# Investigation by Parkinson's Disease Research Group of United Kingdom into excess mortality seen with combined levodopa and selegiline treatment in patients with early, mild Parkinson's disease: further results of randomised trial and confidential inquiry

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## Abstract

**Objective:** To determine whether the excess mortality observed in patients who received both levodopa and selegiline in a randomised trial could be explained by revised diagnosis of Parkinson's disease, autonomic or cardiovascular effects, more rapid disease progression, or drug interactions.

**Design:** Open randomised trial and blind comparison and reclassification of the cause of death of patients who were recruited from 93 hospitals between 1985 and 1990 and who had died before December 1993 in arms 1 and 2.

**Setting:** United Kingdom.

**Subjects:** 624 patients with early Parkinson's disease who were not receiving dopaminergic treatment and a subgroup of 120 patients who died during the trial.

**Interventions:** Levodopa and a dopa decarboxylase inhibitor (arm 1), levodopa and a dopa decarboxylase inhibitor in combination with selegiline (arm 2), or bromocriptine alone (arm 3).

**Main outcome measures:** All cause mortality for 520 subjects in arms 1 and 2 and for 104 subjects who were randomised into these arms from arm 3. Cause specific mortality for people who died in the original arms 1 and 2 on the basis of the opinion of a panel, revised diagnosis and disability ratings, evidence from clinical records of either autonomic or cardiovascular episodes, other clinical features before death, and drug interactions.

**Results:** After extended follow up (mean 6.8 years) until the end of September 1995, when arm 2 was terminated, the hazard ratio for arm 2 compared with arm 1 was 1.32 (95% confidence interval 0.98 to 1.79). For subjects who were randomised from arm 3 the hazard ratio for arm 2 was 1.54 (0.83 to 2.87). When all subjects were included the hazard ratio was 1.33 (1.02 to 1.74) and after adjustment for other baseline factors it was 1.30 (0.99 to 1.72). The excess mortality seemed to be greatest in the third and fourth year of follow up. Cause specific death rates showed an excess of deaths from Parkinson's disease only (hazard ratio 2.5 (1.3 to 4.7)). No significant differences were found for revised diagnosis, disability rating scores, autonomic or cardiovascular events, other clinical features, or drug interactions. Patients who died in arm 2 were more likely to have had possible dementia and a history of falls before death compared with those who died in arm 1.

**Conclusion:** The results consistently show excess mortality in patients treated with combined levodopa and selegiline. Revised diagnosis, autonomic or cardiovascular events, or drug interactions could not explain this finding, but falls and possible dementia were more common in arm 2. The results do not support combined treatment in patients with newly diagnosed Parkinson's disease. In more advanced disease, combined treatment should perhaps be avoided in patients with postural hypotension, frequent falls, confusion, or dementia.


## Introduction

The Parkinson's Disease Research Group of the United Kingdom reported increased mortality in patients with early, mild Parkinson's disease who were randomly allocated combined levodopa and selegiline treatment (arm 2) compared with levodopa alone (arm 1).[1] Relative mortality was increased by about 60%, equivalent to one excess death for every 54 patients treated for 1 year. No clinically important differences in disability ratings were noted after either 1[2] or 4 years.[1] These results were unexpected as selegiline was thought to protect against nigral cell death,[3] to slow disease progression,[4] and to reduce death rates.[5]

This trial has generated much controversy about the role of selegiline in the management of Parkinson's disease. The number of selegiline prescriptions has almost halved in the United Kingdom since the findings of the trial were published (fig 1). Objections about the validity of the findings include inconsistency with other studies, the inappropriate use of an intention to treat analysis, lack of adjustment of results for early termination of arm 2, overall death rates being too high, the unreliability of death certification, and the possibility of differential misdiagnosis.[6–9]

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Despite many of these criticisms being addressed,[10 11] the reason for the excess mortality remains unclear. One suggested mechanism was that selegiline might increase the risk of a disturbance of cardiac rhythm or compromise the cardiovascular system through orthostatic hypotension.[1] Other possibilities are that combination treatment may have accelerated nigral cell death or that selegiline may have had an adverse drug interaction with a drug not included in the trial.

We report updated and new death rates in subjects in arms 1 and 2 and in those who were randomised from arm 3 (bromocriptine) to arms 1 or 2. Results are also presented from the cause of death inquiry study, which reviewed the clinical course, cause of death, and circumstances around the time of death for all participants who died before December 1993.

## Subjects and methods

The trial methods have been reported.[1 2] Briefly, 782 patients with early, mild Parkinson's disease were randomly allocated to one of three treatment arms: levodopa and a dopa decarboxylase inhibitor alone (arm 1); levodopa, a dopa decarboxylase inhibitor, and selegiline (arm 2); and bromocriptine alone (arm 3). If a patient could not tolerate the drugs or showed little functional improvement they could be rerandomised to one of the other two arms. The principal outcomes were mortality and disability ratings. After an interim analysis of deaths up to December 1993 it was decided to terminate arm 2; patients were informed of this in October 1995.

The clinical record of every death before December 1993 was obtained from the relevant consultant, general practitioner, or nursing home. The records were systematically examined by JO, who recorded all drug treatment before death and deleted any references to antiparkinsonian drugs to conceal the trial arm. Data on severity of the disease within 3 months of death, comorbidity within 1 month of death, mobility within 1 month of death, and mode of death were recorded by AC on a standardised form.

A clinical summary of the clinical course, atypical clinical features, and comorbid medical conditions and a detailed résumé of events around the terminal illness was produced. Details of special investigations such as radiography and pathological and postmortem examination were included when available, but there was no access to the cause of death from the death certificate. A panel comprising a neurologist (AJL), geriatrician (PO), general practitioner (BH), and clinical epidemiologist (YB-S) reviewed each summary and assigned a cause of death according to ICD-9 (international classification of diseases, 9th revision).[12] The panel was blind to the death certificate and trial arm. Parkinson's disease was coded as the underlying cause of death if it contributed to the death because of severe debility.

The panel rated diagnostic certainty for the cause of death from 1 (confident) to 5 (guessing)[13] and determined whether the diagnosis of Parkinson's disease might have been incorrect and whether the patient might have had dementia.

The reliability of the panel was ascertained by presenting again 20 cases selected at random and stratified on confidence rating at least 3 months later. This was to maximise the likelihood that the cases had been forgotten. Cause specific mortality rates were recalculated using the panel's classification to ascertain whether this altered the results based on death certificates in the previous report.[1] When the panel was unable to reach a diagnosis the cause was taken from the death certificate.

### Statistical analysis

The death rates in arms 1 and 2 were compared using the log rank test and Kaplan-Meier survival curves. The relative mortality hazard ratio and 95% confidence intervals were calculated using Cox's proportional hazards model, which enabled adjustment for possible prognostic factors. The adequacy of the proportional hazards model was tested using a log-time interaction with treatment group to check whether the hazard ratio changed with follow up.[14]

Codes for specific causes were grouped under the standard classification headings except for the more common conditions such as ischaemic heart disease (410-414) and cerebrovascular disease (430-438). Comparison of categorical and continuous variables were analysed using the $\chi^2$ test or Fisher's exact test for categorical variables and the *t* test for continuous variables.

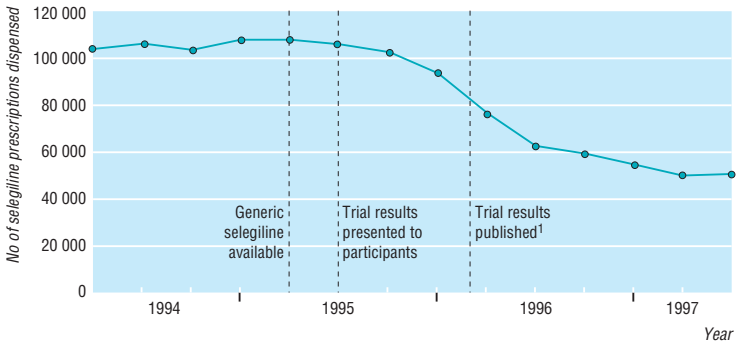


**Fig 1** Quarterly tracking data for selegiline prescriptions dispensed in United Kingdom before and after publication of results of Parkinson's Disease Research Group of the United Kingdom.[1] Source: Scriptcount (Taylor Nelson AGB)—volume of prescriptions dispensed based on representative sample of 300 pharmacies projected to give total for United Kingdom

## Results

### Mortality

Our previous paper reported the results of the interim analysis of December 1994.[1] This analysis included deaths only before the end of 1993 because of the delay in notification of deaths from the NHS central register. This report provides data on mortality up to the end of September 1995, when arm 2 was terminated, providing an additional 21 months of follow up (average 6.8 years) and new results on 104 patients randomised from the bromocriptine arm to either arm 1 (53 patients) or 2 (51 patients).

Death rates were similar in arms 1 and 2 during the additional follow up (table 1). They were higher in patients who were rerandomised to arm 2 (levodopa and selegiline) than in those rerandomised to arm 1 (levodopa alone) (hazard ratio 1.54 (95% confidence interval 0.83 to 2.87)). The overall hazard ratio for

mortality in arm 2 (levodopa and selegiline) compared with arm 1 (levodopa alone) when subjects who had been randomised a second time were included was 1.33 (1.02 to 1.74) (P = 0.038 in log rank test); this was little altered when subjects who had been rerandomised were excluded. The confidence intervals have not been adjusted to take account of the early termination of arm 2; the inclusion of additional information means that this updated result is much less affected by the decision to stop treatment early. After adjustment for other baseline factors—age, sex, duration of Parkinson's disease, disability before treatment, year of entry to trial—the hazard ratio was 1.30 (0.99 to 1.72). Analysis based on patients receiving treatment ("on treatment analysis") gave a hazard ratio of 1.39 (0.94 to 2.05).

Figure 2 shows the updated Kaplan-Meier curve. Although a test of departure from the assumption of proportional hazards was not significant, the excess mortality was greatest in the third and fourth years of follow up and was more apparent for the on treatment analysis (table 2).

As entry to the trial stopped in September 1990, information on mortality was complete for the first 5 years of follow up, so the results for the first 5 years were unaffected by the early termination of arm 2. The hazard ratio for the first 5 years for arm 2 compared with arm 1 was 1.38 (0.95 to 2.04).

**Table 1** Numbers of deaths (person years) and hazard ratios (95% confidence intervals) in patients treated with levodopa and selegiline (arm 2) and levodopa alone (arm 1)

| Variable | Deaths (person years) | | Hazard ratio (95% CI) |
|---|---|---|---|
| | Arm 1 | Arm 2 | |
| Deaths before 1994 (previously reported)[1] | 44 (1372.6) | 76 (1500.5) | 1.57 (1.09 to 2.30) |
| Deaths during additional follow up to end of September 1995 | 29 (336.6) | 27 (334.3) | 1.05 (0.60 to 1.86) |
| All deaths to end of September 1995 | 73 (1709.2) | 103 (1834.8) | 1.32 (0.98 to 1.79) |
| Patients randomised from arm 3 | 21 (368.0) | 21 (280.5) | 1.54 (0.83 to 2,87) |
| All patients including those rerandomised | 94 (2077.2) | 124 (2115.3) | 1.33 (1.02 to 1.74) |

**Table 2** Hazard ratios by duration of follow up in on treatment and intention to treat analyses

| Months after randomisation | Treatment arm | On treatment analysis | | Intention to treat analysis | |
|---|---|---|---|---|---|
| | | No of deaths | Hazard ratio (95% CI) | No of deaths | Hazard ratio (95% CI) |
| -24 | 1 | 9 | 1.09 (0.45 to 2.69) | 9 | 1.35 (0.58 to 3.15) |
| | 2 | 10 | | 13 | |
| 25-48 | 1 | 10 | 2.36 (1.14 to 4.92) | 21 | 1.79 (1.06 to 3.05) |
| | 2 | 25 | | 39 | |
| >48 | 1 | 23 | 1.09 (0.63 to 1.88) | 64 | 1.17 (0.83 to 1.64) |
| | 2 | 30 | | 72 | |
| All | 1 | 42 | 1.39 (0.94 to 2.05) | 94 | 1.33 (1.02 to 1.74) |
| | 2 | 65 | | 124 | |

*All patients randomly allocated to arms 1 and 2, including those randomised from arm 3.

**Table 3** Causes of death and death rates as classed by panel in comparison with cause given on death certificate

| | Cause of death on certificate | | Mortality per 1000 patients years (No of deaths) | |
|---|---|---|---|---|
| | Same | Different | Arm 1 | Arm 2 |
| **Panel's opinion** | | | | |
| Unknown | 0 | 30* | | |
| Ischaemic heart disease | 13 | 6 | 9.5 (13) | 6.7 (10) |
| Cerebrovascular disease | 7 | 3 | 2.2 (3) | 6.0 (9) |
| Other cardiovascular disease | 1 | 3 | 2.2 (3) | 3.3 (5) |
| Cancer | 11 | 0 | 4.4 (6) | 6.0 (9) |
| Parkinsonian syndrome | 19 | 15 | 9.5 (13) | 23.3 (35) |
| Respiratory disease | 2 | 2 | 2.2 (3) | 1.3 (2) |
| Other | 2 | 6 | 2.2 (3) | 4.0 (6) |
| All causes | 55 | 35 | 32.1 (44) | 50.7 (76) |

*When panel could not reach diagnosis, cause from death certificate was used for calculating mortality.

## Cause of death

Up to December 1993, 120 patients died (44/249 (17.7%) in arm 1 and 76/271 (28.0%) in arm 2). Twenty four cases had information from a postmortem examination. As information was not available for 21 cases because notes had been destroyed or lost, we relied only on information from the trial assessments, which may not have had information about the terminal event. The kappa coefficient[15] for the 20 cases classified by the panel on the two occasions was 0.76 for the underlying cause of death, 0.73 for the confidence rating, and 1.0 for the diagnosis of Parkinson's disease (kappa >0.75, excellent; 0.40 to 0.75, fair to good; >0.40, poor). The panel reached a diagnosis in 90 cases. It decided that information was insufficient for the remaining 30 cases to be certain of the cause of death. The pattern of cause specific mortality based on the panel's classification was similar to that previously reported (table 3). Only Parkinson's disease showed an excess of deaths (hazard ratio 2.50 (1.32 to 4.73), whereas for other causes combined the hazard ratio was 1.21 (0.76 to 1.93).

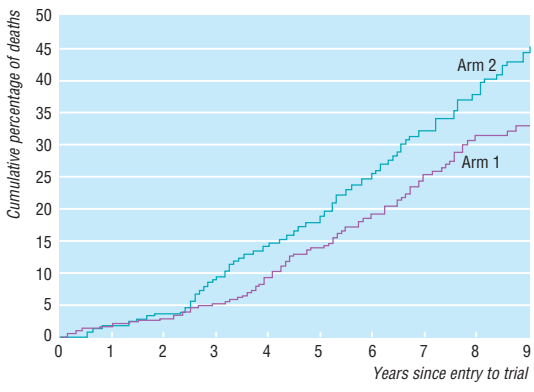


**Fig 2** Cumulative percentage of deaths by treatment arm (Kaplan-Meier estimate). All patients randomly allocated to arms 1 and 2, including those randomised from arm 3. Numbers of patients surviving from years 1 to 9 were 294, 290, 282, 270, 254, 200, 146, 98, and 73 (arm 1); 317, 310, 291, 274, 258, 210, 140, 98, and 66 (arm 2)

When arms 1 and 2 were compared there were no significant differences between any of the clinical features and the mode of death (table 4). Patients in arm 2 were more likely to have possible dementia, and within three months of death they were more likely to have falls, postural dizziness, and shortness of breath. However, the proportion of cases with a revised diagnosis—for example, multiple system atrophy, progressive supranuclear palsy, Alzheimer's disease, and cerebrovascular disease—was slightly greater in arm 1.

The mean confidence score was slightly worse in arm 2 (3.00 *v* 2.59, P = 0.19) and the postmortem rate was slightly lower. In arm 2 more deaths were classified as sudden, but the proportion of unexpected deaths

and the proportion of deaths that occurred at home were similar. There was no evidence that patients in arm 2 had greater cardiovascular comorbidity as assessed by clinical disease or cardiac drugs, and patients in arm 2 were less likely to be taking antidepressants before death.

### Disability subscales

Previous analyses showed that progression of disability was similar in the two treatment groups. As this contrasts with the excess mortality from Parkinson's disease seen in arm 2, we examined this further by analysing the disability rating before death (table 5). There were no significant differences in any of the subscales between the two arms. Fifty two per cent of the disability ratings (91/176) were made within the year preceding death, 20% (35/176) within 1-2 years before death, and 28% (50/176) more than 2 years before death. This distribution was similar for arms 1 and 2.

### Drugs

Ascertainment of the type of drugs taken around the time of death is important if the excess mortality observed with selegiline and levodopa is due to some acute toxic mechanism. We obtained drug information on 91 of the 120 patients who died, which was similar for arm 1 (31/44 (71%)) and arm 2 (60/76 (79%)) Almost all of the patients were taking levodopa 3 months before death (arm 1, 30/31 (97%); arm 2, 59/60 (98%)). In contrast, 23% (7/31) of the patients in arm 1 were no longer in the arm of treatment to which they had been randomised compared with 87% (52/60) taking selegiline in arm 2.

**Table 4** Results from the cause of death inquiry study on clinical features before and at the time of death

| Clinical feature | No (%) of patients Arm 1 (n=44) | Arm 2 (n=76) | Difference (95% CI) |
|---|---|---|---|
| **Diagnosis** | | | |
| Probable Parkinson's disease | 37 (84.1) | 68 (89.5) | –5.4 (–18.2 to 7.4) |
| **Features 1 month before death** | | | |
| Angina, myocardial infarction | 6 (13.6) | 8 (10.5) | 3.1 (–9.2 to 14.4) |
| Heart failure | 7 (15.9) | 12 (15.8) | 0.1 (–13.4 to 13.7) |
| Bedbound | 11 (25.0) | 22 (28.9) | –4.0 (–20.3 to 12.4) |
| Faints | 4 (9.1) | 4 (5.3) | 3.8 (–6.0 to 13.7) |
| Postural dizziness | 2 (4.6) | 8 (10.5) | –6.0 (–15.2 to 3.3) |
| Postural hypotension | 4 (9.1) | 9 (11.8) | –2.3 (–13.9 to 8.4) |
| Supine hypotension | 7 (15.9) | 12 (15.8) | 0.1 (–13.4 to 13.7) |
| Shortness of breath | 6 (13.6) | 17 (22.4) | –8.7 (–22.5 to 5.1) |
| Falls* | 7 (15.9) | 19 (25.0) | –9.1 (–23.6 to 5.5) |
| **Other drug treatment 3 months before death** | | | |
| Cardiac drugs | 22 (50.0) | 34 (44.7) | 5.3 (–13.3 to 23.8) |
| Antidepressants | 13 (29.5) | 17 (22.4) | 7.2 (–9.2 to 23.6) |
| **Features at time of death** | | | |
| Died during day | 13 (29.5) | 22 (28.9) | 0.6 (–16.3 to 17.5) |
| Died at home | 8 (18.2) | 11 (14.5) | 3.7 (–10.2 to 17.6) |
| Sudden death | 7 (15.9) | 18 (23.7) | –7.8 (–22.2 to 6.7) |
| Unexpected death | 7 (15.9) | 11 (14.5) | 1.4 (–12 to 14.8) |
| Postmortem examination | 10 (22.7) | 14 (18.4) | 4.3 (–10.8 to 19.4) |
| Witnessed | 24 (54.5) | 42 (55.3) | –0.7 (–19.2 to 17.8) |
| **Panel coding** | | | |
| Possible dementia | 9 (20.5) | 23 (30.3) | –9.8 (–25.6 to 6.0) |
| Uncertain cause | 11 (25.0) | 18 (23.7) | 1.3 (–14.7 to 17.3) |

*Within 3 months of death.

**Table 5** Average disability scores by treatment arm based on last disability rating before death for 176 patients who died among those originally randomised to arms 1 and 2

| | Arm 1 (n=73) | Arm 2 (n=103) |
|---|---|---|
| Hoehn and Yahr score | 3.0 | 3.0 |
| **North Western University disability subscales*** | | |
| Walking | 6.2 | 6.9 |
| Dressing | 6.7 | 6.9 |
| Hygiene | 6.2 | 6.8 |
| Eating and feeding | 7.3 | 7.5 |
| Speech | 7.4 | 7.8 |
| Total | 33.8 | 35.8 |
| **Webster subscales‡** | | |
| Bradykinesia of hands | 1.7 | 1.7 |
| Rigidity | 1.4 | 1.4 |
| Posture | 1.4 | 1.3 |
| Upper extremity swing | 2.2 | 2.2 |
| Gait | 1.7 | 1.4 |
| Tremor | 0.8 | 0.7 |
| Facies | 1.3 | 1.3 |
| Seborrhoea | 0.5 | 0.6 |
| Speech | 1.3 | 1.2 |
| Self care | 1.6 | 1.4 |
| Balance | 1.2 | 1.1 |
| Rising from chair | 1.3 | 1.2 |
| Total | 16.4 | 15.5 |

*Scored from 0 to 10, where 10=normal.
‡Scored from 0 to 3, where 0=normal.

## Discussion

The updated results show a relatively increased mortality for the combined levodopa and selegiline treatment compared with treatment with levodopa alone of around 35%, equivalent to one excess death per 75 patients treated for 1 year. The mortality ratios were remarkably consistent regardless of whether all deaths, deaths of patients who were rerandomised, or deaths in the first 5 years were considered. These estimates are lower than previously reported[1] and are more realistic, as the previous result was based on an interim analysis. Although our confidence intervals are comparatively narrow, they are all around unity so that some results are significant while others are not. Had arm 2 of the trial continued, it is possible that the mortality would have diminished further, and both previous and current results could simply reflect chance. However, the similarity of the size of the effect in patients rerandomised from arm 3 provides an independent replication of the findings seen for the main group allocated to arms 1 and 2. Whereas subjects withdrawn from arm 3 may be unrepresentative, the randomisation process ensures that the internal comparison is valid and can be viewed as a separate trial. In addition, the complete mortality results based on the first 5 years of follow up were not affected by the decision to terminate arm 2 of the trial and so are less likely to represent a random high value.

We emphasise that this trial fails to support the hope that combined treatment might be associated with reduced mortality or improvement in disability rating scales. Unfortunately, no data were collected on quality of life or mood, so we cannot comment on whether combined treatment may have benefited these measures.

**Possible explanations**

One problem with the observed excess mortality is the lack of a clear reason for this observation. Other conditions which mimic Parkinson's disease are difficult to diagnose as atypical features often develop only after several years[16] and they have a worse prognosis than Parkinson's disease.[17 18] We did not, however, find a higher rate of revised diagnosis in arm 2 compared with arm 1 (11% *v* 15%). Another criticism was that an intention to treat analysis was inappropriate because of the comparatively large number of patients who withdrew.[9] Ideally, we would like to have had accurate drug data on all of the patients, including those who withdrew at the time arm 2 was terminated. For the subgroup of patients who died for whom data were available, most patients in arm 2 were still receiving combined treatment while only a fifth of patients in arm 1 had selegiline added to their drug regimen before they died.

Since the original publication two studies have shown that selegiline diminishes autonomic responsiveness and increases risk of orthostatic hypotension.[19 20] We postulated that if this mechanism was clinically important we should observe more sudden or unexpected deaths, hypotensive episodes, falls, and possibly a higher postmortem rate in arm 2. Our findings provide limited support for this hypothesis, though none of the differences were significant. However, retrospective analysis of clinical notes is likely to significantly underestimate the true rate of any hypotensive effect of selegiline and levodopa. The most marked difference in clinical characteristics between the two arms was for falls before death and possible dementia. Falls commonly occur among patients with severe Parkinson's disease because of postural instability and akinesia as well as any autonomic effect. A randomised controlled trial of selegiline, α tocopherol, or placebo for Alzheimer's disease noted a significant increase in falls and syncope in patients receiving selegiline in combination with α tocopherol.[21]

Dementia is not uncommon in association with Parkinson's disease and is a poor prognostic factor.[22 23] Selegiline and levodopa treatment may directly result in increased confusion. Alternatively, dementia may be a marker for general frailty and increased risk of adverse drug effects.[24]

One explanation could be that selegiline and levodopa contribute to hypotensive episodes which increase the risk of either a heart attack or stroke, especially in elderly patients with pre-existing atherosclerotic disease. However, both our analyses of cause specific mortality and of comorbidity did not support this notion. If combined treatment actually accelerated disease progression, and hence death from Parkinson's disease, subjects in arm 2 would be expected to have worse disability scores and to be more disabled or bedbound before death. The data do not, however, support this hypothesis either. The use of cardiac or antidepressant drugs was no greater in arm 2 than arm 1, although we cannot rule out the possibility of a drug interaction because some of the patients' records were destroyed.

One remaining possibility is that combined treatment is harmful to a subgroup of patients. This might explain why the greatest comparative mortality ratio was seen for the analysis of patients on allocated treatment between 2 and 4 years. If susceptible subjects are selectively removed from arm 2 the mortality ratios would be expected to return to unity with further follow up because only non-susceptible subjects would then remain in the study.

**Key messages**

- New data from the trial of the Parkinson's Disease Research Group of the United Kingdom still show higher death rates in patients with early, mild Parkinson's disease treated with combined selegiline and levodopa compared with those treated with levodopa alone
- No specific cause, other than Parkinson's disease, could be found for this excess mortality
- Combined selegiline and levodopa treatment seems to offer no advantage to patients with early, mild Parkinson's disease
- In advanced Parkinson's disease, selegiline may help manage symptoms but is best avoided in patients with postural hypotension, frequent falls, confusion, and dementia

**Clinical implications**

Despite uncertainties there are some clear clinical implications from these results. There is no evidence that combined treatment with levodopa and selegiline confers advantages over levodopa treatment alone in terms of mortality or morbidity in patients with early, mild Parkinson's disease. There seems little logic in giving patients with newly diagnosed disease combined treatment, although treatment might be started with selegiline alone and then withdrawn if levodopa treatment was indicated. Clinicians should determine whether the addition of selegiline for severely disabled patientd provides additional symptomatic benefit. In these patients quality of life is generally more important than quantity of life, and each case should be reviewed on its merits. However, if patients have clinically significant orthostatic hypotension, cardiac arrhythmias, confusional states, hallucinations, or deteriorating cognitive function, gradual and slow withdrawal of selegiline over 4 to 6 weeks should be seriously considered.

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Contributors: YB-S participated in designing, analysing, and interpreting results from the cause of death inquiry study, as well as in interpreting the results of the Parkinson's Disease Research Group of the United Kingdom trial and in writing the paper. JH participated in the design, analysis, and interpretation of the

trial of the Parkinson's Disease Research Group of the United Kingdom, as well as helping to write the paper. JO participated in the design of the cause of death inquiry study, procured all the material, and blinded all the notes for the drugs for Parkinson's disease. AJL was involved in the design and conduct of the trial of the Parkinson's Disease Research Group of the United Kingdom as well as helping to write the paper; he will also act as guarantor for the paper. AC designed the standardised form, reviewed all the case notes, and produced the vignettes for the cause of death inquiry study. BH, PO, YB-S, and AJL reviewed all the vignettes and assigned the causes of death for the cause of death inquiry study. All the contributors read and critically commented on the paper.

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# Why do children have chronic abdominal pain, and what happens to them when they grow up? Population based cohort study

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## Abstract

**Objective:** To test the hypotheses that children with abdominal pain have anxious parents and come from families with high rates of physical illness and that they grow up to suffer from high rates of medically unexplained symptoms and psychiatric disorders.
**Design:** Population based birth cohort study.
**Setting:** General population.
**Subjects:** Participants in the Medical Research Council (MRC) national survey of health and development, a population based birth cohort study established in 1946.
**Main outcome measures:** Abdominal pain present throughout childhood in the absence of defined organic disease, and measures of physical symptoms and psychiatric disorder at age 36 years.
**Results:** There were high rates of complaints about physical health among the parents of children with persistent abdominal pain, and the mothers had higher neuroticism scores. Children with persistent abdominal pain were more likely to suffer from psychiatric disorders in adulthood (odds ratio 2.72 (95% confidence interval 1.65 to 4.49)) but were not especially prone to physical symptoms once psychiatric disorder was controlled for (odds ratio 1.39 (0.83 to 2.36)).
**Conclusions:** Persistent abdominal pain is associated with poor health and emotional disorder in the parents. Children with abdominal pain do not necessarily continue to experience physical symptoms into adulthood but are at increased risk of adult psychiatric disorders.

## Introduction

Recurrent abdominal pain is a common reason for children to see a doctor.[1–3] In most cases no defined organic diagnosis can be found, and this has led researchers to seek psychosocial explanations for recurrent abdominal pain.[4] Children presenting with abdominal pain may come from anxious families[5–8]

and from families in which one or more members suffer from physical health complaints.[9–12] Most studies have drawn from relatively small clinical samples, which may introduce selection bias with, for example, the most severely symptomatic children and the most anxious parents being overrepresented.

There is comparatively little literature on the long term outcome of children with recurrent abdominal pain. Studies from clinical samples suggest that between 25% and 50% continue to experience symptoms into adulthood.[13–15] It seems plausible that children with recurrent abdominal pain might also grow up to suffer from irritable bowel syndrome and other functional (or medically unexplained) symptoms. As one of the commonest functional symptoms in childhood, it is tempting to view it as a precursor to non-specific physical symptoms in adulthood. In addition, the evidence that childhood recurrent abdominal pain is associated with a range of psychosocial risk factors suggests that common mental disorders (such as anxiety and depression) may be more common in later life.

This study describes the results of the Medical Research Council's national survey of health and development, a birth cohort which has followed the same group of 5362 subjects from birth in 1946 until the most recent wave of data gathering in 1989 (at age 43 years). We used this long follow up to test the hypotheses that children with persistent abdominal pain come from families with high rates of psychiatric disorder and neuroticism and physical illness and that children with persistent abdominal pain will have high rates of psychiatric disorders and medically unexplained symptoms in adulthood.

## Subjects and methods

*The MRC national survey of health and development*—The national survey of health and development is a national birth cohort study set up in 1946.[16] The survey was based on a sample stratified for social class of all single legitimate births that occurred in England, Wales, and Scotland in one week of March 1946. The sampling procedure and follow up has been described in detail elsewhere.[16] The stratification was based on father's social class: all children born to non-manual workers and agricultural workers were surveyed, while those born to other manual labourers were sampled in a ratio of 1:4. Since 1946, 19 waves of data gathering have been performed. At each wave, information on admission to hospital has been sought. Whenever admission is reported the hospital is contacted for details of diagnosis and treatment.

*Definition of cases of recurrent abdominal pain and controls*—The usual definition of recurrent abdominal pain is of pain severe enough to affect activities and that occurs at least three times over a period of at least 3 months.[1] The data collected in the survey did not allow for this precise definition. Abdominal pain over the previous year was asked about on three occasions in childhood (at ages 7, 11, and 15 years). We therefore defined persistent abdominal pain as abdominal pain reported at each of these three points in time, which suggested that the pain was chronic. Hospital records for all such children were scrutinised by a paediatrician (SC), and those with a defined organic cause of pain that was judged to have been present throughout childhood were excluded from the sample. Controls were defined as survey members who participated in the same waves of data collection during childhood but in whom either no abdominal pain was reported or it occurred only once or twice.

*Parental illness in childhood*—Parental illness was assessed when the survey members were aged 15. The mother was given a list of seven physical illnesses and asked to indicate whether she or her husband had any of them. The illnesses were asthma, cough, rheumatism in joints, anaemia, heart trouble, kidney trouble, and other health complaints. From this list it was possible to determine the number of health complaints each parent suffered from. The mother was also asked to indicate if either parent had "nervous" complaints. In addition, information was collected on the mother's perception of her and her husband's health. This was rated on a questionnaire as "excellent, good, average, not very good, bad." Finally, maternal neuroticism was assessed with the Maudsley personality inventory.[17]

*Absence from school*—Absence from school was assessed twice during childhood. Firstly, school records from the period 1952-6 (at ages 6-10 years) were used to determine the number and distribution of 1 week periods off school over that time. Secondly, the teachers were asked whether the child was below average, average, or above average in terms of absences at the age of 13 years and again at 15 years.

*Childhood personality and behaviour*—Two main sources of information were used. The children had the Pintner personality inventory administered at the

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**Table 1** Relation between childhood abdominal pain and parental health complaints and maternal neuroticism

| Risk factor (age (years) of child at assessment) | No exposed | No (%) cases | Odds ratio (95% CI)* | Ir $\chi^2$ for trend; P value |
|---|---|---|---|---|
| **Maternal neuroticism on Maudsley personality inventory (13)** | | | | |
| 0 | 1144 | 16 (1.4) | 1.00 | 13.62;0.0002 |
| 1 | 765 | 11 (1.4) | 0.76 (0.37 to 1.12 | |
| 2–3 | 1037 | 23 (2.2) | 1.05 (0.49 to 2.24) | |
| ⩾4 | 511 | 21 (4.1) | 2.61 (1.23 to 5.52) | |
| **Parental ailments (15)** | | | | |
| 0 | 1604 | 15 (0.9) | 1.00 | 13.62;0.0002 |
| 1 | 1055 | 25 (2.4) | 2.37 (1.12 to 5.01) | |
| 2 | 500 | 16 (3.2) | 3.01 (1.31 to 6.91) | |
| 3 | 204 | 7 (3.4) | 2.57 (0.85 to 7.74) | |
| | 125 | 8 (6.4) | 4.96 (1.73 to 14.17) | |
| **Mother's perception of own health (15)** | | | | |
| Excellent/good | 2353 | 24 (1.4) | 1.00 | 13.64;0.0002 |
| Average | 920 | 27 (2.9) | 1.39 (0.75 to 2.58) | |
| Not very good/bad | 171 | 1 (5.9) | 4.54 (2.00 to 10.30) | |
| **Mother's perception of father's health (15)** | | | | |
| Excellent/good | 2453 | 37 (1.5) | 1.00 | 6.13;0.01 |
| Average | 723 | 22 (3.0) | 1.69 (0.89 to 3.20) | |
| Not very good/bad | 204 | 7 (3.4) | 2.06 (0.80 to 5.29) | |
| **Mother's self reporting of "nerves" (15)** | | | | |
| No | 3059 | 54 (1.8) | 1.00 | 6.13;0.01 |
| Yes | 394 | 17 (4.3) | 2.12 (1.05 to 4.31) | |
| **Mother reports "nerves" in father (15)** | | | | |
| No | 3193 | 64 (2.0) | 1.00 | 0.46;0.5 |
| Yes | 148 | 4 (2.7) | 1.44 (0.43 to 4.79) | |
| **Reported continual or repeated colds in other family members (6)** | | | | |
| No | 2181 | 24 (1.1) | 1.00 | 14.2; 0.0002 |
| Yes | 1427 | 48 (3.4) | 2.48 (1.39 to 4.41) | |

Ir = likelihood ratio test.
*Odds ratios corrected for sex and father's social class, weighted for sampling.

**Table 2** Relation between abdominal pain and childhood personality and behaviour and school absences

| Risk factor (assessor) | No exposed | No (%) affected | Odds ratio (95% CI)* | lr $\chi^2$ for trend; P value |
|---|---|---|---|---|
| **Neuroticism on Pintner personality inventory** | | | | |
| Non-neurotic | 1183 | 21 (1.8) | 1.00 | 0.99; 0.32 |
| Mid-neurotic | 1042 | 19 (1.8) | 1.07 (0.50 to 2.25) | |
| Neurotic | 1026 | 23 (2.2) | 1.34 (0.67 to 2.68) | |
| **Introversion on Pinter personality inventory** | | | | |
| Introvert | 975 | 24 (2.5) | 1.00 | 0.57; 0.45 |
| Ambivert | 1104 | 17 (1.5) | 0.83 (0.40 to 1.68) | |
| Extravert | 1172 | 22 (1.9) | 0.79 (0.39 to 1.60) | |
| **Energy level at age 13 (teacher)** | | | | |
| Never tired | 233 | 1 (0.4) | 1.00 | 1.82; 0.18 |
| Normally energetic | 3026 | 62 (2.1) | 2.48 (0.34 to 18.12) | |
| Always tired | 187 | 5 (2.7) | 3.33 (0.37 to 30.08) | |
| **Day dreaming in class at age 13 (teacher)** | | | | |
| Seldom or never | 1664 | 25 (1.5) | 1.00 | 4.77; 0.03 |
| Sometimes | 1602 | 36 (2.3) | 1.55 (0.84 to 2.87) | |
| Frequently | 212 | 8 (3.8) | 2.37 (0.88 to 6.33) | |
| **Disobedience in class at age 13 (teacher)** | | | | |
| Seldom or never | 3145 | 64 (2.0) | 1.00 | 0.74; 0.4 |
| Sometimes | 321 | 321 (0.9) | 0.45 (0.19 to 1.02) | |
| Frequently | 26 | 2 (7.7) | 2.90 (0.77 to 10.93) | |
| **Lying in class at age 13 (teacher)** | | | | |
| Seldom or never | 2926 | 55 (1.9) | 1.00 | 0.04; 0.83 |
| Sometimes | 483 | 13 (2.7) | 1.36 (0.61 to 2.60) | |
| Frequently | 49 | 1 (2.0) | 0.36 (0.05 to 2.71) | |
| **Periods of absence (weeks) at ages 6-10 (school doctor)** | | | | |
| 0-2 | 855 | 14 (1.6) | 1.00 | 5.3; 0.02 |
| 3-4 | 717 | 9 (1.3) | 0.61 (0.22 to 1.69) | |
| 5-8 | 851 | 22 (2.6) | 1.66 (0.76 to 3.66) | |
| ⩾9 | 622 | 19 (3.1) | 1.75 (0.77 to 4.01) | |
| **School absence at age 13 (teacher)** | | | | |
| Seldom or never | 824 | 12 (1.5) | 1.00 | 2.24; 0.13 |
| Sometimes | 888 | 13 (1.5) | 1.07 (0.41 to 2.79) | |
| Frequently | 851 | 24 (2.8) | 1.71 (0.70 to 4.14) | |

lr = likelihood ratio test. *Odds ratios corrected for sex and father's social class, weighted for sampling.

age of 13, which defined personality according to two dimensions "neuroticism" and "extroversion."[18] The second source of information on personality was from the child's form teacher, who was asked to rate the survey members on the following items: lying, disobedience, being a disciplinary problem, restlessness, quality of work, and energy levels. For each item they were asked to say whether the child was above average, average, or below average.

*Other variables*—Sex and social class were possible confounders. Social class was assessed according to the father's occupation in 1961 (when survey members were aged 15) and was classified as manual versus non-manual social group.

*Adulthood variables*—Outcomes during adulthood were measured at 36 years. Two main outcomes were used: psychiatric disorder and physical symptoms. The present state examination, a semistructured psychiatric interview which generates levels of severity of psychiatric disorder (the index of definition), was used for the first outcome.[19] An index of definition of 5 is considered to be threshold for psychiatric disorder. The second outcome was self reported physical symptoms. These were headache, back pain, abdominal pain, dizziness, chest pain, and rheumatism. We identified survey members who suffered from inflammatory bowel disease during adulthood from self report and hospital notes. The survey collects death records for all survey members, and these were available to determine whether persistent abdominal pain in childhood was associated with increased mortality.

*Analytical strategy and statistical methods*—Odds ratios and 95% confidence intervals were calculated to assess the strength of associations between childhood risk factors and persistent abdominal pain. These were subsequently controlled for father's social class and sex in a logistic regression analysis weighted for the sampling. Likelihood trend tests were used for ordered categorical variables. Ordinal regression was used for the adult outcomes, which were ordered categorical variables (index of definition and number of physical symptoms). This generated a single odds ratio for ordered categorical outcomes which represent the odds of having the outcome for those in the group with pain relative to those unaffected by pain.[20] Cox's proportional hazards were used to determine whether death rates for those with abdominal pain in childhood (corrected for sex, social class, and sampling weights) were raised during adulthood.

## Results

At the age of 7 years, a fifth of survey members had suffered abdominal pain; at 11 years it was 19% and at 15 years it was 17%. Two fifths were reported to have suffered abdominal pain at least once in childhood and 10% at least twice. Seventy six (2.1%) of the 3637 children who participated at the three points in time had recurrent abdominal pain. Of these, three had hospital records that suggested that the pain was caused by a chronic disease, leaving 73 (2.0%) with persistent pain of unexplained origin. Of this group, 52 (71%) had consulted a doctor at least once during childhood. The follow up and representativeness of the survey have been described in more detail elsewhere.[16] Of the risk set, 32 were followed up to the age of 36 years, and this proportion did not differ according to pain status in childhood ($\chi^2 = 0.001$; $P = 0.97$).

Children with persistent abdominal pain were evenly distributed between the sexes (odds ratio for girls 0.97; 95% confidence interval 0.56 to 1.68). Children whose fathers had manual occupations were more likely to suffer from pain (1.75; 1.02 to 3.03). Table 1 shows the relation between persistent abdominal pain and various measures of parental and family health during childhood. There was a strong association between pain and parental health complaints, parental ratings of health, maternal "nerves," maternal neuroticism, and reporting of the family being prone to "colds." Because the relation between pain and parental physical health complaints and health ratings could have been due to maternal neuroticism an additional logistic model, which included maternal neuroticism with these complaints, was included, but this caused only a modest reduction in these associations (results not shown).

Childhood personality and its association with persistent abdominal pain is shown in table 2. Neuroticism and introversion were not associated. The teacher's ratings suggested that persistent abdominal pain was no more common in children with antisocial traits such as lying, disobedience, or having disciplinary problems. There was a modest association between traits such as day dreaming in class and having low levels of energy and persistent abdominal pain. Children with abdomi-

**Table 3** Relation between childhood abdominal pain and adult psychiatric disorder and physical symptoms at age 36 years

| Outcome | No of children | No (%) with abdominal pain | Odds ratio* (95% CI) |
|---|---|---|---|
| **Persistent abdominal pain** | | | |
| No | 2383 | 45 (1.9) | 1.30 (0.50 to 3.38) |
| Yes | 226 | 7 (3.1) | 1.03 (0.39 to 2.73)† |
| **Persistent headache** | | | |
| No | 2045 | 38 (1.9) | 1.51 (0.73 to 3.13) |
| Yes | 563 | 14 (2.5) | 1.20 (0.57 to 2.56)† |
| **Index of definition on present state examination** | | | |
| 1 | 1239 | 13 (1.1) | 2.72 (1.65 to 4.49)‡ |
| 2 | 811 | 19 (2.3) | |
| 3 | 225 | 9 (4.0) | |
| 4 | 158 | 5 (3.2) | |
| 5 | 129 | 1 (0.8) | |
| 6 | 24 | 4 (16.7) | |
| 7 | 6 | 1 (16.7) | |
| **No of common somatic symptoms** | | | |
| 0 | 1312 | 20 (1.5) | 1.74 (1.04 to 2.92)‡ |
| 1 | 786 | 16 (2.0) | 1.39 (0.83 to 2.36)†‡ |
| 2 | 345 | 9 (2.6) | |
| 3 | 130 | 5 (3.9) | |
| 4 | 30 | 1 (3.3) | |
| 5 | 7 | 1 (14.3) | |

*Derived by logistic regression unless marked otherwise.
†Corrected for psychiatric disorder at age 36 (see text).
‡Ordinal regression, corrected for sex, father's social class, marital status at age 36, and educational status. Note that ordinal regression derives single odds ratio describing increased risk of having outcome in abdominal pain group compared with "no pain" group, independent of level of severity of outcome.

nal pain had more absence from school between the ages of 6 and 10 years, but only a modest non-significant increase in absence was evident at 13 years.

The outcome of children with pain is shown in table 3. Persistent abdominal pain in childhood was associated with psychiatric disorder, and this association remained after correction for potential confounders in an ordinal regression model. Childhood pain was only very weakly associated with abdominal pain and headache at 36 years but was associated with increasing numbers of physical symptoms at this age. Because there is a strong association between psychiatric disorder and physical symptoms, psychiatric disorder was added to the model, and this led to the association between persistent abdominal pain and physical symptoms in adulthood failing to reach significance. None of the children with persistent abdominal pain developed inflammatory bowel disease during the period of follow up. Only one subject with abdominal pain in childhood died over the follow up period, and this was lower than the rate for the rest of the cohort (hazard ratio (controlled for sex and social class) 0.15; 0.02 to 1.06).

## Discussion

This study used population based data to follow up a group of children with persistent abdominal pain over a period of 20 years. There were three main findings. Firstly, persistent abdominal pain in childhood was associated with physical ill health in the parents. Secondly, persistent abdominal pain in childhood did not predict abdominal pain in adulthood but was modestly associated with other common physical symptoms in adulthood. Thirdly, persistent abdominal pain in childhood was a predictor of psychiatric disorder in adulthood.

### Methodological concerns

We were not able to define recurrent abdominal pain in the conventional manner. We believe, however, that our sample of children was likely to be symptomatic for much of childhood and to reflect clinical samples of children with recurrent abdominal pain. They were somewhat more likely to have been absent from school for long periods during middle childhood. The population base of this sample and the lack of differences in follow up rates for children with abdominal pain and those without make it unlikely that these results are due to selection bias. The results reported here compare those with persistent abdominal pain with children who never experienced pain. When those who had experienced pain once or twice in childhood were included in the control group the results were not substantially altered, although some of the odds ratios were slightly reduced (results not shown).

### Family ill health and symptoms

The relation between sickness in the family and medically unexplained symptoms in adulthood has been reported in several retrospective studies. The relation between persistent abdominal pain present in childhood and ill health in the parents suggests that the parental anxiety and preoccupations with physical health may reinforce the child's concern about physiological and minor medical bodily sensations. From the clinical viewpoint this suggests that in the treatment of children with persistent abdominal pain it is important to understand parental beliefs and experiences and to avoid behaviours that might reinforce pain behaviour in the child. This is a component of treatments which have been shown to be effective.[4 21]

While the parents of children with persistent abdominal pain were more likely to have psychiatric disorders, the children themselves did not seem especially maladjusted. They did not score especially high on neuroticism but were more likely to be "day dreamers" and there was a non-significant trend for them to be lacking in energy. These behaviours may be akin to inhibited traits (such as shyness, fearfulness, and being easily upset), which are recognised to be predictors of adult depression.[22]

So far as we know, this is the largest and longest follow up of abdominal pain in children to date. The survey members were growing up in the 1950s, and it is interesting to speculate whether the same associations would have been detected in a modern sample. With an increasingly health conscious population the parents of children with abdominal pain may be less readily reassured than they were 40 years ago. Modern medical advances may mean that these children would be more extensively investigated today than previously and that a proportion may avoid unnecessary operations, but it may also reinforce illness beliefs.

Overall the results suggest that the outcome in terms of symptoms of persistent pain is good. Though there is some evidence that persistent abdominal pain in childhood is associated with medically unexplained physical symptoms in adult life it is a more powerful predictor of adult psychiatric disorder. Apley's "little

**Key messages**

- Persistent abdominal pain in childhood is more common in families with high rates of reported physical illness and psychological symptoms
- The outcome for persistent abdominal pain is good in terms of mortality
- Children with persistent abdominal pain are not at greatly increased risk of developing physical symptoms in adulthood
- Abdominal pain in childhood is associated with considerably increased risk of psychiatric disorders in adulthood

belly-achers"[13] do not grow up to be big belly achers but do grow up to suffer from anxiety or depression.

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Contributors: MH is the guarantor for this paper. He was responsible for formulating initial hypotheses, collecting data on admission in childhood, analysing data, and writing early drafts. The other authors all participated in further refinement of hypotheses and study design. MW, as director of the Medical Research Council national survey of health and development, was responsible for recent data collection. SC rated data on the children's physical ailments. All authors commented on early results and considered additional analyses to perform. All commented on later drafts.

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# Randomised controlled trial of aminosidine (paromomycin) *v* sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India

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## Abstract

**Objectives:** To assess the efficacy and tolerability of aminosidine compared with sodium stibogluconate for treating visceral leishmaniasis.
**Design:** Randomised, unblinded, controlled trial with 180 day follow up.
**Setting:** Kala-Azar Research Centre, Brahmpura, Muzaffarpur, Bihar, India.
**Subjects:** People of either sex aged 6-50 years with symptoms and signs suggestive of visceral leishmaniasis (fever, loss of appetite, enlarged spleen) with leishmania amastigotes detected in Giemsa stained aspirates of spleen or bone marrow.
**Interventions:** Aminosidine at three daily doses (12, 16, and 20 mg/kg) for 21 days and sodium stibogluconate 20 mg/kg/day for 30 days.
**Main outcome measures:** Laboratory measures of efficacy: parasite count, haemoglobin concentration, white cell count, platelet count, serum albumin concentration. Clinical measures of efficacy: spleen size, fever, body weight, and liver size. Measures of safety: liver and renal function tests, reports of adverse events.
**Results:** Of the 120 patients enrolled (30 per treatment arm), 119 completed treatment and follow up. Cure at end of follow up was achieved in 23 (77%), 28 (93%), and 29 (97%) patients treated with 12, 16, and 20 mg aminosidine/kg/day respectively, and in 19 (63%) patients given sodium stibogluconate. At 16 and 20 mg/kg/day, aminosidine was significantly more active than sodium stibogluconate in both clinical and laboratory measures of efficacy. No significant clinical or laboratory toxicity occurred in any treatment group.
**Conclusions:** A 21 day course of aminosidine 16 or 20 mg/kg/day should be considered as first line treatment for visceral leishmaniasis in Bihar.

## Introduction

Bihar state, in the north east of India, carries the burden of about half of the world's annual cases of visceral leishmaniasis. In recent years these infections have become increasingly unresponsive to first line treatment with pentavalent antimony compounds. While a daily dose of 20 mg/kg sodium stibogluconate for 20-40 days was efficacious in the 1980s, up to 25% unresponsiveness is now reported even with high doses and longer administration.[1–8] In consequence, as well as increased morbidity and mortality, treatment costs have risen because of increased doses, prolonged hospitalisation, and need for retreatment. Alternative drug treatments for areas with endemic visceral leishmaniasis are badly needed.

Aminosidine is an aminoglycoside antibiotic identical to paromomycin.[9] An injectable formulation of 500 mg aminosidine sulphate has been on the market in several countries for over 30 years for treating bacterial and parasitic infections. Aminosidine was first shown to have anti-leishmanial activity in the 1960s,[10 11] and it has been shown to act synergistically with antimony drugs.[12] Clinical trials with injectable aminosidine for treating visceral leishmaniasis have been conducted in Africa (Kenya and Sudan),[13 14] India (Bihar),[15 16] and in complicated cases imported into the United Kingdom.[17] Most patients received aminosidine combined with antimony compounds, and the combinations were found to be highly efficacious and well tolerated. Minimal comparative data are available thus far on treatment with aminosidine alone.

This study was therefore undertaken to determine the efficacy and safety of aminosidine alone in treating visceral leishmaniasis and to establish the optimum dose for a fixed duration of 21 days in comparison with standard treatment. This study is part of the aminosidine development project of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, the aim of which is to produce data to support the registration and use of aminosidine in control programmes for visceral leishmaniasis.

## Methods

### Protocol

*Study design*

This randomised, unblinded, controlled trial was designed to evaluate the ratio of risk to benefit of three doses of aminosidine compared with the standard dose of antimony. This study was undertaken at the Kala-Azar Research Centre in Muzaffarpur, Bihar, which is situated in the centre of the hyperendemic area spread over a radius of 70 km. Patients were randomly assigned to one of four treatment arms: aminosidine (Gabbromycin, Farmitalia-Carlo Erba, Milan, Italy, now Pharmacia-Upjohn) given intramuscularly at a dose of 12, 16, or 20 mg/kg/day for 21 days, or sodium stibogluconate 20 mg/kg/day (Albert David, Calcutta, India, 30 ml vial containing 100 mg/ml) to a maximum of 8.5 ml/day for 30 days. Patients were hospitalised for treatment and, after discharge, were followed up at 30, 90, and 180 days after treatment was completed.

At initial assessment, at end of treatment, and at each follow up, subjects were examined by means of parasitology on Giemsa stained aspirates of spleen or bone marrow to assess the parasite burden (measured in accordance with the WHO Technical Series No 793[18]), electrocardiography, and audiometry. At initial assessment, at weekly intervals during treatment, and at each follow up, subjects were also assessed by means of measurement of spleen and liver size (from the costal margin along the anterior axillary line of supine patients); blood chemistry (liver and renal function tests); haematology (complete blood count, including haemoglobin concentration, white cell count, and platelet count); prothrombin and bleeding time; and urine analysis.

*Inclusion and exclusion criteria*

Patients aged 6-50 years with symptoms and signs suggestive of visceral leishmaniasis and aspirates of spleen or bone marrow positive for leishmania amastigotes were eligible for inclusion in the study if they gave signed informed consent. Exclusion criteria were a known allergy to aminoglycosides, treatment in the previous 12 months with a drug with recognised or presumed anti-leishmanial action, serious concomitant diseases, pregnancy or lactation (women underwent a pregnancy test at initial assessment), failure to agree to return for all follow up evaluations, and being critically ill from leishmaniasis. Definitions for critical illness from leishmaniasis included the spleen reaching to the pelvic crest, haemoglobin concentration $<50$ g/l, white cell count $<2\times10^9$/l,[3] platelet count $<80\times10^9$/l,[3] aspartate aminotransferase concentration $>4\times$upper limit of normal, serum albumin concentration $<20$ g/l, and urine urea or creatinine concentration $>2\times$upper limit of normal.

*Ethics*

The study received formal clearance from the drug controller of the Indian government, the local ethics committee, and the WHO Secretarial Committee on Research Involving Human Subjects and was conducted in accordance with the Declaration of Helsinki. Patients were informed of the purpose of the trial and had to give their signed informed consent before being enrolled.

*Efficacy variables*

The primary parameter of efficacy was final cure (clinical improvement and parasitological cure persisting at 180 days after treatment completed). Parasitological definitions of efficacy were cure (negative aspirates for leishmania amastigotes after treatment completed), improvement (reduction of parasitic load $\geq2$ grades after treatment completed), failure (reduction of parasitic load by $<2$ grades), and relapse (positive aspirates after initial conversion to negative aspirate). Clinical improvement was defined as defervescence and improvement in one or more clinical sign—that is, increase in body weight by 2 kg, in haemoglobin concentration by 20 g/l, in white cell count by $1\times10^9$/l, and in albumin concentration by 5 g/l and reduction in spleen size by 40%.

*Statistical methods*

We decided that 30 patients with visceral leishmaniasis should be enrolled into each treatment arm (total 120

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**Table 1** Selected baseline characteristics of patients with visceral leishmaniasis by treatment. Values are means (SD) unless stated otherwise

| | Aminosidine | | | Sodium stibogluconate 20 mg/kg/day (n=30) | Comparison (P value)* |
|---|---|---|---|---|---|
| | 12 mg/kg/day (n=30) | 16 mg/kg/day (n=30) | 20 mg/kg/day (n=30) | | |
| Male:female ratio | 18:12 | 18:12 | 23:7 | 24:6 | 0.19 |
| Age (years) | 29.83 (14.77) | 23.73 (12.02) | 29.10 (14.67) | 26.07 (12.58) | 0.28 |
| Weight (kg) | 37.85 (12.80) | 35.87 (11.39) | 37.63 (12.53) | 37.25 (12.44) | 0.60 |
| Duration of illness (No of days with fever) | 73.57 (57.07) | 69.73 (49.28) | 90.47 (59.20) | 62.33 (40.50) | 0.2 |
| Spleen size (cm) | 5.96 (3.59) | 6.44 (3.70) | 6.36 (4.70) | 5.55 (3.45) | 0.80 |
| Haemoglobin concentration (g/l) | 86 (14.2) | 76 (20.1)† | 82.5 (10.3) | 89.2 (13.1)† | 0.0064 |
| White cell count ($10^9$/l) | 4.05 (1.16) | 3.59 (0.89) | 4.04 (1.07) | 4.15 (1.13) | 0.19 |
| Platelet count ($10^9$/l) | 210 (66)† | 178 (34) | 168 (56)† | 178 (50) | 0.016 |
| Albumin concentration (g/l) | 30.7 (5.0) | 30.7 (3.8) | 29.9 (4.0)† | 33.2 (5.2)† | 0.015 |
| Parasite burden (grade) | 2.20 (0.96) | 2.03 (0.96) | 2.40 (0.81) | 1.93 (0.74) | 0.18 |

*Calculated from one way analysis of variance, except for male:female ratio calculated from $\chi^2$ test.
†Significant on Tukey's honest significance difference.

patients). With this number, we thought it unlikely that we would be able to demonstrate significant differences in efficacy, but it was considered a satisfactory balance between scientific purposes and practical constraints.

All 120 patients enrolled were included in the analyses on the basis of intention to treat. We used descriptive statistics to summarise baseline values, and we used the $\chi^2$ test to compare dichotomous variables between groups and one way analysis of variance for continuous variables. We assessed changes in continuous variables from baseline over time by using paired *t* tests within groups and, for comparisons between groups, used the one way analysis of variance with post hoc multiple comparison using Tukey's honest significance difference. Both actual values and changes from baseline were compared across the groups. All results were assessed at a significance level of $P = 0.05$.

Values were compared at each follow up visit. Since patients given antimony were treated for 30 days while those given aminosidine were treated for 21 days, we created the category "end of treatment" (day 30 for antimony, day 21 for aminosidine). In this paper we present detailed comparisons only for day 21 and end of treatment.

*Data quality assurance*

The sources of data were verified, values were keyed in using DataBase III and double checked at the clinical site. Further checks with SPSS for Windows were made after transferring the data to Geneva for analyses.

### Assignment

Treatment was unblinded. Patient eligibility was evaluated before randomisation to treatment with a computer generated randomisation list. Treatment was administered by nurses at the hospital. The doctor assessing clinical efficacy was unaware of the dose of aminosidine given, and technicians assessing laboratory measures of efficacy were unaware of the treatment administered.

**Table 2** Overall efficacy of treatments for visceral leishmaniasis. Values are number (percentage) of patients

| Treatment | Final cure (at end of follow up) | Failure (at end of treatment) | Relapse (during follow up) | Defaulters |
|---|---|---|---|---|
| Aminosidine*: | | | | |
| 12 mg/kg/day (n=30) | 23(77) | 2 | 5 | 0 |
| 16 mg/kg/day (n=30) | 28(93) | 0 | 1 | 1 |
| 20 mg/kg/day (n=30) | 29(97) | 0 | 1 | 0 |
| Sodium stibogluconate 20 mg/kg/day (n=30)† | 19(63) | 8 | 3 | 0 |

*Treatment given for 21 days. †Treatment given for 30 days.

## Results

### Subjects

*Patient disposition*—Between June 1993 and August 1995, 2007 patients who attended the centre with complaints of fever were screened for visceral leishmaniasis. Visceral leishmaniasis was diagnosed in 507 patients, of whom 120 met the inclusion criteria.

*Baseline characteristics*—Table 1 shows that the baseline characteristics of the four groups allocated to different treatment arms did not differ significantly except for haemoglobin concentration (higher in the group allocated antimony compared with those allocated aminosidine 16 mg/kg/day), platelet counts (higher in those allocated aminosidine 12 mg/kg/day than in those allocated 20 mg/kg/day), and albumin concentration (higher in the antimony group than in those allocated aminosidine 20 mg/kg/day).

### Efficacy evaluation

*Overall assessment*—Table 2 shows that a final cure (clinical cure, clinical improvement, and parasitological cure at 180 days after end of treatment) was achieved in 23, 28, and 29 patients given aminosidine 12, 16, and 20 mg/kg/day respectively, compared with 19 of the patients given antimony ($\chi^2$ test, $P = 0.003$). Of the three doses of aminosidine, only treatment with 12 mg/kg/day did not differ significantly from antimony treatment ($P = 0.26$).

*Parasitological outcome*—At the end of treatment tissue aspirates were negative for leishmania amastigotes in 27, 28, and 27 patients given aminosidine 12, 16, and 20 mg/kg/day respectively, compared with 22 patients given antimony (table 3). All three doses of aminosidine were significantly more effective than antimony ($\chi^2$ test, $P = 0.002$). Only two failures were recorded in the group given aminosidine 12 mg/kg/day compared with eight in the antimony group. During follow up, a total of 10 patients relapsed after apparent clearance of parasites (5, 1, and 1 given aminosidine 12, 16, and 20 mg/kg/day respectively,

**Table 3** Parasitological measures of efficacy of treatments for visceral leishmaniasis. Values are number of patients

| | Time after start of treatment | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 21 days | | 30 days | | | 60 days | | | 90 days | | 120 days | | 180 days | |
| Treatment | Cured | Improved | Cured | Improved | Failed | Cured | Failed | Relapsed | Cured | Relapsed | Cured | Relapsed | Cured | Relapsed |
| Aminosidine*: | | | | | | | | | | | | | | |
| 12 mg/kg/day (n=30) | 27 | 3 | 28 | 0 | 2 | 28 | 0 | 0 | 27 | 1 | 26 | 1 | 23 | 3 |
| 16 mg/kg/day (n=30) | 28 | 2 | 30 | 0 | 0 | 30 | 0 | 0 | 30 | 0 | 30 | 0 | 29 | 1 |
| 20 mg/kg/day (n=30) | 27 | 3 | 30 | 0 | 0 | 30 | 0 | 0 | 29 | 1 | 29 | 0 | 29 | 0 |
| Sodium stibogluconate 20 mg/kg/day (n=30)† | 19 | 2 | 22 | 2 | 6 | 21 | 2 | 1 | 21 | 0 | 20 | 1 | 19 | 1 |

*Treatment given for 21 days. †Treatment given for 30 days.

and 3 given antimony). Parasitological outcome was independent of initial parasite burden.

*Changes from baseline*

*Comparisons within groups*—With few exceptions, the parasite burden, spleen and liver size, and body temperature were significantly lower and body weight, haemoglobin concentration, and platelet counts were significantly higher than baseline values at every assessment during treatment with all four treatment regimens (paired *t* tests). Compared with baseline, albumin concentration was significantly higher at all assessments in the patients given aminosidine 20 mg/kg/day, on days 14 and 21 in the patients given aminosidine 12 and 16 mg/kg/day, and on days 14, 21, and 30 in those given antimony.

*Comparisons between groups*—At the end of treatment (21 days for aminosidine and 30 days for antimony), aminosidine was significantly more effective than antimony for most of the variables considered (table 4). At both day 21 and end of treatment, the changes from baseline values of parasite counts and white cell counts were significantly greater for all groups given aminosidine than for those given antimony. For other parameters, only the patients given the two higher doses of aminosidine showed significantly greater changes from baseline than did those who were given antimony.

**Safety evaluation**

No clinically relevant differences in laboratory values were recorded in any of the treatment groups, and no renal toxicity was apparent with any of the doses of aminosidine (table 5). During the study, six patients experienced adverse events that did not require discontinuation of treatment (see box). Overall, both drugs were well tolerated. Aminosidine did not produce any substantial degree of ototoxicity or renal toxicity.

## Discussion

Although the activity of aminosidine (paromomycin) against *Leishmania* has been known since the 1960s,[10 11] the drug was not clinically evaluated for treating human leishmaniasis until the late 1980s.[13–16] Two stud-

**Table 4** Changes from baseline value in measures of efficacy of treatments for visceral leishmaniasis on day 21 (end of aminosidine treatment) and day 30 (end of sodium stibogluconate treatment) after start of treatment. Values are mean (SD) unless stated otherwise

| | Aminosidine on day 21 | | | Sodium stibogluconate 20 mg/kg/day (n=30) | | Comparison (P value)* | |
|---|---|---|---|---|---|---|---|
| | 12 mg/kg/day (n=30) | 16 mg/kg/day (n=30) | 20 mg/kg/day (n=30) | Day 21 | Day 30 | Day 21 | End of treatment |
| Body weight (kg) | 2.10 (1.82) | 2.40 (1.90) | 2.00 (1.57) | 2.03 (1.84) | 2.55 (1.82) | 0.82 | 0.60 |
| Fever (°C) | –1.64 (0.47) | –1.82 (0.60)† | –1.75 (0.42) | –1.33 (0.94)† | –1.46 (0.91) | 0.023 | 0.14 |
| Spleen size (cm) | –4.12 (1.91) | –4.75 (2.56)† | –5.1 (3.83)†‡ | –2.5 (2.57)† | –2.88 (3.12)‡ | 0.0032 | 0.023 |
| Haemoglobin concentration (g/l) | 17.9 (10.2) | 24.1 (16.1)† | 21.0 (8.9)† | 12.5 (12.6)† | 16.3 (15.8) | 0.003 | 0.11 |
| White cell count ($10^9$/l) | 3.05 (1.50)†‡ | 3.44 (1.48)†‡ | 3.12 (1.30)†‡ | 1.79 (1.48)† | 1.90 (1.85)‡ | 0.001 | 0.001 |
| Platelet count ($10^9$/l) | 110 (96) | 122 (74) | 142 (79)† | 82 (70)† | 100 (89) | 0.037 | 0.25 |
| Albumin concentration (g/l) | 9.1 (3.8)† | 8.9 (3.7)† | 9.8 (3.5)† | 5.8 (6.3)† | 7.8 (8.1) | 0.004 | 0.54 |
| Parasite burden (grade) | –2.07 (0.87)†‡ | –1.97 (0.93)†‡ | –2.30 (0.75)†‡ | –1.30 (0.91)† | –1.23 (1.14)‡ | 0.0002 | 0.002 |

*Comparison between groups done by one way analysis of variance with post hoc Tukey's honest significance difference.
†Significant differences between groups on day 21. ‡Significant differences between groups at end of treatment.

**Table 5** Changes from baseline value in measures of safety of treatments for visceral leishmaniasis on day 21 (end of aminosidine treatment) and day 30 (end of sodium stibogluconate treatment) after start of treatment. Values are mean (SD) unless stated otherwise

| | Aminosidine on day 21 | | | Sodium stibogluconate 20 mg/kg/day (n=30) | | Comparison (P value)* | |
|---|---|---|---|---|---|---|---|
| | 12 mg/kg/day (n=30) | 16 mg/kg/day (n=30) | 20 mg/kg/day (n=30) | Day 21 | Day 30 | Day 21 | End of treatment |
| Creatinine concentration (μmol/l) | –11.5 (29.2) | –10.6 (23.9) | –10.6 (15.9) | –10.6 (26.5) | –13.3 (23.9) | 0.99 | 0.97 |
| Blood urea nitrogen (mmol/l) | 0.43 (2.05) | 0.39 (1.61) | 0.32 (1.81) | –0.62 (1.56) | –0.54 (1.52) | 0.071 | 0.11 |
| Bilirubin (μmol/l) | 47.0 (260.1) | –1.0 (222.3) | –0.2 (2.1) | –0.5 (2.7) | –0.5 (2.2) | 0.40 | 0.40 |
| Aspartate aminotransferase (U/l) | –16.43 (32.57) | –7.00 (40.30) | –18.73 (39.15) | –1.67 (50.03) | –8.37 (45.51) | 0.33 | 0.59 |

*Comparison between groups done by one way analysis of variance with post hoc Tukey's honest significance difference.

ies were conducted in African patients (Kenya and Sudan),[13 14] in which aminosidine was administered at 14 or 16 mg/kg/day for 14-19 days, either alone or in combination with sodium stibogluconate 20 mg/kg/day administered for 21 days, and compared with sodium stibogluconate 20 mg/kg/day given for 30 days. In both studies the combinations of aminosidine plus antimony were at least 95% effective at end of treatment and were significantly more effective than sodium stibogluconate alone. The combination of aminosidine plus antimony was evaluated in two trials in Bihar, India.[15 16] The highest dose, aminosidine 12 mg/kg/day in combination with sodium stibogluconate 20 mg/kg/day for 21 days, was 82-88% effective. However, these studies produced limited data on the efficacy of aminosidine used alone.

This prompted us to compare the efficacy of aminosidine alone with that of the standard treatment with antimony. At 180 days after end of treatment, the final cure rate with sodium stibogluconate given for 30 days was 63%, confirming that antimony can no longer be considered the drug of choice in this region. Aminosidine given at 12 mg/kg/day for 21 days produced a final cure rate of 77%; although this was not significantly better than the rate with sodium stibogluconate, it was achieved one week earlier. The higher doses of aminosidine, 16 and 20 mg/kg/day for 21 days, were significantly more effective than antimony, with final cure rates of 93% and 97% respectively. No significant difference was detected between these two doses. These two regimens proved significantly more effective than antimony on almost all measures of efficacy that we evaluated.

Our results are substantially better than those obtained earlier in Bihar with the combination of aminosidine 12 mg/kg/day plus sodium stibogluconate 20 mg/kg/day for 21 days, suggesting that antimony played a minor role in this regimen.[15 16]

We actively sought our patients for follow up visits, and only one patient defaulted. Statistical analyses were done on an intention to treat basis. One potential limitation of our study design was that it was conducted in an unblinded fashion. However, measures of concealment were applied to both clinical and laboratory evaluations to limit potential bias.

**Adverse events recorded during study**

*Aminosidine 12 mg/kg/day*
- One case of vomiting, possibly drug related, relieved with symptomatic treatment

*Aminosidine 20 mg/kg/day*
- One case of gradual onset of ototoxicity, determined by audiogram, definitely drug related (grade 2 mixed deafness at end of treatment, worsened to grade 3 and persisted during follow up)
- One case of gradual onset of ototoxicity, determined by audiogram, thought to be drug related (grade 1 conductive deafness before enrolment, deteriorated to grade 1 sensorineural deafness at end of treatment, reversed to baseline state at day 30 of follow up)

*Sodium stibogluconate 20 mg/kg/day*
- Two cases of reversible myocarditis, diagnosed by electrocardiography, definitely drug related
- One case of epileptic seizure, not drug related (patient had concealed a history of seizures)

**Key messages**

- Bihar in north east India accounts for about half the annual worldwide cases of visceral leishmaniasis, and resistance to standard treatment with sodium stibogluconate has been increasing
- We compared the safety and efficacy of three doses of aminosidine with standard regimen of sodium stibogluconate for treating visceral leishmaniasis in Bihar
- Aminosidine given at 16 or 20 mg/kg/day for 21 days was significantly more effective in producing final cure than sodium stibogluconate 20 mg/kg/day for 30 days
- Aminosidine had a low incidence of adverse reactions, including ototoxicity and renal toxicity, and was well tolerated
- Intramuscular injection of aminosidine 16 mg/kg/day for 21 days should be considered as a new first line treatment for visceral leishmaniasis in Bihar

**Conclusions**

Aminosidine at either 16 or 20 mg/kg/day for 21 days is effective in treating visceral leishmaniasis in Bihar, where the response to standard treatment with antimony for 30 days has become unacceptably low. We propose a 21 day regimen with aminosidine 16 mg/kg/day as the new first line treatment for visceral leishmaniasis in Bihar. An additional advantage of aminosidine over sodium stibogluconate is the lower overall burden to the health system, deriving from the lower cost of the drug and the shorter period of hospitalisation.

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Contributors: TKJ was the principal investigator and participated in data analysis and writing the protocol and paper. PO initiated clinical development of aminosidine for leishmaniasis (following studies by R Neal and L Donno), wrote the protocol (with TKJ, A Bryceson, and R Davidson), analysed the data, and wrote the regulatory report and paper. TPK participated in data analysis and writing the protocol and paper.

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Conflict of interest: None.

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# Commentary: Some good news for treatment of visceral leishmaniasis in Bihar

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Bihar is again the centre of an epidemic of visceral leishmaniasis (kala-azar) with an official estimate of 430 000 cases over the past 11 years. Antimony has been the treatment of choice since 1920, but treatment is arduous, requiring daily intravenous injections for 21 days, and up to 83% of patients experience side effects of myalgia or arthralgia.[1] The Bihar epidemic has also been exacerbated by a sharp increase in drug resistance, and in this paper 37% of patients were not cured by antimony.[2]

New drugs are urgently needed. Amphotericin B was the first alternative assessed, and in an open randomised trial produced significantly better parasite clearance (100% *v* 70%), resolution of fever, improvements in leucocyte and platelet counts, and regression of spleen size than antimony (sodium stibogluconate).[3] The toxicity profile of amphotericin B in this population is poor, and it causes unpredictable drug induced myocarditis as well as anorexia, nausea, and vomiting.[4] It has been successfully used in a lipid complex preparation but is prohibitively expensive.[5]

The aminoglycoside aminosidine has only recently been used in visceral leishmaniasis.[6] Jha and colleagues' well designed study shows that in Bihar aminosidine is more effective than sodium stibogluconate.[2] Patients were appropriately recruited and randomly allocated to either the antimony compound or aminoglycoside, with an impressively high follow up rate in difficult conditions. The study could have been strengthened by blinding of treatments and by detailed auditory testing and HIV testing before treatment. Parasite culture and assessment of in vitro sensitivity to sodium stibogluconate would have produced interesting supplementary data. HIV infection is a risk factor for the development of visceral leishmaniasis[7] and affects the response to treatment and the occurrence of side effects. The toxicity profile of aminosidine will be a crucial factor determining its usefulness in the field. The aminoglycosides are neuro-ototoxic and have been reported to cause high tone deafness.[6] The present article does not document the specific side effects that were monitored for.

The epidemic of visceral leishmaniasis has been expensive, costing an estimated $250m for treatment alone. It is difficult to calculate the full cost of treatment, but the cheapest drug costs per course are sodium stibogluconate (locally produced in India, $16), aminosidine ($50), amphotericin ($60), and AmBisome ($2000) (A Bryceson, personal communication).

The authors' recommendation of using aminosidine alone may cause future problems. Monotherapy is problematic when used for controlling any intracellular organism; drug resistance developed in both leprosy and tuberculosis during the eras of monotherapy. Other studies suggest that a combination of aminosidine and sodium stibogluconate is more effective than the latter alone.[8]

A final irony is that aminosidine is not currently being marketed. Farmitalia-Carlo Erba originally produced the drug, but during a series of takeovers production slowed and marketing stopped. Once again the needs of patients with a tropical disease have not been able to compete with the high finances of drug companies.

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*Endpiece*

## Asherisms

Blind faith in doctors, though convenient, is not always to their benefit.

From *A Sense of Asher*, selected by Ruth Holland (BMA Publications, 1984)

# Suicide in patients with stroke: epidemiological study

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In the United States stroke is the third most common cause of death among those aged over 70. In Europe the incidence of stroke is 2 per 1000 population a year.[1] Survivors are often incapacitated. The frequency of depression after stroke is estimated at 18-60%.[2] Other neurological disorders that may result in mental and cognitive disorders are associated with an increased risk of suicidal behaviour.[3] Studies on the possible increased risk of suicide among patients with stroke have never been performed. We therefore aimed to estimate, on the basis of a cohort of patients with stroke in a selected area in Denmark, whether the risk of suicide was higher than in the background population (the common reference in previous studies on suicide risk[3 4]).

## Materials, method, and results

All patients admitted to hospital in the county of Funen, Denmark, with a discharge diagnosis of stroke (code 430-438 according to the international classification of diseases, eighth revision) during 1 April 1973 to 31 December 1989 were registered.

Only admitted patients were included, biasing the study towards the patients with the most severe strokes. Danish patients with stroke, however, are almost always admitted, thus reducing this bias.

Age, date of birth, sex, time of first admittance, and department of admittance were registered. In patients who had died, the date of death was also registered. Information was collected for the study period from the National Board of Health on *(a)* the causes of death in the deceased patients, and *(b)* the frequency of suicide comparable for age and sex in the total population of the county of Funen (the background population). We then calculated standardised mortality ratios for suicide for men and women separately in the age groups ⩽49 years, 50-59, 60-69, 70-79, and ⩾80. The study was approved by the regional ethics committee for the county of Funen and Vejle and the Danish Data Protecting Agency.

At the end of the study, of the 37 869 patients with stroke (19 266 men), 7365 (3614 men) were alive and 30 504 (15 652 men) had died. Altogether, 140 patients (80 women) committed suicide. The table shows the number of suicides, the person years at risk, and the standardised mortality ratios in the five age groups for women and men.

## Comment

We have shown that patients with stroke have a significantly increased risk of suicide, especially in the age groups up to age 60 and in women.

The high suicide risk in the youngest age groups is in agreement with studies on suicide in multiple sclerosis,[3] epilepsy, Huntington's chorea, spinal cord lesions, and diabetes.[4] The lowered risk of suicide in the oldest age groups is also in agreement with the findings for Parkinson's disease.[4]

In multiple sclerosis, men had the highest suicide risk, whereas in stroke, women did. A Danish study found an increased risk of depression in female patients with stroke,[5] which might explain the finding. Because we included all admitted patients with stroke in the area (possible because of good registration practice), selection bias could not explain the results. Furthermore, the large number of patients included in the study makes the results reliable.

Although only 140 in a population of almost 38 000 patients with stroke committed suicide (7.2% of all the suicides in the area), an unknown, but probably larger number of patients may have attempted suicide, and a third may have depression.[2] Furthermore, the number of suicides may be underestimated as some deaths would not be registered as suicides. The high suicide risk in patients with stroke suggests that society should take more interest in the psychosocial aspects of living with the impairment imposed by stroke.

Contributors: CM, ENS, and ES wrote the project protocol. CM and ENS coordinated the collection of the data. ENS wrote the initial version of the paper, which was discussed and accepted by all authors. ES had the original idea for the study and participated in the discussion of the protocol and data sampling and in the discussion of the paper. JB was responsible for the data analysis and made all the data analyses. Afterwards the results were discussed by all the authors.

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Conflict of interest: None.

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Number of suicides and standardised mortality ratios (95% confidence interval) for suicide in women and men with stroke in five age groups

| | Women | | | Men | | |
|---|---|---|---|---|---|---|
| Age group | Suicides | Years at risk | Standardised mortality ratio | Suicides | Years at risk | Standardised mortality ratio |
| ⩽49 | 7 | 1964.2 | 1376 (646 to 2996) | 6 | 2771.1 | 656 (324 to 1352) |
| 50-59 | 22 | 4096.3 | 1378 (896 to 2129) | 20 | 7514.8 | 580 (338 to 823) |
| 60-69 | 7 | 11 263.2 | 224 (120 to 426) | 9 | 15 031.0 | 76 (38 to 157) |
| 70-79 | 25 | 21 481.6 | 184 (112 to 304) | 15 | 18 680.2 | 161 (98 to 224) |
| ⩾80 | 19 | 17 640.7 | 133 (73 to 244) | 10 | 9192.8 | 131 (84 to 205) |

# Effect of electrical cardioversion on myocardial cells in patients in intensive care

G Neumayr, P Schratzberger, G Friedrich, H Gänzer, C J Wiedermann

For about 30 years electrical cardioversion has been routine for converting arrhythmias.[1] Whether the application of shocks in the usual dosage is safe is still controversial as minimal myocardial cell injury cannot be excluded.[2] If simultaneous muscle damage occurs the measurement of common cardiac markers, especially creatine kinase and its isoenzyme creatine kinase MB, lacks specificity. We therefore also measured the concentration of cardiac troponin T as this is the most sensitive and specific marker to date.

## Patients, methods, and results

Over the past three years in this unit 69 non-selected patients with atrial fibrillation (aged 21-87, mean 63.7 years) underwent elective countershock using a direct current. Serum samples were taken before and 24 hours after cardioversion. The concentrations of cardiac troponin T, total creatine kinase, and creatine kinase MB were measured by enzyme linked immunosorbent assay (Boehringer, Germany) (reference ranges $<0.1$ µg/l, 10-80 U/l, and $<12$ U/l, $<6$% respectively). A total of 153 shocks was delivered, amounting to an average cumulative energy of 286 J per patient. Cardioversion was started with 50 J of stored energy, and subsequent shocks comprised 100, 200, 300, and 360 J. The procedure was terminated after restoration of sinus rhythm or after two attempts of 360 J each.

Four patients received the highest amount of cumulative energy (1370 J). Sixty seven patients converted to sinus rhythm, and no major complications occurred. At follow up 24 hours later 60 patients had restored sinus rhythm. All measurements of cardiac troponin T activity before and after cardioversion were below 0.1 µg/l. The baseline concentrations and peak activities of creatine kinase and creatine kinase MB were within the normal range except in three cases. In one patient the peak activity of total creatine kinase increased from 13 to 103 U/l but that of creatine kinase MB was normal. In the other two patients the peak activity of creatine kinase was increased from 32 to 363 U/l and from 18 to 512 U/l and that of creatine kinase MB by 33 U/l and by 42 U/l respectively.

## Comment

Experiments in animals have shown that necrosis of myocardial cells occurs after repeated countershocks using direct currents of high energy.[3] Evidence that electrical cardioversion may result in myocardial damage in humans is based on the increased concentrations of various cardiac enzymes measured after cardioversion.[4]

To overcome the problem of insufficient specifity of cardiac enzymes we measured the activity of cardiac troponin T. Cardiac troponin T is not detectable in the serum of healthy people and can be differentiated from its isoforms in skeletal muscle by immunological techniques; its cross reactivity to mixed skeletal muscle is 1-2%, and its specificity is 95% in the presence of skeletal damage.[5] Currently, cardiac troponin T is the best marker for detecting minimal myocardial damage, especially when skeletal muscles are also injured.

In our non-selected patient population countershock using direct current was highly effective and without major complications. As we did not find any increase in plasma activity of cardiac troponin T we conclude that myocardial cell injury by electrical cardioversion is unlikely when applying cumulative energies of up to 1370 J. As two patients had raised concentrations of total creatine kinase and creatine kinase MB but not of cardiac troponin T, we conclude that these enzymes originated from injured skeletal muscle. We therefore suggest that the increased concentrations of creatine kinase and creatine kinase MB reported previously in cases of myocardial damage could also have originated from injured skeletal muscle.

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*Endpiece*

**Who's out there?**

Communication today has four characteristics; it is global, permanent, immediate, and immaterial. Previously only God had these qualities.

Ignatio Ramonet (of *Le Monde Diplomatique*) quoted in *UNESCO Sources*, April 1997

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