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Veterinary Clinical Research Database for Homeopathy: Placebo-controlled trials

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Summary
Background: Veterinary homeopathy has led a somewhat shadowy existence since its first introduction. Only in the last three decades has the number of clinical trials increased considerably. This literature is generally not well perceived, which may be partly a consequence of the diffuse and somewhat inaccessible nature of some of the relevant research publications. The Veterinary Clinical Research Database for Homeopathy (VetCR) was launched in 2006 to provide information on existing clinical research in veterinary homeopathy and to facilitate the preparation of systematic reviews.
Objective: The aim of the present report is to provide an overview of this first database on clinical research in veterinary homeopathy, with a special focus on its content of placebo controlled clinical trials and summarising what is known about placebo effects in animals.
Results: In April 2012, the VetCR database contained 302 data records. Among these, 203 controlled trials were identified: 146 randomised and 57 non-randomised. In 97 of those 203 trials, the homeopathic medical intervention was compared to placebo.
Comment: A program of formal systematic reviews of peer-reviewed randomised controlled trials in veterinary homeopathy is now underway; detailed findings from the program's data extraction and appraisal approach, including the assessment of trial quality (risk of bias), will be reported in due course.

Introduction

Homeopathy was originally developed to treat human patients,[1] but already in 1815, the founder of homeopathy, Samuel Hahnemann, stated that animals most probably would also benefit from homeopathic treatment (cited in[2]). Further early contributions were made, for example, by Genzke (provings in animals), Günther (handbook on veterinary homeopathy) and von Bönninghausen (various case reports) in the middle of the 19th century.[3–7]

Despite its promising start in the 19th century (for an overview see[8,9]), veterinary homeopathy has led a somewhat shadowy existence since these first contributions. Only in the last three decades has the number of clinical trials increased considerably. This literature is generally not well perceived, which may be partly a consequence of the diffuse and somewhat inaccessible nature of some of the relevant research publications. The Veterinary Clinical Research Database for Homeopathy (VetCR,

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Table 1 Peer reviewed status of RCTs and NRCTs in veterinary homeopathy.

	# of records	# of trial records: placebo control	# of placebo controlled trial records in repeat publications	# of trial records: ''OTP''[a]	# of publications	Mean year of publication
Non-peer reviewed, non-randomised, controlled clinical trials	45	17	–	28	30	1994
Peer reviewed, non-randomised, controlled clinical trials	12	3	–	9	12	2005
(Sub totals of NRCTs)	(57)	(20)	–	(37)	(42)	(1997)
Non-peer reviewed, randomised, controlled clinical trials	92	47	10	45	78	1993
Peer reviewed, randomised, controlled clinical trials	54	30	3	24	48	1999
(Sub totals of RCTs)	(146)	(77)	(13)	(69)	(126)	(1995)
Sum	203	97[b]	13	106	168	
Δ (=unique placebo controlled trials)			84[c]			

[a] ''Other than placebo'' control.
[b] 17 of these trials include additional control groups besides the placebo group.
[c] See online Table 1.

http://www.carstens-stiftung.de/clinresvet/index.php) was launched in 2006 to provide information on existing clinical research in veterinary homeopathy and to facilitate the preparation of systematic reviews on the subject.[10]

Here we present an updated overview of the first database on clinical research in veterinary homeopathy with focus on its content of placebo-controlled clinical trials. We also summarise the knowledge on placebo effects in animals.

Materials and methods

Setup of database: Studies to be included in the VetCR database (http://www.carstens-stiftung.de/clinresvet/index.php) were identified by searching MEDLINE database (www.pubmed.org) and by analysing e-mail alerts of various journals with the keywords ''homeopathy'', ''homeopathic'', ''veterinary'' and ''clinical research''. Further publications were found by screening of dissertation abstracts, by citation tracking and hand-searching of complementary medicine journals. Besides observational studies and clinical trials, selected case reports and case series were included, but no basic research experiments were incorporated; the latter are the subject of the HomBRex database.[11]

For identification of controlled clinical trials in the VetCR database the search strategy was as follows: Design = ''randomised controlled clinical trial'' or ''controlled clinical trial''.

The peer review status of each relevant journal was identified by inspection of that journal's published information or its historical peer-review status was identified from The Serials Directory,[12] where its presence in the Peer Reviewed Index enabled its designation ''peer reviewed''. If no information on the peer reviewed status was available, journals were designated ''non-peer reviewed''. Books, abstracts, conference proceedings, theses/dissertations, newsletters, letters, reports and internet reports were automatically defined as ''non-peer reviewed''.

Results and discussion

In April 2012, the database contained 302 records. About half of the listed records were randomised, controlled clinical trials (RCTs: $n = 146$). In addition, 57 non-randomised, controlled clinical trials (NRCTs), 60 observational studies, 3 drug provings (or in modern terms, ''homeopathic pathogenetic trials''), 11 case series and 24 case reports were found. In one case, the study design was unknown (original publication not available). The 146 + 57 = 203 controlled trials are the subject of Table 1.

Each publication may contain multiple numbers of trials, resulting in more than one database record for the given publication. The 57 NRCTs were published in 42 different publications and the 146 RCTs in 126 different publications. The mean year of publication was 1997 and 1995 for NRCTs (peer reviewed and non-peer reviewed) and RCTs (peer reviewed and non-peer reviewed), respectively. Most of the listed publications ($n = 148$; 88%) were published in the last 30 years (Fig. 1), peaking between 2005 and 2009 ($n = 43$; 26%), irrespective of randomised ($n = 31$) or non-randomised design ($n = 12$).

Of the 57 NRCT records, 12 (21%) were published in peer reviewed journals (Table 1), whereas 37% ($n = 54$) of the 146 RCT records passed the process of peer review. Altogether, the number of non-peer reviewed publications was almost double the number of peer reviewed publications (108:60), but the proportion of peer reviewed publications (regardless of design) clearly increased in recent years (Fig. 2). The ratio of RCTs to NRCTs (roughly 3:1) has been rather stable in 5-year periods since 1975; there is no trend towards a higher percentage of RCTs (data not shown).

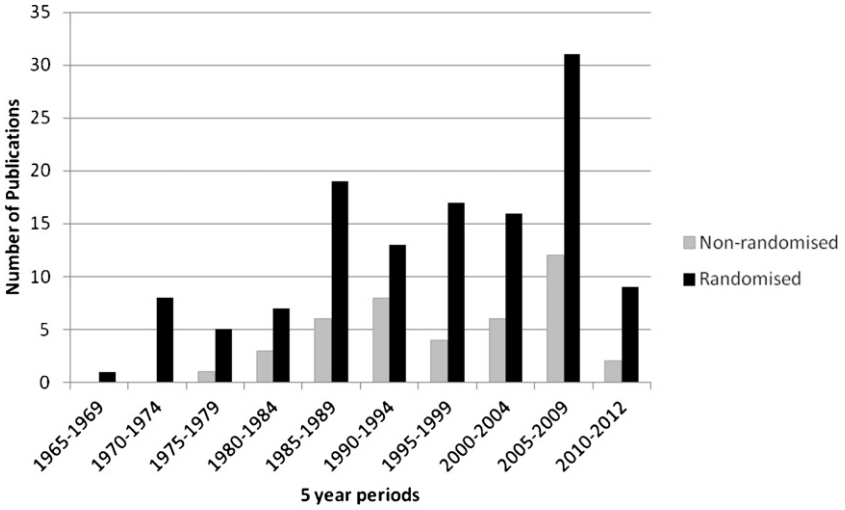

Figure 1 Absolute numbers of publications reporting on randomised (black, $n = 126$) and non-randomised (grey, $n = 42$) controlled clinical trials from 1965 to 2012. The last column only covers a 3-year period.

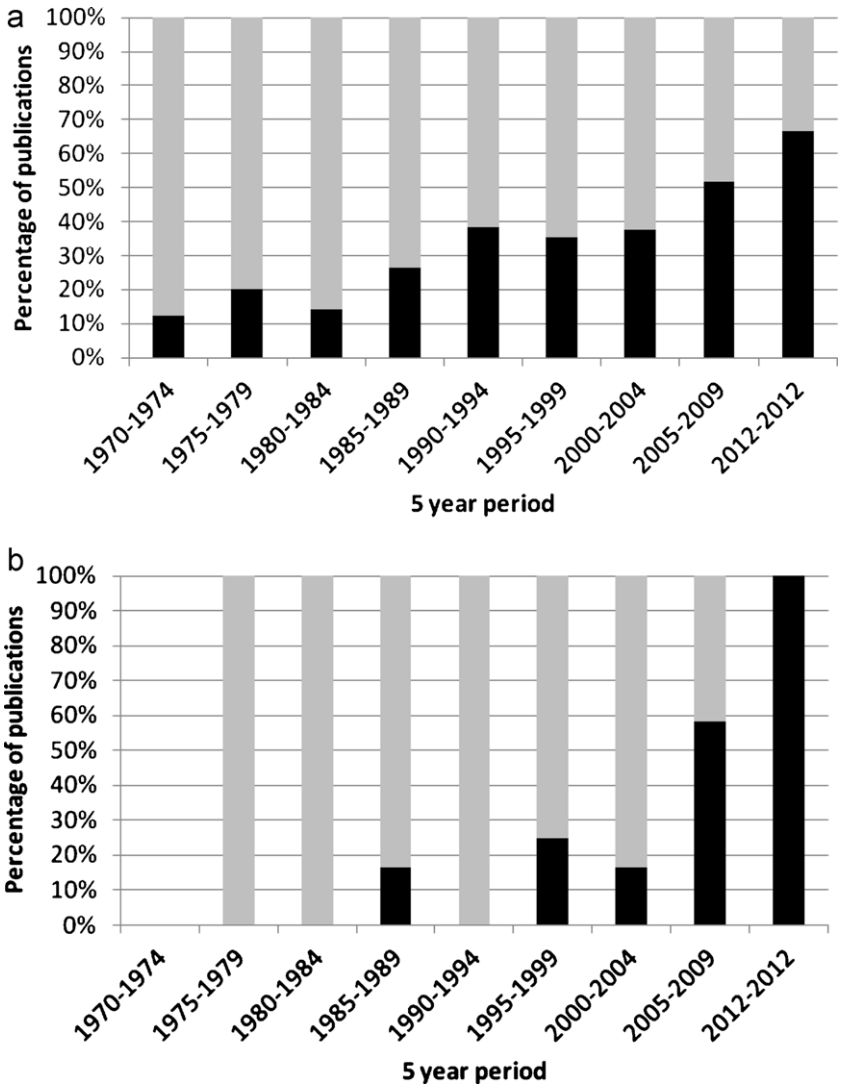

Figure 2 Percentage of peer reviewed publications (black) to non-peer reviewed publications (grey). (a) Randomised controlled clinical trials. Between 1965 and 1969, only one trial was published in a peer reviewed journal (data omitted for clarity). (b) Non-randomised controlled clinical trials.

Table 2 Disorders/outcomes in 84 unique placebo controlled trials.

Disorder/outcome	Cattle	Pig	Horse	Dog	Hare/rabbit	Sheep	Goat	Chicken	Fish	Guineafowl	Sum[a]
Mastitis	19										19
Postpartum disorders	11	2									13
Skin disorders			1	3	1						5
Diarrhoea	2	2	1								5
Infections	2	2		1							5
Musculoskeletal disorders			2	1							3
Behavioural disorders				3							3
Liver disorders			2								2
Gastroenteritis										1	1
Immunomodulation	2						1	1			4
Performance (reproduction)	7	2	2		5	2					18
Performance (growth/health)	4	5					1		1		11
Sum[a]	47	13	8	8	6	2	2	1	1	1	

[a] Some trials, more than one main outcome was investigated.

In NRCTs, homeopathy was tested against placebo-treated animals (Table 1; total = 20 records: 3 peer reviewed, 17 non-peer reviewed) or other controls than placebo (28 + 9 = 37 records).

In 47 of the non-peer reviewed RCTs, homeopathy was tested against placebo-treated animals (Table 1). In 45 trials, placebo was not the control. The main proportion of non-peer reviewed RCTs were theses ($n = 52$, 57%).

Thirty of the peer reviewed RCTs tested homeopathy against placebo-treated animals (Table 1). In 24 trials, placebo was not the control.

In total, placebo controls were almost equally applied in peer reviewed trials (3 + 30 = 33 records, 50%) and non-peer reviewed (17 + 47 = 64 records, 44%, Table 1) trials (total: 97 trials).

Of the 97 placebo controlled trials (see Table 1), 13 (=10 + 3) records were repeat publications (leaving 84 records of unique placebo controlled trials). In 44 of those 84 records (52%), authors reported at least one test where the effect of homeopathic treatment was significantly better than placebo treatment. However, this also included trials, where, for example, more than 80 tests were performed and only one test yielded a significant difference in favour of homeopathic treatment. Moreover, only a small number of those trials (fewer than 10%) accounted statistically for the problem of multiple testing. In addition, in some of those trials, placebo treatment yielded significantly better results than homeopathic treatment.

Ten different animal species and 12 different disorders/outcomes were investigated in the 84 unique records of placebo controlled trials (summarised in Table 2). Farm animals were more often investigated compared to companion animals. Cattle were the study subjects most often employed ($n = 43$), followed by pigs ($n = 12$) and dogs and horses ($n = 8$ each). Most trials investigated the benefit of homeopathic prophylaxis or treatment in mastitis control (19) and postpartum disorders (13). In addition, 29 trials investigated the effects of homeopathy application for performance improvement (health, growth, reproduction). A complete reference list of all 84 trials can be found in the online version at http://www.sciencedirect.com/ (online Table 1).

The quality of the 84 trials appears to be extremely diverse and a formal quality assessment is taking place within a program of systematic reviews of RCTs of veterinary homeopathy that involves two of the present authors.[13] In the course of this program, a full data extraction, including risk-of-bias assessment according to Cochrane standards (http://www.cochrane.org/), will be carried out.

Only six trials compared homeopathic treatment, placebo treatment and untreated animals at the same time (online Table 2; published in online version at http://www.sciencedirect.com/ as supplementary data). In five of six trials, no significant differences were found between homeopathic treatment and placebo treatment. In addition, few significant differences were found between homeopathic/placebo treatment on the one hand and the untreated individuals on the other hand, even if the tendency of the majority of test results was favourable for either homeopathic or placebo treatment. With only six trials, the VetCR database does not provide substantial information whether the treatment and/or context effect (homeopathic or placebo) is better than no treatment at all. However, some additional information on placebo effects in animals can be retrieved from the conventional veterinary and animal research literature and have been reviewed in 1999 by McMillan.[14] With respect to the classical concept of placebo, animals cannot discriminate between drug and food or *verum* and placebo and therefore have no expectation regarding recovery (provided they have not been conditioned — see below).[15] But with respect to modern concepts of the placebo effect or context effects,[16–18] various aspects have been reported to elicit a placebo response in animals.

Probably best known from Pavlov's dog experiments[19] is the phenomenon of classical conditioning.[18] Animals can recognise known people and circumstances and can recall learned cycles.[20] Recently it has been shown that exposure of rats to a drink of novel taste (conditioned stimulus) followed by an injection of the immune suppressor cyclosporine (unconditioned stimulus) is capable of priming

rats in such a way that subsequent sole exposure to the drink suppresses the immune system to the same or similar extent as another injection of cyclosporine. This is true after 3 days' break without conditioning procedure but also after 11 days; the effect has also been confirmed in humans.[21]

In addition, caring treatment (e.g. petting and gentle handling) can increase viability under stress, improve health, promote growth and increase productivity of animals.[22–27] It has been shown that a positive relationship between dairy cows and stockpersons correlates with improved udder health.[28] In this context, the intensive individual consultation in homeopathy is of importance.[29] Empathy/person effects can influence the heart rate and blood pressure of dogs depending on which attendant is entering the study room.[30,31] Similar effects have been reported in rabbits and horses and various other animals.[32] In addition, animals can respond to emotional states of humans[33] and the presence of an unafraid rat is capable of calming a fearful rat.[34]

Finally, the expectancy of owners may have substantial effects on the study outcome in such trials where the outcome is assessed by the owners of companion animals.[35–40] The same holds true for therapists if they are not completely blinded (therapist expectancy).[15,41]

In summary, placebo effects can have an impact on the outcome of veterinary studies, but if the study design is adapted accordingly, their influence can be minimised[29] (drug application via drinking water, no caring treatment, no owner assessment, complete blinding, allocation concealment and randomisation, adequate run-in and follow-up time).

Clinical research in veterinary homeopathy has some inherent disadvantages. The interview-based repertorisation is limited to objective parameters and interrogations of the animal owners. Only few drug provings in animals exist and few remedies are listed in a *Materia Medica* (e.g.[42]). In several cases, a human repertory (a collection of symptoms attained after drug provings) and *Materia Medica* are used to find the matching homeopathic remedy (*Similimum*), an approach that is questioned by some authors.[43–47]

However, clinical research in veterinary homeopathy also has some inherent advantages compared to clinical research in human homeopathy: The environmental conditions can be considered as rather stable and comparable for all patients when located in the same isolated pen, kennel, etc. It is easier, in principle, to acquire larger numbers of participants, at least of livestock animals, and to maintain blinding. Therefore, studies of veterinary homeopathy that account for the above mentioned adaptations of the study design may be more useful in investigating whether homeopathic remedies have specific effects over and above those of placebo.[29]

Conflict of interest statement

We declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ctim.2012.11.009.

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