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Review

Review of the Use of Pre-Visit Pharmaceuticals for Reducing Fear-Related Behaviours in Dogs

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Abstract

Fear, anxiety, and stress (FAS) in canine patients is a growing concern for the veterinary industry. FAS affects the health of the patient while also increasing the risk to veterinary staff. Studies show that many veterinarians do not feel confident in managing behavioural issues like FAS, making engaging effectively with clients more difficult. Pre-visit pharmaceuticals (PVPs) can be an important tool in mitigating the effects of FAS; however, conclusive research is lacking on the efficacy of many of the medications and combinations currently used for this purpose. A comprehensive literature search was conducted in multiple databases. The most current research available on medications identified as widely used for treating FAS, and available for use in New Zealand, has been reviewed and discussed. Combinations selected for inclusion were the 'chill protocol' of acepromazine, gabapentin, and melatonin. Single agents included are clonidine, dexmedetomidine, gabapentin, and trazodone. Research into the use of the 'chill protocol' suggests this may be a combination particularly useful in highly stressed and aggressive dogs; however, additional studies need to be conducted to strengthen the evidence for its use. A multimodal approach has been identified as being desirable when addressing FAS in a clinical setting, with less evidence to support the use of single-agent medications in mitigating problematic behaviours.

Keywords: fear, anxiety, stress (FAS); canine; pre-visit pharmaceuticals

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1. Introduction

1.1. Fear, Anxiety, and Stress: The Implications for Patients, Staff, and Clients

Managing fear, anxiety, and stress (FAS) in canine patients is an increasingly important issue in veterinary medicine. Clinical signs of FAS can be varied in both their presentation and the extent to which they impact the ability of veterinary staff to complete a physical examination on a patient. Patients showing signs of FAS may exhibit avoidant behaviours such as hiding, trying to escape, or refusing to enter a clinic or exam room [1]. In more extreme cases, this can escalate to aggressive behaviours such as growling, snarling, and biting, risking the safety of all parties involved [1].

Aggression is a common way through which FAS manifests in patients, leading to an increased risk to veterinary staff, owners, and the patients themselves [2]. Up to 75% of vets have reported being injured by a patient [2], and there are a number of unfortunate examples involving serious injuries to clinicians, as well as patients that have been ordered to be destroyed due to attacks on staff [3]. An example that received nationwide attention in New Zealand involved a veterinary surgeon sustaining significant injuries to her forearm, including a fractured ulna and nerve damage, following a sudden attack by a patient [3]. It

is important to acknowledge that even if the behaviour does not rise to a level that impedes the ability of veterinary staff to examine or conduct routine procedures like vaccinations, there is still cause for concern, and action to mitigate FAS should be initiated, due to the impact stress and anxiety it can have on a patient's overall health [1–5].

Negative health implications associated with patients exhibiting signs of FAS in a clinical environment include poorer outcomes when hospitalization is required, reduced access to preventative health care, such as vaccinations, due to a client's reluctance to expose their dog to a known stressful environment, and an inability of clinicians to complete a thorough clinical examination [2,4]. High FAS scores are also associated with increased rates of anesthesia complications and a reduction in the effectiveness of sedatives [5]. Finally, patients with FAS are at a higher risk of early age euthanasia due to behavioural concerns [2,6], with behavioural issues noted as the most common reason for both surrendering a dog and premature euthanasia [4,7].

FAS has a negative effect on client–clinic relationships [8], with research indicating that one in every five dog owners would attend veterinary appointments more often if it were less stressful for them and their pet [9]. As a compounding factor, a recent survey of graduating veterinary students in the United States found they did not feel confident in their ability to manage behavioural issues in their patients [10]. In addition, clients are reportedly resistant to the use of behaviour-modifying pharmaceuticals [11]. Recommended strategies for managing this reluctance include clear communication around the benefits of pre-visit medications, such as a potential reduction in the number of sedative agents required to anesthetise a highly stressed or anxious patient, which can both reduce costs and anesthetic complications [2,4,5,8]. In the study conducted by van Haaften et al. [11], evidence supporting the efficacy of a medication or protocol was reported as the most important consideration by owners; therefore, the ability to reference quality research to support their use may be critical in achieving the best outcome for patients with FAS.

1.2. The Impact of COVID-19

Societal changes associated with the response to the COVID-19 pandemic created ideal conditions for dogs to develop behaviours associated with FAS. During this period, an increase in dog adoptions was noted worldwide, coupled with 'lockdowns' that necessitated the closure of dog parks and training clubs, resulting in 'pandemic puppies' that have had minimal exposure to novel stimulation and socialization opportunities [12]. Several studies have found that a lack of socialization is a predicator for displaying signs of FAS as an adult dog [13,14]-and the veterinary industry has seen a rise in patients exhibiting problem behaviours due to the impact of the COVID-19 lockdowns [12], with the coining of the term "COVID dogs" [12,15].

While these unusual societal conditions may have increased the frequency of these behaviours, patients exhibiting clinical signs of FAS during veterinary examinations have been an ongoing concern, with the original "Chill Protocol" (acepromazine, gabapentin, and melatonin) routinely used at Tufts University since 2014 [16], and research on medications such as trazodone being conducted in the mid-1990s [17].

1.3. Pre-Visit Pharmaceuticals (PVPs): An Overview

With these clear areas of concern associated with FAS, it is important for veterinary professionals to explore ways to mitigate and reduce the impact of FAS on the provision of veterinary care. While the dispensing of PVPs is becoming more common, Hargrave notes that sedation is still under-utilized as a tool to reduce the impact of FAS on patients [4]. Research shows that there is a cumulative effect of negative experiences in patients [4,5]. Each poor experience serves to increase stress on the patient and causes a heightened

response during future visits [4]. It is, therefore, important to reduce both the number of negative visits as well as the intensity of the response. An example of the way in which behaviours associated with FAS is illustrated in Ryan (2017) as a ladder of behaviours that describe the escalation from low-stress indicators, such as yawning and nose licking, through to creeping with ears back and to snapping and biting [1].

While a multi-pronged approach involving desensitization and counterconditioning is key to long-term success [5], this review will focus on the use of short-acting pre-visit pharmaceuticals (PVPs) to reduce FAS in patients during clinical visits. The aim of this review is to assess the strength of evidence supporting the use of PVPs to enable veterinary professionals in New Zealand to advocate for patients and discuss different protocols effectively with clients. While these medications will still need to be discussed with, and prescribed by, a licenced veterinarian, veterinary nurses are commonly involved in discussions with clients about behavioural concerns and are also at risk from patients displaying aggression, as important members of the veterinary team. The medications mentioned in this research review have all been found suitable for administration to dogs for a variety of ailments; however, it should be noted that their use in mitigating fear-related behaviours, specifically in dogs, is considered 'off-label'.

2. Methods

2.1. PICO

The PICO framework for systematic review was used to identify search terms and formulate the research question for this review [18]. The elements of the PICO are listed below:

Population: Canines with FAS located in New Zealand.
Intervention: Administering pre-visit pharmaceuticals.
Comparison: Different medications and/or combinations.
Outcome: Reduction in FAS and increase in patient compliance, leading to safer and more frequent access to veterinary care.

Identifying these elements assisted in formulating the research question addressed by this review: Which pre-visit pharmaceuticals provide the greatest reduction in FAS, while increasing patient compliance, in dogs treated clinically in New Zealand?

2.2. Literature Search

An initial literature search in both Articles Express and Google Scholar revealed ProQuest, ScienceDirect, AVMA, and EBSCO to be the most relevant databases, and an advanced literature search was then conducted on 8 May 2024 using the following search terms:

Behavio * AND canine OR dog AND veteran * AND [medication name/combination]

As the aim of this literature review is to investigate medications that can be used to facilitate a reduction in FAS in a clinical setting, the studies reviewed have been limited to only medications and combinations that are used primarily for this purpose. Therefore, short-acting medications for behaviour modification are included, while longer-acting medications and those that are designed to be used for chronic behavioural issues have been excluded.

2.3. Inclusion Criteria

Inclusion criteria for medications focused on those that have been commonly used for this purpose and reported on in the peer-reviewed literature, and medications available in New Zealand.

From the original "Chill Protocol", acepromazine, melatonin, and gabapentin warranted inclusion [16]. The remaining medications included in this review were chosen from

among those discussed in three recent, peer-reviewed literature reviews (Table 1). The reference lists from these reviews were also searched for relevant articles.

Table 1. Literature reviews on treating FAS during clinical visits, from which the medications included for review were drawn.

Reference	Title	Medications Discussed
Riemer et al., 2021 [5]	"A review on mitigating fear and aggression in dogs and cats in a veterinary setting"	Acepromazine, alprazolam *, clonidine, dexmedetomidine [OTM], gabapentin, and trazodone.
Erickson et al., 2021 [19]	"A review of pre-appointment medications to reduce fear and anxiety in dogs and cats at veterinary visits"	Alprazolam *, dexmedetomidine [OTM], gabapentin, and trazodone.
Warnes et al., 2022 [20]	"The use of behaviourally-active medication in companion animals part 1"	Alprazolam *, clonidine, dexmedetomidine [OTM], diazepam *, gabapentin, imepitoin *, and trazodone.

* not included in this review.

The resulting list of medications included acepromazine, clonidine, dexmedetomidine, gabapentin, and trazodone.

2.4. Exclusion Criteria

Alprazolam was excluded due to its being unavailable in New Zealand [21]. A decision was made to exclude benzodiazepines generally, along with imepitoin (Pexion, Boehringer Ingelheim, Auckland, New Zealand), due to the potential side effect of behavioural disinhibition, which was associated with aggression [20].

Search limits were set to exclude articles that were not peer-reviewed, were not published in English, and articles that were published prior to 2014. Articles that did not focus on dogs or did not focus on the medications selected for review were also excluded.

2.5. Limitations and Challenges

Some limitations around using consistent search terms became apparent during the initial stages of the search. While some medications had a number of recent, high-quality studies published, others had less robust or older evidence to support their use. This necessitated including articles published prior to 2014, namely a 2002 study evaluating acepromazine [22] and a 2011 study into the efficacy of clonidine [23]. In addition, for some commonly used agents, namely gabapentin and trazodone, there was very limited clinical research in existence that was specific to the focus of this review. The author is aware of only a single clinical study into each of these medications for the treatment of FAS in dogs during veterinary visits, despite their wide use for this purpose.

FAS can be represented as a rating on a scale determined by observable behaviour (available through Fear Free Pet Wellbeing group) with 1 being the lowest level, indicating little to no stress, and 5 being the highest rating, indicating the patient has a history of extreme levels of FAS, including escalation to growling and biting [24]. This review was completed with a view to providing research that attempts to mitigate even the highest levels of FAS. The clinical studies selected for inclusion in the review are presented in Table 2.

Table 2. Clinical studies selected for inclusion in this extended literature review.

Reference	Medication	Sample Size	Population	Hypotheses/Aims/ Objectives	Methodology				Main Findings
					Article Type	Randomized	Double-Blinded	Placebo-Controlled	
Costa et al. (2023) [25]	Chill Protocol (Acepromazine, melatonin, gabapentin)	45	Healthy dogs with a history of FAS, aggressive dogs not excluded	That the 'chill protocol' would reduce FAS in over 75% of subjects	Clinical trial	No	No	No	FAS was reduced in 91.1% of subjects Increased patient compliance
Vaisanen et al. (2002) [22]	Acepromazine	42	Healthy female dogs, undergoing ovariohysterectomy	To compare acepromazine to medetomidine to find which agent produces the lower stress scores	Clinical trial	Yes	Yes	No	Medetomidine was more effective than acepromazine at reducing clinical markers of stress
Kim et al. (2022) [26]	Trazodone	20	Healthy dogs with a history of FAS	That trazodone dosed at 9–12 mg/kg 90 min before a veterinary appointment would show reduced signs of FAS	Crossover clinical trial	Yes	Yes	Yes	Lower stress scores in the trazodone group compared with the placebo group
Stollar et al. (2022) [27]	Gabapentin	22	Healthy dogs	To evaluate a single dose of gabapentin as a treatment for FAS prior to a veterinary appointment	Clinical trial	Yes	Yes	Yes	Lower stress scores in the gabapentin group compared with the placebo group
Ogata & Dodman, (2011) [23]	Clonidine	22	Healthy dogs with a history of behavioural issues including separation anxiety, storm phobia, noise phobia and fear aggression	To evaluate clonidine as a treatment of fear-based behaviours when used on an 'as required' basis.	Open trial	No	No	No	82% of dogs showed improvement on clonidine Of the dogs that showed improvement, most were recorded as being more than 50% better with the clonidine
Hauser et al. (2020) [28]	Dexmedetomidine oromucosal gel	40	Healthy dogs with a history of FAS, excludes aggressive dogs	To investigate the efficacy of dexmedetomidine gel for the treatment of FAS in dogs when administered in a clinical environment	Clinical trial	Yes	Yes	Yes	Showed a statistically significant reduction in FAS when treated with dexmedetomidine gel Did not show an increase in patient compliance
Korpivaara et al. (2021) [29]	Dexmedetomidine oromucosal gel	76	Healthy dogs with a history of FAS, excludes aggressive dogs	Evaluate efficacy and safety of dexmedetomidine gel to treat FAS during veterinary visits	Clinical pilot study	Yes	Yes	Yes	Dexmedetomidine gel was shown to be safe and effective at reducing signs of FAS Some evidence to support increased patient compliance, however the strength of this was weak

3. Pre-Visit Pharmaceuticals

3.1. Acepromazine

Acepromazine is a phenothiazine and is used clinically as a sedative and tranquilliser; it is not known to have anxiolytic properties [8,22,25]. Costa et al. noted that when used in combination with other medications, acepromazine can enhance the sedative and anxiolytic properties of other agents [25]. The use of acepromazine as a single agent is no longer recommended for the treatment of FAS, with studies showing no change in stress or anxiety scoring when used alone [5]. Research into the use of acepromazine as a sedative agent in dogs being transported via airplane found that both the control group and the group sedated with acepromazine showed physiological signs of an increased stress response, including an increase in both salivary cortisol concentration and heart rate [30]. This supports the view that acepromazine alone is unsuitable as a treatment for FAS in dogs.

3.1.1. Mechanism

As a phenothiazine, acepromazine acts as a depressant on the central nervous system, causing sedation and vasodilation [31]. Although acepromazine may work synergistically with other sedative and anxiolytic agents when used in combination, enhancing their effect [25], it is not known to possess any anxiolytic effects itself [5]. It is, therefore, important to acknowledge that successfully treating FAS cannot be achieved by simply sedating or tranquillising a patient, as while this may result in a patient who is compliant

for examination, if the patient is still experiencing anxiety and stress, it is also still subject to the ill effects associated with FAS.

3.1.2. Evidence

Limited research into the use of acepromazine to treat FAS exists. One study comparing the effects of either acepromazine or medetomidine on perioperative stress levels in dogs has been conducted [22]. Although not specifically targeted at FAS during veterinary visits, the study evaluated physiological markers of stress in canine patients in a clinical environment, and therefore, still has some relevance to this review. The authors referred to acepromazine being widely used to provide chemical restraint and sedation [22], and prior to acepromazine falling out of favour for this purpose, it was certainly the case [32].

The authors compared the clinical signs of stress in patients administered a pre-medication dose of either acepromazine in combination with butorphanol (an opiate), designated as group ACE, or medetomidine in combination with butorphanol, designated group MED [22]. A group of 42 female dogs booked for ovariohysterectomy (OHE), who were 'in good health' and between 15 and 40 kg and 2–7 years old, were selected for inclusion in the study [22]. Brachycephalic breeds and greyhound breeds were excluded from the trial, and the authors did not screen for behavioural issues [22].

The results of the study indicated that medetomidine was more effective at reducing stress, with lower levels of cortisol, epinepherine, and norepinephrine reported in this group [22]. The authors discussed the possibility that the higher cortisol levels noted in the ACE group may be related to acepromazine producing less of a sedative effect than medetomidine and specifically noted that patients in the ACE group appeared less sedated prior to surgery [22]. The results of this study are similar to those reported by [30].

It should be noted that butorphanol, as a partial opioid agonist, would no longer be considered to provide an appropriate level of analgesia for a canine OHE surgery, with a strong preference for a full mu-opioid, such as methadone or morphine [33]. It is, therefore, possible that increased cortisol levels during the post-operative phase may have been impacted by inadequate analgesia.

3.1.3. Dose Rates and Safety

Dose rates for acepromazine vary depending on the way in which it is administered. When given intravenously (IV), the dose is 0.01–0.02 mg/kg [31]. The intramuscular (IM) dosage is listed as 0.01–0.05 mg/kg [31]. These dose rates assume the agent is being used as a sedative or pre-anesthetic medication. In a study comparing acepromazine to medetomidine as a mitigating agent for perioperative stress levels, acepromazine was administered IM in conjunction with butorphanol at a dose rate of 0.05 mg/kg [22].

In studies investigating acepromazine as a treatment for FAS, the injectable formulation can also be administered orally, and again, dose rates vary. The listed dose for acepromazine when given orally is 1–3 mg/kg [31]. Bergeron et al. used a fairly low dose rate of 0.5 mg/kg when studying the effect of acepromazine on stress in dogs being transported by airplane [30]. The results of this study did not show that acepromazine, at this dose, was effective at reducing clinical signs of stress [30].

The use of acepromazine in patients already experiencing high levels of FAS is contraindicated due to its potential to exacerbate these symptoms [5]. Additionally, note sensitivity to noise as a reported side effect [25], and the BSAVA Small Animal Formulary Part A: Canine and Feline (10th edition) advises against the use of acepromazine for the management of sound phobias in dogs [31]. It is also not recommended for use in Boxers and sight-hounds [31]. Acepromazine is used off-label to treat stress and anxiety in dogs [31,34].

3.2. Clonidine

Clonidine is an alpha-2 agonist, used as an anti-hypertensive in human medicine, although it is also commonly used to treat psychiatric disorders, including post-traumatic stress disorder, and as a treatment for ADHD [23]. In veterinary medicine, clonidine has been used to treat fear-based behaviours, and although limited studies have been performed, the results have been encouraging, and it may be under-utilized as a treatment for FAS [23].

3.2.1. Mechanism

As an alpha-2 agonist, clonidine acts on the locus ceruleus (LC) and inhibits the production of norepinephrine (NE), reducing responsiveness to fearful stimuli [23]. Clonidine exhibits sedative, anxiolytic, and analgesic properties [23]. Research into clonidine in human medical studies indicates that it is effective at reducing the perception of threats and other stressors, leading Ogata and Dodman (2011) to investigate its use as a treatment for fear-based behaviours in dogs [23].

3.2.2. Evidence

An open study into clonidine as a treatment for fear-based behavioural issues was conducted by Ogata & Dodman in 2011. The study included 22 dogs that had been diagnosed with fear-based behavioural issues, split into two groups [23]. Group A (10 dogs) were diagnosed with phobias and separation anxiety, but were not fear aggressive, and Group B (12 dogs) were classified as having aggressive behaviours [23]. All the dogs included in the study were medicated concurrently with longer-acting behaviour-modifying medications, including fluoxetine, sertraline, buspirone, and clomipramine [20,23]. The study involved owners medicating their dogs in the home with a prescribed dose of clonidine on an as-required basis; the owners then reported their assessment of their dogs' behaviour after medicating with clonidine, during follow-up telephone conversations [23].

Although multiple limitations were noted, the study reported that 82% (18 dogs) had a positive response, with a reduction in the intensity of signs of fear-based aggression, as scored by owners [23]. A further 83% of dogs in this category were scored by owners as more than 50% improved on clonidine compared to being unmedicated [23]. The results of Group B (dogs with aggressive behaviours) were very encouraging, with 11 out of 12 owners reporting an improvement on clonidine [23]. These results would suggest that further research into clonidine as a treatment for FAS should be conducted.

The subjective nature of the owner assessments is a limitation when interpreting the strength of evidence supporting the use of clonidine. Additionally, it would have been advantageous to have a comparative group treated with only clonidine, as all the subjects included in the study were being treated concurrently with other behaviour-modifying medications. This study did not investigate the efficacy of clonidine with specific regard to FAS in a veterinary environment. However, the results of the study with respect to treating fear-based behavioural issues are encouraging and may suggest some evidence to support the use of clonidine for fear-based behaviours associated with veterinary visits.

3.2.3. Dose Rates and Safety

Ogata & Dodman started with a dose of 0.01 mg/kg one to two times daily, increasing to 0.05 mg/kg if tolerated by the patient with no adverse effects [23]. The BSAVA Small Animal Formulary Part A: Canine and Feline (10th edition) takes their listed dose from Ogata & Dodman's 2011 study [23,31]. A more recent study also used a dose of 0.05 mg/kg [35]. This study combined clonidine with tramadol as part of a pre-anesthetic protocol, and the authors concluded with a warning that there may be an interaction between these

two medications, as two of the eight patients in the study experienced a second-degree atrioventricular block and died during the trial [35]. For this reason, while the authors supported further investigation into clonidine as a treatment for fear-based behaviours, they strongly advised against its use in conjunction with tramadol due to the potential for adverse cardiovascular effects [35]. The BSAVA Formulary lists renal and cardiovascular disease as a contraindication and adds a warning advising that clonidine should not be used concurrently with opiates, barbiturates, or antihypertensive agents [31]. Clonidine is used off-label to treat fear and anxiety in dogs in New Zealand [34].

3.3. Dexmedetomidine Oromucosal Gel (Sileo®)

Dexmedetomidine is an alpha-2 agonist, commonly used as a sedative either as a single agent or in combination with an opioid. Available as an oromucosal gel (Sileo® by Zoetis, Parsippany, NJ, USA) for ease of use by owners, dexmedetomidine has been safely used in clinical trials investigating its efficacy as a treatment for both noise phobia and FAS during veterinary visits [28,29,36].

3.3.1. Mechanism

Dexmedetomidine is an alpha-2 agonist, and similarly to clonidine, it acts on the locus coeruleus (LC) and decreases the patient's response to stressors by inhibiting the production of noradrenaline [19,20]. This mechanism of action results in sedative, anxiolytic, and analgesic effects [28,31]. Dexmedetomidine is known to cause vasoconstriction, leading to a compensatory reduction in heart rate, with the potential for bradycardia at higher doses [20,31]. When used as an oromucosal gel, a lower dosage is used (sub-sedative), and these cardiovascular effects are not expected [20].

3.3.2. Evidence

In two clinical studies on the use of dexmedetomidine oromucosal gel to treat FAS during veterinary visits, dogs with a noted history of FAS were invited to take part in studies that were randomized, double-blind blind, and placebo-controlled [28,29]. Methodology differed between the two studies; however, dogs showing signs of, or with a history of, aggression were excluded from both studies. Hauser et al. elected to have the owners administer the gel in the consultation room 5 min after arriving at the veterinary clinic, with a veterinarian then entering the room after 20 min to conduct a standardized examination [28]. Korpivaara et al. had the client administer the gel at home "in a stress-free environment" 45 min–1 h prior to the appointment [29]. Hauser et al. made note of the reality of dogs presenting to veterinary clinics with no previous history of behavioural issues and referenced the quick action time of dexmedetomidine oromucosal gel (20 min) in support of their investigation into its use in these cases [28]. This difference in methodology may have some bearing on the differences reported in their respective results.

Korpivaara et al. reported that the ease of carrying out a physical examination was significantly improved in the patients who had received dexmedetomidine oromucosal gel compared to the placebo group [29]. The placebo group reported 17.4% of examinations as 'not possible', while the active groups scored 14.8% 'not possible' for the label dose (125 mcg/m^2) group, and just 8.3% 'not possible' for the higher dose (250 mcg/m^2) group [29]. The Hauser et al. study, however, reported that while signs of FAS (vocalization and avoidance behaviours) were reduced in the group that received dexmedetomidine, there was no difference in the ease of performing a physical examination [28]. There are several possible explanations for this difference. In the trial conducted by Korpivaara et al., giving the medication while the dog was relaxed and comfortable at home may have increased its efficacy [29], with Hauser et al. noting in their discussion that administering

the dexmedetomidine to an already stressed patient may affect effectiveness [28]. Another possibility may be found in the results section of the Korpivaara study, where they acknowledge that the majority of dogs in the trial scored between 'fair' and 'excellent' during the screening appointment for 'ability to perform an examination' [29]. If the dogs were fairly easy to examine prior to receiving the dexmedetomidine, this may have increased the chance of them scoring well after medication.

These differences in results make it difficult to consider the evidence supporting the use of dexmedetomidine gel to treat FAS during veterinary visits as conclusive. Both studies were able to conclude that dexmedetomidine gel reduced the signs of FAS in dogs during veterinary appointments [28,29]; however, the evidence supporting its use as a tool to enable clinicians to carry out a physical examination on patients with FAS is still subject to some debate.

As randomized, double-blinded, placebo-controlled trials, the data obtained is of a high standard. However, both studies reported conflicts of interest, with Zoetis (the distributor of Sileo®) and Orion Corporation (the manufacturer of Sileo®) sponsoring or funding the studies.

3.3.3. Dose Rates and Safety

Only the oromucosal gel formulation of dexemedetomidine has been investigated in this review; therefore, dose rates presented are for this formulation, not the injectable solution. The licenced dose rate for dexmedetomidine gel is 125 mcg/m^2. There has also been research conducted at double the listed dose, 250 mcg/m^2, with no reported safety concerns [29,36]. Sileo® is manufactured as a 3 mL pre-filled syringe with graduated 'dot' markers to enable easy dosing for weight; the concentration is 0.1 mg/mL. Sileo® is used off-label to treat fear and anxiety during clinical visits in dogs, but is licenced for the treatment of acute fear and anxiety in response to noise [34].

3.4. Gabapentin

Gabapentin is a gabapentoid, used as an anticonvulsant and analgesic [20]. Evidence around the use of gabapentin as a single agent to treat FAS in dogs has previously been based on research performed on cats [37] and on storm phobias in dogs [38]. More recently, Stollar et al. conducted a clinical study on the efficacy of a single dose of gabapentin as a treatment for FAS during veterinary visits [27]. To the authors' knowledge, this is the only study into the use of gabapentin for this purpose.

3.4.1. Mechanism

Gabapentin belongs to the drug class gabapentoid, although it does not bind to GABA receptors [39]. The mechanism of action for gabapentin is not conclusively proven; however, it is thought to work by inhibiting the release of excitatory neurotransmitters [39].

3.4.2. Evidence

Limited studies on the efficacy of gabapentin as a sedative or anxiolytic agent exist in dogs; however, it has been widely used for this purpose [8,20]. A recent study found that a single dose of 50 mg/kg given prior to veterinary visits significantly reduced signs of FAS in dogs [27].

Stollar et al. investigated the use of gabapentin as a treatment for FAS through a double-blinded, placebo-controlled study [27]. The sample population was small, with just 22 clinically healthy dogs included in the study, with dogs showing a history or signs of aggression excluded [27]. The dose administered to subjects was fairly high, at 50 mg/kg, with similar studies (albeit either not for this specific purpose or in conjunction with other medications) dosing at 20–30 mg/kg [16,25,27,38].

The results of the study reported a reduction in some behaviours indicative of FAS, compared to the placebo group, and also established that there were no significant adverse effects reported, with no dogs needing to be withdrawn from the trial [27]. Stollar et al. also tested salivary cortisol concentrations in both groups and found no significant differences between the two [27]. The authors referenced several potential explanations for this, including the possibility that the mode of action of gabapentin is more sedative than anxiolytic, and suggested further research to investigate this is warranted [27].

In addition to the small sample size, a limitation of the study was that it did not specifically include dogs with a history of FAS [27]. An important consideration when evaluating the efficacy of a medication to treat FAS during veterinary visits is whether it facilitates an easier physical examination by the clinician. In conducting the study on healthy dogs, without previously reported signs of FAS during veterinary visits, it is, therefore, difficult to establish from Stollar et al.'s study whether gabapentin is effective for this purpose [27].

3.4.3. Dose Rates and Safety

Gabapentin has a published dose range of 10–20 mg/kg in dogs [31], with some studies suggesting that doses at the higher end of the range (20 mg/kg) are necessary to see anxiolytic or sedative effects [5,19,39].

Gabapentin has been given at doses of up to 50 mg/kg with the study reporting no adverse effects, indicating a strong safety range in dogs [27]. Gabapentin is used off-label to treat fear and anxiety in dogs [34].

3.5. Trazodone

Trazodone is a serotonin antagonist and reuptake inhibitor [26], with primarily anxiolytic properties [40]. A large number of studies on trazodone as a treatment for FAS exist [17,32,41–43]; however, only one specifically addresses its use in treating FAS for veterinary appointments [26].

3.5.1. Mechanism

As an atypical antidepressant SARI, trazodone is used as an anxiolytic medication in both human and veterinary medicine [31,40]. Functioning as a serotonin reuptake inhibitor, clinical studies have shown trazodone causes a reduction in anxious behaviours in dogs [40].

3.5.2. Evidence

Kim et al. investigated the effect of a single dose of trazodone, given prior to a veterinary appointment, on stress levels in dogs [26]. In this crossover trial, 20 healthy dogs were selected and randomly assigned to two groups, with each group receiving either a placebo or an active agent prior to attending a veterinary visit and standardized examination [26]. Aggressive dogs were excluded from the study.

Two veterinary visits were conducted, and if a patient received the placebo before the first visit, it received the active agent (trazodone dosed at 9–12 mg/kg) before the second visit [26]. Both the owners and research staff completed a behavioural assessment survey, the visits were videoed, and clinical information (heart rate, respiration rate, and serum cortisol concentrations) was obtained from the patients [26]. The results of the study showed a significant reduction in the dog stress score (DSS) when the patients were medicated with trazodone prior to the appointment, and owners reported their dogs appearing less stressed [26]. Although the reporting from the owners is encouraging, the research staff did not record a significant difference in behavioural scores between the two groups [26]. The authors noted that since owners have been found to avoid veterinary visits

if their dog finds them stressful, just the perception of owners that trazodone makes the visits less stressful may increase the likelihood of them attending visits more frequently [26]. It was also noted that the patients did not appear sedated, and as this has also been a factor in clients refusing PVPs, this may likewise increase the chances of owners 'opting in' to their use [26].

The authors acknowledged that multiple other research avenues into the use of trazodone to treat FAS exist, including medication protocols involving multiple dosages, a common example is a dose the night before the veterinary visit and a second dose 90 min prior to the appointment [26]. Also, the study was partially funded by Fear Free Pets LLC; however, this organization does not have a particular PVP that they recommend, so it is unlikely to result in the potential for bias. In addition, the authors reported no conflicts of interest.

3.5.3. Dose Rates and Safety

The dose rate used in the Kim et al. study, at 9–12 mg/kg, is higher than the dose rates used in similar studies [26]; however, the published range is quite broad, at 4–12 mg/kg, up to 300 mg per dog [31].

A study into the use of trazodone to mitigate stress during post-surgical confinement used doses of 3.5–10 mg/kg [32]. An earlier review of cases where trazodone was used as adjunctive treatment for canine anxiety found doses varied from 1.9 mg/kg to a maximum dose of 19.5 mg/kg [17]. Trazodone is used off-label to treat fear and anxiety in dogs [34].

3.6. The "Chill Protocol" (Acepromazine, Gabapentin, and Melatonin)

The "Chill Protocol" [25] was developed at Cummings School of Veterinary Medicine, Tufts University, and has been used since 2014. The protocol combines acepromazine, gabapentin, and melatonin in a multimodal approach to treating FAS in dogs [16].

3.6.1. Mechanism

Mechanisms of action for acepromazine and gabapentin have been noted in the previous sections. The mechanism of action for melatonin with regard to its use as an anxiolytic has not been established; however, studies in human medicine have shown a reduction in perioperative anxiety, and anxiolytic effects have been noted when used to treat storm phobia in dogs [25].

3.6.2. Evidence

Costa et al. carried out a clinical study investigating the efficacy of the protocol on 45 client-owned dogs with a history of FAS during veterinary visits [25]. The clinical trial compared signs of FAS and the level of sedation after receiving a combination of gabapentin, melatonin, and acepromazine (GMA) against an established baseline [25]. This trial aimed to provide evidence supporting the use of the chill protocol, with the authors acknowledging that although the use of PVPs has increased, specific data on efficacy and consistency are lacking [25]. It was hypothesized that the use of the chill protocol would reduce FAS in more than 70% of the subjects included in the study [25]. The study compared a baseline FAS score without any medication to FAS scores at a second visit with the medication on board [25].

This trial was directed specifically at dogs with a pre-existing history of FAS and did not exclude aggressive patients [25]. For this reason, the trial was not double-blinded or placebo-controlled. However, the methodology was robust, with patients being videoed during a screening appointment, at which a standardized physical examination was attempted, before returning after a two-week "wash-out" period medicated with the GMA protocol [25]. The second appointment was also videoed, and the same standardized

examination was attempted, with the data collected blinded by assigning a reference code to each patient and then randomly assigned and analyzed by four trained observers [25].

The authors reported a reduction in FAS in 91.1% of the dogs included in the study and concluded that the protocol was effective in reducing FAS [25]. Of particular importance is the additional conclusion that the protocol improved "handleability and increased compliance during examination" [25]. It was noted that overall, the patients experienced signs of sedation, corresponding with lower stress scores, which was attributed to the use of gabapentin, with this effect being more profound in older patients [25]. The authors discussed the likelihood of subclinical levels of renal impairment, common in geriatric patients, being a contributing factor, with around a third of the gabapentin dose excreted as urine after metabolizing [25].

Limitations of the study were identified as a lack of control or comparative groups, where one or two of the agents could be given, compared to the full GMA protocol [25]. The potential for the results of the second appointment to have been impacted by desensitization from the first visit was discussed but largely discounted as it would be more typical to experience an increase, rather than a decrease, in FAS at a second visit [1,4]. Additionally, desensitization and counter-conditioning take time to effectively manage FAS, and the short timeframe and single screening visit were unlikely to achieve this [2].

3.6.3. Dose Rates and Safety

The protocol involves the use of three agents given at the dose rate, frequency, and mechanism of delivery [25]. In the Costa et al. clinical study, acepromazine was given oromucosally at a dose of 0.05 mg/kg [25]. This dose is at the higher end of that initially published (0.025–0.05 mg/kg) but is still within a generally accepted dose range when treating FAS [8,16]. This is a comparatively low dosage when delivered orally, with published dose rates for oral acepromazine being listed at 1–3 mg/kg [31], although this dose is more likely to be recommended for profound sedation prior to anesthesia, rather than for the management of FAS.

The chill protocol dose for gabapentin is 20–25 mg/kg [16,25]. This dose is in line with research suggesting doses in this range are more likely to achieve sedation [5,19,39]. The BSAVA Small Animal Formulary Part A: Canine and Feline (10th edition) lists the dose for melatonin at 3–6 mg/dog; however, there is no dose specific to the treatment of FAS, so it is used 'off license' for this purpose [31]. The dose used in the GMA protocol for anxiolysis falls within this dose range, at 1–5 mg/dog [16,25]. Further, no safety concerns were discussed with regard to the study, and the authors did not report having to withdraw any subjects for this reason.

4. Discussion

Although reviewing the current evidence supporting the use of pre-visit pharmaceuticals revealed some recent, encouraging clinical studies, the strength of evidence is still weak for several widely used medications.

4.1. Study Aims and Objectives

It was noted that while many studies were able to report a reduction in signs of FAS, several were unable to make a corresponding conclusion with regard to an improvement in patient compliance, facilitating a better clinical examination. While reducing signs of FAS is a positive improvement for patient welfare and can avoid an escalation in stress-related behaviours, if the patient is still unable to be physically examined in a clinical setting, then there is an ongoing risk to the patient's health.

Not all studies reviewed were specifically aimed at increasing patient compliance, and additional research into medications that can provide this outcome is needed to give clinicians confidence in recommending their use. With clients already reticent to use behaviour-modifying medications, having strong evidence to present in their favour is needed in order to increase client confidence and obtain the best outcome for the patient [11].

A number of studies identified that if clients are visibly able to see their pet is less stressed during veterinary visits, this may result in them seeking out veterinary care more readily [26,28,29]. As efficacy is reported as the main contributor to the client deciding whether to utilize PVPs [11], this visible perception of the medication effectively reducing signs of FAS may have the biggest impact on a client's 'buy in'. Discussing the goals of treatment with PVPs is important to manage client expectations, and pharmaceuticals should be used concurrently with behaviour modification training. Additionally, discussions should be held with clients regarding what a 'successful' visit and treatment outcome looks like, with a long-term goal of being able to reduce dosages over time.

4.2. Conflicts of Interest and Bias

A common concern with the clinical studies reviewed involved potential bias and conflicts of interest. Both trials of dexmedetomidine oromucosal gel were funded by the manufacturer or distributor of Sileo®, and the authors had strong connections to these companies. The lead author of the study on the combination referred to as the 'chill protocol' was also listed as the lead author on the original article published in Clinician's Brief in 2019 and had been introduced and used since 2014 [16,25].

4.3. Sample Size and Selection

Sample sizes for all clinical studies were fairly small, ranging from 20 [26] to 76 [29] healthy, client-owned dogs.

With the exception of Costa et al. [25] and Ogata and Dodman [23,25], the clinical studies all excluded patients with a history of high levels of FAS and/or aggression. Although it should be noted that a limitation in Ogata & Dodman's study was a reliance on owner assessments [23]. The intervention was carried out at home and then reported by owners, rather than being assessed by clinicians [23]. Kim et al.'s study into trazodone excluded patients with a history of aggression [26]. Stollar et al. also excluded patients with a history of aggression in their investigation of gabapentin [27]. Behaviour was not addressed as an inclusion criterion in a study into acepromazine [22]. Both Hauser et al. and Korpivaara et al. excluded dogs with a history of aggression in their clinical trials on the effect of dexmedetomidine oromucosal gel on FAS in dogs during veterinary visits [28,29]. These exclusions make it difficult to assess whether the study findings can be relied upon in patients exhibiting high levels of FAS during clinical appointments.

4.4. Further Research

Clinical studies on widely used combinations of medications are needed to provide evidence for their use. An example is trazodone and gabapentin, which are commonly used as a treatment protocol for FAS during veterinary visits but have yet to have any published research to support their use for this purpose in dogs, with clinicians relying on studies conducted in cats to support their use [20]. There has, however, been a recent study into electroretinographic responses in dogs published, which was able to report no safety concerns when gabapentin and trazodone were used concurrently [44].

Clonidine has had encouraging results in previous clinical trials; however, these need to be repeated in order to strengthen the evidence for its use. As there are concerns around the safety of clonidine when used in combination with tramadol [35], careful consideration

should be given to its use in conjunction with opioids, and dexmedetomidine may be a safer alpha-2 agonist alternative.

Dexmedetomidine oromucosal gel (Sileo®) has also had a number of encouraging clinical studies; however, there have been differing results with regard to an increase in patient compliance, and therefore, repeating these studies with a standardized dosing protocol would be beneficial to strengthening the evidence for its use as a single agent. Another avenue of research may be the combination of dexmedetomidine gel with another agent, with the aim of both reducing FAS and increasing patient compliance, or developing a protocol utilizing dexmedetomidine gel that is targeted at patients with high FAS scores.

5. Conclusions

There is a lack of robust research to support the use of the majority of the medications commonly used to treat FAS. While the recent clinical study undertaken by Costa et al. showed promising results [25], the clinical trial needs to be repeated and the sample size increased. Although there are weaknesses and potential bias in the clinical study on the 'chill protocol', the results of the study are very encouraging and may support the use of a multimodal approach, rather than relying on a single agent to treat FAS during veterinary visits. The objective of the study meant that randomization and controls were not utilized, as the authors specifically included patients with high FAS and histories of aggressive behaviour [25].

At present, the most promising single-agent medication is dexmedetomidine oromucosal gel (Sileo®). Unfortunately, findings regarding its impact on patient compliance differ, but this may be due to a difference in methodologies between two clinical studies [28,29]. When given 90 min–1 h prior to veterinary appointments, an increase in patient compliance was reported [29]. A similar study that involved dosing the patients after arrival at the veterinary clinic, and only waiting 20 min after administration, was unable to report the same results [28]. Both studies recorded a significant reduction in signs of FAS and strong evidence suggesting dexmedetomidine gel can be used safely at a wide dose range [28,29]. Owners also reported that the gel can be used easily at home [28,29]. While further research is needed, there is potential for this medication to be a strong tool in mitigating FAS during veterinary visits.

Both trazodone and gabapentin have shown evidence of reducing signs of FAS; however, these studies are unable to show a corresponding increase in patient compliance. More studies on their use and in combination with other medications are needed to provide evidence for their use in treating FAS during veterinary visits. It is possible that they may have value in treating FAS in patients who are not aggressive in the clinic or score lower on the FAS scale.

There were an encouraging number of recently published studies aimed at addressing exactly this concern—using pre-visit pharmaceuticals to manage canine patients with significant levels of FAS and potentially fear–aggressive behaviours. There were also several studies that were the first of their kind to be published on medications that are already commonly used to treat FAS during veterinary visits, giving important insights and evidence on their efficacy.

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