Minaprine in Depression
A Controlled Trial with Amitriptyline

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Minaprine (200 mg daily, either once or divided b.d.) was compared with amitriptyline (25–50 mg t.d.s.) over six weeks in 144 patients with major depression. Significant reductions in HRSD scores at the end of six weeks' treatment were recorded with both dose regimes of minaprine and with amitriptyline, with no significant differences between them. There was a significantly greater incidence of drowsiness and dry mouth with amitriptyline than with minaprine.
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Minaprine is an amino-phenylpyridazine compound synthesised by Wermuth & Exinger (1972) which facilitates serotonergic, dopaminergic, and cholinergic transmission. The compound has been shown to exert antidepressant effects in most animal models of depression (Biziere *et al*, 1982) and in clinical trials against placebo (Jouvent *et al*, 1984), imipramine and maprotiline (Radmayr *et al*, 1984), nomifensine (Mikus *et al*, 1984), and mianserin (Wheatley, 1989).

The main advantages claimed for minaprine are that it is relatively free from anticholinergic effects, cardiotoxicity, drowsiness, and weight gain. In a previous study undertaken by our group (Wheatley, 1989) equivalent antidepressant activity was recorded against mianserin; the incidence of anticholinergic effects was negligible with either drug, but drowsiness was significantly more frequent with mianserin. Mianserin was chosen for that trial as being a comparable non-anticholinergic compound, although drowsiness (Wakeling, 1983) and weight gain (Harris & Harper, 1980) are common with it. However, in order to confirm the freedom from anticholinergic and sedative effects, a comparison to a standard tricyclic antidepressant is required and, of those available, amitriptyline is probably the most widely used and documented from these points of view (Mindham, 1979).

Method

In our previous study, minaprine 100 mg twice daily was as effective as 100 mg thrice daily and so the former dose was used for the present study. The trial was double-blind and an additional comparison to once-daily medication was also included, patients being randomly allocated to one of the following:

(a) minaprine 200 mg single dose for six weeks (200 mg morning, placebo midday and evening)
(b) minaprine 100 mg b.d. for six weeks (100 mg morning, placebo midday, 100 mg evening)
(c) amitriptyline 25 mg t.d.s. for one week (25 mg morning, 25 mg midday, 25 mg evening); amitriptyline 50 mg t.d.s. for five weeks (50 mg morning, 50 mg midday, 50 mg evening) (these doses were halved in patients aged 65 years and older).

All doses, irrespective of nature, were contained in identical capsules, individually blister-packed and labelled: 'Morning', 'Midday', and 'Evening'. The opened blister packs provided a means of verifying drug compliance.

Although it is common practice to administer amitriptyline as a single dose at night, being the standard for this trial it was felt important to adhere to the makers' recommendations which postulate divided dosage. For ethical reasons a placebo group was not included because of risk of suicide in these unsupervised patients in the community.

The trial was undertaken by 16 general practitioner members of the group who treated 144 patients attending their surgeries and suffering from major depression according to DSM–III–R criteria (American Psychiatric Association, 1987) with a minimum score on the Hamilton Rating Scale for Depression (HRSD) of 19 (Hamilton, 1960). Those taking part had previously attended training sessions to validate inter-rater reliability in completing the HRSD (Loudon & Tiplady, 1981). As compared to hospital out-patients, depression is seen at an earlier and more acute stage in general practice, when response to antidepressant drugs is more likely to be effective (Wheatley, 1973).

Patients were excluded if they were suffering from schizophrenia, chronic brain syndrome, senile dementia, epilepsy, cardiac, renal or hepatic failure, or peptic ulcer, as were women who might be pregnant or breast feeding. Furthermore, patients were excluded if they were being treated with lithium, had an abnormal EEG or ECG, or were suicidal. Written informed consent was obtained from all patients before the start of the trial.

On breaking the code, it was found that the allocation of patients to treatment groups was as follows: minaprine o.d. 53, minaprine b.d. 45, and amitriptyline 46. As in the previous study, females outnumbered males, the sex ratios for the three groups being minaprine (o.d.) 2.8 : 1, minaprine (b.d.) 1.4 : 1, and amitriptyline 1.9 : 1. In the three groups respectively, the mean ages were: 48.6, 43.4 and 49.0 years and this was the first episode of depression in 53%, 62% and 67% respectively.

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Table 1
Mean scores on the HRSD in the three treatment groups as the trial progressed

Week	Minaprine o.d.	Minaprine b.d.	Amitriptyline
0	23.4	23.2	23.3
1	19.8	19.4	18.7
2	17.2	16.1	15.7
3	14.8	14.3	12.8
4	12.7	10.8	10.9
6	11.3	11.0	11.0

Results

The full six-week trial was completed by 42 patients in the minaprine (o.d.) group, 35 in the minaprine (b.d.) group, and 34 in the amitriptyline group. The 'last visit carried forward' (LVCF) method was used for all patients completing at least two weeks and these were then included in the analysis of the results, giving totals of 49, 41 and 37 in the three groups respectively (total $n = 127$). The paired t-test was used to test for pre-post differences, and the t-test for between-group differences. The results are shown in Table 1.

The differences in HRSD from baseline became statistically significant at week one in all three groups ($P<0.01$) and all other differences were highly significant from baseline. The greatest change in mean score was recorded in the amitriptyline group, namely a reduction of 12.3, closely followed by minaprine b.d. with a reduction of 12.2 and minaprine o.d. with a reduction of 12.1. Comparison of the change scores from week 0 to week 6 in the three groups showed no significant between-drug differences.

Analysis of mean HRSD scores during the trial is useful to allow comparisons between the three treatment groups, but does not give any indication as to the numbers either completely or partially relieved of symptoms or in whom there was no effect. As in the previous study, cases were classified into three categories in relation to the final HRSD score: cured <6, improved 7–17, and no better or worse >18. Using these criteria, at the end of the trial the numbers 'cured' were minaprine (o.d.) 15 (31%), minaprine (b.d.) 14 (34%), and amitriptyline 12 (32%); 'improved' 27 (55%), 18 (44%) and 16 (43%) respectively; and 'no better or worse' 7 (14%), 9 (22%) and 9 (24%) respectively. However these differences were not statistically significant (χ^2).

A check-list of all possible side-effects was provided and this was recorded before treatment and after each week of treatment. Initially, patients were asked whether they had any of these symptoms and subsequently only a general question: "Have the capsules upset you in any way?"

There were no reported side-effects in 77% of patients on minaprine o.d., 71% on minaprine b.d. and 61% on amitriptyline. (NS for all comparisons χ^2.) However, drowsiness occurred much more frequently with amitriptyline (20%) than with either minaprine o.d. (2%) ($P<0.01$) or minaprine b.d. (4%) ($P<0.05$). So did dry mouth: amitriptyline (17%), minaprine o.d. (4%) ($P<0.05$) and minaprine b.d (2%) ($P<0.02$). On the other hand, nausea/vomiting was higher in both minaprine groups – o.d. 6% (NS) and b.d. 7% (NS) – as compared to amitriptyline (0%).

The majority of patients dropping out did so because of side-effects (amitriptyline 5, minaprine o.d. 2 and b.d. 1). Two patients in each treatment group (six in all) were lost to follow-up due to defaulting, while one patient had to be admitted to hospital because of a suicide attempt and one other patient dropped out because he found the capsules too big to swallow. The drop-out rate due to side-effects was significantly greater with amitriptyline than both minaprine groups combined ($\chi^2 = 9.954$, $P<.005$).

Discussion

As is the usual experience with trials of new antidepressant drugs, this study showed no significant differences between minaprine and the 'standard' amitriptyline, in respect of either rapidity of onset of action or overall antidepressant effect. These are similar findings to those in the previous study against mianserin, thus providing further evidence for the effectiveness of minaprine. Although, of course, the possibility of a type II statistical error cannot be ruled out, the numbers in each group were sufficient to give a 50% chance ($P<0.05$) of a difference of at least 20% being demonstrated between treatments (Clark & Downie, 1966).

Any advantages for the new drug depend therefore on a more effective side-effect profile and, of course, its safety, although the latter is not the subject of this report. With regard to the incidence of side-effects, there was a clear advantage for minaprine 200 mg either as a single daily dose or divided twice daily, over the control standard drug, amitriptyline 75–150 mg divided thrice daily. This advantage was demonstrated in respect of drowsiness and dry mouth, two of the commonest side-effects with the tricyclic antidepressants.

A major problem with antidepressants is motivation of patients to continue treatment for the vital first two to three weeks, before any appreciable antidepressant effect becomes apparent. By nature of the illness, depressed patients are apathetic or even antagonistic to drug therapy and will use any excuse to terminate it. Side-effects may occur within the first 24 hours of treatment and are commonly used as this excuse. Therefore, a new antidepressant drug, even although not therapeutically superior to those already available, may ensure better patient compliance in treatment. Minaprine would appear to fulfil this requirement.

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Depression and 'Hassles' in Globus Pharyngis

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A group of 25 patients (16 women, 9 men) attending an ENT department with globus sensation and 25 matched ENT controls were assessed using the Beck Depression Inventory and scales for daily stressful events ('hassles'). Globus patients of both sexes were significantly more depressed than controls and had Beck scores suggestive of significant depression. Thirteen patients, but only two controls, had an independent life event within two months of disease onset, and patients had higher hassles scores than controls.
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Our previous psychological investigations of globus patients (Wilson *et al*, 1988; Deary *et al*, 1989) have found increasing self-ratings of free-floating anxiety, somatisation and depression, and low extraversion in women when compared with age-matched controls. Lehtinen & Puhakka (1976) found depressive and obsessive characteristics in 11 women with globus sensation, but men were similar to controls. The results were not, however, subjected to statistical analysis. Pratt *et al* (1976), in contrast, found that men in their study had a higher incidence of depression and hypochondriasis. Brown *et al* (1986) have since reported some success in therapy of globus sensation with antidepressants.

In our previous study (Deary *et al*, 1989) depression and somatisation were assessed using the Crown Crisp Experiential Index – a brief research questionnaire covering several aspects of neurotic illness. The aim of the present study was to assess, in greater detail, stress and depression in globus patients. Over the past five years, we have noticed that many globus patients of both sexes spontaneously identify a strong temporal relationship between the onset of their symptoms and a stressful life-event or repeated daily stressors. Therefore, we examined the degree to which globus patients experience everyday 'hassles' (Kanner, 1981) as a measure of perceived regular stress, and a preliminary attempt was made to compare the numbers of major independent life

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