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SERTRALINE IN STROKE-ASSOCIATED LABILITY OF MOOD

ALISTAIR BURNS,[1]* EVE RUSSELL,[2] HILARY STRATTON-POWELL,[3] PIPPA TYRELL,[4] PAUL O'NEILL[5] AND ROBERT BALDWIN[6]
[1]*Professor of Old Age Psychiatry, Department of Old Age Psychiatry, Withington Hospital, Manchester, UK*
[2]*Consultant in Old Age Psychiatry, Department of Old Age Psychiatry, Withington Hospital, Manchester, UK*
[3]*Research Nurse, Department of Old Age Psychiatry, Withington Hospital, Manchester, UK*
[4]*Consultant Geriatrician, Hope Hospital, Salford, Manchester, UK*
[5]*Consultant Geriatrician, Withington Hospital, Manchester, UK*
[6]*Consultant in Old Age Psychiatry, Manchester Royal Infirmary, Manchester, UK*

SUMMARY

Objective. To assess whether a selective serotonin reuptake inhibitor is effective in the treatment of stroke-associated lability of mood.

Methods. Twenty-eight non-depressed patients suffering from post-stroke lability of mood took part in an 8-week double-blind randomized placebo-controlled trial of a selective serotonin reuptake inhibitor (50 mg sertraline per day).

Results. There were statistically significant improvements in a global rating of emotionalism and a specific benefit on tearfulness. The results are discussed in the light of proposed serontonergic mechanisms for emotional lability following stroke.

Conclusions. 50 mg of sertraline per day may be an effective and well-tolerated treatment for stroke-associated lability of mood in the absence of depression. This is supportive evidence for the serontonergic hypothesis of lability of mood following stroke. Copyright © 1999 John Wiley & Sons, Ltd.

KEY WORDS—sertraline; lability; stroke

The physical sequelae of stroke have been well documented and, more recently, there has been increasing awareness of associated psychological distress including psychiatric disturbance (Allman, 1991). Depression is a well-recognized consequence of stroke (Starkstein and Robinson, 1989; Allman, 1991), with studies indicating an incidence of between 20 and 50% in the first year post-stroke (House *et al*., 1991; Robinson *et al*., 1987). The association of vascular brain disease and depression in older people has recently been emphasized (Alexopoulos *et al*., 1997; Krishnan *et al*., 1997). We have documented the presence of post-traumatic stress disorder in 10% of patients following stroke which may be a causal mechanism for conceptualizing the various symptoms occurring after the event, including lability of mood (Sembi *et al*., 1998). Emotional changes post-stroke have been described variously as 'emotionalism', 'lability of mood', 'pathological crying' and the ugly and outdated term 'emotional incontinence'. These sequelae, in common with neuropsychiatric features of dementia, are more frequent than is generally appreciated and cause distress to carers and patients alike. Clinically, they commonly interfere with the rehabilitative process and have been reported in 15% of patients at 1 month and 21% at 6 months (House *et al*., 1989). Anderson (1992) described the sequelae of stroke, finding that most cited problems were mood and personality change, that the quality of contact between patient and supporter were strongly to the latter's subjective feeling of burden, with the conclusion that patients' emotional and social behaviour has a significant impact on the carer, more so than the physical level of disability.

Emotionalism has been treated with a variety of remedies including tricyclic antidepressants, many

*Correspondence to: Professor A. Burns, Department of Old Age Psychiatry, Withington Hospital, West Didsbury, Manchester M20 8LR, UK. Tel/Fax: 0161 291 4364. E-mail: A_Burns@fs1.with.man.ac.uk

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studies of which have shown beneficial effects (Lawson and Macleod, 1969; Schiffer *et al*., 1983, 1985). Levodopa has also been used with success (Wolf *et al*., 1979; Udaka *et al*., 1984). More recently, selective serotonin reuptake inhibitors (SSRIs) have been used to good effect (Sloan *et al*., 1992; Seliger *et al*., 1992; Anderson *et al*., 1993), their relatively better safety index and lower side-effect profile (in particular cerebro- and cardiovascular effects) compared to tricyclic antidepressants being advantageous. Also, there is circumstantial evidence that serotonergic mechanisms may underlie the lability of mood seen following stroke, with lesions more commonly found in the raphe nuclei (an area rich in serotonergic neurones) in patients with lability of mood. Anderson *et al*. (1993) reported a placebo-controlled double-blind trial of citalopram in patients with post-stroke pathological crying, showing it to be an effective and well-tolerated treatment.

This study is an attempt to broaden previous work using a well-established SSRI (sertraline) in a larger group of subjects with post-stroke lability of mood.

DESIGN OF STUDY

Sample

Patients were recruited from three hospitals in Manchester where specialist stroke services exist. Referrals were taken from a wide variety of sources and consisted of patients known to the services, whether they were inpatients, outpatients or entirely supported in the community. Inclusion criteria of the study were: clinically documented stroke (with or without computed tomography evidence of infarction); presence of lability of mood observed by the referring clinician; at least 1 month having elapsed since stroke; absence of depression and dementia according to DSM-III-R criteria (APA, 1987). One month post-stroke was taken as an inclusion criterion to concentrate on patients with chronic and persistent emotional disorders. The study was approved by the appropriate local ethics committees.

Assessments

Basic demographic data were obtained on the sample including sex, age, site of stroke (determined clinically) and time elapsed since stroke. The following assessments were carried out on each patient on entry to the study and at the times outlined in Table 1.

Primary outcome measures

Emotionalism/lability of mood. Seven questions were asked, based on those in the study by House *et al*. (1989), to establish the presence or absence of lability of mood:

'Have you been more tearful in the last 2 weeks than you were before your stroke?'
'Have you actually cried more in the last 2 weeks?'
'Does the weepiness come suddenly at times when you weren't expecting it?'
'If you feel the tears coming on, can you control yourself to stop them?'
'Have you been unable to stop yourself crying in front of other people?'
'Is that a new experience for you?'

These were rated on a yes/no basis, scoring 1 for yes and 0 for no.

'How frequent are your episodes of tearfulness?'

This was rated on a four-point scale (0—one episode less than once per week, 1—episodes more than once a week but less than once a day, 2—episodes up to five times a day, 3—episodes six or

Table 1. Assessments during the study

	Baseline	2-week placebo run-in	Placebo or sertraline				2-week placebo washout
Week	−2	0	2	4	6	8	10
Lability scale	✓	✓	✓	✓	✓	✓	✓
CIBIC		✓	✓	✓	✓	✓	✓
MMSE	✓	✓		✓		✓	✓
MADRS	✓	✓		✓		✓	✓

Note: Assessments took place at the end of the study period described.

more times a day). The total maximum score for the scale was 9, and anyone scoring 1 or above was regarded as having lability of mood.

Clinician's Interview-Based impression of Change (CIBIC). This is a seven-point rating scale which measures a global change in the patient's condition, rated by the research nurse (HSP) taking into account all information about the clinical condition of the patient, including opinions of observers where possible.

Secondary outcome measures

Mini-Mental State Examination (MMSE) (Folstein et al., 1975). A 30-item rating of cognitive impairment; the greater the score, the less the impairment.

Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). A standardized scale of depression, marked out of 28, known to be sensitive to change in mood state.

Other clinical measures

Barthel Index (Mahoney and Barthel, 1965). A brief rating of functional ability with emphasis on physical functions.

Scandinavian stroke scale (Lindenstrom et al., 1991). A descriptive scale for severity of stroke.

Frenchay aphasia battery (Enderby et al., 1987). Assesses the degree of language dysfunction.

Study design

This is summarized in Table 1. The study was carried out according to a double-blind placebo-controlled parallel group design. After randomization (in blocks of four using a random number allocation list produced by the Department of Medical Statistics at Withington Hospital) to either drug or placebo, there was a 2-week run-in period (single-blind in order to exclude transient reversible emotional states with patients excluded if symptoms resolved during this period) followed by 8 weeks on placebo or sertraline in a fixed dose of 50 mg per day. Finally, there was a 2-week single-blind placebo phase with follow-up assessments at 3 months. Active agent and placebo were packed in gelatine capsules with an identical appearance. Compliance was monitored by a capsule count at each visit. Emergency code breaks were held in the pharmacy but were not used.

Statistical analysis

Statistics were computed employing the SAS system (Release 6.11) using Fisher's exact test for categorical variables, Wilcoxon rank sum tests for continuous data and Cochran Mantel Haenszel tests for identification of predictors of improvement.

RESULTS

Twenty-eight patients were randomized—14 to placebo and 14 to the sertraline group. No patients were excluded during the 2-week run-in period. Four patients did not complete the study. Two withdrew in the sertraline group—one after week 8 following the development of a skin rash and one following a hospital admission in the last week of the study because of a fractured hip. Two patients died, one in each group, both from fatal strokes, one at week 6 and the other between completion of the study and follow-up. Two more patients reported adverse events during the study, one of sleeplessness and the other of constipation. Both were on placebo. Results are presented on an intention to treat basis, with the last observation carried forward for those who did not complete the study.

The demographic characteristics of the sample and the results of the primary and secondary outcome variables are presented in Table 2. Seventeen patients had a left-sided stroke, 11 a right-sided stroke. There were no differences in the primary or secondary outcome variables at baseline and results are presented for the outcome measures taken at the beginning of week 4 (4 weeks into treatment) and the beginning of week 8 (the end of the active phase) and at week 10 (the end of the 2-week washout period).

Mean MADRS score at entry to the study was 0.7 (SD 1.3) in the placebo group and 1.6 (SD 2.2) in the sertraline group. The baseline scores on the MMSE were 24.6 in the placebo group (SD 7.4) and 20.9 (SD 9.6) in the sertraline group. Neither of these measures changed significantly during the study. There was no difference in the other measures between the placebo and sertraline group in Barthel Index (mean value 12.3 (SD 7.1)

Table 2. Demographic characteristics and results of primary and secondary outcome variables

	Placebo	Sertraline
N	14	14
M:F	8:6	5:9
Age(yr)		
Mean (SD)	67.6 (8.5)	73.4 (9.1)
Months from stroke		
Median (range)	10.5 (1–156)	5.5 (1.5 – 48)

Assessments	After week	Placebo	Sertraline
Improvements on CIBIC;	4*	9 (64%)	14 (100%)
N (%)†	8*	9 (64%)	13 (93%)
	10	9 (64%)	10 (71%)
Improvement on lability scale;	4	9 (64%)	12 (86%)
N (%)‡	8*	9 (64%)	13 (93%)
	10	9 (64%)	5 (36%)
Diminished tearfulness;	4	9 (64%)	13 (93%)
N (%)†	8*	9 (64%)	14 (100%)
	10	8 (57%)	10 (71%)

Note: The 10-week assessment is after 2 weeks on placebo.
*Assessments scored as improved, worsened and no change. Difference between treatment and placebo groups $p = 0.041$ (Fisher's exact test).
†In addition to the nine subjects improving on placebo, five showed no change, significant on a 3×2 chi-square (improved, worse or no change treatment group).
‡In addition to the nine subjects improving on placebo, five showed no significant change, one subject on sertraline deteriorated. Significant on a 3×2 chi-square (improved, worse or no change treatment group).

and 12.2 (SD 7.2) respectively), Scandinavian stroke scale (mean value 32.2 (SD 13.4) and 29.7 (SD 14.7) respectively) or Frenchay aphasia score (mean value 21.6 (SD 7.6) and 19.8 (SD 7.8) respectively).

There was a significant improvement in lability score (and, in particular, episodes of tearfulness) and CIBIC compared to baseline at 4 and 8 weeks. Tearfulness significantly diminished after 2 weeks (50% of patients in the placebo group and 97% in the treatment group) and remained significantly lower throughout the trial. All scores became non-significant after the 2-week washout.

A stepwise logistic regression was performed to explore factors influencing improvement in tearfulness. The small dataset did not allow for a full explanatory model, so Cochran Mantel Haenszel tests were carried out to analyse each variable at a time. Two explanatory variables revealed an independent association with improvement in tearfulness—length of time since stroke and score on the Frenchay aphasia battery. Patients who scored greater than 20 on the Frenchay aphasia better did better, as did patients who had had their stroke at least 6 months earlier (although there were large differences between time since stroke and treatment in the two groups). Because of the small numbers, these results need to be interpreted with caution, but they suggest that the presence of aphasia and the fact that a patient has had a stroke several months earlier should not deter active treatment of emotionalism.

DISCUSSION

While this is a relatively small study, as far as we are aware, it is the largest placebo-controlled double-blind trial of an antidepressant of the SSRI group in stroke-associated lability of mood. It suggests that sertraline is effective in its lowest dose (50 mg per day) and reduces lability of mood as measured by the patient on a self-rating scale and on an independent measure (the CIBIC). It seems to have a particularly beneficial effect on tearfulness. The drug was well tolerated without serious side-effects. The positive response was achieved within 4 weeks of treatment of patients

without coexisting depression and disappeared within 2 weeks of stopping the drug. The absence of significant depression and the speed of response in some patients make it unlikely that the results were due to a primary effect on depressed mood.

There does not appear to be a differential response to sertraline in terms of symptom profile but the specific effect on tearfulness may be explained by a direct effect of the drug on the serotonergic-rich raphe nuclei. Even though the statistical significance was marginal, the sample size was small and many of the patients in this study reported an almost instantaneous decrease in tearfulness.

In conclusion, this study suggests that sertraline may be an effective and well-tolerated drug in the treatment of emotional lability following stroke.

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