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Treatment of separation anxiety in dogs with clomipramine: results from a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial

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Abstract

The efficacy and tolerability of clomipramine in the treatment of separation anxiety in dogs was tested in a prospective, randomized, double-blind, placebo-controlled, parallel-group, international multicenter clinical trial. For a diagnosis of separation anxiety, dogs had to exhibit at least one of the following signs in the absence of their owner: destruction, defecation, urination and/or vocalization, as well as the behaviour suggestive of ''hyper-attachment'' to their owner. A total of 95 dogs were randomized to receive one of the three treatments for 2–3 months: ''standard-dose'' clomipramine (1 to < 2 mg/kg, PO, q. 12 h); ''low-dose'' clomipramine (0.5 to < 1 mg/kg, PO, q. 12 h); and placebo (PO, q. 12 h). All dogs received behavioural therapy. Dogs were examined at four time points (days 0, 28, 56 and 84) after the initiation of therapy. Improvement in each dog's behaviour at days 28, 56 and 84 was evaluated in comparison to its behaviour at day 0.

The results showed that, compared to placebo, dogs receiving standard-dose clomipramine were rated improved at least three times faster for the signs destruction, defecation and urination. At most time points, more dogs in the standard-dose clomipramine group were rated improved for the signs destruction, defecation and urination, and in an owner's global assessment of the dog's overall behaviour ($p < 0.05$ at certain time points). However, there were no statistically signifi-

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cant differences at any time point between the standard dose and the placebo groups in the sign vocalization. The low-dose clomipramine group produced no statistically significant effect when compared with placebo. Mild and transient vomiting was noted as a side effect of clomipramine in a small number of dogs.

It is concluded that addition of standard-dose (1 to < 2 mg/kg, PO, q. 12 h) clomipramine to conventional behavioural therapy for 2–3 months ameliorated the signs of separation anxiety in dogs.

Keywords: Separation anxiety; Dogs; Clomipramine; Behavioural therapy

1. Introduction

Separation anxiety is a common behavioural disorder in dogs (Pageat, 1995; Voith and Borchelt, 1996; Overall, 1997a). It is characterized by signs of destructiveness, inappropriate elimination (defecation, urination) and vocalization when an affected dog is left alone or is separated from its attachment figure, usually its owner (McCrave, 1991). In the owner's absence, dogs may also show signs of autonomic arousal, such as hyper-salivation, trembling or diarrhoea. Other signs include motor restlessness such as pacing, circling, digging or excessive licking (McCrave, 1991). The aetiology of the disorder is uncertain, but may be related to heritable characteristics, early experience (Serpell and Jagoe, 1995) or environmental factors. Separation anxiety is often considered to be an extreme manifestation of the social nature of dogs. Certain individuals may develop such a strong attachment to certain human beings that they become distressed when separated from them (Elliot and Scott, 1961; O'Farrell, 1992; Pageat, 1995; Serpell and Jagoe, 1995; Askew, 1996). Treatment of separation anxiety is important for a number of reasons. First, for welfare reasons, it is necessary to relieve the distress of affected dogs. Second the signs of anxiety, e.g., destruction, elimination in the house and vocalization, can become so intolerable to the owner, partners, or neighbours, that without treatment, abandonment or euthanasia of the pet is the outcome (Houpt et al., 1996; Miller et al., 1996).

Although behavioural treatment plans for separation anxiety are documented (Tuber et al., 1982; O'Farrell, 1992; Voith and Ganster, 1993; Voith and Borchelt, 1996; Pageat, 1995; Askew, 1996; Overall, 1997b; Nack, 1999), at the time of the initiation of the study, there were no reported controlled studies of the pharmacological treatment of this condition. Particularly for anxiety disorders, the concomitant use of behavioural therapy and psychotropic medication may yield the most favorable outcome (Hart and Cooper, 1996). Recently, results of placebo-controlled, blinded studies with clomipramine in separation anxiety have been reported from France and UK (Petit et al., 1999; Podberscek et al., 1999).

In the present study, the drug clomipramine hydrochloride, herein described as clomipramine, was evaluated for the treatment of separation anxiety in dogs when used in combination with behavioural therapy. Clomipramine, classified in the human literature as a tricyclic antidepressant, is unique in this class for the predominance of its effects on the neurotransmitter serotonin. Clomipramine inhibits the neuronal reuptake

of both serotonin and noradrenaline in vivo (Waldmeier and Baumann, 1979; Maitre et al., 1982). There is evidence from preclinical studies that, in dogs, clomipramine should lead to relatively selective inhibition of neuronal reuptake of serotonin and have lesser effects on neuronal reuptake of noradrenaline (Hewson et al., 1998a; King et al., 2000). At therapeutic doses, clomipramine does not appear to have significant anticholinergic effects in dogs (Pouchelon et al., 2000).

Clomipramine is effective in a wide range of behavioural disorders in human beings including depression, generalized anxiety, obsessive–compulsive disorder, panic attacks and phobias (McTavish and Benfield, 1990; Modigh, 1990; Trimble, 1990; Dodson, 1991). Clomipramine has been demonstrated to be effective in reducing stereotypic behaviour in dogs (Goldberger and Rapoport, 1991; Rapoport et al., 1992; Overall, 1994; Thornton, 1995; Mertens and Dodman, 1996; Hewson et al., 1998b; Moon-Fanelli and Dodman, 1998) and has been reported to be useful in the treatment of a number of other canine behavioural disorders including aggression, anxieties, phobias and separation anxiety (Pageat, 1995; Simpson, 1997a; Simpson and Simpson, 1996; Overall, 1997a,b, 1998; Petit et al., 1999). Clomipramine may be suitable for use in combination with behavioural modification techniques as it does not impair (and may even improve) learning and memory (Nurten et al., 1996; Valzelli et al., 1988).

The aim of this study was to evaluate the efficacy and safety of clomipramine when used in combination with a behavioural treatment plan in cases of canine separation anxiety. The study was a prospective, randomized, double-blind, parallel-group design clinical trial.

2. Animals, materials and methods

Dogs with separation anxiety were recruited into the trial at sites in France, the UK and the US. The diagnosis was made based on a behavioural evaluation and veterinary examination. Specific inclusion and exclusion criteria were employed (Table 1). Dogs were recruited from primary veterinarians and newspaper announcements and were diagnosed with separation anxiety based on a detailed behavioural history and interview with the owner. A veterinary medical history was obtained from the owner and verified from records obtained from the dog's primary veterinarian. Dogs with known chronic systemic diseases were excluded.

In order to rule out medical problems that might confound the study, and to establish a baseline for comparison during the trial, a comprehensive veterinary examination was made at day 0 (visit 1). This included a physical examination and routine haematology (including haematocrit, RBC and WBC counts) and plasma biochemistry (including creatinine, urea, alanine-aminotranferase, gamma-glutamyltransferase, total protein, albumin).

Dogs fulfilling the entry criteria were enrolled into the trial at day 0. In all cases, the written consent of the dog's owner was obtained. Behavioural therapy (Table 2) was described to each owner. Owners were instructed not to change their dog's environment during the trial.

Table 1
Inclusion and exclusion entry criteria

Inclusion criteria
(A) Dogs must show at least one of the following signs when isolated from their owner and these signs must have been present for at least 1 month.
(1) Destructive behaviour.
(2) Inappropriate defecation in the house.
(3) Inappropriate urination in the house.
(4) Excessive vocal behaviour, including whining, barking or howling.
(B) Dogs must show all of the three following signs, suggesting a high degree of ''hyper-attachment'' to their owner:
(1) Usually follows the owner about the house and tries to maintain physical contact with the owner (within 1 m).
(2) Becomes distressed with increasing distance of separation from the owner.
(3) Becomes distressed when the owner prepares to leave the home and greets the owner excessively on his/her return.

Exclusion criteria: any one of the following would exclude a dog from admission into the trial
(A) Dog is under 6 months of age.
(B) Duration of signs of separation anxiety is less than 1 month.
(C) Destructive behaviour occurs in the presence of the owner.
(D) Behavioural conditions other than separation anxiety are present, which may cause destruction, vocalization or inappropriate defecation or urination, e.g., destructive behaviour and vocalization due to dominance aggression or territorial protection; urination in males due to marking behaviour; inadequate house-training.
(E) Medical conditions are present that might confound the diagnosis or interpretation of results, including urogenital disorders causing abnormal or difficult urination; gastrointestinal disease causing vomiting or disorders of defecation.

Other criteria
All drugs with a known action on the CNS including antidepressants, anxiolytics, monoamine oxidase inhibitors or phenothiazines must be stopped at least 2 weeks before starting the trial. In multi-dog households, the dog suffering from separation anxiety has to be identified without ambiguity.

The dogs were assigned to one of the following treatment groups at random: ''standard-dose'' clomipramine (1.0 to <2.0 mg/kg, PO, q. 12 h, equivalent to 2 to <4 mg/kg/day), ''low-dose'' clomipramine (0.5 to <1.0 mg/kg, PO, q. 12 h, equivalent to 1 to <2 mg/kg/day), or placebo (0 mg/kg, PO, q. 12 h). Randomization was balanced every six cases per investigator.

The test article was supplied as meat-flavoured tablets containing clomipramine hydrochloride (Clomicalm®, Novartis Animal Health, Basel, Switzerland). Placebo tablets, identical in appearance to the tablets containing clomipramine, consisted of the vehicle minus clomipramine. All investigators and owners remained blinded to the treatment groups for the duration of the trial. The test treatments were administered two times daily at intervals as close to 12 h as possible (defined as q. 12 h).

Except as described below, the dogs were treated for a minimum of 2 months (56 days). If all signs of separation anxiety disappeared after 2 months, the dog could be withdrawn from the trial. If the signs were not completely resolved at day 56, the treatment was continued for an additional 1 month (i.e., for a total of 84 days). Owners could elect to remove their dog from the trial at day 28 if it had shown no improvement.

Table 2
Behavioural plan explained to the owners of all dogs in the trial. This plan was based on an original proposal of P. Pageat (France) with additional input from D. Appleby (UK) and K.L. Overall (US)

At home
Stop all forms of retrospective reprimand or punishment for destruction or elimination in the house.
All interactions between the dog and the owner must take place on the owner's initiative. Attempts by the dog to seek physical contact with the owner should be ignored. The owner may play with or touch the dog, but only when the dog is relaxed and only at the command and initiative of the owner.
The dog may sleep in the owner's bedroom, but only on the initiative of the owner.
When leaving home
The owner should pay no attention to the dog during the 30-min period before he/she leaves. The only interaction permitted is to put the dog in a place where it normally stays while the owner is absent.
The owner may leave items impregnated with his/her scent or that occupy the dog's attention (e.g., toys).
Owners may practice leaving routines and then not leave the house.
When returning home
On returning to the house, the owner should ignore the dog until it is relaxed.

Veterinary and behavioural examinations were performed on day 0 (visit 1), day 28 (visit 2), day 56 (visit 3), and in some cases, on day 84 (visit 4). Haematology and plasma biochemistry values were obtained on day 0 and at the last visit (day 56 or 84).

2.1. Concomitant treatments not permitted

Concomitant treatments that could affect the symptoms of separation anxiety were not permitted during the trial. These included drugs with a known action on the central nervous system (CNS), including antidepressants, antiepileptics, anxiolytics and neuroleptics. The administration of certain CNS-acting drugs, such as general anaesthetics, was permitted to allow emergency surgical procedures of short duration. Investigators were instructed to postpone elective surgical procedures until the completion of the trial. Monoamine oxidase inhibitors were not permitted for 14 days before the start of, and during the trial, as serious interactions with selective serotonin-reuptake inhibitors have been reported in man (Trimble, 1990; Dodson, 1991) and dogs (Simpson and Davidson, 1996). Drugs affecting gastrointestinal motility (including anti-emetics, anti-diarrhoea treatments) or urinary function (including diuretics) could not be started during the trial. However, therapy with these agents could continue if the dog was already receiving them at the start of the study.

2.2. Efficacy assessment and statistics

The efficacy of the treatments was assessed subjectively by the investigator in response to specific questions directed to the owner at days 28, 56 and 84, as compared to day 0 (baseline).

Similar scoring schemes are standard in the evaluation of medicines for CNS diseases in humans (Hamilton, 1959; Montgomery and Asberg, 1979; Goodman et al., 1989). Assessments were made based on the severity and frequency of the signs of separation anxiety and on the owner's global assessment. At the visits on days 28, 56 and 84, each

of the four signs of separation anxiety (destruction, defecation, urination and vocalization) were rated as ''worse'', ''no change'', ''improved'', ''disappeared'' or ''newly appeared'', as compared to the baseline visit (day 0). ''Disappeared'' was defined as the total absence of the sign in the previous 1 month, since the last visit. ''Newly appeared'' was defined as the appearance of the sign since the last visit. A rating of ''improved'' or ''worse'' was based on the frequency and/or severity of the behaviour. Treatment success was defined as signs ''disappeared'' or ''improved''. For the statistical analyses, the frequency of such cases was compared between treatment groups. The last recorded value was inserted at subsequent visits for cases withdrawn from the study at day 28 due to lack of efficacy or at day 56 due to the disappearance of signs.

Each owner made a ''global'' assessment of the change in his/her dog's behaviour at the visits on days 28, 56 and 84. Owners were asked to rate the change in their dog's global behaviour as ''no improvement'', ''little improvement'', ''moderate improvement'', ''much improvement'' or ''cured'' as compared to day 0. ''Cured'' was defined as the disappearance of signs. The global assessment took into consideration the signs exhibited in the owner's absence, including destruction, defecation, urination and vocalization, as well as other signs not assessed individually, such as excessive salivation. The global assessment also incorporated the dog's overall behaviour in the owner's presence. For statistical analysis, treatment success was defined as ''moderate improvement'', ''much improvement'' or ''cured''. The frequency of such cases was compared between treatment groups.

An estimate of the rate of response in each of the three treatment groups was made by evaluating the time, measured in the number of visits, taken to reach a defined response (e.g., 80% of dogs rated as ''improved'').

Significance is reported with a two-tailed p value less than 5% ($p < 0.05$) using the Fisher's exact test (Proc FREQ; SAS Institute, SAS/STAT User's Guide, Version 6, 4th edn., Vol. 1, SAS Institute, Cary, NC, 1989, pp. 851–889). Differences were considered to approach significance with a two-tailed p value between 5% and 10% ($0.1 < p < 0.05$).

2.3. Hyper-attachment and efficacy of the behavioural plan

A simple assessment of the dog–owner relationship was made at days 0, 28, 56 and 84. The following parameters were recorded: owner reprimands dog for destruction, defecation or urination; dog follows owner (around the home); dog initiates the interaction between dog and owner; dog is anxious when owner leaves (the home); dog excessively greets owner (when he/she returns home); and dog sleeps in owner's bed. Each of these parameters was assessed as occurring ''always'', ''usually'', ''rarely'' or ''never''. The objective of these assessments was to evaluate (albeit simplistically) the compliance and effectiveness of the behavioural plan.

2.4. Tolerability assessment

The tolerability of the test treatments was evaluated by a veterinarian at each visit by a clinical examination of the dog and by questioning the owner for reported adverse

events. The assessment was based on the reported frequency and severity of undesirable events, and the suspicion that it was caused by the test treatment (rated as mild, moderate or high suspicion).

3. Results

Cases were recruited by the following investigators (location of the center and number of cases recruited): K.L. Overall, Philadelphia, PA, US (22); B.S. Simpson, Southern Pines, NC, US (14); D. Appleby, Defford, UK (12); C. Ross, Edinburgh, UK (9); J.P. Chaurand, Taverny, France (8); S. Heath, Brackley, UK (8); C. Beata, Toulon, France, (7); A.B. Weiss, Beauselle, France (7); G. Muller, Lille, France (6); T. Paris, St. Martin d'Heres, France (4); B.G. Bataille, Sevrier, France (1); P. Pageat, L'Isle sur la Sorgue, France (1).

A total of 99 cases were recruited and included in the baseline demography data and tolerability assessments. A total of 95 cases were included in the efficacy analyses as four cases were withdrawn prematurely from the study (noncompliance with the test article administration, withdrawal of owner consent, inability of owner to assess target behaviours and breaking of the blinding code after an accidental overdose of the test treatment). A total of 28 cases received standard-dose clomipramine (1.0 to < 2.0 mg/kg, PO q. 12 h), 35 received low-dose clomipramine (0.5 to < 1.0 mg/kg, PO q. 12 h) and 32 received placebo (PO q. 12 h). The cases were distributed approximately evenly between the three countries: 34 cases in France, 27 cases in UK and 34 cases in US.

3.1. Baseline data

The sex, age and body weight of the dogs are listed below. The study population was predominantly male (63%) adult dogs aged between 1 and 5 years (55%) and weighing between 10 and 40 kg (67%). The dogs were 29 intact males, 33 castrated males, 12 entire females and 25 spayed females. The number of dogs aged between 6 months and 1 year was 21, > 1–5 years was 54, > 5–10 years was 20 and > 10 years was 4. The number of dogs weighing > 1.25–5 kg was 5, > 5–10 kg was 26, > 10–20 kg was 20, > 20–40 kg was 42 and > 40 kg was 5. A total of 33 recognized breeds of dogs (74% of animals) were represented and the remaining dogs (26% of animals) were mixed breed.

Cases were assigned to treatment groups at random. For each treatment group, we calculated the mean number of target behaviours (destruction, defecation, urination or vocalization) exhibited by each dog at day 0. The results were similar in the three treatment groups with a mean of 2.3, 2.2 and 2.5 behaviours present in the standard-dose clomipramine, low-dose clomipramine and placebo groups, respectively. However, the duration of time the signs had been present was noticeably longer (mean 31.6 months) in the standard-dose clomipramine group as compared to the other two groups (mean values of 17.2 and 17.6 months, respectively for the low-dose clomipramine and placebo groups).

All cases fulfilled the inclusion criteria, with the exception of 6 cases which did not fulfill all three of the criteria for hyper-attachment. These cases were included nevertheless in the analysis, according to the ''intention-to-treat'' principle.

3.2. Efficacy assessment

The frequency of cases in which signs were rated as ''worse'', ''no change'', ''improved'' or ''disappeared'' are shown in Tables 3–6. In no case was any sign rated ''newly appeared'' when it had been absent at day 0. For three of the signs of separation anxiety (destruction, defecation and urination), there was a higher frequency of cases with treatment success, defined as a rating of either ''improved'' or ''disappeared'', in the standard-dose clomipramine group as compared to the low-dose clomipramine and placebo groups at all three time points (days 28, 56 and 84) (Tables 3–5).

However, when the individual signs were evaluated separately for either the ''disappeared'' or ''improved'' ratings, differences between the standard-dose clomipramine and placebo groups reached statistical significance ($p < 0.05$) at only certain visits. This was shown for ''disappeared'' and ''improved'' for the sign destruction at days 28 and 56; ''improved'' for the sign defecation at days 56 and 84; and ''improved'' for the sign urination at day 56. Therefore, in this study, statistical significance for the rating ''disappeared'' was only reached between the standard-dose clomipramine and placebo groups for one sign (destruction) at two time points (days 28 and 56).

Table 3
Cases with destruction exhibited in the owner's absence

	Worse	No change	Improved	Disappeared	Total improved + disappeared	Total
Day 28						
Placebo, q. 12 h	3 (12%)	15 (58%)	8 (31%)	0 (0%)	8 (31%)	26
CLO 0.5 to <1 mg/kg, q. 12 h	0 (0%)	13 (43%)	15 (50%)	2 (7%)	17 (57%)	30
CLO 1 to <2 mg/kg, q. 12 h	0 (0%)	3 (19%)	10 (63%)	3 (19%)	13 (81%)	16
				$p = 0.049$	$p = 0.001$	
Day 56						
Placebo, q. 12 h	4 (16%)	9 (36%)	10 (40%)	2 (8%)	12 (48%)	25
CLO 0.5 to <1 mg/kg, q. 12 h	2 (7%)	10 (35%)	13 (45%)	4 (14%)	17 (59%)	29
CLO 1 to <2 mg/kg, q. 12 h	0 (0%)	1 (7%)	8 (53%)	6 (40%)	14 (93%)	15
				$p = 0.036$	$p = 0.001$	
Day 84						
Placebo, q. 12 h	3 (12%)	8 (32%)	8 (32%)	6 (24%)	14 (56%)	25
CLO 0.5 to <1 mg/kg, q. 12 h	1 (4%)	9 (32%)	11 (39%)	7 (25%)	18 (64%)	28
CLO 1 to <2 mg/kg, q. 12 h	0 (0%)	2 (13%)	5 (33%)	8 (53%)	13 (87%)	15
				$p = 0.089$	$p = 0.08$	

Cases for which the sign was present at day 0 were subsequently assessed at days 28, 56 and 84 and rated as worse, no change, improved or disappeared based on the frequency and/or severity of the behaviour. Results are the frequency of each response (% of total). CLO = clomipramine. *P* values are two-tailed comparisons to the placebo group at the respective time point using Fisher's exact test.

Table 4
Cases with defecation exhibited in the owner's absence

	Worse	No change	Improved	Disappeared	Total improved + disappeared	Total
Day 28						
Placebo, q. 12 h	1 (7%)	6 (43%)	2 (14%)	5 (36%)	7 (50%)	14
CLO 0.5 to < 1 mg/kg, q. 12 h	0 (%)	4 (44%)	3 (33%)	2 (22%)	5 (56%)	9
CLO 1 to < 2 mg/kg, q. 12 h	0 (0%)	2 (17%)	5 (42%)	5 (42%)	10 (83%)	12
Day 56						
Placebo, q. 12 h	1 (7%)	6 (43%)	2 (14%)	5 (36%)	7 (50%)	14
CLO 0.5 to < 1 mg/kg, q. 12 h	0 (%)	2 (22%)	4 (44%)	3 (33%)	7 (78%)	9
CLO 1 to < 2 mg/kg, q. 12 h	0 (0%)	0 (0%)	4 (33%)	8 (67%)	12 (100%), $p = 0.001$	12
Day 84						
Placebo, q. 12 h	1 (7%)	6 (43%)	2 (14%)	5 (36%)	7 (50%)	14
CLO 0.5 to < 1 mg/kg, q. 12 h	0 (0%)	3 (33%)	2 (22%)	4 (44%)	6 (67%)	9
CLO 1 to < 2 mg/kg, q. 12 h	0 (0%)	1 (8%)	6 (50%)	5 (42%)	11 (92%), $p = 0.036$	12

See Table 2 for explanation.

At the last time point (day 84), statistical significance was only reached between the standard dose and placebo groups for the ''improved'' rating for one sign (defecation). Significance was approached ($p < 0.1$) for the ratings ''disappeared'' and ''improved'' for the sign destruction at days 28, 56 and 84; ''improved'' for the sign defecation at

Table 5
Cases of urination exhibited in the owner's absence

	Worse	No change	Improved	Disappeared	Total improved + disappeared	Total
Day 28						
Placebo, q. 12 h	1 (7%)	7 (50%)	3 (21%)	3 (21%)	6 (43%)	14
CLO 0.5 to < 1 mg/kg, q. 12 h	0 (0%)	4 (31%)	6 (46%)	3 (23%)	9 (69%)	13
CLO 1 to < 2 mg/kg, q. 12 h	1 (6%)	3 (18%)	9 (53%)	4 (24%)	13 (77%), $p = 0.075$	17
Day 56						
Placebo, q. 12 h	1 (7%)	5 (36%)	4 (29%)	4 (29%)	8 (57%)	14
CLO 0.5 to < 1 mg/kg, q. 12 h	0 (0%)	2 (15%)	6 (46%)	5 (39%)	11 (85%)	13
CLO 1 to < 2 mg/kg, q. 12 h	0 (0%)	1 (6%)	9 (53%)	7 (41%)	16 (94%), $p = 0.028$	17
Day 84						
Placebo, q. 12 h	1 (7%)	5 (36%)	4 (29%)	4 (29%)	8 (57%)	14
CLO 0.5 to < 1 mg/kg, q. 12 h	0 (0%)	7 (54%)	3 (23%)	3 (23%)	6 (46%)	13
CLO 1 to < 2 mg/kg, q. 12 h	0 (0%)	3 (18%)	8 (47%)	6 (35%)	14 (82%)	17

See Table 2 for explanation.

Table 6
Cases with vocalization exhibited in the owner's absence

	Worse	No change	Improved	Disappeared	Total improved + disappeared	Total
Day 28						
Placebo, q. 12 h	1 (4%)	14 (54%)	9 (35%)	2 (8%)	11 (42%)	26
CLO 0.5 to <1 mg/kg, q. 12 h	2 (8%)	11 (44%)	9 (36%)	3 (12%)	12 (48%)	25
CLO 1 to <2 mg/kg, q. 12 h	0 (0%)	8 (42%)	9 (47%)	2 (11%)	11 (58%)	19
Day 56						
Placebo, q. 12 h	2 (8%)	10 (40%)	8 (32%)	5 (20%)	13 (52%)	25
CLO 0.5 to <1 mg/kg, q. 12 h	2 (8%)	7 (29%)	12 (50%)	3 (13%)	15 (63%)	24
CLO 1 to <2 mg/kg, q. 12 h	0 (0%)	3 (16%)	12 (63%)	4 (21%)	16 (84%), $p = 0.052$	19
Day 84						
Placebo, q. 12 h	1 (4%)	8 (32%)	8 (32%)	8 (32%)	16 (64%)	25
CLO 0.5 to <1 mg/kg, q. 12 h	0 (0%)	8 (35%)	9 (39%)	6 (26%)	15 (65%)	23
CLO 1 to <2 mg/kg, q. 12 h	0 (0%)	4 (21%)	9 (47%)	6 (32%)	15 (79%)	19

See Table 2 for explanation.

days 56 and 84; and ''improved'' for the sign urination at days 28 and 56. For the signs destruction, defecation and urination, the frequency of cases rated with signs ''improved'' in the standard-dose clomipramine groups at the first visit (day 28) was higher than the values obtained at any of the three visits (days 28, 56 or 84) in the placebo group, suggesting that the response rate to this dose of clomipramine was at least three times faster than obtained in the placebo group.

For vocalization, more cases were rated as ''improved'' with standard-dose clomipramine as compared to placebo at all three time points, although significance was only approached ($p < 0.1$) for one time (day 56) (Table 6). There were no differences in the number of cases rated as ''disappeared''. A total of 64% of cases were rated as ''improved'' in the placebo group at day 84, while 58% and 84% of cases obtained this rating in the standard-dose clomipramine group, respectively at days 28 and 56. Therefore, the response rate for vocalization can be estimated as occurring between 1.5 and 3 times faster with this dose of clomipramine as compared to placebo.

There were no statistically significant ($p > 0.1$) differences in the frequency of ratings ''disappeared'' or ''improved'' for the four signs of separation anxiety between the low-dose clomipramine and placebo groups (Tables 3–6). In some cases (standard-dose clomipramine $n = 11$, low-dose clomipramine $n = 20$, placebo $n = 10$), dogs were given worse scores for one or more of the four signs of separation anxiety at a subsequent visit as compared to the previous examination (e.g., a dog was rated as ''improved'' at day 28 and ''no change'' at day 56). This occurred (respectively in the standard-dose clomipramine, low-dose clomipramine and placebo groups) in one, two and three dogs at day 28; two, nine and three dogs at day 56; and eight, nine and four dogs at day 84. These numbers do not take into account the dogs withdrawn from the study due to lack of efficacy at day 28 (zero in the standard-dose clomipramine group, one in the low-dose clomipramine and three in the placebo group).

More cases were rated ''moderate improvement'', ''much improvement'' or ''cured'' for the owner's global assessment in the standard-dose clomipramine group as compared to the placebo group at all three time points (Table 7). Differences reached statistical significance ($p < 0.05$) at days 28 and 56, and approached significance ($p < 0.1$) at day 84. Similarly, more cases were rated as ''much improvement'' or ''cured'' in the standard-dose clomipramine group as compared to the placebo group at all three time points and differences reached statistical significance ($p < 0.05$) at day 84 and approached significance ($p < 0.1$) at day 28. Only 17 out of the total of 86 dogs (20%) were rated as ''cured'' at the last visit (day 84), with only slightly more (27%) in the standard-dose clomipramine group as compared to the placebo (21%). Differences did not approach statistical significance ($p > 0.1$).

3.3. Cases withdrawn

The numbers (% of all cases) withdrawn at day 28 due to lack of efficacy were zero (0%), one (3%) and three (9%), in the standard-dose clomipramine, low-dose clomipramine and placebo groups, respectively. Differences did not reach statistical significance ($p > 0.1$, between standard-dose clomipramine and placebo).

The number (% of all cases) withdrawn at day 56 with disappearance of all signs of separation anxiety were three (10%), one (3%) and three (9%) in the standard-dose clomipramine, low-dose clomipramine and placebo groups, respectively.

3.4. Hyper-attachment

Results of the dog–owner relationship are given in Table 8. The behavioural plan instructed owners not to reprimand their dogs for destruction, defecation or urination caused in their absence. The results show that 51% of owners reported reprimanding or punishing their dogs at day 0. Few owners (0–7%) reported reprimanding their dogs at days 28, 56 and 84 in all three treatment groups, suggesting that there might have been good compliance with this part of the behavioural plan. However, we could not verify that the owners reported correctly these results. Two parameters describing owner/dog interactions, ''dog follows owner'' and ''dog initiates interaction'', were intended to assess the compliance with the behavioural plan and its effect on ''hyper-attachment'' of the dog to its owner. A total of three owners reported that their dogs rarely or never followed their owner in the house at day 0, which, as noted previously, was a violation of the inclusion criteria. Nevertheless, most dogs initiated interactions and followed their owners in the residence at day 0, and these numbers declined with time, approximately equally, in all three treatment groups.

The parameter, ''dog is anxious when owner leaves'' was designed to evaluate the degree of anxiety shown by the dog when anticipating separation from its owner. As noted previously, one dog was reported not to show this sign at day 0, which is a violation of the inclusion criteria. The remainder of the dogs (96–100% per group) were anxious when the owner left at day 0, and this number declined during the trial in all three treatment groups. Although fewer dogs were anxious in the standard-dose

Table 7
Owner's global assessment of dog's behaviour

	No improvement	Little improvement	Moderate improvement	Much improvement	Cured	Total moderate + much improvement + cured	Total much improvement + cured	Total
Day 28								
Placebo, q. 12 h	11 (36%)	11 (36%)	6 (19%)	2 (7%)	1 (3%)	9 (29%)	3 (10%)	31
CLO 0.5 to <1 mg/kg, q. 12 h	6 (17%)	16 (46%)	7 (20%)	6 (17%)	0 (0%)	13 (37%)	6 (17%)	35
CLO 1 to <2 mg/kg, q. 12 h	4 (15%)	6 (22%)	9 (33%)	8 (30%)	0 (0%)	17 (63%), $p = 0.017$	8 (30%), $p = 0.091$	27
Day 56								
Placebo, q. 12 h	6 (20%)	7 (23%)	6 (20%)	7 (23%)	4 (13%)	17 (57%)	11 (37%)	30
CLO 0.5 to <1 mg/kg, q. 12 h	2 (6%)	13 (41%)	8 (25%)	7 (22%)	2 (6%)	17 (53%)	9 (28%)	32
CLO 1 to <2 mg/kg, q. 12 h	2 (8%)	1 (4%)	7 (27%)	13 (50%)	3 (12%)	23 (89%), $p = 0.016$	16 (62%)	26
Day 84								
Placebo, q. 12 h	5 (17%)	6 (21%)	6 (21%)	6 (21%)	6 (21%)	18 (62%)	12 (41%)	29
CLO 0.5 to <1 mg/kg, q. 12 h	3 (10%)	9 (29%)	6 (19%)	9 (29%)	4 (13%)	19 (61%)	13 (42%)	31
CLO 1 to <2 mg/kg, q. 12 h	3 (12%)	1 (4%)	3 (12%)	12 (46%)	7 (27%)	22 (85%), $p = 0.076$	19 (73%), $p = 0.029$	26

The improvement of the dog's behaviour was assessed at days 28, 56 and 84 as compared to baseline (day 0).
Results are the frequency of each response (% of total). CLO = clomipramine.
P values are two-tailed comparisons to the placebo group at the respective time point using Fisher's exact test.

Table 8
Assessment of the dog–owner relationship

	Day 0	Day 28	Day 56	Day 84
Owner reprimands dog				
Placebo, q. 12 h	11/21 (34%)	2/29 (6%)	2/27 (0%)	2/27 (0%)
CLO 0.5 to <1 mg/kg, q. 12 h	20/15 (57%)	1/34 (3%)	0/34 (3%)	0/34 (7%)
CLO 1 to <2 mg/kg, q. 12 h	17/11 (61%)	0/28 (0%)	0/26 (0%)	0/26 (0%)
Dog follows owner				
Placebo, q. 12 h	32/0 (100%)	25/5 (83%)	10/17(37%)	10/10 (50%)
CLO 0.5 to <1 mg/kg, q. 12 h	33/2 (94%)	23/12 (66%)	23/7 (77%)	15/13 (54%)
CLO 1 to <2 mg/kg, q. 12 h	27/1 (96%)	19/9 (70%)	12/14 (46%)	8/13 (38%)
Dog initiates interaction				
Placebo, q. 12 h	28/4 (88%)	15/15 (50%)	9/18 (33%)	6/14 (30%)
CLO 0.5 to <1 mg/kg, q. 12 h	32/3 (91%)	25/10 (71%)	17/14 (55%)	13/15 (46%)
CLO 1 to <2 mg/kg, q. 12 h	27/1 (96%)	18/10 (64%)	11/15 (42%)	8/13 (38%)
Dog is anxious when owner leaves				
Placebo, q. 12 h	33/0 (100%)	28/3 (90%)	20/8 (71%)	14/7 (67%)
CLO 0.5 to <1 mg/kg, q. 12 h	34/0 (100%)	24/10 (71%)	18/12 (60%)	15/12 (56%)
CLO 1 to <2 mg/kg, q. 12 h	27/1 (96%)	22/6 (79%)	12/14 (46%)	11/10 (52%)
Dog excessively greets owner				
Placebo, q. 12 h	31/1 (97%)	23/7 (77%)	22/5 (81%)	13/7 (65%)
CLO 0.5 to <1 mg/kg, q. 12 h	33/2 (94%)	21/14 (60%)	20/11 (65%)	17/11 (61%)
CLO 1 to <2 mg/kg, q. 12 h	28/0 (100%)	21/7 (75%)	19/7 (73%)	16/5 (76%)
Dog sleeps in owners bed				
Placebo, q. 12 h	20/12 (63%)	18/12 (60%)	7/20 (26%)	7/13 (35%)
CLO 0.5 to <1 mg/kg, q. 12 h	20/15 (57%)	16/19 (46%)	11/20 (35%)	10/18 (36%)
CLO 1 to <2 mg/kg, q. 12 h	17/11 (61%)	16/12 (57%)	11/15 (43%)	11/10 (52%)

Results show the number of cases for which the behaviour was rated as ''always or usually'' present/''rarely or never'' present (percentage of cases rated as ''always or usually'').
CLO = Clomipramine.

clomipramine as compared to the placebo group at days 28, 56 and 84, differences did not reach statistical significance. Most dogs (97%) were reported at day 0 to ''excessively greet their owner'' when the latter returned to the house. The number of positive scores for this parameter was reduced during the trial (67% at day 84) with approximately equal reduction in all three groups. A total of 60% of dogs were reported to sleep in or on the bed of the owner at day 0, and this number was reduced during the trial (41% at day 84) in all three treatment groups.

3.5. Tolerability

The frequency of reported undesirable events is provided in Table 9, regardless of the severity of the event and the causality assessment. Most cases were reported to have been unrelated to the test treatment. There were no significant changes in body weight,

Table 9
Reported undesirable medical events

Treatment group (no. of cases)	Placebo, PO, q. 12 h, $N = 33$	0.5 to <1 mg/kg, PO, q. 12 h, CLO, $N = 36$	1 to <2 mg/kg, PO, q. 12 h, CLO, $N = 30$
Gastrointestinal signs / appetite			
Intermittent vomiting/gastritis	3	13	8
Intermittent diarrhoea/colitis	2	5	0
Anorexia/weight loss	0	1	2
Increased appetite/weight gain	2	0	3
Constipation	1	0	0
Increased thirst	0	0	1
Neurological signs			
Lethargy/sleepiness	2	2	4
Trembling/discomfort	1	0	1
Aggression	1	1	1
Collapse and possible DIC	0	0	1
Other medical conditions			
Upper respiratory	1	0	0
Conjunctivitis	1	1	0
Seborrhoea	0	0	1
Vaginitis (mild)	0	0	1

Results are the number of dogs for which each event was recorded, unrelated to the duration of treatment, the severity of the reaction or judged relation to the test treatment. See Section 3.5 for details.
CLO = clomipramine, DIC = disseminated intravascular coagulation.

rating of physical condition, haematology or plasma biochemistry values during the trial. The only medical events observed more frequently in the clomipramine treated groups as compared to the placebo group, were intermittent incidents of vomiting/gastritis and lethargy/sleepiness. Intermittent vomiting was reported in eight dogs in the standard-dose clomipramine group, but in only two cases was there rated to be a ''high suspicion'' of a relationship to the test article. All cases of vomiting in the standard-dose clomipramine group were transient and of mild severity. No dogs were withdrawn due to occurrences of vomiting. Lethargy or sleepiness was reported in four dogs in the standard-dose clomipramine group as compared to two cases in the placebo group. One case of sedation in the standard-dose clomipramine group was rated with ''mild suspicion'' as being related to the test treatment, the remaining three cases were reported as unrelated.

During the trial, dogs received a variety of antibiotics, anti-inflammatory agents, anti-parasitic drugs, general anaesthetics, opiate analgesics and vaccines. In no case was a reaction to a concomitant medication noted.

One dog, with a previous history of two to three seizures per year, received the standard dose of clomipramine during the trial. This dog was included in the analyses as, although epilepsy was a pre-admission exclusion criterion, the dog's history of seizures was not known at the time of inclusion. No episodes of seizures occurred in the trial.

The only serious medical event reported during the trial was a four-year-old, castrated male greyhound which collapsed after receiving 21 days treatment with the standard

dose (1.2 mg/kg q12 h) of clomipramine. The dog developed a transient high fever (111°F) attributed to increased motor activity and possibly disseminated intravascular coagulation (DIC). The reaction was judged by the investigator as being possibly due to the administration of clomipramine. The dog was withdrawn from the study, clomipramine was discontinued and the dog recovered without consequences. A total of two other greyhounds completed the trial without incident.

A total of three dogs (one in each treatment group) reported aggression during the trial with no history of aggression pre-trial. The cases involving clomipramine were mild. One case was directed against other dogs (standard dose). One case was directed toward the owner (low dose). One case, receiving placebo, was judged to be serious. This dog had no previous history of aggression. It was withdrawn from the study at day 56 because of the appearance of dominance aggression towards members of the family and strangers. The aggression disappeared in the following month, coinciding with the withdrawal of the test treatment (placebo) and alteration of the dog's management.

4. Discussion

We employed detailed inclusion and exclusion criteria in an attempt to include only cases of separation anxiety according to the definition of the disorder made by Pageat (1995). In order to be suitable for the trial, dogs have to show at least one of the four target signs (destruction, defecation, urination or excessive vocalization) of anxiety while the owner was absent. In addition, dogs have to show three additional behavioural signs (following owner in the house, distress when owner prepared to leave and ''excessive greeting'' when owner returned) indicating a close relationship between the dog and its owner. Some authors state that this relationship, often described as ''hyper-attachment'', is critical to the etiology of the disorder (Pageat, 1995); however, others disagree (Overall, 1997b). Therefore, the results of this study (involving dogs with anxiety plus hyper-attachment) may not be relevant to cases of anxiety exhibited in the owner's absence in which no hyper-attachment is present. A small number of cases (six) did not fulfill all three of the hyper-attachment inclusion criteria, but were included in the data analysis, nevertheless, according to the ''intention-to-treat'' principle.

The efficacy of the test treatment was assessed in two ways. First, for each of the four signs of separation anxiety (destruction, defecation, urination and vocalization), the frequency of cases rated as ''improved'' or ''disappeared'' was used to indicate treatment success. The results show that more dogs were rated as ''improved'' for destruction, defecation and urination at all three time points in the standard-dose (1 to < 2 mg/kg, PO, q. 12 h) clomipramine group as compared to the placebo, although statistical significance was only reached at one or two of the three time points for each of the signs. Second, ratings of ''moderate improvement'', ''much improvement'' or ''cured'' for the owner's global assessment of the dog's behaviour were used as indices of treatment success. More cases were rated as ''moderately'' or ''markedly improved'' for the global score in the standard-dose clomipramine as compared to the placebo group at all three time points, with statistical significance being reached for one or two of the three time points. The low dose of clomipramine (0.5 to < 1 mg/kg, PO, q. 12 h) had no statistically significant effect.

Although these results demonstrate a beneficial effect of the standard-dose clomipramine in reducing the frequency and/or severity of signs of anxiety as compared to placebo, some observations are pertinent. First, the efficacy of clomipramine for vocalization was equivocal. One reason for this result may be that the owner could quantify destruction, defecation and urination in the house relatively easily and reliably. In contrast, vocalization could be assessed directly by the owner only when leaving or returning to the house, vocalization during much of the owner's absence could be assessed only by indirect means, e.g., by questioning neighbours. Therefore, our assessment of vocalization was not optimal and might not be suitable for distinguishing differences between treatment groups. An additional factor might be that vocalization may not be specific to anxiety: canine vocalization serves numerous functions, ranging from distress to excitement (Simpson, 1997b). The nature of vocalizations exhibited by the dogs was not recorded in this study. Second, although an excellent response was achieved with standard-dose clomipramine for the ''improved'' rating, the efficacy of the drug was equivocal for the rating ''disappeared''. For the latter, statistical significance was only reached for destruction (at days 28 and 56). However, the limitations of the scoring schemes must be acknowledged. For the four individual signs (destruction, defecation, urination and vocalization), the ''disappeared'' category represented a high hurdle for the treatment, as this rating was given only when the dog did not show signs at any time in the preceding 28 days. This may explain the low incidence of ''disappeared'' ratings in the trial. The single ''improved'' rating, on the other hand, represented a large range from very slight to very marked improvement. The choice of only two categories (improved and disappeared) for assessing the success of the treatment for the four signs makes it difficult to interpret clinically relevant differences between groups.

In this respect, the global scores may be more useful since the ''improvement'' category was divided into ''little improvement'', ''moderate improvement'' or ''much improvement'' subgroups. A beneficial effect of clomipramine in producing a higher frequency of ''moderate improvement'' or ''much improvement'' for the global score was evident, although no effect on the ''cured'' rating was shown.

Overall, the study suggests a clear beneficial effect of adding clomipramine to behavioural therapy in reducing the frequency or severity of the signs of separation anxiety in dogs. The efficacy of clomipramine in assisting the total disappearance of signs remains unproven, except perhaps for destruction, although the trial had inadequate power (low number of cases, limitations of the scoring schemes) to test adequately this aspect. Nevertheless, the results suggest that the complete disappearance of signs of separation anxiety may be difficult to achieve within 3 months in many dogs, even with the combination of behavioural therapy and clomipramine.

The results of the study also clearly demonstrate the benefit of adding clomipramine to behavioural therapy in producing faster improvement of the signs of separation anxiety in dogs. We could not determine accurately the increase in speed of response, but estimated values of at least three times faster for destruction, defecation and urination, and between 1.5 and 3 times faster for vocalization. In view of the issues discussed previously, we recommend that future trials employ more objective endpoints, e.g., daily recording of the frequency and severity of signs.

For each of the four signs of anxiety (destruction, defecation, urination and vocalization), the difference between the standard-dose clomipramine and placebo groups in the number of cases rated as improved was greater at day 56 as compared to day 84. This observation is paralleled by the less frequent attainment of statistical significance between the groups at day 84 (defecation and global score) as compared to day 56 (destruction, defecation, urination and global score). It is therefore possible that, with sufficient time, the response in the placebo group might have approached that obtained in the clomipramine group, leaving a faster onset of improvement as the only benefit of clomipramine. However, this scenario remains speculative for several reasons: (1) a statistically significant effect of clomipramine was still present at the end of the trial (day 84) for defecation and the global score; (2) a higher number of responders was obtained in the clomipramine as compared to the placebo at day 84 for destruction and urination, suggesting that the lack of statistical significance of these parameters was only a function of insufficient power in the study; and (3) there was no consistent change in the number of responders in the clomipramine and placebo groups for the global score between days 56 and 84. Therefore, it remains untested whether the response with behavioural therapy alone would ever catch-up that obtained with the combination of clomipramine plus behavioural therapy.

For some parameters, a lower number of positive ratings were obtained in the clomipramine groups at day 84 as compared to day 56, giving the impression that the efficacy of the drug decreased during long-term treatment. However, this impression is misleading, at least for the standard clomipramine group. Furthermore, there is no evidence that dogs (or humans) become tolerant to clomipramine during long-term administration (Modigh, 1990; Trimble, 1990; Dodson, 1991). We found that the ratings of some dogs in all groups ''deteriorated'' during the study, i.e., obtained worse scores at one visit as compared to the previous time. There are many possible reasons for these results including the changes in the environment or reduced compliance with the behavioural therapy by the owners (especially if the dog's behaviour had initially improved). A total of 10 dogs receiving placebo ''deteriorated'' in the trial and a further three were withdrawn at day 28 due to the lack of efficacy. A similar number of dogs (11), receiving standard-dose clomipramine ''deteriorated'' in the study but none were withdrawn due to lack of efficacy. However, significantly more dogs were rated as improved at days 28 and 56 in the clomipramine group, and therefore, more animals were eligible to be rated as worse at days 56 and 84. Therefore, we conclude that the behaviour of relatively fewer dogs deteriorated during the trial with standard-dose clomipramine as compared to placebo. Interestingly, a high number of dogs (20) receiving the low dose of clomipramine ''deteriorated'' during the study trial and one was withdrawn due to lack of efficacy at day 28. It would be wrong to conclude that this dose of clomipramine was having negative effects, however, as the total number of dogs in this group responding was generally higher as compared to the placebo. However, the low dose of clomipramine cannot be recommended for clinical use to treat cases of separation anxiety as it produced no statistically significant improvement as compared to placebo, and the standard dose of clomipramine gave a clearly superior result.

The behavioural plan was designed to modify the dog–owner relationship, particularly the interactions that could be related to ''hyper-attachment''. The primary objective

of the trial was to test the efficacy of clomipramine and not to test the effectiveness of the behavioural plan, or its individual components, per se. Nevertheless, some information was obtained during the trial on the dog–owner relationship. One objective of recording these data was to check on the compliance of the behavioural plan. A fundamental point was that owners should not reprimand their dog for any destruction, defecation or urination produced in their absence: compliance with this part of the plan was reported to have been very good but we have no means to check that the owners reported this parameter correctly.

A second objective of the dog–owner questions was to determine the extent to which the ''hyper-attachment'' between the dog and the owner changed during the trial. The presence of ''hyper-attachment'' was an inclusion criterion for the trial and some of the investigators believe that breaking ''hyper-attachment'' is an integral part of the treatment of separation anxiety (Pageat, 1995). ''Hyper-attachment'' was assessed via two parameters, ''dog follows the owner around the house'' and ''dog initiates interactions with the owner''. The frequency of these parameters declined during the trial, indicating less attachment of the dog to its owner. However, the changes in hyper-attachment were the same in all three treatment groups although the progression of signs of separation anxiety differed significantly between groups. Furthermore, only reducing attachment with behavioural therapy did not produce optimal improvement of the signs of anxiety, at least during the time of the trial. The best control of the signs of separation anxiety was obtained when a combination of behavioural therapy and standard-dose clomipramine was employed. These results suggest that the relation between hyper-attachment and anxiety was not simple in our trial population of dogs. Further studies are needed to examine the relationship between ''hyper-attachment'' and separation anxiety, as our trial was not designed to test this point.

Clomipramine was well tolerated in most dogs. The adverse events encountered in the trial that could be attributed reliably to clomipramine were gastritis/vomiting and lethargy/sleepiness, but these were mild and transient in all cases. No dogs were withdrawn from the trial due to these side effects. One greyhound receiving the standard dose of clomipramine collapsed with hyperthermia and may have subsequently developed DIC. The dog recovered after the withdrawal of clomipramine and supportive treatment. The cause of this response is uncertain, but could have been an idiosyncratic reaction to clomipramine. However, there have been no other reports of collapse or DIC following clomipramine administration in dogs, either in the literature or during its first year of commercialization, and neither effects were observed following the administration of elevated doses (50 mg/kg, PO, q. 24 h) of the drug for 1 year to Beagle dogs (J.N. King, unpublished data).

There were a few cases of lethargy/sleepiness observed in dogs in all three treatment groups (low or standard-dose clomipramine as well as placebo). This side effect is noted in some humans receiving clomipramine, but it generally disappears after a few days (Simpson and Simpson, 1996). Results of a follow-up questionnaire made after the completion of the trial showed no adverse effects after abrupt termination of treatment with the standard dose of clomipramine and a low incidence of return of signs of separation anxiety (CLOCSA Group, unpublished data). Therefore, no special precautions appear necessary when stopping treatment with clomipramine.

Similar results to these, obtained in our trial were reported in a French study, which employed similar inclusion criteria and evaluation methods (Petit et al., 1999). However, a recent paper from the UK failed to demonstrate a clear benefit of clomipramine in cases of separation-related problems (Podberscek et al., 1999), although the inclusion criteria and behavioural therapy in that trial were different from our study. Furthermore, that study may not have had sufficient power to test reliably the effect of clomipramine, as there were significant differences between the groups at baseline and the trial involved a relatively small number of cases (Podberscek et al., 1999).

5. Conclusions

Clomipramine at a dosage of 1 to < 2 mg/kg, PO, q. 12 h produced significant improvement in the signs of separation anxiety as compared to placebo when used in combination with a programme of behavioural therapy, and may therefore be a useful aid in the treatment of this disorder.

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