the context of illicitly manufactured fentanyl (IMF)	N/A	N/A	N/A	N/A	CDC, 2023a

wr/mm7226a4.htm	increased by 276%, rising from 2.9% in January 2019 to 10.9% in June 2022.					
Report https://blogs.cdc.gov/nchs/2023/06/30/7408/	Males were at least twice as likely to die from overdoses involving xylazine each year from 2018 to 2021. The highest rate of overdose deaths involving xylazine in 2021 were among the 35-44 age group.	N/A	N/A	N/A	N/A	CDC, 2023b
Report https://www.dea.gov/alert/dea-reports-widespread-threat-fentanyl-mixed-xylazine	Public Safety Alert was announced in November 2022 warning the public of the increasing reports of fentanyl mixed with xylazine, stating that will be the deadliest drug threat the US has ever faced. The Drug Enforcement Administration reported the seizure of xylazine-fentanyl mixture in 48 of 50 states.	N/A	N/A	N/A	N/A	DEA, 2022b
Report https://www.emcdda.europa.eu/publications/european-drug-report/2023/drug-situation-in-europe-up-to-2023_en	Ketamine seizures remain high, often found in MDMA mixtures. The rise of 'Pink cocaine'—ketamine mixed with other synthetics—reflects growing consumer interest.	N/A	N/A	N/A	N/A	EUDA, 2023g
Report https://www.emcdda.europa.eu/publications/risk-assessments/ketamine_en	Hospitals, veterinary clinics and pharmaceutical distribution are ways ketamine is diverted for recreational use as sources have concluded the synthesis of ketamine as difficult. 12 deaths where ketamine had been identified occurred between 1987 and 2000. Concerns are present due to the 'near death' experiences and the unpredictability of the drug.	N/A	N/A	N/A	N/A	EUDA, 2002

Report https://www.emcdda.europa.eu/publications/data-factsheet/syringe-residues-analysis-data-escape-project_en	Carfentanil was frequently identified in syringes from Vilnius (92%) and Riga (29%). Xylazine was found in 13% of syringes from Riga, often co-occurring with isotonitazene, metonitazene, or carfentanil.	N/A	N/A	N/A	N/A	EUDA, 2023h
Report https://www.emcdda.europa.eu/publications/european-drug-report/2023/other-drugs_en	Quantity of ketamine seized and reported to EU Early Warning System remains relatively high in recent years, suggesting it is consistently available in national drug markets, where it has been found in mixtures sold as 'pink cocaine'. A seized mixture in 2022 from Estonia included a mixture of protonitazene, metonitazene and xylazine.	N/A	N/A	N/A	N/A	EUDA, 2023b
Report https://www.emcdda.europa.eu/publications/european-drug-report/2023/injecting-drug-use_en	In Riga, Xylazine was found in 13% (25/194) of syringes. It was consistently mixed with isotonitazene or metonitazene in all 25 syringes and co-occurring with carfentil in 3 syringes. Carfentanil was commonly found in syringes from Vilnius (92%) and Riga (29%).	N/A	N/A	N/A	N/A	EUDA, 2023a
Report https://www.emcdda.europa.eu/publications/rapid-communication/new-psychoactive-substances-global-markets-glocal-threats-and-covid-19-pandemic_en	In 2019 there was 234 seizures of carfentanil (10044.2g). 17kg of new opioids were seized with 12kg being in the form of powders - 84% was carfentanil. In 2018, the total quantity to be seized was 1.9kg.	N/A	N/A	N/A	N/A	EUDA, 2020

Report https://www.emcdda.europa.eu/publications/european-drug-report/2023/harm-reduction_en	Increasing polydrug consumption adds to the challenges of developing effective responses to reduce drug overdose deaths and drug-related poisonings. Mixtures containing novel benzodiazepines, novel opioids and the tranquiliser xylazine, has been reported in Estonia.	N/A	N/A	N/A	N/A	EUDA, 2023f
Report https://www.emcdda.europa.eu/publications/european-drug-report/2023/drug-induced-deaths_en	Xylazine was identified in one fatality in 2022.	N/A	N/A	N/A	N/A	EUDA, 2023c
Report https://www.emcdda.europa.eu/news/2023/european-drug-report-2023-highlights_en	The increasing diversity in drug supply and usage poses novel challenges for drug policy and healthcare in Europe. The mixtures of novel benzodiazepines and opioids, with xylazine, has the potential to impact European health.	N/A	N/A	N/A	N/A	EUDA, 2023e
Report https://www.emcdda.europa.eu/ews25_en	In 2020, approximately 1.2 tonnes of seized material consisted mainly of aryl cyclohexylamines, with ketamine making up the vast majority at 1.1 tonnes (93%). In 2020, carfentanil made up 52% of opioid seizures. Argentina has reported the adulteration of cocaine with carfentanil, leading to deaths and non-fatal poisonings.	N/A	N/A	N/A	N/A	EUDA, 2022b
Report https://www.emcdda.europa.eu/publications/risk-assessments/carfentanil_en	Carfentanil is mainly seized as a powder but has been seen as a liquid, although in Europe it is typically administered via intravenous injection. Carfentanil misuse may be under-reported due to not being part of most routine drug screening. There is	N/A	N/A	N/A	N/A	EUDA, 2018

	limited information regarding the dose regimens of carfentanil and the abuse liability in humans.					
Report https://www.emcdda.europa.eu/publications/european-drug-report/2023_en	Around 930 new psychoactive substances were being monitored by the EMCDDA by the end of 2022. Ketamine has gained prominence as a preferred drug among certain demographics.	N/A	N/A	N/A	N/A	EUDA, 2023d
Report https://www.emcdda.europa.eu/publications/edr/trends-developments/2022_en	Belgium and the Netherlands announced the dismantling of laboratories producing ketamine. 1600 seizures and 240kgs of ketamine was reported by 16 EU countries. 13% of people who used drugs in the last 12 months used ketamine, from the European Web Survey on Drugs.	N/A	N/A	N/A	N/A	EUDA, 2022a
Report https://www.emcdda.europa.eu/publications/edr/trends-developments/2021_en	Until 2021, there was inadequate monitoring of ketamine, which restricted the comprehension of its usage and its impact on public health. Denmark reported a last year prevalence of ketamine of 0.6% in 2017, and Romania 0.8% in 2019.	N/A	N/A	N/A	N/A	EUDA, 2021
Report https://www.emcdda.europa.eu/publications/joint-reports/carfentanil_en	Until 2017, the EMCDDA had 755 seizures of carfentanil reported by seven Member States. Seizures reported carfentanil was mixed with other opioids or the synthetic cathinone alpha-PHP. 48 deaths were reported to the EMCDDA up until 2017 - 85% were male and 15% female.	N/A	N/A	N/A	N/A	EUDA, 2017

Report https://www.wedinos.org/resources/downloads/Annual-Report-22-23-English.pdf	In 2022/2023, ketamine was the 5th most identified psychoactive. Ketamine was the 7th most intended purchased drug but was 6th most common drug identified post analysis. Ketamine was the second most common drug identified (206) from the 1112 samples analysed from 22 Nighttime Economy Venues and 2 festivals. 204 samples of ketamine were submitted during 2021-2022, with 6% of these containing no ketamine. The initial sample of xylazine was received in January 2020, followed by 10 subsequent samples containing xylazine. Among the 9 samples received between April 2022 and March 2023, none were submitted with xylazine listed as the intended purchase.	N/A	N/A	N/A	N/A	WEDINOS, 2023
Report https://www.wedinos.org/resources/downloads/Annual-Report-21-22-English.pdf	Ketamine was the 4th most identified psychoactive substance. 213 samples of ketamine were identified from the 1102 samples from 24 Nighttime Economy Venues and 3 festivals - making it the second most identified substance after cocaine. 160 samples were submitted as ketamine, with 8% containing no ketamine.	N/A	N/A	N/A	N/A	WEDINOS, 2022
Report https://www.wedinos.org/resources/downloads/Annual-Report-20-21-English.pdf	Ketamine was the 3rd most prevalent drug submitted by individuals aged 0-17 years. Ketamine was the 7th most intended purchased drug but was the 10th most common drug identified post analysis.	N/A	N/A	N/A	N/A	WEDINOS, 2021

Report https://www.wedinos.org/resources/downloads/PHILTRE-AR-Eng-19-20.pdf	Ketamine was the 4th most identified psychoactive substance. Ketamine was the 6th most intended purchased drug but the 8th most common identified drug post analysis. From the 1048 samples received from Nighttime Economy and Festivals, ketamine was the 3rd most common drug identified, after cocaine and MDMA.	N/A	N/A	N/A	N/A	WEDINOS, 2020
Report https://www.wedinos.org/resources/downloads/Annual_Report_201819.pdf	Ketamine was the 3rd most prevalent substance identified, after cocaine and MDMA. From the 339 samples identified from Nighttime Economy and Festivals, ketamine was the most prevalent drug.	N/A	N/A	N/A	N/A	WEDINOS, 2019
Report https://www.wedinos.org/resources/downloads/Philtre_Annual_Report_2017-18.pdf	Ketamine was 5th most identified NPS. A sample submitted with intent to be ketamine was identified as beta-hydroxy fentanyl.	N/A	N/A	N/A	N/A	WEDINOS, 2018
Report https://www.wedinos.org/resources/downloads/Philtre_Annual_Report_2016-17.pdf	Ketamine was the 6th most identified NPS. Ketamine bought by users were analysed and sampled to be cocaine or furanylfentanyl.	N/A	N/A	N/A	N/A	WEDINOS, 2017
Report https://www.wedinos.org/resources/downloads/WEDINOS_Annual_Report_2015-16_FINAL.pdf	Ketamine was a new entry and was the 3rd most identified NPS.	N/A	N/A	N/A	N/A	WEDINOS, 2016

Supplementary Table 2 - A list of commonly misused drugs, including brand names, used to analyse concomitant drug use

Opioids	Benzodiazepines/Z-drugs	CNS Depressants	Stimulants	Other
Fentanyl	Adinazolam	Xylazine	Caffeine	Ketamine
Morphine	Deracyn	Dexmedatomidine	Nicotine	Ketamine HCl
Hydrocodone	Alprazolam	Medetomidine	Cocaine	Ketamine Hydrocloride
Methadone	Xanax	Pentobarbital	Amphetamine	Cannabis
Oxycodone	Helex	Phenobarbital	Concerta	Marijuana
Carfentanil	Xanor	Alcohol	Ritalin	LSD
Buprenorphine	Trankimazin	Ethanol	Methylphenidate	Mescaline
Hydromorphone	Onax	Nembutal	Adderall	PCP
Codeine	Alprox	Gamma-hydroxybutyrate	Methamphetamine	Psilocybin
Heroin	Misar	GHB	Dextroampheta mine	Salvia
Oxymorphone	Restyl	Sodium oxybate	Khat	Ayahuasca
Anexsia	Solanax	Xyrem	Kratom	Amyl nitrate
Co-Gesic	Tafil	Acepromazine	MDMA	Ketalar
Embeda	Neurol		Desoxyn	Spravato
Exalgo	Frontin		Clenbuterol	Ketaset
Hycet	Kalma			Dextromethorphan
Hycodan	Ksalol			Nandrolone
Hydromet	Farmapram			Oxandrin
Ibudone	Bentazepam			Oxandrolone
Kadian	Thiadipona			Anadrol
Liquicet	Bretazenil			Oxymetholone
Lorcet	Bromazepam			Anadrol-50
Lortab	Lexotanil			Testosterone cypionate
Maxidone	Lexotan			Depo-testosterone
MS Contin	Lexilium			Gabapentin
Norco	Lectopam			Levothyroxine
Opana	Lexaurin			Levothyroxine Sodium
OxyContin	Lexatin			Furosemide
Palladone	Bromam			Amitriptyline
Percocet	Bromazolam			Phenylbutazone
Percodan	Brotizolam			Carprofen
Reprexain	Lendormin			Pregabalin
Rezira	Dormex			Promethazine
Roxicet	Sintonal			Pheniramine

Targiniq	Noctilan
TussiCaps	Camazepam
Tussionex	Albego
Tuzlstra	Limpidon
Vicodin	Librium
Vicoprofen	Risolid
Vituz	Elenium
Xartemis	Cinazepam
Xodol	Levana
Zolvit	Cinolazepam
Zutripo	Gerodorm
Zydone	Clobazam
Actiq	Onfil
Duragesic	Frisium
Sublimaze	Urbanol
Zohyrdo	Clonazepam
Dilaudid	Rivatril
Meperidine	Rivotril
Demerol	Klonopin
Dolophine	Iktorivil
Methadose	Paxam
Duramorph	Clonazolam
Zohydro	Clorazepate
Tramadol	Tranxene
Tramadol HCl	Tranxilium
Butorphanol	Clotiazepam
Loperamide Hydrochloride	Veratran
	Clozan
	Rize
	Cloxazolam
	Cloxam
	Sepazon
	Olcadil
	Delorazepam
	Dadumir
	Chloretizolam
	Diazepam
	Antenex
	Apaurin
	Apzepam
	Apozepam

Diazepan
Hexalid
Normabel
Pax
Stesolid
Stedon
Tranquirit
Valium
Vival
Valaxona
Diclazepam
Estazolam
Ethyl carfluzepate
Etizolam
Etilaam
Etizest
Pasaden
Depas
Ethyl lofazepate
Victan
Meilax
Ronlax
Flualprazolam
Flubromazepam
Templex
Flubromazolam
Remnon
Flubrotizolam
Fluclotizolam
Flunitrazepam
Rohypnol
Hipnosedon
Vulbegal
Fluscand
Flunipam
Ronal
Rohydorm
Hypnodorm
Flunirtazolam
Fluazepam
Dalmadorm
Dalmane

Fluzepam
Flutazolam
Coreminal
Flutemazepam
Flutoprazepam
Restas
Halazepam
Alapryl
Paxipam
Ketazolam
Anxon
Sedotime
Loprazolam
Dormonoct
Havlane
Lorazepam
Atvian
Orfidal
Lorenin
Lorsailan
Temesta
Tavor
Lorabenz
Lormetazepam
Loramet
Noctamid
Pronoctan
Meclonzepam
Medazepam
Nobrium
Ansilan
Mazepam
Rudotel
Raporan
Metizolam
Mexazolam
Midazolam
Dormicum
Flormidal
Versed
Hypnovel
Dormonid

Nifoxipam
Nimetazepam
Erimin
Lavol
Nitemazepam
Nitrazepam
Mogadon
Alodorm
Pacisyn
Dulmolid
Nitrazadon
Nitrazolam
Nordazepam
Norfluazepam
Oxazepam
Seresta
Serax
Serenid
Serepax
Sobril
Oxabenz
Oxapax
Oxascand
Ox-Pam
Opamox
Alepam
Medopam
Murelax
Noripam
Purata
Phenezepam
Phenzitat
Pinazepam
Domar
Duna
Prazepam
Demetrin
Lysanxia
Prazene
Centrax
Premazepam
Pyrazolam

Quazepam
Doral
Quiedorm
Rilmazefone
Temezepam
Restoril
Normison
Euuhypnos
Temaze
Tenox
Tetrazepam
Myolastan
Clinoxam
Epsipam
Musaril
Triazolam
Halcion
Rilamir
Notison
Somese
Flumazenil
Anexate
Lanexat
Romazicon
Mazixcon
Eszopiclone
Lunesta
Zaleplon
Sonata
Starnoc
Zolpidem
Ambien
Nytamel
Snaval
Stilnoct
Stilnox
Sublinox
Xolnox
Zoldem
Zolnod
Zopiclone
Imovane

	Rhovane
	Ximovan
	Zileze
	Zimoclone
	Zimovane
	Zopitan
	Zoeclone
	Zopiklone
	Lunesta
	Atvian
	Clorazepate Dipotassium
	Chlordiazepoxide

Training and Achievements

Throughout my MRes studies, I attended the Postgraduate Research 6-week writing course, to further develop and enhance my writing skills to produce publishable work. This 6-week writing course covered essential aspects such as structuring and maintaining flow in academic writing, developing critical writing techniques, and effectively organising each chapter of a thesis.

Additionally, I participated in the CFSRE's 12-part online course – "The Role of Comprehensive Medicolegal Death Investigation as part of a Public Health Improvement Strategy", where online webinars took place to discuss drug-related trends in the US. This series included webinars discussing drug-related trends in the US, which was particularly valuable given that the veterinary drugs investigated in my study often emerge there first. Gaining insights into US drug trends has provided a foundation for predicting similar patterns in the UK and globally.

As of September 2024, the chapter titled "Exploring the Confluence of Animal Medicine and its Implications for Human Health: A Systematic Literature Review" has been accepted for publication and is currently "in press" in the journal *Current Neuropharmacology*. This publication not only highlights the quality of my research but validates the importance of this work to the wider scientific community. The subsequent chapter, "Exploring Human Misuse and Abuse of Veterinary Drugs: A Descriptive Pharmacovigilance Analysis Utilising the Food and Drug Administration's Adverse Events Reporting System (FAERS)," is under review in *Toxics*, within the Drug Toxicity section. The final chapter, "From Veterinary Medicine to Illicit Drug Supply: Utilising Social Media to Explore the Rising Emergence of Veterinary Medicines in Human Health," is currently in preparation and will be submitted to *Expert Opinion on Drug Safety*.

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Exploring the Confluence of Animal Medicine and its Implications for Human Health: A Systematic Literature Review

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Affiliations + expand

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Abstract

Introduction: The abuse of veterinary drugs has emerged as a concerning trend, with global fatalities on the rise. Our understanding of this phenomenon remains limited. This study aims to identify the veterinary drugs being misused, the reasons behind their misuse, and how they are obtained.

Methods: Utilising PubMed, Scopus, and Web of Science databases, along with related grey literature, we applied the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) framework for data collection. Screening and cross-referencing yielded 66 relevant articles, encompassing case reports, surveys, reports, and systemic literature reviews. The analysis identified 28 distinct veterinary drugs being misused in humans, primarily falling into categories, e.g., α-2- and β-2-adrenergic receptor agonists, GABAergic receptor modulators, opioid receptor agonists, nonsteroidal anti-inflammatory drugs (NSAIDs), and N-methyl-D-aspartate (NMDA) receptor antagonists. These drugs were used for various purposes, including recreational use, weight loss, bodybuilding, pain relief, and self-medication for stress-related symptoms.

Results: Routes of administration predominantly included parenteral, oral, and inhalation methods. Veterinary workers/assistants and individuals connected to animals were identified as contributors to the misuse of these medications. Motivations for their utilisation ranged from affordability and accessibility to the ease of obtaining multiple prescriptions from various veterinary sources, often in conjunction with other illicit substances. Dependence and addiction were common outcomes of

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