Homeopathy (2009) 98, 17–25

doi:10.1016/j.homp.2008.11.006, available online at http://www.sciencedirect.com

ORIGINAL PAPER

Observational study of homeopathic and conventional therapies in patients with diabetic polyneuropathy

Raffaella Pomposelli[1], Valeria Piasere[2], Cristina Andreoni[1], Gavina Costini[1], Elena Tonini[1], Antonietta Spalluzzi[3], Daniela Rossi[3], Chiara Quarenghi[3], Maria Elisabetta Zanolin[4] and Paolo Bellavite[2,*]

[1]*"Belladonna" Medical Association, Milan, Italy*
[2]*Department of Morphological-Biomedical Sciences, University of Verona, Italy*
[3]*Quarenghi Clinic, S. Pellegrino, Bergamo, Italy*
[4]*Department of Medicine and Public Health (Biomedical Statistics Section), University of Verona, Italy*

Methods: **The feasibility and outcomes of homeopathic therapy in a group of type-2 diabetes mellitus patients with diabetic neuropathy were studied in a prospective observational study. Patients were followed from baseline (T0) for 6 months (T1) and for 12 months (T2), treatment was adjusted as necessary. Primary outcome was diabetic neuropathy symptom (DNS) score, secondary outcomes were clinical evolution and short-form-36 (SF-36)-evaluated quality of life (QOL).**

Results: **Homeopathy was used in 45 patients, 32 of whom completed the observation study, and in parallel the conventional therapy outcomes were observed in 32 patients, 29 of whom completed the study. DNS improved in both groups during the observation period, but the change with respect to baseline was statistically significant only in Homeopathic group at T1 ($P = 0.016$). Over the course of the observation there was a substantial stability of the electroneurophysiological values, blood pressure and body weight in both groups, a slight decrease of fasting blood glucose and glycated haemoglobin in Homeopathic group. QOL scores showed an improvement in Homeopathic group only. The cost of conventional drugs decreased in Homeopathic group from 114 €/month to 94 €/month at T1.**

Conclusion: **Complementary homeopathic therapy of diabetic neuropathy was feasible and promising effects in symptom scores and cost savings were observed.** *Homeopathy* (2009) **98, 17–25.**

Keywords: diabetes; diabetic neuropathy; homeopathy; observational study; quality of life; pharmacoeconomics

Introduction

Public demand for complementary therapies including particular for homeopathy is increasing, because patients are not completely satisfied with conventional treatments for many conditions. It is therefore necessary to initiate constructive and documented comparison between the different therapies and their possible integration, particularly in situations where conventional medicine is limited. Recent multi-practitioner pilot studies have indicated that systematic recording of clinical data in homeopathy is both feasible and capable of informing future research.[1–6]

In this study, diabetic neuropathy in a group of type-2 diabetes mellitus patients was considered. Patients affected with this disease often have polyneuropathies causing pain, functional limitations and worsening of the quality of life (QOL). Diabetes is often (>50% of cases) complicated by peripheral neuropathy: a painful, often debilitating

*Correspondence: Paolo Bellavite, Dipartimento di Scienze Morfologico-Biomediche, Università di Verona, Piazza L.A. Scuro 10, 37134 Verona, Italy. Tel./fax: +39 458027485.
E-mail: paolo.bellavite@univr.it
Received 6 February 2008; revised 27 October 2008; accepted 18 November 2008

condition, which may be associated with ulcers of the lower limbs and in even death due to autonomic neuropathy.

Unfortunately, in terms of therapy little can be done for the neuropathy. So, while future hopes lie in the advancement of research into potential pharmacological agents, for the present particular emphasis is placed on prevention, especially the early and careful control of glycaemia. It is common experience that most type-2 diabetic patients, besides dietary interventions, receive more than one drug, including oral antidiabetic drugs and insulin; however, good control of glycaemia may be achieved in only about 25% of patients. To obtain better results, the treatment should include multidisciplinary efforts. A simple biochemical-laboratory approach is not sufficient, other mental, emotional and spiritual dimensions also need to be treated.[7-9]

Given this, an attempt at treatment based on associating homeopathy with traditional therapy appears justified. On the basis of our previous experience in other chronic and neurological pathologies,[1,10] the hypothesis that justifies the homeopathic approach is that it might bring further improvement in the local symptoms of the disease and in the QOL compared to conventional therapy alone. A first exploratory, observational, study was thus undertaken, taking advantage of the existence of a long-standing collaboration between homeopaths and conventional doctors in the Quarenghi Clinic (Bergamo, I), which has a formal agreement with Lombardia Region of the Italian National Health Service, for care and rehabilitation services. Participation in this observational study was proposed to the patients who came to this medical centre. For ethical reasons and due to the observational nature of the design, the choice whether to take advantage of the homeopathic treatment (free of charge) was left to the patient after he/she had been given adequate information. The study comprised two nonrandomised groups, treated for 1 year either with homeopathic therapy (and conventional therapy when necessary), or with conventional therapy alone.

In addition to the specific symptoms and signs of the pathology, the objectives of the study included evaluation of the changes in QOL, assessed by the short-form-36 (SF-36) questionnaire, which is well validated[11-14] and has been used for studies in non-conventional or complementary medicine.[1,15,16] Thus documentation of the clinical and psychological evolution and the peculiarity of the homeopathy, which is never directed solely to the removal of a symptom but to the overall treatment of the person, were respected.

Study design

This was a nonrandomised, prospective, observational study, with a follow-up of 12 months, of the clinical evolution and the QOL, in a group of patients receiving homeopathic treatment as complementary care and in another group receiving conventional therapy only. The patients of Homeopathic group were treated according to homeopathic therapy based on criteria of classical (individualized) homeopathy.[1,7] The protocol was approved by the Scientific Technical Committee of the Regione Lombardia Health Service, and formally recorded the 24th of February 2004. For such observational studies, the Ethical Committee approval was not required.

Patients with diabetic neuropathy, being treated at the Quarenghi Clinic by the team of general medicine specialist (C.Q.), diabetologist (A.S.) and neurologist (D.R.), were classified according to severity, measured by diabetic neuropathy symptom (DNS) scores. If the patient was eligible, he was informed as to the possible treatment options, taking care to present the possibility of homeopathic therapy in an objective and neutral manner. All the patients who agreed to participate in the study received thorough information concerning the possible therapies and the study, including an information sheet, then signed the informed consent form and the agreement to data processing.

Patients who choose homeopathic therapy received homeopathic prescription from one of the four medical doctors expert in classic homeopathy involved in this study (R.P., C.A., G.C., E.T.). These doctors were qualified in Italian post-graduate 3-year course Homeopathy Schools, recognised by the Homeopathic Scientific Medical Society (Federazione Italiana delle Associazioni dei Medici e dei Veterinari Omeopati) and had a minimum 6-year experience of homeopathic practice. The follow-up required 2–3 further homeopathic visits in 1 year, with the same doctor who made the first prescription. All the appointments were at the Quarenghi Clinic. The follow-up of the diabetic disease and of neuropathy, irrespective of the study group to which patients belonged, was carried out by means of the diagnostic tests and the conventional treatments available (diet, insulin or oral hypoglycaemic agent, physiotherapy) by the conventional medical team of the Quarenghi Clinic (A.S., D.R., C.Q.). The University Department received the documentation, both conventional and homeopathic, in a coded and anonymous form and the results were analysed by three researchers (P.B., V.P., M.E.Z.). All the data were collected and catalogued in three phases: (1) Time 0 (T0, baseline, before treatment), (2) Time 1 (T1, 6 months of treatment), and (3) Time 2 (T2, 12 months of treatment).

Criteria for inclusion or exclusion

All consecutive patients attending to the Clinic during the recruitment period and having suitable characteristics were asked to participate in the study. Patients with a diagnosis of diabetic polyneuropathy were included, with the exclusion of other possible causes of polyneuropathy. The following patients were excluded: patients with neoplasia, acquired immune deficiency syndrome (AIDS), chronic inflammatory diseases (e.g. Crohn's Disease, rheumatoid arthritis), patients with a history of or currently suffering from alcohol abuse, Alzheimer's disease, patients who were mentally unstable or for any reason incapable of completing the questionnaires, patients with homeopathic therapies already in progress, macrocytic anaemia due to folic acid and B12 deficiencies. Patients were withdrawn from the study if deviation from protocol occurred, for life threatening conditions, and according to patient's choice or inability to attend the Clinic.

End points

The primary outcome measure was DNS score.[17] We used this because it is one of the most utilized scores for diabetic neuropathy, it is routinely used in the clinic where the study was conducted, and is less subjective than QOL scores, because it is scored by the physician. The score goes from 0 (polyneuropathy absent) to 4 (one point for the presence of each of the following symptoms more than once per week in the last two weeks: (a) unsteadiness in walking; (b) burning, pain or weakness in the legs or feet; (c) tingling sensation in the legs and feet; (d) areas of numbness, insensibility in the legs or feet). The DNS score is validated, easy to carry out and has a high predictive value in the screening of diabetic polyneuropathy.

Over the course of the observation other clinical data including normal monitoring of diabetes, such as arterial blood pressure, weight, fasting blood glucose, glycated haemoglobin were obtained and systematically filed. Function of sensory and motor nerves was assessed by electroneurophysiological tests (Time 0 and 2). The studies on electrical conductivity of the nerves were carried out by stimulating a peripheral nerve (e.g. ulnar, sural, or peroneal) and recording the rate of transmission and amplitude of the signal.

The homeopathic symptoms were obtained and the homeopathic follow-up was carried out according to the methods of classical, individualized homeopathy. In brief, the symptoms under evaluation (homeopathic symptoms) must reflect the particular details expressed by the patient, rather than the typical symptoms of the pathology. Homeopathic symptoms of the patient collected in this manner must not be too many or too few (no less than three and a maximum of 10, but this may change according to the individual). When selecting symptoms, the homeopath gives preference to symptoms that are intense or unusual and present both at the time of the visit and during the previous months or years (historical symptoms). The prescribing requires the use of the repertory and it is preferable (although not obligatory) to use a computerised repertory. Once the homeopathic symptoms have been chosen and a series of candidate remedies selected with the help of the repertory, the doctor prescribes a single medicine, by comparing the ensemble of the symptoms and the signs presented by the patient with those associates with various medicines proposed in the Materia Medica. When carrying out the follow-up, any new symptoms that may appear are judged according to the so-called Hering principle. The dilutions of the homeopathic medicines were at the homeopathic doctors discretion, but the Centesimal Hahnemannian (CH) scale was generally used.

The SF-36 score comprises 8 dimensions.[11,18,19] The score in each dimension ranges from 0 (worst possible) to 100 (optimal). These dimensions are: Physical functioning (low scores indicate difficulties in physical activities including walking, dressing or bathing, work), Role limitations due to physical problems (difficulty with work or other daily activity because of physical health), Bodily pain, General health (subjective consideration of his/her health and perspectives for the future), Vitality (tiredness, absence of physical energy), Social function (interference of physical and emotional problems with social activities), Role limitations due to emotional problems (difficulty with work or other daily activity due to emotional problems), and finally Mental health (anxiety or depression). The patients completed the questionnaire on alone according to the instructions given orally. The doctors involved in the study were instructed in detail on administering the questionnaire. Once the responses had been completed, the questionnaire was given back to the doctor or nurse, who checked if it was complete (if not, it was returned to the patient for completion). Patients did not have access to their earlier responses. Under no circumstances did the homeopathic doctors have access to the questionnaires, nor could they influence the patients at the moment of completing them.

Cost of medicines

The monthly cost of the drugs taken was calculated on the basis of the consumption of medicines in the previous month and their costs. For conventional medicines, this is obtained by multiplying the Unit Cost, (the cost of each tablet, capsule or vial), by the number of tablets, capsules or vials taken in 1 month. The monthly cost for insulin was obtained in a similar manner multiplying the cost of 1 International Unit by the monthly consumption. For eye drops the cost of one drop was multiplied by the monthly consumption. The price of the pharmaceutical products was taken from the following sources: Ministero della Salute (Ministry of Health), Department for the Evaluation of Medicines and Pharmacovigilance: *Guide for the use of pharmaceuticals*, 2003 and A. Menarini: *Pharmaceutical Repertory SSN*, September 2004. The medicines were supplied by the Clinic, with no additional costs to the patient. The costs for medicines for homeopathic therapy lasting a period of 1 month considering 1 single-dose and 5 drops three times per day are as follows: (a) 30 CH or 200 CH single-dose €4.30; (b) cost of 1000 CH single-dose €10.00; (c) 30 ml bottle of drops €14.00.

Statistics

Due to the small sample size, different baseline values and drop-outs (see Results), the two groups were statistically compared only at the baseline. The comparisons were carried out using the Pearson χ^2 test for categorical variables, the independent Student t test for continuous variables with normal distribution and the Mann–Whitney test for variables with non-normal distribution. The outcomes were evaluated in each group as changes of the values at various observation times with respect to the values at baseline. In each group (Homeopathic and Conventional), the changes of the values at different times were analysed using analysis of variance (ANOVA) test for repeated measures followed by *post-hoc* comparisons with Bonferroni correction (for variables with normal distribution) or the Friedman test followed by *post-hoc* comparisons with Wilcoxon test (non-normal distribution). Differences with $P < 0.05$ were considered significant. The analysis of the outcomes as compared to the baseline values was carried out according

to the "intention to treat" (ITT) principle which takes into account the drop-outs considering them cases that are not improved.[20] In order to describe the effects, we calculated also effect sizes as standardised mean differences (d) according to the formula: (MEANpost – MEANbaseline)/SDbaseline.[16,21] Effect sizes are regarded as being small where $d < 0.3$, moderate where $d < 0.8$, high where $d > 0.8$.[16,21] The data were processed using Stata 9.2 software (www.stata.com).

Results

Patients included and drop-outs

45 patients were included in Homeopathic group (homeopathic treatment and conventional treatment) and 32 patients in Conventional group (conventional therapy alone) (Table 1). Patients who withdrew from the study were 13 from the Homeopathic group (6 voluntary unspecified withdrawals, 2 could not be contacted for follow-up, 1 serious heart disease, 1 stroke, 1 cognitive decline, 2 neoplasias) and 3 from the Conventional group (1 deceased, 1 neoplasia, 1 could not be contacted for follow-up). The 6 patients who withdrew without specifying the reasons were followed up by the diabetologist, who noted that their withdrawal was not due to a specific dissatisfaction with the treatment, but to practical difficulties in attending the additional homeopathic appointments. No serious adverse effects directly attributable to the homeopathic medicines were reported either by patients or by doctors.

The characteristics of age and sex of the patients included in the study are reported in Table 2. The two groups did not show statistically significant differences in composition for gender distribution (Pearson χ^2: $P = 0.651$). In the Conventional group the patients were on average older than the homeopathic group, but the difference was not statistically significant (Mann–Whitney test: $P = 0.216$).

All the patients in the two groups were affected by type-2 diabetes mellitus and at the recruitment in the study they were under the following treatments: in Homeopathic group, 15.6% diet only, 44.4% diet plus oral antidiabetic drugs, 26.7% diet plus insulin, 13.3% diet plus oral antidiabetic drugs plus insulin; in Conventional group, 21.9% diet only, 59.4% diet plus oral antidiabetic drugs, 16.6% diet plus insulin, 3.1% diet plus oral antidiabetic drugs plus insulin (the difference in treatment types was not statistically significant: Pearson χ^2: $P = 0.220$).

Diabetic neuropathy score

The primary objective of the study concerned the severity of the symptoms of polyneuropathy, evaluated using the DNS score. These data are reported in Table 3. At baseline (T0), the distribution of the scores (frequency of cases and % of total) and the means were similar in the two groups (Mann–Whitney test: $P = 0.596$). There was a slight improvement in both groups over the course of time: in fact, the number of cases with higher DNS scores and mean values decreased during time. This improvement was statistically significant in the Homeopathic group only (Friedman test: $P = 0.044$), particularly at the T1 (effect size: −0.27; Wicoxon test: $P = 0.016$).

Electroneurophysiological parameters

The studies on the electrical conductivity of the nerves are reported in Table 4. There were no differences between groups at the baseline (t test: $P = 0.45$ and 0.96 for sural and ulnar nerves, respectively). Over the course of the year of observation, in both groups there was essentially no change in the values for those sensory nerves. No significant changes were observed in either the values for the peroneal motor nerve and for the ulnar motor nerve (data not shown).

Other clinical data

Means of body weight and blood pressure (systolic and diastolic) did not show differences between the two groups or variations over the period of observation (data not shown). Regarding the determination of fasting blood glucose (Table 5) a slightly worse initial state was found in Homeopathic group but this was not statistically significant (t test: $P = 0.39$). A slight improvement over time was seen in this group, so that the glycaemia at T2 appeared to be lower in Homeopathic group than in Conventional group (8.60 and 8.78 mmol/L, respectively), but these changes were not statistically significant. Glycaemia trends were confirmed by the glycated haemoglobin (data not shown), which at T0 appeared to be slightly higher in Homeopathic group. A slight drop in the glycated haemoglobin in Homeopathic group and an increase in Conventional group were observed over the course of time, but did not reach statistical significance.

Quality of life (QOL)

The results of the different variables of QOL are shown in Figure 1 and two examples concerning specific parameters

Table 1 Cases treated and observation times (values in months)

	Homeopathic group					*Conventional group*				
	N	*Observation times*				N	*Observation times*			
		Mean	*SD*	*Min*	*Max*		*Mean*	*SD*	*Min*	*Max*
Time 0 (no. patients included)	45	–	–	–	–	32	–	–	–	–
Completed 6 months (Time 1)	35	6.7	1.0	6	10	31	6.3	0.5	6	7
Completed 12 months (Time 2)	32	12.6	1.2	9	15	29	12.3	0.8	10	14
Drop-outs between T0 and T1	10					1				
Drop-outs between T1 and T2	3					2				

Table 2 Age and sex of patients included

	Homeopathic group			*Conventional group*		
	Male	*Female*	*Total*	*Male*	*Female*	*Total*
Sex	29 (64%)	16 (36%)	45	19 (59%)	13 (41%)	32
Age						
Average	65.2	67.4	66.0	67.9	67.5	67.7
SD	8.3	8.8	8.5	8.7	13.9	10.9
Median	66	67	66	68	73	71

are given in Tables 6 and 7. At Time 0 the Physical Function (Figure 1 and Table 6) was slightly but not significantly worse in Homeopathic group (Mann–Whitney test: $P = 0.58$). This variable of the QOL, linked to motor capacity, improved in Homeopathic group over the entire period of observation (Friedman test: $P = 0.019$), and *post-hoc* analysis showed statistical significance at T2 (Wilcoxon test: $P = 0.019$). In the Conventional group there were significant modifications in Physical Function (Friedman test: $P = 0.018$), but the changes first showed a slight deterioration, then a recovery, so that after 12 months this variable was almost unchanged.

Role limitations due to physical factors showed improvements in Homeopathic group, while in Conventional group a worsening at T2 was observed. However, because of the broad variations between patients and with time, these changes were not statistically significant. Bodily Pain (pain due to physical problems) improved in Homeopathic group and worsened in Conventional group during the observation period, but these changes were not statistically significant. Similar trends, showing better outcomes in the Homeopathic group, without reaching statistical significance, appeared in the General Health and the Vitality scales.

Social Functions showed a significant difference between groups at the beginning (Mann–Whitney test: $P = 0.02$), then a slight improvement in both groups. In the Homeopathic group, the improvement of Social Function in the first 6 months (T1 *vs.* T0) was statistically significant (Wilcoxon test: $P = 0.04$). The scores in the Role limitations (work or other daily activities) due to emotional problems were similar to those of the social functioning, with a significant difference between the two groups at T0 and a statistically significant improvement in Homeopathic group, during the first 6 months. Mental Health did not show significant differences between the two groups at Time 0 (independent *t* test: $P = 0.14$) and exhibited an improvement in Homeopathic group, with a borderline statistical significance (ANOVA: $P = 0.064$), limited to the first 6-month phase (paired *t* test with *post-hoc* Bonferroni: T1 *vs.* T0, $P = 0.052$) (Figure 1 and Table 7).

Consumption and costs of medicines

Table 8 reports the monthly cost of conventional medicines, with reference to month prior to the visit at the three observation times. At T0 the consumption of medicines was higher in Homeopathic group than in the Conventional group (Mann–Whitney test: $P = 0.007$). In the first 6 months there was a decrease in consumption in Homeopathic group and an increase in Conventional group. These changes approached but did not reach the statistical significance (Wilcoxon test: $P = 0.071$ and 0.089, respectively). In the second 6 months there was increased consumption in Homeopathic group while Conventional group remained substantially stable.

The homeopathic medicines prescribed most often were *Calcarea Carbonica* (6 cases), *Ignatia* (3), *Phosphorus*

Table 3 Diabetic neuropathy scores at the three observational times

Time	*DNS scores*	*Homeopathic group*			*Conventional group*		
		Frequency of cases	*% of total*	*Mean score ± SD*	*Frequency of cases*	*% of total*	*Mean score ± SD*
T0	0	12	26.7	1.40 ± 1.21	10	31.2	1.26 ± 1.06
	1	15	33.3		10	31.2	
	2	9	20		7	21.9	
	3	6	13.3		5	15.6	
	4	3	6.7		0	0	
T1	0	21	46.7	**1.07 ± 1.25**	14	43.8	1.06 ± 1.15
	1	10	22.2		8	25.0	
	2	6	13.3		6	18.8	
	3	6	13.3		3	9.4	
	4	2	4.4		1	3.1	
T2	0	17	37.8	1.22 ± 1.27	16	50	0.94 ± 1.21
	1	13	28.9		8	25	
	2	6	13.3		3	9.4	
	3	6	13.3		4	12.5	
	4	3	6.7		1	3.1	
*P**			**0.044**			0.259	
T1 *vs.* T0	Effect size§			**−0.27**			−0.19
	*P***			**0.016**			0.350
T2 *vs.* T0	Effect size§			−0.15			−0.30
	*P***			0.146			0.182

* Friedman test.
§ Negative values indicate clinical improvement, positive values indicate worsening.
** Signed-rank test (Wilcoxon).

Table 4 Electrophysiological conductivity studies of sensory nerves

Time	*Parameter*		*Homeopathic group*			*Conventional group*		
			N	*Mean*	*SD*	N	*Mean*	*SD*
T0	Sural^		45	2.71	2.7	32	3.17	2.64
	Right ulnar		44	17.39	11.4	31	17.27	12.69
T2	Sural^		45	2.88	2.97	32	3.15	2.58
	Right ulnar		44	18.8	12.93	31	16.74	15.38
T2 *vs.* T0	Sural^	Effect size§		0.063			−0.008	
		*P**		0.26			0.93	
	Right ulnar	Effect size§		0.124			−0.042	
		*P**		0.38			0.80	

Mean and SD values are *P–P* Amp. (μV).
^ Values of sural nerve are mean of left and right legs measurements.
§ Positive values indicate clinical improvement, negative values indicate worsening.
* Paired *t* test.

(3), *Medhorrinum* (3), *Thuja* (2), *Nux Vomica* (2), *Lycopodium* (2), *Natrum muriaticum* (2), *Carcinosinum* (2), followed by numerous others prescribed in individual cases. The dilutions/dynamizations most used were 30 CH (21 cases), followed by 15 CH (9 cases) and by 200 CH (6 cases), and other sporadic occasions 5 CH, 7 CH, MCH and MK were used. In general, it was noted that in the second and third prescriptions the homeopathic potency prescribed tended to increase. The overall cost for 1 month of therapy with homeopathic medicines was from €18.30 (30 CH or 200 CH dilutions) to €24.00 (1000 CH).

Discussion

The object of this research was homeopathic therapy in diabetic neuropathy, carried out at professional practice level, in a Clinic where the collaboration with conventional doctors was operative. Through this observational study new knowledge was gained regarding the results of homeopathic therapy and conventional therapy

Table 5 Fasting blood glucose

Time		*Homeopathic group*			*Conventional group*		
		N	*Mean*	*SD*	N	*Mean*	*SD*
T0		45	8.79	2.59	32	8.34	1.79
T1		45	8.73	3.15	32	8.78	2.96
T2		45	8.60	3.60	31	8.78	2.97
*P**			0.703			0.419	
T1 *vs.* T0	Effect size§		−0.023			0.246	
	*P***		1.00			0.68	
T2 *vs.* T0	Effect size§		−0.073			0.246	
	*P***		1.00			0.50	

Mean and SD values are mmol/L.
* Repeated measures ANOVA.
§ Negative values indicate clinical improvement, positive values indicate worsening.
** Paired *t* test with Bonferroni *post-hoc* correction.

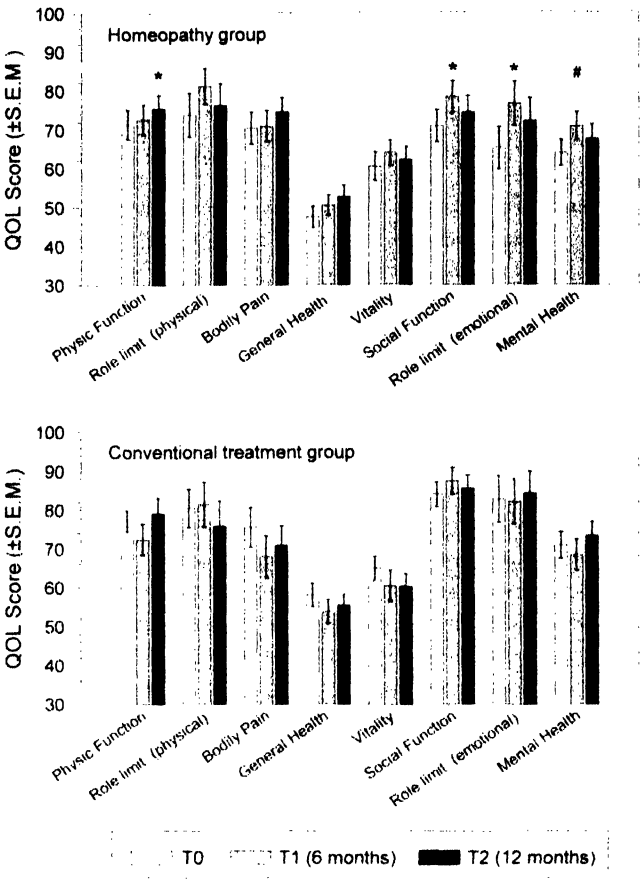

Figure 1 QOL scores (SF-36) in the two observation groups. *: $P < 0.05$ (Wilcoxon test); #: $P = 0.052$ (Bonferroni test).

in a serious chronic illness. The study proved to be feasible with little difficulty and the cooperation of the various specialists treating the patients proved to be effective. The treating doctor (homeopath or conventional) was personally fully responsible in his area of expertise. In any case the diabetes specialist had full control of the treatment of the diabetes and regulated the conventional therapy according to the conventional clinical data. In cases of emergency, the Diabetes specialist could prescribe or discontinue any therapy without consulting the Homeopath. There were no cases in which this proved to be necessary.

Because of ethical issues and the precise choice of method, it was necessary to respect the homeopathic which required in-depth and often repeated conversation with the patient, as well as possible succession of different medicines, so this protocol was not designed as blinded. On the other hand, it did face the question – important from a practical point of view – concerning the effect size of the therapy in the actual conditions where the treatment is applied. Therefore, an approach of this kind could bridge the distance between clinical experimentation and the therapeutic decisions of individual doctors, who often have to base their choices on personal experience only.[22,23]

In this study, a recruitment respected the free choice of the patient concerning whether or not to accept homeopathic treatment in addition to conventional treatment. The option of homeopathy was presented by the

Table 6 Physical Function (SF-36)

Time		*Homeopathic group*			*Conventional group*		
		N	*Mean score*	*SD*	N	*Mean score*	*SD*
T0		45	71.3	24.7	32	77.1	15.3
T1		45	72.7	24.9	32	72.5	22.4
T2		45	75.3	23.7	32	79.0	22.4
*P**			**0.019**			**0.018**	
T1 *vs.* T0	Effect size§		0.057			-0.301	
	*P***		0.208			0.125	
T2 *vs.* T0	Effect size§		0.162			0.124	
	*P***		**0.019**			0.189	

* Friedman test.
§ Positive values indicate clinical improvement, negative values indicate worsening.
** Sign-rank test (Wilcoxon).

Table 8 Monthly costs of conventional drugs. Mean and SD values are €/month

Time		*Homeopathic group*			*Conventional group*		
		N	*Mean*	*SD*	N	*Mean*	*SD*
T0		44	114.07	112.52	32	68.66	55.30
T1		44	94.44	63.84	32	78.25	58.44
T2		43	110.50	71.51	32	77.39	55.22
*P**			0.071			0.089	
T1 *vs.* T0	Effect size§		-0.17			0.17	
	*P***		0.078			0.139	
T2 *vs.* T0	Effect size§		-0.03			0.16	
	*P***		0.432			0.074	

* Friedman test.
§ Negative values indicate decrease of costs, positive values indicate increase.
** Sign-rank test (Wilcoxon).

conventional doctor of the clinic in a neutral manner in order to avoid generating either unjustified expectations or fears. A previous study in the same clinic included interviews by nurses uninvolved in the research, regarding the reasons why patients chose homeopathy.[10] The major reason was for the extra possibility it would give them, and incomplete satisfaction with conventional treatment. About one third of patients had favourable expectations, either due to positive information received from relatives or friends or to advice of the family doctor. The most prevalent motivation for not choosing homeopathy was the fear of taking medicine the effects of which were unknown.

There were more withdrawals in the Homeopathic group, but this was not due to adverse effects, or to dissatisfaction with the treatment but to practical difficulties in attending the additional appointments and probably also to the greater severity of the clinical conditions of the patients in that group. The ITT analysis takes into account the drop-outs considering them cases that had not improved, thus reducing bias effects due to patients with clinical progress that is different (either better or worse) from the average of the group they belong to.

Despite the limitations due to the small sample size, the results of this study permit the quantification of the clinical changes during 1 year of observation with the two therapeutic approaches. The primary objective relative to the DNS score indicated that symptoms of diabetic neuropathy showed slight improvement, statistically significant in the Homeopathic group, particularly in the first 6 months.

Among the secondary objectives, some clinical parameters such as body weight, arterial pressure, electrophysiological tests and glucose levels did not show significant variations over the course of the observation. However, it should be noted that the blood glucose seemed to be controlled slightly better in Homeopathic group, showing a slight decline. This might suggest that an observation time of 1 year is insufficient to express the full effect of this type of treatment in this pathology.

According to the homeopathic method, the objective of the treatment is the whole person and only secondarily the treatment of the disease on an organic level. It is significant that homeopathic theory and practice have always aimed at activating the so-called vital energy,[7,24–26] and in homeopathic research methodology, apart from the specific symptoms of the pathology, it is useful to evaluate changes in the QOL. Effect sizes in the QOL from baseline to post-treatment showed small, but often statistically significant, positive effects in the Homeopathic group. It is interesting to note that the dimensions with the greatest improvements in the area of homeopathy were social functions and emotional problems. The differences in the behaviour of the two groups are interesting and some parameters that show differences in favour of Homeopathic group tend to lead one to believe that adjunctive homeopathic therapy gives a better result than conventional therapy alone. Clearly, such a suggestion of a greater effectiveness in the homeopathic approach, emerging from this first observational study, should be tested by randomised studies.

The improvement of DNS and QOL in Homeopathic group, particularly in the first 6 months of therapy, was

Table 7 Mental health (SF-36)

Time		*Homeopathic group*			*Conventional group*		
		N	*Mean score*	*SD*	N	*Mean score*	*SD*
T0		44	63.80	22.30	32	71.00	19.20
T1		44	70.70	23.60	32	68.50	22.70
T2		43	67.50	23.90	32	73.30	20.60
*P**			0.064			0.124	
T1 *vs.* T0	Effect size§		0.31			-0.13	
	*P***		0.052			0.664	
T2 *vs.* T0	Effect size§		0.17			0.12	
	*P***		0.500			0.558	

* Repeated measures ANOVA.
§ Positive values indicate clinical improvement, negative values indicate worsening.
** Paired *t* test with Bonferroni *post-hoc* correction.

accompanied by a drop in the prescription of pharmaceuticals on the part of the conventional treating doctor (diabetes specialist). The result was not maintained in the second 6 months, but it may suggest further attention to this possible cost saving in future research. It should be also considered that for this protocol the medical homeopaths worked without payment, but in the normal setting of the cure the overall costs should include also the 2–3 visits/year with a medical homeopath (€100 for the first appointment and €80 for subsequent).

For several parameters, improvements experienced in the first 6 months were not maintained or even get worse. It is difficult to find a clinical or psycho-social factor that could explain this, apart from the natural progression of the disease. The homeopathic doctors report that in several cases they noted a worsening immediately after flu immunisation, but these are sporadic cases that may be motivation for further research that could focus on this aspect of the data.

In summary, this study produced the following results:

1. It was possible to treat patients with homeopathy, monitored by the conventional diabetes specialist, without any major problem of compatibility between the two forms of therapy.
2. The method of recruiting permitted two groups to be formed that were sufficiently similar as to severity in the DNS scores and electroneurophysiological data, but different regarding the other variables such as the QOL and the consumption of medicines. The homeopathic patients generally had a worse clinical condition at entry.
3. Evaluated according to laboratory and instrumental parameters, the course of diabetic neuropathy was not significantly improved in the Homeopathy group, nor in the Conventional group.
4. A number of significant improvements in symptoms, as reported by DNS and QOL score, were found in the homeopathy group, possibly associated with a decrease in conventional drug consumption in the first 6 months of observation. The extent and the type of improvements could help planning randomised studies.

Competing interests declaration

Homeopathic medical doctors (R. Pomposelli, MD, C. Andreoni, MD, G. Costini, MD, and E. Tonini, MD) worked on a voluntary basis and did not receive supplementary compensation for the research. The doctors of the Quarenghi Clinic were A. Spalluzzi, MD (Diabetologist), D. Rossi, MD (Neurophysiologist) and C. Quarenghi, MD, (Internist). Dr. V. Piasere, MD, has received a grant from Belladonna Association. P. Bellavite, MD, and M.E. Zanolin are Professors at University of Verona (School of Medicine). No affiliation nor financial relationship of any author with the drug companies existed.

Acknowledgements

The study was financed by a grant from "Belladonna" Association (Milan, Italy), a medical non-profit cultural association having the statutory purpose of supporting the research in homeopathy, and in part by Italian Ministry of Research (60%). Homeopathic medicines were provided free by Siffra (Strada in Chianti, Italy). We thank Yves Doessant for revision of manuscript.

References

1 Muscari-Tomaioli G, Allegri F, Miali E, *et al.* Observational study of quality of life in patients with headache, receiving homeopathic treatment. *Br Homeopath J* 2001; **90**(4): 189–197.
2 Thompson EA, Reilly D. The homeopathic approach to symptom control in the cancer patient: a prospective observational study. *Palliat Med* 2002; **16**(3): 227–233.
3 Van Wassenhoven M, Ives G. An observational study of patients receiving homeopathic treatment. *Homeopathy* 2004; **93**(1): 3–11.
4 Steinsbekk A, Ludtke R. Patients' assessments of the effectiveness of homeopathic care in Norway: a prospective observational multicentre outcome study. *Homeopathy* 2005; **94**(1): 10–16.
5 Spence DS, Thompson EA, Barron SJ. Homeopathic treatment for chronic disease: a 6-year, university-hospital outpatient observational study. *J Altern Complement Med* 2005; **11**(5): 793–798.
6 Mathie RT, Robinson TW. Outcomes from homeopathic prescribing in medical practice: a prospective, research-targeted, pilot study. *Homeopathy* 2006; **95**(4): 199–205.
7 Vithoulkas G. *The science of homeopathy*. New York: Grove Press Inc., 1980.
8 Bellavite P. Complexity science and homeopathy. A synthetic overview. *Homeopathy* 2003; **92**: 203–212.
9 Bell IR, Koithan M. Models for the study of whole systems. *Integr Cancer Ther* 2006, **5**(4): 293–307.
10 Pomposelli R, Codecà G, Bergonzi R, *et al.* Terapia omeopatica in pazienti con patologia artroreumatica. *Medicina Naturale* 2003; **13**: 44–50.
11 Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30**(6): 473–483.
12 Garratt AM, Ruta DA, Abdalla MI, Buckingham JK, Russell IT. The SF36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? *Br Med J* 1993; **306**(6890): 1440–1444.
13 Apolone G, Mosconi P. The Italian SF-36 health survey: translation, validation and norming. *J Clin Epidemiol* 1998; **51**: 1025–1036.
14 Brazier JE, Harper R, Jones NM, *et al.* Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *Br Med J* 1992; **305**(6846): 160–164.
15 Walach H, Guthlin C. Effects of acupuncture and homeopathy: prospective documentation. Interim results. *Br Homeopath J* 2000; **89**: S31–S34.
16 Guthlin C, Lange O, Walach H. Measuring the effects of acupuncture and homoeopathy in general practice: an uncontrolled prospective documentation approach. *BMC Public Health* 2004; **4**(1): 6.
17 Meijer JW, Smit AJ, Sonderen EV, Groothoff JW, Eisma WH, Links TP. Symptom scoring systems to diagnose distal polyneuropathy in diabetes: the Diabetic Neuropathy Symptom score. *Diabet Med* 2002; **19**(11): 962–965.
18 Apolone G, Mosconi P, Ware JE Jr. *Questionario sullo stato di salute SF-36. Manuale d'uso e interpretazione dei risultati*. Milano: Guerini e Ass., 1997.
19 Mingardi G, Cornalba L, Cortinovis E, Ruggiata R, Mosconi P, Apolone G. Health-related quality of life in dialysis patients. A report from an Italian study using the SF-36 Health Survey. DIA-QOL Group. *Nephrol Dial Transplant* 1999; **14**(6): 1503–1510.
20 Everitt BS, Dunn G. *Statistical analysis of medical data*. London: Arnold, 1998.
21 Cohen J. *Statistical power analysis for the behavioral sciences*. Hillsdale: Lawrence Erlbaum, 1987.

22 Oberbaum M, Vithoulkas G, van Haselen R. Clinical trials of classical homeopathy: reflections on appropriate research designs. *J Altern Complement Med* 2003; **9**(1): 105–111.

23 Walach H, Falkenberg T, Fonnebo V, Lewith G, Jonas WB. Circular instead of hierarchical: methodological principles for the evaluation of complex interventions. *BMC Med Res Methodol* 2006; **6**: 29.

24 Hahnemann CFS. *Organon of medicine*. Edited from the 5th and 6th edition (1842) by Joseph Reves. Haifa: Homeopress Ltd, 1994.

25 Teut M. Homeopathy between vital force and self-organization. *Forsch Komplementarmed Klass Naturheilkd* 2001; **8**(3): 162–167.

26 Bell IR, Lewis DA, Lewis SE, Brooks AJ, Schwartz GE, Baldwin CM. Strength of vital force in classical homeopathy: bio-psycho-social-spiritual correlates within a complex systems context. *J Altern Complement Med* 2004; **10**(1): 123–131.