A CLINICAL COMPARISON OF NOMIFENSINE AND AMITRIPTYLINE

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- 1 The study consists of a double-blind evaluation of nomifensine and amitriptyline in a group of 37 patients with primary depressive illness.
- 2 The patients were referred by their family doctors on the basis that they would ordinarily have been prescribed a tricyclic antidepressant drug. Random allocation to the treatment groups took place. Assessment took place at weekly intervals over a 4-week period using the Visual Analogue Scale for depression and anxiety, and a side-effects check-list. Patients were also assessed on the Hamilton Depression Scale before the onset and at the end of the trial.
- 3 No significant difference was found between the two groups as regards relief from depression and anxiety, although marginal differences were found in favour of the amitriptyline group.
- 4 The overall frequency of side-effects was similar in the nomifensine and amitriptyline patients. But the development of *severe* side-effects was significantly more common in the amitriptyline group.

Introduction

This study consists of a double-blind evaluation of antidepressant medication carried out in patients with primary depressive illness. The patients were referred by their general practitioners on the basis that they would ordinarily have regarded the depression as requiring the prescription of a tricyclic antidepressant drug. The aims of the trial were to compare nomifensine and amitriptyline in respect of therapeutic efficacy, rate of response and frequency and severity of side-effects.

Methods

Patients were selected for the study as described previously (Little *et al.*, 1977). A group of 39 patients fulfilling the criteria for inclusion was assembled over a period of 2.5 yr (Table 1). Two patients had to be withdrawn from the series: one failed to keep subsequent appointments and the other deteriorated and required electroconvulsive therapy (ECT). The distribution of the patients included in the trial in relation to age and sex is shown in Table 2.

An initial clinical interview which took into account the symptomatology of the disorder, life events before the onset, previous psychiatric medication, previous psychiatric episodes, family history of mental disorder and social variables, was carried out. A depressive diagnosis was confirmed and each patient was then

allocated to depressive neurosis (ICD 300.4) or depressive psychosis (ICD 296.2, 298.0) subgroupings in line with the eighth edition of the International Classification of Diseases and the British Glossary to it. Four patients, in whom neither the 'reactive' nor the 'endogenous' elements clearly predominated, were diagnosed as 'mixed depressions' (Table 3).

Random blind allocation to the nomifensine and amitriptyline treatment groups took place by code. The capsules were matched for size, shape and colour. The dosage was 25 mg three times daily, of amitriptyline or nomifensine for 3-7 d, which was then increased to 50 mg three times daily unless contra-indicated. In addition, diazepam up to 5 mg three times daily and nitrazepam up to 10 mg at night was permitted if felt to be necessary.

The patients were assessed at weekly intervals for 4 weeks. The instruments used to measure the mood changes were the Hamilton Depression Scale (HDS) (Hamilton, 1960), administered before the onset and at the end of the trial only, and the Visual Analogue Scale (VAS) (Aitken, 1969) for anxiety and depressed mood. The VAS scores observer ratings made by the authors. A side-effects check-list was also administered to each patient (Table 4). The side-effects were scored only when they had developed or become worse during the treatment period. If they were worse by one grade—for example, if the side-effect changed from mild to moderate, a grade of 1 was

Table 1 Patient allocation to treatment groups

<i>Nomifensine</i>	<i>Amitriptyline</i>	<i>Withdrawals</i>	<i>Total</i>
20	17	2	39

Table 2 Age and sex distribution (age range 18-64 years)

		<i>Male</i>	<i>Female</i>
<i>Nomifensine</i>	Mean age	42.8	48.5
	Number	8	12
<i>Amitriptyline</i>	Mean age	45.7	38.4
	Number	9	8

Table 3 Distribution by diagnosis

	<i>Nomifensine</i>	<i>Amitriptyline</i>
Depressive neurosis	8	9
Endogenous depression	9	6
Mixed depression	2	2
Reactive depressive psychosis	1	0
	20	17

Table 4

Drowsiness	0	1	2	3
Dry mouth	0	1	2	3
Weakness	0	1	2	3
Dizziness	0	1	2	3
Postural hypotension	0	1	2	3
Sweating	0	1	2	3
Restlessness	0	1	2	3
Excitement	0	1	2	3
Apprehension	0	1	2	3
Tachycardia	0	1	2	3
Blurred vision	0	1	2	3
Constipation	0	1	2	3
Insomnia	0	1	2	3

given; if they changed by two grades (for example, mild to severe), a grade of 2 was given; and, if the change was from none to severe, a grade of 3 was given.

Results

The mean scores on the HDS in the amitriptyline and nomifensine groups immediately before treatment and 4 weeks later (at the end of the trial), and also the change in scores in the two groups, are shown in Table 5. The mean scores were similar and the differences not statistically significant.

Table 5 HDS (mean $\pm$ s.e.)

	<i>Amitriptyline</i>	<i>Nomifensine</i>
Initial	27 $\pm$ 2.3	24.8 $\pm$ 1.4
Final	10.6 $\pm$ 1.4	12.3 $\pm$ 2.1
Change	16.4 $\pm$ 2.7	12.6 $\pm$ 2.5

The course of the two groups at weekly intervals, as reflected by the VAS scores for depressed mood, is shown in Figure 1. The difference is slight but consistently in favour of the amitriptyline group. A trend analysis demonstrated, however, that the difference was not significant. The trend in favour of amitriptyline as regards the VAS scores for anxiety is also seen to be marginal (Figure 2).

Pooling the total changes on the side-effects scores (see Table 4), to gain an overall impression, an average of 8.4 side-effects per patient was found for nomifensine and 7.5 for amitriptyline. The only

Figure 1 VAS scores for depression (mean $\pm$ s.d.). ▲, Nomifensine; ●, amitriptyline. **Figure 2** VAS scores for anxiety (mean $\pm$ s.d.). ▲, Nomifensine; ●, amitriptyline.

Figure 3 Severity of side-effects. a, Nomifensine; b, amitriptyline.

significant individual side-effect difference in terms of frequency was the higher incidence of dry mouth among the amitriptyline patients ($P < 0.05$). More important, however, a significantly higher percentage of patients in the amitriptyline group ($P < 0.01$) developed side-effects of *severe* degree (Figure 3). No serious side-effects occurred, although one patient in each group developed a symptomless deterioration in tests of liver function, which in both cases returned to normal gradually after treatment was stopped.

Discussion

This study compares the therapeutic efficacy and frequency of unwanted side-effects in a group of 37 patients treated with amitriptyline or nomifensine over a 4 week period with primary depressive illness

referred directly, and without previous treatment, by their family doctors. The medication was allocated on a random double-blind basis. Amitriptyline is a tricyclic drug of established antidepressant value in the treatment of depressive disorders, whereas nomifensine is a tetra-hydroisoquinoline, a member of a group unrelated to the tricyclics or monoamine oxidase (MAO) inhibitors, and only recently investigated for psychotropic activity (Hanks, 1977). The present findings showed no significant difference in terms of antidepressant efficacy or rate of response between amitriptyline and nomifensine. The slight difference in favour of amitriptyline, both as regards depression and anxiety, may possibly relate to the higher proportion of patients with endogenous depression in the nomifensine group (Table 3).

The frequency of side-effects was similar in the two groups. But, and this is perhaps the main finding of the study, *severe* side-effects were more likely to occur with amitriptyline than with nomifensine.

As the patients were treated and assessed in different parts of the country (Newcastle and Dumfries), it was felt important to establish the reliability of the assessments made by the authors working in the two areas. The fact that the level of inter-rates reliability was acceptably high in relation to the diagnosis, the VAS and the HDS, was therefore established at an early stage of the trial and is reported elsewhere (Little *et al.*, 1977).

We thank Mr Andrew Hewett of Hoechst Pharmaceuticals for statistical help; and Dr G.W. Hanks of Hoechst Pharmaceuticals for assistance during the trial. This study was approved by the Ethical Committees of Newcastle Area Health Authority (Teaching) Group and of the Crichton Royal Hospital.

References

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Discussion

PROFESSOR TURNER (Chairman) pointed out that the low incidence of adverse, including autonomic, effects attributable to nomifensine, would have been difficult to recognize without a placebo control trial.

DR DAVISON (Newcastle) wanted to know how long it took to collect 40 patients from a single general practice, as the trial by Drs Kerr and McClelland took 2.5 yr to collect 39 patients.

DR NICHOLSON (London) replied that the trial took place during a period of 2 yr and that patients were selected from a six partner group practice, presumably with a population of 15-17,000 patients.

PROFESSOR TURNER then asked if the additional expense of Dr Little's recording devices, introduced to remove observer bias, could be justified in view of the fact that there was a correlation coefficient of 0.9 between Dr Little and Dr Kerr.