

In: **Recent Advances in Companion Animal Behavior Problems**, Houpt K.A. (Ed.)
Publisher: International Veterinary Information Service (www.ivis.org)

Pharmacological Management of Separation Anxiety (11 Oct 2000)

J.N. King

Novartis Animal Health Inc., Postfach, Basel, Switzerland.

Summary

The treatment of separation anxiety in dogs involves the combination of behaviour modification therapy, environmental management and pharmacotherapy. Tricyclic antidepressants with strong serotonin-reuptake inhibiting properties appear to be the first choice for drug therapy, with additional administration of benzodiazepines in severe cases. With proper management, cases of separation anxiety carry a good prognosis.

Introduction

Separation anxiety is a distressing disorder for both the dog and its owner. It is a common problem; accounting for between 5 and 21% of cases in behaviour practice [1]. A diagnosis of separation anxiety may be made when a dog shows signs of anxiety (notably defecation, urination, destruction or vocalisation) in the absence of the owner [1-3]. It is very important before any treatment is started that an accurate diagnosis is made, and other causes with similar signs (e.g. destruction due to boredom, inappropriate defecation or urination due to lack of house-training, barking at people approaching the house) are excluded. A critical factor in the aetiology of many cases of separation anxiety appears to be a high degree of attachment (termed hyperattachment) between the dog and its owner. Therefore, in lay terms, the dog becomes emotionally dependent on the company of certain people, and shows anxiety when they are absent. Management of separation anxiety is important for several reasons including:

1. welfare of the dog (chronic anxiety must be considered unhealthy and we can assume that anxious dogs are suffering);
2. repeated destruction or soiling of the house is unacceptable to the owners of the dog;
3. barking in the absence of the owner can be intolerable for neighbours.

It is doubtful if one can ever "cure" a case of separation anxiety in the sense of producing irreversible normalisation of the dog's behaviour. However, the condition can certainly be "controlled" in most cases to establish a situation that is acceptable to both the dog and humans. Management of separation anxiety involves environmental management and behaviour modification, with or without additional pharmacological therapy [1,4]. Optimal control appears to be achievable when all three are combined [1,4-8].

Behaviour Modification and Environmental Management

It is outside the scope of this review to discuss behaviour and environmental programs for separation anxiety, several have been published [1,3,4,6]. The principles of behaviour modification involve: no punishment (e.g. for destruction or elimination in the house), increase exercise, relaxation training, reduce excitement at departures and reunions, uncoupling of departure cues, and desensitization to departure and absence of the owner [8].

Results of clinical trials show that behaviour therapy leads to improvements in the behaviour of some dogs [6,7,9], although there is no hard data to prove its efficacy since time or placebo alone might lead to improvements. In the largest trial of separation anxiety published to date, improvement in destruction,

defecation or urination was reported in 50 - 57% of dogs with 3 months behavioural therapy [6]. Two principle limitations of behaviour therapy were identified in this trial:

1. many dogs did not respond, a 50% response rate is equivalent to a 50% non-response rate;
2. the onset of improvement was not fast, for example only 31% of dogs were reported to have improved for destruction after a month of therapy [6].

The limitations of behaviour therapy alone were recently re-emphasised, an important point being that, in practice, owners are not willing to implement full behaviour therapy programs [8]. Therefore, although behaviour therapy and environmental modification alone might certainly be sufficient in some cases, combination with drug therapy appears to offer the optimal control of separation anxiety [6,8]. Likewise, although using drugs alone may control effectively the signs of separation anxiety, it can be assumed that the relapse rate would be high once the drug was stopped, since the underlying (behavioural) cause of the problem would not be corrected [5].

Pharmacological Treatment

A number of drugs from different classes may be useful to manage separation anxiety in dogs. Although drugs can (in theory) be used as monotherapy, it is recommended that they be used only as adjuncts in addition to behaviour therapy and environmental modification. The objective of medical therapy is to relieve anxiety and not to treat or suppress specific symptoms (e.g. destruction, vocalisation). The most extensively documented drug, and the only one approved worldwide for separation anxiety in dogs, is clomipramine hydrochloride (Clomicalm®), commonly described as clomipramine. L-deprenyl (Anipryl®), also known as selegiline (Selgian®), is approved worldwide in dogs, but has an approval for "separation problems" only in certain European countries. However, to the knowledge of this author, no data from controlled trials showing the efficacy of L-deprenyl in separation anxiety have ever been published in referred journals.

Due to limited space, only a short review of different classes of drugs that may be useful to treat separation anxiety in dogs is given below [3,4,10,11]. This is followed by a more detailed summary on clomipramine. It should be emphasised, that with the exception of clomipramine and L-deprenyl/selegiline, none of the drugs discussed below are registered for separation anxiety in dogs, and their efficacy and tolerability in this species may not have been studied in detail. Although it is possible to extrapolate some information from the human literature, the pharmacology of drugs may differ significantly between humans and animals. Before starting therapy with non-licensed products, therefore, veterinarians should discuss the benefit-risk ratio with owners of dogs. It is important that any drug being used to manage separation anxiety should not interfere with any behaviour modification being attempted; therefore drugs that are heavily sedative or impair memory or learning are not suitable for long-term use.

Tricyclic Antidepressants (TCAs)

These drugs block the neuronal reuptake of noradrenaline and (additionally for certain agents) serotonin [10-13]. Examples include clomipramine and amitriptyline. Blockade of reuptake of noradrenaline or serotonin seems to confer antidepressant activity in humans, but blockade of serotonin reuptake appears to be necessary for anti-anxiety activity. Many TCAs also antagonise cholinergic muscarinic receptors, and this action is the origin of most of their adverse effects in humans: dry mouth, inhibition of bladder contractility, increased intra-ocular pressure and tachycardia with arrhythmias. The drugs also reduce the convulsion threshold and can worsen pre-existing epilepsy. The commonest side effects of clomipramine in dogs are sedation and vomiting [6].

Logically, TCAs with predominately serotonin reuptake inhibiting properties should be the most suitable in dogs with separation anxiety. Certainly, clomipramine appears to be highly selective as a serotonin reuptake inhibitor in dogs and has no detectable anticholinergic properties at therapeutic doses [14,15]. Although some authors have attributed the beneficial effects of clomipramine in controlling the signs of separation anxiety to anticholinergic actions, the evidence available indicates that this is not the case and that inhibition of serotonin-reuptake is the principle mechanism of action [14,15].

A second TCA, amitriptyline, has been recommended by some authors for separation anxiety in dogs [11,16]. Although less expensive than newer TCAs or SSRIs, amitriptyline is less selective for serotonin reuptake than clomipramine, and is reported to be less effective and have more anticholinergic and sedative effects [14,16]. Neither amitriptyline nor clomipramine have effects on cardiac rhythm in healthy dogs [15,17]. In addition,

neither drug negatively affects memory or learning, at least in rats [18,19]. Although not proven, it is possible that these drugs may improve the ability of dogs to benefit from behaviour therapy, since the animals may be more responsive to this therapy when less anxious. TCAs with serotonin reuptake inhibiting properties, notably clomipramine, are the drugs of first choice for the management of stereotypic behaviours in dogs [20-24], and this property is useful in cases of separation anxiety which have additional stereotypic components to their behaviours.

Selective Serotonin-Reuptake Inhibitors (SSRIs)

These agents selectively inhibit serotonin reuptake and have few effects on noradrenaline reuptake or cholinergic receptors. They can be expected to have a profile in dogs similar to clomipramine. Although hard data on these agents is lacking, they should in theory be useful drugs in cases of separation anxiety. Use of fluoxetine at a dose of approximately 1 mg/kg per day was described in 6 dogs with separation anxiety [25].

Benzodiazepines

These drugs are potent anxiolytics and work through potentiation of the (inhibitory) neurotransmitter γ -aminobutyric acid [10]. Although these agents are potent anxiolytics, their effects on anxiety are frequently associated with sedation. Benzodiazepines are therefore not suitable for long-term use in separation anxiety, as they impair memory and would be expected to diminish the dog's receptivity to behaviour therapy. In addition, they may induce dependence or tolerance with long-term treatment, and therefore need to be withdrawn gradually after long-term use [10]. Although no controlled studies have been published, benzodiazepines are reported to be useful as short-term agents, for example at the start of the therapy in severely affected dogs or in refractory cases [4]. Since benzodiazepines have a short duration of action, they should be administered shortly before the maximal anti-anxiety effect is desired. Benzodiazepines are reported to be disappointing when used alone in cases of separation anxiety, but may be very useful when used in combination. For example, a case receiving clomipramine may benefit at the start of treatment with alprazolam administered one hour before the planned departure of the owner [4]. Once the anxiety at departure has been controlled, the alprazolam can be slowly withdrawn leaving the dog to be maintained on the TCA. If a benzodiazepine is used in combination with a TCA such as clomipramine, reduction of the dose of both or either of the drugs might be necessary as these classes of drugs may have additive effects, notably producing sedation. Unfortunately no guidelines on doses of benzodiazepines and TCAs when used in combination have been published. Extreme care must be exercised with the use of benzodiazepines in dogs exhibiting aggressive behaviour, which may be worsened.

Monoamine Oxidase Inhibitors

These agents act primarily to increase brain levels of dopamine, and are therefore used in humans to treat Parkinson's disease and depression [26]. In addition, they have neuroprotective properties that may account for the use of L-deprenyl to treat cognitive dysfunction in dogs. Although L-deprenyl is registered in some European countries for "separation problems" in dogs, no controlled efficacy data have been published. From a mechanistic view, strong anti-anxiety properties would not be expected.

Monoamine oxidase inhibitors may have serious interactions with many classes of drugs including TCAs and SSRIs. In the absence of data in dogs, it is advised not to use these drugs in combination, and to allow a washout period (e.g. 2 weeks) when changing treatment.

Azaperones

The azaperone buspirone has relatively selective anti-anxiety properties working via serotonin. It is reported not to produce sedation, and in theory could be useful to manage cases of separation anxiety in dogs [10]. However no data have been published in dogs. In man, buspirone has the disadvantage of having a slow onset of action.

Antipsychotics

Also termed neuroleptics or major tranquillisers, the antipsychotics act as dopamine antagonists [10]. They include the phenothiazines. Acepromazine is registered for use in dogs (but not for separation anxiety). The low potency antipsychotics, such as acepromazine, are not recommended for long-term use in cases of separation anxiety, as their anti-anxiety effects are not selective, and by non-selectively reducing responsiveness would be expected to impair the effectiveness of behaviour therapy. The high potency

antipsychotics produce less sedation but more extrapyramidal side effects than their low potency counterparts. Although the antipsychotics might, at least in theory, be useful for short-term control of the signs of separation anxiety, the benzodiazepines appear to be more suitable.

Table 1. List of drugs that may be useful for the therapy of separation anxiety in dogs. All agents are given orally [10,11].	
Tricyclic Antidepressants	
Amitriptyline	1 - 2 mg/kg q12h to start
Clomipramine	1 - 2 mg/kg q12h (or 2 - 4 mg/kg q24h)
Selective Serotonin Reuptake Inhibitors	
Fluoxetine	1 mg/kg q24h
Paroxetine	1 mg/kg q24h
Benzodiazepines	
Alprazolam	0.01 - 0.1 mg/kg
Clozapate	0.55 - 2.2 mg/kg
Diazepam	0.55 - 2.2 mg/kg
Others	
Buspirone	1 mg/kg q24h
Selegiline	0.5 mg/kg q24h

Management of Separation Anxiety with Clomipramine (Clomicalm®)

Clomipramine is the only drug that is been either registered worldwide or shown in well-controlled published studies to be effective in separation anxiety in dogs. Although a preliminary study found no clear effect in dogs with "separation problems" [9], four well-controlled studies have demonstrated clear advantages of adding clomipramine to behaviour therapy in dogs with separation anxiety [6,7,27,28]. The benefits of clomipramine were to produce a much faster control of signs of destruction, defecation and urination, and the advantages were maintained throughout the 2 - 3 month trial (example of results in Fig. 1, [6]). A reduction in vocalisation in cases of separation anxiety has recently been demonstrated [29]. The use of clomipramine is described in more detail below. Similar properties might be expected with other drugs with strong serotonin reuptake inhibiting actions.

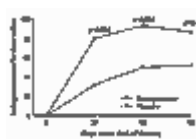


Figure 1. Response of dogs with separation anxiety for the sign destruction receiving behaviour therapy alone (placebo) or the combination of behaviour therapy and clomipramine (Clomicalm® at a dose of 1-2 mg/kg PO q12h). P values illustrate statistical comparisons between groups (significance is $p < 0.05$). - To view this image in full size go to the IVIS website at www.ivis.org . -

Use Instructions

It is recommended in cases of separation anxiety to use clomipramine only in combination with behaviour therapy. Once the signs of anxiety have been controlled, and the dog-owner relationship "normalised", the clomipramine may be withdrawn. However the owner needs to keep working to maintain an appropriate dog-owner relationship (e.g. behaviour therapy may need to be continued). The dose of clomipramine hydrochloride is 1 - 2 mg/kg administered twice daily or 2 - 4 mg/kg administered once daily. Although not recommended on the label, some dogs may respond better with higher doses (up to 3 mg/kg twice daily, [3]). Clomipramine may be given with or without food; in cases where vomiting occurs it is worth trying to give the drug with food.

Beneficial effects of clomipramine appear rapidly, within the first week, although maximal control of the signs of separation anxiety may take longer [6,28]. In severe cases, clomipramine alone may not be sufficient to control immediately the signs of separation anxiety; in these dogs addition of a benzodiazepine (e.g. alprazolam) at the start of therapy may be considered [4].

The optimal time in the day to administer clomipramine has not been determined. Voith recommended to administer amitriptyline approximately one hour before the desired maximum effect [11]. A similar recommendation might be made for clomipramine as peak concentrations in plasma are achieved within one hour after oral administration [14]. However, the bradycardia noted with elevated doses of clomipramine administered once daily was maximal approximately 12 hours after administration, which is consistent with a central mechanism of action [15]. Therefore, it is possible that clomipramine administered once daily would be most effective given at least 6 hours before the maximum effect is desired, e.g. when the owner must leave the dog.

There appears to be no need to taper the dose of clomipramine at the end of therapy, in trials sudden withdrawal of the drug after 2 - 3 months treatment was not associated with any adverse effects. Nevertheless, worsening of signs of anxiety or stereotypic behaviour has been observed in man with sudden withdrawal of TCAs including clomipramine [30]; therefore tapering of the dose after long-term administration remains a sensible precaution.

There are no hard data on the optimal duration of therapy with clomipramine, the only advice that can be given is treat as long as is necessary but no longer. In clinical trials, the response rate was good and the relapse rate was low when clomipramine was administered for 2 or 3 months and then withdrawn [6,7]. Therefore a minimum treatment time of 2 months can be recommended, although individual dogs may require longer treatment. Some dogs have received clomipramine continuously for years, the drug was tolerated well and the signs of separation anxiety were controlled successfully. If long-term treatment is necessary, it is worth trying to reduce gradually the dosage to the minimally effective dose. It is not known how long therapy with clomipramine should be continued once the signs of separation anxiety have been controlled. In man, the relapse rate in cases of panic attacks and stereotypies is higher when clomipramine therapy is withdrawn too soon [30]. Therefore it would seem logical to continue with clomipramine for at least a few weeks in dogs even once the signs of separation anxiety have been controlled. Simplistically one can imagine that a period of normalised brain serotonin function in addition to an absence of anxiety and a normalised dog-owner relation is required to produce the changes in the brain chemistry of dogs that are necessary to produce long-term resolution of the problem. In a general article, Voith recommended halving the dose of anti-anxiety drugs after 15 - 20 successful absences, and withdrawing the drug once the dose was so low that it was probably ineffective [11]. Simpson recommended continuing with clomipramine for 1 - 2 months after the signs had been controlled [4].

Tolerability and Safety

The commonest side effects of clomipramine in dogs are sedation and vomiting, although in trials these signs were mild and transient and were not sufficient reason to stop therapy [6,7]. The sedation occurs typically at the start of therapy and is usually self-limiting, as dogs become tolerant to it [4]. Less commonly there may be changes in appetite and body weight. By virtue of its relatively selective activity on serotonin as compared to noradrenaline or cholinergic receptors, clomipramine appears to produce fewer adverse effects and be safer to use in dogs as compared to humans [6,14]. Clomipramine has no detectable anticholinergic effects at therapeutic doses in dogs, and therefore side effects reported in humans such as retention of urine or faeces, dry mouth or tachycardia should not be expected. Studies in dogs have shown no significant effects on intra-ocular pressure, plasma prolactin levels, or heart rate and rhythm in healthy dogs. Nevertheless, the label for Clomicalm® carries warnings to use the drug with caution in dogs with pre-existing cardiac disease, epilepsy or glaucoma, since the safety of clomipramine has not been tested adequately at present in these conditions [28]. Although previous texts have recommended monitoring of the ECG in all dogs receiving TCAs, recent work has suggested that this is not necessary in healthy dogs, although it might be prudent to do so in dogs in which the clinician suspects an abnormal cardiac rhythm [15,17]. Studies in dogs have shown that clomipramine does not effect heart rate and rhythm in dogs at therapeutic doses, and produces benign changes (reduction in heart rate) at super-therapeutic doses [15,17].

The US label for Clomicalm® carries a precaution not to use the drug in dogs with aggression [28]. This appears to be a defensive precaution as no cases of clomipramine worsening cases of aggression have been reported. However, it is prudent to manage any aggressive dogs with caution, and this includes when using

clomipramine. One small trial reported no negative (or positive) effects of clomipramine in cases of dominance aggression in dogs [31].

References

1. Horowitz DF. Diagnosis and treatment of canine separation anxiety and the use of clomipramine hydrochloride (Clomicalm). *J Am Anim Hosp Assoc* 2000; 36:107-109.
2. McCrave EA. Diagnostic criteria for separation anxiety in the dog. *Vet Clin North Am Small Anim Pract* 1991; 21:247-255. - PubMed -
3. Overall KL. *Clinical Behavioral Medicine for Small Animals*. St. Louis: Mosby 1997; 210-219. - Available from amazon.com -
4. Simpson BS. Canine separation anxiety. *Comp Cont Edu Pract Vet* 2000; 22:328-339.
5. Hart BL, Cooper LL. Integrating use of psychotropic drugs with environmental management and behavioral modification for treatment of problem behavior in animals. *J Am Vet Med Assoc* 1996; 209:1549-1551. - PubMed -
6. King JN, Simpson BS, Overall KL, et al. Treatment of separation anxiety in dogs with clomipramine: Results from a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial. *Appl Anim Beh Sci* 2000; 67:255-275.
7. Petit S, Pageat P, Chaurand JP, et al. Efficacy of clomipramine in the treatment of separation anxiety in dogs: Clinical trial. *Rev Méd Vét* 1999; 150:133-140.
8. Takeuchi Y, Houpt KA, Scarlett JM. Evaluation of treatments for separation anxiety in dogs. *J Am Vet Med Assoc* 2000; 217:342-345. - PubMed -
9. Podberscek AL, Hsu Y, Serpell JA. Evaluation of clomipramine as an adjunct to behavioural therapy in the treatment of separation-related problems in dogs. *Vet Rec* 1999; 145:365-369. - PubMed -
10. Simpson BS, Simpson DM. Antipsychotics and antidepressants. *Behavioral pharmacotherapy Part I*. *Comp Cont Edu* 1996; 18:1067-1081.
11. Voith VL. Behavioral disorders. In: *Textbook of Veterinary Internal Medicine*. Philadelphia: WB Saunders Co, 1989; 227-238.
12. Dodson L. Review of clomipramine: An effective antiobsessional agent. *Hosp Formul* 1991; 26:489-499.
13. McTavish D, Benfield P. Clomipramine: An overview of its pharmacological properties and a review of its therapeutic use in obsessive compulsive disorder and panic disorder. *Drugs* 1990; 39:136-153. - PubMed -
14. King JN, Maurer MP, Altmann B, et al. Pharmacokinetics of clomipramine in dogs following single-dose and repeated-dose oral administration. *Am J Vet Res* 2000; 61:80-85. - PubMed -
15. Pouchelon JL, Martel E, Champeroux P, et al. Effect of clomipramine hydrochloride on heart rate and rhythm in healthy dogs. *Am J Vet Res* 2000; 61:960-964. - PubMed -
16. Overall KL. Use of clomipramine to treat ritualistic stereotypic behaviors in three dogs. *J Am Vet Med Assoc* 1994; 205:1733-1741. - PubMed -
17. Reich MR, Ohad DG, Overall KL, et al. Electrocardiographic assessment of antianxiety medication in dogs and correlation with serum drug concentration. *J Am Vet Med Assoc* 2000; 216:1571-1575. - PubMed -

18. Nurten A, Yamantürk P, Enginar N. The effects of amitriptyline and clomipramine on learning and memory in an elevated plus-maze test in mice. *Eur. Neuropsychopharmacol* 1996; 6:26.
19. Valzelli L, Skorupska M, Kozak W, et al. Difference in learning and retention by Albino-Swiss mice. Part 5. Effect of some antidepressants. *Meth Find Exp Clin Pharmacol* 1988; 10:427-430. - PubMed -
20. Goldberger RL, Rapoport JL. Canine acral lick dermatitis: response to the antiobsessional drug clomipramine. *J Am Anim Hosp Assoc* 1991; 27:179-182.
21. Rapoport JL, Ryland DH, Kriete M. Drug treatment of canine acral lick. An animal model of obsessive-compulsive disorder. *Arch Gen Psychiatry* 1992; 49:517-521. - PubMed -
22. Mertens PA, Dodman NH. Drug treatment for acral lick dermatitis in dogs. *Kleintierpraxis* 1996; 41:327-337.
23. Hewson CJ, Luescher A, Parent JM, et al. Efficacy of clomipramine in the treatment of canine compulsive disorder. *J Am Vet Med Assoc* 1998; 213:1760-1766. - PubMed -
24. Moon-Fanelli AA, Dodman NH. Description and development of compulsive tail chasing in terriers and response to clomipramine treatment. *J Am Vet Med Assoc* 1998; 212:1252-1257. - PubMed -
25. Melman SA. Use of Prozac in animals for selected dermatological and behavioral conditions. *Vet Forum* 1995; 12:19-27.
26. Bentue-Ferrer D, Menard G, Allain H. Monoamine oxidase B inhibitors. Current status and future potential. *CNS Drugs* 1996; 6:217-236.
27. Novartis Animal Health. Internal report on a clinical trial with clomipramine in dogs in Japan, 1997.
28. FDA. Freedom of information summary, Clomicalm (clomipramine hydrochloride), Novartis Animal Health, Greensboro, NC. Washington, DC: USFDA, 1998.
29. Overall KL, Agulneck L, Dunham AE. Qualitative and quantitative differences in vocalizations by dogs affected with separation anxiety and unaffected dogs using sonographic analyses. (in preparation).
30. Modigh K. The pharmacology of clomipramine in anxiety disorders. In: *Anxiety*. Dunedin: University of Otago Press 1990; 93-100.
31. White MM, Neilson JC, Hart BL, et al. Effects of clomipramine hydrochloride on dominance-related aggression in dogs. *J Am Vet Med Assoc* 1999; 215:1288-1291. - PubMed -

All rights reserved. This document is available on-line at www.ivis.org. Document No. A0807.1000 .

