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EFFECTS OF TREATING BEHAVIOURAL PROBLEMS: COMBINING BEHAVIOURAL THERAPY AND PSYCHOTHERAPEUTICS

Influences of medication and changes therein, behavioural therapy and other factors on the outcomes of cases in the behavior clinic

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Abstract

Behavioural problems of animals can cause difficulties for their owners, their environment and themselves. Dangerous situations may arise and welfare is at stake. Behavioural therapy can be used successfully as treatment, sometimes (especially in the more severe cases) the combination with psychotherapeutics is useful and necessary. However, even though knowledge of these problems and the pathogenesis is improving, there is still little knowledge about the effects of drugs for dogs when treating specific problems. In this thesis data of dogs that have been treated with Clomipramine, Fluoxetine or Methylphenidate at the behavioural department of the university clinic of Utrecht has been analysed. The following data was collected: name, patient number, breed, gender, date of birth, weight, date of examination, examined by therapist, owner information, problem presented by the owner, problem category, previous treatment, prescribed medication and dose, prescribed behavioural therapy, prescribed food supplements, change in the medication or dose during treatment, results of treatment, side effects, follow up of the patient. This was done in order to get an insight into what treatment plans gave which results, looking both at the original plan and the actually implemented therapies by owners. We were specifically interested in what factors may influence results.

For the 77 dogs that fit our criteria, the following results were reported: 24,7% (19 dogs) improved to the owners satisfaction (problem solved), 54,6% (42 dogs) improved at least slightly, for 18,2% (14 dogs) treatment was reported to have no effect, and for 2,6% (2 dogs) a negative effect was reported. We also looked at the results achieved with the different psychotherapeutics and for specific problem behaviours. A loglinear analysis was done to assess which factors could have influenced results. No significant statistical higher order interaction was found for the used variables and result. Some lower order interactions did prove statistically significant after correction. Significant partial associations found when combining all variables: Effect*Therapist (P 0,003), Category*Sex (P 0,003), Category*Change in medication (P 0,004). After looking at smaller groups, we found the significant partial association of Therapist * Change in medication (P 0,002) for combined group of 'generalized anxiety + separation anxiety'. When looking at the combined group of 'aggression + fear induced aggression', Effect * Change in medication proved significant (P 0,001). Unfortunately, no significant conclusion could be drawn from this data. It is suggested that the absence of statistically significant data might be explained by the small research group. Another important influencing factor is owner feedback, which was shown to be inconsistent at times. The gathered information did show that the amount of patients that improved with therapy is 79,3%. Hopefully the gathered information will help us to understand and improve the treatment of behavioural problems in dogs even more.

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Chapter 1

Introduction

Dogs with behavioural problems can cause problems for owners. Aggression is one of the most common behavioural problems in dogs and can have a negative influence on public health, animal welfare and the bond between humans and animals[1]. Anxiety disorders can often be accompanied by a loss of impulse control. This may lead to inappropriate behaviour such as destructiveness, excessive barking and aggression[2]. It is therefore important to do something about these problems. Behavioural problems can have different underlying factors. There is a social factor or behavioural component (e.g. (early) socialization, genetics, an owner's response to situations, the amount of exercise, traumatic experiences etc.) and there is a biochemical factor (several neurotransmitter systems can be involved). When treating behavioural problems, it is important to try and identify these underlying factors. Behavioural therapy can be used as successful treatment and sometimes medication is a necessary supplement[3]. Certain drugs can effectively reduce an animal's anxiety, fear or aggressiveness[3]. This makes it easier to desensitize the animal to a stimulus, lessening the response[3].

At the behavioural department of the university clinic of Utrecht such therapies are being pursued. Currently the most common psychotherapeutics being prescribed there are:

- Alprazolam;
- Clomipramine (also known under its brand name; Clomicalm);
- Fluoxetine, and;
- Methylphenidate (also known as Ritalin)

(In this thesis we will focus on clomipramine, fluoxetine and methylphenidate.)

In the treatment of behavioural problems there are many unknown factors. There is often incomplete knowledge on pathogenesis. Knowledge of the pharmacokinetics of the psychotropic drugs in dogs is limited. Also, there is little scientific knowledge about the correct

dosage, the most effective intervals and the effect compared with and combined with other drugs. There are no double blind studies.

The scientific basis for treating animals with behavioural problems is limited as research is only possible in a limited way. After all, an owner who arrives at the clinic with a problem that is sufficiently severe (and possibly results in dangerous situations), wants immediate treatment. Ethical issues would arise when giving a placebo to these patients, or even when solely giving drugs without behavioural management techniques, to assess the effect of the drug alone. To solve the behavioural problem as efficiently as possible, behavioural management techniques and drugs must be combined for an optimal effect. This makes it hard to differentiate which measures lead to the best results. This is made even more difficult by the fact that it is nearly impossible to know which behavioural measures are actually and adequately executed by owners.

Behavioural therapy usually starts after medication leads to a sufficient response (around 4-6 weeks). By doing so an animal's anxiety, fear or aggressiveness can be reduced, it becomes easier to desensitize the animal to a stimulus[3]. Currently little is known about the effects of drugs for dogs when treating specific problems, such as the difference of response to a certain drug for fearful dogs compared to aggressive dogs. There are many other questions that remain unanswered. In this thesis we will focus on the following questions:

Does the combination of psychotherapeutics with behavioural measures contribute to a solution of behavioural problems? What are the most influential factors determining a case's prognosis?

What are the effects of the drugs before behavioural therapy starts? Which dosage needs to be used for which drug in the average patient? Which drugs are most effective for which problems? Is the right drug dosage given at the right moments? What happens when owners run out of the medication? (If there is a relapse of the problem, this might be indicative of a drugs' success.) It is also useful to gather information about side effects, which ones are common and what is the severity of these effects perceived by an owner? Are these side effects a reason for owners to stop giving the medication? Are all behavioural management techniques used consequently and over a longer period of time? Are drugs a useful supplement to behavioural management?

We will try to evaluate which treatment plans gave what results and to get an insight into the extent treatment plans have been implemented. Analysis of this data will give us an insight into which factors are important on the outcome of cases in the behavioural clinic. To this end, we gathered and evaluated data of patients with behavioural problems that have been treated at the faculty for the past 3 years. Looking at treatment plans, evaluating feedback and gathering missing information by calling owners, we hoped to sample sufficient information to answer some of these questions.

Chapter 2

Treatable problems

Behavioural problems in dogs that can be treated with medication and behavioural therapy

Behavioural problems in dogs can be very serious. When they cannot be controlled, dangerous situations may arise or welfare may be at stake. Medication can be used to control and resolve these problems, if training techniques have not proven to provide sufficient results. Medication can facilitate the training process, can make a situation more safe, and can be beneficial for a dog's welfare by reducing stress and anxiety. What behavioural problems can get so serious that drug therapy may be needed?

2.1 Aggression

Of all behavioural problems that are being treated by veterinary behaviourists, aggression is the most common one[3,4]. Both public safety and a risk to family members are a concern, because aggression results in a risk of injury[3]. Bites can be dangerous and biting incidents are seen often in the USA[1,3,5,6], most children are bitten by dogs with which they are familiar[3,7,8]. Aggression has an impact on the human-animal bond, it may lead to emotional stress, a decrease in welfare, and an increased risk of relinquishment or euthanasia of the dog involved[3,9].

The definition of aggression is a physical act or threat of action by one individual, that reduces freedom or genetic fitness of another[3,10]. This not only includes bites, but also behaviours such as subtle body postures and facial expressions[3]. Most types of aggression are treatable, but not all of them are curable[3]. Treatment has a better prognosis if initiated shortly after the

onset of the aggressive problematic behaviour[3]. However, even when a problem cannot be cured life can be made more pleasant and safe for both owner and dog by management leading to improvement.

Underlying factors for the onset of aggression are being researched. A genetic component is likely in certain breeds, pathophysiologic changes have been reported in the English springer spaniel and the English cocker spaniel[3,11-14]. Pain can cause or contribute to aggression[3]. Therefore, medical causes of aggression always should be ruled out before commencing (drug) treatment. Neutering may affect behaviour, but the reported results regarding aggression are conflicting[3,15-25]. Aggression can affect all breeds and both sexes[3]. Dominance was thought to be a major factor in owner-directed aggression, but more recent studies have suggested that dogs in these situations are most often fearful and in a state of conflict[3,26,27].

Aggressive dogs undergo physiological effects. Aggressive behaviour usually includes the 'fight or flight' response, resulting in an immediate elevated hart rate, blood pressure, respiratory rate, and vasoconstriction to internal organs, as well as glycogen and fat breakdown for immediate energy[3,28]. Stress can decrease the threshold for aggression[3]. A dog is more likely to remember behaviour and its results during a physiologic stress reaction, compared to when it is calm[3,28]. This explains why it takes more time to desensitize and countercondition a dog from a certain stimulus compared to learning the response initially. Aggression is often linked to arousal.

A dog with a high level of arousal can benefit from selective serotonin reuptake inhibitors (SSRIs), or any other forms of medication and supplements that reduce anxiety, reactivity and impulsivity[3]. If aggressive behaviour is abnormal, drug therapy should be considered in combination with management and behavioural modification[3]. Abnormal behaviour includes a lack of impulse control, an out of context response, an excessive response to the threat, aggressiveness to benign challenges, and aggressiveness that lacks predictability[3]. It is important to identify whether it is truly a case of abnormal behaviour before commencing (drug) treatment. It is possible that not abnormal behaviour, but learned effects result in a for the owner unpredictable situation[3]. For example, a dog may have learned not to show the anxiety related behaviour in a situation if it has been punished for this behaviour. This would not diminish the anxious emotion, causing it to try other coping techniques such as lunging or biting[3]. If the owner then recoils, this is a negative reinforcement of the unwanted behaviour[3]. In such situations, management and teaching owners how to respond is very important.

Types of aggression can be differentiated in different ways, most generally classification is based upon target or situation. Depending on the underlying factors, onset, severity etc. treatment plans can be implemented. Prevention would be the most ideal way to ensure welfare and well-being of both dog and owner. Management and behaviour modification can lead to good results. In the more severe cases medication is a necessary supplement that enables the dog to be more receptive to behavioural treatment[3].

2.2 Anxiety disorders

Anxiety, fear and phobias play a major role in a majority of canine behaviour disorders[3]. Physiologically anxiety, fear, or stress in a pet leads to a stimulation of the sympathetic system

and the hypothalamic-pituitary-adrenal (HPA) axis as a response[3,29]. From the sympathetic system, norepinephrine and epinephrine are released, resulting in a fight or flight reaction[3]. The stimulated HPA axis leads to a cortisol release which can be useful in the immediate response, but of which a chronic elevation can lead to medical and behavioural changes related to chronic stress[3]. It is important to make sure of a pet's mental well-being, studies have shown that psychological factors may stimulate the HPA axis more than physical factors do[3,30,31].

The amygdala (a part of the limbic system) is thought to be the area where external and internal fear evoking triggers are being processed[3]. Its input comes from the sensory organs, through the thalamus[3,32]. After perceiving a stimulus, the amygdala puts two pathways in motion. One is the immediate physiologic fear or startle response, the other is a slower pathway to the cortex in order to determine if the threat is real[3]. However, once started it may be hard to inhibit the emotional state that has been created. The amygdala stimulates the HPA axis by signalling the hypothalamus to release corticotrophin releasing factor[3,33]. This leads to a release of norepinephrine from the locus ceruleus[3,33]. Dysregulation of this locus may be associated with panic attacks, attention deficit hyperactivity disorder, sleep and arousal disorders, and affective disorders[3]. The amygdala can integrate prior learning and memory to stimulate other brain centres to initiate the autonomic stress response[3,34]. The hippocampus is also of importance in the limbic system, thought to be responsible for processing contextual information and differentiating between safe and dangerous[3]. Dysfunction can lead to severe anxiety reactions in not-dangerous or barely threatening situations, such as in posttraumatic stress disorder in humans[3,35]. Chronic stress can lead to damage, and even a reduction[36], in the hippocampus. Resulting in the loss of its controlling function of the HPA axis, leading to very high levels of cortisol[3,33]. The dorsal and medial raphe nuclei provide almost all serotonin input into the forebrain[37]. Limbic projections of the raphe nuclei may help modulate fear and anxiety, the dorsal nuclei seems to modulate cognitive and motor components, and thereby inhibit the fight or flight response[3,37]. A functioning forebrain is necessary to unlearn fear responses[3].

A fearful response can include aggression, cowering, shaking, freezing, escaping, and a fearful appearance such as a low posture[3]. But also displacement behaviours such as yawning, lip or snout licking, whining, (out-of-context) grooming, or circling[3]. Clinical signs of anxiety disorders can be a result of dysregulation of fear pathways, often due to alterations in a number of neurotransmitters (including; serotonin, norepinephrine, and gamma-aminobutyric acid(GABA))[3]. Both serotonin and GABA are typically seen as inhibitors of the stress response[3].

Severe fear or anxiety can have a genetic or environmental cause, such as an inadequate early life (environmental experiences and socialization), a conditioned fear due to unpleasant experience(s), medical or behavioural pathology, or a combination of factors[3]. Especially the first year of development seems to be of special importance, fearful behaviours are often linked back to this period[3]. Not only adequate exposure to the world, but also maintaining this exposure to social and environmental experiences is necessary[3,38]. Sexual maturity might be a second, more sensitive period[3,38,39]. Punishment-based training for young adolescents is linked to fear conditioning and increased avoidance[3,15,40-44]. If an animal encounters a stimulus it perceives as pleasant, no fearful reaction will occur. Encountering a situation that was

previously perceived as unpleasant in a pleasant way, may cause a reduction of the fear response[3]. However, experience with a negative stimulus will lead to avoidance of or increasingly fearful reactions to the stimulus[3]. Increase of frequency of a stimulus may result in an increase of further fear and phobias[3]. When a stimulus is intensely unpleasant, a single exposure can be enough to induce a fearful response in the future (one-trial learning)[3]. Specific stimuli can be differentiated (discrimination), and generalization also occurs[3]. Events remembered as preceding an unpleasant situation can also evoke a fear response[3].

A fear response leads to high states of arousal and anxiety, in which the pet cannot make conscious decisions as to how to respond[3]. Therefore, it is necessary to use means to calm a pet before desensitisation or retraining can be implemented[3]. Training methods, certain devices to help control the pet (such as head halters), and drugs can be useful[3]. Each fear evoking event that does not end positively, will aggravate the problem further[3]. Therefore, punishment must be avoided. If possible, a stimulus should be avoided until controlled and successful exposure training can be implemented[3]. Owners should also realise that their emotional responses may increase the pet's anxiety[3], possibly causing a negative result[3]. If a pet can escape from a situation or uses aggression to successfully get rid of the stimulus, this negatively reinforces the behaviour because the stimulus is removed[3]. Therefore, it is important that owners know what they are doing and how to respond. Techniques widely used to manage fear and phobias are: controlled exposure, habituation, systematic desensitization, counterconditioning, shaping response substation, and positive reinforcement[3,45-49]. They can be combined for optimal results. Safety must be considered, confinement, a head halter and leash, or a muzzle can prevent aggression and retreat[3].

The prognosis of treatment is good if the duration is short, the pet has a stable temperament, the pet had a good socialization period, and if the owner can control further exposure to the stimulus[3]. A pet that reacts in an aggressive way, is more difficult to treat[3]. A genetic cause, a very early emergence of the problem, an inadequate socialization period, and an environment that cannot be fully controlled result in a poorer prognosis[3]. Prevention might be the only safe way to minimize stress in these cases[3], in some cases relocation may be considered.

2.3 Attention deficit hyperactivity disorder (ADHD)

A dysregulation of the locus ceruleus may be associated with attention deficit hyperactivity disorder[3]. However, hyperactivity in dogs (and other species) can have many causes, most of which are not due to physiological disorders. For example attention deficit disorders (ADD's) in humans are associated with lack of impulse control, over activity, and lack of attention, all of which interferes with the ability to learn[3]. In certain cases of hyperactivity, learning deficits, and aggression in dogs, central nervous system (CNS) stimulants may have a calming effect, quite like they do for humans with ADD[3]. ADHD dogs may exhibit this paradoxical response to treatment with for example methylphenidate[3,50]. The response is called paradoxical because normally these drugs stimulate the CNS, but dogs with ADHD become less active and more attentive[3]. Sometimes a (less serotonergic) SSRI such as fluoxetine may also be useful in cases of ADHD[3], but methylphenidate currently remains the most prescribed drug for these cases. In a European trial of dogs with ADHD, 55% improved after receiving a methylphenidate therapy[3].

It seems that true hyperactivity disorders are rare in dogs[3]. Most overactive dogs are either under stimulated, genetically predisposed to high levels of energy and activity (working dogs), or the behaviour is or has been inadvertently rewarded[3]. Problem situations mostly occur when the need for exercise, proper social interaction, and or control is neglected[3]. Dogs that the family cannot get under control, respond poorly to commands, and engage in behaviours the family finds obnoxious are often called 'unruly'[3]. Sometimes a compulsive disorder can give a presentation of a dog that is being overly active and out of control[3]. Therefore, it is important to understand the underlying factors. Training that leads to an increase in expended energy, better obedience, better control over the dog when leashed, and others can be used to give owners more control[3]. They must be used to correct the problems with hyperactivity disorders, but it is important to adjust a program to suit the individual[3].

Dogs with ADHD may have symptoms such as: over activity, poor attention span, lack of trainability, aggressive displays, and failure to calm down in neutral situations[3]. The prognosis is based upon the presentation and cause of the hyperactivity[3]. Behaviour modification techniques can help owners to deal with their dogs. Young dogs that are playful and active may improve with maturity, but those cases of dogs that have an innately high energy level and insufficient outlets in their current situation may be more practically resolved by relocation[3]. When the problem is truly ADHD, drugs may facilitate training and behaviour modification techniques. Increasing the amount of daily exercise is often be helpful, teaching the brain something new can also be very tiring for the dog and therefore useful[3]. Situations that make the dog particularly excited should be avoided as much as possible. Obedience training is an important part of helping owners to handle their dogs[3]. After learning basic commands these can be used preceding the dog getting anything from the owner[3], creating an obedient, and sometimes even calm, moment before giving a reward. It is also possible to learn a specific 'calm' command. After exercise and play, it can be helpful to guide the dog to something such as a resting placing to help it settle down[3]. Wanted (calm) behaviours should be rewarded, and all negative (attention seeking) behaviours should be ignored[3]. To prevent hyperactivity problems a regular daily routine should be followed, that meets the individual's needs of play, exercise, mental stimulation and social interaction.

2.4 Stereotypic and compulsive disorders (OCD)

Compulsive disorders are also known as obsessive-compulsive disorders or stereotypies[3,51,52]. They have been reported in humans, companion animals, farm, zoo, and laboratory animal species[3]. Stereotypies have been described as an abnormal invariant, a repetition of a motor pattern that serves no apparent function[3]. They may be 'behaviours induced by frustration, inability to cope, or central nervous system dysfunction'[3,53], but because of the phenotypic diagnosis and unknown biological causes, the term 'abnormal repetitive behaviour' seems most fitting right now[3,53,54]. These abnormal repetitive behaviours can vary in form and may be fixated on a goal[3,55]. Behaviours seen in dogs such as tail chasing, rhythmic barking, or self-traumatic behaviours fit the description[3]. It is very important to rule out medical causes before labelling a problem as behavioural, medical problems can be an underlying factor for many compulsive behaviours[3].

Compulsive behaviours arise in situations of conflict, frustration, or confinement[3]. Maternal deprivation has also been proven to be a contributing factor to the development of abnormal

repetitive behaviours[3,54]. Maternal deprivation can make offspring more fearful, anxious, and cause altered responses to stress[3,54]. Therefore, there is a greater chance to develop compulsive behaviours later on[3,54]. A genetic predisposition is possible, several either proven or suspected[3,51,56-60]. Compulsive behaviours often arise after recognizable periods of change or distress, and/or in the prepubertal period or prior to social maturity, when behavioural needs are not being fully met[3,51,61,62]. In the early stages of developing such a disorder, it might be seen as a coping mechanism, possibly successfully reducing stress[3]. However, many repetitive behaviours can cause lifelong changes in CNS function, affecting an animal's well-being[3]. Starting out as a mechanism to cope, they evolve into repetitive actions outside of the original context[3,52]. These behaviours are not fully under the animal's control, it may be impossible to initiate or stop at specific moments, even up to the point where they might be difficult for an owner to interrupt[3]. Originally it may have been a normal behaviour, e.g.; grooming, predation, ingestion, or locomotion related[3]. When a certain behaviour does not help to cope with a situation and interferes with normal function, it is seen as compulsive[3,51]. Coping behaviours may become inappropriate, out of context or redirected[3]. Conflict can occur when a pet wants to perform two opposing behaviours, but is uncertain about the results because of unpredictable factors or for example inconsistent previous responses by the owner[3]. Repeated exposure to such conflicting situations can lead to developing habits, to developing a compulsive behaviour[3]. Therefore, to prevent stereotypic behaviours it is important to create an environment for animals that is predictable (controllable), safe and enriching, thereby reducing stress[3]. It is important to let the pet engage in desirable behaviours without giving much chance for the undesirable, and to react consequently to a situation.

There are several specific presentations of compulsive disorders: dermatologic, locomotor and predatory, neurologic, or ingestive[3]. General approaches to treatment apply to all groups, but there may be additional considerations to diagnosing and treating specific problems[3]. Some of the most common presentations of compulsive disorders in dogs are: self-trauma; tail chasing, spinning; pacing, circling; chasing lights/shadows; rhythmic barking; freezing, staring; fence running; hallucinatory; and oral/ingestive manifestations[3].

A compulsive behaviour can cause pathological changes in the brain[3]. To treat patients it is important to address both the environment (stressors), the behavioural management and to use drugs for an optimal result[3]. Regarding pathophysiology, much is speculated but little is known. Looking at the effective medications, beta-endorphins, dopamine, glutamate, and serotonin have all been implicated[3]. Oral stereotypies may involve the mesolimbic dopaminergic system, whilst locomotor stereotypies involve activation of the nigrostriatal dopaminergic system[3,63]. However, abnormal serotonin transmission seems to be the primary mechanism for inducing a compulsive disorder[3]. Studies with animals have proven direct serotonin involvement[3,64]. When treating humans with compulsive disorders, the inhibition of serotonin reuptake is very effective[3,64,65]. In several studies drugs such as Clomipramine and Fluoxetine (inhibiting serotonin reuptake) have been proven most effective when treating cats and dogs with compulsive disorders[3,51,66-72]. In certain studies clomipramine seems most effective compared to other drugs[67], in other studies both clomipramine and fluoxetine were equally effective[60].

The prognosis is variable, because of the vast amount of possible presentations of compulsive disorders that may be encountered[3]. If an accurate diagnosis can be made, owner response related compulsive disorders, or compulsive disorders developed due to a medical problem that can be treated, should give a fairly good prognosis[3]. But it may take some time to find the best therapy. Drugs and behavioural methods need to be combined and this may be a very long-term treatment plan, especially if there are underlying genetic factors[3]. Within 4-6 weeks a first response to medication should be observed, medication has to be continued for at least 6 months and it might be possible that it is necessary to continue for as long as the pet lives[3]. Sometimes it might be better to let an animal perform certain behaviours, if they are not damaging or reducing the animal's welfare, for treatment might be more disruptive than the behaviour itself[3].

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Chapter 3

Psychopharmaceutics

Psychopharmaceutics in dogs

It is clear that behavioural problems in dogs can result in very severe and possibly dangerous situations for both owner and dog. A quick and effective treatment of behavioural problems is the aim when treating patients, controlling clinical signs[3]. As mentioned earlier, certain drugs can effectively reduce an animal's anxiety, fear or aggressiveness[3]. This makes it possible to desensitize the animal to a stimulus and lessen the response[3]. However, little information is known on drug therapy for companion animals. Most data comes from either clinical experience of veterinarians or inferred comparisons between human psychiatric conditions and behavioural problems of pets[3]. There are not many published trials, in part due to ethical concerns. Therefore, particularly the placebo effect (which may be responsible for 50% or more of the effects in some behavioural studies) is relatively unresearched[3].

In laboratory situations it is possible to test the efficacy of a product, but it is not comparable to the effect on dogs with specific behavioural problems in a domestic environment with many influencing factors[3]. Extrapolating data from human medicine is very useful. However, even when disposition and metabolism for some drug are determined in pets, this is not the case for all[3]. Therefore, when basing a dose on human medicine, drug metabolism (including metabolites, half-life, route of excretion) as well as neurotransmitter and receptor effects may vary[3].

In clinical trials a drug is usually used to treat a specific problem, such as separation anxiety[3]. We should keep in mind that the drugs used do not treat a specific diagnosis, but modify an emotional state[3]. Certain drugs can effectively reduce an animal's anxiety, fear, aggressiveness, or the inability to behaviour mechanisms[3]. Psychotherapeutics have an effect on the 'diffuse modulatory neurotransmitters' (such as serotonin, dopamine, norepinephrine), these neurons

come from small nuclei in the brainstem but are projected into a large area of the brain[3]. They affect (or modulate) a wide range of behavioural control aspects, which can be the same for different behavioural conditions[3]. Many psychotropic drugs affect not one but multiple neurotransmitter systems[3]. Therefore, the same drug can sometimes be used to treat different problems. Sometimes drugs working on the same neurotransmitter system can be combined, because they use different receptors[3]. Because of these differences in pharmacologic actions, some drugs may be more efficient than others even though they seem very similar[3]. Side effects can be a major reason for picking one over the other. It is important to realise that different drugs can effectively be used for the same problem[3]. Individual (or breed) differences may cause generally effective drugs to be less so.

Drugs should only be used when this is absolutely necessary. Side effects can be severe and veterinarians also have to take into account the risk of (owner) abuse with certain drugs. Clinical perspectives where drug therapy is necessary are: using it combined with behavioural therapy, in drug desensitization, when drugs are necessary as a primary mode of treatment, when there is an underlying pathology[3]. Cases that are sent to the university behavioural clinic of Utrecht are often the more severe ones, likely to need drugs to help the owner and patient. Drugs may lead to a quicker, safer way of resolving a problem, but it is also possible that a problem only improves slightly (or not at all) and that it is necessary to administer these drugs for as long as the pet lives[3].

When treating behavioural problems such as separation anxiety, fears, and aggression, drugs may very likely be a useful adjunct to behavioural therapy[3]. Compulsive disorders, attention deficit hyperactivity disorders (ADHDs), and generalized anxiety disorders might actually need medication for an effective treatment[3]. In these cases behavioural changes may have altered neurotransmitter function[3].

3.1 Antidepressants

Antidepressants mainly work on serotonin pathways, this group includes the tricyclic anti-depressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs)[3]. They are primarily used for behaviour sequence regulation. They may help a pet control the initiation, termination and intensity of a behaviour[3]. They are used for problems such as (but not limited to): phobias, anxiety disorders, aggression, and compulsive disorders[3]. Antidepressants have a few advantages over other drugs. They are non-addicting, less sedating, and unlikely to affect either learning or training[3].

Clomipramine and fluoxetine are the most widely used drugs in this category[3]. Effects can be observed quite quickly, but it is recommended to continue treatment for at least 4-6 weeks to allow for an effect build over time that may induce changes in the expression of receptors[3,73]. Chronic administration of these drugs may stimulate neurogenesis in the hippocampus[3,74]. Side-effects vary between drugs, because neurotransmitters are affected in (slightly) different ways. Side-effects may include gastrointestinal signs, in appetence, lethargy, paradoxical agitation, and neurological signs such as tremors or seizures[3]. Side effects can vary greatly, due to the many different neurotransmitters and receptors that can be involved, and genetic diversity.

3.2 Clomipramine

Clomipramine is a tricyclic antidepressant (TCA) that is often used for the treatment of anxiety related behavioural problems in companion animals[75], such as separation anxiety and compulsive behaviours. Clomipramine is also known under its brand name Clomicalm. Behavioural problems are often associated with a loss of impulse control, but Clomipramine does not seem to have an influence on an animal's impulse control[2]. Clomipramine was proven effective when treating compulsive behaviours in dogs[3,51,76]. Especially combined with behavioural therapy, a significant decrease of frequency and intensity of clinical signs was achieved[51].

Much is unclear regarding the pharmacokinetics of Clomipramine for dogs. However, it has been proven that it is not similar to humans. For example, its half-life is much shorter[77]. Therefore, dosage frequency needs to be higher for an optimal clinical effect[77]. Clomipramine mainly blocks the reuptake of serotonin and, to a lesser extent, norepinephrine. It also has actions on acetylcholine and histamine[3]. It is absorbed from the gastrointestinal tract and metabolized in the liver before excretion through the kidneys. In the liver it is metabolized in to the active metabolite desmethylclomipramine. In 1-3 hours peak levels are reached for clomipramine and desmethylclomipramine[3]. Terminal half-life is 4 hours or less[3]. An increase in dose, leads to residence times and therefore also to increased terminal half-lives[3,78]. A steady state can be achieved in 1-4 days[3]. Side-effects are sedation, dry mouth, retained urine or stool, tachycardia, hypotension, and dizziness[3]. Possibly caused by the mild anticholinergic effect, moderate antihistaminic effect and potent alpha-1 antagonist properties of clomipramine, proven in humans[3]. In dogs side-effects seem to be less, possibly due to shorter half-life and quicker elimination[3,78]. In dogs the ratio between clomipramine and desmethylclomipramine is also different (3:1, compared to 1:2,5 in humans) [3,78]. Desmethylclomipramine is responsible for most anticholinergic effects, the difference in ratio may also be part of the explanation for less side effects[3,78].

Clomipramine is widely used in veterinary medicine. In a retrospective study of compulsive disorders in dogs and cats, clomipramine was proven to be the significantly better drug compared to amitriptyline[3,51]. The relative success rate of Clomipramine compared to Amitriptyline was 0.83 compared to 0.59 (log likelihood ratio test statistic Gadj = 6.03; $P < 0.05$)[51]. Frequency and intensity of clinical signs of OCD may decrease by over 50% using behaviour modification techniques and treatment with clomipramine[51]. The use of clomipramine combined with a behaviour modification plan is an effective treatment for separation anxiety[3,51,79,80]. Clomipramine was effective when treating compulsive and anxiety disorders in dogs and cats [3,66,67,72,81]. A dog that was treated for shadow chasing started improving from day 7, after 2 months of treatment clinical improvement was measured[76]. Shadow chasing was drastically reduced and dopamine transporter binding regained normal values[76]. The dog relapsed after Clomipramine therapy was stopped[76]. Long term administration does not seem to cause adverse effects or relapse and may lead to further improvement, cessation of administering the drug can cause a relapse but this does not have to be the case[3,82].

In one study no significant difference was seen between treating dogs with separation anxiety with clomipramine and behaviour modification or behaviour modification alone[3,83]. However, the effects where only followed for 6 weeks. In another study, the use of clomipramine for the treatment of separation anxiety lead to a greater and faster improvement in the drugs combined with behaviour modification group compared with the just behaviour modification group[3]. Clomipramine was not proven effective when treating owner-related aggression

cases[3,84]. Clomipramine can be combined with other anxiolytics[3]. In one study clomipramine in combination with behaviour modification and alprazolam as needed was effective for the treatment of storm phobias[3,85]. TCA's, such as clomipramine, are more effective at calming than SSRIs due to a certain sedative aspect[3]. Short term administration of clomipramine seems to be effective at reducing plasma cortisol following transport, it appears to slightly reduce fear, anxiety, or both during transport[86]. When using clomipramine for the treatment of separation anxiety (a standard dose compared to placebo), dogs improved three times faster for the signs destruction, defecation and urination and in the owners global assessment. However, the sign vocalization never improved statistically significant[79]. When treating storm phobia in dogs, 30 out of 32 dogs that completed the study improved to a degree with a combination of clomipramine, alprazolam and behavioural therapy[85].

3.3 Fluoxetine

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI)[87,88] and is frequently used as an antidepressant[88]. SSRIs are selective for serotonin reuptake, because of this they may have fewer side effects than TCAs[3,89]. Little is known about the pharmacokinetics of fluoxetine. The concentration of certain neuro-hormones (possibly Prolactin) in blood, might give an indication of the expected efficacy in comparison with other conventional methods[90]. Fluoxetine has a T_{max} of 1.8 hours, this is 12.8 hours for the active metabolite norfluoxetine, and it reaches a steady state around 10 days[3]. The clearance half-life is 6,2 hours and 49 hours for norfluoxetine[3]. Therefore, it is important to wait long enough before starting new medications.
Side-effects may include a reduced appetite and lowering of the threshold for epileptic insults[3].

In dogs SSRIs are mostly used to treat separation anxiety, compulsive disorders, fear related problems, most specifically fear- and anxiety related aggression, and impulse control disorders. At the faculty of veterinary medicine of Utrecht it is mostly used for problems such as: severe anxiety, aggression and compulsive behaviours. In a controlled clinical trial, treatment of compulsive disorders in dogs with fluoxetine seemed to be effective[87]. However, they did report results were ambiguous and they did not look at the effect of synergism with other medication and/or behavioural measures[87]. The use of fluoxetine in combination with behavioural therapy for treating separation anxiety in dogs has proven very effective[73] and also significantly more effective than either just fluoxetine or just behaviour medication[3,85]. When using Fluoxetine for the treatment of separation anxiety, dogs that received fluoxetine improved quicker (within one week) compared to placebo-treated dogs. At the end of the study the group that was treated with fluoxetine had improved substantially more as well (72% compared to 50% of the placebo-treated group)[73]. Fluoxetine was proven useful for generalized anxiety[3,91], canine aggression[3,92,93], and compulsive disorders[3,69,94]. When treating dogs with fluoxetine for compulsive disorders, an odds ratio of 8.7 was found for the likelihood of dogs decreasing in severity of compulsive behaviours[71]. It is suggested that fluoxetine is more effective than other drugs such as sertraline, when treating hyperactivity, aggression and compulsive disorders[3]Tryptophan is the precursor to serotonin. It has been suggested that supplementing tryptophan can lead to better results (enhancing mood and memory and treating impulsive behaviour), but no clinical benefits have been reported[3]. As an

augmentation to clomipramine or SSRIs it might be useful to enhance the clinical response (if this was inadequate at first), but it also increases risks of for example serotonin syndrome[3].

3.4 Methylphenidate

Methylphenidate, also known as Ritalin, is the first choice of medication for the treatment of attention deficit hyperactivity disorder (ADHD) in humans. Dogs can develop similar problems and in these cases Ritalin can be prescribed. Ritalin is a central nervous system (CNS) stimulant. Working mechanisms are based upon the release of dopamine and reuptake inhibition of dopamine and norepinephrine[3,95]. Apparently this helps to enhance inhibitory output, improving concentration and impulse control and decreasing motor activity[3]. Humanely much is known about the pharmacokinetics. In dogs a quicker absorption rate, lower biological availability and a higher elimination rate have been reported compared to humans[95]. Therefore, dosages must be given at different intervals than we do for humans. It is being speculated that dogs should get a higher dose that humans[95]. In a trial of dogs with hypersensitivity-hyperactivity disorders, 55% of the dogs improved with methylphenidate therapy[3].

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Chapter 4

Material & Methods

4.1 Animal selection and data collection

Searching through the patient database (Vetware) of the behavioural faculty of the university clinic of Utrecht, patient records were reviewed to select dogs that had been treated with either clomipramine, fluoxetine, or methylphenidate in the past 3 years. Of these patients, the following data was collected: name, patient number, breed, gender, date of birth, weight, date of examination, examined by therapist, owner information, problem presented by the owner, problem category, previous treatment, prescribed medication and dose, prescribed behavioural therapy, prescribed food supplements, change in the medication or dose during treatment, results of treatment, side effects, follow up of the patient.

Most of the data of these patients was already complete in Vetware, 48 dogs fit the criteria. If data was missing (e.g., no feedback had been given after the initial consult) a phone survey was executed to collect the missing information. The phone survey did not exist of a questionnaire, but was executed by specifically asking owners about the missing information. Eventually this led to more detailed knowledge on those cases was feedback had not yet been received. Especially compared to the data obtained from Vetware, since owners were very eager to share a lot of information regarding the treatment process. This led to more detailed information on another 29 cases.

If missing data could not be gathered or if medication had never been administered (or had only been given for 1 week and effects could only be expected after at least 4 weeks), dogs

were excluded from the data. Eventually 77 dogs fit the criteria. The data was fed into Microsoft Excel 2010, after which it was processed by using SPSS Statistics 22.

4.2 Data processing and statistical analysis

An analysis of the data in SPSS Statistics 22 was made. To look at numbers and percentages of success, tables could easily be made using the custom tables function.

A loglinear analysis was done to assess which factors could have influenced results. This type of analysis is especially useful when testing the relationship between more than two categorical variables[96]. It is also possible to see the significance of the retained effects. The analysis does not only measure the relationship between all variables at the same time, but also the relationship between a few variables. Each variable is coded so all categories will be taken into account.

However, due to the small sample size (n=77) and the huge amount of categories within each variable, the variables had to be redefined to include more patients per group. For example, breed was excluded due to the large amount of breeds included in this research (41). A more specific version of the side-effects variable had 28 options and was replaced by a more compact version with 2 categories (side effect or no side effects).

The selected variables and their categories are: effect (observed or not observed by owner), therapist, category (generalized anxiety, separation anxiety , fear induced aggression, aggression, ADHD, OCD, and other), sex (male, female, castrated male, castrated female, or chemically castrated male), medication (clomipramine, fluoxetine, or methylphenidate), dose (0.5 mg/kg, 1 mg/kg, 1.5 mg/kg, 2 mg/kg, 2.5 mg/kg, or 3 mg/kg), times a day given (1x, 2x, 3x), behavioural therapy (given or not given), change in medication (none, higher dose, or lower dose), Side-effects (observed or not observed by owner).

This gave us the following variables with their amount of categories (or range):

- Effect (0-1)
- Therapist (1-4)
- Category (1-6)
- Sex (1-5)
- Medication (1-3)
- Dose (1-6)
- Times a day given (1-3)
- Behavioural therapy (0-1)
- Change in medication (1-3)
- Side-effects (1-2)

By looking at the partial associations table, it is possible to see which interactions between variables cause significant results[96].

Chapter 5

Results

Of the 77 dogs whose treatment and results have been analysed, 19 (24,7%) had been labelled as solved, 42 (54,6%) were labelled partially improved, for 14 dogs (18,2%) there was no effect, and for 2 dogs (2,6%) a negative effect had been reported. Table 1 shows which behavioural problems the dogs were treated for. The percentage in Table 1 shows the observed percentage of results obtained within a specific category (which is why the sum of each category is 100%). Table 2 shows the results obtained with the different drugs and Table 3 shows a percentage of how many times side effects were seen for each drug. Out of 77 dogs, side effects were reported for 33 (42,9%) patients.

Table 1: Behavioural problems for which the dogs were treated

	Problem Solved		Partial effect		No effect		Partially negative effect	
Category	N	%	N	%	N	%	N	%
Generalized fear	5	25,0	9	45,0	5	25,0	1	5,0
Separation anxiety	0	0,0	5	71,4	2	28,6	0	0,0
Fear aggression	4	40,0	5	50,0	1	10,0	0	0,0
Aggression	4	30,8	5	38,5	4	30,8	0	0,0
ADHD	3	16,7	14	77,8	1	5,6	0	0,0
OCD	0	0,0	4	66,7	1	16,7	1	16,7
Other	3	100,0	0	0,0	0	0,0	0	0,0
Total N	**19**		**42**		**14**		**2**	

Table 2: results obtained with different drugs

	Problem Solved		Partial effect		No effect		Partially negative effect	
Medication	N	%	N	%	N	%	N	%
Clomipramine	8	25,8	16	51,6	6	19,4	1	3,2
Fluoxetine	10	26,3	19	50,0	8	21,1	1	2,6
Methylphenidate	1	12,5	7	87,5	0	0,0	0	0,0
Total N	**19**		**42**		**14**		**2**	

Table 3: Side effects per drug

	Side effects		No side effects	
Medication	N	%	N	%
Clomipramine	11	35,5	20	64,5
Fluoxetine	19	50,0	19	50,0
Methylphenidate	3	37,5	5	62,5
Total N	**33**		**44**	

The side effects can differ greatly in severity. A very common side effect such as dogs reported to be 'dull' or 'drowsy' may not be cause for too much concern, but when a dog did not even want to walk anymore it's owners decided to immediately stop with the drug therapy. Therefore, it is necessary to differentiate between reported side effects. An owner's perception of the severity of a side effect is of importance when considering treatment options and the chance of success. Owners reported many different combinations of side effects for each drug, as shown in Table 4. The percentage once again shows how many times each side effect was seen for each drug.

Of the 29 cases who were interviewed in the phone survey, 22 owners had stopped administering the drug therapy. Out of 22 owners who have stopped giving the prescribed medication without consulting the university clinic, 7 mentioned side effects as the primary reason and for two of these owners dullness was one of the side effects reported. If we look at frequency, dullness is reported most often (12 times; 6 times for clomipramine, 5 times for fluoxetine and 1 time for methylphenidate). Dullness in itself is not considered to be an inacceptable side effect, nevertheless gradations of severity may exist and some owners did mention dullness as part of the reason to stop giving medication. Some owners felt that the dullness was a sign of the drug suppressing the dog's actions rather than aiding the dog and themselves with dealing with the problem. Especially in combination with other (more severe) side effects, such a common and in theory acceptable side effect can be a reason to stop therapy. A more common reason to stop with the prescribed drug therapy without consulting the faculty clinic was the absence of a satisfactory outcome. This was specifically mentioned by 8 out of the 22 owners who participated in the phone survey and had stopped giving the prescribed medication. In those cases were contact with the university clinic was maintained, side effects and/or the absence of expected results usually led to a change in drug dosage. Table 5 shows us how often the initial dose of each drug was adjusted by the behavioural therapist for all patients. The percentages show the observed percentage for each drug. A reduced dose can mean either a reduction or a complete stop.

Table 4: Reported side effects for each drug

	Clomipramine		Fluoxetine		Methylphenidate	
Reported side effects	N	%	N	%	N	%
None	20	64,5	19	50,0	5	62,5
Nausea and decreased appetite	1	3,2	2	5,3	0	0,0
Dull*	2	6,5	1	2,6	0	0,0
Dull* and lower stimulus threshold	0	0,0	1	2,6	0	0,0
Dull* and decreased appetite	1	3,2	0	0,0	0	0,0
Dull* and weight gain	1	3,2	0	0,0	0	0,0
Dull* and gluttony	0	0,0	1	2,6	0	0,0
Increased fearfulness	0	0,0	1	2,6	0	0,0
Dampening all forms of behaviour	1	3,2	0	0,0	0	0,0
Deterioration of the problem	0	0,0	1	2,6	1	12,5
Dull* and not wanting to walk	1	3,2	0	0,0	0	0,0
Increased aggression	1	3,2	0	0,0	0	0,0
Dull* and increased fearfulness	0	0,0	1	2,6	0	0,0
Smacking, eating grass, and polyuria	0	0,0	1	2,6	0	0,0
Bleary eyes	0	0,0	1	2,6	0	0,0
Increased sexual activity	0	0,0	1	2,6	0	0,0
Dull* and eating grass	0	0,0	1	2,6	0	0,0
Not wanting to walk	0	0,0	1	2,6	0	0,0
Skin problems, diarrhoea, and anorexia	0	0,0	1	2,6	0	0,0
Depression, weird smell, and difficulty eating	0	0,0	1	2,6	0	0,0
Dry mouth and smacking	0	0,0	1	2,6	0	0,0
Diarrhoea	0	0,0	0	0,0	1	12,5
Nausea, not eating or drinking (following dose increase)	1	3,2	0	0,0	0	0,0
Increased water intake	0	0,0	0	0,0	1	12,5
Sleeping too much/too deep	1	3,2	1	2,6	0	0,0
Dull*, not wanting to walk, and anorexia	1	3,2	0	0,0	0	0,0
Throwing up, incontinence	0	0,0	1	2,6	0	0,0
Dull*, sleeping a lot, and stumbling when jumping in the car (loss of coordination)	0	0,0	1	2,6	0	0,0
N Total	**31**		**38**		**8**	

* Dull is being used to combine several terms mentioned by owners, such as: dull, drowsy, tired, or slow.

Table 5: Number of adjusted dosing

	No change		Reduced dose		Increased dose	
Medication	N	%	N	%	N	%
Clomipramine	9	29,0	9	29,0	13	41,9
Fluoxetine	13	34,2	6	15,8	19	50,0
Methylphenidate	0	0,0	2	25,0	6	75,0

5.1 Loglinear analysis

The 10-way loglinear analysis produced a final model that retained all effects. The likelihood ratio of this model was $\chi^2(0) = 0$. However, the highest order interaction was not significant. There was no statistical significance that the used 10 variables have a specific statistical interaction. When taking away any of the interactions, no significance was seen. Therefore, chosen variables have no statistically significant influence upon results.

In the partial associations table these results were broken down to look at individual interactions. Several low in hierarchy interactions (with only a few of the variables) did show significant results. These significant results are reported in the following table (Table 6). It can be concluded that these significant lower interactions stand for a possible relation with the variable combinations that are significant.

Table 6: Significant Partial Associations Results found when combining all variables. N = 77

Variables	df	Partial χ^2	Sig.	Iterations
Effect * Therapist	3	14,031	0,003	9
Effect* Category	6	17,422	0,008	10
Therapist * Category	18	30,704	0,031	8
Effect * Sex	4	10,110	0,039	10
Category * Sex	24	47,972	0,003	8
Therapist * Change in medication	6	14,093	0,029	11
Category * Change in medication	12	29,044	0,004	10
Dose * Change in medication	10	21,965	0,015	12
Change in medication * Side-effects	4	13,576	0,009	10

To diminish the amount of interactions that needed to be computed, the category variable was also split up in its seven categories. For each of these categories (e.g., a file containing solely dogs with the problem specification of generalized anxiety) a separate analysis was done. Significant results were found in for the aggression and for the fearfulness categories, giving us the following results (Table 7 and Table 8). The other categories did not have significant results.

Table 7: Significant Partial Associations Results found for 'Aggression'. N = 12

Variables	df	Partial χ^2	Sig.	Iterations
Effect * Change in medication	2	8,991	0,011	3

Table 8: Significant Partial Associations Results found for 'Generalized anxiety'. N = 20

Variables	df	Partial χ^2	Sig.	Iterations
Therapist * Change in medication	6	15,157	0,019	5

When combining categories with certain similarities to get a bigger N, more significant results were found for the combinations 'generalized anxiety + separation anxiety' and 'aggression + fear induced aggression' as shown in table 8.1 and 8.2.

Table 9: Significant Partial Associations Results found for 'generalized anxiety + separation anxiety'. N = 27

Variables	df	Partial χ^2	Sig.	Iterations
Therapist * Change in medication	6	20,902	0,002	5
Behavioural therapy * Change in medication	2	6,519	0,038	8

Table 10: Significant Partial Associations Results found for 'aggression + fear induced aggression'. N = 22

Variables	df	Partial χ^2	Sig.	Iterations
Effect* Therapist	3	9.621	0,022	11
Effect * Sex	4	13,336	0,010	7
Effect * Behavioural therapy	1	5,744	0,017	14
Dose * Behavioural therapy	5	11,083	0,050	12
Effect * Change in medication	2	15,104	0,001	8
Sex * Change in medication	8	15,641	0,048	9
Behavioural therapy * Change in medication	2	9,120	0,010	12

It is important to mention that no correction has been used on this data. Due to the high amount of – values (780), the Dunn-Sidak method was used. This formula ($\alpha = 1 - [1 - 0.05]\text{^}(1/F)$), with F representing the amount of variables (10), gives a corrected P-value of 0,005116. After correction, only the underlined values are significant.

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Chapter 6

Discussion

The absence of significant results from the loglinear analysis after correction can mean several things. It is possible that none of the researched variables are of significant influence upon each other and therefore upon results. However, the absence of significant data is more likely due to other factors. Logically, it would make sense that the type of medication is significantly related to the dose and to the amount of times a certain medication is given each day. Used guidelines are different for these three drugs, these differences should show in data but this is not the case. Another explanation for the absence of statistically significant data is that the research group may have been too small. There is an N of 77 dogs, but the amount of variables and subcategories of these variables make very small subgroups. For example there are only 8 dogs who received methylphenidate therapy. If only 1 or 2 dogs would have had different results, the found percentages would differ enormously. A larger study may give other results. When merging categories within variables or combining groups, we gain a larger N. However, specific and subtle relations may be lost. It is also possible that there is no predicting value for results, but there might be small influences that we have missed due to the small sample size.

Interpretation of the significant lower interaction relations is also complicated. The different log-linear analyses did not all have the same significant variable combinations. They could simply be not strong enough to be found in all groups, or some groups might be too small. Or are they false positives, created by the small groups? As mentioned above, a change of 1 or 2 cases in a small group can cause a huge difference in results.

So the question remains whether there is indeed a relationship between the (after correction still) found significant interactions. We do not see the same interactions in all groups, but the variable *category* was not taken into account in the extra analyses done to see if a bigger group would give different results. For choosing related categories in bigger groups, and not taking category into account was the way groups size was increased. Therefore, it is hard to draw conclusions from these results. Especially because we only know that a relation between variables might exist, and not what that relation is. It would be interesting to look into these significant variable interactions. If dosage is indeed changed more often in a certain way for a certain problem category, this might lead to new insights on what the initial dosage should be. If certain problems are related to gender and whether or not a dog is neutered, advice can be given accordingly. It seems to make sense that the variables *effect* and *change in medication* are related, for if an owner reports an insufficient response to treatment changes have to be made. The phone surveys showed that owners did not want to continue treatment in the same way, if insufficient results were achieved. But why does this somewhat expected relation only show in the aggression group? The relations between *therapist* and *effect* and *therapist* and *change in medication* are also had to draw conclusions from. The therapists have not treated the same amount of dogs, they may have used slightly different techniques, and the cases may have differed greatly as well.

The data gathered in Vetware might not be entirely complete. An owner has a big influence upon the results. Almost all owners received instructions on how to use behavioural therapy alongside the drug therapy. But of those spoken to in the phone survey, several did not remember receiving instructions of behavioural methods. Obviously they did not use the behavioural methods, even though they were mentioned in the treatment plan. Even regarding drug therapy, these interpretational differences become clear. One person said they gave the drugs regularly, but did skip a day or two every once in a while. Another said they always gave the drugs, but did know how the dog responded to a day or two without it. Without asking more information than is being offered, these cases would seem very different. Therefore, owners should be seen as a major influential factor in this study. People can interpret thing in different ways. Some owners may be willing to share even the tiniest detail, whereas others give just the bare minimum or don't stay in touch at all. Owners were not asked about specific details, but gave information which they thought was relevant regarding the treatment of their dog.

Side effects have been identified, but if nothing else this made clear how important an owner's perception is. The same side effect was acceptable for some as something that would go away or as a minor effect, but for others it was a reason to stop the drug therapy. It is important to tell owners what to expect and for them to stay in touch, so dose alterations or alternative therapies can be discussed if needed.

When comparing the information gathered in Vetware and the information gathered from owners of those patients that had not given any feedback or had missing information, more extensive knowledge was obtained in the phone survey. However, since some patients had been treated almost 3 years ago, the newly gathered data may have been incomplete or changed by time as memories fade. At least one case had reported side effects initially, but could not remember any side effects during the phone survey. On the other hand, there was

also a case were no side effects had been mentioned during early correspondence, but during the phone survey the owner retrospectively (after quitting the drug therapy) did believe certain side effects had occurred. Therefore, if another study on this subject would be made, it might be more useful to gather new data from new patients. With an extensive questionnaire and a standard follow up procedure. This was not possible within the time limit of this study, since patients may need to be followed for at least a year or longer. Also, since the initial design of this study was explorative and not testing, it was of more interest to look at the available data of patients already treated at the Utrecht University Behavioural Clinic.

Even without statistically significant results from the loglinear analysis, several other results are of interest and they do answer some of our questions. The majority of cases redirected to the behavioural clinic of Utrecht University are severe cases, owners have often tried many things before asking for help. 19% of all cases treated with either clomipramine, fluoxetine or methylphenidate, were reported to be solved. Another 42% reported at least partial improvement. It may not be clear what variables have an influence upon results, but it is clear that good progress can be made with these more challenging cases. When looking at the results of each drug separately, it should be taken into account that the drugs are prescribed for very different indications. Clomipramine is more often prescribed for the less severe anxiety related problems, whereas fluoxetine is usually given in the more severe (and possibly more dangerous) anxiety and aggression cases.

It is hard for owners to judge whether or not a drug has effect, for changes can be gradual and behavioural methods are being used at the same time. A fall-back after stopping drug therapy with continued behavioural training methods is easier to observe. In the phone surveys a fall-back after quitting dug therapy was reported 3 times for clomipramine, and 2 times for fluoxetine. For methylphenidate one owner reported no fall-back, even though initial improvement had been obvious after starting the drug therapy.

Methylphenidate seems to have the highest success rate, with all patients having either a partial effect (some improvement) or being solved. It might be that the patients this drug is being prescribed to respond better to therapy. Maybe because it is a specific problem (ADHD) that is being treated, or maybe because an initial test can be done to see if the dog responds to the dug. After long term use some owners do stop therapy and do not notice a difference. This may lead some of them to believe that the medication did not have any effect, but that the behavioural methods and possible changes of routine, establishing leadership, and tiring challenges that are being provided for the dogs caused all improvement. This may be the case, but it is also possible that medication facilitated this process. And, in the case of ADHD (a problem humanely recognized as linked to certain areas in the brain) an altogether different explanation seems acceptable. In humans, a difference in brain volume between kids with ADHD and a control group has been seen[97]. Several areas, most prominent in cerebral prefrontal regions, develop later in kids with ADHD[98]. Which explains why we often hear about kids with ADHD, but not so much about adults. It is possible to outgrow ADHD. It might be so that this is the same for dogs. This could explain why sometimes there is no setback after quitting the methylphenidate therapy, it may be so that these areas are underdeveloped in dogs as well and that they can outgrow it too.

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