Ultrasound treatment for treating the carpal tunnel syndrome: randomised "sham" controlled trial

Gerold R Ebenbichler, Karl L Resch, Peter Nicolakis, Günther F Wiesinger, Frank Uhl, Abdel-Halim Ghanem, Veronika Fialka

Abstract

Objective: To assess the efficacy of ultrasound treatment for mild to moderate idiopathic carpal tunnel syndrome.
Design: Randomised, double blind, "sham" controlled trial with assessments at baseline, after 2 weeks' and 7 weeks' treatment, and at a follow up assessment 6 months later (8 months after baseline evaluation).
Setting: Outpatient clinic of a university department of physical medicine and rehabilitation in Vienna.
Subjects: 45 patients with mild to moderate bilateral carpal tunnel syndrome as verified by electroneurography.
Intervention: 20 sessions of ultrasound (active) treatment (1 MHz, 1.0 W/cm^2, pulsed mode 1:4, 15 minutes per session) applied to the area over the carpal tunnel of one wrist, and indistinguishable sham ultrasound treatment applied to the other. The first 10 treatments were performed daily (5 sessions/week); 10 further treatments were twice weekly for 5 weeks.
Main outcome measures: Score of subjective symptom ratings assessed by visual analogue scale; electroneurographic measures (for example, motor distal latency and sensory antidromic nerve conduction velocity).
Results: Improvement was significantly more pronounced in actively treated than in sham treated wrists for both subjective symptoms ($P < 0.001$, paired *t* test) and electroneurographic variables (motor distal latency $P < 0.001$, paired *t* test; sensory antidromic nerve conduction velocity $P < 0.001$, paired *t* test). Effects were sustained at 6 months' follow up.
Conclusion: Results suggest there are satisfying short to medium term effects due to ultrasound treatment in patients with mild to moderate idiopathic carpal tunnel syndrome. Findings need to be confirmed, and ultrasound treatment will have to be compared with standard conservative and invasive treatment options.

Introduction

The carpal tunnel syndrome, caused by compression of the median nerve at the wrist, is considered the most common entrapment neuropathy.[1] Patients complain of paraesthesia (with or without numbness or pain) involving the fingers innervated by the median nerve, and a weakness of thumb abduction. Symptoms are worst at night and often wake the patient. Standard treatments include splints, local injection of corticosteroids, and surgical decompression. Benefit from non-surgical treatment, however, seems to be limited,[2] and not all patients respond to surgery.[3 4]

Ultrasound treatment within an intensity range of 0.5-2.0 W/cm^2 may have the potential to induce various biophysical effects within tissue.[5 6] Experiments on the stimulation of nerve regeneration[7] and on nerve conduction by ultrasound treatment[8 9] and findings of an anti-inflammatory effect of such treatment[10] support the concept that ultrasound treatment might facilitate recovery from nerve compression.[7] However, few studies report a benefit of ultrasound treatment in the carpal tunnel syndrome under clinical conditions.[11 12] We sought to investigate the clinical efficacy of pulsed ultrasound in the treatment of idiopathic carpal tunnel syndrome by means of a rigorous, controlled clinical trial.

Material and methods

Patients

Over two years patients with clinically suspected carpal tunnel syndrome referred to the outpatient clinic of the department of physical medicine and rehabilitation of the University of Vienna were invited to take part in this randomised, double blind study of ultrasound treatment versus "sham" ultrasound treatment (fig 1).

We diagnosed the carpal tunnel syndrome by using standard electrophysiological criteria.[13 14] Criteria for inclusion in the study were bilateral, idiopathic carpal tunnel syndrome; mild to moderate pain lasting more than three months; and written informed consent. Patients were excluded if they had secondary entrapment neuropathies, systemic diseases with increased risk of the carpal tunnel syndrome, or electroneurographic and clinical signs for axonal degeneration of the median nerve; had gained surgical relief of the syndrome; had been treated with ultrasound for the syndrome; had a history of steroid injections into the carpal tunnel; or had required regular analgesic or anti-inflammatory drugs.

Intervention

Ultrasound treatment was administered as monotherapy for 15 minutes per session to the area over the

Department of Physical Medicine and Rehabilitation, University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria
Gerold R Ebenbichler, *assistant doctor*
Peter Nicolakis, *assistant doctor*
Günther F Wiesinger, *assistant doctor*
Abdel-Halim Ghanem, *assistant doctor*
Veronika Fialka, *head of department*
Department of Complementary Medicine, University of Exeter, Exeter
Karl L Resch, *senior lecturer*
Department of Neurology, University of Vienna
Frank Uhl, *professor*
Correspondence to: Dr Ebenbichler

BMJ 1998;316:731–5

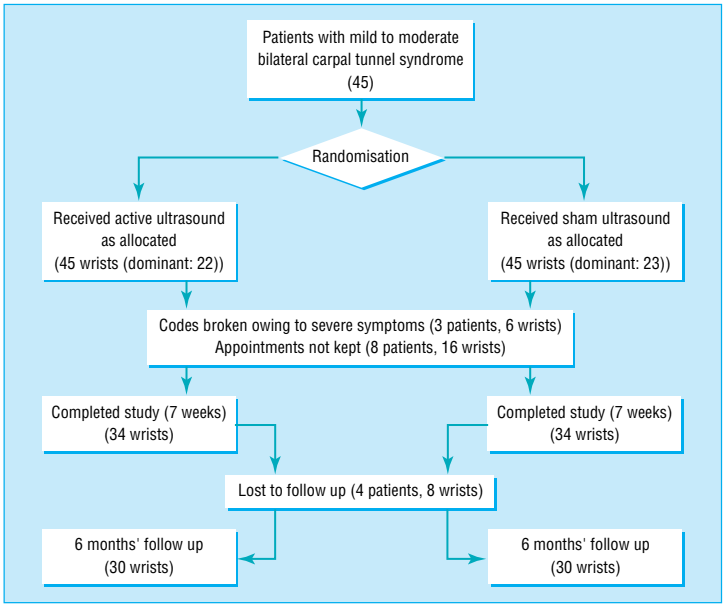


Fig 1 Trial profile

carpal tunnel at a frequency of 1 MHz and an intensity of 1.0 W/cm^2, pulsed mode 1:4, with a transducer of 5 cm^2 (Sonodyn, Siemens) and with aquasonic gel as couplant. The machine was standardised initially, and the output was controlled regularly on a simple underwater radiation balance. An on/off key introduced into the transducer circuit allowed mock insonation to be given to a sham group without affecting the normal ultrasonic output when the key was turned to the "on" position. The first 10 treatments of a total of 20 ultrasound treatments were performed daily 5 times a week for 2 weeks, and the second 10 treatments twice a week for another 5 weeks.

For occasional pain relief, analgesics (usually tramadol) were allowed, but not non-steroidal or steroidal antirheumatics.

Outcome measures

Primary

Primary outcome measures for each wrist comprised *(a)* a sum score of subjective symptoms consisting of ratings of main complaints and sensory loss and *(b)* quantification of electroneurographic measurements. Main complaints were defined as complaints related to pain or paraesthesia, or to both, which the patient considered the most important ones at baseline. Severity of complaints at the clinical examination, and the worst complaints experienced within 3 days before the consultation were quantified by the study physician (GRE) by means of a coloured visual analogue scale, on which the patients could indicate their assessment along a distance of 10 cm, ranging from white ("no complaints at all") to red ("the most intense complaints I can imagine"). Sensory loss (hypalgesia or hyperpathia, or both) was assessed by means of a sharp pin wheel and compared with "normal" sensation in the fifth digit. Quantification was again by coloured visual analogue scale ("no difference at all" to "greatest possible difference").

All electroneurographic measurements were performed with a Viking II Nicolet (EMS, Madison, USA) electromyography device. Briefly, median motor nerve conduction was measured at the wrist and elbow with bipolar surface disc electrodes. Median distal motor latency was recorded with cathodes 6.5 cm apart. Antidromic sensory nerve action potentials were recorded from the wrist to the second digit, with ring electrodes placed around the proximal and distal interphalangeal joints. At least 15 sensory nerve action potentials were averaged, and antidromic sensory nerve conduction velocity was calculated as appropriate. The skin temperature of the forearm was kept constant at 32-33°C during all treatments.[15]

Secondary

Secondary outcome measures comprised *(a)* quantification of physical functioning and *(b)* the patients' general improvement. Tests of physical functioning comprised dynamometric measurements (dynamometer by Preston, New York) of hand grip and finger pinch strength. The patients' positioning was standardised, and the average force of three consecutive trials was calculated. The patients rated their overall change at the end of the treatment series on a five point ordinal scale (1 = free of symptoms, 5 = much worse).

Other factors

At each appointment the patients rated their main complaint without being reminded of the ratings they had made at previous appointments. Drugs taken for pain relief were registered and side effects of the ultrasound treatment reported.

Electrophysiological measurements and clinical examinations were performed before the first treatment session, after 10 sessions (week 2), and after the last session (week 7). A follow up was performed six months later (8 months after baseline evaluation). After the follow up examination the treatment code was broken, and patients were either discharged or offered an alternative treatment.

Sample size

A sample size calculation was performed based on the assumptions that the main outcome measurement (changes in sum score between baseline and end of treatment on visual analogue scale) is continuous in nature, fairly normally distributed, and that an additional improvement in the intervention side of 10 percentage points (standard deviation = 15 percentage points) is considered clinically relevant. If the incidence of the carpal tunnel syndrome on one wrist could be considered completely independent from the incidence on the other wrist, 36 independent observations in each group would be necessary to detect that difference at the 5% level ($\alpha = 0.05$) with an 80% chance ($\beta = 0.2$). Synchronicity of the carpal tunnel syndrome in both wrists happens in about one third of all cases, but to our knowledge no evidence exists that the natural course of symptoms goes strictly in parallel in these cases. In addition, systemic interventions that would probably affect both wrists, such as pain killers, were among the exclusion criteria. Taken together, 45 to 50 independent observations in each group might be a sensible estimate.

Statistics

Longitudinal changes between wrists were compared, with two tailed *t* tests for paired samples for fairly normally distributed variables (visual analogue scores and force measurements) and Wilcoxon tests for skewed data. Subsequently, a χ^2 analysis was performed on dichotomised data of the mean score of subjective symptoms, with an overall improvement of more than 35 percentage points from baseline values as cut off point.

Assignment

A randomisation list was produced with a random number generator of a popular spreadsheet program (Lotus Symphony). After the eligible patients had been enrolled, an ultrasound therapist not involved in the treatment allocated the dominant wrist of each consecutive patient to ultrasound or sham treatment (the patient's other wrist received the other treatment) by means of sequentially numbered sealed opaque envelopes containing the group allocation (active or sham). This therapist was the only person aware of treatment allocation during the trial.

Blinding

The patients, GRE, and the therapists who delivered the ultrasound treatment were all unaware of the treatment allocation. Only the therapist who was in charge of group allocation switched the ultrasonic generator to the respective modes before each treatment session (see above). This procedure allowed blinding of both the patients and the therapists delivering the treatment. Intensity of ultrasound treatment was below sensitivity threshold.

Results

Baseline evaluation

Forty five patients with bilateral carpal tunnel syndrome (90 wrists) fulfilled all inclusion criteria; 11 (24%) of these patients discontinued treatment after randomisation (8 patients early after randomisation because of non-compliance in keeping appointments, and 3 patients because of excessive pain requiring additional therapeutic measures). Thus 34 patients—that is, 34 actively treated and 34 sham treated wrists—completed the study. Their characteristics did not differ from the original 45 patients in the study. Thirty of them (67% of the initial 45 patients) completed a follow up at 6 months.

The wrists were similar in terms of the duration of current episodes of main complaints regardless of randomisation group (table 1). There were slight group imbalances at baseline. Most complaints in the actively treated group were significantly more severe ($P=0.05$, Wilcoxon test) when rated on the visual analogue scale. Baseline differences were also present in the mean score of physical functioning and strength of hand grip, whereas finger pinch was comparable.

Other subjective symptoms—for example, scores of main complaints, sensory loss, and the mean score of all subjective symptoms—were similar at baseline. Electroneurography, motor distal latency, peak to peak amplitude, and antidromic sensory nerve conduction velocity did not differ significantly between wrists.

Table 1 Demographic data and baseline characteristics of patients who completed study, according to which group (active or sham ultrasound) their dominant wrist was randomised to. Values are means (SD) unless stated otherwise

Variable	Treatment	
	Active	Sham
No of subjects who completed the study	34	
Age (years)	51 (15)	
Body mass index (kg/m^2)	25.9 (5.1)	
No of wrists with complaints	29	27
No of wrists with sensory loss	25	19
Duration of current episode of main complaints (months)	7.8 (6.7)	7.2 (6.5)
Subjective symptoms:		
Score of all subjective symptoms	4.1 (2.1)	3.3 (1.5)
Main complaint (cm)*	3.3 (2.8)	2.0 (1.9)
Worst complaint (cm)*	6.5 (2.6)	5.8 (2.8)
Sensory loss (cm)*	2.4 (2.4)	2.0 (2.4)
Physical functioning:		
Score of physical functioning	21.3 (11.9)	25.5 (11.3)
Handgrip strength (kg)	15.8 (10.9)	19.8 (10.0)
Finger pinch (×0.2 kg)	5.5 (1.8)	5.8 (1.8)
Electroneurography:		
Motor distal latency (ms)	5.2 (1.0)	5.2 (1.2)
Peak to peak amplitude	14.5 (3.4)	14.6 (3.7)
Antidromic sensory nerve conduction velocity wrist-digit II (m/s)	40.0 (7.2)	42.1 (7.2)

*Distance along a coloured visual analogue scale, on which the patients indicated their assessment (white, 0=minimum complaint; red, 10=maximum complaint). See methods section for further details.

Effect of treatment

Subjective symptoms

Table 2 and figure 2 show longitudinal changes of subjective symptoms. Improvement in the mean score of all ratings of subjective symptoms was significantly more pronounced in the actively treated wrists at week 2 ($P<0.008$), at the end of treatment ($P<0.0001$), and at the 6 month follow up ($P<0.0001$).

Satisfactory improvement or complete remission of symptoms was observed in 68% (23/34) of the wrists receiving active treatment versus 38% (13/34) of those receiving sham treatment ($P<0.001$; relative risk reduction 48%) at the end of the treatment series, and in 74% (22/30) versus 20% (6/30) ($P<0.001$; 67%) at 6 months' follow up.

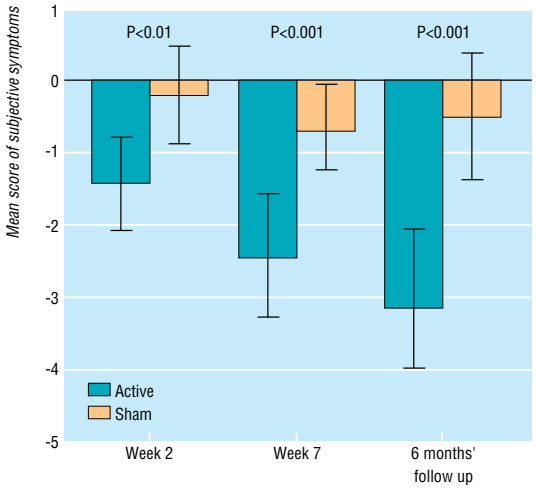


Fig 2 Mean change (and 95% confidence intervals) from baseline score for all subjective symptoms (active versus sham treatment) at week 2, end of treatment, and 6 months' follow up (paired *t* test)

Table 2 Mean change (95% confidence interval) from baseline values for outcome measures at week 2, at end of treatment (week 7), and 6 months later

Outcome measure	Week 2	End of therapy	6 months' follow up
Subjective symptoms			
Mean change in main complaints (cm)*:			
Sham	0.05 (–0.48 to 0.58)	–0.17 (–0.92 to 0.57)	–0.08 (–1.06 to 0.90)
Active	–1.05 (–1.91 to –0.19)	–2.14 (–3.15 to –1.12)	–2.76 (–3.79 to –1.73)
Paired difference (*t* test)	1.1 (0.23 to 1.98)	1.96 (0.91 to 3.01)	2.26 (1.49 to 3.88)
P value (2 tailed)	0.015	0.001	<0.0005
Mean change in worst complaints (cm)*:			
Sham	–0.90 (–2.24 to 0.43)	–1.56 (–2.58 to –0.54)	–0.95 (–2.43 to 0.54)
Active	–2.20 (–3.16 to –1.25)	–3.91 (–5.07 to –2.75)	–4.78 (–5.85 to –3.70)
Paired difference (*t* test)	1.30 (–0.38 to 2.98)	2.35 (0.92 to 3.78)	3.83 (2.32 to 5.34)
P value (2 tailed)	0.125	0.002	<0.0005
Mean change in sensory loss (cm)*:			
Sham	0.42 (–0.29 to 1.13)	–0.07 (–0.86 to 0.72)	–0.08 (–0.91 to 0.76)
Active	–0.82 (–1.69 to 0.05)	–1.14 (–1.99 to –0.29)	–1.60 (–2.55 to –0.65)
Paired difference (*t* test)	1.24 (0.33 to 2.15)	1.07 (0.31 to 1.83)	1.53 (0.85 to 2.20)
P value (2 tailed)	0.009	0.007	<0.0005
Physical functioning			
Mean change in hand grip strength (kg):			
Sham	–0.61 (–1.88 to 0.66)	–0.09 (–2.04 to 1.85)	–1.99 (–4.08 to 0.09)
Active	0.71 (–1.35 to 2.77)	3.87 (2.06 to 5.67)	5.44 (2.91 to 7.96)
Paired difference (*t* test)	–1.32 (0.35 to –2.99)	–3.96 (–2.01 to –5.90)	–7.43 (–5.22 to –9.64)
P value (2 tailed)	0.118	<0.0005	<0.0005
Mean change in pinch strength (kg):			
Sham	–0.20 (–0.25 to –0.15)	0.06 (–0.26 to 0.38)	–0.22 (–0.38 to –0.06)
Active	–0.01 (–0.13 to 0.12)	0.33 (0.17 to 0.50)	0.49 (0.28 to 0.70)
Paired difference (*t* test)	–0.19 (0.43 to –0.81)	–0.27 (0.37 to –0.91)	–0.71 (–0.15 to –1.27)
P value (2 tailed)	0.537	0.392	0.014
Electroneurography			
Mean change in motor distal latency (ms):			
Sham	0.04 (–0.08 to 0.15)	0.06 (–0.08 to 0.21)	0.04 (–0.10 to 0.19)
Active	–0.23 (–0.37 to –0.10)	–0.55 (–0.71 to –0.39)	–0.31 (–0.45 to –0.18)
Paired difference (*t* test)	0.27 (0.11 to 0.42)	0.61 (0.43 to 0.79)	0.36 (0.18 to 0.54)
P value (2 tailed)	0.001	<0.0005	<0.0005
Mean change in antidromic sensory nerve conduction velocity (m/s):			
Sham	–0.84 (–1.07 to –0.62)	–0.89 (–1.11 to –0.66)	–0.27 (–0.51 to –0.03)
Active	4.50 (4.34 to 4.66)	7.35 (6.98 to 7.71)	2.69 (2.39 to 2.99)
Paired difference (*t* test)	–5.34 (–3.58 to –7.11)	–8.23 (–6.22 to –10.24)	–2.96 (–1.66 to –4.66)
P value (2 tailed)	<0.0005	p<0.0005	0.001

*Distance along a coloured visual analogue scale, on which the patients indicated their assessment (white, 0=minimum complaint; red, 10=maximum complaint). See methods section for further details.

Electroneurography

The results of electroneurography are shown in table 2. Motor distal latency decreased with active treatment and remained unchanged with sham treatment both at the end of treatment and at 6 months' follow up (end of treatment: active −0.55 ms (95% confidence interval −0.71 to −0.39) and sham 0.06 ms (−0.08 to 0.21); at follow up: −0.31 ms (−0.45 to −0.18) and 0.04 ms (−0.10 to 0.19); $P < 0.001$ for both time periods).

Similar significant changes in the velocity of sensory nerve conduction were observed at the end of treatment and at 6 months' follow up with active treatment, whereas velocity remained unchanged with sham treatment ($P < 0.0001$ between groups).

Physical functioning

Hand grip and finger pinch strength had improved significantly with active treatment at the end of treatment and at 6 months' follow up (table 2).

Other measurements

Patients' ratings of overall improvement at the end of treatment significantly favoured active over sham treatment (Mann-Whitney U test $P = 0.002$). Good or excellent treatment results were stated by 76% (26/34) of the patients for actively treated wrists versus 32% (11/34) for sham treated wrists.

At 6 months' follow up 28 patients showed an unsatisfactory outcome (9 actively treated and 19 sham treated wrists) and were offered further treatment. Subsequently 13 patients were offered ultrasound treatment and splints for their sham treated wrists, and 10 wrists (3 sham treated) were injected with steroids. Surgical relief of the carpal tunnel syndrome was planned for 5 patients (3 sham treated wrists).

Average consumption of analgesics during treatment and follow up phase was low: 8 out of the 34 patients occasionally took analgesics, and three patients were off work. No side effects due to ultrasound treatment were reported.

Discussion

An increase in pressure in the carpal tunnel is usually caused by non-specific flexor tenosynovitis.[16] Chronic focal compression of a nerve trunk can cause focal demyelination by mechanical stress deforming the myelin lamellae. Ischaemia also plays a pathogenic role

Key messages

- Chronic entrapment of the median nerve at the wrist (the carpal tunnel syndrome) is probably the most common peripheral nerve lesion
- No satisfactory conservative treatment is available at present
- Twenty sessions of ultrasound treatment show good short and medium term efficacy in patients with bilateral, mild to moderate forms of the carpal tunnel syndrome
- Optimal treatment schedules of ultrasound treatment alone or in combination with other non-surgical treatments await elucidation

in the carpal tunnel syndrome. It could account for intermittent paraesthesia that occurs at night or with wrist flexion.[2] The carpal tunnel syndrome is often observed bilaterally. Symptoms are usually markedly worse on one (mostly the dominant) side.

Conservative treatment approaches seem to offer clear advantages over surgical treatment of the carpal tunnel syndrome. Recent studies have confirmed short term effects of steroid injections into the carpal tunnel, with modest or complete pain relief in up to 92% of the patients, although long term recurrence rates seem variable.[17–19] Potential adverse effects to nerves and tendons with repeated injections have limited the value of this treatment.[20 21] Palmar wrist splints worn at night seem suitable only when symptoms are mainly nocturnal,[22] and ergonomic strategies have not yet been evaluated.

The findings of the present study confirm preliminary data that ultrasound treatment may facilitate recovery from the carpal tunnel syndrome.[11 12] Given the favourable response rate of 68% of patients at the end of treatment, ultrasound treatment may be similar in effectiveness to steroid injections or wrist splinting; improvements persisting for at least 6 months in most patients might even suggest the potential superiority of ultrasound treatment.

Serial ratings by patients of overall improvement suggest that ultrasound treatment would be best administered every day. Frequent treatment, however, is time consuming (as seen by the relatively high drop out rate in our study), but ultrasound treatment could be performed by compliant patients at home.

According to the pathophysiology of the carpal tunnel syndrome, ultrasonography might elicit anti-inflammatory and tissue stimulating effects, as already shown experimentally[23] and in recent clinical trials.[10 24]

Conclusion

Our trial suggests that ultrasound treatment has good short term effectiveness and even yields satisfying medium term effects in patients with mild to moderate idiopathic carpal tunnel syndrome. Further research is required to confirm independently these findings, to evaluate optimal treatment schedules with this method, and to investigate whether ultrasound treatment or one of the non-surgical treatments alone or in combination is superior, or whether early decompression may provide better long term results with fewer eventual neurological deficits.

We thank the therapists Helene Göttel, Beate Grabner, Renate Humenberger, Elfriede Jöbstel, Brigitte Kalleitner, Ilse Kirchweger, Constantin Ofner, and Renate Sedlacek for their help in the study, and Professor Brigitte Stanek for helpful review of the manuscript.

Contributors: GRE initiated the study, coordinated the formulation of the primary research hypothesis, designed the study, participated in data collection and data analysis, interpreted the findings, and wrote the paper. KLR participated in the design, carried out the data analysis and interpretation, and wrote the paper. PN, GFW, FU, and A-HG participated in the design, data collection, and the interpretation of results and helped to write the paper. VF participated in the design and the interpretation of results and helped to write the paper. GRE and KLR are guarantors for the paper.

Funding: None.

Conflict of interest: None.

1 Diagnosis of the carpal tunnel syndrome [editorial]. *Lancet* 1985;i:854-8.
2 Dawson DM. Entrapment neuropathies of the upper extremities. *N Engl J Med* 1993;329:2013-8.
3 Cotton P. Symptoms may return after carpal tunnel surgery. *JAMA* 1991;265:1921-2.
4 O'Malley MJ, Evanoff M, Terrono AL, Millender LH. Factors that determine reexploration treatment of carpal tunnel syndrome. *J Hand Surg (Am)* 1992;17:638-41.
5 Barnett SB, Ter Haar GR, Ziskin MC, Nyborg WL, Maeda K, Bang J. Current status of research on biophysical effects of ultrasound. *Ultrasound Med Biol* 1994;20:205-18.
6 Dyson M. Mechanisms involved in therapeutic ultrasound. *Physiotherapy* 1987;73:116-20.
7 Hong CZ, Liu HH, Yu J. Ultrasound thermotherapy effect on the recovery of nerve conduction in experimental compression neuropathy. *Arch Phys Med Rehabil* 1988;69:410-4.
8 Currier DP, Greathouse D, Swift T. Sensory nerve conduction: effect of ultrasound. *Arch Phys Med Rehabil* 1978;59:181-5.
9 Kramer JF. Effect of therapeutic ultrasound intensity on subcutaneous tissue temperature and ulnar nerve conduction velocity. *Am J Phys Med* 1989;64:1-9.
10 El Hag M, Coghlan K, Christmas P, Harvey W, Harris M. The anti-inflammatory effects of dexamethasone and therapeutic ultrasound in oral surgery. *Br J Oral Maxillofac Surg* 1985;23:17-23.
11 Edel H, Bergmann P. Studies on the effect of ultrasonics in different dosage on the neural conduction velocity in man. *Arch Phys Ther Leipz* 1970;22:255-9.
12 Mayr H, Ammer K. Impulsgalvanisation und Ultraschall zur Therapie des Carpaltunnelsyndromes. *Österr Z Phys Med* 1994;4:95-9.
13 Stevens JC. AAEE minimonograph #26: the electrodiagnosis of the carpal tunnel syndrome. *Muscle Nerve* 1987;10:99-113.
14 Ludin HP. *Praktische Elektromyographie*. 4th ed. Stuttgart: Enke, 1993.
15 Baysal AI, Chang CW, Oh SJ. Temperature effects on nerve conduction studies in patients with carpal tunnel syndrome. *Acta Neurol Scand* 1993;88:213-6.
16 Gelberman RH, Hergenroeder PT, Hargens AR, Lundborg GN, Akeson WH. The carpal tunnel syndrome. A study of carpal canal pressures. *J Bone Joint Surg (Am)* 1981;63:380-3.
17 Gelberman RH, Aronson D, Weisman MH. Carpal tunnel result of a prospective trial of steroid injection and splinting. *J Bone Joint Surg (Am)* 1980;62:1181-4.
18 Giannini F, Passero S, Cioni R, Paradiso C, Battistini N, Giordano N, et al. Electrophysiologic evaluation of local steroid injection in carpal tunnel syndrome. *Arch Phys Med Rehabil* 1991;72:738-42.
19 Girlanda P, Dattola R, Venuto C, Mangiapane R, Nicolosi C, Messina C. Local steroid treatment in idiopathic carpal tunnel syndrome: short and long term efficacy. *J Neurol* 1993;240:187-90.
20 McConnell JR, Bush DC. Intraneural steroid injection as a complication in the management of carpal tunnel syndrome. *Clin Orthop* 1990;250:181-4.
21 Burton RI, Littler J. Entrapment syndromes of the retinacular or restraining systems of the hand: carpal tunnel syndrome. *Curr Probl Surg* 1975;12(suppl 7):17.
22 Burke DT, McHale Burke M, Stewart GW, Cambre A. Splinting in carpal tunnel syndrome: in search of the optimal angle. *Arch Phys Med Rehabil* 1994;75:1241-4.
23 Byl NN, McKenzie AL, West JM, Whitney JAD, Hunt T, Scheuenstuhl H. Low-dose ultrasound effects on wound healing. A controlled study with Yucatan pigs. *Arch Phys Med Rehabil* 1992;3:656-64.
24 Binder A, Hodge G, Greenwood AM, Hazelman BL, Page Thomas DP. Is therapeutic ultrasound effective in treating soft tissue lesions? *BMJ* 1985;290:512-4.

(Accepted 11 November 1997)

Variations in population health status: results from a United Kingdom national questionnaire survey

Paul Kind, Paul Dolan, Claire Gudex, Alan Williams

Centre for Health Economics, University of York, York YO1 5DD
Paul Kind, *senior research fellow*
Paul Dolan, *research fellow*
Claire Gudex, *research fellow*
Alan Williams, *professor of economics*
Correspondence to: Dr Kind pk1@york.ac.uk

BMJ 1998;316:736–41

Abstract

Objective: To measure the health of a representative sample of the population of the United Kingdom by using the EuroQoL EQ-5D questionnaire.
Design: Stratified random sample representative of the general population aged 18 and over and living in the community.
Setting: United Kingdom.
Subjects: 3395 people resident in the United Kingdom.
Main outcome measures: Average values for mobility, self care, usual activities, pain or discomfort, and anxiety or depression.
Results: One in three respondents reported problems with pain or discomfort. There were differences in the perception of health according to the respondent's age, social class, education, housing tenure, economic position, and smoking behaviour.
Conclusions: The EQ-5D questionnaire is a practical way of measuring the health of a population and of detecting differences in subgroups of the population.

Introduction

The measurement of health is central to the evaluation of health care. By observing the extent of changes in health the benefits and disbenefits of health care for both patients and groups of patients can be evaluated; over the past 25 years several generic measures of health have been developed for use in this way.[1–8] These instruments were designed for use as general purpose measures of health, independent of diagnostic categorisation or disease severity. Information based on such measures is useful for establishing the degrees of morbidity in the community, enabling different population subgroups to be compared, which would help in assessing health needs or in informing those responsible for allocating health resources. Periodic reassessment of health could provide important data on the extent of any changes in the health of a population—for example, the extent to which the population is achieving national targets for health. If such standardised information was also routinely collected on individual patients it would provide a simple means of evaluating the outcomes of their health care.

We report on a study in which the EuroQoL EQ-5D questionnaire[9] was fielded in a survey of the population of the United Kingdom, conducted as part of a wider study of practical ways of measuring health related quality of life.[10]

Subjects and methods

EQ-5D questionnaire

The EQ-5D questionnaire is a generic measure of health status developed by the EuroQoL Group, an international research network established in 1987 by researchers from Finland, the Netherlands, Sweden, and the United Kingdom. The EQ-5D questionnaire defines health in terms of five dimensions: mobility, self care, usual activities (work, study, housework, family, or leisure), pain or discomfort, and anxiety or depression. Each dimension is subdivided into three categories, which indicate whether the respondent has no problem, a moderate problem, or an extreme problem (appendix). Combinations of these categories define a total of 243 health states. The EQ-5D questionnaire comprises two pages; on the first page respondents record the extent of their problem in each of the five dimensions and on the second page they record their perception of their overall health on a visual analogue scale (0 denoting the worst imaginable health state and 100 denoting the best imaginable health state). The validity and reliability of the EQ-5D questionnaire have been tested,[11–13] as has its application in a range of patient groups.[14–16] Since the original survey reported here, the EQ-5D questionnaire has been fielded in three national surveys, including the English national health survey—an interview-based survey of about 16 000 people. The EQ-5D questionnaire has also been used in population surveys in Spain, Germany, and Canada.

Survey design and methods

Members of the public aged 18 and over were interviewed as part of a national survey. No upper age limit was stipulated. The sample was based on addresses in England, Scotland, and Wales, selected by postcode.[17] Eighty postcode areas were chosen, proportionately to the number of addresses in each area, after these areas had been stratified by regional health authority, socioeconomic group, and population density. Seventy six addresses were selected from each postcode area, yielding a total of 6080 addresses. At each of these addresses one adult aged 18 or over was selected using a Kish grid.[18] Individuals in institutions, hostels, care homes, or bed and breakfast accommodation were excluded from the sample. Of the selected addresses, 12% were unproductive as they were non-residential, empty, or untraceable. The final sample comprising 3395 subjects was representative of the general population with respect to age, sex, and social class. During the interview, respondents completed the EQ-5D questionnaire and provided information on age, sex, marital state, education, employment, housing tenure, and smoking behaviour. The interviews took place during the last quarter of 1993.

Analysis mainly compared the differences between the population subgroups. It was hypothesised that more health problems would be reported with increasing age, with lower social class, for those registered sick or disabled, and for smokers. χ^2 Tests were used for the analysis of the descriptive profile data, and Student's t test was used to test for subgroup differences in the visual analogue scale data.

Results

A moderate problem on at least one dimension was reported by 42% of respondents, whereas only 6% of respondents reported any extreme problem (table 1). Problems were most often recorded in the pain or discomfort dimension. In subsequent analyses, moderate and extreme categories of each dimension were combined.

The mean state of health recorded on the visual analogue scale was 82.5 (SD 17).

Table 1 Numbers (percentages) of respondents reporting a problem in each EuroQoL dimension

	Problem		
EuroQoL dimension	Moderate	Extreme	Any
Mobility	620 (18.3)	3 (0.1)	623 (18.4)
Self care	139 (4.1)	5 (0.1)	144 (4.2)
Usual activities	481 (14.2)	70 (2.1)	551 (16.3)
Pain/discomfort	988 (29.2)	129 (3.8)	1117 (33.0)
Anxiety/depression	648 (19.1)	62 (1.8)	710 (20.9)
Any dimensions*	1441 (42.4)	212 (6.2)	1456 (43.1)

*Although row totals within dimension are internally consistent, there is apparent anomaly in the final row. 1441 respondents reported a moderate problem in at least one dimension and 212 reported an extreme problem; these two dimensions are not mutually exclusive as respondents may have reported an extreme problem in one dimension, with no intermediate level of problem being reported for remaining dimension. Hence total of 1456 does not equate to addition of two previous table entries.

Health and age

The rates of reported problems increased significantly with age ($P<0.001$) for all dimensions (table 2); an exception to this general pattern was the anxiety/depression dimension, which peaked at 28% of respondents aged 60 to 69 and then decreased slightly.

Figure 1 shows the mean visual analogue scale values for each age group and the 95% confidence interval. The mean value decreased from about 87 in the youngest age group to 72 in the oldest age group. Mean values did not differ significantly in the 20 to 49 age range but decreased significantly for respondents aged ≥50 ($P<0.001$).

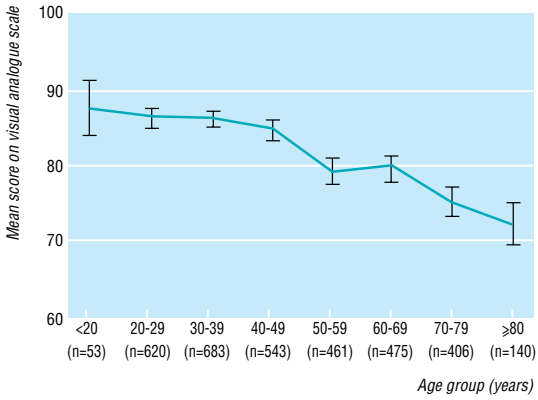


Fig 1 Mean self rated health status of respondents

Health and sex

Women aged ≥70 tended to report higher rates of problems than did men of the same age (table 2). A systematic difference in rates was found across all age groups on the anxiety/depression dimension, with women reporting significantly higher rates than men ($P<0.05$). No significant differences were found in the visual analogue scale scores for men and women.

Health and marital status

Respondents who were widowed, separated, or divorced reported significantly more problems on all five dimensions ($P<0.001$). Scores on the visual analogue scale for this group were also significantly lower than for respondents living alone or for those with a partner (means 77, 84, and 84 respectively, $P<0.001$).

Health and social class

After the effects of age were controlled for, there were significant differences in the rates of reported problems when respondents were grouped according to social class (table 3).

Table 2 Numbers (percentages) of respondents reporting any problem, by age group and sex

	Age group (years)						
EuroQoL dimension	20-29	30-39	40-49	50-59	60-69	70-79	≥80
Mobility							
All respondents	31 (5.0)	53 (7.8)	56 (10.3)	101 (21.9)	140 (29.3)	162 (39.8)	80 (56.7)
Men	15 (5.7)	24 (8.0)	23 (9.3)	53 (25.9)	73 (34.6)	57 (33.5)	21 (45.7)
Women	16 (4.5)	29 (7.6)	33 (11.1)	48 (18.7)	67 (25.1)	105 (44.3)	59 (62.1)
Self care							
All respondents	6 (1.0)	11 (1.6)	23 (4.2)	24 (5.2)	27 (5.7)	30 (7.4)	23 (16.3)
Men	3 (1.1)	6 (2.0)	10 (4.0)	13 (6.3)	15 (7.1)	13 (7.6)	5 (10.9)
Women	3 (0.8)	5 (1.3)	13 (4.4)	11 (4.3)	12 (4.5)	17 (7.2)	18 (18.9)
Usual activity							
All respondents	44 (7.1)	59 (8.6)	59 (10.8)	101 (21.9)	118 (24.7)	107 (26.3)	62 (44.0)
Men	23 (8.7)	22 (7.3)	23 (9.3)	51 (25.0)	61 (28.9)	42 (24.7)	19 (41.3)
Women	21 (5.9)	37 (9.7)	36 (12.1)	50 (19.4)	57 (21.4)	65 (27.4)	43 (45.3)
Pain/discomfort							
All respondents	98 (15.8)	132 (19.3)	141 (25.9)	202 (43.7)	221 (46.2)	228 (56.0)	85 (60.3)
Men	39 (14.8)	56 (18.7)	59 (24.0)	85 (41.5)	105 (49.8)	86 (50.6)	25 (54.3)
Women	59 (16.6)	76 (19.8)	82 (27.5)	117 (45.5)	116 (43.4)	142 (59.9)	60 (63.2)
Anxiety/depression							
All respondents	83 (13.4)	119 (17.4)	102 (18.7)	126 (27.2)	134 (28.0)	103 (25.3)	35 (24.8)
Men	27 (10.2)	46 (15.3)	39 (15.8)	53 (25.9)	54 (25.6)	29 (17.1)	8 (17.4)
Women	56 (15.8)	73 (19.1)	63 (21.1)	73 (28.3)	80 (30.0)	74 (31.2)	27 (28.4)

Table 3 Numbers (percentages) of respondents reporting any problem, by age group and social class (based on respondent's own current or most recent occupation as classified by registrar general)

	Age group (years)						
EuroQoL dimension	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**⩾80**
Mobility							
Social class:							
I and II	6 (3.6)	18 (7.6)	15 (7.6)	17 (14.3)	42 (28.4)	24 (29.6)	11 (47.8)
III	12 (4.4)	21 (7.3)	26 (11.8)	47 (23.5)	56 (26.7)	80 (39.8)	36 (57.1)
IV and V	11 (7.7)	9 (6.3)	15 (12.4)	36 (26.5)	40 (36.7)	52 (46.4)	28 (59.6)
Self care							
Social class:							
I and II	1 (0.6)	4 (1.7)	7 (3.5)	5 (4.2)	7 (4.8)	3 (3.7)	3 (13.0)
III	2 (0.7)	4 (1.4)	10 (4.5)	10 (5.0)	12 (5.7)	17 (8.5)	7 (11.8)
IV and V	2 (1.4)	2 (1.4)	6 (5.0)	9 (6.7)	7 (6.4)	10 (8.9)	11 (23.4)
Usual activities							
Social class:							
I and II	11 (6.5)	16 (6.8)	19 (9.6)	17 (14.3)	37 (25.0)	19 (23.5)	8 (34.8)
III	16 (5.9)	20 (7.0)	23 (10.4)	45 (22.5)	46 (21.9)	54 (26.9)	28 (44.4)
IV and V	13 (9.1)	18 (12.6)	16 (13.2)	38 (27.9)	32 (29.6)	32 (28.6)	21 (44.7)
Pain/discomfort							
Social class:							
I and II	24 (14.3)	39 (16.5)	38 (19.2)	33 (27.7)	62 (41.9)	36 (44.4)	9 (39.1)
III	42 (15.6)	45 (15.7)	69 (31.4)	98 (49.0)	93 (44.3)	111 (55.2)	43 (68.3)
IV and V	26 (18.2)	41 (28.7)	33 (27.3)	69 (50.7)	62 (56.9)	77 (68.8)	29 (61.7)
Anxiety/depression							
Social class:							
I and II	15 (8.9)	37 (15.6)	31 (15.7)	25 (21.0)	28 (18.9)	14 (17.3)	6 (26.1)
III	36 (13.3)	47 (16.4)	41 (18.6)	59 (29.4)	58 (27.6)	55 (27.4)	13 (20.6)
IV and V	25 (17.5)	33 (23.1)	29 (24.0)	39 (28.7)	45 (41.3)	31 (27.7)	14 (29.8)

Rates of reported problems from respondents in social classes III and IV were between 20% and 120% higher than rates in respondents from social classes I and II; the largest differences were for the pain/discomfort ($P<0.01$) and anxiety/depression ($P<0.01$) dimensions. Rates did not differ significantly for the mobility and self care dimensions. Figure 2 shows that respondents from social classes I and II had consistently higher levels of reported health as measured by the visual analogue scale than respondents from the two other social classes. Respondents from social classes I and II had a 5 point advantage on the visual analogue scale over respondents from social classes IV and V of the same age group. The difference was significant for all age groups except for respondents aged 40 to 49 years. The mean scores on the visual analogue scale for respondents from social classes I and II remained above the level of the youngest respondents from social classes IV and V until the 50 to 59 age group.

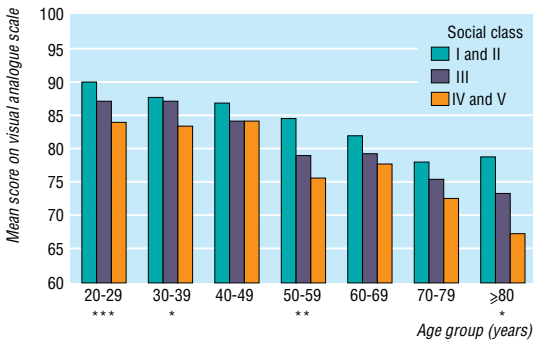


Fig 2 Effect of social class on self rated health status. *P<0.05; **P<0.01; ***P<0.001

Health and education

When respondents were classified by education rather than by social class, a similar pattern of differences emerged. Respondents who had received higher or further education reported significantly lower rates of problems with mobility ($P<0.05$), usual activities ($P<0.05$), pain/discomfort ($P<0.01$), and anxiety/depression ($P<0.01$) than did those who had received no education after leaving school. A similar pattern was seen on the visual analogue scale, with significantly higher scores reported for those who had received higher or further education ($P<0.001$).

Health and economic status

Significantly higher rates of problems were reported by respondents who were unemployed, sick or disabled, or retired, compared with those in employment or full time education ($P<0.001$) (table 4). Rates of reported problems for unemployed people were almost twice those of respondents in a salaried job.

When respondents were grouped according to housing tenure, significantly higher rates of problems were recorded on all the dimensions for those living in rented property compared with owner occupiers.

The mean scores on the visual analogue scale of people in work or of people who were studying was significantly higher than for people who were unemployed (87.5 and 82.0 respectively, $P<0.001$). Similarly, the scores of owner occupiers were significantly higher than for people who rented their accommodation (85.1 and 77.2 respectively, $P<0.001$).

Table 4 Numbers (percentages) of respondents reporting problems, by employment

Employment	No of respondents	EuroQoL dimension				
		Mobility	Self care	Usual activities	Pain/discomfort	Anxiety/depression
Studying	92	5 (5.4)	1 (1.1)	8 (8.7)	20 (21.7)	15 (16.3)
Salaried job	1636	106 (6.5)	11 (0.7)	109 (6.7)	337 (20.6)	223 (13.6)
Unemployed	196	24 (12.2)	5 (2.6)	21 (10.7)	53 (27.0)	52 (26.5)
Sick or disabled	128	101 (78.9)	48 (37.5)	110 (85.3)	112 (86.8)	79 (61.2)
Retired	761	280 (36.8)	53 (7.0)	211 (27.7)	393 (51.6)	186 (24.4)
Looking after home	524	93 (17.7)	23 (4.4)	79 (15.1)	179 (34.2)	138 (26.3)

*The table excludes 45 respondents whose employment was classed as other and 12 respondents whose details were missing.

Health and smoking behaviour

Respondents who smoked reported significantly higher rates of problems than non-smokers on all dimensions. Non-smokers also recorded significantly higher scores on the visual analogue scale than respondents who smoked (83.4 and 80.4 respectively, $P<0.001$).

Analysis of variance

Analysis of variance was used to investigate the collective influence of background variables. With the score on the visual analogue scale as the dependent variable and age as a covariate, a main effects model indicated a significant contribution for education ($P<0.01$), employment ($P<0.001$), and smoking behaviour ($P<0.001$). Housing tenure, marital status, and social class were not significant variables in this model.

Disability rates from other national surveys

Respondents who reported any problem in any dimension could be distinguished from respondents who reported no problems whatsoever. This dichotomy can be used to form an arbitrary definition of disability, enabling data to be compared with the findings of other surveys. The general household survey incorporates questions on longstanding illness and recent interference with usual activities.[19] The responses to these questions are combined to give rates of limiting longstanding illness which are published annually. The disability survey by the Office of Population Censuses and Surveys conducted in 1985 included a questionnaire comprising 10 categories: locomotion, reaching and stretching, dexterity, seeing, hearing, personal care, continence, communication, behaviour, and intellectual functioning.[20] The rates of disability in people grouped into five year age groups were reported in this survey.[20] These data were plotted against disability rates determined from our survey (fig 3). Disability rates based on responses to the EQ-5D questionnaire were 20% to 25% higher than rates from the general household survey for all age groups and about 30% to 40% higher than the 1985 disability survey, until the age of 80.

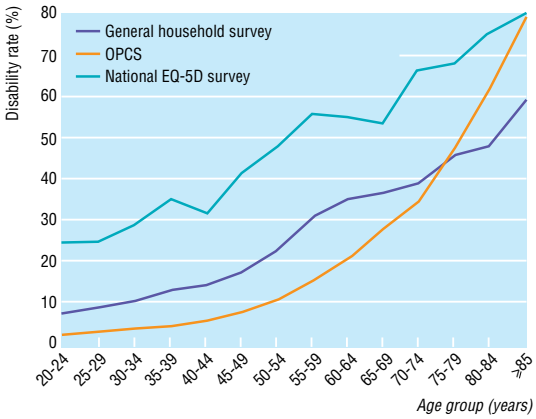


Fig 3 Disability rates from three national surveys

Discussion

This survey provides an important insight into the health status of the population of the United Kingdom at any one time. Although extreme problems with mobility and self care were rarely reported in this survey, there was a high level of reported problems with pain or discomfort. Over 50% of respondents aged ≥70 and about 20% of the youngest respondents reported some problem in this dimension. This finding has important implications. Pain does not seem to be a dimension of interest in a national disability survey despite being widely experienced in the community. The omission of a pain category means that it is assigned a zero weight, despite good evidence that it has a powerful influence on society's valuations of states of health.[21] These factors combine to disadvantage a significant proportion of the general population.

Significant differences were found between population subgroups with respect to age, social class, marital status, employment, education, and smoking behaviour. These findings compare with findings reported elsewhere.[22–24] Disability rates based on the EuroQoL classification reflected similar trends to those seen in the general household survey and surveys of the Office of Population Censuses and Surveys, although rates in these surveys were somewhat lower as they were based on a narrower definition of disability.

Population averages

The representativeness of the survey suggests that the results are indicative of the average health status in the general population of the United Kingdom, although it should be borne in mind that sampling was limited to individuals living in the community and tended to exclude people who had extreme problems with mobility or with self care and therefore likely to be dependent on others for their daily needs. Current investigation of specific patient groups—for example, people attending their general practice surgeries—reveals a wider distribution of reported problems. Thus, to the extent that this survey excluded people who were likely to yield responses indicating more severe problems, the results may well underestimate the health related quality of life of the general population.

Key messages

- Measurement of health outcome requires the observation of states of health
- Patients' involvement in recording and assessing their own state of health is a major element in the process of evaluating the impact of health care
- The EuroQoL EQ-5D questionnaire highlights variations in states of health which are consistent with previously published results
- High degrees of pain are reported in the general population. A category for pain is absent and thus undetected in the survey of disability by the Office of Population Censuses and Surveys

Our data can be treated as descriptive population "norms." As such, they could provide baseline values for monitoring variations in health for specific population groups, particularly if this information was also linked to local epidemiological data. In aggregate form, such information could be used to complement national targets by providing a measure based on health status rather than mortality. The capacity of the EQ-5D questionnaire to generate quantifiable and usable information on the health status of a population led to its inclusion in the 1996 health survey for England.[25]

Measuring outcomes

However, it is the measurement of change in health status for which the need is greatest. There can be few circumstances in which healthcare workers are not concerned with the measurement of outcome, and the EQ-5D questionnaire provides the capacity to measure change in health status, and hence outcomes, in a simple standardised way. The information on self reported problems recorded on the first page of the EQ-5D questionnaire identifies a unique health status for which there is a corresponding index value based on the views of the general population.[21] Changes in health status and the value of that change can be used to quantify outcomes for clinical and economic evaluation; the latter role was recommended for the EQ-5D questionnaire in a report commissioned by the United States Department of Public Health.[26] There is "an increasing consensus regarding the centrality of the patient's point of view in monitoring medical care outcomes,"[6] and the EQ-5D questionnaire has the obvious potential to contribute to that process. The national survey data reported in this paper show what can be achieved by using an uncomplicated instrument for measuring health status. The further exploitation of its potential is open to us all.

Survey work for the 1993 survey was conducted by Social and Community Planning Research, and we thank the trained fieldwork staff for their help in the collection of the data.

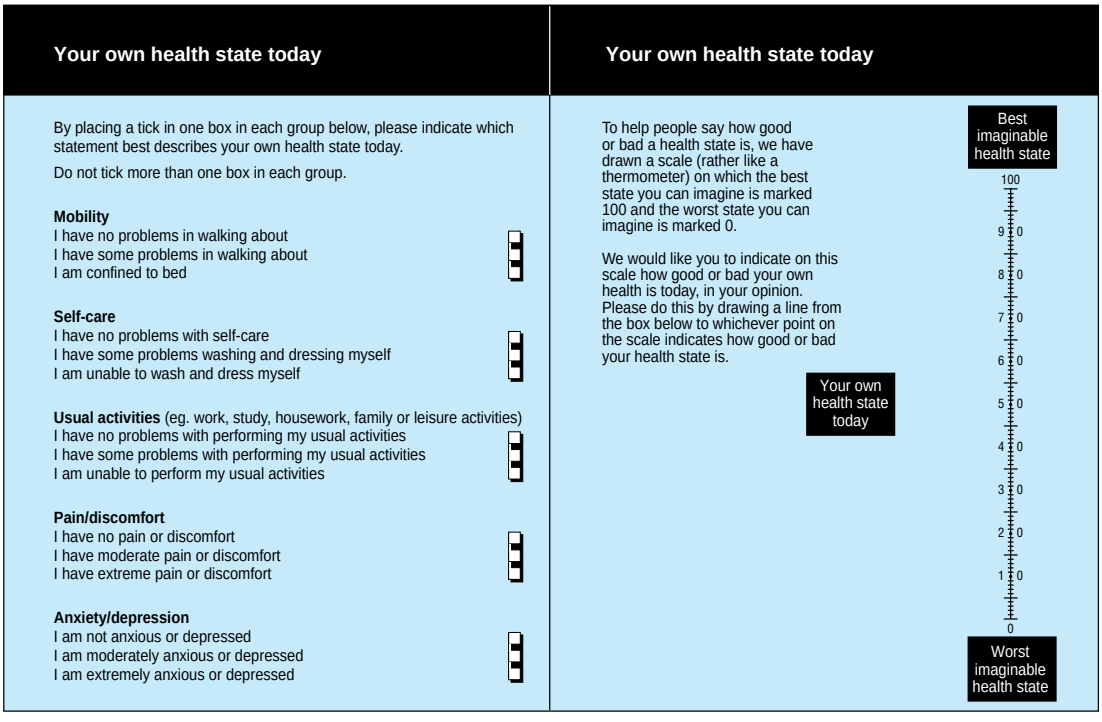
Contributors: All four authors shared equally in the design and execution of the research reported in this paper. Social and Community Planning Research provided significant additional expertise in the design and management of the national survey. PK will act as guarantor for the paper.

Funding: The project was funded by the Department of Health. The views expressed are those of the authors and not necessarily of the Department of Health.

Conflict of interest: None.

1 Patrick DL, Bush JW, Chen MM. Methods for measuring levels of well-being for a health status index. *Health Serv Res* 1973;11:516.
2 Rosser RM, Watts V. The measurement of hospital output. *Int J Epidemiol* 1972;1:361-8.

Appendix



Your own health state today

By placing a tick in one box in each group below, please indicate which statement best describes your own health state today.

Do not tick more than one box in each group.

Mobility
I have no problems in walking about
I have some problems in walking about
I am confined to bed

Self-care
I have no problems with self-care
I have some problems washing and dressing myself
I am unable to wash and dress myself

Usual activities (eg. work, study, housework, family or leisure activities)
I have no problems with performing my usual activities
I have some problems with performing my usual activities
I am unable to perform my usual activities

Pain/discomfort
I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort

Anxiety/depression
I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed

Your own health state today

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is.

Your own health state today

Best imaginable health state
100
90
80
70
60
50
40
30
20
10
0
Worst imaginable health state

EQ-5D questionnaire

3 Bergner M, Bobbitt RA, Kressel S, Pollard WE, Gilson BS, Morris JR. The sickness impact profile: conceptual formulation and methodology for the development of a health status measure. *Int J Health Serv* 1976;6:393-415.
4 Hunt SM, McKenna SP, McEwen J, Backett EM, Williams J, Papp E. A quantitative approach to perceived health status: a validation study. *J Epidemiol Community Health* 1980;34:281-6.
5 Torrance GW, Furlong W, Feeny D, Boyle M. Multi-attribute preference functions. *Pharmacoeconomics* 1995;7:503-20.
6 Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
7 Sintonen H. An approach to measuring and valuing health states. *Soc Sci Med* 1981;15:55-65.
8 EuroQoL Group. EuroQoL—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.
9 Brooks RG. EuroQoL—the current state of play. *Health Policy* 1996;37:53-72.
10 Williams AH. *The measurement and valuation of health: a chronicle*. University of York: Centre for Health Economics, 1995. (Discussion paper 136.)
11 Brazier J, Jones N, Kind P. Testing the validity of the EuroQoL and comparing it with the SF-36 health survey questionnaire. *Qual Life Res* 1993;2:169-80.
12 Van Agt H, Essink-Bot M-L, Krabbe P, Bonsel G. Test-retest reliability of health state valuations collected with the EuroQoL questionnaire. *Soc Sci Med* 1994;39:1537-44.
13 Essink-Bot M-L, Krabbe P, Bonsel G, Aaronson N. An empirical comparison of four generic health status measures: the Nottingham health profile, the medical outcomes study 36-item short-form health survey, the COOP/WONCA charts, and the EuroQoL Instrument. *Med Care* 1997;35:522-37.
14 Hurst NP, Jobanputra P, Hunter M, Lambert M, Lochead A, Brown H. Validity of EuroQoL—a generic health status instrument—in patients with rheumatoid arthritis. *Br J Rheumatol* 1994;33:655-62.
15 Sculpher M, Dwyer N, Byford S, Stirrat G. Randomised trial comparing hysterectomy and transcervical endometrial resection: effect on health related quality of life and costs two years after surgery. *Br J Obstet Gynaecol* 1996;103:142-94.
16 Hollingworth W, Mackenzie R, Todd CJ, Dixon AK. Measuring changes in quality of life following magnetic resonance imaging of the knee: SF-36, EuroQoL or Rosser index? *Qual Life Res* 1995;4:325-34.
17 Erens B. *Health-related quality of life: general population survey*. London: Social and Community Planning Research, 1994. (Technical report.)
18 Kish L. *Survey sampling*. New York: Wiley, 1965.
19 Thomas M, Goddard E, Hickman M, Hunter P. *The general household survey 1992*. London: HMSO, 1994. (OPCS Series GHS No 23.)
20 Martin J, Letzer H, Elliot D. The prevalence of disability among adults. *OPCS surveys of disability in Great Britain. Report 1*. London: HMSO, 1988.
21 Dolan P, Gudex C, Kind P, Williams A. *A social tariff for EuroQoL: results from a UK general population survey*. University of York: Centre for Health Economics, 1995. (Discussion paper 138.)
22 Department of Health and Social Security. *Prevention and health: everybody's business. A reassessment of public and personal health*. London: HMSO, 1976.
23 Black D, Morris JN, Smith C, Townsend P. Black Report. *Inequalities in health: report of a research working group*. London: Department of Health and Social Security, 1980.
24 Rahkonen O, Arber S, Lahelma E. Health inequalities in early adulthood: a comparison of young men and women in Britain and Finland. *Soc Sci Med* 1995;41:163-71.
25 Prescott-Clarke P, Primatesta P, eds. *Health survey for England, 1996*. London: Stationery Office, 1998.
26 Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA* 1996;276:1253-8.

(Accepted 31 October 1997)

Use of calcium channel blockers and risk of suicide: ecological findings confirmed in population based cohort study

Gunnar Lindberg, Kerstin Bingefors, Jonas Ranstam, Lennart Råstam, Arne Melander

Abstract

Objective: To investigate possible associations between use of cardiovascular drugs and suicide.
Design: Cross sectional ecological study based on rates of use of eight cardiovascular drug groups by outpatients. A population based cohort study including users of drugs to control hypertension.
Subjects: The ecological study included 152 of Sweden's 284 municipalities. The cohort study included all inhabitants of one Swedish municipality who during 1988 or 1989 had purchased cardiovascular agents from pharmacies within the municipality. Six hundred and seventeen subjects (18.2%) were classified as users of calcium channel blockers and 2780 (81.8%) as non-users.
Main outcome measures: Partial correlations (least squares method) between rates of use of cardiovascular drugs and age standardised mortality from suicide in Swedish municipalities. Hazard ratios for risk of suicide with adjustments for difference in age and sex in users of calcium channel blockers compared with users of other hypertensive drugs.
Results: Among the Swedish municipalities the use of each cardiovascular drug group except angiotensin converting enzyme inhibitors correlated significantly and positively with suicide rates. After adjustment for the use of other cardiovascular drug groups, as a substitute for the prevalence of cardiovascular morbidity, only the correlation with calcium channel blockers remained significant ($r = 0.29$, $P < 0.001$). In the cohort study, five users and four non-users of calcium channel blockers committed suicide during the follow up until the end of 1994. The absolute risk associated with use of calcium channel blockers was 1.1 suicides per 1000 person years. The relative risk, adjusted for differences in age and sex, among users versus non-users was 5.4 (95% confidence interval 1.4 to 20.5).
Conclusions: Use of calcium channel blockers may increase the risk of suicide.

Introduction

A recent epidemiological study reported an excess risk of depression requiring pharmacological treatment after treatment with calcium channel blockers and angiotensin converting enzyme inhibitors but not after treatment with digoxin, anti-arrhythmics, nitrates, diuretics, or β blockers.[1] There have also been case reports suggesting depression[2–5] as well as psychosis[6] after treatment with calcium channel blockers. As depression may promote suicide we investigated possible ecological associations between suicide rates and the rates of use of eight cardiovascular drug groups in 152 Swedish municipalities. In addition, we investigated the risk of suicide in users and non-users of calcium channel blockers who had purchased prescription drugs mainly used to treat hypertension.

Swedish Network for Pharmacoepidemiology, Foundation, Malmö University Hospital, SE-205 02 Malmö, Sweden
Gunnar Lindberg, *clinical epidemiologist*
Jonas Ranstam, *biostatistician*
Arne Melander, *professor*
Department of Pharmaceutical Services Research, Uppsala University, Box 586, SE-751 23 Uppsala, Sweden
Kerstin Bingefors, *senior lecturer*
Department of Community Medicine, Lund University, Malmö University Hospital, SE-205 02 Malmö
Lennart Råstam, *professor*
Correspondence to: Dr Lindberg gunnar.lindberg@nepi.a.se

BMJ 1998;316:741–5

Methods

This report concerns two different studies: firstly, an ecological study with data from Swedish municipalities on rates of suicide and rates of use of eight groups of cardiovascular drug groups; secondly, the hypothesis generated by this study tested in a cohort study on historical data from users of different antihypertensive drugs.

The ecological study

Sweden is administratively divided into 284 municipalities. Suicide rates for men and women standardised for age for these municipalities during the 5 year period 1989-93 were obtained from the epidemiological centre of the Swedish Board of Health and Welfare. Data on incidence of cause specific mortality were missing for eight municipalities. Data on suicide mortality (ICD-9 (international classification of diseases, 9th revision), codes E950-E959 and E980-E989) were available for 152 municipalities in which the expected number of people committing suicide during the 5 year period was more than five men and five women, as assumed from the overall suicide rates in Sweden.

Rates of use of cardiovascular drugs by outpatients, defined by the Anatomical Therapeutical Chemical (ATC) classification[7] and expressed as pharmacy dispensed numbers of defined daily doses per 1000 inhabitants per year, were obtained from Apoteksbolaget (the Swedish Corporation of Pharmacies) for each of the 152 municipalities during each of the years 1989-93. The geometric means of the annual rates of use were used in the calculations.

The rates of use of eight cardiovascular drug groups—diuretics, β blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, lipid lowering agents, low dose aspirin, nitrates, and cardiac glycosides—were correlated with suicide rates by using Pearson's correlation coefficient. Partial correlation coefficients between suicide rates and rates of use of the cardiovascular drug groups were assessed to estimate a correlation coefficient for each drug group independent of variations in the rates of use of the seven other groups to use as a proxy for cardiovascular disease prevalence. All tests were two sided.

The cohort study

Data on individual prescription drug use in a municipality located in mid-eastern Sweden (population about 20 000 in 1989) have been compiled and studied since the 1970s. All prescription drugs purchased by residents from pharmacies within the municipality are registered according to the ATC system.[7] For the purpose of the present study all inhabitants of the municipality were identified who during 1988 or 1989 had purchased cardiovascular medications with ATC codes (in 1988 and 1989) C02 (centrally acting antiadrenergic agents, ganglion blocking antiadrenergic agents, peripherally acting antiadrenergic agents, calcium channel blockers, angiotensin converting enzyme inhibitors), C03 (diuretics), and C07 (β blockers). ATC codes for calcium channel blockers and angiotensin converting enzyme inhibitors were later changed to C08 and C09, respectively. The subjects were classified as users or non-users of calcium channel blockers. Mortality data for the cohort until the end of 1994, including the cause of death, were derived from the Swedish mortality register.[8] Deaths from suicide were defined by the ICD-9 codes E950-E959 and E980-E989. The codes E980-E989 include cases with uncertain intention for suicide. Data on purchased medications and cause of death were linked by the Swedish personal identification number.

Differences in risk of suicide were evaluated by the Kaplan-Meier method and the log rank test. Multivariate adjustments for differences in age and sex were performed with the proportional hazards method. All P values are two sided.

Results

The ecological study

The number of suicides in the 152 municipalities during the 5 year period ranged from 5 to 652. The total number of suicides in the municipalities during this period was 5648. The total population was 7.3 million, and the mean (range) municipality population was 48 042 (13 722 - 679 364) in 1991. Age adjusted suicide rates varied from 0.76 to 3.69 deaths per 10 000 inhabitants per year. The mean (SD) suicide rate for the 152 municipalities was 2.06 (0.49) suicides per 10 000 inhabitants per year. The rates of use were 79.7 defined daily doses per 1000 inhabitants per day for diuretics, 36.8 for β blockers, 22.5 for calcium channel blockers, 20.4 for nitrates, 16.0 for angiotensin converting enzyme inhibitors, 15.3 for cardiac glycosides, 9.4 for low dose aspirin, and 2.9 for lipid lowering agents.

The correlation coefficients for the relations between rates of drug use and rates of suicide are given in table 1. Except for angiotensin converting enzyme

Table 1 Correlation coefficients for rates of use of cardiovascular drug groups and rates of suicide in 152 Swedish municipalities, 1989-93

Drug group	Unadjusted	Adjusted†
Diuretics	0.27**	0.14
β blockers	0.20*	–0.11
Calcium channel blockers	0.36***	0.29***
ACE inhibitors	0.11	–0.09
Lipid lowering agents	0.19**	0.16
Low dose aspirin	0.18*	–0.03
Nitrates	0.17*	–0.12
Cardiac glycosides	0.20*	–0.06

ACE=Angiotensin converting enzyme inhibitors.
†Adjusted for differences in rates of use of all other cardiovascular agents.
*P<0.05; **P<0.01; ***P<0.001.

Table 2 Correlation coefficients for rates of use of calcium channel blockers and rates of suicide in 152 Swedish municipalities, 1989-93

Drug	Unadjusted	Adjusted†
All vasoselective drugs	0.31***	0.21*
Felodipine	0.24**	0.14
Nifedipine	0.21**	0.12
All cardioselective drugs	0.39***	0.17*
Verapamil	0.22**	0.08
Diltiazem	0.28**	0.19*

†Adjusted for differences in rates of use of all agents included in table 1 except calcium channel blockers.
*P<0.05; **P<0.01; ***P<0.001.

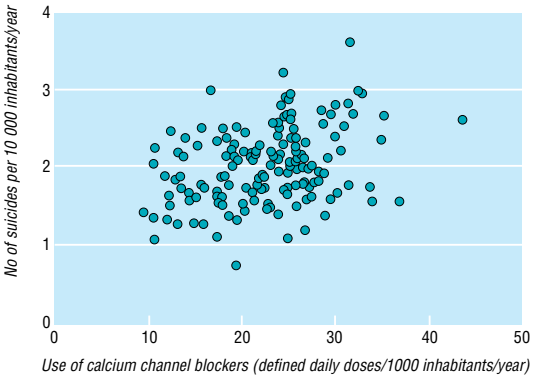


Fig 1 Correlation between rates of use of calcium channel blockers and rates of suicide in 152 Swedish municipalities

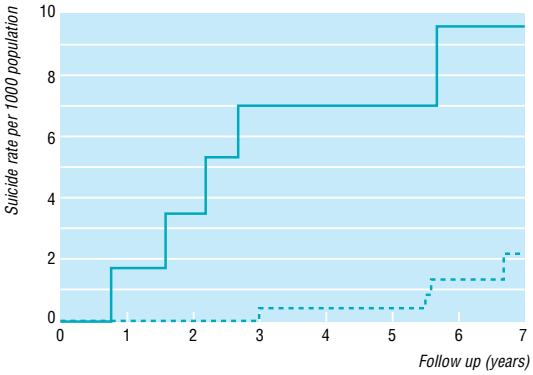


Fig 2 Cumulative rate of suicide over 7 years' follow up in 617 users (continuous line) and 2780 non-users (dotted line) of calcium channel blockers

inhibitors, the rates of use correlated significantly with the suicide rates. The highest correlation coefficient was seen for calcium channel blockers ($r=0.36$, $P<0.001$) (figure 1). After adjustment for differences in the rates of use of the other drug groups, only the rates of use of calcium channel blockers correlated significantly with the suicide rates ($r=0.29$, $P<0.001$) (table 1). Additional adjustment for the proportion of men living in the municipality did not alter this result.

The rates of use of two predominantly cardioselective and two predominantly vasoselective calcium channel blockers also correlated significantly with suicide rates (table 2). After adjustment for the rates of use of the seven other types of cardiovascular drug groups, the use of both dihydropyridine and benzothiazepine derivatives remained significantly correlated with suicide rates. When we adjusted for differences in use of the seven other cardiovascular drug groups, the correlation coefficient was 0.21 for dihydropyridine derivates and 0.18 for benzothiazepine derivatives. The rates of use of diltiazem had the closest correlation with suicide rates (table 2).

The cohort study

In all, 3397 patients were identified as purchasers of drugs with ATC codes C02, C03, and C07 in 1988 and 1989. Of them, 617 (18.2%) were classified as users of calcium channel blockers (nifedipine, verapamil, diltiazem, and felodipine) and 2780 (81.8%) as non-users. During the follow up, from the date of purchase until the end of 1994, five users of calcium channel blockers (three men and two women, one with uncertain intent) and four non-users (three men and one woman, none with uncertain intent) committed suicide. The 7 year suicide risks were 9.7 and 2.2 per 1000 persons for calcium channel blocker users and non-users, respectively. The difference in suicide risk was significant ($P=0.002$.) The average annual absolute risk associated with use of calcium channel blockers was therefore 1.1 suicides per 1000 persons. After adjustment for differences in age and sex the relative risk among users versus non-users was 5.4 (95% confidence interval 1.4 to 20.5). Figure 2 illustrates the cumulative suicide rates during follow up of users and non-users of calcium channel blockers.

Discussion

In the past several groups of cardiovascular drug have been associated with depressive disorders. As suicide is a serious consequence of depression, the current studies were undertaken to evaluate the possible influence of widely used drugs on risk of suicide. The correlation between use of calcium channel blockers and suicide rates found in the ecological study led us to design a cohort study to test if, among users of antihypertensive drugs, subjects using calcium channel blockers had a higher risk of suicide than subjects not using calcium channel blockers.

Diltiazem,[2] nifedipine,[3] and verapamil[4] have been associated with depressive disorders in case reports and also in a previous epidemiological study that used data on individual prescriptions of calcium channel blockers and antidepressants.[1] The two current studies imply that calcium channel blockers may also promote suicide. In the ecological study the estimated correlation suggests that about one tenth of the intermunicipality variation in risk of suicide is related to the use of calcium channel blockers. In the cohort study the suicide risk in users of calcium channel blockers adjusted for sex and age was fivefold compared with the risk in non-users treated with other antihypertensive agents.

Clinical trials have a limited ability to detect infrequent or late adverse effects or adverse effects resulting in common symptoms. They also often use a number of inclusion and exclusion criteria, thus reducing their generalisability. Studies with a long follow up and studies encompassing the whole population are therefore needed.

In contrast with most clinical trials the current cohort study included all identified users of the study drugs. Consequently the generalisability of the study is high. In the ecological study low populated municipalities with few expected suicides were excluded, so the influence from extreme rates in combination with small number of events was avoided.

In Sweden, as in most other countries, men have a higher incidence of suicide than women. Men are also more likely to be prescribed a calcium channel blocker (unpublished data on file). In our cohort study the estimated rates of suicide were adjusted for differences in age and sex, and, in the ecological study, the suicide rates were adjusted for differences in age. Additional

adjustment of the ecological correlations for the proportion of men in the municipalities did not affect the results (no data given), thus we can eliminate age or sex differences as confounders.

Comorbidity such as cardiovascular diseases might have promoted depressive disorders and suicide. In the ecological study this problem was dealt with by adjusting the correlation for each tested cardiovascular drug group with the rate of use of the seven other drug groups. In the cohort study all subjects were treated with antihypertensive drugs. It follows that although no detailed clinical data were available, users and non-users of calcium channel blockers most probably had similar medical backgrounds.

Populations with a high prevalence of cardiovascular diseases also have a high suicide risk. In the ecological study the rates of use of all but one evaluated cardiovascular drug group also correlated significantly with the suicide rates before adjustment for the rates of use of the other drug groups. After adjustment, however, only the rate of use of calcium channel blockers was significantly and positively correlated with suicide rates (see table 1). Accordingly, the increased suicide risk linked to use of calcium channel blockers would seem independent of cardiovascular comorbidity.

Links with depression

Calcium channel blockers are often prescribed to treat angina pectoris. If angina pectoris causes depression, this might form a link to suicidal behaviour. Nitrates are also prescribed to treat angina pectoris, however, and the rates of use of nitrates did not correlate with suicide rates when we adjusted for the rates of use of other cardiovascular drug groups. Neither did the use of angiotensin converting enzyme inhibitors, often prescribed to patients with diabetes, correlate with suicide rates. Thus, it seems unlikely that the presence of angina pectoris or diabetes help to explain the linking of calcium channel blockers to depression and increased suicide risk.

Other reasons to prescribe calcium channel blockers might have been greater difficulty in achieving control of blood pressure or adverse effects from other antihypertensive drugs. Again, it is not very likely that such circumstances have enough penetrative power to link calcium channel blockers to depression and suicide risk.

In the late 1980s β blockers were suspected of inducing depression.[9] Therefore, other antihypertensive or antiangina drugs might have been chosen for patients with depression. If calcium channel blockers were used particularly often in depressed patients, an increased suicide risk would appear in users of calcium channel blockers even though the drugs per se would not promote depression and suicide. To behave as a confounder, however, the confounding variable has to be substantially correlated to the tested exposition as well as to the outcome. Therefore, to achieve a high increase in suicide risk by confounding from selective prescribing of calcium channel blockers to depressed patients, most depressed patients with increased risk of suicide and few non-depressed patients should have been prescribed calcium channel blockers. Only about half of depressed patients are correctly diagnosed by their primary care physicians,[10] however, and use of calcium channel blockers is also obviously common in patients without depression.

Key messages

- Clinical trials have a limited ability to detect infrequent adverse effects, so postmarketing reports on adverse effects and observational epidemiological studies are necessary
- The present investigations, including one cross sectional ecological study and one population based cohort study, suggest an increased risk of suicide in users of calcium channel blockers
- The results are in accordance with a depressive effect of calcium channel blockers suggested by case reports and a recent epidemiological study
- Channel blockers should be considered a possible cause of depression and suicide

In the cohort study population patients were classified as users and non-users of calcium channel blockers at the time of inclusion. Some of the former might have stopped taking calcium channel blockers shortly after inclusion and some non-users might have been prescribed calcium channel blockers after inclusion. Moreover, both studies take drugs purchased from pharmacies into account. It is not certain that each purchased drug was used, and some inhabitants may not have purchased drugs from pharmacies in their home municipality. Provided that the misclassification was independent of the outcome, however, misclassification of exposure would probably have resulted in underestimation of the true association.

One way to interpret the results of the ecological study is to assume that most, if not all, cardiovascular agents have some depressive effect, calcium channel blockers being most prominent. As the studied cardiovascular agents were very heterogeneous, however, a common effect on mood is unlikely.

In contrast with most other cardiovascular agents, calcium channel blockers influence secretory and contractile mechanisms in many different types of cells. Because of their lipophilic properties they easily penetrate the blood-brain barrier. Hence they have access to and may interfere with neurones and receptors involved in the regulation of mood. As calcium channel blockers differ in selectivity and in kinetics their influence on the central nervous system may vary. In the ecological study, however, the rates of use of both dihydropyridine and benzothiazepine derivatives correlated significantly and those of phenylalkylamine derivatives non-significantly with suicide rates after adjustment for the rates of use of other cardiovascular drug groups. Hence it seems likely that calcium channel blockade per se is involved in the increased risk of suicide. A calcium channel effect of dihydropyridines in affective disorders has also been suggested previously.[5]

In conclusion, use of calcium channel blockers may increase risk of suicide. A depressive effect of these drugs has been suggested and may constitute a link with risk of suicide. The consequences of treatment with calcium channel blockers should be further inves-

tigated with respect to depressive disorders and suicide. Calcium channel blockers should be considered as a possible cause of depression and suicide

Contributors: GL initiated the ecological and cohort studies, formulated the study aims, designed the layouts, organised the data collection, and participated in the statistical analysis and interpretation of results and in writing the paper. KB participated in collecting and interpreting results for the cohort study. JR participated in the statistical analysis and interpretation of the data and contributed to writing the paper. LR participated in the interpretation of the data and the writing of the paper. AM, head of the Swedish Network for Pharmacoepidemiology (NEPI), participated in the interpretation of the data and contributed to writing and editing the paper.

Funding: The NEPI Foundation (the Swedish Network of Pharmacoepidemiology) and the Swedish National Institute of Public Health.

Conflict of interest: None.

1 Hallas J. Evidence of depression provoked by cardiovascular medication: a prescription sequence symmetry analysis. *Epidemiology* 1996;7:478-84.
2 Biriell C, McEwen J, Sanz E. Depression associated with diltiazem. *BMJ* 1989;299:796.
3 Hullett FJ, Potkin SG, Levy AB, Ciasca R. Depression associated with nifedipine-induced calcium channel blockade. *Am J Psychiatry* 1988;145:1277-9.
4 Dassylva B. Verapamil may cause depression. *Can J Psychiatry* 1993:38:299-300.
5 McAllister-Williams RH. Calcium-channel blockade and depressive illness. *Br J Psychiatry* 1990;157:618-9.
6 Kahn JK. Nifedipine-associated acute psychosis. *Am J Med* 1986;81:705-6.
7 Capellà D. Descriptive tools and analysis. In: Dukes MNG, ed. *Drug utilisation studies: methods and uses*. Copenhagen: WHO Regional Office for Europe, 1993:55-78. (WHO regional publication. European series: No 45.)
8 Bolander AM. Mortality statistics in Sweden and its neighbouring countries. Advantages and hazards inherent in systems and materials. In: Boström H, Lungstedt N, eds. *Medical aspects of mortality statistics*. Stockholm: Almquist and Wiksell, 1981:236-55.
9 Avorn J, Everitt DE, Weiss S. Increased antidepressant use in patients prescribed beta-blockers. *JAMA* 1986;255:357-60.
10 Nielsen AC, Williams TA. Depression in ambulatory medical patients. Prevalence by self-reported questionnaire and recognition by non-psychiatric physicians. *Arch Gen Psychiatry* 1980;37:999-1004.

(Accepted 11 November 1997)

QT and QTc dispersion are accurate predictors of cardiac death in newly diagnosed non-insulin dependent diabetes: cohort study

Abdul A O Naas, Neil C Davidson, Chris Thompson, Fraser Cummings, Simon A Ogston, Roland T Jung, Ray W Newton, Allan D Struthers

Patients with non-insulin dependent diabetes mellitus have an excess risk of dying from cardiovascular disease. One small study suggested that a prolonged QT interval could predict cardiac death in patients with diabetic nephropathy who have received insulin treatment. The question now is whether the same is true in newly diagnosed diabetes in patients who have no apparent complications. In addition, QT dispersion, a new but related electrocardiographic variable, predicts cardiac death in patients who have chronic heart failure, peripheral vascular disease, or essential hypertension.[1–3] We investigated whether it also predicted cardiac death in diabetic patients.

Subjects, methods, and results

The study group of 182 patients with non-insulin dependent diabetes mellitus (103 men; mean age 52.8 (SD 8.5) years) represented the Dundee cohort of the United Kingdom prospective diabetes study, which was recruited between 1982 and 1988. Patients were followed up for a mean of 10.3 (1.7) years. The inclusion and exclusion criteria of the study have been reported elsewhere. Patients with overt cardiac disease at baseline were excluded. A single observer (AAON) measured QT intervals as described previously.[1–3] Cardiac death was mostly classified at the coordinating centre in Oxford, using the codes of the international classification of diseases, ninth revision. All analysis was done by Cox regression analysis, with cardiac death as the sole end point. We used forward stepwise analysis, each time using all three QT variables along with age, systolic blood pressure, sex, smoking, blood glucose concentration, and antihypertensive drug. As a result, we identified age, systolic blood pressure, sex, diuretics, and all QT variables as the potentially important variables. Finally we fitted the regression using these four variables with each of the three QT variables.

In those who had a cardiac death, the mean time of death after the baseline electrocardiogram was 7.3 (3.2) years; after the 3 year electrocardiogram it was 4.9 (2.3) years and after the 6 year electrocardiogram 3.8 (1.0) years. The table shows that QTc max, QTc dispersion, and QT dispersion are all highly significant and independent predictors of cardiac death at baseline, at 3 years, and at 6 years. In multivariate analysis they outperformed all other predictors.

Comment

Our main finding was that QT dispersion, QTc dispersion, and QTc max are excellent predictors of cardiac death in patients with non-insulin dependent diabetes mellitus. QTc interval analysis has two major advantages over other possible ways of stratifying risk in patients. Firstly, measurements of QTc interval are easily obtained with a non-invasive routine test: other potential predictors of cardiac death often require extra testing with specialised equipment. Secondly, comparisons between QTc dispersion and microalbuminuria suggest that QTc dispersion is a better predictor of cardiac death.[4] A QTc dispersion >78 ms at year 6 in this study had 100% sensitivity and 90% specificity, giving an odds ratio of 9.0, whereas the odds

Department of Clinical Pharmacology and Therapeutics, Ninewells Hospital and Medical School, Dundee DD1 9SY
Abdul A O Naas, *clinical research fellow*
Neil C Davidson, *British Heart Foundation research fellow*
Allan D Struthers, *consultant physician*
Diabetes Centre, Ninewells Hospital and Medical School
Chris Thompson, *senior registrar*
Fraser Cummings, *medical student*
Roland T Jung, *consultant physician*
Ray W Newton, *consultant physician*
Department of Epidemiology, Ninewells Hospital and Medical School
Simon A Ogston, *senior lecturer*
Correspondence to: Professor Struthers

BMJ 1998;316:745–6

Cox multivariate regression analysis for prediction of cardiac death from data at various time points

	B	SE	Wald χ^2 statistic	P value
Baseline				
QTc dispersion	0.021	0.0069	9.40	0.002**
Age	0.080	0.0312	6.61	0.010*
Systolic blood pressure	0.016	0.0080	4.16	0.041*
Sex	0.682	0.5130	1.77	0.183
QT dispersion	0.018	0.0068	7.07	0.008**
Age	0.075	0.0314	5.74	0.017*
Systolic blood pressure	0.016	0.0081	3.96	0.047*
Sex	0.534	0.5016	1.13	0.287
QTc max	0.0166	0.0042	15.45	0.0001**
Age	0.0699	0.0322	4.69	0.0303*
Sex	1.143	0.5269	4.71	0.0300*
Systolic blood pressure	0.0139	0.0077	3.27	0.0707
Year 3				
QTc dispersion	0.017	0.0074	5.15	0.023*
Systolic blood pressure	0.019	0.0118	2.58	0.108
Age	0.046	0.0371	1.51	0.219
Sex	0.569	0.6090	0.87	0.351
QT dispersion	0.018	0.0070	6.46	0.011*
Systolic blood pressure	0.018	0.0115	2.46	0.117
Age	0.045	0.0370	1.48	0.225
Sex	0.539	0.0604	0.80	0.372
QTc max	0.017	0.0054	9.79	0.002**
Sex	0.910	0.6440	2.00	0.157
Age	0.051	0.0380	1.85	0.174
Systolic blood pressure	0.015	0.0117	1.63	0.202
Year 6				
QTc dispersion	0.036	0.0113	10.29	0.001**
Sex	1.667	0.9790	2.90	0.089
Age	0.034	0.0610	0.31	0.575
Systolic blood pressure	0.000	0.0160	0.00	0.986
QT dispersion	0.024	0.0105	5.37	0.020*
Sex	1.219	0.8530	2.04	0.153
Age	0.050	0.0540	0.87	0.351
Systolic blood pressure	0.003	0.0160	0.04	0.838
QTc max	0.035	0.0110	10.36	0.001**
Sex	1.827	0.9210	3.94	0.047*
Age	0.038	0.5400	0.51	0.477
Systolic blood pressure	0.015	0.0190	0.599	0.439

*P<0.05, **P<0.005. Although diuretics were significant in univariate analysis, they were not significant in multivariate analysis.

ratio for microalbuminuria was only 1.8 in a recent overview.[5]

The question arises why analysis of QT interval should be able to predict cardiac death. QT dispersion may be a composite term reflecting electrical inhomogeneity as a result of ischaemia, left ventricular dilatation, left ventricular hypertrophy, cardiac fibrosis, and autonomic neuropathy. Each one of these individually confers increased cardiac risk, and this may be why QT dispersion, as a composite of them, is highly predictive of cardiac death. The clinical value of analysing the QT interval may therefore be that it could be used as a screening test to select diabetic patients for more extensive cardiac investigations. Importantly, the time between measuring a prolonged QT interval and the subsequent cardiac death is many years, which provides ample opportunity to intervene.

We thank Professor Robert Turner (Oxford) and Mr Phillip Bassett (United Kingdom prospective diabetes study centre) for their assistance. We would also like to thank Lynda G Dick and Marlyn F H Foster for their help in the Ninewells Diabetes Centre with the patients from the study.

Contributors: AAON analysed all the electrocardiograms and wrote the first draft of the paper. SO performed the statistical analysis. CT, NCD, and FC helped to extract data on each patient. RWN and RTJ ran the United Kingdom prospective diabetes study in Dundee. ADS supervised the project and wrote the final draft of the paper.

Funding: NCD was supported by the British Heart Foundation.

Conflict of interest: None.

1 Barr CS, Naas AO, Freeman M, Lang CC, Struthers AD. QT dispersion and sudden unexpected death in chronic heart failure. *Lancet* 1994;343:327-9.
2 Fu GS, Meissner A, Simon R. Repolarization dispersion and sudden cardiac death in patients with impaired left ventricular function. *Eur Heart J* 1997;18:281-9.
3 Darbar D, Luck J, Davidson N, Pringle T, Main G, McNeill G, et al. Sensitivity and specificity of QT dispersion for identification of risk of cardiac death in patients with peripheral vascular disease. *BMJ* 1996;312:874-8.
4 Sawicki PT, Meinhold J, Kiwitt S, Bender R. QT interval dispersion is an important predictor or mortality in NIDDM patients. *Diabetes* 1996;45(suppl 2):128A.
5 Dineen S, Gerstein H. Microalbuminuria and mortality in NIDDM: a systematic overview of the literature. *Diabetes* 1995;44(suppl 1):124A.

(Accepted 16 September 1997)

How often does surgery for peptic ulceration eradicate *Helicobacter pylori*? Systematic review of 36 studies

John Danesh, Paul Appleby, Richard Peto

Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Clinical Medicine, University of Oxford, Radcliffe Infirmary, Oxford OX2 6HE

continued over

BMJ 1998;316:746–7

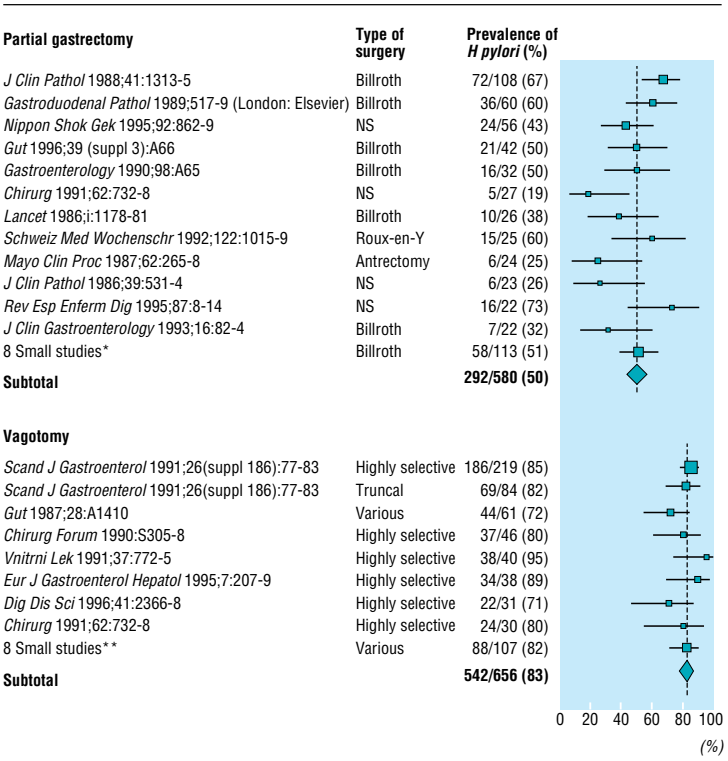
Most peptic ulceration is due to chronic infection with *Helicobacter pylori*, and antibiotic treatments can generally cure both the infection and the ulceration.[1] In previous decades, however, persistent peptic ulceration was often treated surgically either by vagotomy, which merely reduces symptoms, or by partial gastrectomy, which removes the ulcer and parts of the stomach likely to be infected with *H pylori*.[2] There have been several surveys on the prevalence of persistent *H pylori* infection in patients who have undergone surgery for peptic ulceration, often many years previously. We present a systematic review of these surveys and compare the type of surgery with the likelihood of persistent *H pylori* infection.

Methods and results

We checked in databases, reference lists, and gastroenterology journals for any studies published before January 1997 that assessed *H pylori* infection after surgery for peptic ulceration. Studies were included if they provided information on the indication for surgery and the type of surgery. We tabulated the type of surgery, the mean interval between surgery and testing

for *H pylori* (average 10 years), the method of testing for *H pylori* (mostly histology), the site and number of gastric biopsies, and the prevalence of infection. Among the 33 reports identified we excluded five: one included unrepresentative patients (*Hepato Gastroenterol* 1994;41:542-5), and four did not provide separate results for patients with peptic ulceration (*Helicobacter* 1996;1:270; *Z Gastroenterol* 1993;31:115-9) or patients who had had partial gastrectomy (*Surg Gynecol Obstet* 1993;176:594-8; *Mat Med Pol* 1994;88:13-6). From 28 publications, 36 studies were included. Prevalences from different studies were combined by direct summation of their numerators and denominators. The results from the small studies—that is, those with fewer than 20 patients—were combined in the figure and when displaying the results from separate studies and calculating standard χ^2 tests of heterogeneity.

Among patients who had undergone vagotomy alone the prevalence of persistent *H pylori* infection was about 83% (542/656), whereas for partial gastrectomy it was only about 50% (292/580; figure). There were insufficient data to compare the prevalence of *H pylori* infection after particular types of partial gastrectomy—for example, Billroth *v* Roux-en-Y—or vagotomy—for example, highly selective *v* truncal. The heterogeneity within the two subtotals ($\chi^2_{12}=47$ and $\chi^2_8=14$) was much less extreme than the heterogeneity between the two subtotals ($\chi^2_1=147$, $P<0.0001$). Thus the difference in prevalence between the subtotals remained informative.



Prevalence of *Helicobacter pylori* after surgery for peptic ulcer: 36 studies. Size of black area proportional to number of patients. NS = not specified (**Dig Dis Sci* 1991;36:1697; *J Clin Gastroenterol* 1993;16:82-4; *Gastroenterology* 1989;96:A247; *Mat Med Pol* 1994;88:9-12; *Gastroenterology* 1989;97:958-64; *Ann Chir* 1991;45:905-8; *Gut* 1989;30:1552-7; *Pol Arch Med Wewn* 1991;86:13-7. ***Lancet* 1986;1:1178-81; *Gastroenterology* 1989;97:958-64; *Gastroduodenal pathology and Campylobacter pylori* (London: Elsevier) 1989: 517-9, 525-7; *Ann Chir* 1991;45:905-8; *Zentralbl Chir* 1995;120:364-72; *Gastroenterology* 1990;98:A65; *Mat Med Pol* 1994;88:9-12)

Comment

Other studies have shown that most patients with active peptic ulcers are infected with *H pylori*—about 95% of those with duodenal ulcer and 85% of those with gastric ulcer.[3] The prevalence of *H pylori* in such patients remains high after vagotomy (83% (95% confidence interval 78% to 86%)) but falls to about 50% (45% to 56%) after partial gastrectomy. This difference cannot be explained by the methods used for testing for *H pylori* or for gastric tissue sampling as both were similar across studies, or by differences in reinfection rates postoperatively. Despite the inclusion of studies reported as abstracts or in languages other than English some publication bias may remain, although this should not alter the main conclusions. Remission of *H pylori* infection after partial gastrectomy may be due partly to the resection of distal gastric tissue, a usual site of infection, and partly to the bactericidal effects of prolonged bile acid reflux in surgical patients.[4] Whatever the reason, this decrease represents one way surgery could contribute to the cure of peptic ulcer disease.

The main clinical implication of the persistently high prevalence of *H pylori* infection postoperatively is that patients who have undergone gastrectomy or particularly vagotomy should be reviewed and considered for antibiotic treatment that will cure their chronic infection.

Carsten Flohr, Sumiyo Iida, and Monika Jakubiecz helped with translations.

Contributors: JD is guarantor; he also initiated the study, identified and abstracted information from publications, performed statistical analyses, interpreted the data, and drafted the report. PA plotted the findings, discussed statistical issues, and edited the report. RP provided the statistical methods, interpreted the data, and drafted the report.

Funding: JD was supported by a Rhodes scholarship and a Balliol College senior scholarship.

Conflict of interest: None.

1 Goodwin CS, Mendall M, Northfield TC. Helicobacter pylori infection. *Lancet* 1997;349:265-9.
2 Fineberg HV, Pearlman LA. Surgical treatment of peptic ulcer in the United States. *Lancet* 1981;i:1305-7.
3 Kuipers EJ, Thijs JC, Festen HPM. The prevalence of Helicobacter pylori in peptic ulcer disease. *Aliment Pharmacol Ther* 1995;9(suppl 2):59-69.
4 O'Connor HJ, Wyatt JI, Ward DC, Dixon MF, Axon ATR, Dewar EP. Effect of duodenal ulcer surgery and enterogastric reflux on Campylobacter pyloridis. *Lancet* 1986;i:1178-81.

(Accepted 24 June 1997)

John Danesh, *Rhodes scholar*
Richard Peto, *professor of medical statistics and epidemiology*
Imperial Cancer Research Fund, Cancer Epidemiology Unit, Gibson Building, Radcliffe Infirmary, Oxford OX2 6HE
Paul Appleby, *research officer*
Correspondence to: Dr Danesh john.danesh@balliol.ox.ac.uk

Corrections

Birth weight and cognitive function in young adult life: historical cohort study

An authors' error occurred in this paper by Henrik Toft Søreson et al (16 August, pp 401-3). The correct mean (SD) score for parity should have been 0-1: 43.6 (9.4); 2: 42.2 (9.7); ≥3, 41.0 (10.1). These values did not lead to any errors in the risk calculations, and there were no consequences for any of the results.

Childhood energy intake and adult mortality from cancer: the Boyd Orr cohort study

An editorial error occurred in this paper by Frankel et al (14 February, pp 499-504). In table 5 the third cause of death under each of the three main headings (Both sexes, Men, and Women) should have read: Cancers not related to smoking [not Cancers not related to cancer, as published].