

**AN ANIMAL MODEL FOR OBSESSIVE
COMPULSIVE DISORDER:**

**FLUOXETINE TREATMENT OF ACRAL LICK
DERMATITIS IN DOGS**

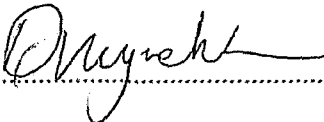
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University of the Witwatersrand, Johannesburg, in partial fulfilment of the
requirements for the degree of Master of Medicine in the branch of
Psychiatry.**

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DECLARATION

I, Dora Rebecca Souleika Mascha Wynchank, declare that this thesis is my own work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.


.....

.....01.....day of.....07....., 1999.

For my parents

Sinclair and Anny Wynchank

Constantly loving and supportive

Both devoted academics

Their lifelong commitment to study and teaching

always my inspiration

PUBLICATIONS AND PRESENTATIONS

Wynchank D. Understanding obsessive compulsive disorder. *Journal of Depression and Anxiety* 1999; 2:14-17.

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ABSTRACT

Acral Lick Dermatitis (ALD) is a self inflicted skin disorder found in dogs. It is caused by excessive licking of paws and flanks. ALD has been proposed to be an animal model of obsessive compulsive disorder (OCD) in humans. In both conditions, serotonergic neural dysfunction is believed to be responsible for aberrant grooming behaviour. ALD is the first animal model proposed for a psychiatric condition. Serotonergic antidepressants are recommended as first line treatment in OCD and preliminary work has shown ALD sufferers to respond to serotonergic antidepressants. *Objective:* The aim of the study was to assess the efficacy and tolerability of fluoxetine treatment of ALD in dogs and to investigate ALD as an animal model of the psychiatric condition, OCD. *Method:* Sixty three dogs with ALD were treated with fluoxetine 20 mg daily, or placebo, for 6 weeks. *Results:* In the fluoxetine group, owners rated both appearance of the lesion ($t = 7.02$, $df = 29$, $p < 0.0001$) and licking behaviour ($t = 10.2$, $df = 29$, $p < 0.0001$) as significantly improved by the end of the trial. Veterinarian-rated pre- and post-treatment photographs showed statistically significant improvement in the fluoxetine group alone (mean = 2.55). There were no significant changes in the placebo group as rated by owners and veterinarians. *Conclusions:* These results demonstrate the efficacy of fluoxetine in the treatment of ALD and lend further support to ALD as an animal model of OCD.

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NOMENCLATURE

ALD	Acral Lick Dermatitis
ANOVA	Analysis of variance
CGI	Clinical Global Assessment
CSF	Cerebrospinal Fluid
CT	Computerised Tomography
DNA	Deoxyribonucleic Acid
DSM IV	Diagnostic and Statistical Manual, Fourth Edition
ECA	Epidemiological Catchment Area
GABA	Gamma-aminobutyric Acid
5HT	5-hydroxytryptamine, serotonin
5HIAA	5 hydroxyindoleacetic acid
<i>m</i> -CPP	<i>meta</i> -chlorophenyl-piperazine
MRI	Magnetic Resonance Imaging
OCD	Obsessive Compulsive Disorder
PANDAS	Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections
PET	Positron Emission Tomography
rCBF	Regional Cerebral Blood Flow
SAVA	South African Veterinary Association
SPECT	Single Photon Emission Computerised Tomography
SRI	Serotonin Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor

TS Tourette's Syndrome

Xe Xenon

CHAPTER 1

1.0 INTRODUCTION

1.1 Obsessive Compulsive Disorder

Obsessive Compulsive Disorder (OCD) has been recognised since antiquity. Case histories from the ecclesiastical literature of the 15th century describe symptoms that are easily recognisable as OCD today (1). Over the centuries, a variety of terms has been used to designate the symptoms of OCD. These terms reflect the different ways OCD has been conceptualised historically. They include: demonic possession, religious melancholy, scruples, *folie de doute* and compulsion neurosis. Obsessive Compulsive Disorder is the name given by the Diagnostic and Statistical Manual (DSM IV) of the American Psychiatric Association (2).

1.1.1 Epidemiology of OCD

As late as 1983 OCD was still thought of as a rare illness with a poor prognosis. In 1988, a publication of the Epidemiologic Catchment Area (ECA) survey indicated that OCD was much more common in the general population than previously recognised, with a lifetime prevalence of 2.5% (3). Following the ECA survey, it became apparent that in the USA, OCD was the fourth most common psychiatric diagnosis (following phobias, substance related disorders and depression).

The average age of onset in OCD is 17 years for males and 21 years for females (4). At least a third of those who develop the disorder have done so by the age of 15 (5). OCD is equally prevalent in women and men, except in adolescence, when males predominate. The underestimation of OCD in previous epidemiological studies was probably because patients seldom sought treatment, fearing stigmatisation. Obsessions and compulsions were viewed as best as silly, and at worst as horrific and 'crazy'. Few people were helped by available treatments. It was only in 1977 that the serotonin reuptake inhibitor (SRI), clomipramine, was shown to be effective in the treatment of the condition (6).

1.1.2 Phenomenology of OCD

An obsession is a recurrent and intrusive thought, feeling, idea or sensation. Attempts are made to ignore or suppress obsessions or to neutralise them with some other thought or action. A compulsion is a conscious, standardised, recurrent thought or behaviour, such as checking, handwashing, counting or avoiding. Compulsions are not realistically connected to that which they are designed to neutralise or prevent. They are clearly excessive. Obsessions exacerbate anxiety and distress; whilst carrying out compulsions reduce it. A person with OCD generally realises the irrationality of the obsessions and recognises both the obsessions and compulsions as egodystonic. OCD can be a most disabling condition because of the excessive time consumed in carrying out obsessions and compulsions. There is significant interference with the person's

routine as well as social, academic and occupational function. OCD symptoms tend to wax and wane over time and the course of the disorder is chronic.

1.1.3 Neurochemical aetiological theories

The aetiology of OCD is multifaceted. Several theories have been proposed regarding genetic, electrophysiological and neuroendocrine factors. Of relevance to this research are the theories concerning neurochemical and neuroanatomical aetiologies. The latter will be dealt with extensively in Chapter 4.

The major hypothesis on the pathophysiology of OCD postulates an involvement of 5-hydroxytryptamine or serotonin (5HT) on the basis of an almost exclusive response of patients to SRIs such as clomipramine and fluoxetine. Serotonin dysregulation has been one of the best studied neurochemical factors in OCD.

However, investigations of the biological correlations of the 5HT hypothesis have had inconsistent results. Two studies have looked at cerebrospinal fluid (CSF) concentrations of the 5HT metabolite, 5 hydroxyindoleacetic acid (5HIAA) in OCD. Thoren and colleagues (7) found a nonsignificant increase of 5HIAA in the CSF of 24 pre-treatment, hospitalised, OCD patients (19%); when compared with 37 healthy volunteers. The findings of Insel and co-workers were more conclusive (8). The levels of 5HIAA were significantly elevated in the CSF of a cohort of eight patients with OCD compared to 23 matched controls. Clearly, these sample sizes are small and the results should be interpreted with caution.

The most widely used agent in pharmacological challenge studies of serotonergic involvement is the 5HT agonist *meta*-chlorophenyl-piperazine (*m*-CPP). *m*-CPP binds with high affinity to several 5HT receptors: namely 5HT₂, 5HT_{1a}, 5HT_{1c} and 5HT_{1d} (9; 10). In healthy human subjects, *m*-CPP is associated with an elevation in plasma prolactin and cortisol concentrations. The effect of *m*-CPP on prolactin in OCD patients remains in dispute. While one study found no difference between untreated OCD patients and controls (11), others found that the prolactin response was blunted in OCD patients compared to healthy controls (12; 13).

Studies measuring the blood and platelet 5HT content in OCD have shown conflicting results and remain inconclusive (14; 15).

On closer inspection, the deductions that can be made about the role of serotonergic dysfunction in OCD remain limited. Responses to treatment provide the most conclusive evidence for the role of the serotonergic neural system in OCD. To account for the conflicting results of the neurochemical investigations listed above, one must take into account that the serotonergic system is extremely complex. To date, more than 14 subtypes of the 5HT receptor have been identified and cloned (16). The serotonergic system does not appear to work in a homogenous and synchronised way. Rather, different segments of the system are implicated in different functions (prolactin release, hypothalamus-pituitary axis, mood, sleep, appetite, thermoregulation, anxiety, obsessions, compulsions etc.). A possible way of understanding and unravelling the serotonergic system would be through its receptors, with research focusing on more specific biological markers and their behavioural correlates in OCD.

1.1.4 Treatment of OCD - literature review

The treatment of OCD is divided into control of the acute episode and maintenance treatment. Important components of any treatment strategy include psychoeducation for patients and families, cognitive behavioural psychotherapy and pharmacotherapy. Support groups also play an important role.

The first drug documented as effective in the treatment of OCD was a monoamine oxidase inhibitor, and not the tricyclic antidepressant, clomipramine, as commonly believed. In 1959, Joel described successful response to iproniazid in six patients with obsessive-compulsive 'psychoneurosis' (17). While the monoamine oxidase inhibitors are rarely used in the treatment of OCD, the SRI clomipramine and the selective serotonin reuptake inhibitors (SSRIs) have become the pharmacology of choice.

In the treatment of OCD, multicentre, double blind trials of six serotonergic antidepressants have demonstrated them to be more effective than placebo and in both adults and children (18 - 25).

Several studies have compared the efficacy of clomipramine versus the SSRIs with interesting results. Clomipramine has emerged superior to the fluoxetine, fluvoxamine and sertraline in three meta-analyses. (26 - 28).

Despite the results of these meta-analyses, questions do remain as to the superiority of clomipramine, particularly as direct comparisons of clomipramine and an SSRI have not

supported the meta-analytic observation that the former is more effective (29). More recently, larger, double blind parallel-design studies have reinforced similarities in efficacy rather than differences between clomipramine and the SSRIs (30).

Possible explanations for the results of the meta-analyses should take into account that clomipramine was the first drug for OCD to be studied in the United States. Study subjects were unlikely to have had prior treatment with potentially effective medications. Studies with the SSRIs occurred later and would have included varying proportions of patients with treatment failures after clomipramine. Hence, the inclusion of more treatment resistant subjects in recent trials may have adversely biased the results. Furthermore, greater baseline severity of OCD in the clomipramine studies may have permitted greater improvement; whereas longer disorder duration may have diminished placebo response.

Dosing and duration of treatment must be sufficient before concluding that a drug used in the treatment of OCD is ineffective (31). Higher doses of SSRIs are usually necessary in OCD as compared to doses used to treat depression. Ten to twelve weeks of therapy with an adequate dose of an SRI may be necessary before improvement is seen. When it is clear that one SRI is not benefiting the patient, switching to another SRI is common practice. After two or three failed trials of SSRIs, a clomipramine trial is often recommended.

Augmentation strategies such as adding lithium carbonate, buspirone, an antipsychotic, clonazepam, triiodothyronine or valproate have all been described in the literature with

varying results. While open label studies do describe some benefits, the double blind evidence for the efficacy of these compounds is disappointing (32).

Behaviour therapy in OCD uses the principles of exposure and response prevention. It is a well established, effective treatment for OCD (33). Best overall results in OCD are obtained using a combination of pharmacotherapy and cognitive behavioural therapies.

Neurosurgery has been used to treat patients who have not responded to an exhaustive array of pharmacological and behavioural treatments and who suffer from severe, debilitating and chronic OCD. Anterior capsulotomy, anterior cingulotomy and subcaudate tractotomy have been an effective and safe intervention for some individuals with incapacitating OCD (34; 35). However, the efficacy of the neurosurgical techniques remains unproven (36).

1.1.5 Prognosis of OCD

The prognosis of OCD has improved significantly with the introduction of effective pharmacological and behavioural strategies. Forty to 60 per cent of patients can expect a significant reduction in symptoms (31). Nevertheless, 20 to 30 per cent have minimal or no response to treatment. Many have significant side effects. SSRIs afford symptom control rather than cure (36). The rate of relapse following discontinuation of treatment is higher in OCD than generally seen in depression. Pato and colleagues (37) found a relapse rate of almost 90% two months after abrupt discontinuation of clomipramine in

18 remitted patients. Tapering the dose of the SRI or SSRI appears to lower the chances of acute relapse but this has yet to be tested in a controlled study.

1.2 Ethology

The concept of drawing inferences about psychiatric conditions from animal behaviour is not new. The search for animal models of psychiatric disorders in humans can be said to have begun over a hundred years ago, with the development of ethology, the study and comparison of animal behaviours. This discipline was founded by Whitman and Heinroth in the late nineteenth century and was brought to recognition by Lorenz in the 1930s. Ethology comprises the scientific observation of animal behaviour in a naturalistic setting. Contemporary researchers are using ethology, and its offspring, neuroethology, to understand the fixed behavioural patterns seen in OCD. Neuroethologists focus on the study of the brain in developing and maintaining fixed behaviours. Lorenz, who won a Nobel prize in 1973 for his work on innate behavioural patterns, described these behaviours as the 'back side of the mirror' (38). By this he meant that in each species, observable behaviour is derived from stored knowledge in the form of genetically transmitted drives and skills.

1.2.1 Fixed action patterns

By studying inborn behaviour patterns in animals in the natural state, Lorenz was able to describe the 'fixed action pattern', a curious, automatic, motor sequence of behaviour

conserved in certain species of animal (38). These innate and adaptive sequential movements may be elicited by specific stimuli or triggers. Lorenz's classic example was the egg-retrieval beak movement found in the graylag goose. This motor pattern was released following egg-like sensory cues. The pattern is seen in all members of the species, even when they are raised in isolation. Some fixed action patterns are present at birth (e.g., the pecking of a newly hatched chick); others are expressed later in development (e.g., courting behaviours). Other examples of fixed action patterns include squirrels' ritual of food storage. Squirrels with extra food, even when in captivity, look for places to hoard the food, and go through covering and packing movements. Nesting is another highly ritualised behaviour. The behaviour in fixed action patterns may appear to be excessive (e.g. hoarding) or inappropriate (e.g. the bird, which pecks at the non-existent worm in a territorial display). However there does seem to be a communicative value by virtue of the formal pattern of the display or the number of times the display is repeated (39).

The early ethologists postulated that in conflictual or frustrating situations, a particular fixed action pattern was both released and inhibited. The behaviour observed in these situations would therefore comprise an excessive or inappropriate sequence of the fixed action pattern movements. Some workers have come to see the rituals of OCD as fixed action patterns: innate behaviours which have become inappropriately released.

1.2.2 Displacement behaviours

When fixed action patterns are performed in an excessive or inappropriate way, in situations of either frustration or conflict, they are termed displacement behaviours (40). These behaviours are species-typical. Naturalistic examples include behaviours such as digging, hoarding and grooming motor rituals. Grooming is frequently observed as a displacement behaviour in animals (41 - 44). Lorenz noted that displacement behaviours occur 'when the normal outlet for a certain motivation is blocked' (38). He summarised: 'a vast majority of motor patterns appearing as displacement activities are common "everyday" activities...the so-called comfort activities of small birds and mammals such as scratching, preening...; when embarrassed, even humans tend to scratch behind the ear - and in other places' (38).

1.2.3 Stereotypies

Stereotypic acts are a variant of displacement behaviour and can be defined as repetitive movements that are repeated without variation and that appear to serve no obvious purpose (45). They tend to be species specific (46) and are common in domestic or captive animals (47).

Zoo stereotypy is the label given to a diverse collection of poorly understood behaviours that are observed in animals that are confined, isolated or chronically frustrated. These behaviours range from scratching or hair pulling, to complex motor acts such as rocking

or pacing. Foraging mammals, particularly carnivores, appear to be most susceptible to this behaviour.

Stereotypic disorders occur where the prevalence of stereotypic behaviours is such that the animal's normal functioning is disrupted. Damage, such as self mutilation, is caused (48). From an ethological perspective, stereotypic disorders can be seen as abnormal expressions of species-typical motor patterns, such as grooming.

The most common grooming stereotype is compulsive self-chewing (Acral Lick Dermatitis, ALD) in dogs. This occurs when dogs repetitiously and seemingly without purpose, lick, scratch or bite specific parts of their bodies. Other stereotypic disorders have been described in a variety of domestic animals. Doberman Pinschers, almost exclusively, show flank sucking (46). Tail chasing is described in bull terriers (49). Certain breeds of cats, particularly the oriental breeds (Siamese, Burmese, Himalayan and Abyssinian) show stereotypic grooming behaviours that may result in baldness (psychogenic alopecia). In this condition, a single site, often on an extremity, abdomen or flank, is licked and chewed (50). Horses show both self mutilation stereotypies and 'crib biting', where a surface area is bitten, neck muscles are tensed, the larynx is retracted and a bolus of air swallowed (51). The cebus monkey has been described to show spontaneous, stereotyped licking behaviour (52). Excessive feather-picking is common in captive birds and may lead to infection, hypothermia and even fatal haemorrhage if 'blood feathers' are picked (53).

The neurochemical underpinning for these phenomena is complex, however, there is evidence for involvement of both the dopaminergic and serotonergic systems (54; 55).

1.3 Acral Lick Dermatitis

Canine ALD was first proposed as an animal model for OCD by owners who noticed a similarity in the ritualistic grooming behaviours of both conditions (56).

1.3.1 Phenomenology of ALD

ALD is a relatively common, self-inflicted, skin disorder found in domestic dogs. It is also known as lick granuloma or neurodermatitis. It is caused by excessive licking, scratching and biting of the carpus, metacarpus and metatarsus. The 'compulsive' licking of a patch of skin leads initially to loss of fur and ultimately to a chronic abrasion of the underlying skin. Interestingly, skin lesions (dermatitis) have also been reported secondary to compulsive washing in humans (57).

There is an interesting phenomenological difference between human OCD and the canine obsessive syndrome. Humans show many forms of compulsions, whereas in dogs there only seem to be two manifestations (ALD and tail chasing). Dogs have a range of behaviour wide enough to include other compulsions, but these have not been described.

1.3.2 Pathology of ALD

Erythema and epidermal excoriations give rise to a single, well circumscribed, ulcerated plaque. Occasionally, lesions are multiple. In severe cases, secondary bacterial infection and pyoderma of the superficial lesions may result. On examination, regional lymph nodes are often swollen. The lesions heal, leaving an alopecic plaque, often with peripheral hyperpigmentation.

Histologically, a sharp transition between hyperplastic and ulcerated epidermis is seen. Superficial dermal fibrosis is usually marked. Collagen fibres in the dermal papillae are often arranged perpendicular to the surface epithelium, called 'vertical streaking'. Perifolliculitis, folliculitis and sometimes furunculosis may accompany more superficial lesions (50).

1.3.3 Aetiology of ALD

Although the aetiology of ALD is uncertain, it has been attributed to psychogenic causes such as loneliness, confinement or boredom. It can also be provoked by local irritation (58).

Certain large breeds appear to be more susceptible: for example, German Shepherds, Labrador Retrievers, St. Bernards, Doberman Pinschers and Great Danes (58).

1.3.4 Treatment of ALD - literature review

ALD is notoriously difficult to treat. Practitioners have used corticosteroids, cobra venom, surgical excision, restrictive collars and radiation or cryotherapy (59 - 61). As in OCD, benzodiazepines are not effective in ALD (49). Following the hypothesis that the opioid system is implicated in self-mutilation, Dodman et al. (62) used narcotic antagonists to treat ALD with some success. An open label pilot study of clomipramine in six dogs suggested that clomipramine might be an effective treatment for ALD (56). Stein and colleagues (55) found similar results with fluoxetine in another open label trial of dogs with ALD.

Rapoport and colleagues were the first to conduct double blind crossover trials in dogs with ALD (59). A pilot challenge study with the 5HT agonist, *m*-CPP, was also attempted, as this drug had previously been shown to worsen OCD after single dose administration (63). However, in the study of Rapoport et al., no useful observations could be made of the effects of *m*-CPP on ALD as all five of the dogs included in the pilot study immediately became somnolent (59).

The study design of Rapoport et al. (59) comprised three, eleven week crossover trials, where three different SSRIs were compared: clomipramine/desipramine (n=13), fluoxetine/fenfluramine (n=14) and sertraline/placebo (n=10). All drugs were given orally and clinical change was measured by the dogs' owners. The results were remarkably similar to what one expects in a clinical OCD population: the placebo response was non-existent and each of the SSRIs was significantly better than the comparison agent. The

SSRIs were found to be effective with a 50% control of symptoms, in a dose similar to the human dose. The improvement was gradual over the five week period. Moreover, as in OCD, the dogs relapsed after stopping treatment with the SSRIs. The results were statistically significant and although the sample size was small, the findings were encouraging and hence, this study was prompted in an attempt to clarify whether ALD is a useful animal model of OCD.

1.4 Animal Models

To start at the beginning: why look for animal models in psychiatric research?

In the literature, there are both advocates of animal models in psychiatric research and those who argue against their use. As regards OCD specifically, the benefit of animal models depends on how the disorder is conceptualised.

Some have viewed OCD as a 'neurosis': a disorder primarily of aberrant thoughts - such as doubt, guilt and aggression. These thoughts are believed to be associated with secondary motor rituals or compulsions. If this is the theoretical underpinning of OCD, animal models are hardly useful. It remains to be proven that any animal, even our closest evolutionary relative, the primate, experiences a thinking process of this type.

Indeed, most psychiatric disorders, such as the psychoses, anxiety and mood disorders, are believed to involve higher brain functions. These are also termed the executive

brain functions and include conceptual thinking, planning, attention and tracking. Anatomically speaking, the executive functions are believed to be controlled by the prefrontal cortex and inferior parietal lobe. Only animals higher up the evolutionary ladder are capable of performing executive brain functions because their brains are sufficiently developed. Therefore, no animal model exists for the bulk of psychiatric disorders.

The contemporary understanding of OCD has veered away from the neurosis model. OCD may be viewed as a disturbance of primitive motor circuits resulting in grooming and checking behaviours. The preoccupation with contamination or doubt might result as a secondary phenomenon, arising from a need to explain the motor behaviour. This conceptualisation of OCD makes it more amenable to an animal model. It does appear that OCD benefits from the use of animal models in the understanding of its underlying neurobiology. Preliminary research has concluded that animal models are both helpful and necessary in OCD (41; 43).

In terms of a putative neuroanatomical site of dysfunction, OCD also appears to be an exception to the majority of psychiatric illnesses. In OCD, higher brain functions are not primarily implicated. The evidence for this is based on the neuroanatomical finding that more ancient parts of the brain - particularly the basal ganglia - appear to be involved. The basal ganglia are ancient in evolutionary terms: they may have been present before the development of the frontal lobes and are seen in animals lower down the evolutionary ladder. The serotonergic neural pathways believed to dysfunction in OCD are thought to be phylogenetically ancient and hence OCD may be related to the

stereotypic behaviours which are found in domestic animals. This has suggested a common neuroethological origin of OCD (55).

1.4.1 The validation of animal models

If an animal model is proposed for a psychiatric disorder, researchers need to have ways of validating it. McKinney and Bunney (64) proposed face validity as a way of validating animal models. ALD appears to be the only animal model of a psychiatric disorder with true face validity. Willner (65; 66) has suggested two other sets of criteria for assessing animal models of depression: predictive and construct validity.

If the only similarity between an animal model and the clinical condition is the treatment response, the validity is termed predictive. In this case, the animal model serves as a behavioural assay for the screening potential of a specific therapy. In contrast, face validity requires the animal model and clinical condition to be similar both in terms of phenomenology and treatment response. Finally, construct validity requires similarities in phenomenology, treatment response, but also a theoretical relationship to the clinical disorder in question. Face validity is particularly useful in the understanding of animal models of OCD.

1.4.2 Displacement behaviours as animal models

There are many similarities between the grooming disorders in both domestic animals and humans. The repetitive, stereotyped cleaning and grooming rituals of OCD can be

compared to both naturalistic and experimental animal behaviours. Displacement behaviour is a well described phenomenon that occurs both in the natural state and experimentally. Holland was the first to point out the phenomenological similarities between displacement behaviours and the compulsive rituals seen in OCD (44).

There are some reservations about the benefit of displacement behaviours as animal models. While there are clear similarities between the hoarding, washing and checking found in OCD and the displacement behaviours found in animals, the extent to which the OCD behaviours can be attributed to conflict or threat, remains highly speculative.

ALD is a disorder characterised by excessive grooming. The licking behaviour in ALD has been viewed as a displacement behaviour and has been attributed to confinement or boredom in the afflicted dog. Furthermore, the grooming behaviour seen in ALD can be likened to the grooming rituals of OCD. As a putative animal model of OCD, ALD can be classified as a form of zoo stereotypy that seems to combine face, predictive and construct validity.

In general, grooming is an important displacement behaviour that has been replicated in the experimental setting. Winslow and Insel (67) set up an experiment to examine the frequency of bouts of displacement grooming in mice. A male mouse (the intruder), was placed in the scent-marked cage of an unfamiliar aggressive mouse (the resident). The intruder's behaviour was compared when given clomipramine (5mg/kg) or desipramine (5mg/kg). When the resident was absent (the anticipatory phase), the intruder's grooming was unaffected by clomipramine but doubled by desipramine. When the

resident was present (displacement phase), the intruder's grooming was decreased by more than half with clomipramine, but unaffected by desipramine.

These results suggest both predictive and face validity for displacement grooming. However, further work needs to be done to ascertain the role of the SSRIs in displacement grooming.

1.5 Aims Of This Study

The primary aim of this study was to assess the efficacy and tolerability of fluoxetine in ALD. ALD was also investigated as an animal model for OCD, using a larger sample size than reported in previous trials. If the pharmacological response to fluoxetine in ALD resembled that in OCD, this would support ALD as an animal model of OCD. It would also provide indirect support for a serotonergic role in complex grooming behaviours in another species.

CHAPTER 2

2.0 MATERIALS AND METHODS

2.1 Experimental Design

The experimental design was a double blind, randomised, placebo controlled trial.

2.2 Study Population

A study population of domestic dogs in Johannesburg was used.

2.3 Recruitment of Subjects

Dogs were recruited from veterinarians in the Johannesburg area. In order to ensure accuracy of diagnosis, a discussion on ALD and the trial itself, was presented to a monthly academic meeting of referring veterinarians. This meeting was hosted by the South African Veterinary Association (SAVA). Letters describing the trial were also sent to all SAVA members in the Johannesburg area.

Widespread community involvement was elicited by an interview held on a local radio station (702), where a well known veterinarian discussed ALD with the researcher and

requested participation from listeners whose dogs had been diagnosed with the condition for at least six months.

2.4 Inclusion and Exclusion Criteria

Inclusion criteria were dogs suffering from ALD which had been diagnosed by a veterinarian at least six months previously and where there was an observable lesion. Other causes of licking behaviour were ruled out by examining the dogs' clinical history, typical lesion appearance and past history of treatment response. The minimum weight of dogs was five kilograms. Dogs undergoing concurrent treatment for ALD were excluded as were dogs with any other medical or surgical condition, currently undergoing treatment.

2.5 Dosage

A dose of fluoxetine, 20mg per day was calculated based on a previous trial which used 0.1mg/kg/day for each dog (59).

2.6 Measurements

The measurement tool was a seven point scale modelled on the Clinical Global Impression (CGI) score. The owners rated the following three factors: licking behaviour, appearance of the lesion and the dogs' general condition (see Appendix A). For

example, as regards licking behaviour, owners scored behaviour using definitions as follows: not rated, no excess licking at all, very mild excess licking, mild excess licking, moderate excess licking, severe excess licking, very severe excess licking. The appearance of the lesion and the dog's general condition were rated on similar seven point scales. The CGI scores were obtained from owners at baseline, and then weekly for the six weeks' duration of the trial. The CGI was explained to owners at the first meeting at home, where the initial assessment was done by the researcher with the owner. At that meeting, owners were interviewed for behavioural and medical histories.

Pre-treatment photographs of the lesions were taken by the researcher at the first consultation (day one of the trial). Post-treatment photographs were obtained at six weeks, the end of the trial. These pre- and post-treatment photographs were rated blind by two independent experienced veterinarians using CGI scores, at the trial end. The veterinarians rated the appearance of the lesion at baseline, at six weeks and compared the two.

2.7 Analysis

A difference between the fluoxetine and placebo groups was calculated to be probably detected with a sample size of 26 per group. The alpha and beta values at 95% confidence levels were respectively 0.05 and 0.01. The data were analysed using paired or group t tests and analysis of variance (ANOVA) tests.

2.8 Ethical Issues

Every owner was approached for informed consent and was given an information booklet about the trial (see Appendix B). Pet owners were able to withdraw their dogs at any point during the trial. Weekly phone calls were made to every owner to discuss potential problems and side effects. The study was accepted by the Animal Ethics Committee of the University of the Witwatersrand.

2.9 Resources

The fluoxetine was provided by the pharmaceutical company, Eli Lilly.

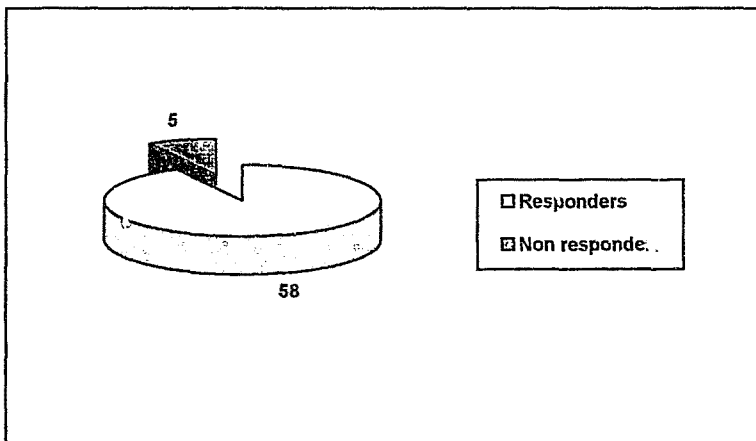
CHAPTER 3

3.0 RESULTS

3.1 Sample Size and Response Rate

Sixty three dogs were entered on the trial and 58 completed the trial. The response rate was therefore 92.0%. Four dogs were withdrawn by their owners during the course of the trial with no reason given; and one dog was underwent euthanasia for an unrelated reason during the trial; (Figure 3.1).

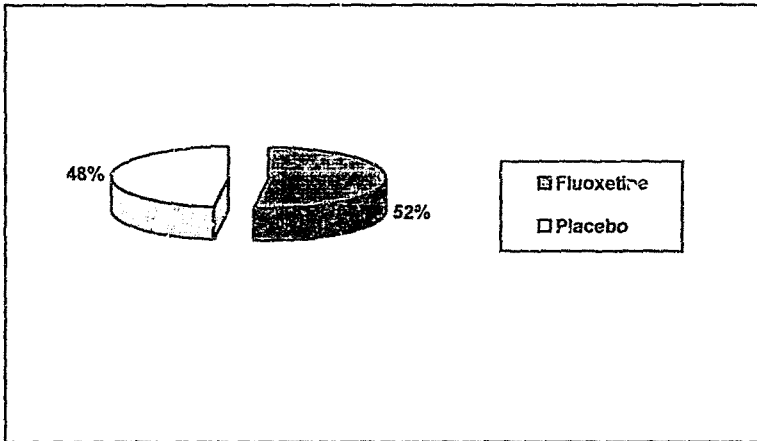
Figure 3.1: Response rates



3.2 Randomisation

There were 30 dogs randomised to the fluoxetine group (51.7%) and 28 dogs to the placebo group (48.3%); (Figure 3.2).

Figure 3.2: Randomisation to the two groups

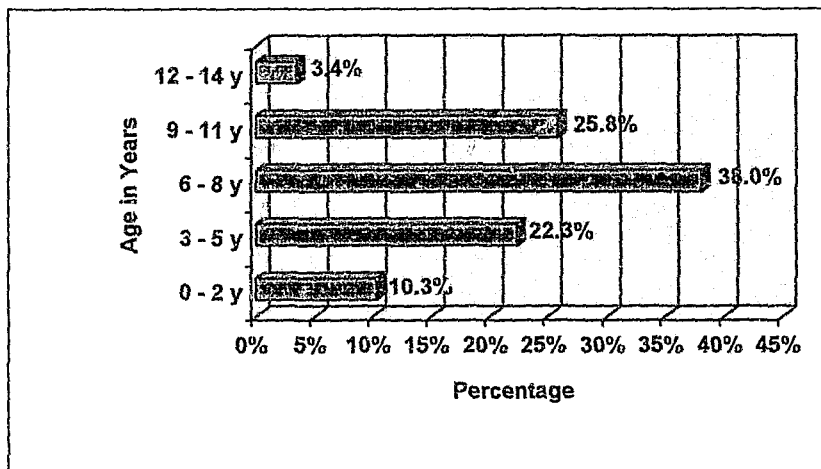


3.3 Demographic Factors

3.3.1 Subjects' ages

The dogs' ages ranged between one and 13 years; (Figure 3.3).

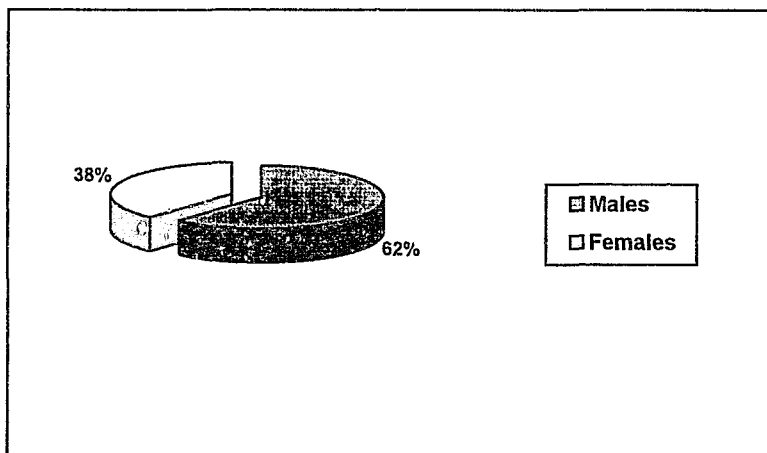
Figure 3.3: Distribution of dogs' ages



3.3.2 Sex of subjects

Males comprised 62.1% of the sample (n=36) and females 37.9% (n=22); (Figure 3.4).

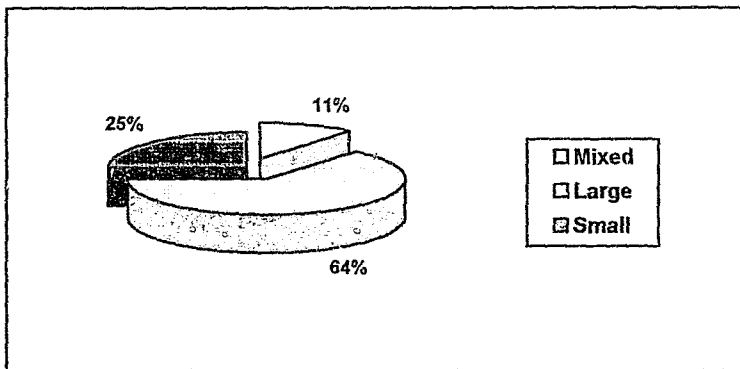
Figure 3.4: Gender distribution



3.3.3 Subjects' breeds

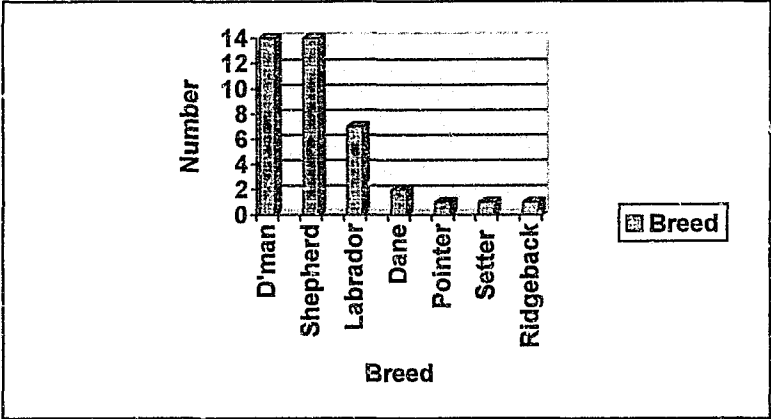
Seven dogs were of mixed breed (11.1%). Of the remaining 56 subjects, the dogs were subdivided into large (n=40; 63.5%) and small breeds (n=16; 25.4%); (Figure 3.5). Dogs classified as belonging to large breeds weighed over ten kilograms whereas dogs belonging to small breeds weighed ten or under ten kilograms.

Figure 3.5: Breed of dogs



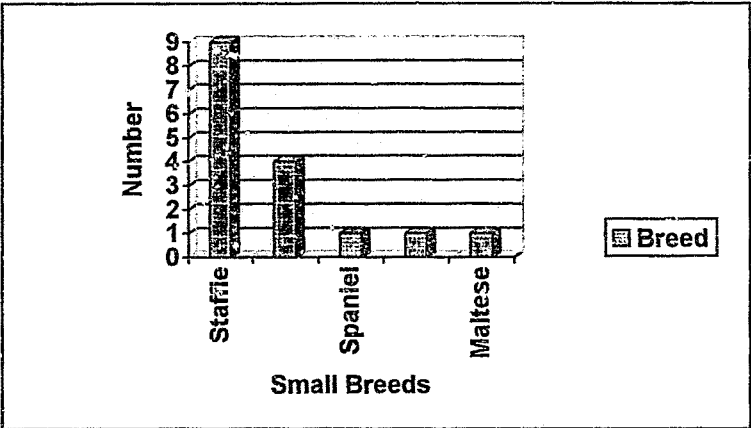
Large breeds comprised the following: Doberman Pinscher (n=14); German Shepherd (n=14); Labrador Retriever (n=7); Great Dane (n=2); German Shorthaired Pointer (n=1); English Setter (n=1); and Rhodesian Ridgeback (n=1); (Figure 3.6).

Figure 3.6: Large breeds



Small breeds comprised the following: Staffordshire Terrier (n=9); Pomeranian (n=4), King Charles Spaniel (n=1); Jack Russell (n=1) and Maltese Poodle (n=1); (Figure 3.7).

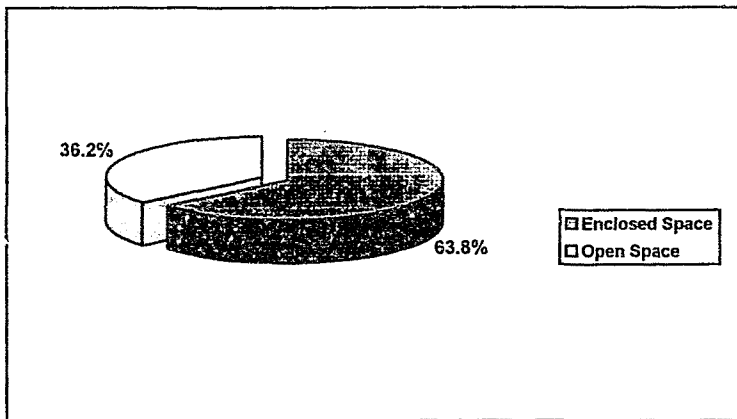
Figure 3.7: Small breeds



3.3.4 Dogs' domestic environment

The majority of the dogs lived in an enclosed space (n= 37; 63.8%), surrounded by a high wall through which they could not see; (Figure 3.8).

Figure 3.8: Subjects' domestic environment

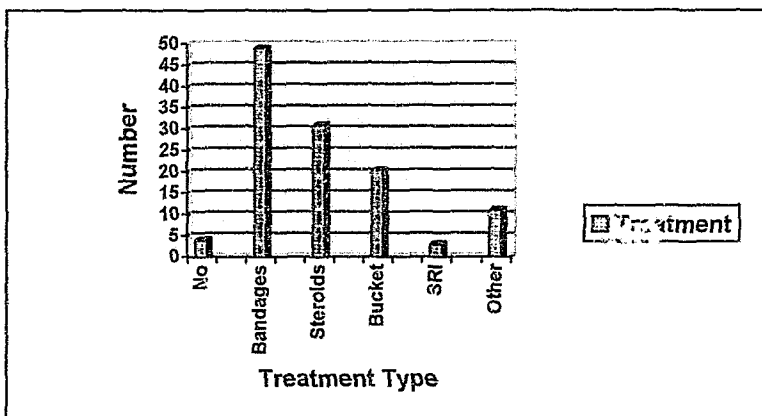


3.4 Previous Treatments for ALD

Only four of the 63 dogs had been on no prior treatment for ALD. Of the remaining 59 subjects, 49 had had bandages applied to the lesion (69.8%); 31 had been on steroids (49.2%); and 25 had had a bucket placed over the head to prevent access to the lesion (39.7%). Three dogs had been on another SRI (clomipramine; 4.7%). Eleven dogs had been on some other form of treatment (17.4%). These included the following: antibiotic treatment (n=8); bitter lime spray to the lesion (n=4); gentian violet (n=3); antihistamine (n=3); surgery (n=2); baby powder (n=1); garlic capsules (n=1), antiseptic ointment

(n=1); wire mesh (n=1); homeopathic medication (n=1); and aloe powder (n=1); (Figure 3.9).

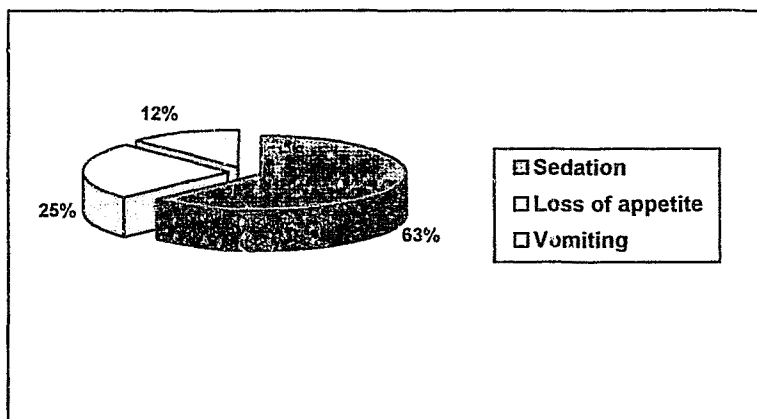
Figure 3.9: Previous treatments for ALD



3.5 Side Effects to Fluoxetine

Of the 58 dogs who completed the trial; side effects to fluoxetine were found in eight dogs. The side effects comprised the following: sedation (n=5, 63%); loss of appetite (n=2, 25%); and vomiting (n=1, 13%); (Figure 3.10).

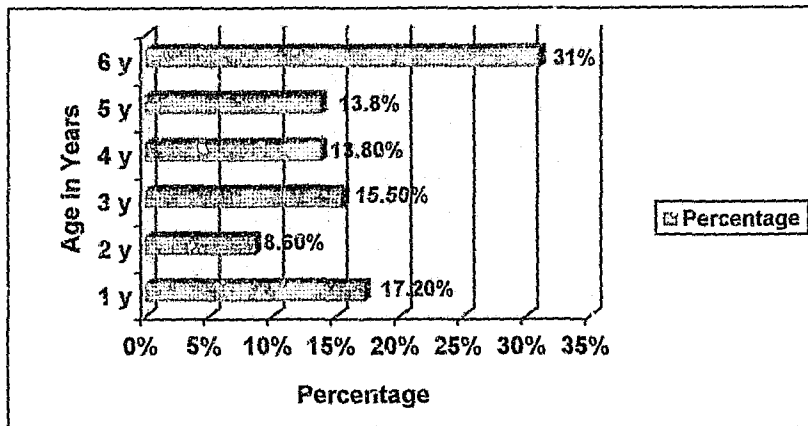
Figure 3.10: Side effects to fluoxetine



3.6 Age of Onset of Licking

The age of onset of licking showed a bimodal distribution with peaks at one year and six or more years; (Figure 3.11).

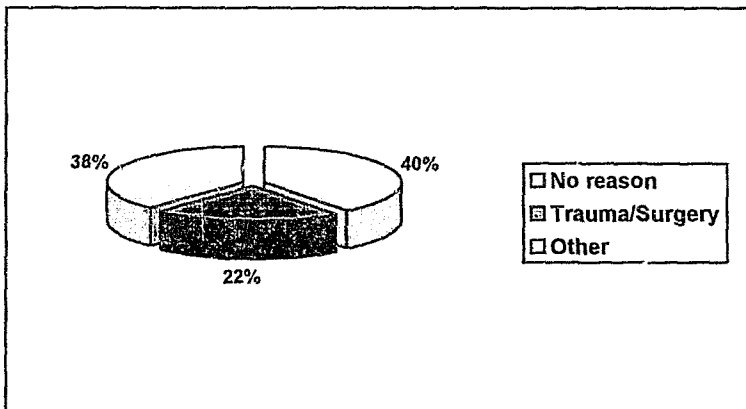
Figure 3.11: Age of onset of licking



3.7 Reason Identified for Onset of Licking

The majority of owners could not identify a subjective reason for the licking behaviour (n=23; 39.6%). For 22.4% of the dogs (n=13), licking had started after an episode of trauma or surgery to the site. In 38.0%, (n=22), owners cited 'other' as a reason for onset of licking. Reasons falling into the 'other' category included recent construction of a high wall or electric fence around the property (Figure 3.12).

Figure 3.12: Reason identified for onset of licking behaviour

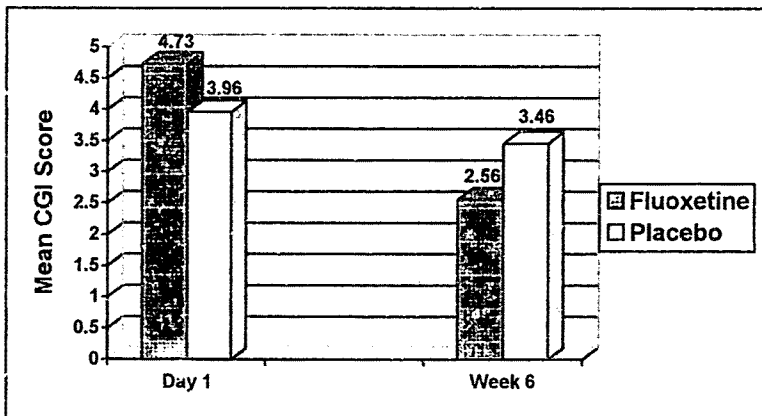


3.8 Licking Behaviour in the Fluoxetine and Placebo Groups

In the fluoxetine group, owners' ratings of licking behaviour on the CGI showed a statistically significant difference between day one of the trial and the end of week six ($p < 0.0001$, $t = 10.2$, paired t test).

By contrast, there were no significant changes in the placebo group. Owners assessed the licking behaviour as minimally changed by the end of the trial ($p = 0.186$, $t = 1.35$); (Figure 3.13).

Figure 3.13: Mean CGI score for licking behaviour

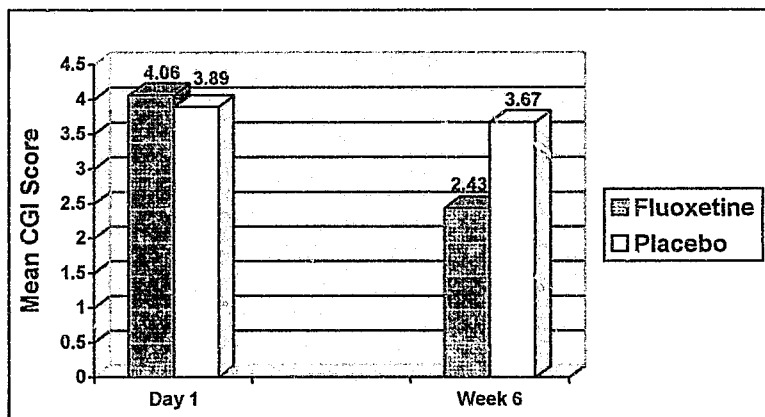


3.9 Appearance of the Lesion in the Fluoxetine and Placebo Groups

Owners rated the appearance of the lesion at the beginning and the end of the trial as significantly improved ($p < 0.0001$, $t = 7.02$).

Owner-rated appearance of the dogs' lesions did not change significantly by the end of the trial in the placebo group ($p = 0.501$, $t = 0.681$); (Figure 3.14).

Figure 3.14: Mean CGI score of appearance of lesion

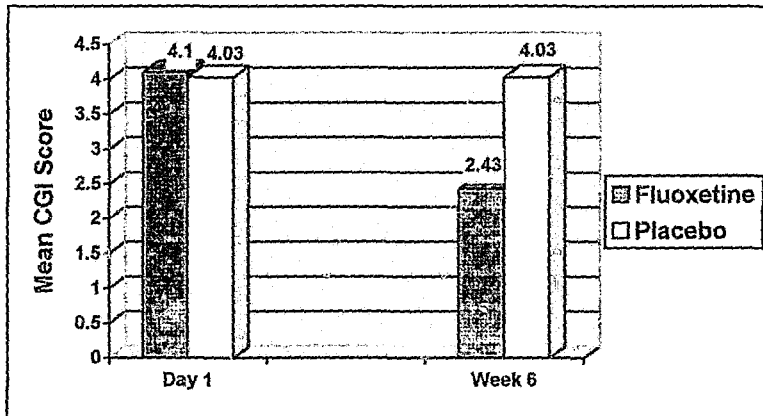


3.10 Dogs' General Condition in the Fluoxetine and Placebo Groups

The amount of change in the dogs' general condition by the end of the trial was also statistically significant in owners' ratings of the fluoxetine group ($p < 0.0001$, $t = 6.90$).

There was no difference in the dogs' general condition in this group by the end of the trial ($p = 1.0$, $t = 0$); (Figure 3.15).

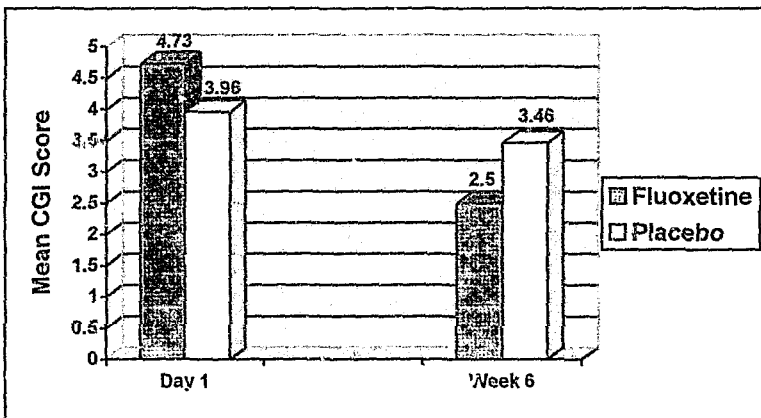
Figure 3.15: Mean CGI score of dogs' general condition



3.11 Baseline Scores

Despite randomisation, the mean owner rated CGI score of licking behaviour was higher at baseline in the fluoxetine group (4.73) than in the placebo group (3.96; $t=2.90$, $p=0.005$, two sample t test). Results were controlled for baseline scores. By the end of week six, the difference in the two groups had reversed with the CGI score in the fluoxetine group significantly lower (2.50) than the placebo group (3.46; $p=0.013$, $t=-2.54$); (Figure 3.16).

Figure 3.16: Baseline CGI score of dogs' general condition



3.12 Comparison between Fluoxetine and Placebo Groups at the Trial End

As regards owners' ratings of the appearance of the lesion ($p=0.0008$ and $t=-3.55$) and general condition of the dog ($p<0.0001$, $t=-4.09$), by the trial's end, the difference between fluoxetine and placebo groups was statistically significant.

3.13 Inter-Rater Reliability in Veterinarian Rating of Clinical Photographs

Using the Pearson correlation coefficients, the ratings by the two veterinarians of pre- and post treatment photographs were found to have good inter-rater reliability ($r=0.869$).

3.14 Veterinarian Ratings of Clinical Photographs

There was a statistically significant improvement in the appearance of the dogs' lesions on fluoxetine. This was measured by subtracting the mean CGI scores at week six from the baseline scores (veterinarian one: mean change=0.933, $t=4.47$, $df=29$, $p<0.0001$; veterinarian two: mean change=1.36, $t=-4.65$, $p<0.0001$). The average of the two veterinarians' ratings was 1.15 ($t=4.97$, $df=29$, $p<0.0001$).

Table 3.1 Veterinarian ratings of clinical photographs

	Veterinarian 1	Veterinarian 2	Mean of 1 + 2
Mean Change	0.933	1.36	1.15
t value	4.47	4.65	4.97

The average of the two veterinarians scores on a CGI scale measuring change in the dog's lesion from baseline to week six, was significantly better in the fluoxetine group (mean=2.55) than in the placebo group (mean=3.66) using the two sample t test ($t=3.36$, $df=56$, $p<0.001$).

CHAPTER 4

4.0 DISCUSSION

4.1 Discussion of Results

4.1.1 Sample size, response rate and randomisation

The sample size of this study is the largest described in the literature for both open label and double blind trials (55; 56; 59).

The response rate in this trial of 92%, can be considered high. It is significantly higher than a placebo response rate. It compares favourably with the only other double blind trial described in the literature (59) where the response rate was 88%. Explanations for the good response in this study may include the high level of motivation of most pet owners, at the start of the trial. Many had tried numerous other therapies for the ALD with little success. They viewed the opportunity to participate in a clinical trial as potentially beneficial to their dogs, who had been suffering from a seemingly intractable and untreatable condition. Secondly, the weekly phone calls to ascertain problems and the weekly completion of CGI scores probably may have helped to motivate the participating pet owners.

The numbers randomised to the two groups were within acceptably similar parameters (n=30 for fluoxetine; n=28 for placebo).

4.1.2 Demographic factors

There are no reports in the literature of the age ranges of dogs with ALD; however in this study, ages spanned one to 13 years.

In this study, the majority of subjects was male (62.1%). Rapoport et al. also reported a *predominance of male subjects (57.1%) versus female (42.8%); (59).*

The majority of dogs belonged to the large breeds (n=40; 63.5%). The finding that most dogs belonged to large breeds is in keeping with descriptions of ALD in the literature (58). In this study, the three most common large breeds were Doberman Pinscher (n=14); German Shepherd (n=14); and Labrador Retriever (n=7). In Rapoport and colleagues' study, albeit in a smaller sample, the breeds of 29 of a total of 42 subjects were identified (59). Labrador Retrievers comprised the majority of subjects (n=11; 37.9%). There were eight Doberman Pinschers (n=8; 27.5%); six Golden Retrievers (n=6; 20.6%) and four German Shepherds (n=4; 13.7%). *Small breeds were the minority of subjects in this trial; which is in keeping with reports of ALD in the literature (58).*

ALD has been recognised to predominate in certain large breeds. It may even occur more frequently within individual families of these breeds, suggesting a genetic

component to the disorder (50). In both OCD and ALD, hereditary factors are important (51; 68).

The results of this study showed that the majority of dogs (n=37; 63.8%) lived in an enclosed environment, surrounded by a high wall. While this may be a spurious finding, as perhaps the majority of all dogs in Johannesburg are housed in such conditions, it is possible that the ALD emerged as a displacement behaviour resulting from frustration at confinement.

4.1.3 Previous treatments

The vast majority of subjects had been on previous treatment trials for ALD (59 of a total of 63). This finding is in keeping with reports in the literature that indicate that ALD is very difficult to treat and numerous treatments are described, with little effect (49; 59; 62).

4.1.4 Side effects

The prevalence of side effects to fluoxetine treatment was low (n=8; 13.7%). This can possibly be explained by the dosing regimen used in the trial, or by the tolerability of fluoxetine in dogs. Dogs cannot report sleep disturbance, headache, dizziness or orgasmic delay. All side effects were reported by owners who may have observed nausea, vomiting or sedation.

4.1.5 Age of onset of licking

The age of onset of licking behaviour was found to be bimodal, with peaks at 1 year or 6 or more years. This finding varies from that of Rapoport et al. (59) where the average age of onset was 4.8 years and no bimodality was observed.

4.1.6 Reason identified for onset of licking

Many dog owners in this study could not identify a subjective reason for the licking behaviour (48.3%). Just under a quarter of owners noted that the licking had started after an episode of trauma or surgery to the site (22.4%). There are descriptions in the veterinary literature that ALD can be provoked by local irritation (58). In the group entitled 'other' (29.3%), the start of licking was sometimes attributed to the construction of a high wall or an electric fence around the property; so that visibility or freedom of movement were impaired.

While the aetiology of ALD is uncertain, it has been suggested that loneliness, confinement and boredom play important roles (56). Dodman et al. (51; 62) have found that stress enhances the stereotypic and compulsive behavioural patterns in dogs with ALD. A similar phenomenon has been described in OCD patients (69).

4.1.7 Treatment effects

In the fluoxetine group only, licking behaviour, lesion appearance and the dogs' general condition all improved significantly by the trial's end. There was no statistically significant change in the placebo group. When the owner ratings for lesion appearance and the dogs' general condition were compared at the end of the trial in the fluoxetine and placebo groups, the difference was statistically significant. This finding was replicated in the veterinarians' blinded ratings of the clinical photographs comparing lesions pre- and post-treatment. The improvement was found in the fluoxetine group alone. In this study, the fluoxetine was effective at a dose similar to that used in humans and within a similar time period. This finding is in keeping with both the two open label trials of SSRIs in ALD (55; 56) and the double blind crossover comparison study of Rapoport et al (59). In the latter study, only the SRI, clomipramine, and two SSRIs (fluoxetine and sertraline) were effective in treating ALD. A placebo and noradrenergic tricyclic antidepressant were not effective; neither was fenfluramine - a 5HT releasing agent. These findings implicate the serotonergic system in ALD.

4.2 Overview of Discussion

From a neurochemical perspective, serotonergic neural systems appear to be a link between OCD and ALD. Serotonergic neural pathways appear to dysfunction in OCD (13; 70). Furthermore, the results of this study implicate serotonergic pathways in ALD. Perhaps there is a subgroup of the 'OCD related disorders' which manifest with

abnormal grooming, where serotonin abnormalities are also a causative factor. Treatment responses in these OCD related disorders have implicated serotonergic pathways (71). Hence, serotonergic pathways are a link between the animal model, ALD and the human condition, OCD. The link between serotonergic pathways and OCD will be discussed in detail in Section 4.3.

There has been much discussion about the putative neuroanatomical site of dysfunction in OCD. The basal ganglia have been proposed as potential sites of dysfunction in OCD and perhaps ALD. Brain imaging studies have implicated the frontal lobes and caudate nuclei in OCD. These studies are discussed in Section 4.6. The results of this study would support a basal ganglia model for OCD. The basal ganglia are phylogenetically ancient structures in the human brain. If OCD is viewed from a neuroethological perspective, then fixed action patterns may be encoded in the basal ganglia and triggered in OCD and ALD.

There is extensive evidence for a basal ganglia model of OCD. The neuropsychiatry of OCD is outlined in Section 4.4. Support for a basal ganglia model of OCD is described in Section 4.5.

4.3 Serotonergic Neural Systems in OCD and ALD

Serotonin is not the monoamine neurotransmitter most often thought of in relation to the basal ganglia, especially as the nigrostriatal dopamine system has been so extensively

studied in the diseases of the basal ganglia. But studies have isolated the 5HT₂ receptors in higher concentrations than previously recognised in the basal ganglia. In these studies of rat brains, concentrations of serotonin were particularly in the nucleus accumbens, caudate and putamen (72; 73).

4.4 The Neuropsychiatry of OCD

Many neurological disorders show obsessive compulsive features as part of their clinical spectrum. If an OCD-like syndrome occurs in these specific neurological conditions, then perhaps inferences can be made about the abnormal neuroanatomy in OCD. Indeed, several neuroanatomical models have been postulated linking OCD to specific brain structures, such as the basal ganglia. The features common to these neuroanatomical models of OCD are involvement of the frontal cortex and basal ganglia, and their reciprocal connections (74 - 77). The basal ganglia are perhaps the structures most strongly implicated in OCD because, in a variety of disorders affecting the basal ganglia, obsessive compulsive features have been documented to occur.

4.4.1 Neurological disorders presenting with obsessive compulsive symptoms

Obsessive compulsive symptoms have been reported in a wide variety of neurological conditions. In epileptic patients, specifically those with temporal lobe epilepsy, episodes resembling OCD have been documented to occur as an ictal phenomenon (78). In stroke patients, particularly those with bilateral lesions to the basal ganglia, obsessive

compulsive symptomatology has also been described (79). In children with mental retardation (80) and the Prader Willi syndrome (81) obsessive compulsive symptoms have been reported. Following herpes simplex encephalitis, diabetes insipidus, multiple sclerosis and acute intermittent porphyria, obsessive compulsive symptoms have been described (82 - 84; 85; respectively). In four case studies of head injury, McKeon et al. reported that obsessive compulsive symptoms developed (86). However, the incidence of these symptoms remains unclear (87).

4.4.2 Neurological insult in the histories of OCD patients

In their clinical histories, OCD patients are often found to have had evidence of neurological insult or injury. An early study of 104 patients with OCD found that 19.4% had associated neurological disorders such as encephalitis, meningitis and epilepsy (88). While other early studies found an association between OCD and birth trauma (89), more recent work has not confirmed this (90; 91).

4.4.3 Soft neurological signs

Seen from another angle, when OCD patients themselves undergo neurological examination, they have been documented to exhibit cognitive and sensory-motor impairment - so called 'soft neurological signs'. In the absence of gross neurological disease, neurological phenomena may occur in a stable and reliable manner over repeated examinations (92). These are termed 'soft neurological signs' and include

involuntary movements, a variety of apraxias, dysdiadochokinesia and dysgraphaesthesia (93).

In an early paper, Schilder suggested that subtle neurological abnormalities were present in a third of OCD patients he studied (94). Denckla studied 54 children and adolescents with OCD and found that choreiform movements in 33%; and neurological deficits including tics and neurodevelopmental delay in 80% (95). Hollander et al. (96) examined 41 adults with OCD matched with 20 normal controls and found that the OCD patients had significantly more soft signs than normals, with abnormalities in fine motor co-ordination, involuntary and mirror movements and visual-spatial dysfunction. Further studies have replicated these results (97; 98).

4.5 The Basal Ganglia Link in OCD

Although the basal ganglia are more commonly associated with motor function, Wise and Rapoport have postulated that selective basal ganglia dysfunction underlies OCD. Obsessive compulsive symptoms have been associated with numerous illnesses and injuries affecting the basal ganglia (76). These conditions are described in detail below and include Tourette's Syndrome, postencephalitic Parkinson's, Sydenham's chorea and other rare conditions. Basal ganglia dysfunction can be linked to OCD on this neuroanatomical basis, and also by the evidence from neuropharmacological and behavioural studies which indicate that the basal ganglia play a complex role in OCD. Clinical response to psychosurgery in OCD sufferers, as well as brain imaging studies, add further to this hypothesis. Wise and Rapoport present a neurobiological model in

which OCD may result from the inappropriate triggering of genetically stored and learnt behaviours by the striatum (76).

4.5.1 Tourette's syndrome and tic disorders

In 1885, Gilles de la Tourette described a syndrome of recurrent motor and vocal tics. In this original description of the disorder that now bears his name, he noted an association between the tics and obsessive compulsive behaviour. Tourette's syndrome (TS) is believed to be associated with basal ganglia dysfunction.

While there is some dispute about the association between OCD and TS per se (99), a subgroup of OCD patients has been found to have tics (100 - 102). Jenike et al. (103) found that motor tic symptoms frequently overlapped with OCD in children diagnosed with OCD. There is increasing evidence that a subgroup of OCD patients also has TS (104).

The genetic link between OCD and TS, particularly the motor and vocal tics (105), has been firmly established. The disorders occur in the same families, but not necessarily in the same individuals (although this does occur frequently). In the relatives of TS patients, family studies demonstrate a high rate of OCD and/or tics (100). In the relatives of OCD patients, family studies reveal a high rate of tics or of TS (106; 107).

4.5.2 Postencephalitic Parkinson's disease

From 1918 to 1920, the 'Great Influenza Epidemic' raged in Europe. Encephalitis lethargica was first reported by von Economo in 1917, after a small local epidemic led to numerous patients being seen in the Vienna Psychiatric Clinic. These patients presented with a variety of symptoms not fitting any then known category. In his study of hundreds of these patients, von Economo provided a comprehensive account of the phenomenology, course and neuropathology of this postencephalitic syndrome.

At autopsy, microscopic inflammatory foci were found in the grey matter of the midbrain and basal ganglia.

The shared clinical features of encephalitis lethargica were an influenza-like prodrome; followed by marked lethargy, sleep disturbance, Parkinsonism and disturbance of ocular movement. In addition, a range of peculiar tics was described, including blepharospasm, mimetic tics of clucking, hissing, yelling or yawning and torticollis (108). Significantly, von Economo reported associated compulsive behaviours reminiscent of OCD, which he attributed to subcortical structure damage, notably of the basal ganglia. These associations have subsequently been confirmed by a series of authors (109).

4.5.3 Sydenham's chorea and PANDAS

Sydenham's chorea is a neurological disorder characterised by sudden involuntary jerking movements of the limbs. It is also known as St. Vitus dance. It occurs as a sequel

to rheumatic fever in 10% to 30% of children (110). In fact, it is the commonest neurological sequel to rheumatic fever and it may serve as a sole diagnostic criterion for acute rheumatic fever. It is primarily seen in prepubertal girls, although recrudescence of symptoms in adulthood, known as chorea gravidarum, has been reported (111).

The clinical presentation is believed to be linked to dysfunction of the basal ganglia. In 1976, Husby et al. reported that antibodies directed against the cytoplasm of the subthalamic and caudate nuclei were present in the sera of nine of 22 children (41%) with Sydenham's chorea (112). Of 50 serum samples taken from children with carditis, seven (14%) contained these antibodies, but no antibodies were isolated from the samples of healthy controls.

A clinical association between OCD and Sydenham's has been noted in several studies since 1958 (88; 113 - 115). Khanna described an association between OCD and Sydenham's chorea in India (82). Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is the name given by Swedo et al. to childhood onset OCD and tic disorders (116). These are characterised by an episodic course of symptom severity and are associated with group A beta haemolytic streptococcal infection and neurological abnormalities. The high prevalence of obsessive-compulsive features among patients with histories of Sydenham's chorea supports the evidence linking OCD to disease of the basal ganglia.

4.5.4 Other presumed basal ganglia disorders and OCD

In the literature, a number of case studies describe discrete damage to the basal ganglia from a variety of causes; followed by obsessive compulsive symptoms. Laplane et al. (117) reported a case of a rare but malignant wasp sting resulting in bilateral basal ganglia lesions; and a neurotoxic reaction including obsessional illness.

Symptoms of OCD have been reported in Huntington's disease (118; 119), idiopathic Parkinson's disease (120; 121), spasmodic torticollis (122), and in Manganese poisoning, a rare cause of basal ganglia damage (123).

4.6 Brain Imaging Studies Linking the Basal Ganglia with OCD

Imaging studies and neurosurgical research have contributed to the development of neuroanatomical models of OCD.

Recently developed brain imaging techniques have enabled the exploration of the brain correlates of OCD. Computed tomography (CT) and magnetic resonance imaging (MRI) depict brain structures. Single photon emission computerised tomography (SPECT), positron emission tomography (PET) and some novel forms of MRI, are used for functional imaging. PET allows for the measurement of regional and global cerebral blood flow (rCBF) and glucose metabolism. ¹³³-Xenon inhalation imaging (Xe flow) is a slightly older technique which followed the now obsolete intra arterial Xe injection.

PET scans have shown increased blood flow and metabolism in the frontal lobes caudate nucleus and cingulum. Abnormally rapid glucose metabolism in the caudate nuclei and orbital gyri is shown on PET scans of patients with OCD (124). Several neuroimaging case reports have noted lesions in the caudate nucleus in occasional patients (115; 125; 126). However, studies of large cohorts of patients with OCD have not shown these findings to be common (127 - 131). Small caudate size has been shown in CT scan volumetric analysis of OCD patients (128).

4.7 Neurosurgery and the Basal Ganglia Connection

As discussed in the Introduction, OCD is one of the few psychiatric disorders for which neurosurgery may be indicated. Surgery disconnecting the orbitofrontal regions from the limbic thalamic and striatal structures has been described to produce symptomatic improvement in OCD. It has been suspected that organic changes in the frontal lobes, basal ganglia, and to a lesser extent, the limbic system, are responsible for the psychopathology in OCD. In capsulotomy, bilateral basal lesions in the anterior limb of the internal capsule are made, which are thought to interrupt frontal-cingulate projections. However, the target zone for the lesion lies within the striatum, adjacent to the caudate nuclei. In 1981, Hassler reported that stereotactic lesions in the mediodorsal and anterior nuclei of the thalamus, and their projection systems to the cortex may diminish both Tourettic and obsessive compulsive behaviours (132). It is important to note that these are the thalamic nuclei providing the main inputs to the

cingulum and frontal cortex. Although the psychosurgical results are far from conclusive, taken together with the other evidence, these data are consistent with a model of OCD involving dysfunction of basal ganglia and frontal lobe-basal ganglia circuits.

4.8 Neuroanatomy of the Basal Ganglia

The basal ganglia (also referred to as the striato-pallido-nigral system) are composed by the following main structures: the caudate nucleus, the lentiform nucleus with its two subdivisions, the putamen and the globus pallidus. The caudate and putamen (the striatum) are really only a single structure, separated by the fibres of the internal capsule. Other structures include the nucleus accumbens and parts of the olfactory tubercle.

The striatum, which is the receptive part of the basal ganglia, receives topographically organised fibres from all parts of the cerebral cortex. The motor-sensory association areas, as well as from the substantia nigra, parts of the amygdala and certain thalamic nuclei supply the striatum.

The major input to the basal ganglia is a glutaminergic, excitatory amino acid projection from the cerebral cortex to the striatum (a). Additional inputs include the well described dopaminergic input from the midbrain's substantia nigra and a serotonergic input from the raphe complex in the brain stem (133).

Within the basal ganglia, inhibitory Gamma-aminobutyric Acid (GABA) neurons project from the striatum to the globus pallidus (b).

The major output of the basal ganglia is a GABAergic inhibitory projection from the globus pallidus to the thalamus (c), which in turn sends an excitatory input to the cortex (d).

Hence, in simplified form, a major pathway to, through and out of the basal ganglia consists of a 'four neurone loop':

- (a) from the cortex to striatum (excitatory, glutamate),
- (b) from striatum to globus pallidus (inhibitory, GABA),
- (c) from globus pallidus to thalamus (inhibitory, GABA), and
- (d) from thalamus to cortex (excitatory).

4.9 A Basal Ganglia Model for OCD

Basal ganglia function has two aspects which are central to the basal ganglia model of OCD. The first is that the basal ganglia may be a repository of innate motor programmes that can be released on detection of an appropriate (key) stimulus. These motor programmes are species specific, fixed action patterns. (134). The second is that the basal ganglia function as a gating mechanism for sensory input (135).

The model for the OCD-basal ganglia relationship proposed by Wise and Rapoport (76) is illustrated in Figure 4.1; and postulates the following:

1. Sensory input is sent from the cortex to the striatum.
2. Striatal neurons detect key stimuli.
3. Striatal neurons project into the pallidum, which disinhibits the thalamic neurons.
4. Fixed action patterns are released.

In more detail:

1. Two sets of processed sensory inputs converge onto the striatum. One set is from the cortical 'association' areas thought to be involved in the recognition of objects and sounds. The superior temporal area directs polysensory and auditory sensory stimuli to the striatum. The inferior temporal area directs visual stimuli to the striatum. The other set is from the anterior cingulate cortex.
2. The striatum consists of cells acting as stimulus detectors.
3. The striatal detection circuits themselves converge onto and inhibit a pallidal output cell group, which is thought to be tonically discharging to inhibit the thalamus - in particular, the mediodorsal and ventroanterior thalamic neurons. The result of the striatal inhibition of the pallidal circuit is that the tonic inhibition of the thalamus is overrun. The thalamic neurons become disinhibited.

4. Thalamic neurons project to the orbito-frontal cortex.

The way in which these circuits are envisioned to perform is as follows: the sensory apparatus relays the appropriate sensory information to the cortex and then to the striatum. If the stimulus matches a stored representation in the striatum, then its cells would begin discharging, thus inhibiting the pallidal cells projecting to the thalamus.

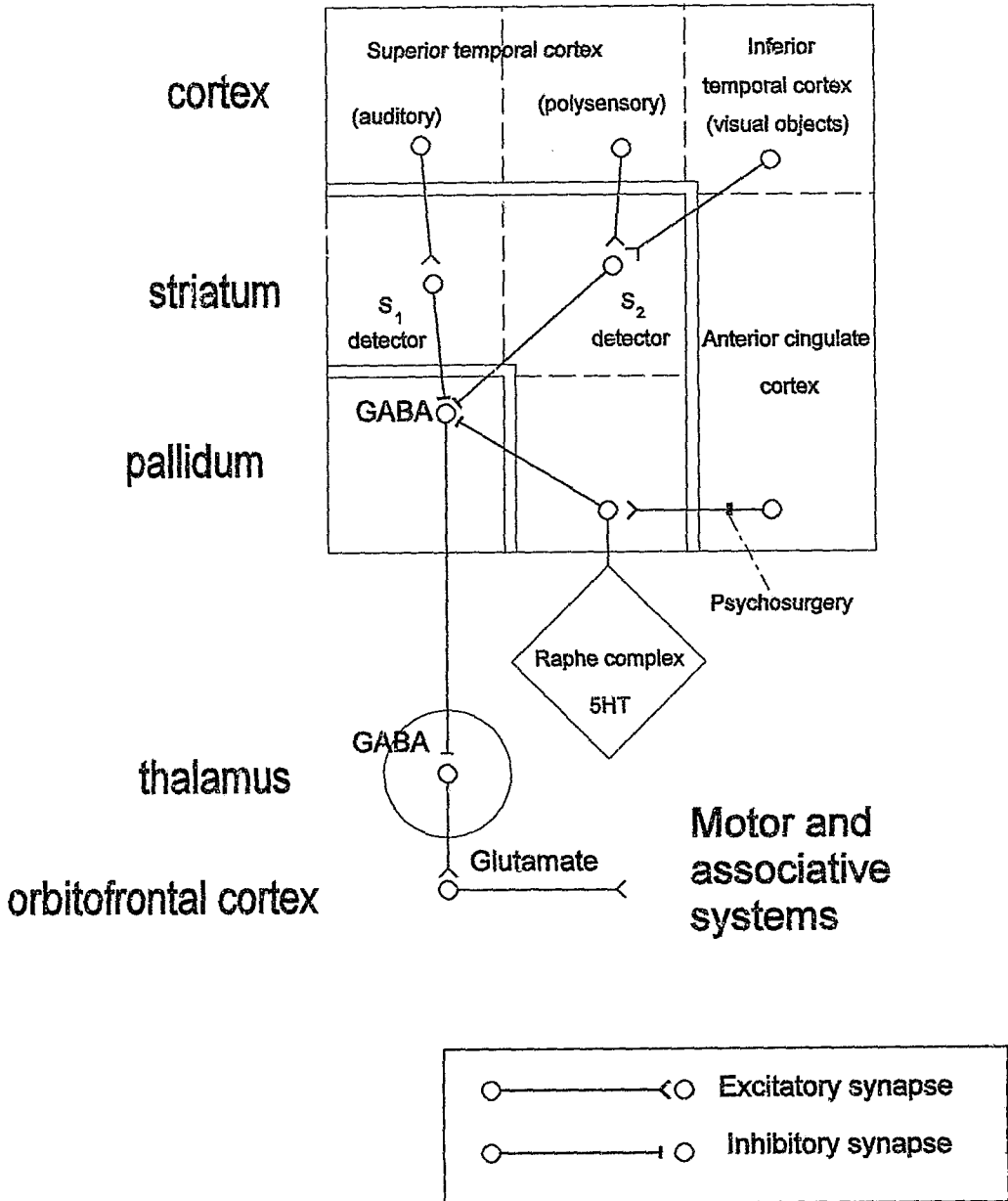
A simple example might involve the recognition of dirtiness. If sensory input to the striatum indicates the hands are dirty, an innately programmed cell group would recognise this input as dirtiness. That cell loop would discharge and stop the tonic discharging of the appropriate pallidal cell. Removal of the inhibitory inputs to the thalamus would release the thalamocortical circuits that lead to the normal behavioural response to dirty hands: hand washing.

In addition to the circuits described above, it is postulated that the anterior cingulate cortex also projects to the striatum with a serotonergic, excitatory modulation. Therefore, the anterior cingulate cortex potentiates inputs to the striatum. From the striatum, a different group of cells project to inhibit the same pallidal cell group. Wise and Rapoport (76) suggest that this particular circuit operates in the absence of an external stimulus. It provides a signal whenever an animal is to perform an act because of exclusively internal motivation. This hypothesis has been corroborated by experimental evidence (136) and corresponds to the 'orbito-frontal loop' of Alexander et al. (137). Thus, the cingulate cortex appears to be involved in generating behaviour in the absence of an appropriate sensory signal. If signals from the cingulate cortex to the striatum converge

onto the same pallidal cell group responsible for producing the fixed action pattern of behaviour, then activation of the cingulate cortex would act to release the behaviour without a sensory stimulus. In the example above, handwashing is now triggered in the absence of any sensory input signalling dirtiness. In OCD, if hyperactivity in the cingulate cortex or striatum occurs, this circuit may be activated in the absence of any motivation to perform an act. The resulting behaviour would be executed compulsively.

What occurs in the absence of a key stimulus? Two sorts of behaviour have been postulated to occur: vacuum behaviours and displacement behaviours. Vacuum behaviours are actions that would normally be directed towards a specific object, but they occur in the absence of the object. For example, Lorenz described how birds snap at non-existent insects and go through the motions of preparing a meal (38). Displacement behaviours have been described previously (1.2.2)

Figure 4.1 A basal ganglia model for OCD



4.10 The Basal Ganglia Model for OCD and the Phenomenology of OCD

Several aspects of the OCD are accounted for by this model. Firstly, the effects of psychosurgery are explained. If the anterior cingulate cortex is destroyed, its thalamic input, efferent pathways to the caudate nucleus or the caudate itself, then the excitatory, serotonergic pathway to the pallidum would be eliminated. Also, lesions of the thalamus, particularly the mediodorsal or ventroanterior nuclei would eliminate the output of this cortico-striato-pallidal loop. Symptomatic improvements in OCD have been reported following these procedures.

4.11 Limitations of the Basal Ganglia Model of OCD

While this model of the abnormalities underlying OCD is a useful conceptual tool, it does have limitations. There is much clinical information which appears to be inconsistent with the model. Firstly, other documented basal ganglia disorders, such as Huntington's disease and idiopathic Parkinson's disease are very rarely associated with obsessive compulsive symptoms. Depression and psychosis are far more common in these two disorders, which also affect different nuclei in the brain.

Secondly, obsessive compulsive symptoms have been documented to occur in the presence of diffuse brain injury. Following head trauma, birth injury or in diabetes, OCD may be an associated finding (136). There is no evidence that in these cases, basal

ganglia damage has occurred to account for the OCD symptomatology. Basal ganglia damage occurring in the context of a generalised brain injury which results in OCD, remains to be proven.

Thirdly, certain clinical features of OCD - namely the time course and behavioural specificity - are not explained for by the model. Onset of OCD is typically in early adulthood. The delay in presentation of symptoms might be accounted for by ongoing degenerative changes in the basal ganglia or orbito-frontal loop, which parallel the time course of the illness. The behavioural specificity of OCD (for one or two thoughts or actions at a time) might be explained by the fact that highly localised brain abnormalities are involved. Circuits producing one species-typical behaviour, such as grooming, might overlap with and share many of the same elements with another behaviour, even cognitive functions like checking for contaminants.

4.12 Other Brain Areas Implicated in OCD

A number of studies are also compatible with the involvement of other brain structures in OCD. The frontal lobe has been implicated in several studies (86; 139; 140), as have other areas (78; 83; 138; 139). Clearly, the preorbital cortex has already been mentioned in the model linking the basal ganglia to OCD. Further research is needed to dissect out the exact basal ganglia-frontal lobe interactions in OCD.

4.13 OCD Related Disorders

Within the realm of the psychiatric disorders, OCD has increasingly been seen as having much in common with other psychiatric illnesses, rather than being tightly defined on its own. It has become recognised that a wide range of psychiatric and medical disorders may be related to OCD and thus, together, may form a family of disorders, referred to as the 'OCD related disorders spectrum' or the 'overlap syndrome'. These diseases are all believed to share the symptoms of obsessive thinking and/or compulsive behaviour. The grouping is based on phenomenological similarities with OCD as well as similar age of onset, clinical course, comorbidity, family histories, biological abnormalities and treatment responses. However, the research supporting this framework is still in a preliminary stage and there are also important differences between the disorders on the spectrum (141).

The OCD spectrum disorders include the body dysmorphic disorder and anorexia nervosa, where there is a obsessive preoccupation with body image and weight (141). Also included are the disorders where there is stereotyped, ritualistic or driven behaviour such as in Tourette's syndrome (142), compulsive hair pulling or trichotillomania (143), sexual compulsions and pathological gambling (141). The impulsive personality disorders (e.g., the borderline personality disorder), have been postulated to belong to this spectrum, as has the somatic subtype of delusional disorder (144). The habit disorders such as compulsive skin picking (145) and onychophagia also fall into the OCD related disorder spectrum (143). Also included are self mutilation and compulsive buying: conditions characterised by impulsive behaviours (144). The

impulse control disorders occur where there is an irresistible impulse to perform harmful or senseless behaviour. Interestingly, the DSM IV uses the word 'impulse' to define an obsession, implying that impulses and obsessions are similar and may even be the same phenomenon (2).

4.13.1 The compulsive - impulsive spectrum

Another way of looking at the OCD related disorders is that they all occur along a spectrum of harm avoidance, with the predominantly compulsive risk averse disorders at one end (OCD, body dysmorphic disorder, hypochondriasis) and the predominantly impulsive risk seeking (pathological gambling, sexual compulsions and impulsive personality disorders) at the other end. What all these disorders have in common is the inability to delay or inhibit repetitive behaviours.

4.13.2 OCD related disorders with abnormal grooming

Among the large array of OCD spectrum disorders, one can subclassify those where there is abnormal grooming behaviour. This is clearly of relevance to this research. Just as animals demonstrate displacement grooming behaviour in response to conflict or frustration, similar grooming behaviours may be inappropriately triggered in humans with these conditions. OCD symptoms themselves have been suggested to be similar to displacement behaviours (44; 102).

The OCD related disorders that involve abnormal grooming behaviours include body dysmorphic disorder, compulsive skin picking, self mutilation, trichotillomania and onychophagia. While there are differences in treatment response amongst the OCD spectrum disorders in general, disorders characterised by abnormal grooming behaviour appear to respond preferentially to the SRIs. This has been shown for body dysmorphic disorder (142; 146) and compulsive skin picking (81; 145; 147; 148). In an open trial, patients with trichotillomania responded to SRIs (149 - 151). These findings were replicated in a double blind trial (152). Treatment response in self mutilation has also been favourable with SRIs (153; 154).

Further strengthening the serotonin link between the OCD related disorders and abnormal grooming is the preliminary finding that pharmacological challenge studies with 5HT agonists such as *m*-CPP have produced symptoms mimicking the naturally occurring symptoms of body dysmorphic disorder, trichotillomania and Tourette's syndrome (142).

While fixed action patterns are of importance in lower animals, learnt behaviour appears to be far more important in primates. Yet there are instances where fixed action patterns of behaviour may be triggered in humans. It may be hypothesised that the brain centre for the control of such fixed action patterns as grooming continue to be present in humans, perhaps within the basal ganglia circuitry. In OCD and the related disorders, there may be pathological triggering of these behaviours, mediated by stressors. This results in such symptoms as repetitive hand washing. Hair pulling in trichotillomania may similarly represent pathological grooming sequences. Hence, fixed action patterns of

grooming behaviour may be released in OCD, the OCD related disorders manifesting with grooming behaviours and in ALD. This suggests a link between OCD and ALD.

In OCD, the serotonergic neural pathways concerned are present in the basal ganglia (the orbito-frontal loop). These pathways are believed to be phylogenetically ancient. Hence release of fixed action patterns in OCD may be related to the displacement behaviours found in domestic animals. This has suggested a common neuroethological origin of OCD (55).

There is very little research about treatment responses in animals with abnormal grooming behaviours, apart from that outlined in the ALD studies. Preliminary results have, however, demonstrated a favourable response to the SSRIs. In an open trial of the treatment of excessive feather picking in psitticine birds, clomipramine was found to be superior to placebo (53).

CHAPTER 5

5.0 CONCLUSIONS

5.1 The Validity of ALD as an Animal Model of OCD

Animal models are useful in the simulation of psychiatric symptoms and investigating both biological and behavioural pathogenesis. Pharmacotherapeutic treatments have also been developed as a result of findings with animal models (155). Naturally occurring animal behavioural disorders, such as ALD, are particularly useful neuroethological models of various psychiatric disorders. The excessive grooming and self mutilation found in dogs with ALD constitute an animal model with both predictive and face validity.

5.1.1 Predictive validity

As an animal model of OCD, ALD meets the criterion for predictive validity. In predictive validity, the only similarity between the animal model and the clinical condition being studied is the treatment response (66). This study verified that the SSRI, fluoxetine, was an effective treatment for ALD.

5.1.2 Face validity

Face validity requires that the animal model and clinical condition be similar both in terms of phenomenology and treatment response (64). ALD meets the criterion for face validity in that the licking behaviour in ALD is similar to the repetitive motor rituals of OCD and the treatment response to the SSRI, fluoxetine, is favourable in both conditions.

Furthermore, there are other similarities which exist between OCD and ALD. In both OCD and ALD, hereditary factors are important (51; 68). In the results of this study, ALD was found to predominate in certain large breeds of dog, in keeping with the findings of other researchers and suggesting a genetic aetiology.

Grooming may be seen as a form of displacement behaviour. Displacement behavioural disorders, such as ALD, are frequently proposed as animal models. An advantage of this model is that the cause of the aberrant behaviour appears to be clear: stress or conflict. Indeed, lifetime stress has been shown to enhance stereotypic and compulsive behavioural patterns in animals with ALD (51; 62). Most subjects in this study were confined behind high walls. While this is a common occurrence in Johannesburg, it may suggest that enforced enclosure and lack of stimulation in the dogs' immediate environment led ultimately to stereotypic self mutilation. This might have led to boredom and loneliness in the dogs, both of which have been suggested as contributing to the aetiology of ALD (56).

On the other hand, displacement behaviours can be criticised as animal models. Their face validity may be only partial, as the behaviours are typically of short duration and rarely interfere with the animal's functioning. In contrast, OCD is a chronic disorder where normal functioning is frequently severely disrupted.

In the study of the aetiology of OCD in humans, some researchers have suggested that loneliness and boredom exacerbate the severity of symptoms (69; 103). However, the extent to which precipitating stress plays a role in OCD is debated in the literature. In particular, the onset of OCD appears most often to be insidious and without a precipitating stressor (6).

5.1.3 Construct validity

Construct validity requires similarities in phenomenology, treatment response and also a theoretical relationship between the animal model and the clinical disorder in question (66). In this category, it is more difficult to prove that ALD is an animal model of OCD.

In both ALD and OCD, the exact pathophysiology is unknown. There is the model of basal ganglia abnormality in OCD, which may explain the release of fixed action patterns in OCD, the OCD related disorders with aberrant grooming and canine ALD. From a neuroanatomical perspective, the basal ganglia appear to be structures that are phylogenetically ancient in the human brain and may be the site of pathology in OCD and the OCD related disorders with aberrant grooming. Basal ganglia involvement can only be surmised in ALD. However, if fixed motor patterns are encoded in the basal

ganglia and triggered in OCD and ALD, involvement of these structures is likely in the pathogenesis of ALD.

However, this model is still only a working hypothesis conjectured for OCD, let alone the OCD related disorders with aberrant grooming and canine ALD.

From a neurochemical perspective, serotonergic neural systems have been implicated in OCD. ~~The results of this study strongly implicate serotonergic pathways in ALD.~~

Treatment responses in the OCD related disorders associated with abnormal grooming behaviours also implicate the serotonergic pathways. Dysfunction in the serotonergic neural pathways is therefore a strong contender for the underlying pathophysiology of OCD, and perhaps the animal model, ALD, too. This might be the causal link between the psychiatric condition and the animal model. Yet, it is unlikely that 5HT acts in isolation in the causation of OCD and ALD. While SSRIs appear to be effective in OCD, there may be numerous neurochemical actions responsible for their clinical effect. It is unlikely to be explained by simply one neurotransmitter. In OCD, there is preliminary evidence that dopamine plays a role in symptom production (156). There is also evidence for dopaminergic dysfunction in animal grooming (49; 52). Furthermore, no neurotransmitter system operates in isolation. In the basal ganglia specifically, dopamine and 5HT appear to be mutually inhibitory, which further complicates the possible interactions (157; 158). Hence, ALD does not meet the ultimate criterion for a successful animal model, that of an identified common underlying biological abnormality.

5.2 Limitations of Animal Models

There are clear limitations to the benefit of animal models. Even amongst members of the same species, behaviour patterns are not consistent and therefore, inferences regarding behavioural disorders must be limited. Neurobiological differences may underlie this behavioural diversity and therefore, neurobiological inferences from treatment responses in these conditions are also limited (46). Furthermore, human behaviour includes complex cognitive and affective phenomena, even when it is observed to be similar to that found in animals. One might argue that egodystonic, reprehensible thoughts are fundamental to OCD. If so, our inability to study thought patterns in other animals would make the use of animal models limited.

A second problem endemic to the search for animal models is the tendency to validate the model by response to pharmacotherapy in the animal model. All three criteria suggested by McKinney and Bunney (64) and Willner (65) include this criterion as a way of measuring whether the model is valid. But how similar are the pharmacokinetics and pharmacodynamics in animals to humans? Species are known to differ in their responsiveness to a given drug, based on absorption, distribution, metabolism, elimination and receptor location. The conservative response would be to use pharmacological response to establish predictive validity only; and not as a criterion for face validity or construct validity.

5.3 Limitations of this Study

One limitation of this study is that rating scales were done by owners. An attempt was made to standardise the assessment of treatment response by taking the clinical photographs and having them assessed by two veterinarians, in a blinded fashion.

Another limitation of the trial is that fluoxetine was the only SSRI studied. While the five *SSRIs available in South Africa all belong to the same class of antidepressant and*

share a common mechanism of action, they do show differences in pharmacological and pharmacokinetic properties (159). These differences may manifest as responses in clinical outcome.

Finally, both OCD and ALD are conditions of unknown origin. Hence, inferences can only be made about the construct validity of ALD as an animal model of OCD.

The work of this thesis could be extended so that the relevance of ALD as an animal model of OCD becomes clearer. As mentioned earlier, novel brain imaging techniques have elucidated the neuroanatomy and brain pathways of OCD. CT and MRI scans depict brain structures and techniques such as 133- Xenon inhalation imaging, SPECT and PET can demonstrate brain function. These techniques could also be applied to examine the brains of dogs with ALD. Any findings in these subjects could be compared to the results of the OCD studies. Indeed, Rapoport has set up a 'canine brain bank' for

neuropathological study of dogs with ALD (59). In vivo imaging studies of these canine brains are a logical research sequel

Both OCD and ALD appear to have genetic influences. Selective breeding of dogs with ALD would allow for DNA linkage and pedigree studies of the condition.

Other aspects of the similarities in treatment response in OCD and ALD could also be studied. For example, when comparing treatment response to SSRIs in OCD and major depressive disorder, it has been recognised that longer exposure to SSRIs is necessary in OCD before response appears (36). This hypothesis was tested in an open label, two month extension phase of fluoxetine treatment in this trial. It was found that in the ALD subjects, clinical improvement continued well into the two month extension phase (160). These findings would need to be verified in a further double blind, randomised, placebo controlled study.

5.4 Final Results

The results of this study clearly indicate the efficacy and tolerability of fluoxetine in the treatment of canine ALD. This has two implications. The first is that fluoxetine appears to be a useful therapeutic modality for this disorder. Secondly, the efficacy of a serotonergic antidepressant implicates central serotonergic pathways in ALD. This suggests that ALD may be a useful naturalistic animal model of OCD. Obsessive Compulsive Disorder has a prevalence that ranges between 1.2% and 3% of the

population (3; 160 - 162). It is a significant psychiatric disorder and is one of the first for which an animal model is proposed. The results of this study suggest that ALD is a potentially fruitful avenue for the further investigation of OCD and the OCD spectrum disorders.

APPENDIX A

CLINICAL GLOBAL QUESTIONNAIRE

Considering your experience with your dog this week, how severe has the licking behaviour been over the last seven days?

No excess licking at all

Very mild excess licking

Mild excess licking

Severe excess licking

Extremely severe excess licking

Considering the appearance of the area your dog usually licks: how severe does it look now compared to the way it was at the start of the study?

Very much improved

Much improved

Minimally improved

Unchanged

Minimally worse

Much worse

Compared to the dog's condition at the start of the study, how much has s/he changed?

Very much improved

Much improved

Minimally improved

Unchanged

Minimally worse

Much worse

APPENDIX B

INFORMATION BOOKLET

Information for pet owners participating in this study

What is Acral Lick Dermatitis?

- ALD is a disease in which dogs continuously lick their paws, tails or flanks - even if there is no sore.
- The cause is unknown. Up to now, there has been no effective treatment for the disease.
- Some researchers have suggested that ALD is caused by abnormal chemicals in the brain which cause excessive grooming behaviour.
- The chemical concerned is called 'serotonin'. It acts as a messenger between nerve cells in the brain. If there is a problem with the serotonin system in the brain, the messages coming from the brain cause abnormal behaviour - such as licking paws continuously, until they become raw.

What does this study examine?

We are aiming to find a way of alleviating the symptoms of ALD.

Fluoxetine is a drug that increases the amount of serotonin in the brain.

This study will examine whether dogs given fluoxetine show any improvement in their licking behaviour.

In order to assess the effects of fluoxetine accurately, it must be compared to placebo.

(A placebo is a pill with no biological effect - like a sugar pill.)

Dogs will be divided into two groups - those that do not get fluoxetine (the active drug), and those that get placebo (the inactive drug). This will be done randomly.

Both the researchers and pet-owners will not know which dog gets which drug until the trial is completed.

What will pet-owners need to do?

As the pet-owner, you will need to understand the design of the trial and agree to participate.

You will need to give your dog a capsule once a day, for 6 weeks.

We will ask you to fill out a short questionnaire before the trial starts, and then once a week for 6 weeks.

The pills will be supplied free of charge.

Fluoxetine has been given to dogs in previous trials with minimal untoward effect.

What will the researcher do?

I will take photographs of your dog's lesion before and after the trial.

Once the trial is over, two veterinarians will compare how severe the lesion was before the trial to after six weeks of fluoxetine or placebo.

I will examine your questionnaires.

In analysing all this information, we will hopefully be able to decide whether fluoxetine is a good treatment for ALD.

APPENDIX C

ABSTRACTS

Wynchank D, Berk M. Fluoxetine treatment of acral lick dermatitis in dogs: a placebo-controlled randomised double blind trial. *Depression and Anxiety* 1998; 8:21-23.

Objective: The aim of the study was to assess the efficacy and tolerability of fluoxetine treatment of acral lick dermatitis (ALD) in dogs and to investigate ALD as an animal model of obsessive compulsive disorder (OCD). **Method:** Sixty three dogs with ALD were treated with fluoxetine 20 mg daily, or placebo, for six weeks. **Results:** In the fluoxetine group, owners rated both the appearance of the lesion ($t = 10.2$, $df = 29$, $p < 0.0001$) and licking behaviour ($t = 10.2$, $df = 29$, $P < 0.0001$) as significantly improved by the end of the trial. Veterinarian rated pre and post treatment photographs showed statistically significant improvement in the fluoxetine group (mean 2.55). There were no significant changes in the placebo group as rated by owners and veterinarians. **Conclusions:** These results demonstrate the efficacy of fluoxetine in the treatment of ALD and lend further support to ALD as an animal model of OCD.

The following two abstracts represent research carried out as an extension of the work described in this thesis.

Wynchank D, Berk M. Behavioural changes in dogs with acral lick dermatitis during a two month extension phase of fluoxetine treatment. *Human Psychopharmacology* 1998; 13:435-437.

Acral Lick Dermatitis (ALD) is a condition in dogs that is believed to be an animal model of obsessive compulsive disorder (OCD) in humans. In both conditions, serotonergic neural dysfunction is believed to be responsible for aberrant grooming behaviour. ALD is the first animal model proposed for a psychiatric condition. Serotonergic antidepressants are recommended as first line treatment in OCD. However, many patients have been discouraged from using these by reports of aggression and suicide-inducing effects of these drugs. This study examined behavioural effects of a 2 month extension phase of fluoxetine treatment in dogs previously diagnosed with ALD. A 2 month extension phase on fluoxetine 20 mg daily, immediately followed on a 6 week, double blind, randomised, placebo controlled trial of fluoxetine in 63 dogs with ALD, diagnosed for at least 6 months. The Dodman scales measured excitability, fearfulness, dominance and territorial aggression at the start and end of the 2 month extension phase. Excitability was rated in 4 settings, referred to as questions 1 to 4. Fifty-four dogs completed the extension phase. Three subjects were withdrawn with no reason given, one for vomiting on fluoxetine. At the end of the extension phase, the analysis of variance showed no significant difference between dogs who received placebo or fluoxetine during the original trial, for scores of fearfulness ($p = 0.127$), dominance ($p =$

0.274) or territorial aggression ($p = 0.172$). Excitability also caused no significant difference on the four questions ($p_1 = 0.822$, $p_2 = 0.607$, $p_3 = 0.975$, $p_4 = 0.820$). After the extension phase, owners assessed dogs as being neither more aggressive nor anxious. Particularly, there was no significant difference in levels of dominance aggression ($p = 1$). Using the paired t test, there was no significantly significant difference between scores obtained both at the end of the 6 week trial and the extension phase for fearfulness ($p = 0.128$), dominance aggression ($p = 1.0$), territorial aggression ($p = 0.422$) and excitability ($p_1 = 0.487$, $p_2 = 0.571$, $p_3 = 0.711$, $p_4 = 0.086$). These results may serve to refute further the reports of the emergence of impulsive aggression in human subjects on fluoxetine treatment as no significant behavioural changes were noted in the dogs treated with fluoxetine for ALD.

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This study aimed to examine the efficacy of fluoxetine follow up treatment in treating sixty two dogs with Acral Lick Dermatitis (ALD). ALD is a condition described in dogs believed to be an animal model of obsessive compulsive disorder. **Method:** Sixty two dogs with ALD were entered into a double blind, randomised, placebo controlled trial of fluoxetine 20 mg per day. The SSRI was found to be significantly effective in treating the condition over 6 weeks. At the trial's end, a two monthly follow up period on fluoxetine was offered to all subjects. **Results:** They showed statistically significant improvement after follow up as compared to the end of the six week trial. This was measured on Clinical Global Impression scores. Licking

behaviour improved significantly ($t = 4.96, p < 0.05$); appearance of the lesion improved ($t = 5.34; p < 0.05$). Longer periods on fluoxetine may be best in the treatment of ALD.

CHAPTER 6

6.0 REFERENCES

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