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REVIEW

Comparison of veterinary drugs and veterinary homeopathy: Part 1

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Summary

We are all trying to understand our own age, and we rightly use the past to help us to do so. But we cannot gain this understanding unless we pay the past the respect it deserves. We must understand just how different it was (Moore 2010).

For many years after its invention around 1796, homeopathy was widely used in humans and later in animals. Over the intervening period (1796-2016) pharmacology emerged as a science from *Materia Medica* (medicinal materials) to become the mainstay of veterinary therapeutics. There remains today a much smaller, but significant, use of homeopathy by veterinary surgeons. Homeopathic products are sometimes administered when conventional drug therapies have not succeeded, but are also used as alternatives to scientifically based therapies and licensed products. The principles underlying the veterinary use of drug-based and homeopathic products are polar opposites; this provides the basis for comparison between them. This two-part review compares and contrasts the two treatment forms in respect of history, constituents, methods of preparation, known or postulated mechanisms underlying responses, legal basis for use and scientific credibility in the 21st century. Part 1 commences with a consideration of why therapeutic products actually work or appear to do so.

1 **Why medicinal products work or seem to work**

2 European Union (EU) terminology refers to medicinal substance-based
3 products. In this review these will be termed drug-based products. A drug
4 may be defined as a medicine or other substance which has a physiological
5 effect or acts on a pathophysiological process, when ingested or otherwise
6 introduced into the body. For drug-based products, clinical use is based on
7 established pharmacological actions and, in many cases, on established
8 molecular mechanisms. In this review, such conventional medicinal
9 products specifically exclude homeopathic products. A summary of the use
10 of homeopathic products in animals in the EU has been provided by the
11 European Council for Classical Homeopathy (2007). The EU definition
12 (Directive 2001/83/EC, as amended) of a homeopathic medicinal product is
13 “*any medicinal product prepared from substances called homeopathic stocks*
14 *in accordance with a homeopathic manufacturing procedure described by the*
15 *European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias*
16 *currently used officially in the Member States. A homeopathic medicinal*
17 *product may contain a number of principles”. For homeopathic medicinal*
18 *products, mechanisms of action are unknown (vide infra). Nevertheless,*
19 *there are several possible explanations as to why and how products in both*
20 *categories work or just appear to. They may possess genuine efficacy*
21 *(something actually happens) or ‘apparent efficacy’ (something is only*
22 *perceived to happen). In addition is ‘indirect or vicarious efficacy’. An*
23 *example is an owner, who wrongly perceives a behavioural problem in a dog,*
24 *and this triggers undesired behaviours in the dog. If treated, by a product of*
25 *either class, the owner might then cease triggering the negative behaviour*
26 *and the product, without direct action, receives credit for achieving a*
27 *positive outcome.*

28 **Coincidence**

29 Commonly, there is an understandable but regrettable reluctance to accept
30 that coincidence might be the explanation for a given observation. The fact
31 that many illnesses resolve, irrespective of treatment given, means that

32 resolution or improvement and treatment may simply be coincidental. If a
33 veterinarian gives a treatment and the animal gets better, there is a strong
34 cognitive bias (the *post hoc ergo propter hoc* bias, Rudolf 1938, Pinto 2001,
35 Gay 2006) to believe that the treatment is responsible, but this assumption
36 might be misplaced.

37 Any cure can be confounded by many factors, which render establishing a
38 causal relationship between treatment and cure difficult. Confounding
39 factors may mask an actual association or, more commonly, falsely indicate
40 an apparent association between treatment and outcome, when there is no
41 actual association (Skelly and others 2012). For every effect, we commonly
42 assume that there must be a specific cause, preferably the one favoured by
43 each of us individually. Factors to be considered, when assessing the
44 efficacy of *any* product, include: specific effects of the treatment, placebo
45 effect, bias in observers' assessment of patients' response to treatment, the
46 natural course of the disease, and effects of concurrent management of the
47 illness, as discussed below.

48 **Specific effect of the treatment**

49 If the treatment *is* actually effective, which efficacy may be underpinned by
50 many pre-clinical studies and manifest in controlled clinical trials, that is
51 called a specific effect. It is the active constituent(s) of the drug-based
52 product or, for a homeopathic product, the unknown mechanism, which
53 provides the claimed benefit. For a drug-based product, efficacy is achieved
54 if a sufficient number of molecules reach and persist at the site of action
55 (the biophase) for a sufficient period of time to act upon a
56 biochemical/physiological pathway. Alternatively, a drug may act on some
57 factor involved in a disease process; this would include a direct or indirect
58 action on a parasite or microorganism present in or on the body. Beyond
59 'working' (or not), the degree of efficacy, i.e. magnitude of response and the
60 establishment of dose-effect relationships, is pivotal to the demonstration of
61 efficacy for drug-based but not for homeopathic products.

62 **Placebo effect**

63 Placebo effects are the principal reason advanced by critics to explain
64 apparent homeopathic effects, and are part of the 'baseline' to which the
65 efficacy of any medication – conventional or homeopathic – is compared in
66 randomised controlled trials (e.g., Hektoen 2005, Shang and others 2005,
67 Kayne 2006 pp146-149, Teixeira and others 2010, Brien and others 2011,
68 Mathie and others 2012, Smith 2012, Vijayakumar 2012, Campbell 2013,
69 Mathie and Clausen 2014). A placebo is a medical intervention that has a
70 non-specific psychological or psychophysiological therapeutic effect and is
71 thus lacking any known specific effect for the condition treated (McMillan
72 1999), but products with specific efficacy can also produce placebo effects.
73 Placebo effects impact patients' perception of their symptoms far more than
74 they do the physiological and pathological processes of disease; any placebo
75 effects on these more objective aspects of disease are typically small in
76 magnitude and clinically irrelevant (Hróbjartsson and Gøtzsche 2010,
77 Wechsler and others 2011). The basis of the placebo effect in humans is
78 experiencing a beneficial effect, arising from belief in the treatment, and
79 based partly on confidence derived from consultations, leading to
80 expectations on the part of the patient. In addition, there may be
81 behavioural conditioning (Enck and others 2013). Mechanisms underlying
82 the placebo effect are still poorly understood; they might be multiple and
83 indeed might differ from circumstance to circumstance. A veterinary
84 example is the display of separation-related behaviour in dogs, for which a
85 conditioned placebo effect, suppressing signs of distress, was demonstrated
86 (Sümegi and others 2014). It is clear that the placebo effect can and
87 sometimes does operate for both homeopathic and drug therapies. Even if
88 the mechanism(s) are obscure, the accepted view is that (in human
89 medicine) a half to one-hour chat with a sympathetic and convincing
90 homeopath can yield positive outcomes; all the collateral benefits of old-
91 fashioned, reassuring, paternalistic medicine. This will be especially true
92 where mind-over-matter considerations are pre-eminent to outcome. In
93 Bavaria, it was reported that 88% of GPs sent human patients home with
94 prescriptions for placebo drugs, the corresponding figure for the whole of
95 Germany being 50% (Jutte and others 2011; Kupferschmidt 2011).

96 In veterinary medicine, it is less easy to conceive if and how an animal
97 can distinguish mentally between a homeopathic and drug-based product, if
98 both are identical in presentation and similarly administered. For the huge
99 majority of medical conditions, a placebo effect seems to be unlikely and
100 counterintuitive, insofar as an animal cannot normally be expected to have
101 such cognitive capacities as expectations regarding recovery or healing. The
102 placebo component of the effect of a homeopathic veterinary product is
103 presumably limited normally to the judgement of outcome, based on the
104 subjective evaluation of the caregiver (veterinarian or animal owner)
105 (Conzemius and Evans 2012; Talbot and others 2013). As in human
106 medicine, a sympathetic veterinarian might provide the basis for placebo-
107 induced benefit in the owner, for both drug-based and homeopathic
108 products. The problem then is that the veterinarian and/or animal owner
109 believes (wholly sincerely) that a beneficial response has occurred, but the
110 animal may continue to suffer. Nevertheless, the potential beneficial effect of
111 human contact on the health and physiological state of animals can be real
112 (Mills and Cracknell 2013). In daily practice, this non-specific treatment
113 effect may be especially important whereas, in a randomised controlled
114 clinical trial, it will be randomly distributed between the treatment and
115 control groups and of lesser importance in animal than in human studies.

116 Insofar as placebo effects occur in animals, for both drug-based and
117 homeopathic products, explanatory theories have been based on: classical
118 conditioning [as recognised by Pavlov in his dogs responding to a saline
119 injection as if it were morphine (Pavlov 1927); cognitive expectancy; and
120 release of endogenous opioids (McMillan 1999; Mills and Cracknell 2013).
121 For further discussion on each of these aspects see Hektoen (2005). For in
122 depth discussion on the placebo effect, see also Meissner and others (2011).
123 In many instances, the placebo effect has been shown to work through
124 recognised physiological/biochemical pathways and encompassing both
125 central and peripheral nervous systems. Enck and others (2013) discuss
126 physiological pathways in placebo analgesia, involving the descending pain

127 modulatory network, and conditioned corticosteroid effects in patients with
128 psoriasis.

129 **Bias in observers' assessment of patients' response to treatment**

130 Doctors or veterinarians sometimes judge that a treatment has had an effect
131 on a patient when, in fact, it has not. There are many examples in medical
132 history of treatments that were thought to be beneficial, but were later
133 proven to be ineffective or even harmful; well-known examples include
134 blood-letting, use of anti-arrhythmics after ischaemic heart disease,
135 hormone replacement therapy to prevent ischaemic heart disease in post-
136 menopausal women, and radical mastectomy rather than more limited
137 surgery for breast cancer (Prasad and Cifu 2015). Medical professionals are
138 naturally inclined to believe that, if a patient improves after a treatment has
139 been given, the improvement must have been a result of that treatment (*post*
140 *hoc ergo propter hoc* bias). This is one example of many cognitive biases that
141 can result in incorrect interpretation of the patient's response to treatment
142 (Rudolf, 1938, Croskerry 2003, Gay 2006, Kahneman 2012, McKenzie 2014,
143 Matute and others 2015, Canfield and others 2016).

144 **Other factors impacting on assessment of treatment efficacy**

145 ***Non-specific healing effects***

146 In addition to placebo effects and observers' bias, other non-specific healing
147 effects, regression to the mean (RTM) and the natural course of disease may
148 all impact on efficacy, perceived or real. As discussed by Hektoen (2005),
149 Mills and Cracknell (2013) and Talbot and others (2013), the elements
150 potentially involved in the total effect of any treatment are: specific
151 treatment effects statistically demonstrated in clinical trials; non-specific
152 effects of treatment (such as the placebo effect); natural resolution of the
153 signs of disease or deranged condition, including self-healing; RTM;
154 concomitant support for treatments e.g. nursing, reduced body weight etc.
155 and combinations of these factors. RTM was first identified by (Galton 1886)
156 and has been discussed more recently by Morton and Torgerson (2003;

157 2005). In a well-designed randomised controlled trial (*vide infra*), all the
158 factors listed, except the specific treatment effect, should be evenly
159 distributed between treatment groups. Thus, the improvement in the
160 placebo group is the sum of factors such as non-specific treatment effects,
161 natural history of the disease, RTM, effects of concurrent nursing etc. These
162 clearly must be non-specific effects, because no treatment with a specific
163 effect was given to the placebo group. In the case of a veterinarian treating
164 an individual patient, in many cases it is not possible to differentiate
165 between non-specific effects and any specific effect of the treatment. For the
166 individual clinical veterinarian treating the individual animal, all of these
167 mechanisms may be operative, often resulting in treatments appearing to be
168 effective when, in fact, they are not.

169 ***Concurrent management of patients***

170 Many medical treatments are associated with additional changes in
171 management of the patient, e.g. nursing, rest, change of diet and treatment
172 with other drugs. Many of these factors can lead to improvements in the
173 disease that may be mis-attributed to the treatment being evaluated. For
174 example, an obese dog given a medical treatment for osteoarthritis and also
175 put on a weight-loss diet may have reduced clinical signs, because of weight
176 loss rather than the medical treatment.

177 ***The natural history of disease***

178 Many diseases have a natural history, leading to mortality or morbidity or,
179 more hopefully, partial or complete restoration of health. As Voltaire said,
180 “*the art of medicine consists in amusing the patient while nature cures the*
181 *disease*”. RTM comprises the natural fluctuation of variables around a
182 mean, and its impact can be considered by way of example. A dog with
183 osteoarthritis shows signs of reduced movement, joint stiffness, pain etc.
184 The owner seeks veterinary advice, a medication is prescribed and the dog
185 shows improvement. If, even in the absence of treatment the signs wax and
186 wane (as may well occur in the osteoarthritic dog) owner and veterinarian
187 understandably, but in part or in whole wrongly, may attribute the benefit

188 to the administered product. Talbot and others (2013) discussed this
189 problem in relation to a feed supplement used in head shaking horses, a
190 condition well known for its intermittency. RTM may occur in an individual
191 animal (as in the example cited above) or group phenomenon and in both
192 cases the observed increase or decrease may be mistakenly attributed to a
193 specific treatment effect (Morton and Torgerson 2005).

194 ***The body's natural healing mechanisms (and their interaction with***
195 ***efficacious medicines)***

196 The natural defence mechanisms of the body in microbial and other diseases
197 can prove highly effective in providing a clinical cure or, better still, a
198 microbiological cure (the gold standard). In microbial disease, the
199 administered drug acts in concert with many immune-based mechanisms,
200 notably the scavenging action of white blood cells, working to defeat the
201 invading pathogen. Drusano and others (2010) calculated that, if
202 antimicrobial therapy drives the bacterial (*Staphylococcus aureus*)
203 population down to between 10^2 and 10^3 colony forming units/g, it is highly
204 likely that the residual population will be eradicated by the immune system
205 and, moreover, achieved with minimal amplification of resistant mutants.

206 In veterinary medicine, the use of antimicrobial drugs in prophylaxis (now
207 under challenge within the EU) is deemed to give the immune-based
208 pathways invaluable support. In metaphylactic use (sometimes referred to
209 as mass medication) drugs are administered collectively to animals, in which
210 the bacterial population exceeds the capacity of the natural defences to work
211 without support. In therapy, especially in the presence of immune
212 deficiencies and heavy bacterial loads, the prudent use of antimicrobial
213 drugs in animals is essential to welfare through restoration of health. Their
214 actions may be attributable to: direct killing; reduced pathogen
215 pathogenicity; enhancement of host immune pathways.

216 With other deviations from normal ranges, the body has the ability,
217 through biochemical, physiological and endocrinological pathways, to
218 restore systems to the normal; this is the homeostasis of the body. These

219 systems are finely balanced and usually integrated, so that for example
220 there is a tonic influence of sympathetic nerves to arterioles to keep them in
221 a state of partial constriction. The same arterioles are under an opposing
222 tonic vasodilator effect of the nitric oxide system. The system can fail,
223 arterial blood pressure may rise and the resulting hypertension may require
224 the attention of a suitable drug. Thus, the homeostatic pathways may be
225 sub-optimal in a hypertensive cat, but they are most likely to be still
226 operational and the pharmacological agent may play only a minor but
227 essential role in assisting the body to restore homeostatic balance.

228 Likewise, there are innumerable integrated systems, keeping within
229 normal ranges blood glucose, blood cell counts etc. Drugs which act on
230 neural, physiological and endocrinological pathways are generally working
231 in concert with the body's enzymes, neurotransmitters, hormones etc. and,
232 even in the presence of a drug or homeopathically energised water, it may be
233 that it is the homeostasis which plays the dominant and even the sole role.
234 There will be many other circumstances, when the drug is required not to
235 work in concert with but to combat a deranged physiological system; if
236 sympathetic vasoconstrictor drive to arterioles is increased, the drug is
237 needed to correct that. Many other drugs are used to counter natural
238 physiological processes, for example anaesthetics, whilst others suppress a
239 natural and useful but unwelcome process, such as inflammation.

240 In summary, placebo effects are those beneficial effects arising from use of
241 a treatment that are not due to the properties of the treatment itself, and
242 therefore must arise from cognitive processes such as belief and
243 expectation.

244 However, placebo effects are only one of many non-specific factors that can
245 give rise to an improvement from treatment. As discussed above, other non-
246 specific effects, that do not arise from the treatment at all, include RTM,
247 other coincidental improvement, effects of concurrent nursing or change of
248 diet, etc. Additional factors can cause perceived but not real improvement,
249 e.g., observer bias and selection bias. All these non-specific effects may
250 occur together, and between them give rise to the improvement seen in the

251 placebo-control group in a randomised controlled trial, i.e. to the
252 improvement that is not due to the specific effect of the treatment. Because
253 all these non-specific effects occur in the placebo-control group, they are
254 sometimes referred to as 'placebo effects' although strictly, this is an error of
255 terminology because true placebo effects are only one contributor to the
256 totality of non-specific effects. In animals, with far less ability to experience
257 beliefs and expectations about the healing effects of treatments, true placebo
258 effects will contribute much less to the non-specific effects than in humans.

259

260 **History**

261 **Homeopathy**

262 The history of homeopathy has been covered elsewhere (e.g., Bellavite and
263 others 2005, Kayne 2006 pp39-58, Loudon 2006, Cook 2008, Campbell
264 2013). Briefly, the fundamental principle of homeopathy, that “like cures
265 like”, was proposed, in 1796, by Samuel Hahnemann (1755-1843), as an
266 alternative to other therapies then in use; primarily herbalism, bleeding,
267 purging, emesis, blistering, sweating (Porter 1997, Wootton 2006). By 1814,
268 Hahnemann was using highly-diluted homeopathic remedies similar to
269 those used by homeopaths today (Hahnemann 1814). Prior to inventing
270 homeopathy, Hahnemann qualified as a doctor, worked as a conventional
271 physician, then as a translator of scientific articles and as a writer. He also
272 studied chemistry. He translated a conventional *Materia Medica* (by William
273 Cullen, 1710-1790) into his native German and found it to be lacking. In its
274 place, he devised and advocated the principles of homeopathy.

275 Homeopathic remedies are based on three central tenets, The Law of
276 Similars (*similia similibus curantur*), The Law of Infinitesimals and The Law of
277 Succussion, each arising from the writings of Hahnemann, in particular his
278 ‘Organon of Medicine’ (Hahnemann 2002). According to The Law of Similars,
279 signs and symptoms can be cured by substances that can cause those signs
280 and symptoms in healthy individuals (Hahneman 2002, Kayne 2006, Owen

281 2015a,b,c). The naming of homeopathic products is usually in Latin, where
282 applicable. Remedies are listed in homeopathic *Materia Medica* (e.g.,
283 Hahnemann 1814, Boericke 2008, several others available at various
284 Internet sites, e.g., International Academy of Classical Homeopathy 2016),
285 together with the signs and symptoms the remedy is thought to be effective
286 for (Lilley 2008). Homeopaths also use repertories, which list signs and
287 symptoms, and for each give the remedies thought to be effective for that
288 sign or symptom (e.g., Boericke 2008). For example, insomnia can be
289 treated by the coffee bean remedy, *Coffea cruda* (Boericke 2008) – coffee
290 contains the CNS stimulants caffeine and theophylline – or a common cold
291 can be treated by the onion remedy *Allium cepa* (Boericke 2008) – onions
292 make the eyes water. For Hahnemann, as for conventional medical doctors
293 in the late 18th century, working before the advent of science and modern
294 medicine, the human body was a black box; a medicine goes in and the
295 effects (any change in symptoms) come out, there being no knowledge of or
296 much interest in “the in between”. How the products of either category
297 worked was unknown and inconsequential.

298 Various forms of like-cures-like concept were present in medical writings
299 long predating Hahnemann, e.g., Hippocrates in the 4th century BC and
300 Paracelsus in the 16th century (Kayne 2006 p47) and the general concept
301 was present among medics in the late 18th century. The Rev. Edward Stone
302 of Chipping Norton described in 1795 (one year ahead of Hahnemann) the
303 treatment of agues by the willow (bark and leaves) noting, “*as this tree*
304 *delights in a moist or wet soil, where agues (fever) chiefly abounds the general*
305 *maxim that many natural remedies carry their cures along with them or that*
306 *remedies lie not far from their causes was so very apposite to this particular*
307 *case that I could not help applying it”* (Wood 2015). We now know that, in this
308 case, there is a conventional pharmacological explanation; the willow
309 contains the glycoside salicin which has anti-inflammatory and antipyretic
310 effects. With advances in chemistry, this led in 1865 to the first synthetic
311 analgesic drug of the non-steroidal anti-inflammatory (NSAID) class,
312 salicylate; this then led in 1895 to acetylated salicylate, aspirin, followed by

313 a plethora of drugs of the NSAID category. However, as a general principle,
314 the like-cures-like concept is arbitrary and has no general credibility,
315 notwithstanding its apparent but superficial symmetry. The general concept
316 of 'like cures like' is a textbook example of sympathetic magic, as practiced
317 by many cultures over the millennia (Fraser 1922).

318 Stone's 'like cures like' is of a qualitatively different type to that of
319 homeopathy. In the Stone example the property of the substance used to
320 treat a disease that is "like" the disease is some observable physical
321 attribute of the substance - in the case of the willow, it grows in damp
322 places, and - in the thinking of the time - diseases tend to occur in damp
323 places. This is a different 'like cures like' concept to homeopathy, in which
324 the property of the substance used to treat a disease that is "like" the
325 disease is the 'symptom picture' induced in healthy volunteers by ingestion
326 of the substance (in the early years of homeopathy) or by ingestion of a
327 remedy made from the substance (for much of the history of homeopathy).

328 Thus, the fundamental principle of homeopathy is that something that
329 induces specific signs and symptoms will also cure the same signs and
330 symptoms. For veterinary medicine, we should note that animals do not
331 have symptoms; symptoms are what humans report (headache, bellyache,
332 disorientation) whilst signs are what we can observe and sometimes
333 measure (rise in body temperature, tachycardia). Therefore, humans can
334 have both symptoms and signs and non-human animals show only signs;
335 the symptoms are known only to the individual animals.

336 Hahnemann's second law, the Law of Infinitesimals challenges the
337 scientifically based principles of biochemistry, physiology, endocrinology and
338 pharmacology, of more molecules producing greater responses; the classical
339 concentration/dose-response relationships (see part 2 of this review; Lees
340 and others 2017). In complete contrast, Hahnemann's second Law states
341 that greater responses are achieved with less, over a huge range of dilutions.
342 With repeated dilutions in (usually) water or alcohol, potency increases. A
343 starting solution (called the "mother tincture") of the 'active' is diluted either

344 1:10 (decimal) or 1:100 (centesimal), then that diluted solution is again
345 diluted by the same degree, and the process continued (Kayne 2006 pp92-
346 100, Kayne 2008). The degree of dilution of a remedy is referred to as its
347 'potency' – a 6c potency remedy has been diluted 1:100 six times (therefore,
348 10^{-12} dilution) and an 8x potency remedy has been diluted 1:10 eight times
349 (10^{-8} dilution). Homeopathic products are provided over a wide range of
350 'potencies'; in the UK 6c, 12c, 30c and 200c seem to be the most commonly
351 used, but homeopaths' preference varies, apparently arbitrarily, from
352 country to country (Kayne 2006 p126). Most over-the-counter homeopathic
353 remedies are 30c.

354 The number of molecules of the 'active' decreases rapidly with dilution
355 and, as implied by Avogadro's number, 6×10^{23} , beyond 12c (a dilution of
356 1×10^{-24}) there is unlikely to be even one molecule of the starting substance
357 present in the remedy (Vickers and Zollman 1999). At 12c dilution of a mole
358 of starting substance, there is a 60.2% chance of one molecule remaining. At
359 30c (10^{-60} dilution), to have one molecule of 'active' remaining would require
360 a mass of water molecules of 2.99×10^{34} kg, more than 15,000 times the
361 mass of the Sun of 1.99×10^{30} kg (Grimes 2012). It is estimated that there are
362 approximately 10^{80} particles in our universe – 10^{80} corresponds to 40c
363 dilution.

364 Succussion is the basis of the third Law. It is a specific type of vigorous
365 shaking or tapping at each dilutional stage (Kayne 2006 pp92-100, Kayne
366 2008); this agitation is believed to "potentise" or "dynamise" the remedy, and
367 is what causes the claimed healing power to not only pass from the less
368 diluted stage to the more diluted stage, but to become more potent as it does
369 so. Hahnemann believed that he had made a breakthrough discovery, whilst
370 transporting his products in a horse drawn carriage. On the basis of
371 uncontrolled observations, he judged that the vigorous shaking this involved
372 increased the potency of his remedies even further beyond the dilution
373 effect. Another equine contribution to homeopathy came in the form of his
374 bespoke striking board used for succussion, constructed by a saddlemaker,
375 with leather on one side and stuffed with horsehair.

376 The preparation of homeopathic products today, as historically, involves
377 shaking or tapping at each dilutional stage. A usual procedure is to strike or
378 whack the container between 10 and 50 times against an elastic object.
379 According to Peter Fisher's (homeopath and Clinical Director and Director of
380 Research at the Royal London Hospital for Integrative Medicine) evidence to
381 the UK House of Commons Science and Technology Committee (2010) "*you*
382 *have to shake it vigorously.... if you just stir it gently, it does not work*";
383 shaken not stirred. Repeated dilution and succussion achieves
384 "potentisation" such that the healing power – the unidentified curative
385 property – imparted to the remedy by the starting substance is retained
386 (indeed increased with each shaking) by the water molecules. As
387 Hahnemann wrote, the whacking procedure releases "*dynamic forces from*
388 *the diluents which were preserved and intensified with subsequent dilutions*".
389 The nature of these "dynamic forces" is not known; like Hahnemann (2002)
390 himself, many contemporary homeopaths refer to them using terms such as
391 'vital force' or 'life energy', as used in homeopathy texts (e.g., Kayne 2006
392 p149-153, Nicolai 2008, Owen 2015d), and apparent from internet searches
393 for these terms with 'homeopathy'. These terms emphasise the mystical,
394 vitalist nature of the belief system underlying homeopathic practice. The
395 mechanisms by which homeopathic remedies effect improvements in signs
396 or symptoms is not known, but homeopaths often refer to their remedies
397 'balancing' unspecified 'energies' in the body, or correcting a disturbance of
398 the body's 'vital force' (e.g., Bell and others 2004, Kayne 2006 pp149-162).
399 However, the nature of these energies is likewise not known and their
400 existence is unproven. They appear not to be detectable grossly, e.g. by sight
401 or touch, or by radiography, scintigraphy, ultrasound or CT or MRI scans.
402 All three Laws of homeopathy – Similaris, Infinitesimals and Succussion –
403 are arbitrary, having been invented by Hahnemann, but never demonstrated
404 to have a physical basis. Homeopaths often speculate that modern scientific
405 concepts such as electromagnetism or quantum effects (see Kayne 2006
406 pp300-306) might underlie the claimed efficacy of their remedies, and
407 frequently refer to the 'vital force' and the action of their remedies in terms

408 of ‘vibrations’ and ‘resonances’ (e.g., Kayne 2006 pp149-153). Thus,
409 homeopathy is pseudoscientific.

410 **Pharmacology**

411 The history of pharmacology spans less than 200 years. It derived from
412 *Materia Medica*, which was practised for at least two millennia up to the late
413 19th/early 20th centuries. Early practitioners were Hippocrates and Galen. In
414 the first known pharmacopoeia, the physician Pedanius Dioscorides wrote,
415 in the first century BC, “*the leaves of the willow being beaten small and*
416 *drank with a little pepper and wine do help such as are troubled with the Iliaco*
417 *Passio (colic). The decoction of the leaves and bark is an excellent fomentation*
418 *for the gout*”. His *De Materia Medica*, was in continual used for more than
419 1,500 years.

420 Writing around the time of Hahnemann (mid 18th century) Voltaire
421 described pharmacology as “*the pouring of drugs of which one knows nothing*
422 *into a patient of whom one knows less*”.

423 **EVOLUTION OF THINKING 1796-2016**

424 In 1796, the year of revelation to Hahnemann, there was, for both human
425 and to a lesser degree for veterinary medicine, *Materia Medica* (the use of
426 plant parts or their extracts), blistering, bleeding, purging, sweating and
427 emesis as the main bases for treatment, together with surgery, which in
428 many cases was savage butchery. The skilled surgeon’s greatest asset was
429 speed rather than quality. Medical treatment was largely based on the
430 concept of balancing the four humours, and bloodletting was the primary
431 treatment (Porter 1997, Wootton 2006).

432 Human doctors not only practised but prided themselves in these
433 procedures. 1780 to 1850 has been described as the period of “heroic
434 medicine”. A popular ditty of the day was penned by John Coakley Lettsome
435 (1744-1815) founder and President of the Medical Society of London (and a
436 leading campaigner for abolition of the slave trade) “*I, John Lettsome,*
437 *blisters, bleeds and sweats ‘em; if, after that, they please to die; I John*

438 *Lettsome*" (Scott and Scott 2008). Perhaps the initial success of homeopathy
439 was due to the fact that it obeyed Hippocrates' first principle of treatment:
440 above all do no harm, giving it, over of the conventional medicine of the time,
441 a better risk:benefit ratio.

442 If the reaction of Hahnemann to these medical practices was derision or
443 despair, one can only, with the benefit of hindsight, sympathise. Now, these
444 barbaric procedures have been swept away, in a tsunami of curiosity,
445 observation, trial and error, experiment and serendipity (the bases of the
446 scientific method), facilitated by the advances in knowledge first of
447 chemistry, then biochemistry/physiology, then cell and molecular biology,
448 all dependent on increasingly sophisticated measuring and analytical
449 techniques. It is true that throughout the 19th century quacks continued to
450 peddle quack medicines, but the ascendancy of the scientific method had
451 largely put paid to the practice of quackery by doctors by the first quarter of
452 the 20th century, as opposed to the practice of quackery by non-medical
453 persons, which continues apace.

454 On the veterinary scene, James White (1816) of Exeter, was way ahead of
455 his time when he wrote; "*within these few years only, has the Veterinary Art
456 acquired a distinct appellation, and a solid foundation in this country. Receipts
457 handed down by traditionary skill, in which ingredients were accumulated
458 without judgment or discrimination, constituted the principles and practice of
459 what was termed Farriery... It is only since the institution of the [London]
460 Veterinary College, that the anatomy and physiology of the horse have been
461 properly investigated, and the effects of medicines on his body correctly
462 ascertained, by numerous and appropriate experiments, both in health and
463 disease; so that a secure foundation is now laid; and, as long as scientific men
464 continue to study and practise the veterinary art, it must necessarily be in a
465 progressive state of improvement*".

466 The quack medicines of earlier centuries were largely based on spurious
467 or unsubstantiated *Materia Medica* products. Now, almost nothing remains
468 in 21st century therapeutics, except for some fine examples of the active

469 constituents of *Materia Medica* remedies; we have quinidine, quinine,
470 morphine, atropine, digitalis glycosides, d-tubocurarine and, derived from
471 the willow, salicylate and its successors. We still have major therapeutic
472 uses for the extracted chemicals of plants, but as drugs in 99% plus purity
473 form. Now, therefore, we have better control of the dose, lesser likelihood of
474 overdose and less opportunity for unwanted effects from the other
475 constituents/adulterants of the plants or their extracts. And, of course, we
476 have over the last 75 years, the example of the magic bullets (penicillin,
477 streptomycin, tetracycline and their derivatives and successors) isolated
478 from soil dwelling microorganisms or produced semi-synthetically or
479 synthetically in the laboratory.

480 The steady development of conventional therapeutics has been an on-
481 going, often unplanned process, proceeding by an incremental, bottom up
482 evolution. It began with the ideas of the Enlightenment. Charles Darwin,
483 Claude Bernard (an early advocate of evidence based medicine [Morabia
484 2006]), Louis Pasteur and Robert Koch were children of The Enlightenment
485 and we are its great, great grandchildren. Johnson (2010) has written that
486 both biological and technological developments comprise a “*gradual but*
487 *relentless probing of the adjacent possible, each new innovation opening up*
488 *new paths to explore*”. As scientific method was refined, and new
489 technologies developed, more was learned about chemistry, biology,
490 physiology, biochemistry, microbiology and pathology, allowing the rational
491 development of treatments. Moreover, in the 20th century medical science
492 developed the randomised controlled clinical trial, allowing the objective
493 testing of novel treatments.

494 In contrast, homeopathy was invented by one man, living at a time of
495 minimal scientific understanding of biology and pathology. It has remained
496 essentially unchanged. Whilst there may now be many more homeopathic
497 remedies, the underlying concepts and philosophy, and the methods of
498 preparation (huge dilutions, succussion etc.), are essentially the same; the
499 Laws are inviolate. Thus, an assumption underlying homeopathy is that
500 disease signs are an expression of a disturbed vital force, affecting the whole

501 organism and the treatment is intended to restore the ‘energetic balance’ of
502 the individual (Bell and others 2004, Kayne 2006, Nicolai 2008, Owen
503 2015d). The actual mechanisms remain obscure, implausible for most
504 people and incompatible with scientific knowledge accumulated over the last
505 two centuries.

506 The belief system of homeopaths is vitalist in that it posits that the
507 phenomena of life are dependent on a force or principle distinct from purely
508 chemical or physical forces - there is something “special” about living tissue,
509 above and beyond its content of atoms and molecules. Vitalism is a
510 discredited scientific hypothesis that Ridley (2015) describes as a
511 superstition in headlong retreat. Vitalism underlies most traditional healing
512 practices, and the Hippocratic ‘four humours’ tradition that dominated
513 Western medicine until disproven by modern science. The superstition of
514 vitalism was dealt its death blows by the advances in pharmacological,
515 biochemical, cellular and molecular biologies, not least by the discovery that
516 “the secret of life” turned out to be an infinitely combinatorial message,
517 written in digital form in three-letter words in a four-letter alphabet. This
518 beautiful discovery is inconsistent with the concept of a ‘vital force’. From
519 psychology, superstitious adults tend to explain biological processes in
520 terms of vitalist causality and energy transmission, and such conceptual
521 confusions are associated with belief in alternative medicine (Lindeman &
522 Saher 2007), which is itself associated with intuitive rather than rational
523 thinking styles (Saher and Lindeman 2005) and belief in other supernatural
524 and paranormal phenomena (Grimmer and White 1990, Saher and
525 Lindeman 2005).

526 In the words of Hahnemann, diseases “*are solely spirit-like (dynamic)*
527 *derangements of the spirit-like power (the vital principle) that animates the*
528 *human body*”. We put the question, does a spirit-like power animate animal
529 bodies too? Contemporary homeopaths still refer to spiritual aspects along
530 with ‘life energy’ or ‘vital force’ when discussing the actions of their remedies
531 (e.g., Kayne 2006 pp151). It is clear that the gulf between homeopaths and
532 the great majority of human and animal doctors is not simply one of how-to-

533 compare using common standards (McKenzie 2012). It is a gulf of mind-set,
534 between the give-me-proof-positive and a proven or plausible mechanism of
535 action of the latter, and the mystical, superstitious beliefs of the former.

536 Whilst homeopaths are vitalists, their belief system spreads more widely.
537 Homeopathic practice implies the belief that there is some property – an
538 ‘essence’ – in each of the substances or objects they make their remedies
539 from; it is that essence which gives rise, via potentisation (dilution,
540 succussion, etc.), to the specific curative properties of the remedy. There
541 are thousands of remedies, each with specific properties, i.e., they treat only
542 certain signs or symptoms or patients and not others, and seemingly no
543 limit to what substances or objects remedies can be made from (*vide infra*)
544 Hence, presumably every substance or object contains an essence. The
545 belief that inanimate substances and objects as well as animate objects
546 such as plants and animals have an essence (especially if that is construed
547 as a ‘vital force’) places homeopathy in the mystical tradition of animism –
548 the belief in a supernatural power that pervades, and can influence, the
549 material universe. Moreover, the essence is beneficial for humans – indeed,
550 potentiating remedies for the treatment of ill humans and animals seems to
551 be the only identified function or use for the essence. Hence, homeopathic
552 beliefs are also “anthropocentric” – believing that the universe, with this
553 essence existing in every substance or object, exists as it does for the benefit
554 of humans. These vitalistic, animistic, anthropocentric beliefs are part of
555 the mystical and magical belief systems universal to human cultures
556 throughout history.

557

558 **CONSTITUENTS**

559 **Homeopathic products**

560 Contemporary homeopaths follow Hahnemann’s example of listing, in
561 *Materia Medica*, their remedies together with the ‘symptom picture’ for each
562 and dosage information (Lilley 2008). The symptom picture is established

563 primarily by means of “provings” or “pathogenetic trials” (*vide infra*) and
564 partly by observations of clinical responses to a remedy, and indicates which
565 signs or symptoms the remedy can be used to treat in a patient (Belon 1995,
566 Kayne 2006 pp51-53, Campbell 2013, Sherr 2015). For homeopathic
567 products in humans, the proving involves a group of several volunteers or
568 just one person. Each imbibes a number of doses of the remedy being
569 ‘proved’, with contemporary provings typically using remedies diluted
570 beyond the Avogadro limit. Each volunteer keeps a diary of the physical
571 and emotional sensations experienced. On completion of the proving, the
572 ‘master prover’ collates information from the diaries and this becomes the
573 ‘symptom picture’ for that remedy and is recorded for homeopaths to
574 reference in practice (Kayne 2006, Riley 2008, Campbell 2013, Sherr 2015).
575 The scientific basis of homeopathic provings is not established.
576 Furthermore, for veterinary products obvious practicalities dictate that these
577 procedures cannot be followed when the recipient is an animal.

578 The components of homeopathic products are water (in some cases
579 alcohol also), dissolved gases, impurities (a variety of inorganic and organic
580 molecules of unknown amounts), and variable amounts of the ‘active’,
581 dependent on the degree of dilution, but less than one molecule at the high
582 dilutions commonly used in practice and supplied as over-the-counter
583 remedies (Kayne 2006 pp81-120). ‘Nanoparticles’ of the starting material
584 have been demonstrated in some commercially-available 30c and 200c
585 remedies made from metals in India (Chikramane and others 2010),
586 presumably due to imperfect dilution, or contamination after dilution,
587 during preparation. There are thousands of remedies in published
588 homeopathic *Materia Medica* (e.g., Boericke 2008) and available via the
589 Internet, with frequent new remedies being homeopathically ‘proved’ and
590 used in practice (Kayne 2006 pp51-53, Riley 2008, Sherr 2015). There
591 appears to be no restriction on what can be used as an ‘active’ to create a
592 remedy; ‘actives’ include viruses, bacteria, animals, plants, minerals,
593 chemicals, conventional drugs, man-made objects, and physical radiations
594 and energy fields (the last two referred to as ‘imponderables’ by Hahnemann

595 and modern homeopaths). Examples include; honey bee (*Apis mel*), emperor
596 dragonfly (*Anax imperator*), duck offal (*Oscilloccinum*), green iguana (*Iguana*
597 *iguana*), human placenta (*Placenta humanum [Welsh]*), Kentucky bluegrass
598 (*Poa pratensis*), lava (*Hekla lava*), gunpowder (*Carbon-sulphur-kali-nitricum*),
599 permethrin, condom (*Latex vulcani*), the Berlin Wall (*Murus Berlinensis*),
600 Hadrian's Wall (*Vallum Aelium*), car exhaust fumes, electricity (*Electricitas*),
601 magnetic field (*Magnetis poli ambo*), emanations from televisions, X-rays (*X-*
602 *ray*), and light from the planet Venus (*Venus stella errans*) – all of which can
603 be found listed in homeopathic *Material Medica* or as homeopathic provings
604 on the Internet, and can be purchased from homeopathic pharmacies (e.g.,
605 www.helios.co.uk). Some homeopathic products contain sugar, but this is
606 not claimed to be essential to efficacy (except in the homeopathic remedy
607 *Saccharum officinale*, prepared from pure cane sugar as the 'active'). Each
608 remedy is claimed to possess specific healing properties, i.e., can be used to
609 treat only certain signs or symptoms, but not others, or only patients with
610 certain characteristics, but not others; yet homeopaths appear to believe
611 that all remedies exert their effects via a single (unknown) process (Kayne
612 2006, Nicolai 2008).

613 Remedies may be dispensed in the liquid form, but can also be mixed with
614 or dropped or sprayed on to other pharmaceutical preparations to create
615 homeopathic creams, ointments, pills and powders, etc. (Kayne 2006 pp100-
616 106, Kayne 2008). Once formulated, there are minimal costs to marketing,
617 only extremely limited regulatory requirements to be negotiated, with no
618 comparisons with other products, homeopathic or otherwise, required.
619 Regulatory authorities recognise that the products are lacking in ingredients
620 with specific actions and it is assumed that no toxicity will arise in the
621 absence of actives. Therefore, it is further assumed that there can be no
622 residues in edible tissues of food producing species and hence no meat/milk
623 withholding periods are required.

624 **Drug-based products**

625 For each drug-based product, there must, by definition, be one or more
626 actives. However, it is rare for drugs to be marketed as the drug substance
627 alone. Almost invariably they are formulated, for oral, parenteral or local
628 administration, as solutions, suspensions, tablets, capsules etc., which
629 contain other compounds, the excipients. Generally, no therapeutic activity
630 is claimed for the excipients, but they are essential to ensure such
631 properties as sterility and syringability and as bulking or flavouring agents.
632 Whilst themselves not active on biological systems, excipients can markedly
633 influence pharmacological and therapeutic outcomes. This occurs
634 principally by affecting the rate and extent of absorption of the active
635 constituents.

636 Each active in conventional drugs is perceived to have a specific chemical,
637 biochemical or physiological mechanism of action by which it brings about
638 its clinical effects, and sometimes other mechanisms of action by which
639 adverse effects arise. For many drugs the mechanism of action is proven,
640 and for most drugs without proven mechanisms of action, scientifically
641 plausible mechanisms exist. For discussion of the bases of efficacy of
642 constituents of homeopathic and drug-based products, and the evidence
643 regarding their clinical efficacy, see Part 2 of this review (Lees and others
644 2017).

645

646 **CONFLICT OF INTEREST**

647 None of the authors of this article has a financial or personal relationship
648 with other people or organisations that could inappropriately influence or
649 bias the content of the paper.

650

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