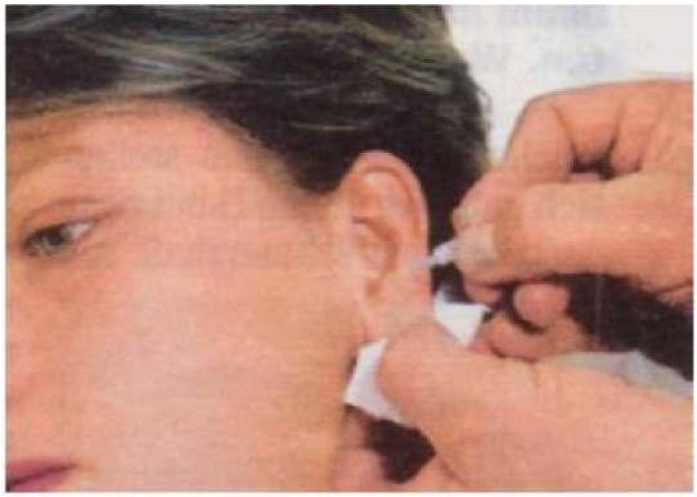
Werth's Parkinson's Implant Therapy (PBS)
- a first retrospective study (2006)

(an interdisciplinary working paper)



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Preface:

This paper takes a statistical approach to examining the financial implications of the innovative method of treatment known as Werth's Parkinson's Implant Therapy, a procedure which not only improves quality of life for Parkinson's patients, but also represents enormous potential savings for the German health service.

The study is addressed in particular to affected patients and their families, but also to health insurance funds, health politicians and pharmaceutical companies interested in helping us to continue our research in this field for the benefit of sufferers.

The implantation method was developed in response to the plasticity of the nervous system, which enables the brain to re-organise itself even after the necrosis of hundreds of thousands of nerve cells, such as can occur with Parkinson's disease. The ability of the brain to act in this way has already been established over extensive years of research in Neurobiology.

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1 Peripheral brain stimulation (PBS) – a new approach to treating Parkinson's syndrome

One characteristic disorder caused by Parkinson's syndrome is the degeneration and consequent loss of dopamine-producing (dopaminergic) neurons in the substantia nigra of the brain. By narrowing its vision to focus on this albeit undeniable aspect of the disease, medicine has developed a fatalistic attitude to prognoses and possible treatments. The consequence has been to fixate on discovering drugs which can substitute for dopamine or increase – temporarily – the efficiency of the dopaminergic synapses by artificial means. Patients go on to develop a life-long dependency on Parkinson's medication, which cannot be regarded as a welcome long-term outcome by any physician with a commitment to the Hippocratic oath. Medical considerations aside, the question arises of the financial efficacy of such an approach. According to the German Federal Office of Statistics, spending on medication has been increasing steadily above the rate of inflation. During the period 2001-2003, for instance, it rose from a little over € 35,000 million to € 37,540 million. This corresponds to an increase of 7.2 % or an annual rise of 2.36 %1, and contrasts with the average growth in the entire health budget of 1.7 % over the same period2. Then again, no form of treatment is quite as marketable as medication. Much of the outlay for the pharmaceutical industry goes into research and development. Average manufacturing costs, on the other hand, can be extremely low. From a purely commercial point of view, then, major potential for rationalisation is to be found in factory production. This being the case, it is hardly surprising that discussions about the potential 'neuroprotective' effect of established drugs are starting to be aired, in order to give existing pharmacotherapy a second wind. In all fairness, it must be admitted that medicine-based treatment has been a great boon for patients in recent years, and will continue to be so in the future, especially in pathological terms. Neurobiological findings, however, appear to show that purely medicine-based treatment doesn't really add up. Because what is true of any other cells in the body is true also of nerve cells, and in particular of dopaminergic cells: that providing relief through the exogenous administration of dopamine substitutes results in accelerated degeneration, and tends to have a negative rather than positive effect on the course of the disease. Extensive years of neurobiological research neurobiology have confirmed that such an association does indeed exist. Consequently, nervous system plasticity should lie at the heart of any consideration of the changes brought

[1] Applying the geometric mean for growth rates
[2] cf. Federal Office of Statistics, w/o author.

about by Parkinson's syndrome, and our approaches to treatment. Viewing the nervous system as a single entity made up of many coactive neuron systems also leaves room for the possibility that the dopaminergic neurons suffer not primary but secondary degeneration and eventual necrosis due to the lack of impulses which, during exposure to particular stresses, causes extreme conditions to affect the entire system. Then again, there are no definitive answers as to why the plasticity of the nervous system should collapse with the onset of morbidity, and whether there are any possible forms of treatment which would restore this plasticity, delivering better results over time. What are needed, then, are new approaches which improve the quality of life of the patient in the long term with fewer side-effects, and which at the same time help lighten the burden on the German health service during its current cost crisis.

One such approach is peripheral brain stimulation (PBS), a method which evolved from ear implant acupuncture. Whereas ear acupuncture using a few needles temporarily inserted into the exterior of the ear sometimes requires many sessions and is ineffective against diseases such as Parkinson's, ear implant acupuncture permanently implants titanium needles, promising a more intensive effect and a greatly reduced risk of infection (1:1000, effectively controlled with Sobelin, 4 x 300).

A study by E. Teschmar (2003) also showed discrete improvements in the treatment group compared with the control group[3]. PBS is an advanced form of ear implant acupuncture, which implants many more titanium needles in accordance with criteria which have yet to be published. It appears that habituation to the stimulation can be ruled out.

PBS seeks to activate neurohumoral factors via subcutaneous receptors in the outer ear, and involves stimulating regions of the brain to different degrees, thereby re-establishing equilibrium. In this way, unstable control circuits can be restabilised, particularly in the extra-pyramidal system, and doses of commonly-prescribed Parkinson's drugs can be reduced over the course of months.

[3] cf. Deutsche Parkinson Vereinigung e.V.

The following questions remain to be answered:

1. Can long-term positive effects also be achieved in a larger patient population and over a longer period?
2. Are these positive effects, for instance in terms of the dose of medication and the associated costs, regarded as a hard criterion?
3. If medication is not reduced, can evidence of overdosing be established?
4. What happens in the case of the untreated control group?
5. What is the effect of prolonged consumption of medication on disease prognosis in terms of increased dosage and cost?
6. What influencing factors are there, and what impact do they have?

A special questionnaire was needed to collect data from treated patients, most of whom lived some distance away. The intention was to reflect the mostly ‘on’ or mostly ‘off’ status of the patients in as objective a way as possible, as well as to take account of important external influencing factors. It also serves as an indicator of medical retrospection.

2 Data collection, descriptive statistics and analysis

Since examining a large number of patient characteristics introduces an equally large number of variables into the equation, from statistical and representative points of view it is essential for the data basis which is used to include the greatest possible number of observations. Conventional studies of Parkinson's patients using the Unified Parkinson's Disease Rating Scale (UPDRS) make it almost impossible, given the detail and comprehensiveness of the scale, to create a large data basis. A new rating scale has been developed in collaboration with neurologists, however, which nonetheless enables conclusions to be drawn which are comparable to those of the UPDRS, and which takes into account the most common symptoms suffered by Parkinson's patients. The precise classification used for this rating scale is explained in 2.1.1.

In order to make a quantitative assessment of the various degrees of severity of symptoms, each of these was assigned a score. More detail is provided about the precise methods used later in the text.

As described above, a data-collection questionnaire was developed which could be sent to a large number of treated patients. This solved the problem of using an insufficiently large sample group. In collaboration with psychologists from the University of Kiel, five arrays of questions were formulated so as to eliminate as far as possible any subjective factors such as the patient's motivation for seeking this form of treatment.

The Institut für Akupunktur und gesunde Medizin provided accurate treatment and patient data by means of a special anonymisation process. This made it possible to send out the questionnaire to 460 Parkinson's patients. A little more than 30 % of these were returned within about seven weeks. At the same time, an equivalent survey of patients who had not yet received Werth's therapy also had to be conducted. Once again, the Institut für Akupunktur und gesunde Medizin in Magdeburg provided support, with untreated patients being asked the same questions as their treated counterparts. This allowed a control group of 78 and a treatment group of 136 to be established.

2.1 Type of information sought

The questionnaires were to be as short as possible but as long as necessary so that the crucial information could be obtained whilst at the same time encouraging the

highest possible return rate by minimising the time required to complete it. The most important parameters appeared to be age (AGE), sex (SEX), body weight (BODYWT) in kg, the period in months between diagnosis and completion of the questionnaire (PARK_DIA), the period in months between first taking medication for Parkinson's and completing the questionnaire (PARK_MEDI), concomitant illnesses, in particular heart failure (HEARTF), the daily dose of medication (converted into cost in Euro (MEDI_COST)) and the state of health of the patient at the time of completing the questionnaire (RAT1, RAT2, RAT3). This enabled a quantitative comparison to be made between the control and treatment groups using a multivariate regression analysis.

2.1.1 Health rating scales

The new rating scales incorporated the most common symptoms observed in Parkinson's patients in clinical practice, and the patients were questioned accordingly.

	always	**often daily**	**some-times**	**seldom monthly**	**never**	
Involuntary movements e.g. of an arm or leg	0	1	2	3	4	
Involuntary twisting motions	0	1	2	3	4	**RAT1**
Restlessness, e.g. inability to sit still	0	1	2	3	4	
Rigidity of body and limbs	4	3	2	1	0	
Feeling rooted to the spot	4	3	2	1	0	
Short, shuffling steps when walking	4	3	2	1	0	
Tremors in the arms and legs	4	3	2	1	0	**RAT2**
Digestive disorders	4	3	2	1	0	
Severely stooped posture	4	3	2	1	0	
Agitation	4	3	2	1	0	
Good mood	0	1	2	3	4	
Feeling of isolation	4	3	2	1	0	**RAT3**
Good contact with friends and acquaintances	0	1	2	3	4	

Fig. 1: Arrays of questions on Parkinson's symptoms and the mood of the patient

The intensity with which symptoms manifested themselves was subdivided into five different categories depending on how often they occurred from four weeks before receipt of the questionnaire until the date of completion. Fig. 1 shows the array of questions put to the patients about their Parkinson's symptoms and their state of mind. Three different scales were developed. Rating scale 1 (RAT1) refers to uncontrolled movements of the patient, which are often observed when an exogenous overdose of a synthetically manufactured dopamine, a derivative or a precursor to dopamine is administered. Rating scale 2 (RAT2) refers exclusively to Parkinson's symptoms such as the frequency of a shuffling gait, tremors in the arms, a severely stooped posture, agitation, etc. Rating scale 3 (RAT3) describes the general state of mind of the patient. Here, the patient was questioned about the frequency of good moods and feelings of isolation and his level of social contacts. Five temporal categories from 'never' to 'always' gave rise to five levels of intensity (scored 0 – 4), which were then used to allocate a numerical value to a symptom. In the interests of simplifying the process as far as possible for the patient, without however allowing his personal assessment of the implant procedure to influence the results, he was asked to indicate the corresponding intensity of the symptoms which he personally observed. Scores were allocated only once the responses had been returned.

2.1.2 Parkinson's medication

In order to minimise potential sources of error when acquiring the data, the questionnaire asked patients to list all the medication they took in a day. They were to specify the name of the medicine, the number of units (tablets, injections, patches) administered per day, and the strength of each unit. The survey was most interested in the dose of Parkinson's medication, however, and this was entered into the database once the questionnaires had been returned. Medicines used to treat or alleviate the side-effects of Parkinson's medication, such as anti-depressants, diuretics or anti-hallucinatory drugs, were not included in the analysis.

Once all the data had been recorded, it was possible to identify 47 different Parkinson's medicines. The use of identical active ingredients and additives, so-called generic drugs, allowed the number of medicines to be reduced further to a final total of 16. In the case of medicines with a delayed action, so-called controlled-release drugs, it was the main active ingredient which was entered into the database. It is only logical to give due credit to the pharmaceutical industry for reducing the cost of the active ingredient by delaying its effect in this way, and for the associated reduction in side-effects. Since there are currently no unequivocal data available for

equivalence doses, it was necessary to resort to costs per milligramme of the active ingredient as a standardised value, and thus as a proxy variable. The study took as its basis the lowest price per milligramme of each active ingredient at 2006 prices.

2.1.3 Length of illness and period of medication

In the questionnaire, patients were asked to state the month and year in which the diagnosis was made and in which Parkinson's medication was first administered. Based on the date on which the patient completed the questionnaire, a figure of duration in months could be derived by subtraction, taking the average number of days per year to be 365.25. The formula shown in Equation 1 was used to calculate the PARK_DIA(MON) variable:

$$(1)\quad \text{PARK\_DIA(MON)} = \frac{(\text{COMPLDAT} - \text{DIAGNOSDAT})}{365.25} \cdot 12$$

A similar procedure was followed to calculate the period of Parkinson's medication. Because Parkinson's is regarded as a degenerative disease, and because it is suspected that the exogenous administration of dopamine accelerates the degenerative process by causing the remaining dopamine-producing cells to shut down production in increasing numbers because of this influx, these parameters are crucial to the analysis.

2.2 Descriptive statistics

The purpose of the following descriptive statistics is to contrast the members of the control and treatment groups in terms of the aforementioned characteristics with the help of the distribution parameters 'mean value' and 'standard deviation'. Table 1 shows the results which were obtained. There were no appreciable differences between the two groups in terms of age, sex or body weight. The length of illness and the period during which medication was taken were, on average, 8 and 4.6 months longer respectively than for the control group.

Despite the progressive course of the disease, the treatment group averaged better scores than the control group on each of the rating scales. Remarkably, even the average cost in Euro per day of medication was € 5.67 below that of the control group, despite the longer periods of illness and medication.

Variable	Description	Control group (n=78) Mean value	Control group (n=78) Standard deviation	Treatment group (n=136) Mean value	Treatment group (n=136) Standard deviation
SEX	0 = Male, 1 = Female	0.31	(0.46)	0.34	(0.48)
AGE	Age of patient in years	69.66	(7.59)	69.33	(7.42)
BODYWT	Body weight in kg	73.81	(10.87)	73.72	(13.48)
PARK_DIA	No. of months since diagnosis	69.25	(59.78)	76.74	(61.05)
PARK_MEDI	No. of months since first medication	64.97	(59.05)	69.33	(61.88)
HEARTF	Heart failure: 0 = No, 1 = Yes	0.12	(0.32)	0.18	(0.38)
RAT1	Score on Scale 1 (involuntary movements)*	7.13	(3.34)	8.48	(3.12)
RAT2	Score on Scale 2 (general Parkinson's symptoms)**	16.42	(6.01)	14.40	(6.01)
RAT3	Score on Scale 3 (mood of patient)	4.17	(2.88)	3.82	(2.59)
ACU_PER	No. of months since implantation	0.00	(0.00)	3.43	(1.85)
MEDI_COST	Cost of medication in € per day	16.29	(21.93)	10.62***	(12.35)

* The higher the score, the fewer the instances of hyperactivity in the patient
** The higher the score, the more pronounced the symptoms of Parkinson's
For variables with binary values (0/1), the mean value indicates the percentage
*** With 20 bootstrap replications in the control group and 15 replications in the treatment group, differs from the mean value of the control group with a probability of error of less than 0.01 %

Table 1: Contrasting the mean value and standard deviation in the control and treatment groups

Fig. 2 illustrates the distribution of length of illness in months (PARK_DIA).

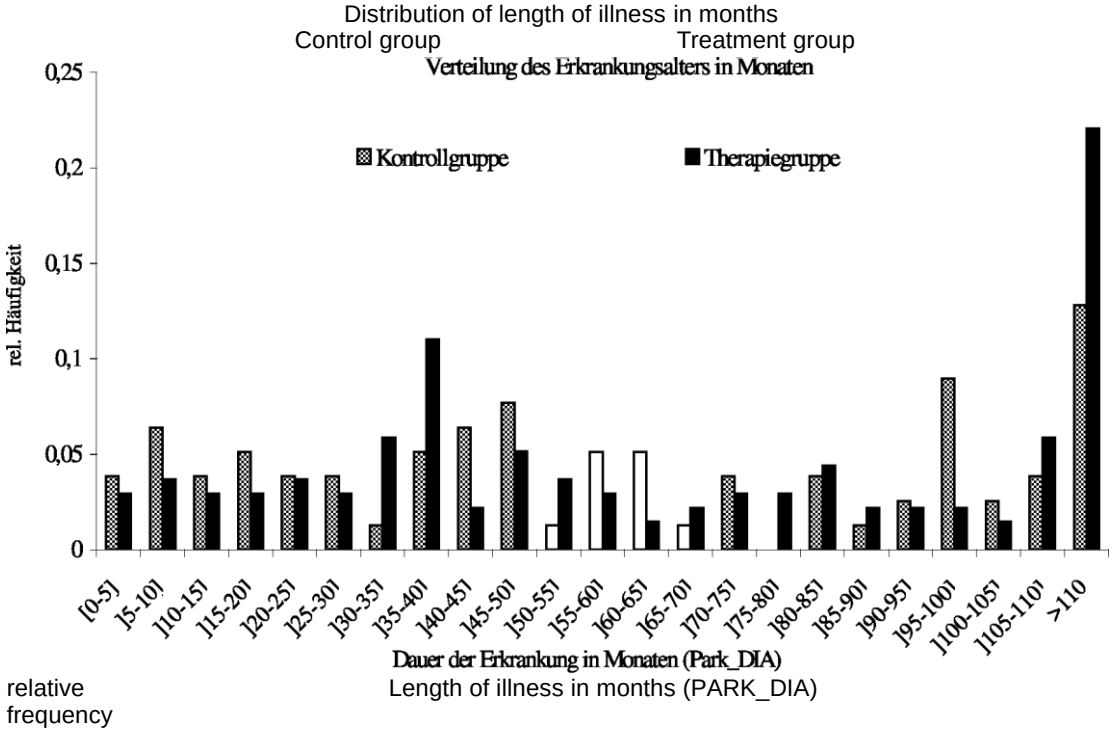

Fig. 2: Distribution of length of illness in the control and treatment groups

This enables any potential anomalies to be identified which unduly distort the mean value. It is apparent that a not insignificant proportion of the treatment group (22 %)

had been ill for longer than 110 months. In the case of the control group, only 12 % had been ill for longer than this period.

The following distributions were observed for the two groups in terms of the daily cost in € of Parkinson's medication.

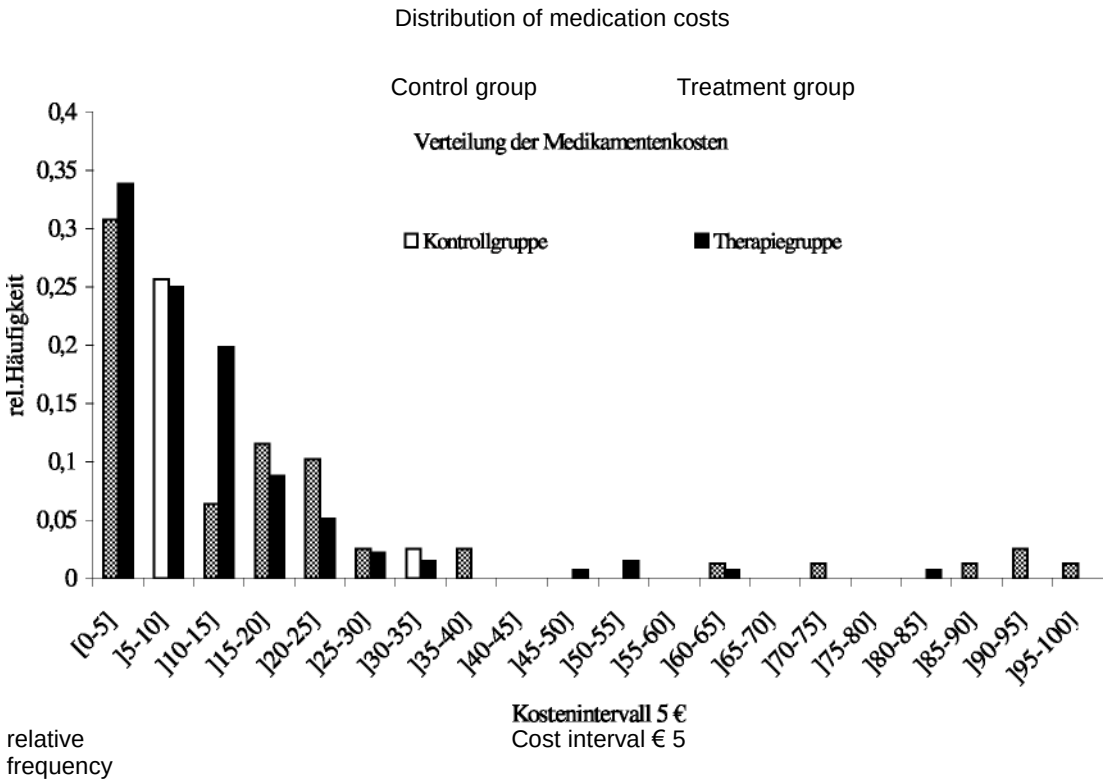

Fig. 3: Distribution of medication costs in the control and treatment groups

Figure 3 demonstrates that the daily costs of medication for the treatment group are more heavily concentrated at the lower end of the scale. Table 1 already showed that the control group costs were more widely distributed, with a higher absolute standard deviation. In order to guard against the possible charge that the mean value was distorted by anomalies, however, a hypothesis test was used to show that the difference in mean value is of a systematic rather than random nature. Fig. 3 provides visual evidence that the costs of medication in the two groups are distributed with positive rather than normal skewness. For this reason, the bootstrapping procedure[4] was applied so as to generate normal distribution through random samples, despite the relatively small size of the sample. An MS Excel programme was used to draw a random sample of identical size fifteen times from the treatment group and twenty times from the control group from the original

[4] For more information, visit the website http://www-stat.stanford.edu/~susan/courses/b494/index/node53.html, Rev. 21 August 2006

population of each group. Then, using the Jarque-Bera test, a check was made to ascertain whether the mean values of these random selections were consistent with normal distribution. After a positive result for both groups was obtained from this test, a conventional t test was used, with independent samples.

Equation 2 shows the t test again in a formal way, together with the result which was obtained.

$$(2) T = \frac{(\overline{X}_{KG} - \overline{X}_{TG})}{S\sqrt{\frac{n_{KG} + n_{TG}}{n_{KG} n_{TG}}}}$$

	Control group	Treatment group
n	20	15
Group variance estimator	4.899	0.602
Mean value	15.615	10.815
Common variance S	3.172	
Mean value difference	4.800	
Factor unequal n	0.342	
Factor n*S	1.084	
t value	4.430	
Degrees of freedom	33	
Critical t value	2.74	
Null hypothesis	Rejection of null hypothesis at 0.01 because 4.430 > 2.74	

Table 2: Results of the hypothesis test after bootstrapping with the null hypothesis: no significant difference in mean value between the groups

Therefore, the difference in mean value between the control and the treatment groups is not a matter of chance, but is systematic and consequently of significance. For two reasons, the mean value difference in medication costs between the two groups in Table 1 is an underestimate. Firstly, all medication to treat the side-effects of Parkinson's medication has been excluded from the study. Just as with any other drug, it is true here too that the more medication is consumed, the more likely and more marked the side-effects. Consequently, the more medication one takes, the more one is compelled to take to combat its side-effects. The correlation between the costs of Parkinson's medication and medication against side-effects has to be positive. No individual evidence is presented here in support of this thesis, because it lies beyond the remit of the study. Secondly, in clinical practice it is often the case that Parkinson's medication is not reduced to the greatest possible degree, either

because the patient has failed to attend a follow-up examination, or because the G.P. or neurologist who continues to treat him has declined to make any such reduction.

2.3 A parametric approach

The relationships between individual variables are of particular interest in a statistical examination of the underlying data. Although it is certainly true that a statistical dependency does not allow conclusions to be drawn about causality with any certainty, as is so frequently attempted. In order to guard against such a charge from the outset, it should be noted that what we have here is merely a collection of statistical relationships.

We were most interested in the relationship between the length of time during which Parkinson's medication was taken (PARK_MEDI) and daily medication costs in € (MEDI_COST). We used the MS Excel programme to calculate the correlation coefficient $\rho_{PARK\_MEDI,\ MEDI\_COST}$ between the two values after *Bravais-Pearson*, using the formula shown in Equation 3, with separate calculations for the control group and the treatment group.[5]

$$(3) \quad \rho_{PARK\_MEDI,\ MEDI\_COST} = \frac{COV\ (PARK\_MEDI,\ MEDI\_COST)}{PARK\_MEDI\ .\ \ MEDI\_COST}$$

where $-1 \quad \rho_{PARK\_MEDI\ :\ MEDI\_COST} \quad 1$

COV(PARK_MEDI, MEDI_COST) represents the covariance between the period of consumption of medication and the cost of medication. The denominator in the fraction in Equation 3 represents the product of the standard deviations of PARK_MEDI and MEDI_COST.

Correlation matrix Group	Variable	Medication costs
Control group	Body weight	0.233
	Age	-0.145
	PARK_DIA	**0.293**
	PARK_MEDI	**0.304**
	RAT1	-0.063
	RAT2	0.000
	RAT3	-0.003
Treatment group	Body weight	0.014
	Age	-0.151
	PARK_DIA	**0.151**
	PARK_MEDI	**0.182**
	RAT1	-0.057
	RAT2	0.036
	RAT3	0.057

Table 3: Results of calculating correlation coefficients after Bravais-Pearson

[5] cf. J. Bleymüller, G. Gehlert, H. Gülicher (2000), p. 145

The results calculated for all variables can be found in Table 3. It is clear that the length of illness and the period of administration of Parkinson's medication have a positive correlation with the level of medication costs, and that this correlation is much weaker in the treatment group than in the control group. All of the other variables exhibit a weak to non-existent statistical relationship with the costs of medication. However, it is apparent that the correlation coefficients of the treatment group are lower in absolute terms than those of the control group, with the exception of those of the variables 'age' and 'RAT2'.

So far, our study has concentrated on scrutinising individual variables. Now, however, we shall go on to use multivariate regression analysis to test other statistical relationships between effects and to support the suspicions raised by correlation analysis. In the following linear regression analysis, daily medication costs (MEDI_COST) in € were regressed on the age of the patient, the period of administration of Parkinson's medication (PARK_MEDI) and group membership for all 214 patients. It transpired that the relationship observed between the named variables was logarithmic in nature. At the same time, examinations revealed that group membership, as a dummy variable, had no significant impact on the parameter of level of the evaluation, but did so on the coefficients of the logarithmised period of administration of Parkinson's medication (ldPARK_MEDI). The Ordinary Least Squares (OLS) method was used for regression analysis, which assumes a linear relationship between the exogenous independent and endogenous dependent variables. As stated above, however, the relationship is logarithmic. If, as shown in Equation 4, one subjects a logarithmisation of all variables to regression analysis, the required linear relationship again becomes apparent.

(4) $ldMEDI\_COST_i = \quad + (\ _1 + \ D_i)\ ldPARK\_MEDI_i + \ _2\ ldAGE_i$
with i = 1…. N [6]

$$D_i = \begin{cases} 0 \text{ if member of control group} \\ 1 \text{ if member of treatment group} \end{cases}$$

Here, variable D_i indicates group membership. It is binary coded, and equals 1 if the patient is a member of the treatment group, and 0 if the patient is a member of the control group. , the coefficient of D_i, represents the difference in the increase in the

[6] cf. mathematical appendix for derivation of the relationship

functions of the two groups. The product of the two is described as the interaction dummy. Parameter indicates the value to which $_1$ must be added to obtain the increase in the treatment group as regards the period of medication consumption.[7] Equation 4 also indicates the function to be estimated. This function was estimated using the MS Excel programme. The results are contained in Table 4.

Regression statistic	
Multiple correlation coefficient	0.558
Coefficient of determination	0.311
Adjusted coefficient of determination	0.301
Standard error	0.966
Observations	214
Degrees of freedom	210
Total variance of residuals	0.919
Estimated variance of residuals (c group)	1.140
Estimated variance of residuals (t group)	0.800

	Coefficients	t statistic	p value
Point of intersection	7.502	2.934	0.004
ldPARK_MEDI	0.449	8.929	0.000
ldPARK_MEDIGR	-0.065	-1.830	0.069
ldAGE	-1.658	-2.751	0.006

Table 4: Results of regression analysis

It should first be noted that all of the parameters of the function lie below the level of significance of 10 %. If significance is actually to be demonstrated, the differences between the estimated and actually observed values, the so-called residuals, must follow a normal distribution pattern. The p value is nothing other than the probability measure of a supposed t distribution which lies to the right of the t value of the t statistic. In this significance test, the null hypothesis states that the parameter under consideration exerts no influence on the endogenous variable. In order to minimise the Type I error risk of the erroneous rejection of the null hypothesis, the level of significance, expressed as probability measure to the right or left (depending on the sign preceding the t value) of the calculated t value, is compared with as small a value as possible. In statistical practice, three values are used. These are the 10 %, 5 % and 1 % levels of significance. If the p value is less than the level of significance for comparison, the null hypothesis is rejected. In the converse case, the null hypothesis is accepted.

With regard to the assumption of normal distribution, a Kolmogorov-Smirnov test conducted with the SPSS statistics programme suggests that the residuals converge

[7] cf. von Auer (2005), pp. 311 ff.

to a normal distribution.[8] Furthermore, the central limit theorem ensures that if a sufficiently large sample size is used (such as in this case, N = 214), the probability distributions of the estimated coefficients converge to normal distributions, and thus the hypothesis tests retain their validity in terms of significance.[9]

Interpreting the coefficients requires further deliberation, however, because the estimated model for comparative statements must be retransformed. This retransformation is usually performed using an inverse function. However, there is a risk of distortion if any group-specific heteroscedasticity[10] is present (cf. Winkelmann (2001)).[11] Group-specific heteroscedasticity can be found using the test statistic represented in Equation 5.

(5) n. ld ^{2} – n_{KG} . ld $^2_{KG}$ – n_{TG} . ld $^2_{TG}$

The values of the estimated variances can be found in Table 4. Thus ^{2} stands for the estimated variance of the residuals in the entire sample, and the two other sigma signs for the estimated variance of the residuals in the control and treatment groups. The following resulting value should be considered.

214 . ld 0.919 – 78 . ld 1.140 – 136 . ld 0.80 = 2.051 < 2.7554

The value calculated from Equation 5 then follows an ^{2} distribution with a degree of freedom, when it does not exceed the critical value (in this case, 2.7554). The underlying null hypothesis in this case is that there is homoscedasticity between the groups. The null hypothesis must be accepted by a narrow margin in this case. The Type II error risk of an erroneous acceptance of the null hypothesis is somewhat more than 10 % here. If one therefore assumes that there is no group-specific heteroscedasticity, the coefficients must be interpreted correctly when comparing the two groups. Equation 6 shows that the coefficient of the variables is to be viewed as elasticity. By using Equation 4 and carrying out partial differentiation, the relationship shown in Equation 6 results for the control group coefficient.

$$(6)\quad {}_1 = \frac{d\,(\mathrm{ld}MEDI\_COST_j)}{d\,(\mathrm{ld}PARK\_MEDI_i)} \qquad \textit{and thus}$$

$$ {}_1 = \frac{dMEDI\_COST_j / MEDI\_COST_j}{dPARK\_MEDI_i / PARK\_MEDI_i}$$

[8] The two-sided level of significance is 89 %; for more on the Kolmogorov-Smirnov test, cf. J. Bleymüller, G. Gehlert, H. Gülicher (2000), pp. 133 ff.

[9] cf. L. von Auer (2005), p. 415

[10] Heteroscedasticity is the violation of the assumption of the OLS that the variance of the residuals remains constant over all N observations.

[11] cf. R. Winkelmann (2001) in 'Jahrbücher für Nationalökonomie und Statistik' ('National Economy and Statistics Yearbooks'), p. 429

Expressed in words, $_1$ indicates by how many percent the costs for Parkinson's medication increase when the period of medication rises by one percent. The coefficient for the treatment group is found by adding $_1$ = 0.449 and = -0.069. Let $_{TG}$ = $_1$ + be the coefficient of the period during which medication was consumed by the treatment group. Then with a 1 % increase in the period of consumption, medication costs will rise by 0.449 % for the control group and 0.384 % for the treatment group. The difference may not appear great at first sight. Its significance becomes clearer, however, if one retransforms the estimated equation. Formula 7 shows the results of this retransformation.

(7) $MEDI\_COST_i = e \ . \ PARK\_MEDI_i^{\ 1} \ . \ AGE_i^{\ 2}$ *for the C group*

$MEDI\_COST_i = e^{\ 12} \ . \ PARK\_MEDI_i^{\ TG} \ . \ AGE_i^{\ 2}$ *for the T group*

Partial differentiation of Formula 7 gives the marginal change in medication costs if one variable changes by one unit. It is interesting to see what value results for medication costs with a marginal change in the period of consumption of the groups in accordance with the estimated regression function. For this purpose, the partial differentiation of Equation 7 is performed with respect to PARK_MEDI.

(8) $$\frac{dMEDI\_COST_i}{dPARK\_MEDI_i} = e \ . \ _1 \ . \ PARK\_MEDI_i^{\ 1-1} \ . \ AGE_i^{\ 3}$$

$_1$ > $_{TG}$ shows that the marginal absolute change which occurs with a one-month increase in PARK_MEDI is also greater for the control group than for the treatment group. The level which is achieved over time is shown in Fig. 4.

[12] For retransformation, cf. mathematical appendix

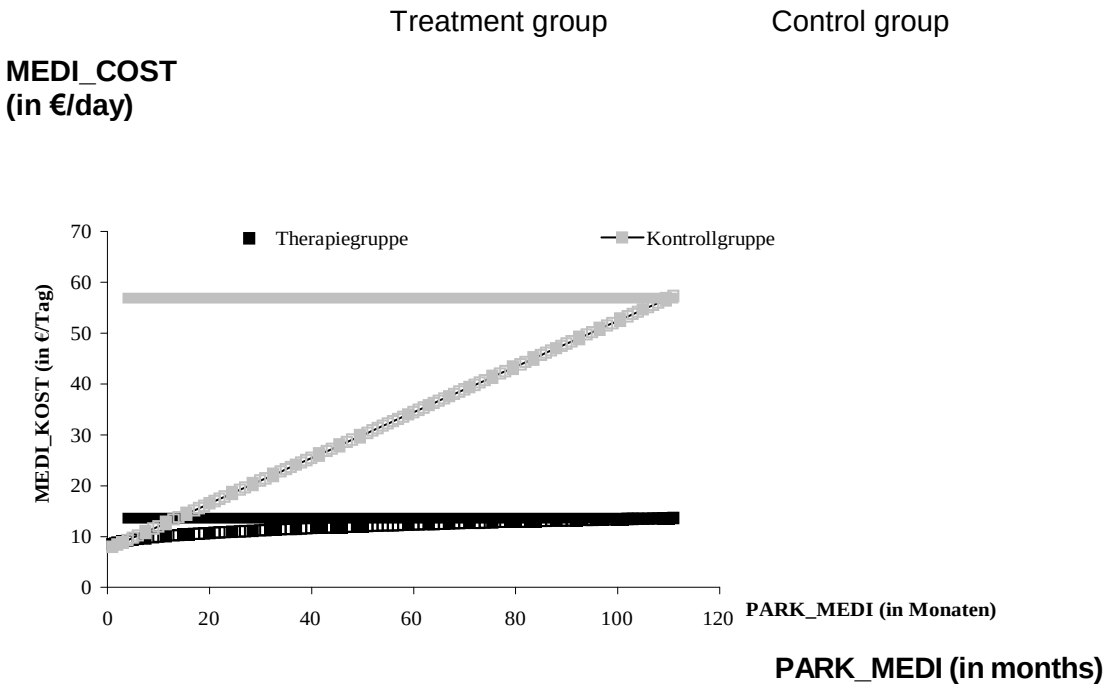

Fig. 4: Bivariate relationship from the OLS estimation between the increase in medication costs in €/day and the period of consumption

Because of the underlying functional form, both the absolute and the relative differences between the two groups increase over time. These statements apply *ceteris paribus* with respect to length of illness and period of consumption. In previous estimations, it was established that all the other variables were firstly of no significance, and secondly, as the correlation matrix has already shown, that they made no additional contribution to medication costs. This should be qualified by noting that the estimation which was made only has a corrected coefficient of determination of 30.1 %. Thus there are also other determinants for medication costs. They do not, however, include comorbidity, sex and body weight. Since the length of the illness and the period of medication are almost perfectly collinear, it was adjudged to be reasonable to use only one of the two variables for the estimation in Equation 4.

3 Interpretation and discussion of results

The descriptive statistics show that patients in the treatment group consumed significantly less Parkinson's medication. And this, despite the fact that some of those questioned inevitably received no follow-up treatment; for instance, there was no consultation with the neurologist who continued to treat them. Patients whose medication was reduced under medical supervision noticed a considerable improvement in their condition. Once a patient becomes physically active, he relearns harmonious body movements. Many patients reported that they had resumed earlier hobbies and activities.

Even more striking than the simple fact alone that Parkinson's patients treated with PBS took lower doses of medication is the conclusion in Fig. 4 that the quantity of medication consumed increases, the longer the period of consumption.[13] The divergence of the two functions over the period of consumption makes this clear. The discrepancy of 0.065 between the rises in the control and the treatment groups initially strikes one as small, but it is nonetheless of great import, because it is a question of elasticities. Suppose the period of medication was to increase by 1 %. This would mean an extra 3.6 days in a 12-month period, during which the medication costs of the control group would rise by 0.449 %. The function of the treatment group, on the other hand, is much less steeply inclined. Moreover, experience at the practice shows that the minor increase which was identified resulted from the large size of the patient group, each of whose members has individually reduced his Parkinson's medication or seen it increase only very slightly.[14]

For individual patients, this means that their Parkinson's has either failed to progress, or has even abated. In parallel with these initially apparently insignificant figures, one finds that the improvement in general wellbeing which results from the receding prospect of nursing care and the resumption of hobbies represents a considerable improvement in quality of life.

We need to re-examine the medical dogma which states that, because Parkinson's kills 450,000 nerve cells in the substantia nigra, there is only one option, namely to provide a medicinal substitute for the neurotransmitter dopamine which is produced by these neurons. To do otherwise would be simply to turn our backs on the

[13] The medication costs were used in the study as a proxy variable for the quantity of medicine consumed, or as a type of equivalence dose, for which there is currently only imprecise information available.

[14] Since this is a cross-sectional analysis.

extensive years of research which have been carried out. The fact is that we have long been aware of the plasticity of the nervous system; in general, nerve cells can take over just about any function of the nervous system which is lost due to the necrosis of other nerve cells. One example is movement disorders in Parkinson's patients. What is crucial for movement is not that all the nerve cells are living, but that the muscles are activated in the proper time sequence and at the appropriate intensity by the action potential of the peripheral nerves. *Are we claiming, then, that this can only be achieved by those 450,000 particular nerve cells which have died in Parkinson's patients?* The so-called neural network in the brain is made up of at least 10,000 million nerve cells with 100 to 100,000 connections per cell. Excitations, which form the material basis of human thought, feeling and movement, pass through this complex network. Changes in the spatial and temporal pattern of excitation are the norm, because each time a synapse is used, it changes. Just as muscles can be trained, so too can nerve cells and their synapses. Disuse leads to atrophy and necrosis. The death of nerve cells and their replacement by others which perform the same function is commonplace in the brain; otherwise, we wouldn't be able to learn, revise our opinions or comprehend the ever-changing diversity of life, progress, and all that surrounds us. The nervous systems of Parkinson's patients can also change in the same way, as treatment with PBS has shown. Neurobiologists have discovered not only that synapses can change their effectiveness (synaptic patency), but also that new synapses can be formed, as neuroanatomists at the Charité in Berlin discovered when they conducted a count of nerve cells. Moreover, undifferentiated stem cells have been discovered in the ventricle of the brain which could take the place of and substitute for necrotic cells.

The results of this study show that, to a large extent, PBS offers an alternative which largely prevents the disease from following its usual course culminating in nursing care, and a way of reducing the consumption of Parkinson's medication. The time is ripe, then, to have done with the old dogma. To conclude, it is possible to have a positive impact on Parkinson's without the incidence of side-effects.

Health politicians should be clearing a place on the agenda for the promotion of this sort of innovation as a recommended form of action. But for this to become a reality, a collective decision in favour of these innovations is required. The logic of collective decision-making states that the implementation of financial policies never meets with organised resistance if the additional burden is shouldered by many.[15] This is precisely what happens in the German health service with respect to all the services

[15] cf. M. Olsen, 'The Logic of Collective Action' from P.R. Krugman, M. Obstfeld (2003), p. 305

of statutory health insurance (treatment from the catalogue of services, medication, remedies, appliances, etc.). For in such cases, the insured citizens of Germany are obliged to bear only a contribution proportionate to their income, and not the actual costs of treatment. Although the efficiency principle applies, whose basis for calculation is income, an individual insured person is not, however, completely in the picture about how additional costs in the health service are met. It is only when there are increases in contribution rates that the public protests, although this is short-lived and disorganised in nature. Moreover, adopting PBS in the catalogue of services offered by statutory health insurance would ensure justice and equality of treatment, because not every sufferer is in a position to fund his own treatment.

From a purely financial point of view, however, further studies need to be carried out to compare the treatment and control groups in terms of the total cost to the health service of Parkinson's disease, so that the genuine net saving becomes apparent, once all factors have been taken into account. Because the costs of treatment must undoubtedly be outweighed by the reduction in spending on medication.

Overview of variables

Variable	Description
ACU_PER	No. of months since implantation
AGE	Age in years of patient at time of survey
Sex	Male = 0, Female = 1
GR	Group membership: 0 = Control group, 1 = Treatment group
HEARTF	Heart failure: 0 = No, 1 = Yes
BODYWT	Body weight in kg of patient at time of survey
ldAGE	Logarithmised age (natural logarithm to the base e)
ldPARK_MEDI	Logarithmised no. of months since start of medication
ldPARK_MEDIGR	Interaction dummy, product of logarithmised period of consumption and group membership
MEDI_COST	Cost in €/day of Parkinson's medication
PARK_DIA	No. of months since diagnosis at time of survey
PARK_MEDI	No. of months since start of medication
RAT1	Score on scale 1 (involuntary movements)
RAT2	Score on scale 2 (general Parkinson's symptoms)
RAT3	Score on scale 3 (mood of patient)

Mathematical appendix

If

y_1 = *MEDI_COST*$_i$, x_{1i} = *PARK_MEDI*$_i$, D_i = *GR*, D_i . x_{1i} = *PARK_MEDIGR*$_i$, x_{2i} = *AGE*

then in general:

$(I)\ \ y_i = \alpha + \beta_1 x_{1i} + \beta_{2i}$ — *the model to be estimated*

$\hat{y}_i = \hat{\alpha} + \hat{\beta}_1 x_{1i} + \hat{\beta}_2 \hat{x}_{2i} + \hat{u}_i$ — *the estimated model*

where

$i = 1.....N$

Because of the structural break in the gradient parameter of x_1, one finds:

$(II)\ \ y_i = \alpha + (\beta_1 + \delta D_i) x_{1i} + \beta_2 x_{2i}$

$\hat{y}_i = \hat{\alpha} + (\hat{\beta}_1 + \hat{\delta} D_i) x_{1i} + \hat{\beta}_2 x_{2i} + \hat{u}_i$

where indicates the gradient parameter of the interaction dummy *D . GR*.

The underlying relationship is not linear, however, as the Ordinary Least Square estimation requires. Instead, it is logarithmic in nature. Consequently, a logarithmic transformation must take place before the OLS method can be applied. Thus:

$(III)\ \ \ln y_i = \alpha + (\beta_1 + \delta D_i) \ln x_{1i} + \beta_2 \ln x_{2i}$

with the following results for the two groups:

$(IV)\ \ \ln y_{KGi} = \alpha + \beta_1 \ln x_{1i} + \beta_2 \ln x_{2i}$ — for the control group

$\ln y_{TGi} = \alpha + (\beta_1 + \delta D_i) \ln x_{1i} + \beta_2 \ln x_{2i}$ — for the treatment group

Since the relationship is now linear again, the OLS method can be applied. The general case (I) is used to derive the coefficients. The Ordinary Least Square method is used to minimise the sum of the squared distances between estimated value and actually observed value *y*. Thus the objective function is

$\min S_{\hat{u}\hat{u}} = \sum_{i=1}^{N} (y_i - \hat{y}_i)^2 = \sum_{i=1}^{N} \hat{u}_i^2$. $S_{\hat{u}\hat{u}}$ signifies the sum of the residual squares with

$\hat{u}_i = y_i - \hat{y}_i = y_i - \hat{\alpha} - \hat{\beta}_1 x_1 - \hat{\beta}_2 x_2$.

Thus the three first-order conditions are:

$$\frac{\partial S_{\hat{u}\hat{u}}}{\partial \hat{\alpha}} = 0, \frac{\partial S_{\hat{u}\hat{u}}}{\partial \hat{\beta}_1} = 0, \frac{\partial S_{\hat{u}\hat{u}}}{\partial \hat{\beta}_2} = 0$$

In order to be able to maintain an overview of the derivation of the normal equations, it is expedient to use the following simplification for the variation of the individual variables, denoted S_{11} for x_1, for instance:

$$S_{11} = \sum x_{1i}^2 - N\bar{x}_1^{\,2}$$

Here, $\bar{x}_1$ stands for the mean value of x_1. x_2 and y are dealt with similarly.

$$\frac{\partial S_{\hat{u}\hat{u}}}{\partial \hat{\alpha}} = \sum 2(y_i - \hat{\alpha} - \hat{\beta}_1 x_{1i} - \hat{\beta}_2 x_{2i}) \cdot (-1) = 0$$

$$\frac{\partial S_{\hat{u}\hat{u}}}{\partial \hat{\beta}_1} = \sum 2(y_i - \hat{\alpha} - \hat{\beta}_1 x_{1i} - \hat{\beta}_2 x_{2i}) \cdot (-x_{1i}) = 0$$

$$\frac{\partial S_{\hat{u}\hat{u}}}{\partial \hat{\beta}_2} = \sum 2(y_i - \hat{\alpha} - \hat{\beta}_1 x_{1i} - \hat{\beta}_2 x_{2i}) \cdot (-x_{2i}) = 0$$

Using the simplifications for the variations, one finds, after a few algebraic conversions:

$$(V) \sum y_i = N\hat{\alpha} + \hat{\beta}_1 \sum x_{1i} + \hat{\beta}_2 \sum x_{2i}$$

$$(VI) \sum x_{1i} y_i = \hat{\alpha} \sum x_{1i} + \hat{\beta}_1 \sum x_{1i}^2 + \hat{\beta}_2 \sum x_{1i} x_{2i}$$

$$(VII) \sum x_{2i} y_i = \hat{\alpha} \sum x_{2i} + \hat{\beta}_1 \sum x_{1i} x_{2i} + \hat{\beta}_2 \sum x_{2i}^2$$

After dividing (V) by N, the estimated value of parameter of level is:

$$\hat{\alpha} = \bar{y} - \hat{\beta}_1 \bar{x}_1 - \hat{\beta}_2 \bar{x}$$

Because $\bar{y} = (1/N)\sum y_i, \bar{x}_1 = (1/N)\sum x_{1i}, \bar{x}_2 = (1/N)\sum x_{2i}$ one finds, after insertion in (VI) and (VII):

$$\sum x_{1i} y_i = N\bar{x}_1(\bar{y} - \hat{\beta}_1 \bar{x}_1 - \hat{\beta}_2 \bar{x}_2) + \hat{\beta}_2 \sum x_{1i}^2 + \hat{\beta}_2 \sum x_{1i} x_{2i}$$

$$\sum x_{2i} y_i = N\bar{x}_2(\bar{y} - \hat{\beta}_1 \bar{x}_1 - \hat{\beta}_2 \bar{x}_2) + \hat{\beta}_1 \sum x_{1i} x_{2i} + \hat{\beta}_2 \sum x_{2i}^2$$

and consequently:

$$S_{1y} = \hat{\beta}_1 S_{11} + \hat{\beta}_2 S_{12}$$

$$S_{2y} = \hat{\beta}_1 S_{12} + \beta_2 S_{22}$$

with S_{1y} the covariation of y and x_1 and S_{2y} the covariation of y and x_2.

Thus the conditional equations for the coefficients of the gradient parameters are:

$$\hat{\beta}_1 = \frac{S_{22}S_{1y} - S_{12}S_{2y}}{S_{11}S_{22} - S_{12}^2}$$

$$\hat{\beta}_2 = \frac{S_{11}S_{2y} - S_{12}S_{1y}}{S_{11}S_{22} - S_{12}^2}$$

In order for it to be possible to interpret the estimated coefficients in the underlying case of the logarithmic function, Equation III must be retransformed by exposure. The function shown in (VIII) results:

$$(VIII)\ y_i = e^{\alpha} \cdot x_{1i}^{(\delta D_i + \beta_1)} \cdot x_{2i}^{\beta_2}$$

with $D_i = \begin{cases} 0 & \text{for control group member} \\ 1 & \text{for treatment group member} \end{cases}$

Bibliography and internet sources

Auer, v. L., (2005), Ökonometrie – Eine Einführung, 3rd edition, Springer Verlag, Berlin, Heidelberg

Bleymüller, J., Gehlert, G., Gülicher, H. (2000), Statistik für Wirtschaftswissenschaftler, 12th edition, Verlag Vahlen

Jarque, C.M., Bera, A.K. (1987), A Test for Normality of Observations and Regression Residuals, International Statistic Review, 55, 163 – 177

Krugman, P.R., Obstfeld, M., (2003), Internationale Wirtschaft – Theorie und Politik, extract from Mancur Olsen, 'The Logic of Collective Action', Cambridge: Havard University Press, 1965, 6th edition, Pearson Studium

Statistisches Bundesamt (2005), 28/8/2006, Gesundheitsausgaben nach Leistungsarten, http://www.destatis.de/basis/d/gesu/gesutab5.php